Applications of Nickel-Catalyzed Cross-Coupling Methods in the Synthesis of Organofluorine Compounds

Thesis by

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To my family, friends and teachers

Acknowledgments

I have been waiting for this moment for a long time. Whenever I reflect on the past five and a half years at MIT and Caltech, the first thing that came to me is not the chemistry itself. It is always about the people. I am fortunate to have met (and known) many talented people during my graduate career. Without them, these five years would have been completely different and I am not even sure if I would have had the courage and motivation to survive in graduate school. It is really my honor to have shared some time with these people.

First of all, I need to thank my supervisor, Professor Gregory C. Fu. It has always been an invaluable experience to work with Greg. He is a special advisor, an excellent chemist, and definitely a role model. As an advisor, Greg did give me several pieces of advice when I was still a junior graduate student. Although many of these suggestions are not actually working for our desired reactions, a few of them are still quite important for my first project. Later on, I received a significant amount of freedom from Greg after becoming a senior graduate student. This is perhaps the most precious asset a student can have from the supervisor. However, Greg is always ready to help and provide his insights on all kinds of topics. Whenever I see the door of his office is open, I will stop by for a chat about some updates on my projects or even just to show off my new Apple products. Thanks to the Fu group retreats, we have the opportunities to brainstorm new projects and pursue them in the lab. I am truly proud of the fact that three of my four projects all originated from my first proposal in the group retreat. This has been quite a unique experience and I am pretty sure that it will benefit me in many ways in the future.

Nevertheless, as one old proverb describes, freedom does not come without a price. As an excellent chemist, Greg always sets very high standards for our chemistry. I probably have spent more time providing him the feasibility and necessity to pursue and publish a project than actually finishing a project. Greg will keep asking me why I think a certain piece of work is worth of investigating and publishing, what is the novelty of a project, and what we can contribute to the community. He likes playing the devil's advocate and I think he really enjoys doing that. I still remember the lesson he told me that we should not only have high standards when judging other people's work, but also hold high standards for our own chemistry. It is never easy to argue with an advisor, not to mention to convince an associated editor of *JACS*. But I did learn a lot from these processes. I might not always win the arguments but they definitely helped me to think in a more critical way. That is always a good thing.

Of course, there is another thing that I need to thank Greg for. Back in September of 2011, I was really enjoying the autumn days in the beautiful city of Boston. One Saturday morning, every member of the Fu group got an email from the boss with the title of "MIT/Caltech". Eight months later, we moved to the gorgeous city of Pasadena. Three and half years after that, I got a degree from Caltech and "fortunately" became the first Ph.D. student with a Caltech degree in the Fu group. I have never even imaged all of these but they actually happened. Although I did miss MIT and Boston, it is still abn invaluable experience to spend time at both great institutes. I think I will definitely miss the sunny days in California after I move to New Jersey. Even for the bright sunshine, I should at least thank Greg for his decisions.

The other members of my thesis committee, Professor Robert H. Grubbs, Professor Brian M. Stoltz, and Professor Jonas C. Peters, also need to be acknowledged. They have provided critical and important feedback during my 4th-year annual meeting and also my propositions exam.

The Caltech Center for Catalysis and Chemical Synthesis, which is founded by the Gordon and Betty Moore Foundation, deserves a special acknowledgment for providing financial support for me for three years. Dr. Scott C. Virgil and his wife Silva S. Virgil are really nice friends to me and always ready to solve all kinds of problems.

Next, I would like to thank every single person that has been working in the Fu group for the past five and a half years. Some of them deserve a specific mention.

Arguably, one of the many advantages of working in the Fu group is that I have had the opportunity to interact with so many amazing postdocs. Dr. Christopher J. Cordier was my first deskmate in the office. I also consider him to be my mentor in the group. This might sound weird since both he and I joined the Fu group at the same time and neither of us had ever done any cross-coupling chemistry before that! Even after spending a few years at Caltech, I still miss those nights that I spent with Chris talking about all kinds of topics back at MIT. We exchanged our opinions on recently published papers, new ideas and proposals, and philosophical topics. Typically when we finished chatting, it was already midnight. We then would tell each other goodbye and say “see you in a few hours!” Chris is one of the very few persons I have met who can always provide very critical and sharp opinions during the discussions in subgroups and group meetings. This sometimes makes people feel uneasy. However, it has always been quite useful to deliver better chemistry. He also deserves certain credit for encouraging me to

propose and actually work on those trifluoromethyl-related projects. I still remember the excitement of that afternoon when I talked to him about this simple idea and both of us were so eager to test the hypothesis. I am really delighted that the program works so well even beyond our wildest imaginations.

Dr. Huan Cong has been my benchmate for over three years since we moved to Caltech. If I say Chris taught me how to do great chemistry, then Huan is a role model for balancing life and work perfectly. This is not to say he only knows how to enjoy life. He managed to drive around 50 miles per day and keep his family happy and at the same time conquered three projects. Countless times he taught me how to live a good life as a person and also how to be an excellent chemist. He always reminds me and also pushes me to plan things earlier and prepare for all sorts of outcomes. Before I applied for a postdoctoral position at Princeton, one of our daily chatting topics was about how important it is to apply at an early time. After I secured a postdoc position, Huan then told me to learn all kinds of surviving skills as soon as possible, such as driving a car. After that, it was about the importance of graduating earlier. As a person with a slow-paced personality, it is quite difficult for me to always pre-organize all kinds of plans. However, without a doubt, I definitely missed those lessons he taught me, especially after he left the group.

Dr. Xin Mu has been a quite valuable friend since he joined the lab in early 2014. As an expert in the area of palladium chemistry and organofluorine chemistry, he shared with me many unique perspectives on these subfields. We discussed all kinds of topics during those more than ten meals we shared in a typical week. His opinions on philosophical topics, political topics, and history-related topics were always inspiring.

Both of us later became big fans of audiobooks and we have exchanged many thoughts on different books we read. He is always a role model for how to be hardworking. Whenever I feel like going home earlier, seeing Xin still working in the lab always makes me to get rid of that thought.

A number of postdocs whom I met at MIT had a tremendous impact on my chemistry and me. Dr. Rylan J. Lundgren and Dr. Alexander S. Dudnik are great pals to talk about anything about chemistry, although most of the time we only had debates on why a certain paper can be published in a certain journal. Dr. Jörg T. Binder was my first and only hoodmate. I am really lucky to have learned a lot of basic skills from him when I first joined the group. Reading his subgroups, which shows more than 500 reactions in 40 days, gave me endless motivation to do more labwork. Yuji Fujiwara defined the meaning of "working machine" when I saw his 30-page group meeting notes. He might be the most efficient chemist that I have ever known. Dr. Hien-Quang Do has never failed to inspire me to work hard. His record of completing 17 table-run entries in less than two weeks made even Greg ask him whether or not he is a prodigy in doing chromatography. Dr. Takuya Ikeda has always been good company for me to talk about a variety of topics, especially on Japanese culture. I also want to thank Dr. Alexander J. Oelke, Dr. Ashraf Wilsily, Dr. E. R. R. Chandrashekar, Dr. Jaclyn M. Murphy, and Dr. Stefan Neufeind for their input and help during my time at MIT.

After we moved to Caltech, I am also fortunate enough to encounter a number of new postdocs. Dr. Nathan D. Schley is a very special friend of mine. His effort to solve more than seven crystal structures for me is definitely worth of mentioning. As an inorganic chemist, we always have debates on organometallic papers from different

perspectives. He is also a tech geek just like me and it is really nice to talk with him about technology related topics. Dr. Xingwen Sun used to live in the same apartment with me and always took care of me just like an elder brother. His unique experience in Fudan University makes him valuable asset for me to understand the atmosphere of doing academia in China. Dr. Linglin Wu is always a bright and passionate person with exhaustless energy.

Three former graduate students in the Fu group are worth special mentioning. I would like to thank Crystal K. Chu for letting me finish her impressive project. It is a real honor to be part of such an amazing project. Shoshana Bachman is a very good friend of mine. We used to talk about all sorts of topics and I practiced the skills of mentoring during the course of helping her with the borylation project. Nicholas E. Bencivenga joined the Fu group at the same time as me. We shared one glovebox and always had a chat while setting up the screenings. His preliminary studies on the asymmetric alkynylation project indeed inspired and helped me to develop a general catalytic system and finally conquer the project.

My fellow graduate students at MIT are a group of really fantastic people. Rong Zhu has never failed to give me enough peer-pressure. I am always curious to know how he managed to publish four papers in four and a half years and still maintained a super healthy life style. Mingjuan Su is the definition of optimism. Whenever I got disappointing results in the lab, talking to her always made me feel that life and chemistry are not so bad. I would also like to thank Phillip Milner, Anna Mork, Eric Standley, Jonathan Weis, Owen Fenton, Tamara Halkina, Nootaree Niljiansku, Sarah Tasker,

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I would also like to thank the following two Caltech graduate students. Yiyang Liu from the Stoltz lab has always been a very good friend of mine since we first met at Peking University. Whenever I had questions about Caltech and Pasadena, Yiyang is definitely the right place to find an answer. Discussion with him on any topic is an enjoyable process and I could not think of any other person who has such a nice personality. Haoxuan Wang from the Reisman lab has also been very helpful during the past three years.

A number of previous graduate students and postdocs who have been working in the Fu group but did not have overlap with me deserve a very special acknowledgement. They include Dr. Christian Fischer, Dr. Xin Dai, Dr. Bunnai Sato, Dr. Neil A. Strotman, Dr. Sha Lou, Dr. Nathan A. Owston, Dr. Jianwei Sun, Dr. Hsyueh-Liang (Dino) Wu, Dr. Jorge Esquivias, Jianrong (Steve) Zhou, Forrest Arp, Sunghee Son, Sean W. Smith, and Pamela M. Lundin. In my opinion, I basically learnt how to do cross-coupling chemistry from reading the subgroup notes of these people. Additionally, the ligands these co-workers have synthesized (and left for the lab) are still playing important roles for the development of new methods. Their results that are preserved in piles of papers and notebooks, no matter positive or negative, never fail to provide me with endless courage and motivation to overcome any difficulties that I have encountered in my own projects. Sometimes, the only thing that really matters is a little bit of hope. Therefore, I feel really lucky to be able to accept the optimism and courage from these former group members.

Professor Rick L. Danheiser, Professor Timothy F. Jamison, Professor Richard R. Schrock, Professor Stephen L. Buchwald, and Professor Gregory C. Fu are great teachers for delivering excellent chemistry courses in the first year of my graduate studies. Professor Patricia W. Brennecke's writing course has always been a relaxing two hours for me after intense studies of chemistry. I also want to thank Professor Timothy M. Swager and Professor Gregory C. Fu for providing opportunities for me to TA for them.

My supervisors and mentors during my undergraduate studies, including Professor Zhen Yang and Professor Jiahua Chen at Peking University and Professor Yefeng Tang at Tsinghua University, have always played very crucial roles in my graduate career. The training I received from the Yang group as an undergraduate has always help to facilitate and assistant my research in the graduate school.

I must also express my gratitude to Professor David W. C. MacMillan at Princeton University for providing me with a postdoctoral position in his group. The chemistry developed in the MacMillan lab has never failed to fascinate me since the beginning of my graduate study and I am really excited to be able to work in different areas.

I would like to thank a few friends at MIT. Zhenlong Zhao and Wenzhe Wei have been my roommates for one year and that period of time has become unforgettable memories for me. Hongkai Zhang was my roommate during my second year at MIT. As an undergraduate at MIT and Ph.D. candidate at Harvard, he always had numerous anecdotes to share with me about these two universities. My friends in the great Boston area, including Wen Sang (MIT), Lei Sun (MIT), Zhe Wang (MIT), Chi Zhang (MIT),

Lu Yang (MIT), Yi Zeng (MIT), Ziyang Zhang (Harvard), and Fanke Meng (Boston College), really make my days at MIT much better.

Several friends in the Caltech community really make my days here colorful. I am so glad to know Dr. Yichen Tan from the Peters lab. Yichen might be the most optimistic person that I have ever known. I used to go shopping and dinning and watch movies with him and his wife Rong Hu in the weekends. I am even more delighted to know that we will have a reunion in New Jersey very soon! The following people from other research groups at Caltech also deserved to be acknowledged: Dr. Fei Sun (the Arnold group), Dr. Chen Xu (the Reisman group), Dr. Wen-Bo (Boger) Liu (the Stoltz group), Dr. Xiangyou Xing (the Stoltz group and the Grubbs group), Dr. Fan Liu (the Goddard group), and Dr. Miles Johnson (the Peters group). My friends in the great Los Angeles area including Dr. Zhongwei Zhu (UC Berkeley), Yumeng Xi (UC Berkeley) and Sino Zheng (USC), should also be included in such a list.

I would like to thank a number of Caltech staff for maintaining the institute in many ways, including Dr. David VanderVelde from the NMR laboratory, Dr. Mona Shahgholi from the mass spectrometry laboratory, Dr. Michael K. Takase, and Larry Henling from the X-ray crystallography facility, administrative assistants Agnes Tong, Anne Penny, Paige Johnson, and Julianne Just, Stockroom manager Joe Drew, and purchasing assistant Steve Gould. Laura Flower Kim and Daniel Yoder from the International Student Programs (ISP) of Caltech have provided me a lot of help in the past three years especially at the time when I transferred to Caltech. I also want to express my thanks to Ivan Shin for his very special friendship.

Several MIT staff also deserve to be thanked for their input and help during my two-year stay, including graduate administrators Susan Brighton and Melinda Cerny, administrative assistants Sarah Fowler, Mary Turner, and Diane Johansen, and Jeffrey Simpson, Anne Gorham, and Li Li from the Department of Chemistry Instrumentation Facility.

I would also like to thank two long-time friends, Fei Qiao and Danping (Geri) Huang, for their support and their very special friendship.

Last but not least, I would like to thank my parents for always supporting me and respecting my decisions even though in many cases they don't really understand what I am doing. Thanks for always believing in me and providing endless courage and comfort to help me overcome all kinds of challenges and difficulties. I love you.

Yufan Liang

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Abstract

The applications of nickel-catalyzed cross-coupling strategy to the synthesis of organofluorine compounds are explored in this thesis.

Chapter 2 describes the development of the first enantioselective cross-coupling method using secondary geminal dihalides as electrophiles. This method provides a unique approach for the generation of enantioenriched tertiary alkyl fluorides. These cross-coupling products can be further transformed into a variety of potentially valuable chiral building blocks.

Chapter 3 describes the development of a practical and versatile Negishi alkylation method employing α-halo-α-perfluoroalkyl secondary electrophiles. Target molecules bearing perfluoroalkyl-substituted (including trifluoromethyl-substituted) tertiary carbons can be easily generated from fluorinated electrophiles. Competition experiments and mechanistic studies have been performed to reveal the unique properties of these electrophiles and also prove the existence of alkyl radicals.

Chapter 4 describes the development of an asymmetric Negishi arylation protocol with α-halo-α-trifluoromethyl secondary electrophiles. This study provides a unique approach to construct trifluoromethyl-substituted tertiary stereocenters. The optimized condition can also be directly applied to substrates bearing an array of fluoroalkyl groups.

Chapter 5 details the progress towards the development of an asymmetric alkynylation method employing α-halo-α-trifluoromethyl secondary electrophiles. Preliminary studies also demonstrate that the protocol we developed has the potential to be used for other non-fluorinated secondary electrophiles.

Published Content and Contributions

1. Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520–5524.

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In this manuscript, Professor Fu conceived the idea to apply geminal dihalides in asymmetric cross-coupling processes. I designed the research and performed all of the experimental work. Professor Fu and I wrote the manuscript together.

2. Liang, Y.; Fu, G. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 9047–9051.

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URL: http://onlinelibrary.wiley.com/doi/10.1002/anie.201503297/abstract

In this manuscript, I conceived the idea to apply perfluoroalkyl-substituted electrophiles in cross-coupling processes. I designed the research and performed all of the experimental work. Professor Fu and I wrote the manuscript together.

3. Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9523–9526.

DOI: 10.1021/jacs.5b04725

URL: http://pubs.acs.org/doi/abs/10.1021/jacs.5b04725

In this manuscript, I conceived the idea to apply trifluoromethyl-substituted electrophiles in asymmetric cross-coupling processes. I designed the research and performed all of the experimental work. Professor Fu and I wrote the manuscript together.

Table of Contents

List of Abbreviations

Å	Ångstrom
$[\alpha]^{25}_{D}$	specific rotation at wavelength of sodium D line
Aq	aqueous
Ar	aryl
BBN	borabicyclononane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
i-Bu	*iso*-butyl
t-Bu	*tert*-butyl
c	concentration for specific rotation measurements
ºC	degrees Celsius
calcd	calculated
cat	catalytic
CF_3	trifluoromethyl
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet
D	deuterium
DMAP	4-dimethylaminopyridine
DMA	*N,N*-dimethylacetamide

DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
e.g.	for example (Latin “exempli gratia”)
eq	equation
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
g	gram(s)
GC	gas chromatography
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
i.e.	that is (Latin “id est”)
IR	infrared (spectroscopy)
J	coupling constant
L	liter

LDA	lithium diisopropylamide
lit.	literature value
m	multiplet; milli
m	meta
m/z	mass to charge ratio
M	metal; molar; molecular ion
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MHz	megahertz
mL	milliliter
μ	micro
min	minute(s)
MS	molecular sieves
N	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution

pin	pinacolato
ppm	parts per million
i-Pr	isopropyl
Py	pyridine
Pybox	pyridine bis(oxazoline)
q	quartet
ref	reference
R_F	perfluoroalkyl
r.t.	room temperature
s	singlet or strong or selectivity factor
sat.	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxy
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight

Ts	*p*-toluenesulfonyl
X	leaving group

CHAPTER 1

An Overview

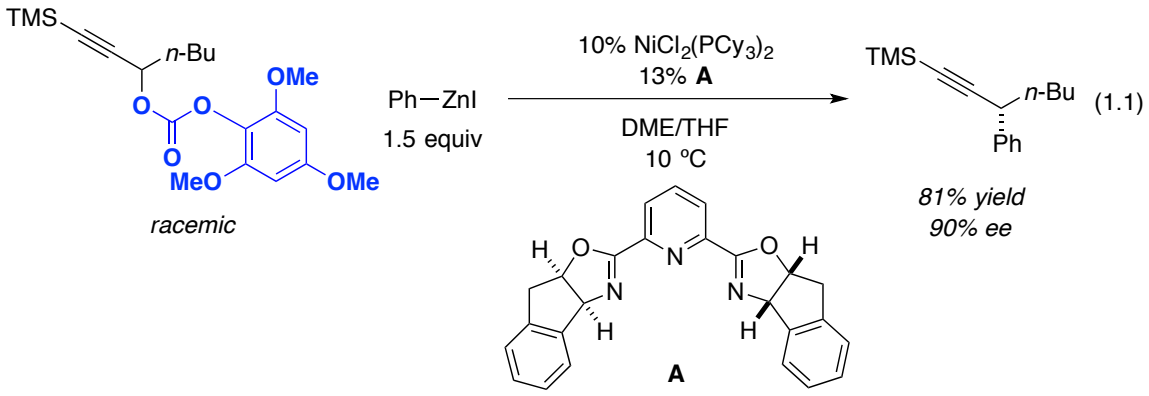
1.1 Nickel-Catalyzed Cross-Coupling Methods Developed in the Fu Group: Recent Developments

Transition-metal catalyzed cross-coupling reactions have become a powerful tool to construct carbon–carbon bonds and carbon–heteroatom bonds.[1] Although early studies in this area mainly focused on using palladium complexes as catalysts, recently more and more evidence has proven that nickel catalysts might be a better choice for certain challenging cases.[2]

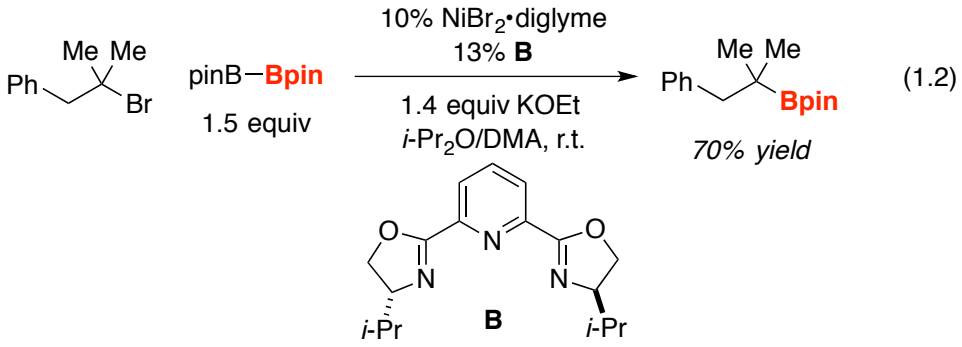
The Fu group started working in the field of cross-coupling more than 15 years ago. Initially, we employed palladium complexes as catalysts and developed a series of non-asymmetric cross-coupling reactions.[3] Later on, we also observed that nickel catalysts are more powerful than their palladium counterparts for more challenging processes, especially when alkyl electrophiles are present. Starting from 2003,[4] we initiated a series of projects employing nickel catalysts in cross-coupling methods with secondary alkyl electrophiles as substrates. In 2005, for the first time we demonstrated that nickel catalyst could promote an enantioselective and stereoconvergent cross-coupling between a *racemic secondary* alkyl electrophile and a *primary* alkyl nucleophile.[5] Since then, our group has devoted tremendous effort towards the developments of novel nickel-catalyzed cross-coupling processes using alkyl electrophiles.[6] We were especially interested in providing new protocols of

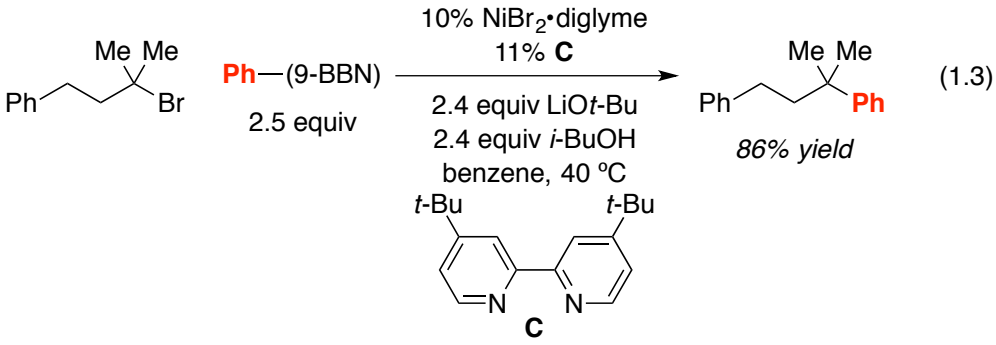
enantioselective cross-coupling reactions starting from *racemic* starting materials. Some of our recent progress (including non-asymmetric methods) will be summarized below.

In terms of exploring new classes of electrophiles, Dr. Alexander J. Oleke and Dr. Jianwei Sun were able to demonstrate that enantioselective Negishi arylations can be performed using secondary alkyl electrophiles bearing an *oxygen* leaving group instead of a halogen atom (eq 1.1).[7]

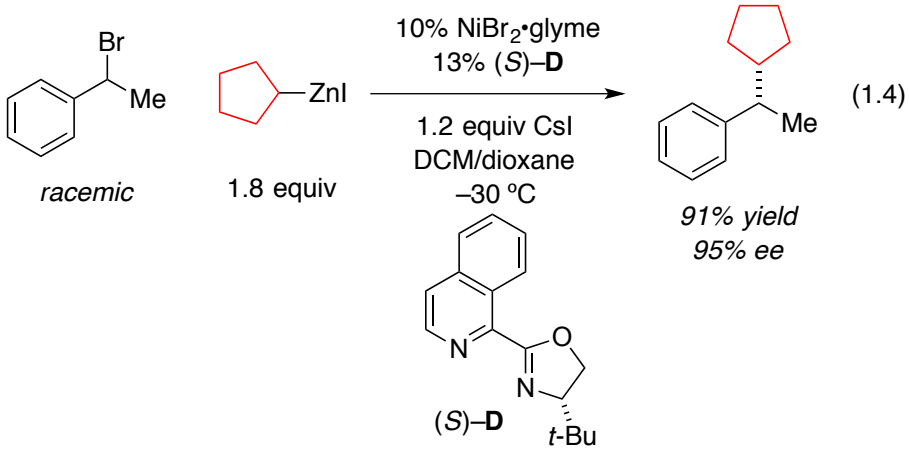


Dr. Alexander S. Dudnik and graduate student Susan L. Zultanski showcased that *unactivated tertiary* alkyl halides can be used in non-asymmetric nickel-catalyzed carbon–boron[8] and carbon–carbon[9] bond-forming processes (eqs 1.2 and 1.3).

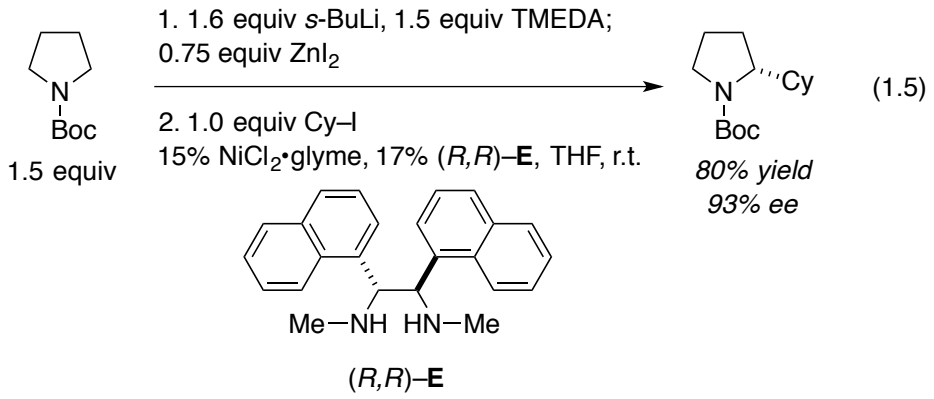




In terms of demonstrating new reactivity of nucleophiles, Dr. Jorge T. Binder and Dr. Christopher J. Cordier demonstrated for the first time that enantioselective *secondary alkyl–secondary alkyl* cross-couplings are feasible (eq 1.4).[10] Although only one stereocenter is formed in such a process, this study provides very promising lead for further investigations on asymmetric cross-couplings using secondary alkyl nucleophiles.

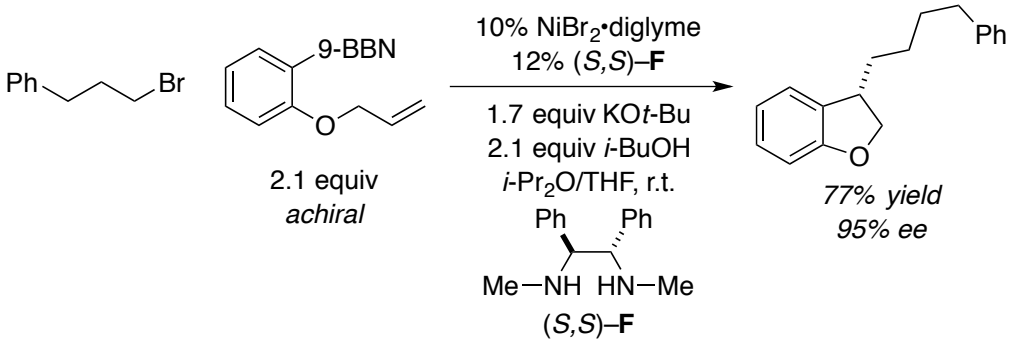


Dr. Christopher J. Cordier and Dr. Rylan J. Lundgren were able to provide a new enantioconvergent cross-coupling employing a *racemic* alkylmetal reagent and unactivated secondary electrophiles (eq 1.5).[11]



(1.5)

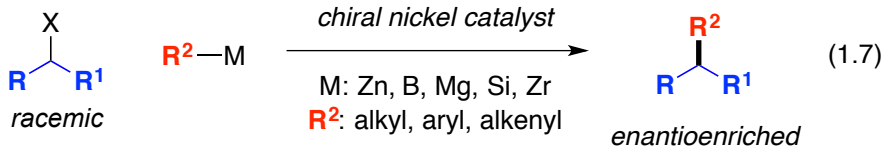
Dr. Huan Cong showcased that stereoselective cross-coupling reactions can also be initiated from *achiral* nucleophiles via a cyclization/cross-coupling sequence (eq 1.6).[12]



(1.6)

Furthermore, Dr. Nathan D. Schley completed the first detailed mechanistic study on an enantioselective Negishi arylation method.[13] The results and observations accumulated in this project might shed some light on the mechanisms of other asymmetric nickel-catalyzed cross-coupling reactions.

Although these studies all serve as proof-of-principle examples that might help us to exploit new territories, by the time I joined the Fu laboratory in early 2011, most of the accomplished and ongoing projects in the group have been focused on the development of novel enantioselective cross-coupling reactions employing *racemic secondary* alkyl electrophiles with all types of nucleophilic organometallic reagents (eq 1.7).



This is a really powerful and versatile method to construct *tertiary* stereocenters through enantioselective carbon-carbon bond-forming processes. A variety of enantioenriched products bearing synthetically valuable functional groups can be generated using this strategy (Figure 1.1). Many recently accomplished projects in the group have been devoted to expanding the electrophile scope of this type of chemistry.[14]

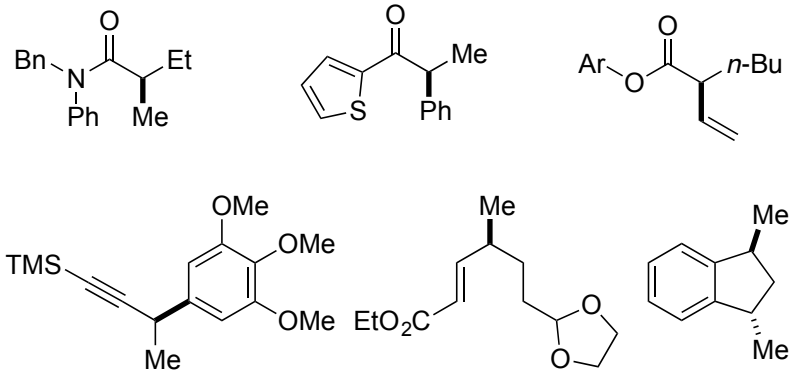


Figure 1.1. Selected Chiral Cross-Coupling Products

The overall theme of my graduate studies is to apply this established strategy to a previously underdeveloped field, namely organofluorine chemistry. We were trying to employ *fluorine*- and *fluoroalkyl*-substituted electrophiles in the cross-coupling methods and generate fluorine-containing compounds as targets. We believed that the success of such a strategy would benefit both nickel-catalyzed cross-coupling chemistry and also organofluorine community.

1.2 Carbon–Carbon Bond-Forming Strategy for the Synthesis of Organofluorine Compounds

During the last decade, substantial progress has been made in the field of organofluorine chemistry.[15] Although numerous methods have been reported for the synthesis of target molecules containing sp^2 C–F[16] and sp^2 C–CF_3[17] moieties, the construction of sp^3 C–F and sp^3 C–CF_3 subunits are still challenging.

We were especially interested in two types of targets (Figure 1.2), namely chiral tertiary alkyl fluorides and chiral molecules containing CF_3-substituted tertiary stereocenters. At the time I joined the Fu group in 2011, there were very few general methods for the asymmetric syntheses of these chiral building blocks. The existing catalytic enantioselective methods also suffer from limited scope. Thus, it left a lot of space for the development of general and novel asymmetric approaches for the construction of these structures.

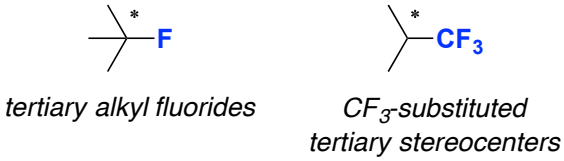


Figure 1.2. Challenging and Interesting Fluorine Compounds

Typically, there are two strategies to create these stereocenters. The first one, which is also the most popular one, is through enantioselective fluorinations or trifluoromethylations (Figure 1.3a).[18] Although some success has been achieved by adopting this method, it is not without limitations. For us, the biggest obstacle to apply this strategy is that transition-metal-catalyzed sp^3 C–F bonds and sp^3 C–CF_3 bonds

formations can be very challenging in a cross-coupling process partially due to the difficulties in the reductive-elimination step.[19] Therefore, we decided to pursue the other approach, namely through carbon–carbon bond-forming processes with fluorinated starting materials (Figure 1.3b). Despite the indirect nature of this strategy, it can sometimes provide certain benefits and solve problems that cannot be tackled by the other strategy.[20]

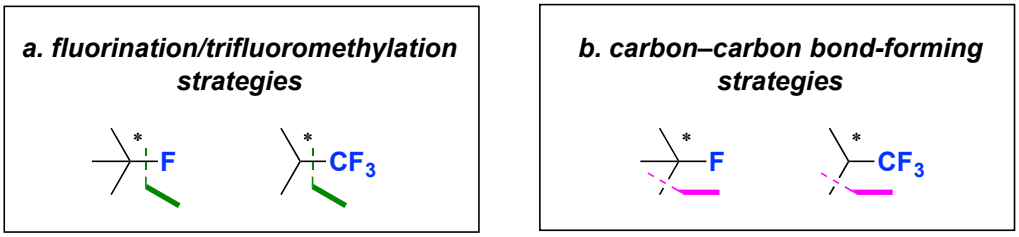


Figure 1.3. Two Strategies to Construct Fluorine and CF_3-Substituted Stereocenters

In order to achieve these transformations using our nickel-catalyzed cross-coupling reactions, we need to develop new types of fluorinated electrophiles. Through my graduate studies, we have introduced two classes of electrophiles in our cross-coupling systems (Figure 1.4)

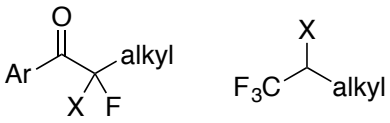


Figure 1.4. New Families of Electrophiles

By applying nickel-catalyzed cross-coupling chemistry to these fluorinated electrophiles, we were able to establish four novel cross-coupling methods, including

three asymmetric protocols. They provide unique approaches to access potentially valuable fluorine-containing building blocks (Figure 1.5) that cannot be synthesized by other existing methods.

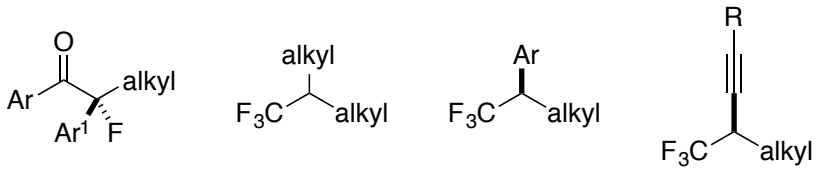
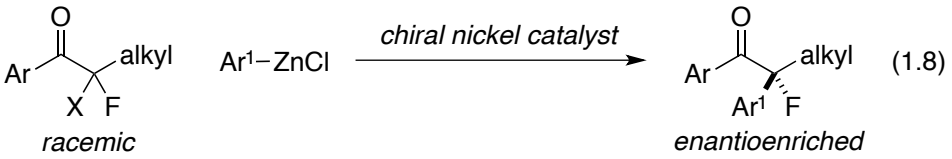


Figure 1.5. Fluorine-Containing Cross-Coupling Products

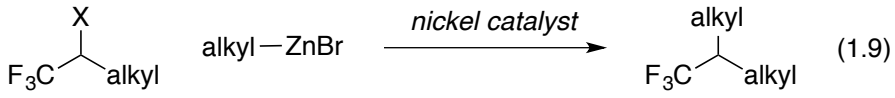
On the other hand, these new methods also help to enrich the cross-coupling chemistry. Specifically, through the development of an asymmetric alkynylation protocol for CF_3-substituted electrophiles (see Chapter 5 for details), we revealed a *universal* method to enantioselectively incorporate an alkynyl nucleophile with a variety of classes of secondary alkyl electrophiles. A longstanding problem in our system, namely, how to enantioselective cross-couple *sp-hybridized* nucleophiles, has been partially solved.

1.3 Overview of Individual Chapters

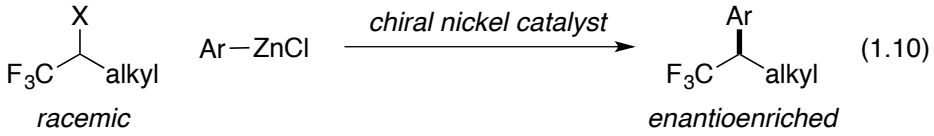
We started our journey by examining the possibility to construct fluorine-containing tertiary stereocenters. In Chapter 2, a catalytic asymmetric Negishi arylation method with germinal dihalides as electrophiles is described (eq 1.8). This method serves as the first example of enantioselective cross-coupling employing alkyl germinal dihalides as substrate. It also demonstrates the idea that our carbon–carbon bond-forming approach can actually be used to generate enantioenriched tertiary alkyl fluorides.



During the course of this study, we were questioning the possibility of applying the same concept to the construction of trifluoromethyl-substituted tertiary carbons. In Chapter 3, as a proof-of-concept, we showcased a Negishi alkylation protocol to cross-couple α-halo-α-trifluoromethyl secondary electrophiles (eq 1.9). This method can also be applied without modifications to other perfluoroalkyl-substituted substrates.

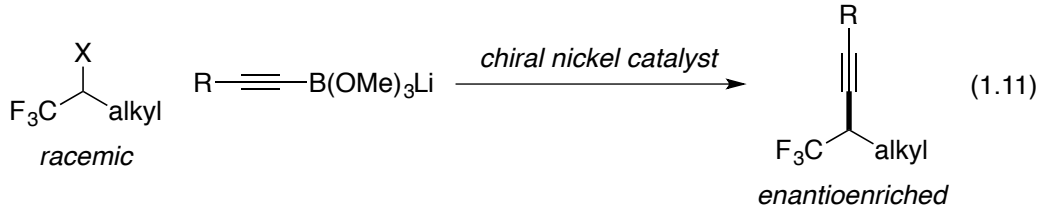


However, despite the practical and versatile nature of this protocol, we were not able to develop an enantioselective version at this stage. Fortunately, at the same time, we obtained very promising leading results by switching the nucleophiles from an *alkylzinc* reagent to an *arylzinc* reagent. Based on these preliminary results, we developed an asymmetric Negishi arylation reaction to generate CF_3-substituted tertiary stereocenters in excellent enantioselectivity and good yield (eq 1.10). Details of this study are provided in Chapter 4.

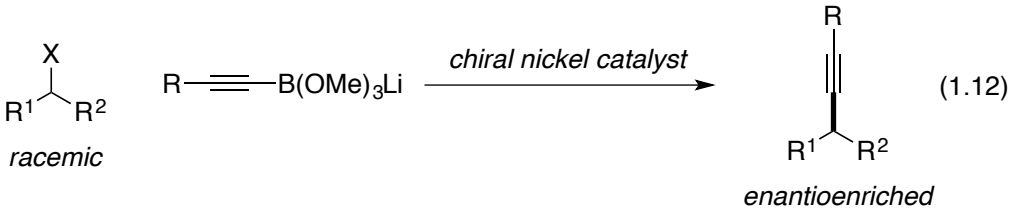


Finally, in Chapter 5, the details of the development of an asymmetric alkynylation method using these trifluoromethyl-substituted electrophiles are provided (eq 1.11). We were able to solve the longstanding alkynylation problem with our fluorine-containing electrophiles and a Suzuki cross-coupling protocol. More importantly,

we were very pleased to realize that this enantioselective alkynylation protocol can be directly applied to an array of racemic secondary alkyl electrophiles (eq 1.12). Some of these preliminary results are also included in Chapter 5.



(1.11)



(1.12)

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(19) For an example, see: Dubinina, G. G.; Brennessel, W. W.; Miller, J. L.; Vicic, D. A. *Organometallics* **2008**, *27*, 3933–3938.

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CHAPTER 2

Asymmetric Negishi Cross-Couplings of Racemic α-Halo-α-Fluoroketones[+]

2.1 Introduction

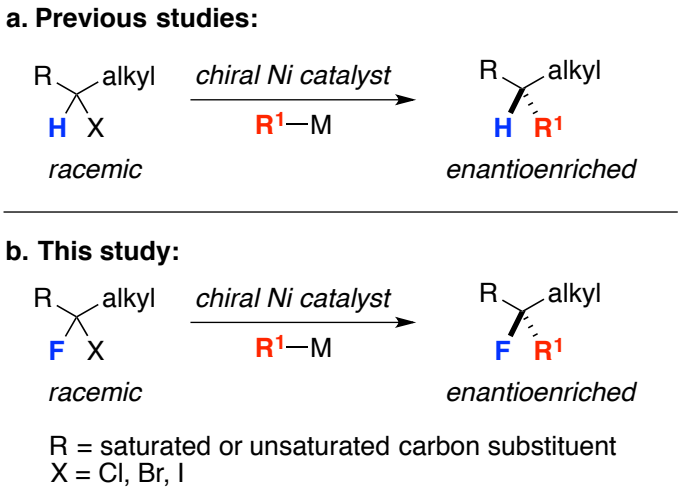
Small molecules containing fluorine atoms have shown potential applications in a variety of disciplines.[1] Thus, significant effort has been made in the development of methods for the preparation of organofluorine compounds.[2] In the case of alkyl fluorides, a number of methods have been reported in the asymmetric synthesis of stereocenters bearing a fluorine atom,[3] particularly α to a carbonyl group. Although the construction of secondary stereocenters has been addressed by many studies,[4] only a few methods have studied the generation of tertiary stereocenters. To date, only cyclic or doubly activated acyclic α-fluorocarbonyl compounds[5] can be synthesized via existing asymmetric catalytic methods.[6] As far as we are aware, no general catalytic asymmetric methods have been developed for the synthesis of simple tertiary α-fluorinated *acyclic* ketones.[7–9]

During the past decade, the Fu group has developed a variety of nickel-catalyzed enantioselective cross-coupling methods, employing *racemic* alkyl electrophiles as substrates.[10] So far, all of the successful electrophiles have been *secondary* alkyl electrophiles (Scheme 2.1a). In order to further explore the power of this carbon–carbon bond-forming strategy, we have now begun to investigate enantioselective cross-couplings of other families of electrophiles, starting with secondary *germinal dihalides*

[+] Portions of this chapter have appeared in the previous publication and the supporting information found therein: Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520–5524.

(Scheme 2.1b). The goal of such a transformation is to achieve *selective cleavage* of the C–X bond with the C–F bond intact and at the same time to form the new C–C bond efficiently and highly enantioselectively. This new strategy would provide an unprecedented enantioselective cross-coupling method employing alkyl germinal dihalides[11] and also a unique approach for the catalytic asymmetric synthesis of tertiary alkyl fluorides.

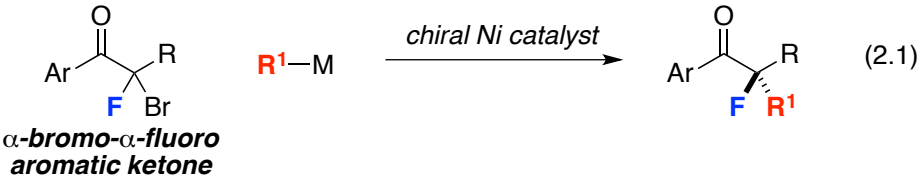
Scheme 2.1. Geminal Dihalides as Electrophiles in Asymmetric Cross-Coupling Reactions



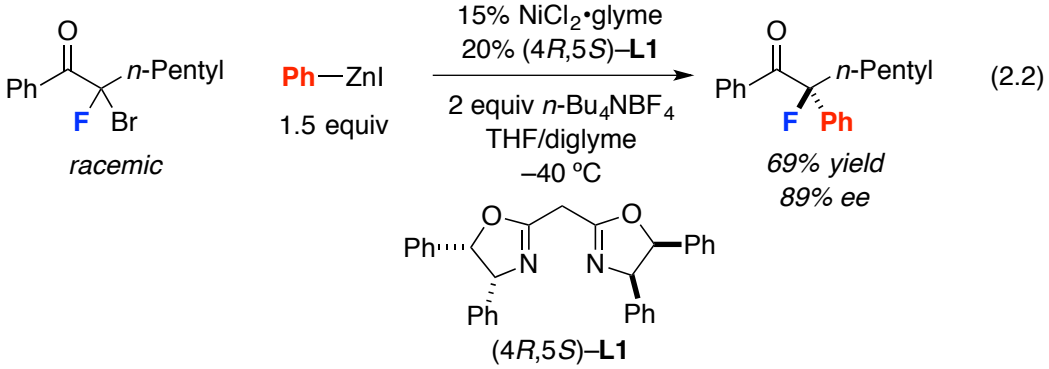
2.2 Optimization

Considering the high interest in the asymmetric synthesis of α-fluorocarbonyl compounds, we decided to start our study by choosing α-bromo-α-fluoro aromatic ketones as the model substrates (eq 2.1). This decision is based on two reasons. First, these electrophiles can be easily prepared from readily available aromatic ketones in two steps using commercially available and cheap fluorinating reagents.[12] Second, our group

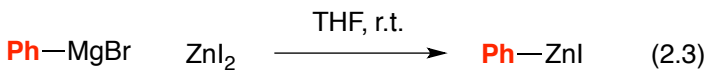
has already reported two enantioselective cross-coupling methods using structurally related α-bromo aromatic ketones as susbtrates.[13] These success can serve as a starting point for the optimization of our desired transformation.



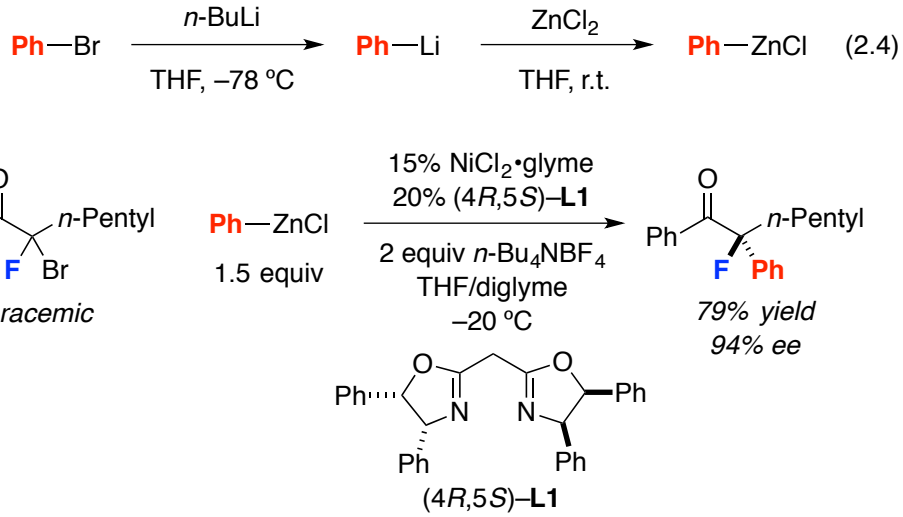
Unfortunately, our attempts to employ the racemic α-bromo-α-fluoroketone under previously developed asymmetric Negishi[13a] and Kumada[13b] conditions failed to give any cross-coupling product (<2% yield). After extensive screening, we identified a suitable condition to provide the cross-coupling product in moderate yield and enantioselectivity (eq 2.2).



Although the condition shown in eq 2.2 led to promising results, further optimization based on this system failed to improve the enantioselectivity. Moreover, a brief survey of the substrate scope also gave very disappointing results. One feature of the reaction shown in eq 2.2 is that the nucleophilic arylzinc reagent is prepared *in situ* from the corresponding aryl Grignard reagent and ZnI_2 (eq 2.3).

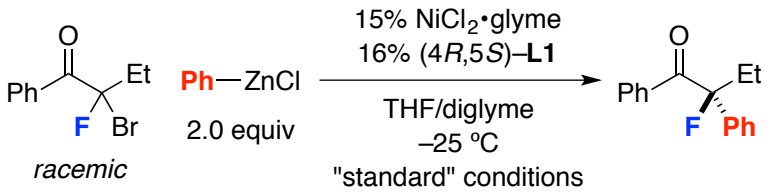


Lei and co-workers have reported that aryl zinc reagents prepared from aryl Grignard reagents and *aryllithium* reagents can display significantly different properties in palladium-catalyzed Negishi arylation reactions.[14] Thus, we decided to test the reactivity of arylzinc reagents which are prepared from aryllithium reagents (eq 2.4). We were delighted to see that this new type of arylzinc reagent provided much better results (eq 2.5) under related conditions. Prior to this study, we have never applied this method to the generation of arylzinc reagents in Negishi cross-coupling methods. Thus, these results also provided an alternative way to *in situ* generate arylzinc reagents from readily available materials.



Further optimization helped to establish a suitable condition that can deliver the cross-coupling product in moderate yield and excellent enantioselectivity (Table 2.1, entry 1). The impact of various reaction parameters on the efficiency of this new method has been provided in Table 2.1.

Table 2.1. Effect of Reaction Parameters[a]



entry	variation from the "standard" conditions	ee (%)	yield (%)[b]
1	none	97	68
2	no $NiCl_2$•glyme	–	<2
3	no (4*R*,5*S*)–**L1**	–	<2
4	10% $NiCl_2$•glyme, 11% (4*R*,5*S*)–**L1**	97	49
5	1.2 equiv PhZnCl	97	51
6	r.t.	83	17
7	THF only	90	38
8	diglyme only	91	19
9	0.1 equiv H_2O	97	65
10	in air in a closed vial	94	27

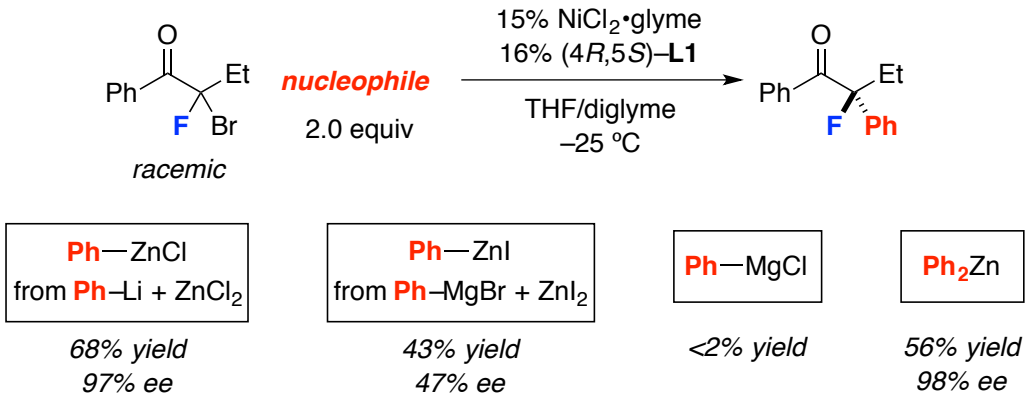
[a]All data are the average of two experiments. [b]The yields were determined through analysis by ^{19}F NMR spectroscopy, with the aid of an internal standard.

In the absence of the nickel source or of the ligand **L1**, essentially no product formation is observed (entries 2 and 3). The employment of less catalyst (entry 4) or less arylzinc reagent (entry 5) leads to a modest decrease in yield. Performing the cross-coupling reaction at room temperature or with a single solvent leads to significantly worse results (entries 6 to 8). The reaction is not very sensitive to moisture (entry 9). Conducting the reaction under air results in decreased efficiency (entry 10). From a practical point of view, both the nickel source and ligand **L1** are commercially available and air-stable.

The choice of the nucleophilic cross-coupling partner is quite crucial to this transformation. A number of previously reported aryl nucleophiles have been tested

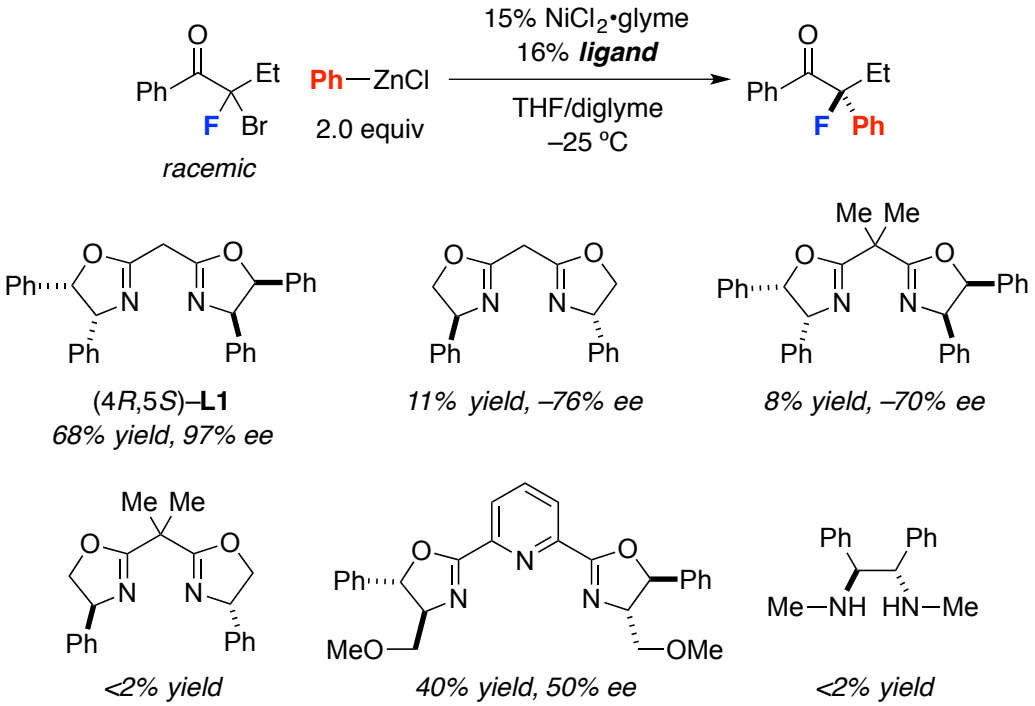
under the optimized conditions. As shown in Scheme 2.2, the arylzinc reagents prepared from aryllithium reagents give the best results.

Scheme 2.2. Effect of Nucleophiles



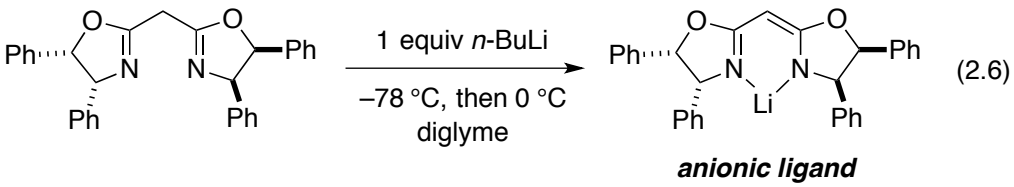
The ligand **L1** plays a vital role in this reaction. Several structurally related or previously employed chiral ligands have been tested under the optimized conditions. As shown in Scheme 2.3, none of these ligands can give even comparable results.

Scheme 2.3. Effect of Ligands

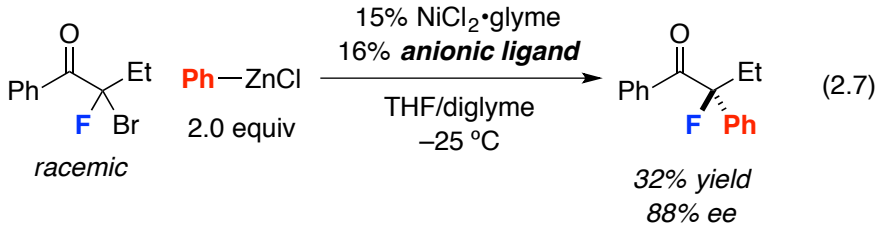


A negative ee value signifies that the major product of the reaction is the opposite (R) enantiomer.

One possible explanation for the importance of ligand **L1** is that the proton in the methylene position is acidic enough to be deprotonated by basic nucleophiles during the course of the reaction. This might lead to active nickel complexes that can display different properties. We performed a control experiment to test this hypothesis. Ligand **L1** is deprotonated with *n*-BuLi and an anionic ligand is generated prior to the cross-coupling reaction (eq 2.6). However, under our optimized conditions, reactions conducted using the anionic ligand cannot provide comparable results (eq 2.7). Thus, the effect of this ligand **L1** might be more complicated than we assumed and further studies are needed to provide more insights.



(2.6)

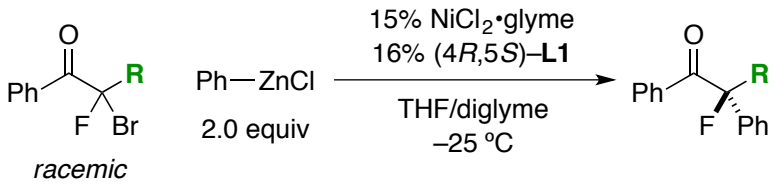


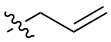
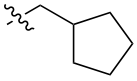
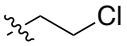
(2.7)

2.3 Scope

With the optimized conditions in hand, we started to explore the scope of this new method. The scope with respect to the alkyl side-chains (R) is fairly broad (Table 2.2). An electrophile bearing a bulky isopropyl substituent can even cross-couple with the nucleophile to give the product in moderate yield and enantioselectivity (entry 5). Functional groups including a terminal olefin (entry 3) and a primary alkyl chloride (entry 6) can both be compatible with our conditions.

Table 2.2. Scope with Respect to the Electrophile: Alkyl Side-Chain[a]

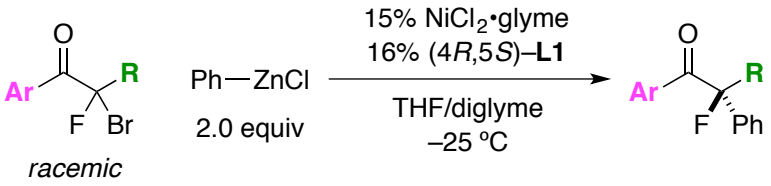


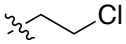
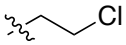
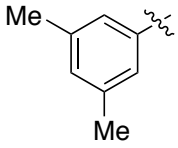
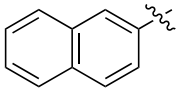
entry	R	ee (%)	yield (%)[b]
1	Et	97	62
2	CH_2Ph	98	73
3		97	43
4		91	59
5	*i*-Pr	82	55
6		98	62

[a]All data are the average of two experiments. [b]Yield of purified product.

Highly enantioselective cross-coupling can be uniformly achieved whether the aryl group (Ar) is para-, meta-, or ortho-substituted, and whether it is electron-rich or electron-deficient (Table 2.3). Additionally, ortho-substituted electrophiles (entries 8 and 9) can deliver the product in good ee, which is quite different from the trends we observed previously in other asymmetric arylation projects.[13]

Table 2.3. Scope with Respect to the Electrophile: Aryl Group[a]

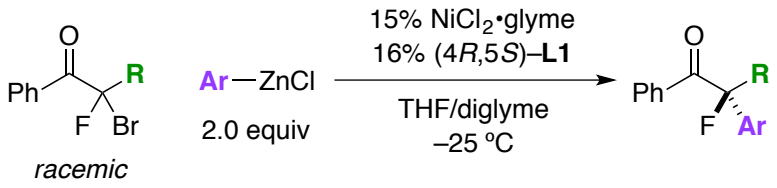


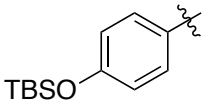
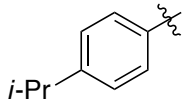
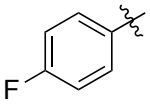
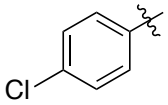
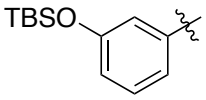
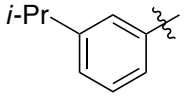
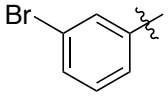
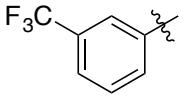
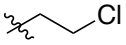
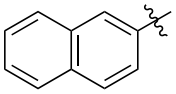
entry	Ar	R	ee (%)	yield (%)[b]
1	X = OMe	CH_2Ph	96	62
2	*t*-Bu		98	76
3	Ph	Et	96	54
4	F		97	63
5	X = OMe	Et	97	54
6	F	CH_2Ph	97	59
7		Et	97	65
8	X = OMe	Et	92	62
9	Me	CH_2Ph	94	70
10		Et	97	51

[a]All data are the average of two experiments. [b]Yield of purified product.

Next, we turned our attention towards the scope of nucleophiles (Table 2.4). A variety of para- and meta-substituted arylzinc reagents can be employed under our optimized conditions. Functional groups including a silyl ether, an aryl chloride, and an aryl bromide can all be tolerated.

Table 2.4. Scope with Respect to the Nucleophile[a]

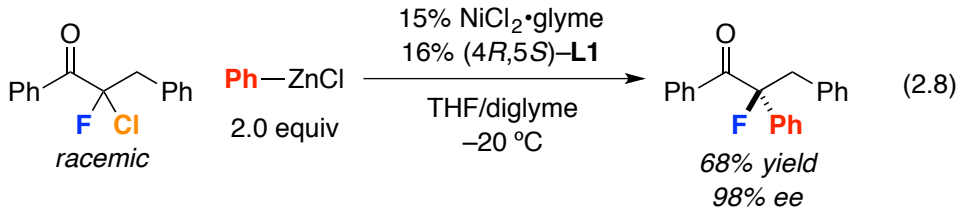


entry	R	Ar	ee (%)	yield (%)[b]
1	CH_2Ph		97	67
2	Et		97	71
3[c]	CH_2Ph		94	65
4[c]	CH_2Ph		93	70
5	CH_2Ph		99	78
6	Et		97	73
7[c]	CH_2Ph		91	58
8[c]	CH_2Ph		90	65
9			98	58

[a]All data are the average of two experiments. [b]Yield of purified product. [c]Reaction temperature: –20 °C.

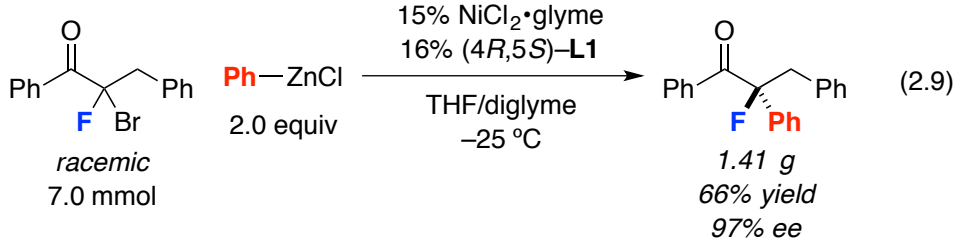
Additionally, we are also pleased to observe that this method is not limited to cross-couple α-bromo-α-fluoroketones. A racemic α-*chloro*-α-fluoroketone can undergo

cross-coupling reaction under related conditions to generate the product in moderate yield and excellent enantioselectivity (eq 2.8).



(2.8)

To test the scalability of this method, a gram-scale experiment was performed (eq 2.9). Using 7.0 mmol electrophile, the reaction proceeded smoothly to generate 1.41 gram product in excellent enantioselectivity.



(2.9)

However, this cross-coupling method is not without limitations. Several unsuccessful electrophiles and nucleophiles under our optimized conditions (entry 1 in Table 2.1) are shown in Figure 2.1.

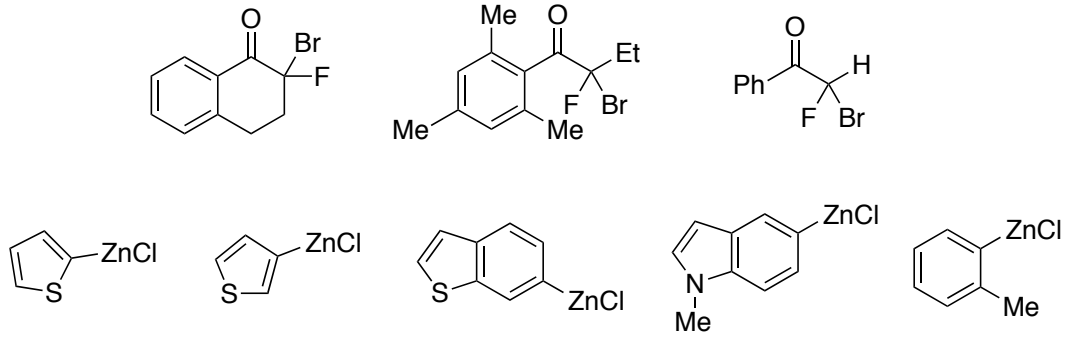


Figure 2.1. Unsuccessful Cross-Coupling Partners

Some other notable features of this cross-coupling method are summarized below:

A. One major side reaction is the hydrodebromination of the electrophiles and the products are generated as racemates.

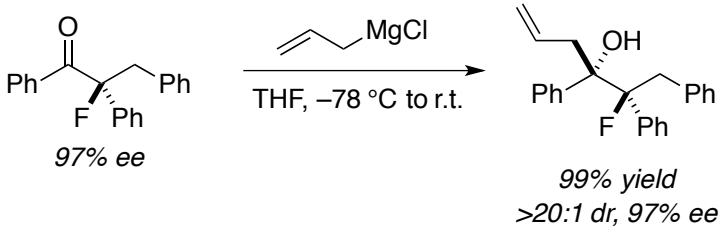
B. No kinetic resolution of the electrophile was observed (<5% ee) during the course of the reaction.

C. The cross-coupling product was stable (no C–F bond cleavage or erosion in ee) under our optimized conditions and its ee value was a constant.

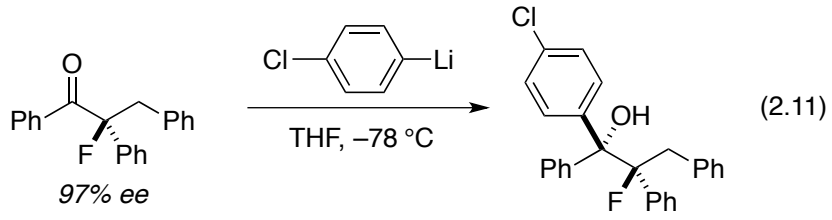
2.4 Derivatization of Cross-Coupling Products

To highlight the utility of these enantioenriched cross-coupling products, we performed a series of transformations to convert them into a variety of valuable chiral organofluorine compounds.

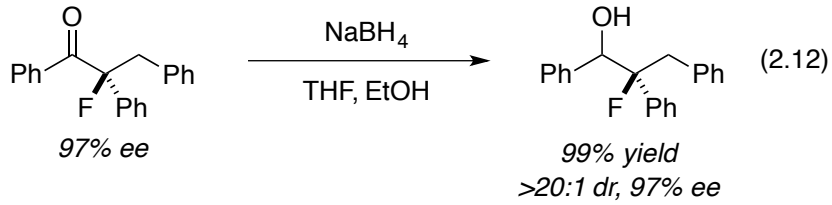
When the enantioenriched α-fluoroketone is treated with an allyl Grignard reagent and an aryllithium reagent, nucleophilic additions to the carbonyl group proceed with excellent diastereoselectivity to generate densely functionalized products (eqs 2.10 and 2.11).[15] Additionally, reducing the ketone moiety with $NaBH_4$ also leads to the alcohol product as a single diastereomer (eq 2.12).[16]



(2.10)

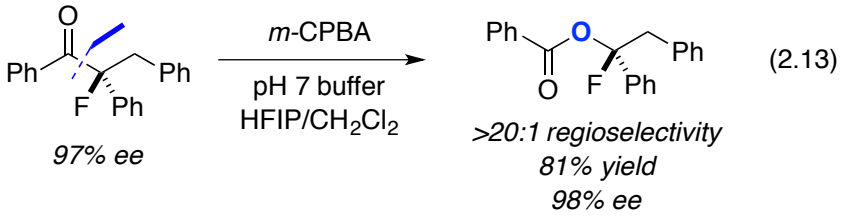


(2.11)

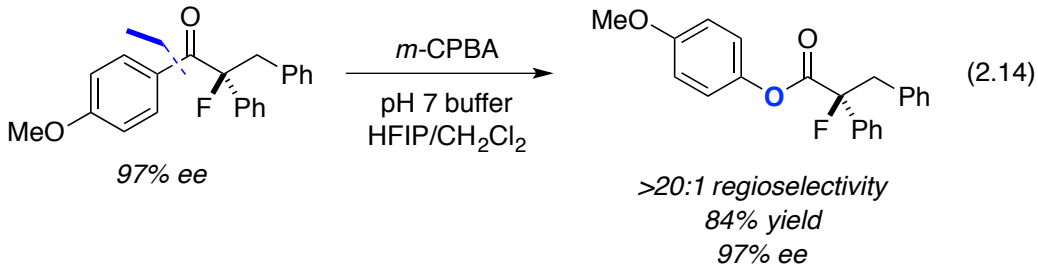


(2.12)

Moreover, *regioselective* Baeyer–Villiger oxidation of the cross-coupling products can be achieved (eqs 2.13 and 2.14, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol).[17] The relative migratory aptitudes of the ketone substituents can determine the regioselectivity of the reaction.[18] To the best of our knowledge, these reactions serve as the first asymmetric synthesis of acylated fluorohydrins[19] and an indirect method for the catalytic enantioselective synthesis of tertiary α-fluoroesters.[20]



(2.13)



(2.14)

2.5 Conclusions

In conclusion, the first catalytic enantioselective cross-coupling method that employs germinal dihalides as substrates has been developed. This method provides a unique approach for the generation of chiral tertiary α-fluoroketones, which can be challenging to synthesize via other existing methods. These enantioenriched products can be further transformed into a variety of valuable chiral fluorine-containing building blocks.

After our study was published in 2014, Gandelman and co-workers adopted the same strategy and developed two nickel-catalyzed cross-coupling methods employing different classes of α-halo-α-fluoro alkyl electrophiles.[21]

2.6 Experimental Section

2.6.1 General Information

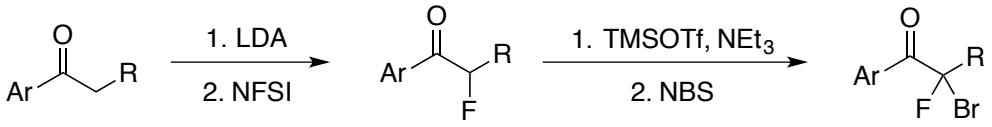
Anhydrous THF and CH_2Cl_2 were purified and dried using a solvent-purification system that contained activated alumina. The following reagents were purchased and used as received: $NiCl_2$•glyme (Aldrich), $ZnCl_2$ (Aldrich; reagent grade, ≥98%), diglyme (Aldrich; anhydrous), *n*-BuLi (Aldrich; ~2.5 M in hexanes; titrated using diphenylacetic acid according to Kofron's method[22]), diisopropylamine (Aldrich; ≥99.5%), *N*-fluorobenzenesulfonimide (Oakwood), trimethylsilyl trifluoromethanesulfonate (Oakwood), triethylamine (Aldrich; ≥99.5%), butyrophenone (Aldrich), 3-phenylpropiophenone (Alfa Aesar), 4-chlorobutyrophenone (Alfa Aesar), 3-methyl-1-phenyl-1-butanone (Aldrich), 4'-*tert*-butyl-4-chlorobutyrophenone (Alfa Aesar), 4-chloro-4'-fluorobutyrophenone (Alfa Aesar), allylmagnesium chloride (Aldrich; 2.0 M in THF), 3-chloroperbenzoic acid (Aldrich; ≤77%), and 1,1,1,3,3,3-hexafluoro-2-propanol

(Oakwood). *N*-Bromosuccinimide (Aldrich) and *N*-chlorosuccinimide (Aldrich) were recrystallized prior to use. Ligand (4*R*,5*S*)-**L1** was purchased from Aldrich. Ligand (4*S*,5*R*)-**L1** was synthesized according to a literature procedure[23] (it is commercially available from Sh-Icon Inc.) All aryl bromides were purchased (Aldrich, Alfa Aesar, TCI, and Oakwood) and used as received.

All reactions were carried out in oven-dried glassware under an inert atmosphere. HPLC analyses were carried out on an Agilent 1100 Series system, using Daicel CHIRALCEL® columns or Daicel CHIRALPAK® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm).

2.6.2 Preparation of Electrophiles

The yields have not been optimized.

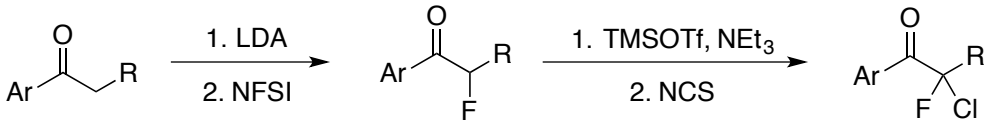


General Procedure A: This was based on published procedures.[24]

Fluorination. *n*-BuLi in hexane (2.30 M; 12.0 mL, 27.5 mmol; 1.10 equiv) was added over 5 min to a solution of diisopropylamine (4.24 mL, 30.3 mmol; 1.21 equiv) in THF (20 mL) at −78 °C. The mixture was allowed to stir for 10 min at −78 °C, and then it was warmed to r.t. and stirred for another 10 min. The clear solution was cooled to −78 °C, and a solution of the ketone (25.0 mmol) in THF (15 mL) was added over 5 min to the freshly prepared solution of LDA. The mixture was stirred at −78 °C for 1.5 h, and then a solution of *N*-fluorobenzenesulfonimide (NFSI; 9.46 g, 30.0 mmol; 1.20 equiv) in THF (30 mL) was added over 5 min to the solution of the enolate at −78 °C. The mixture

was allowed to stir at −78 °C for 5 min, and then it was allowed to warm to r.t. (white or light-yellow suspension) and stirred for 6–12 h. Next, aqueous solutions of NH_4Cl (saturated; 20 mL) and of HCl (1 N; 50 mL) were added in turn. The mixture was extracted with CH_2Cl_2 (3 × 70 mL), and the organic layers were combined, dried over Na_2SO_4, and concentrated. The desired product was purified by flash chromatography on silica gel (10:1 hexane/diethyl ether, unless otherwise noted).

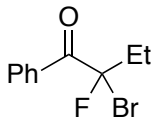
Bromination. Et_3N (3.07 mL, 22.0 mmol; 1.10 equiv) and trimethylsilyl trifluoromethanesulfonate (TMSOTf; 3.62 mL, 20.0 mmol; 1.00 equiv) were added to a solution of the α-fluoroketone (20.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to warm to r.t., and then it was stirred for 2.5 h. Next, *N*-bromosuccinimide (NBS; 4.63 g, 26.0 mmol; 1.30 equiv) was added in one portion to the reaction mixture, followed by CH_2Cl_2 (20 mL). The orange or red solution was allowed to stir at r.t. for 16 h, during which it became dark red. Then, the reaction was quenched with water (30 mL), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The desired product was purified by flash chromatography on silica gel (100:1 hexane/dichloromethane, unless otherwise noted).



General Procedure B: The first step is the same as for General Procedure A.

Chlorination. Et_3N (3.07 mL, 22.0 mmol; 1.10 equiv) and trimethylsilyl trifluoromethanesulfonate (TMSOTf; 3.62 mL, 20.0 mmol; 1.00 equiv) were added to a

solution of the α-fluoroketone (20.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to warm to r.t., and then it was stirred for 2.5 h. Next, *N*-chlorosuccinimide (NCS; 3.47 g, 26.0 mmol; 1.30 equiv) was added in one batch to the reaction mixture, followed by the addition of CH_2Cl_2 (20 mL). The orange or red solution was allowed to stir at r.t. for 16 h, during which it became dark red. Then, the reaction was quenched with water (30 mL), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The desired product was purified by flash chromatography on silica gel (100:1 hexane/dichloromethane, unless otherwise noted).



2-Bromo-2-fluoro-1-phenylbutan-1-one [76650-11-8]. The title compound was synthesized according to General Procedure A from butyrophenone. The overall yield (2 steps) was 64%. The title compound was isolated as a colorless oil.

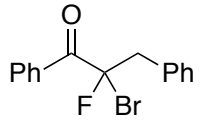
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 – 8.16 (m, 2H), 7.63 – 7.59 (m, 1H), 7.50 – 7.47 (m, 2H), 2.66 – 2.50 (m, 2H), 1.17 (t, 3H, J = 7.3 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1 (d, J = 28.5 Hz), 133.8, 132.1 (d, J = 3.6 Hz), 130.6 (d, J = 5.8 Hz), 128.4, 106.0 (d, J = 272.2 Hz), 34.2 (d, J = 21.1 Hz), 8.6 (d, J = 3.8 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −118.1 (t, 1F, J = 21.8 Hz);

FT-IR (film) 2982, 2944, 1690, 1598, 1448, 1262, 1152, 887, 828 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{10}H_{10}FO$: 165, found: 165.



2-Bromo-2-fluoro-1,3-diphenylpropan-1-one. The title compound was synthesized according to General Procedure A from 3-phenylpropiophenone. The overall yield (2 steps) was 43%. The title compound was isolated as a white solid.

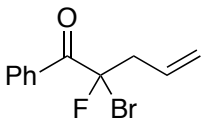
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.06 (m, 2H), 7.60 – 7.57 (m, 1H), 7.46 – 7.43 (m, 2H), 7.36 – 7.30 (m, 5H), 3.99 (dd, 1H, *J* = 14.7, 25.6 Hz), 3.86 (dd, 1H, *J* = 14.7, 20.8 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.4 (d, *J* = 28.3 Hz), 133.8, 133.3, 132.2 (d, *J* = 3.7 Hz), 131.1, 130.4 (d, *J* = 5.7 Hz), 128.4, 128.3, 127.6, 103.7 (d, *J* = 274.1 Hz), 46.4 (d, *J* = 19.8 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −116.5 (dd, 1F, *J* = 20.7, 25.7 Hz);

FT-IR (film) 3063, 3032, 1690, 1597, 1448, 1262, 1135, 1087, 955, 885, 846, 743 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{15}H_{12}FO$: 227, found: 227.



2-Bromo-2-fluoro-1-phenylpent-4-en-1-one. The title compound was synthesized according to General Procedure A from 1-phenylpent-4-en-1-one. The overall yield (2 steps) was 38%. The title compound was isolated as a colorless oil (it should be stored in a refrigerator (~5 °C)).

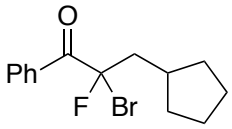
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 – 8.16 (m, 2H), 7.63 – 7.60 (m, 1H), 7.50 – 7.47 (m, 2H), 5.94 – 5.86 (m, 1H), 5.33 – 5.29 (m, 2H), 3.36 – 3.29 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.8 (d, J = 27.9 Hz), 133.9, 132.0 (d, J = 3.9 Hz), 130.6 (d, J = 5.8 Hz), 129.8 (d, J = 2.8 Hz), 128.4, 121.4, 103.5 (d, J = 273.0 Hz), 45.0 (d, J = 20.9 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −116.7 (tt, 1F, J = 1.9, 22.1 Hz);

FT-IR (film) 3077, 1694, 1598, 1448, 1263, 1137, 932, 870, 711 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{11}H_{10}{}^{79}BrFO$: 256, found: 256, 258 (M^++2).



2-Bromo-3-cyclopentyl-2-fluoro-1-phenylpropan-1-one. The title compound was synthesized according to General Procedure A from 3-cyclopentyl-1-phenylpropan-1-one. The overall yield (2 steps) was 50%. The title compound was isolated as a yellow oil.

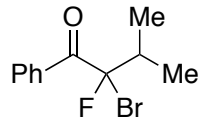
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 – 8.14 (m, 2H), 7.63 – 7.59 (m, 1H), 7.50 – 7.46 (m, 2H), 2.70 (d, 1H, J = 6.6 Hz), 2.66 (dd, 1H, J = 1.1, 6.5 Hz), 2.15 – 2.06 (m, 1H), 1.91 – 1.82 (m, 2H), 1.67 – 1.60 (m, 2H), 1.56 – 1.48 (m, 2H), 1.30 – 1.12 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.7 (d, J = 28.2 Hz), 133.7, 132.3 (d, J = 3.3 Hz), 130.6 (d, J = 5.6 Hz), 128.4, 105.5 (d, J = 273.7 Hz), 46.2 (d, J = 19.7 Hz), 37.0, 33.3 (dd, J = 1.5, 21.5 Hz), 24.7 (d, J = 23.1 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −114.6 (t, 1F, J = 23.6 Hz);

FT-IR (film) 2953, 2869, 1693, 1598, 1448, 1258, 1144, 915, 704 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{14}H_{16}FO$: 219, found: 219.



2-Bromo-2-fluoro-3-methyl-1-phenylbutan-1-one. The title compound was synthesized according to General Procedure A from 3-methyl-1-phenyl-1-butanone. The overall yield (2 steps) was 49%. The title compound was isolated as a light-yellow oil.

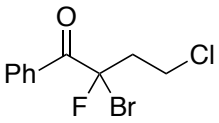
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.11 (m, 2H), 7.62 – 7.59 (m, 1H), 7.50 – 7.46 (m, 2H), 2.91 – 2.81 (m, 1H), 1.35 (d, 3H, *J* = 6.8 Hz), 1.07 (dd, 3H, *J* = 0.8, 6.7 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.2 (d, *J* = 27.6 Hz), 133.6, 132.9 (d, *J* = 3.4 Hz), 130.3 (d, *J* = 6.2 Hz), 128.4, 109.9 (d, *J* = 275.6 Hz), 37.5 (d, *J* = 20.6 Hz), 17.6 (d, *J* = 2.9 Hz), 17.0 (d, *J* = 3.3 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −127.1 (d, 1F, *J* = 26.8 Hz);

FT-IR (film) 2980, 2940, 1692, 1598, 1448, 1263, 1026, 913, 843, 817 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{11}H_{12}FO$: 179, found: 179.



2-Bromo-4-chloro-2-fluoro-1-phenylbutan-1-one. The title compound was synthesized according to General Procedure A from 4-chlorobutyrophenone. The overall yield (2 steps) was 26%. The title compound was isolated as a light-yellow oil.

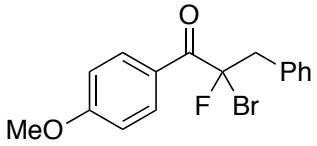
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 – 8.16 (m, 2H), 7.65 – 7.62 (m, 1H), 7.52 – 7.48 (m, 2H), 3.83 (ddd, 1H, *J* = 5.5, 9.6, 10.9 Hz), 3.74 (ddd, 1H, *J* = 6.2, 9.7, 10.9 Hz), 3.13 – 2.98 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.1 (d, *J* = 27.4 Hz), 134.2, 131.3 (d, *J* = 3.9 Hz), 130.7 (d, *J* = 5.5 Hz), 128.5, 102.4 (d, *J* = 272.7 Hz), 43.3 (d, *J* = 20.2 Hz), 38.4 (d, *J* = 4.1 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −117.1 (t, 1F, *J* = 19.9 Hz);

FT-IR (film) 3063, 2970, 1691, 1597, 1448, 1269, 1249, 1175, 1139, 1086, 898, 822 cm^{-1};

GC-MS (EI) *m/z* (M^+−Cl) calcd for $C_{10}H_9{}^{79}BrFO$: 243, found: 243, 245 (M^+−Cl+2).



2-Bromo-2-fluoro-1-(4-methoxyphenyl)-3-phenylpropan-1-one. The title compound was synthesized according to General Procedure A from 1-(4-methoxyphenyl)-3-phenylpropan-1-one. The overall yield (2 steps) was 45%. The title compound was isolated as a light-yellow oil.

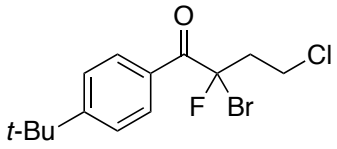
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.09 (m, 2H), 7.35 – 7.28 (m, 5H), 6.93 – 6.90 (m, 2H), 3.96 (dd, 1H, *J* = 14.7, 24.9 Hz), 3.88 – 3.79 (m, 4H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.5 (d, *J* = 27.1 Hz), 164.0, 133.5, 133.0 (d, *J* = 6.4 Hz), 131.1, 128.2, 127.5, 124.7 (d, *J* = 4.0 Hz), 113.7 (d, *J* = 1.2 Hz), 104.2 (d, *J* = 274.4 Hz), 55.5, 46.4 (d, *J* = 19.8 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −115.3 (dd, 1F, J = 21.7, 24.7 Hz);

FT-IR (film) 3032, 2935, 2840, 1680, 1601, 1511, 1263, 1177, 1134, 1029, 853, 725 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{16}H_{14}FO_2$: 257, found: 257.



2-Bromo-1-(4-(*tert*-butyl)phenyl)-4-chloro-2-fluorobutan-1-one. The title compound was synthesized according to General Procedure A from 4'-*tert*-butyl-4-chlorobutyrophenone. The overall yield (2 steps) was 34%. The title compound was isolated as a light-yellow oil.

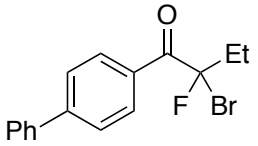
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.11 (m, 2H), 7.53 – 7.50 (m, 2H), 3.82 (ddd, 1H, J = 5.6, 9.7, 10.8 Hz), 3.73 (ddd, 1H, J = 6.1, 9.8, 10.8 Hz), 3.12 – 2.97 (m, 2H), 1.36 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.6 (d, J = 27.3 Hz), 158.3, 130.7 (d, J = 5.7 Hz), 128.5 (d, J = 3.7 Hz), 125.6 (d, J = 0.7 Hz), 102.6 (d, J = 273.0 Hz), 43.4 (d, J = 20.2 Hz), 38.5 (d, J = 4.0 Hz), 35.3, 31.0;

^{19}F NMR (282 MHz, $CDCl_3$) δ −116.6 (t, 1F, J = 19.9 Hz);

FT-IR (film) 2965, 2905, 2869, 1687, 1604, 1272, 1136, 1112, 899, 853 cm^{-1};

GC-MS (EI) *m/z* (M^+−Cl) calcd for $C_{14}H_{17}{}^{79}BrFO$: 299, found: 299, 301 (M^+−Cl+2).



1-([1,1'-Biphenyl]-4-yl)-2-bromo-2-fluorobutan-1-one. The title compound was synthesized according to General Procedure A from 1-([1,1'-biphenyl]-4-yl)butan-1-one. The overall yield (2 steps) was 59%. The title compound was isolated as a light-yellow solid.

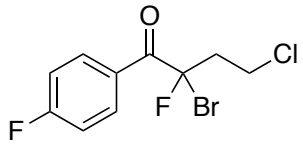
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 – 8.27 (m, 2H), 7.73 – 7.70 (m, 2H), 7.67 – 7.64 (m, 2H), 7.51 – 7.48 (m, 2H), 7.45 – 7.41 (m, 1H), 2.70 – 2.53 (m, 2H), 1.20 (t, 3H, J = 7.3 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.6 (d, J = 27.9 Hz), 146.5, 139.6, 131.2 (d, J = 5.9 Hz), 130.7 (d, J = 3.8 Hz), 129.0, 128.4, 127.3, 127.0, 106.2 (d, J = 272.2 Hz), 34.2 (d, J = 21.1 Hz), 8.6 (d, J = 3.7 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −117.9 (t, 1F, J = 21.8 Hz);

FT-IR (film) 2981, 1687, 1604, 1264, 1152, 885, 856, 745, 723 cm^{-1};

GC-MS (EI) *m/z* (M^+−HBr) calcd for $C_{16}H_{13}FO$: 240, found: 240.



2-Bromo-4-chloro-2-fluoro-1-(4-fluorophenyl)butan-1-one. The title compound was synthesized according to General Procedure A from 4-chloro-4'-fluorobutyrophenone. The overall yield (2 steps) was 42%. The title compound was isolated as a light-yellow oil.

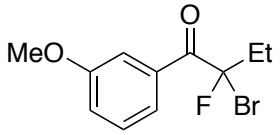
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 – 8.20 (m, 2H), 7.19 – 7.14 (m, 2H), 3.82 (ddd, 1H, *J* = 5.5, 9.5, 10.9 Hz), 3.73 (ddd, 1H, *J* = 6.2, 9.6, 10.9 Hz), 3.11 – 2.96 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 187.5 (d, *J* = 27.5 Hz), 166.2 (d, *J* = 258.0 Hz), 133.6 (dd, *J* = 5.9, 9.5 Hz), 127.5, 115.9 (d, *J* = 22.2 Hz), 102.4 (d, *J* = 272.5 Hz), 43.2 (d, *J* = 20.1 Hz), 38.4 (d, *J* = 4.1 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −102.2 (m, 1F), −117.0 (t, 1F, *J* = 20.0 Hz);

FT-IR (film) 2971, 1695, 1599, 1506, 1412, 1277, 1241, 1162, 1139, 899, 854, 710 cm^{-1};

GC-MS (EI) *m/z* (M^+−Cl) calcd for $C_{10}H_8{}^{79}BrF_2O$: 261, found: 261, 263 (M^+−Cl+2).



2-Bromo-2-fluoro-1-(3-methoxyphenyl)butan-1-one. The title compound was synthesized according to General Procedure A from 1-(3-methoxyphenyl)butan-1-one. The overall yield (2 steps) was 52%. The title compound was isolated as a light-yellow oil.

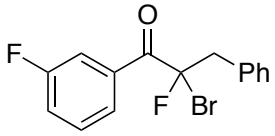
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dddd, 1H, *J* = 0.9, 1.6, 2.2, 7.7 Hz), 7.66 (dt, 1H, *J* = 1.5, 2.8 Hz), 7.39 (t, 1H, *J* = 8.0 Hz), 7.15 (ddd, 1H, *J* = 0.9, 2.7, 8.3 Hz), 3.86 (s, 3H), 2.65 – 2.49 (m, 2H), 1.16 (t, 3H, *J* = 7.3 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.9 (d, *J* = 28.0 Hz), 159.4, 133.3 (d, *J* = 3.4 Hz), 129.4 (d, *J* = 1.2 Hz), 123.2 (d, *J* = 7.4 Hz), 120.3, 114.9 (d, *J* = 4.6 Hz), 106.0 (d, *J* = 272.5 Hz), 55.4, 34.3 (d, *J* = 21.2 Hz), 8.6 (d, *J* = 3.7 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −117.9 (t, 1F, *J* = 21.7 Hz);

FT-IR (film) 2979, 2943, 1694, 1598, 1580, 1489, 1463, 1428, 1271, 1226, 1152, 1039, 719 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{11}H_{12}{}^{79}BrFO_2$: 274, found: 274, 276 ($M^+$+2).



2-Bromo-2-fluoro-1-(3-fluorophenyl)-3-phenylpropan-1-one. The title compound was synthesized according to General Procedure A from 1-(3-fluorophenyl)-3-phenylpropan-1-one. The overall yield (2 steps) was 31%. The title compound was isolated as a light-yellow oil.

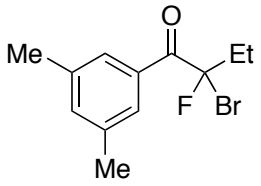
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dtd, 1H, *J* = 1.0, 1.7, 7.9 Hz), 7.73 (ddt, 1H, *J* = 1.6, 2.9, 9.6 Hz), 7.42 (td, 1H, *J* = 5.6, 8.1 Hz), 7.33 – 7.28 (m, 6H), 3.96 (dd, 1H, *J* = 14.7, 25.9 Hz), 3.84 (dd, 1H, *J* = 14.7, 20.6 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.2 (dd, *J* = 2.3, 28.4 Hz), 162.3 (d, *J* = 247.9 Hz), 134.0 (dd, *J* = 3.7, 4.8 Hz), 133.1, 131.1 (d, *J* = 1.0 Hz), 130.1 (dd, *J* = 0.8, 7.7 Hz), 128.4, 127.7, 126.2 (dd, *J* = 3.1, 6.4 Hz), 120.9 (d, *J* = 21.4 Hz), 117.3 (dd, *J* = 5.7, 23.4 Hz), 103.5 (d, *J* = 273.5 Hz), 46.4 (d, *J* = 19.7 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −111.5 (m, 1F), −117.1 (dd, 1F, *J* = 20.6, 25.6 Hz);

FT-IR (film) 3067, 3034, 1694, 1587, 1440, 1270, 1124, 894, 721 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{15}H_{11}F_2O$: 245, found: 245.



2-Bromo-1-(3,5-dimethylphenyl)-2-fluorobutan-1-one. The title compound was synthesized according to General Procedure A from 1-(3,5-dimethylphenyl)butan-1-one. The overall yield (2 steps) was 61%. The title compound was isolated as a colorless oil.

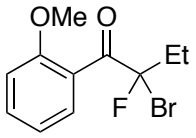
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.77 (m, 2H), 7.25 – 7.24 (m, 1H), 2.63 – 2.50 (m, 2H), 2.39 (s, 6H), 1.15 (t, 3H, *J* = 7.3 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.6 (d, *J* = 27.9 Hz), 138.0, 135.5, 132.3 (d, *J* = 3.6 Hz), 128.2 (d, *J* = 5.7 Hz), 106.1 (d, *J* = 272.7 Hz), 34.3 (d, *J* = 21.2 Hz), 21.3, 8.6 (d, *J* = 3.7 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −117.7 (t, 1F, *J* = 21.8 Hz);

FT-IR (film) 2980, 2944, 2919, 1690, 1604, 1459, 1301, 1215, 1152, 1060, 922, 869 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{12}H_{14}{}^{79}BrFO$: 272, found: 272, 274 (M^++2).



2-Bromo-2-fluoro-1-(2-methoxyphenyl)butan-1-one. The title compound was synthesized according to General Procedure A from 1-(2-methoxyphenyl)butan-1-one.

The overall yield (2 steps) was 60%. The title compound was isolated as a light-yellow oil.

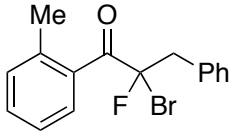
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dt, 1H, *J* = 1.4, 7.6 Hz), 7.46 (ddd, 1H, *J* = 1.7, 7.5, 8.3 Hz), 7.01 (td, 1H, *J* = 0.9, 7.5 Hz), 6.97 (dd, 1H, *J* = 0.9, 8.4 Hz), 3.84 (s, 3H), 2.59 – 2.47 (m, 2H), 1.16 (t, 3H, *J* = 7.3 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.2 (d, *J* = 31.8 Hz), 157.5 (d, *J* = 0.8 Hz), 132.7, 129.6 (d, *J* = 2.8 Hz), 125.2 (d, *J* = 2.4 Hz), 120.3, 111.4, 106.0 (d, *J* = 272.0 Hz), 55.7, 34.0 (d, *J* = 21.0 Hz), 8.6 (d, *J* = 3.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −119.8 (t, 1F, *J* = 20.9 Hz);

FT-IR (film) 2982, 2943, 2839, 1719, 1599, 1488, 1462, 1435, 1291, 1256, 1162, 1021, 893, 753 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{11}H_{12}FO_2$: 195, found: 195.



2-Bromo-2-fluoro-3-phenyl-1-(*o*-tolyl)propan-1-one. The title compound was synthesized according to General Procedure A from 3-phenyl-1-(*o*-tolyl)propan-1-one. The overall yield (2 steps) was 22%. The title compound was isolated as a light-yellow oil.

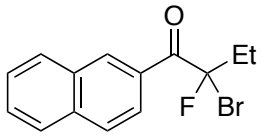
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (ddd, 1H, *J* = 1.3, 3.9, 8.0 Hz), 7.35 – 7.29 (m, 6H), 7.20 (dt, 1H, *J* = 0.7, 7.8 Hz), 7.14 (tdd, 1H, *J* = 0.6, 1.3, 7.4 Hz), 4.04 (dd, 1H, *J* = 14.4, 30.7 Hz), 3.85 (dd, 1H, *J* = 14.4, 15.7 Hz), 2.18 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.4 (d, *J* = 29.9 Hz), 138.4, 133.5 (d, *J* = 2.8 Hz), 133.2, 131.4, 131.3, 131.1 (d, *J* = 1.3 Hz), 128.8 (d, *J* = 8.1 Hz), 128.5, 127.8, 124.9, 103.2 (d, *J* = 274.9 Hz), 47.0 (d, *J* = 19.5 Hz), 19.9;

^{19}F NMR (282 MHz, $CDCl_3$) δ −115.6 (ddd, 1F, *J* = 4.0, 15.8, 30.7 Hz);

FT-IR (film) 3064, 3033, 2930, 1700, 1496, 1455, 1264, 1226, 1122, 940, 886, 724 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{16}H_{14}FO$: 241, found: 241.



2-Bromo-2-fluoro-1-(naphthalen-2-yl)butan-1-one. The title compound was synthesized according to General Procedure A from 1-(naphthalen-2-yl)butan-1-one. The overall yield (2 steps) was 41%. The title compound was isolated as a light-yellow oil.

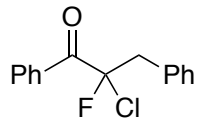
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 – 8.80 (m, 1H), 8.17 (dt, 1H, *J* = 1.7, 8.7 Hz), 7.99 (dd, 1H, *J* = 0.7, 8.2 Hz), 7.92 – 7.87 (m, 2H), 7.65 – 7.61 (m, 1H), 7.58 – 7.55 (m, 1H), 2.73 – 2.56 (m, 2H), 1.22 (t, 3H, *J* = 7.3 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.0 (d, *J* = 27.9 Hz), 135.7, 132.9 (d, *J* = 7.8 Hz), 132.2 (d, *J* = 0.7 Hz), 130.0, 129.3 (d, *J* = 3.6 Hz), 129.1, 128.2 (d, *J* = 0.8 Hz), 127.7, 126.8, 125.6 (d, *J* = 4.0 Hz), 106.3 (d, *J* = 272.2 Hz), 34.3 (d, *J* = 21.2 Hz), 8.6 (d, *J* = 3.7 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −117.4 (t, 1F, *J* = 21.6 Hz);

FT-IR (film) 3060, 2981, 2942, 1686, 1627, 1462, 1280, 1230, 1151, 1123, 1108, 979, 910, 868, 741 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{14}H_{12}{}^{79}BrFO$: 294, found: 294, 296 (M^++2).



2-Chloro-2-fluoro-1,3-diphenylpropan-1-one [1062229-21-3]. The title compound was synthesized according to General Procedure B from 3-phenylpropiophenone. The overall yield (2 steps) was 40%. The title compound was isolated as a light-yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.07 (m, 2H), 7.61 – 7.58 (m, 1H), 7.47 – 7.44 (m, 2H), 7.36 – 7.29 (m, 5H), 3.86 (dd, 1H, *J* = 14.5, 22.5 Hz), 3.70 (dd, 1H, *J* = 14.6, 22.2 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.0 (d, *J* = 29.8 Hz), 133.9, 132.6, 132.1 (d, *J* = 3.8 Hz), 131.2, 130.4 (d, *J* = 5.5 Hz), 128.4 (d, *J* = 0.6 Hz), 128.3, 127.6, 109.0 (d, *J* = 262.1 Hz), 45.1 (d, *J* = 20.8 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −114.9 (t, 1F, *J* = 22.4 Hz);

FT-IR (film) 3065, 3033, 1694, 1598, 1497, 1455, 1448, 1264, 1135, 893, 853, 749 cm^{-1};

GC-MS (EI) *m/z* (M^+−Cl) calcd for $C_{15}H_{12}FO$: 227, found: 227.

2.6.3 Asymmetric Negishi Cross-Couplings

General procedure for the preparation of solutions of the arylzinc reagent (0.30 M): In the air, $ZnCl_2$ (Aldrich; reagent grade, ≥98%; dried with a heat gun under high vacuum for 20 min before the reaction; 2.04 g, 15.0 mmol; 1.50 equiv) was added

quickly to an oven-dried 20 mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap and then evacuated and back-filled with nitrogen (three cycles). THF (8.5 mL) was added to this vial, and the resulting mixture was stirred vigorously until the $ZnCl_2$ had completely dissolved. THF was then added to provide a 1.50 M solution of $ZnCl_2$. Next, an oven-dried 40 mL vial equipped with a stir bar was charged with the aryl bromide (9.00 mmol) and then closed with a PTFE septum cap. The vial was evacuated and back-filled with nitrogen (three cycles), and then THF (6.5 mL) was added to this vial.

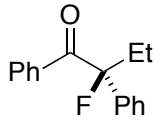
A solution of *n*-BuLi (2.61 M; 3.45 mL, 9.00 mmol; 1.00 equiv) was added over ~5 min to the vial that contained the solution of the aryl bromide, which had been cooled to −78 °C. The mixture was allowed to stir at −78 °C for another 5 min, and then the solution of $ZnCl_2$ (1.50 M; 9.00 mL, 13.5 mmol; 1.50 equiv) was added to the vial. The mixture was allowed to warm to r.t., and then it was stirred for 40 min at r.t.

The arylzinc solution was titrated using I_2 according to Knochel's method[25] (concentration ~0.4 M). This solution was then diluted with THF to generate a 0.30 M solution in an oven-dried 40 mL vial.

General procedure for asymmetric Negishi cross-couplings: In the air, $NiCl_2$•glyme (33.0 mg, 0.150 mmol) and (4*R*,5*S*)-**L1** (73.4 mg, 0.160 mmol) were added to an oven-dried 40 mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap and then evacuated and back-filled with nitrogen (three cycles). Diglyme (2.5 mL) was added to the vial, and the mixture was vigorously stirred at r.t. for 45 min. In the air, an oven-dried 4 mL vial was charged with the α-bromo-α-fluoroketone (1.00 mmol),

and then the vial was sparged with nitrogen for 10 min. Diglyme (0.9 mL) was added, and the resulting solution was transferred via syringe to the 40 mL reaction vial. The 4 mL vial was rinsed with diglyme (0.8 mL × 2), and the washings were transferred to the reaction vial. The reaction vial was wrapped with electrical tape and then cooled to −25 °C for 15 min; at the same time, an oven-dried 40 mL vial that contained the arylzinc solution (0.30 M) was also cooled to −25 °C for 15 min (a nitrogen-filled balloon was attached to each vial). To the vigorously stirred solution of catalyst and electrophile was added the solution of the arylzinc reagent (0.30 M; 6.67 mL, 2.00 mmol; 2.00 equiv) over 3 min, during which the reaction mixture turned to orange. The balloon was removed, and the septum cap was sealed with grease. The mixture was stirred vigorously at −25 °C for 36 h. Then, the reaction was quenched by the addition of EtOH (2 mL), and the mixture was allowed to warm to r.t. and then diluted with Et_2O (100 mL) and washed with deionized water (25 mL × 4). The organic layer was dried over Na_2SO_4 and then concentrated, and the residue was purified by flash chromatography.

A second run was performed with the (4*S*,5*R*)-**L1**.



(*S*)-2-Fluoro-1,2-diphenylbutan-1-one (Table 2.2, Entry 1) [1355165-74-0]. 2-Bromo-2-fluoro-1-phenylbutan-1-one (245 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: (1) normal-phase silica, 5%→7.5%→10%→12.5% dichloromethane in hexane; (2) reverse-

phase silica (C-18), 40%→50% MeCN in water. The title compound was isolated as a colorless oil.

Run 1, 151 mg (62% yield, 97% ee); Run 2, 150 mg (62% yield, 97% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 8.4 min (minor), 14.1 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 2H), 7.52 – 7.47 (m, 3H), 7.41 – 7.30 (m, 5H), 2.51 – 2.39 (m, 1H), 2.26 – 2.14 (m, 1H), 0.93 (t, 3H, J = 7.4 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5 (d, J = 28.2 Hz), 138.8 (d, J = 22.1 Hz), 135.1 (d, J = 3.5 Hz), 132.9, 129.9 (d, J = 6.4 Hz), 128.7 (d, J = 1.8 Hz), 128.1, 124.1 (d, J = 9.3 Hz), 103.7 (d, J = 189.5 Hz), 32.8 (d, J = 23.7 Hz), 7.5 (d, J = 4.2 Hz);

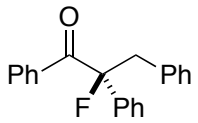
^{19}F NMR (282 MHz, $CDCl_3$) δ −165.2 (t, 1F, J = 24.6 Hz);

FT-IR (film) 3061, 2978, 2940, 1683, 1447, 1259, 974, 858, 842, 754, 709 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{16}H_{15}FNaO$: 265, found: 265;

$[\alpha]^{25}_D = -176°$ (c = 1.00, $CHCl_3$); 97% ee, from (4*R*,5*S*)-**L1**.

The spectral data are in agreement with literature data.[9d]



(*S*)-2-Fluoro-1,2,3-triphenylpropan-1-one (Table 2.2, Entry 2). 2-Bromo-2-fluoro-1,3-diphenylpropan-1-one (307 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 20:1→10:1 hexane/dichloromethane. The title compound was isolated as a white solid.

Run 1, 224 mg (74% yield, 98% ee); Run 2, 218 mg (72% yield, 97% ee).

This compound was also prepared on a 7.00 mmol scale (eq 2.9), using 2-bromo-2-fluoro-1,3-diphenylpropan-1-one (2.15 g, 7.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene (0.30 M, 46.7 mL, 14.0 mmol; 2.00 equiv). Following the general procedure, the title compound was isolated in 66% yield (1.41 g) and 97% ee.

The ee was determined on an AD-H column (2% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 12.4 min (minor), 14.3 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.76 (m, 2H), 7.46 – 7.42 (m, 3H), 7.37 – 7.29 (m, 5H), 7.20 – 7.17 (m, 3H), 7.09 – 7.07 (m, 2H), 3.74 (dd, 1H, *J* = 14.4, 24.7 Hz), 3.47 (dd, 1H, *J* = 14.4, 26.1 Hz);

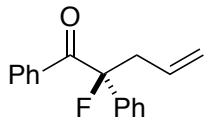
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1 (d, *J* = 28.1 Hz), 138.3 (d, *J* = 22.1 Hz), 135.0 (d, *J* = 3.5 Hz), 134.6, 132.9, 130.9, 129.9 (d, *J* = 6.2 Hz), 128.6 (d, *J* = 2.1 Hz), 128.3 (d, *J* = 0.7 Hz), 128.1, 127.8, 126.7, 124.2 (d, *J* = 9.0 Hz), 102.7 (d, *J* = 191.7 Hz), 45.5 (d, *J* = 22.5 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −160.9 (t, 1F, *J* = 25.4 Hz);

FT-IR (film) 3062, 3031, 1686, 1598, 1496, 1447, 1261, 1075, 1029, 942, 763 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{21}H_{17}FNaO$: 327, found: 327;

$[\alpha]^{25}_D$ = −215° (*c* = 1.03, $CHCl_3$); 98% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-1,2-diphenylpent-4-en-1-one (Table 2.2, Entry 3). 2-Bromo-2-fluoro-1-phenylpent-4-en-1-one (257 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 25:1→10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 104 mg (41% yield, 97% ee); Run 2, 115 mg (45% yield, 96% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 12.5 min (minor), 19.5 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.87 (m, 2H), 7.51 – 7.46 (m, 3H), 7.41 – 7.31 (m, 5H), 5.73 (ddt, 1H, *J* = 7.0, 10.2, 17.2 Hz), 5.15 – 5.08 (m, 2H), 3.18 (dddt, 1H, *J* = 1.2, 7.0, 14.8, 25.7 Hz), 2.94 (dddt, 1H, *J* = 1.3, 7.0, 14.8, 24.3 Hz);

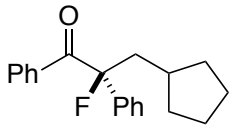
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8 (d, *J* = 27.9 Hz), 138.4 (d, *J* = 22.2 Hz), 134.8 (d, *J* = 3.6 Hz), 133.0, 131.1 (d, *J* = 3.4 Hz), 130.0 (d, *J* = 6.3 Hz), 128.7 (d, *J* = 1.9 Hz), 128.3, 128.1, 124.1 (d, *J* = 9.2 Hz), 119.7, 102.5 (d, *J* = 190.4 Hz), 44.0 (d, *J* = 22.8 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −161.8 (t, 1F, *J* = 24.9 Hz);

FT-IR (film) 3074, 3028, 1687, 1598, 1448, 1259, 1239, 923, 759, 723 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{17}H_{15}FNaO$: 277, found: 277;

$[\alpha]^{25}_D$ = −208° (*c* = 1.00, $CHCl_3$); 97% ee, from (4*R*,5*S*)-**L1**.



(*S*)-3-Cyclopentyl-2-fluoro-1,2-diphenylpropan-1-one (Table 2.2, Entry 4). 2-Bromo-3-cyclopentyl-2-fluoro-1-phenylpropan-1-one (299 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: (1) normal-phase silica, 5%→10% dichloromethane in hexane; (2) reverse-phase silica (C-18), 70% MeCN in water. The title compound was isolated as a colorless oil.

Run 1, 174 mg (59% yield, 91% ee); Run 2, 175 mg (59% yield, 90% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 11.5 min (minor), 14.8 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.87 (m, 2H), 7.54 – 7.42 (m, 2H), 7.50 – 7.46 (m, 1H), 7.41 – 7.30 (m, 5H), 2.48 (ddd, 1H, *J* = 6.2, 14.8, 25.8 Hz), 2.31 (ddd, 1H, *J* = 5.6, 14.8, 26.7 Hz), 1.84 – 1.77 (m, 2H), 1.64 – 1.51 (m, 3H), 1.47 – 1.36 (m, 2H), 1.19 – 1.03 (m, 2H);

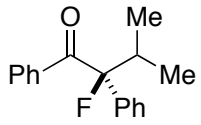
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9 (d, *J* = 28.4 Hz), 139.3 (d, *J* = 22.6 Hz), 135.1 (d, *J* = 3.4 Hz), 132.8, 129.9 (d, *J* = 6.3 Hz), 128.7 (d, *J* = 1.9 Hz), 128.1, 128.0, 124.1 (d, *J* = 9.2 Hz), 104.0 (d, *J* = 190.3 Hz), 45.2 (d, *J* = 22.1 Hz), 35.7, 33.7 (dd, *J* = 1.4, 9.7 Hz), 24.8 (d, *J* = 17.0 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −162.3 (t, 1F, *J* = 26.2 Hz);

FT-IR (film) 3061, 2952, 2868, 1687, 1683, 1598, 1447, 1259, 757, 712 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{20}H_{21}FNaO$: 319, found: 319;

$[\alpha]^{25}_D = -154°$ (*c* = 1.02, $CHCl_3$); 91% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-3-methyl-1,2-diphenylbutan-1-one (Table 2.2, Entry 5). 2-Bromo-2-fluoro-3-methyl-1-phenylbutan-1-one (259 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 25:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 142 mg (55% yield, 83% ee); Run 2, 140 mg (55% yield, 81% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 10.6 min (minor), 17.0 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.86 (m, 2H), 7.57 – 7.54 (m, 2H), 7.50 – 7.46 (m, 1H), 7.41 – 7.35 (m, 4H), 7.32 – 7.29 (m, 1H), 2.87 (ddq, 1H, J = 6.8, 13.7, 32.1 Hz), 1.09 (d, 3H, J = 6.7 Hz), 0.74 (d, 3H, J = 7.0 Hz);

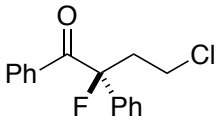
^{13}C NMR (126 MHz, $CDCl_3$) δ 200.1 (d, J = 29.3 Hz), 138.2 (d, J = 22.5 Hz), 136.0 (d, J = 3.4 Hz), 132.7, 129.6 (d, J = 6.3 Hz), 128.6 (d, J = 2.2 Hz), 128.1 (d, J = 0.8 Hz), 128.0, 124.4 (d, J = 10.1 Hz), 106.0 (d, J = 194.8 Hz), 36.6 (d, J = 22.6 Hz), 17.2 (d, J = 4.6 Hz), 15.8 (d, J = 3.1 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −180.3 (d, 1F, J = 32.1 Hz);

FT-IR (film) 2973, 1685, 1598, 1447, 1259, 1012, 836, 749 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{17}H_{17}FNaO$: 279, found: 279;

$[\alpha]^{25}_D$ = −94.0° (c = 1.00, $CHCl_3$); 83% ee, from (4*R*,5*S*)-**L1**.



(*S*)-4-Chloro-2-fluoro-1,2-diphenylbutan-1-one (Table 2.2, Entry 6). 2-Bromo-4-chloro-2-fluoro-1-phenylbutan-1-one (280 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 25:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 171 mg (62% yield, 98% ee); Run 2, 168 mg (61% yield, 98% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 15.9 min (minor), 24.0 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.87 (m, 2H), 7.51 – 7.48 (m, 3H), 7.43 – 7.40 (m, 2H), 7.38 – 7.33 (m, 3H), 3.60 (td, 1H, *J* = 5.6, 10.8 Hz), 3.45 (td, 1H, *J* = 4.9, 10.7 Hz), 2.91 (dddd, 1H, *J* = 5.6, 10.8, 14.5, 23.5 Hz), 2.70 (dddd, 1H, *J* = 4.9, 10.9, 14.5, 22.9 Hz);

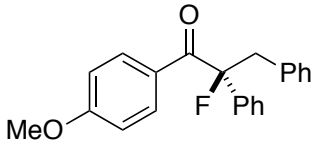
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6 (d, *J* = 27.4 Hz), 137.6 (d, *J* = 21.8 Hz), 134.1 (d, *J* = 3.5 Hz), 133.0, 130.1 (d, *J* = 5.7 Hz), 129.1 (d, *J* = 2.1 Hz), 128.7, 128.3 (d, *J* = 0.6 Hz), 123.8 (d, *J* = 9.1 Hz), 102.1 (d, *J* = 190.5 Hz), 42.6 (d, *J* = 22.6 Hz), 38.6 (d, *J* = 5.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −163.2 (t, 1F, *J* = 23.2 Hz);

FT-IR (film) 3061, 2971, 1686, 1597, 1448, 1265, 1065, 758, 709 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{16}H_{14}ClFNaO$: 299, found: 299;

$[\alpha]^{25}_D$ = −201° (*c* = 0.99, $CHCl_3$); 98% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-1-(4-methoxyphenyl)-2,3-diphenylpropan-1-one (Table 2.3, Entry 1). 2-Bromo-2-fluoro-1-(4-methoxyphenyl)-3-phenylpropan-1-one (337 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 8:1→3:1 hexane/dichloromethane. The title compound was isolated as a white solid.

Run 1, 205 mg (61% yield, 97% ee); Run 2, 212 mg (63% yield, 95% ee).

The ee was determined on an AD-H column (2% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 23.7 min (minor), 25.1 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 2H), 7.40 – 7.38 (m, 2H), 7.34 – 7.27 (m, 3H), 7.18 – 7.15 (m, 3H), 7.07 – 7.04 (m, 2H), 6.80 – 6.77 (m, 2H), 3.79 (s, 3H), 3.71 (dd, 1H, J = 14.4, 23.8 Hz), 3.45 (dd, 1H, J = 14.4, 27.0 Hz);

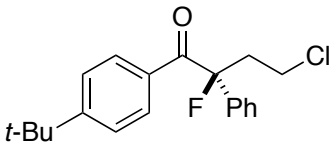
^{13}C NMR (126 MHz, $CDCl_3$) δ 195.9 (d, J = 26.8 Hz), 163.3, 138.7 (d, J = 22.2 Hz), 134.8, 132.6 (d, J = 6.7 Hz), 130.9, 128.5 (d, J = 2.0 Hz), 128.1, 127.8, 127.5 (d, J = 3.6 Hz), 126.6, 124.2 (d, J = 8.9 Hz), 113.4 (d, J = 1.2 Hz), 102.8 (d, J = 191.7 Hz), 55.3, 45.4 (d, J = 22.6 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −160.1 (t, 1F, J = 25.2 Hz);

FT-IR (film) 3031, 1676, 1600, 1259, 1175, 1030, 839, 751 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{22}H_{19}FNaO_2$: 357, found: 357;

$[\alpha]^{25}_D$ = −157° (c = 0.98, $CHCl_3$); 97% ee, from (4*R*,5*S*)-**L1**.



(*S*)-1-(4-(*tert*-Butyl)phenyl)-4-chloro-2-fluoro-2-phenylbutan-1-one (Table 2.3, Entry 2). 2-Bromo-1-(4-(*tert*-butyl)phenyl)-4-chloro-2-fluorobutan-1-one (336 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 25:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 245 mg (74% yield, 98% ee); Run 2, 257 mg (77% yield, 98% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 17.1 min (minor), 23.2 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.83 (m, 2H), 7.50 – 7.47 (m, 2H), 7.42 – 7.32 (m, 5H), 3.59 (td, 1H, *J* = 5.5, 10.8 Hz), 3.45 (td, 1H, *J* = 4.9, 10.8 Hz), 2.90 (dddd, 1H, *J* = 5.5, 10.9, 14.5, 23.8 Hz), 2.68 (dddd, 1H, *J* = 4.9, 11.0, 14.4, 22.6 Hz), 1.28 (s, 9H);

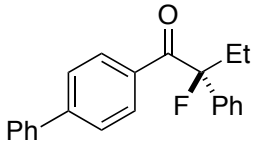
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0 (d, *J* = 26.8 Hz), 157.2, 137.8 (d, *J* = 22.0 Hz), 131.4 (d, *J* = 3.5 Hz), 130.2 (d, *J* = 6.0 Hz), 129.0 (d, *J* = 1.8 Hz), 128.6, 125.3, 123.8 (d, *J* = 9.1 Hz), 102.2 (d, *J* = 190.5 Hz), 42.6 (d, *J* = 22.6 Hz), 38.7 (d, *J* = 5.0 Hz), 35.1, 30.9;

^{19}F NMR (282 MHz, $CDCl_3$) δ −162.9 (t, 1F, *J* = 23.3 Hz);

FT-IR (film) 2965, 1681, 1605, 1449, 1269, 1106, 707 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{20}H_{22}ClFNaO$: 355, found: 355;

$[\alpha]^{25}_D$ = +124° (*c* = 1.02, $CHCl_3$); 98% ee, from (4*S*,5*R*)-**L1**.



(*S*)-1-([1,1'-Biphenyl]-4-yl)-2-fluoro-2-phenylbutan-1-one (Table 2.3, Entry 3). 1-([1,1'-Biphenyl]-4-yl)-2-bromo-2-fluorobutan-1-one (321 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 20:1→10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 161 mg (51% yield, 96% ee); Run 2, 181 mg (57% yield, 95% ee).

The ee was determined on an AD-H column (2% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 13.9 min (minor), 17.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.99 (m, 2H), 7.60 – 7.53 (m, 6H), 7.46 – 7.32 (m, 6H), 2.48 (ddq, 1H, *J* = 7.3, 14.6, 24.9 Hz), 2.23 (ddq, 1H, *J* = 7.4, 14.8, 24.4 Hz), 0.95 (t, 3H, *J* = 7.3 Hz);

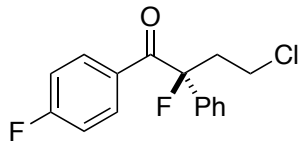
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8 (d, *J* = 27.9 Hz), 145.6, 139.9, 138.8 (d, *J* = 22.2 Hz), 133.7 (d, *J* = 3.8 Hz), 130.6 (d, *J* = 6.7 Hz), 128.9, 128.7 (d, *J* = 1.8 Hz), 128.2, 128.1, 127.2, 126.8 (d, *J* = 0.9 Hz), 124.1 (d, *J* = 8.8 Hz), 103.8 (d, *J* = 189.5 Hz), 32.8 (d, *J* = 23.8 Hz), 7.5 (d, *J* = 4.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −165.0 (t, 1F, *J* = 24.7 Hz);

FT-IR (film) 3059, 3030, 2978, 2939, 2882, 1681, 1604, 1448, 1259, 1008, 857, 760, 748, 738 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{22}H_{19}FNaO$: 341, found: 341;

$[\alpha]^{25}_D$ = −46.2° (*c* = 1.02, $CHCl_3$); 96% ee, from (4*R*,5*S*)-**L1**.



(*S*)-4-Chloro-2-fluoro-1-(4-fluorophenyl)-2-phenylbutan-1-one (Table 2.3, Entry 4). 2-Bromo-4-chloro-2-fluoro-1-(4-fluorophenyl)butan-1-one (298 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 25:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 181 mg (61% yield, 97% ee); Run 2, 192 mg (65% yield, 97% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 17.5 min (minor), 20.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (ddd, 2H, *J* = 1.7, 5.4, 9.0 Hz), 7.47 – 7.34 (m, 5H), 7.04 – 7.01 (m, 2H), 3.59 (td, 1H, *J* = 5.6, 10.7 Hz), 3.44 (td, 1H, *J* = 4.9, 10.7 Hz), 2.90 (dddd, 1H, *J* = 5.6, 10.7, 14.5, 23.4 Hz), 2.70 (dddd, 1H, *J* = 4.9, 10.8, 14.5, 23.2 Hz);

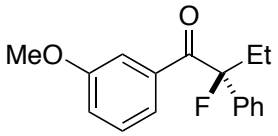
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8 (d, *J* = 27.1 Hz), 165.7 (d, *J* = 256.6 Hz), 137.4 (d, *J* = 22.0 Hz), 133.0 (dd, *J* = 6.6, 9.5 Hz), 130.3 (t, *J* = 3.4 Hz), 129.1 (d, *J* = 2.0 Hz), 128.8 (d, *J* = 0.9 Hz), 123.7 (d, *J* = 9.1 Hz), 115.5 (d, *J* = 21.5 Hz), 102.2 (d, *J* = 190.3 Hz), 42.4 (d, *J* = 22.6), 38.5 (d, *J* = 5.1 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −103.9 (m, 1F), −163.0 (t, 1F, *J* = 23.3 Hz);

FT-IR (film) 1685, 1599, 1506, 1449, 1263, 1239, 1160, 845, 743 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{16}H_{13}ClF_2NaO$: 317, found: 317;

$[\alpha]^{25}_D$ = +174° (*c* = 1.06, $CHCl_3$); 97% ee, from (4*S*,5*R*)-**L1**.



(*S*)-2-Fluoro-1-(3-methoxyphenyl)-2-phenylbutan-1-one (Table 2.3, Entry 5). 2-Bromo-2-fluoro-1-(3-methoxyphenyl)butan-1-one (275 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 10:1→5:1 hexane/dichloromethane. The title compound was isolated as a white solid.

Run 1, 154 mg (57% yield, 97% ee); Run 2, 140 mg (51% yield, 97% ee).

The ee was determined on an AD-H column (2% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 9.9 min (minor), 11.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 3H), 7.42 – 7.37 (m, 3H), 7.33 – 7.30 (m, 1H), 7.27 – 7.24 (m, 1H), 7.03 (ddd, 1H, *J* = 1.0, 2.7, 8.2 Hz), 3.78 (s, 3H), 2.45 (ddq, 1H, *J* = 7.3, 14.6, 24.6 Hz), 2.20 (ddq, 1H, *J* = 7.4, 14.7, 24.5 Hz), 0.93 (t, 3H, *J* = 7.3 Hz);

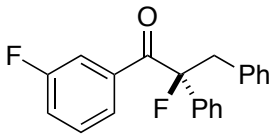
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1 (d, *J* = 28.6 Hz), 159.2, 138.8 (d, *J* = 22.1 Hz), 136.2 (d, *J* = 3.5 Hz), 129.1 (d, *J* = 1.5 Hz), 128.7 (d, *J* = 1.8 Hz), 128.1, 124.0 (d, *J* = 9.0 Hz), 122.6 (d, *J* = 7.6 Hz), 119.4, 114.2 (d, *J* = 5.0 Hz), 103.6 (d, *J* = 190.0 Hz), 55.3, 32.7 (d, *J* = 23.7 Hz), 7.4 (d, *J* = 4.5 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −165.2 (t, 1F, *J* = 24.6 Hz);

FT-IR (film) 2975, 2942, 1686, 1579, 1446, 1431, 1270, 1218, 763, 734 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{17}H_{17}FNaO_2$: 295, found: 295;

$[\alpha]^{25}_D$ = −158° (*c* = 1.03, $CHCl_3$); 97% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-1-(3-fluorophenyl)-2,3-diphenylpropan-1-one (Table 2.3, Entry 6). 2-Bromo-2-fluoro-1-(3-fluorophenyl)-3-phenylpropan-1-one (325 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 7.5%→10%→12.5% dichloromethane in hexane. The title compound was isolated as a white solid.

Run 1, 197 mg (61% yield, 97% ee); Run 2, 185 mg (57% yield, 97% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 12.4 min (minor), 14.0 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dtd, 1H, *J* = 1.0, 1.7, 7.8 Hz), 7.46 (ddt, 1H, *J* = 1.5, 2.8, 9.7 Hz), 7.43 – 7.41 (m, 2H), 7.38 – 7.26 (m, 4H), 7.21 – 7.18 (m, 3H), 7.15 (tdd, 1H, *J* = 1.0, 2.7, 8.3 Hz), 7.10 – 7.07 (m, 2H), 3.73 (dd, 1H, *J* = 14.4, 25.3 Hz), 3.45 (dd, 1H, *J* = 14.4, 25.7 Hz);

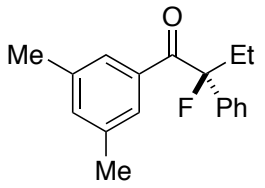
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8 (dd, *J* = 2.3, 28.4 Hz), 162.1 (d, *J* = 247.2 Hz), 137.9 (d, *J* = 22.1 Hz), 136.7 (dd, *J* = 3.5, 6.6 Hz), 134.4, 130.9 (d, *J* = 0.7 Hz), 129.7 (d, *J* = 7.9 Hz), 128.7 (d, *J* = 1.9 Hz), 128.5, 127.9, 126.8, 125.7 (dd, *J* = 3.2, 6.7 Hz), 124.2 (d, *J* = 8.9 Hz), 119.9 (d, *J* = 21.4 Hz), 116.7 (dd, *J* = 6.3, 23.1 Hz), 102.8 (d, *J* = 191.8 Hz), 45.5 (d, *J* = 22.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −112.2 (m, 1F), −161.3 (t, 1F, *J* = 25.5 Hz);

FT-IR (film) 1687, 1643, 1586, 1438, 1269, 770, 733 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{21}H_{16}F_2NaO$: 345, found: 345;

$[\alpha]^{25}_{D}$ = +192° (*c* = 0.98, $CHCl_3$); 97% ee, from (4*S*,5*R*)-**L1**.



(*S*)-1-(3,5-Dimethylphenyl)-2-fluoro-2-phenylbutan-1-one (Table 2.3, Entry 7). 2-Bromo-1-(3,5-dimethylphenyl)-2-fluorobutan-1-one (273 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 20:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 166 mg (61% yield, 97% ee); Run 2, 187 mg (69% yield, 96% ee).

The ee was determined on an AD-H column (0.05% *i*-PrOH/hexane, flow rate 0.3 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 21.2 min (minor), 22.3 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 4H), 7.41 – 7.38 (m, 2H), 7.34 – 7.30 (m, 1H), 7.13 – 7.12 (m, 1H), 2.44 (ddq, 1H, *J* = 7.3, 14.7, 25.4 Hz), 2.29 (s, 6H), 2.19 (ddq, 1H, *J* = 7.4, 14.7, 23.8 Hz), 0.93 (t, 3H, *J* = 7.4 Hz);

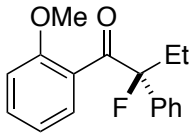
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.0 (d, *J* = 28.2 Hz), 138.9 (d, *J* = 22.1 Hz), 137.7, 135.2 (d, *J* = 3.4 Hz), 134.6, 128.6 (d, *J* = 1.8 Hz), 128.0 (d, *J* = 1.0 Hz), 127.6 (d, *J* = 6.3 Hz), 124.1 (d, *J* = 9.2 Hz), 103.7 (d, *J* = 189.9 Hz), 32.9 (d, *J* = 23.7 Hz), 21.2, 7.5 (d, *J* = 4.4 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −165.0 (t, 1F, *J* = 24.6 Hz);

FT-IR (film) 2977, 2923, 1682, 1604, 1448, 1303, 1207, 1060, 975, 762, 733 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{18}H_{19}FNaO$: 293, found: 293;

$[\alpha]^{25}_D = -132°$ (*c* = 1.02, $CHCl_3$); 97% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-1-(2-methoxyphenyl)-2-phenylbutan-1-one (Table 2.3, Entry 8). 2-Bromo-2-fluoro-1-(2-methoxyphenyl)butan-1-one (275 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 10:1→5:1 hexane/dichloromethane. The title compound was isolated as a light-yellow oil.

Run 1, 174 mg (64% yield, 92% ee); Run 2, 160 mg (59% yield, 92% ee).

The ee was determined on an AD-H column (2% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 11.4 min (minor), 26.7 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 2H), 7.41 – 7.36 (m, 3H), 7.34 – 7.31 (m, 1H), 7.06 (ddd, 1H, *J* = 0.8, 1.7, 7.7 Hz), 6.91 – 6.88 (m, 2H), 3.67 (s, 3H), 2.46 (ddq, 1H, *J* = 7.3, 14.6, 24.3 Hz), 2.20 (ddq, 1H, *J* = 7.4, 14.7, 24.0 Hz), 0.94 (t, 3H, *J* = 7.4 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.4 (d, *J* = 33.4 Hz), 157.2 (d, *J* = 1.5 Hz), 138.6 (d, *J* = 22.8 Hz), 131.9, 128.4 (d, *J* = 3.1 Hz), 128.2 (d, *J* = 2.0 Hz), 128.0 (d, *J* =

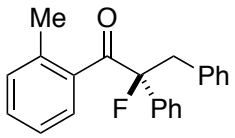
2.2 Hz), 127.7, 124.5 (d, J = 9.6 Hz), 120.0, 111.2, 103.0 (d, J = 190.4 Hz), 55.3, 33.0 (d, J = 23.1 Hz), 7.5 (d, J = 4.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −169.3 (t, 1F, J = 24.1 Hz);

FT-IR (film) 2976, 2940, 1708, 1598, 1488, 1462, 1290, 1256, 1024, 754 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{17}H_{17}FNaO_2$: 295, found: 295;

$[\alpha]^{25}_D$ = −96.5° (*c* = 1.03, $CHCl_3$); 92% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-2,3-diphenyl-1-(*o*-tolyl)propan-1-one (Table 2.3, Entry 9). 2-Bromo-2-fluoro-3-phenyl-1-(*o*-tolyl)propan-1-one (321 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 7.5%→10%→12.5% dichloromethane in hexane. The title compound was isolated as a colorless oil.

Run 1, 219 mg (69% yield, 94% ee); Run 2, 224 mg (70% yield, 94% ee).

The ee was determined on an AD-H column (2% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 6.9 min (minor), 9.0 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.57 (m, 2H), 7.45 – 7.41 (m, 2H), 7.40 – 7.36 (m, 1H), 7.27 – 7.23 (m, 6H), 7.13 (dt, 1H, J = 0.7, 7.7 Hz), 7.03 – 6.99 (m, 1H), 6.88 (ddd, 1H, J = 1.3, 3.2, 7.8 Hz), 3.82 (dd, 1H, J = 14.3, 31.1 Hz), 3.44 (dd, 1H, J = 14.3, 19.8 Hz), 2.00 (s, 3H);

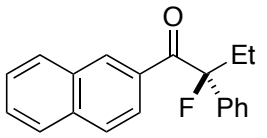
^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5 (d, *J* = 31.8 Hz), 138.3 (d, *J* = 22.6 Hz), 137.2, 136.4 (d, *J* = 2.5 Hz), 134.7, 131.1 (d, *J* = 1.1 Hz), 131.0, 130.5, 128.6 (d, *J* = 1.7 Hz), 128.4, 128.0, 127.8 (d, *J* = 7.1 Hz), 126.9, 124.5, 124.4 (d, *J* = 9.5 Hz), 102.6 (d, *J* = 192.8 Hz), 45.8 (d, *J* = 21.7 Hz), 19.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ −161.4 (ddd, 1F, *J* = 3.1, 19.8, 31.1 Hz);

FT-IR (film) 3063, 3031, 2927, 1694, 1496, 1455, 1448, 1253, 934, 761, 746, 732 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{22}H_{19}FNaO$: 341, found: 341;

$[\alpha]^{25}_D$ = −138° (*c* = 1.03, $CHCl_3$); 94% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-1-(naphthalen-2-yl)-2-phenylbutan-1-one (Table 2.3, Entry 10). 2-Bromo-2-fluoro-1-(naphthalen-2-yl)butan-1-one (295 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 25:1→20:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 145 mg (50% yield, 97% ee); Run 2, 151 mg (52% yield, 96% ee).

The ee was determined on an AD-H column (0.5% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 16.0 min (minor), 23.7 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.95 (dt, 1H, *J* = 1.7, 8.7 Hz), 7.88 (dd, 1H, *J* = 1.2, 8.2 Hz), 7.82 – 7.79 (m, 2H), 7.59 – 7.54 (m, 3H), 7.51 – 7.48 (m, 1H),

7.43 – 7.40 (m, 2H), 7.35 – 7.31 (m, 1H), 2.53 (ddq, 1H, J = 7.3, 14.6, 24.8 Hz), 2.27 (ddq, 1H, J = 7.4, 14.7, 24.5 Hz), 0.98 (t, 3H, J = 7.3 Hz);

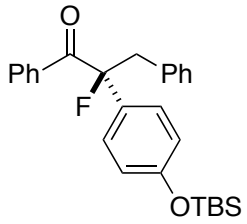
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2 (d, J = 27.7 Hz), 138.9 (d, J = 22.2 Hz), 135.3, 132.24 (d, J = 3.5 Hz), 132.18 (d, J = 1.2 Hz), 132.13 (d, J = 8.6 Hz), 129.8, 128.7 (d, J = 1.8 Hz), 128.5, 128.1, 127.8, 127.6, 126.5, 125.4 (d, J = 4.5 Hz), 124.1 (d, J = 8.9 Hz), 103.9 (d, J = 189.6 Hz), 32.8 (d, J = 23.6 Hz), 7.5 (d, J = 4.5 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −164.6 (t, 1F, J = 24.6 Hz);

FT-IR (film) 3060, 2978, 2940, 1681, 1627, 1448, 1278, 775, 762, 749 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{20}H_{17}FNaO$: 315, found: 315;

$[\alpha]^{25}_D$ = −10.2° (*c* = 1.05, $CHCl_3$); 97% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-2-fluoro-1,3-diphenylpropan-1-one (Table 2.4, Entry 1). 2-Bromo-2-fluoro-1,3-diphenylpropan-1-one (307 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from (4-bromophenoxy)(*tert*-butyl)dimethylsilane were used. Solvent system for chromatography: 20:1→10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 300 mg (69% yield, 97% ee); Run 2, 277 mg (64% yield, 97% ee).

The ee was determined of 2-fluoro-2-(4-hydroxyphenyl)-1,3-diphenylpropan-1-one (obtained by deprotection of the TBS group with TBAF) on an AD-H column (10%

i-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 16.0 min (minor), 18.4 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.76 (m, 2H), 7.46 – 7.43 (m, 1H), 7.33 – 7.29 (m, 2H), 7.28 – 7.25 (m, 2H), 7.19 – 7.17 (m, 3H), 7.07 – 7.05 (m, 2H), 6.83 – 6.80 (m, 2H), 3.68 (dd, 1H, *J* = 14.3, 24.0 Hz), 3.45 (dd, 1H, *J* = 14.4, 26.7 Hz), 0.98 (s, 9H), 0.19 (s, 6H);

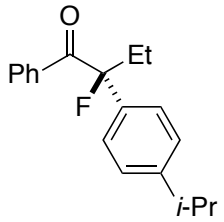
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3 (d, *J* = 28.1 Hz), 155.7, 135.0 (d, *J* = 3.2 Hz), 134.7, 132.8, 130.94 (d, *J* = 22.4 Hz), 130.94, 129.9 (d, *J* = 5.9 Hz), 128.0, 127.8, 126.6, 125.6 (d, *J* = 8.5 Hz), 120.2 (d, *J* = 1.5 Hz), 102.6 (d, *J* = 190.7 Hz), 45.4 (d, *J* = 22.7 Hz), 25.6, 18.2, −4.4 (d, *J* = 2.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −159.6 (t, 1F, *J* = 25.4 Hz);

FT-IR (film) 2955, 2929, 2857, 1686, 1606, 1508, 1260, 913, 839, 782, 698 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{27}H_{31}FNaO_2Si$: 457, found: 457;

$[\alpha]^{25}_D$ = −156° (*c* = 1.05, $CHCl_3$); 97% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-2-(4-isopropylphenyl)-1-phenylbutan-1-one (Table 2.4, Entry 2). 2-Bromo-2-fluoro-1-phenylbutan-1-one (245 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from 1-bromo-4-isopropylbenzene were used. Solvent system for chromatography: 20:1 hexane/dichloromethane. The title compound was isolated as a light-yellow oil.

Run 1, 205 mg (72% yield, 97% ee); Run 2, 198 mg (70% yield, 97% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.7 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 8.4 min (minor), 12.5 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.90 (m, 2H), 7.50 – 7.46 (m, 1H), 7.44 – 7.41 (m, 2H), 7.38 – 7.35 (m, 2H), 7.26 – 7.24 (m, 2H), 2.93 – 2.88 (m, 1H), 2.45 (ddq, 1H, J = 7.3, 14.6, 25.6 Hz), 2.19 (ddq, 1H, J = 7.4, 14.7, 23.6 Hz), 1.24 (dd, 6H, J = 1.4, 6.9 Hz), 0.94 (t, 3H, J = 7.3 Hz);

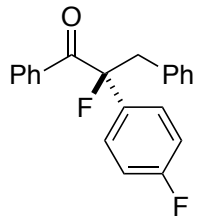
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7 (d, J = 28.4 Hz), 148.7, 136.1 (d, J = 22.1 Hz), 135.2 (d, J = 3.4 Hz), 132.8, 130.0 (d, J = 6.3 Hz), 128.1, 126.7 (d, J = 1.8 Hz), 124.1 (d, J = 9.0 Hz), 103.8 (d, J = 189.0 Hz), 33.7, 32.8 (d, J = 23.6 Hz), 23.9 (d, J = 2.7 Hz), 7.5 (d, J = 4.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −164.6 (t, 1F, J = 24.6 Hz);

FT-IR (film) 2961, 2871, 1671, 1448, 1260, 1219, 826 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{19}H_{21}FNaO$: 307, found: 307;

$[\alpha]^{25}_D$ = +38.4° (c = 0.97, $CHCl_3$); 97% ee, from (4*S*,5*R*)-**L1**.



(*S*)-2-Fluoro-2-(4-fluorophenyl)-1,3-diphenylpropan-1-one (Table 2.4, Entry 3). 2-Bromo-2-fluoro-1,3-diphenylpropan-1-one (307 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from 1-bromo-4-fluorobenzene were used. The reaction was

run at −20 °C for 36 h. Solvent system for chromatography: 20:1→10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 210 mg (65% yield, 94% ee); Run 2, 211 mg (65% yield, 93% ee).

The ee was determined on an AD-H column (1% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 12.1 min (minor), 14.4 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.74 (m, 2H), 7.48 – 7.45 (m, 1H), 7.41 – 7.37 (m, 2H), 7.34 – 7.31 (m, 2H), 7.21 – 7.18 (m, 3H), 7.07 – 7.02 (m, 4H), 3.71 (dd, 1H, J = 14.4, 23.8 Hz), 3.45 (dd, 1H, J = 14.4, 27.2 Hz);

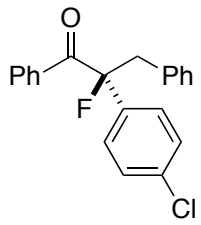
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1 (d, J = 27.8 Hz), 162.6 (d, J = 246.7 Hz), 134.8 (d, J = 3.3 Hz), 134.3, 134.1 (dd, J = 3.1, 22.7 Hz), 133.0, 130.9, 129.9 (d, J = 6.2 Hz), 128.1, 127.9, 126.8, 126.2 (t, J = 8.7 Hz), 115.6 (dd, J = 1.7, 21.8 Hz), 102.5 (d, J = 192.3 Hz), 45.5 (d, J = 22.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −113.7 (m, 1F), −159.8 (t, 1F, J = 25.4 Hz);

FT-IR (film) 3064, 3031, 2927, 1686, 1508, 1260, 1236, 1162, 837 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{21}H_{16}F_2NaO$: 345, found: 345;

$[\alpha]^{25}_D$ = +191° (*c* = 1.06, $CHCl_3$); 93% ee, from (4*S*,5*R*)-**L1**.



(*S*)-2-(4-Chlorophenyl)-2-fluoro-1,3-diphenylpropan-1-one (Table 2.4, Entry 4). 2-Bromo-2-fluoro-1,3-diphenylpropan-1-one (307 mg, 1.00 mmol) and the arylzinc

chloride reagent prepared from 1-bromo-4-chlorobenzene were used. The reaction was run at −20 °C for 36 h. Solvent system for chromatography: 20:1→10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 232 mg (68% yield, 93% ee); Run 2, 243 mg (72% yield, 93% ee).

The ee was determined on an AD-H column (1% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 13.3 min (minor), 18.2 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.73 (m, 2H), 7.48 – 7.45 (m, 1H), 7.36 – 7.30 (m, 6H), 7.20 – 7.18 (m, 3H), 7.07 – 7.05 (m, 2H), 3.70 (dd, 1H, *J* = 14.4, 23.7 Hz), 3.44 (dd, 1H, *J* = 14.4, 27.2 Hz);

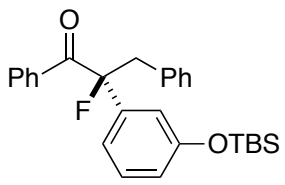
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9 (d, *J* = 27.7 Hz), 136.8 (d, *J* = 22.8 Hz), 134.7 (d, *J* = 3.5 Hz), 134.4, 134.2, 133.1, 130.9 (d, *J* = 1.0 Hz), 129.8 (d, *J* = 6.1 Hz), 128.8 (d, *J* = 1.8 Hz), 128.2, 127.9, 126.9, 125.8 (d, *J* = 9.0 Hz), 102.4 (d, *J* = 192.6 Hz), 45.4 (d, *J* = 22.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −160.6 (t, 1F, *J* = 25.6 Hz);

FT-IR (film) 3063, 3031, 1684, 1490, 1260, 1094, 1083, 733, 698 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{21}H_{16}ClFNaO$: 361, found: 361;

$[\alpha]^{25}_D = -195°$ (*c* = 1.00, $CHCl_3$); 93% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)-2-fluoro-1,3-diphenylpropan-1-one (Table 2.4, Entry 5). 2-Bromo-2-fluoro-1,3-diphenylpropan-1-one (307 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from (3-bromophenoxy)(*tert*-butyl)dimethylsilane were used. Solvent system for chromatography: 15:1→10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 338 mg (78% yield, 99% ee); Run 2, 334 mg (77% yield, 99% ee).

The ee was determined of 2-fluoro-2-(3-hydroxyphenyl)-1,3-diphenylpropan-1-one (obtained by deprotection of the TBS group with TBAF) on an AD-H column (10% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 13.5 min (minor), 18.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.78 (m, 2H), 7.47 – 7.43 (m, 1H), 7.33 – 7.29 (m, 2H), 7.21 – 7.16 (m, 4H), 7.08 – 7.06 (m, 2H), 7.00 – 6.97 (m, 1H), 6.89 – 6.88 (m, 1H), 6.76 (ddd, 1H, *J* = 1.0, 2.4, 8.1 Hz), 3.68 (dd, 1H, *J* = 14.4, 22.9 Hz), 3.47 (dd, 1H, *J* = 14.4, 28.2 Hz), 0.95 (s, 9H), 0.12 (d, 6H, *J* = 1.0 Hz);

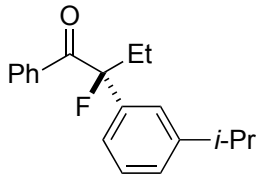
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7 (d, *J* = 28.0 Hz), 155.9 (d, *J* = 2.3 Hz), 139.7 (d, *J* = 22.2 Hz), 134.8 (d, *J* = 3.4 Hz), 134.6, 132.9, 130.9, 129.9 (d, *J* = 5.8 Hz), 129.7 (d, *J* = 1.7 Hz), 128.1, 127.8, 126.7, 120.0, 117.2 (d, *J* = 8.4 Hz), 116.1 (d, *J* = 9.6 Hz), 102.4 (d, *J* = 191.7 Hz), 45.2 (d, *J* = 22.4 Hz), 25.7, 18.2, −4.5 (d, *J* = 4.5 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −160.5 (dd, 1F, *J* = 22.9, 28.1 Hz);

FT-IR (film) 2956, 2929, 2858, 1685, 1599, 1484, 1280, 1258, 946, 830, 783, 696 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{27}H_{31}FNaO_2Si$: 457, found: 457;

$[\alpha]^{25}_D$ = +180° (*c* = 1.05, $CHCl_3$); 99% ee, from (4*S*,5*R*)-**L1**.



(*S*)-2-Fluoro-2-(3-isopropylphenyl)-1-phenylbutan-1-one (Table 2.4, Entry 6). 2-Bromo-2-fluoro-1-phenylbutan-1-one (245 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from 1-bromo-3-isopropylbenzene were used. Solvent system for chromatography: 20:1 hexane/dichloromethane. The title compound was isolated as a light-yellow oil.

Run 1, 202 mg (71% yield, 98% ee); Run 2, 213 mg (75% yield, 96% ee).

The ee was determined on an AD-H column (100% hexane, flow rate 0.4 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 16.0 min (minor), 17.5 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.88 (m, 2H), 7.50 – 7.46 (m, 1H), 7.38 – 7.30 (m, 5H), 7.20 – 7.18 (m, 1H), 2.95 – 2.89 (m, 1H), 2.46 (ddq, 1H, J = 7.3, 14.6, 25.6 Hz), 2.20 (ddq, 1H, J = 7.4, 14.7, 23.6 Hz), 1.25 (dd, 6H, J = 0.7, 6.9 Hz), 0.94 (t, 3H, J = 7.3 Hz);

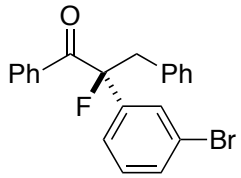
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6 (d, J = 28.8 Hz), 149.4 (d, J = 1.8 Hz), 138.7 (d, J = 22.3 Hz), 135.3 (d, J = 3.0 Hz), 132.8, 129.9 (d, J = 5.8 Hz), 128.6 (d, J = 1.6 Hz), 128.1, 126.1, 122.3 (d, J = 8.9 Hz), 121.6 (d, J = 9.3 Hz), 103.9 (d, J = 188.9 Hz), 34.2, 32.9 (d, J = 23.7 Hz), 23.9 (d, J = 11.0), 7.5 (d, J = 4.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −164.6 (m, 1F);

FT-IR (film) 2962, 2882, 1682, 1598, 1447, 1258, 795, 703 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{19}H_{21}FNaO$: 307, found: 307;

$[\alpha]^{25}_{D} = -121°$ (c = 1.00, $CHCl_3$); 98% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-(3-Bromophenyl)-2-fluoro-1,3-diphenylpropan-1-one (Table 2.4, Entry 7). 2-Bromo-2-fluoro-1,3-diphenylpropan-1-one (307 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from 1,3-dibromobenzene were used. The reaction was run at −20 °C for 36 h. Solvent system for chromatography: 15:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 224 mg (58% yield, 92% ee); Run 2, 221 mg (58% yield, 90% ee).

The ee was determined on an AS-H column (0.05% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 18.0 min (major), 22.2 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.73 (m, 2H), 7.59 (t, 1H, J = 1.9 Hz), 7.49 – 7.43 (m, 2H), 7.37 – 7.31 (m, 3H), 7.24 – 7.18 (m, 4H), 7.09 – 7.07 (m, 2H), 3.71 (dd, 1H, J = 14.4, 25.3 Hz), 3.42 (dd, 1H, J = 14.4, 25.6 Hz);

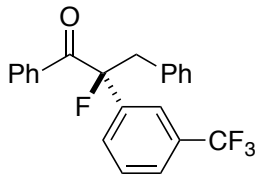
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7 (d, J = 27.9 Hz), 140.6 (d, J = 22.5 Hz), 134.7 (d, J = 3.6 Hz), 134.1, 133.1, 131.5, 130.9 (d, J = 1.2 Hz), 130.2 (d, J = 1.9 Hz), 129.8 (d, J = 6.2 Hz), 128.2, 128.0, 127.4 (d, J = 9.7 Hz), 126.9, 123.0 (d, J = 8.9 Hz), 122.9 (d, J = 2.3 Hz), 102.2 (d, J = 193.8 Hz), 45.6 (d, J = 22.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −160.5 (t, 1F, J = 25.4 Hz);

FT-IR (film) 3063, 3031, 1685, 1596, 1567, 1260, 1076, 781, 715, 692 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{21}H_{16}{}^{79}BrFNaO$: 405, found: 405, 407 ($M+Na^+$+2);

$[\alpha]^{25}_D = -180°$ (*c* = 1.00, $CHCl_3$); 92% ee, from (4*R*,5*S*)-**L1**.



(*S*)-2-Fluoro-1,3-diphenyl-2-(3-(trifluoromethyl)phenyl)propan-1-one (Table 2.4, Entry 8). 2-Bromo-2-fluoro-1,3-diphenylpropan-1-one (307 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from 1-bromo-3-(trifluoromethyl)benzene were used. The reaction was run at −20 °C for 36 h. Solvent system for chromatography: 20:1→15:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 237 mg (64% yield, 90% ee); Run 2, 247 mg (66% yield, 90% ee).

The ee was determined on an OJ-H column (0.5% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 21.6 min (minor), 25.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.74 (m, 2H), 7.71 – 7.70 (m, 1H), 7.65 – 7.63 (m, 1H), 7.60 – 7.57 (m, 1H), 7.50 – 7.46 (m, 2H), 7.35 – 7.32 (m, 2H), 7.21 – 7.18 (m, 3H), 7.08 – 7.06 (m, 2H), 3.76 (dd, 1H, *J* = 14.4, 24.9 Hz), 3.46 (dd, 1H, *J* = 14.4, 26.2 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8 (d, *J* = 27.9 Hz), 139.4 (d, *J* = 22.7 Hz), 134.7 (d, *J* = 3.6 Hz), 133.9, 133.2, 130.8 (d, *J* = 1.1 Hz), 129.8 (d, *J* = 6.4 Hz), 129.1 (d,

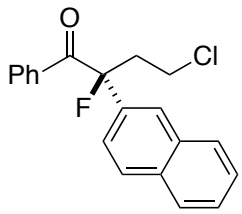
J = 2.0 Hz), 128.2, 128.0, 127.7 (m), 127.0, 125.2 (m), 124.9, 122.7, 121.3 (m), 102.4 (d, J = 193.9), 45.7 (d, J = 22.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −62.7 (s, 3F), −160.7 (t, 1F, J = 25.6 Hz);

FT-IR (film) 3065, 3032, 1685, 1448, 1332, 1169, 1129, 1078, 699 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{22}H_{16}F_4NaO$: 395, found: 395;

$[\alpha]^{25}_D$ = −151° (*c* = 1.00, $CHCl_3$); 90% ee, from (4*R*,5*S*)-**L1**.



(*S*)-4-Chloro-2-fluoro-2-(naphthalen-2-yl)-1-phenylbutan-1-one (Table 2.4, Entry 9). 2-Bromo-4-chloro-2-fluoro-1-phenylbutan-1-one (280 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from 2-bromonaphthalene were used. Solvent system for chromatography: 20:1→15:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 190 mg (58% yield, 98% ee); Run 2, 190 mg (58% yield, 97% ee).

The ee was determined on an AD-H column (1% *i*-PrOH/hexane, flow rate 0.8 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 15.5 min (minor), 22.0 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 1.9 Hz), 7.93 – 7.83 (m, 5H), 7.58 (dd, 1H, J = 1.9, 8.6 Hz), 7.55 – 7.50 (m, 2H), 7.48 (ddt, 1H, J = 1.3, 7.2, 8.7 Hz), 7.36 – 7.33 (m, 2H), 3.64 (td, 1H, J = 5.5, 10.8 Hz), 3.48 (td, 1H, J = 4.9, 10.7 Hz), 3.00 (dddd, 1H, J = 5.5, 10.7, 14.5, 23.1 Hz), 2.81 (dddd, 1H, J = 4.9, 10.9, 14.5, 23.3 Hz);

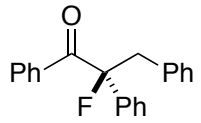
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6 (d, J = 27.0 Hz), 134.9 (d, J = 22.0 Hz), 134.1 (d, J = 3.5 Hz), 133.03 (d, J = 0.8 Hz), 132.99 (d, J = 1.8 Hz), 133.0, 130.2 (d, J = 6.3 Hz), 129.2 (d, J = 2.0 Hz), 128.29, 128.26, 128.25, 127.7, 126.8 (d, J = 3.9 Hz), 123.1 (d, J = 9.6 Hz), 121.2 (d, J = 8.6 Hz), 102.3 (d, J = 190.6 Hz), 42.5 (d, J = 22.5 Hz), 38.7 (d, J = 4.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ −162.6 (t, 1F, J = 23.2 Hz);

FT-IR (film) 3059, 2968, 1684, 1597, 1448, 1264, 1244, 819, 748, 708 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{20}H_{16}ClFNaO$: 349, found: 349;

$[\alpha]^{25}_D$ = +202° (c = 0.60, $CHCl_3$); 97% ee, from (4*S*,5*R*)-**L1**.



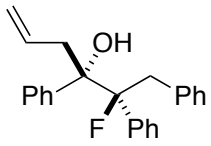
(*S*)-2-Fluoro-1,2,3-triphenylpropan-1-one (eq 2.8). 2-Chloro-2-fluoro-1,3-diphenylpropan-1-one (263 mg, 1.00 mmol) and the arylzinc chloride reagent prepared from bromobenzene were used. The reaction was run at −20 °C for 36 h. Solvent system for chromatography: 20:1→10:1 hexane/dichloromethane. The title compound was isolated as a white solid.

Run 1, 205 mg (67% yield, 98% ee); Run 2, 206 mg (68% yield, 98% ee).

The ee was determined on an AD-H column (2% *i*-PrOH/hexane, flow rate 0.6 mL/min); retention times for compound obtained using (4*R*,5*S*)-**L1**: 12.4 min (minor), 14.3 min (major).

For the characterization data, see Table 2.2, Entry 2 (above).

2.6.4 Derivatization of the Cross-Coupling Products



(2*S*,3*S*)-2-Fluoro-1,2,3-triphenylhex-5-en-3-ol (eq 2.10). A solution of allylmagnesium chloride (2.0 M in THF; 0.21 mL, 0.42 mmol; 1.2 equiv) was added over 1 min to a solution of (*S*)-2-fluoro-1,2,3-triphenylpropan-1-one (107 mg, 0.350 mmol; 98% ee; Table 2.2, entry 2; from a Negishi cross-coupling reaction using (4*R*,5*S*)-**L1**) in THF (1.0 mL) at −78 °C. The mixture was allowed to stir at −78 °C for 10 min, and then it was stirred at r.t. for 60 min. Next, the reaction mixture was cooled to 0 °C, and aqueous NH_4Cl (saturated; 2 mL) was added to quench the reaction. The mixture was washed with brine and extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography on silica gel. Solvent system for chromatography: 50%→75% dichloromethane in hexane. The title compound was isolated as a white solid.

Run 1, 121 mg (100% yield, >20:1 dr, 97% ee); Run 2, 119 mg (98% yield, >20:1 dr, 97% ee).

The ee was determined on an AS-H column (1% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention time: 7.5 min (major), 9.9 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 5H), 7.14 – 7.08 (m, 3H), 7.06 – 7.03 (m, 3H), 6.98 – 6.93 (m, 4H), 5.54 – 5.45 (m, 1H), 5.19 (d, 1H, *J* = 17.1 Hz), 5.09 (d, 1H, *J* = 10.2, Hz), 3.87 (dd, 1H, *J* = 10.3, 14.6 Hz), 3.20 (dd, 1H, *J* = 14.6, 41.7 Hz), 2.94-2.83 (m, 2H), 2.64 (s, 1H);

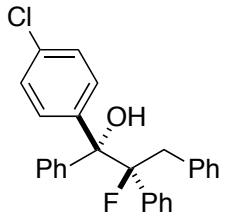
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0 (d, *J* = 2.4 Hz), 137.9 (d, *J* = 22.1 Hz), 136.0, 133.4, 130.7 (d, *J* = 1.8 Hz), 128.0 (d, *J* = 1.6 Hz), 127.5, 127.3, 127.23, 127.19, 127.0, 126.8, 126.0, 120.0, 102.6 (d, *J* = 185.9 Hz), 79.5 (d, *J* = 24.7 Hz), 40.3 (d, *J* = 3.9 Hz), 39.5 (d, *J* = 20.9 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −165.2 (dd, 1F, *J* = 10.3, 41.7 Hz);

FT-IR (film) 3552, 3060, 3029, 1497, 1446, 1032, 1000, 977, 722, 700 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{24}H_{23}FNaO$: 369, found: 369;

$[\alpha]^{25}_D = -73.3°$ (*c* = 0.97, $CHCl_3$).



(1*R*,2*S*)-1-(4-Chlorophenyl)-2-fluoro-1,2,3-triphenylpropan-1-ol (eq 2.11). A solution of *n*-BuLi in hexane (2.61 M; 0.17 mL, 0.46 mmol; 1.3 equiv) was added over 1 min to a solution of 1-chloro-4-bromobenzene (95.8 mg, 0.500 mmol; 1.43 equiv) in THF (0.7 mL) at −78 °C. The mixture was stirred at −78 °C for 10 min, and then a solution of (*S*)-2-fluoro-1,2,3-triphenylpropan-1-one (107 mg, 0.350 mmol; 98% ee; Table 2.2, entry 2; from a Negishi cross-coupling reaction using (4*R*,5*S*)-**L1**) in THF (1.0 mL) was added to the aryllithium solution at −78 °C. The mixture was allowed to stir at −78 °C for 60 min, and then the reaction was quenched with aqueous NH_4Cl (saturated; 2 mL). The mixture was washed with brine and extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash

chromatography on silica gel. Solvent system for chromatography: 15%→50% dichloromethane in hexane. The title compound was isolated as a white solid.

Run 1, 137 mg (94% yield, >20:1 dr, 98% ee); Run 2, 143 mg (98% yield, >20:1 dr, 98% ee).

The ee was determined on an AS-H column (2% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times: 12.1 min (major), 15.6 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 2H), 7.39 – 7.36 (m, 2H), 7.33 – 7.31 (m, 2H), 7.22 – 7.20 (m, 2H), 7.15 – 7.11 (m, 6H), 7.06 – 7.04 (m, 3H), 6.91 – 6.89 (m, 2H), 3.62 – 3.45 (m, 2H), 2.83 (s, 1H);

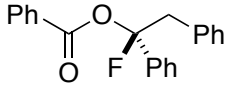
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9 (d, J = 1.3 Hz), 142.0 (d, J = 2.2 Hz), 138.4 (d, J = 22.3 Hz), 135.6 (d, J = 1.5 Hz), 133.2, 130.6 (d, J = 1.3 Hz), 129.3 (d, J = 5.2 Hz), 128.1, 127.57, 127.56, 127.4 (d, J = 1.2 Hz), 127.3 (d, J = 2.1 Hz), 127.2 (d, J = 2.2 Hz), 127.1 (m), 126.1, 102.6 (d, J = 190.6 Hz), 81.0 (d, J = 25.6 Hz), 41.4 (d, J = 20.3 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −161.3 (dd, 1F, J = 11.4, 37.6 Hz);

FT-IR (film) 3568, 3069, 3031, 1491, 1446, 1013, 746, 699 cm^{-1};

MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{27}H_{22}ClFNaO$: 439, found: 439;

$[\alpha]^{25}_D$ = +65.6° (*c* = 0.99, $CHCl_3$).



(*S*)-1-Fluoro-1,2-diphenylethyl benzoate (eq 2.13). This procedure is based on a published procedure.[17] To a solution of (*S*)-2-fluoro-1,2,3-triphenylpropan-1-one (122 mg, 0.400 mmol; 98% ee; Table 2.2, entry 2; from a Negishi cross-coupling reaction using (4*R*,5*S*)-**L1**) and 3-chloroperbenzoic acid (*m*-CPBA, ≤77% purity; 448 mg, 2.00

mmol; 5.00 equiv) in CH_2Cl_2 (1.0 mL) was added 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP; 1.0 mL) and phosphate buffer solution (pH 7; 0.4 mL). The mixture was stirred vigorously at r.t. for 36 h. The reaction was then quenched with aqueous $Na_2S_2O_3$ (saturated; 7 mL). The mixture was washed with aqueous $NaHCO_3$ (saturated; 15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography on silica gel. Solvent system for chromatography: (1) flash chromatography on silica, 15%→30% dichloromethane in hexane; (2) preparative TLC on silica, 15% ethyl acetate in hexane. The title compound was isolated as a white solid.

Run 1, 104 mg (81% yield, 98% ee); Run 2, 104 mg (81% yield, 98% ee).

The ee was determined on an AD-H column (5% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times: 8.3 min (major), 10.6 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 8.02 (m, 2H), 7.61 – 7.58 (m, 1H), 7.48 – 7.44 (m, 2H), 7.35 – 7.33 (m, 5H), 7.28 – 7.25 (m, 3H), 7.15 – 7.13 (m, 2H), 3.63 – 3.51 (m, 2H);

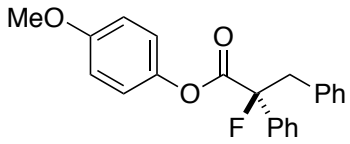
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 138.7 (d, J = 26.2 Hz), 133.5, 133.3 (d, J = 3.5 Hz), 130.9, 129.9, 129.8, 128.7 (d, J = 1.2 Hz), 128.5, 128.2, 128.0, 127.1, 124.7 (d, J = 6.9 Hz), 113.8 (d, J = 236.4 Hz), 47.4 (d, J = 26.4 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −113.5 (t, 1F, J = 17.5 Hz);

FT-IR (film) 3063, 3032, 2929, 1740, 1451, 1265, 1135, 1084, 1066, 1024, 1008, 999, 707, 701, 603 cm^{-1};

MS (ESI) *m/z* (M+Na$^+$) calcd for $C_{21}H_{17}FNaO_2$: 343, found: 343;

$[\alpha]^{25}_D$ = −74.2° (c = 0.97, $CHCl_3$).



4-Methoxyphenyl (*S*)-2-fluoro-2,3-diphenylpropanoate (eq 7). This procedure is based on a published procedure.[17] To a solution of (*S*)-2-fluoro-1-(4-methoxyphenyl)-2,3-diphenylpropan-1-one (117 mg, 0.350 mmol; 97% ee; Table 2.3, entry 1; from a Negishi cross-coupling reaction using (4*R*,5*S*)-**L1**) and 3-chloroperbenzoic acid (*m*-CPBA, 77% purity; 392 mg, 1.75 mmol; 5.00 equiv) in CH_2Cl_2 (1.0 mL) was added 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP; 1.0 mL) and phosphate buffer solution (pH 7; 0.4 mL). The mixture was stirred vigorously at r.t. for 36 h. The reaction was quenched with aqueous $Na_2S_2O_3$ (saturated; 7 mL). The mixture was washed with aqueous $NaHCO_3$ (saturated; 15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography on silica gel. Solvent system for chromatography: (1) flash chromatography on silica, 20%→50% dichloromethane in hexane; (2) preparative TLC on silica, 20% ethyl acetate in hexane. The title compound was isolated as a white solid.

Run 1, 104 mg (85% yield, 97% ee); Run 2, 100 mg (82% yield, 97% ee).

The ee was determined on an AD-H column (5% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times: 15.6 min (minor), 20.7 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.68 (m, 2H), 7.47 – 7.39 (m, 3H), 7.36 – 7.29 (m, 5H), 6.83 – 6.80 (m, 2H), 6.74 – 6.70 (m, 2H), 3.78 (dd, 1H, J = 14.5, 32.9 Hz), 3.76 (s, 3H), 3.51 (dd, 1H, J = 14.5, 18.4 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8 (d, J = 27.1 Hz), 157.5, 143.5, 137.7 (d, J = 22.6 Hz), 134.1, 130.7 (d, J = 1.5 Hz), 128.8 (d, J = 1.3 Hz), 128.6 (d, J = 1.5 Hz), 128.3,

127.3, 124.8 (d, J = 9.3 Hz), 121.9, 114.4, 96.8 (d, J = 194.2 Hz), 55.5, 44.9 (d, J = 21.4 Hz);

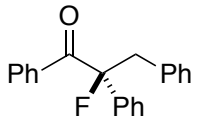
^{19}F NMR (282 MHz, $CDCl_3$) δ −161.8 (dd, 1F, J = 18.5, 32.8 Hz);

FT-IR (film) 3062, 3032, 2931, 2836, 1774, 1753, 1503, 1248, 1189, 1031, 696 cm^{-1};

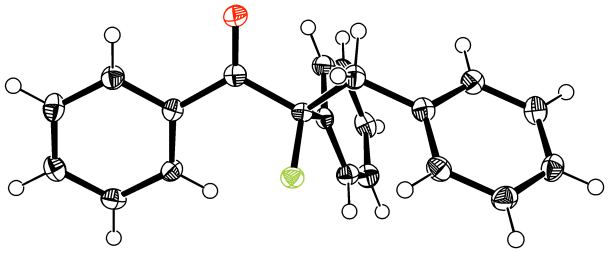
MS (ESI) *m/z* ($M+H^+$) calcd for $C_{22}H_{20}FO_3$: 351, found: 351;

$[\alpha]^{25}_D$ = +9.7° (c = 1.02, $CHCl_3$).

2.6.5 Assignment of the Absolute Stereochemistry of the Cross-Coupling Products



Absolute stereochemistry of product from Entry 2.2 of Table 2 (run with (4*R*,5*S*)-L1). (*S*)-2-Fluoro-1,2,3-triphenylpropan-1-one.



A crystal of $C_{21}H_{17}F_1O_1$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Rigkau Saturn944+ with filtered Cu-Kα radiation at a temperature of 93 K. Using Olex2 [1], the structure was solved with the ShelXS [2]

structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement, and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341.

2. SHELXS, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

3. SHELXL, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

Table 2.5. Crystal Data and Structure Refinement for Crystal_001.

Identification code	crystal_001	
Empirical formula	C_{21} H_{17} F_1 O_1	
Formula weight	304.36	
Temperature	93 K	
Wavelength	1.54187 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.89490(10) Å	α= 90°.
	b = 15.2807(3) Å	β= 90 °.
	c = 17.2167(12) Å	γ = 90 °.
Volume	1550.85(12) $Å^3$	
Z	4	
Density (calculated)	1.303 Mg/m^3	

Absorption coefficient	0.697 mm^{-1}
F(000)	640
Crystal size	0.2 x 0.05 x 0.05 mm^3
Theta range for data collection	3.868 to 68.146°.
Index ranges	-7<=h<=7, -18<=k<=18, -20<=l<=20
Reflections collected	53111
Independent reflections	2831 [R(int) = 0.0685]
Completeness to theta = 67.687°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.902
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2831 / 0 / 208
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0252, wR2 = 0.0621
R indices (all data)	R1 = 0.0258, wR2 = 0.0626
Absolute structure parameter	0.06(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.102 and -0.154 $e/Å^{-3}$

Table 2.6. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_001. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	1126(2)	6163(1)	7538(1)	21(1)
O(1)	-3721(2)	5645(1)	6546(1)	27(1)
C(1)	-392(3)	6179(1)	5945(1)	19(1)
C(2)	-1906(3)	6014(1)	6624(1)	20(1)
C(3)	-1220(3)	6315(1)	7451(1)	18(1)
C(4)	-2440(3)	5754(1)	8058(1)	21(1)
C(5)	1456(3)	6748(1)	5966(1)	21(1)
C(6)	2811(3)	6861(1)	5316(1)	23(1)
C(7)	2325(3)	6410(1)	4638(1)	24(1)
C(8)	465(3)	5855(1)	4608(1)	26(1)
C(9)	-891(3)	5737(1)	5257(1)	23(1)
C(10)	-1677(3)	7287(1)	7554(1)	18(1)
C(11)	-3756(3)	7631(1)	7329(1)	23(1)
C(12)	-4232(3)	8511(1)	7445(1)	25(1)
C(13)	-2646(3)	9056(1)	7786(1)	25(1)
C(14)	-574(3)	8713(1)	8014(1)	25(1)
C(15)	-82(3)	7833(1)	7900(1)	22(1)
C(16)	-1913(3)	5999(1)	8888(1)	20(1)
C(17)	-3448(3)	6488(1)	9323(1)	22(1)
C(18)	-2990(3)	6698(1)	10091(1)	25(1)
C(19)	-997(3)	6417(1)	10435(1)	25(1)
C(20)	550(3)	5933(1)	10009(1)	25(1)
C(21)	97(3)	5726(1)	9239(1)	23(1)

Table 2.7. Bond Lengths [Å] and Angles [°] for Crystal_001.

F(1)-C(3)	1.4103(17)
O(1)-C(2)	1.216(2)
C(1)-C(2)	1.492(2)
C(1)-C(5)	1.394(2)
C(1)-C(9)	1.396(2)
C(2)-C(3)	1.551(2)
C(3)-C(4)	1.529(2)
C(3)-C(10)	1.520(2)
C(4)-C(16)	1.510(2)
C(5)-C(6)	1.385(2)
C(6)-C(7)	1.386(3)
C(7)-C(8)	1.388(3)
C(8)-C(9)	1.385(2)
C(10)-C(11)	1.388(2)
C(10)-C(15)	1.392(2)
C(11)-C(12)	1.388(2)
C(12)-C(13)	1.383(3)
C(13)-C(14)	1.385(3)
C(14)-C(15)	1.390(2)
C(16)-C(17)	1.392(2)
C(16)-C(21)	1.394(2)
C(17)-C(18)	1.388(2)
C(18)-C(19)	1.384(3)
C(19)-C(20)	1.384(3)
C(20)-C(21)	1.390(2)
C(5)-C(1)-C(2)	123.58(14)
C(5)-C(1)-C(9)	119.24(15)
C(9)-C(1)-C(2)	117.18(15)
O(1)-C(2)-C(1)	121.19(15)
O(1)-C(2)-C(3)	117.93(14)
C(1)-C(2)-C(3)	120.87(14)
F(1)-C(3)-C(2)	107.73(12)
F(1)-C(3)-C(4)	107.24(12)
F(1)-C(3)-C(10)	108.79(12)
C(4)-C(3)-C(2)	109.77(13)
C(10)-C(3)-C(2)	110.49(13)
C(10)-C(3)-C(4)	112.64(13)
C(16)-C(4)-C(3)	114.25(14)
C(6)-C(5)-C(1)	120.48(15)
C(5)-C(6)-C(7)	119.99(16)
C(6)-C(7)-C(8)	119.84(17)
C(9)-C(8)-C(7)	120.45(17)
C(8)-C(9)-C(1)	119.98(16)

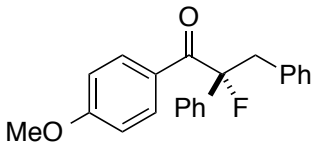
C(11)-C(10)-C(3)	119.62(14)
C(11)-C(10)-C(15)	119.22(15)
C(15)-C(10)-C(3)	121.09(15)
C(10)-C(11)-C(12)	120.36(16)
C(13)-C(12)-C(11)	120.50(16)
C(12)-C(13)-C(14)	119.28(16)
C(13)-C(14)-C(15)	120.61(17)
C(14)-C(15)-C(10)	120.03(16)
C(17)-C(16)-C(4)	120.56(16)
C(17)-C(16)-C(21)	118.68(16)
C(21)-C(16)-C(4)	120.74(15)
C(18)-C(17)-C(16)	120.72(17)
C(19)-C(18)-C(17)	120.01(17)
C(18)-C(19)-C(20)	119.98(16)
C(19)-C(20)-C(21)	119.99(17)
C(20)-C(21)-C(16)	120.61(17)

Table 2.8. Anisotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_001. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

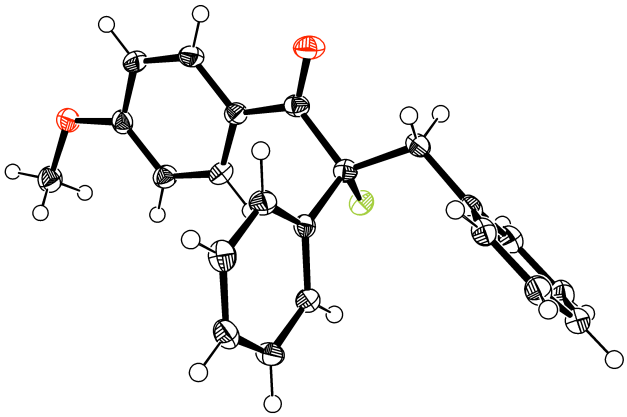
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	18(1)	21(1)	22(1)	0(1)	-2(1)	3(1)
O(1)	24(1)	34(1)	24(1)	-4(1)	1(1)	-10(1)
C(1)	21(1)	17(1)	18(1)	2(1)	-1(1)	2(1)
C(2)	21(1)	17(1)	22(1)	0(1)	0(1)	1(1)
C(3)	15(1)	20(1)	19(1)	0(1)	-1(1)	0(1)
C(4)	24(1)	19(1)	21(1)	0(1)	1(1)	-2(1)
C(5)	22(1)	22(1)	19(1)	0(1)	-3(1)	-2(1)
C(6)	19(1)	25(1)	26(1)	5(1)	-1(1)	-2(1)
C(7)	26(1)	25(1)	22(1)	3(1)	5(1)	3(1)
C(8)	35(1)	22(1)	21(1)	-4(1)	3(1)	0(1)
C(9)	26(1)	20(1)	23(1)	-1(1)	1(1)	-3(1)
C(10)	20(1)	17(1)	15(1)	1(1)	2(1)	-1(1)
C(11)	21(1)	24(1)	23(1)	2(1)	-1(1)	-1(1)
C(12)	24(1)	26(1)	27(1)	5(1)	4(1)	6(1)
C(13)	32(1)	17(1)	26(1)	4(1)	8(1)	2(1)
C(14)	30(1)	20(1)	26(1)	-3(1)	2(1)	-4(1)
C(15)	21(1)	21(1)	23(1)	1(1)	-2(1)	-1(1)
C(16)	24(1)	14(1)	21(1)	3(1)	2(1)	-2(1)
C(17)	24(1)	21(1)	23(1)	3(1)	0(1)	1(1)
C(18)	32(1)	21(1)	23(1)	0(1)	3(1)	3(1)
C(19)	33(1)	23(1)	20(1)	1(1)	-1(1)	-5(1)
C(20)	24(1)	27(1)	24(1)	6(1)	-4(1)	-3(1)
C(21)	23(1)	22(1)	25(1)	3(1)	3(1)	0(1)

Table 2.9. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_001.

	x	y	z	U(eq)
H(4A)	-4063	5805	7976	25
H(4B)	-2027	5147	7977	25
H(5)	1780	7055	6419	26
H(6)	4046	7239	5335	28
H(7)	3244	6480	4203	29
H(8)	125	5561	4150	32
H(9)	-2134	5362	5233	27
H(11)	-4835	7269	7100	27
H(12)	-5628	8736	7291	30
H(13)	-2967	9645	7862	30
H(14)	498	9076	8246	30
H(15)	1313	7609	8056	26
H(17)	-4796	6675	9096	27
H(18)	-4024	7028	10376	30
H(19)	-696	6554	10951	30
H(20)	1893	5746	10239	30
H(21)	1144	5402	8955	28



Absolute stereochemistry of product from Entry 1 of Table 2.3 (run with (4*S*,5*R*)-L1). (*R*)-2-Fluoro-1-(4-methoxyphenyl)-2,3-diphenylpropan-1-one.



A crystal of $C_{22}H_{19}F_1O_2$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Rigkau Saturn944+ with filtered Cu-Kα radiation at a temperature of 93 K. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement, and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341.

2. SHELXS, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

3. SHELXL, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

Table 2.10. Crystal Data and Structure Refinement for Crystal_002.

Identification code	crystal_002	
Empirical formula	C_{22} H_{19} F_1 O_2	
Formula weight	334.37	
Temperature	93 K	
Wavelength	1.54187 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.86120(10) Å	α= 90°.
	b = 15.7648(3) Å	β= 90 °.
	c = 18.3237(13) Å	γ = 90 °.
Volume	1693.12(13) $Å^3$	
Z	4	
Density (calculated)	1.312 Mg/m^3	
Absorption coefficient	0.731 mm^{-1}	
F(000)	704	
Crystal size	0.15 x 0.05 x 0.05 mm^3	
Theta range for data collection	3.699 to 68.208°.	
Index ranges	-7<=h<=7, -18<=k<=18, -21<=l<=22	
Reflections collected	58234	
Independent reflections	3085 [R(int) = 0.0587]	
Completeness to theta = 67.687°	99.9 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	1.000 and 0.912
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3085 / 0 / 227
Goodness-of-fit on F^2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0237, wR2 = 0.0599
R indices (all data)	R1 = 0.0238, wR2 = 0.0600
Absolute structure parameter	-0.01(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.109 and -0.166 e.$Å^{-3}$

Table 2.11. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_002. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	-1506(2)	-9122(1)	-7196(1)	21(1)
O(1)	3412(2)	-9778(1)	-8002(1)	28(1)
O(2)	-2372(2)	-8682(1)	-10727(1)	27(1)
C(1)	1652(3)	-9363(1)	-7999(1)	20(1)
C(2)	862(2)	-8975(1)	-7264(1)	19(1)
C(3)	2025(3)	-9430(1)	-6627(1)	22(1)
C(4)	404(3)	-9191(1)	-8689(1)	19(1)
C(5)	-1648(3)	-8745(1)	-8735(1)	22(1)
C(6)	-2659(3)	-8565(1)	-9401(1)	23(1)
C(7)	-1597(3)	-8832(1)	-10040(1)	22(1)
C(8)	435(3)	-9294(1)	-10001(1)	24(1)
C(9)	1410(3)	-9473(1)	-9339(1)	23(1)
C(10)	1425(3)	-9081(1)	-5884(1)	20(1)
C(11)	2943(3)	-8551(1)	-5519(1)	22(1)
C(12)	2455(3)	-8252(1)	-4822(1)	25(1)
C(13)	434(3)	-8480(1)	-4484(1)	24(1)
C(14)	-1107(3)	-9001(1)	-4844(1)	25(1)
C(15)	-619(3)	-9299(1)	-5541(1)	23(1)
C(16)	1281(3)	-8024(1)	-7265(1)	17(1)
C(17)	3364(3)	-7707(1)	-7509(1)	22(1)
C(18)	3794(3)	-6842(1)	-7503(1)	25(1)
C(19)	2163(3)	-6281(1)	-7243(1)	24(1)
C(20)	96(3)	-6593(1)	-6993(1)	25(1)
C(21)	-349(3)	-7461(1)	-7003(1)	21(1)
C(22)	-4298(3)	-8134(1)	-10802(1)	29(1)

Table 2.12. Bond Lengths [Å] and Angles [°] for Crystal_002.

F(1)-C(2)	1.4127(17)
O(1)-C(1)	1.222(2)
O(2)-C(7)	1.3585(18)
O(2)-C(22)	1.429(2)
C(1)-C(2)	1.549(2)
C(1)-C(4)	1.487(2)
C(2)-C(3)	1.531(2)
C(2)-C(16)	1.520(2)
C(3)-C(10)	1.511(2)
C(4)-C(5)	1.395(2)
C(4)-C(9)	1.402(2)
C(5)-C(6)	1.386(2)
C(6)-C(7)	1.392(2)
C(7)-C(8)	1.398(2)
C(8)-C(9)	1.371(2)
C(10)-C(11)	1.391(2)
C(10)-C(15)	1.396(2)
C(11)-C(12)	1.391(2)
C(12)-C(13)	1.385(2)
C(13)-C(14)	1.387(2)
C(14)-C(15)	1.391(2)
C(16)-C(17)	1.393(2)
C(16)-C(21)	1.390(2)
C(17)-C(18)	1.387(2)
C(18)-C(19)	1.387(2)
C(19)-C(20)	1.385(2)
C(20)-C(21)	1.393(2)
C(7)-O(2)-C(22)	117.34(12)
O(1)-C(1)-C(2)	117.93(13)
O(1)-C(1)-C(4)	120.60(14)
C(4)-C(1)-C(2)	121.35(13)
F(1)-C(2)-C(1)	107.80(11)
F(1)-C(2)-C(3)	107.06(12)
F(1)-C(2)-C(16)	108.70(11)
C(3)-C(2)-C(1)	110.19(12)
C(16)-C(2)-C(1)	109.88(12)
C(16)-C(2)-C(3)	113.03(12)
C(10)-C(3)-C(2)	114.42(12)
C(5)-C(4)-C(1)	124.58(13)
C(5)-C(4)-C(9)	118.12(14)
C(9)-C(4)-C(1)	117.26(14)
C(6)-C(5)-C(4)	121.65(14)
C(5)-C(6)-C(7)	119.18(14)

O(2)-C(7)-C(6)	125.24(15)
O(2)-C(7)-C(8)	115.02(14)
C(6)-C(7)-C(8)	119.74(14)
C(9)-C(8)-C(7)	120.50(15)
C(8)-C(9)-C(4)	120.78(15)
C(11)-C(10)-C(3)	120.15(14)
C(11)-C(10)-C(15)	118.75(14)
C(15)-C(10)-C(3)	121.07(14)
C(12)-C(11)-C(10)	120.84(15)
C(13)-C(12)-C(11)	119.92(15)
C(12)-C(13)-C(14)	119.86(15)
C(13)-C(14)-C(15)	120.19(15)
C(14)-C(15)-C(10)	120.42(15)
C(17)-C(16)-C(2)	119.69(13)
C(21)-C(16)-C(2)	121.25(13)
C(21)-C(16)-C(17)	119.02(14)
C(18)-C(17)-C(16)	120.59(15)
C(19)-C(18)-C(17)	120.29(15)
C(20)-C(19)-C(18)	119.39(14)
C(19)-C(20)-C(21)	120.51(15)
C(16)-C(21)-C(20)	120.19(15)

Symmetry transformations used to generate equivalent atoms

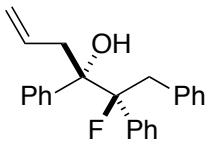
Table 2.13. Anisotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_002. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	18(1)	23(1)	22(1)	-1(1)	2(1)	-3(1)
O(1)	24(1)	30(1)	29(1)	-6(1)	-2(1)	8(1)
O(2)	38(1)	25(1)	18(1)	0(1)	-2(1)	7(1)
C(1)	20(1)	16(1)	24(1)	-2(1)	1(1)	-1(1)
C(2)	16(1)	20(1)	21(1)	0(1)	0(1)	0(1)
C(3)	24(1)	18(1)	23(1)	2(1)	-1(1)	4(1)
C(4)	22(1)	16(1)	21(1)	-2(1)	2(1)	-2(1)
C(5)	22(1)	26(1)	20(1)	-3(1)	4(1)	1(1)
C(6)	21(1)	25(1)	23(1)	-1(1)	2(1)	1(1)
C(7)	29(1)	17(1)	19(1)	1(1)	0(1)	-3(1)
C(8)	32(1)	21(1)	21(1)	-3(1)	6(1)	2(1)
C(9)	25(1)	18(1)	26(1)	-2(1)	3(1)	3(1)
C(10)	22(1)	16(1)	21(1)	4(1)	-2(1)	3(1)
C(11)	22(1)	22(1)	22(1)	4(1)	0(1)	0(1)
C(12)	30(1)	21(1)	23(1)	1(1)	-4(1)	-2(1)
C(13)	31(1)	22(1)	20(1)	1(1)	1(1)	5(1)
C(14)	23(1)	27(1)	25(1)	6(1)	2(1)	2(1)
C(15)	24(1)	20(1)	25(1)	3(1)	-3(1)	-2(1)
C(16)	19(1)	18(1)	15(1)	0(1)	-3(1)	1(1)
C(17)	19(1)	24(1)	24(1)	0(1)	1(1)	2(1)
C(18)	22(1)	26(1)	27(1)	3(1)	-1(1)	-5(1)
C(19)	32(1)	18(1)	23(1)	2(1)	-5(1)	-2(1)
C(20)	28(1)	20(1)	26(1)	-2(1)	0(1)	6(1)
C(21)	21(1)	22(1)	21(1)	1(1)	3(1)	2(1)
C(22)	29(1)	34(1)	24(1)	3(1)	-2(1)	4(1)

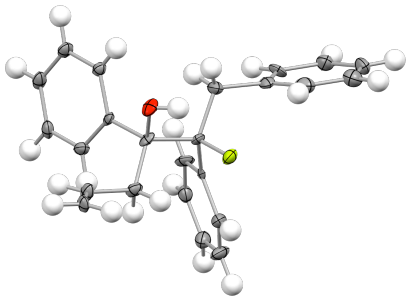
Table 2.14. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters (Å^{2}x 10^3) for Crystal_002.

	x	y	z	U(eq)
H(3A)	1611	-10026	-6642	26
H(3B)	3665	-9394	-6692	26
H(5)	-2355	-8564	-8308	27
H(6)	-4030	-8269	-9421	28
H(8)	1130	-9482	-10428	29
H(9)	2754	-9786	-9321	28
H(11)	4302	-8395	-5744	27
H(12)	3486	-7899	-4584	30
H(13)	111	-8285	-4016	29
H(14)	-2470	-9150	-4618	30
H(15)	-1662	-9646	-5780	27
H(17)	4476	-8079	-7678	27
H(18)	5182	-6637	-7674	30
H(19)	2454	-5702	-7236	29
H(20)	-1004	-6220	-6818	30
H(21)	-1741	-7664	-6833	26
H(22A)	-3947	-7590	-10595	44
H(22B)	-5582	-8375	-10553	44
H(22C)	-4657	-8067	-11310	44

2.6.6 Assignment of the Stereochemistry of the Derivatization Products



Relative stereochemistry of product from eq 2.10 (run with the product of a cross-coupling conducted with (4*R*,5*S*)-L1). (2*S*,3*S*)-2-Fluoro-1,2,3-triphenylhex-5-en-3-ol.



A crystal of $C_{24}H_{23}F_1O_1$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Smart with filtered Mo-Kα radiation at a temperature of 100 K. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimization. The absolute stereochemistry could not be determined on the basis of the absolute structure parameter, but was instead assigned by reference to the tertiary stereocenter in the starting material ((*S*)-2-fluoro-1,2,3-triphenylpropan-1-one).

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement, and analysis program. *J.*

Appl. Cryst. **2009**, *42*, 339–341.

2. SHELXS, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

3. SHELXL, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

Table 2.15. Crystal Data and Structure Refinement for Crystal_004.

Identification code	crystal_004	
Empirical formula	C_{24} H_{23} F O	
Formula weight	346.42	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C_2	
Unit cell dimensions	a = 16.777(6) Å	α= 90°.
	b = 15.082(5) Å	β= 110.639(6) °.
	c = 15.600(6) Å	γ = 90 °.
Volume	3694(2) $Å^3$	
Z	8	
Density (calculated)	1.246 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	1472	
Crystal size	0.27 x 0.21 x 0.17 mm^3	
Theta range for data collection	1.395 to 26.357°.	
Index ranges	-20<=h<=20, -18<=k<=18, -19<=l<=19	

Reflections collected	25299
Independent reflections	7544 [R(int) = 0.1056]
Completeness to theta = 25.242°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7544 / 1 / 471
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0797, wR2 = 0.1624
R indices (all data)	R1 = 0.1120, wR2 = 0.1746
Absolute structure parameter	-0.5(5)
Largest diff. peak and hole	0.334 and -0.379 e/$Å^{-3}$

Table 2.16. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for Crystal_004. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	1016(2)	1283(2)	191(2)	23(1)
O(1)	459(3)	-295(3)	-636(3)	22(1)
C(1)	1455(4)	912(4)	-357(4)	16(1)
C(2)	1352(4)	-117(4)	-277(4)	16(1)
C(3)	1762(4)	-618(4)	-873(4)	14(1)
C(4)	2605(5)	-914(4)	-521(4)	20(2)
C(5)	2962(5)	-1357(4)	-1074(4)	20(1)
C(6)	2495(5)	-1518(4)	-1975(4)	24(2)
C(7)	1667(5)	-1233(4)	-2346(4)	21(2)
C(8)	1294(5)	-801(4)	-1793(4)	16(1)
C(9)	1698(5)	-412(4)	728(4)	20(2)
C(10)	1571(4)	-1379(4)	866(4)	21(2)
C(11)	1105(4)	-1680(4)	1319(4)	18(1)
C(12)	979(5)	1245(4)	-1329(4)	26(2)
C(13)	926(4)	2236(4)	-1457(4)	22(2)
C(14)	355(5)	2730(5)	-1188(5)	34(2)
C(15)	250(5)	3644(5)	-1350(5)	32(2)
C(16)	713(5)	4059(5)	-1813(5)	32(2)
C(17)	1290(5)	3585(5)	-2094(4)	29(2)
C(18)	1380(5)	2673(4)	-1921(4)	28(2)
C(19)	2370(4)	1211(4)	60(4)	16(1)
C(20)	2704(5)	1510(4)	962(4)	22(2)
C(21)	3555(5)	1745(5)	1350(4)	30(2)
C(22)	4088(5)	1683(4)	848(5)	28(2)
C(23)	3764(4)	1384(4)	-43(4)	22(2)
C(24)	2919(5)	1156(4)	-439(4)	24(2)
F(1B)	-1077(2)	-1387(2)	-5179(2)	21(1)
O(1B)	-359(3)	-2912(3)	-4322(3)	22(1)
C(1B)	-1411(4)	-1774(4)	-4552(4)	15(1)
C(2B)	-1270(4)	-2804(4)	-4616(4)	17(1)
C(3B)	-1590(4)	-3340(4)	-3988(4)	15(1)
C(4B)	-2425(4)	-3634(4)	-4252(4)	19(1)
C(5B)	-2708(5)	-4135(4)	-3680(4)	23(2)
C(6B)	-2166(5)	-4346(4)	-2807(5)	28(2)
C(7B)	-1331(5)	-4069(4)	-2522(4)	22(2)
C(8B)	-1034(4)	-3573(4)	-3096(4)	18(1)
C(9B)	-1665(4)	-3114(4)	-5627(4)	17(1)

C(10B)	-1501(4)	-4077(4)	-5750(4)	21(2)
C(11B)	-1125(6)	-4372(5)	-6301(6)	47(3)
C(12B)	-884(5)	-1389(4)	-3617(4)	24(2)
C(13B)	-857(5)	-392(4)	-3562(4)	22(2)
C(14B)	-328(5)	97(5)	-3902(4)	25(2)
C(15B)	-299(5)	1010(5)	-3825(5)	31(2)
C(16B)	-765(5)	1464(4)	-3402(4)	27(2)
C(17B)	-1292(5)	992(4)	-3069(4)	24(2)
C(18B)	-1342(5)	67(4)	-3149(4)	24(2)
C(19B)	-2339(4)	-1537(4)	-4850(4)	12(1)
C(20B)	-2771(4)	-1204(4)	-5730(4)	15(1)
C(21B)	-3633(4)	-1034(4)	-6025(4)	20(2)
C(22B)	-4087(5)	-1199(4)	-5467(5)	29(2)
C(23B)	-3672(5)	-1520(4)	-4597(5)	27(2)
C(24B)	-2806(5)	-1678(4)	-4290(4)	19(2)

Table 2.17. Bond Lengths [Å] and Angles [°] for Crystal_004.

F(1)-C(1)	1.426(7)
O(1)-C(2)	1.428(8)
C(1)-C(2)	1.572(8)
C(1)-C(12)	1.527(8)
C(1)-C(19)	1.509(9)
C(2)-C(3)	1.534(8)
C(2)-C(9)	1.534(8)
C(3)-C(4)	1.398(9)
C(3)-C(8)	1.400(8)
C(4)-C(5)	1.383(9)
C(5)-C(6)	1.368(9)
C(6)-C(7)	1.372(10)
C(7)-C(8)	1.393(9)
C(9)-C(10)	1.500(8)
C(10)-C(11)	1.307(9)
C(12)-C(13)	1.507(9)
C(13)-C(14)	1.390(11)
C(13)-C(18)	1.389(10)
C(14)-C(15)	1.402(10)
C(15)-C(16)	1.384(11)
C(16)-C(17)	1.393(10)
C(17)-C(18)	1.399(9)
C(19)-C(20)	1.393(8)
C(19)-C(24)	1.403(9)
C(20)-C(21)	1.386(10)
C(21)-C(22)	1.384(11)
C(22)-C(23)	1.378(9)
C(23)-C(24)	1.374(10)
F(1B)-C(1B)	1.414(6)
O(1B)-C(2B)	1.440(8)
C(1B)-C(2B)	1.579(9)
C(1B)-C(12B)	1.529(8)
C(1B)-C(19B)	1.502(9)
C(2B)-C(3B)	1.508(8)
C(2B)-C(9B)	1.553(8)
C(3B)-C(4B)	1.386(9)
C(3B)-C(8B)	1.419(8)
C(4B)-C(5B)	1.374(8)
C(5B)-C(6B)	1.383(10)
C(6B)-C(7B)	1.377(10)
C(7B)-C(8B)	1.388(8)
C(9B)-C(10B)	1.503(8)
C(10B)-C(11B)	1.311(10)
C(12B)-C(13B)	1.507(9)

C(13B)-C(14B)	1.396(9)
C(13B)-C(18B)	1.387(10)
C(14B)-C(15B)	1.380(10)
C(15B)-C(16B)	1.371(10)
C(16B)-C(17B)	1.373(10)
C(17B)-C(18B)	1.400(9)
C(19B)-C(20B)	1.400(8)
C(19B)-C(24B)	1.380(8)
C(20B)-C(21B)	1.378(9)
C(21B)-C(22B)	1.367(10)
C(22B)-C(23B)	1.377(10)
C(23B)-C(24B)	1.381(10)

F(1)-C(1)-C(2)	104.2(5)
F(1)-C(1)-C(12)	105.4(5)
F(1)-C(1)-C(19)	106.7(4)
C(12)-C(1)-C(2)	111.7(5)
C(19)-C(1)-C(2)	112.6(5)
C(19)-C(1)-C(12)	115.2(5)
O(1)-C(2)-C(1)	106.5(5)
O(1)-C(2)-C(3)	107.5(5)
O(1)-C(2)-C(9)	108.3(5)
C(3)-C(2)-C(1)	110.6(5)
C(9)-C(2)-C(1)	110.8(4)
C(9)-C(2)-C(3)	112.8(5)
C(4)-C(3)-C(2)	121.8(5)
C(4)-C(3)-C(8)	117.6(6)
C(8)-C(3)-C(2)	120.6(6)
C(5)-C(4)-C(3)	120.7(6)
C(6)-C(5)-C(4)	120.6(7)
C(5)-C(6)-C(7)	120.4(6)
C(6)-C(7)-C(8)	119.6(6)
C(7)-C(8)-C(3)	121.0(6)
C(10)-C(9)-C(2)	114.0(5)
C(11)-C(10)-C(9)	123.9(6)
C(13)-C(12)-C(1)	116.3(5)
C(14)-C(13)-C(12)	120.4(7)
C(18)-C(13)-C(12)	121.5(6)
C(18)-C(13)-C(14)	117.8(6)
C(13)-C(14)-C(15)	121.9(7)
C(16)-C(15)-C(14)	118.8(7)
C(15)-C(16)-C(17)	120.8(7)
C(16)-C(17)-C(18)	118.9(7)
C(13)-C(18)-C(17)	121.7(7)
C(20)-C(19)-C(1)	121.2(6)
C(20)-C(19)-C(24)	118.1(6)

C(24)-C(19)-C(1)	120.7(5)
C(21)-C(20)-C(19)	120.6(7)
C(22)-C(21)-C(20)	120.4(6)
C(23)-C(22)-C(21)	119.3(7)
C(24)-C(23)-C(22)	120.9(7)
C(23)-C(24)-C(19)	120.7(6)
F(1B)-C(1B)-C(2B)	105.0(5)
F(1B)-C(1B)-C(12B)	105.4(5)
F(1B)-C(1B)-C(19B)	107.9(5)
C(12B)-C(1B)-C(2B)	112.6(5)
C(19B)-C(1B)-C(2B)	112.2(5)
C(19B)-C(1B)-C(12B)	113.1(5)
O(1B)-C(2B)-C(1B)	104.9(5)
O(1B)-C(2B)-C(3B)	108.3(5)
O(1B)-C(2B)-C(9B)	108.3(5)
C(3B)-C(2B)-C(1B)	113.0(5)
C(3B)-C(2B)-C(9B)	112.1(5)
C(9B)-C(2B)-C(1B)	109.9(4)
C(4B)-C(3B)-C(2B)	122.2(5)
C(4B)-C(3B)-C(8B)	117.3(5)
C(8B)-C(3B)-C(2B)	120.5(6)
C(5B)-C(4B)-C(3B)	121.8(6)
C(4B)-C(5B)-C(6B)	120.5(7)
C(7B)-C(6B)-C(5B)	119.3(6)
C(6B)-C(7B)-C(8B)	120.7(6)
C(7B)-C(8B)-C(3B)	120.3(6)
C(10B)-C(9B)-C(2B)	112.8(5)
C(11B)-C(10B)-C(9B)	124.3(6)
C(13B)-C(12B)-C(1B)	115.4(5)
C(14B)-C(13B)-C(12B)	121.1(7)
C(18B)-C(13B)-C(12B)	120.9(6)
C(18B)-C(13B)-C(14B)	118.0(6)
C(15B)-C(14B)-C(13B)	120.1(7)
C(16B)-C(15B)-C(14B)	122.1(7)
C(15B)-C(16B)-C(17B)	118.4(6)
C(16B)-C(17B)-C(18B)	120.6(7)
C(13B)-C(18B)-C(17B)	120.8(7)
C(20B)-C(19B)-C(1B)	120.7(5)
C(24B)-C(19B)-C(1B)	121.7(5)
C(24B)-C(19B)-C(20B)	117.6(6)
C(21B)-C(20B)-C(19B)	121.0(6)
C(22B)-C(21B)-C(20B)	120.5(6)
C(21B)-C(22B)-C(23B)	119.4(7)
C(22B)-C(23B)-C(24B)	120.4(6)
C(19B)-C(24B)-C(23B)	121.1(6)

Table 2.18. Anisotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_004. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

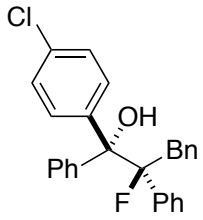
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	31(2)	19(2)	18(2)	-7(2)	7(2)	-2(2)
O(1)	17(3)	20(2)	30(3)	-9(2)	8(2)	-7(2)
C(1)	20(4)	17(3)	10(3)	-7(2)	3(3)	2(3)
C(2)	15(4)	14(3)	18(3)	-7(2)	6(3)	-8(3)
C(3)	23(4)	7(3)	12(3)	-3(2)	6(3)	-3(3)
C(4)	28(4)	15(3)	14(3)	-1(2)	3(3)	-1(3)
C(5)	28(4)	12(3)	22(3)	2(3)	12(3)	4(3)
C(6)	44(5)	18(3)	16(3)	2(3)	17(3)	5(3)
C(7)	32(4)	18(3)	12(3)	-2(2)	8(3)	-2(3)
C(8)	25(4)	12(3)	12(3)	-1(2)	7(3)	-3(3)
C(9)	30(4)	16(3)	14(3)	-1(2)	8(3)	-8(3)
C(10)	37(4)	10(3)	19(3)	0(2)	13(3)	-3(3)
C(11)	31(4)	9(3)	18(3)	2(2)	12(3)	-2(3)
C(12)	33(5)	19(3)	16(3)	0(3)	-6(3)	1(3)
C(13)	22(4)	19(3)	15(3)	-4(3)	-5(3)	-3(3)
C(14)	38(5)	34(4)	22(4)	1(3)	-1(3)	-3(4)
C(15)	33(5)	31(4)	26(4)	0(3)	4(3)	7(3)
C(16)	46(5)	17(3)	22(3)	5(3)	-3(4)	4(3)
C(17)	41(5)	26(4)	17(3)	4(3)	7(3)	3(3)
C(18)	35(5)	24(4)	15(3)	8(3)	-1(3)	7(3)
C(19)	27(4)	5(3)	8(3)	3(2)	-1(3)	1(3)
C(20)	26(4)	19(3)	17(3)	-2(2)	2(3)	3(3)
C(21)	29(5)	37(4)	19(3)	-14(3)	1(3)	5(3)
C(22)	26(4)	23(4)	29(4)	-5(3)	3(3)	3(3)
C(23)	26(4)	16(3)	25(3)	1(3)	10(3)	5(3)
C(24)	37(5)	25(4)	8(3)	1(2)	4(3)	-8(3)
F(1B)	20(2)	31(2)	14(2)	7(2)	8(2)	-6(2)
O(1B)	13(3)	34(3)	17(2)	11(2)	3(2)	1(2)
C(1B)	18(4)	19(3)	8(3)	1(2)	5(3)	-9(3)
C(2B)	13(4)	26(3)	11(3)	6(2)	5(3)	-1(3)
C(3B)	15(3)	17(3)	15(3)	2(2)	8(3)	0(3)
C(4B)	23(4)	20(3)	19(3)	1(3)	14(3)	-1(3)
C(5B)	37(4)	15(3)	29(4)	-13(3)	24(3)	-9(3)
C(6B)	45(5)	19(3)	26(4)	-4(3)	20(4)	-12(3)
C(7B)	38(5)	17(3)	13(3)	4(3)	10(3)	3(3)
C(8B)	27(4)	17(3)	13(3)	-2(2)	11(3)	-3(3)
C(9B)	20(4)	20(3)	11(3)	3(2)	6(3)	0(3)

C(10B)	28(4)	22(3)	12(3)	4(3)	7(3)	-1(3)
C(11B)	73(7)	30(4)	64(5)	-31(4)	55(5)	-32(4)
C(12B)	28(4)	26(4)	14(3)	9(3)	3(3)	-8(3)
C(13B)	31(4)	22(3)	9(3)	5(2)	1(3)	-9(3)
C(14B)	21(4)	29(4)	19(3)	10(3)	0(3)	-7(3)
C(15B)	30(5)	32(4)	23(4)	9(3)	-2(3)	-14(3)
C(16B)	35(4)	17(3)	22(3)	8(3)	1(3)	1(3)
C(17B)	28(4)	22(3)	18(3)	3(3)	2(3)	5(3)
C(18B)	33(4)	20(3)	15(3)	5(3)	4(3)	-4(3)
C(19B)	16(3)	11(3)	11(3)	-1(2)	6(2)	-4(2)
C(20B)	23(4)	12(3)	10(3)	1(2)	5(3)	2(3)
C(21B)	20(4)	12(3)	20(3)	4(2)	-1(3)	3(3)
C(22B)	23(4)	19(3)	45(4)	6(3)	12(4)	7(3)
C(23B)	27(4)	20(4)	43(4)	3(3)	24(4)	6(3)
C(24B)	33(4)	12(3)	15(3)	-4(2)	10(3)	0(3)

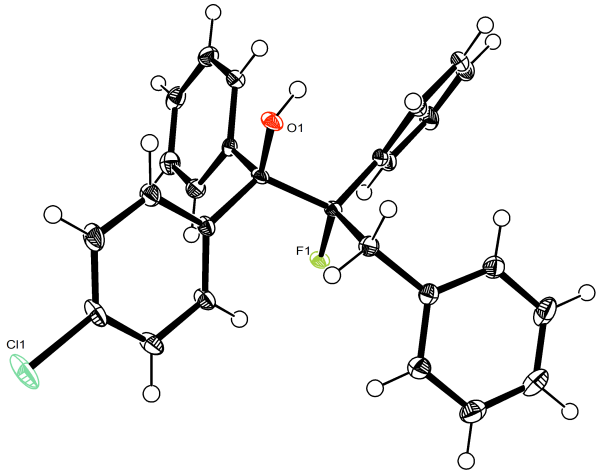
Table 2.19. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters (Å^2 x 10^3) for Crystal_004.

	x	y	z	U(eq)
H(1)	195	129	-511	33
H(4)	2936	-809	104	24
H(5)	3537	-1551	-826	24
H(6)	2745	-1829	-2346	29
H(7)	1349	-1331	-2976	25
H(8)	713	-628	-2045	19
H(9A)	2315	-278	987	24
H(9B)	1414	-61	1075	24
H(10)	1846	-1797	608	25
H(11A)	823	-1278	1585	22
H(11B)	1049	-2301	1383	22
H(12A)	1259	994	-1737	32
H(12B)	392	1006	-1532	32
H(14)	26	2439	-886	41
H(15)	-133	3972	-1146	38
H(16)	636	4676	-1941	39
H(17)	1617	3876	-2399	35
H(18)	1762	2345	-2127	33
H(20)	2345	1553	1314	27
H(21)	3774	1950	1965	36
H(22)	4671	1845	1114	33
H(23)	4128	1333	-388	26
H(24)	2705	960	-1057	29
H(1B)	-163	-2568	-4622	33
H(4B)	-2812	-3486	-4844	22
H(5B)	-3281	-4337	-3887	28
H(6B)	-2367	-4680	-2408	34
H(7B)	-954	-4218	-1925	27
H(8B)	-455	-3388	-2891	22
H(9BA)	-2287	-3010	-5848	21
H(9BB)	-1426	-2751	-6008	21
H(10B)	-1681	-4499	-5404	25
H(11C)	-937	-3967	-6656	57
H(11D)	-1041	-4991	-6346	57
H(12C)	-1117	-1617	-3157	28
H(12D)	-293	-1612	-3445	28
H(14B)	14	-198	-4187	30
H(15B)	55	1333	-4074	38
H(16B)	-724	2091	-3342	32
H(17B)	-1625	1295	-2780	29
H(18B)	-1713	-249	-2919	29

H(20B)	-2466	-1094	-6129	18
H(21B)	-3913	-800	-6622	23
H(22B)	-4683	-1093	-5678	34
H(23B)	-3984	-1633	-4204	32
H(24B)	-2527	-1887	-3683	23



Relative and absolute stereochemistry of product from eq 2.11 (run with the product of a cross-coupling conducted with (4*R*,5*S*)-L1). (1*R*,2*S*)-1-(4-Chlorophenyl)-2-fluoro-1,2,3-triphenylpropan-1-ol (for the sake of simplicity, disordered solvent molecules (CH_2Cl_2) have been omitted)**.**



A crystal of a solvate of $C_{27}H_{22}Cl_1F_1O_1$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Apex-II with filtered Mo-Kα radiation at a temperature of 100 K. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimization. The disordered and partially occupied dichloromethane solvent was refined with similarity restraints placed on the appropriate atom bond lengths and displacement parameters. The occupancy of the

dichloromethane was also refined. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement, and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341.

2. SHELXS, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

3. SHELXL, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

Table 2.20. Crystal Data and Structure Refinement for Crystal_005.

Identification code	crystal_005	
Empirical formula	$C_{27}\ H_{22}\ Cl_1\ F\ O \cdot (0.58\ CH_2Cl_2)$	
Formula weight	466.24	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.4485(6) Å	α = 90°.
	b = 5.9142(3) Å	β = 91.076(3) °.
	c = 17.0352(8) Å	γ = 90 °.
Volume	1153.23(10) $Å^3$	
Z	2	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	0.326 mm^{-1}	

F(000)	484.8
Crystal size	0.3 x 0.1 x 0.05 mm^3
Theta range for data collection	1.779 to 37.564°.
Index ranges	-19<=h<=19, -9<=k<=10, -28<=l<=28
Reflections collected	62094
Independent reflections	11432 [R(int) = 0.0601]
Completeness to theta = 25.242°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11432 / 68 / 321
Goodness-of-fit on F^2	0.957
Final R indices [I>2sigma(I)]	R1 = 0.0499, wR2 = 0.1202
R indices (all data)	R1 = 0.0773, wR2 = 0.1290
Absolute structure parameter	-0.005(18)
Largest diff. peak and hole	0.818 and -0.637 $e/Å^{-3}$

Table 2.21. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for Crystal_005. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)	Occ
Cl(1)	-3149(1)	-8113(1)	-3825(1)	33(1)	
F(1)	-3173(1)	-9003(2)	-7865(1)	14(1)	
O(1)	-3390(1)	-3198(2)	-7234(1)	16(1)	
C(1)	-2872(2)	-6682(3)	-7856(1)	11(1)	
C(2)	-3704(2)	-5518(3)	-7253(1)	12(1)	
C(3)	-3090(2)	-5802(3)	-8686(1)	12(1)	
C(4)	-2652(2)	-3711(3)	-8930(1)	16(1)	
C(5)	-2846(2)	-2956(4)	-9698(1)	18(1)	
C(6)	-3464(2)	-4295(4)	-10232(1)	21(1)	
C(7)	-3910(2)	-6353(4)	-9993(1)	20(1)	
C(8)	-3730(2)	-7103(3)	-9224(1)	15(1)	
C(9)	-1579(2)	-6523(3)	-7607(1)	14(1)	
C(10)	-804(2)	-8115(4)	-8052(1)	15(1)	
C(11)	-491(2)	-7697(4)	-8830(1)	20(1)	
C(12)	216(2)	-9199(5)	-9226(1)	27(1)	
C(13)	629(2)	-11144(4)	-8862(1)	25(1)	
C(14)	347(2)	-11570(4)	-8090(1)	24(1)	
C(15)	-371(2)	-10072(4)	-7688(1)	21(1)	
C(16)	-3531(2)	-6300(3)	-6398(1)	13(1)	
C(17)	-3843(2)	-4760(3)	-5813(1)	18(1)	
C(18)	-3740(2)	-5302(4)	-5022(1)	22(1)	
C(19)	-3313(2)	-7411(4)	-4810(1)	20(1)	
C(20)	-3022(2)	-8995(4)	-5373(1)	19(1)	
C(21)	-3140(2)	-8431(3)	-6168(1)	17(1)	
C(22)	-4982(2)	-5871(3)	-7507(1)	13(1)	
C(23)	-5592(2)	-4212(3)	-7925(1)	17(1)	
C(24)	-6762(2)	-4514(4)	-8141(1)	21(1)	
C(25)	-7343(2)	-6478(4)	-7942(1)	21(1)	
C(26)	-6739(2)	-8158(4)	-7531(1)	20(1)	
C(27)	-5575(2)	-7861(3)	-7317(1)	16(1)	
Cl(2)	762(3)	-18036(7)	-5767(2)	136(1)	0.581(3)
Cl(3A)	-738(8)	-13650(20)	-5696(6)	156(2)	0.235(3)
C(28)	381(9)	-15326(17)	-5956(7)	141(2)	0.581(3)
Cl(3B)	144(19)	-12920(40)	-5390(13)	158(3)	0.106(3)
Cl(3C)	-295(9)	-15040(20)	-5084(6)	169(3)	0.240(3)

Table 2.22. Bond Lengths [Å] and Angles [°] for Crystal_005.

Cl(1)-C(19)	1.7347(19)
F(1)-C(1)	1.416(2)
O(1)-C(2)	1.419(2)
C(1)-C(2)	1.573(2)
C(1)-C(3)	1.522(2)
C(1)-C(9)	1.535(2)
C(2)-C(16)	1.537(2)
C(2)-C(22)	1.533(3)
C(3)-C(4)	1.400(3)
C(3)-C(8)	1.394(3)
C(4)-C(5)	1.397(3)
C(5)-C(6)	1.389(3)
C(6)-C(7)	1.384(3)
C(7)-C(8)	1.394(3)
C(9)-C(10)	1.508(3)
C(10)-C(11)	1.402(3)
C(10)-C(15)	1.399(3)
C(11)-C(12)	1.386(3)
C(12)-C(13)	1.386(4)
C(13)-C(14)	1.383(3)
C(14)-C(15)	1.397(3)
C(16)-C(17)	1.402(3)
C(16)-C(21)	1.392(3)
C(17)-C(18)	1.387(3)
C(18)-C(19)	1.386(3)
C(19)-C(20)	1.386(3)
C(20)-C(21)	1.399(3)
C(22)-C(23)	1.393(3)
C(22)-C(27)	1.399(3)
C(23)-C(24)	1.393(3)
C(24)-C(25)	1.384(3)
C(25)-C(26)	1.392(3)
C(26)-C(27)	1.386(3)
Cl(2)-C(28)	1.691(10)
Cl(3A)-C(28)	1.687(11)

F(1)-C(1)-C(2)	106.29(13)
F(1)-C(1)-C(3)	106.66(14)
F(1)-C(1)-C(9)	107.18(14)
C(3)-C(1)-C(2)	111.50(14)
C(3)-C(1)-C(9)	112.15(14)
C(9)-C(1)-C(2)	112.61(14)
O(1)-C(2)-C(1)	106.35(14)
O(1)-C(2)-C(16)	104.00(14)

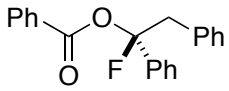
O(1)-C(2)-C(22)	112.20(15)
C(16)-C(2)-C(1)	114.78(14)
C(22)-C(2)-C(1)	110.06(14)
C(22)-C(2)-C(16)	109.34(14)
C(4)-C(3)-C(1)	121.57(16)
C(8)-C(3)-C(1)	119.78(16)
C(8)-C(3)-C(4)	118.64(16)
C(5)-C(4)-C(3)	120.55(18)
C(6)-C(5)-C(4)	120.1(2)
C(7)-C(6)-C(5)	119.63(18)
C(6)-C(7)-C(8)	120.50(19)
C(3)-C(8)-C(7)	120.55(19)
C(10)-C(9)-C(1)	113.33(15)
C(11)-C(10)-C(9)	121.90(18)
C(15)-C(10)-C(9)	120.05(16)
C(15)-C(10)-C(11)	118.05(18)
C(12)-C(11)-C(10)	120.6(2)
C(11)-C(12)-C(13)	120.8(2)
C(14)-C(13)-C(12)	119.5(2)
C(13)-C(14)-C(15)	120.1(2)
C(14)-C(15)-C(10)	120.9(2)
C(17)-C(16)-C(2)	116.65(16)
C(21)-C(16)-C(2)	125.05(16)
C(21)-C(16)-C(17)	118.23(17)
C(18)-C(17)-C(16)	121.49(19)
C(19)-C(18)-C(17)	119.00(19)
C(18)-C(19)-Cl(1)	119.94(16)
C(18)-C(19)-C(20)	121.06(18)
C(20)-C(19)-Cl(1)	119.00(17)
C(19)-C(20)-C(21)	119.28(19)
C(16)-C(21)-C(20)	120.90(17)
C(23)-C(22)-C(2)	121.02(17)
C(23)-C(22)-C(27)	118.07(18)
C(27)-C(22)-C(2)	120.91(16)
C(22)-C(23)-C(24)	121.01(19)
C(25)-C(24)-C(23)	120.45(19)
C(24)-C(25)-C(26)	119.03(19)
C(27)-C(26)-C(25)	120.6(2)
C(26)-C(27)-C(22)	120.89(19)
Cl(3A)-C(28)-Cl(2)	134.6(11)

Table 2.23. Anisotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_005. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$.

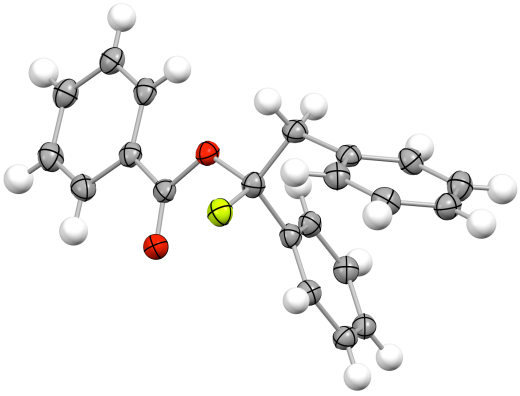
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	60(1)	29(1)	9(1)	4(1)	0(1)	-10(1)
F(1)	21(1)	7(1)	14(1)	0(1)	1(1)	-1(1)
O(1)	28(1)	7(1)	13(1)	0(1)	3(1)	-1(1)
C(1)	16(1)	7(1)	11(1)	0(1)	1(1)	0(1)
C(2)	19(1)	7(1)	9(1)	0(1)	1(1)	0(1)
C(3)	15(1)	11(1)	10(1)	1(1)	4(1)	2(1)
C(4)	18(1)	14(1)	15(1)	2(1)	3(1)	0(1)
C(5)	21(1)	18(1)	16(1)	6(1)	6(1)	3(1)
C(6)	22(1)	29(1)	12(1)	6(1)	3(1)	5(1)
C(7)	22(1)	27(1)	11(1)	0(1)	1(1)	0(1)
C(8)	18(1)	16(1)	12(1)	0(1)	2(1)	-1(1)
C(9)	17(1)	14(1)	12(1)	-1(1)	0(1)	0(1)
C(10)	13(1)	17(1)	15(1)	-1(1)	0(1)	-1(1)
C(11)	17(1)	26(1)	17(1)	2(1)	0(1)	4(1)
C(12)	19(1)	43(1)	18(1)	-5(1)	2(1)	10(1)
C(13)	16(1)	29(1)	31(1)	-9(1)	-1(1)	5(1)
C(14)	19(1)	18(1)	36(1)	0(1)	2(1)	2(1)
C(15)	19(1)	20(1)	23(1)	3(1)	2(1)	1(1)
C(16)	18(1)	11(1)	10(1)	0(1)	2(1)	-2(1)
C(17)	27(1)	14(1)	13(1)	-2(1)	3(1)	1(1)
C(18)	34(1)	20(1)	12(1)	-3(1)	5(1)	-1(1)
C(19)	30(1)	20(1)	10(1)	3(1)	0(1)	-7(1)
C(20)	31(1)	14(1)	13(1)	3(1)	-1(1)	-2(1)
C(21)	27(1)	12(1)	11(1)	0(1)	1(1)	-1(1)
C(22)	17(1)	13(1)	8(1)	-1(1)	3(1)	2(1)
C(23)	22(1)	16(1)	14(1)	3(1)	4(1)	4(1)
C(24)	22(1)	24(1)	16(1)	1(1)	1(1)	9(1)
C(25)	19(1)	27(1)	16(1)	-6(1)	1(1)	4(1)
C(26)	21(1)	21(1)	18(1)	-3(1)	1(1)	-2(1)
C(27)	21(1)	14(1)	15(1)	0(1)	1(1)	1(1)
Cl(2)	132(2)	156(3)	116(2)	-63(2)	-62(2)	26(2)
Cl(3A)	136(4)	181(4)	150(4)	-49(4)	-42(3)	3(4)
C(28)	105(4)	181(5)	134(4)	-52(5)	-65(4)	2(4)
Cl(3B)	139(5)	183(5)	151(5)	-41(5)	-49(4)	10(5)
Cl(3C)	140(4)	189(5)	176(5)	-36(5)	-37(4)	2(4)

Table 2.24. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters (Å^2 x 10^3) for Crystal_005.

	x	y	z	U(eq)	Occ
H(1)	-3514	-2623	-7679	24	
H(4)	-2218	-2799	-8569	19	
H(5)	-2556	-1525	-9856	22	
H(6)	-3580	-3801	-10758	25	
H(7)	-4342	-7261	-10355	24	
H(8)	-4045	-8513	-9066	18	
H(9A)	-1306	-4954	-7689	17	
H(9B)	-1504	-6860	-7039	17	
H(11)	-765	-6370	-9088	24	
H(12)	418	-8893	-9754	32	
H(13)	1103	-12177	-9141	30	
H(14)	642	-12882	-7833	29	
H(15)	-568	-10386	-7160	25	
H(17)	-4133	-3313	-5961	22	
H(18)	-3958	-4242	-4633	26	
H(20)	-2745	-10447	-5221	23	
H(21)	-2951	-9518	-6556	20	
H(23)	-5205	-2853	-8064	21	
H(24)	-7162	-3364	-8428	25	
H(25)	-8143	-6676	-8084	25	
H(26)	-7127	-9519	-7396	24	
H(27)	-5174	-9025	-7038	20	
H(28A)	1081	-14455	-5790	169	0.581
H(28B)	363	-15250	-6537	169	0.581



Absolute stereochemistry of product from eq 2.13 (run with the product of a cross-coupling conducted with (4*R*,5*S*)-L1). (*S*)-1-Fluoro-1,2-diphenylethyl benzoate.



A crystal of $C_{21}H_{17}F_1O_2$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Rigkau Saturn944+ with filtered Cu-Kα radiation at a temperature of 93 K. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement, and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341.

2. SHELXS, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

3. SHELXL, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

Table 2.25. Crystal Data and Structure Refinement for Crystal_003.

Identification code	crystal_003	
Empirical formula	C_{21} H_{17} F_1 O_2	
Formula weight	320.36	
Temperature	93 K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	C 1 2 1	
Unit cell dimensions	a = 23.9583(4) Å	α= 90°.
	b = 5.74320(10) Å	β= 98.352(7) °.
	c = 11.8825(8) Å	γ = 90 °.
Volume	1617.66(12) $Å^3$	
Z	4	
Density (calculated)	1.315 Mg/m^3	
Absorption coefficient	0.743 mm^{-1}	
F(000)	672	
Crystal size	0.3 x 0.15 x 0.1 mm^3	
Theta range for data collection	3.730 to 68.193°.	
Index ranges	-28<=h<=28, -6<=k<=6, -14<=l<=14	
Reflections collected	17522	
Independent reflections	2923 [R(int) = 0.0897]	
Completeness to theta = 67.687°	99.6 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	1.000 and 0.742
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2923 / 1 / 217
Goodness-of-fit on F^2	1.138
Final R indices [I>2sigma(I)]	R1 = 0.0427, wR2 = 0.1153
R indices (all data)	R1 = 0.0440, wR2 = 0.1173
Absolute structure parameter	0.1(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.172 and -0.227 e/$Å^{-3}$

Table 2.26. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_003. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	946(1)	3233(3)	6557(1)	32(1)
O(1)	1179(1)	3964(3)	4361(2)	32(1)
O(2)	827(1)	6566(3)	5507(2)	28(1)
C(1)	928(1)	5744(5)	4476(2)	28(1)
C(2)	1132(1)	5518(5)	6505(2)	27(1)
C(3)	944(1)	6845(5)	7497(2)	29(1)
C(4)	1242(1)	6041(5)	8638(2)	27(1)
C(5)	1090(1)	3966(5)	9131(2)	31(1)
C(6)	1386(1)	3197(5)	10155(2)	34(1)
C(7)	1834(1)	4486(6)	10705(2)	34(1)
C(8)	1985(1)	6552(6)	10225(2)	35(1)
C(9)	1693(1)	7309(5)	9200(2)	31(1)
C(10)	1762(1)	5559(5)	6497(2)	25(1)
C(11)	2102(1)	3735(5)	6945(2)	28(1)
C(12)	2684(1)	3855(5)	6969(2)	29(1)
C(13)	2927(1)	5805(5)	6552(2)	29(1)
C(14)	2589(1)	7632(5)	6101(2)	30(1)
C(15)	2008(1)	7532(5)	6079(2)	28(1)
C(16)	695(1)	7307(5)	3528(2)	26(1)
C(17)	754(1)	6595(5)	2424(2)	32(1)
C(18)	556(1)	8001(6)	1505(2)	34(1)
C(19)	303(1)	10121(5)	1687(2)	34(1)
C(20)	244(1)	10830(5)	2775(2)	32(1)
C(21)	444(1)	9419(5)	3702(2)	29(1)

Table 2.27. Bond Lengths [Å] and Angles [°] for Crystal_003.

F(1)-C(2)	1.390(3)
O(1)-C(1)	1.204(3)
O(2)-C(1)	1.367(3)
O(2)-C(2)	1.432(3)
C(1)-C(16)	1.484(4)
C(2)-C(3)	1.526(4)
C(2)-C(10)	1.512(3)
C(3)-C(4)	1.511(4)
C(4)-C(5)	1.399(4)
C(4)-C(9)	1.391(4)
C(5)-C(6)	1.389(4)
C(6)-C(7)	1.387(4)
C(7)-C(8)	1.387(5)
C(8)-C(9)	1.384(4)
C(10)-C(11)	1.385(4)
C(10)-C(15)	1.401(4)
C(11)-C(12)	1.391(4)
C(12)-C(13)	1.387(4)
C(13)-C(14)	1.385(4)
C(14)-C(15)	1.390(4)
C(16)-C(17)	1.401(4)
C(16)-C(21)	1.382(4)
C(17)-C(18)	1.384(4)
C(18)-C(19)	1.390(5)
C(19)-C(20)	1.383(4)
C(20)-C(21)	1.395(4)

C(1)-O(2)-C(2)	117.5(2)
O(1)-C(1)-O(2)	123.4(2)
O(1)-C(1)-C(16)	124.6(2)
O(2)-C(1)-C(16)	112.0(2)
F(1)-C(2)-O(2)	107.8(2)
F(1)-C(2)-C(3)	107.7(2)
F(1)-C(2)-C(10)	109.9(2)
O(2)-C(2)-C(3)	104.9(2)
O(2)-C(2)-C(10)	112.3(2)
C(10)-C(2)-C(3)	113.9(2)
C(4)-C(3)-C(2)	112.7(2)
C(5)-C(4)-C(3)	121.2(2)
C(9)-C(4)-C(3)	120.3(3)
C(9)-C(4)-C(5)	118.5(2)
C(6)-C(5)-C(4)	120.5(3)
C(7)-C(6)-C(5)	120.3(3)
C(8)-C(7)-C(6)	119.6(3)

C(9)-C(8)-C(7)	120.1(3)
C(8)-C(9)-C(4)	121.1(3)
C(11)-C(10)-C(2)	121.2(2)
C(11)-C(10)-C(15)	119.7(2)
C(15)-C(10)-C(2)	119.0(2)
C(10)-C(11)-C(12)	120.1(2)
C(13)-C(12)-C(11)	120.2(2)
C(14)-C(13)-C(12)	119.8(2)
C(13)-C(14)-C(15)	120.3(3)
C(14)-C(15)-C(10)	119.8(2)
C(17)-C(16)-C(1)	117.1(2)
C(21)-C(16)-C(1)	122.8(2)
C(21)-C(16)-C(17)	120.1(3)
C(18)-C(17)-C(16)	119.9(3)
C(17)-C(18)-C(19)	119.7(3)
C(20)-C(19)-C(18)	120.6(3)
C(19)-C(20)-C(21)	119.8(3)
C(16)-C(21)-C(20)	119.9(3)

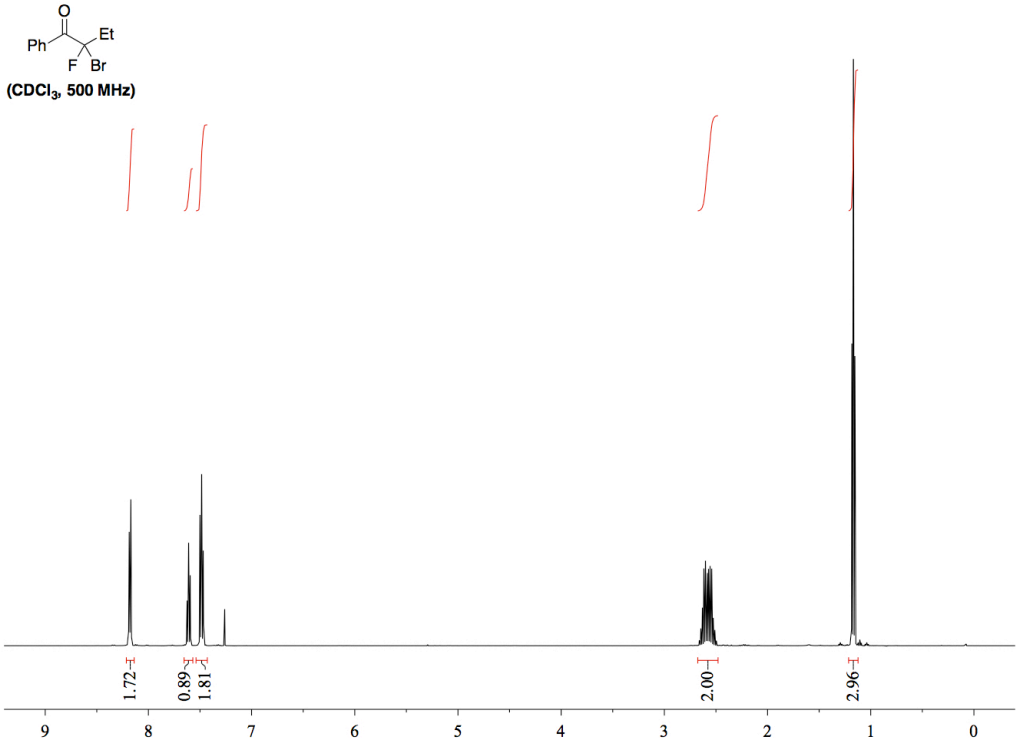
Table 2.28. Anisotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal_003. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	30(1)	31(1)	34(1)	-1(1)	5(1)	-5(1)
O(1)	32(1)	33(1)	31(1)	-4(1)	1(1)	4(1)
O(2)	26(1)	36(1)	22(1)	-1(1)	3(1)	4(1)
C(1)	22(1)	34(1)	28(1)	-5(1)	3(1)	-1(1)
C(2)	28(1)	28(1)	25(1)	2(1)	2(1)	-1(1)
C(3)	27(1)	35(2)	26(1)	-1(1)	6(1)	4(1)
C(4)	25(1)	31(1)	25(1)	-1(1)	7(1)	3(1)
C(5)	30(1)	36(2)	29(1)	0(1)	8(1)	-3(1)
C(6)	40(2)	32(2)	31(1)	3(1)	10(1)	0(1)
C(7)	35(2)	41(2)	25(1)	2(1)	4(1)	6(1)
C(8)	34(1)	43(2)	28(1)	0(1)	4(1)	-3(1)
C(9)	37(1)	31(1)	27(1)	-1(1)	7(1)	-2(1)
C(10)	27(1)	29(1)	20(1)	-2(1)	3(1)	-1(1)
C(11)	29(1)	29(1)	26(1)	2(1)	6(1)	0(1)
C(12)	28(1)	34(2)	26(1)	1(1)	3(1)	4(1)
C(13)	26(1)	33(1)	27(1)	-4(1)	4(1)	-2(1)
C(14)	30(1)	33(2)	27(1)	0(1)	5(1)	-4(1)
C(15)	32(1)	30(1)	23(1)	1(1)	1(1)	1(1)
C(16)	21(1)	33(1)	26(1)	-1(1)	4(1)	-3(1)
C(17)	29(1)	36(2)	31(1)	-6(1)	7(1)	-4(1)
C(18)	36(1)	43(2)	24(1)	0(1)	6(1)	-2(1)
C(19)	32(1)	39(2)	30(2)	5(1)	2(1)	-3(1)
C(20)	26(1)	35(2)	33(2)	2(1)	3(1)	-2(1)
C(21)	23(1)	39(2)	26(1)	-2(1)	4(1)	-5(1)

Table 2.29. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for crystal_003.

	x	y	z	U(eq)
H(3A)	1018	8526	7407	35
H(3B)	532	6641	7475	35
H(5)	782	3077	8762	38
H(6)	1281	1781	10481	41
H(7)	2036	3958	11406	41
H(8)	2290	7447	10601	42
H(9)	1803	8719	8875	38
H(11)	1938	2399	7236	33
H(12)	2916	2596	7273	35
H(13)	3325	5887	6575	34
H(14)	2755	8959	5806	36
H(15)	1777	8799	5781	34
H(17)	929	5150	2305	38
H(18)	592	7519	755	41
H(19)	170	11091	1057	41
H(20)	68	12275	2892	38
H(21)	408	9908	4451	35

2.6.7 ^{1}H NMR Spectra of Selected Compounds


O
Ph
Et
F
Br
(CDCl3, 500 MHz)
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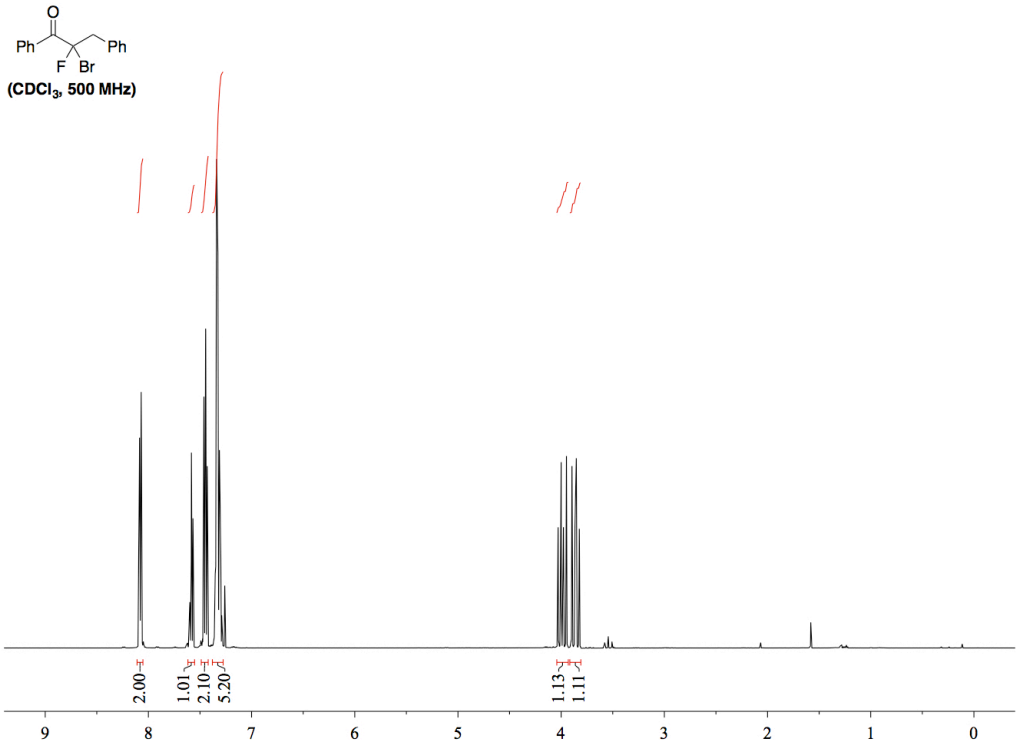
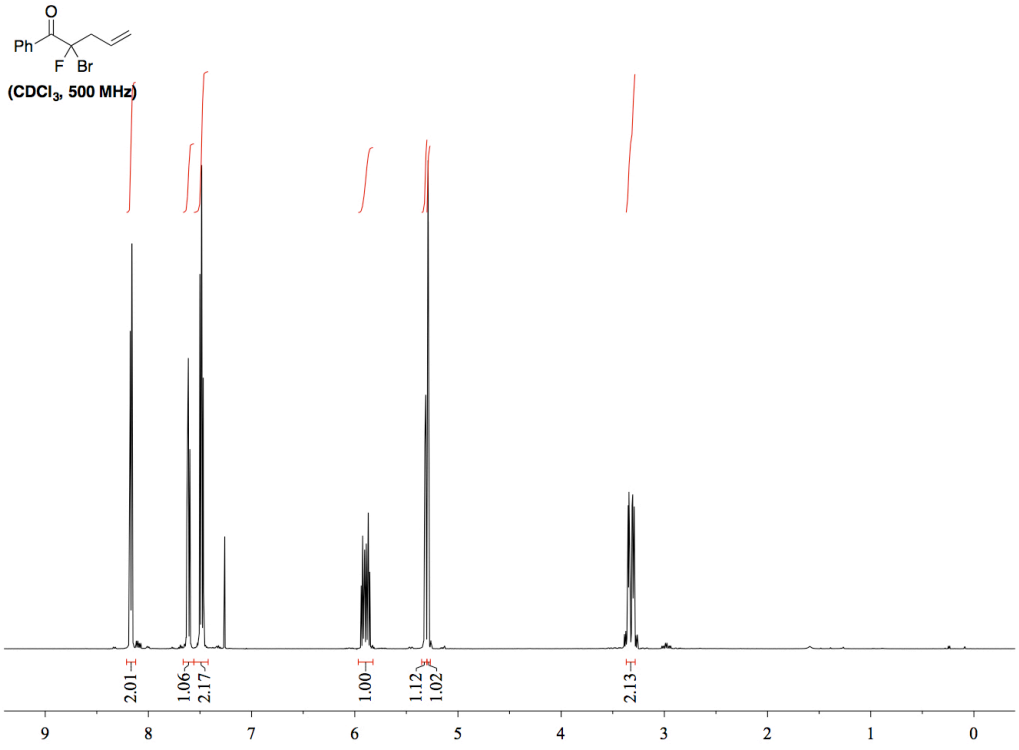
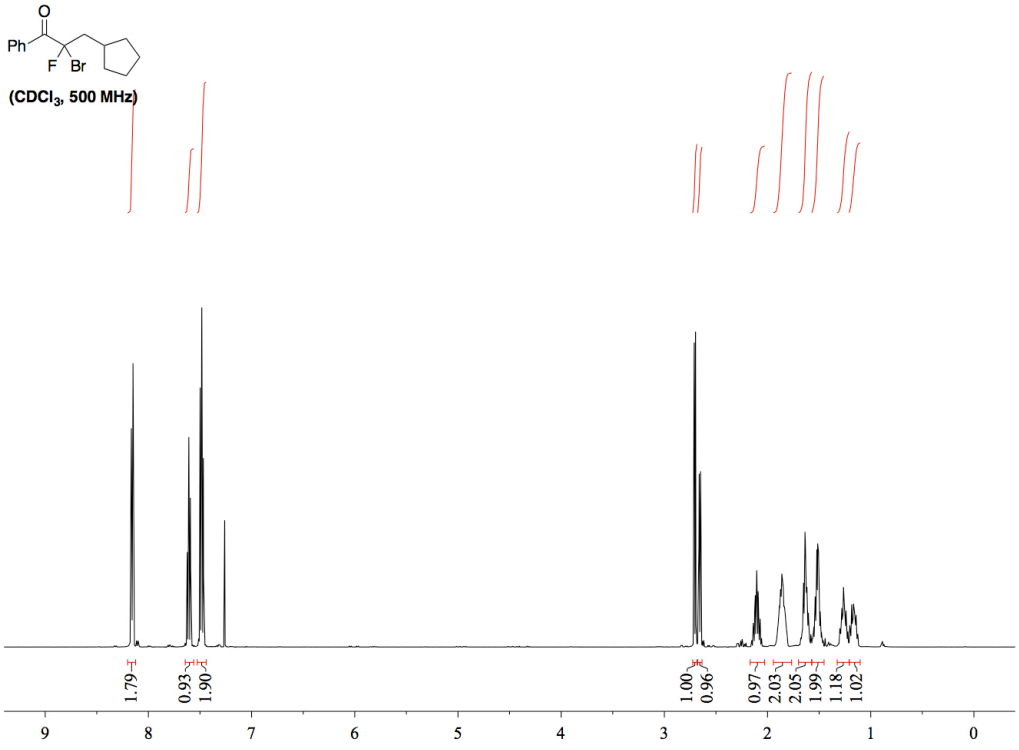
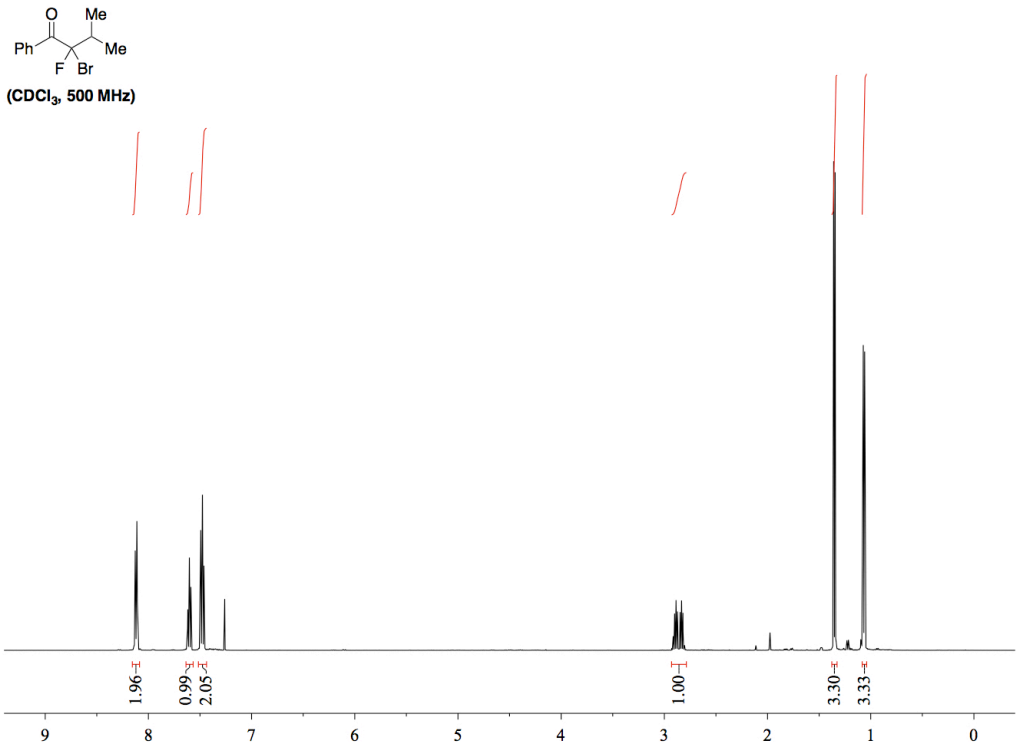
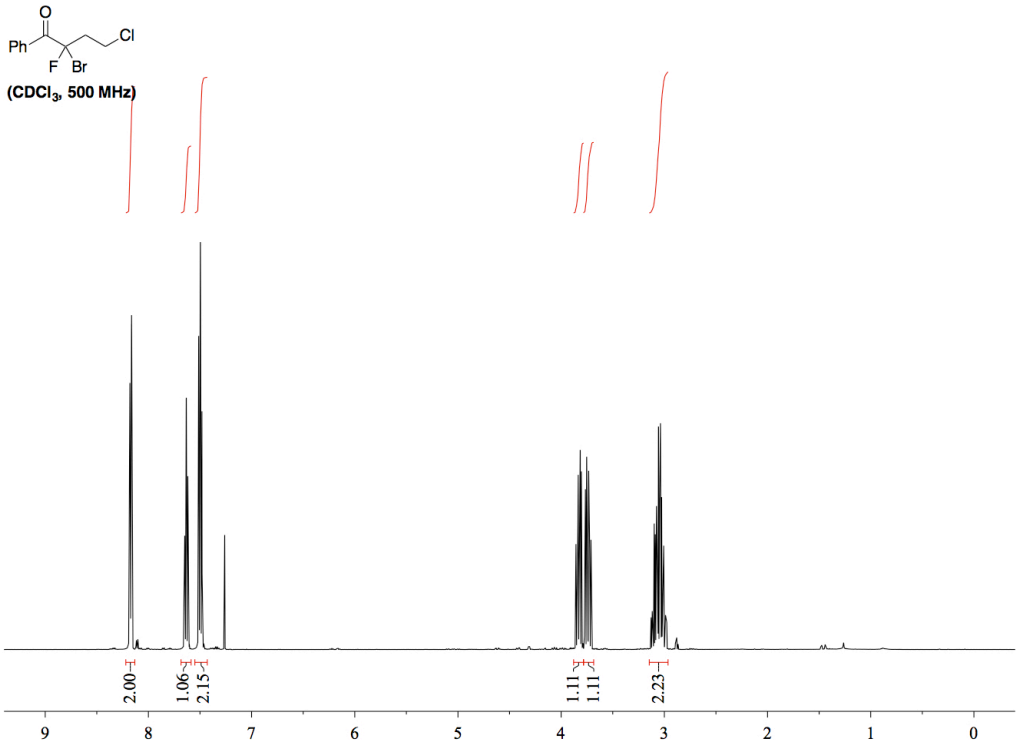
0.89
1.81
2.00
2.96
9
8
7
6
5
4
3
2
1
0

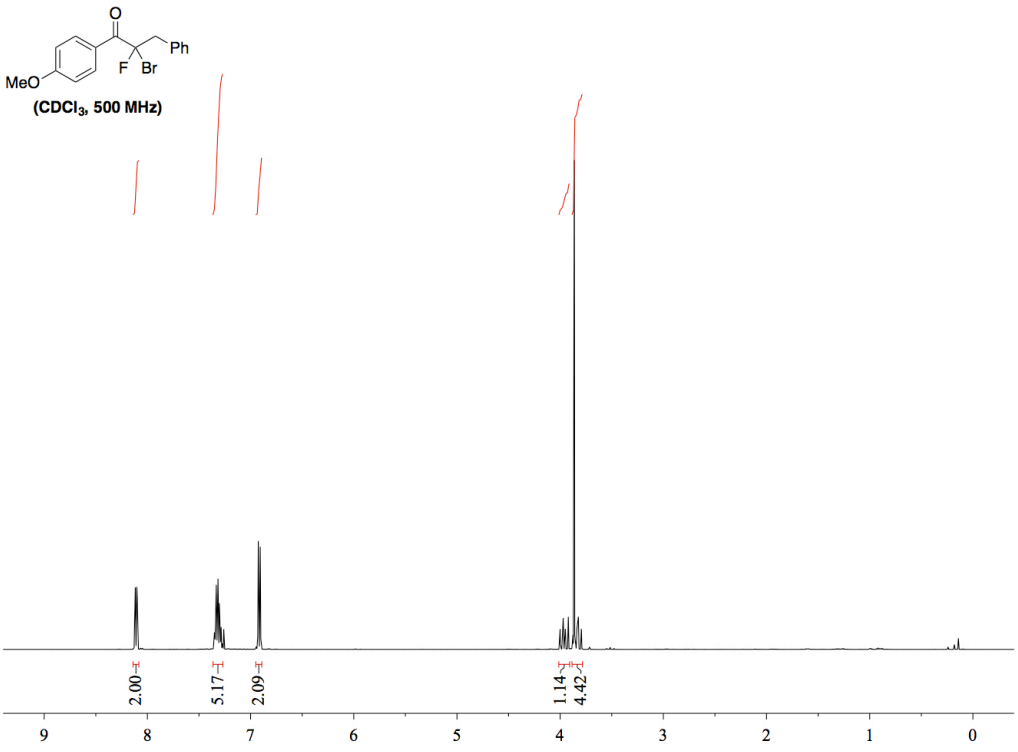

O
Ph
Ph
F
Br
(CDCl3, 500 MHz)
2.00
1.01
2.10
5.20
1.13
1.11
9
8
7
6
5
4
3
2
1
0

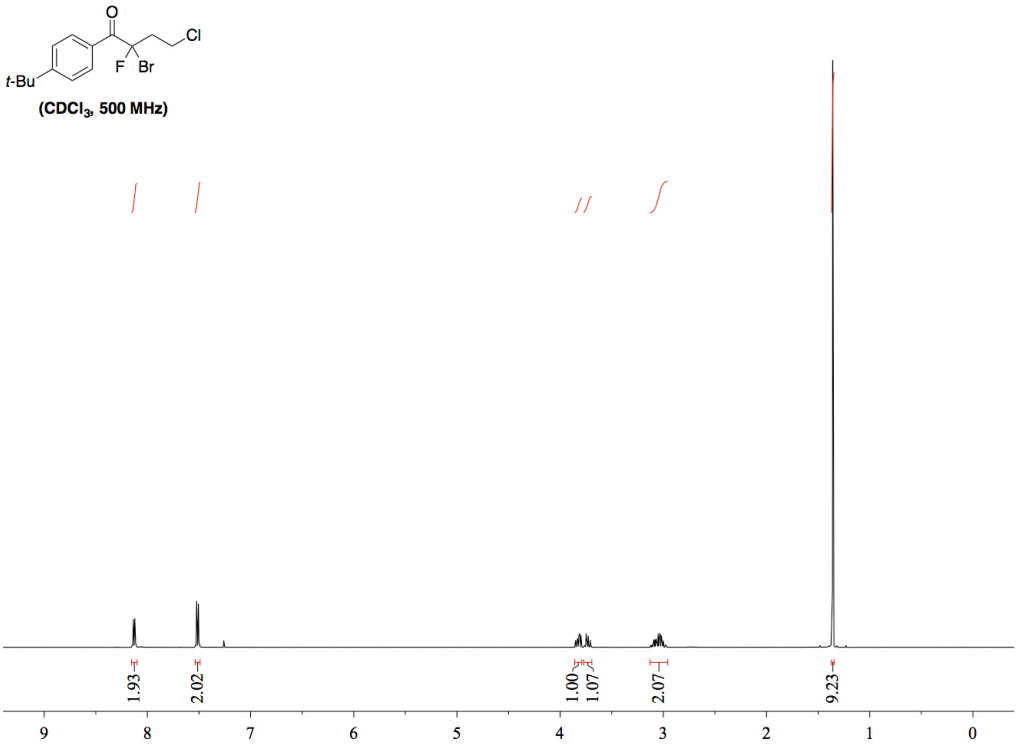

O
Ph
F Br
(CDCl3, 500 MHz)
2.01
1.06
2.17
1.00
1.12
1.02
2.13
9 8 7 6 5 4 3 2 1 0

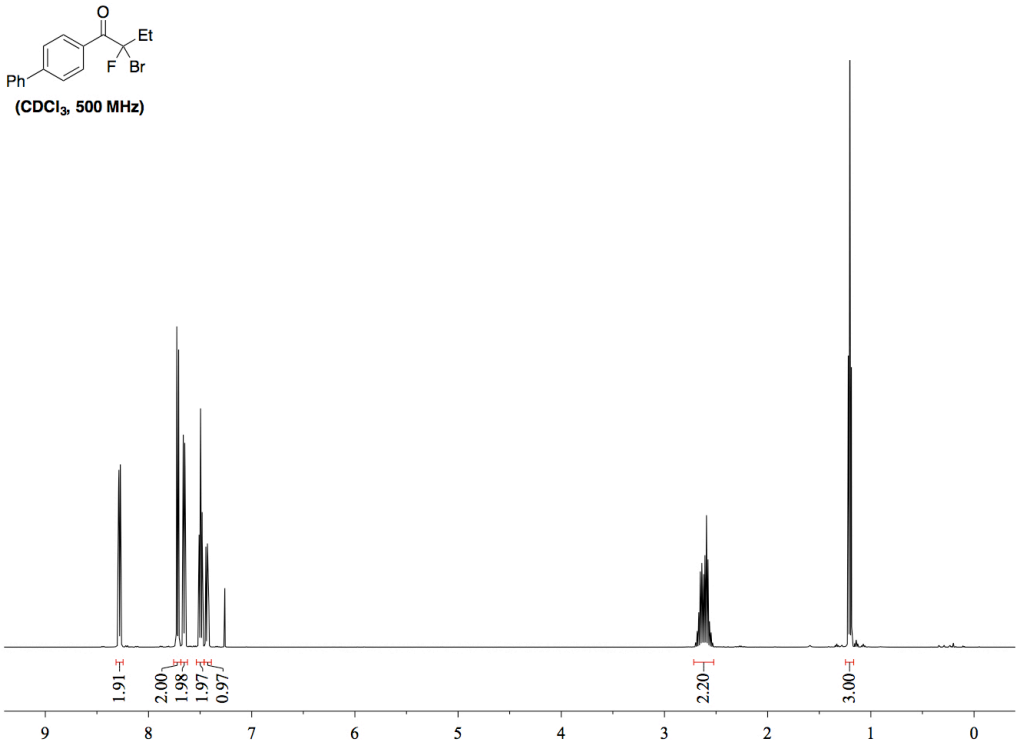

O
Ph
F Br
(CDCl3, 500 MHz)
1.79
0.93
1.90
1.00
0.96
0.97
2.03
2.05
1.99
1.18
1.02
9 8 7 6 5 4 3 2 1 0

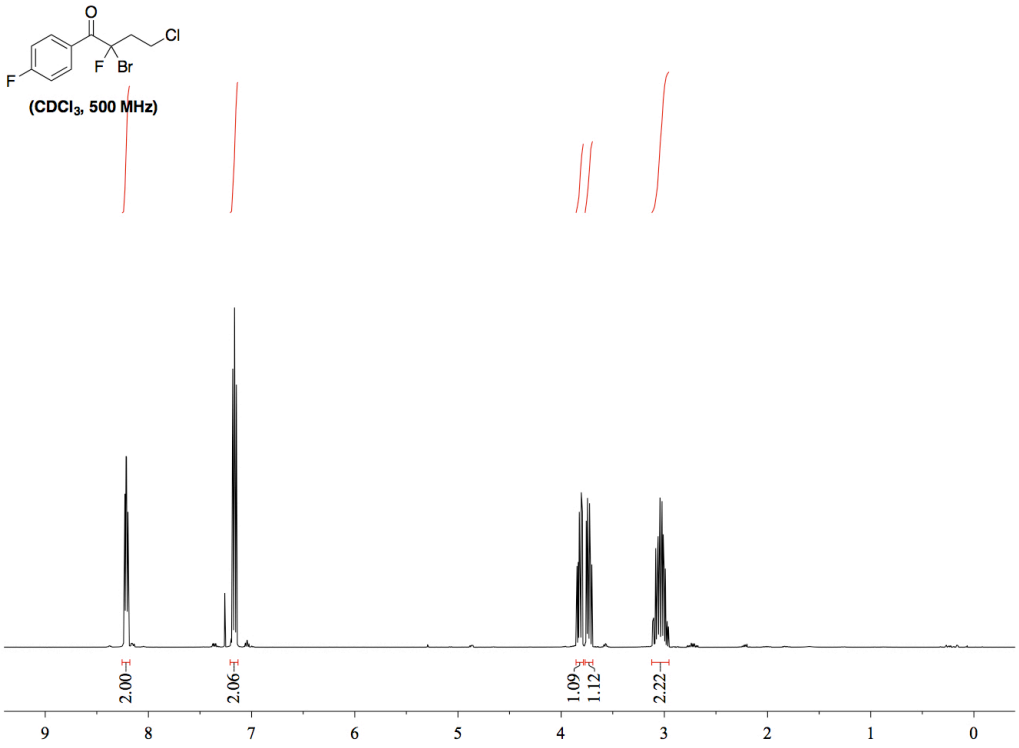

O
Me
Ph
Me
F
Br
(CDCl3, 500 MHz)
1.96
0.99
2.05
1.00
3.30
3.33
9
8
7
6
5
4
3
2
1
0

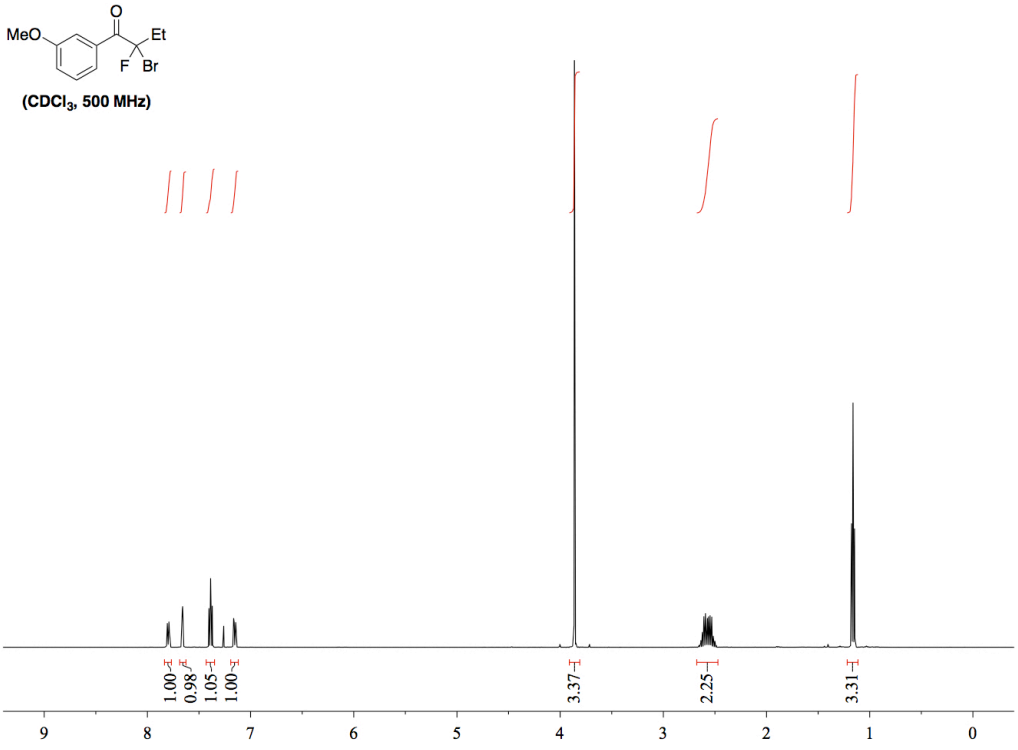

O
Ph
Cl
F
Br
(CDCl3, 500 MHz)
2.00
1.06
2.15
1.11
1.11
2.23
9
8
7
6
5
4
3
2
1
0

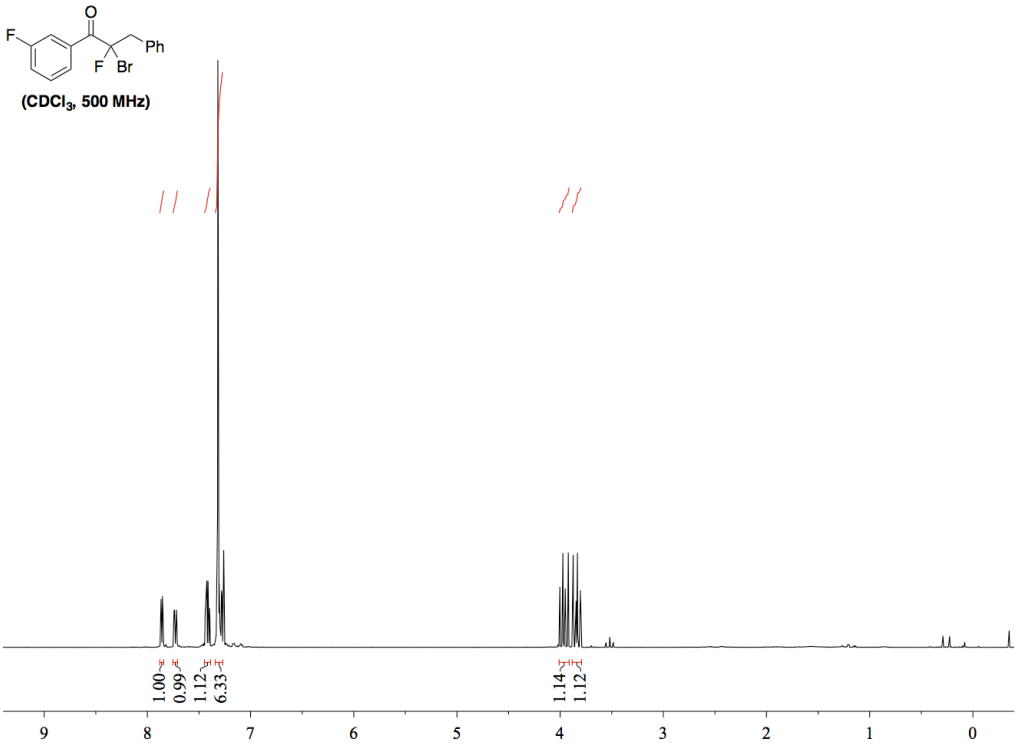

O
Ph
F Br
MeO
(CDCl3, 500 MHz)
2.00
5.17
2.09
1.14
4.42
9 8 7 6 5 4 3 2 1 0

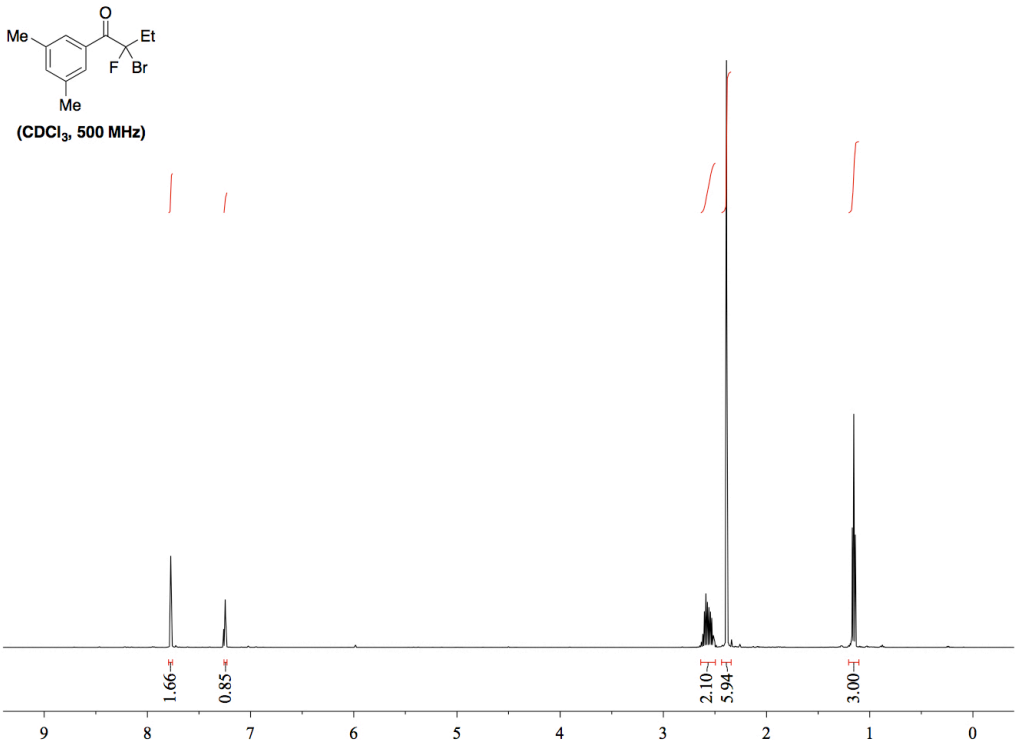

O
Cl
F Br
t-Bu
(CDCl3, 500 MHz)
1.93
2.02
1.00
1.07
2.07
9.23
9 8 7 6 5 4 3 2 1 0

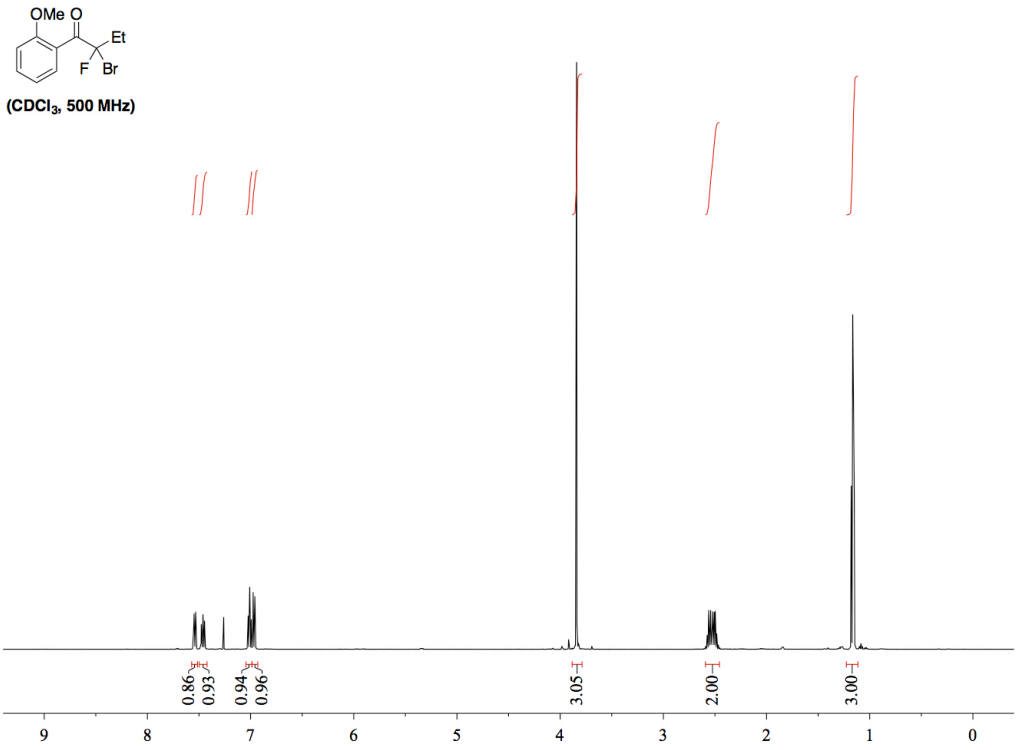

O
Et
F Br
Ph
(CDCl3, 500 MHz)
1.91
2.00
1.98
1.97
0.97
2.20
3.00
9
8
7
6
5
4
3
2
1
0

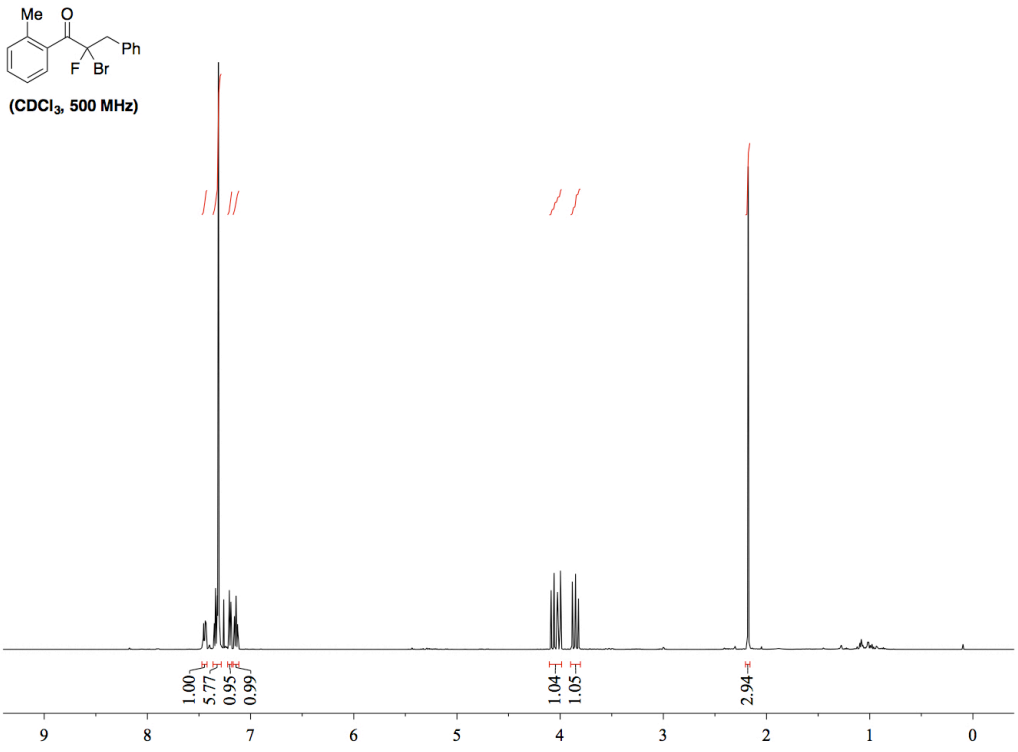

O
Cl
F Br
F
(CDCl3, 500 MHz)
2.00
2.06
1.09
1.12
2.22
9
8
7
6
5
4
3
2
1
0

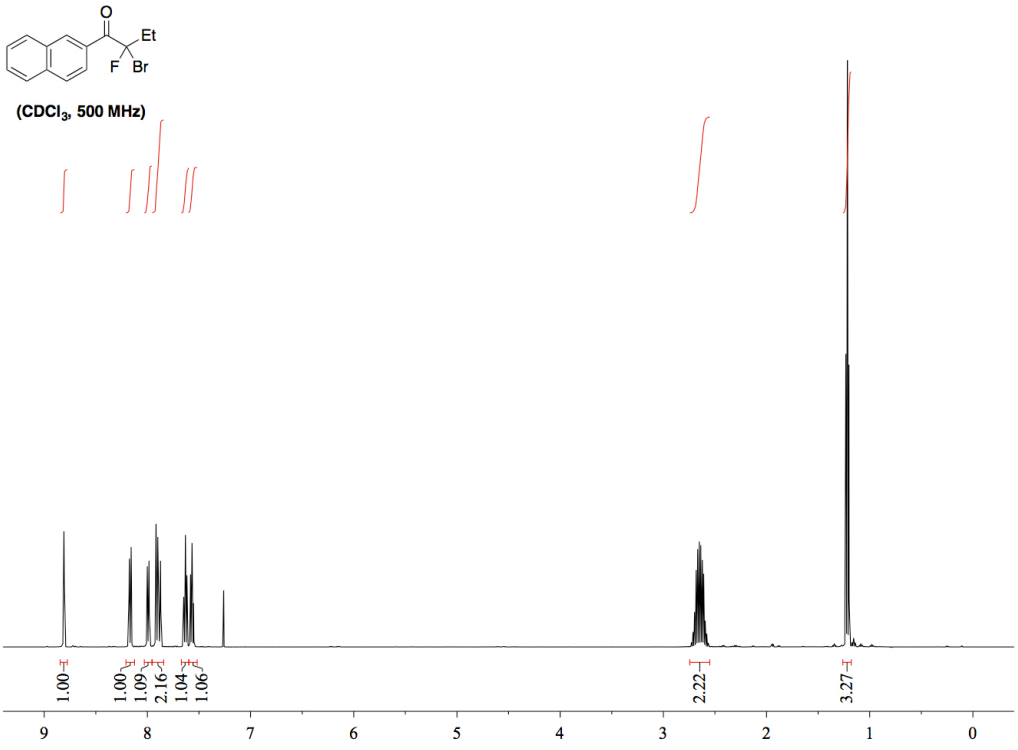

MeO
O
Et
F Br
(CDCl3, 500 MHz)
1.00
0.98
1.05
1.00
3.37
2.25
3.31
9
8
7
6
5
4
3
2
1
0

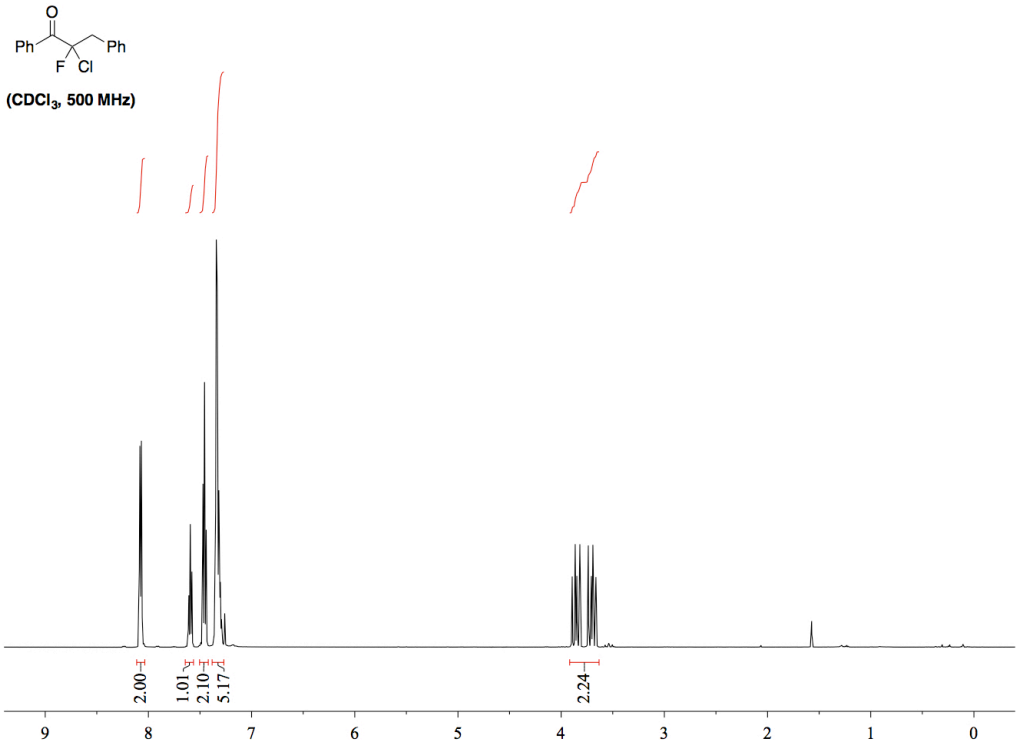

F
O
Ph
F Br
(CDCl3, 500 MHz)
1.00
0.99
1.12
6.33
1.14
1.12
9
8
7
6
5
4
3
2
1
0

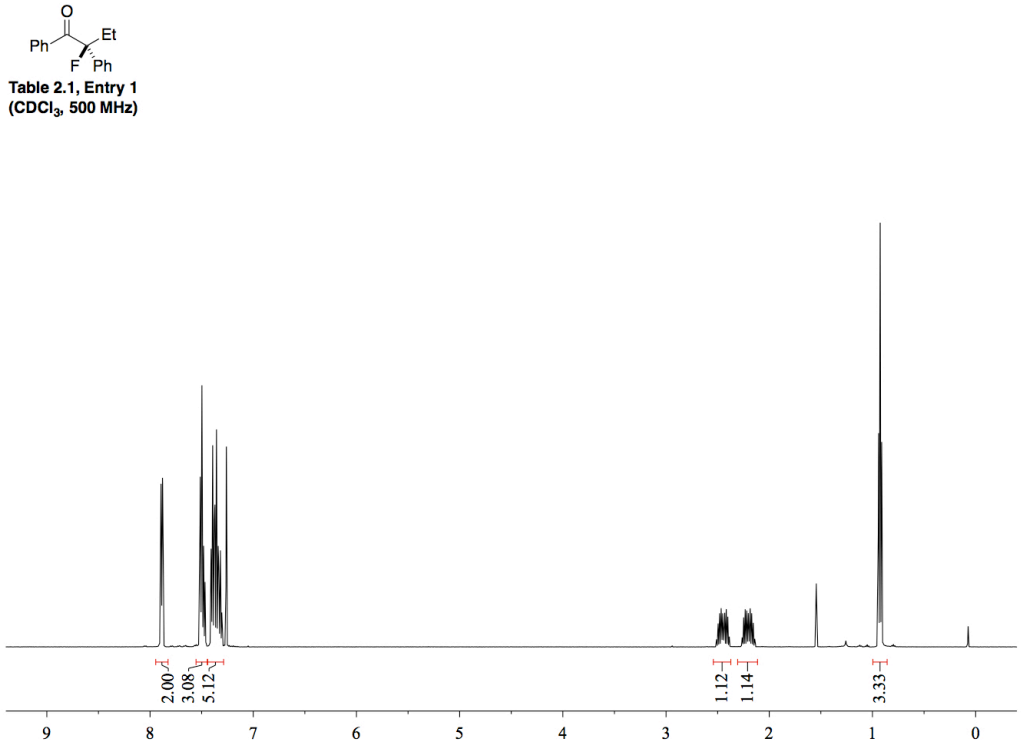

Me
O
Et
F
Br
Me
(CDCl3, 500 MHz)
1.66
0.85
2.10
5.94
3.00
9
8
7
6
5
4
3
2
1
0


OMe
O
Et
F
Br
(CDCl3, 500 MHz)
0.86
0.93
0.94
0.96
3.05
2.00
3.00
9
8
7
6
5
4
3
2
1
0


Me
O
Ph
F
Br
(CDCl3, 500 MHz)
1.00
5.77
0.95
0.99
1.04
1.05
2.94
9
8
7
6
5
4
3
2
1
0


O
Et
F
Br
(CDCl3, 500 MHz)
1.00
1.00
1.09
2.16
1.04
1.06
2.22
3.27
9
8
7
6
5
4
3
2
1
0


O
Ph
Ph
F
Cl
(CDCl3, 500 MHz)
2.00
1.01
2.10
5.17
2.24
9
8
7
6
5
4
3
2
1
0


O
Ph
Et
F
Ph
Table 2.1, Entry 1
(CDCl3, 500 MHz)
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3.08
5.12
1.12
1.14
3.33
9
8
7
6
5
4
3
2
1
0

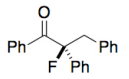

Table 2.2, Entry 2
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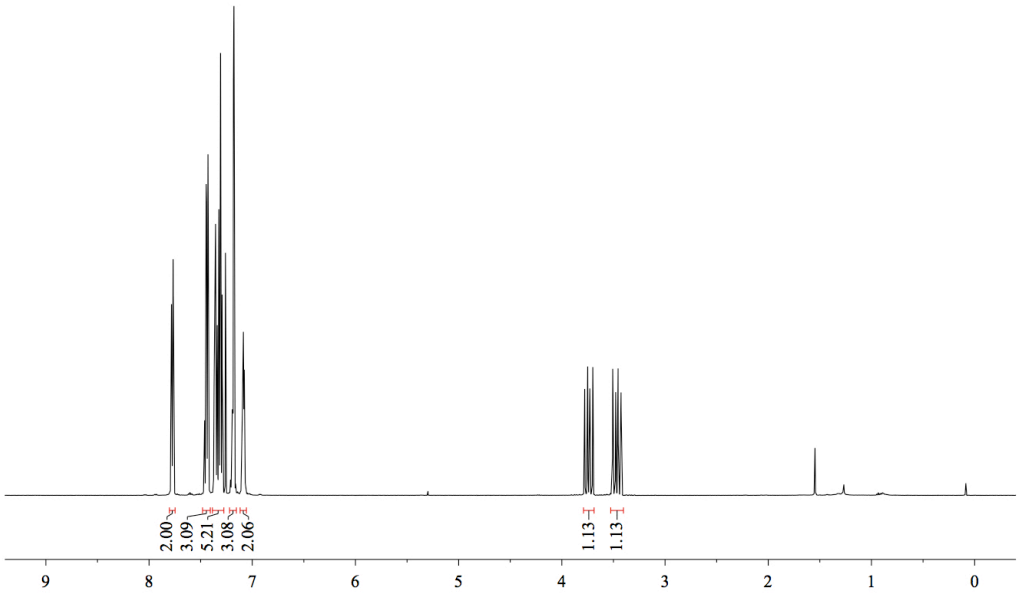


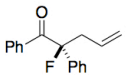
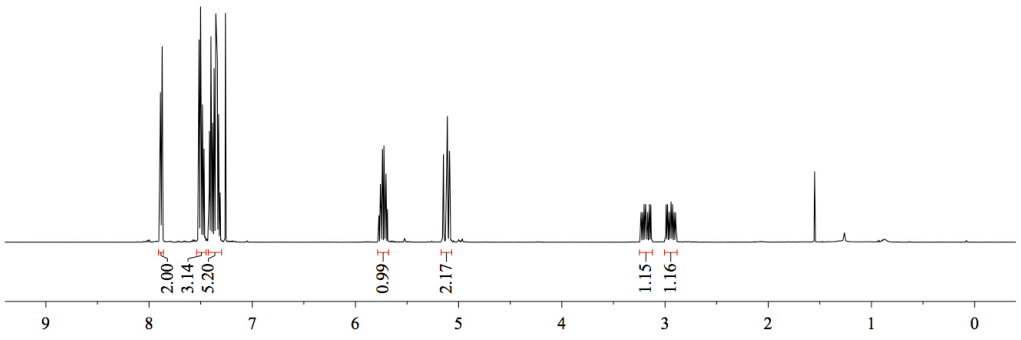


Table 2.2, Entry 3
($CDCl_3$, 500 MHz)



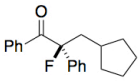
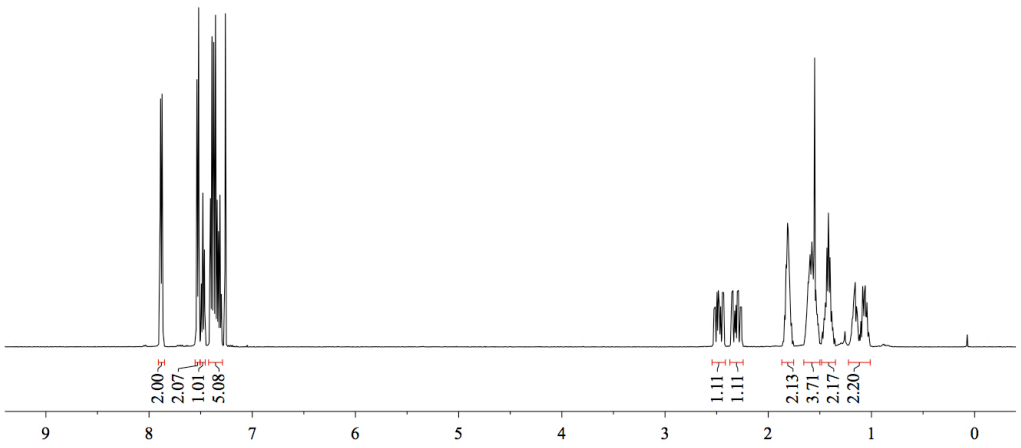


Table 2.2, Entry 4
($CDCl_3$, 500 MHz)



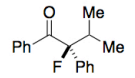
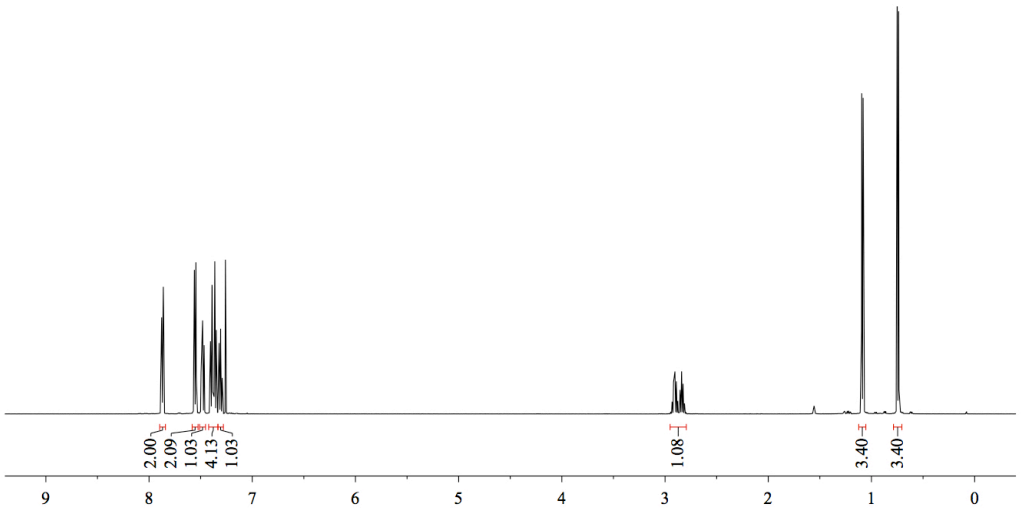


Table 2.2, Entry 5
($CDCl_3$, 500 MHz)



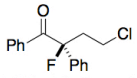
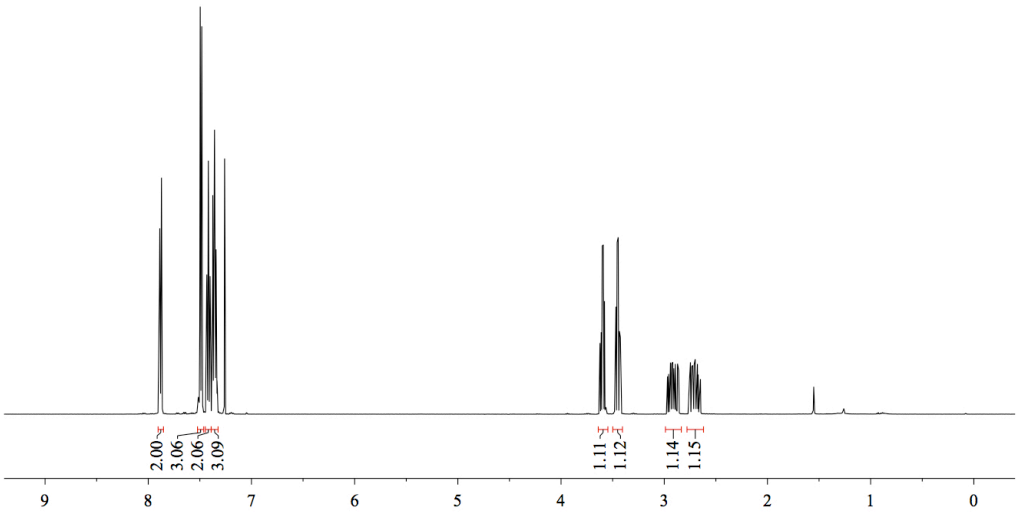


Table 2.2, Entry 6
($CDCl_3$, 500 MHz)



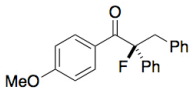
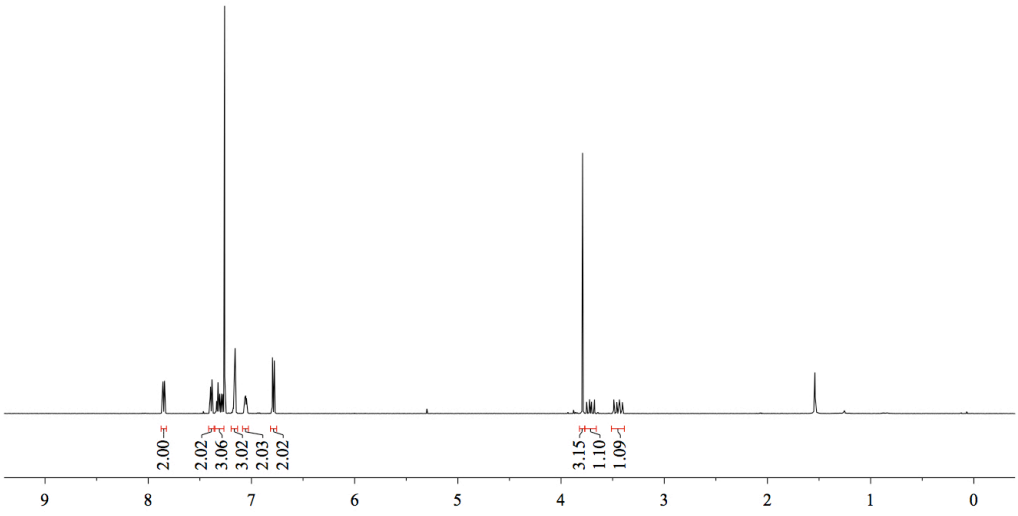


Table 2.3, Entry 1
($CDCl_3$, 500 MHz)



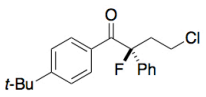


Table 2.3, Entry 2
($CDCl_3$, 500 MHz)

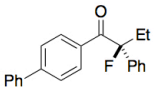


Table 2.3, Entry 3
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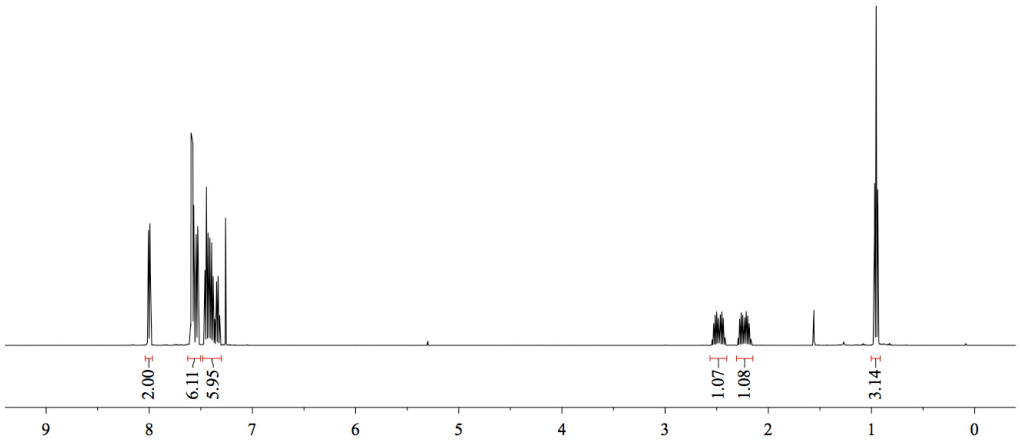

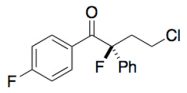

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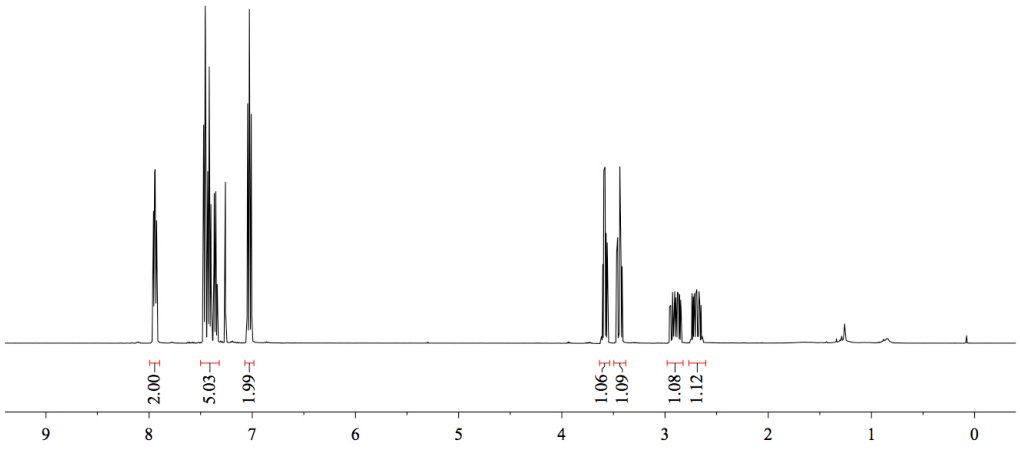

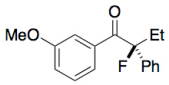

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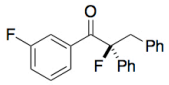

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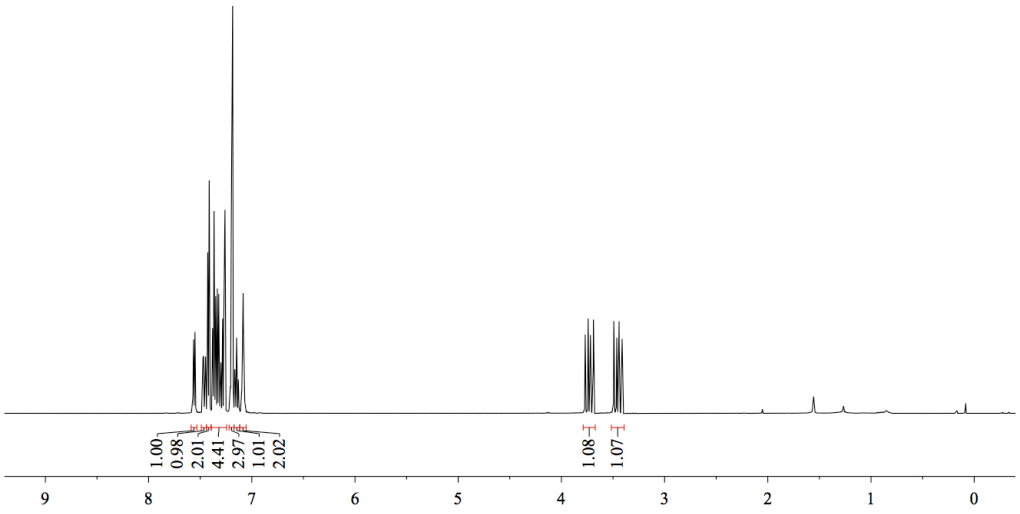

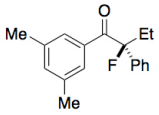

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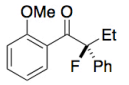

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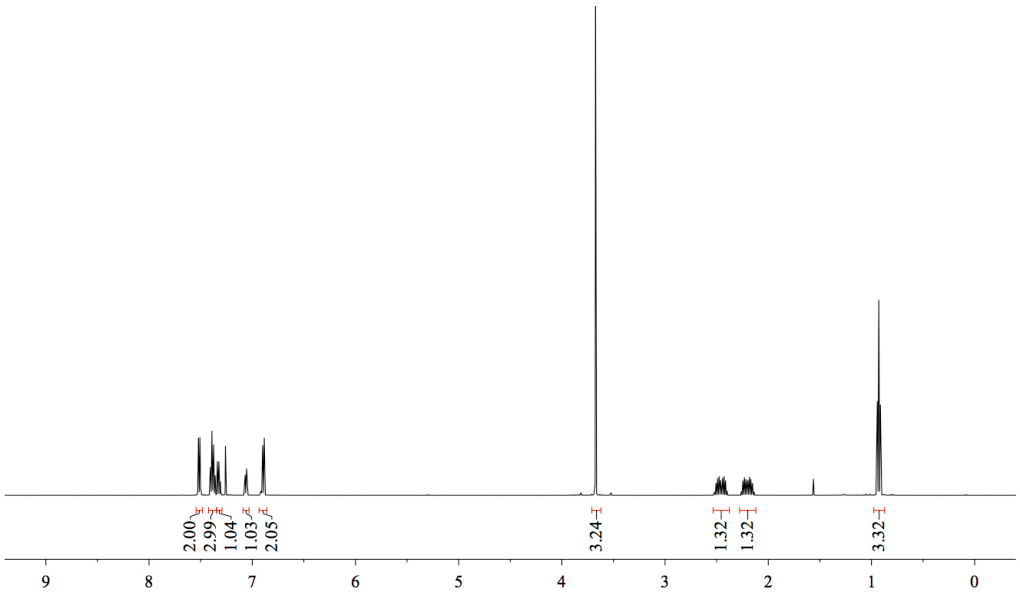

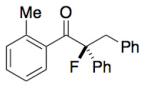

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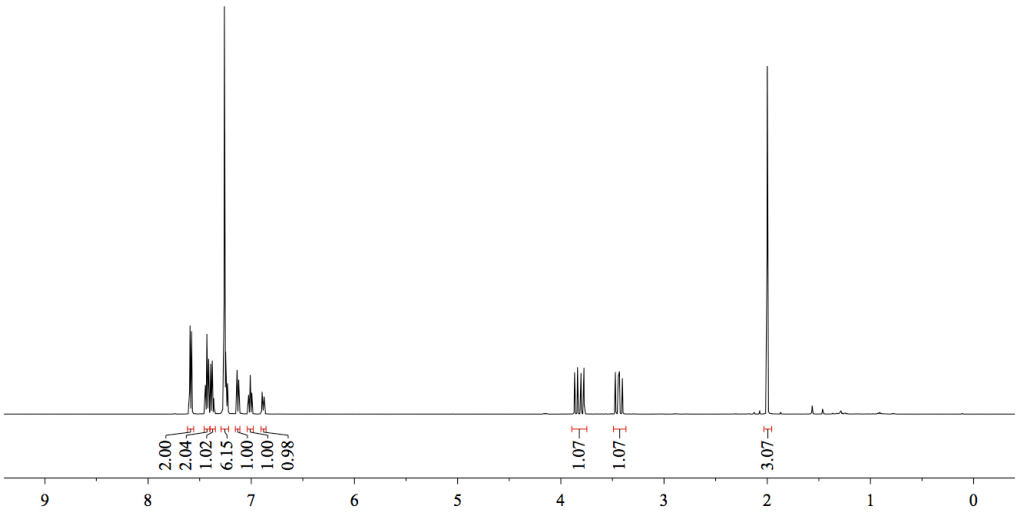

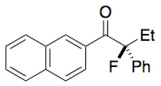

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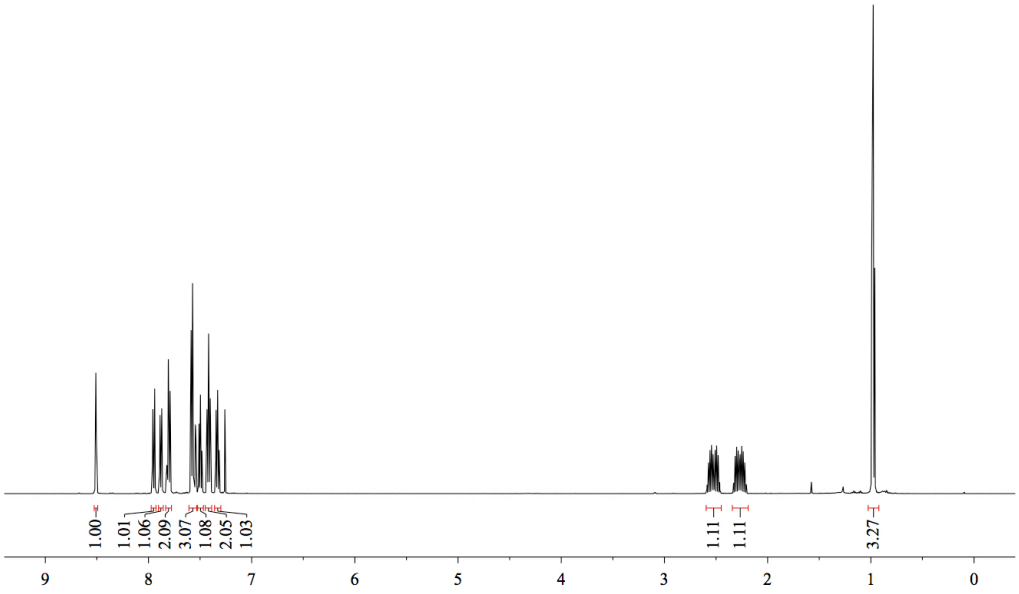

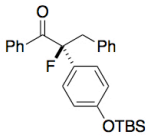

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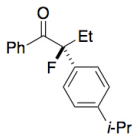

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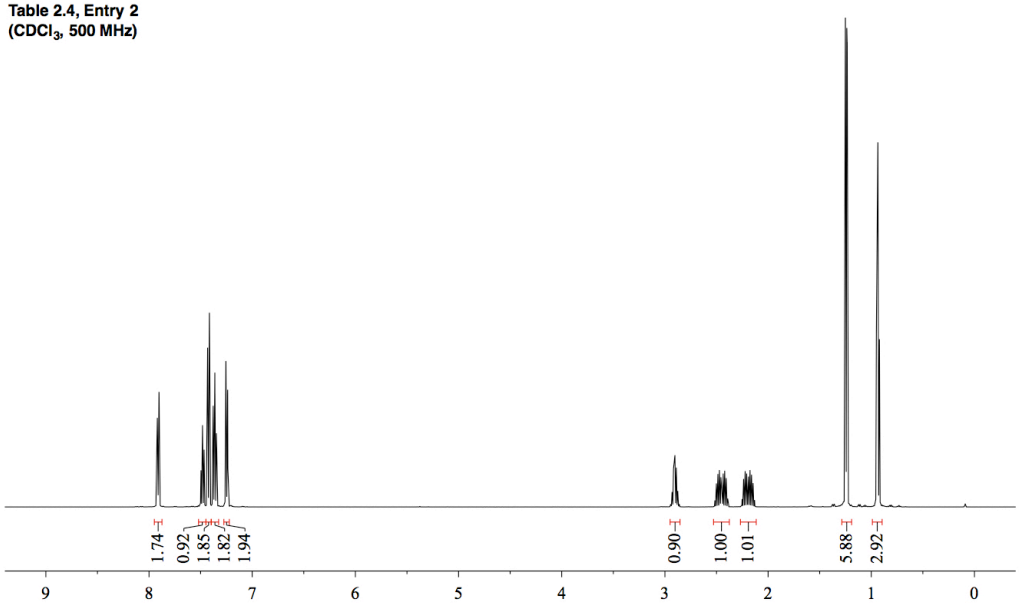

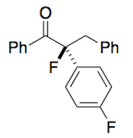

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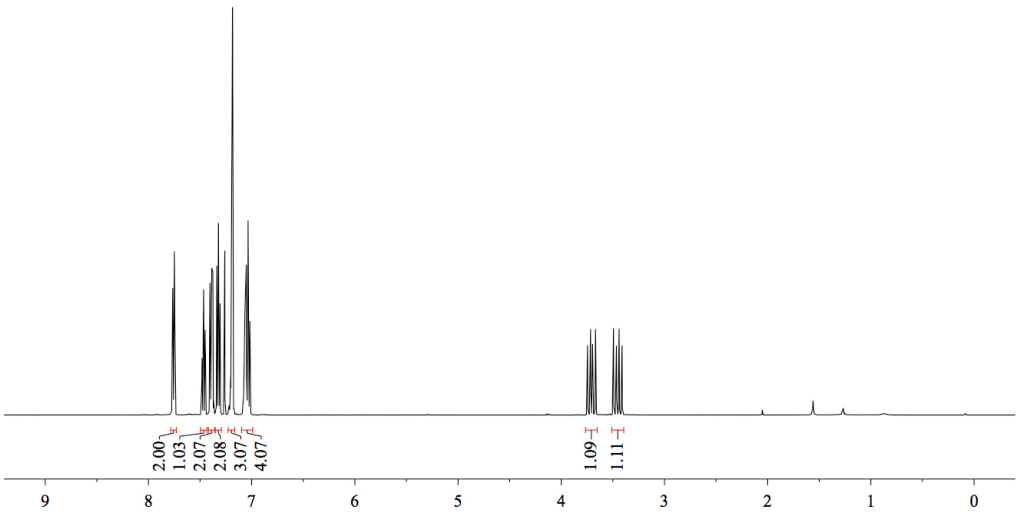

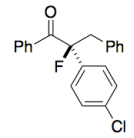

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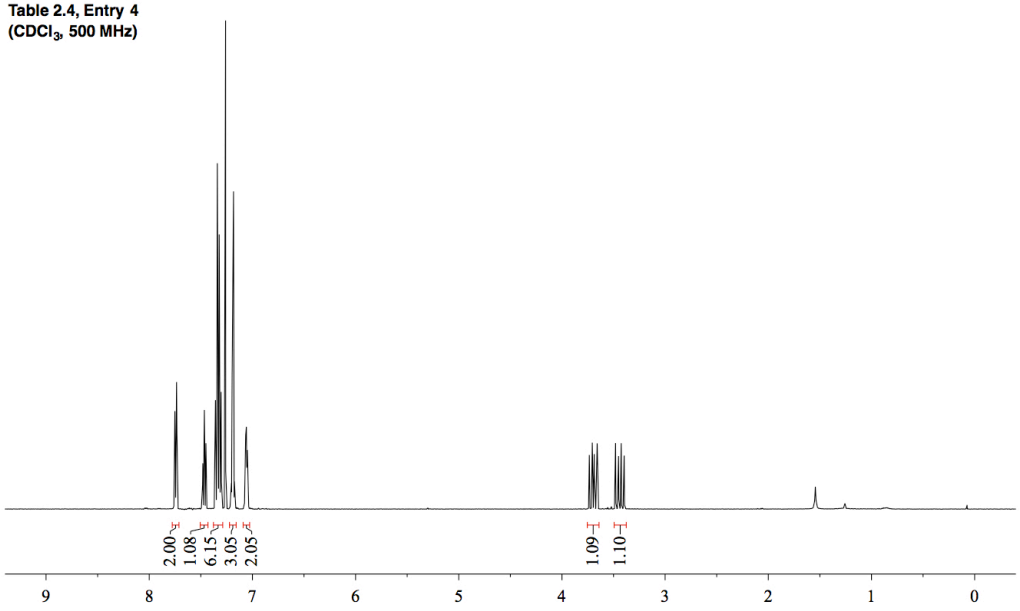

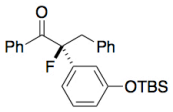

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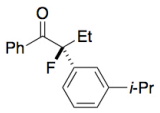

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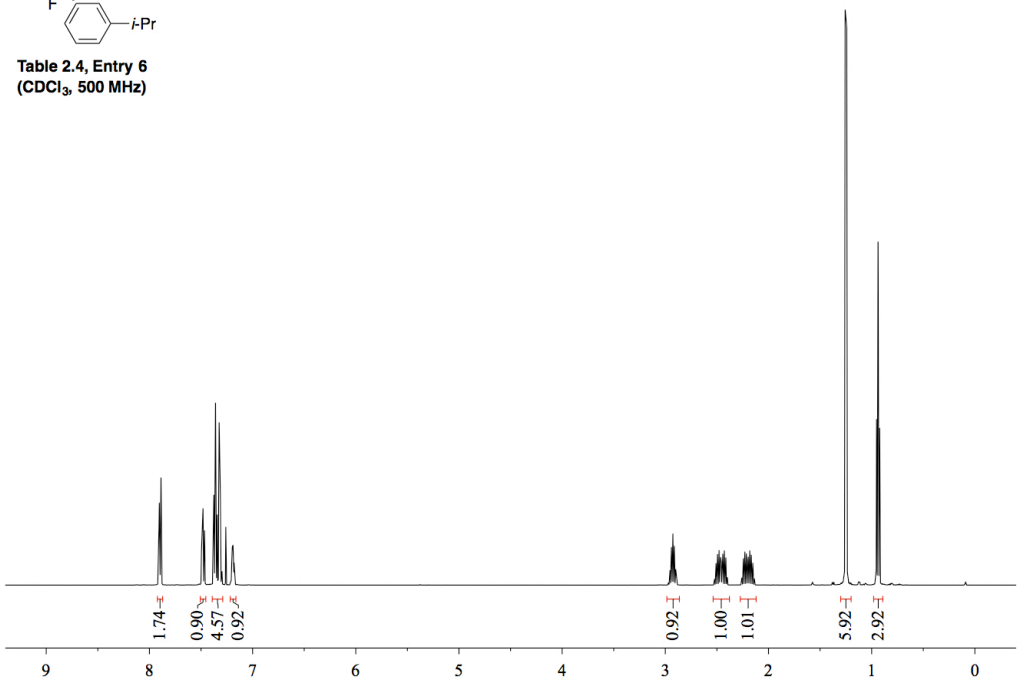

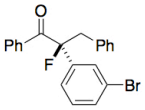

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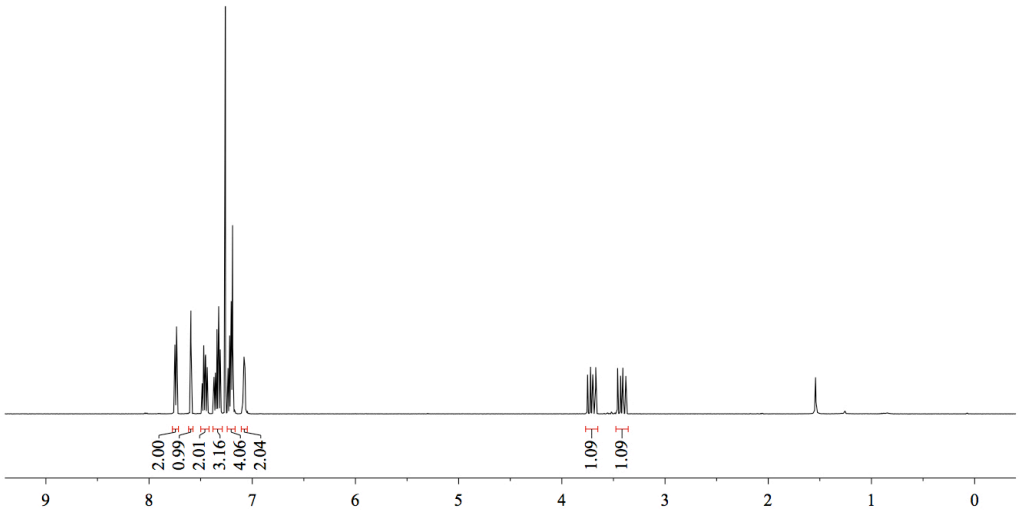

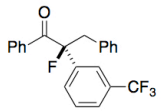

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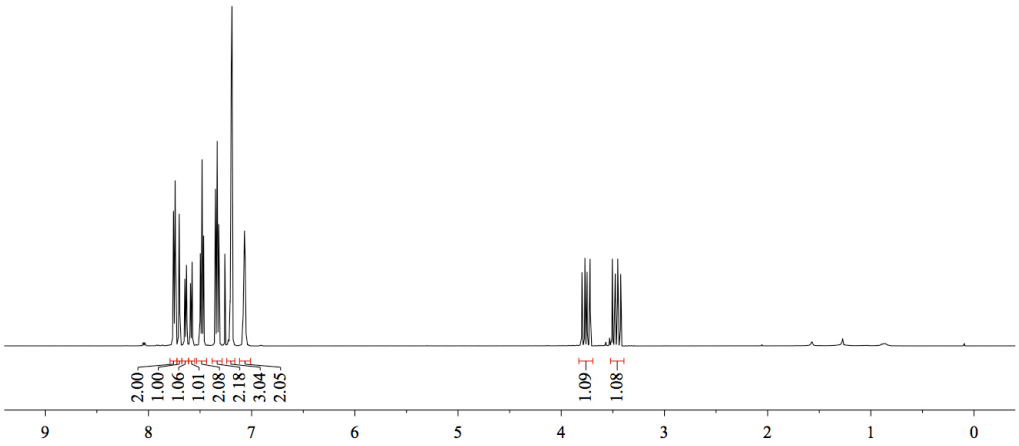

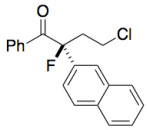

Table 2.4, Entry 9
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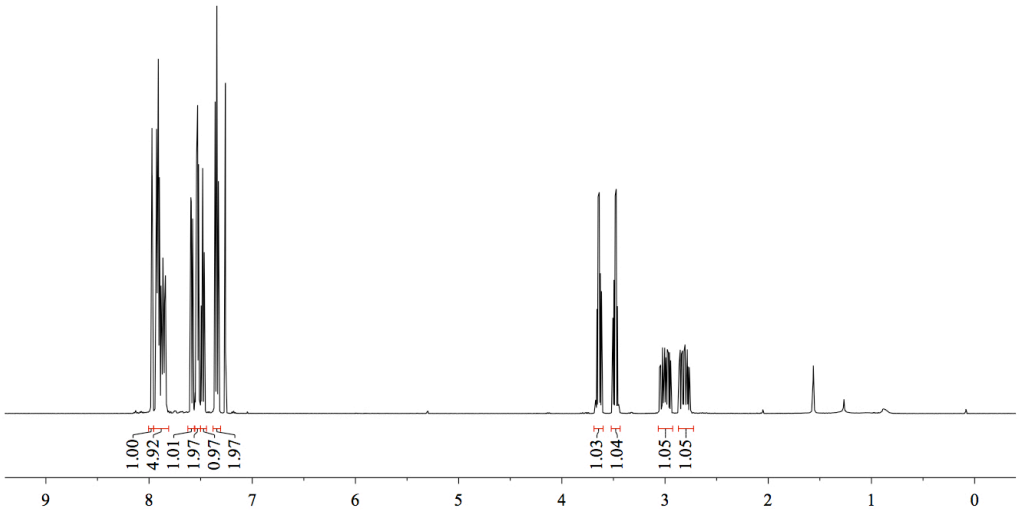
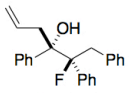
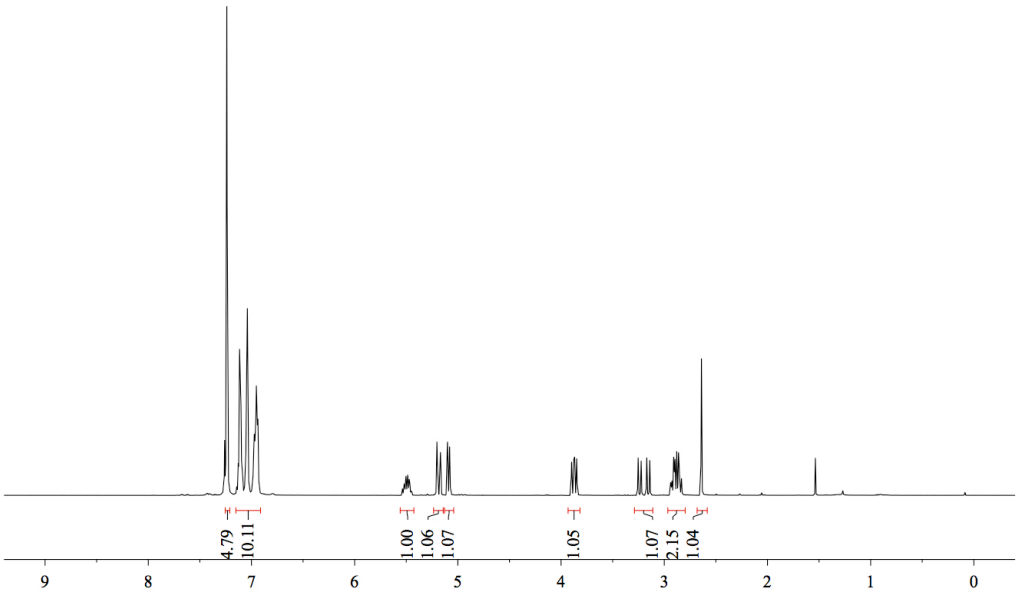
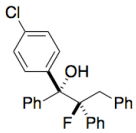


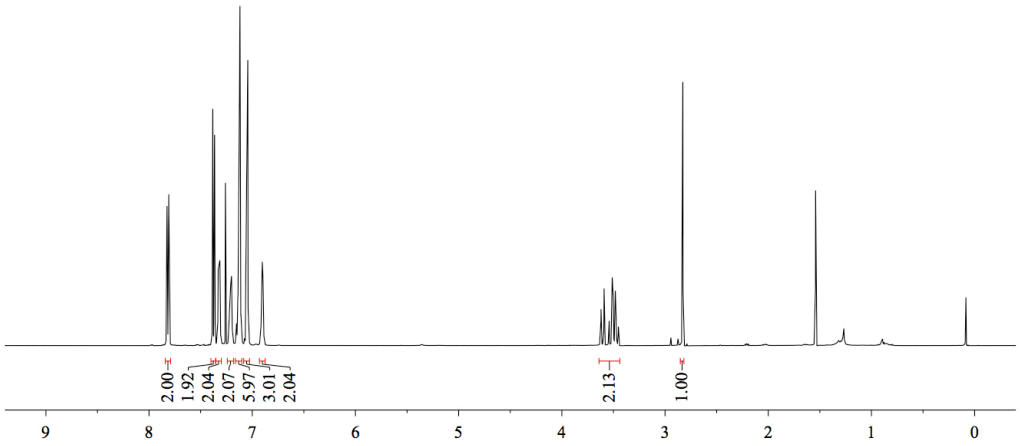


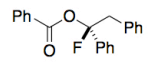
Eq 2.10
($CDCl_3$, 500 MHz)



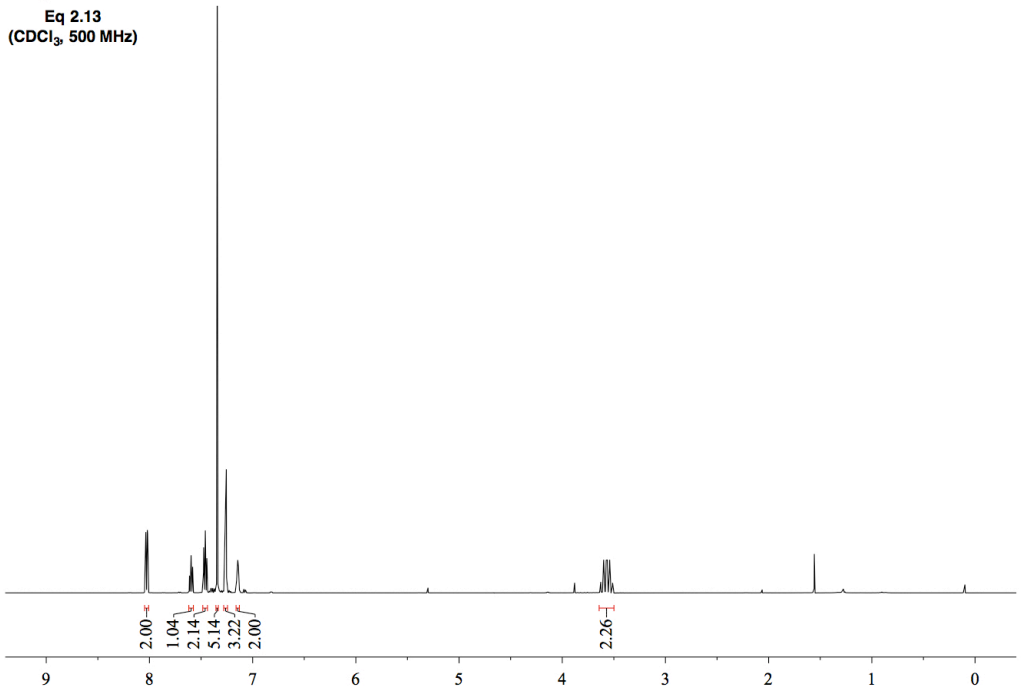


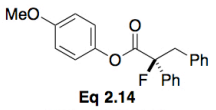
Eq 2.11
($CDCl_3$, 500 MHz)



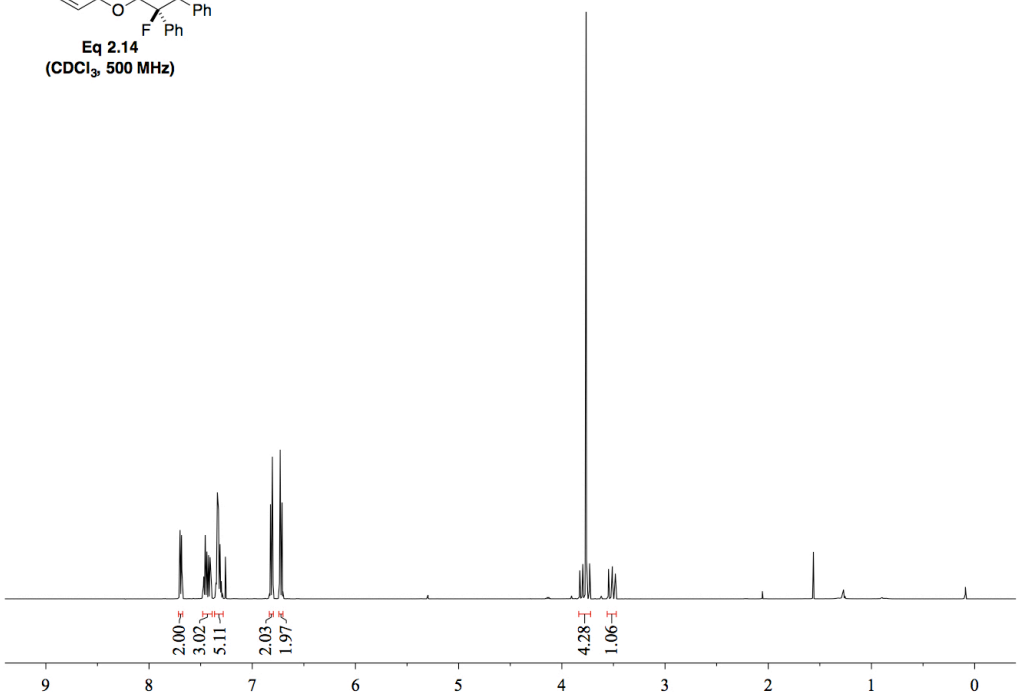


Eq 2.13
($CDCl_3$, 500 MHz)





Eq 2.14
($CDCl_3$, 500 MHz)



2.7 Notes and References

(1) (a) *Fluorine in Pharmaceutical and Medicinal Chemistry;* Grouverneur, V., Müller, K., Eds.; Imperial College Press: London, 2012. (b) *Fluorine-Related Nanoscience with Energy Applications;* Nelson, D. L., Brammer, C. N., Eds.; American Chemical Society: Washington, DC, 2011. (c) *Fluorine in Medicinal Chemistry and Chemical Biology;* Ojima, I., Ed.; John Wiley & Sons; Chichester, UK, 2009.

(2) (a) *Efficient Preparations of Fluorine Compounds;* Roesky, H. W., Ed.; John Wiley & Sons: Hoboken, NJ, 2013. (b) *Science of Synthesis;* Percy, J. M., Ed.; Georg Thieme: Stuttgart, Germany, 2006; Volume 34.

(3) Fore recent reviews, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264. (b) Valero, G.; Companyó, X.; Rios, R. *Chem. Eur. J.* **2011**, *17*, 2018–2037. (c) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558–568. (d) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708–2732.

(4) For early examples of asymmetric α-fluorination of aldehydes, see: (a) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703–3706. (b) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem. Int. Ed.* **2005**, *44*, 3706–3710. (c) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828.

(5) For selected examples, see: (a) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 4204–4207. (b) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem. Int. Ed.* **2005**, *44*, 7248–7251. (c) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am.*

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(6) For selected examples of the catalytic asymmetric synthesis of other families of tertiary alkyl fluorides, see: (a) Phipps, R. J.; Hiramatsu,K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376–8379. (b) Shunatona, H. P.; Früh, N.; Wang, Y.-M.; Rauniyar, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 7724–7727. (c) Wu, J.; Wang, Y.-M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 13729–13733.

(7) For a recent study with limited scope, see: Shibatomi, K.; Futatsugi, K.; Kobayashi, F.; Iwasa, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2010**, *132*, 5625–5627.

(8) For a recent example with esters, see: Tengeiji, A.; Shiina, I. *Molecules* **2012**, *17*, 7356–7378.

(9) For examples of methods for the synthesis of racemic products, see: (a) Wang, W.; Jasinski, J.; Hammond, G. B.; Xu, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 7247–7252. (b) Guo, Y.; Tao, G.-H.; Blumenfeld, A.; Shreeve, J. M. *Organometallics* **2010**, *29*, 1818–1823. (c) Zhang, W.; Hu, J. *Adv. Synth. Catal.* **2010**, *352*, 2799–2804. (d) Guo, C.; Wang, R.-W.; Guo, Y.; Qing, F.-L. *J. Fluorine Chem.* **2012**, *133*, 86–96.

(10) For a recent review on the topic of enantioselective and enantiospecific cross-coupling reactions, see: Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587–9652.

(11) At the time that we began our studies in 2011, we were not aware of any precedent for selective nickel-catalyzed cross-couplings of α-halo-α-fluoro compounds. However, in early 2013, Ando and co-workers reported a *diastereoselective* Kumada reactions with α-bromo-α-fluoro-β-lactams with aryl Grignard nucleophiles, see: Tarui, A.; Kondo, S.; Sato, K.; Omote, M.; Minami, H.; Miwa, Y.; Ando, A. *Tetrahedron* **2013**, *69*, 1559–1565.

(12) See the experimental sections for details.

(13) (a) Negishi arylations: Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 154–156. (b) Kumada arylations: Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266.

(14) Jin, L.; Liu, C.; Liu, J.; Hu, F.; Lan, Y.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 16656–16657.

(15) For a review of the effect of a fluorine substituent on the conformation of molecules, see: Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, No. 38.

(16) At this stage, we are not able to establish the relative stereochemistry of this alcohol.

(17) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron* **2003**, *59*, 1547–1552.

(18) For discussions of the fluorine effect in Baeyer–Villiger reactions, see: (a) Crudden, C.; M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2851–

2855. (b) Grein, F.; Chen, A. C.; Edwards, D.; Crudden, C. M. *J. Org. Chem.* **2006**, *71*, 861–872.

(19) For examples of applications of this class of compounds, see: (a) Rye, C. S.; Baell, J. B.; Street, I. *Tetrahedron* **2007**, *63*, 3306–3311. (b) Demoute, J. P.; Hoemberger, G.; Pazenok, S.; Babin, D. 5-Halo-4-fluoro-4,7,7-trimethyl-3-oxabicyclo[4.1.0]heptane-2-ones, Method for Their Production and Their Use in the Production of Cyclopropane Caboxylic Acids. WO 2001034592 A1, May 17, 2001. (c) Ishibashi, M. Method for Screening Therapeutic Agent for Glomerular Disorder. U.S. Patent 20090041719 A1, Feb. 12, 2009.

(20) For a recent example of direct asymmetric synthesis of tertiary α-fluoroesters, see: Lee, S. Y.; Neufeind, S.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 8899–8902.

(21) (a) Jiang, X.; Sakthivel, S.; Kulbitski, K.; Nisnevich, G.; Gandelman, M. *J. Am. Chem. Soc.* **2014**, *136*, 9548–9551. (b) Jiang, X.; Gandelman, M. *J. Am. Chem. Soc.* **2015**, *137*, 2542–2547.

(22) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.

(23) Masamune, S.; Lowenthal, R. E. Cu Complexes of Bis-Oxazolines and Their Use. U.S. Patent 5,298,623, March 29, 1994.

(24) (a) Shibatomi, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5796–5798. (b) Mohanta, P. K.; Davis, T. A.; Gooch, J. R.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2005**, *127*, 11896–11897.

(25) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890–891.

CHAPTER 3

Nickel-Catalyzed Negishi Alkylations of α-Halo-α-Perfluoroalkyl Electrophiles[+]

3.1 Introduction

Organic molecules bearing fluorine atoms usually exhibit unique properties, including biological activity, and have been found to have important applications in a variety of fields.[1] Although significant progress has been made in the development of general methods for the synthesis of fluorinated aromatic molecules,[2,3] current approaches to the preparation of compounds bearing a C_{sp3}–R_F moiety (R_F = a perfluoroalkyl group) are still narrow in scope.[4]

Figure 3.1 shows a few interesting molecules wherein a perfluoroalkyl group is connected to an sp^3-hybridized tertiary carbon.[5]

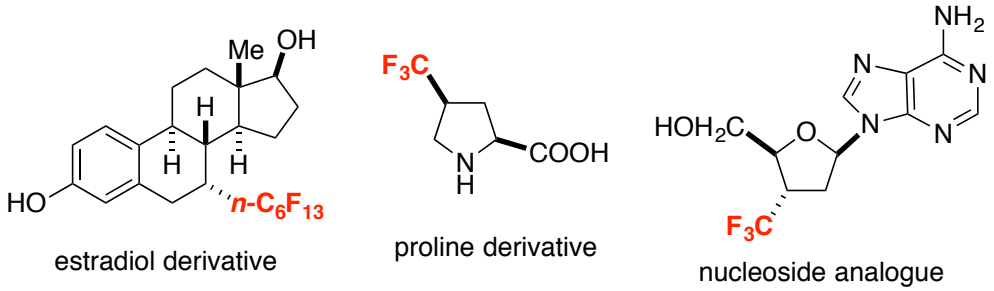

Figure 3.1. Compounds Bearing Perfluoroalkyl-Substituted Tertiary Carbons

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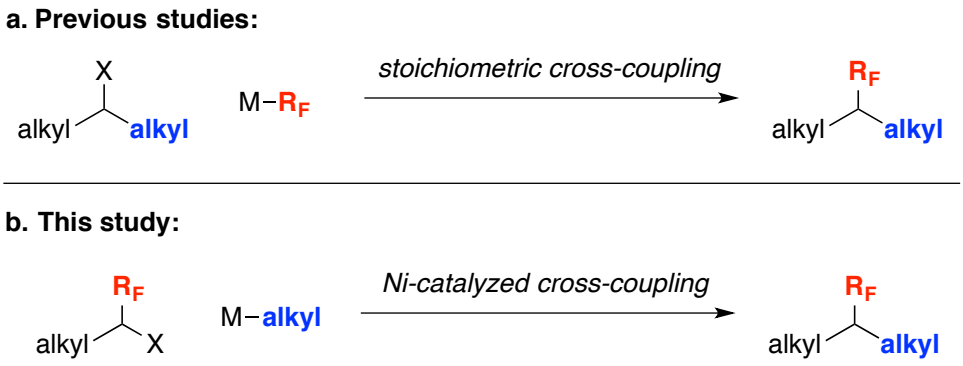
[+] Portions of this chapter have appeared in the previous publication and the supporting information found therein: Liang, Y.; Fu, G. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 9047–9051. Copyright 2015 John Wiley & Sons, Inc.

In order to construct this type of structure, one commonly employed strategy is to perform an alkyl-alkyl cross-coupling reaction with a perfluoroalkyl nucleophile (Scheme 3.1a). However, only stoichiometric cross-coupling methods have been reported when unactivated alkyl electrophiles are used as substrates.[6] Additionally, the reluctance of a fluoroalkyl group to participate in the reductive elimination step might also add difficulties to adopting this strategy.[7]

Scheme 3.1. Two Types of Cross-Coupling Strategies

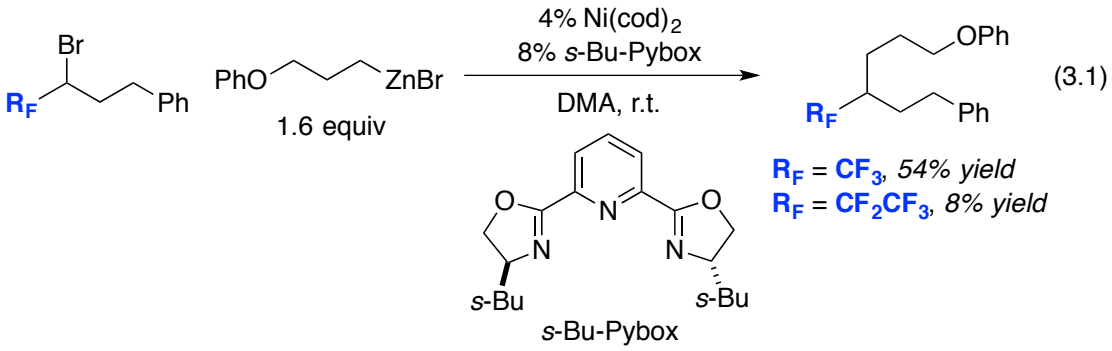


We envisioned that an alternative approach in which an α-halo-α-perfluoroalkyl *secondary* alkyl electrophile is cross-coupled with an alkyl nucleophile can also be a promising strategy (Scheme 3.1b). Although success has been achieved in cross-coupling aryl, alkenyl, and alkynyl nucleophiles with *primary* alkyl electrophiles bearing a CF_3 group (specifically, CF_3I and CF_3OTs),[8] to the best of our knowledge, secondary alkyl electrophiles with a perfluoroalkyl group have never been employed in such a method. In this chapter, we describe a nickel-catalyzed Negishi alkylation method with α-halo-α-perfluoroalkyl *secondary* alkyl electrophiles as substrates. This new route provides a

versatile and practical approach for the generation of valuable building blocks bearing perfluoroalkyl-substituted tertiary carbons.

3.2 Optimization

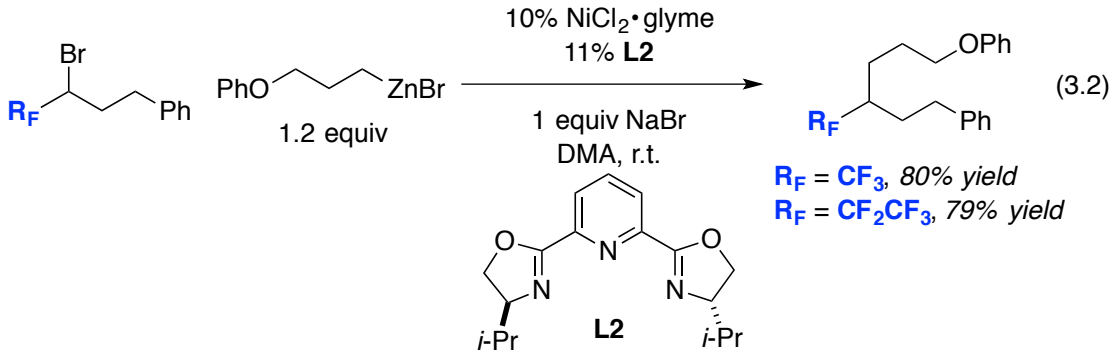
We chose to start our study by choosing alkylzinc reagents as the nucleophilic cross-coupling partners due to their ready accessibility and high functional-group tolerance.[9] In 2003, our group reported the first Ni-catalyzed Negishi alkylation method with *unactivated* secondary alkyl electrophiles as substrates.[10] Applying these conditions to the cross-coupling of an alkyl electrophile bearing a perfluoroalkyl group, we obtained promising results (eq 3.1).



(3.1)

Although this catalytic system could deliver the CF_3-substituted product in moderate yield, the efficiency of the reaction with the C_2F_5-substituted electrophile is very disappointing. In order to develop a general method that can cross-couple electrophiles bearing all kinds of perfluoroalkyl groups, we decided to optimize the reaction conditions using the C_2F_5-substituted alkyl bromide as model substrate. After extensive screening, we finally identified a suitable condition that can provide both cross-coupling products in good yield (eq 3.2). From a practical point of view, both the nickel

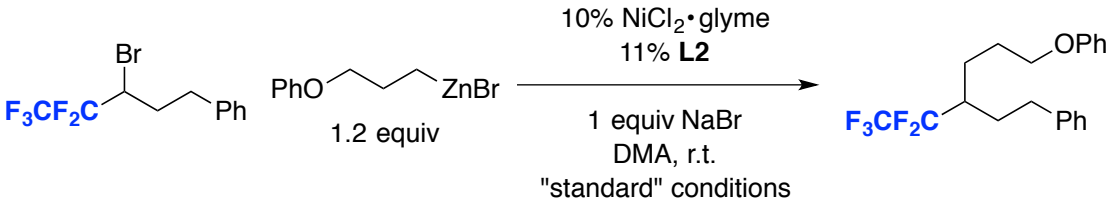
source and ligand **L2** shown in eq 3.2 are commercially available and can be handled in air.



(3.2)

As shown in Table 3.1, in the absence of nickel source, no product is formed (entry 2). Without the ligand **L2**, the cross-coupling product is generated in moderate yield (entry 3). The use of less alkylzinc reagent leads to only a small drop in yield (entry 4). The employment of 5% catalyst affords a moderate decreased in efficiency (entry 5). The addition of small amount of water or the changes in temperature has no significant effect towards the outcome of the reaction, whereas performing the reaction under air leads to decreased yield (entries 6 to 9).

Table 3.1. Effect of Reaction Parameters[a]

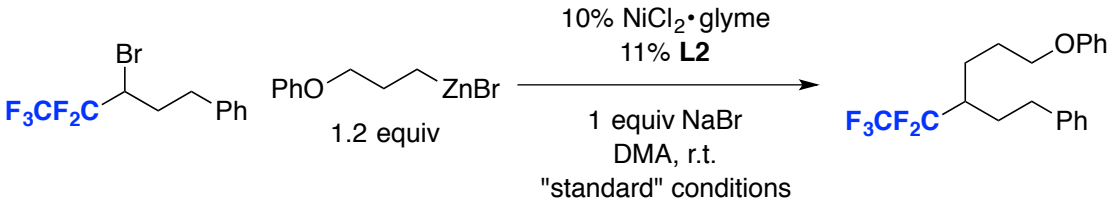


entry	variation from the "standard" conditions	yield (%)[b]
1	none	79
2	no $NiCl_2$•glyme	<1
3	no **L2**	49
4	1.0 equiv of organozinc reagent	71
5	5.0% $NiCl_2$•glyme, 5.5% **L2**	64
6	+ 0.1 equiv H_2O	79
7	under air in a closed vial	60
8	40 °C, instead of r.t.	72
9	0 °C, instead of r.t.	75

[a]All data are the average of two experiments. [b]The yields were determined through analysis by ^{19}F NMR spectroscopy with the aid of an internal standard.

The introducing of NaBr as additive is very crucial for this transformation. Several other related additives have been tested under the optimized conditions and NaBr turns out to be the best (Table 3.2). Possible explanations for the beneficial effects of NaBr include but are not restricted to an increase in the ionic strength of reaction medium and activation of alkylzinc reagents via the formation of ate complexes.[11]

Table 3.2. Effect of Additive[a]

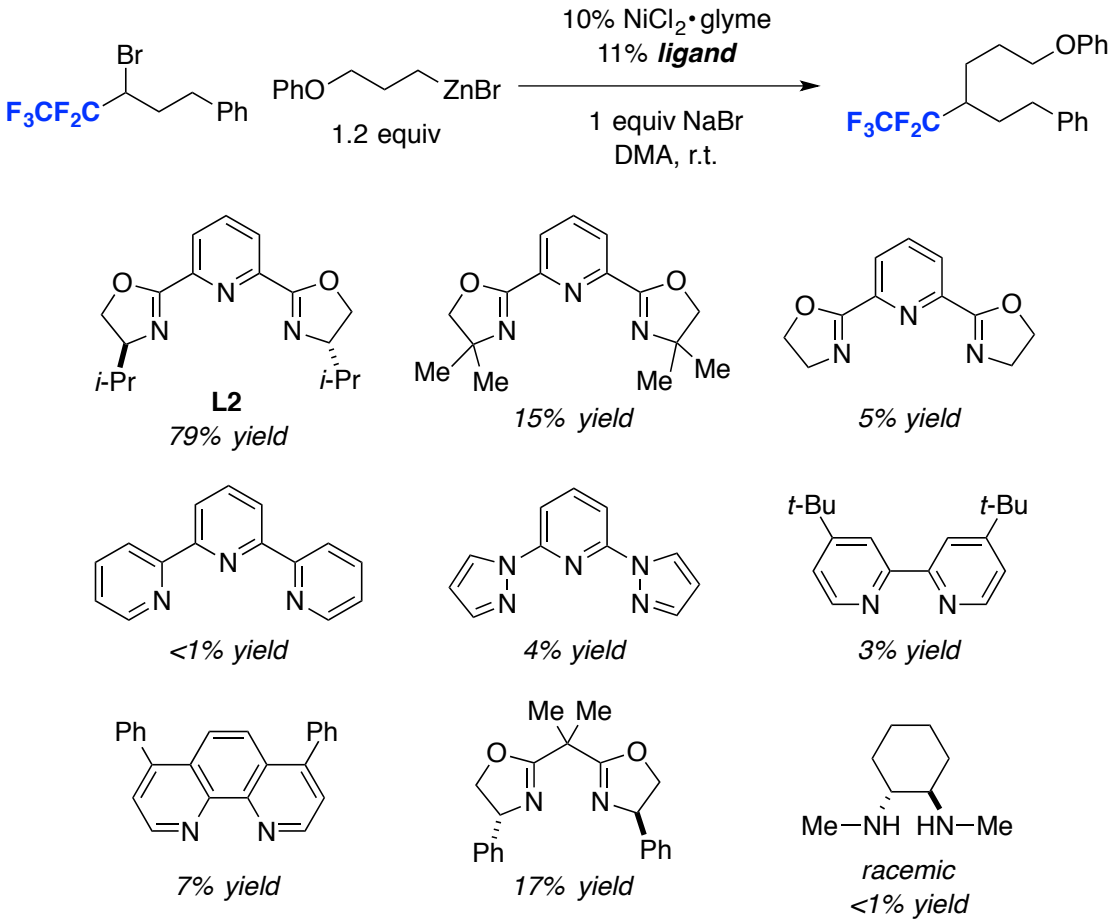


entry	variation from the "standard" conditions	yield (%)[b]
1	none	79
2	no NaBr	28
3	LiBr, instead of NaBr	75
4	KBr, instead of NaBr	66
5	CsBr, instead of NaBr	61
6	(*n*-Bu)$_4$NBr, instead of NaBr	74
7	NaI, instead of NaBr	59
8	NaCl, instead of NaBr	66
9	NaF, instead of NaBr	27

[a]All data are the average of two experiments. [b]The yields were determined through analysis by ^{19}F NMR spectroscopy with the aid of an internal standard.

Several tridentated and bidentated chiral or achiral ligands have been explored under our optimized conditions (Scheme 3.2). None of these previously employed ligands can even provide comparable results.

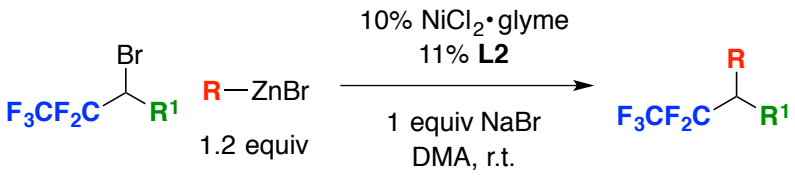
Scheme 3.2. Effect of Ligands

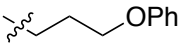
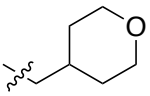
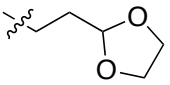
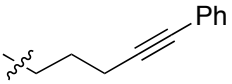
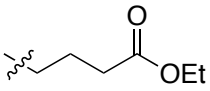
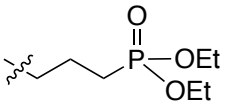
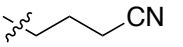
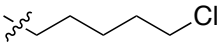
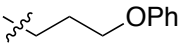


3.3 Scope

With the optimized conditions in hand, we started to explore the scope of this new method. A variety of alkylzinc reagents can be employed in this Negishi alkylation method (Table 3.3). Functional groups including an ether (entries 1, 2, and 8), an acetal (entry 3), an internal alkyne (entry 4), an ester (entry 5), a phosphonate (entry 6), a nitrile (entry 7), and a primary alkyl chloride (entry 8) can all be compatible with the optimized conditions.

Table 3.3. Negishi Alkylations to Generate Pentafluoroethyl-Substituted Products: Scope[a]

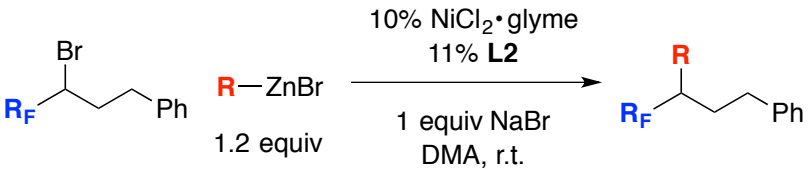


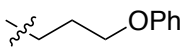
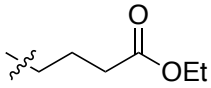
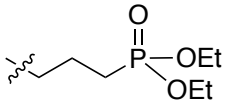
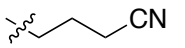
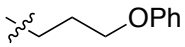
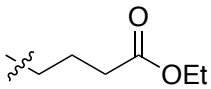
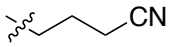
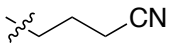
entry	R^1	R	yield (%)[b]
1	CH_2CH_2Ph		74
2	CH_2CH_2Ph		55
3	CH_2CH_2Ph		61
4	CH_2CH_2Ph		59
5	CH_2CH_2Ph		66
6	CH_2CH_2Ph		70
7	CH_2CH_2Ph		77
8			64

[a]All data are the average of two experiments. [b]Yield of purified product.

Next, we are delighted to observe that this method can also be applied to electrophiles bearing higher order perfluoroalkyl groups without any modifications (Table 3.4).

Table 3.4. Scope with Respect to the Perfluoroalkyl Group[a]

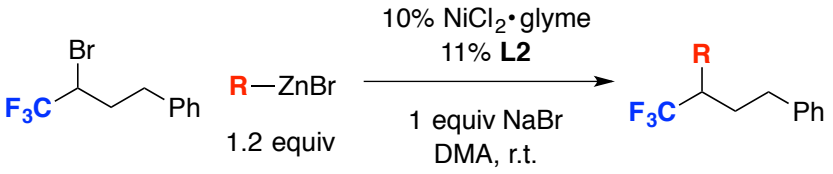


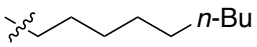
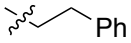
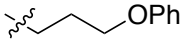
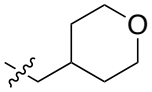
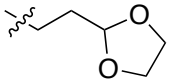
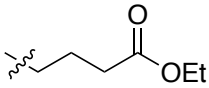
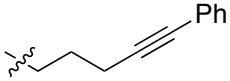
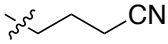
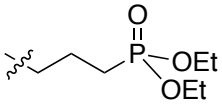
entry	R_F	R	yield (%)[b]
1	*n*-C_3F_7		65
2	*n*-C_3F_7		54
3	*n*-C_3F_7		51
4	*n*-C_3F_7		69
5	*n*-C_4F_9		67
6	*n*-C_4F_9		54
7	*n*-C_4F_9		69
8	*n*-C_9F_{19}		66

[a]All data are the average of two experiments. [b]Yield of purified product.

Considering the unique properties of the trifluoromethyl (CF_3) group, the construction of molecules bearing C–CF_3 moieties has recently attracted much attention. Although a few methods have been developed in the generation of targets that include a trifluoromethyl group connected to a tertiary carbon, a general method that provides the products in good efficiency is still desirable.[4,12] As shown in Table 3.5 and Table 3.6, our method can be directly used to access these targets and the functional-group tolerance is very satisfactory.

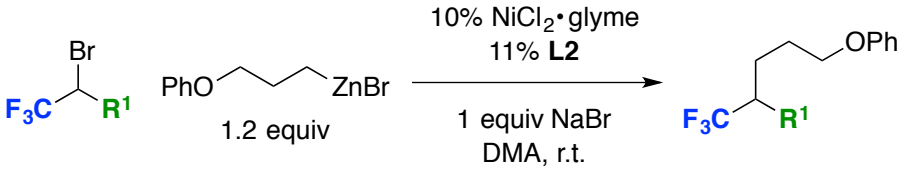
Table 3.5. Negishi Alkylations to Generate Trifluoromethyl-Substituted Products: Scope with Respect to the Nucleophile[a]



entry	R	yield (%)[b]
1		79
2		78
3		83
4		74
5		72
6		83
7		67
8		83
9		89

[a]All data are the average of two experiments. [b]Yield of purified product.

Table 3.6. Negishi Alkylations to Generate Trifluoromethyl-Substituted Products: Scope with Respect to the Electrophile[a]



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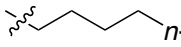
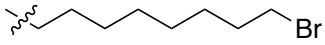
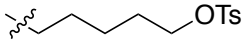
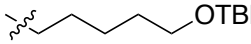
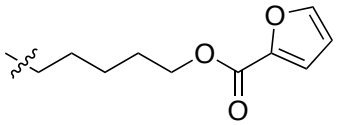
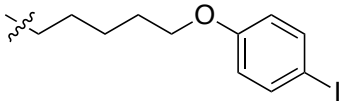
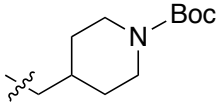
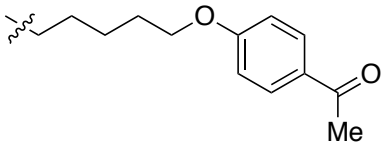
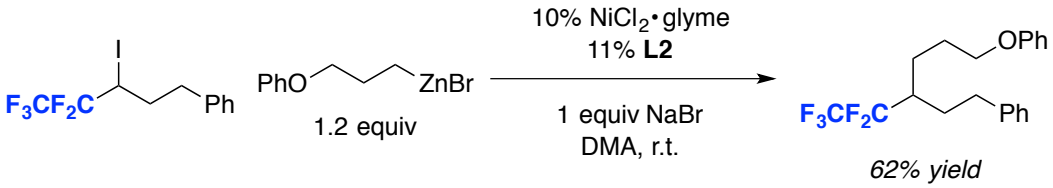
1		86
2		79
3		76
4[c]		72
5		83
6[c]		81
7		80
8		86

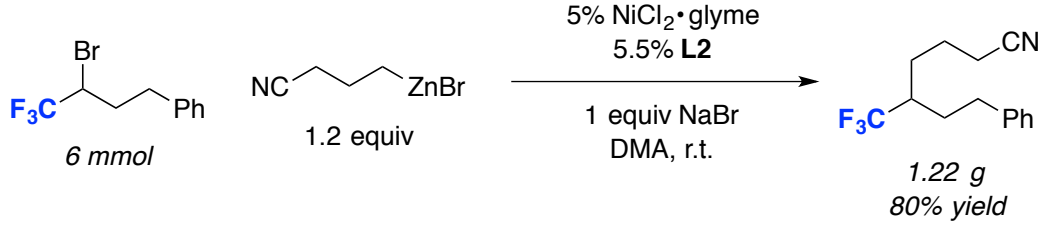
[a]All data are the average of two experiments. [b]Yield of purified product. [c]Nucleophile: $BrZnCH_2CH_2CH_2CN$.

Our new method is not limited to cross-couplings of secondary alkyl bromides. Under the same conditions, a fluorinated alkyl *iodide* can also cross-couple with an alkylzinc reagent in moderate efficiency (eq 3.3).



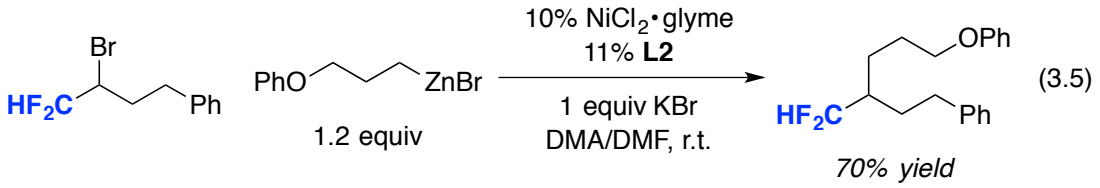
(3.3)

To probe the scalability of this method, we perform a large-scale experiment using a trifluoromethyl-containing electrophile (eq 3.4). The cross-coupling reaction proceeds in good yield in the presence of only 5% catalyst.

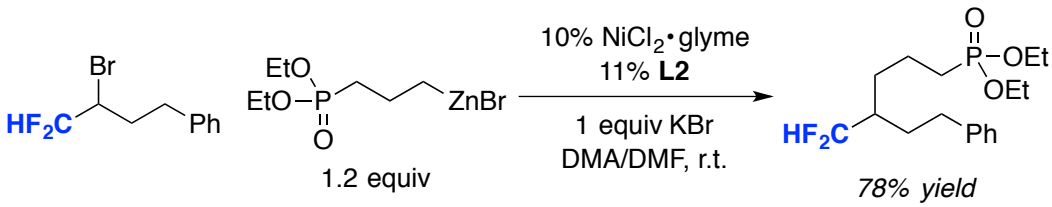


(3.4)

Although we initially optimized the reaction conditions with α-bromo-α-*perfluoroalkyl* secondary electrophiles, we were also delighted to observe that an α-bromo-α-*difluoromethyl* secondary electrophile can react with alkylzinc reagents under related conditions (eqs 3.5 and 3.6). Thus it provides us with an efficient way to generate difluoromethyl-substituted compounds, which is complementary to other strategies.[13,14]



(3.5)



(3.6)

A number of electrophiles that give low yield under our optimized conditions (eq 3.2) are summarized in Figure 3.2.

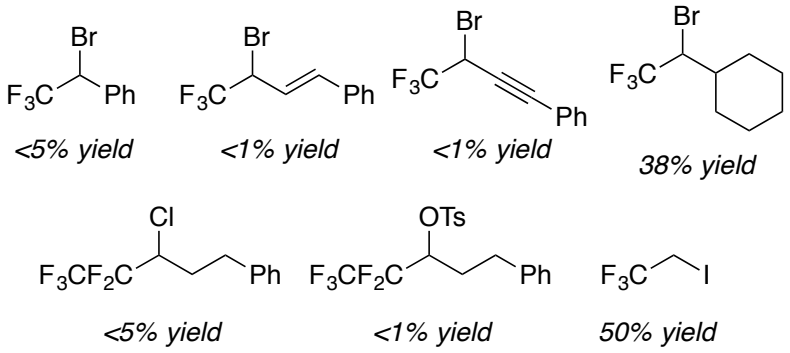


Figure 3.2. Unsuccessful Electrophiles.

Other features of this cross-coupling method are listed below.

A. A secondary alkylzinc reagent (cyclopentyl–ZnBr) is not suitable cross-coupling partner.

B. The cross-coupling product is stable under our standard conditions. No C–F bond cleavage has been observed.

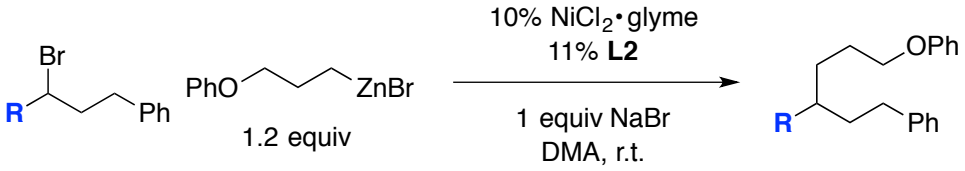
C. The major side reaction of this method is the debromodefluorination of the electrophile.

3.4 Competition Experiments

From a practical perspective, we are delighted to observe that this cross-coupling reaction is typically very fast. Full conversion of electrophiles can be achieved even within a few *minutes* (less than 10 minutes for eq 3.2). We were curious about the unique reactivity of these perfluoroalkylated electrophiles and therefore subjected a few

structurally related fluorinated electrophiles to the reaction condition. These results are summarized in Table 3.7.

Table 3.7. Differences in Reactivity[a]

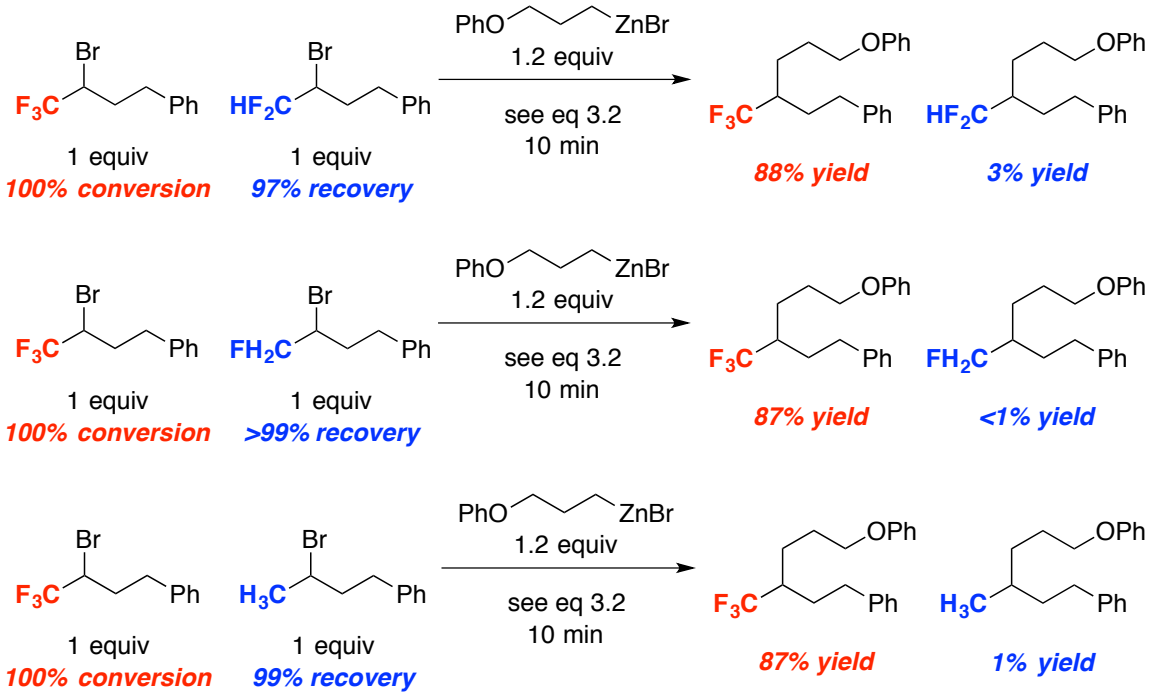


entry	R	reaction time	SM conversion (%)[b]	Yield(%)[b]
1	CF_3	10 min	100	88
2	CF_2H	5 h	85	44
3	CFH_2	5 h	64	<1
4	CH_3	5 h	31	13

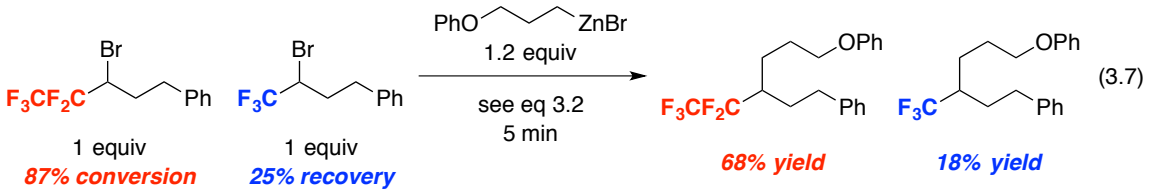
[a]All data are the average of two experiments. [b]Yields and conversion are determined by ^{19}F NMR analysis and calibrated GC analysis versus internal standards.

As shown in Table 3.7, the trifluoromethyl-substituted electrophile is indeed more reactive than partially fluorinated electrophiles and non-fluorinated electrophile under our standard condition. Thus, we were wondering if this enhanced reactivity could lead to highly selective Negishi alkylations that might be synthetically useful. A series of competition experiments have been performed and the results are shown in Scheme 3.3. Highly chemoselective cross-coupling reactions can be achieved under the standard conditions. In each case, the less reactive electrophile can be recovered almost quantitatively. Although we are not sure about the origins of this selectivity, it is not uncommon for fluorine atoms to play important roles in determining the reacitivity of organofluorine compounds.[15]

Scheme 3.3. Competition Experiments (CF_3, CF_2H, CFH_2 and CH_3)



Additionally, we also performed a similar competition experiment using a *pentafluoroethyl*-substituted electrophile and a *trifluoromethyl*-substituted electrophile under the standard condition (eq 3.7). It turned out that the latter is less reactive. However, quantitative recovery of the less reactive substrate is not feasible at this stage.



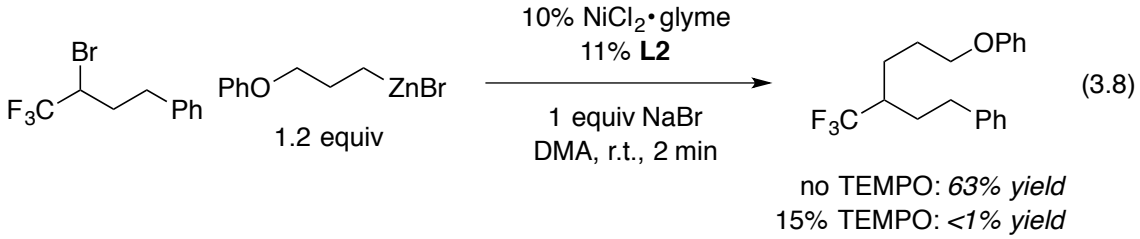
(3.7)

3.5 Mechanistic Studies

Previously, for some nickel-catalyzed cross-couplings employing alkyl electrophiles, we have suggested that the electrophile may react to generate an alkyl

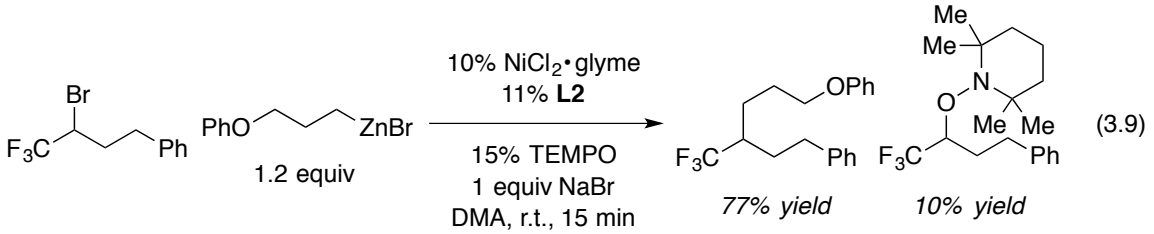
radical during the oxidative-addition step of the catalytic cycle.[16] For this new method, we also obtained some evidence that is consistent with the existence of alkyl radicals as reaction intermediates.

This cross-coupling reaction can be inhibited by the addition of catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as shown in eq 3.8.

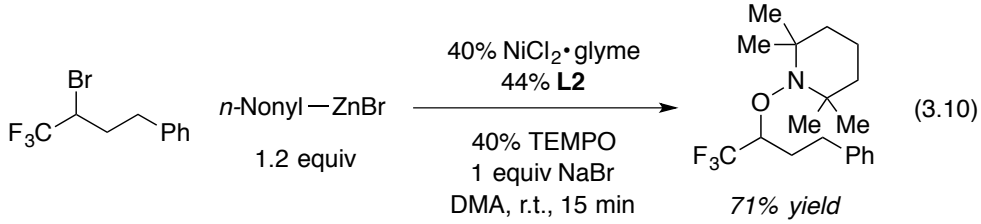


(3.8)

The above cross-coupling reaction resumes after the TEMPO (15 mol%) has been consumed. After 15 minutes, the cross-coupling product is generated in 77% yield (eq 3.9). We also identified a side product in this reaction. This side product can be independently synthesized and isolated according to conditions shown in eq 3.10. Presumably, this adduct is generated from the trapping of TEMPO with an alkyl radical.[17]



(3.9)

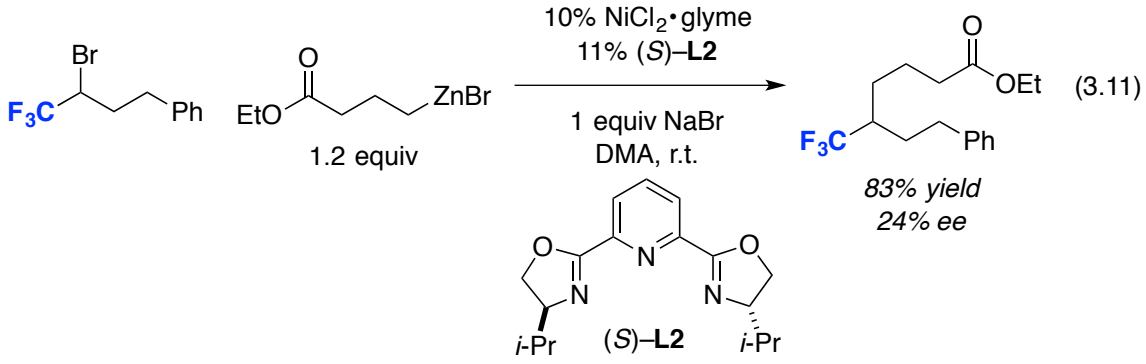


(3.10)

3.6 Conclusions

In summary, we have developed the first catalytic cross-coupling method employing α-bromo-α-perfluoroalkyl secondary electrophiles. Primary alkylzinc reagents can cross-couple with these electrophiles under mild conditions (at room temperature) in short reaction time (several minutes to hours) with the aid of commercially available catalyst components. Particularly, the catalytic system can be applied directly to α-bromo-α-trifluoromethyl electrophiles to generate products bearing trifluoromethyl-substituted tertiary carbons. Competition experiments and preliminary mechanistic studies reveal unique properties of these electrophiles and also provide evidence to support the existence of alkyl radical intermediates.

One remaining question within this project is whether or not an *enantioselective* Negishi alkylation protocol can be developed. Although ligand **L2** leads to a quite efficient bond-formation process, the level of stereoinduction is quite low under our standard condition (eq 3.11). Extensive optimization has been conducted and a synthetically useful level of enantioselectivity could not be achieved under all conditions.



(3.11)

At the same time, we also studied asymmetric Negishi *arylations* using these perfluoroalkyl-substituted electrophiles and quickly identified very promising results. Following these preliminary studies, we have successfully developed an asymmetric Negishi arylation method and it will be discussed in detail in the next chapter.

3.7 Experimental Section

3.7.1 General Information

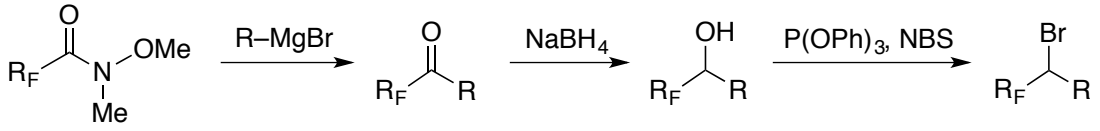
^{1}H NMR data and ^{13}C NMR data were collected on a VARIAN 500 MHz spectrometer at ambient temperature. ^{19}F NMR data and ^{31}P NMR data were collected on a VARIAN 300 MHz spectrometer at ambient temperature.

Anhydrous THF, CH_2Cl_2, and toluene were purified and dried using a solvent-purification system that contained activated alumina. The following reagents were purchased and used as received: $NiCl_2$•glyme (Strem), ligand **L2** (Aldrich), DMA (Aldrich; anhydrous), DMF (Aldrich; anhydrous), zinc powder (Alfa-Aesar; ~100 mesh, 99.9%), iodine (Alfa-Aesar; crystalline, 99.5%), $NaBH_4$ (Oakwood), triphenyl phosphite (Aldrich), *N*-bromosuccinimide (Aldrich), *N*-iodosuccinimide (AK Scientific), oxalyl chloride (Aldrich), DMSO (Aldrich; ≥99.5%), Et_3N (Aldrich), trifluoromethyltrimethylsilane (Oakwood), TBAF (Aldrich; 1.0 M in THF), triphenylphosphine (Oakwood), and tetrabromomethane (TCI). NaBr (Aldrich; ≥99%; granular) and KBr (Aldrich; ≥99%; granular) were dried at 140 °C for 12 h prior to use. All alkyl bromides were purchased (Aldrich, Alfa Aesar, TCI, and Oakwood) and used as received.

All reactions were carried out in oven-dried glassware under an inert atmosphere.

3.7.2 Preparation of Electrophiles

These procedures have not been optimized.



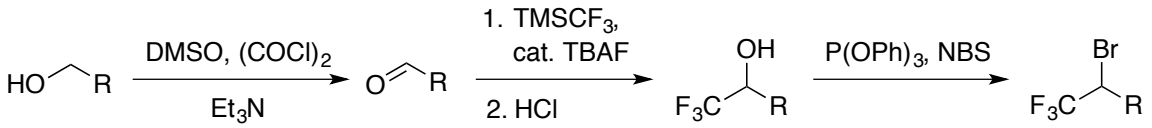
General Procedure A: Synthesis of Electrophiles with a Perfluoroalkyl Group

Preparation of the ketone using a Grignard reagent. A solution of the Grignard reagent in THF (1.0 M, 40 mmol; 1.0 equiv) was added by syringe to a solution of the Weinreb amide[18] (40 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and then it was allowed to warm to r.t. and stirred for 15 h. Next, water was added to quench the reaction at 0 °C. A solution of 1 N HCl (50 mL) was added, and then the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel.

Reduction of the ketone to the alcohol. $NaBH_4$ (2.3 g, 60 mmol; 3.0 equiv) was added in portions to a solution of the ketone (20 mmol) in Et_2O (20 mL) and MeOH (20 mL) at 0 °C (CAUTION: very exothermic). After the addition was complete, the mixture was stirred at 0 °C for 30 min, and then it was allowed to warm to r.t. and stirred for 30 min. Next, Et_2O (30 mL) was added to dilute the reaction mixture, the mixture was cooled to 0 °C, and then deionized water (30 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel.

Bromination of the alcohol.[19] Triphenylphosphite (4.0 g, 3.4 mL; 1.3 equiv) was added over 5 min to a solution of *N*-bromosuccinimide (2.3 g, 13 mmol; 1.3 equiv) in CH_2Cl_2 (10 mL) at 0 °C (CAUTION: exothermic). Next, a solution of the alcohol (10 mmol) in CH_2Cl_2 (12 mL) was added to the mixture at 0 °C. The reaction mixture was

heated to 40 °C and then stirred at 40 °C for 12 h. Next, the solvent was evaporated, and the product was purified by flash chromatography on silica gel.



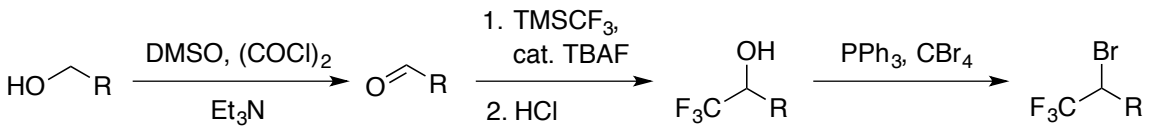
General Procedure B: Synthesis of Electrophiles with a CF_3 Group

Swern oxidation of the alcohol. DMSO (2.9 mL, 40 mmol; 2.0 equiv) was added slowly to a solution of oxalyl chloride (2.0 mL, 24 mmol; 1.2 equiv) in CH_2Cl_2 (150 mL) at −78 °C. The resulting mixture was allowed to stir at −78 °C for 30 min. Next, a solution of the alcohol (20 mmol) in CH_2Cl_2 (30 mL) was added over 5 min to the mixture. The resulting mixture was stirred at −78 °C for 45 min, and then NEt_3 (11 mL, 80 mmol; 4.0 equiv) was added in one portion. The mixture was allowed to warm to r.t., and then it was stirred at r.t. for 2 h. Next, an aqueous saturated solution of NH_4Cl (30 mL) was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (3 × 70 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel.

Trifluoromethylation of the aldehyde.[20] A solution of TBAF (1.0 M in THF; 0.20 mL, 0.20 mmol; 0.013 equiv) was added over 3 min to a solution of the aldehyde (15 mmol) and trifluoromethyltrimethylsilane (2.7 mL, 18 mmol; 1.2 equiv) in THF (20 mL) at 0 °C (CAUTION: very exothermic). The reaction mixture was allowed to warm to r.t., and it was stirred for 1 h. Next, an aqueous solution of 1 N HCl (30 mL) was added, and the mixture was allowed to stir at r.t. for another 2 h. Then, the mixture was extracted

with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel.

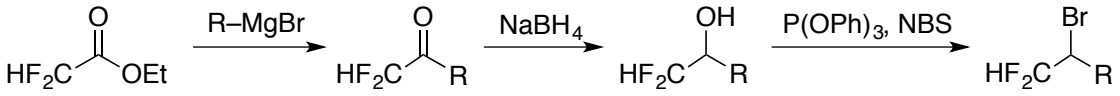
The bromination step is the same as in General Procedure A.



General Procedure C: Synthesis of Electrophiles with a CF_3 Group

The first two steps are the same as in General Procedure B.

Bromination of the alcohol.[8e] Triphenylphosphine (4.2 g, 16 mmol; 2.0 equiv) and tetrabromomethane (5.3 g, 16 mmol; 2.0 equiv) were added to a solution of the alcohol (8.0 mmol) in toluene (20 mL). The resulting mixture was heated to 110 °C and stirred at 110 °C for 3 h, at which time it had turned into a yellow suspension. Then, CH_2Cl_2 (50 mL) was added to the reaction mixture until it became a clear solution. The solvents were then evaporated, and the crude product was purified by flash chromatography on silica gel.

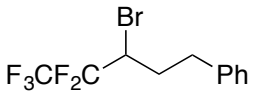


General Procedure D: Synthesis of Electrophiles with a Difluoromethyl Group

Preparation of the ketone using a Grignard reagent. A solution of the Grignard reagent in THF (1.0 M, 20 mmol; 1.0 equiv) was added by syringe to a solution of ethyl 2,2-difluoroacetate (40 mmol; 2.0 equiv) in THF (40 mL) at –78 ºC. The reaction

mixture was stirred at –78 °C for 1 hour. Next, aqueous NH_4Cl solution (30 mL) was added to quench the reaction at –78 ºC. A solution of 1 N HCl (30 mL) was added, and then the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel.

The next two steps are the same as in General Procedure A.



(3-Bromo-4,4,5,5,5-pentafluoropentyl)benzene. The title compound was synthesized according to General Procedure A, using 2,2,3,3,3-pentafluoro-*N*-methoxy-*N*-methylpropanamide and a Grignard reagent prepared from (2-bromoethyl)benzene. The overall yield was 30% (3 steps). The title compound was isolated as a colorless oil.

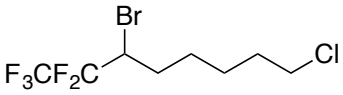
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.28 – 7.21 (m, 3H), 4.10 – 4.01 (m, 1H), 3.10 – 3.02 (m, 1H), 2.82 – 2.75 (m, 1H), 2.42 – 2.34 (m, 1H), 2.25 – 2.15 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 128.1, 117.8, 117.5, 115.7, 109.2 – 101.3 (m), 35.3 – 34.3 (m), 21.6, 21.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.0 (s, 3F), −114.2 (dd, 1F, J = 269.4, 12.4 Hz), −117.0 (dd, 1F, J = 269.4, 13.0 Hz);

FT-IR (film) 3030, 1497, 1456, 1324, 1200, 1129, 1104, 1029, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{11}H_{10}{}^{79}BrF_5$: 316, found: 316, 318 (M^++2).



3-Bromo-8-chloro-1,1,1,2,2-pentafluorooctane. The title compound was synthesized according to General Procedure A, using 2,2,3,3,3-pentafluoro-*N*-methoxy-*N*-methylpropanamide and a Grignard reagent prepared from 1-bromo-5-chloropentane. The overall yield was 9% (3 steps). The title compound was isolated as a colorless oil.

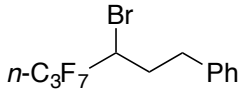
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 – 4.10 (m, 1H), 3.55 (t, 2H, J = 6.6 Hz), 2.11 – 2.01 (m, 1H), 1.95 – 1.69 (m, 4H), 1.60 – 1.43 (m, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 120.5 – 111.9 (m), 46.5 (dd, J = 25.4, 23.7 Hz), 44.7, 32.1, 30.5, 26.3, 25.9;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.0 (s, 3F), −114.5 (dd, 1F, J = 269.3, 12.6 Hz), −117.2 (dd, 1F, J = 269.3, 12.7 Hz);

FT-IR (film) 2944, 2867, 1196, 1022, 719 cm^{-1};

GC-MS (EI) *m/z* (M^+−HBr) calcd for $C_8H_{10}ClF_5$: 236, found: 236.



(3-Bromo-4,4,5,5,6,6,6-heptafluorohexyl)benzene. The title compound was synthesized according to General Procedure A, using 2,2,3,3,4,4,4-heptafluoro-*N*-methoxy-*N*-methylbutanamide and a Grignard reagent prepared from (2-bromoethyl)benzene. The overall yield was 24% (3 steps). The title compound was isolated as a colorless oil.

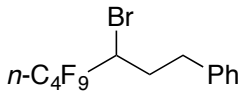
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 3H), 7.28 – 7.22 (m, 2H), 4.19 – 4.08 (m, 1H), 3.06 (ddd, 1H, *J* = 13.3, 8.4, 4.4 Hz), 2.80 (dt, 1H, *J* = 13.9, 8.2 Hz), 2.43 – 2.36 (m, 1H), 2.27 – 2.17 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 128.8, 128.5, 126.7, 121.5 – 108.5 (m), 46.5 (t, *J* = 24.5 Hz), 32.6, 32.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (t, 3F, *J* = 10.7 Hz), −109.2 – −115.5 (m, 2F), –123.3 (dd, 2F, *J* = 20.0, 8.1 Hz);

FT-IR (film) 3029, 2936, 1497, 1456, 1348, 1235, 1182, 1108, 964, 927, 750, 724, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{12}H_{10}{}^{79}BrF_7$: 366, found: 366, 368 (M^++2).



(3-Bromo-4,4,5,5,6,6,7,7,7-nonafluoroheptyl)benzene. The title compound was synthesized according to General Procedure A, using 2,2,3,3,4,4,5,5,5-nonafluoro-*N*-methoxy-*N*-methylpentanamide and a Grignard reagent prepared from (2-bromoethyl)benzene. The overall yield was 31% (3 steps). The title compound was isolated as a colorless oil.

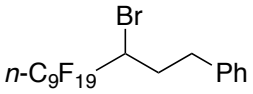
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 7.27 – 7.21 (m, 3H), 4.20 – 4.10 (m, 1H), 3.06 (ddd, 1H, *J* = 13.3, 8.4, 4.4 Hz), 2.79 (dt, 1H, *J* = 13.9, 8.2 Hz), 2.43 – 2.35 (m, 1H), 2.21 (dddd, 1H, *J* =15.1, 11.1, 8.3, 4.4 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 128.8, 128.5, 126.7, 119.5 – 111.5 (m), 47.0 – 46.4 (m), 32.7, 32.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 – −80.9 (m, 3F), −108.5 – −115.4 (m, 2F), −119.8 – −120.0 (m, 2F), −126.0 – −126.2 (m, 2F)

FT-IR (film) 3030, 2929, 1497, 1456, 1353, 1238, 1136, 750, 717, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{13}H_{10}{}^{79}BrF_9$: 416, found: 416, 418 (M^++2).



(3-Bromo-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-nonadecafluorododecyl)benzene. The title compound was synthesized according to General Procedure A, using 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluoro-*N*-methoxy-*N*-methyldecanamide and a Grignard reagent prepared from (2-bromoethyl)benzene. The overall yield was 21% (3 steps). The title compound was isolated as a white solid.

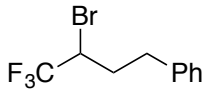
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.27 – 7.20 (m, 3H), 4.20 – 4.10 (m, 1H), 3.06 (ddd, 1H, *J* = 13.3, 8.4, 4.4 Hz), 2.79 (dt, 1H, *J* = 13.9, 8.2 Hz), 2.45 – 2.35 (m, 1H), 2.25 – 2.17 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 128.8, 128.5, 126.7, 115.7 – 103.7 (m), 47.3 – 46.4 (m), 32.7, 32.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (m, 3F), −108.3 – −115.0 (m, 2F), −118.6 – −119.2 (m, 2F), −121.3 – −122.2 (m, 8F), −122.6 – −122.9 (m, 2F), −126.1 – −126.3 (m, 2F);

FT-IR (film) 3030, 2936, 1497, 1456, 1215, 1151, 1097, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+−HBr−C_9F_{19}) calcd for C_9H_9: 117, found: 117.



(3-Bromo-4,4,4-trifluorobutyl)benzene [136832-35-4]. The title compound was synthesized according to General Procedure A, using 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide and a Grignard reagent prepared from (2-bromoethyl)benzene. The overall yield was 34% (3 steps). The title compound was isolated as a colorless oil.

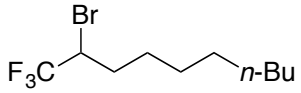
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.29 – 7.22 (m, 3H), 4.03 – 3.96 (m, 1H), 3.02 (ddd, 1H, *J* = 13.4, 8.3, 4.6 Hz), 2.81 – 2.75 (m, 1H), 2.40 – 2.33 (m, 1H), 2.21 (dddd, 1H, *J* = 14.6, 11.0, 8.2, 4.6 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 128.8, 128.5, 126.7, 124.0 (q, *J* = 278.2 Hz), 46.7 (q, *J* = 32.6 Hz), 32.9 (d, *J* = 1.4 Hz), 32.5;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.1 (d, 3F, *J* = 7.1 Hz);

FT-IR (film) 3029, 1258, 1168, 1111, 750, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{10}H_{10}{}^{79}BrF_3$: 266, found: 266, 268 (M^++2).



2-Bromo-1,1,1-trifluorodecane [1349717-60-7]. The title compound was synthesized according to General Procedure A, using 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide and a Grignard reagent prepared from 1-bromooctane. The overall yield was 30% (3 steps). The title compound was isolated as a colorless oil.

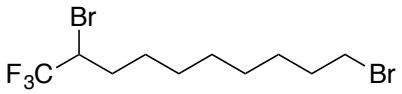
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dqd, 1H, *J* = 10.5, 7.2, 3.3 Hz), 2.02 (dddd, 1H, *J* = 14.6, 9.8, 6.1, 3.3 Hz), 1.91 – 1.81 (m, 1H), 1.43 – 1.21 (m, 12H), 0.89 (t, 3H, *J* = 7.2 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 124.1 (q, J = 278.0 Hz), 47.7 (q, J = 32.3 Hz), 31.8, 31.4 (d, J = 1.5 Hz), 29.23, 29.15, 28.6, 26.8, 22.6, 14.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.4 (d, 3F, J = 7.2 Hz);

FT-IR (film) 2956, 2928, 2857, 1266, 1173, 1124, 1105, 678 cm^{-1};

GC-MS (EI) *m/z* (M^+–C_4H_9) calcd for $C_6H_9{}^{79}BrF_3$: 217, found: 217, 219 (M^+–C_4H_9+2).



2,10-Dibromo-1,1,1-trifluorodecane. The title compound was synthesized according to General Procedure B from 9-bromononan-1-ol. The overall yield was 50% (3 steps). The title compound was isolated as a colorless oil.

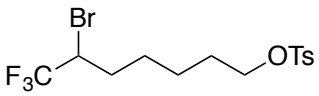
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dqd, 1H, J = 10.5, 7.1, 3.3 Hz), 3.41 (t, 2H, J = 6.8 Hz), 2.02 (dddd, 1H, J = 14.5, 9.8, 6.1, 3.3 Hz), 1.89 – 1.82 (m, 3H), 1.47 – 1.28 (m, 10H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 124.0 (q, J = 278.2 Hz), 47.7 (q, J = 32.4 Hz), 33.9, 32.7, 31.3 (d, J = 1.5 Hz), 29.0, 28.56, 28.48, 28.0, 26.7;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, J = 7.1 Hz);

FT-IR (film) 2931, 2857, 1267, 1169, 1110, 677 cm^{-1};

GC-MS (EI) *m/z* (M^+–C_3H_6Br) calcd for $C_7H_{11}{}^{79}BrF_3$: 231, found: 231, 233 (M^+–C_3H_6Br+2).



6-Bromo-7,7,7-trifluoroheptyl 4-methylbenzenesulfonate. The title compound was synthesized according to General Procedure B from 6-hydroxyhexyl 4-methylbenzenesulfonate.[21] The overall yield was 52% (3 steps). The title compound was isolated as a colorless oil.

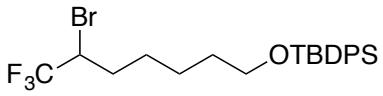
^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.83 – 7.79 (m, 2H), 7.51 – 7.46 (m, 2H), 4.55 (dqd, 1H, *J* = 10.7, 7.4, 3.3 Hz), 4.07 (t, 2H, *J* = 6.3 Hz), 2.46 (s, 3H), 2.04 – 1.99 (m, 1H), 1.85 – 1.76 (m, 1H), 1.73 – 1.55 (m, 3H), 1.52 – 1.30 (m, 3H);

^{13}C NMR (126 MHz, CD_3COCD_3) δ 145.9, 134.5, 131.0, 128.8, 125.5 (q, *J* = 277.2 Hz), 71.4, 48.4 (q, *J* = 32.0 Hz), 32.0 (d, *J* = 1.6 Hz), 29.3, 26.9, 25.2, 21.6;

^{19}F NMR (282 MHz, CD_3COCD_3) δ −72.9 (d, 3F, *J* = 7.4 Hz);

FT-IR (film) 2948, 1598, 1359, 1189, 1176, 1117, 1098, 951, 815, 664 cm^{-1};

GC-MS (EI) *m/z* (M^+–OTs) calcd for $C_7H_{11}{}^{79}BrF_3$: 231, found: 231, 233 (M^+–OTs+2).



((6-Bromo-7,7,7-trifluoroheptyl)oxy)(*tert*-butyl)diphenylsilane. The title compound was synthesized according to General Procedure B from 6-((*tert*-butyldiphenylsilyl)oxy)hexan-1-ol.[22] The overall yield was 23% (3 steps). The title compound was isolated as a colorless oil.

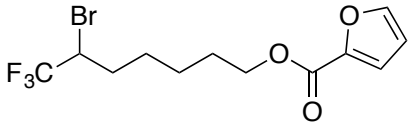
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.46 – 7.37 (m, 6H), 4.04 (dqd, 1H, *J* = 10.5, 7.2, 3.4 Hz), 3.69 (t, 2H, *J* = 6.3 Hz), 2.02 (dddd, 1H, *J* = 14.4, 9.8, 5.6, 3.3 Hz), 1.90 – 1.81 (m, 1H), 1.69 – 1.54 (m, 3H), 1.49 – 1.35 (m, 3H), 1.07 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 134.0, 129.6, 127.6, 124.1 (q, J = 278.2 Hz), 63.5, 47.6 (q, J = 32.4 Hz), 32.1, 31.4 (d, J = 1.4 Hz), 26.9, 26.5, 24.9, 19.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, J = 7.1 Hz);

FT-IR (film) 2932, 2858, 1428, 1259, 1171, 1113, 823, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+–C_4H_9) calcd for $C_{19}H_{21}{}^{79}BrF_3OSi$: 429, found: 429.



6-Bromo-7,7,7-trifluoroheptyl furan-2-carboxylate. The title compound was synthesized according to General Procedure B from 6-hydroxyhexyl furan-2-carboxylate.[23] The overall yield was 62% (3 steps). The title compound was isolated as a light-yellow oil (it should be stored in a refrigerator (~5 °C)).

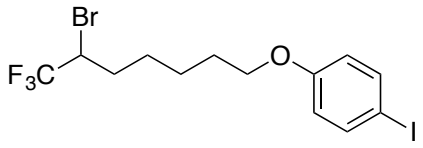
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, 1H, J = 1.8, 0.9 Hz), 7.17 (dd, 1H, J = 3.5, 0.9 Hz), 6.51 (dd, 1H, J = 3.5, 1.7 Hz), 4.31 (t, 2H, J = 6.6 Hz), 4.07 (dqd, 1H, J = 10.5, 7.1, 3.4 Hz), 2.05 (dddd, 1H, J = 14.7, 10.3, 5.6, 3.3 Hz), 1.93 – 1.84 (m, 1H), 1.82 – 1.68 (m, 3H), 1.55 – 1.42 (m, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 146.3, 144.7, 124.0 (q, J = 278.1 Hz), 117.8, 111.8, 64.6, 47.4 (q, J = 32.5 Hz), 31.3 (d, J = 1.5 Hz), 28.4, 26.5, 25.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, J = 7.0 Hz);

FT-IR (film) 2949, 2866, 1726, 1582, 1571, 1475, 1400, 1297, 1260, 1180, 1118, 1014, 958, 885, 764, 677 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{12}H_{14}{}^{79}BrF_3O_3$: 342, found: 342, 344 ($M^+$+2).



1-((6-Bromo-7,7,7-trifluoroheptyl)oxy)-4-iodobenzene. The title compound was synthesized according to General Procedure B from 6-(4-iodophenoxy)hexan-1-ol.[24] The overall yield was 33% (3 steps). The title compound was isolated as a colorless oil (it should be stored in a refrigerator (~5 °C)).

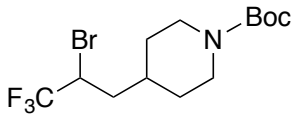
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 6.69 – 6.65 (m, 2H), 4.08 (dqd, 1H, *J* = 10.5, 7.1, 3.4 Hz), 3.93 (t, 2H, *J* = 6.3 Hz), 2.07 (dddd, 1H, *J* = 14.3, 9.9, 5.5, 3.4 Hz), 1.95 – 1.86 (m, 1H), 1.85 – 1.68 (m, 3H), 1.60 – 1.46 (m, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 138.2, 124.0 (q, *J* = 278.2 Hz), 116.9, 82.6, 67.6, 47.5 (q, *J* = 32.5 Hz), 31.3 (d, *J* = 1.4 Hz), 28.8, 26.6, 25.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, *J* = 7.1 Hz);

FT-IR (film) 2944, 1587, 1487, 1473, 1283, 1245, 1175, 1117, 820 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{13}H_{15}{}^{79}BrF_3IO$: 450, found: 450, 452 ($M^+$+2).



***tert*-Butyl 4-(2-bromo-3,3,3-trifluoropropyl)piperidine-1-carboxylate.** The title compound was synthesized according to General Procedure C from *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate. The overall yield was 26% (3 steps). The title compound was isolated as a white solid.

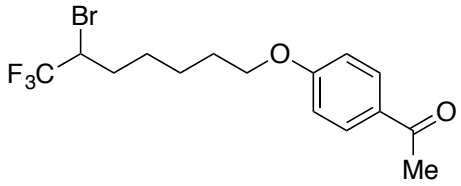
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 – 4.09 (m, 3H), 2.72 – 2.68 (m, 2H), 1.94 – 1.85 (m, 1H), 1.85 – 1.72 (m, 2H), 1.68 – 1.63 (m, 2H), 1.44 (s, 9H), 1.23 (tdd, 1H, *J* = 12.8, 11.0, 4.4 Hz), 1.03 (tdd, 1H, *J* = 12.7, 11.0, 4.5 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 124.1 (q, *J* = 278.1 Hz), 79.5, 44.8 (q, *J* = 32.7 Hz), 37.6, 33.2, 32.4, 30.0, 28.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.5 (d, 3F, *J* = 7.0 Hz);

FT-IR (film) 2977, 2931, 2850, 1691, 1425, 1366, 1262, 1252, 1172, 1129, 1110, 967, 685 cm^{-1};

GC-MS (EI) *m/z* (M^+–Boc) calcd for $C_8H_{12}{}^{79}BrF_3N$: 258, found: 258, 260 (M^+–Boc+2).



1-(4-((6-Bromo-7,7,7-trifluoroheptyl)oxy)phenyl)ethan-1-one. The title compound was synthesized according to General Procedure C from 1-(4-((6-hydroxyhexyl)oxy)phenyl)ethan-1-one.[25] The overall yield was 57% (3 steps). The title compound was isolated as a light-yellow oil (it should be stored in a refrigerator (~5 °C)).

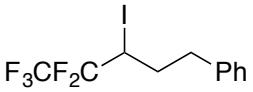
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 2H), 6.93 – 6.89 (m, 2H), 4.12 – 4.05 (m, 1H), 4.03 (t, 2H, *J* = 6.3 Hz), 2.55 (s, 3H), 2.07 (dddd, 1H, *J* = 14.4, 10.1, 5.6, 3.4 Hz), 1.94 – 1.80 (m, 3H), 1.78 – 1.68 (m, 1H), 1.62 – 1.47 (m, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 162.9, 130.6, 130.2, 124.0 (q, *J* = 278.2 Hz), 114.0, 67.8, 47.4 (q, *J* = 32.4 Hz), 31.3 (d, *J* = 1.4 Hz), 28.7, 26.5, 26.3, 25.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, J = 7.1 Hz);

FT-IR (film) 2946, 2867, 1676, 1602, 1576, 1509, 1358, 1257, 1172, 1117, 834 cm^{-1};

GC-MS (EI) *m/z* (M^+–CH_3) calcd for $C_{14}H_{15}{}^{79}BrF_3O_2$: 351, found: 351, 353 ($M^+$–$CH_3$+2).



(4,4,5,5,5-Pentafluoro-3-iodopentyl)benzene. The title compound was synthesized according to General Procedure A, using 2,2,3,3,3-pentafluoro-*N*-methoxy-*N*-methylpropanamide and a Grignard reagent prepared from (2-bromoethyl)benzene. *N*-iodoosuccinimide, rather than *N*-bromosuccinimide, was used in the last step. The overall yield was 9% (3 steps). The title compound was isolated as a colorless oil (it should be stored in a refrigerator (~5 °C)).

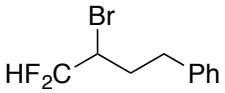
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.27 – 7.20 (m, 3H), 4.18 – 4.08 (m, 1H), 3.03 (dt, 1H, J = 13.3, 6.4 Hz), 2.72 (dt, 1H, J = 14.0, 8.2 Hz), 2.20 – 2.13 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 128.8, 128.5, 126.7, 121.6 – 112.0 (m), 34.9, 33.6, 24.3 – 23.9 (m);

^{19}F NMR (282 MHz, $CDCl_3$) δ −79.5 (s, 3F), −101.6 (dd, 1F, J = 265.8, 8.8 Hz), −114.8 (dd, 1F, J = 265.7, 19.6 Hz);

FT-IR (film) 3029, 2934, 1497, 1455, 1318, 1207, 1120, 1019, 712, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{11}H_{10}F_5I$: 364, found: 364.



(3-Bromo-4,4-difluorobutyl)benzene. The title compound was synthesized according to General Procedure D, using ethyl 2,2-difluoroacetate and a Grignard reagent prepared from (2-bromoethyl)benzene. The overall yield (3 steps) was 38%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.27 – 7.22 (m, 3H), 5.84 (td, 1H, *J* = 55.9, 3.6 Hz), 3.94 – 3.85 (m, 1H), 2.99 (ddd, 1H, *J* = 13.5, 8.5, 4.8 Hz), 2.78 (dt, 1H, *J* = 13.9, 8.2 Hz), 2.33 – 2.26 (m, 1H), 2.19 – 2.09 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7, 128.7, 128.5, 126.5, 117.0 – 112.6 (m), 49.8 (t, *J* = 24.0 Hz), 32.6, 32.3 (m);

^{19}F NMR (282 MHz, $CDCl_3$) δ −117.4 (ddd, 1F, *J* = 277.0, 55.7, 10.8 Hz), −122.4 (ddd, 1F, *J* = 277.0, 56.0, 13.1 Hz);

FT-IR (neat) 3028, 2949, 1497, 1455, 1381, 1136, 1086, 1044, 752, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{10}H_{11}{}^{79}BrF_2$: 248, found: 248, 250 (M^++2);

3.7.3 Nickel-Catalyzed Negishi Alkylations

General procedure for the preparation of alkylzinc solutions (0.50 M).[26]

In the air, zinc powder (589 mg, 9.00 mmol; 1.50 equiv) was added to an oven-dried 20-mL vial equipped with a stir bar. The vial was heated at 80 °C under high vacuum for 30 min. After back-filling with nitrogen, iodine chips (76 mg, 0.30 mmol; 0.050 equiv) were added to the vial. Then, the vial was evacuated and back-filled with nitrogen (three cycles). DMA (5 mL) was added to the mixture, and the mixture was stirred until the red color had faded. Next, the alkyl bromide (6.0 mmol; 1.0 equiv) was

added. The reaction mixture was stirred at 80 °C for 12 h, and then the mixture was allowed to cool to r.t. The gray solution was filtered under an inert atmosphere by injection through a syringe filter directly into a nitrogen-filled, 20-mL vial sealed with a PTFE septum cap. The alkylzinc solution was titrated using I_2 according to Knochel's method[27] (the concentration was ~0.9 M). This solution was diluted into a 0.50 M solution by the addition of DMA.

These solutions of organozinc bromides can be stored at r.t. under an inert atmosphere for several weeks without deterioration.

General Procedure A: Negishi Alkylations of α-Halo-α-Perfluoroalkyl Electrophiles

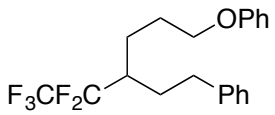
In the air, the electrophile (0.80 mmol) and NaBr (82 mg, 0.80 mmol; 1.0 equiv) were added to an oven-dried 20-mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap and then evacuated and back-filled with nitrogen (three cycles). In the air, $NiCl_2$•glyme (17.6 mg, 0.080 mmol) and ligand **L2** (26.5 mg, 0.088 mmol) were added to an oven-dried 4-mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap and then evacuated and back-filled with nitrogen (three cycles). DMA (2.0 mL) was added to the 4-mL vial, and the mixture was vigorously stirred at r.t. for 25 min. The resulting solution was transferred via syringe to the 20-mL reaction vial that contained the electrophile. The 4-mL vial was rinsed with DMA three times (0.7 mL, 0.7 mL, and 0.6 mL), and the washings were transferred to the 20-mL reaction vial. The resulting solution was allowed to stir at r.t. for 1 min. Then, the reaction vial was wrapped with electrical tape, and the alkylzinc solution (0.50 M; 1.9 mL, 0.95 mmol; 1.2

equiv) was added over 1 min. The mixture was stirred vigorously at r.t. for 5 h. Then, the reaction was quenched by the addition of MeOH (0.5 mL). The resulting mixture was allowed to stir for 1 min, and then it was diluted with Et_2O (100 mL) and washed with deionized water (20 mL × 4). The organic layer was dried over Na_2SO_4 and then concentrated, and the residue was purified by flash chromatography.

General Procedure B: Negishi Alkylations of α-Bromo-α-Difluoromethyl Electrophiles

In the air, the electrophile (0.80 mmol) and KBr (95 mg, 0.80 mmol; 1.0 equiv) were added to an oven-dried 20-mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap and then evacuated and back-filled with nitrogen (three cycles). In the air, $NiCl_2$•glyme (17.6 mg, 0.080 mmol) and ligand **L2** (26.5 mg, 0.088 mmol) were added to an oven-dried 4-mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap and then evacuated and back-filled with nitrogen (three cycles). DMF (2.0 mL) was added to the 4-mL vial, and the mixture was vigorously stirred at r.t. for 25 min. The resulting solution was transferred via syringe to the 20-mL reaction vial that contained the electrophile. The 4-mL vial was rinsed with DMF three times (0.7 mL, 0.7 mL, and 0.6 mL), and the washings were transferred to the 20-mL reaction vial. The resulting solution was allowed to stir at r.t. for 1 min. Then, the reaction vial was wrapped with electrical tape, and the alkylzinc solution in DMA (0.50 M; 1.9 mL, 0.95 mmol; 1.2 equiv) was added over 1 min. The mixture was stirred vigorously at r.t. for 5 h. Then, the reaction was quenched by the addition of MeOH (0.5 mL). The resulting mixture was allowed to stir for 1 min, and then it was diluted with Et_2O (100 mL) and

washed with deionized water (20 mL × 4). The organic layer was dried over Na_2SO_4 and then concentrated, and the residue was purified by flash chromatography.



((5,5,6,6,6-Pentafluoro-4-phenethylhexyl)oxy)benzene (Table 3.3, Entry 1). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,5-pentafluoropentyl)benzene (254 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 10:1 → 3:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 217 mg (73% yield); Run 2, 220 mg (74% yield).

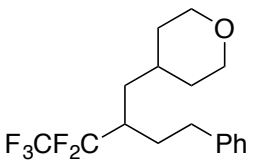
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 4H), 7.25 – 7.17 (m, 3H), 6.99 – 6.95 (m, 1H), 6.93 – 6.89 (m, 2H), 3.96 (t, 2H, *J* = 5.8 Hz), 2.81 – 2.67 (m, 2H), 2.30 – 2.17 (m, 1H), 2.13 – 2.02 (m, 1H), 1.98 – 1.69 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 141.0, 129.5, 128.6, 128.3, 126.2, 121.0 – 115.1 (m), 120.8, 114.4, 67.1, 39.6 (t, *J* = 19.9 Hz), 32.9, 28.5, 26.3, 23.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.7 (s, 3F), −117.0 (d, 2F, *J* = 16.1 Hz);

FT-IR (film) 2960, 1601, 1587, 1497, 1472, 1246, 1203, 1171, 754, 700, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{20}H_{21}F_5O$: 372, found: 372.



4-(3,3,4,4,4-Pentafluoro-2-phenethylbutyl)tetrahydro-*2H*-pyran (Table 3.3, Entry 2). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,5-pentafluoropentyl)benzene (254 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-(bromomethyl)tetrahydro-2*H*-pyran. Solvent system for chromatography: 15:1 → 12:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 147 mg (55% yield); Run 2, 144 mg (54% yield).

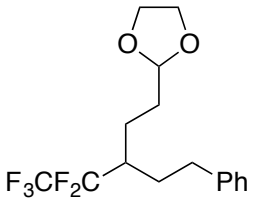
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.24 – 7.16 (m, 3H), 3.96 – 3.87 (m, 2H), 3.38 – 3.30 (m, 1H), 3.28 – 3.19 (m, 1H), 2.76 – 2.64 (m, 2H), 2.26 – 2.14 (m, 1H), 2.11 – 2.00 (m, 1H), 1.76 – 1.66 (m, 1H), 1.64 – 1.43 (m, 3H), 1.42 – 1.23 (m, 3H), 1.20 – 1.09 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 128.6, 128.4, 126.3, 121.6 – 114.0 (m), 67.8, 67.7, 36.5 (t, J = 19.9 Hz), 34.5, 33.5, 33.2, 32.5, 32.3, 29.7;

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.4 (s, 3F), −116.2 – −118.3 (m, 2F);

FT-IR (film) 2934, 2843, 1455, 1201, 1108, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{21}F_5O$: 336, found: 336.



2-(4,4,5,5,5-Pentafluoro-3-phenethylpentyl)-1,3-dioxolane (Table 3.3, Entry 3). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,5-pentafluoropentyl)benzene (254 mg, 0.80 mmol) and an alkylzinc

bromide reagent prepared from 2-(2-bromoethyl)-1,3-dioxolane. Solvent system for chromatography: 10:1 → 4:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 166 mg (61% yield); Run 2, 161 mg (60% yield).

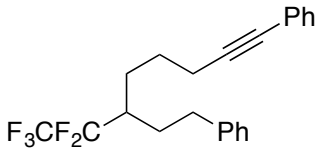
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 4.86 (t, 1H, J = 4.3 Hz), 4.02 – 3.94 (m, 2H), 3.91 – 3.83 (m, 2H), 2.75 (ddd, 1H, J = 13.8, 10.6, 5.7 Hz), 2.67 (ddd, 1H, J = 13.7, 10.4, 6.2 Hz), 2.29 – 2.16 (m, 1H), 2.02 (ddt, 1H, J = 19.6, 10.8, 5.1 Hz), 1.92 – 1.62 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 128.5, 128.3, 126.2, 121.2 – 116.1 (m), 103.9, 64.97, 64.94, 39.6 (t, J = 19.9 Hz), 32.8, 30.6, 28.5, 20.7;

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.7 (s, 3F), −117.1 (d, 2F, J = 16.1 Hz);

FT-IR (film) 2958, 2885, 1203, 1143, 1096, 1008, 700 cm^{-1};

GC-MS (EI) m/z (M^+) calcd for $C_{16}H_{19}F_5O_2$: 338, found: 338.



(6-(Perfluoroethyl)oct-1-yne-1,8-diyl)dibenzene (Table 3.3, Entry 4). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,5-pentafluoropentyl)benzene (254 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (5-bromopent-1-yn-1-yl)benzene. Solvent system for chromatography: 20:1 → 15:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 173 mg (57% yield); Run 2, 183 mg (60% yield).

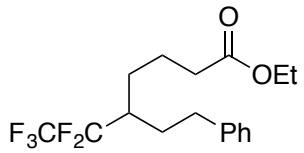
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.33 – 7.28 (m, 5H), 7.25 – 7.18 (m, 3H), 2.82 – 2.67 (m, 2H), 2.44 (t, 2H, *J* = 6.6 Hz), 2.27 – 2.14 (m, 1H), 2.06 (dddd, 1H, *J* = 14.8, 10.7, 6.4, 4.4 Hz), 1.93 (ddt, 1H, *J* = 13.0, 8.2, 4.1 Hz), 1.86 – 1.62 (m, 4H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 131.5, 128.5, 128.3, 128.2, 127.7, 126.2, 123.7, 121.5 – 115.0 (m), 89.1, 81.4, 39.5 (t, *J* = 20.0 Hz), 32.9, 28.5, 25.9, 25.7, 19.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.7 (s, 3F), −117.0 (d, 2F, *J* = 16.2 Hz);

FT-IR (film) 3028, 2959, 1490, 1454, 1202, 1171, 1122, 1094, 1008, 756, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{22}H_{21}F_5$: 380, found: 380.



Ethyl 6,6,7,7,7-pentafluoro-5-phenethylheptanoate (Table 3.3, Entry 5). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,5-pentafluoropentyl)benzene (254 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from ethyl 4-bromobutanoate. Solvent system for chromatography: 2:1 → 1:1.5 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 192 mg (68% yield); Run 2, 180 mg (64% yield).

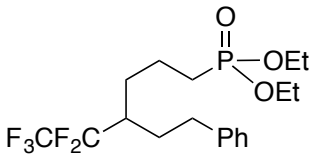
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 4.15 (q, 2H, *J* = 7.1 Hz), 2.78 – 2.64 (m, 2H), 2.31 (t, 2H, *J* = 6.8 Hz), 2.21 – 2.08 (m, 1H), 2.06 – 1.99 (m, 1H), 1.85 – 1.51 (m, 5H), 1.27 (t, 3H, *J* = 7.1 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 141.0, 128.5, 128.3, 126.2, 121.1 – 114.8 (m), 60.4, 39.7 (t, J = 20.0 Hz), 34.1, 32.9, 28.5, 26.2, 22.0, 14.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.7 (s, 3F), −117.1 (d, 2F, J = 16.2 Hz);

FT-IR (film) 2963, 1735, 1201, 1123, 1095, 1007, 753, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{21}F_5O_2$: 352, found: 352.



Diethyl (5,5,6,6,6-pentafluoro-4-phenethylhexyl)phosphonate (Table 3.3, Entry 6). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,5-pentafluoropentyl)benzene (254 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from diethyl (3-bromopropyl)phosphonate. Solvent system for chromatography: 1:1 → 1:2.5 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 237 mg (71% yield); Run 2, 230 mg (69% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.15 (m, 3H), 4.16 – 4.03 (m, 4H), 2.75 – 2.63 (m, 2H), 2.17 – 2.07 (m, 1H), 2.05 – 1.96 (m, 1H), 1.84 – 1.56 (m, 7H), 1.32 (t, 6H, J = 7.1 Hz);

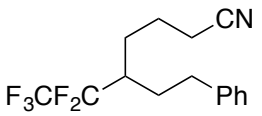
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9, 128.5, 128.3, 126.2, 121.2 – 114.7 (m), 61.6 (d, J = 6.6 Hz), 39.7 (t, J = 20.0 Hz), 32.9, 28.5, 27.6 (d, J = 16.7 Hz), 25.7 (d, J = 141.8 Hz), 20.0 (d, J = 4.9 Hz), 16.4 (d, J = 6.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.7 (s, 3F), −116.9 (t, 2F, J = 16.9 Hz);

^{31}P NMR (121 MHz, $CDCl_3$) δ 31.2;

FT-IR (film) 2981, 1244, 1203, 1169, 1058, 1031, 960, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{26}F_5O_3P$: 416, found: 416.



6,6,7,7,7-Pentafluoro-5-phenethylheptanenitrile (Table 3.3, Entry 7). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,5-pentafluoropentyl)benzene (254 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-bromobutanenitrile. Solvent system for chromatography: 10:1 → 3:1 hexane/ethyl acetate. The title compound was isolated as a yellow oil.

Run 1, 190 mg (78% yield); Run 2, 183 mg (75% yield).

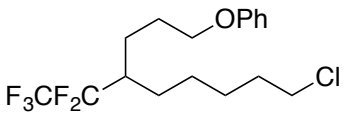
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.25 – 7.21 (m, 1H), 7.20 – 7.17 (m, 2H), 2.80 – 2.64 (m, 2H), 2.35 – 2.29 (m, 2H), 2.22 – 2.02 (m, 2H), 1.90 – 1.64 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 128.6, 128.3, 126.4, 120.5 – 114.8 (m), 118.9, 39.3 (t, J = 20.1 Hz), 32.8, 28.3, 26.0, 22.6, 17.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.7 (s, 3F), −116.3 (dd, 1F, J = 274.0, 15.2 Hz), −117.6 (dd, 1F, J = 273.9, 16.4 Hz);

FT-IR (film) 2952, 2247, 1497, 1455, 1335, 1203, 1173, 1124, 1096, 1007, 753, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{15}H_{16}F_5N$: 305, found: 305.



((9-Chloro-4-(perfluoroethyl)nonyl)oxy)benzene (Table 3.3, Entry 8). The title compound was prepared according to the General Procedure with 3-bromo-8-chloro-1,1,1,2,2-pentafluorooctane (254 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 10:1 → 8:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 188 mg (63% yield); Run 2, 192 mg (64% yield).

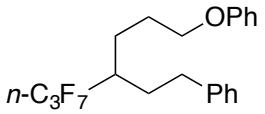
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 6.97 – 6.94 (m, 1H), 6.92 – 6.88 (m, 2H), 4.01 – 3.94 (m, 2H), 3.53 (t, 2H, J = 6.6 Hz), 2.23 – 2.12 (m, 1H), 1.95 – 1.62 (m, 7H), 1.56 – 1.33 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 129.5, 120.8, 119.6 – 115.9 (m), 114.4, 67.2, 44.9, 40.2 (t, J = 19.8 Hz), 32.3, 26.9, 26.6, 26.5, 26.1, 23.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.7 (s, 3F), −117.2 (dd, 2F, J = 16.2, 13.2 Hz);

FT-IR (film) 2954, 2871, 1601, 1587, 1498, 1471, 1246, 1202, 1018, 755, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{22}ClF_5O$: 372, found: 372.



(4,4,5,5,6,6,6-Heptafluoro-3-(3-phenoxypropyl)hexyl)benzene (Table 3.4, Entry 1). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,6,6,6-heptafluorohexyl)benzene (294 mg, 0.80 mmol) and an alkylzinc

bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 10:1 → 3:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 220 mg (65% yield); Run 2, 220 mg (65% yield).

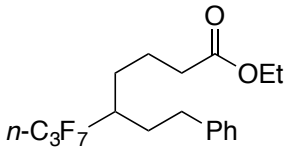
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 4H), 7.25 – 7.17 (m, 3H), 6.99 – 6.95 (m, 1H), 6.93 – 6.89 (m, 2H), 3.99 – 3.94 (m, 2H), 2.79 (ddd, 1H, *J* = 13.8, 10.4, 5.7 Hz), 2.70 (ddd, 1H, *J* = 13.7, 10.2, 6.2 Hz), 2.39 – 2.24 (m, 1H), 2.14 – 2.04 (m, 1H), 2.00 – 1.72 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 141.0, 129.5, 128.6, 128.4, 126.2, 121.1 – 109.7 (m), 120.8, 114.4, 67.2, 39.9 (t, *J* = 20.1 Hz), 32.9, 28.5, 26.3, 23.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.7 (t, 3F, *J* = 11.0 Hz), −114.1 – −114.4 (m, 2F), −124.6 – −124.8 (m, 2F);

FT-IR (film) 3029, 2952, 1601, 1498, 1226, 1173, 1111, 753, 699, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{21}H_{21}F_7O$: 422, found: 422.



Ethyl 6,6,7,7,8,8,8-heptafluoro-5-phenethyloctanoate (Table 3.4, Entry 2). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,6,6,6-heptafluorohexyl)benzene (294 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from ethyl 4-bromobutanoate. Solvent system for chromatography: 2:1 → 1:1.5 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 174 mg (54% yield); Run 2, 174 mg (54% yield).

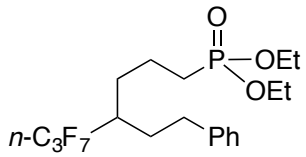
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 4.15 (q, 2H, *J* = 7.1 Hz), 2.79 – 2.64 (m, 2H), 2.31 (t, 2H, *J* = 6.7 Hz), 2.28 – 2.18 (m, 1H), 2.09 – 2.00 (m, 1H), 1.86 – 1.53 (m, 5H), 1.27 (t, 3H, *J* = 7.1 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 141.0, 128.5, 128.3, 126.2, 121.9 – 107.1 (m), 60.4, 40.1 (t, *J* = 20.0 Hz), 34.1, 32.9, 28.5, 26.1, 22.0, 14.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (t, 3F, *J* = 11.0 Hz), −114.1 – −114.4 (m, 2F), −124.7 – −124.8 (m, 2F);

FT-IR (film) 2963, 1736, 1225, 1178, 1107, 748, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{21}F_7O_2$: 402, found: 402.



Diethyl (5,5,6,6,7,7,7-heptafluoro-4-phenethylheptyl)phosphonate (Table 3.4, Entry 3). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,6,6,6-heptafluorohexyl)benzene (294 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from diethyl (3-bromopropyl)phosphonate. Solvent system for chromatography: 1:1 → 1:2.5 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 186 mg (50% yield); Run 2, 190 mg (51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.15 (m, 3H), 4.16 – 4.03 (m, 4H), 2.77 – 2.62 (m, 2H), 2.28 – 2.14 (m, 1H), 2.08 – 1.98 (m, 1H), 1.88 – 1.59 (m, 7H), 1.32 (t, 6H, *J* = 7.1 Hz);

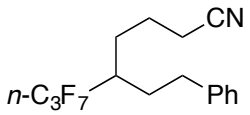
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9, 128.5, 128.3, 126.2, 121.7 – 107.0 (m), 61.6 (d, J = 6.5 Hz), 40.1 (t, J = 20.0 Hz), 32.9, 28.5, 27.6 (d, J = 17.0 Hz), 25.7 (d, J = 141.8 Hz), 19.9 (d, J = 4.8 Hz), 16.4 (d, J = 6.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (t, 3F, J = 11.0 Hz), −114.0 – −114.3 (m, 2F), −124.6 – −124.8 (m, 2F);

^{31}P NMR (121 MHz, $CDCl_3$) δ 31.2;

FT-IR (film) 2981, 1349, 1231, 1176, 1103, 1059, 1031, 958, 749, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{26}F_7O_3P$: 466, found: 466.



6,6,7,7,8,8,8-Heptafluoro-5-phenethyloctanenitrile (Table 3.4, Entry 4). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,6,6,6-heptafluorohexyl)benzene (294 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-bromobutanenitrile. Solvent system for chromatography: 10:1 → 4:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 200 mg (70% yield); Run 2, 190 mg (67% yield).

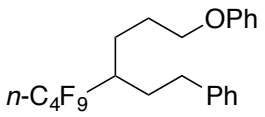
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.27 – 7.16 (m, 3H), 2.81 – 2.65 (m, 2H), 2.37 – 2.18 (m, 3H), 2.13 – 2.06 (m, 1H), 1.92 – 1.66 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 128.6, 128.3, 126.4, 121.7 – 107.5 (m), 118.9, 39.6 (t, J = 20.3 Hz), 32.9, 28.3, 26.0, 22.6, 17.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.7 (t, 3F, J = 11.0 Hz), −114.0 – −114.4 (m, 2F), −124.6 – −124.9 (m, 2F);

FT-IR (film) 2952, 2247, 1497, 1455, 1350, 1225, 1176, 1108, 748, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{16}F_7N$: 355, found: 355.



(4,4,5,5,6,6,7,7,7-Nonafluoro-3-(3-phenoxypropyl)heptyl)benzene (Table 3.4, Entry 5). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,6,6,7,7,7-nonafluoroheptyl)benzene (334 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: hexane → 4:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 255 mg (67% yield); Run 2, 250 mg (66% yield).

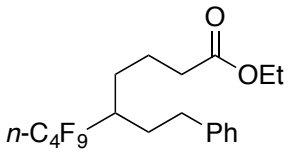
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.25 – 7.17 (m, 3H), 6.99 – 6.95 (m, 1H), 6.93 – 6.89 (m, 2H), 4.00 – 3.94 (m, 2H), 2.81 – 2.67 (m, 2H), 2.39 – 2.28 (m, 1H), 2.14 – 2.04 (m, 1H), 2.01 – 1.71 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 141.0, 129.5, 128.6, 128.3, 126.2, 121.9 – 116.0 (m), 120.8, 114.4, 67.2, 40.1 (t, J = 20.2 Hz), 32.9, 28.5, 26.3, 23.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 – −81.0 (m, 3F), −113.5 – −113.8 (m, 2F), −121.3 – −121.6 (m, 2F), −126.0 – −126.2 (m, 2F);

FT-IR (film) 3029, 2952, 1601, 1498, 1236, 1172, 1133, 752, 699, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{22}H_{21}F_9O$: 472, found: 472.



Ethyl 6,6,7,7,8,8,9,9,9-nonafluoro-5-phenethylnonanoate (Table 3.4, Entry 6). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,6,6,7,7,7-nonafluoroheptyl)benzene (334 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from ethyl 4-bromobutanoate. Solvent system for chromatography: hexane → 1:1.5 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 200 mg (55% yield); Run 2, 188 mg (52% yield).

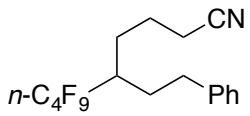
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 4.15 (q, 2H, J = 7.2 Hz), 2.78 – 2.65 (m, 2H), 2.34 – 2.18 (m, 3H), 2.10 – 2.00 (m, 1H), 1.86 – 1.54 (m, 5H), 1.27 (t, 3H, J = 7.1 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 141.0, 128.5, 128.3, 126.2, 121.8 – 115.4 (m), 60.4, 40.3 (t, J = 20.2 Hz), 34.1, 32.9, 28.5, 26.1, 22.0, 14.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 – −81.0 (m, 3F), −113.6 – −113.9 (m, 2F), −121.4 – −121.6 (m, 2F), −126.0 – −126.3 (m, 2F);

FT-IR (film) 2963, 1735, 1235, 1133, 750, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{21}F_9O_2$: 452, found: 452.



6,6,7,7,8,8,9,9,9-Nonafluoro-5-phenethylnonanenitrile (Table 3.4, Entry 7). The title compound was prepared according to the General Procedure A with (3-bromo-

4,4,5,5,6,6,7,7,7-nonafluoroheptyl)benzene (334 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-bromobutanenitrile. Solvent system for chromatography: hexane → 4:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 221 mg (68% yield); Run 2, 227 mg (70% yield).

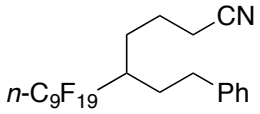
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.26 – 7.21 (m, 1H), 7.21 – 7.17 (m, 2H), 2.80 – 2.65 (m, 2H), 2.37 – 2.21 (m, 3H), 2.15 – 2.05 (m, 1H), 1.92 – 1.66 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 128.7, 128.3, 126.4, 121.6 – 116.0 (m), 118.9, 39.8 (t, J = 20.3 Hz), 32.9, 28.3, 26.0, 22.6, 17.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 – −81.0 (m, 3F), −113.4 – −113.8 (m, 2F), −121.3 – −121.6 (m, 2F), −126.0 – −126.2 (m, 2F);

FT-IR (film) 2952, 2247, 1354, 1235, 1133, 1019, 750, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{16}F_9N$: 405, found: 405.



6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,14-Nonadecafluoro-5-phenethyltetradecanenitrile (Table 3.4, Entry 8). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-nonadecafluorododecyl)benzene (534 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-bromobutanenitrile.

Solvent system for chromatography: hexane → 4:1 hexane/ethyl acetate. The title compound was isolated as a colorless viscous oil.

Run 1, 340 mg (65% yield); Run 2, 351 mg (67% yield).

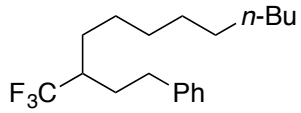
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.25 – 7.17 (m, 3H), 2.81 – 2.65 (m, 2H), 2.37 – 2.21 (m, 3H), 2.14 – 2.06 (m, 1H), 1.92 – 1.66 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 128.7, 128.3, 126.4, 120.2 – 105.1 (m), 118.9, 40.0 (t, J = 20.2 Hz), 32.9, 28.4, 26.0, 22.6, 17.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (t, 3F, J = 10.0 Hz), −113.2 – −113.6 (m, 2F), −120.3 – −120.7 (m, 2F), −121.5 – −122.2 (m, 8F), −122.6 – −123.0 (m, 2F), −126.0 – 126.4 (m, 2F);

FT-IR (film) 2954, 2247, 1497, 1455, 1209, 1100, 739, 702, 658 cm^{-1};

GC-MS (EI) *m/z* (M^+−C_9F_{19}) calcd for $C_{13}H_{16}N$: 186, found: 186.



(3-(Trifluoromethyl)dodecyl)benzene (Table 3.5, Entry 1). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 1-bromononane. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 199 mg (79% yield); Run 2, 197 mg (78% yield).

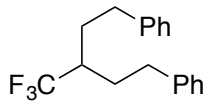
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.24 – 7.18 (m, 3H), 2.71 (t, 2H, *J* = 8.2 Hz), 2.12 – 2.01 (m, 1H), 1.99 – 1.89 (m, 1H), 1.80 – 1.71 (m, 1H), 1.68 – 1.59 (m, 1H), 1.52 – 1.22 (m, 15H), 0.90 (t, 3H, *J* = 6.9 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 128.7 (q, *J* = 280.4 Hz), 128.5, 128.4, 126.1, 41.9 (q, *J* = 24.8 Hz), 33.1, 31.9, 29.64, 29.61, 29.5, 29.4, 29.3, 27.8 (q, *J* = 2.3 Hz), 26.7, 22.7, 14.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (d, 3F, *J* = 9.5 Hz);

FT-IR (film) 2926, 2855, 1455, 1260, 1153, 1129, 1104, 746, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{29}F_3$: 314, found: 314.



(3-(Trifluoromethyl)pentane-1,5-diyl)dibenzene (Table 3.5, Entry 2). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (2-bromoethyl)benzene. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 182 mg (78% yield); Run 2, 182 mg (78% yield).

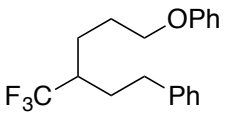
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 4H), 7.26 – 7.21 (m, 2H), 7.19 – 7.15 (m, 4H), 2.77 – 2.65 (m, 4H), 2.19 – 2.08 (m, 1H), 2.00 (dddd, 2H, *J* = 14.8, 9.2, 6.8, 5.7 Hz), 1.82 (ddt, 2H, *J* = 13.7, 9.4, 6.7 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 128.58 (q, *J* = 281.1 Hz), 128.53, 128.4, 126.2, 41.2 (q, *J* = 25.0 Hz), 32.9, 29.7 (d, *J* = 2.4 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, *J* = 9.4 Hz);

FT-IR (film) 3027, 2937, 1497, 1454, 1260, 1145, 1113, 747, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{19}F_3$: 292, found: 292.



(6-Phenoxy-3-(trifluoromethyl)hexyl)benzene (Table 3.5, Entry 3). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 6:1 → 5:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 213 mg (83% yield); Run 2, 213 mg (83% yield).

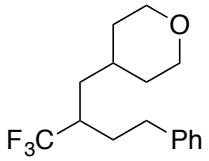
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.25 – 7.18 (m, 3H), 6.99 – 6.96 (m, 1H), 6.93 – 6.89 (m, 2H), 3.96 (t, 2H, *J* = 5.9 Hz), 2.81 – 2.69 (m, 2H), 2.21 – 2.13 (m, 1H), 2.01 (dddd, 1H, *J* = 14.2, 9.4, 6.7, 5.6 Hz), 1.93 – 1.69 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 141.1, 129.5, 128.54 (q, *J* = 280.3 Hz), 128.52, 128.4, 126.2, 120.7, 114.4, 67.2, 41.6 (q, *J* = 25.1 Hz), 32.9, 29.5 (q, *J* = 2.4 Hz), 26.4, 24.4 (q, *J* = 2.5 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (d, 3F, *J* = 9.4 Hz);

FT-IR (film) 2953, 2874, 1601, 1497, 1246, 1152, 1120, 754, 700, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{21}F_3O$: 322, found: 322.



4-(4-Phenyl-2-(trifluoromethyl)butyl)tetrahydro-2*H*-pyran (Table 3.5, Entry 4). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-(bromomethyl)tetrahydro-2*H*-pyran. Solvent system for chromatography: 12:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 167 mg (73% yield); Run 2, 169 mg (74% yield).

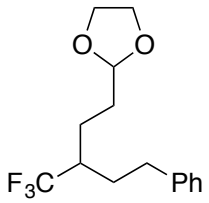
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 3.97 – 3.87 (m, 2H), 3.35 (td, 1H, *J* = 11.8, 2.1 Hz), 3.27 (td, 1H, *J* = 11.8, 2.3 Hz), 2.78 – 2.65 (m, 2H), 2.19 – 2.09 (m, 1H), 1.98 (ddt, 1H, *J* = 14.3, 9.2, 6.2 Hz), 1.74 – 1.66 (m, 1H), 1.59 – 1.51 (m, 3H), 1.40 – 1.12 (m, 4H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 128.6 (q, *J* = 280.2 Hz), 128.5, 128.4, 126.2, 67.82, 67.76, 38.4 (q, *J* = 25.0 Hz), 35.4 (q, *J* = 2.3 Hz), 33.2, 33.0, 32.7, 32.3, 30.2 (q, *J* = 2.3 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.3 (d, 3F, *J* = 9.2 Hz);

FT-IR (film) 2935, 2842, 1261, 1239, 1160, 1134, 1105, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{21}F_3O$: 286, found: 286.



2-(5-Phenyl-3-(trifluoromethyl)pentyl)-1,3-dioxolane (Table 3.5, Entry 5). The title compound was prepared according to the General Procedure A with (3-bromo-

4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 2-(2-bromoethyl)-1,3-dioxolane. Solvent system for chromatography: 10:1 → 6:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 163 mg (71% yield); Run 2, 166 mg (72% yield).

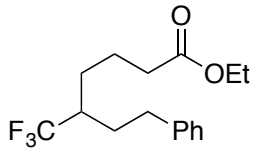
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.23 – 7.17 (m, 3H), 4.85 (t, 1H, J = 4.2 Hz), 4.01 – 3.93 (m, 2H), 3.90 – 3.82 (m, 2H), 2.78 – 2.66 (m, 2H), 2.21 – 2.09 (m, 1H), 1.96 (dddd, 1H, J = 14.3, 9.5, 6.8, 5.7 Hz), 1.83 – 1.70 (m, 4H), 1.69 – 1.62 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 128.49, 128.48 (q, J = 280.5 Hz), 128.3, 126.1, 103.9, 64.95, 64.92, 41.6 (q, J = 25.1 Hz), 32.8, 30.7, 29.5 (q, J = 2.3 Hz), 21.8 (q, J = 2.6 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (d, 3F, J = 9.4 Hz);

FT-IR (film) 2955, 2881, 1454, 1396, 1263, 1145, 1116, 1031, 749, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{15}H_{19}F_3O_2$: 288, found: 288.



Ethyl 7-phenyl-5-(trifluoromethyl)heptanoate (Table 3.5, Entry 6). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from ethyl 4-bromobutanoate. Solvent system for chromatography: 2:1 → 1:1.5 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 198 mg (82% yield); Run 2, 200 mg (83% yield).

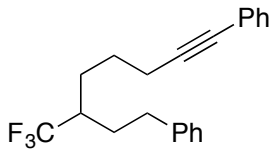
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 4.15 (q, 2H, *J* = 7.1 Hz), 2.74 – 2.68 (m, 2H), 2.30 (t, 2H, *J* = 7.0 Hz), 2.13 – 2.04 (m, 1H), 2.01 – 1.92 (m, 1H), 1.81 – 1.62 (m, 4H), 1.56 – 1.49 (m, 1H), 1.27 (t, 3H, *J* = 7.1 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 141.1, 128.5, 128.4 (q, *J* = 280.4 Hz), 128.3, 126.2, 60.4, 41.7 (q, *J* = 25.0 Hz), 34.1, 32.9, 29.4 (q, *J* = 2.4 Hz), 27.2 (q, *J* = 2.5 Hz), 22.0, 14.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (d, 3F, *J* = 9.4 Hz);

FT-IR (film) 2942, 1734, 1262, 1184, 1147, 1114, 748, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{21}F_3O_2$: 302, found: 302.



(6-(Trifluoromethyl)oct-1-yne-1,8-diyl)dibenzene (Table 3.5, Entry 7). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (5-bromopent-1-yn-1-yl)benzene. Solvent system for chromatography: 20:1 → 15:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 175 mg (66% yield); Run 2, 176 mg (67% yield).

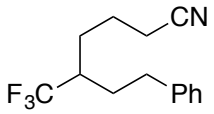
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.33 – 7.27 (m, 5H), 7.24 – 7.18 (m, 3H), 2.81 – 2.69 (m, 2H), 2.43 (t, 2H, *J* = 6.6 Hz), 2.21 – 2.08 (m, 1H), 2.00 (dddd, 1H, *J* = 14.2, 9.5, 6.8, 5.6 Hz), 1.89 – 1.66 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 131.5, 128.52 (q, J = 280.4 Hz), 128.51, 128.3, 128.2, 127.7, 126.2, 123.7, 89.2, 81.3, 41.5 (q, J = 25.0 Hz), 32.9, 29.5 (q, J = 2.4 Hz), 26.9 (q, J = 2.4 Hz), 25.7, 19.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (d, 3F, J = 9.4 Hz);

FT-IR (film) 2951, 1490, 1262, 1146, 1114, 756, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{21}H_{21}F_3$: 330, found: 330.



7-Phenyl-5-(trifluoromethyl)heptanenitrile (Table 3.5, Entry 8). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-bromobutanenitrile. Solvent system for chromatography: 10:1 → 4:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 170 mg (83% yield); Run 2, 170 mg (83% yield).

This compound was also prepared on a 6.00 mmol scale (eq 3.4), using (3-bromo-4,4,4-trifluorobutyl)benzene (1.60 g, 6.00 mmol) and an alkylzinc bromide reagent prepared from 4-bromobutanenitrile (0.50 M; 14.4 mL, 7.20 mmol; 1.20 equiv). Following the General Procedure A using 5.0% $NiCl_2$·glyme (65.9 mg, 0.300 mmol) and 5.5% ligand **1** (99.5 mg, 0.330 mmol), the title compound was isolated in 80% yield (1.22 g).

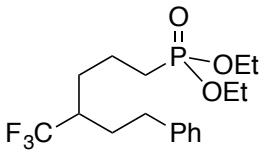
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.25 – 7.18 (m, 3H), 2.79 – 2.68 (m, 2H), 2.32 (t, 2H, *J* = 6.8 Hz), 2.15 – 2.06 (m, 1H), 2.02 (dddd, 1H, *J* = 14.5, 8.9, 6.9, 5.6 Hz), 1.82 – 1.62 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 128.6, 128.3, 128.1 (q, *J* = 280.3 Hz), 126.3, 119.0, 41.2 (q, *J* = 25.3 Hz), 32.8, 29.4 (q, *J* = 2.4 Hz), 26.9 (q, *J* = 2.5 Hz), 22.6, 17.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, *J* = 9.1 Hz);

FT-IR (film) 3028, 2946, 2877, 2247, 1497, 1462, 1455, 1396, 1263, 1195, 1149, 1115, 1031, 751, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{14}H_{16}F_3N$: 255, found: 255.



Diethyl (6-phenyl-4-(trifluoromethyl)hexyl)phosphonate (Table 3.5, Entry 9). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (214 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from diethyl (3-bromopropyl)phosphonate. Solvent system for chromatography: 4:1 → 1:3 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 258 mg (88% yield); Run 2, 260 mg (89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 4.15 – 4.02 (m, 4H), 2.70 (t, 2H, *J* = 8.1 Hz), 2.10 – 2.02 (m, 1H), 1.94 (dddd, 1H, *J* = 14.4, 8.7, 7.3, 5.8 Hz), 1.78 – 1.52 (m, 7H), 1.31 (t, 6H, *J* = 7.1 Hz);

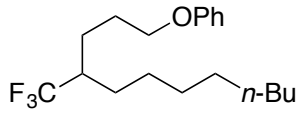
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9, 128.5, 128.34 (q, J = 280.3 Hz), 128.28, 126.2, 61.5 (d, J = 6.5 Hz), 41.6 (q, J = 25.4 Hz), 32.9, 29.4 (d, J = 2.3 Hz), 28.6 (dd, J = 16.7, 2.4 Hz), 25.6 (d, J = 141.8 Hz), 19.9 (d, J = 4.8 Hz), 16.4 (d, J = 5.9 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (d, 3F, J = 9.3 Hz);

^{31}P NMR (121 MHz, $CDCl_3$) δ 31.3;

FT-IR (film) 2981, 2940, 1257, 1161, 1107, 1058, 1030, 960, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{26}F_3O_3P$: 366, found: 366.



((4-(Trifluoromethyl)dodecyl)oxy)benzene (Table 3.6, Entry 1). The title compound was prepared according to the General Procedure A with 2-bromo-1,1,1-trifluorodecane (220 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: hexane → 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 225 mg (85% yield); Run 2, 230 mg (87% yield).

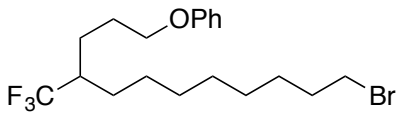
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 6.97 – 6.93 (m, 1H), 6.92 – 6.88 (m, 2H), 3.97 (t, 2H, J = 6.1 Hz), 2.10 (dddd, 1H, J = 15.7. 9.6, 6.4, 3.6 Hz), 1.94 – 1.84 (m, 2H), 1.83 – 1.73 (m, 1H), 1.71 – 1.59 (m, 2H), 1.50 – 1.23 (m, 13H), 0.90 (t, 3H, J = 6.9 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 129.4, 128.6 (q, J = 280.4 Hz), 120.7, 114.4, 67.4, 42.3 (q, J = 24.8 Hz), 31.8, 29.7, 29.4, 29.2, 27.8 (q, J = 2.4 Hz), 26.8, 26.6, 24.5 (q, J = 2.3 Hz), 22.7, 14.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.1 (d, 3F, J = 9.5 Hz);

FT-IR (film) 2927, 2856, 1601, 1498, 1245, 1160, 1133, 753, 691 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{29}F_3O$: 330, found: 330.



((12-Bromo-4-(trifluoromethyl)dodecyl)oxy)benzene (Table 3.6, Entry 2). The title compound was prepared according to the General Procedure A with 2,10-dibromo-1,1,1-trifluorodecane (283 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 10:1 → 6:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 259 mg (79% yield); Run 2, 260 mg (79% yield).

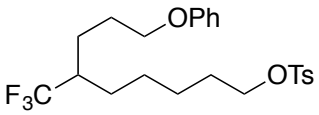
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 6.97 – 6.93 (m, 1H), 6.92 – 6.88 (m, 2H), 3.97 (t, 2H, J = 6.1 Hz), 3.41 (t, 2H, J = 6.8 Hz), 2.11 (ddtd, 1H, J = 15.6, 9.6, 5.9, 3.4 Hz), 1.92 – 1.73 (m, 5H), 1.71 – 1.59 (m, 2H), 1.51 – 1.25 (m, 11H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 129.4, 128.6 (q, J = 280.5 Hz), 120.7, 114.4, 67.3, 42.3 (q, J = 24.8 Hz), 34.0, 32.8, 29.5, 29.2, 28.7, 28.1, 27.8 (q, J = 2.5 Hz), 26.7, 26.6, 24.4 (q, J = 2.5 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.1 (d, 3F, J = 9.5 Hz);

FT-IR (film) 2931, 2856, 1601, 1498, 1245, 1162, 1121, 754, 691 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{28}{}^{79}BrF_3O$: 408, found: 408, 410 ($M^+$+2).



9-Phenoxy-6-(trifluoromethyl)nonyl 4-methylbenzenesulfonate (Table 3.6, Entry 3). The title compound was prepared according to the General Procedure A with 6-bromo-7,7,7-trifluoroheptyl 4-methylbenzenesulfonate (322 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 10:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 275 mg (75% yield); Run 2, 278 mg (76% yield).

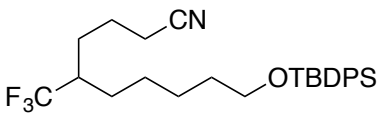
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 2H), 7.36 – 7.32 (m, 2H), 7.31 – 7.25 (m, 2H), 6.96 – 6.92 (m, 1H), 6.91 – 6.86 (m, 2H), 4.03 – 3.92 (m, 4H), 2.44 (s, 3H), 2.15 – 2.00 (m, 1H), 1.90 – 1.80 (m, 2H), 1.79 – 1.71 (m, 1H), 1.69 – 1.53 (m, 4H), 1.46 – 1.25 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 144.7, 133.1, 129.8, 129.4, 128.4 (q, J = 281.0 Hz), 127.8, 120.7, 114.4, 70.3, 67.2, 42.2 (q, J = 24.8 Hz), 28.6, 27.6 (d, J = 2.7 Hz), 26.5, 26.1, 25.5, 24.4 (d, J = 2.7 Hz), 21.6;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.0 (d, 3F, J = 9.5 Hz);

FT-IR (film) 2946, 1600, 1498, 1360, 1246, 1189, 1177, 1157, 955, 815, 756, 664 cm^{-1};

LC-MS (ESI) *m/z* ($M+H^+$) calcd for $C_{23}H_{30}F_3O_4S$: 459, found: 459.



10-((*tert*-Butyldiphenylsilyl)oxy)-5-(trifluoromethyl)decanenitrile (Table 3.6, Entry 4). The title compound was prepared according to the General Procedure A with ((6-bromo-7,7,7-trifluoroheptyl)oxy)(*tert*-butyl)diphenylsilane (390 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-bromobutanenitrile. Solvent system for chromatography: 10:1 → 8:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 268 mg (70% yield); Run 2, 281 mg (74% yield).

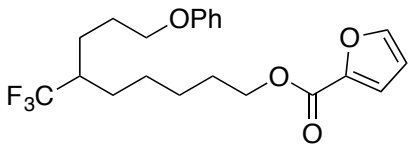
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.46 – 7.37 (m, 6H), 3.68 (t, 2H, J = 6.3 Hz), 2.38 – 2.33 (m, 2H), 2.08 – 2.01 (m, 1H), 1.83 – 1.68 (m, 3H), 1.68 – 1.54 (m, 4H), 1.44 – 1.33 (m, 5H), 1.06 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 134.0, 129.5, 128.2 (q, J = 280.3 Hz), 127.6, 119.0, 63.7, 42.1 (q, J = 25.2 Hz), 32.2, 27.7 (q, J = 2.4 Hz), 27.1 (q, J = 2.4 Hz), 26.8, 26.5, 25.8, 22.8, 19.2, 17.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (d, 3F, J = 9.3 Hz);

FT-IR (film) 2933, 2858, 2247, 1428, 1258, 1153, 1112, 703 cm^{-1};

GC-MS (EI) *m/z* (M^+−C_4H_9) calcd for $C_{23}H_{27}F_3NOSi$: 418, found: 418.



9-Phenoxy-6-(trifluoromethyl)nonyl furan-2-carboxylate (Table 3.6, Entry 5). The title compound was prepared according to the General Procedure A with 6-bromo-7,7,7-trifluoroheptyl furan-2-carboxylate (274 mg, 0.80 mmol) and an alkylzinc bromide

reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 20:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 267 mg (84% yield); Run 2, 258 mg (81% yield).

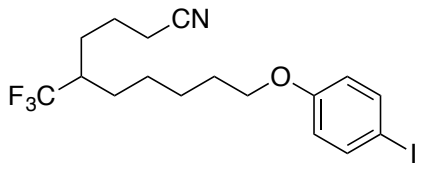
^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.80 (dd, 1H, *J* = 1.8, 0.8 Hz), 7.30 – 7.25 (m, 2H), 7.22 (dd, 1H, *J* = 3.5, 0.9 Hz), 6.96 – 6.89 (m, 3H), 6.63 (dd, 1H, *J* = 3.5, 1.8 Hz), 4.27 (t, 2H, *J* = 6.6 Hz), 4.03 (t, 2H, *J* = 6.1 Hz), 2.38 – 2.25 (m, 1H), 1.94 – 1.64 (m, 7H), 1.60 – 1.43 (m, 5H);

^{13}C NMR (126 MHz, CD_3COCD_3) δ 160.1, 159.1, 147.9, 146.0, 130.4, 130.1 (q, *J* = 279.8 Hz), 121.5, 118.7, 115.5, 112.9, 68.2, 65.4, 43.0 (q, *J* = 24.6 Hz), 29.4, 28.6 (q, *J* = 2.5 Hz), 27.4, 27.3, 26.9, 25.3 (q, *J* = 2.7 Hz);

^{19}F NMR (282 MHz, CD_3COCD_3) δ −70.6 (d, 3F, *J* = 9.9 Hz);

FT-IR (film) 2948, 2871, 1722, 1601, 1586, 1498, 1475, 1398, 1297, 1246, 1180, 1120, 1078, 755, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{21}H_{25}F_3O_4$: 398, found: 398.



10-(4-Iodophenoxy)-5-(trifluoromethyl)decanenitrile (Table 3.6, Entry 6). The title compound was prepared according to the General Procedure A with 1-((6-bromo-7,7,7-trifluoroheptyl)oxy)-4-iodobenzene (361 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from 4-bromobutanenitrile. Solvent system for chromatography: 10:1 → 4:1 hexane/ethyl acetate. The title compound was isolated as a white solid.

Run 1, 283 mg (81% yield); Run 2, 285 mg (81% yield).

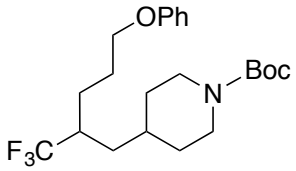
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 6.69 – 6.64 (m, 2H), 3.92 (t, 2H, *J* = 6.3 Hz), 2.40 – 2.35 (m, 2H), 2.14 – 2.02 (m, 1H), 1.84 – 1.59 (m, 7H), 1.51 – 1.41 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 138.1, 128.1 (q, *J* = 280.3 Hz), 119.0, 116.9, 82.5, 67.7, 42.1 (q, *J* = 25.3 Hz), 28.9, 27.7 (q, *J* = 2.4 Hz), 27.1 (q, *J* = 2.4 Hz), 26.5, 26.1, 22.8, 17.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (d, 3F, *J* = 9.3 Hz);

FT-IR (film) 2943, 2246, 1586, 1487, 1244, 1174, 1153, 1125, 821 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{21}F_3INO$: 439, found: 439.



***tert*-Butyl 4-(5-phenoxy-2-(trifluoromethyl)pentyl)piperidine-1-carboxylate (Table 3.6, Entry 7).** The title compound was prepared according to the General Procedure A with *tert*-butyl 4-(2-bromo-3,3,3-trifluoropropyl)piperidine-1-carboxylate (288 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 25:1 → 15:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 267 mg (80% yield); Run 2, 265 mg (80% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.97 – 6.93 (m, 1H), 6.90 – 6.86 (m, 2H), 4.16 – 4.02 (m, 2H), 3.99 – 3.95 (m, 2H), 2.73 – 2.57 (m, 2H), 2.27 – 2.16

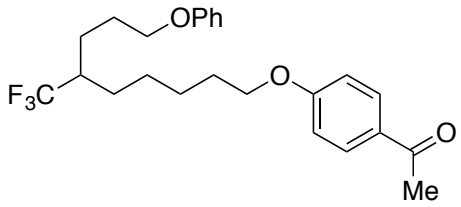
(m, 1H), 1.94 – 1.75 (m, 3H), 1.71 – 1.61 (m, 3H), 1.60 – 1.50 (m, 2H), 1.46 (s, 9H), 1.38 – 1.30 (m, 1H), 1.15 – 1.01 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 154.7, 129.5, 128.5 (q, J = 280.0 Hz), 120.8, 114.4, 79.3, 67.1, 39.2 (q, J = 25.1 Hz), 34.9, 33.4, 32.3, 31.9, 28.4, 26.4, 25.1 (d, J = 2.5 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.4 (d, 3F, J = 9.3 Hz);

FT-IR (film) 2973, 2933, 2870, 1692, 1498, 1424, 1366, 1246, 1171, 1138, 755, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+−Boc) calcd for $C_{17}H_{23}F_3NO$: 314, found: 314.



1-(4-((9-Phenoxy-6-(trifluoromethyl)nonyl)oxy)phenyl)ethan-1-one (Table 3.6, Entry 8). The title compound was prepared according to the General Procedure A with 1-(4-((6-bromo-7,7,7-trifluoroheptyl)oxy)phenyl)ethan-1-one (294 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 10:1 → 4:1 hexane/ethyl acetate. The title compound was isolated as a yellow oil.

Run 1, 291 mg (86% yield); Run 2, 287 mg (85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H), 7.31 – 7.25 (m, 2H), 6.98 – 6.86 (m, 5H), 4.01 (t, 2H, J = 6.4 Hz), 3.96 (t, 2H, J = 6.0 Hz), 2.55 (s, 3H), 2.13 (dddd,

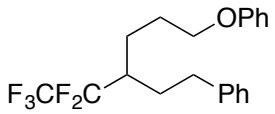
1H, J = 14.7, 8.8, 5.8, 3.1 Hz), 1.93 – 1.74 (m, 5H), 1.72 – 1.62 (m, 2H), 1.57 – 1.42 (m, 5H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 163.0, 158.8, 130.6, 130.2, 129.4, 128.5 (q, J = 280.4 Hz), 120.7, 114.4, 114.1, 67.9, 67.3, 42.2 (q, J = 25.0 Hz), 28.9, 27.7 (d, J = 2.3 Hz), 26.6, 26.5, 26.3, 26.1, 24.5 (d, J = 2.5 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.0 (d, 3F, J = 9.5 Hz);

FT-IR (film) 2945, 1676, 1601, 1254, 1172, 1158, 1124, 834, 755, 692 cm^{-1};

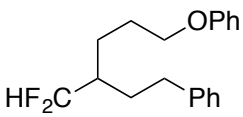
LC-MS (ESI) *m/z* ($M+H^+$) calcd for $C_{24}H_{30}F_3O_3$: 423, found: 423.



((5,5,6,6,6-Pentafluoro-4-phenethylhexyl)oxy)benzene (eq 3.3). The title compound was prepared according to the General Procedure A with (4,4,5,5,5-pentafluoro-3-iodopentyl)benzene (291 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 10:1 → 3:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 186 mg (62% yield); Run 2, 183 mg (61% yield).

For the characterization data, see Table 3.3, Entry 1 (above).



(3-(Difluoromethyl)-6-phenoxyhexyl)benzene (eq 3.5). The title compound was prepared according to General Procedure B with (3-bromo-4,4-difluorobutyl)benzene

(199 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from (3-bromopropoxy)benzene. Solvent system for chromatography: 6:1 → 4:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 170 mg (70% yield); Run 2, 168 mg (69% yield).

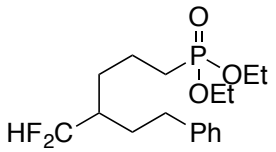
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 4H), 7.24 – 7.18 (m, 3H), 6.97 (tt, 1H, *J* = 7.3, 1.1 Hz), 6.93 – 6.89 (m, 2H), 5.80 (td, 1H, *J* = 56.7, 3.3 Hz), 3,96 (t, 2H, *J* = 6.2 Hz), 2.73 (t, 2H, *J* = 7.9 Hz), 1.97 – 1.83 (m, 4H), 1.79 – 1.70 (m, 2H), 1.67 – 1.60 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 141.6, 129.4, 128.5, 128.3, 126.0, 120.7, 118.8 (t, *J* = 242.6 Hz), 114.4, 67.4, 41.1 (t, *J* = 18.6 Hz), 33.0, 29.5 (t, *J* = 4.4 Hz), 26.5, 24.3 (t, *J* = 4.6 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −122.4 (dd, 2F, *J* = 56.6, 15.5 Hz);

FT-IR (neat) 2948, 1600, 1586, 1497, 1246, 1081, 1037, 754, 692 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{22}F_2O$: 304, found: 304;



Diethyl (4-(difluoromethyl)-6-phenylhexyl)phosphonate (eq 3.6). The title compound was prepared according to General Procedure B with 3-bromo-4,4-difluorobutyl)benzene (199 mg, 0.80 mmol) and an alkylzinc bromide reagent prepared from diethyl (3-bromopropyl)phosphonate. Solvent system for chromatography: 1:2 → 1:3 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 215 mg (77% yield); Run 2, 217 mg (78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 5.74 (td, 1H, *J* = 56.6, 3.2 Hz), 4.15 – 4.02 (m, 4H), 2.67 (t, 2H, *J* = 7.9 Hz), 1.88 – 1.75 (m, 2H), 1.74 – 1.58 (m, 6H), 1.54 – 1.44 (m, 1H), 1.32 (t, 6H, *J* = 7.1 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 128.4, 128.3, 126.0, 118.5 (t, *J* = 242.6 Hz), 61.5 (d, *J* = 6.5 Hz), 41.2 (td, *J* = 18.8, 1.8 Hz), 33.0, 29.4 (t, *J* = 4.3 Hz), 28.6 (dt, *J* = 16.9, 4.5 Hz), 25.8 (d, *J* = 141.3 Hz), 19.9 (d, *J* = 5.0 Hz), 16.4 (d, *J* = 6.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −122.4 – −122.7 (m, 2F);

^{31}P NMR (121 MHz, $CDCl_3$) δ 31.6;

FT-IR (neat) 2981, 2938, 1241, 1054, 1030, 961, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{27}F_2O_3P$: 348, found: 348;

Competition Experiments (Scheme 3.3 and eq 3.7).

In a nitrogen-filled glovebox, $NiCl_2$•glyme (2.2 mg, 0.010 mmol), ligand **L2** (3.3 mg, 0.011 mmol), and NaBr (10.3 mg, 0.10 mmol) were added to an oven-dried 4-mL vial equipped with a stir bar. DMA (0.25 mL) was added to the 4-mL vial, and the vial was closed with a PTFE septum cap. The mixture was vigorously stirred at r.t. for 25 min. Then, a solution in DMA of each of the two alkyl electrophiles (0.10 mmol in 0.25 mL of DMA) was added in turn to the 4-mL vial. The combined mixture was allowed to stir at r.t. for 1 min. Next, the solution of the alkylzinc reagent (0.50 M; 0.24 mL, 0.12 mmol; 1.2 equiv) was added in one portion. The reaction mixture was stirred vigorously at r.t. for 10 min, and then the reaction was quenched with MeOH (0.2 mL). A solution of $PhCF_3$ (0.20 M; 0.50 mL, 0.10 mmol; 1.0 equiv) in $CDCl_3$ was added to the vial as an internal standard, and the reaction mixture was analyzed by ^{19}F NMR spectroscopy.

When (3-bromobutyl)benzene was used as the electrophile, *n*-tetradecane (26 μL) was added to the vial as another internal standard, and the reaction mixture was also analyzed by GC.

Study of the effect of TEMPO:

Eq 3.8, without TEMPO: In a nitrogen-filled glovebox, $NiCl_2$•glyme (2.2 mg, 0.010 mmol), ligand **L2** (3.3 mg, 0.011 mmol), and NaBr (10.3 mg, 0.10 mmol) were added to an oven-dried 4-mL vial equipped with a stir bar. DMA (0.25 mL) was added to the 4-mL vial, and the vial was closed with a PTFE septum cap. The mixture was stirred vigorously at r.t. for 25 min. Then, a solution of the alkyl electrophile in DMA (0.10 mmol in 0.25 mL of DMA) was added to this solution. The resulting solution was allowed to stir at r.t. for 1 min. Next, a solution of the alkylzinc reagent (0.50 M; 0.24 mL, 0.12 mmol; 1.2 equiv) was added in one portion. The mixture was stirred vigorously at r.t. for 2 min, and then the reaction was quenched with MeOH (0.2 mL). A solution of $PhCF_3$ (0.20 M; 0.50 mL, 0.10 mmol; 1.0 equiv) in $CDCl_3$ was added to the vial as an internal standard, and the reaction mixture was analyzed by ^{19}F NMR spectroscopy.

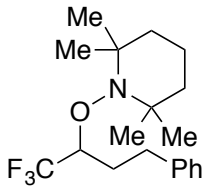
Eq 3.8, with TEMPO: In a nitrogen-filled glovebox, (3-bromo-4,4,4-trifluorobutyl)benzene (26.7 mg, 0.10 mmol) and NaBr (10.3 mg, 0.10 mmol) were added to an oven-dried 4-mL vial equipped with a stir bar. DMA (0.25 mL) was added to this vial, and then a solution of TEMPO in DMA (0.15 M; 0.10 mL, 0.015 mmol; 0.15 equiv) and a solution of the alkylzinc reagent (0.50 M; 0.24 mL, 0.12 mmol; 1.2 equiv).

In a nitrogen-filled glove box, $NiCl_2$•glyme (6.6 mg, 0.030 mmol) and ligand **L2** (9.9 mg, 0.033 mmol) were added to a second oven-dried 4-mL vial equipped with a stir bar. DMA (0.75 mL) was added to this vial, and the vial was closed with a PTFE septum cap. The mixture was vigorously stirred at r.t. for 25 min. Next, 0.25 mL of this catalyst stock solution was added to the 4-mL reaction vial in one portion. The resulting mixture was stirred vigorously at r.t. for 2 min, and then the reaction was quenched with MeOH (0.2 mL). A solution of $PhCF_3$ (0.20 M; 0.50 mL, 0.10 mmol; 1.0 equiv) in $CDCl_3$ was added to the vial as an internal standard, and the reaction mixture was analyzed by ^{19}F NMR spectroscopy.

Eq 3.9: In a nitrogen-filled glovebox, (3-bromo-4,4,4-trifluorobutyl)benzene (26.7 mg, 0.10 mmol) and NaBr (10.3 mg, 0.10 mmol) were added to an oven-dried 4-mL vial equipped with a stir bar. DMA (0.25 mL) was added to this vial, and then a solution of TEMPO in DMA (0.15 M; 0.10 mL, 0.015 mmol; 0.15 equiv) and a solution of the alkylzinc reagent (0.50 M; 0.24 mL, 0.12 mmol; 1.2 equiv).

In a nitrogen-filled glove box, $NiCl_2$•glyme (6.6 mg, 0.030 mmol) and ligand **L2** (9.9 mg, 0.033 mmol) were added to a second oven-dried 4-mL vial equipped with a stir bar. DMA (0.75 mL) was added to this vial, and the vial was closed with a PTFE septum cap. The mixture was vigorously stirred at r.t. for 25 min. Next, 0.25 mL of this catalyst stock solution was added to the 4-mL reaction vial in one portion. The resulting mixture was stirred vigorously at r.t. for 15 min, and then the reaction was quenched with MeOH (0.2 mL). A solution of $PhCF_3$ (0.20 M; 0.50 mL, 0.10 mmol; 1.0 equiv) in $CDCl_3$ was

added to the vial as an internal standard, and the reaction mixture was analyzed by ^{19}F NMR spectroscopy.



2,2,6,6-Tetramethyl-1-((1,1,1-trifluoro-4-phenylbutan-2-yl)oxy)piperidine (eq 3.10; preparation of an authentic sample). The title compound was prepared according to the General Procedure A with (3-bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an alkylzinc bromide reagent prepared from 1-bromononane, in the presence of TEMPO (94 mg, 0.40 mmol), $NiCl_2$•glyme (88 mg, 0.40 mmol), and ligand **L2** (133 mg, 0.44 mmol). Solvent system for chromatography: hexane → 7:1 hexane/dichloromethane. The title compound was isolated as a colorless oil (98 mg, 71% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 4.32 – 4.24 (m, 1H), 2.84 (ddd, 1H, *J* = 16.2, 11.4, 5.0 Hz), 2.75 (ddd, 1H, *J* = 14.0, 10.6, 6.5 Hz), 2.49 – 2.40 (m, 1H), 2.07 – 1.97 (m, 1H), 1.67 – 1.40 (m, 5H), 1.37 – 1.28 (m, 1H), 1.21 – 1.06 (m, 12H);

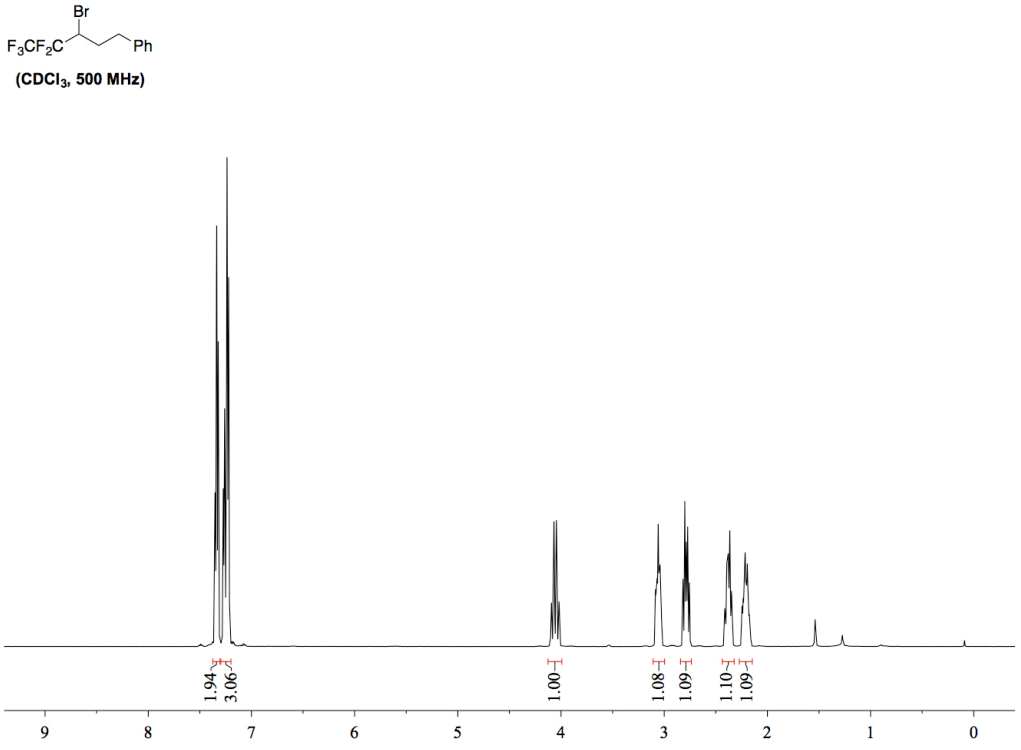
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 128.44, 128.36, 126.0, 125.3 (q, *J* = 283.3 Hz), 79.5 (q, *J* = 27.5 Hz), 61.1, 60.2, 40.5, 33.9, 33.4, 31.6 (d, *J* = 1.7 Hz), 29.8 (d, *J* = 1.3 Hz), 20.3, 17.1;

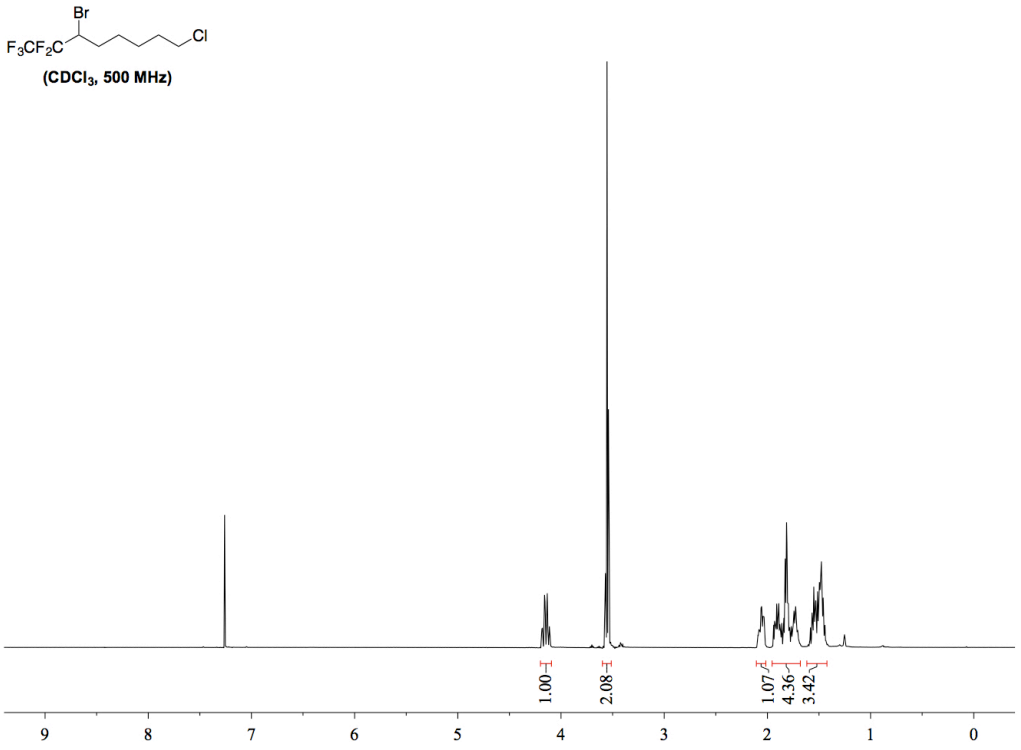
^{19}F NMR (282 MHz, $CDCl_3$) δ −73.3 (d, 3F, *J* = 6.9 Hz);

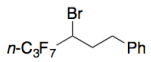
FT-IR (film) 2976, 2933, 2873, 1457, 1378, 1363, 1264, 1189, 1159, 1132, 1090, 748, 698 cm^{-1};

HRMS (ESI) *m/z* ($M+H^+$) calcd for $C_{19}H_{29}F_3NO$: 344.2201, found: 344.2194.

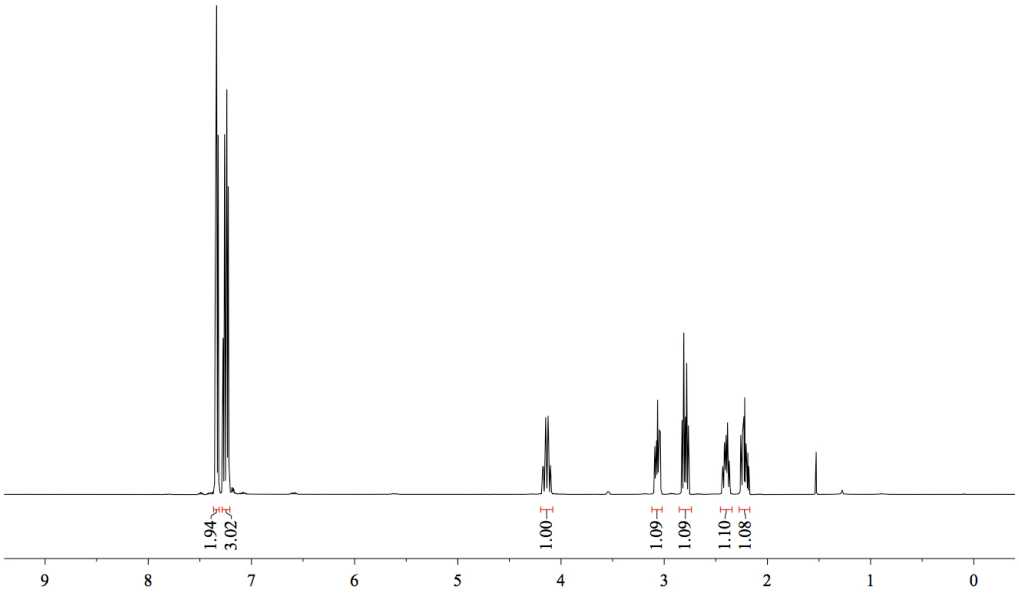
3.7.4 ^{1}H NMR Spectra of Selected Compounds

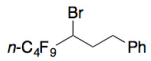

Br
F3CF2C
Ph
(CDCl3, 500 MHz)
1.94
3.06
1.00
1.08
1.09
1.10
1.09
9
8
7
6
5
4
3
2
1
0


Br
F3CF2C
Cl
(CDCl3, 500 MHz)
1.00
2.08
1.07
4.36
3.42
9
8
7
6
5
4
3
2
1
0

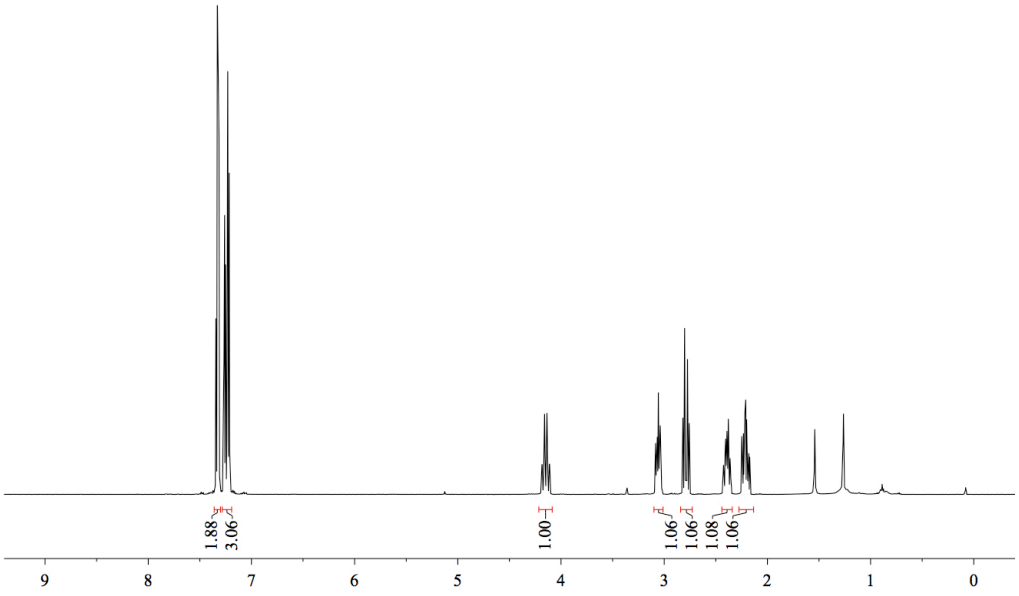


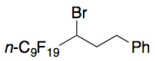
($CDCl_3$, 500 MHz)



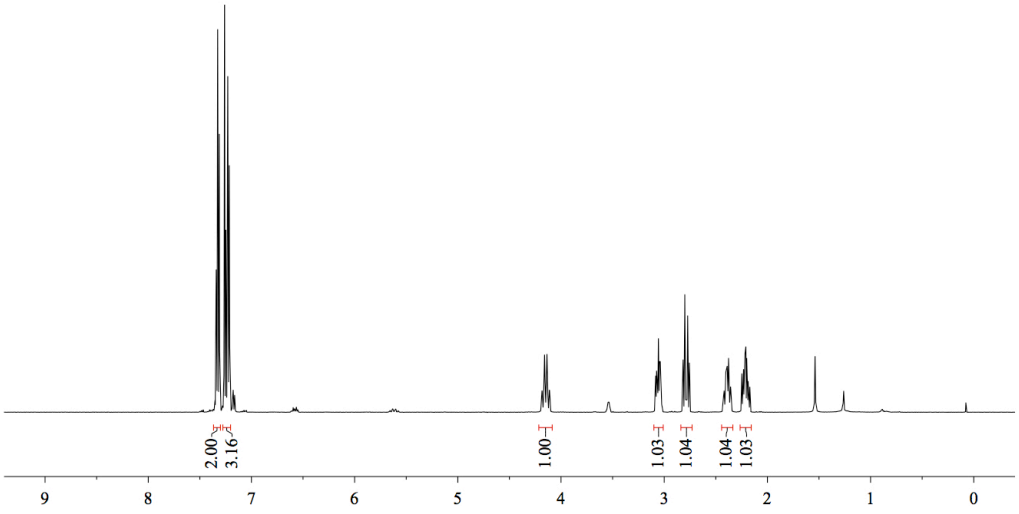


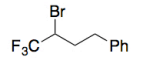
($CDCl_3$, 500 MHz)



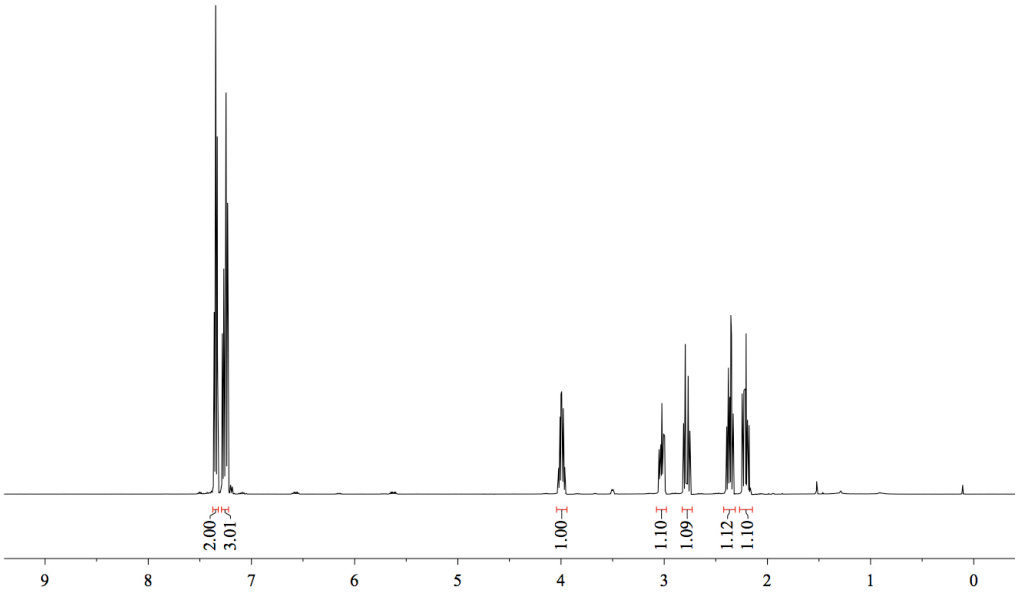


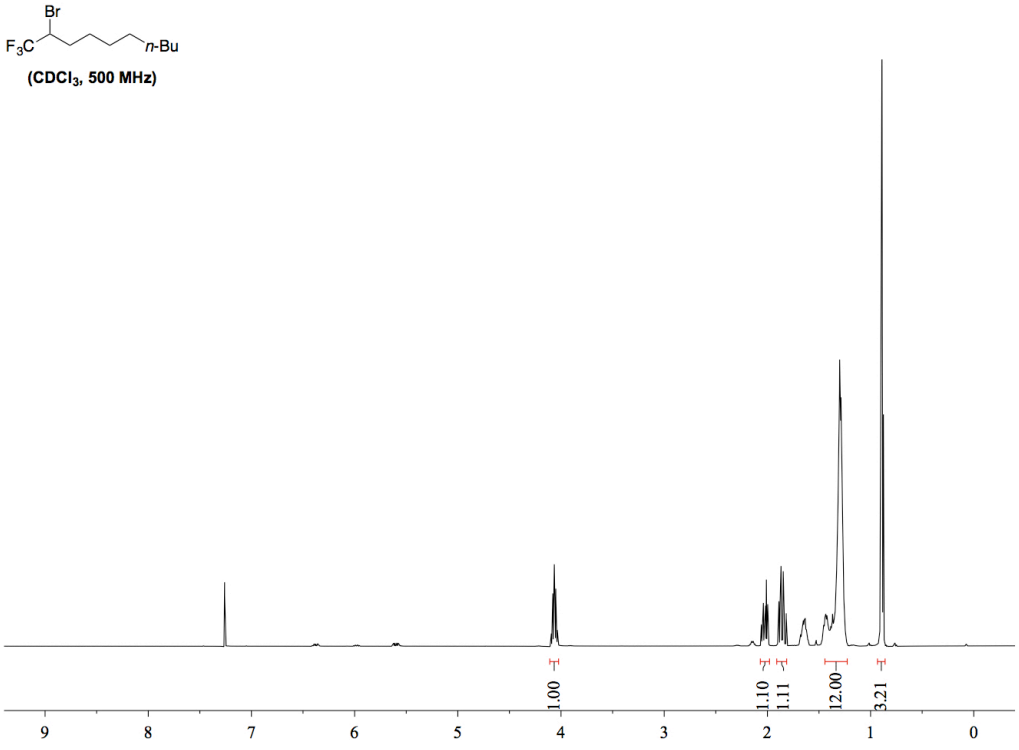
($CDCl_3$, 500 MHz)

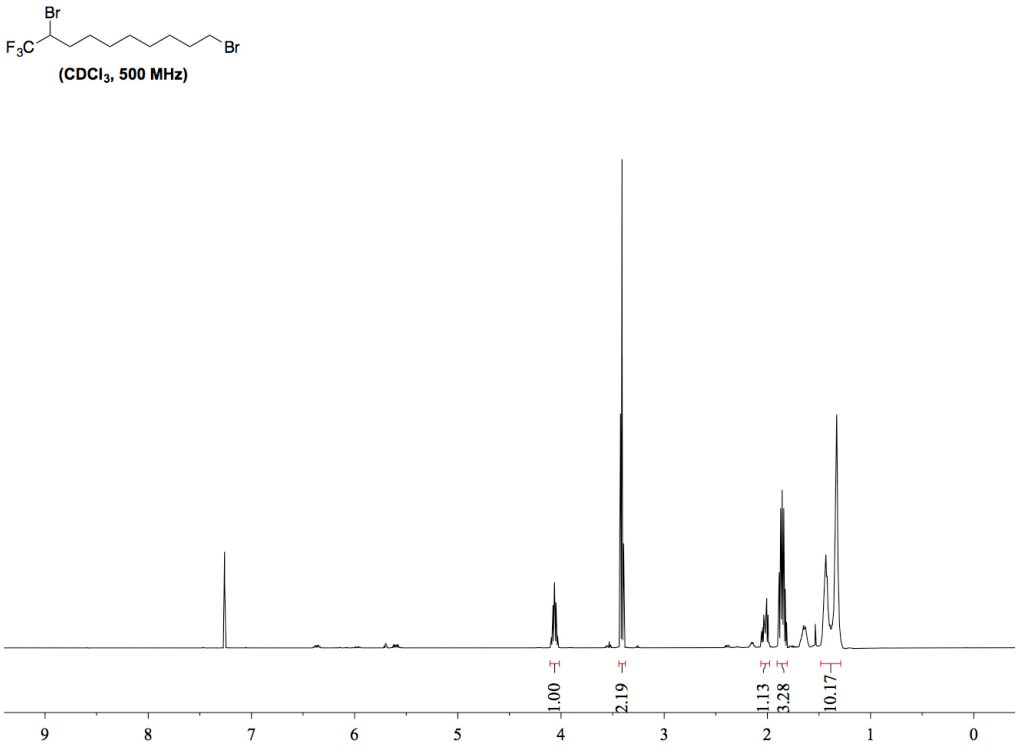




($CDCl_3$, 500 MHz)




Br
F3C
n-Bu
(CDCl3, 500 MHz)
1.00
1.10
1.11
12.00
3.21
9
8
7
6
5
4
3
2
1
0


Br
F3C
Br
(CDCl3, 500 MHz)
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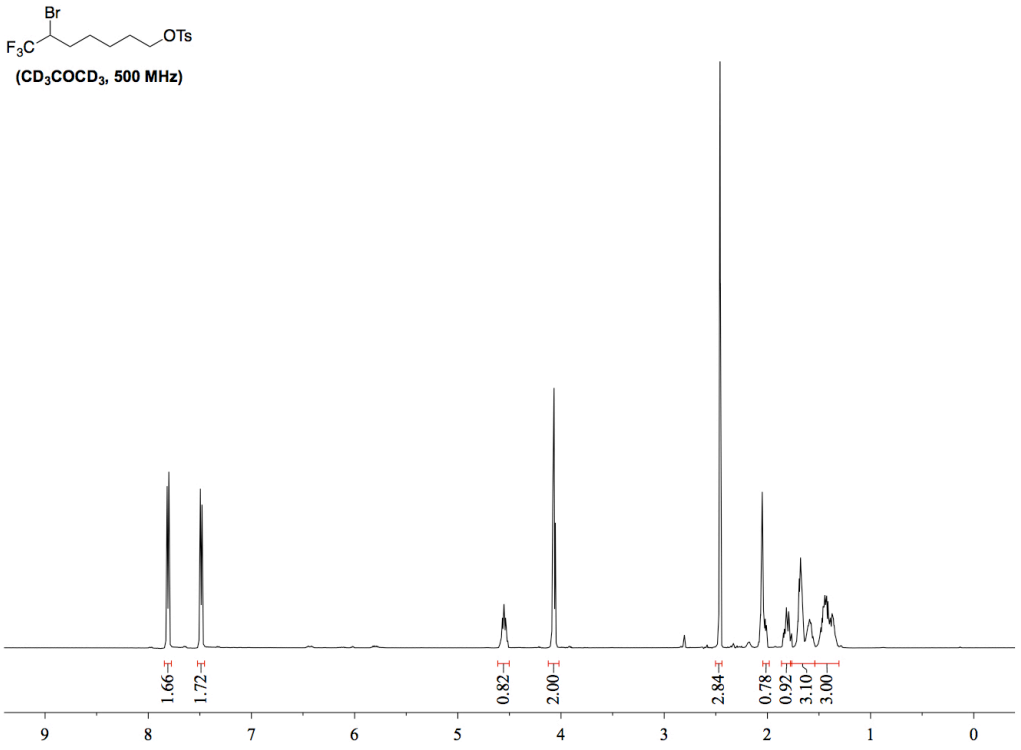
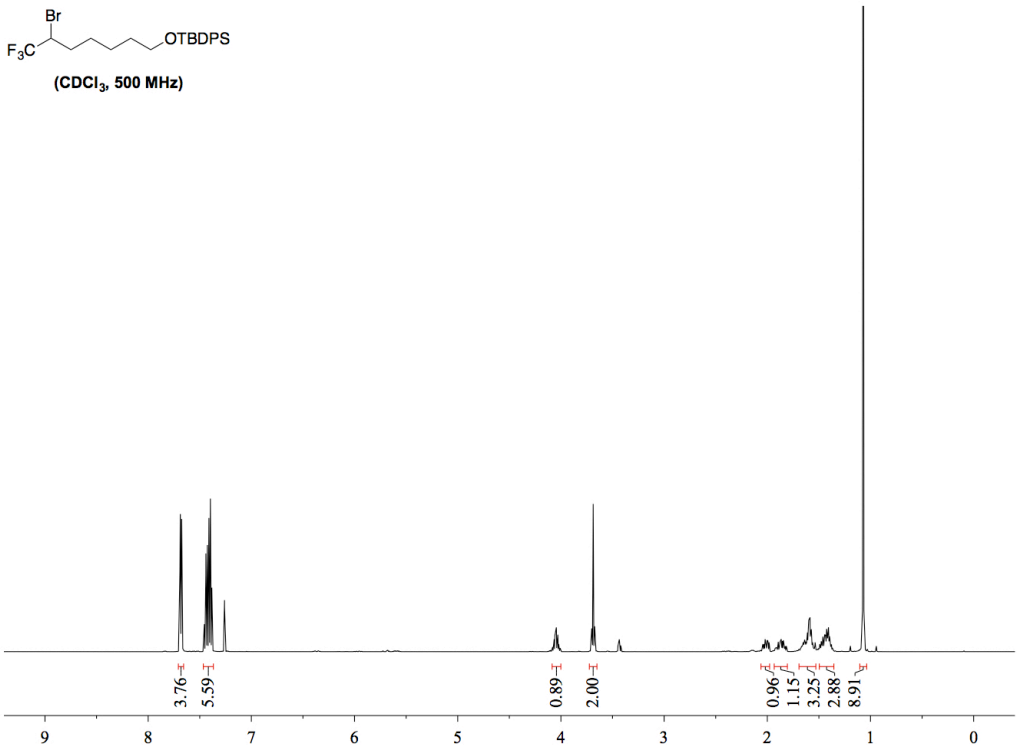
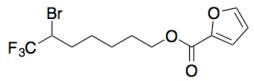
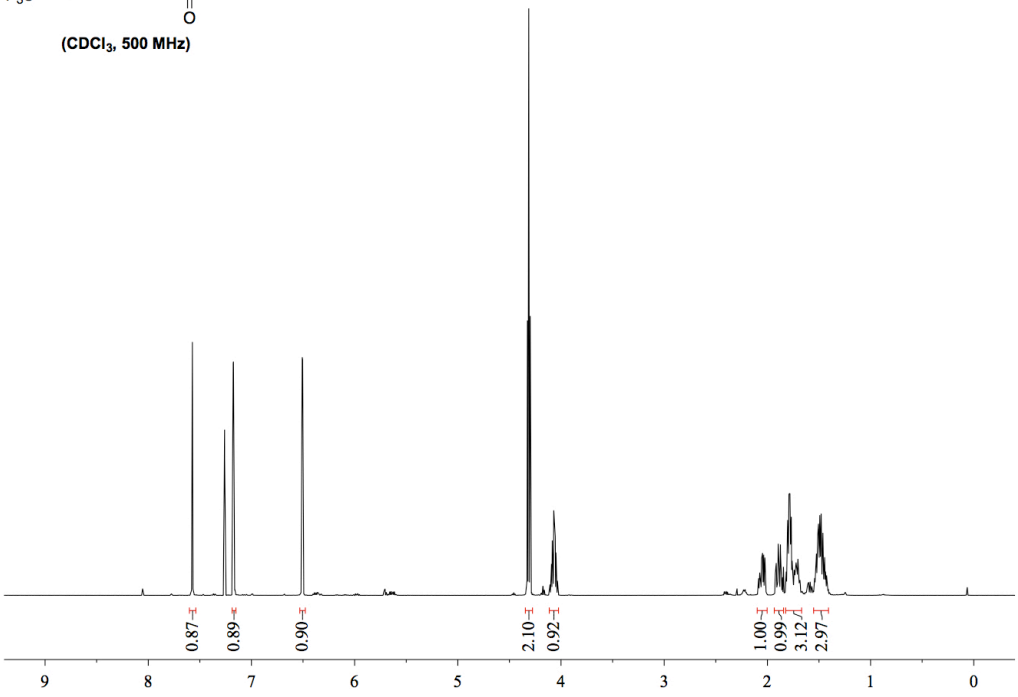
2.19
1.13
3.28
10.17
9
8
7
6
5
4
3
2
1
0

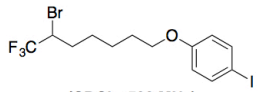

Br
F3C
OTs
(CD3COCD3, 500 MHz)
1.66
1.72
0.82
2.00
2.84
0.78
0.92
3.10
3.00
9
8
7
6
5
4
3
2
1
0


Br
F3C
OTBDPS
(CDCl3, 500 MHz)
3.76
5.59
0.89
2.00
0.96
1.15
3.25
2.88
8.91
9
8
7
6
5
4
3
2
1
0

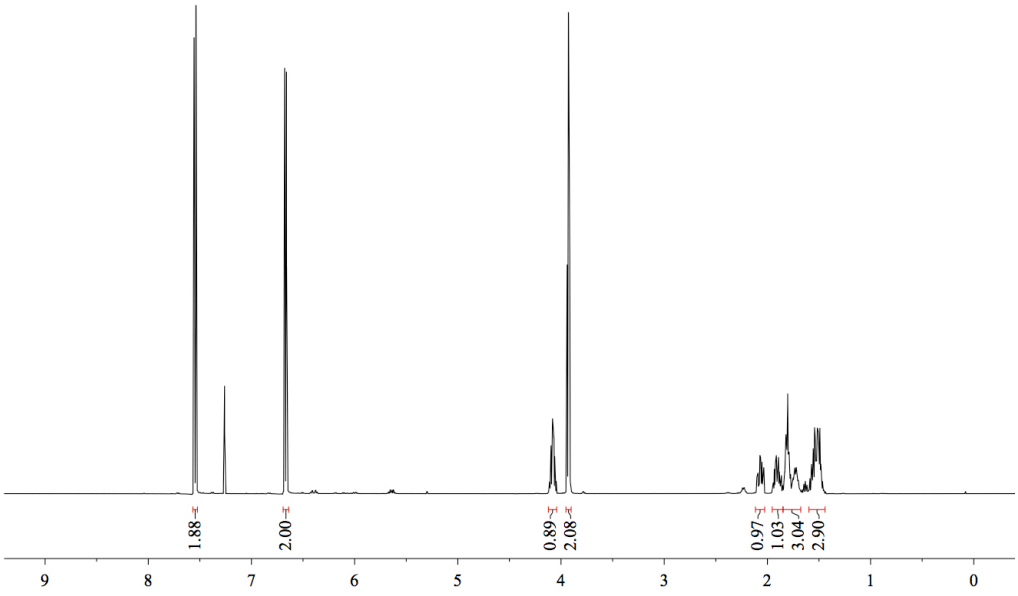


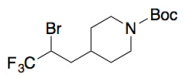
($CDCl_3$, 500 MHz)



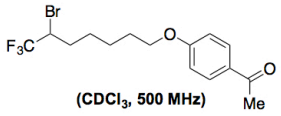


($CDCl_3$, 500 MHz)

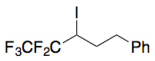




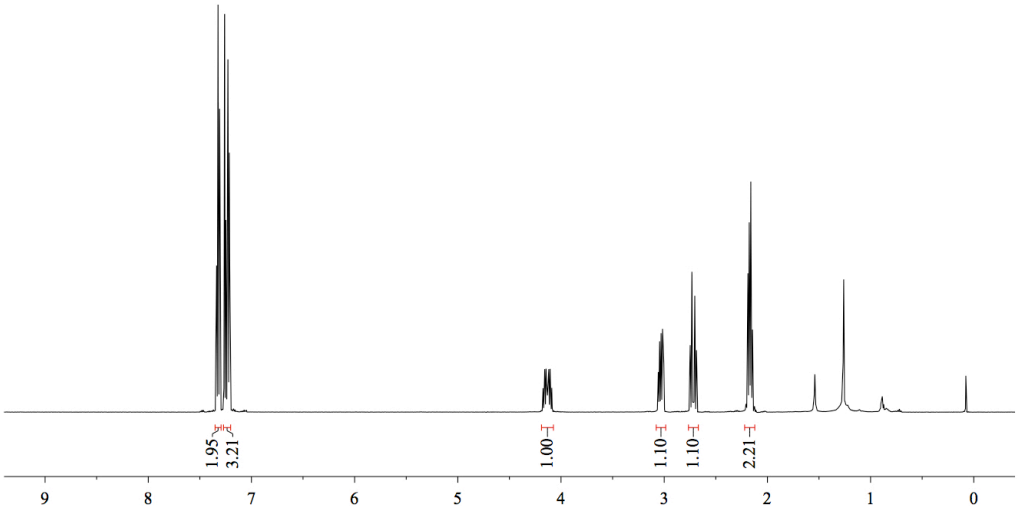
($CDCl_3$, 500 MHz)

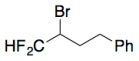


($CDCl_3$, 500 MHz)

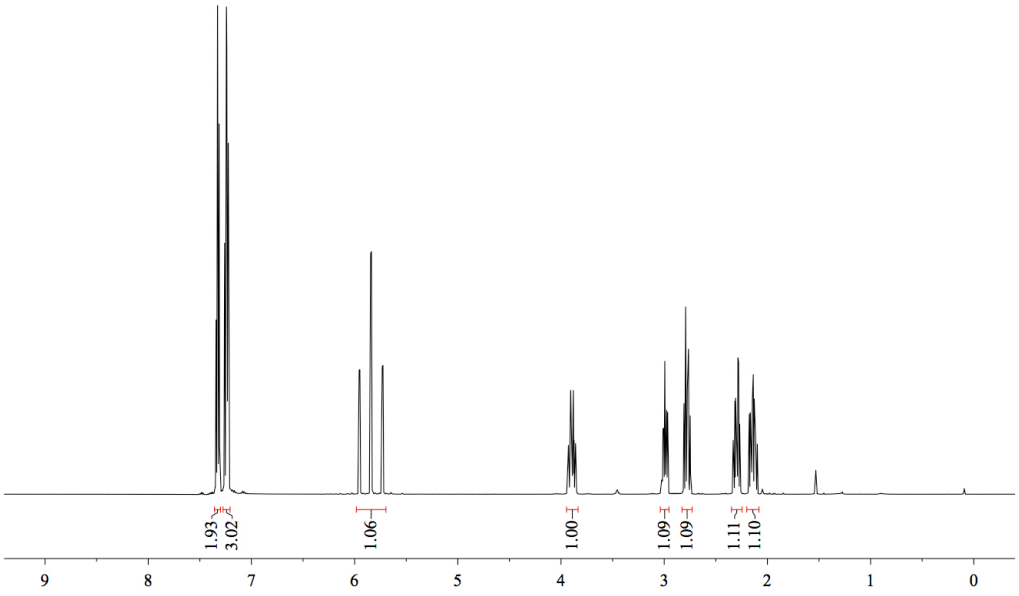


($CDCl_3$, 500 MHz)





($CDCl_3$, 500 MHz)



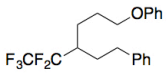
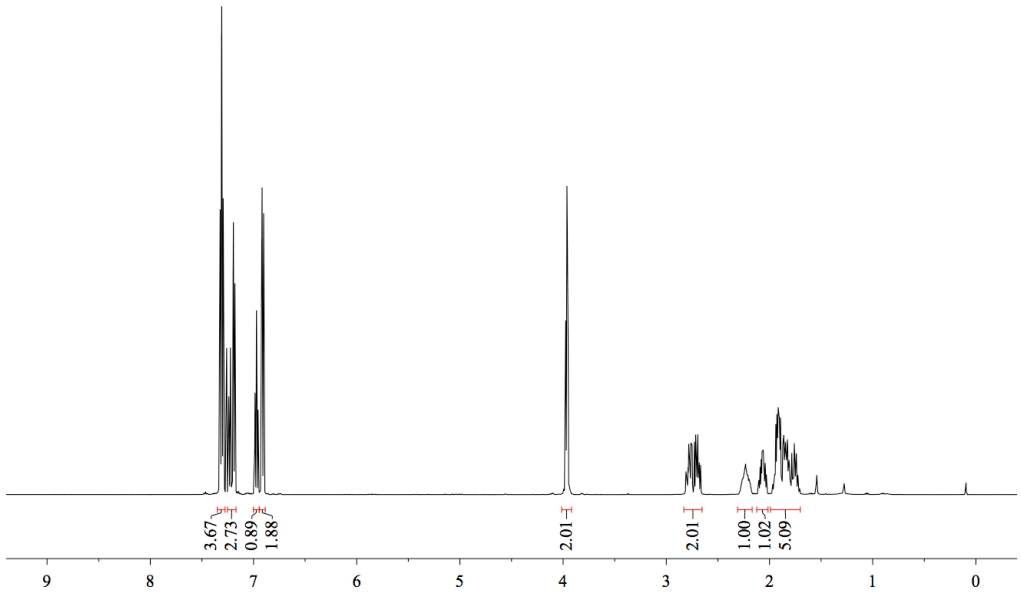


Table 3.3, Entry 1
($CDCl_3$, 500 MHz)



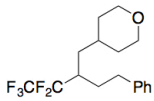
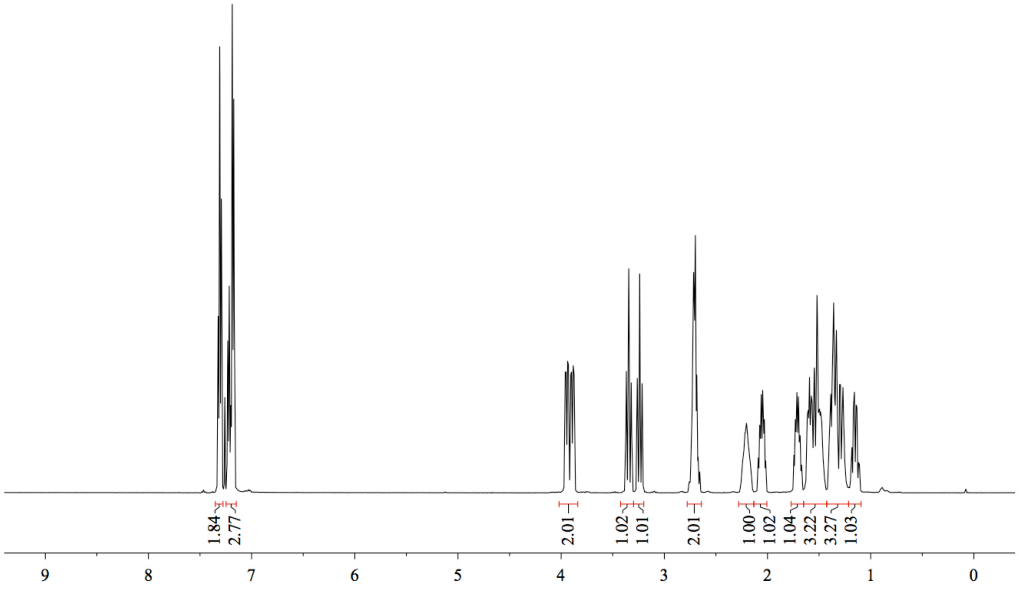


Table 3.3, Entry 2
($CDCl_3$, 500 MHz)



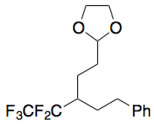
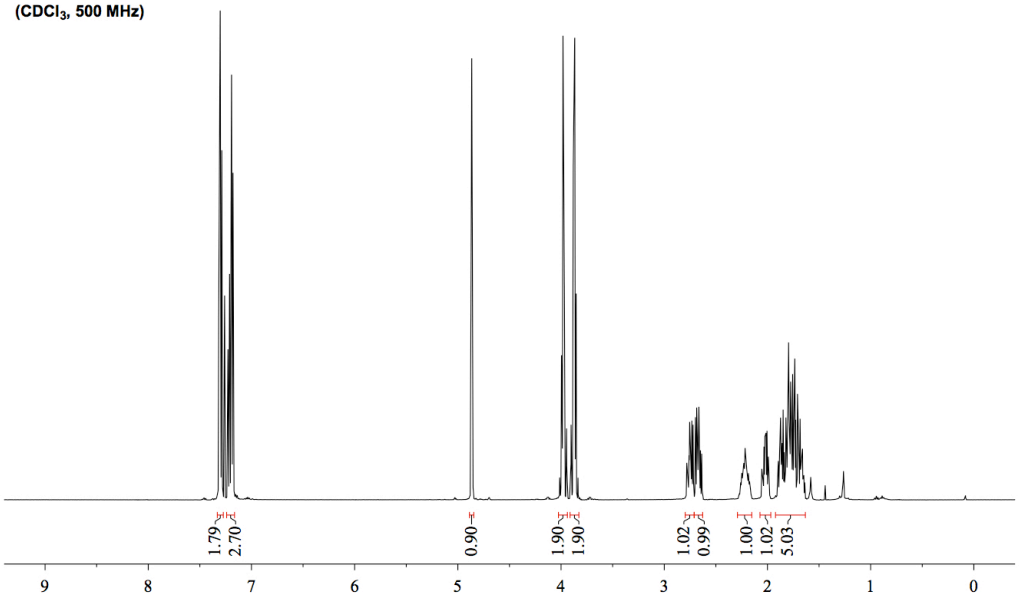


Table 3.3, Entry 3
($CDCl_3$, 500 MHz)



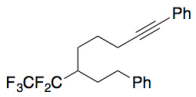
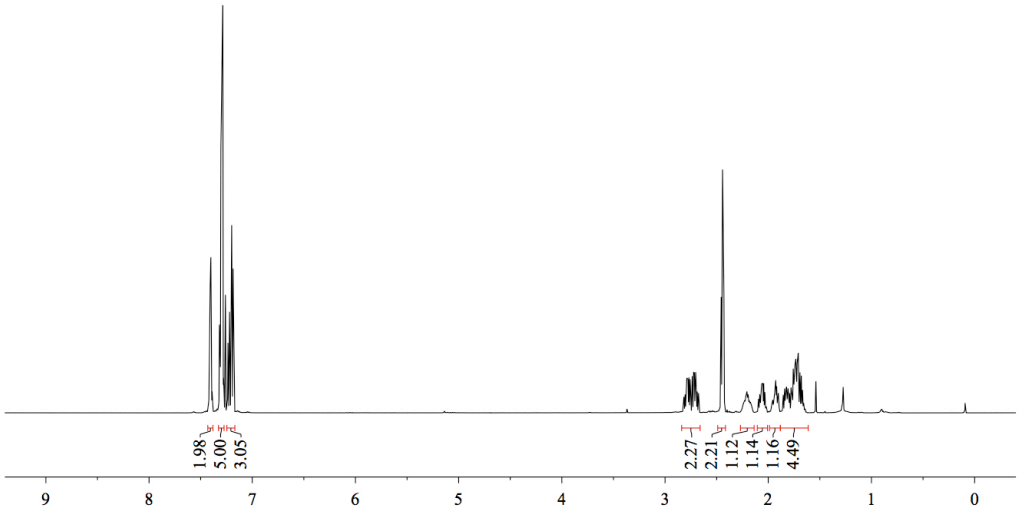


Table 3.3, Entry 4
($CDCl_3$, 500 MHz)



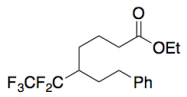
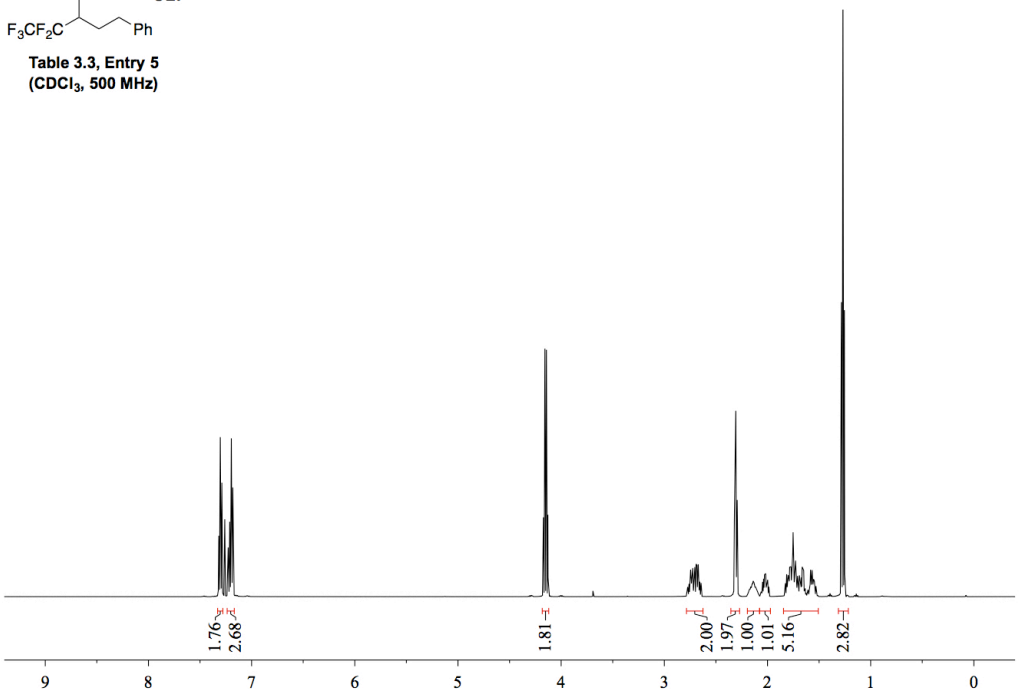


Table 3.3, Entry 5
($CDCl_3$, 500 MHz)



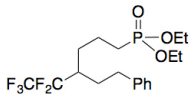
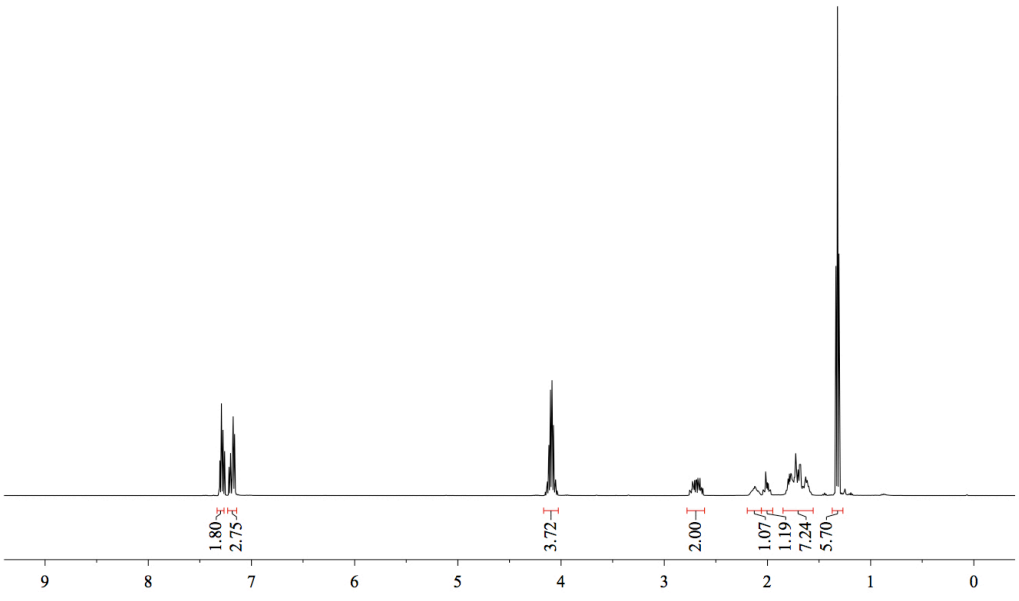


Table 3.3, Entry 6
($CDCl_3$, 500 MHz)



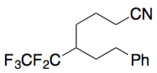
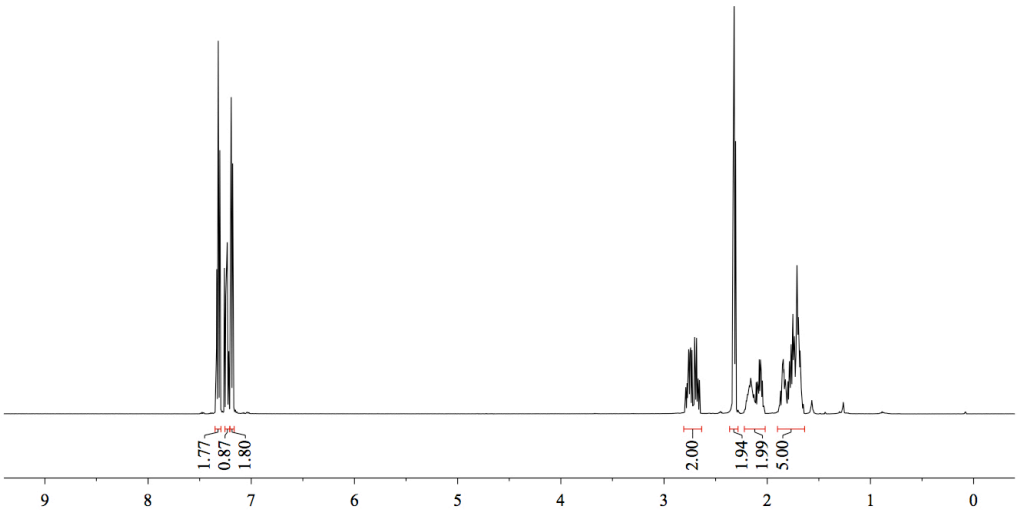


Table 3.3, Entry 7
($CDCl_3$, 500 MHz)



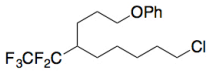
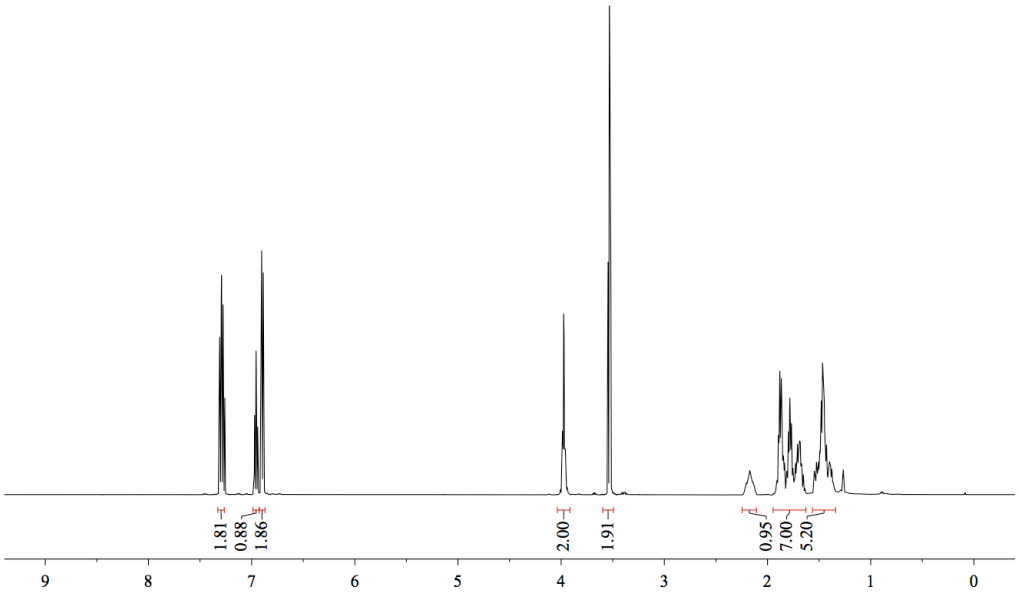


Table 3.3, Entry 8
($CDCl_3$, 500 MHz)



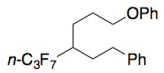
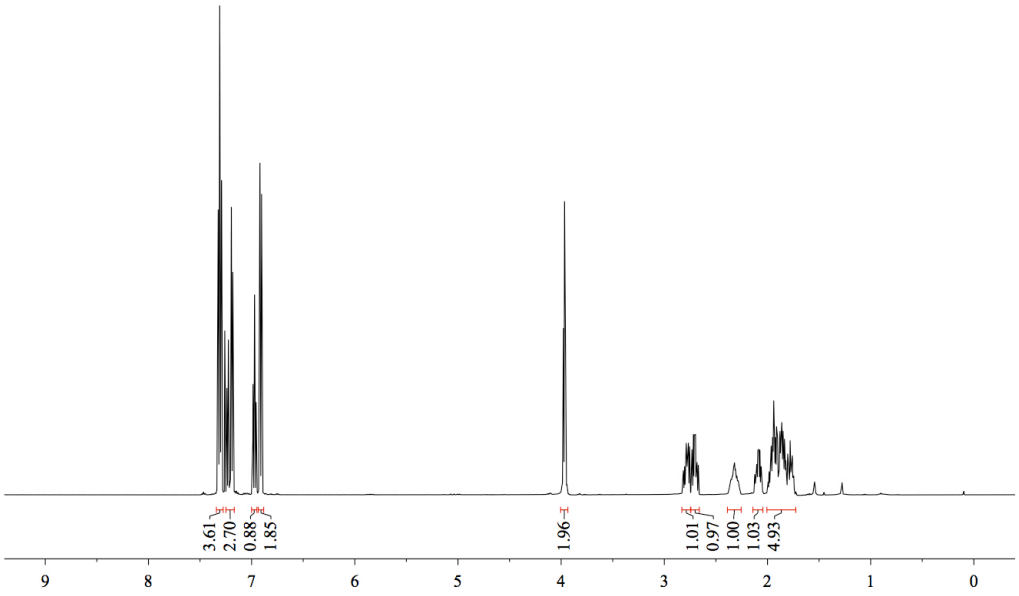


Table 3.4, Entry 1
($CDCl_3$, 500 MHz)



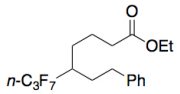
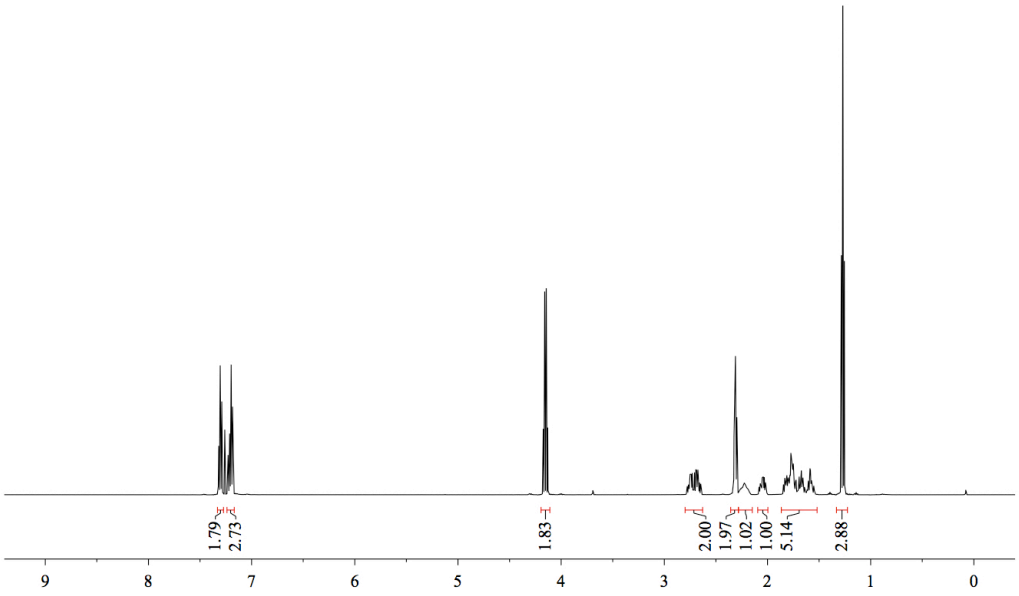


Table 3.4, Entry 2
($CDCl_3$, 500 MHz)



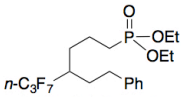
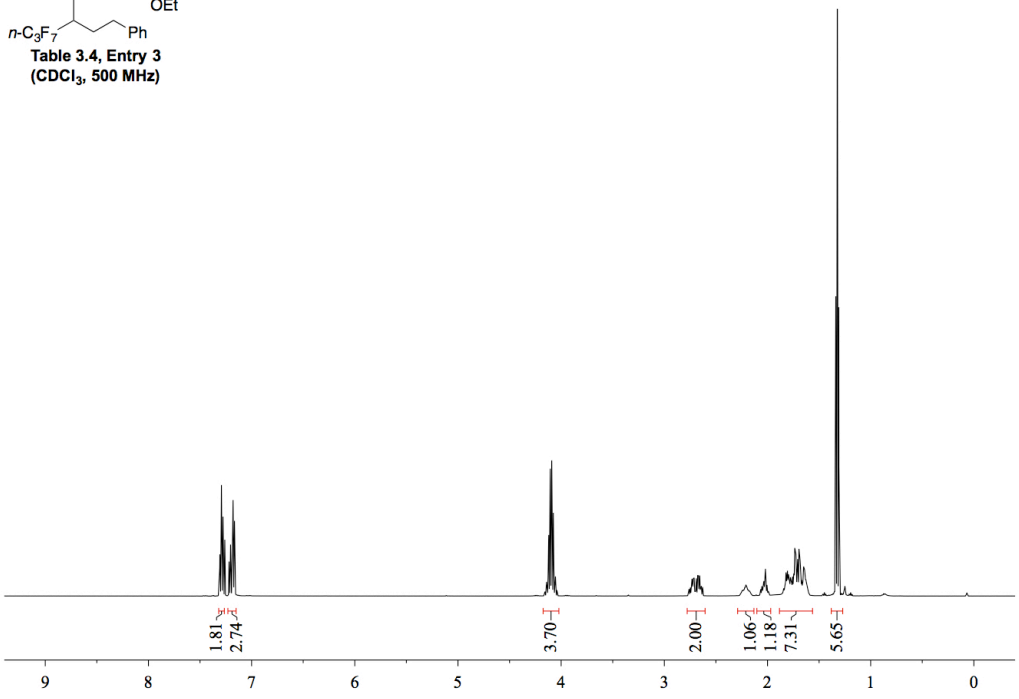


Table 3.4, Entry 3
($CDCl_3$, 500 MHz)



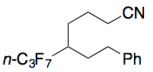
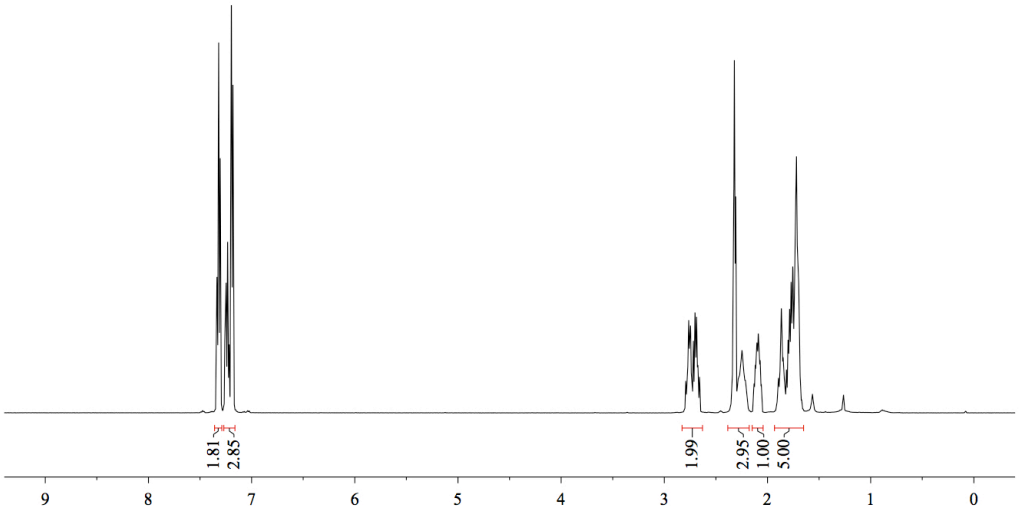


Table 3.4, Entry 4
($CDCl_3$, 500 MHz)



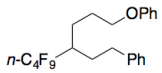
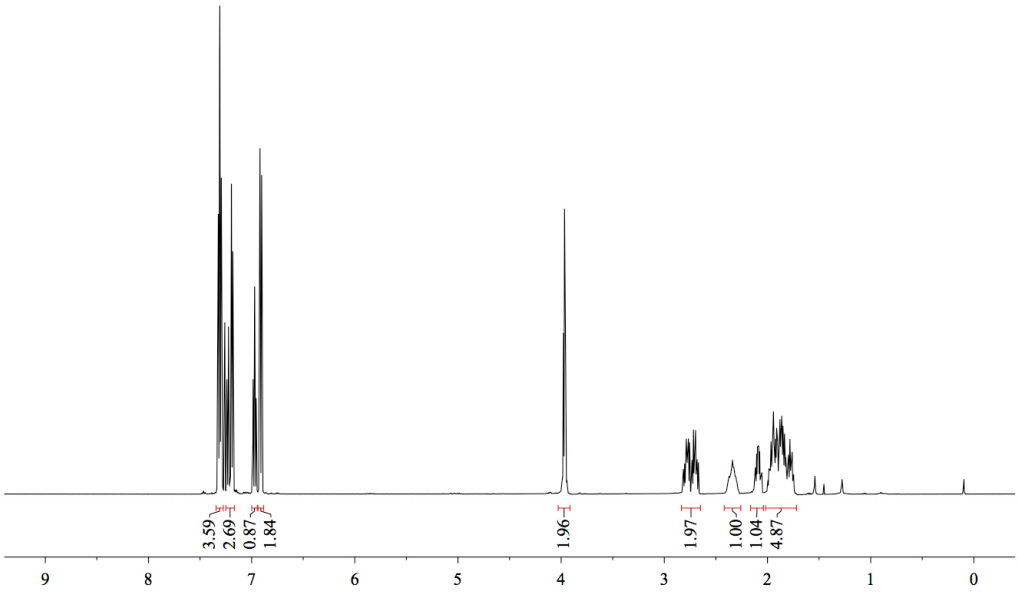


Table 3.4, Entry 5
($CDCl_3$, 500 MHz)



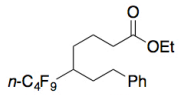


Table 3.4, Entry 6
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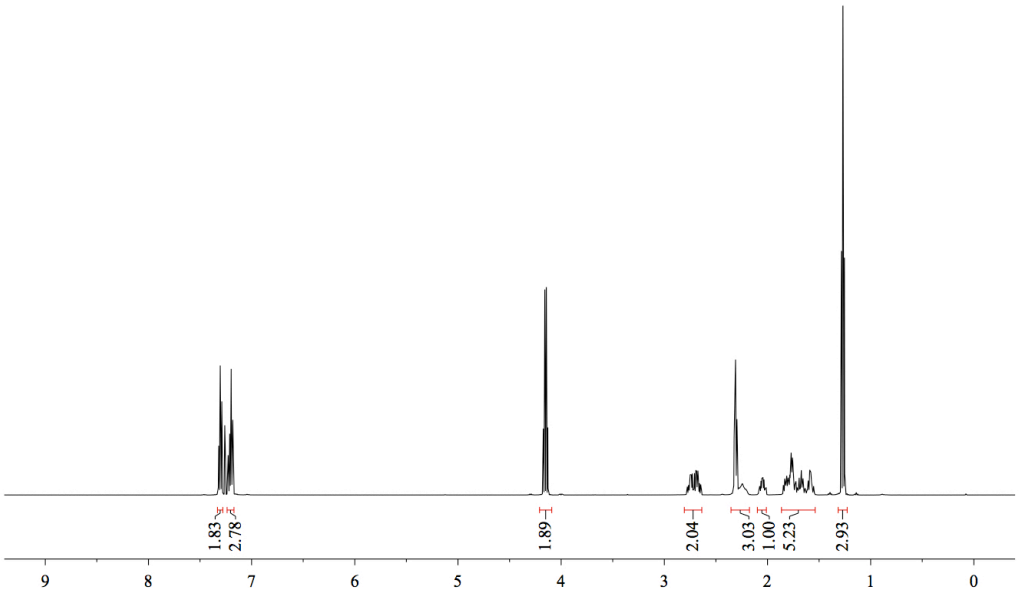


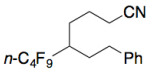
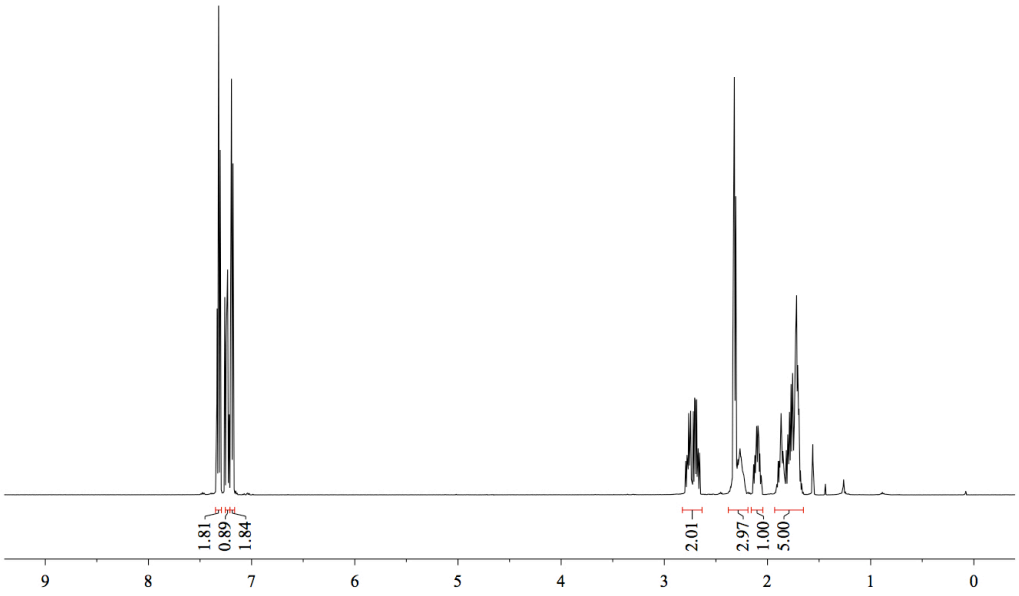
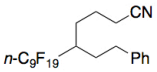


Table 3.4, Entry 7
($CDCl_3$, 500 MHz)





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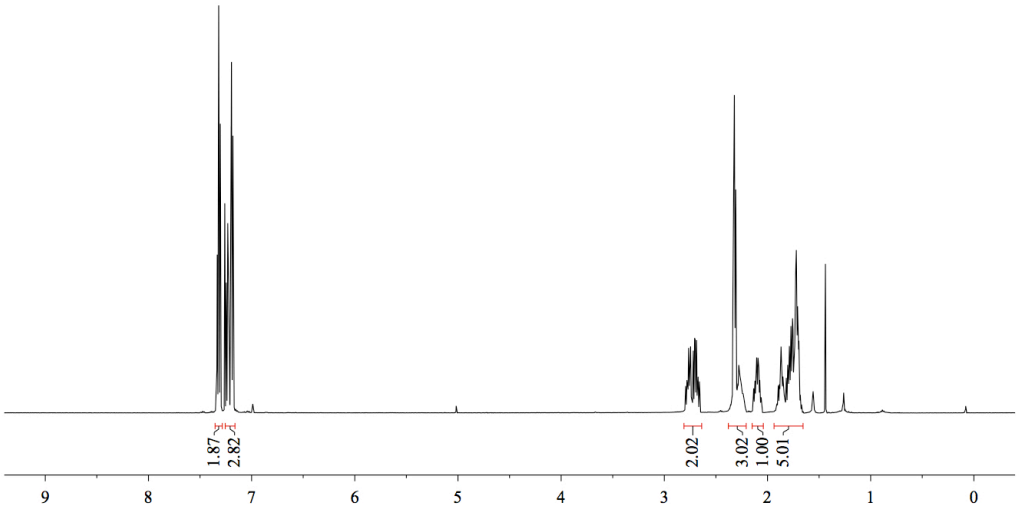

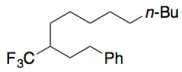

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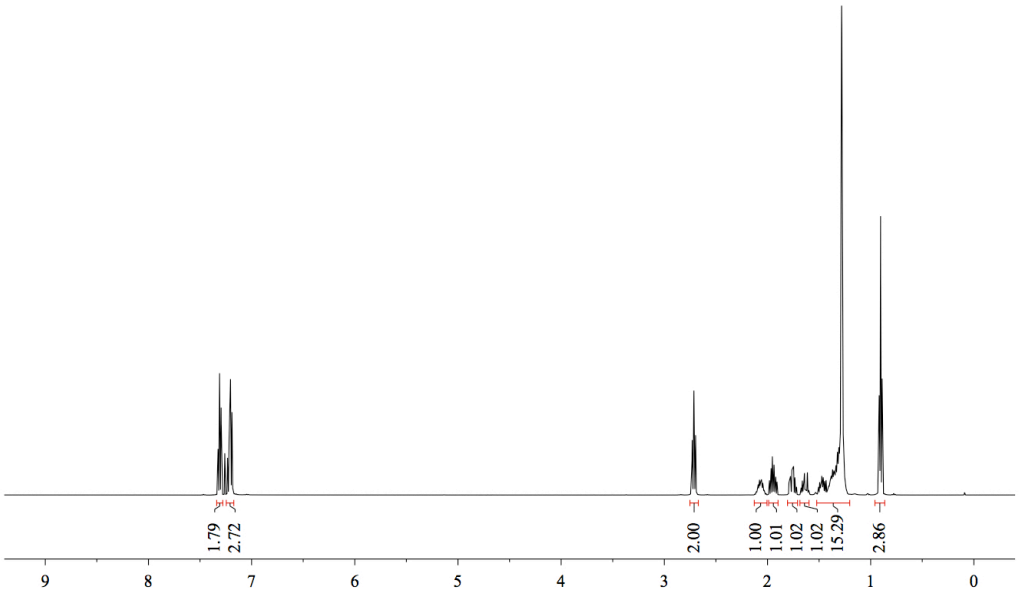

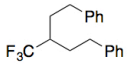

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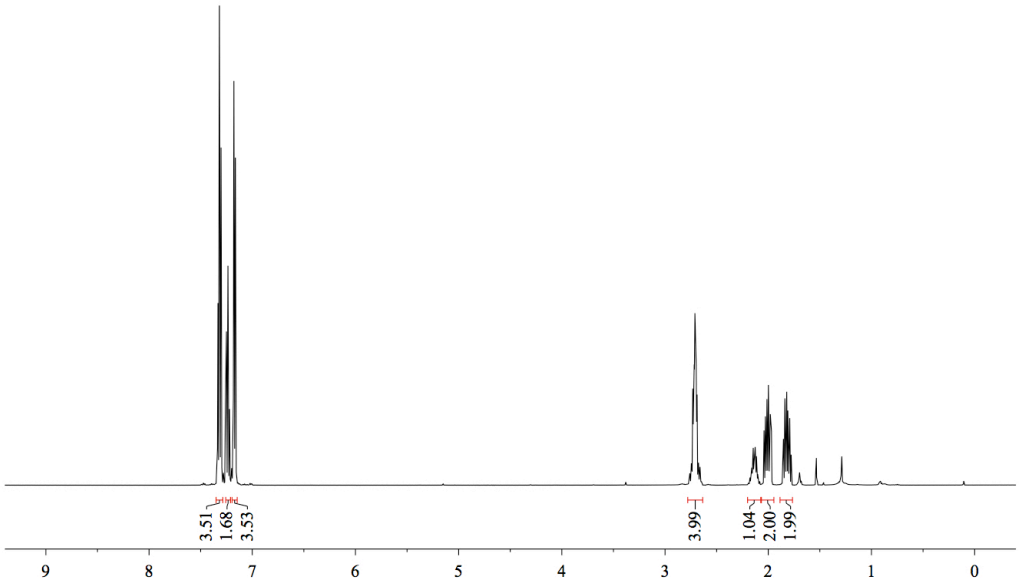

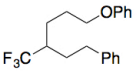

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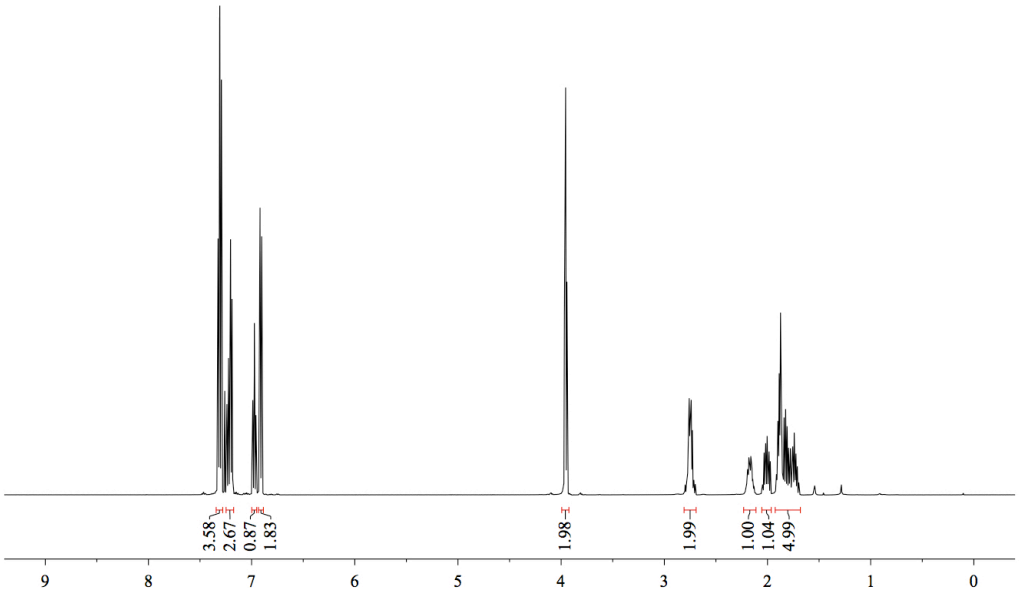

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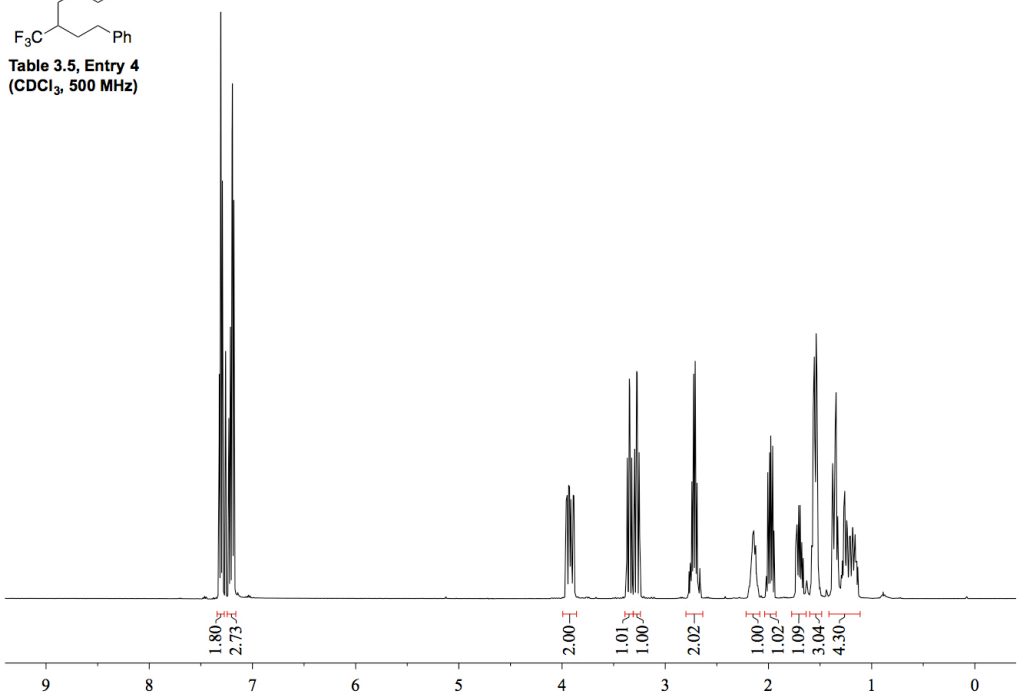

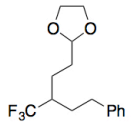

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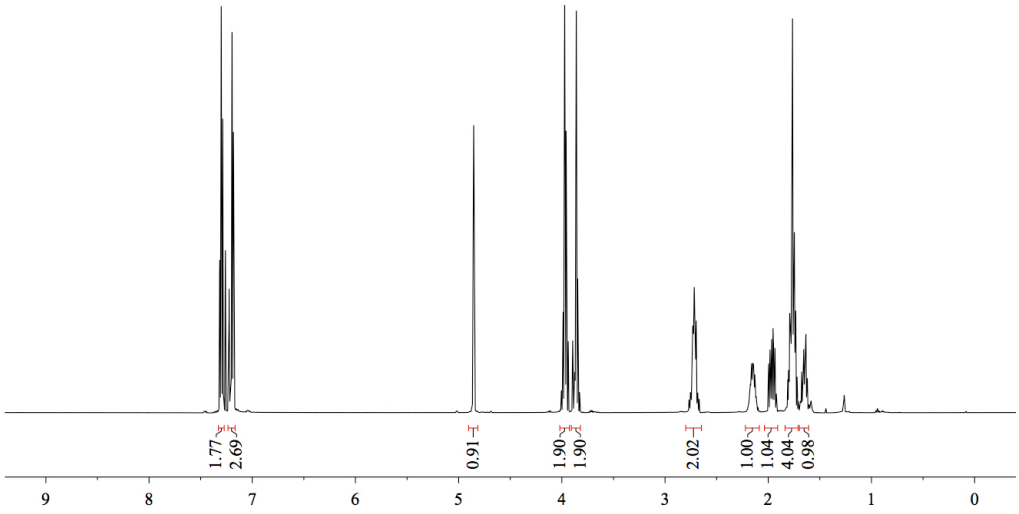

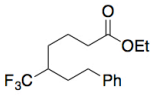

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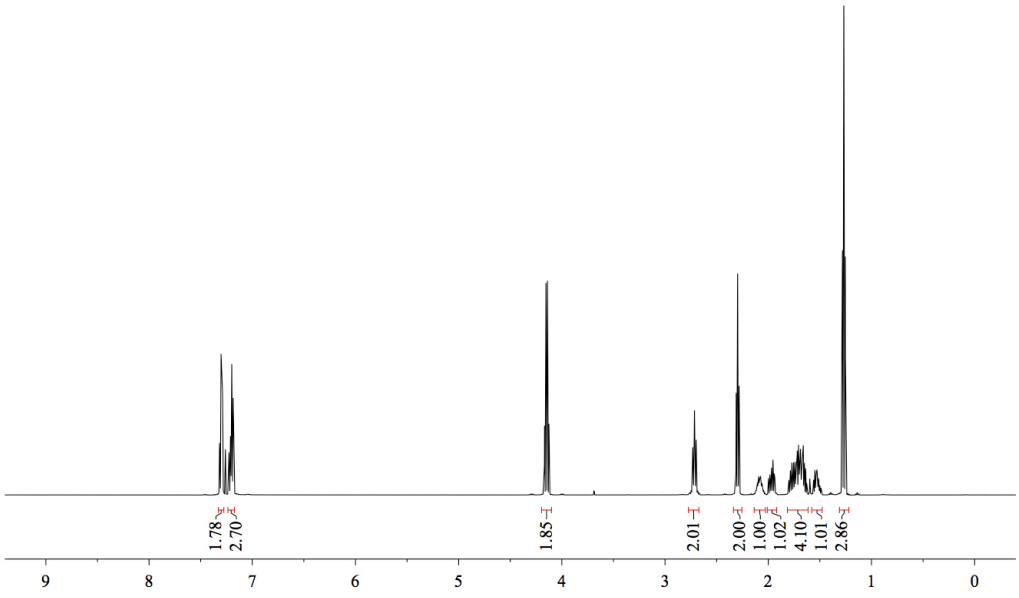
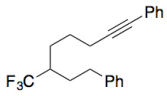
($CDCl_3$, 500 MHz)





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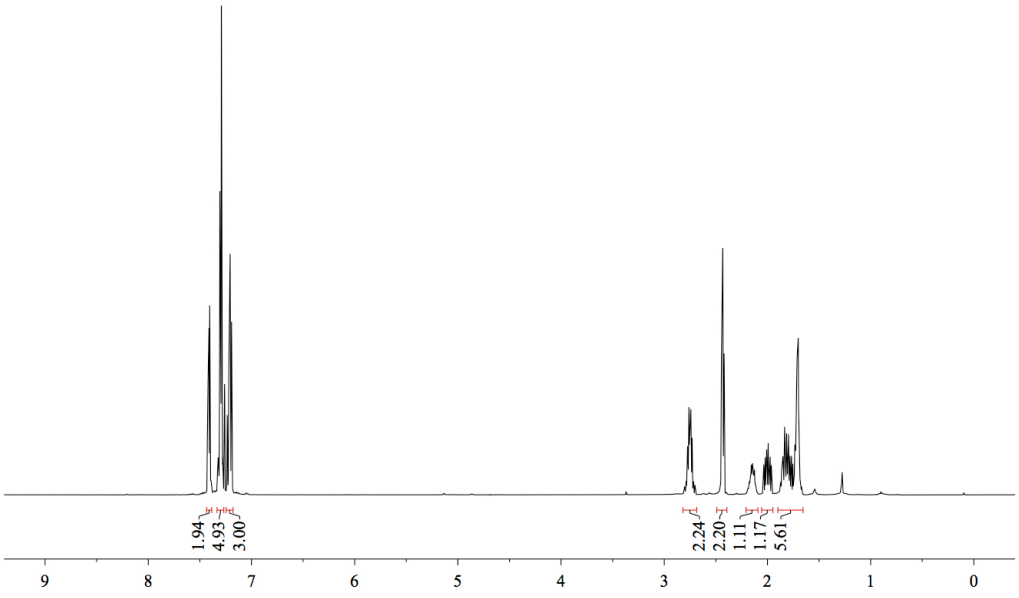

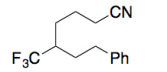

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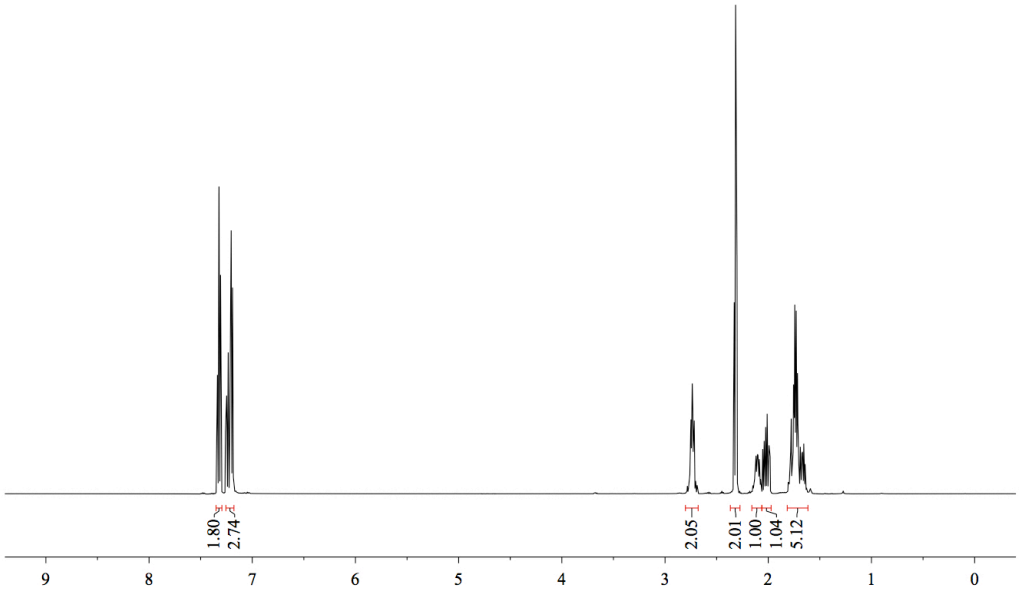

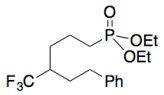

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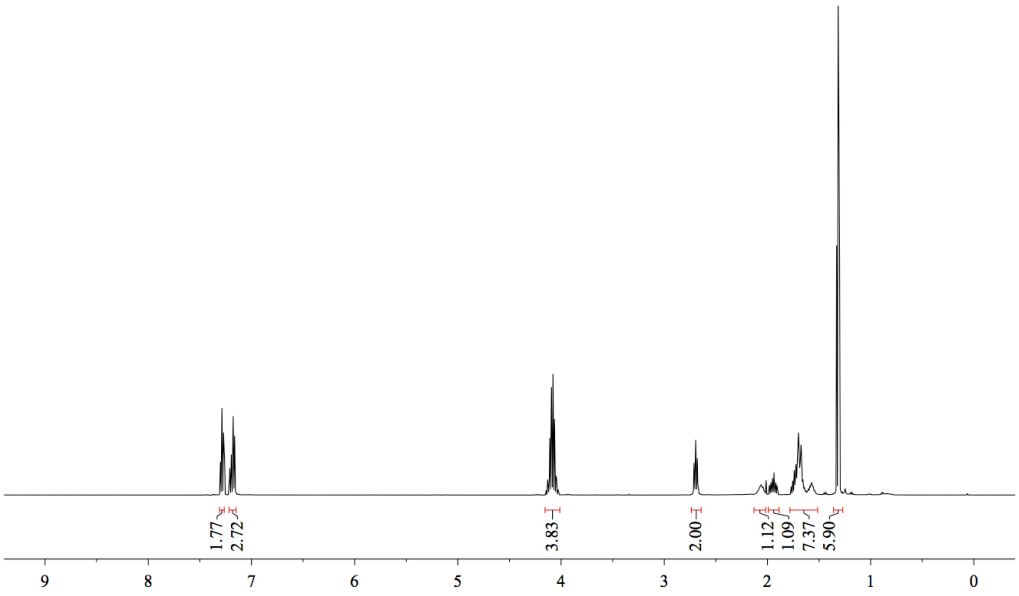

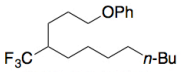

Table 3.6, Entry 1
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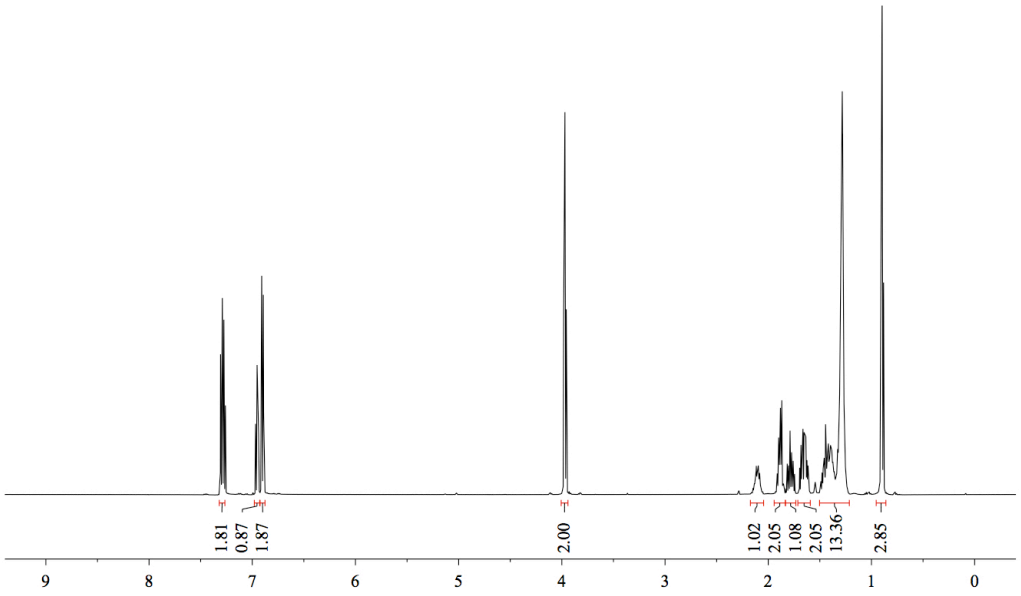

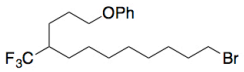

Table 3.6, Entry 2
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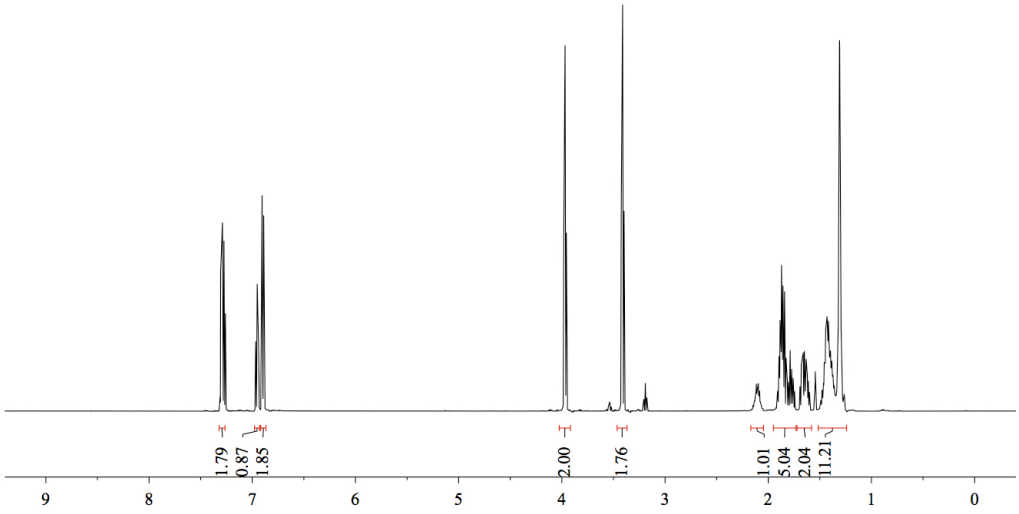

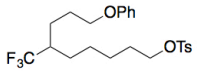

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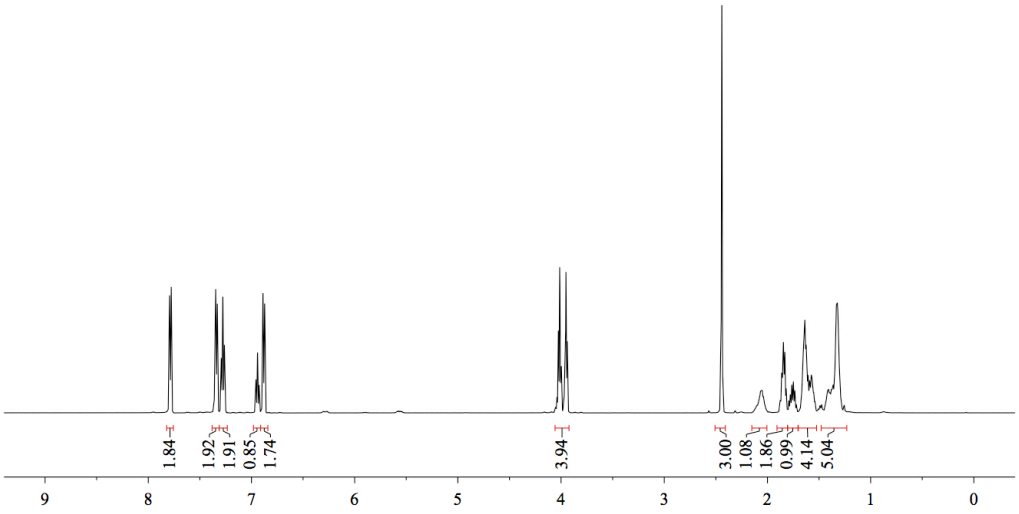

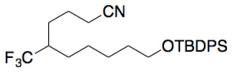

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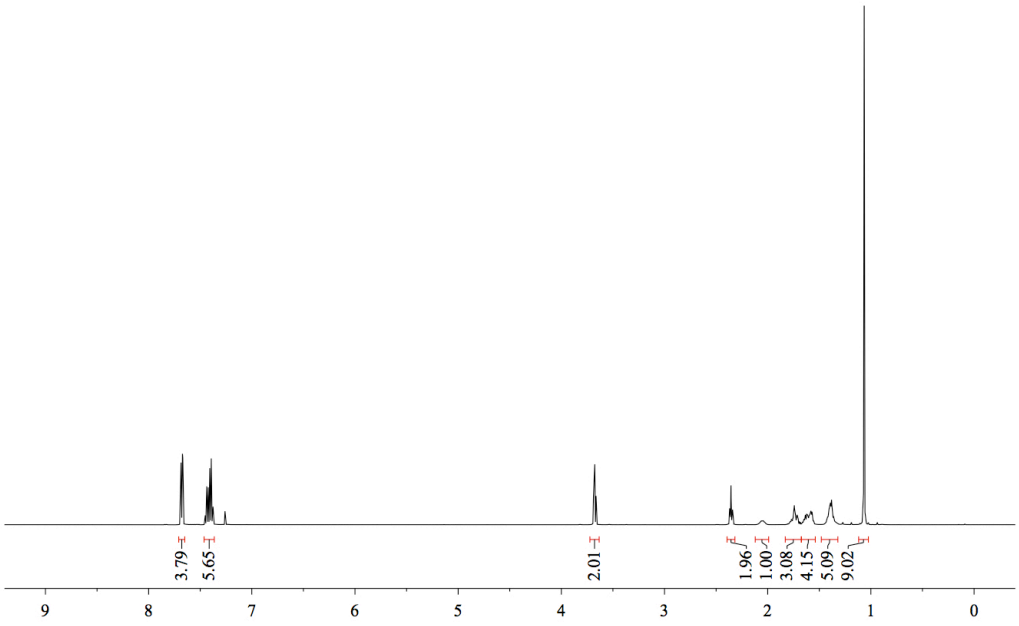


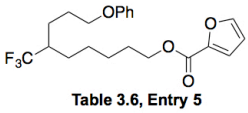
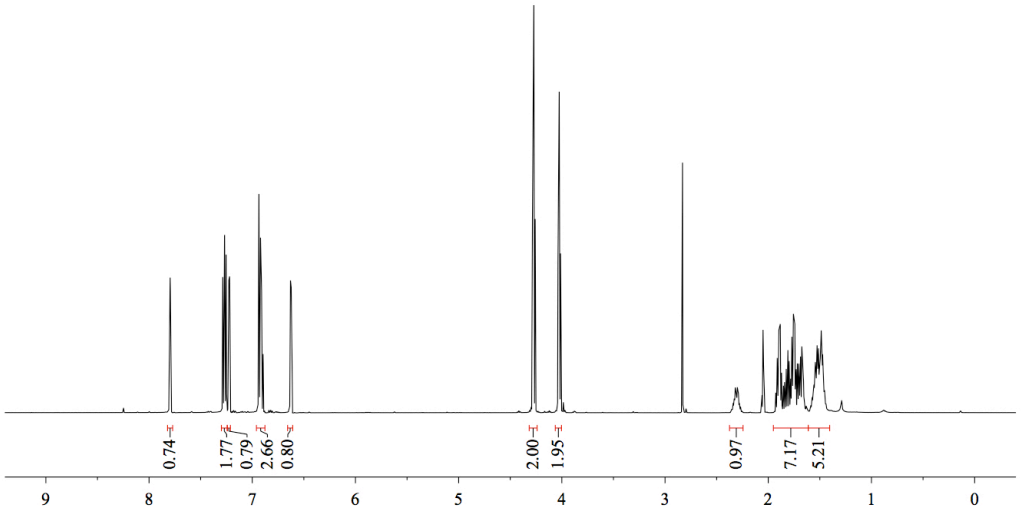


Table 3.6, Entry 5
(CD_3COCD_3, 500 MHz)



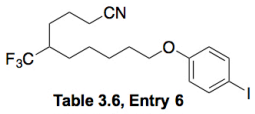
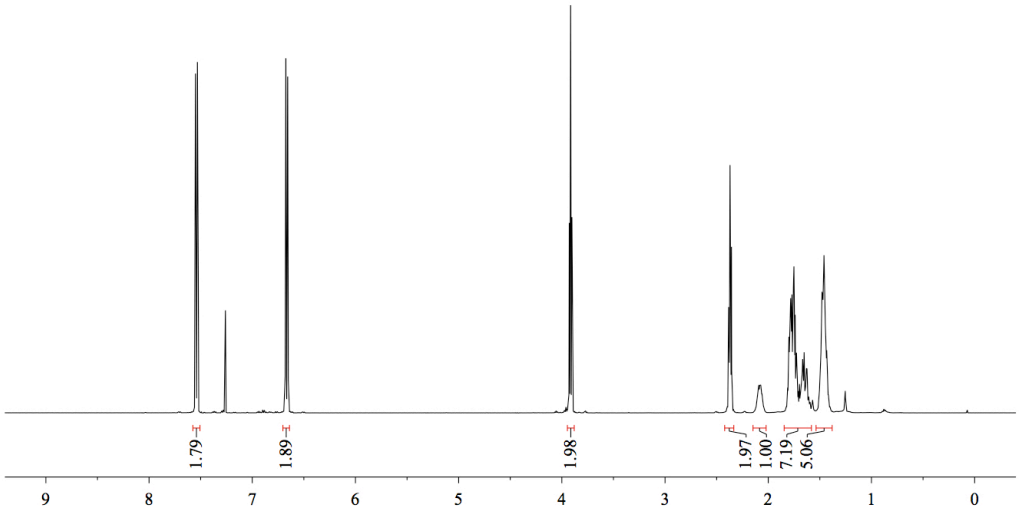
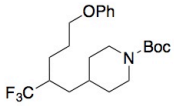


Table 3.6, Entry 6
($CDCl_3$, 500 MHz)





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($CDCl_3$, 500 MHz)

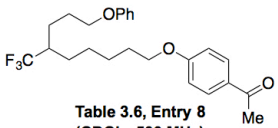
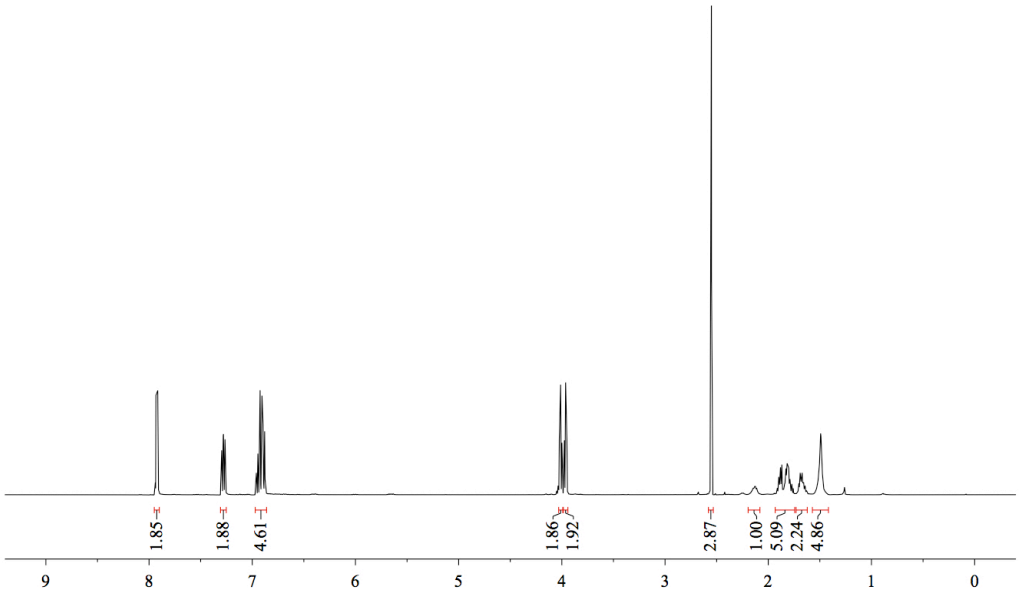
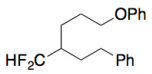
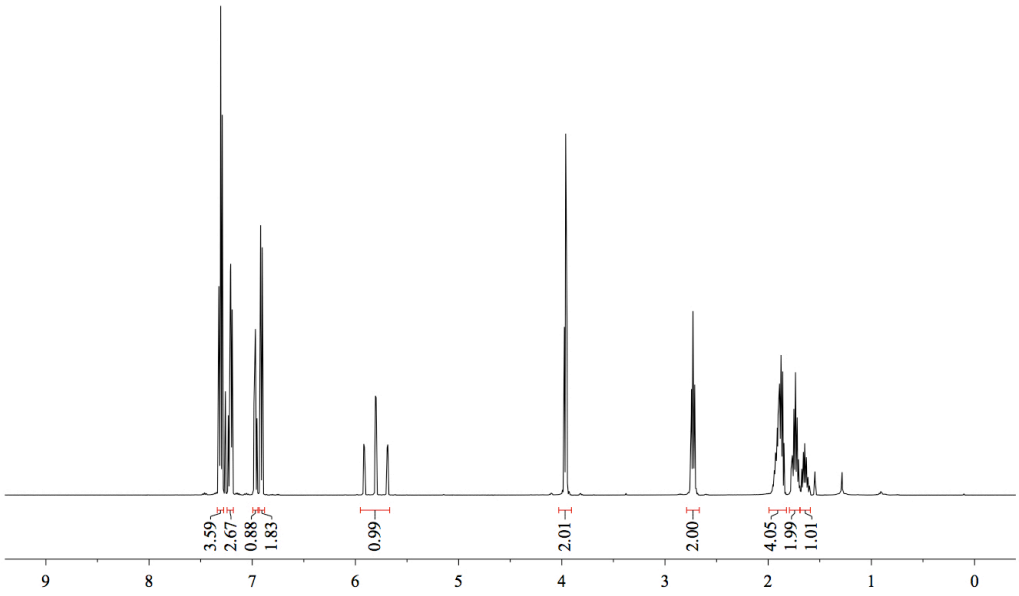


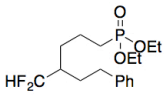
Table 3.6, Entry 8
($CDCl_3$, 500 MHz)



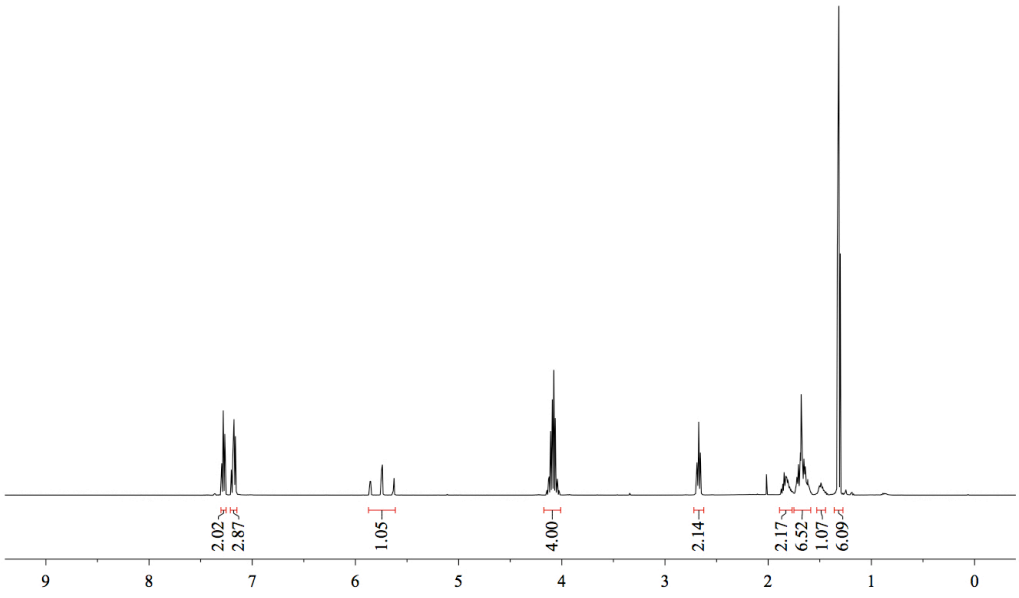


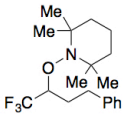
Eq 3.5
($CDCl_3$, 500 MHz)



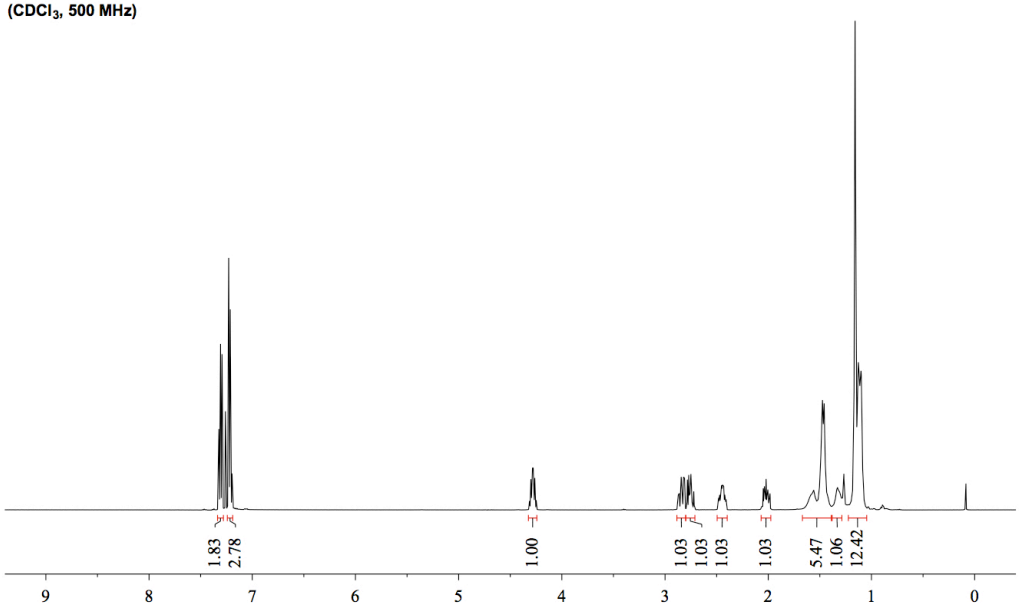


Eq 3.6
($CDCl_3$, 500 MHz)





Eq 3.10
($CDCl_3$, 500 MHz)



3.8 Notes and References

(1) (a) *Fluorine in Pharmaceutical and Medicinal Chemistry;* Grouverneur, V., Müller, K., Eds.; Imperial College Press: London, 2012. (b) *Fluorine-Related Nanoscience with Energy Applications;* Nelson, D. L., Brammer, C. N., Eds.; American Chemical Society: Washington, DC, 2011. (c) *Fluorine in Medicinal Chemistry and Chemical Biology;* Ojima, I., ED.; John Wiley & Sons; Chichester, UK, 2009.

(2) For Ar–F, see: (a) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612–633. (b) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661–1664.

(3) For Ar–CF_3, see: (a) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847–1935. (b) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37–54. (c) Chen, P.; Liu, G. *Synthesis* **2013**, *45*, 2919–2939. (d) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679–1681.

(4) For a recent review, see: Xu, J.; Liu, X.; Fu, Y. *Tetrahedron Lett.* **2014**, *55*, 585–594.

(5) (a) Proline derivative: Del Valle, J. R.; Goodman, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 1600–1602. Qiu, X.-l.; Qing, F.-l. *J. Org. Chem.* **2002**, *67*, 7162–7164. (b) For a review on fluorinated amino acids, see: Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Koksch, B. *Chem. Soc. Rev.* **2012**, *41*, 2135–2171. (c) Nucleoside analogue: Jeannot, F.; Gosselin, G.; Standring, D.; Bryant, M.; Sommadossi, J.-P.; Loi, A. G.; La Colla, P.; Mathé, C. *Bioorg. Med. Chem.* **2002**, *10*, 3153–3161. (d) For a review on the synthesis and applications of fluorinated nucleosides, see: Wójtowicz-Rajchel, H. *J.*

Fluorine Chem. **2012**, *143*, 11–48. (e) Estradiol derivative: Blazejewski, J.-C.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seo, H.-S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11*, 335–345.

(6) Catalytic methods are only limited to activated electrophiles. For selected examples, see: (a) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186–5191. (b) Chen, Q.-Y.; Wu, S.-W. *J. Chem. Soc., Chem. Commun.* **1989**, 705–706. (c) Miyake, Y.; Ota, S.-i.; Nishibayashi, Y. *Chem. Eur. J.* **2012**, *18*, 13255–13258. (d) Miyake, Y.; Ota, S.-i.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013**, *49*, 7809–7811. (e) Miyake, Y.; Ota, S.-i.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Org. Biomol. Chem.* **2014**, *12*, 5594–5596.

(7) (a) Jover, J.; Miloserdov, F. M.; Benet-Buchholz, J.; Grushin, V. V.; Maseras, F. *Organometallics* **2014**, *33*, 6531–6543. (b) Dubinina, G. G.; Brennessel, W. W.; Miller, J. L.; Vicic, D. A. *Organometallics* **2008**, *27*, 3933–3938.

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(14) For selected examples of difluoromethylation methods to generate sp^3 C–CF_2H moieties, see: (a) Cao, P.; Duan, J.-X.; Chen, Q.-Y. *J. Chem. Soc., Chem. Commun.* **1994**, 737–738. (b) Rozen, S.; Zamir, D. *J. Org. Chem.* **1991**, *56*, 4695–4700. (c) Martínez, A. G.; Barcina, J. O.; Rys, A. Z.; Subramanian, L. R. *Tetrahedron Lett.* **1992**, *33*, 7787–7788. (d) Bujok, R.; Makosza, M. *Synlett* **2002**, 1285–1286. (e) Sasson, R.; Hagooly, A.; Rozen, S. *Org. Lett.* **2003**, *5*, 769–771. (f) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050–5053. (g) Liu, G.; Wang, X.; Lu, X.; Xu, X.-H.; Tokunaga, E.; Shibata, N. *ChemistryOpen* **2012**, *1*, 227–231. (h) Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S.; Mikami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 9535–9538.

(15) For a recent review, see: Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135–147.

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(17) Notes: (a) Without the nickel source or the nucleophile, the TEMPO-electrophile adduct cannot be generated. (b) This TEMPO-electrophile adduct is stable under the cross-coupling reaction and also does not inhibit the carbon-carbon bond-forming process.

(18) Prepared from the corresponding acid anhydride, acid chloride, or ester, based on published procedures: (a) Regan, J. et al. *J. Med. Chem.* **2006**, *49*, 7887–7896. (b) Bergeron, M.; Johnson, T.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2011**, *50*, 11112–11116.

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(20) Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984−989.

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(22) Prepared according to a literature procedure: Yuan, H.; He, R.; Wan, B.; Wang, Y.; Pauli, G. F.; Franzblau, S. G.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5311–5315.

(23) Prepared from hexane-1,6-diol and furan-2-carbonyl chloride.

(24) Prepared from 6-chlorohexan-1-ol and 4-iodophenol.

(25) Prepared from 6-chlorohexan-1-ol and 1-(4-hydroxyphenyl)ethan-1-one.

(26) (a) Huo, S. *Org. Lett.* **2003**, *5*, 423–425. (b) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757.

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CHAPTER 4

Nickel-Catalyzed Asymmetric Negishi Arylations of α-Halo-α-Trifluoromethyl Electrophiles[+]

4.1 Introduction

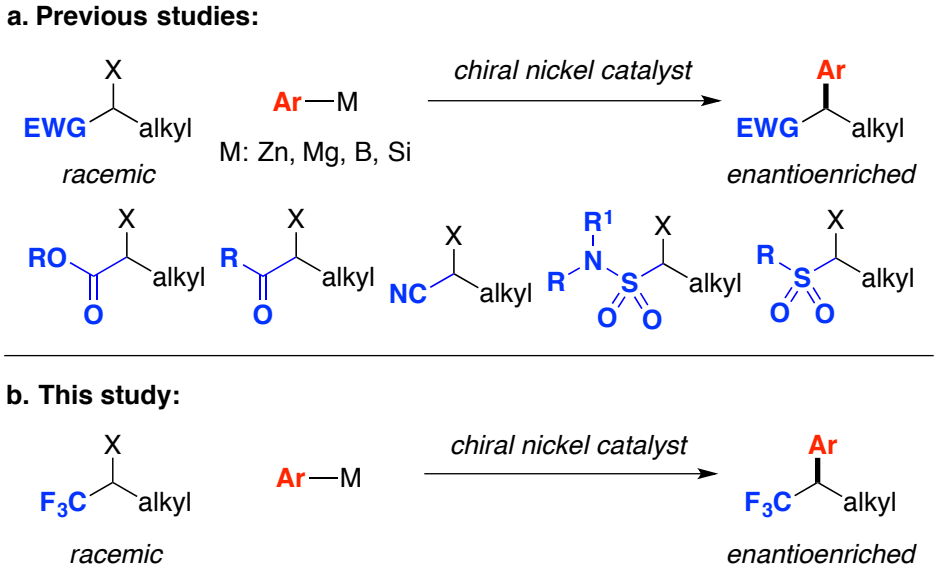
In Chapter 3, we describe our effort towards the development of a Negishi alkylation method using trifluoromethyl-substituted secondary electrophiles. Although the new method is quite versatile and practical, the attempt to extend it into an *enatioselective* alkylation method did not yield very positive results. We were still quite interested in exploring the possibility of providing such an approach to the construction of tertiary stereocenters bearing a trifluoromethyl (CF_3) group. Examples in the literature of catalytic enantioselective reactions that can generate this type of structures include the α-trifluoromethylation of aldehydes,[1] the hydrogenation of CF_3-containing olefins,[2] the nucleophilic trifluoromethylation of allylic electrophiles,[3] and the conjugate addition of CF_3-substituted electron-poor alkenes.[4] Many of these methods often require adjacent directing and/or activating groups (such as an aryl, alkenyl and carbonyl substituent) to achieve the bond formation and high levels of enantioselectivity. Therefore, the development of a general strategy without the need of pre-installed functional groups could complement existing methods. Our desired nickel-catalyzed cross-couplings of α-halo-α-trifluoromethyl electrophiles can be considered as a promising candidate to

[+] Portions of this chapter have appeared in the previous publication and the supporting information found therein: Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9523–9526.

achieve these goals. If a chiral catalyst can distinguish a trifluoromethyl (CF_3) group and an alkyl group effectively, high enantioselectivity can be obtained without the help from adjacent functional groups.

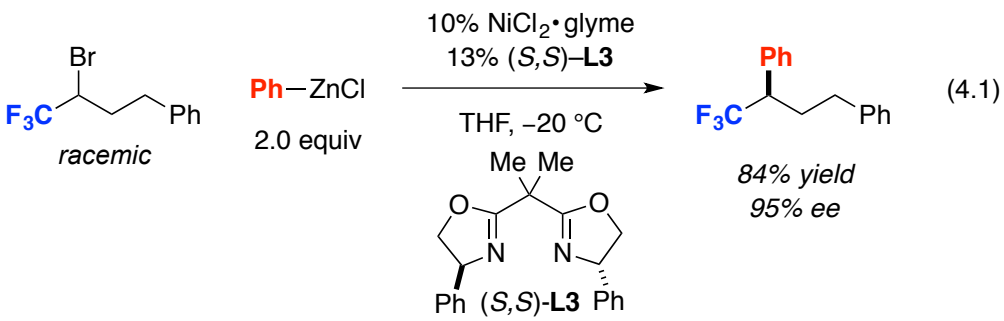
Our group has already reported a series of enantioselective arylation methods employing a variety of secondary alkyl electrophiles (Scheme 4.1a). One common feature of these reactions is that a halogen atom and an *electron-withdrawing group* are connected to the same carbon. Although the detailed conditions for each family of electrophiles may vary, to date, we have shown that secondary electrophiles including α-haloesters,[5] α-haloketones,[6] α-halonitriles,[7] α-halosulfones[8] and α-halosulfonamides[8] can all be suitable cross-coupling partners for enantioselective arylations. Considering the electron-withdrawing nature of a CF_3 group, it might be possible to achieve asymmetric arylations with α-halo-α-trifluoromethyl electrophiles when suitable catalysts are chosen (Scheme 4.1b). Therefore, this new method will provide a unique approach for the generation of tertiary trifluoromethyl-substituted stereocenters and at the same time expand the territory our nickel-catalyzed cross-coupling chemistry.

Scheme 4.1. Design of the Project



4.2 Optimization

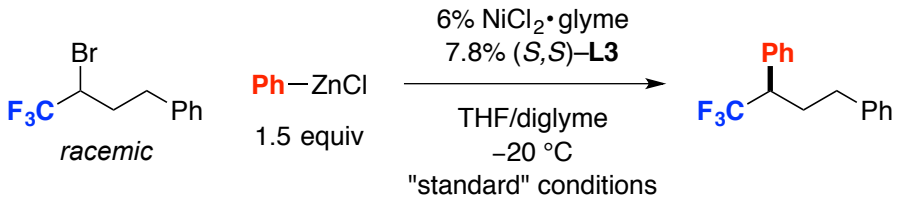
We decided to start this study by examining arylzinc reagents as the nucleophiles and quickly identified a very promising result. In the presence of a commercially available bis(oxazoline) ligand **L3**, the Negishi arylation reaction provides the product in good yield and excellent enantioselectivity (eq 4.1).



(4.1)

Further optimization based on this promising result led to a more general and practical condition (Table 4.1, entry 1). The impact of various reaction parameters on the outcome of this method is shown in Table 4.1.

Table 4.1. Effect of Parameters[a]



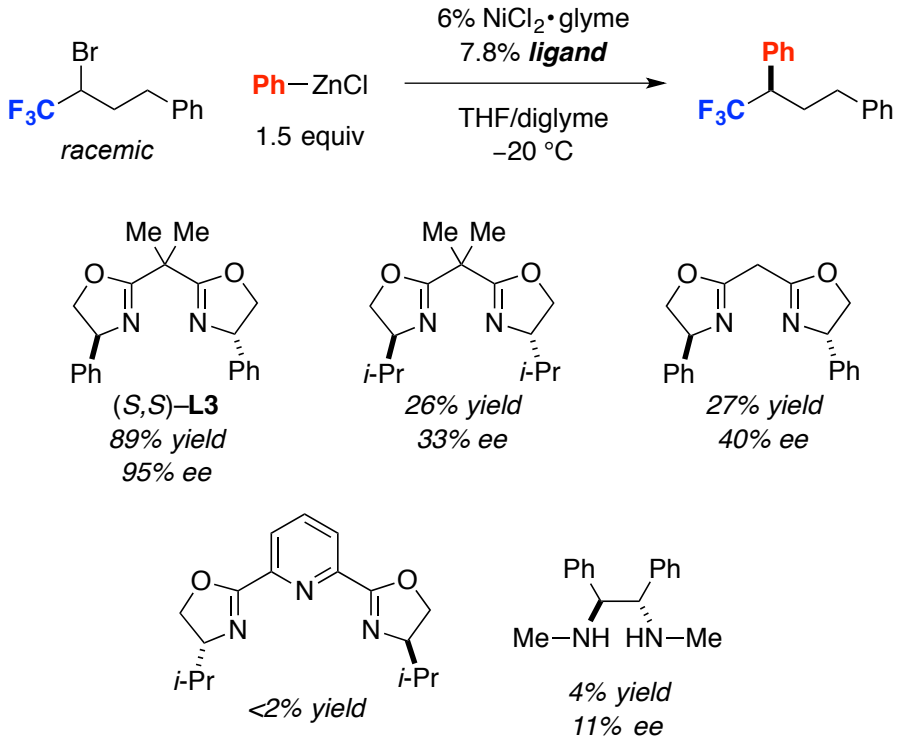
entry	variation from the "standard" conditions	ee (%)	yield (%)[b]
1	none	95	89
2	no $NiCl_2$•glyme	–	<2
3	no (*S,S*)-**L3**	–	3
4	1.1 equiv Ph–ZnCl	95	78
5	3.0% $NiCl_2$•glyme, 3.9% (*S,S*)-**1**	94	72
6	THF only	95	82
7	r.t., instead of –20 °C	86	15
8	0.1 equiv H_2O added	95	88

[a]All data are the average of two experiments. [b]The yields were determined through analysis by ^{19}F NMR spectroscopy with the aid of an internal standard.

Both the nickel source and the chiral ligand **L3** are important for this transformation (entries 2 and 3). When less amount of nucleophile or catalyst is employed, the product is generated in decreased yield but the enantioselectivity still maintained (entries 4 and 5). Diglyme serves as a co-solvent to increase the efficiency of the reaction (entry 6). At room temperature, the efficiency and stereoselectivity drop significantly (entry 7). Finally, the reaction condition is not sensitive to a small amount of water (entry 8).

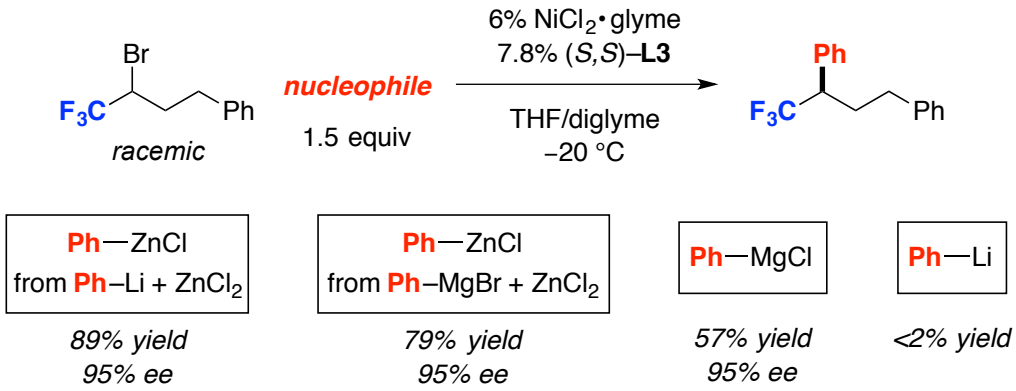
A number of structurally related or previously employed chiral ligands have been surveyed under our optimized conditions and the results are displayed in Scheme 4.2. All of these ligands provide the product in lower yields and ee values. From a practical perspective, both enantiomers of ligand **L3** are commercially available.

Scheme 4.2. Effect of Ligands



Additionally, similar to the trend we observed for the project described in Chapter 2, the nucleophilic arylating reagent also plays a very crucial role in this transformation (Scheme 4.3). Arylzinc reagents that are derived from aryllithium nucleophiles give the best results. However, arylzinc reagents prepared from aryl Grignard reagents and aryl Grignard reagents themselves can also be employed to deliver the cross-coupling products in good enantioselectivity with moderate yields.

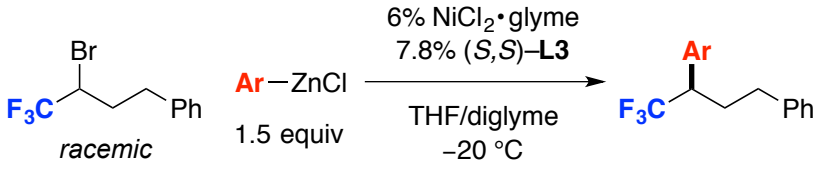
Scheme 4.3. Effect of Nucleophiles

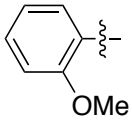
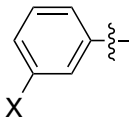
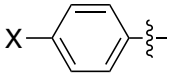


4.3 Scope

With the optimized conditions in hand, we decided to explore the scope of this new method. As shown in Table 4.2, a variety of ortho-, meta- and para-substituted arylzinc reagents are compatible nucleophilic cross-coupling partners. Both electron-rich and electron-poor nucleophiles can generate the products in good yields and enantioselectivity. Functional groups such as an aryl ether (entries 1 and 2), an aryl halide (entries 5, 6, 10, and 11), an aryl thioether (entry 9) can all be tolerated.

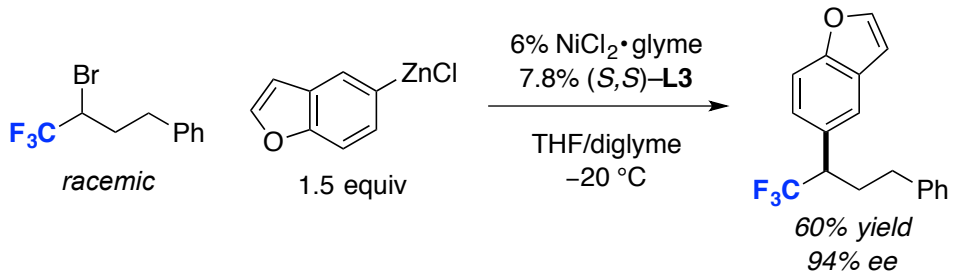
Table 4.2. Scope with Respect to the Nucleophile[a]



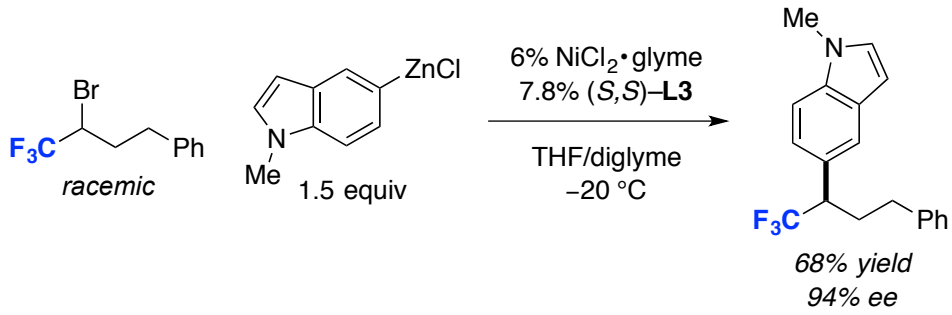
entry	Ar		ee (%)	yield (%)[b]
1			87	50
2		X = OMe	96	90
3		Me	95	90
4[c]		CF_3	97	87
5[c]		F	96	79
6[c]		Cl	96	86
7		X = H	95	86
8		Me	95	89
9		SMe	94	52
10[c]		F	96	84
11[c]		Br	95	87

[a]All data are the average of two experiments. [b]Yield of purified product. [c]Reaction temperature: –15 °C.

Arylzinc reagents with an oxygen heterocycle and a nitrogen heterocycle are also feasible nucleophiles for this transformation (eqs 4.2 and 4.3).



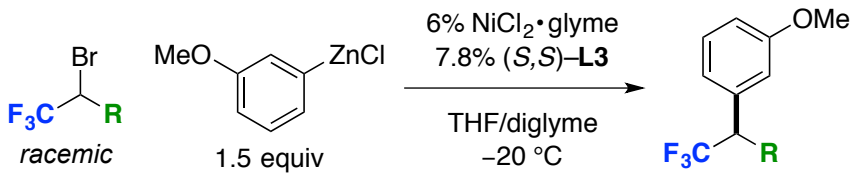
(4.2)

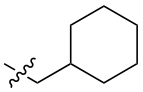
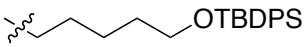
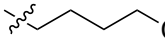
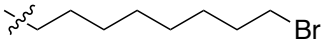
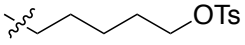
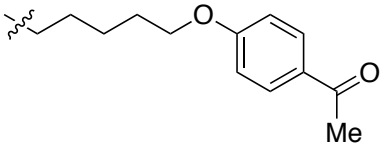
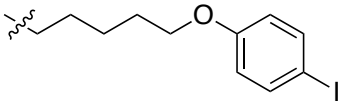
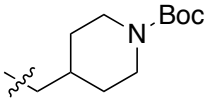
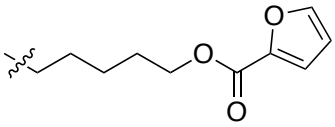


(4.3)

The scope with regard to the electrophilic cross-coupling partners is also fairly broad (Table 4.3). Synthetically useful functional groups including a silyl ether protecting group (entry 4), a primary alkyl chloride (entry 5), a primary alkyl bromide (entry 6), a primary alkyl tosylate (entry 7), an aromatic ketone (entry 8), an aryl iodide (entry 9), a carbamate (entry 10), and a furan-containing ester (entry 11) can all be compatible with our standard conditions. Also, the chiral catalyst can even effectively distinguish between a CF_3 group and a CH_3 group (entry 1) to provide the product in good stereoselectivity.[9]

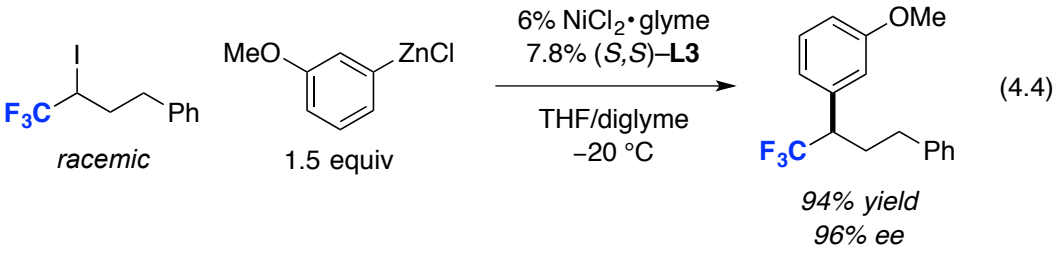
Table 4.3. Scope with Respect to the Electrophile[a]



entry	R	ee (%)	yield (%)[b]
1	Me	91	81
2	*n*-Oct	95	88
3		96	81
4		94	77
5		96	89
6		96	80
7		97	91
8		96	89
9		95	60
10		97	82
11		96	81

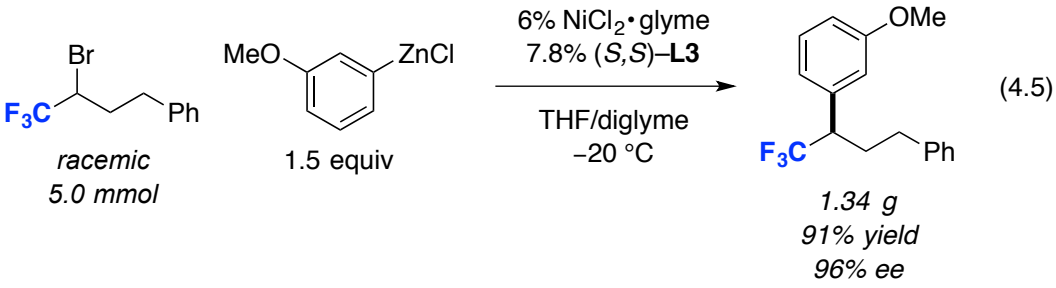
[a]All data are the average of two experiments. [b]Yield of purified product.

Although we initially optimized the reactions using alkyl bromides as substrates, we are delighted to observe that an alkyl iodide can also be a suitable electrophile for this new method (eq 4.4).

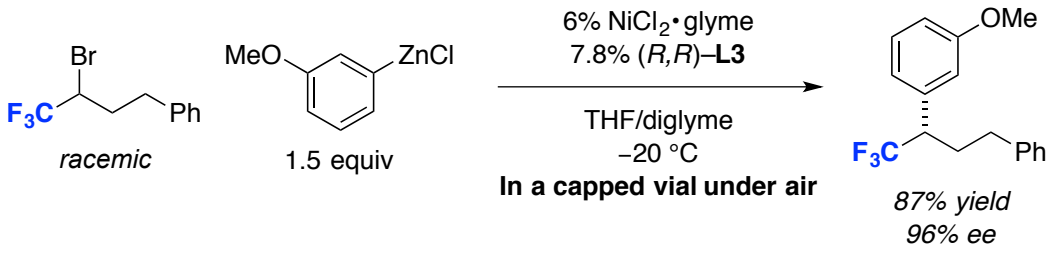


(4.4)

To demonstrate the scalability of this method, we performed a Negishi arylation reaction at a larger scale and the product was still generated in good yield and enantioselectivity (eq 4.5). Moreover, conducting the cross-coupling reaction in a closed vial under air led to similar efficiency (eq 4.6).



(4.5)



(4.6)

This method is not without limitations. Figure 4.1 summarizes a few electrophiles and nucleophiles that are not suitable cross-coupling partners under our optimized conditions (Table 4.1, entry 1).

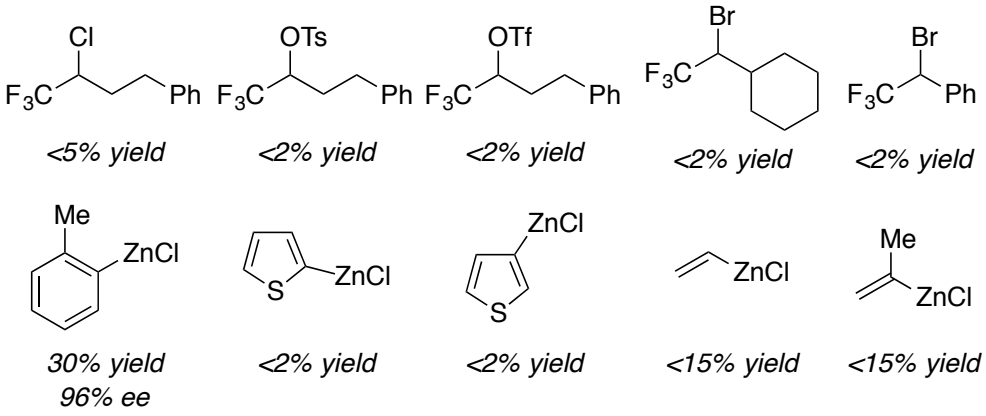


Figure 4.1. Unsuccessful Electrophiles and Nucleophiles

Other features of this method are provided below:

A. During the course of these cross-couplings, no kinetic resolution of the electrophile (<5% ee) was observed.

B. The ee value stays constant in the course of the reaction.

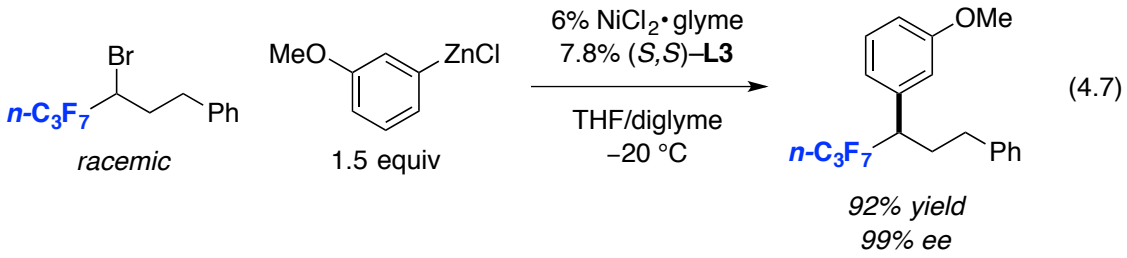
C. The cross-coupling product is stable under our reaction system. No C–F bond cleavage has been observed.

D. Major side reaction of this method is the hydrodebromination of the electrophile.

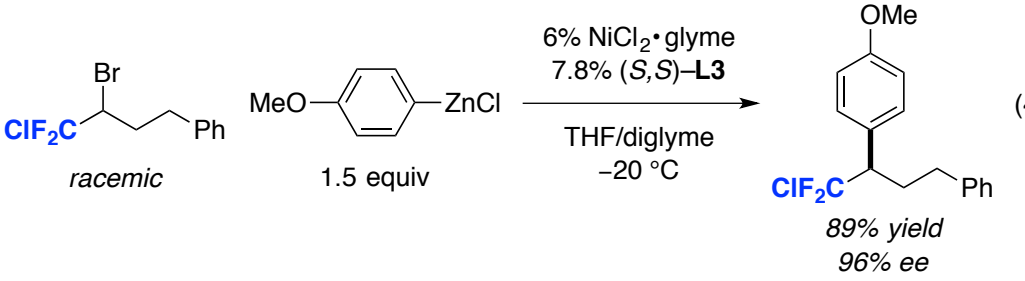
4.4 Scope of Other Fluorinated Electrophiles

This cross-coupling method can also be applied to substrates bearing an electron-withdrawing group other than CF_3. Electrophiles with a perfluoroalkyl group, a chlorodifluoromethyl group, a CF_2COPh substituent and a CF_2COOEt substituent can all undergo Negishi arylations to provide the products in good yield and excellent enantioselectivity (eqs 4.7, 4.8, 4.9, and 4.10). To the best of our knowledge, our method

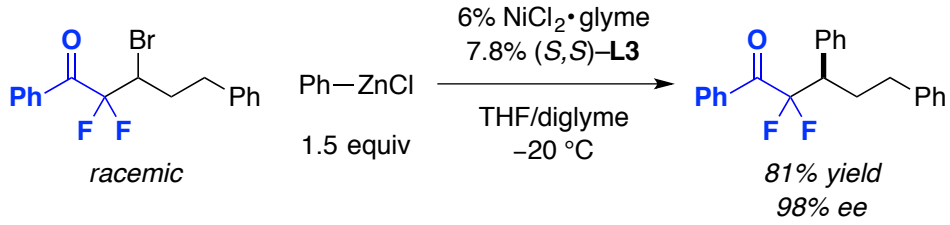
serves as the first method for the asymmetric of tertiary stereocenters containing these fluoroalkyl groups.[10]



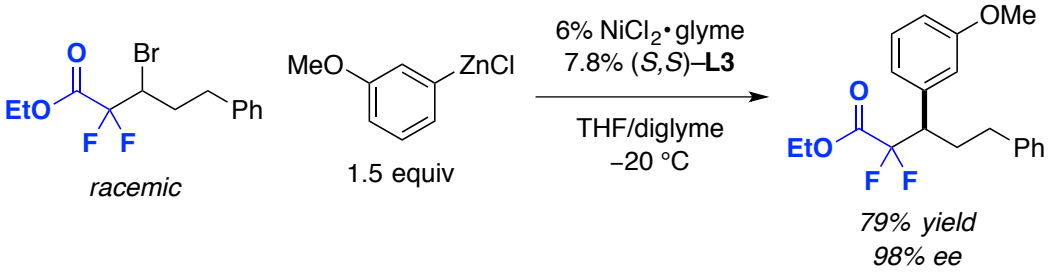
(4.7)



(4.8)



(4.9)



(4.10)

However, despite this success, our method still cannot be applied to any kinds of fluoroalkyl-containing electrophiles. A few unsuccessful cases are shown in Figure 4.2 (see entry 1 of Table 4.1 for reaction condition).

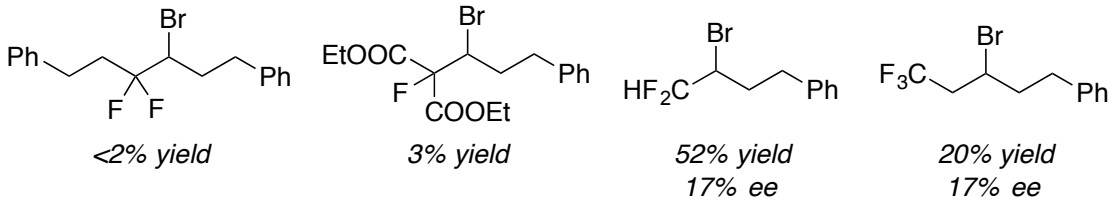


Figure 4.2. Problematic Fluoroalkyl-Containing Electrophiles

4.5 Conclusions

In summary, a highly enantioselective and versatile nickel-catalyzed Negishi arylation protocol has been developed employing α-halo-α-trifluoromethyl secondary electrophiles. This method not only provides a unique approach for the construction of tertiary CF_3-containing stereocenters without the necessity to pre-install directing or activating groups, but also expands our asymmetric Negishi arylation system to previously unknown substrates. Additionally, the ability to apply these conditions directly to substrates bearing a variety of fluoroalkyl groups also makes it a valuable strategy for the synthesis of potentially interesting fluorine-containing chiral building blocks.

After our method was published in early 2015, Zhang and co-workers reported a nickel-catalyzed *non*-asymmetric reductive cross-coupling method using the same type of electrophiles that we developed and aryl halides.[11]

4.6 Experimental Section

4.6.1 General Information

The following reagents were purchased and used as received: $NiCl_2$•glyme (Strem), ligand (*R,R*)–**L3** (Aldrich), ligand (*S,S*)–**L3** (Aldrich), $ZnCl_2$ (Aldrich; reagent grade, ≥98%), diglyme (Aldrich; anhydrous), *n*-BuLi (Aldrich; 2.5 M in hexanes). All

aryl bromides were purchased (Aldrich, Alfa Aesar, TCI, and Oakwood) and used as received. Anhydrous THF was purified and dried using a solvent-purification system that contained activated alumina.

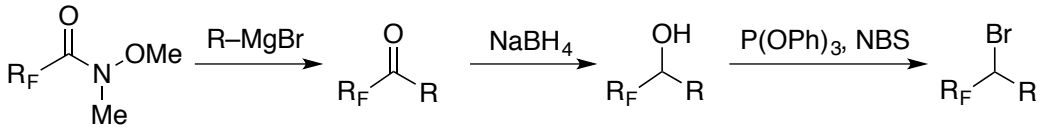
All reactions were carried out in oven-dried glassware under an inert atmosphere.

HPLC analyses were carried out on an Agilent 1100 Series system, using Daicel CHIRALCEL® columns or Daicel CHIRALPAK® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm).

^{1}H NMR data and ^{13}C NMR data were collected on a Varian 500 MHz spectrometer at ambient temperature. ^{19}F NMR data were collected on a Varian 300 MHz spectrometer at ambient temperature.

4.6.2 Preparation of Electrophiles

These procedures have not been optimized.



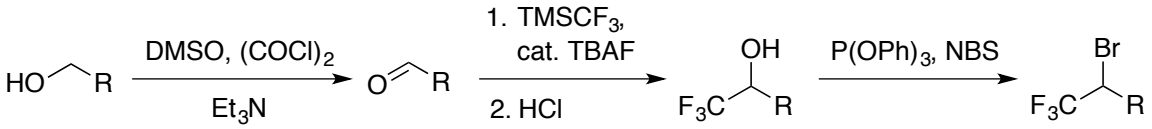
General Procedure A

Preparation of the ketone using a Grignard reagent. A solution of the Grignard reagent in THF (1.0 M, 40 mmol; 1.0 equiv) was added by syringe to a solution of the Weinreb amide[12] (40 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and then it was allowed to warm to r.t. and stirred for 15 h. Next, water was added to quench the reaction at 0 °C. A solution of 1 N HCl (50 mL) was added, and then the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic

layers were combined, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel.

Reduction of the ketone to the alcohol. $NaBH_4$ (2.3 g, 60 mmol; 3.0 equiv) was added in portions to a solution of the ketone (20 mmol) in Et_2O (20 mL) and MeOH (20 mL) at 0 °C (CAUTION: very exothermic). After the addition was complete, the mixture was stirred at 0 °C for 30 min, and then it was allowed to warm to r.t. and stirred for 30 min. Next, Et_2O (30 mL) was added to dilute the reaction mixture, the mixture was cooled to 0 °C, and then deionized water (30 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel.

Bromination of the alcohol.[13] Triphenylphosphite (4.0 g, 3.4 mL; 1.3 equiv) was added over 5 min to a solution of *N*-bromosuccinimide (2.3 g, 13 mmol; 1.3 equiv) in CH_2Cl_2 (10 mL) at 0 °C (CAUTION: exothermic). Next, a solution of the alcohol (10 mmol) in CH_2Cl_2 (12 mL) was added to the mixture at 0 °C. The reaction mixture was heated to 40 °C and then stirred at 40 °C for 12 h. Next, the solvent was evaporated, and the product was purified by flash chromatography on silica gel.



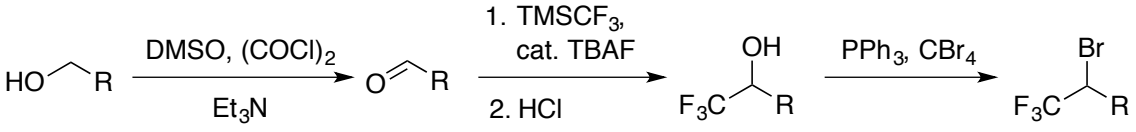
General Procedure B

Swern oxidation of the alcohol. DMSO (2.9 mL, 40 mmol; 2.0 equiv) was added slowly to a solution of oxalyl chloride (2.0 mL, 24 mmol; 1.2 equiv) in CH_2Cl_2 (150 mL)

at −78 °C. The resulting mixture was allowed to stir at −78 °C for 30 min. Next, a solution of the alcohol (20 mmol) in CH_2Cl_2 (30 mL) was added over 5 min to the mixture. The resulting mixture was stirred at −78 °C for 45 min, and then NEt_3 (11 mL, 80 mmol; 4.0 equiv) was added in one portion. The mixture was allowed to warm to r.t., and then it was stirred at r.t. for 2 h. Next, an aqueous saturated solution of NH_4Cl (30 mL) was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (3 × 70 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel.

Trifluoromethylation of the aldehyde.[14] A solution of TBAF (1.0 M in THF; 0.20 mL, 0.20 mmol; 0.013 equiv) was added over 3 min to a solution of the aldehyde (15 mmol) and trifluoromethyltrimethylsilane (2.7 mL, 18 mmol; 1.2 equiv) in THF (20 mL) at 0 °C (CAUTION: very exothermic). The reaction mixture was allowed to warm to r.t., and it was stirred for 1 h. Next, an aqueous solution of 1 N HCl (30 mL) was added, and the mixture was allowed to stir at r.t. for another 2 h. Then, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel.

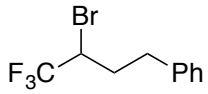
The bromination step is the same as in General Procedure A.



General Procedure C

The first two steps are the same as in General Procedure B.

Bromination of the alcohol.[15] Triphenylphosphine (4.2 g, 16 mmol; 2.0 equiv) and tetrabromomethane (5.3 g, 16 mmol; 2.0 equiv) were added to a solution of the alcohol (8.0 mmol) in toluene (20 mL). The resulting mixture was heated to 110 °C and stirred at 110 °C for 3 h, at which time it had turned into a yellow suspension. Then, CH_2Cl_2 (50 mL) was added to the reaction mixture until it became a clear solution. The solvents were then evaporated, and the crude product was purified by flash chromatography on silica gel.



(3-Bromo-4,4,4-trifluorobutyl)benzene [136832-35-4]. The title compound was synthesized according to General Procedure A, using 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide and a Grignard reagent prepared from (2-bromoethyl)benzene. The overall yield was 34% (3 steps). The title compound was isolated as a colorless oil.

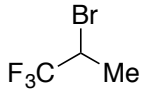
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.29 – 7.22 (m, 3H), 4.03 – 3.96 (m, 1H), 3.02 (ddd, 1H, J = 13.4, 8.3, 4.6 Hz), 2.81 – 2.75 (m, 1H), 2.40 – 2.33 (m, 1H), 2.21 (dddd, 1H, J = 14.6, 11.0, 8.2, 4.6 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 128.8, 128.5, 126.7, 124.0 (q, J = 278.2 Hz), 46.7 (q, J = 32.6 Hz), 32.9 (d, J = 1.4 Hz), 32.5;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.1 (d, 3F, J = 7.1 Hz);

FT-IR (film) 3029, 1258, 1168, 1111, 750, 700 cm^{-1};

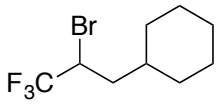
GC-MS (EI) *m/z* (M^+) calcd for $C_{10}H_{10}{}^{79}BrF_3$: 266, found: 266, 268 (M^++2).



2-Bromo-1,1,1-trifluoropropane [421-46-5]. The title compound was synthesized from 1,1,1-trifluoropropan-2-ol according to a literature procedure[16] in 68% yield (colorless oil; it should be stored in a refrigerator (~5 °C)).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (hept, 1H, *J* = 7.0 Hz), 1.81 (d, 3H, *J* = 7.0 Hz);

The NMR spectral data are in agreement with literature data.[17]



(2-Bromo-3,3,3-trifluoropropyl)cyclohexane. The title compound was synthesized according to General Procedure B, using 3-cyclohexyl-1,1,1-trifluoropropan-2-ol, in 46% yield (colorless oil).

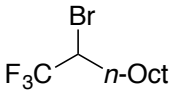
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (dqd, 1H, *J* = 3.7, 7.1, 10.8 Hz), 1.88 – 1.65 (m, 7H), 1.65 – 1.56 (m, 1H), 1.35 – 1.24 (m, 2H), 1.23 – 1.11 (m, 1H), 1.08 – 1.00 (m, 1H), 0.87 – 0.79 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 124.3 (q, *J* = 277.8 Hz), 45.5 (q, *J* = 32.4 Hz), 38.4, 34.5, 33.7, 31.0, 26.3, 26.1, 25.7;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.5 (d, 3F, *J* = 7.0 Hz);

FT-IR (film) 2925, 2854, 1450, 1314, 1291, 1271, 1258, 1180, 1157, 1128, 1109, 681 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_9H_{14}{}^{79}BrF_3$: 258, found: 258, 260 (M^++2).



2-Bromo-1,1,1-trifluorodecane [1349717-60-7]. The title compound was synthesized according to General Procedure A, using 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide and a Grignard reagent prepared from 1-bromooctane. The overall yield was 30% (3 steps). The title compound was isolated as a colorless oil.

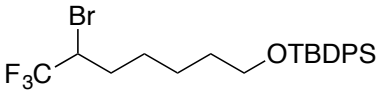
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dqd, 1H, J = 10.5, 7.2, 3.3 Hz), 2.02 (dddd, 1H, J = 14.6, 9.8, 6.1, 3.3 Hz), 1.91 – 1.81 (m, 1H), 1.43 – 1.21 (m, 12H), 0.89 (t, 3H, J = 7.2 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 124.1 (q, J = 278.0 Hz), 47.7 (q, J = 32.3 Hz), 31.8, 31.4 (d, J = 1.5 Hz), 29.23, 29.15, 28.6, 26.8, 22.6, 14.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.4 (d, 3F, J = 7.2 Hz);

FT-IR (film) 2956, 2928, 2857, 1266, 1173, 1124, 1105, 678 cm^{-1};

GC-MS (EI) *m/z* (M^+–C_4H_9) calcd for $C_6H_9{}^{79}BrF_3$: 217, found: 217, 219 (M^+–C_4H_9+2).



((6-Bromo-7,7,7-trifluoroheptyl)oxy)(*tert*-butyl)diphenylsilane. The title compound was synthesized according to General Procedure B from 6-((*tert*-butyldiphenylsilyl)oxy)hexan-1-ol.[18] The overall yield was 23% (3 steps). The title compound was isolated as a colorless oil.

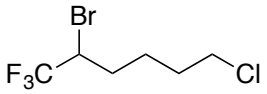
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.46 – 7.37 (m, 6H), 4.04 (dqd, 1H, *J* = 10.5, 7.2, 3.4 Hz), 3.69 (t, 2H, *J* = 6.3 Hz), 2.02 (dddd, 1H, *J* = 14.4, 9.8, 5.6, 3.3 Hz), 1.90 – 1.81 (m, 1H), 1.69 – 1.54 (m, 3H), 1.49 – 1.35 (m, 3H), 1.07 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 134.0, 129.6, 127.6, 124.1 (q, *J* = 278.2 Hz), 63.5, 47.6 (q, *J* = 32.4 Hz), 32.1, 31.4 (d, *J* = 1.4 Hz), 26.9, 26.5, 24.9, 19.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, *J* = 7.1 Hz);

FT-IR (film) 2932, 2858, 1428, 1259, 1171, 1113, 823, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+–C_4H_9) calcd for $C_{19}H_{21}{}^{79}BrF_3OSi$: 429, found: 429.



2-Bromo-6-chloro-1,1,1-trifluorohexane. The title compound was synthesized according to General Procedure B from using 6-chloro-1,1,1-trifluorohexan-2-ol. The overall yield was 44% yield (3 steps). The title compound was isolated as a colorless oil.

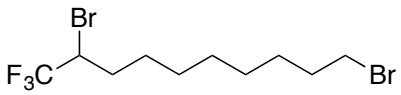
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 (dqd, 1H, *J* = 3.3, 7.1, 10.5 Hz), 3.58 – 3.55 (m, 2H), 2.11 – 2.04 (m, 1H), 1.94 – 1.78 (m, 4H), 1.66 – 1.57 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 123.9 (q, *J* = 278.1 Hz), 47.2 (q, *J* = 32.6 Hz), 44.3, 31.5, 30.8 (d, *J* = 1.5 Hz), 24.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, *J* = 7.1 Hz);

FT-IR (film) 2957, 1330, 1259, 1167, 1111, 677 cm^{-1};

GC-MS (EI) *m/z* (M^+−HBr) calcd for $C_6H_8ClF_3$: 172, found: 172.



2,10-Dibromo-1,1,1-trifluorodecane. The title compound was synthesized according to General Procedure B from 9-bromononan-1-ol. The overall yield was 50% (3 steps). The title compound was isolated as a colorless oil.

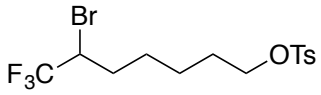
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dqd, 1H, *J* = 10.5, 7.1, 3.3 Hz), 3.41 (t, 2H, *J* = 6.8 Hz), 2.02 (dddd, 1H, *J* = 14.5, 9.8, 6.1, 3.3 Hz), 1.89 – 1.82 (m, 3H), 1.47 – 1.28 (m, 10H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 124.0 (q, *J* = 278.2 Hz), 47.7 (q, *J* = 32.4 Hz), 33.9, 32.7, 31.3 (d, *J* = 1.5 Hz), 29.0, 28.56, 28.48, 28.0, 26.7;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, *J* = 7.1 Hz);

FT-IR (film) 2931, 2857, 1267, 1169, 1110, 677 cm^{-1};

GC-MS (EI) *m/z* (M^+–C_3H_6Br) calcd for $C_7H_{11}{}^{79}BrF_3$: 231, found: 231, 233 (M^+–C_3H_6Br+2).



6-Bromo-7,7,7-trifluoroheptyl 4-methylbenzenesulfonate. The title compound was synthesized according to General Procedure B from 6-hydroxyhexyl 4-methylbenzenesulfonate.[19] The overall yield was 52% (3 steps). The title compound was isolated as a colorless oil.

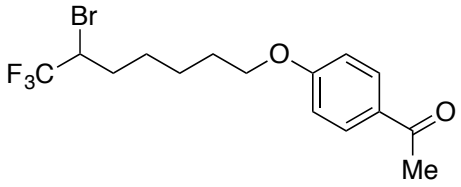
^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.83 – 7.79 (m, 2H), 7.51 – 7.46 (m, 2H), 4.55 (dqd, 1H, *J* = 10.7, 7.4, 3.3 Hz), 4.07 (t, 2H, *J* = 6.3 Hz), 2.46 (s, 3H), 2.04 – 1.99 (m, 1H), 1.85 – 1.76 (m, 1H), 1.73 – 1.55 (m, 3H), 1.52 – 1.30 (m, 3H);

^{13}C NMR (126 MHz, CD_3COCD_3) δ 145.9, 134.5, 131.0, 128.8, 125.5 (q, *J* = 277.2 Hz), 71.4, 48.4 (q, *J* = 32.0 Hz), 32.0 (d, *J* = 1.6 Hz), 29.3, 26.9, 25.2, 21.6;

^{19}F NMR (282 MHz, CD_3COCD_3) δ −72.9 (d, 3F, *J* = 7.4 Hz);

FT-IR (film) 2948, 1598, 1359, 1189, 1176, 1117, 1098, 951, 815, 664 cm^{-1};

GC-MS (EI) *m/z* (M^+–OTs) calcd for $C_7H_{11}{}^{79}BrF_3$: 231, found: 231, 233 (M^+–OTs+2).



1-(4-((6-Bromo-7,7,7-trifluoroheptyl)oxy)phenyl)ethan-1-one. The title compound was synthesized according to General Procedure C from 1-(4-((6-hydroxyhexyl)oxy)phenyl)ethan-1-one.[20] The overall yield was 57% (3 steps). The title compound was isolated as a light-yellow oil (it should be stored in a refrigerator (~5 °C)).

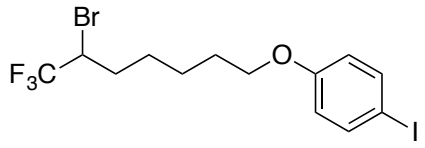
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 2H), 6.93 – 6.89 (m, 2H), 4.12 – 4.05 (m, 1H), 4.03 (t, 2H, *J* = 6.3 Hz), 2.55 (s, 3H), 2.07 (dddd, 1H, *J* = 14.4, 10.1, 5.6, 3.4 Hz), 1.94 – 1.80 (m, 3H), 1.78 – 1.68 (m, 1H), 1.62 – 1.47 (m, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 162.9, 130.6, 130.2, 124.0 (q, *J* = 278.2 Hz), 114.0, 67.8, 47.4 (q, *J* = 32.4 Hz), 31.3 (d, *J* = 1.4 Hz), 28.7, 26.5, 26.3, 25.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, *J* = 7.1 Hz);

FT-IR (film) 2946, 2867, 1676, 1602, 1576, 1509, 1358, 1257, 1172, 1117, 834 cm^{-1};

GC-MS (EI) *m/z* (M^+–CH_3) calcd for $C_{14}H_{15}{}^{79}BrF_3O_2$: 351, found: 351, 353 ($M^+$–$CH_3$+2).



1-((6-Bromo-7,7,7-trifluoroheptyl)oxy)-4-iodobenzene. The title compound was synthesized according to General Procedure B from 6-(4-iodophenoxy)hexan-1-ol.[21] The overall yield was 33% (3 steps). The title compound was isolated as a colorless oil (it should be stored in a refrigerator (~5 °C)).

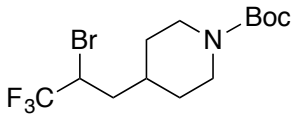
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 6.69 – 6.65 (m, 2H), 4.08 (dqd, 1H, *J* = 10.5, 7.1, 3.4 Hz), 3.93 (t, 2H, *J* = 6.3 Hz), 2.07 (dddd, 1H, *J* = 14.3, 9.9, 5.5, 3.4 Hz), 1.95 – 1.86 (m, 1H), 1.85 – 1.68 (m, 3H), 1.60 – 1.46 (m, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 138.2, 124.0 (q, *J* = 278.2 Hz), 116.9, 82.6, 67.6, 47.5 (q, *J* = 32.5 Hz), 31.3 (d, *J* = 1.4 Hz), 28.8, 26.6, 25.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, *J* = 7.1 Hz);

FT-IR (film) 2944, 1587, 1487, 1473, 1283, 1245, 1175, 1117, 820 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{13}H_{15}{}^{79}BrF_3IO$: 450, found: 450, 452 ($M^+$+2).



***tert*-Butyl 4-(2-bromo-3,3,3-trifluoropropyl)piperidine-1-carboxylate.** The title compound was synthesized according to General Procedure C from *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate. The overall yield was 26% (3 steps). The title compound was isolated as a white solid.

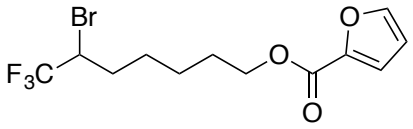
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 – 4.09 (m, 3H), 2.72 – 2.68 (m, 2H), 1.94 – 1.85 (m, 1H), 1.85 – 1.72 (m, 2H), 1.68 – 1.63 (m, 2H), 1.44 (s, 9H), 1.23 (tdd, 1H, *J* = 12.8, 11.0, 4.4 Hz), 1.03 (tdd, 1H, *J* = 12.7, 11.0, 4.5 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 124.1 (q, *J* = 278.1 Hz), 79.5, 44.8 (q, *J* = 32.7 Hz), 37.6, 33.2, 32.4, 30.0, 28.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.5 (d, 3F, *J* = 7.0 Hz);

FT-IR (film) 2977, 2931, 2850, 1691, 1425, 1366, 1262, 1252, 1172, 1129, 1110, 967, 685 cm^{-1};

GC-MS (EI) *m/z* (M^+–Boc) calcd for $C_8H_{12}{}^{79}BrF_3N$: 258, found: 258, 260 (M^+–Boc+2).



6-Bromo-7,7,7-trifluoroheptyl furan-2-carboxylate. The title compound was synthesized according to General Procedure B from 6-hydroxyhexyl furan-2-carboxylate.[22] The overall yield was 62% (3 steps). The title compound was isolated as a light-yellow oil (it should be stored in a refrigerator (~5 °C)).

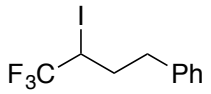
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, 1H, *J* = 1.8, 0.9 Hz), 7.17 (dd, 1H, *J* = 3.5, 0.9 Hz), 6.51 (dd, 1H, *J* = 3.5, 1.7 Hz), 4.31 (t, 2H, *J* = 6.6 Hz), 4.07 (dqd, 1H, *J* = 10.5, 7.1, 3.4 Hz), 2.05 (dddd, 1H, *J* = 14.7, 10.3, 5.6, 3.3 Hz), 1.93 – 1.84 (m, 1H), 1.82 – 1.68 (m, 3H), 1.55 – 1.42 (m, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 146.3, 144.7, 124.0 (q, *J* = 278.1 Hz), 117.8, 111.8, 64.6, 47.4 (q, *J* = 32.5 Hz), 31.3 (d, *J* = 1.5 Hz), 28.4, 26.5, 25.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3 (d, 3F, J = 7.0 Hz);

FT-IR (film) 2949, 2866, 1726, 1582, 1571, 1475, 1400, 1297, 1260, 1180, 1118, 1014, 958, 885, 764, 677 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{12}H_{14}{}^{79}BrF_3O_3$: 342, found: 342, 344 ($M^+$+2).



(4,4,4-Trifluoro-3-iodobutyl)benzene. The title compound was synthesized according to General Procedure A, using 1,1,1-trifluoro-4-phenylbutan-2-ol, in 48% yield (colorless oil; it should be stored in a refrigerator (~5 °C)); *N*-iodosuccinimide, rather than *N*-bromosuccinimide, was used.

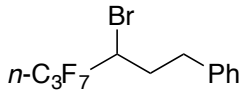
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 7.28 – 7.22 (m, 3H), 4.09 – 4.00 (m, 1H), 3.00 (dt, 1H, J = 6.4, 13.4 Hz), 2.71 (dt, 1H, J = 8.2, 13.9 Hz), 2.23 – 2.16 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 128.8, 128.5, 126.7, 124.6 (q, J = 276.5 Hz), 34.4, 34.2 (d, J = 1.6 Hz), 23.6 (q, J = 31.1 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −68.8 (d, 3F, J = 8.0 Hz);

FT-IR (film) 3028, 1455, 1257, 1161, 1094, 1075, 749 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{10}H_{10}F_2I$: 314, found: 314.



(3-Bromo-4,4,5,5,6,6,6-heptafluorohexyl)benzene. The title compound was synthesized according to General Procedure A, using 2,2,3,3,4,4,4-heptafluoro-*N*-

methoxy-*N*-methylbutanamide and a Grignard reagent prepared from (2-bromoethyl)benzene. The overall yield was 24% (3 steps). The title compound was isolated as a colorless oil.

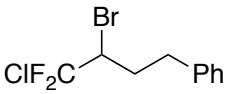
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 3H), 7.28 – 7.22 (m, 2H), 4.19 – 4.08 (m, 1H), 3.06 (ddd, 1H, J = 13.3, 8.4, 4.4 Hz), 2.80 (dt, 1H, J = 13.9, 8.2 Hz), 2.43 – 2.36 (m, 1H), 2.27 – 2.17 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 128.8, 128.5, 126.7, 121.5 – 108.5 (m), 46.5 (t, J = 24.5 Hz), 32.6, 32.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (t, 3F, J = 10.7 Hz), −109.2 – −115.5 (m, 2F), –123.3 (dd, 2F, J = 20.0, 8.1 Hz);

FT-IR (film) 3029, 2936, 1497, 1456, 1348, 1235, 1182, 1108, 964, 927, 750, 724, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{12}H_{10}{}^{79}BrF_7$: 366, found: 366, 368 (M^++2).



(3-Bromo-4-chloro-4,4-difluorobutyl)benzene. The title compound was synthesized according to General Procedure A, using 1-chloro-1,1-difluoro-4-phenylbutan-2-ol, in 48% yield (colorless oil).

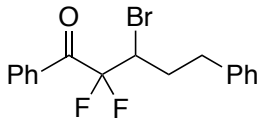
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 2H), 7.27 – 7.23 (m, 3H), 4.12 (tdd, 1H, J = 2.6, 5.6, 11.1 Hz), 3.04 (ddd, 1H, J = 4.5, 8.3, 13.3 Hz), 2.78 (dt, 1H, J = 8.3, 13.9 Hz), 2.50 – 2.43 (m, 1H), 2.22 (dddd, 1H, J = 4.4, 8.1, 11.0, 14.5 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 128.7, 128.5, 127.6 (dd, J = 292.5, 294.2 Hz), 126.7, 53.7 (t, J = 27.0 Hz), 34.2, 32.6;

^{19}F NMR (282 MHz, $CDCl_3$) δ −53.7 (dd, 1F, *J* = 5.7, 162.3 Hz), −57.5 (dd, 1F, *J* = 11.1, 162.4 Hz);

FT-IR (film) 3029, 2929, 1497, 1455, 1256, 1203, 1169, 1116, 1080, 1031, 947, 751, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{10}H_{10}{}^{79}BrClF_2$: 282, found: 282, 284 ($M^+$+2);



3-Bromo-2,2-difluoro-1,5-diphenylpentan-1-one. The title compound was synthesized according to General Procedure B, using 2,2-difluoro-3-hydroxy-1,5-diphenylpentan-1-one,[23] in 44% yield (colorless oil).

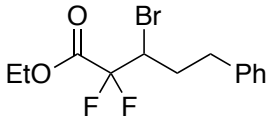
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 8.05 (m, 2H), 7.67 – 7.64 (m, 1H), 7.52 – 7.48 (m, 2H), 7.34 – 7.30 (m, 2H), 7.27 – 7.22 (m, 3H), 4.46 (dtd, 1H, *J* = 2.6, 11.1, 14.9 Hz), 3.08 (ddd, 1H, *J* = 4.5, 8.7, 13.5 Hz), 2.80 (dt, 1H, *J* = 8.3, 13.9 Hz), 2.45 – 2.38 (m, 1H), 2.30 – 2.22 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.3 (dd, *J* = 28.9, 30.6 Hz), 139.6, 134.4, 132.2 (t, *J* = 2.3 Hz), 130.0 (dd, *J* = 2.7, 4.1 Hz), 128.7, 128.6, 128.5, 126.4, 116.1 (dd, *J* = 256.9, 261.0 Hz), 49.6 (dd, *J* = 24.1, 26.9 Hz), 32.8, 32.2 (t, *J* = 2.2 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −101.1 (dd, 1F, *J* = 11.1, 275.8 Hz), −105.7 (dd, 1F, *J* = 14.9, 275.7 Hz);

FT-IR (film) 3063, 3028, 2930, 1702, 1598, 1497, 1449, 1281, 1251, 1203, 1185, 1046, 923, 898, 754, 717, 700, 687 cm^{-1};

GC-MS (EI) *m/z* (M^+−Br) calcd for $C_{17}H_{15}F_2O$: 273, found: 273.



Ethyl 3-bromo-2,2-difluoro-5-phenylpentanoate. The title compound was synthesized according to General Procedure B, using ethyl 2,2-difluoro-3-hydroxy-5-phenylpentanoate,[24] in 87% yield (colorless oil).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.31 (m, 2H), 7.26 – 7.21 (m, 3H), 4.35 (q, 2H, *J* = 7.1 Hz), 4.23 – 4.15 (m, 1H), 3.03 (ddd, 1H, *J* = 4.6, 8.5, 13.5 Hz), 2.76 (dt, 1H, *J* = 8.3, 13.9 Hz), 2.36 – 2.29 (m, 1H), 2.20 (dddd, 1H, *J* = 4.6, 8.5, 11.1, 14.8 Hz), 1.34 (t, 3H, *J* = 7.1 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 (t, *J* = 32.3 Hz), 139.6, 128.7, 128.5, 126.5, 113.5 (dd, *J* = 253.1, 258.0 Hz), 63.4, 49.2 (dd, *J* = 25.5, 28.0 Hz), 32.7, 31.9, 13.8;

^{19}F NMR (282 MHz, $CDCl_3$) δ −105.1 (dd, 1F, *J* = 9.0, 255.8 Hz), −114.4 (dd, 1F, *J* = 15.9, 255.8 Hz);

FT-IR (film) 3028, 2984, 1776, 1760, 1497, 1455, 1373, 1311, 1251, 1218, 1102, 1061, 753, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{13}H_{15}{}^{79}BrF_2O_2$: 320, found: 320, 322 ($M^+$+2).

4.6.3 Stereoconvergent Negishi Cross-Couplings

General procedure for the preparation of a solution of the arylzinc reagent (0.30 M): $ZnCl_2$ (Aldrich; reagent grade, ≥98%) was fused through drying with a heat gun under high vacuum for 20 min before use. *n*-BuLi (Aldrich; ~2.5 M in hexanes) was titrated using diphenylacetic acid, according to Kofron's method.[25]

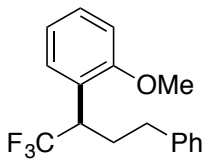
In the air, $ZnCl_2$ (1.43 g, 10.5 mmol) was added quickly to an oven-dried 20 mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap, and then it was evacuated and back-filled with nitrogen (three cycles). THF (6.0 mL) was added to the vial, and the resulting mixture was stirred vigorously until the $ZnCl_2$ had completely dissolved. THF (0.5 mL) was then added, thereby providing a 1.50 M solution of $ZnCl_2$. Next, an oven-dried 40 mL vial equipped with a stir bar was charged with the aryl bromide (9.00 mmol), and then it was closed with a PTFE septum cap. The vial was next evacuated and back-filled with nitrogen (three cycles), and then THF (6.5 mL) was added to this vial. The vial that contained the solution of the aryl bromide was cooled to −78 °C. A solution of *n*-BuLi in hexanes (2.57 M; 3.50 mL, 9.00 mmol; 1.00 equiv) was added over ~4 min to the solution of the aryl bromide. After the addition was complete, the resulting mixture was stirred at −78 °C for 7 min. Next, the solution of $ZnCl_2$ (1.50 M; 6.00 mL, 9.00 mmol; 1.00 equiv) was added to the vial. The resulting mixture was allowed to warm to r.t., and then it was stirred for 45 min at r.t. The solution of the arylzinc reagent was titrated using I_2, according to Knochel's method[26] (the concentration was typically ~0.4 M). This solution was then diluted to a 0.30 M solution using THF.

These solutions of organozinc reagents can be stored at r.t. under an inert atmosphere for several weeks without deterioration.

General Procedure for stereoconvergent Negishi arylations: In the air, an oven-dried 20 mL vial equipped with a stir bar was charged with the electrophile (1.00 mmol). The vial was closed with a PTFE septum cap, and then it was evacuated and back-filled with nitrogen (three cycles). In the air, $NiCl_2$·glyme (13.2 mg, 0.060 mmol)

and (*R,R*)–**L3** (26.1 mg, 0.078 mmol) were added to an oven-dried 4 mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap, and then it was evacuated and back-filled with nitrogen (three cycles). Diglyme (1.5 mL) was added to the vial, and the mixture was vigorously stirred at r.t. for 30 min. The resulting solution was transferred via syringe to the 20 mL reaction vial that contained the electrophile. The 4 mL vial was rinsed with THF three times (0.8 mL, 0.8 mL, and 0.7 mL), and the washings were transferred to the reaction vial. The resulting solution was stirred at r.t. for 3 min. Then, the joint of the reaction vial was wrapped with electrical tape, and the vial was cooled to −20 °C. Meanwhile, an oven-dried 40 mL vial that contained the solution of the arylzinc reagent was also cooled to −20 °C. Nitrogen-filled balloons were attached to both of the vials. To the vigorously stirred solution of catalyst and electrophile was added the solution of the arylzinc reagent (0.30 M; 5.0 mL, 1.5 mmol; 1.5 equiv) over 3 min, leading to an orange reaction mixture. The balloon was removed, and the puncture hole in the septum cap was covered with grease. The mixture was stirred vigorously at −20 °C for 14 h, and then the reaction was quenched by the addition of MeOH (2 mL). The resulting mixture was allowed to warm to r.t., and then it was diluted with Et_2O (100 mL) and washed with deionized water (20 mL × 4). The organic layer was dried over Na_2SO_4, filtered, and then concentrated, and the residue was purified by flash chromatography.

A second run was performed with (*S,S*)–**L3**.



(*R*)-1-Methoxy-2-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (Table 4.2, Entry 1). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-2-methoxybenzene were used. The reaction was run at −20 °C for 40 h. Solvent system for chromatography: 15:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 150 mg (51% yield, 88% ee); Run 2, 140 mg (48% yield, 86% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 15.5 min (minor), 16.4 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 1H), 7.33 (ddd, 1H, *J* = 1.7, 7.4, 8.2 Hz), 7.30 – 7.26 (m, 2H), 7.22 – 7.18 (m, 1H), 7.11 – 7.09 (m, 2H), 7.03 (td, 1H, *J* = 1.1, 7.5 Hz), 6.95 (dd, 1H, *J* = 1.1, 8.3 Hz), 4.08 (dqd, 1H, *J* = 4.2, 9.7, 11.2 Hz), 3.82 (s, 3H), 2.57 – 2.44 (m, 2H), 2.33 (dddd, 1H, *J* = 4.2, 7.1, 9.8, 13.4 Hz), 2.18 (dddd, 1H, *J* = 5.1, 9.5, 11.0, 13.5 Hz);

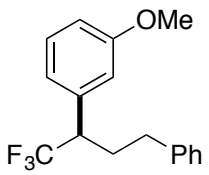
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 141.1, 129.0, 128.4, 128.3, 128.2, 127.2 (q, *J* = 280.9 Hz), 126.0, 123.1, 120.8, 110.9, 55.6, 39.8 (q, *J* = 27.2 Hz), 32.6, 30.4 (d, *J* = 2.5 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.5 (d, 3F, *J* = 9.6 Hz);

FT-IR (film) 2941, 1603, 1496, 1464, 1246, 1148, 1118, 1030, 753, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{17}F_3O$: 294, found: 294;

$[\alpha]^{25}_D$ = +12° (*c* = 1.01, $CHCl_3$); 86% ee, from (*S,S*)-**L3**.



(*R*)-1-Methoxy-3-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (Table 4.2, Entry 2). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 5:1 → 4:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 268 mg (91% yield, 96% ee); Run 2, 260 mg (88% yield, 96% ee).

This compound was also prepared on a 5.00 mmol scale (eq 4.5), using (3-bromo-4,4,4-trifluorobutyl)benzene (1.34 g, 5.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene (0.30 M; 25 mL, 7.5 mmol; 1.5 equiv). Following the General Procedure, the title compound was isolated in 91% yield (1.34 g) and 96% ee.

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 20.4 min (minor), 32.2 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 3H), 7.24 – 7.20 (m, 1H), 7.13 – 7.10 (m, 2H), 6.93 – 6.89 (m, 2H), 6.87 – 6.84 (m, 1H), 3.84 (s, 3H), 3.21 (dqd, 1H, J = 3.9, 9.3, 11.1 Hz), 2.61 (ddd, 1H, J = 4.9, 9.1, 13.9 Hz), 2.44 (ddd, 1H, J = 7.8, 8.9, 13.8 Hz), 2.34 (dddd, 1H, J = 3.9, 7.7, 9.1, 13.2 Hz), 2.21 (dddd, 1H, J = 4.9, 9.0, 11.2, 13.8 Hz);

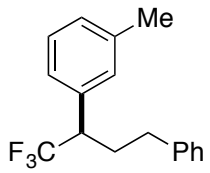
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 140.6, 135.9 (d, J = 2.0 Hz), 129.7, 128.5, 128.4, 126.9 (q, J = 280.6 Hz), 126.2, 121.5, 115.2, 113.3, 55.2, 49.2 (q, J = 26.5 Hz), 32.5, 30.2 (d, J = 2.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.6 (d, 3F, J = 9.3 Hz);

FT-IR (film) 3028, 2956, 1603, 1586, 1496, 1454, 1258, 1157, 1110, 1044, 781, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{17}F_3O$: 294, found: 294;

$[\alpha]^{25}_D$ = +48° (*c* = 0.97, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.



(*R*)-1-Methyl-3-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (Table 4.2, Entry 3). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methylbenzene were used. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 247 mg (89% yield, 95% ee); Run 2, 252 mg (91% yield, 95% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 12.4 min (minor), 13.5 min (major).

^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.35 – 7.12 (m, 9H), 3.48 – 3.37 (m, 1H), 2.58 – 2.44 (m, 2H), 2.37 (s, 3H), 2.35 – 2.21 (m, 2H);

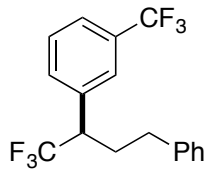
^{13}C NMR (126 MHz, CD_3COCD_3) δ 142.0, 139.3, 135.4 (d, J = 2.1 Hz), 130.9, 129.9, 129.6, 129.4, 129.3, 128.4 (q, J = 279.9 Hz), 127.3, 127.1, 49.8 (q, J = 26.1 Hz), 33.4, 31.1 (d, J = 2.2 Hz), 21.5;

^{19}F NMR (282 MHz, CD_3COCD_3) δ −70.2 (d, 3F, J = 9.7 Hz);

FT-IR (film) 3028, 2955, 1496, 1454, 1259, 1171, 1147, 1110, 785, 708, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{17}F_3$: 278, found: 278;

$[\alpha]^{25}_D$ = −46° (*c* = 0.97, $CHCl_3$); 95% ee, from (*S,S*)-**L3**.



(*R*)-1-(1,1,1-Trifluoro-4-phenylbutan-2-yl)-3-(trifluoromethyl)benzene (Table 4.2, Entry 4). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-(trifluoromethyl)benzene were used. The reaction was run at −15 °C for 14 h. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 287 mg (86% yield, 96% ee); Run 2, 288 mg (87% yield, 97% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 14.6 min (minor), 17.4 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.63 (m, 1H), 7.56 – 7.48 (m, 3H), 7.33 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 7.10 – 7.05 (m, 2H), 3.30 (dqd, 1H, J = 3.6, 9.0, 10.8 Hz), 2.65 – 2.56 (m, 1H), 2.47 – 2.36 (m, 2H), 2.30 – 2.20 (m, 1H);

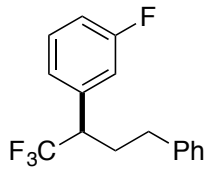
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 135.5 (d, J = 2.2 Hz), 132.5, 131.2 (q, J = 32.5 Hz), 129.3, 128.6, 128.3, 126.5 (q, J = 280.7 Hz), 126.4, 126.1 (q, J = 3.9 Hz), 125.2 (q, J = 3.7 Hz), 123.9 (q, J = 271.4 Hz), 49.0 (q, J = 26.9 Hz), 32.4, 29.9 (d, J = 2.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −62.7 (s, 3F), −69.7 (d, 3F, J = 9.1 Hz);

FT-IR (film) 3029, 2958, 1497, 1454, 1332, 1258, 1169, 1115, 1077, 802, 711, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{14}F_6$: 332, found: 332;

$[\alpha]^{25}_D$ = +42° (*c* = 0.98, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.



(*R*)-1-Fluoro-3-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (Table 4.2, Entry 5). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-fluorobenzene were used. The reaction was run at −15 °C for 14 h. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 225 mg (80% yield, 96% ee); Run 2, 220 mg (78% yield, 96% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 16.7 min (minor), 19.7 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 1H), 7.32 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.13 – 7.01 (m, 5H), 3.29 – 3.17 (m, 1H), 2.61 (ddd, 1H, J = 4.9, 8.8, 13.5 Hz), 2.47 – 2.32 (m, 2H), 2.20 (dddd, 1H, J = 4.9, 8.6, 11.2, 13.7 Hz);

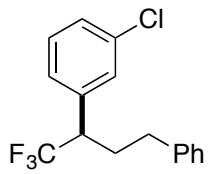
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 (d, J = 246.6 Hz), 140.2, 136.9 (m), 130.2 (d, J = 8.3 Hz), 128.6, 128.4, 126.6 (q, J = 280.6 Hz), 126.3, 125.1 (d, J = 2.9 Hz), 116.0 (d, J = 22.0 Hz), 115.3 (d, J = 21.0 Hz), 48.9 (qd, J = 1.9, 26.9 Hz), 32.4, 30.1 (d, J = 2.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, J = 9.2 Hz), −112.4 (m, 1F);

FT-IR (film) 3029, 2957, 1616, 1593, 1491, 1454, 1258, 1174, 1157, 1143, 1112, 787, 709, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{14}F_4$: 282, found: 282;

$[\alpha]^{25}_D$ = +49° (*c* = 0.97, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.



(*R*)-1-Chloro-3-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (Table 4.2, Entry 6). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-chlorobenzene were used. The reaction was run at −15 °C for 14 h. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 260 mg (87% yield, 96% ee); Run 2, 255 mg (85% yield, 96% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 18.0 min (minor), 23.3 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 7.25 – 7.17 (m, 2H), 7.12 – 7.08 (m, 2H), 3.21 (dqd, 1H, *J* = 3.9, 9.2, 11.0 Hz), 2.61 (ddd, 1H, *J* = 4.9, 8.8, 13.5 Hz), 2.47 – 2.32 (m, 2H), 2.20 (dddd, 1H, *J* = 4.9, 8.5, 11.1, 13.7 Hz);

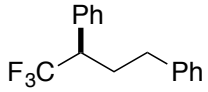
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.2, 136.4 (d, *J* = 2.0 Hz), 134.7, 130.0, 129.3, 128.6, 128.5, 128.3, 127.4, 126.6 (q, *J* = 280.7 Hz), 126.4, 48.9 (q, *J* = 26.9 Hz), 32.4, 30.0 (d, *J* = 2.1 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.6 (d, 3F, *J* = 9.1 Hz);

FT-IR (film) 3028, 2957, 1599, 1576, 1497, 1479, 1454, 1434, 1257, 1170, 1157, 1113, 786, 713, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{14}ClF_3$: 298, found: 298;

$[\alpha]^{25}_D$ = +54° (*c* = 1.01, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.



(*R*)-(4,4,4-Trifluorobutane-1,3-diyl)dibenzene (Table 4.2, Entry 7). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 230 mg (87% yield, 95% ee); Run 2, 225 mg (85% yield, 95% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 15.6 min (minor), 16.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 3H), 7.34 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 7.13 – 7.09 (m, 2H), 3.24 (dqd, 1H, *J* = 3.9, 9.4, 11.0 Hz), 2.61 (ddd, 1H, *J* = 4.9, 8.9, 13.6 Hz), 2.49 – 2.32 (m, 2H), 2.25 (dddd, 1H, *J* = 4.8, 8.7, 11.1, 13.8 Hz);

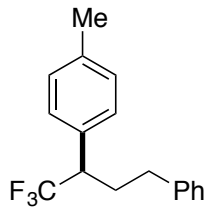
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 134.4 (d, *J* = 2.0 Hz), 129.2, 128.7, 128.5, 128.4, 128.2, 126.9 (q, *J* = 280.6 Hz), 126.2, 49.2 (q, *J* = 26.5 Hz), 32.5, 30.1 (d, *J* = 2.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, *J* = 9.3 Hz);

FT-IR (film) 3030, 2956, 1496, 1455, 1258, 1148, 1109, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{15}F_3$: 264, found: 264;

$[\alpha]^{25}_D$ = −47° (*c* = 0.99, $CHCl_3$); 95% ee, from (*S,S*)-**L3**.



(*R*)-1-Methyl-4-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (Table 4.2, Entry 8). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-4-methylbenzene were used. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 246 mg (88% yield, 95% ee); Run 2, 250 mg (90% yield, 94% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 12.1 min (minor), 13.1 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.19 (m, 5H), 7.13 – 7.10 (m, 2H), 3.20 (dqd, 1H, *J* = 3.9, 9.4, 11.2 Hz), 2.61 (ddd, 1H, *J* = 4.9, 9.1, 13.8 Hz), 2.47 – 2.41 (m, 1H), 2.40 (s, 3H), 2.35 (dddd, 1H, *J* = 3.9, 7.7, 9.1, 13.2 Hz), 2.22 (dddd, 1H, *J* = 4.9, 9.0, 11.2, 13.7 Hz);

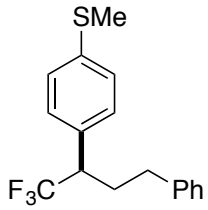
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 138.0, 131.3 (d, *J* = 2.0 Hz), 129.5, 129.0, 128.5, 128.4, 127.0 (q, *J* = 280.5 Hz), 126.2, 48.7 (q, *J* = 26.5 Hz), 32.5, 30.1 (d, *J* = 2.1 Hz), 21.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (d, 3F, *J* = 9.4 Hz);

FT-IR (film) 3028, 2955, 1517, 1496, 1454, 1259, 1169, 1148, 1108, 814, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{17}F_3$: 278, found: 278;

$[\alpha]^{25}_D$ = +52° (*c* = 0.99, $CHCl_3$); 95% ee, from (*R,R*)-**L3**.



(*R*)-Methyl(4-(1,1,1-trifluoro-4-phenylbutan-2-yl)phenyl)sulfane (Table 4.2, Entry 9). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from (4-bromophenyl)(methyl)sulfane were used. Solvent system for chromatography: 15:1 → 5:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 162 mg (52% yield, 94% ee); Run 2, 160 mg (52% yield, 93% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 19.4 min (minor), 20.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 4H), 7.24 – 7.20 (m, 3H), 7.12 – 7.07 (m, 2H), 3.23 – 3.14 (m, 1H), 2.60 (ddd, 1H, *J* = 4.9, 8.9, 13.7 Hz), 2.52 (s, 3H), 2.46 – 2.29 (m, 2H), 2.20 (dddd, 1H, *J* = 4.8, 8.7, 11.2, 13.7 Hz);

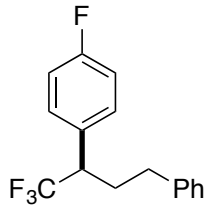
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 138.7, 131.0 (d, *J* = 2.3 Hz), 129.6, 128.5, 128.4, 126.8 (q, *J* = 280.6 Hz), 126.6, 126.2, 48.6 (q, *J* = 26.6 Hz), 32.4, 30.0 (d, *J* = 2.1 Hz), 15.5;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (d, 3F, *J* = 9.3 Hz);

FT-IR (film) 3027, 2922, 1601, 1496, 1256, 1169, 1149, 1109, 816, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{17}F_3S$: 310, found: 310;

$[\alpha]^{25}_D$ = +68° (*c* = 0.98, $CHCl_3$); 94% ee, from (*R,R*)-**L3**.



(*R*)-1-Fluoro-4-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (Table 4.2, Entry 10). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-4-fluorobenzene were used. The reaction was run at −15 °C for 14 h. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 235 mg (83% yield, 96% ee); Run 2, 241 mg (85% yield, 96% ee).

The ee was determined on an OD-H column (hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 26.3 min (minor), 29.8 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 4H), 7.25 – 7.20 (m, 1H), 7.13 – 7.07 (m, 4H), 3.22 (dqd, 1H, *J* = 3.7, 9.2, 11.0 Hz), 2.60 (ddd, 1H, *J* = 4.6, 8.0, 12.2 Hz), 2.46 – 2.32 (m, 2H), 2.24 – 2.14 (m, 1H);

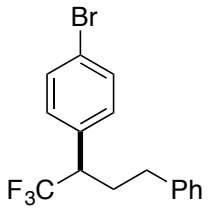
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (d, *J* = 247.3 Hz), 140.3, 130.8 (d, *J* = 8.0 Hz), 130.1 (d, *J* = 1.7 Hz), 128.5, 128.4, 126.7 (q, *J* = 280.4 Hz), 126.3, 115.7 (d, *J* = 21.5 Hz), 48.4 (q, *J* = 26.8 Hz), 32.4, 30.1 (d, *J* = 2.1 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.0 (d, 3F, *J* = 9.2 Hz), −113.9 (m, 1F);

FT-IR (film) 3028, 2956, 1609, 1513, 1497, 1455, 1258, 1230, 1163, 1111, 831, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{14}F_4$: 282, found: 282;

$[\alpha]^{25}_D$ = −45° (*c* = 1.04, $CHCl_3$); 96% ee, from (*S,S*)-**L3**.



(*R*)-1-Bromo-4-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (Table 4.2, Entry 11). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1,4-dibromobenzene were used. The reaction was run at −15 °C for 14 h. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 296 mg (86% yield, 95% ee); Run 2, 300 mg (87% yield, 95% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 20.0 min (minor), 22.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 7.32 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 7.10 – 7.07 (m, 2H), 3.20 (dqd, 1H, *J* = 3.8, 9.2, 10.9 Hz), 2.60 (ddd, 1H, *J* = 4.5, 7.8, 11.8 Hz), 2.46 – 2.31 (m, 2H), 2.24 – 2.13 (m, 1H);

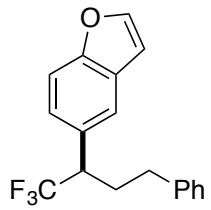
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.2, 133.4 (d, *J* = 1.9 Hz), 132.0, 130.8, 128.6, 128.3, 126.5 (q, *J* = 280.6 Hz), 126.3, 122.4, 48.6 (q, *J* = 26.7 Hz), 32.3, 29.9 (d, *J* = 2.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (d, 3F, *J* = 9.3 Hz);

FT-IR (film) 3028, 2956, 1491, 1454, 1256, 1170, 1156, 1114, 1076, 1012, 819, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{14}{}^{79}BrF_3$: 342, found: 342, 344 (M^++2);

$[\alpha]^{25}_D$ = +61° (*c* = 0.99, $CHCl_3$); 95% ee, from (*R,R*)-**L3**.



(*R*)-5-(1,1,1-Trifluoro-4-phenylbutan-2-yl)benzofuran (eq 4.2). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 5-bromobenzofuran were used. Solvent system for chromatography: 20:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 184 mg (61% yield, 94% ee); Run 2, 178 mg (59% yield, 94% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 21.8 min (minor), 22.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 1H, *J* = 2.2 Hz), 7.57 – 7.53 (m, 2H), 7.32 – 7.28 (m, 2H), 7.26 – 7.20 (m, 2H), 7.13 – 7.09 (m, 2H), 6.80 (dd, 1H, *J* = 1.0, 2.2 Hz), 3.35 (dqd, 1H, *J* = 3.7, 9.3, 11.1 Hz), 2.66 – 2.57 (m, 1H), 2.50 – 2.38 (m, 2H), 2.34 – 2.24 (m, 1H);

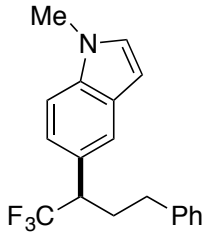
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 145.7, 140.6, 128.8 (q, *J* = 2.1 Hz), 128.5, 128.4, 127.8, 127.0 (q, *J* = 280.7 Hz), 126.2, 125.3, 121.8, 111.6, 106.6, 49.0 (q, *J* = 26.6 Hz), 32.5, 30.4 (d, *J* = 2.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (d, 3F, *J* = 9.4 Hz);

FT-IR (film) 3028, 2955, 1471, 1454, 1259, 1157, 1127, 1107, 1031, 742, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{15}F_3O$: 304, found: 304;

$[\alpha]^{25}_D$ = +56° (*c* = 1.00, $CHCl_3$); 94% ee, from (*R,R*)-**L3**.



(*R*)-1-Methyl-5-(1,1,1-trifluoro-4-phenylbutan-2-yl)-1*H*-indole (eq 4.3). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 5-bromo-1-methyl-1*H*-indole were used. Solvent system for

chromatography: 20:1 → 12:1 hexane/dichloromethane. The title compound was isolated as a light-green color solid.

Run 1, 209 mg (66% yield, 94% ee); Run 2, 222 mg (70% yield, 94% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 23.0 min (major), 24.8 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.59 (m, 1H), 7.37 (d, 1H *J* = 8.4 Hz), 7.33 – 7.29 (m, 2H), 7.25 – 7.18 (m, 2H), 7.15 – 7.10 (m, 3H), 6.54 (dd, 1H, *J* = 0.9, 3.1 Hz), 3.83 (s, 3H), 3.35 (dqd, 1H, *J* = 3.6, 9.3, 11.0 Hz), 2.66 – 2.60 (m, 1H), 2.51 – 2.29 (m, 3H);

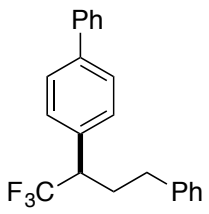
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 136.5, 129.5, 128.6, 128.43, 128.40, 127.3 (q, *J* = 280.5 Hz), 126.1, 125.0 (q, *J* = 2.0 Hz), 122.4, 121.7, 109.4, 101.0, 49.2 (q, *J* = 26.3 Hz), 32.9, 32.5, 30.5 (d, *J* = 2.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (d, 3F, *J* = 9.4 Hz);

FT-IR (film) 3027, 2951, 1514, 1495, 1453, 1336, 1258, 1138, 1103, 799, 724, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{18}F_3N$: 317, found: 317;

$[\alpha]^{25}_D$ = +63° (*c* = 1.00, $CHCl_3$); 94% ee, from (*R,R*)-**L3**.



(*R*)-4-(1,1,1-Trifluoro-4-phenylbutan-2-yl)-1,1'-biphenyl (for determination of absolute stereochemistry). (3-Bromo-4,4,4-trifluorobutyl)benzene (267 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 4-bromo-1,1'-biphenyl were used. Solvent system for chromatography: hexane → 10:1 hexane/dichloromethane. The title compound was isolated as a white solid.

Run 1, 160 mg (47% yield, 94% ee); Run 2, 158 mg (46% yield, 93% ee).

The ee was determined on an OD-H column (1.0% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 7.0 min (minor), 11.1 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.62 (m, 4H), 7.50 – 7.45 (m, 2H), 7.42 – 7.36 (m, 3H), 7.33 – 7.29 (m, 2H), 7.25 – 7.20 (m, 1H), 7.15 – 7.11 (m, 2H), 3.29 (dqd, 1H, J = 3.9, 9.3, 11.0 Hz), 2.65 (ddd, 1H, J = 4.9, 9.0, 13.8 Hz), 2.53 – 2.35 (m, 2H), 2.27 (dddd, 1H, J = 4.9, 8.8, 11.1, 13.8 Hz);

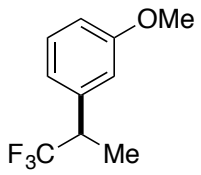
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 140.6, 140.5, 133.4 (d, J = 2.0 Hz), 129.6, 128.8, 128.5, 128.4, 127.5, 127.4, 127.1, 126.9 (q, J = 280.6 Hz), 126.2, 48.8 (q, J = 26.5 Hz), 32.5, 30.1 (d, J = 2.0 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.6 (d, 3F, J = 9.3 Hz);

FT-IR (film) 3061, 3030, 2955, 1496, 1487, 1454, 1256, 1168, 1148, 1108, 1009, 833, 765, 737, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{22}H_{19}F_3$: 340, found: 340;

$[\alpha]^{25}_D$ = −69° (*c* = 0.96, $CHCl_3$); 93% ee, from (*S,S*)-**L3**.



(*R*)-1-Methoxy-3-(1,1,1-trifluoropropan-2-yl)benzene (Table 4.3, Entry 1). 2-Bromo-1,1,1-trifluoropropane (177 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 15:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 166 mg (81% yield, 92% ee); Run 2, 164 mg (80% yield, 90% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 19.5 min (minor), 29.0 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 1H), 6.93 – 6.91 (m, 1H), 6.89 – 6.87 (m, 2H), 3.82 (s, 3H), 3.40 (qq, 1H, J = 7.2, 9.2 Hz), 1.51 (d, 3H, J = 7.3 Hz);

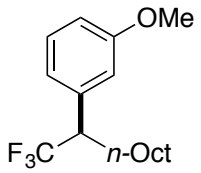
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 137.9, 129.5, 127.1 (q, J = 280.5 Hz), 120.8, 114.6, 113.1, 55.2, 44.2 (q, J = 27.5 Hz), 14.6 (d, J = 2.8 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.4 (d, 3F, J = 9.3 Hz);

FT-IR (film) 2992, 2948, 2839, 1604, 1588, 1496, 1465, 1291, 1261, 1237, 1172, 1126, 1041, 991, 781, 703 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{10}H_{11}F_3O$: 204, found: 204;

$[\alpha]^{25}_D$ = −9.8° (*c* = 1.04, $CHCl_3$); 90% ee, from (*S,S*)-**L3**.



(*R*)-1-Methoxy-3-(1,1,1-trifluorodecan-2-yl)benzene (Table 4.3, Entry 2). 2-Bromo-1,1,1-trifluorodecane (275 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 15:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 265 mg (88% yield, 94% ee); Run 2, 263 mg (87% yield, 96% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 10.8 min (minor), 15.5 min (major).

^{1}H NMR (500 MHz, CD_3CN) δ 7.31 – 7.27 (m, 1H), 6.93 – 6.87 (m, 3H), 3.78 (s, 3H), 3.43 – 3.32 (m, 1H), 1.99 – 1.84 (m, 2H), 1.35 – 1.06 (m, 12H), 0.86 (t, 3H, J = 7.0 Hz);

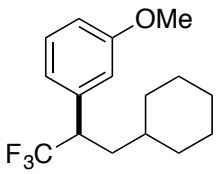
^{13}C NMR (126 MHz, CD_3CN) δ 160.9, 137.6 (d, J = 2.1 Hz), 130.7, 128.5 (q, J = 279.2 Hz), 122.3, 116.1, 114.2, 56.0, 50.2 (q, J = 25.9 Hz), 32.6, 30.0, 29.9, 29.8, 29.1 (q, J = 2.3 Hz), 27.3, 23.4, 14.4;

^{19}F NMR (282 MHz, CD_3CN) δ −70.3 (d, 3F, J = 9.7 Hz);

FT-IR (film) 2926, 2856, 1603, 1587, 1496, 1456, 1436, 1259, 1161, 1125, 1104, 1047, 708 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{25}F_3O$: 302, found: 302;

$[\alpha]^{25}_D$ = −42° (*c* = 1.04, $CHCl_3$); 96% ee, from (*S,S*)-**L3**.



(*R*)-1-(3-Cyclohexyl-1,1,1-trifluoropropan-2-yl)-3-methoxybenzene (Table 4.3, Entry 3). (2-Bromo-3,3,3-trifluoropropyl)cyclohexane (259 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 25:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 230 mg (80% yield, 96% ee); Run 2, 231 mg (81% yield, 96% ee).

The ee was determined on an OJ-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 9.1 min (minor), 9.7 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 1H), 6.90 – 6.81 (m, 3H), 3.82 (s, 3H), 3.33 (dqd, 1H, J = 4.0, 9.4, 11.2 Hz), 1.86 – 1.71 (m, 3H), 1.68 – 1.54 (m, 4H), 1.18 – 1.02 (m, 4H), 1.00 – 0.82 (m, 2H);

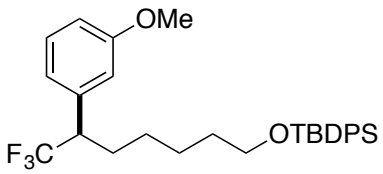
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 136.6 (d, J = 2.0 Hz), 129.5, 127.2 (q, J = 280.5 Hz), 121.5, 115.2, 112.9, 55.2, 47.2 (q, J = 26.2 Hz), 36.0 (d, J = 2.0 Hz), 34.2, 33.9, 31.8, 26.4, 26.0, 25.8;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (d, 3F, J = 9.4 Hz);

FT-IR (film) 2926, 2852, 1604, 1587, 1490, 1452, 1261, 1183, 1155, 1113, 1050, 779, 710 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{21}F_3O$: 286, found: 286;

$[\alpha]^{25}_D$ = +52° (*c* = 1.00, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.



(*R*)-*tert*-Butyldiphenyl((7,7,7-trifluoro-6-(3-methoxyphenyl)heptyl)oxy)silane (Table 4.3, Entry 4). ((6-Bromo-7,7,7-trifluoroheptyl)oxy)(*tert*-butyl)diphenylsilane (487 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 4:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 390 mg (76% yield, 94% ee); Run 2, 395 mg (77% yield, 94% ee).

The ee was determined on an OD-H column (1.0% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 4.7 min (minor), 7.8 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 4H), 7.46 – 7.35 (m, 6H), 7.30 – 7.23 (m, 1H), 6.90 – 6.81 (m, 3H), 3.82 (s, 3H), 3.65 – 3.59 (m, 2H), 3.17 (dqd, 1H, *J* = 4.0, 9.3, 11.0 Hz), 2.03 – 1.92 (m, 1H), 1.90 – 1.79 (m, 1H), 1.57 – 1.27 (m, 4H), 1.23 – 1.14 (m, 2H), 1.06 (s, 9H);

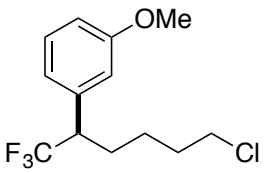
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 136.4 (d, *J* = 2.0 Hz), 135.5, 134.0 (d, *J* = 1.4 Hz), 129.6, 129.5, 127.6, 126.9 (q, *J* = 280.7 Hz), 121.4, 115.0, 113.0, 63.7, 55.2, 50.0 (q, *J* = 26.3 Hz), 32.2, 28.7 (d, *J* = 2.2 Hz), 26.9, 26.5, 25.5, 19.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.6 (d, 3F, *J* = 9.3 Hz);

FT-IR (film) 2933, 2858, 1603, 1587, 1490, 1472, 1428, 1260, 1161, 1113, 702 cm^{-1};

GC-MS (EI) *m/z* ($M^+-C_4H_9$) calcd for $C_{26}H_{28}F_3O_2Si$: 457, found: 457;

$[\alpha]^{25}_D$ = +24° (*c* = 1.03, $CHCl_3$); 94% ee, from (*R,R*)-**L3**.



(*R*)-1-(6-Chloro-1,1,1-trifluorohexan-2-yl)-3-methoxybenzene (Table 4.3, Entry 5). 2-Bromo-6-chloro-1,1,1-trifluorohexane (253 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 15:1 → 12:1 → 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 250 mg (89% yield, 96% ee); Run 2, 248 mg (88% yield, 96% ee).

The ee was determined on an OJ-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 26.1 min (minor), 27.5 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 1H), 6.89 – 6.86 (m, 2H), 6.83 – 6.82 (m, 1H), 3.82 (s, 3H), 3.52 – 3.42 (m, 2H), 3.19 (dqd, 1H, *J* = 4.1, 9.2 ,11.0 Hz), 2.05 – 1.96 (m, 1H), 1.94 – 1.68 (m, 3H), 1.43 – 1.28 (m, 2H);

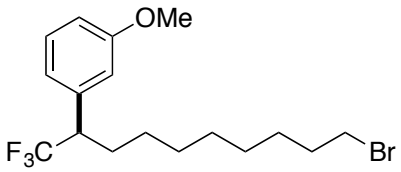
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 136.0 (d, *J* = 2.3 Hz), 129.7, 126.8 (q, *J* = 280.7 Hz), 121.3, 115.0, 113.2, 55.2, 50.0 (q, *J* = 26.6 Hz), 44.4, 32.1, 28.1 (d, *J* = 2.2 Hz), 24.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, *J* = 9.3 Hz);

FT-IR (film) 2954, 1603, 1490, 1456, 1257, 1159, 1109, 1043, 781, 707 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{13}H_{16}ClF_3O$: 280, found: 280;

$[\alpha]^{25}_D$ = +51° (*c* = 0.99, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.



(*R*)-1-(10-Bromo-1,1,1-trifluorodecan-2-yl)-3-methoxybenzene (Table 4.3, Entry 6). 2,10-Dibromo-1,1,1-trifluorodecane (354 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 15:1 → 12:1 → 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 309 mg (81% yield, 96% ee); Run 2, 300 mg (79% yield, 95% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 14.9 min (minor), 25.4 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 1H), 6.88 – 6.86 (m, 2H), 6.83 – 6.82 (m, 1H), 3.82 (s, 3H), 3.39 (t, 2H, J = 6.8 Hz), 3.18 (dqd, 1H, J = 4.0, 9.3, 11.1 Hz), 1.97 (dddd, 1H, J = 4.1, 7.7, 9.2, 13.4 Hz), 1.89 – 1.78 (m, 3H), 1.45 – 1.13 (m, 10H);

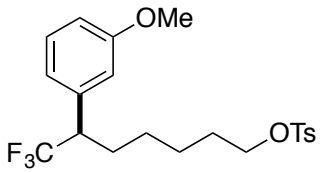
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 136.5 (d, J = 2.2 Hz), 129.5, 126.9 (q, J = 280.7 Hz), 121.4, 115.1, 113.0, 55.2, 50.1 (q, J = 26.3 Hz), 33.9, 32.7, 29.1, 29.0, 28.64 (d, J = 2.0 Hz), 28.57, 28.0, 26.6;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, J = 9.3 Hz);

FT-IR (film) 2929, 2856, 1603, 1490, 1457, 1437, 1257, 1158, 1109, 1050, 780, 708 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{24}{}^{79}BrF_3O$: 380, found: 380, 382 ($M^+$+2);

$[\alpha]^{25}_D$ = +33° (c = 0.99, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.



(*R*)-7,7,7-Trifluoro-6-(3-methoxyphenyl)heptyl 4-methylbenzenesulfonate (Table 4.3, Entry 7). 6-Bromo-7,7,7-trifluoroheptyl 4-methylbenzenesulfonate (403 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 1:1 → 1:1.5 → 1:2 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 391 mg (91% yield, 97% ee); Run 2, 393 mg (91% yield, 97% ee).

The ee was determined on an OJ-H column (10% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 32.0 min (minor), 34.7 min (major).

^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.80 – 7.76 (m, 2H), 7.48 – 7.44 (m, 2H), 7.33 – 7.28 (m, 1H), 6.95 – 6.90 (m, 3H), 3.99 (td, 2H, J = 1.1, 6.4 Hz), 3.80 (s, 3H), 3.46 – 3.37 (m, 1H), 2.45 (s, 3H), 1.96 – 1.83 (m, 2H), 1.63 – 1.50 (m, 2H), 1.40 – 1.06 (m, 4H);

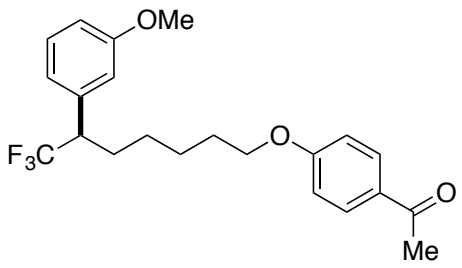
^{13}C NMR (126 MHz, CD_3COCD_3) δ 160.9, 145.8, 137.3 (d, J = 2.1 Hz), 134.5, 130.9, 130.6, 128.7, 128.3 (q, J = 279.9 Hz), 122.1, 116.1, 114.1, 71.4, 55.6, 50.2 (q, J = 26.1 Hz), 29.2, 29.0 (d, J = 2.2 Hz), 26.8, 25.7, 21.6;

^{19}F NMR (282 MHz, CD_3COCD_3) δ −70.2 (d, 3F, J = 9.6 Hz);

FT-IR (film) 2945, 1600, 1496, 1457, 1358, 1258, 1176, 1118, 956, 815, 708, 663 cm^{-1};

GC-MS (EI) *m/z* (M^+−OTs) calcd for $C_{14}H_{18}F_3O$: 259, found: 259;

$[\alpha]^{25}_{D}$ = +25° (*c* = 0.99, $CHCl_3$); 97% ee, from (*R,R*)-**L3**.



(*R*)-1-(4-((7,7,7-Trifluoro-6-(3-methoxyphenyl)heptyl)oxy)phenyl)ethan-1-one (Table 4.3, Entry 8). 1-(4-((6-Bromo-7,7,7-trifluoroheptyl)oxy)phenyl)ethan-1-one (367 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 15:1 → 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 357 mg (91% yield, 95% ee); Run 2, 342 mg (87% yield, 96% ee).

The ee was determined on an AD-H column (5% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 14.4 min (minor), 17.4 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 2H), 7.28 – 7.25 (m, 1H), 6.89 – 6.82 (m, 5H), 3.97 – 3.94 (m, 2H), 3.81 (s, 3H), 3.19 (dqd, 1H, *J* = 4.1, 9.3, 11.0 Hz), 2.55 (s, 3H), 2.05 – 1.97 (m, 1H), 1.92 – 1.84 (m, 1H), 1.79 – 1.69 (m, 2H), 1.54 – 1.38 (m, 2H), 1.31 – 1.23 (m, 2H);

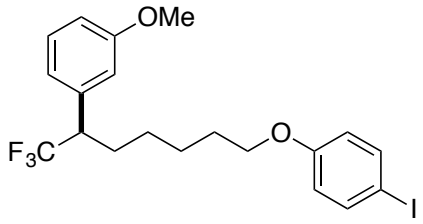
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 162.9, 159.7, 136.3 (d, *J* = 2.0 Hz), 130.5, 130.2, 129.6, 126.9 (q, *J* = 280.6 Hz), 121.3, 115.1, 114.1, 113.0, 67.9, 55.2, 50.0 (q, *J* = 26.4 Hz), 28.7, 28.6 (d, *J* = 2.2 Hz), 26.4, 26.3, 25.7;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, *J* = 9.3 Hz);

FT-IR (film) 2943, 1675, 1601, 1255, 1170, 1117, 834, 708 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{22}H_{25}F_3O_3$: 394, found: 394;

$[\alpha]^{25}_D$ = +34° (*c* = 0.97, $CHCl_3$); 95% ee, from (*R,R*)-**L3**.



(*R*)-1-Methoxy-3-(1,1,1-trifluoro-7-(4-iodophenoxy)heptan-2-yl)benzene

(Table 4.3, Entry 9). 1-((6-Bromo-7,7,7-trifluoroheptyl)oxy)-4-iodobenzene (451 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 10:1 → 5:1 → 4:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 282 mg (59% yield, 95% ee); Run 2, 292 mg (61% yield, 95% ee).

The ee was determined on an OD-H column (10% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 12.6 min (minor), 22.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.30 – 7.24 (m, 1H), 6.90 – 6.81 (m, 3H), 6.66 – 6.61 (m, 2H), 3.85 (t, 2H, *J* = 6.4 Hz), 3.81 (s, 3H), 3.19 (dqd, 1H, *J* = 4.1, 9.3, 11.0 Hz), 2.07 – 1.96 (m, 1H), 1.93 – 1.83 (m, 1H), 1.78 – 1.63 (m, 2H), 1.54 – 1.36 (m, 2H), 1.32 – 1.19 (m, 2H);

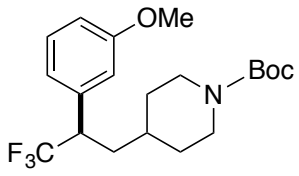
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 158.8, 138.1, 136.3 (d, *J* = 2.1 Hz), 129.6, 126.9 (q, *J* = 280.7 Hz), 121.3, 116.9, 115.1, 113.0, 82.5, 67.7, 55.2, 50.0 (q, *J* = 26.4 Hz), 28.8, 28.6 (d, *J* = 2.1 Hz), 26.4, 25.7;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, J = 9.3 Hz);

FT-IR (film) 2942, 1586, 1486, 1472, 1244, 1174, 1118, 820, 708 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{20}H_{22}F_3IO_2$: 478, found: 478;

$[\alpha]^{25}_D$ = +28° (c = 0.98, $CHCl_3$); 95% ee, from (*R,R*)-**L3**.



***tert*-Butyl (*R*)-4-(3,3,3-trifluoro-2-(3-methoxyphenyl)propyl)piperidine-1-carboxylate (Table 4.3, Entry 10)**. *tert*-Butyl 4-(2-bromo-3,3,3-trifluoropropyl)piperidine-1-carboxylate (360 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 15:1 → 10:1 hexane/dichloromethane. The title compound was isolated as a light-yello solid.

Run 1, 320 mg (83% yield, 96% ee); Run 2, 315 mg (81% yield, 97% ee).

The ee was determined on an OJ-H column (2.0% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 8.5 min (minor), 13.0 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 1H), 6.89 – 6.81 (m, 3H), 4.02 (br, 2H), 3.81 (s, 3H), 3.36 – 3.27 (m, 1H), 2.54 (br, 2H), 1.90 (ddd, 1H, J = 4.4, 11.4, 13.8 Hz), 1.78 (ddd, 1H, J = 4.0, 9.4, 13.7 Hz), 1.68 – 1.64 (m, 1H), 1.52 – 1.48 (m, 1H), 1.43 (s, 9H), 1.27 – 1.04 (m, 3H);

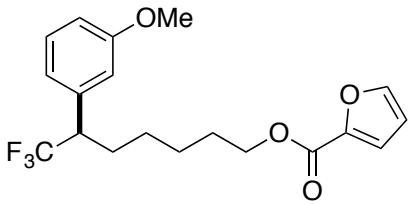
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 154.7, 136.0 (d, *J* = 1.9 Hz), 129.7, 126.9 (q, *J* = 280.7 Hz), 121.3, 115.1, 113.0, 79.3, 55.2, 47.1 (q, *J* = 26.5 Hz), 35.2 (d, *J* = 1.9 Hz), 32.7, 32.5, 30.8, 28.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (d, 3F, *J* = 9.2 Hz);

FT-IR (film) 2932, 1690, 1456, 1424, 1366, 1259, 1162, 1118, 1098, 969, 711 cm^{-1};

GC-MS (EI) *m/z* (M^+–Boc) calcd for $C_{15}H_{19}F_3NO$: 286, found: 286;

$[\alpha]^{25}_D$ = −49° (*c* = 0.99, $CHCl_3$); 97% ee, from (*S,S*)-**L3**.



(*R*)-7,7,7-Trifluoro-6-(3-methoxyphenyl)heptyl furan-2-carboxylate (Table 4.3, Entry 11). 6-Bromo-7,7,7-trifluoroheptyl furan-2-carboxylate (343 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 1:1 → 1:1.2 → 1:1.5 hexane/dichloromethane. The title compound was isolated as a yellow oil.

Run 1, 298 mg (81% yield, 96% ee); Run 2, 298 mg (81% yield, 96% ee).

The ee was determined on an OJ-H column (5% *i*-PrOH/hexane, flow rate 1.0 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 25.6 min (minor), 33.0 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, 1H, *J* = 0.9, 1.8 Hz), 7.29 – 7.24 (m, 1H), 7.14 (dd, 1H, *J* = 0.8, 3.5 Hz), 6.89 – 6.80 (m, 3H), 6.50 (dd, 1H, *J* = 1.7, 3.5 Hz), 4.24 (t,

2H, J = 6.6 Hz), 3.80 (s, 3H), 3.18 (dqd, 1H, J = 4.1, 9.3, 11.0 Hz), 1.99 (dddd, 1H, J = 4.1, 7.1, 9.7, 13.7 Hz), 1.91 – 1.81 (m, 1H), 1.76 – 1.61 (m, 2H), 1.50 – 1.32 (m, 2H), 1.29 – 1.21 (m, 2H);

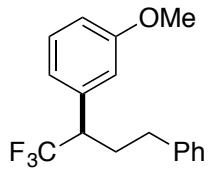
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 158.7, 146.2, 144.7, 136.3 (d, J = 2.2 Hz), 129.6, 126.9 (q, J = 280.6 Hz), 121.3, 117.7, 115.0, 113.0, 111.8, 64.7, 55.2, 50.0 (q, J = 26.4 Hz), 28.6 (d, J = 2.0 Hz), 28.4, 26.4, 25.6;

^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (d, 3F, J = 9.2 Hz);

FT-IR (film) 2947, 1727, 1603, 1584, 1473, 1297, 1259, 1180, 1119, 765, 709 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{21}F_3O_4$: 370, found: 370;

$[\alpha]^{25}_D$ = +32° (*c* = 0.94, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.

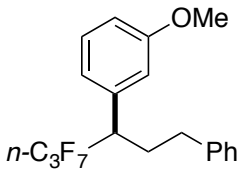


(*R*)-1-Methoxy-3-(1,1,1-trifluoro-4-phenylbutan-2-yl)benzene (eq 4.4). (4,4,4-Trifluoro-3-iodobutyl)benzene (314 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 5:1 → 4:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 277 mg (94% yield, 96% ee); Run 2, 277 mg (94% yield, 96% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 ml/min); retention times for compound obtained using (*S,S*)-**L3**: 20.2 min (minor), 32.3 min (major).

For the characterization data, see Table 4.2, Entry 2 (above).



(*R*)-1-(4,4,5,5,6,6,6-Heptafluoro-1-phenylhexan-3-yl)-3-methoxybenzene (eq 4.7). (3-Bromo-4,4,5,5,6,6,6-heptafluorohexyl)benzene (367 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 15:1 → 12:1 → 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 363 mg (92% yield, 99% ee); Run 2, 361 mg (92% yield, 99% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*S,S*)-**L3**: 12.8 min (minor), 15.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 3H), 7.24 – 7.20 (m, 1H), 7.11 – 7.09 (m, 2H), 6.93 – 6.90 (m, 2H), 6.86 – 6.85 (m, 1H), 3.84 (s, 3H), 3.34 – 3.25 (m, 1H), 2.60 – 2.53 (m, 1H), 2.45 – 2.34 (m, 2H), 2.26 – 2.17 (m, 1H);

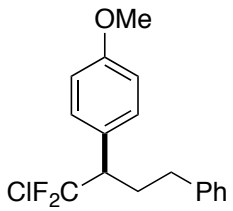
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 140.5, 135.5 (d, J = 5.4 Hz), 129.6, 128.5, 128.4, 126.2, 122.0, 119.5 – 115.2 (m), 115.6, 113.2, 112.1 – 107.0 (m), 55.2, 47.1 (t, J = 21.0 Hz), 32.4, 29.3;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.7 (dd, 3F, *J* = 10.2, 11.9 Hz), −112.9 – −116.8 (m, 2F), −122.6 – −125.6 (m, 2F);

FT-IR (film) 2961, 1603, 1587, 1496, 1456, 1348, 1219, 1174, 1116, 1045, 933, 728, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{17}F_7O$: 394, found: 394;

$[\alpha]^{25}_D$ = +40° (*c* = 0.93, $CHCl_3$); 99% ee, from (*R,R*)-**L3**.



(*R*)-1-(1-Chloro-1,1-difluoro-4-phenylbutan-2-yl)-4-methoxybenzene (eq 4.8). (3-Bromo-4-chloro-4,4-difluorobutyl)benzene (283 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-4-methoxybenzene were used. Solvent system for chromatography: 6:1 → 4:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 274 mg (88% yield, 96% ee); Run 2, 278 mg (89% yield, 96% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 29.1 min (minor), 34.4 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 5H), 7.11 – 7.08 (m, 2H), 6.96 – 6.92 (m, 2H), 3.85 (s, 3H), 3.30 (qd, 1H, *J* = 3.1, 11.5 Hz), 2.63 – 2.57 (m, 1H), 2.45 – 2.36 (m, 2H), 2.27 – 2.19 (m, 1H);

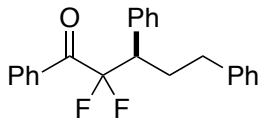
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 140.7, 131.2 (t, *J* = 296.2 Hz), 130.6, 128.5, 128.4, 126.8 (t, *J* = 2.5 Hz), 126.2, 114.0, 55.2, 54.8 (t, *J* = 22.3 Hz), 32.6, 30.8 (t, *J* = 2.2 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −53.9 (dd, 1F, *J* = 10.9, 160.5 Hz), −54.7 (dd, 1F, *J* = 11.9, 160.7 Hz);

FT-IR (film) 3026, 2956, 1612, 1515, 1496, 1454, 1306, 1251, 1180, 1114, 1034, 947, 826, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{17}ClF_2O$: 310, found: 310;

$[\alpha]^{25}_D$ = +43° (*c* = 0.93, $CHCl_3$); 96% ee, from (*R,R*)-**L3**.



(*R*)-2,2-Difluoro-1,3,5-triphenylpentan-1-one (eq 4.9). 3-Bromo-2,2-difluoro-1,5-diphenylpentan-1-one (353 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from bromobenzene were used. Solvent system for chromatography: 10:1 → 5:1 → 2:1 hexane/dichloromethane. The title compound was isolated as a white solid.

Run 1, 283 mg (81% yield, 98% ee); Run 2, 280 mg (80% yield, 97% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 20.1 min (minor), 20.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.59 – 7.55 (m, 1H), 7.43 – 7.39 (m, 2H), 7.35 – 7.24 (m, 7H), 7.20 – 7.17 (m, 1H), 7.10 – 7.07 (m, 2H), 3.62 – 3.52 (m, 1H), 2.58 (ddd, 1H, *J* = 4.7, 9.3, 13.6 Hz), 2.46 – 2.33 (m, 2H), 2.29 – 2.22 (m, 1H);

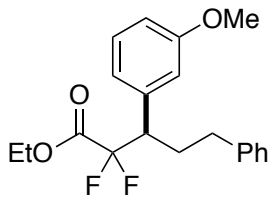
^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1 (t, *J* = 30.0 Hz), 141.0, 135.02, 134.98, 133.9, 132.8, 129.84, 129.79 (t, *J* = 3.5 Hz), 128.6, 128.5, 128.4, 127.9, 126.0, 119.4 (t, *J* = 258.1 Hz), 49.2 (t, *J* = 21.5 Hz), 32.8, 29.6 (t, *J* = 3.6 Hz);

^{19}F NMR (282 MHz, $CDCl_3$) δ −103.1 (dd, 1F, *J* = 15.4, 272.5 Hz), −105.4 (dd, 1F, *J* = 17.3, 272.5 Hz);

FT-IR (film) 3028, 1701, 1598, 1496, 1454, 1161, 1089, 1065, 912, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{23}H_{20}F_2O$: 350, found: 350;

$[\alpha]^{25}_D = -9.7°$ (*c* = 0.94, $CHCl_3$); 97% ee, from (*S,S*)-**L3**.



Ethyl (*R*)-2,2-difluoro-3-(3-methoxyphenyl)-5-phenylpentanoate (eq 4.10). Ethyl 3-bromo-2,2-difluoro-5-phenylpentanoate (321 mg, 1.00 mmol) and an arylzinc chloride reagent prepared from 1-bromo-3-methoxybenzene were used. Solvent system for chromatography: 2:1 → 1.5:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 271 mg (78% yield, 98% ee); Run 2, 278 mg (80% yield, 98% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 mL/min); retention times for compound obtained using (*R,R*)-**L3**: 22.9 min (minor), 28.8 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 3H), 7.21 – 7.18 (m, 1H), 7.11 – 7.09 (m, 2H), 6.89 – 6.82 (m, 3H), 4.13 (qd, 2H, *J* = 1.1, 7.2 Hz), 3.82 (s, 3H), 3.30

(dddd, 1H, J = 3.6, 11.3, 12.9, 19.6 Hz), 2.58 (ddd, 1H, J = 4.8, 9.3, 14.0 Hz), 2.42 (ddd, 1H, J = 7.5, 9.3, 13.9 Hz), 2.28 (dddd, 1H, J = 3.6, 7.6, 9.3, 13.1 Hz), 2.19 (dddd, 1H, J = 4.9, 9.2, 11.3, 13.9 Hz), 1.13 (t, 3H, J = 7.1 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8 (t, J = 32.8 Hz), 159.7, 141.0, 136.3 (d, J = 6.3 Hz), 129.6, 128.39, 128.38, 126.1, 121.9, 116.5 (dd, J = 254.4, 257.5 Hz), 115.4, 113.3, 62.5, 55.2, 49.4 (dd, J = 21.2, 23.0 Hz), 32.7, 29.2 (dd, J = 1.8, 4.6 Hz), 13.7;

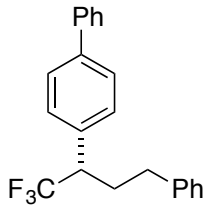
^{19}F NMR (282 MHz, $CDCl_3$) δ −107.1 (dd, 1F, J = 12.9, 252.1 Hz), −113.7 (dd, 1F, J = 19.6, 252.1 Hz);

FT-IR (film) 2940, 1771, 1602, 1490, 1456, 1257, 1103, 1064, 774, 751, 698 cm^{-1};

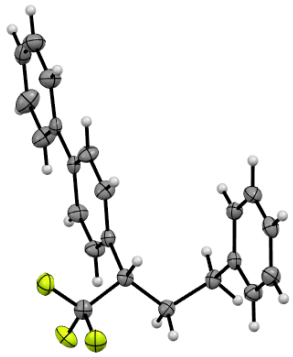
GC-MS (EI) *m/z* (M^+) calcd for $C_{20}H_{22}F_2O_3$: 348, found: 348;

$[\alpha]^{25}_D$ = +27° (*c* = 1.05, $CHCl_3$); 98% ee, from (*R,R*)-**L3**.

4.6.4 Determination of the Absolute Configuration of the Cross-Coupling Products



(*S*)-4-(1,1,1-Trifluoro-4-phenylbutan-2-yl)-1,1'-biphenyl. This compound was prepared according to the General Procedure using (3-bromo-4,4,4-trifluorobutyl)benzene and an arylzinc chloride reagent prepared from 4-bromo-1,1'-biphenyl (run with (*R,R*)-**L3**).



A suitable crystal of $C_{22}H_{19}F_3$ was selected for analysis. All measurements were made on a Bruker APEX-II CCD with filtered Cu-Kα radiation at a temperature of 120 K. Using Olex2,[1] the structure was solved with the ShelXS[2] structure solution program using Direct Methods and refined with the ShelXL[2] refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

1. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339.

2. Sheldrick, G. M. *Acta Crystallogr. A* **2008**, *64*, 112.

Table 4.4. Crystal Data and Structure Refinement for Crystal01.

Identification code	crystal01
Empirical formula	$C_{22}H_{19}F_3$
Formula weight	340.37
Temperature	120 K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$

Unit cell dimensions	a = 11.0486(3) Å	α = 90°.
	b = 5.4958(2) Å	β = 96.3784(11) °.
	c = 14.1940(4) Å	γ = 90 °.
Volume	856.54(5) $Å^3$	
Z	2	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.814 mm^{-1}	
F(000)	356	
Crystal size	0.161 x 0.036 x 0.031 mm^3	
Theta range for data collection	3.133 to 71.808°.	
Index ranges	-13<=h<=13, -6<=k<=6, -17<=l<=17	
Reflections collected	16914	
Independent reflections	3123 [R(int) = 0.0295]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8644 and 0.7825	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3123 / 1 / 226	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0282, wR2 = 0.0776	
R indices (all data)	R1 = 0.0286, wR2 = 0.0780	
Absolute structure parameter (Flack)	0.05(4)	
Largest diff. peak and hole	0.218 and -0.180 $e/Å^{-3}$	

Table 4.5. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for Crystal01. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	4828(1)	5608(2)	2905(1)	36(1)
F(2)	5550(1)	3642(2)	1786(1)	35(1)
F(3)	5939(1)	7458(2)	1980(1)	33(1)
C(1)	6808(2)	3676(4)	5793(1)	28(1)
C(2)	6772(2)	5381(4)	6511(1)	30(1)
C(3)	7706(2)	7058(4)	6688(1)	28(1)
C(4)	8678(2)	7010(4)	6150(1)	28(1)
C(5)	8705(2)	5311(4)	5426(1)	25(1)
C(6)	7767(1)	3635(3)	5235(1)	21(1)
C(7)	7762(2)	1825(3)	4432(1)	24(1)
C(8)	6759(2)	2328(3)	3621(1)	22(1)
C(9)	6939(1)	4755(3)	3122(1)	21(1)
C(10)	5822(2)	5359(4)	2446(1)	25(1)
C(11)	8076(1)	4830(3)	2603(1)	20(1)
C(12)	8296(2)	3054(3)	1948(1)	26(1)
C(13)	9316(2)	3184(3)	1457(1)	26(1)
C(14)	10156(1)	5072(3)	1603(1)	20(1)
C(15)	9940(2)	6825(3)	2277(1)	27(1)
C(16)	8915(2)	6704(3)	2764(1)	26(1)
C(17)	11251(2)	5188(3)	1073(1)	22(1)
C(18)	11495(2)	3363(4)	441(2)	35(1)
C(19)	12520(2)	3444(4)	-43(2)	38(1)
C(20)	13331(2)	5346(4)	96(1)	32(1)
C(21)	13103(2)	7173(5)	713(2)	38(1)
C(22)	12072(2)	7101(4)	1195(1)	34(1)

Table 4.6. Bond Lengths [Å] and Angles [°] for Crystal01.

F(1)-C(10)	1.3449(19)
F(2)-C(10)	1.340(2)
F(3)-C(10)	1.343(2)
C(1)-C(2)	1.388(3)
C(1)-C(6)	1.392(2)
C(2)-C(3)	1.386(3)
C(3)-C(4)	1.386(2)
C(4)-C(5)	1.391(3)
C(5)-C(6)	1.390(3)
C(6)-C(7)	1.512(2)
C(7)-C(8)	1.533(2)
C(8)-C(9)	1.533(2)
C(9)-C(10)	1.513(2)
C(9)-C(11)	1.526(2)
C(11)-C(12)	1.388(2)
C(11)-C(16)	1.387(2)
C(12)-C(13)	1.391(2)
C(13)-C(14)	1.392(2)
C(14)-C(15)	1.397(2)
C(14)-C(17)	1.496(2)
C(15)-C(16)	1.391(2)
C(17)-C(18)	1.392(3)
C(17)-C(22)	1.387(3)
C(18)-C(19)	1.389(3)
C(19)-C(20)	1.377(3)
C(20)-C(21)	1.373(3)
C(21)-C(22)	1.392(3)
C(2)-C(1)-C(6)	120.97(16)
C(3)-C(2)-C(1)	120.03(16)
C(2)-C(3)-C(4)	119.65(17)
C(3)-C(4)-C(5)	120.10(17)
C(6)-C(5)-C(4)	120.80(15)
C(1)-C(6)-C(7)	120.04(15)
C(5)-C(6)-C(1)	118.43(15)
C(5)-C(6)-C(7)	121.52(15)
C(6)-C(7)-C(8)	112.91(14)
C(7)-C(8)-C(9)	112.59(14)
C(10)-C(9)-C(8)	110.19(14)
C(10)-C(9)-C(11)	110.23(13)
C(11)-C(9)-C(8)	113.71(13)
F(1)-C(10)-C(9)	111.55(14)
F(2)-C(10)-F(1)	106.19(15)
F(2)-C(10)-F(3)	106.70(13)

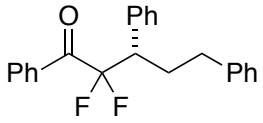
F(2)-C(10)-C(9)	113.11(14)
F(3)-C(10)-F(1)	106.23(15)
F(3)-C(10)-C(9)	112.58(15)
C(12)-C(11)-C(9)	121.26(15)
C(16)-C(11)-C(9)	120.77(14)
C(16)-C(11)-C(12)	117.96(15)
C(11)-C(12)-C(13)	120.75(16)
C(12)-C(13)-C(14)	121.83(16)
C(13)-C(14)-C(15)	116.98(15)
C(13)-C(14)-C(17)	121.35(15)
C(15)-C(14)-C(17)	121.65(15)
C(16)-C(15)-C(14)	121.17(16)
C(11)-C(16)-C(15)	121.28(16)
C(18)-C(17)-C(14)	121.23(16)
C(22)-C(17)-C(14)	121.62(15)
C(22)-C(17)-C(18)	117.14(16)
C(19)-C(18)-C(17)	121.47(19)
C(20)-C(19)-C(18)	120.45(19)
C(21)-C(20)-C(19)	118.95(17)
C(20)-C(21)-C(22)	120.7(2)
C(17)-C(22)-C(21)	121.30(19)

Table 4.7. Anisotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal01. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

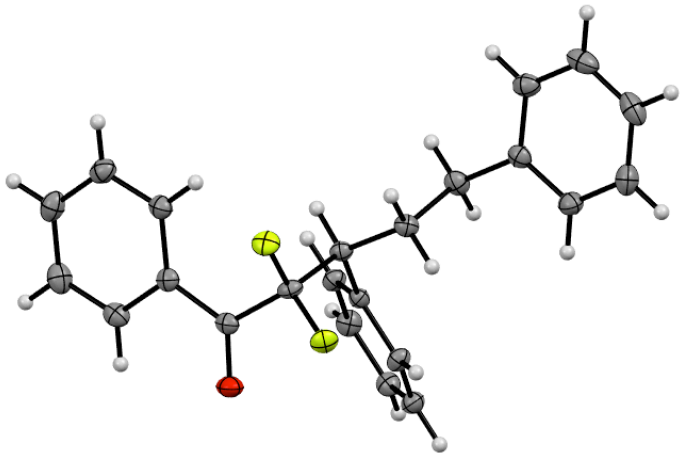
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	26(1)	48(1)	37(1)	3(1)	10(1)	10(1)
F(2)	32(1)	39(1)	33(1)	-11(1)	-7(1)	4(1)
F(3)	35(1)	32(1)	32(1)	8(1)	2(1)	6(1)
C(1)	29(1)	30(1)	25(1)	-3(1)	5(1)	-5(1)
C(2)	28(1)	37(1)	25(1)	-4(1)	7(1)	1(1)
C(3)	33(1)	28(1)	20(1)	-4(1)	-1(1)	5(1)
C(4)	29(1)	29(1)	26(1)	-1(1)	-2(1)	-4(1)
C(5)	24(1)	30(1)	21(1)	2(1)	2(1)	0(1)
C(6)	26(1)	20(1)	18(1)	2(1)	0(1)	4(1)
C(7)	31(1)	19(1)	22(1)	0(1)	4(1)	3(1)
C(8)	27(1)	21(1)	21(1)	-2(1)	4(1)	-1(1)
C(9)	24(1)	20(1)	19(1)	-3(1)	4(1)	1(1)
C(10)	26(1)	25(1)	25(1)	-1(1)	5(1)	4(1)
C(11)	23(1)	20(1)	17(1)	0(1)	2(1)	2(1)
C(12)	27(1)	25(1)	27(1)	-8(1)	5(1)	-4(1)
C(13)	31(1)	24(1)	25(1)	-10(1)	6(1)	-2(1)
C(14)	24(1)	20(1)	16(1)	4(1)	0(1)	3(1)
C(15)	31(1)	19(1)	32(1)	-5(1)	8(1)	-4(1)
C(16)	33(1)	19(1)	27(1)	-7(1)	8(1)	0(1)
C(17)	24(1)	24(1)	16(1)	6(1)	0(1)	4(1)
C(18)	41(1)	27(1)	39(1)	-6(1)	17(1)	-3(1)
C(19)	46(1)	33(1)	40(1)	-3(1)	22(1)	3(1)
C(20)	26(1)	43(1)	27(1)	10(1)	6(1)	8(1)
C(21)	30(1)	47(1)	38(1)	-1(1)	7(1)	-9(1)
C(22)	32(1)	37(1)	32(1)	-8(1)	8(1)	-5(1)

Table 4.8. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal01.

	x	y	z	U(eq)
H(1)	6168	2521	5681	33
H(2)	6107	5397	6882	36
H(3)	7679	8236	7175	33
H(4)	9327	8138	6276	34
H(5)	9372	5296	5058	30
H(7A)	7650	168	4682	28
H(7B)	8563	1872	4182	28
H(8A)	5960	2345	3875	27
H(8B)	6747	993	3151	27
H(9)	7027	6050	3619	25
H(12)	7744	1734	1834	31
H(13)	9442	1952	1009	32
H(15)	10502	8122	2406	33
H(16)	8787	7929	3214	32
H(18)	10947	2033	337	42
H(19)	12663	2177	-472	46
H(20)	14037	5395	-229	38
H(21)	13654	8499	811	46
H(22)	11929	8388	1615	40



(*S*)-2,2-Difluoro-1,3,5-triphenylpentan-1-one (eq 4.9). This compound was prepared with (*R,R*)-**L3**.



A suitable crystal of $C_{23}H_{20}F_2O$ was selected for analysis. All measurements were made on a Bruker APEX-II CCD with filtered Cu-Kα radiation at a temperature of 120 K. Using Olex2,[1] the structure was solved with the ShelXS[2] structure solution program using Direct Methods and refined with the ShelXL[2] refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

1. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339.

2. Sheldrick, G. M. *Acta Crystallogr. A* **2008**, *64*, 112.

Table 4.9. Crystal Data and Structure Refinement for Crystal02.

Identification code	crystal02	
Empirical formula	$C_{23}H_{20}F_2O$	
Formula weight	350.39	
Temperature	120 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.66013(10) Å	α = 90°.
	b = 13.3182(2) Å	β = 90 °.
	c = 23.7538(4) Å	γ = 90 °.
Volume	1790.63(5) $Å^3$	
Z	4	
Density (calculated)	1.300 Mg/m^3	
Absorption coefficient	0.755 mm^{-1}	
F(000)	736	
Crystal size	0.133 x 0.057 x 0.012 mm^3	
Theta range for data collection	3.721 to 71.834°.	
Index ranges	-6<=h<=6, -16<=k<=16, -28<=l<=29	
Reflections collected	21566	
Independent reflections	3486 [R(int) = 0.0407]	
Completeness to theta = 67.679°	99.8 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.7535 and 0.6828
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3486 / 0 / 235
Goodness-of-fit on F^2	1.061
Final R indices [I>2sigma(I)]	R1 = 0.0280, wR2 = 0.0726
R indices (all data)	R1 = 0.0290, wR2 = 0.0734
Absolute structure parameter (Flack)	0.04(4)
Largest diff. peak and hole	0.158 and -0.181 e/$Å^{-3}$

Table 4.10. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal02. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	1883(2)	3098(1)	-253(1)	23(1)
F(2)	4614(2)	3949(1)	181(1)	23(1)
O(1)	4293(2)	5356(1)	-544(1)	25(1)
C(1)	-1167(3)	4179(1)	-1024(1)	21(1)
C(2)	-2795(3)	4277(1)	-1456(1)	25(1)
C(3)	-2562(3)	5041(2)	-1850(1)	27(1)
C(4)	-679(4)	5708(1)	-1815(1)	27(1)
C(5)	975(3)	5605(1)	-1391(1)	23(1)
C(6)	749(3)	4842(1)	-989(1)	18(1)
C(7)	2613(3)	4794(1)	-546(1)	18(1)
C(8)	2411(3)	4046(1)	-52(1)	18(1)
C(9)	621(3)	4361(1)	396(1)	17(1)
C(10)	977(3)	5461(1)	551(1)	16(1)
C(11)	2992(3)	5781(1)	839(1)	19(1)
C(12)	3298(3)	6793(1)	964(1)	21(1)
C(13)	1600(3)	7492(1)	810(1)	21(1)
C(14)	-401(3)	7179(1)	524(1)	22(1)
C(15)	-717(3)	6166(1)	394(1)	19(1)
C(16)	719(3)	3646(1)	903(1)	20(1)
C(17)	-1172(3)	3896(1)	1344(1)	23(1)
C(18)	-1094(3)	3172(1)	1833(1)	20(1)
C(19)	-2859(3)	2457(1)	1908(1)	25(1)
C(20)	-2738(4)	1764(1)	2343(1)	30(1)
C(21)	-835(4)	1774(1)	2711(1)	30(1)
C(22)	919(4)	2488(2)	2645(1)	28(1)
C(23)	796(3)	3182(1)	2210(1)	24(1)

Table 4.11. Bond Lengths [Å] and Angles [°] for Crystal02.

F(1)-C(8)	1.3822(18)
F(2)-C(8)	1.3698(18)
O(1)-C(7)	1.211(2)
C(1)-C(2)	1.386(2)
C(1)-C(6)	1.401(2)
C(2)-C(3)	1.388(3)
C(3)-C(4)	1.390(3)
C(4)-C(5)	1.382(3)
C(5)-C(6)	1.400(2)
C(6)-C(7)	1.491(2)
C(7)-C(8)	1.545(2)
C(8)-C(9)	1.527(2)
C(9)-C(10)	1.524(2)
C(9)-C(16)	1.536(2)
C(10)-C(11)	1.396(2)
C(10)-C(15)	1.393(2)
C(11)-C(12)	1.391(2)
C(12)-C(13)	1.389(2)
C(13)-C(14)	1.384(3)
C(14)-C(15)	1.396(2)
C(16)-C(17)	1.535(2)
C(17)-C(18)	1.511(2)
C(18)-C(19)	1.392(2)
C(18)-C(23)	1.394(2)
C(19)-C(20)	1.387(3)
C(20)-C(21)	1.388(3)
C(21)-C(22)	1.383(3)
C(22)-C(23)	1.389(3)
C(2)-C(1)-C(6)	119.93(16)
C(1)-C(2)-C(3)	120.33(17)
C(2)-C(3)-C(4)	120.08(17)
C(5)-C(4)-C(3)	119.95(17)
C(4)-C(5)-C(6)	120.49(16)
C(1)-C(6)-C(7)	124.17(15)
C(5)-C(6)-C(1)	119.21(16)
C(5)-C(6)-C(7)	116.62(15)
O(1)-C(7)-C(6)	122.16(15)
O(1)-C(7)-C(8)	116.94(15)
C(6)-C(7)-C(8)	120.84(14)
F(1)-C(8)-C(7)	109.98(12)
F(1)-C(8)-C(9)	110.34(13)
F(2)-C(8)-F(1)	104.46(12)
F(2)-C(8)-C(7)	107.49(13)

F(2)-C(8)-C(9)	110.44(12)
C(9)-C(8)-C(7)	113.69(13)
C(8)-C(9)-C(16)	110.57(13)
C(10)-C(9)-C(8)	110.17(13)
C(10)-C(9)-C(16)	113.65(13)
C(11)-C(10)-C(9)	121.34(14)
C(15)-C(10)-C(9)	119.48(14)
C(15)-C(10)-C(11)	119.17(15)
C(12)-C(11)-C(10)	120.19(15)
C(13)-C(12)-C(11)	120.46(16)
C(14)-C(13)-C(12)	119.58(16)
C(13)-C(14)-C(15)	120.33(15)
C(10)-C(15)-C(14)	120.27(15)
C(17)-C(16)-C(9)	112.08(13)
C(18)-C(17)-C(16)	111.50(13)
C(19)-C(18)-C(17)	120.90(15)
C(19)-C(18)-C(23)	118.43(16)
C(23)-C(18)-C(17)	120.63(15)
C(20)-C(19)-C(18)	120.97(17)
C(19)-C(20)-C(21)	120.07(18)
C(22)-C(21)-C(20)	119.53(17)
C(21)-C(22)-C(23)	120.38(18)
C(22)-C(23)-C(18)	120.61(17)

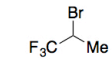
Table 4.12. Anisotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal02. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	27(1)	13(1)	29(1)	-4(1)	1(1)	0(1)
F(2)	15(1)	24(1)	29(1)	0(1)	-1(1)	5(1)
O(1)	22(1)	24(1)	28(1)	-2(1)	3(1)	-7(1)
C(1)	22(1)	20(1)	22(1)	-3(1)	3(1)	-1(1)
C(2)	22(1)	27(1)	26(1)	-7(1)	0(1)	0(1)
C(3)	28(1)	30(1)	24(1)	-4(1)	-4(1)	8(1)
C(4)	35(1)	22(1)	24(1)	2(1)	1(1)	5(1)
C(5)	25(1)	18(1)	25(1)	-1(1)	4(1)	0(1)
C(6)	19(1)	17(1)	20(1)	-4(1)	3(1)	2(1)
C(7)	18(1)	16(1)	21(1)	-5(1)	5(1)	0(1)
C(8)	14(1)	15(1)	24(1)	-4(1)	-1(1)	0(1)
C(9)	14(1)	17(1)	20(1)	-1(1)	0(1)	1(1)
C(10)	14(1)	18(1)	17(1)	-1(1)	2(1)	1(1)
C(11)	17(1)	20(1)	21(1)	-2(1)	-3(1)	4(1)
C(12)	20(1)	23(1)	22(1)	-2(1)	-1(1)	-1(1)
C(13)	25(1)	16(1)	22(1)	-2(1)	3(1)	0(1)
C(14)	22(1)	19(1)	25(1)	0(1)	0(1)	6(1)
C(15)	16(1)	20(1)	21(1)	-1(1)	-1(1)	2(1)
C(16)	19(1)	17(1)	22(1)	1(1)	1(1)	1(1)
C(17)	21(1)	25(1)	24(1)	2(1)	2(1)	4(1)
C(18)	19(1)	20(1)	21(1)	-2(1)	4(1)	2(1)
C(19)	21(1)	25(1)	29(1)	-5(1)	3(1)	-1(1)
C(20)	30(1)	22(1)	39(1)	-2(1)	14(1)	-5(1)
C(21)	43(1)	24(1)	24(1)	3(1)	11(1)	5(1)
C(22)	35(1)	31(1)	20(1)	-1(1)	-2(1)	4(1)
C(23)	24(1)	24(1)	25(1)	-3(1)	0(1)	-5(1)

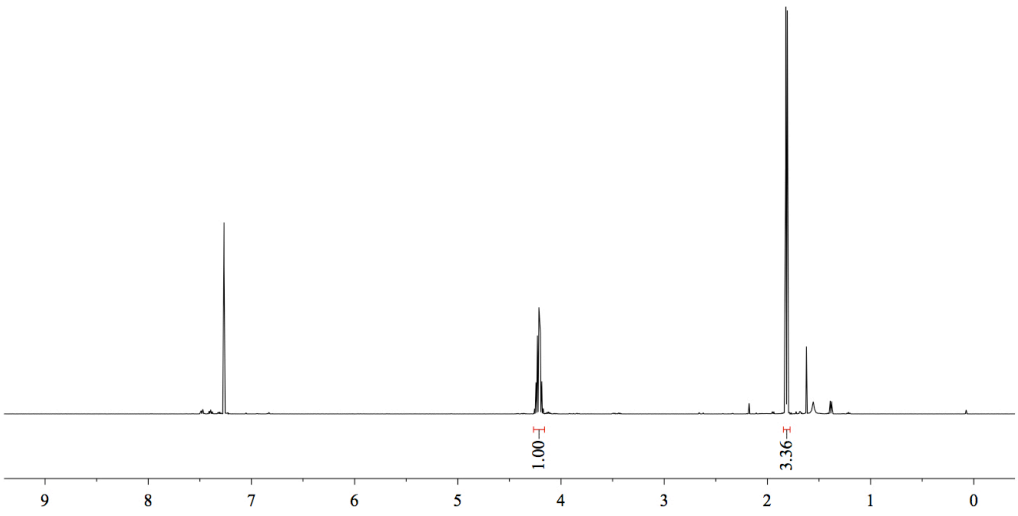
Table 4.13. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for Crystal02.

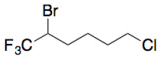
	x	y	z	U(eq)
H(1)	-1351	3663	-751	25
H(2)	-4076	3818	-1484	30
H(3)	-3692	5109	-2143	33
H(4)	-527	6233	-2083	33
H(5)	2274	6055	-1372	28
H(9)	-987	4298	225	20
H(11)	4158	5307	948	23
H(12)	4679	7006	1158	26
H(13)	1810	8182	899	25
H(14)	-1565	7656	417	27
H(15)	-2092	5957	197	23
H(16A)	488	2948	771	23
H(16B)	2300	3688	1079	23
H(17A)	-918	4588	1485	28
H(17B)	-2753	3869	1167	28
H(19)	-4165	2443	1657	30
H(20)	-3961	1282	2389	36
H(21)	-736	1293	3005	36
H(22)	2214	2503	2899	34
H(23)	2010	3669	2169	29

4.6.5 ^{1}H NMR Spectra of Selected Compounds

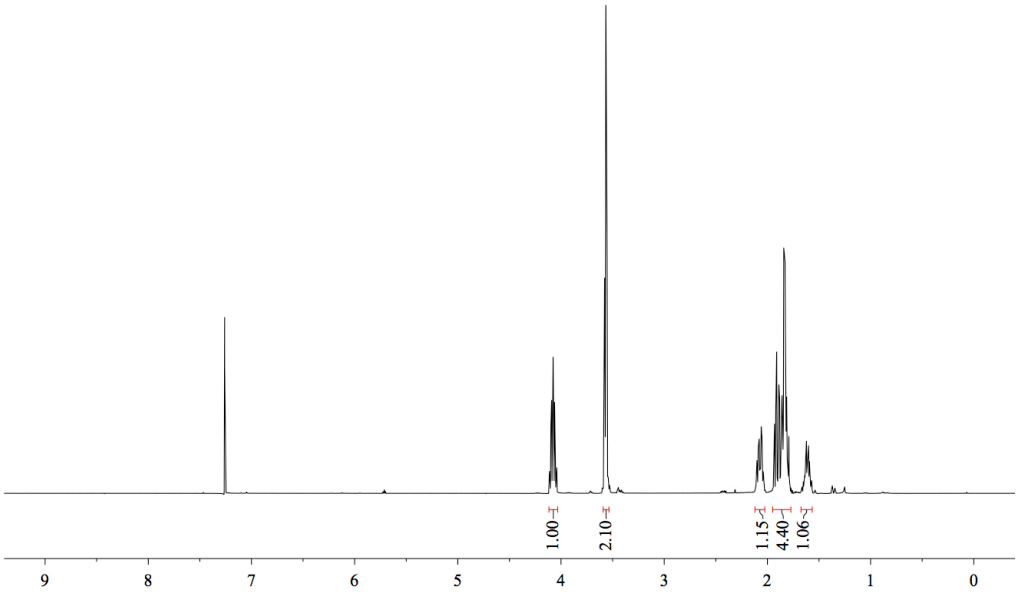


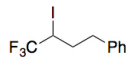
($CDCl_3$, 500 MHz)



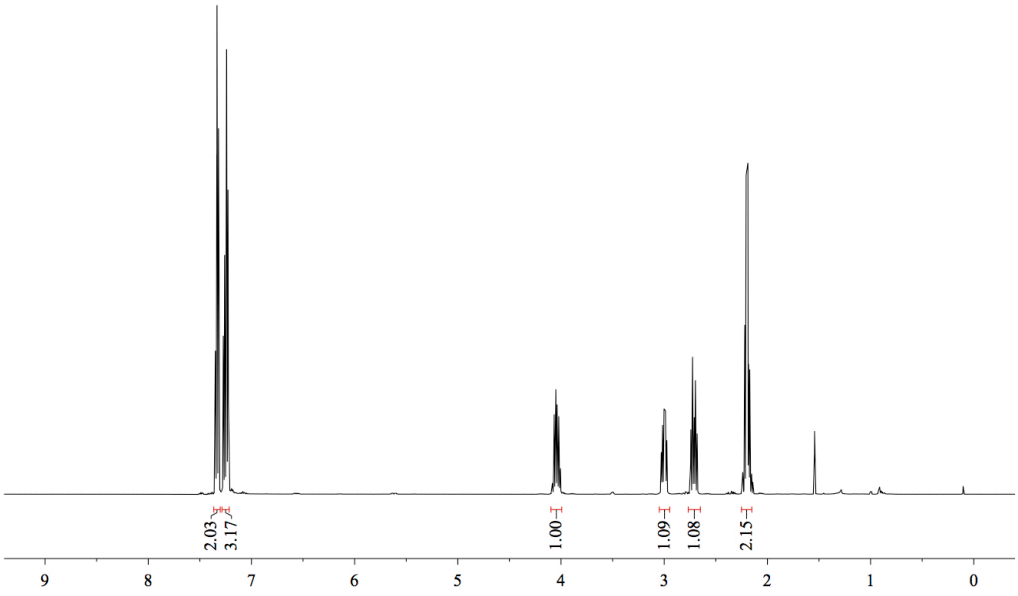


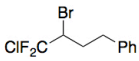
($CDCl_3$, 500 MHz)



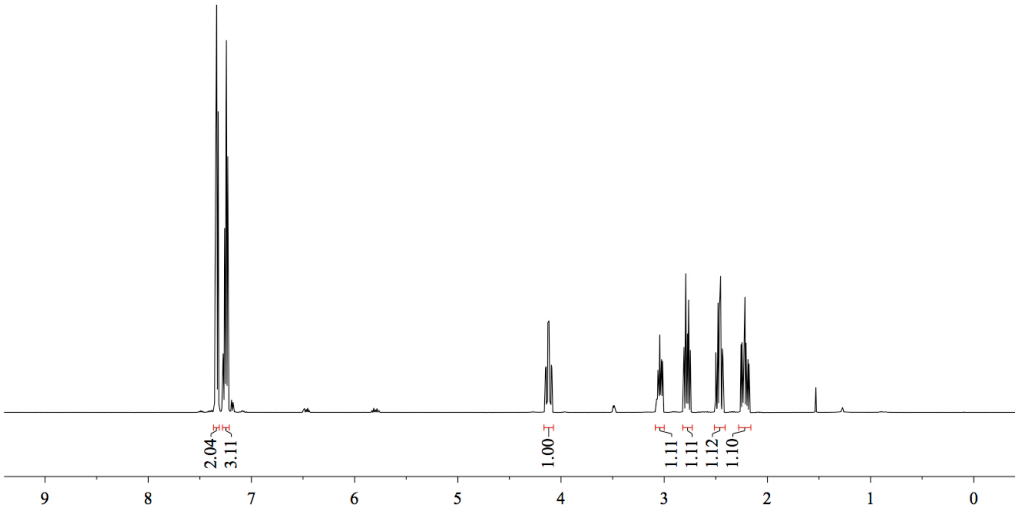


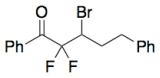
($CDCl_3$, 500 MHz)



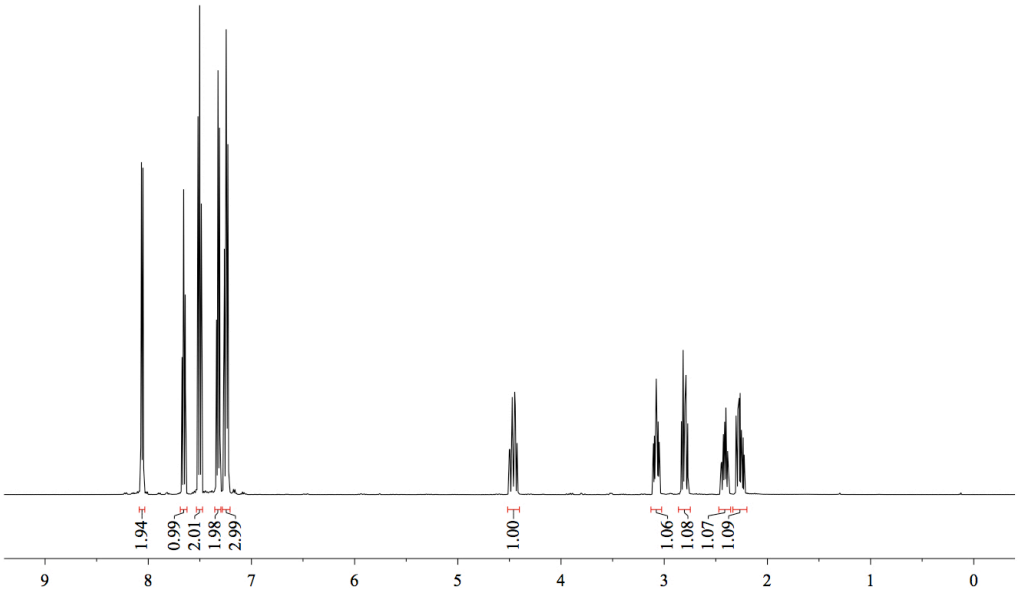


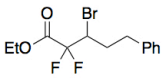
($CDCl_3$, 500 MHz)



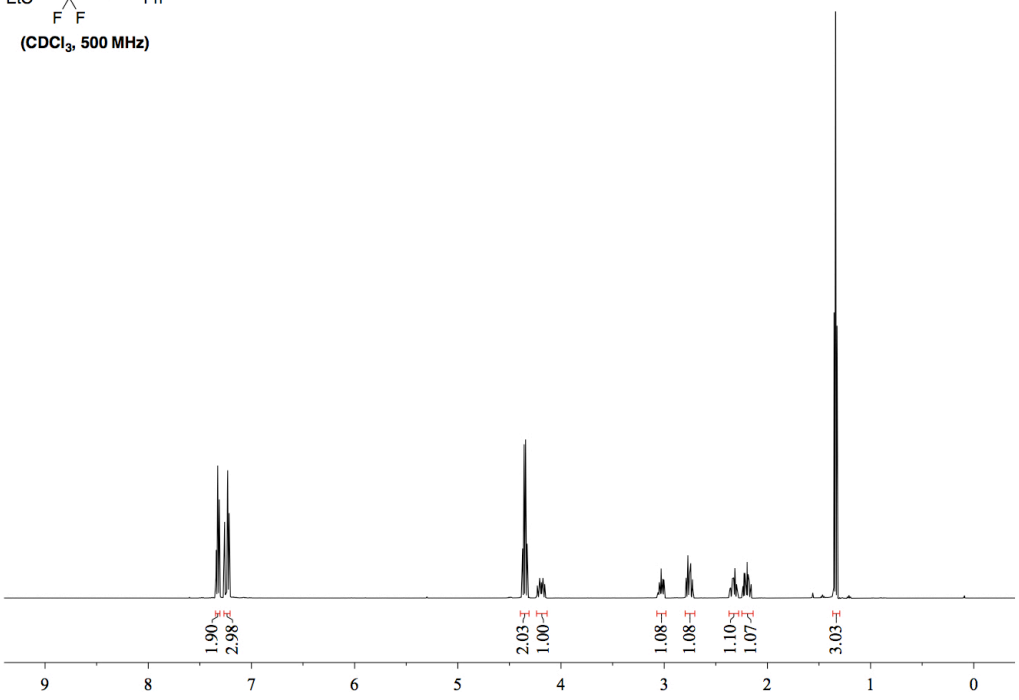


($CDCl_3$, 500 MHz)





($CDCl_3$, 500 MHz)



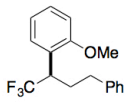
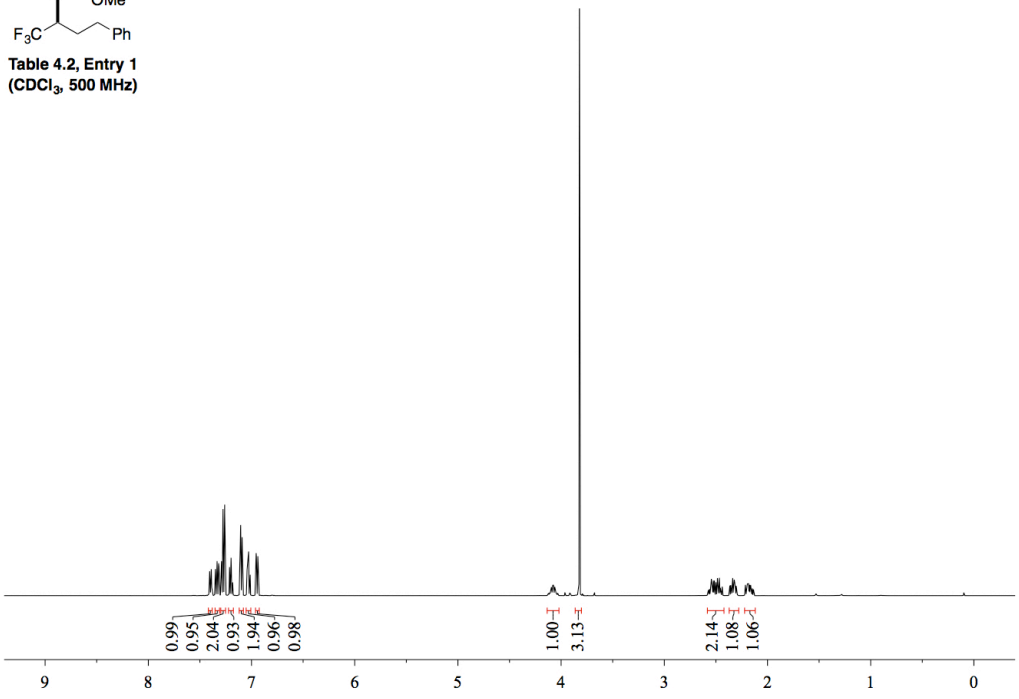


Table 4.2, Entry 1
($CDCl_3$, 500 MHz)



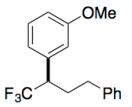
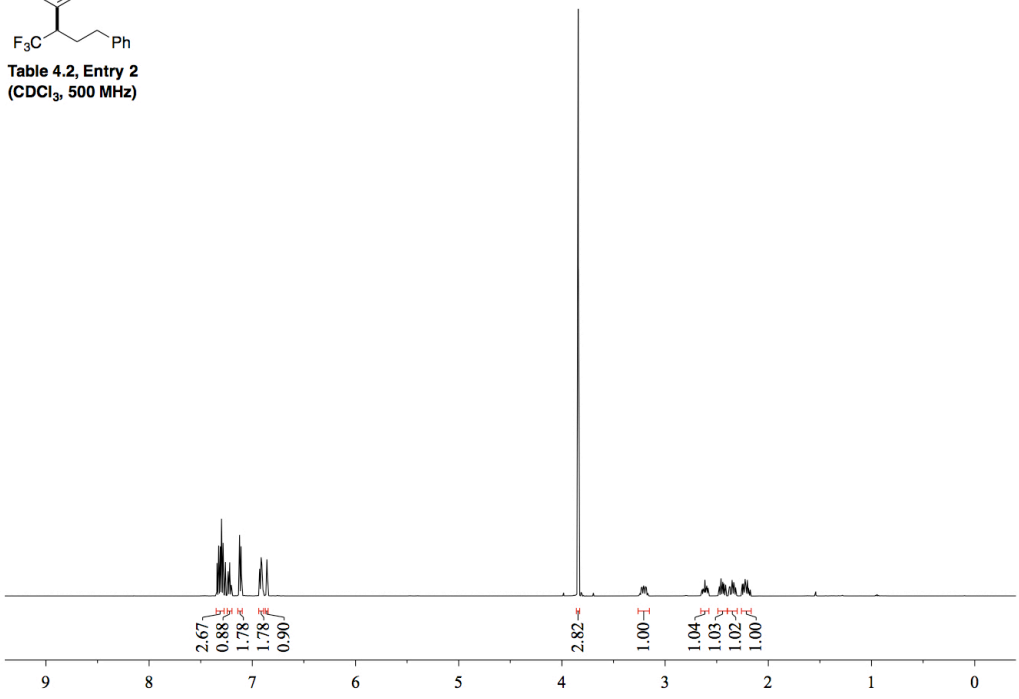


Table 4.2, Entry 2
($CDCl_3$, 500 MHz)



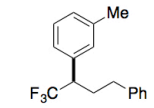
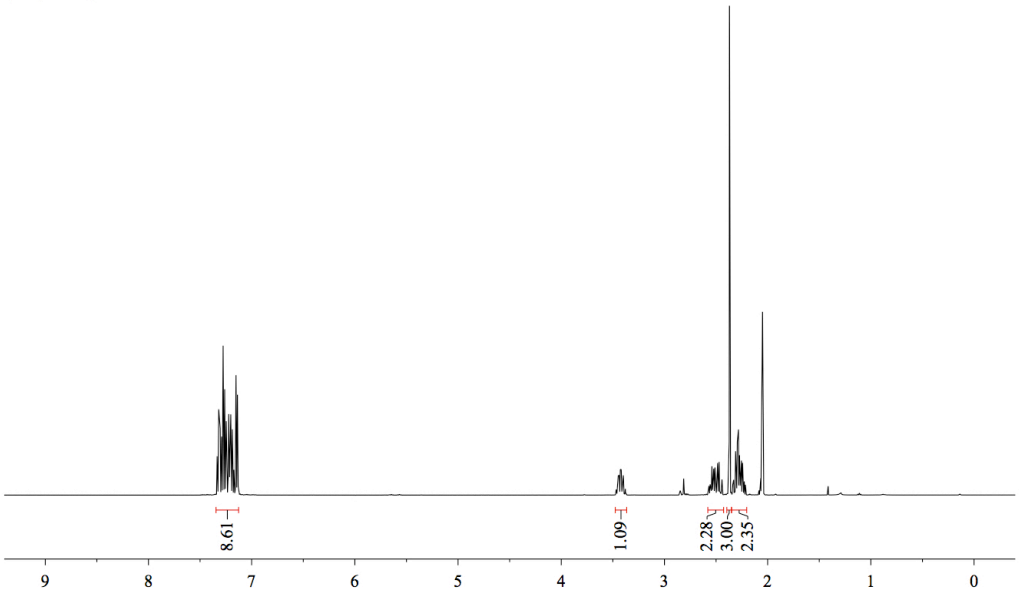


Table 4.2, Entry 3
(CD_3COCD_3, 500 MHz)



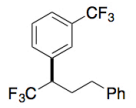
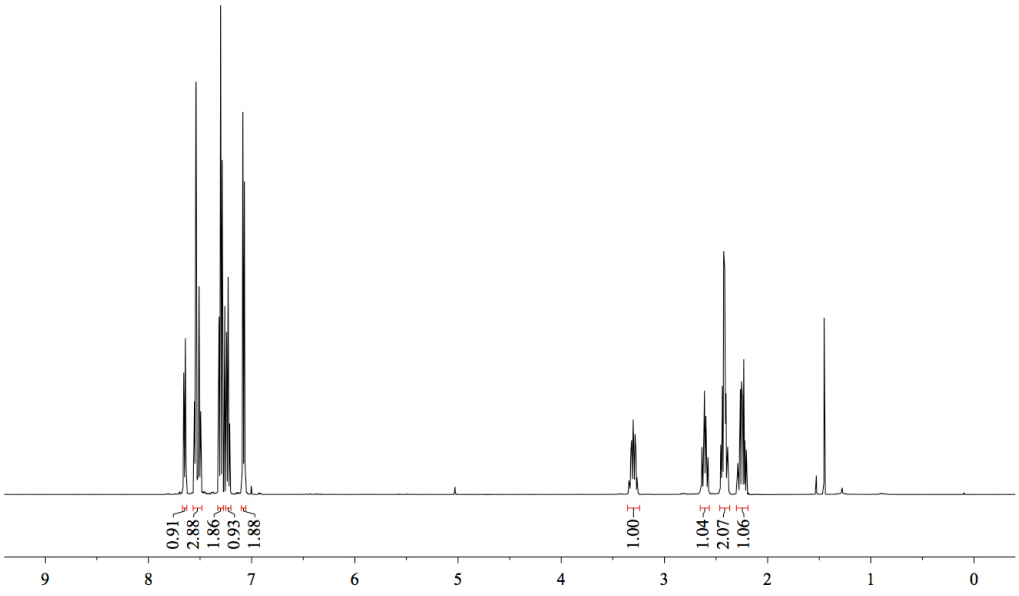


Table 4.2, Entry 4
($CDCl_3$, 500 MHz)



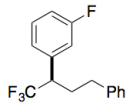
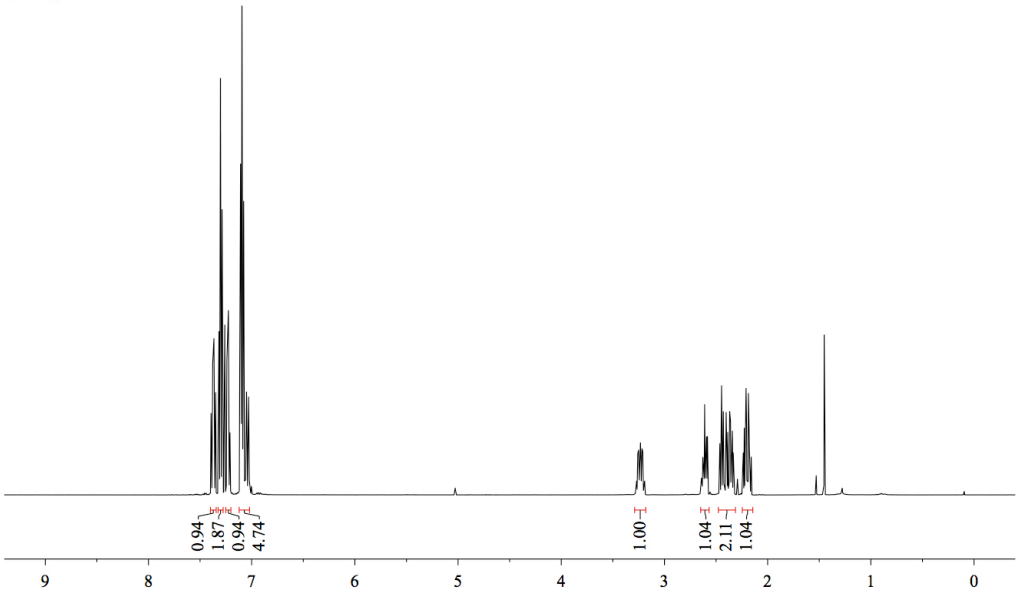


Table 4.2, Entry 5
($CDCl_3$, 500 MHz)



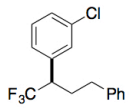
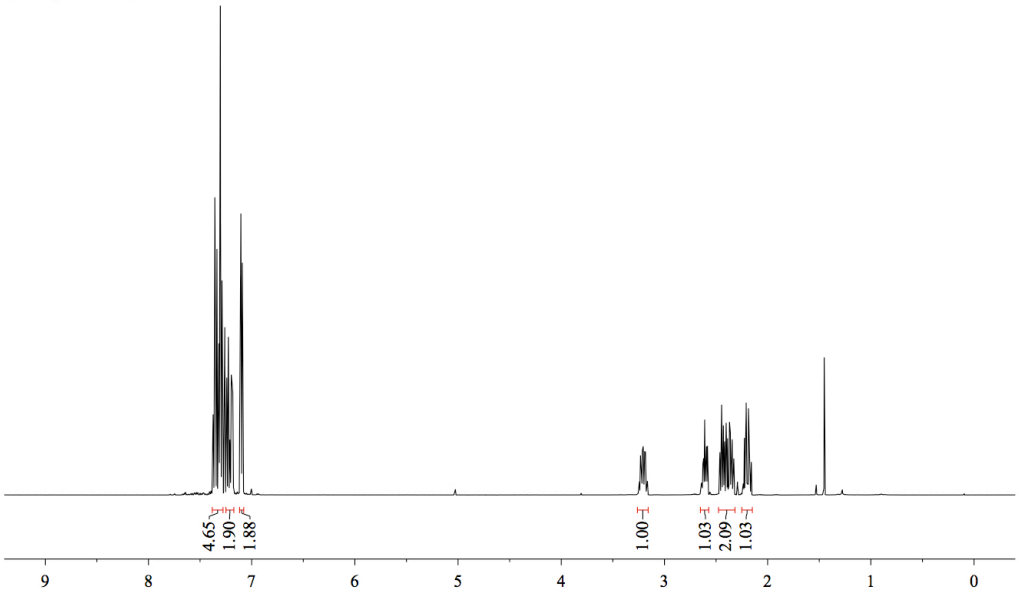


Table 4.2, Entry 6
($CDCl_3$, 500 MHz)



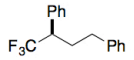
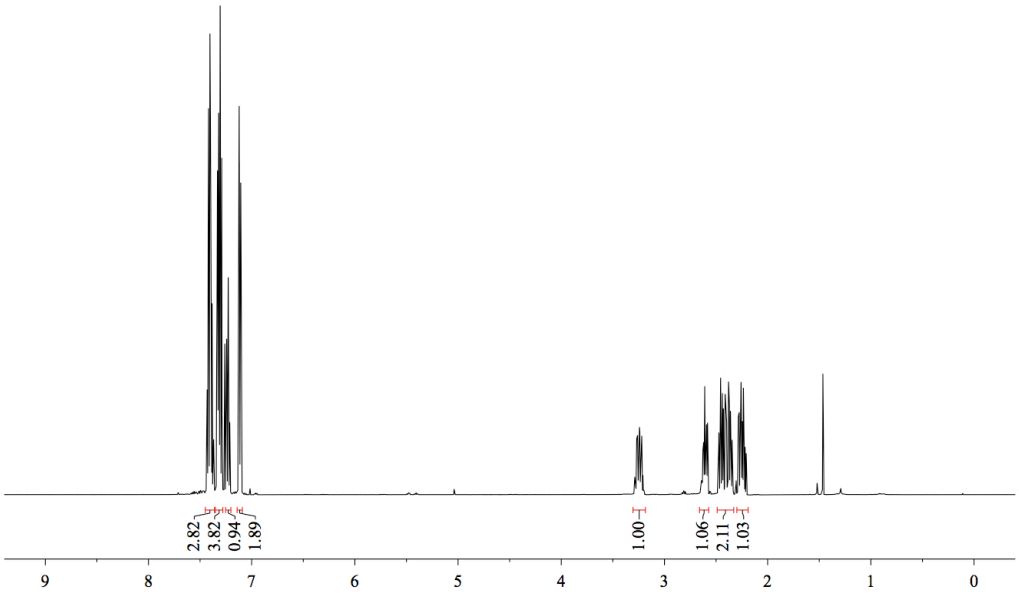


Table 4.2, Entry 7
($CDCl_3$, 500 MHz)



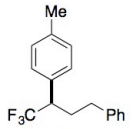


Table 4.2, Entry 8
($CDCl_3$, 500 MHz)

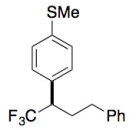
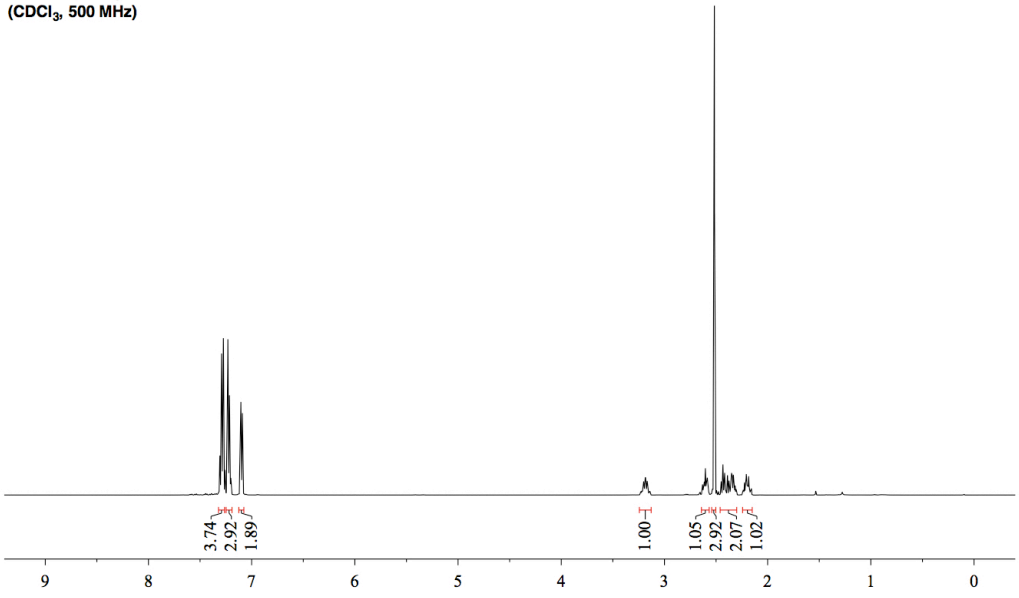


Table 4.2, Entry 9
($CDCl_3$, 500 MHz)



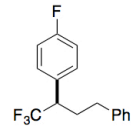
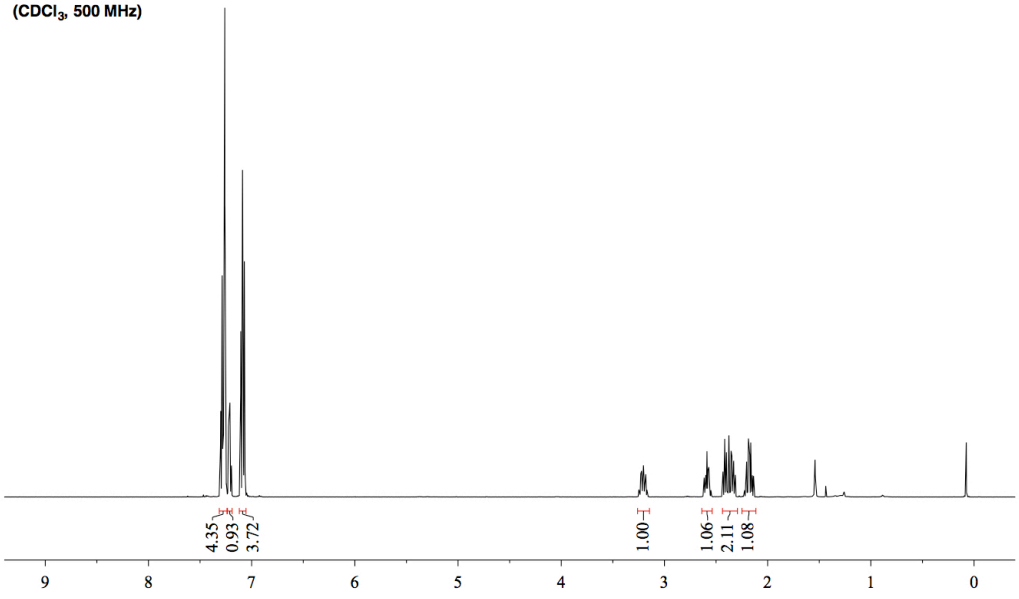


Table 4.2, Entry 10
($CDCl_3$, 500 MHz)



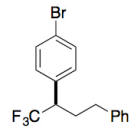
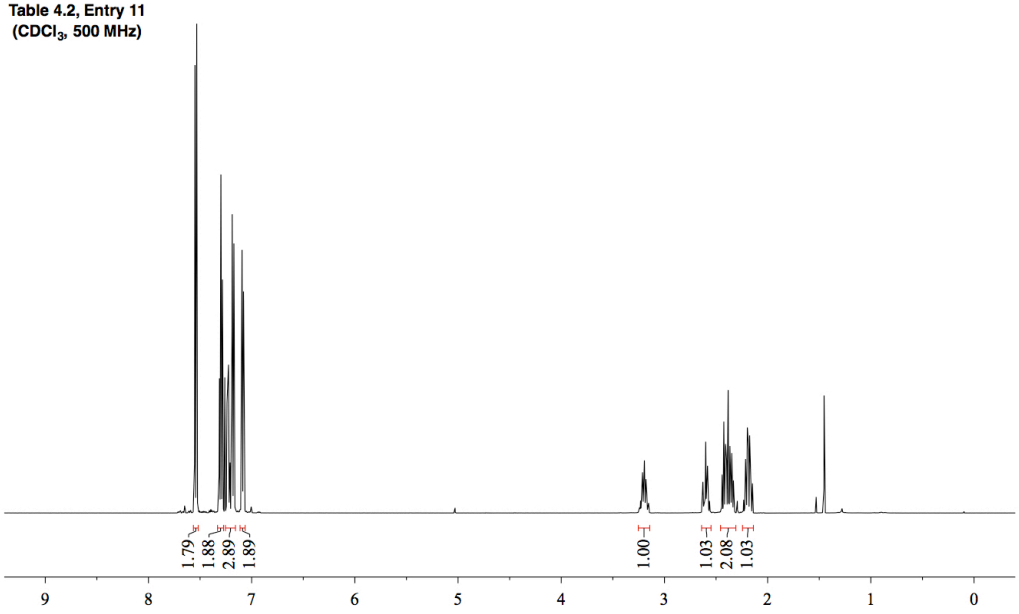
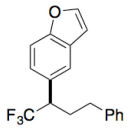
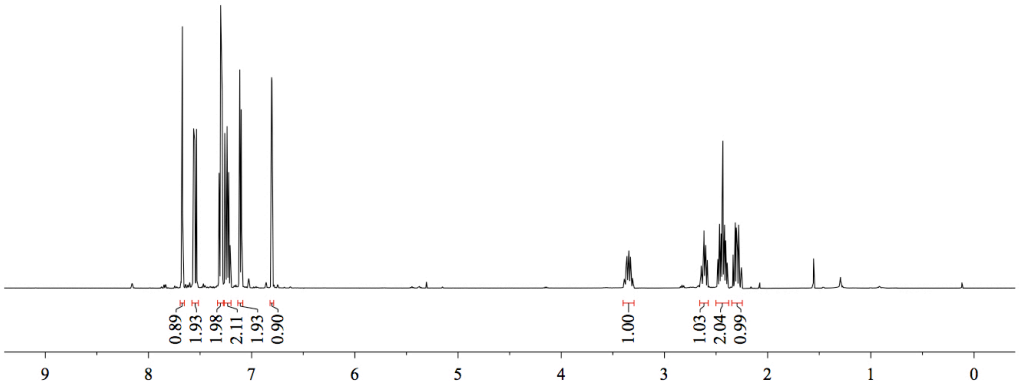


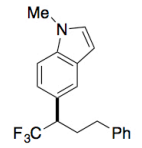
Table 4.2, Entry 11
($CDCl_3$, 500 MHz)



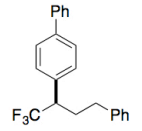


Eq 4.2
($CDCl_3$, 500 MHz)

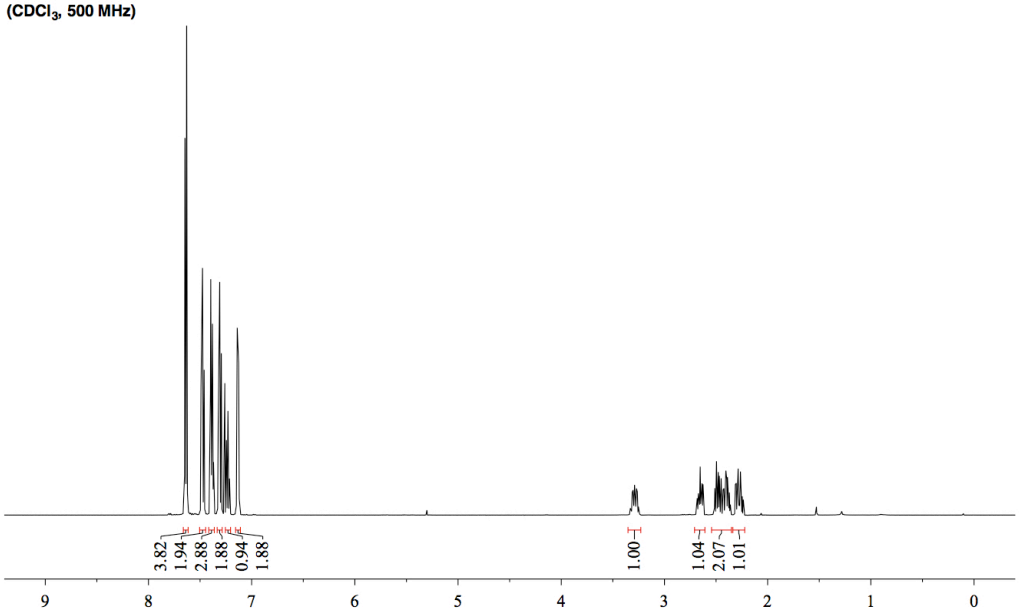




Eq 4.3
($CDCl_3$, 500 MHz)



($CDCl_3$, 500 MHz)



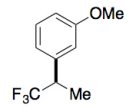
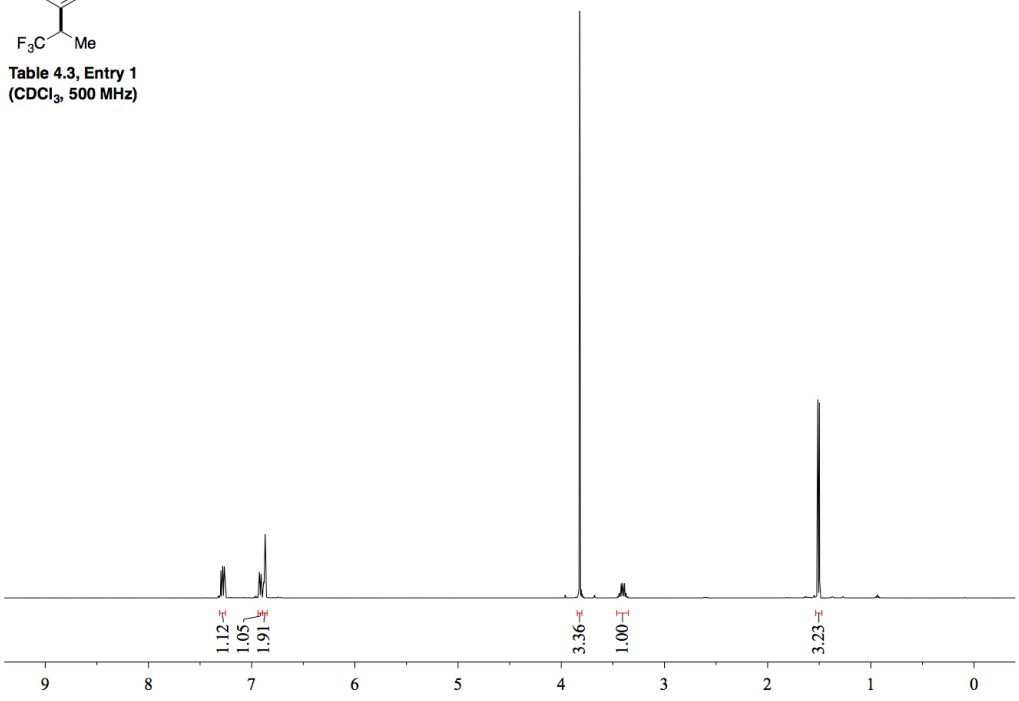


Table 4.3, Entry 1
($CDCl_3$, 500 MHz)



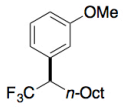


Table 4.3, Entry 2
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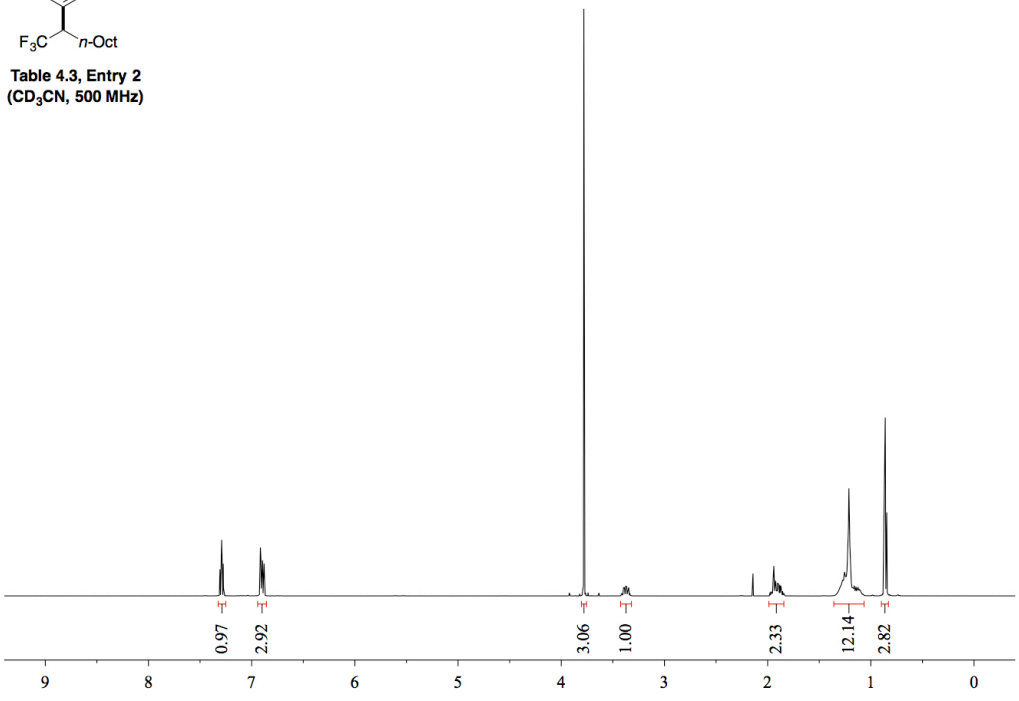

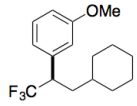

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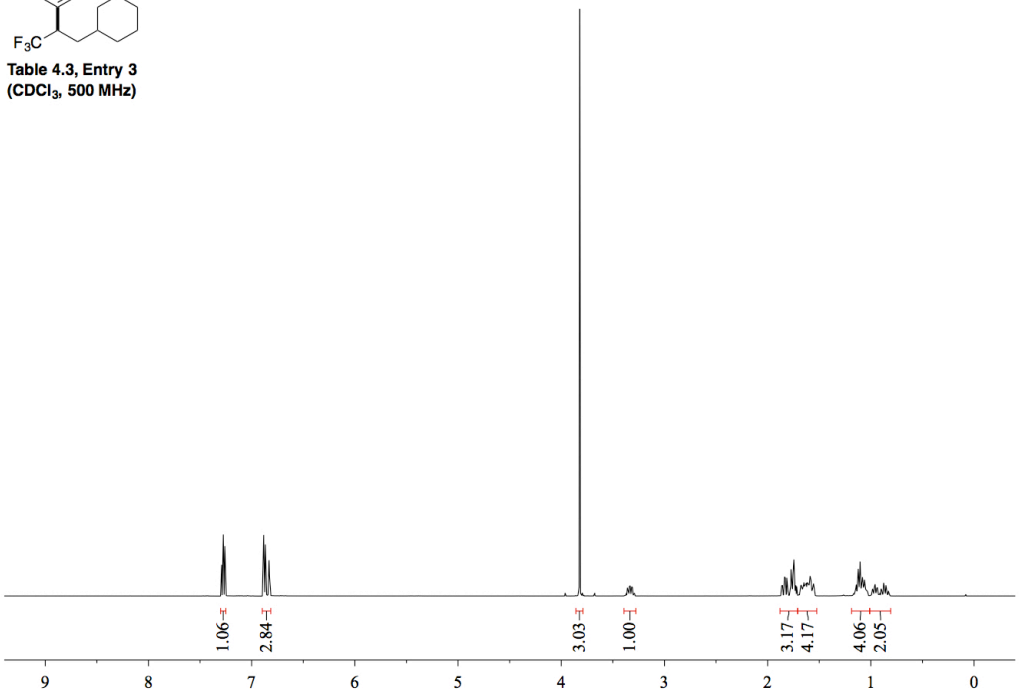

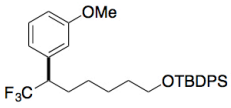

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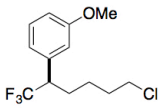

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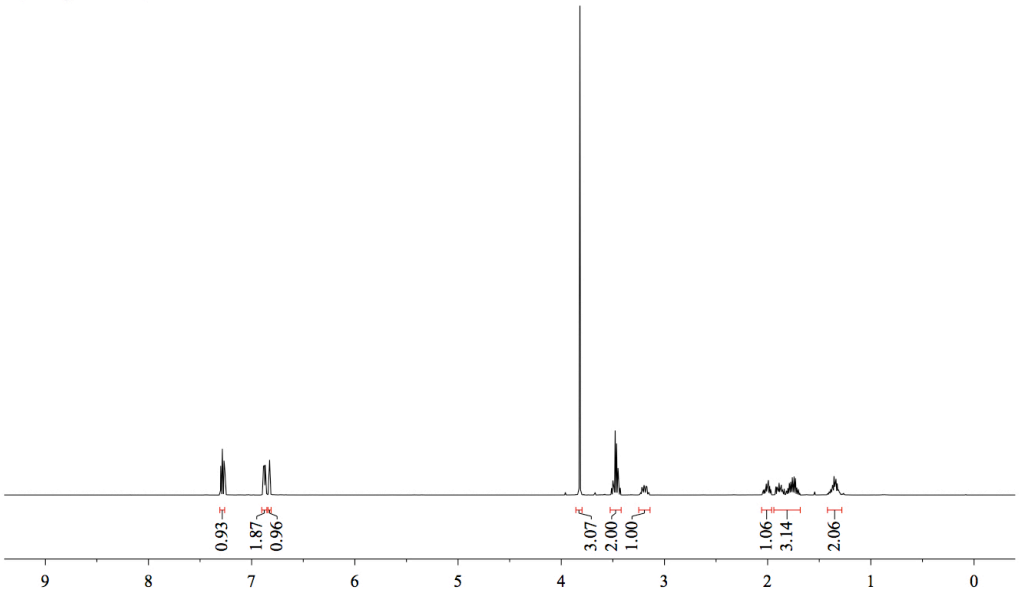

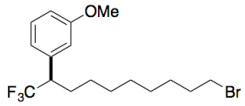

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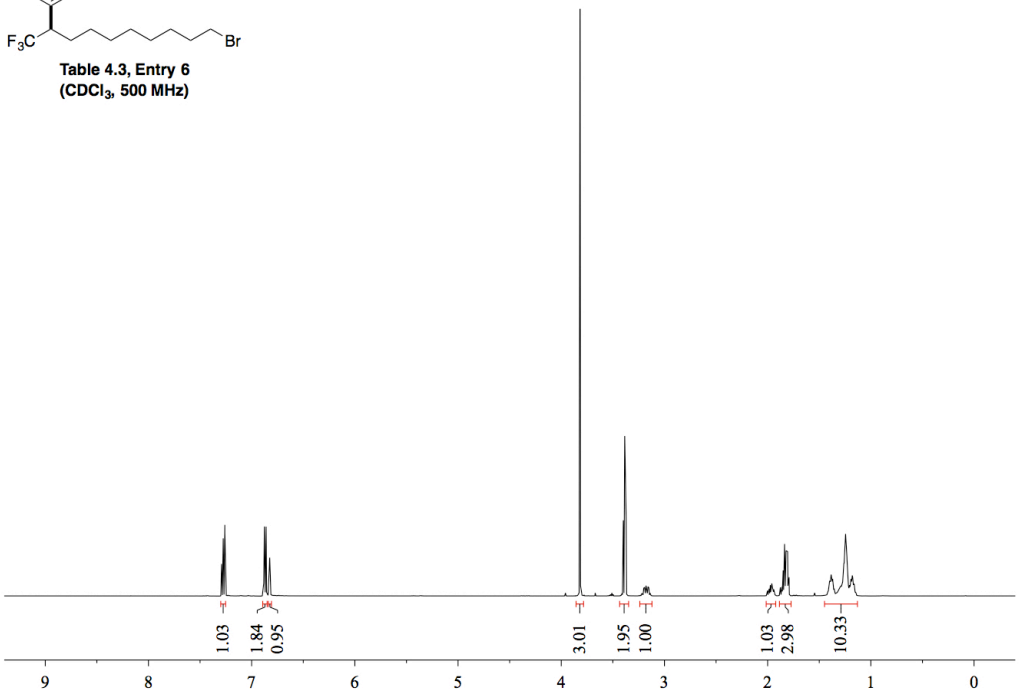

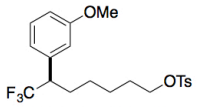

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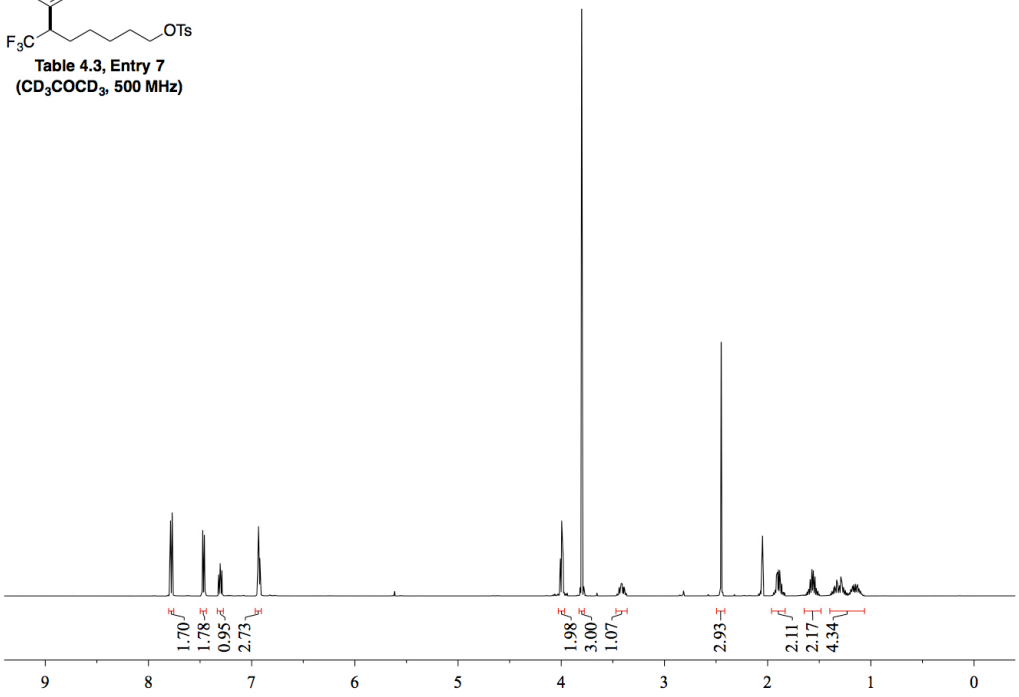

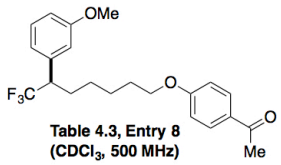

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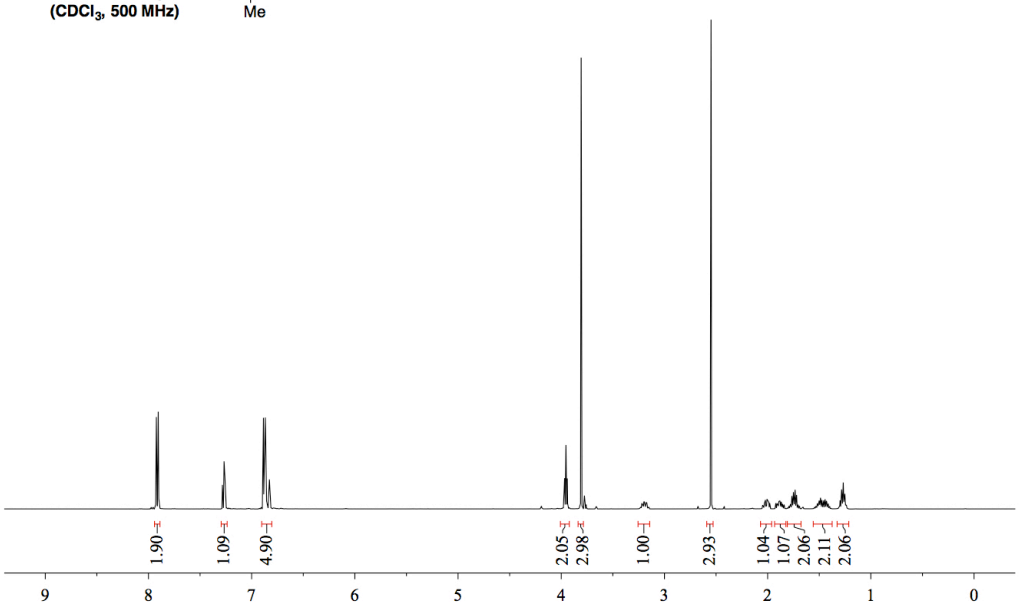

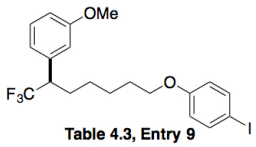

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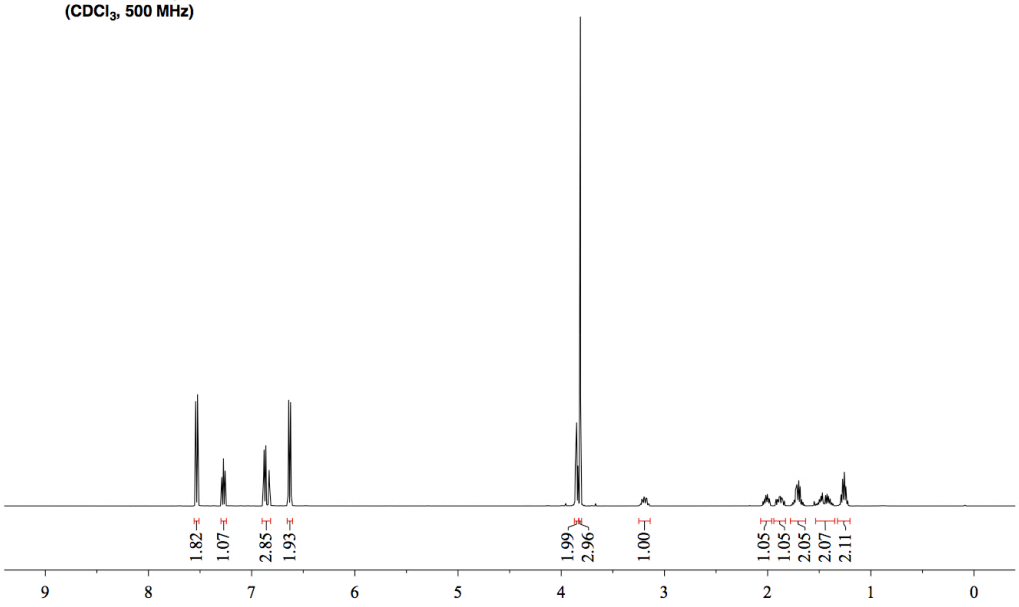

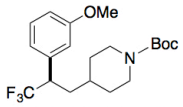

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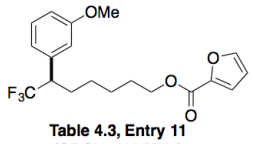

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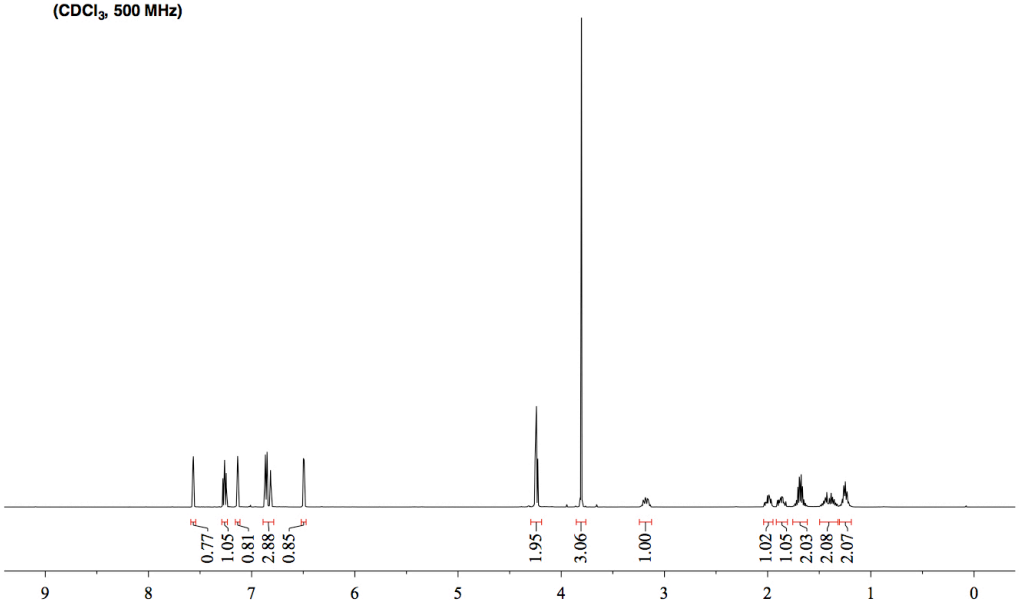

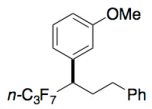

Eq 4.7
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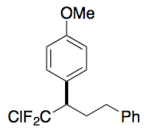

Eq 4.8
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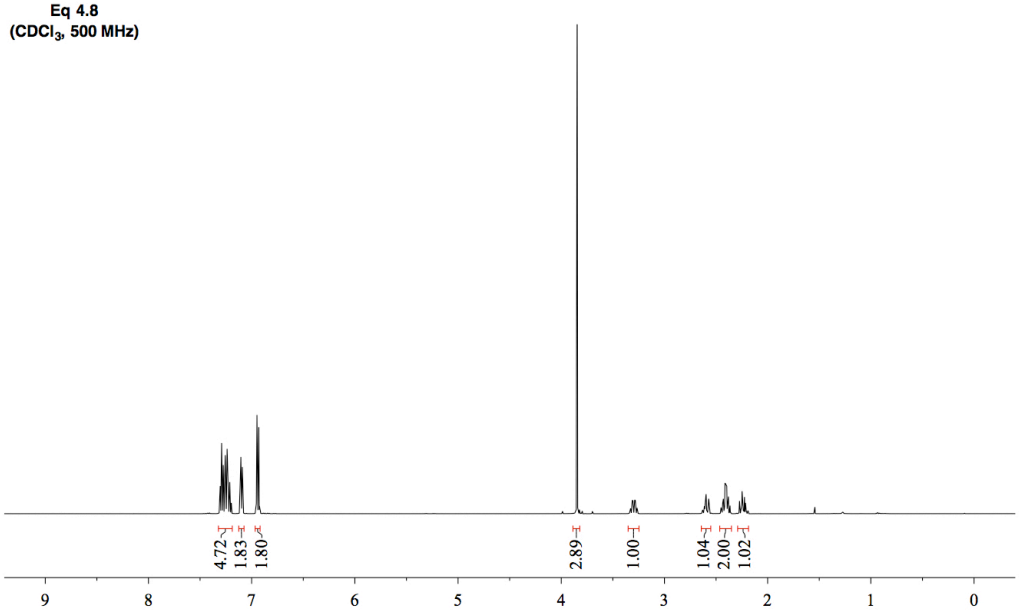

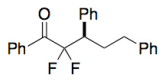

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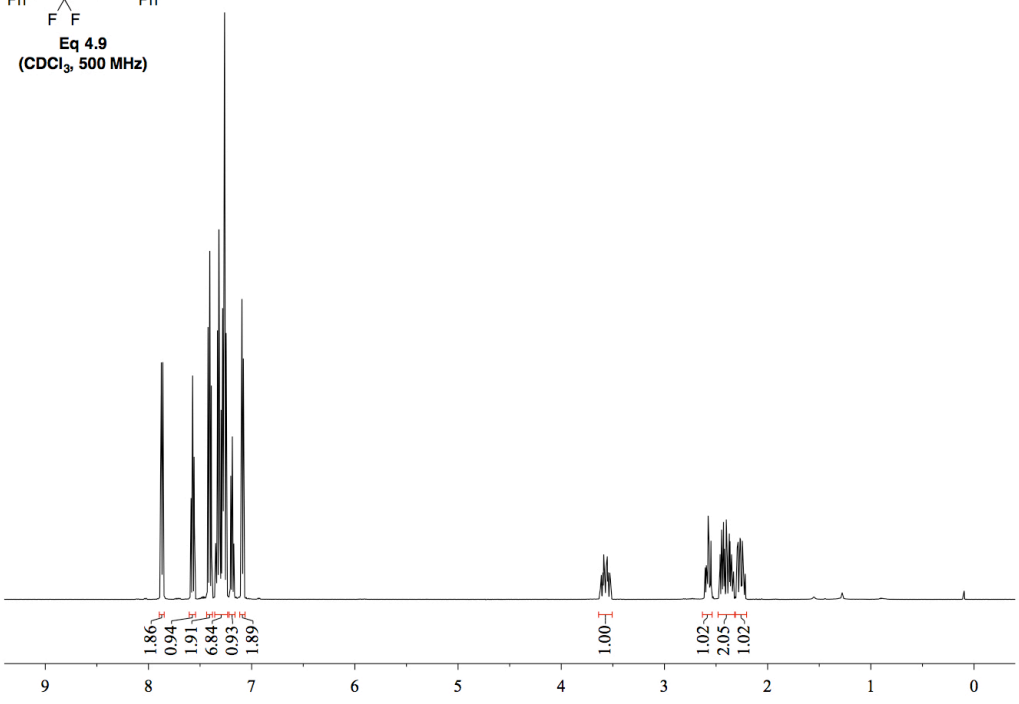

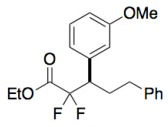

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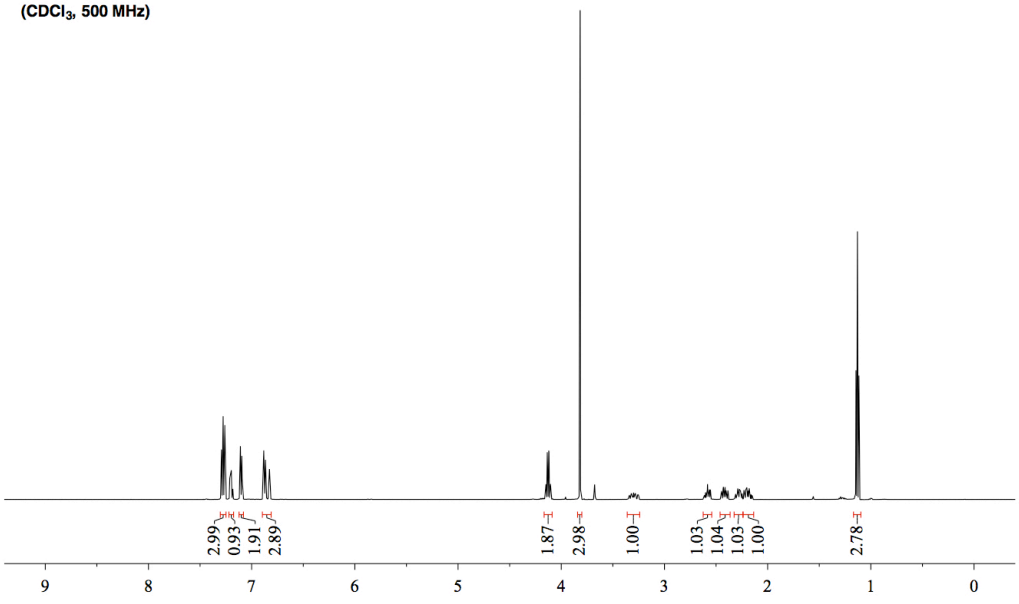

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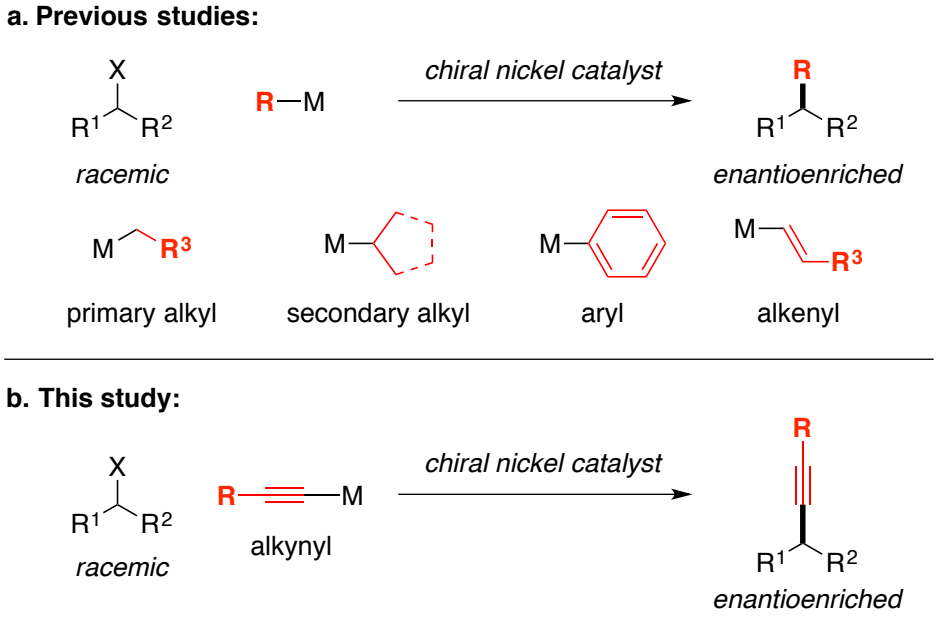
CHAPTER 5

Nickel-Catalyzed Asymmetric Suzuki Alkynylations of α-Halo-α-Trifluoromethyl Electrophiles

5.1 Introduction

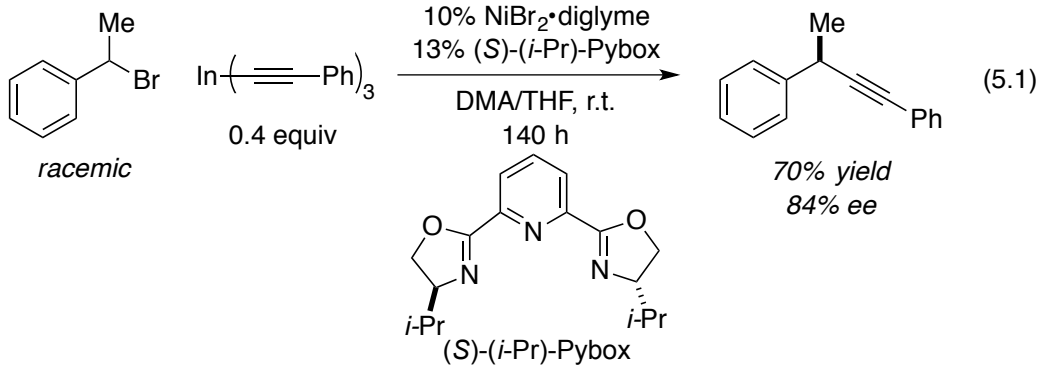
In the last decade, our group has developed a series of enantioselective cross-coupling methods of racemic secondary alkyl electrophiles with different families of nucleophiles. To date, we have demonstrated that sp^3-hybridized nucleophiles, including primary alkyl and symmetrical secondary alkyl nucleophiles, and sp^2-hybridized nucleophiles, including aryl and alkenyl nucleophiles, are suitable substrates for this type of reactions (Scheme 5.1a). One of the new directions in our group's chemistry is to explore new types of nucleophilic cross-coupling partners. In this chapter, our effort towards the development of an enantioselective cross-coupling method employing a new class of nucleophiles, namely *sp-hybridized alkynyl organoboron reagents*, is described (Scheme 5.1b).

Scheme 5.1. Enantioselective Cross-Couplings with Alkynyl Nucleophiles

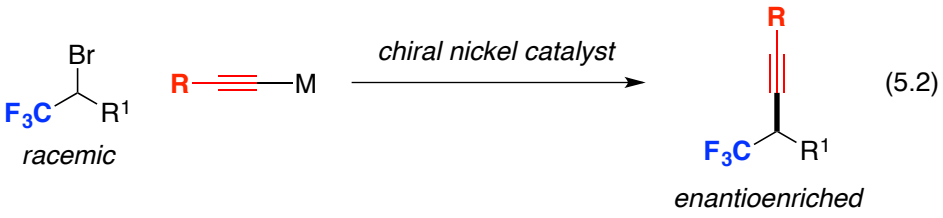


Chiral molecules bearing an alkynyl-substituted tertiary stereocenter are valuable building blocks due to the versatility of the alkynyl functional groups.[1] Cross-couplings of a secondary alkyl electrophile and an alkynyl organometallic reagent is one of the most straightforward approaches to construct such a stereocenter (Scheme 5.1b). However, although *non-asymmetric* cross-coupling methods using secondary alkyl electrophiles and alkynyl nucleophiles have been reported with a number of different transition-metal catalysts[2] (including nickel catalysts[3]), the enantioselective version of this transformation has been largely underdeveloped. In 2008, Sestelo, Sarandeses, and co-workers reported an nickel-catalyzed asymmetric alkynylation method employing secondary benzylic bromides and alkynylindium reagents (eq 5.1).[4] The yield and enantioselectivity of this method are moderate and the scope with respect to the electrophiles is quite limited.

Additionally, the cross-coupling conditions used by these researchers are actually first disclosed by our group in 2005 for an enantioselective Negishi alkylation method.[5]



Despite these drawbacks, this study is still the only reported method using an alkynyl nucleophile in enantioselective cross-coupling reactions. In order to investigate the field of asymmetric alkynylation cross-coupling and also further explore the utilities of fluorine-containing electrophiles, we decided to start our studies by choosing α-bromo-α-trifluoromethyl secondary electrophiles as our model substrates. The success of such a transformation will provide a convenient approach for the synthesis of chiral building blocks bearing a trifluoromethyl-substituted *propargylic* stereocenter.[6]

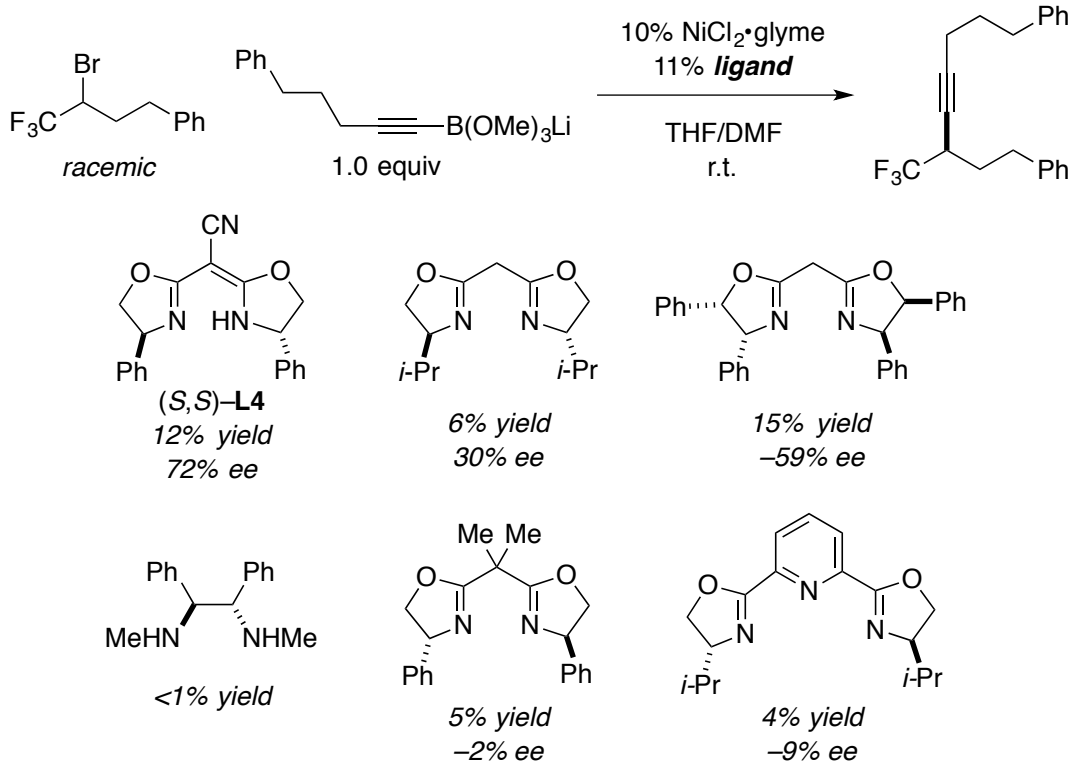


5.2 Optimization

We started our journey by conducting a variety of screenings using alkynyllzinc and alkynyl Grignard reagents as nucleophiles. Unfortunately, we cannot identify a

suitable condition (>20% yield) to continue further optimization. By switching the nucleophilic cross-coupling partner to an alkynylboron reagent which is *in situ* generated from the corresponding alkynyllithium reagent and $B(OMe)_3$, we quickly obtained a promising lead. In a ligand screening, we observed that performing the reaction with a chiral cyano-substituted bis(oxazoline) ligand **L4** generates the cross-coupling product in low yield but moderate enantioselectivity (Scheme 5.2).

Scheme 5.2. Preliminary Results from a Ligand Screening

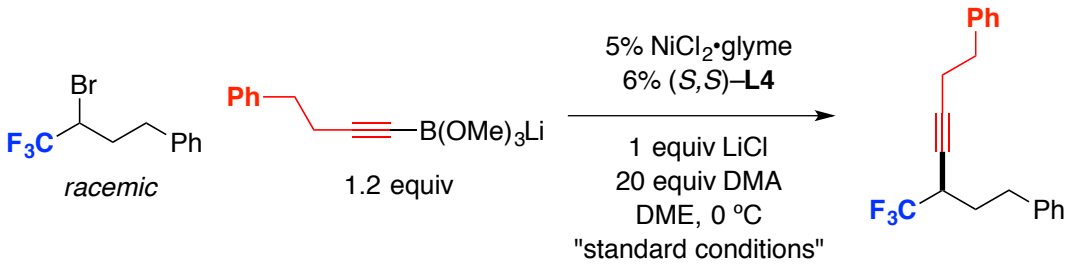


A negative ee value signifies that the major product of the reaction is the opposite (S) enantiomer.

Further optimization was performed to increase the efficiency and stereoselectivity based on these results. Finally, we identified a suitable condition to

deliver the cross-coupling product in good yield and enantioselectivity (Table 5.1, entry 1). The impact of reaction parameters on the efficiency of this transformation is provided in Table 5.1.

Table 5.1. Effect of Reaction Parameters[a]



entry	variation from the "standard" conditions	ee (%)	yield (%)[b]
1	none	92	88
2	no $NiCl_2$•glyme	–	<2
3	no (*S,S*)–**L4**	–	3
4	no LiCl	91	67
5	no DMA	92	68
6	1.0 equiv of nucleophile	92	75
7	1% $NiCl_2$•glyme, 1.2% (*S,S*)–**1**	92	78
8	r.t., instead of 0 °C	90	79
9	+ 0.1 equiv H_2O	92	88
10	in a closed vial under air	92	87

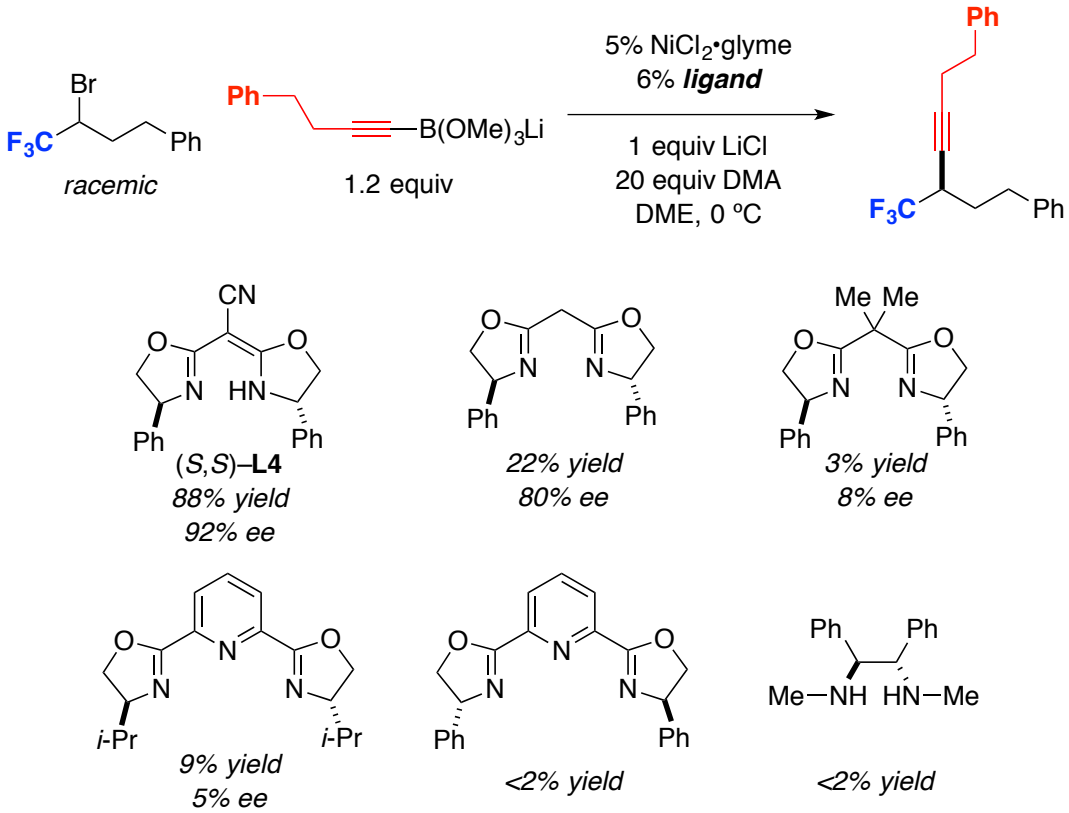
[a]All data are the average of two experiments. [b]Yields determined by ^{19}F NMR analysis versus an internal standard.

Essentially no bond-formation can be observed without the nickel source or the ligand **L4** (entries 2 and 3). The addition of both LiCl and DMA leads to increased yield for the transformation without any changes in enantioselectivity (entries 4 and 5). The use of a smaller amount of nucleophile or catalyst or performing the reaction at room temperature leads to slightly decreased efficiency (entries 6, 7, and 8). To our delight, the optimized condition is not very sensitive to a small amount of water or air (entries 9 and

10). From a practical perspective, both the nickel source and the ligand **L4** are commercially available and air-stable.

The chiral ligand **L4** is very crucial for the success of this transformation. A number of other bidentated and tridentated chiral ligands have been surveyed under the optimized conditions and none of them can provide comparable efficiency (Scheme 5.3). Previously, we have never employed this family of chiral bis(oxazoline) ligands in any of our asymmetric nickel-catalyzed cross-coupling methods.[7] Thus, this study introduced this new family of ligand to our system.

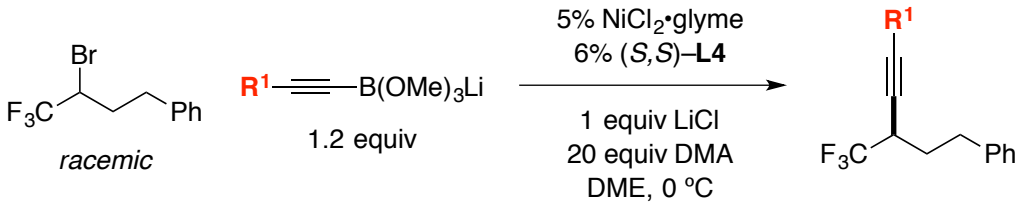
Scheme 5.3. Effect of Ligands

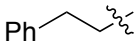
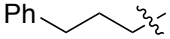
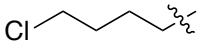
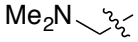
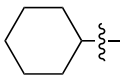


5.3 Scope

With the optimized conditions in hand, we started to explore the scope of this new method. As shown in Table 5.2, it is delighted that a number of *alkyl*-substituted alkynyl nucleophiles are suitable substrates for this transformation (entries 1 to 5). Functional groups including a primary alkyl chloride (entry 3) and a tertiary amine (entry 4) can both be tolerated. Also, a nucleophile bearing a terminal *silyl* protecting group is able to deliver the product in good yield and enantioselectivity (entry 6).

Table 5.2. Scope with Respect to the Nucleophile: Part I[a]



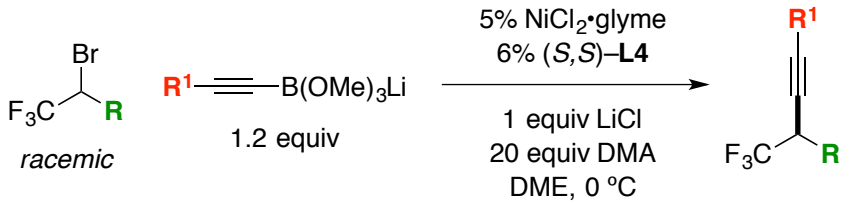
entry	R[1]	ee (%)	yield (%)[b]
1		92	86
2		92	86
3		93	81
4[c]		91	80
5		94	78
6[d]	TIPS	93	93

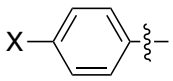
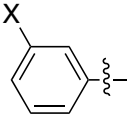
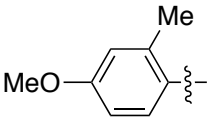
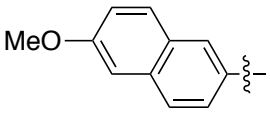
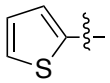
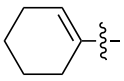
[a]All data are the average of two experiments. [b]Yield of purified product. [c]10% $NiCl_2$•glyme, 12% (*S*,*S*)–**L4.** [d]Reaction temperature: r.t.

Moreover, the current method can also be applied to *aryl*- and *alkenyl*-substituted alkynyl nucleophiles (Table 5.3). High enantioselectivity and yield are uniformly

obtained whether the aromatic ring is para- (entries 2 to 4), meta- (entries 5 and 6), and ortho-substituted (entry 7), and whether it is electron-poor or electron-rich. Nucleophiles containing a naphthalene ring (entry 8) and a thiophene ring (entry 9) are both applicable under our optimized conditions.

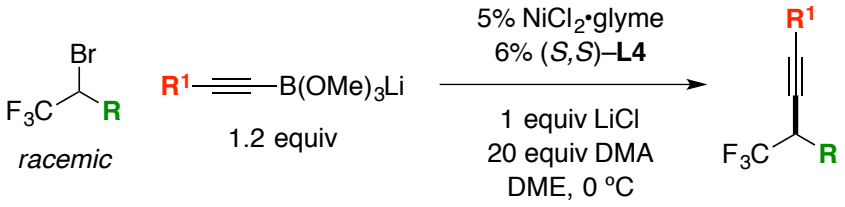
Table 5.3. Scope with Respect to the Nucleophile: Part II[a]



entry	R	R¹	ee (%)	yield (%)[b]
1	CH_2CH_2Ph	Ph	94	98
2[c]	CH_2CH_2Ph	 X = Cl	94	94
3	CH_2CH_2Ph	OMe	94	99
4	CH_2CH_2Ph	NMe_2	93	92
5[c]	CH_2CH_2Ph	 X = F	94	80
6	CH_2CH_2Ph	OMe	95	99
7	CH_2CH_2Ph		93	97
8	CH_2CH_2Ph		94	97
9[d]	*n*-Oct		94	62
10	CH_2CH_2Ph		95	91

[a]All data are the average of two experiments. [b]Yield of purified product. [c]Reaction temperature: 10 °C. [d]10% $NiCl_2$•glyme, 12% (*S,S*)–**L4.**

Table 5.4. Scope with Respect to the Electrophile[a]



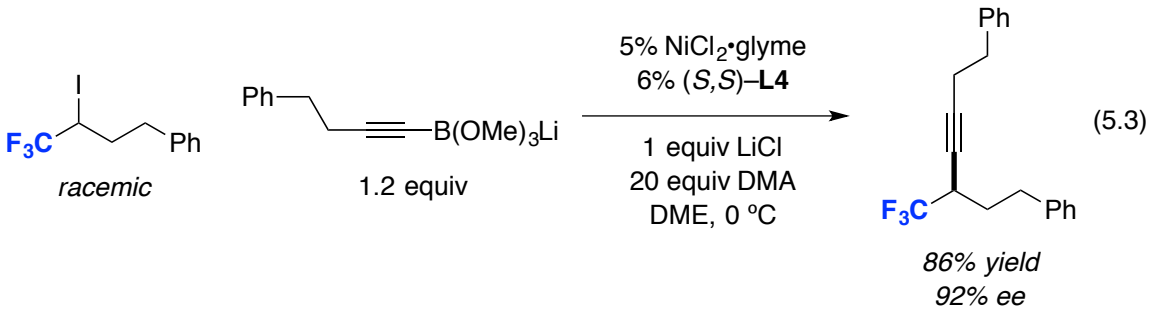
entry	R	R[1]	ee (%)	yield (%)[b]
1	*n*-Oct	MeO–	92	94
2	OTBDPS	$PhCH_2CH_2$	91	78
3	Cl	$PhCH_2CH_2$	92	84
4	O, O, Me	MeO–	93	97
5[c]	O, I	Ph	94	87
6	N, Boc	MeO–	97	97
7[c]	O, O, O	MeO–	94	87

[a]All data are the average of two experiments. [b]Yield of purified product.
[c]10% $NiCl_2$•glyme, 12% (*S*,*S*)–**L4.**

The scope with respect to the electrophile is also fairly broad (Table 5.4). An array of synthetically useful functional groups including a silyl ether (entry 2), a primary alkyl chloride (entry 3), an aromatic ketone (entry 4), an aryl iodide (entry 5), a

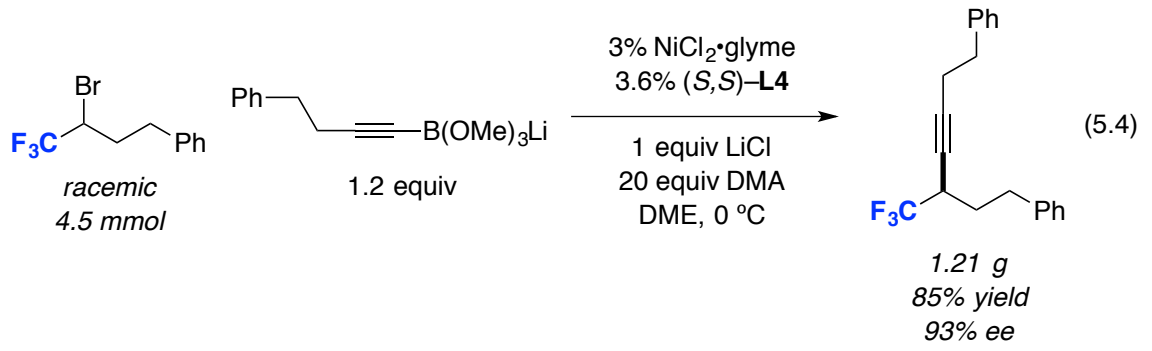
carbamate (entry 6), a furan ring (entry 7), and an ester (entry 7) can all be compatible with our conditions.

Although initially we optimized the reactions using an alkyl bromide as electrophile, we are glad that an alkyl iodide is also a suitable substrate for this transformation (eq 5.3).



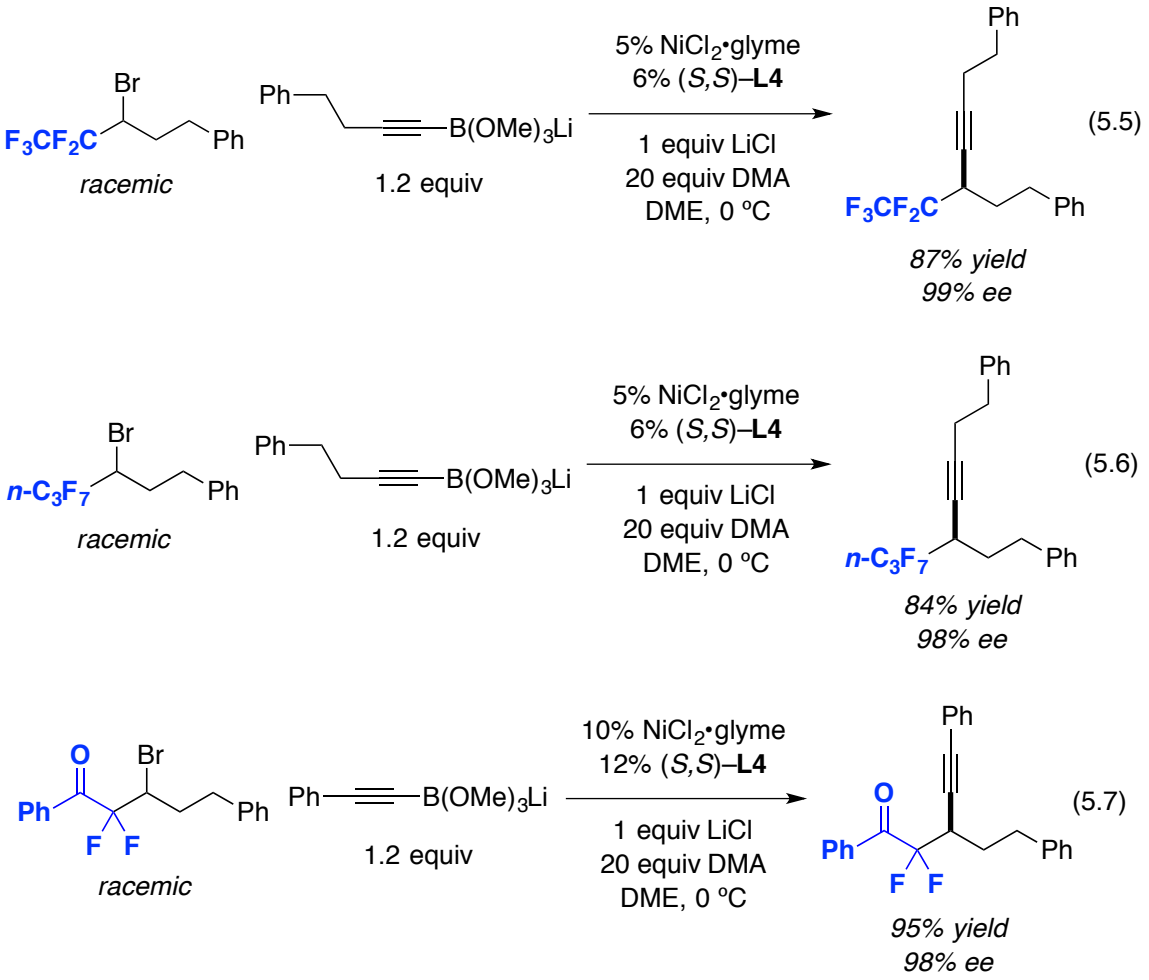
(5.3)

The scalability of this method is quite satisfactory. As shown in eq 5.4, a 4.5-mmol scale cross-coupling reaction is performed in the presence of 3% catalyst. More than 1 gram of product can still be generated in good yield and enantioselectivity.



(5.4)

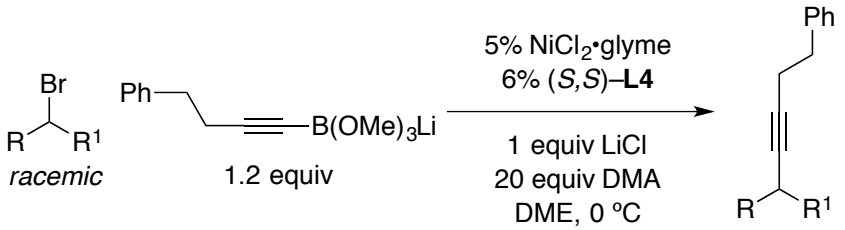
Similar to the findings in Chapter 4, the current method is not limited to cross-couple CF_3-substituted electrophiles. Racemic secondary electrophiles bearing a perfluoroethyl group (eq 5.5), a perfluoropropyl group (eq 5.6), and a CF_2COPh group (eq 5.7) can all be suitable substrates for this transformation under our standard conditions.

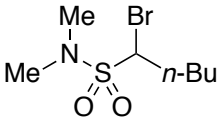
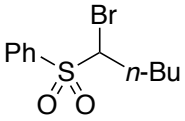
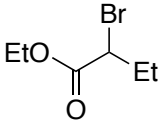
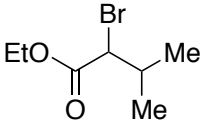
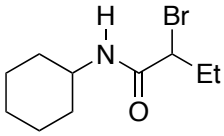
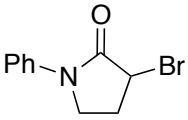
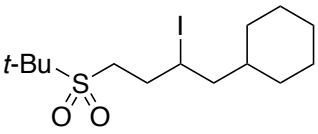


5.4 Preliminary Results of Asymmetric Alkynylations of Other Alkyl Electrophiles

Serving as a proof-of-concept, the current Suzuki alkynylation protocol successfully demonstrates that alkynyl nucleophiles can be employed in nickel-catalyzed asymmetric cross-coupling processes. However, we are more interested in developing asymmetric alkynylations methods using other families of electrophiles. Some of our preliminary results are presented in Table 5.5.

Table 5.5. Scope with Respect to Other Alkyl Electrophiles[a]



entry	electrophile	ee (%)	yield (%)[b]
1		98	89
2		93	85
3[c]		85	88
4[c]		97	80
5		87	93
6[c]		91	83
7[c,d]		86	96

[a]All data are the average of two experiments. [b]Yield of purified product. [c]No LiCl. [d]10% $NiCl_2$•glyme, 12% (*S*,*S*)–**L4.**

We were very delighted to observe that our standard conditions can be applied to cross-couple an α-bromo sulfone (entry 1) and an α-bromo sulfonamide (entry 2). α-Bromo esters (entries 3 and 4) are also feasible substrates under slightly modified conditions (without the addition of LiCl). A sterically more hindered electrophile also cross-couples in good efficiency and excellent enantioselectivity (entry 4).[8] Moreover, an α-bromo *secondary* amide (entry 5) and an α-bromo *lactam* can also cross-couple with the nucleophile in good yield and enatioselectivity. This is the first time that we apply an asymmetric cross-coupling protocol to these families of electrophiles. Finally, it is even more surprising to observe that the current method can cross-couple an *unactivated* secondary alkyl iodide. This is also the first time in our studies that an asymmetric cross-coupling method can be applied to both *activated* and *unactivated* racemic secondary alkyl electrophiles.

5.5 Conclusions

In summary, the first enantioselective Suzuki alkynylation method of secondary alkyl electrophiles has been described in this chapter. In the presence of commercially available catalysts and nucleophiles that can be easily prepared from readily available terminal alkynes, an array of α-bromo-α-trifluoromethyl secondary electrophiles cross-couple with a variety of alkynylboron nucleophiles to generate products in good efficiency and excellent stereoselectivity. Furthermore, the generality of this protocol has been examined using other alkyl electrophiles. Our preliminary studies have shown that the current method is quite general for the construction of a variety of tertiary

stereocenters bearing an alkynyl group. Further studies to disclose the full scope of this method and also examine the mechanism of these transformations are underway.

5.6 Experimental Section

5.6.1 General Information

The following reagents were purchased and used as received: $NiCl_2$•glyme (Strem), $B(OMe)_3$ (Aldrich; ≥99.5%), DMA (Aldrich; anhydrous), LiCl (Alfa Aesar; ultra dry, ≥99.995%), *n*-BuLi (Aldrich; ~2.5 M in hexanes; titrated using diphenylacetic acid according to Kofron's method[9]). All terminal alkynes were purchased (Aldrich, Alfa Aesar, TCI, Oakwood, Ak Scintific and Combi-Blocks) and used as received. Anhydrous DME was purified and dried using a solvent-purification system that contained activated alumina. Ligand (*S*,*S*)–**L4** was purchased from Aldrich and used as received. Ligand (*R*,*R*)–**L4** was synthesized according to a literature procedure.[10]

All reactions were carried out in oven-dried glassware under an inert atmosphere.

HPLC analyses were carried out on an Agilent 1100 Series system, using Daicel CHIRALCEL® columns or Daicel CHIRALPAK® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm).

^{1}H NMR data and ^{13}C NMR data were collected on a Varian 500 MHz spectrometer at ambient temperature. ^{19}F NMR data were collected on a Varian 300 MHz spectrometer at ambient temperature.

5.6.2 Preparation of Electrophiles

These procedures have not been optimized.

All of the fluorinated electrophiles are prepared according to literature procedures.[11]

All of the electrophiles shown in Table 5.5 are prepared according to literature procedures[12] or purchased and used as received.

5.6.3 Enantioselective Suzuki Cross-Couplings

Preparation of alkynylboron reagents (0.47 M):

In the air, an oven-dried 20 mL vial equipped with a stir bar was charged with the alkyne (2.0 mmol) and closed with a PTFE septum cap. The vial was evacuated and back-filled with nitrogen (three cycles), and then DME (2 mL) was added to this vial.

A solution of *n*-BuLi (2.54 M; 0.79 mL, 2.0 mmol; 1.0 equiv) was added over 1 min to this 20-mL vial, which had been cooled to 0 °C for 10 min. The mixture was allowed to stir at 0 °C for another 5 min and then warmed to room temperature. After stirring at room temperature for 10 min, DME was added to produce a total volume of 4.0 mL (0.5 M). Next, $B(OMe)_3$ (0.25 mL; 2.2 mmol; 1.1 equiv) was added to the alkynyllithium solution to provide an alkynylboron solution (0.47 M). The mixture was allowed to stir for 30 min at room temperature and used directly in the cross-coupling reaction.

General procedure for asymmetric alkynylation:

Preparation of a catalyst–ligand stork solution.

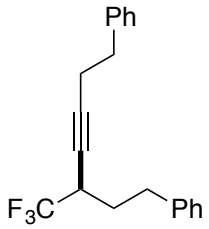
In the air, $NiCl_2$·glyme (6.6 mg, 0.060 mmol) and (*R*,*R*)–**L4** (12 mg, 0.072 mmol) were added to an oven-dried 4 mL vial equipped with a stir bar. The vial was closed with

a PTFE septum cap and the evacuated and back-filled with nitrogen three times. DME (1.5 mL) was added to the 4 mL vial and the mixture was vigorously stirred at room temperature for 30 min.

Asymmetric Suzuki alkynylation.

In the air, the electrophile (0.50 mmol) and LiCl (21 mg, 0.50 mmol; 1.0 equiv) were added to an oven-dried 20 mL vial equipped with a stir bar. The vial was closed with a PTFE septum cap and then evacuated and back-filled with nitrogen three times. DMA (0.93 mL, 10 mmol; 20 equiv) and DME (1.25 mL) were added to this 20 mL vial. The catalyst–ligand stork solution (1.25 mL; 0.050 mmol $NiCl_2$·glyme and 0.060 mmol (*R*,*R*)–**L4**) was added to the same vial and the mixture was allowed to stir at room temperature for 1 min. Next, this 20 mL vial was wrapped with electrical tape and cooled to 0 °C. Meanwhile, a 20 mL vial that contained the solution of the alkynylboron reagent was also cooled to 0 °C. Nitrogen-filled balloons were attached to both of the vials. To the vigorously stirred solution of catalyst and electrophile was added the solution of the alkynylboron reagent (0.47 M; 1.3 mL, 0.60 mmol; 1.2 equiv) over 1 min. The balloons were removed and the puncture hole in the septum cap was covered with grease. The mixture was stirred vigorously at 0 °C for 4 to 24 hours, and then MeOH (1 mL) was added to the reaction mixture. The resulting mixture was allowed to warm to room temperature, and then it was diluted with Et_2O (100 mL) and washed with deionized water (20 mL × 3). The organic layer was dried over Na_2SO_4, filtered, and then concentrated, and the crude material was purified by flash chromatography.

A second run was performed with (*S*,*S*)–**L4**.



(*R*)-(5-(Trifluoromethyl)hept-3-yne-1,7-diyl)dibenzene (Table 5.2, entry 1). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 4 h. Solvent system for chromatography: 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 135 mg (85% yield, 92% ee); Run 2, 137 mg (87% yield, 92% ee).

This compound was also prepared on a 4.5 mmol scale (eq 5.4), using (3-Bromo-4,4,4-trifluorobutyl)benzene (1.2 g, 4.5 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene (0.47 M; 11.5 mL, 5.4 mmol; 1.2 equiv). Following the General Procedure using 3.0% $NiCl_2$·glyme (30 mg, 0.14 mmol) and 3.6% (*S*,*S*)–**L4** (54 mg, 0.16 mmol), the title compound was isolated in 85% yield (1.21 g) and 93% ee.

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 9.4 min (major), 13.6 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H), 7.31 – 7.23 (m, 4H), 7.20 – 7.16 (m, 2H), 3.04 – 2.86 (m, 1H), 2.93 – 2.85 (m, 3H), 2.66 (dt, 1H, *J* = 13.8, 8.5 Hz), 2.60 (td, 1H, *J* = 7.4, 2.3 Hz), 2.06 – 1.98 (m, 1H), 1.97 – 1.88 (m, 1H);

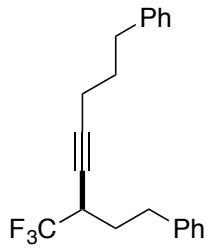
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.38, 140.37, 128.50, 128.49, 128.47, 128.4, 126.3, 126.2, 125.5 (q, *J* = 280.3 Hz), 85.0, 73.6 (q, *J* = 3.5 Hz), 37.0 (q, *J* = 30.2 Hz), 34.8, 32.4, 30.1 (d, *J* = 1.7 Hz), 20.8;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.3 (d, 3F, J = 8.0 Hz);

FT-IR (film) 3028, 2932, 2243, 1604, 1497, 1454, 1260, 1165, 1118, 750, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{20}H_{19}F_3$: 316, found: 316;

$[\alpha]^{25}_D$ = +86° (*c* = 1.0, $CHCl_3$); 92% ee, from (*R,R*)-**L4**.



(*R*)-(3-(Trifluoromethyl)oct-4-yne-1,8-diyl)dibenzene (Table 5.2, entry 2). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from pent-4-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 16 h. Solvent system for chromatography: 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 140 mg (85% yield, 92% ee); Run 2, 143 mg (87% yield, 92% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 7.2 min (minor), 7.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H), 7.27 – 7.20 (m, 6H), 3.10 – 2.95 (m, 2H), 2.81 – 2.73 (m, 3H), 2.28 (td, 2H, J = 7.0, 2.3 Hz), 2.10 – 1.85 (m, 4H);

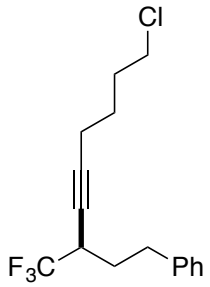
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 140.4, 128.55, 128.51, 128.46, 128.38, 126.3, 125.9, 125.5 (q, J = 280.1 Hz), 85.4, 73.4 (q, J = 3.5 Hz), 37.0 (q, J = 30.2 Hz), 34.7, 32.5, 30.22, 30.16, 18.0;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.4 (d, 3F, J = 8.0 Hz);

FT-IR (film) 3063, 3027, 2940, 2862, 2242, 1603, 1497, 1454, 1259, 1165, 1117, 747, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{21}H_{21}F_3$: 330, found: 330;

$[\alpha]^{25}_D$ = −60° (*c* = 1.0, $CHCl_3$); 92% ee, from (*S,S*)-**L4**.



(*R*)-(9-Chloro-3-(trifluoromethyl)non-4-yn-1-yl)benzene (Table 5.2, entry 3). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from 6-chlorohex-1-yne were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 123 mg (81% yield, 93% ee); Run 2, 121 mg (80% yield, 93% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 6.6 min (minor), 7.5 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.25 – 7.20 (m, 3H), 3.60 (t, 2H, *J* = 6.5 Hz), 3.05 – 2.91 (m, 2H), 2.73 (dt, 1H, *J* = 13.8, 8.5 Hz), 2.31 (td, 2H, *J* = 7.0, 2.3 Hz), 2.07 – 1.98 (m, 1H), 1.98 – 1.89 (m, 3H), 1.76 – 1.69 (m, 2H);

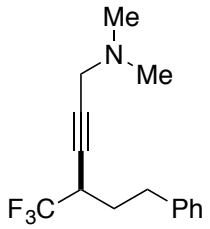
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.3, 128.6, 128.4, 126.3, 125.5 (q, *J* = 280.1 Hz), 84.9, 73.5 (q, *J* = 3.6 Hz), 44.5, 37.0 (q, *J* = 30.2 Hz), 32.5, 31.4, 30.1, 25.7, 17.9;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.4 (d, 3F, *J* = 8.0 Hz);

FT-IR (film) 2942, 2243, 1455, 1259, 1164, 1117, 751, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{18}ClF_3$: 302, found: 302;

$[\alpha]^{25}_D = -76°$ (*c* = 1.0, $CHCl_3$); 93% ee, from (*S,S*)-**L4**.



(*R*)-*N*,*N*-Dimethyl-6-phenyl-4-(trifluoromethyl)hex-2-yn-1-amine (Table 5.2, entry 4). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from *N*,*N*-dimethylprop-2-yn-1-amine were used. 10% $NiCl_2$·glyme (11 mg, 0.050 mmol) and 12% **L4** (20 mg, 0.060 mmol) were used. The reaction was run at 0 ºC for 16 h. Solvent system for chromatography: 1:1 hexane/ethyl acetate. The title compound was isolated as a yellow oil.

Run 1, 107 mg (79% yield, 91% ee); Run 2, 110 mg (81% yield, 91% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 12.5 min (minor), 18.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 7.25 – 7.20 (m, 3H), 3.34 (d, 2H, *J* = 2.0 Hz), 3.12 – 3.02 (m, 1H), 2.97 (ddd, 1H, *J* = 13.8, 8.8, 4.9 Hz), 2.75 (dt, 1H, *J* = 13.8, 8.5 Hz), 2.33 (s, 6H), 2.10 – 1.93 (m, 2H);

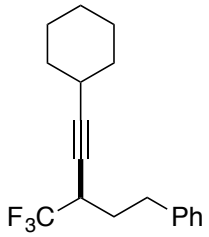
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.2, 128.6, 128.4, 126.4, 125.4 (q, *J* = 280.1 Hz), 80.3, 77.9 (q, *J* = 3.4 Hz), 47.9, 44.0, 37.0 (q, *J* = 30.3 Hz), 32.5, 30.0;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.2 (d, 3F, *J* = 7.9 Hz);

FT-IR (film) 2941, 2860, 2823, 2778, 1604, 1497, 1454, 1259, 1164, 1118, 1035, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{15}H_{18}F_3N$: 269, found: 269;

$[\alpha]^{25}_D$ = +74° (*c* = 1.0, $CHCl_3$); 91% ee, from (*R,R*)-**L4**.



(*R*)-(5-Cyclohexyl-3-(trifluoromethyl)pent-4-yn-1-yl)benzene (Table 5.2, entry 5). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from ethynylcyclohexane were used. The reaction was run at 0 ºC for 17 h. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 113 mg (77% yield, 93% ee); Run 2, 116 mg (79% yield, 94% ee).

The ee was determined on an OD-H column (hexane, flow rate 0.3 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 18.5 min (minor), 19.4 min (major).

^{1}H NMR (500 MHz, CD_3CN) δ 7.33 – 7.29 (m, 2H), 7.26 – 7.20 (m, 3H), 3.20 – 3.10 (m, 1H), 2.93 (ddd, 1H, *J* = 13.9, 9.3, 4.7 Hz), 2.78 – 2.70 (m, 1H), 2.52 – 2.44 (m, 1H), 2.02 (dddd, 1H, *J* = 13.2, 9.3, 7.8, 4.0 Hz), 1.90 – 1.76 (m, 3H), 1.75 – 1.66 (m, 2H), 1.55 – 1.42 (m, 3H), 1.42 – 1.31 (m, 3H);

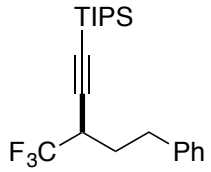
^{13}C NMR (126 MHz, CD_3CN) δ 141.7, 129.5, 129.4, 127.2, 126.9 (q, *J* = 279.1 Hz), 91.0, 73.7, 37.6 (q, *J* = 29.9 Hz), 33.2, 33.1, 31.1 (d, *J* = 1.6 Hz), 29.5, 26.5, 25.3;

^{19}F NMR (282 MHz, CD_3CN) δ −72.1 (d, 3F, *J* = 8.3 Hz);

FT-IR (film) 2931, 2855, 2242, 1497, 1450, 1260, 1165, 1118, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{21}F_3$: 294, found: 294;

$[\alpha]^{25}_D = -83°$ (*c* = 1.0, $CHCl_3$); 94% ee, from (*S,S*)-**L4**.



(*R*)-Triisopropyl(5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)silane (Table 5.2, entry 6). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from ethynyltriisopropylsilane were used. The reaction was run at r.t. for 4 h. Solvent system for chromatography: hexane. The title compound was isolated as a colorless oil.

Run 1, 170 mg (92% yield, 92% ee); Run 2, 174 mg (94% yield, 93% ee).

The ee was determined on an OD-H column (hexane, flow rate 0.3 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 14.2 min (minor), 15.1 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.26 – 7.21 (m, 3H), 3.12 – 2.96 (m, 2H), 2.79 (dt, 1H, *J* = 13.8, 8.6 Hz), 2.10 – 1.94 (m, 2H), 1.13 – 1.11 (m, 21H);

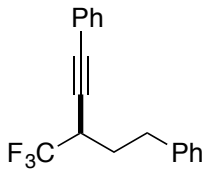
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.3, 128.6, 128.5, 126.4, 125.3 (q, *J* = 280.0 Hz), 100.1 (q, *J* = 3.3 Hz), 86.9, 37.9 (q, *J* = 30.4 Hz), 32.5, 30.2 (d, *J* = 1.7 Hz), 18.5, 11.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.2 (d, 3F, *J* = 7.9 Hz);

FT-IR (film) 2944, 2892, 2866, 2184, 1462, 1259, 1167, 1121, 883, 701, 679, 666 cm^{-1};

GC-MS (EI) *m/z* ($M^+ - C_3H_7$) calcd for $C_{18}H_{24}F_3Si$: 325, found: 325;

$[\alpha]^{25}_D = -80°$ (*c* = 1.0, $CHCl_3$); 93% ee, from (*S,S*)-**L4**.



(*R*)-(3-(Trifluoromethyl)pent-1-yne-1,5-diyl)dibenzene (Table 5.3, entry 1). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from ethynylbenzene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 50:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 140 mg (97% yield, 94% ee); Run 2, 141 mg (98% yield, 94% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 14.0 min (minor), 15.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.40 – 7.33 (m, 5H), 7.30 – 7.25 (m, 2H), 3.34 – 3.23 (m, 1H), 3.06 (ddd, 1H, *J* = 13.7, 8.6, 5.0 Hz), 2.86 (dt, 1H, *J* = 13.9, 8.5 Hz), 2.22 – 2.06 (m, 2H);

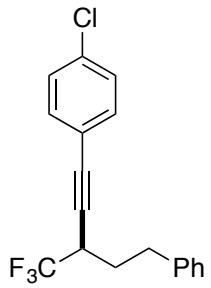
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.2, 131.9, 128.7, 128.6, 128.5, 128.3, 126.4, 125.3 (q, *J* = 280.4 Hz), 122.3, 85.3, 81.9 (q, *J* = 3.5 Hz), 37.6 (q, *J* = 30.5 Hz), 32.5, 30.0;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.9 (d, 3F, *J* = 7.9 Hz);

FT-IR (film) 3028, 2939, 1600, 1491, 1444, 1256, 1163, 1118, 755, 690 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{15}F_3$: 288, found: 288;

$[\alpha]^{25}_D$ = +140° (*c* = 1.0, $CHCl_3$); 94% ee, from (*R,R*)-**L4**.



(*R*)-1-Chloro-4-(5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)benzene (Table 5.3, entry 2). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from 1-chloro-4-ethynylbenzene were used. The reaction

was run at 10 ºC for 16 h. Solvent system for chromatography: 50:1 hexane/dichloromethane. The title compound was isolated as a light-yellow oil.

Run 1, 150 mg (93% yield, 94% ee); Run 2, 151 mg (94% yield, 94% ee).

The ee was determined on an OD-H column (hexane, flow rate 0.5 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 34.6 min (major), 38.1 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.37 – 7.32 (m, 4H), 7.28 – 7.24 (m, 3H), 3.30 – 3.24 (m, 1H), 3.04 (ddd, 1H, *J* = 13.7, 8.6, 5.0 Hz), 2.83 (dt, 1H, *J* = 13.9, 8.4 Hz), 2.22 – 2.06 (m, 2H);

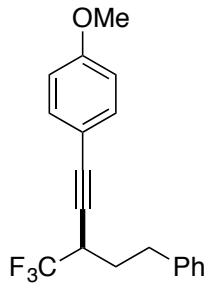
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1, 134.1, 133.1, 128.7, 128.6, 128.5, 126.4, 125.2 (q, *J* = 280.3 Hz), 120.7, 84.2, 82.9 (q, *J* = 3.5 Hz), 37.6 (q, *J* = 30.5 Hz), 32.5, 29.9;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.8 (d, 3F, *J* = 7.9 Hz);

FT-IR (film) 3028, 2939, 1490, 1257, 1163, 1120, 1092, 1015, 828, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{14}ClF_3$: 322, found: 322;

$[\alpha]^{25}_D$ = −141° (*c* = 1.0, $CHCl_3$); 94% ee, from (*S,S*)-**L4**.



(*R*)-1-Methoxy-4-(5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)benzene (Table 5.3, entry 3). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an

alkynylboron reagent prepared from 1-ethynyl-4-methoxybenzene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 6:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 156 mg (98% yield, 94% ee); Run 2, 157 mg (99% yield, 94% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 10.9 min (major), 12.5 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.35 – 7.31 (m, 2H), 7.28 – 7.22 (m, 3H), 6.89 – 6.86 (m, 2H), 3.83 (s, 3H), 3.29 – 3.20 (m, 1H), 3.03 (ddd, 1H, J = 13.7, 8.6, 5.0 Hz), 2.83 (dt, 1H, J = 13.9, 8.5 Hz), 2.18 – 2.04 (m, 2H);

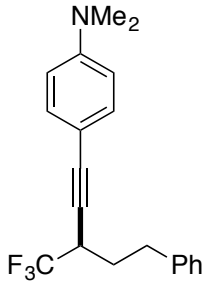
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 140.3, 133.3, 128.6, 128.5, 126.4, 125.4 (q, J = 280.4 Hz), 114.3, 113.9, 85.2, 80.4 (q, J = 3.7 Hz), 55.3, 37.6 (q, J = 30.4 Hz), 32.6, 30.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.9 (d, 3F, J = 7.9 Hz);

FT-IR (film) 2937, 2237, 1607, 1510, 1457, 1292, 1251, 1172, 1119, 1037, 832, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{17}F_3O$: 318, found: 318;

$[\alpha]^{25}_D$ = −155° (*c* = 1.0, $CHCl_3$); 94% ee, from (*S,S*)-**L4**.



(*R*)-*N*,*N*-Dimethyl-4-(5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)aniline (Table 5.3, entry 4). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from 4-ethynyl-*N*,*N*-dimethylaniline were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 3:1 hexane/dichloromethane. The title compound was isolated as a pink oil.

Run 1, 150 mg (90% yield, 93% ee); Run 2, 155 mg (93% yield, 93% ee).

The ee was determined on an OD-H column (1.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*R,R*)-**L4**: 5.9 min (minor), 7.6 min (major).

^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.36 – 7.29 (m, 6H), 7.25 – 7.20 (m, 1H), 6.74 – 6.69 (m, 2H), 3.49 (dqd, 1H, *J* = 10.7, 8.3, 4.0 Hz), 3.03 (ddd, 1H, *J* = 14.0, 9.4, 4.9 Hz), 2.98 (s, 6H), 2.90 – 2.79 (m, 1H), 2.14 (dddd, 1H, *J* = 12.9, 9.4, 7.6, 4.1 Hz), 2.04 – 1.96 (m, 1H);

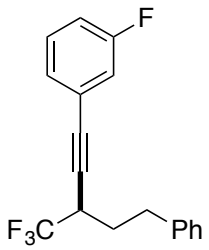
^{13}C NMR (126 MHz, CD_3COCD_3) δ 151.7, 141.8, 133.8, 129.6, 129.5, 127.3, 127.0 (q, *J* = 279.4 Hz), 112.8, 109.7, 87.4, 80.2 (q, *J* = 3.7 Hz), 40.4, 38.5 (q, *J* = 29.9 Hz), 33.4, 31.4 (d, *J* = 1.7 Hz);

^{19}F NMR (282 MHz, CD_3COCD_3) δ −71.7 (d, 3F, *J* = 8.2 Hz);

FT-IR (film) 2922, 2231, 1609, 1523, 1359, 1257, 1160, 1116, 816, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{20}H_{20}F_3N$: 331, found: 331;

$[\alpha]^{25}_D = -146°$ (*c* = 1.0, $CHCl_3$); 93% ee, from (*S,S*)-**L4**.



(*R*)-1-Fluoro-3-(5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)benzene (Table 5.3, entry 5). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from 1-ethynyl-3-fluorobenzene were used. The reaction was run at 10 ºC for 16 h. Solvent system for chromatography: 50:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 120 mg (78% yield, 94% ee); Run 2, 124 mg (81% yield, 93% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 6.2 min (minor), 6.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 7H), 7.23 – 7.19 (m, 1H), 7.12 – 7.06 (m, 1H), 3.32 – 3.22 (m, 1H), 3.04 (ddd, 1H, J = 13.7, 8.5, 5.0 Hz), 2.84 (dt, 1H, J = 13.9, 8.4 Hz), 2.22 – 2.06 (m, 2H);

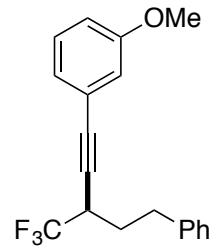
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, J = 246.6 Hz), 140.0, 129.9 (d, J = 8.6 Hz), 128.6, 128.5, 127.8 (d, J = 2.8 Hz), 126.5, 124.0 (d, J = 9.3 Hz), 125.2 (q, J = 280.3 Hz), 118.7 (d, J = 22.6 Hz), 116.1 (d, J = 21.1 Hz), 84.1 (d, J = 3.4 Hz), 82.9 (q, J = 3.5 Hz), 37.5 (q, J = 30.5 Hz), 32.5, 29.9;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.8 (d, 3F, J = 7.9 Hz), −112.8 (m, 1F);

FT-IR (film) 3028, 2942, 1608, 1582, 1488, 1435, 1258, 1172, 1151, 1119, 875, 784, 699, 680 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{14}F_4$: 306, found: 306;

$[\alpha]^{25}_D$ = +131° (*c* = 1.0, $CHCl_3$); 94% ee, from (*R,R*)-**L4**.



(*R*)-1-Methoxy-3-(5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)benzene (Table 5.3, entry 6). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from 1-ethynyl-3-methoxybenzene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 5:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 158 mg (99% yield, 95% ee); Run 2, 158 mg (99% yield, 95% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 12.4 min (minor), 16.1 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.29 – 7.23 (m, 4H), 7.11 (ddd, 1H, *J* = 7.6, 1.5, 1.0 Hz), 7.03 (dd, 1H, *J* = 2.6, 1.4 Hz), 6.93 (ddd, 1H, *J* = 8.3, 2.6, 1.0 Hz), 3.84 (s, 3H), 3.32 – 3.22 (m, 1H), 3.04 (ddd, 1H, *J* = 13.7, 8.5, 5.1 Hz), 2.84 (dt, 1H, *J* = 13.9, 8.5 Hz), 2.20 – 2.05 (m, 2H);

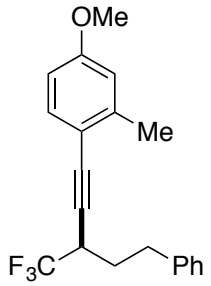
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 140.2, 129.4, 128.6, 128.5, 126.4, 125.3 (q, *J* = 280.4 Hz), 124.4, 123.2, 116.7, 115.2, 85.3, 81.7 (q, *J* = 3.6 Hz), 55.3, 37.6 (q, *J* = 30.4 Hz), 32.5, 30.0;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.8 (d, 3F, J = 7.9 Hz);

FT-IR (film) 3027, 2940, 1598, 1576, 1490, 1455, 1319, 1287, 1258, 1161, 1118, 1046, 700, 686 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{17}F_3O$: 318, found: 318;

$[\alpha]^{25}_D$ = −54° (*c* = 1.0, $CHCl_3$); 95% ee, from (*S,S*)-**L4**.



(*R*)-4-Methoxy-2-methyl-1-(5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)benzene (Table 5.3, entry 7). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from 1-ethynyl-4-methoxy-2-methylbenzene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 5:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 161 mg (97% yield, 94% ee); Run 2, 160 mg (96% yield, 92% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 ml/min); retention times for compound obtained using (*R,R*)-**L4**: 22.2 min (minor), 22.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, 1H, J = 8.5 Hz), 7.36 – 7.31 (m, 2H), 7.28 – 7.22 (m, 3H), 6.79 – 6.77 (m, 1H), 6.74 – 6.68 (m, 1H), 3.82 (s, 3H), 3.29 (dtt, 1H, J =

15.7, 7.9, 3.9 Hz), 3.05 (ddd, 1H, *J* = 13.7, 8.7, 4.9 Hz), 2.85 (dt, 1H, *J* = 13.8, 8.5 Hz), 2.46 (s, 3H), 2.19 – 2.04 (m, 2H);

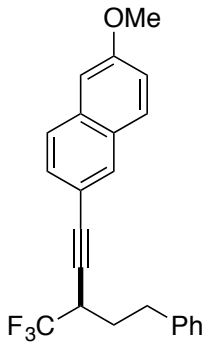
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 142.3, 140.3, 133.4, 128.6, 128.5, 126.4, 125.5 (q, *J* = 280.3 Hz), 115.0, 114.3, 111.2, 84.3 (q, *J* = 3.6 Hz), 84.2, 55.2, 37.7 (q, *J* = 30.4 Hz), 32.6, 30.2, 20.9;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.1 (d, 3F, *J* = 7.9 Hz);

FT-IR (film) 3028, 2941, 2235, 1606, 1497, 1455, 1297, 1258, 1236, 1162, 1118, 1043, 750, 701 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{20}H_{19}F_3O$: 332, found: 332;

$[\alpha]^{25}_D$ = −91° (*c* = 1.0, $CHCl_3$); 92% ee, from (*S,S*)-**L4**.



(*R*)-2-Methoxy-6-(5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)naphthalene (Table 5.3, entry 8). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from 2-ethynyl-6-methoxynaphthalene were used. The reaction was run at 0 ºC for 17 h. Solvent system for chromatography: 6:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 178 mg (97% yield, 94% ee); Run 2, 178 mg (97% yield, 94% ee).

The ee was determined on an OD-H column (1.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 7.8 min (major), 14.2 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.95 (m, 1H), 7.74 – 7.69 (m, 2H), 7.52 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.38 – 7.33 (m, 2H), 7.31 – 7.25 (m, 3H), 7.21 – 7.17 (m, 1H), 7.14 – 7.11 (m, 1H), 3.94 (s, 3H), 3.35 – 3.29 (m, 1H), 3.09 (ddd, 1H, *J* = 13.7, 8.5, 5.2 Hz), 2.89 (dt, 1H, *J* = 13.9, 8.4 Hz), 2.24 – 2.10 (m, 2H);

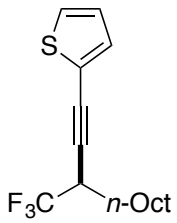
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 140.2, 134.3, 131.7, 129.3, 129.0, 128.6, 128.5, 128.3, 126.8, 126.4, 125.4 (q, *J* = 280.3 Hz), 119.5, 117.1, 105.7, 85.8, 81.4 (q, *J* = 3.6 Hz), 55.3, 37.7 (q, *J* = 30.4 Hz), 32.6, 30.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.8 (d, 3F, *J* = 7.9 Hz);

FT-IR (film) 3027, 2937, 2236, 1630, 1602, 1498, 1484, 1390, 1258, 1198, 1162, 1118, 1031, 854, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{23}H_{19}F_3O$: 368, found: 368;

$[\alpha]^{25}_D$ = −144° (*c* = 1.0, $CHCl_3$); 94% ee, from (*S,S*)-**L4**.



(*R*)-2-(3-(Trifluoromethyl)undec-1-yn-1-yl)thiophene (Table 5.3, entry 9). 2-Bromo-1,1,1-trifluorodecane (138 mg, 0.50 mmol) and an alkynylboron reagent prepared from 2-ethynylthiophene were used. 10% $NiCl_2$·glyme (11 mg, 0.050 mmol) and 12% **L4**

(20 mg, 0.060 mmol) were used. The reaction was run at 0 ºC for 16 h. Solvent system for chromatography: hexane. The title compound was isolated as a light yellow oil.

Run 1, 90 mg (60% yield, 94% ee); Run 2, 96 mg (64% yield, 94% ee).

The ee was determined on an OD-H column (hexane, flow rate 0.3 ml/min); retention times for compound obtained using (*R,R*)-**L4**: 17.2 min (minor), 19.4 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, 1H, *J* = 5.2, 1.2 Hz), 7.23 (dd, 1H, *J* = 3.7, 1.2 Hz), 6.97 (dd, 1H, *J* = 5.2, 3.6 Hz), 3.30 (dqd, 1H, *J* = 10.4, 8.0, 4.3 Hz), 1.87 – 1.60 (m, 3H), 1.52 – 1.43 (m, 1H), 1.41 – 1.23 (m, 10H), 0.89 (t, 3H, *J* = 6.7 Hz);

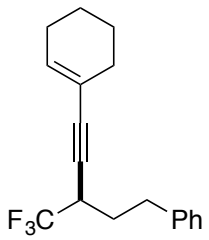
^{13}C NMR (126 MHz, $CDCl_3$) δ 132.5, 127.2, 126.9, 125.3 (q, *J* = 280.5 Hz), 122.3, 86.3 (q, *J* = 3.6 Hz), 77.9, 38.6 (q, *J* = 30.3 Hz), 31.8, 29.2, 29.1, 29.0, 28.3, 26.7, 22.7, 14.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −70.9 (d, 3F, *J* = 8.0 Hz);

FT-IR (film) 2955, 2927, 2856, 2234, 1261, 1168, 1132, 1107, 852, 831, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{21}F_3S$: 302, found: 302;

$[\alpha]^{25}_D$ = +42° (*c* = 1.0, $CHCl_3$); 94% ee, from (*R,R*)-**L4**.



(*R*)-(5-(Cyclohex-1-en-1-yl)-3-(trifluoromethyl)pent-4-yn-1-yl)benzene (Table 5.3, entry 10). (3-Bromo-4,4,4-trifluorobutyl)benzene (134 mg, 0.50 mmol) and an alkynylboron reagent prepared from 1-ethynylcyclohex-1-ene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: hexane. The title compound was isolated as a light-yellow oil.

Run 1, 133 mg (91% yield, 95% ee); Run 2, 133 mg (91% yield, 95% ee).

The ee was determined on an OD-H column (hexane, flow rate 0.3 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 23.2 min (minor), 24.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.25 – 7.21 (m, 3H), 6.21 – 6.17 (m, 1H), 3.13 (dqd, 1H, J = 12.0, 8.0, 4.1 Hz), 2.96 (ddd, 1H, J = 13.7, 8.8, 4.9 Hz), 2.75 (dt, 1H, J = 13.8, 8.5 Hz), 2.20 – 1.93 (m, 6H), 1.70 – 1.57 (m, 4H);

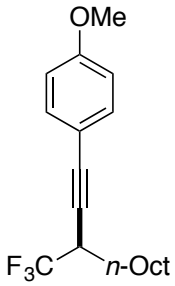
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 135.8, 128.54, 128.49, 126.3, 125.4 (q, J = 280.3 Hz), 119.9, 87.2, 79.0 (q, J = 3.7 Hz), 37.4 (q, J = 30.1 Hz), 32.5, 30.1, 29.1, 25.6, 22.2, 21.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.2 (d, 3F, J = 7.9 Hz);

FT-IR (film) 2934, 2227, 1455, 1259, 1161, 1119, 919, 750, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{18}H_{19}F_3$: 292, found: 292;

$[\alpha]^{25}_D = -114°$ (c = 1.0, $CHCl_3$); 95% ee, from (*S,S*)-**L4**.



(*R*)-1-Methoxy-4-(3-(trifluoromethyl)undec-1-yn-1-yl)benzene (Table 5.4, entry 1). 2-Bromo-1,1,1-trifluorodecane (138 mg, 0.50 mmol) and an alkynylboron reagent prepared from 1-ethynyl-4-methoxybenzene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 12:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 152 mg (93% yield, 92% ee); Run 2, 154 mg (94% yield, 92% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 10.4 min (major), 12.4 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 2H), 6.85 – 6.82 (m, 2H), 3.81 (s, 3H), 3.30 – 3.22 (m, 1H), 1.85 – 1.62 (m, 3H), 1.53 – 1.43 (m, 1H), 1.42 – 1.22 (m, 10H), 0.89 (t, 3H, J = 6.7 Hz);

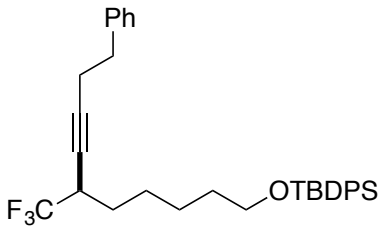
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 133.3, 125.5 (q, J = 280.4 Hz), 114.5, 113.8, 84.5, 80.9 (q, J = 3.5 Hz), 55.3, 38.3 (q, J = 30.1 Hz), 31.8, 29.3, 29.2, 29.1, 28.4, 26.7, 22.7, 14.1;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.2 (d, 3F, J = 8.0 Hz);

FT-IR (film) 2955, 2927, 2856, 2238, 1608, 1511, 1466, 1291, 1250, 1172, 1132, 1106, 1034, 831 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{19}H_{25}F_3O$: 326, found: 326;

$[\alpha]^{25}_{D} = -26°$ (c = 1.0, $CHCl_3$); 92% ee, from (*S,S*)-**L4**.



(*R*)-*tert*-Butyldiphenyl((10-phenyl-6-(trifluoromethyl)dec-7-yn-1-yl)oxy)silane (Table 5.4, entry 2). ((6-Bromo-7,7,7-trifluoroheptyl)oxy)(*tert*-butyl)diphenylsilane (244 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 9 h. Solvent system for chromatography: 15:1 to 10:1 to 5:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 210 mg (78% yield, 91% ee); Run 2, 210 mg (78% yield, 91% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 0.5 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 19.4 min (major), 25.5 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 4H), 7.46 – 7.38 (m, 6H), 7.32 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 3.68 (t, 2H, J = 6.4 Hz), 3.02 – 2.94 (m, 1H), 2.82 (t, 2H, J = 7.4 Hz), 2.50 (td, 2H, J = 7.4, 2.2 Hz), 1.71 – 1.64 (m, 1H), 1.63 – 1.46 (m, 4H), 1.45 – 1.26 (m, 3H), 1.08 (s, 9H);

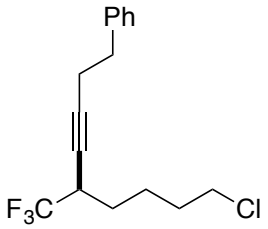
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 135.5, 134.0, 129.5, 128.5, 128.3, 127.6, 126.3, 125.6 (q, J = 280.2 Hz), 84.3, 73.9 (q, J = 3.6 Hz), 63.7, 37.7 (q, J = 29.9 Hz), 34.9, 32.2, 28.4, 26.9, 26.3, 25.3, 20.8, 19.2;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.4 (d, 3F, J = 8.1 Hz);

FT-IR (film) 3070, 3028, 2932, 2858, 1472, 1463, 1454, 1428, 1262, 1169, 1145, 1125, 1112, 823, 741, 700 cm^{-1};

GC-MS (EI) *m/z* (M^+−TBDPS) calcd for $C_{17}H_{20}F_3O$: 297, found: 297;

$[\alpha]^{25}_D = -16°$ (*c* = 1.0, $CHCl_3$); 91% ee, from (*S,S*)-**L4**.



(*R*)-(9-Chloro-5-(trifluoromethyl)non-3-yn-1-yl)benzene (Table 5.4, entry 3). 2-Bromo-6-chloro-1,1,1-trifluorohexane (127 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 15:1 to 10:1 hexane/dichloromethane. The title compound was isolated as a light-yellow oil.

Run 1, 127 mg (84% yield, 92% ee); Run 2, 127 mg (84% yield, 92% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 6.5 min (major), 7.7 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 3.56 – 3.48 (m, 2H), 3.05 – 2.97 (m, 1H), 2.83 (t, 2H, *J* = 7.4 Hz), 2.51 (td, 2H, *J* = 7.4, 2.2 Hz), 1.84 – 1.42 (m, 6H);

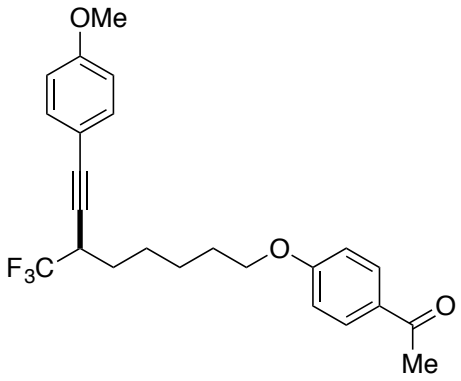
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 128.5, 128.3, 126.3, 125.4 (q, *J* = 280.2 Hz), 84.7, 73.5 (q, *J* = 3.7 Hz), 44.5, 37.6 (q, *J* = 30.1 Hz), 34.8, 32.0, 27.8, 23.9, 20.8;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.5 (d, 3F, J = 8.3 Hz);

FT-IR (film) 2957, 2870, 2246, 1455, 1263, 1170, 1153, 1117, 749, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{18}ClF_3$: 302, found: 302;

$[\alpha]^{25}_D$ = −29° (*c* = 1.0, $CHCl_3$); 92% ee, from (*S,S*)-**L4**.



(*R*)-1-(4-((8-(4-Methoxyphenyl)-6-(trifluoromethyl)oct-7-yn-1-yl)oxy)phenyl)ethan-1-one (Table 5.4, entry 4). 1-(4-((6-Bromo-7,7,7-trifluoroheptyl)oxy)phenyl)ethan-1-one (184 mg, 0.50 mmol) and an alkynylboron reagent prepared from 1-ethynyl-4-methoxybenzene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 10:1 to 5:1 hexane/ethyl acetate. The title compound was isolated as a yellow solid. It should be stored in a refrigerator (~5 ºC).

Run 1, 199 mg (95% yield, 93% ee); Run 2, 205 mg (98% yield, 92% ee).

The ee was determined on an AD-H column (5.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 16.2 min (major), 17.4 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 2H), 7.38 – 7.34 (m, 2H), 6.93 – 6.88 (m, 2H), 6.84 – 6.79 (m, 2H), 4.03 (t, 2H, *J* = 6.3 Hz), 3.80 (s, 3H), 3.34 – 3.24 (m, 1H), 2.55 (s, 3H), 1.91 – 1.71 (m, 5H), 1.64 – 1.50 (m, 3H);

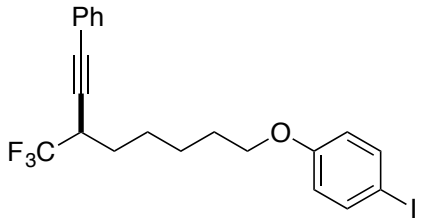
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 162.9, 159.7, 133.2, 130.5, 130.1, 125.4 (q, *J* = 280.2 Hz), 114.3, 114.1, 113.8, 84.7, 80.6 (q, *J* = 3.5 Hz), 67.9, 55.3, 38.2 (q, *J* = 30.2 Hz), 28.8, 28.3, 26.4, 26.3, 25.5;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.1 (d, 3F, *J* = 8.0 Hz);

FT-IR (film) 2938, 2869, 2234, 1674, 1602, 1510, 1358, 1253, 1172, 1127, 1031, 833 cm^{-1};

LC-MS (ESI) *m/z* ($M+H^+$) calcd for $C_{24}H_{26}F_3O_3$: 419, found: 419;

$[\alpha]^{25}_D$ = −44° (*c* = 1.0, $CHCl_3$); 92% ee, from (*S,S*)-**L4**.



(*R*)-1-Iodo-4-((8-phenyl-6-(trifluoromethyl)oct-7-yn-1-yl)oxy)benzene (Table 5.4, entry 5). 1-((6-Bromo-7,7,7-trifluoroheptyl)oxy)-4-iodobenzene (226 mg, 0.50 mmol) and an alkynylboron reagent prepared from ethynylbenzene were used. 10% $NiCl_2$·glyme (11 mg, 0.050 mmol) and 12% **L4** (20 mg, 0.060 mmol) were used. The reaction was run at 0 ºC for 17 h. Solvent system for chromatography: 10:1 to 8:1 hexane/dichloromethane. The title compound was isolated as a light-yellow oil. It should be stored in a refrigerator (~5 ºC).

Run 1, 207 mg (88% yield, 94% ee); Run 2, 200 mg (85% yield, 94% ee).

The ee was determined on an OD-H column (0.25% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 17.4 min (major), 19.8 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.46 – 7.41 (m, 2H), 7.36 – 7.28 (m, 3H), 6.69 – 6.64 (m, 2H), 3.93 (t, 2H, *J* = 6.3 Hz), 3.35 – 3.27 (m, 1H), 1.91 – 1.72 (m, 5H), 1.64 – 1.49 (m, 3H);

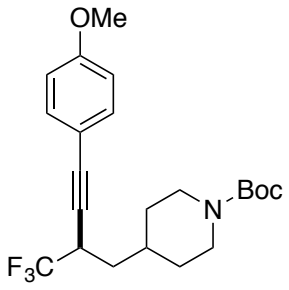
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 138.1, 131.8, 128.6, 128.3, 125.3 (q, *J* = 280.5 Hz), 122.2, 116.8, 84.8, 82.5, 82.1 (q, *J* = 3.6 Hz), 67.7, 38.3 (q, *J* = 30.3 Hz), 28.8, 28.3, 26.4, 25.6;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.0 (d, 3F, *J* = 7.9 Hz);

FT-IR (film) 2940, 2868, 1587, 1486, 1471, 1283, 1244, 1174, 1127, 819, 756, 691 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{21}H_{20}F_3IO$: 472, found: 472;

$[\alpha]^{25}_D = -36°$ (*c* = 1.0, $CHCl_3$); 94% ee, from (*S,S*)-**L4**.



***tert*-butyl (*R*)-4-(4-(4-methoxyphenyl)-2-(trifluoromethyl)but-3-yn-1-yl)piperidine-1-carboxylate (Table 5.4, entry 6**). *tert*-Butyl 4-(2-bromo-3,3,3-trifluoropropyl)piperidine-1-carboxylate (180 mg, 0.50 mmol) and an alkynylboron

reagent prepared from 1-ethynyl-4-methoxybenzene were used. The reaction was run at 0 ºC for 17 h. Solvent system for chromatography: 20:1 to 15:1 hexane/ethyl acetate. The title compound was isolated as a yellow oil.

Run 1, 196 mg (95% yield, 97% ee); Run 2, 201 mg (98% yield, 97% ee).

The ee was determined on an OD-H column (3.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 7.7 min (major), 12.5 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H), 6.86 – 6.81 (m, 2H), 4.25 – 3.97 (m, 2H), 3.81 (s, 3H), 3.36 (dqd, 1H, *J* = 11.9, 7.8, 4.1 Hz), 2.85 – 2.60 (m, 2H), 1.85 – 1.68 (m, 4H), 1.65 – 1.57 (m, 1H), 1.45 (s, 9H), 1.30 – 1.18 (m, 1H), 1.13 – 1.04 (m, 1H);

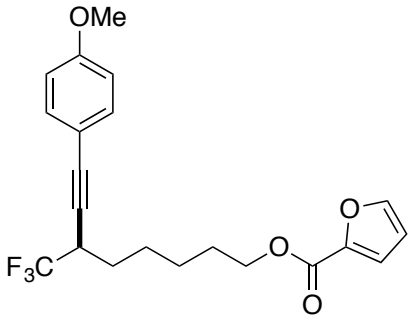
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 154.8, 133.3, 114.2, 113.9, 125.5 (q, *J* = 280.3 Hz), 84.8, 80.3 (q, *J* = 3.5 Hz), 79.4, 55.3, 35.8 (q, *J* = 30.5 Hz), 34.8, 33.2, 32.6, 30.7, 28.4;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.4 (d, 3F, *J* = 7.8 Hz);

FT-IR (film) 2975, 2930, 2848, 2237, 1692, 1607, 1511, 1425, 1366, 1285, 1250, 1172, 1128, 833 cm^{-1};

GC-MS (EI) *m/z* (M^+ −Boc) calcd for $C_{17}H_{19}F_3NO$: 310, found: 310;

$[\alpha]^{25}_D$ = +62° (*c* = 1.0, $CHCl_3$); 97% ee, from (*R,R*)-**L4**.



(*R*)-8-(4-Methoxyphenyl)-6-(trifluoromethyl)oct-7-yn-1-yl furan-2-carboxylate (Table 5.4, entry 7). 6-Bromo-7,7,7-trifluoroheptyl furan-2-carboxylate (172 mg, 0.50 mmol) and an alkynylboron reagent prepared from 1-ethynyl-4-methoxybenzene were used. 10% $NiCl_2$·glyme (11 mg, 0.050 mmol) and 12% **L4** (20 mg, 0.060 mmol) were used. The reaction was run at 0 ºC for 17 h. Solvent system for chromatography: 10:1 hexane/ethyl acetate. The title compound was isolated as a light-yellow oil. It should be stored in a refrigerator (~5 ºC).

Run 1, 171 mg (87% yield, 94% ee); Run 2, 171 mg (87% yield, 93% ee).

The ee was determined on an OD-H column (1.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 18.6 min (major), 23.1 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, 1H, *J* = 1.8, 0.9 Hz), 7.39 – 7.35 (m, 2H), 7.17 (dd, 1H, *J* = 3.5, 0.9 Hz), 6.85 – 6.80 (m, 2H), 6.49 (dd, 1H, *J* = 3.5, 1.7 Hz), 4.32 (t, 2H, *J* = 6.6 Hz), 3.80 (s, 3H), 3.32 – 3.23 (m, 1H), 1.88 – 1.69 (m, 5H), 1.60 – 1.43 (m, 3H);

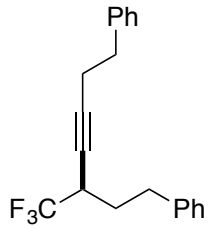
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 158.8, 146.2, 144.7, 133.3, 125.4 (q, *J* = 280.4 Hz), 117.8, 114.3, 113.8, 111.8, 84.7, 80.6 (q, *J* = 3.7 Hz), 64.7, 55.2, 38.2 (q, *J* = 30.2 Hz), 28.5, 28.3, 26.4, 25.5;

^{19}F NMR (282 MHz, $CDCl_3$) δ −71.1 (d, 3F, J = 8.0 Hz);

FT-IR (film) 2953, 2234, 1725, 1607, 1511, 1475, 1296, 1250, 1172, 1125, 1032, 1014, 833, 764 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{21}H_{21}F_3O_4$: 394, found: 394;

$[\alpha]^{25}_D$ = −37° (*c* = 1.0, $CHCl_3$); 93% ee, from (*S,S*)-**L4**.

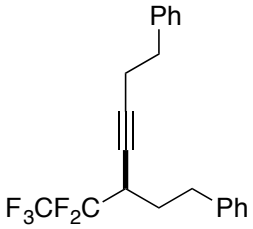


(*R*)-(5-(Trifluoromethyl)hept-3-yne-1,7-diyl)dibenzene (eq 5.3). (4,4,4-trifluoro-3-iodobutyl)benzene (157 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 5 h. Solvent system for chromatography: 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 139 mg (88% yield, 92% ee); Run 2, 131 mg (83% yield, 92% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 7.9 min (major), 10.5 min (minor).

For the characterization data, see Table 5.2, entry 1 (above).



(*R*)-(5-(Perfluoroethyl)hept-3-yne-1,7-diyl)dibenzene (eq 5.5). (3-Bromo-4,4,5,5,5-pentafluoropentyl)benzene (159 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 5 h. Solvent system for chromatography: 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 161 mg (88% yield, 99% ee); Run 2, 155 mg (85% yield, 99% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 6.2 min (major), 7.3 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H), 7.28 – 7.22 (m, 4H), 7.18 – 7.14 (m, 2H), 3.05 – 2.95 (m, 1H), 2.94 – 2.85 (m, 3H), 2.64 (dt, 1H, *J* =13.8, 8.5 Hz), 2.57 (td, 1H, *J* = 7.4, 2.3 Hz), 2.05 (dtd, 1H, *J* = 12.4, 8.5, 3.7 Hz), 1.92 (dddd, 1H, *J* = 13.3, 11.1, 8.9, 4.7 Hz);

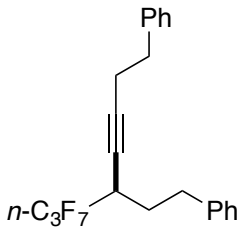
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.37, 140.36, 128.51, 128.46, 128.42, 128.38, 126.33, 126.27, 120.8 – 109.5 (m), 85.8, 72.9 (dd, *J* = 9.6, 3.1 Hz), 34.8, 34.7 (dd, *J* = 26.5, 22.8 Hz), 32.5, 29.0, 20.7;

^{19}F NMR (282 MHz, $CDCl_3$) δ −81.5 (s, 3F), −117.0 (dd, *J* = 265.3, 8.6 Hz), −121.0 (dd, *J* = 265.3, 19.0 Hz);

FT-IR (film) 3028, 2931, 2238, 1497, 1455, 1194, 1119, 1068, 1031, 750, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{21}H_{19}F_5$: 366, found: 366;

$[\alpha]^{25}_D$ = +68° (*c* = 1.0, $CHCl_3$); 99% ee, from (*R,R*)-**L4**.



(*R*)-(5-(Perfluoropropyl)hept-3-yne-1,7-diyl)dibenzene (eq 5.6). (3-Bromo-4,4,5,5,6,6,6-heptafluorohexyl)benzene (184 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 12 h. Solvent system for chromatography: 20:1 to 10:1 hexane/dichloromethane. The title compound was isolated as a colorless oil.

Run 1, 175 mg (84% yield, 98% ee); Run 2, 172 mg (83% yield, 98% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 6.0 min (major), 7.7 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 4H), 7.28 – 7.21 (m, 4H), 7.18 – 7.15 (m, 2H), 3.11 – 3.00 (m, 1H), 2.95 – 2.85 (m, 3H), 2.64 (dt, 1H, *J* = 13.8, 8.5 Hz), 2.57 (td, 1H, *J* = 7.4, 2.3 Hz), 2.06 (dtd, 1H, *J* = 12.4, 8.5, 3.7 Hz), 1.93 (dddd, 1H, *J* = 13.3, 11.0, 9.0, 4.7 Hz);

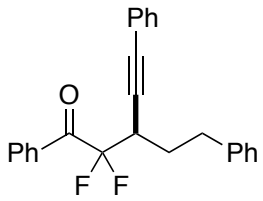
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.39, 140.37, 128.51, 128.46, 128.42, 128.37, 126.33, 126.27, 119.5 – 106.2 (m), 85.8, 72.9 (d, *J* = 10.0 Hz), 34.9 (dd, *J* = 26.8, 22.7 Hz), 34.8, 32.5, 28.9, 20.8;

^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (dd, 3F, *J* = 11.8, 9.1 Hz), −113.7 – −118.1 (m, 2F), −122.9 – −126.1 (m, 2F);

FT-IR (film) 3064, 3029, 2930, 2863, 1604, 1497, 1455, 1349, 1224, 1185, 1117, 750, 698 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{22}H_{19}F_7$: 416, found: 416;

$[\alpha]^{25}_D$ = +59° (*c* = 1.0, $CHCl_3$); 98% ee, from (*R,R*)-**L4**.



(*R*)-2,2-Difluoro-3-phenethyl-1,5-diphenylpent-4-yn-1-one (eq 5.7). 3-Bromo-2,2-difluoro-1,5-diphenylpentan-1-one (177 mg, 0.50 mmol) and an alkynylboron reagent prepared from ethynylbenzene were used. 10% $NiCl_2$·glyme (11 mg, 0.050 mmol) and 12% **L4** (20 mg, 0.060 mmol) were used. The reaction was run at 0 ºC for 17 h. Solvent system for chromatography: 4:1 to 2:1 hexane/dichloromethane. The title compound was isolated as a colorless oil. It should be stored in a refrigerator (~5 ºC).

Run 1, 178 mg (95% yield, 98% ee); Run 2, 178 mg (95% yield, 98% ee).

The ee was determined on an AD-H column (0.25% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 6.6 min (minor), 7.2 min (major).

^{1}H NMR (500 MHz, CD_3COCD_3) δ 8.12 – 8.08 (m, 2H), 7.77 – 7.72 (m, 1H), 7.63 – 7.57 (m, 2H), 7.42 – 7.28 (m, 9H), 7.25 – 7.19 (m, 1H), 3.67 (dtd, 1H, *J* = 17.6,

10.9, 3.8 Hz), 3.08 (ddd, 1H, *J* = 13.9, 9.2, 4.8 Hz), 2.89 (ddd, 1H, *J* = 13.7, 9.1, 7.8 Hz), 2.24 – 2.16 (m, 1H), 2.11 – 2.06 (m, 1H);

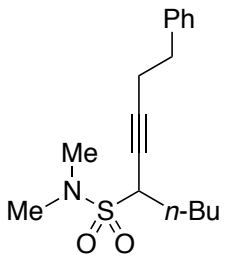
^{13}C NMR (126 MHz, CD_3COCD_3) δ 190.0 (t, *J* = 28.7 Hz), 141.9, 135.6, 133.6, 132.6, 130.8 (t, *J* = 3.5 Hz), 130.0, 129.7, 129.55, 129.53, 129.51, 127.2, 123.5, 119.2 (dd, *J* = 259.6, 257.2 Hz), 86.9, 84.8 (dd, *J* = 9.4, 2.8 Hz), 38.5 (dd, *J* = 27.3, 23.1 Hz), 33.7, 30.3f;

^{19}F NMR (282 MHz, CD_3COCD_3) δ −103.6 (dd, 1F, *J* = 266.6, 10.9 Hz), −107.1 (dd, 1F, *J* = 266.6, 17.5 Hz);

FT-IR (film) 3062, 3027, 2940, 1704, 1598, 1491, 1449, 1275, 1185, 1129, 1070, 916, 757, 720, 690, 664 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{25}H_{20}F_2O$: 374, found: 374;

$[\alpha]^{25}_D$ = +92° (*c* = 1.0, $CHCl_3$); 98% ee, from (*R,R*)-**L4**.



***N,N*-Dimethyl-1-phenylnon-3-yne-5-sulfonamide (Table 5.5, entry 1**). 1-Bromo-*N,N*-dimethylpentane-1-sulfonamide (129 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 22 h. Solvent system for chromatography: 5:1 to 4:1 hexane/ethyl acetate. The title compound was isolated as a colorless oil.

Run 1, 138 mg (90% yield, 98% ee); Run 2, 136 mg (88% yield, 98% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*R,R*)-**L4**: 37.0 min (major), 40.8 min (minor).

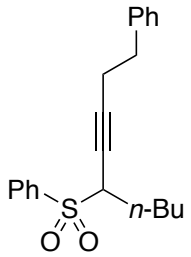
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 3.79 (ddt, 1H, J = 10.7, 4.2, 2.2 Hz), 2.89 (s, 6H), 2.86 – 2.79 (m, 2H), 2.58 – 2.52 (m, 2H), 2.03 – 1.94 (m, 1H), 1.85 – 1.75 (m, 1H), 1.57 – 1.47 (m, 1H), 1.40 – 1.28 (m, 3H), 0.91 (t, 3H, J = 7.2 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1, 128.43, 128.37, 126.4, 87.0, 73.6, 54.4, 38.5, 34.6, 29.8, 28.7, 22.1, 20.9, 13.8;

FT-IR (film) 3027, 2953, 2918, 2859, 2359, 2235, 1456, 1336, 1280, 1142, 964, 746, 697 cm^{-1};

LC-MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{17}H_{25}NNaO_2S$: 330, found: 330;

$[\alpha]^{25}_D$ = –29° (*c* = 1.0, $CHCl_3$); 98% ee, from (*R,R*)-**L4**.



((1-Phenylnon-3-yn-5-yl)sulfonyl)benzene (Table 5.5, entry 2). ((1-Bromopentyl)sulfonyl)benzene (146 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 22 h. Solvent system for chromatography: 10:1 hexane/ethyl acetate. The title compound was isolated as a light-yellow oil.

Run 1, 143 mg (84% yield, 93% ee); Run 2, 144 mg (85% yield, 93% ee).

The ee was determined on an AD-H column (5.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*R,R*)-**L4**: 10.9 min (major), 14.3 min (minor).

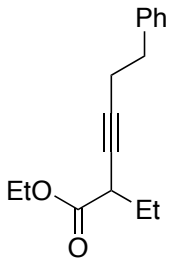
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 2H), 7.67 – 7.63 (m, 1H), 7.54 – 7.50 (m, 2H), 7.30 – 7.25 (m, 2H), 7.23 – 7.18 (m, 1H), 7.15 – 7.11 (m, 2H), 3.78 (ddt, 1H, *J* = 11.1, 3.8, 2.3 Hz), 2.73 (t, 2H, *J* = 7.4 Hz), 2.45 (td, 2H, *J* = 7.4, 2.3 Hz), 2.07 (dddd, 1H, *J* = 12.6, 9.6, 5.5, 3.8 Hz), 1.63 (dddd, 1H, *J* = 12.6, 11.0, 9.5, 4.4 Hz), 1.54 – 1.43 (m, 1H), 1.35 – 1.26 (m, 3H), 0.88 (t, 3H, *J* = 7.2 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1, 136.8, 133.8, 129.5, 128.6, 128.35, 128.33, 126.3, 88.2, 73.1, 59.6, 34.5, 28.8, 28.3, 22.1, 20.9, 13.8;

FT-IR (film) 3062, 3027, 2957, 2930, 2870, 2236, 1453, 1447, 1319, 1308, 1148, 1084, 750, 699, 689 cm^{-1};

LC-MS (ESI) *m/z* ($M+Na^+$) calcd for $C_{21}H_{24}NaO_2S$: 363, found: 363;

$[\alpha]^{25}_D$ = +0.63° (*c* = 1.0, $CHCl_3$); 93% ee, from (*S,S*)-**L4**.



Ethyl 2-ethyl-6-phenylhex-3-ynoate (Table 5.5, entry 3). Ethyl 2-bromobutanoate (98 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. LiCl was not added for this reaction. The reaction was run at

0 ºC for 24 h. Solvent system for chromatography: 1:1 hexane/dichloromethane. The title compound was isolated as a colorless oil. It should be stored in a freezer (–20 ºC).

Run 1, 105 mg (86% yield, 85% ee); Run 2, 109 mg (89% yield, 85% ee).

The ee was determined on an OD-H column (0.5% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*R,R*)-**L4**: 11.4 min (minor), 17.4 min (major).

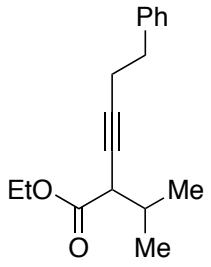
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 4.19 (q, 2H, J = 7.1 Hz), 3.21 (ddt, 1H, J = 7.8, 6.1, 2.3 Hz), 2.83 (t, 2H, J = 7.6 Hz), 2.53 – 2.47 (m, 2H), 1.87 – 1.68 (m, 2H), 1.28 (t, 3H, J = 7.1 Hz), 0.97 (t, 3H, J = 7.4 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 140.7, 128.5, 128.2, 126.2, 83.0, 77.1, 61.2, 39.6, 35.2, 26.1, 21.0, 14.1, 11.5;

FT-IR (film) 3027, 2970, 2934, 2875, 1741, 1496, 1454, 1250, 1181, 1024, 750, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{16}H_{20}O_2$: 244, found: 244;

$[\alpha]^{25}_D$ = +10° (*c* = 1.0, $CHCl_3$); 85% ee, from (*S,S*)-**L4**.



Ethyl 2-isopropyl-6-phenylhex-3-ynoate (Table 5.5, entry 4). Ethyl 2-bromo-3-methylbutanoate (105 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. LiCl was not added for this reaction. The reaction was run at

0 ºC for 12 h. Solvent system for chromatography: 1:1 hexane/dichloromethane. The title compound was isolated as a light-yellow oil. It should be stored in a freezer (–20 ºC).

Run 1, 100 mg (78% yield, 97% ee); Run 2, 105 mg (81% yield, 97% ee).

The ee was determined on an OD-H column (1.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*R,R*)-**L4**: 5.0 min (minor), 7.3 min (major).

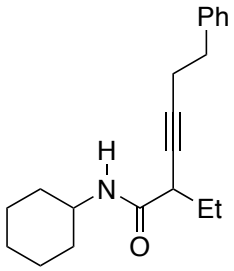
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.24 – 7.18 (m, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 3.11 (dt, 1H, *J* = 6.5, 2.3 Hz), 2.84 (t, 2H, *J* = 7.5 Hz), 2.55 – 2.49 (m, 2H), 2.21 – 2.08 (m, 1H), 1.28 (t, 3H, *J* = 7.1 Hz), 0.97 (d, 3H, *J* = 1.5 Hz), 0.96 (d, 3H, *J* = 1.6 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 140.7, 128.5, 128.3, 126.1, 83.9, 75.8, 61.1, 45.7, 35.2, 31.1, 21.0, 20.7, 19.0, 14.2;

FT-IR (film) 3027, 2963, 2930, 2872, 1741, 1454, 1253, 1180, 1156, 1031, 748, 699 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{17}H_{22}O_2$: 258, found: 258;

$[\alpha]^{25}_{D} = -7.3°$ (*c* = 1.0, $CHCl_3$); 97% ee, from (*R,R*)-**L4**.



***N*-Cyclohexyl-2-ethyl-6-phenylhex-3-ynamide (Table 5.5, entry 5)**. 2-Bromo-*N*-cyclohexylbutanamide (124 mg, 0.50 mmol) and an alkynylboron reagent prepared

from but-3-yn-1-ylbenzene were used. The reaction was run at 0 ºC for 22 h. Solvent system for chromatography: 5:1 hexane/ethyl acetate. The title compound was isolated as a white solid.

Run 1, 138 mg (93% yield, 87% ee); Run 2, 138 mg (93% yield, 86% ee).

The ee was determined on an AD-H column (2.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 10.2 min (major), 11.3 min (minor).

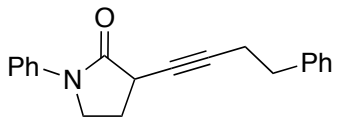
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.19 (m, 5H), 6.33 – 6.26 (m, 1H), 3.73 – 3.65 (m, 1H), 3.13 – 3.08 (m, 1H), 2.85 (t, 2H, J = 7.3 Hz), 2.62 – 2.53 (m, 2H), 1.91 – 1.54 (m, 7H), 1.41 – 1.27 (m, 2H), 1.22 – 0.99 (m, 3H), 0.94 (t, 3H, J = 7.4 Hz);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 140.3, 128.4, 128.3, 126.4, 85.9, 78.6, 48.0, 41.0, 35.0, 32.9, 32.6, 26.1, 25.5, 24.70, 24.68, 20.6, 11.0;

FT-IR (film) 3276, 2925, 2852, 1641, 1550, 1449, 1379, 1314, 1245, 1219, 1154, 1103, 1076, 981, 753, 732, 694 cm^{-1};

GC-MS (EI) *m/z* (M^+) calcd for $C_{20}H_{27}NO$: 297, found: 297;

$[\alpha]^{25}_{D} = -3.3°$ (c = 1.0, $CHCl_3$); 86% ee, from (*S,S*)-**L4**.



1-Phenyl-3-(4-phenylbut-1-yn-1-yl)pyrrolidin-2-one (Table 5.5, entry 6). 3-Bromo-1-phenylpyrrolidin-2-one (120 mg, 0.50 mmol) and an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. LiCl was not added for this reaction. The

reaction was run at 0 ºC for 22 h. Solvent system for chromatography: 7:1 to 6:1 hexane/ethyl acetate. The title compound was isolated as a white solid.

Run 1, 120 mg (83% yield, 91% ee); Run 2, 120 mg (83% yield, 91% ee).

The ee was determined on an AD-H column (20% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*R,R*)-**L4**: 11.5 min (minor), 14.7 min (major).

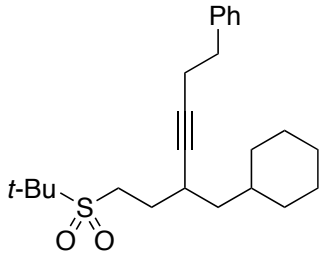
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H), 7.41 – 7.35 (m, 2H), 7.31 – 7.25 (m, 2H), 7.24 – 7.15 (m, 4H), 3.86 – 3.75 (m, 2H), 3.53 (tt, 1H, *J* = 8.5, 2.3 Hz), 2.85 (t, 2H, *J* = 7.7 Hz), 2.52 (td, 2H, *J* = 7.6, 2.3 Hz), 2.45 (dddd, 1H, *J* = 12.9, 8.6, 7.1, 4.5 Hz), 2.21 – 2.12 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 140.7, 139.2, 128.8, 128.5, 128.3, 126.2, 124.7, 119.8, 83.0, 77.0, 46.7, 36.6, 35.1, 26.8, 21.1;

FT-IR (film) 3061, 3028, 2928, 1683, 1600, 1497, 1454, 1398, 1315, 1225, 1208, 757, 745, 701, 690 cm^{-1};

LC-MS (ESI) *m/z* ($M+H^+$) calcd for $C_{20}H_{20}NO$: 290, found: 290;

$[\alpha]^{25}_{D}$ = +79° (*c* = 1.0, $CHCl_3$); 91% ee, from (*S,S*)-**L4**.



(7-(*tert*-Butylsulfonyl)-5-(cyclohexylmethyl)hept-3-yn-1-yl)benzene (Table 5.5, entry 7). (4-(*tert*-butylsulfonyl)-2-iodobutyl)cyclohexane (193 mg, 0.50 mmol) and

an alkynylboron reagent prepared from but-3-yn-1-ylbenzene were used. LiCl was not added for this reaction. 10% $NiCl_2$·glyme (11 mg, 0.050 mmol) and 12% **L4** (20 mg, 0.060 mmol) were used. The reaction was run at 0 ºC for 20 h. Solvent system for chromatography: 6:1 hexane/ethyl acetate. The title compound was isolated as a yellow oil.

Run 1, 185 mg (95% yield, 87% ee); Run 2, 186 mg (96% yield, 85% ee).

The ee was determined on an AD-H column (1.0% *i*-PrOH/hexane, flow rate 1.0 ml/min); retention times for compound obtained using (*S,S*)-**L4**: 10.5 min (major), 12.2 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 3.11 (ddd, 1H, *J* = 13.0, 11.1, 4.9 Hz), 2.90 (ddd, 1H, *J* = 13.0, 11.0, 5.0 Hz), 2.79 (t, 2H, *J* = 7.4 Hz), 2.57 – 2.50 (m, 1H), 2.47 (td, 2H, *J* = 7.4, 2.2 Hz), 2.07 – 1.98 (m, 1H), 1.84 – 1.76 (m, 1H), 1.76 – 1.60 (m, 6H), 1.39 (s, 9H), 1.30 – 1.11 (m, 5H), 0.95 – 0.74 (m, 2H);

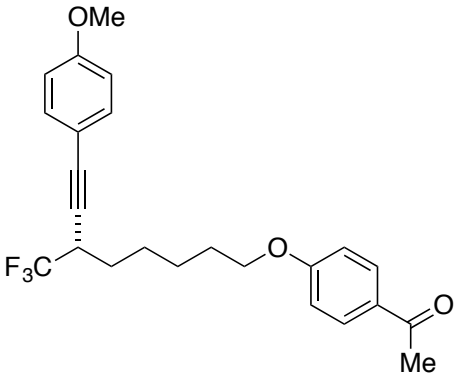
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 128.4, 128.3, 126.2, 82.3, 82.0, 58.9, 44.0, 43.2, 35.3, 35.1, 33.7, 32.4, 28.4, 26.5, 26.4, 26.2, 26.1, 23.4, 20.8;

FT-IR (film) 2921, 2849, 1449, 1300, 1270, 1116, 750, 699, 664 cm^{-1};

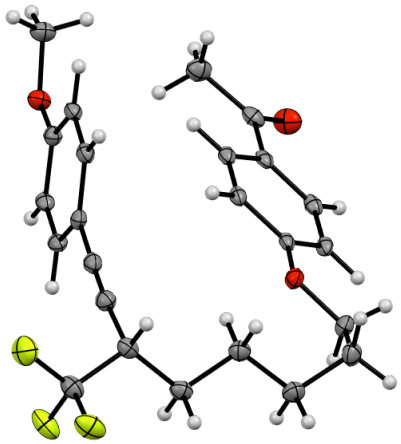
LC-MS (ESI) *m/z* ($M+H^+$) calcd for $C_{24}H_{36}NaO_2S$: 411, found: 411;

$[\alpha]^{25}_D$ = +11° (*c* = 1.0, $CHCl_3$); 87% ee, from (*R,R*)-**L4**.

5.6.4 Assignments of the Absolute Stereochemistry of the Cross-Coupling Products



Absolute stereochemistry of product from entry 4 of Table 5.4 (run with (*R*,*R*)–L4). (*S*)-1-(4-((8-(4-Methoxyphenyl)-6-(trifluoromethyl)oct-7-yn-1-yl)oxy)phenyl)ethan-1-one



A suitable crystal of $C_{24}H_{25}F_3O_3$ was selected for analysis. All Measurements were made on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100.0 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341.

2. SHELXS, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

3. SHELXL, G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

Crystal structure determination of p16037_a.

Crystal Data for $C_{24}H_{25}F_3O_3$ (M =418.44 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 5.4627(5) Å, b = 25.165(2) Å, c = 7.6160(8) Å, β = 91.544(5)°, V = 1046.60(17) Å^3, Z = 2, T = 100.0 K, μ(CuKα) = 0.875 mm^{-1}, *Dcalc* = 1.328 g/cm^3, 48849 reflections measured (7.024° ≤ 2Θ ≤ 145.006°), 4128 unique (R_{int} = 0.0406, R_{sigma} = 0.0169) which were used in all calculations. The final R_1 was 0.0348 (I > 2σ(I)) and wR_2 was 0.0979 (all data).

Table 5.6 Crystal Data and Structure Refinement for P16037_a.

Identification code	p16037_a
Empirical formula	$C_{24}H_{25}F_3O_3$
Formula weight	418.44
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.4627(5)
b/Å	25.165(2)

c/Å	7.6160(8)
α/°	90
β/°	91.544(5)
γ/°	90
Volume/$Å^3$	1046.60(17)
Z	2
$\rho_{calc}g/cm^3$	1.328
μ/mm^{-1}	0.875
F(000)	440.0
Crystal size/mm^3	0.22 × 0.21 × 0.2
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.024 to 145.006
Index ranges	$-6 \leq h \leq 6$, $-31 \leq k \leq 31$, $-9 \leq l \leq 9$
Reflections collected	48849
Independent reflections	4128 [R_{int} = 0.0406, R_{sigma} = 0.0169]
Data/restraints/parameters	4128/1/273
Goodness-of-fit on F^2	1.196
Final R indexes [I>=2σ (I)]	R_1 = 0.0348, wR_2 = 0.0979
Final R indexes [all data]	R_1 = 0.0349, wR_2 = 0.0980
Largest diff. peak/hole / e $Å^{-3}$	0.20/-0.30
Flack parameter	0.079(19)

Table 5.7. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for P16037_a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F001	2859(4)	6964.8(8)	10045(3)	36.1(4)
F002	5516(4)	7449.0(7)	8783(3)	33.5(4)
F003	6712(4)	6812.3(7)	10474(2)	34.3(4)
O004	2064(4)	3449.3(7)	9960(3)	21.3(4)
O005	8097(3)	5065.6(7)	3903(2)	19.0(4)
O006	8303(4)	2550.6(8)	4540(3)	29.4(5)
C007	5013(5)	6951.5(11)	9243(4)	24.3(6)
C008	647(5)	4260(1)	8485(3)	17.5(5)
C009	1088(5)	4793.9(11)	8164(3)	18.2(5)
C00A	5490(5)	3830.9(11)	5364(3)	17.1(5)
C00B	5862(5)	4365.5(10)	5061(3)	17.1(5)
C00C	3172(5)	5048.3(10)	8866(3)	17.4(5)
C00D	4364(4)	4222.8(11)	10276(3)	17.7(5)
C00E	6825(5)	2870.5(11)	5095(3)	21.3(6)
C00F	4788(5)	4750.2(11)	9940(3)	18.7(5)
C00G	7457(5)	6564(1)	6786(4)	21.0(5)
C00H	4971(5)	6582.5(10)	7674(3)	19.6(5)
C00I	7146(5)	3450.8(10)	4764(3)	16.4(5)
C00J	10162(5)	5260.6(11)	2966(4)	21.0(5)
C00K	9602(4)	4158.9(11)	3561(3)	17.1(5)
C00L	2290(5)	3971.4(10)	9547(3)	17.2(5)
C00M	7911(5)	4533.9(11)	4155(3)	15.1(5)
C00N	4179(5)	6046.5(11)	8193(4)	20.5(5)
C00O	9791(5)	6206.4(11)	4196(4)	24.4(6)
C00P	3676(5)	5595.4(11)	8508(3)	19.5(5)
C00Q	9807(6)	5845.2(11)	2575(4)	24.2(6)
C00R	9189(5)	3624.6(10)	3865(3)	18.4(5)
C00S	4684(6)	2690.0(11)	6141(4)	26.6(6)
C00T	-80(5)	3174.4(11)	9336(4)	24.8(6)
C00U	7357(5)	6223.6(11)	5122(4)	21.5(5)

Table 5.8. Anisotropic Displacement Parameters ($Å^2$ x 10^3) for P16037_a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F001	36.1(10)	34.6(10)	38.1(10)	-12.2(8)	8.9(8)	4.8(8)
F002	43.1(11)	17.2(8)	39.6(10)	-5.1(7)	-6.6(8)	-0.9(7)
F003	44.0(11)	33.5(9)	24.8(8)	-7.8(7)	-11.0(8)	8.5(8)
O004	21.8(10)	19.0(9)	22.9(9)	0.5(7)	-3.2(7)	-1.6(7)
O005	18.4(9)	20.3(9)	18.4(8)	-0.8(7)	4.5(7)	0.4(7)
O006	27.5(11)	22.2(10)	38.5(12)	-3.6(9)	0.5(9)	5.1(8)
C007	26.9(15)	23.0(14)	22.8(13)	-4.1(11)	-2.3(11)	3.4(11)
C008	16.4(12)	23.2(13)	12.8(11)	-2.3(9)	-1.2(9)	-0.7(10)
C009	17.2(13)	22.7(13)	14.5(11)	-1.2(10)	-0.6(9)	1.7(10)
C00A	13.4(12)	25.1(13)	12.6(11)	-2.1(9)	-1.5(9)	0.4(10)
C00B	14.2(12)	24.1(13)	12.9(11)	-2.9(9)	-0.4(9)	3.5(9)
C00C	16.9(12)	21.4(13)	14.1(11)	-2.2(9)	3.9(9)	-0.1(9)
C00D	12.9(11)	24.8(13)	15.1(11)	-1.9(10)	-1.5(9)	2.8(10)
C00E	22.6(14)	22.3(13)	18.6(13)	-2.9(10)	-6.7(10)	1.4(11)
C00F	12.4(12)	25.2(13)	18.5(12)	-4.1(10)	0.0(9)	-0.2(10)
C00G	22.9(13)	17.2(12)	22.9(13)	-0.8(10)	-1.8(10)	-2.6(10)
C00H	21.9(13)	17.7(12)	19.1(12)	-1.1(10)	-2.3(10)	0.1(10)
C00I	14.6(12)	21.8(13)	12.4(11)	-2.4(9)	-4.5(9)	1.7(9)
C00J	18.8(13)	26.3(14)	18.2(12)	-0.1(10)	5.1(10)	-1.7(10)
C00K	11.5(11)	25.8(13)	14.0(11)	-1.9(10)	0.8(9)	2.7(10)
C00L	16.9(12)	18.0(12)	16.7(12)	-2.1(9)	1.3(10)	0.6(9)
C00M	13.3(11)	22.0(12)	9.9(10)	-2.5(9)	-1.8(8)	1.5(9)
C00N	19.9(13)	21.2(13)	20.3(12)	-2.2(10)	0.6(10)	-0.1(10)
C00O	25.5(15)	22.8(13)	25.2(14)	-1.0(11)	3.8(11)	-5.7(11)
C00P	17.3(12)	25.5(15)	16.0(12)	-2.8(10)	1.8(9)	1(1)
C00Q	29.1(15)	25.5(13)	18.2(13)	2.6(10)	4.3(11)	-2.2(11)
C00R	15.7(12)	24.8(14)	14.5(11)	-3.9(10)	-2.7(9)	6.1(10)
C00S	28.8(15)	21.7(13)	29.4(15)	1.4(11)	0.2(12)	-2.7(11)
C00T	23.3(15)	22.0(14)	28.9(14)	-1.0(11)	-2.3(11)	-5.0(11)
C00U	23.2(14)	20.0(12)	21.5(13)	-0.9(10)	0.9(10)	-2.3(10)

Table 5.9. Bond Lengths for P16037_a.

Atom	Atom	Length/Å
F001	C007	1.341(3)
F002	C007	1.331(3)
F003	C007	1.348(3)
O004	C00L	1.357(3)
O004	C00T	1.430(3)
O005	C00J	1.438(3)
O005	C00M	1.356(3)
O006	C00E	1.224(4)
C007	C00H	1.513(3)
C008	C009	1.388(4)
C008	C00L	1.396(4)
C009	C00C	1.400(4)
C00A	C00B	1.381(4)
C00A	C00I	1.402(4)
C00B	C00M	1.397(4)
C00C	C00F	1.404(4)
C00C	C00P	1.432(4)
C00D	C00F	1.372(4)
C00D	C00L	1.400(4)
C00E	C00I	1.493(4)
C00E	C00S	1.503(4)
C00G	C00H	1.534(4)
C00G	C00U	1.529(4)
C00H	C00N	1.474(4)
C00I	C00R	1.396(4)
C00J	C00Q	1.512(4)
C00K	C00M	1.404(3)
C00K	C00R	1.384(4)
C00N	C00P	1.194(4)
C00O	C00Q	1.533(4)
C00O	C00U	1.523(4)

Table 5.10. Bond Angles for P16037_a.

Atom	Atom	Atom	Angle/°
C00L	O004	C00T	118.0(2)
C00M	O005	C00J	118.03(19)
F001	C007	F003	106.6(2)
F001	C007	C00H	112.4(2)
F002	C007	F001	106.7(2)
F002	C007	F003	106.5(2)
F002	C007	C00H	111.6(2)
F003	C007	C00H	112.7(2)
C009	C008	C00L	119.6(2)
C008	C009	C00C	121.2(2)
C00B	C00A	C00I	120.7(2)
C00A	C00B	C00M	120.1(2)
C009	C00C	C00F	118.1(2)
C009	C00C	C00P	121.7(2)
C00F	C00C	C00P	120.3(2)
C00F	C00D	C00L	120.1(2)
O006	C00E	C00I	120.3(3)
O006	C00E	C00S	121.0(3)
C00I	C00E	C00S	118.8(2)
C00D	C00F	C00C	121.2(2)
C00U	C00G	C00H	111.7(2)
C007	C00H	C00G	111.9(2)
C00N	C00H	C007	110.4(2)
C00N	C00H	C00G	111.1(2)
C00A	C00I	C00E	122.2(2)
C00R	C00I	C00A	118.6(2)
C00R	C00I	C00E	119.2(2)
O005	C00J	C00Q	109.4(2)
C00R	C00K	C00M	119.2(2)
O004	C00L	C008	125.2(2)
O004	C00L	C00D	115.0(2)
C008	C00L	C00D	119.7(2)
O005	C00M	C00B	115.7(2)
O005	C00M	C00K	124.4(2)
C00B	C00M	C00K	119.9(2)
C00P	C00N	C00H	174.3(3)
C00U	C00O	C00Q	114.4(2)
C00N	C00P	C00C	177.6(3)
C00J	C00Q	C00O	114.9(2)
C00K	C00R	C00I	121.5(2)
C00O	C00U	C00G	112.8(2)

Table 5.11. Torsion Angles for P16037_a.

A	B	C	D	Angle/°
F001	C007	C00H	C00G	-179.1(2)
F001	C007	C00H	C00N	-54.8(3)
F002	C007	C00H	C00G	61.2(3)
F002	C007	C00H	C00N	-174.6(2)
F003	C007	C00H	C00G	-58.6(3)
F003	C007	C00H	C00N	65.6(3)
O005	C00J	C00Q	C00O	65.2(3)
O006	C00E	C00I	C00A	179.5(2)
O006	C00E	C00I	C00R	-2.0(4)
C008	C009	C00C	C00F	-1.3(4)
C008	C009	C00C	C00P	178.4(2)
C009	C008	C00L	O004	179.9(2)
C009	C008	C00L	C00D	-0.1(4)
C009	C00C	C00F	C00D	0.9(4)
C00A	C00B	C00M	O005	179.1(2)
C00A	C00B	C00M	C00K	-0.4(4)
C00A	C00I	C00R	C00K	0.1(3)
C00B	C00A	C00I	C00E	178.9(2)
C00B	C00A	C00I	C00R	0.4(3)
C00E	C00I	C00R	C00K	-178.4(2)
C00F	C00D	C00L	O004	179.7(2)
C00F	C00D	C00L	C008	-0.4(4)
C00H	C00G	C00U	C00O	179.0(2)
C00I	C00A	C00B	C00M	-0.2(4)
C00J	O005	C00M	C00B	-179.5(2)
C00J	O005	C00M	C00K	0.0(3)
C00L	C008	C009	C00C	0.9(4)
C00L	C00D	C00F	C00C	-0.1(4)
C00M	O005	C00J	C00Q	170.9(2)
C00M	C00K	C00R	C00I	-0.8(4)
C00P	C00C	C00F	C00D	-178.8(2)
C00Q	C00O	C00U	C00G	176.9(2)
C00R	C00K	C00M	O005	-178.6(2)
C00R	C00K	C00M	C00B	0.9(3)
C00S	C00E	C00I	C00A	-1.4(4)
C00S	C00E	C00I	C00R	177.1(2)
C00T	O004	C00L	C008	-3.2(4)
C00T	O004	C00L	C00D	176.8(2)
C00U	C00G	C00H	C007	-175.7(2)
C00U	C00G	C00H	C00N	60.4(3)
C00U	C00O	C00Q	C00J	-81.0(3)

Table 5.12. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for P16037_a.

Atom	*x*	*y*	*z*	U(eq)
H008	-764	4092	7984	21
H009	-46	4990	7453	22
H00A	4095	3719	5985	20
H00B	4722	4619	5470	21
H00D	5481	4028	11005	21
H00F	6202	4917	10443	22
H00C	7961	6930	6481	25
H00E	8703	6417	7620	25
H00H	3738	6723	6798	24
H00G	10319	5061	1854	25
H00I	11682	5208	3682	25
H00K	11013	4271	2959	21
H00J	11076	6083	5043	29
H00L	10222	6572	3834	29
H00M	8237	5891	1913	29
H00N	11134	5964	1806	29
H00R	10322	3370	3451	22
H00O	4803	2306	6348	40
H00P	3157	2769	5487	40
H00Q	4694	2877	7270	40
H00S	-155	3183	8049	37
H00T	-1539	3347	9794	37
H00U	-15	2805	9737	37
H00V	6876	5857	5435	26
H00W	6084	6367	4303	26

5.6.5 ^{1}H NMR Spectra of Selected Compounds

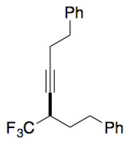
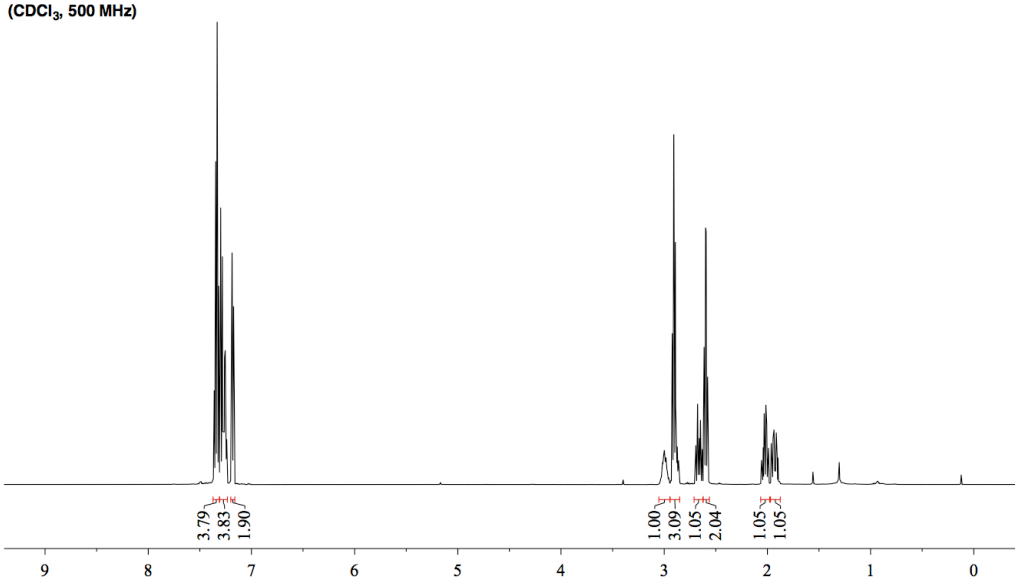


Table 5.2, Entry 1
($CDCl_3$, 500 MHz)



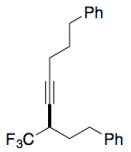
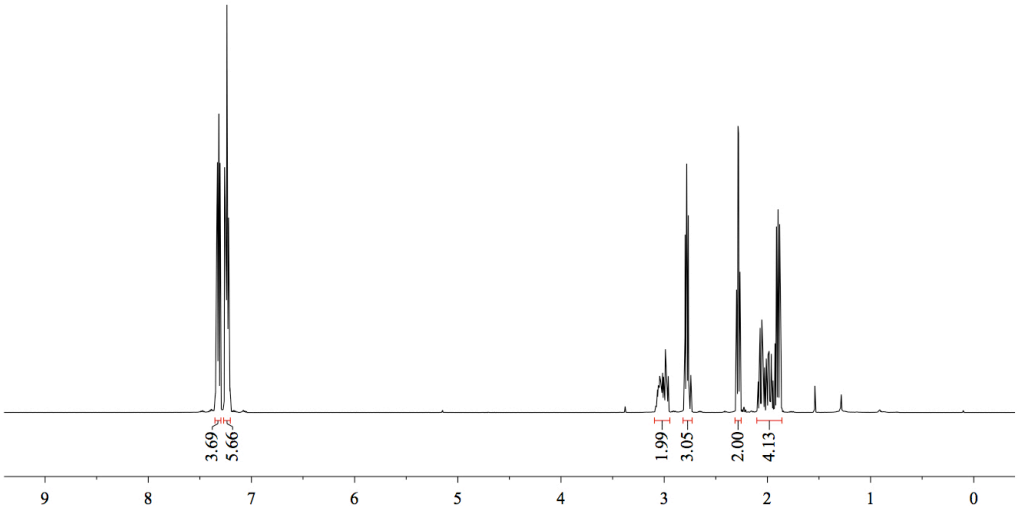


Table 5.2, Entry 2
($CDCl_3$, 500 MHz)



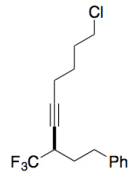


Table 5.2, Entry 3
($CDCl_3$, 500 MHz)

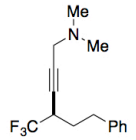
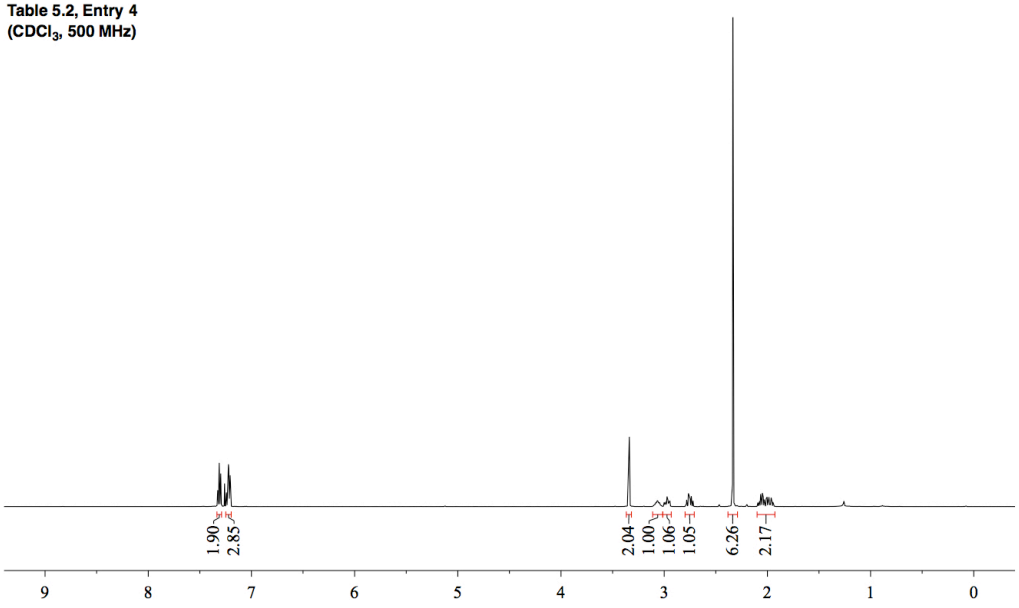


Table 5.2, Entry 4
($CDCl_3$, 500 MHz)



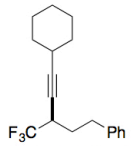
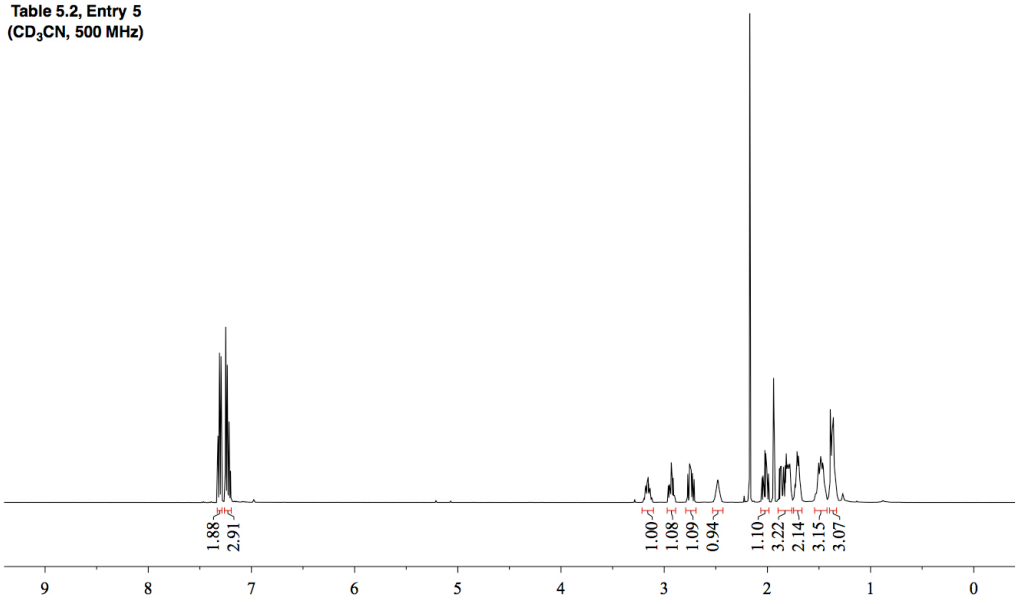


Table 5.2, Entry 5
(CD_3CN, 500 MHz)



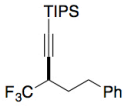


Table 5.2, Entry 6
($CDCl_3$, 500 MHz)

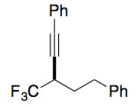
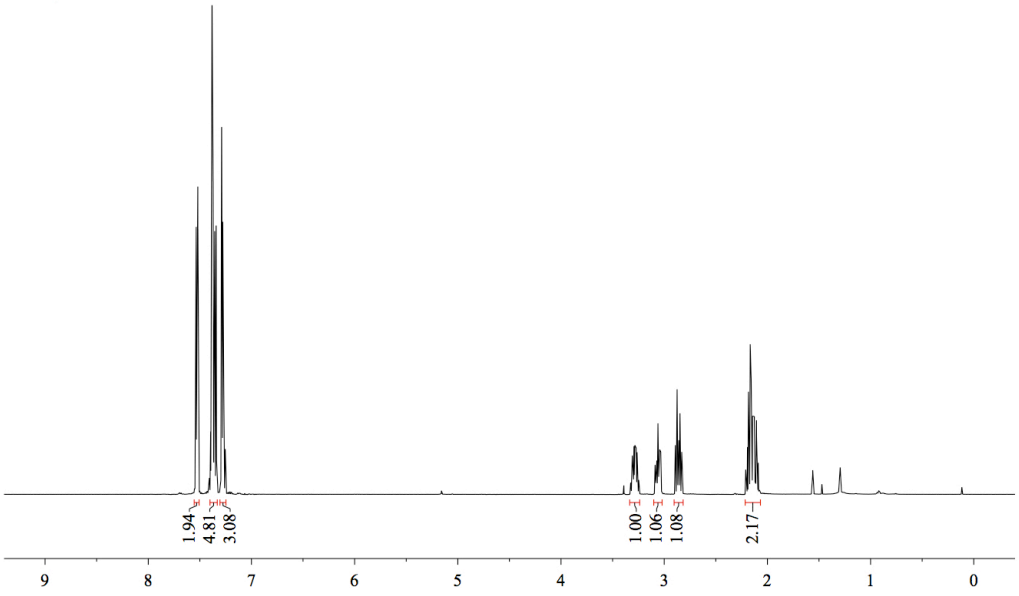


Table 5.3, Entry 1
($CDCl_3$, 500 MHz)



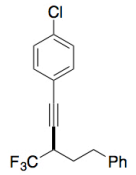
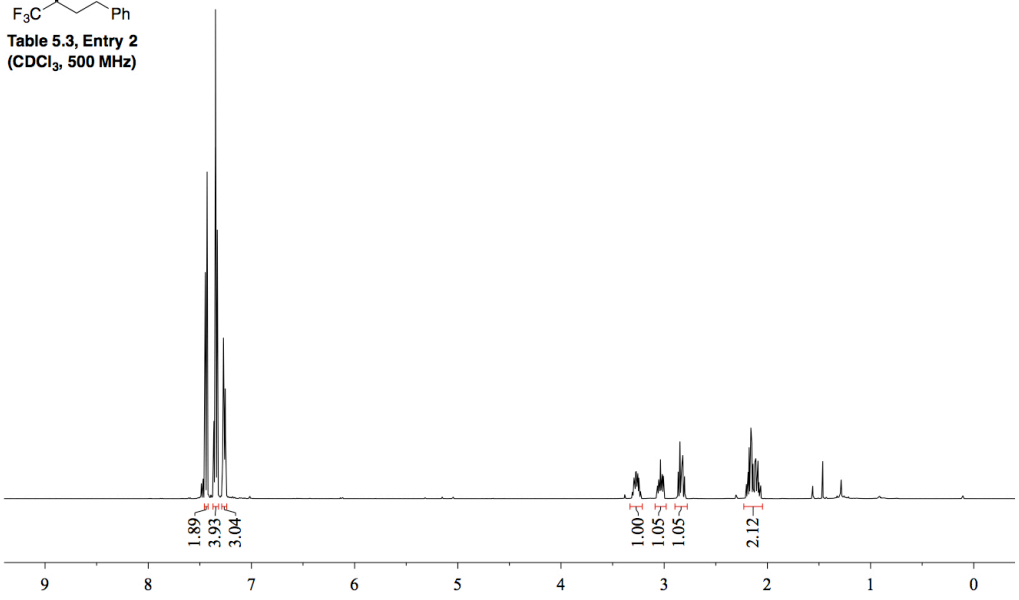


Table 5.3, Entry 2
($CDCl_3$, 500 MHz)



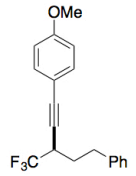


Table 5.3, Entry 3
($CDCl_3$, 500 MHz)

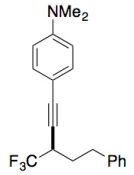


Table 5.3, Entry 4
(CD_3COCD_3, 500 MHz)

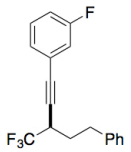
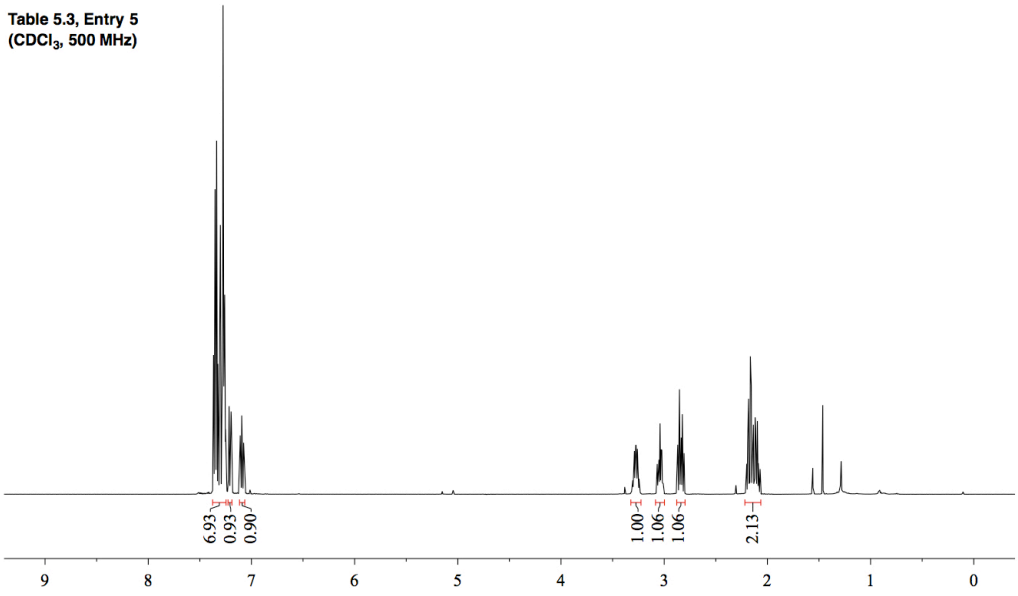


Table 5.3, Entry 5 ($CDCl_3$, 500 MHz)



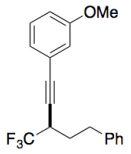
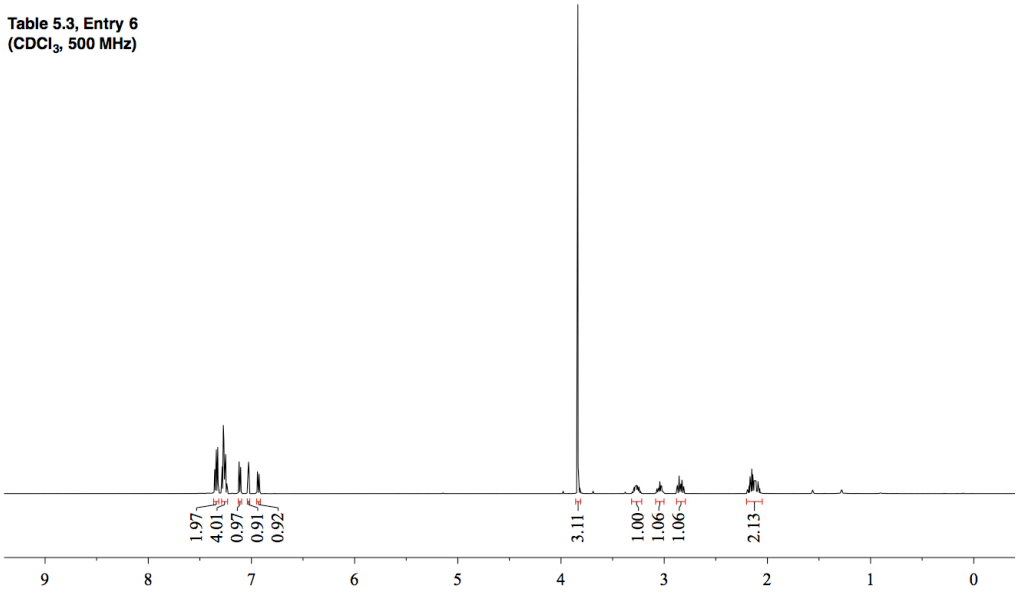


Table 5.3, Entry 6 ($CDCl_3$, 500 MHz)



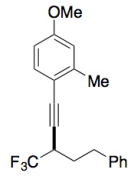


Table 5.3, Entry 7
($CDCl_3$, 500 MHz)

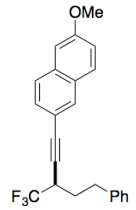


Table 5.3, Entry 8
($CDCl_3$, 500 MHz)

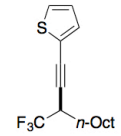
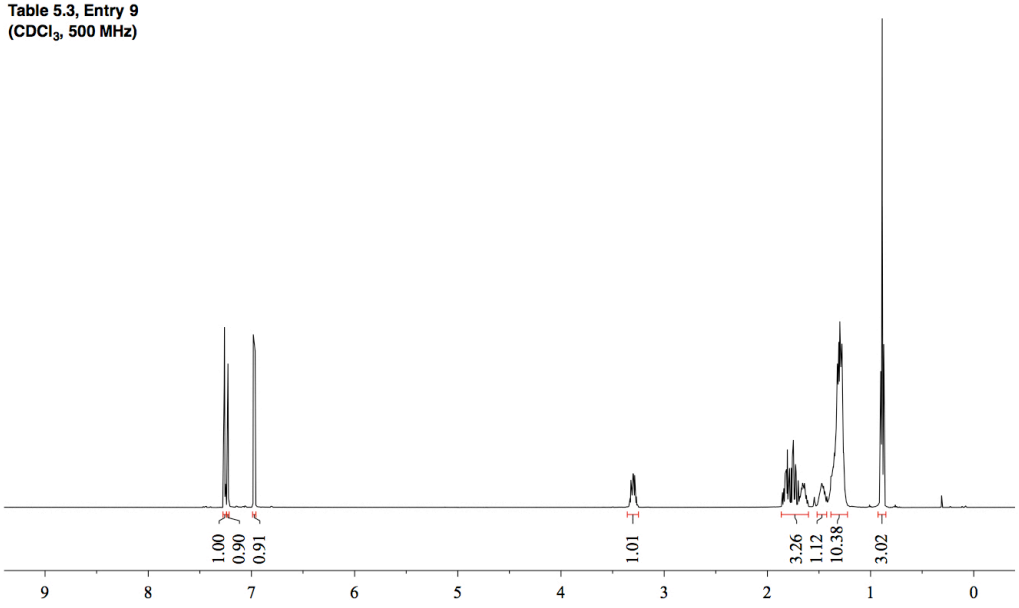


Table 5.3, Entry 9
($CDCl_3$, 500 MHz)



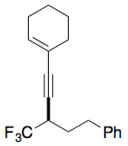
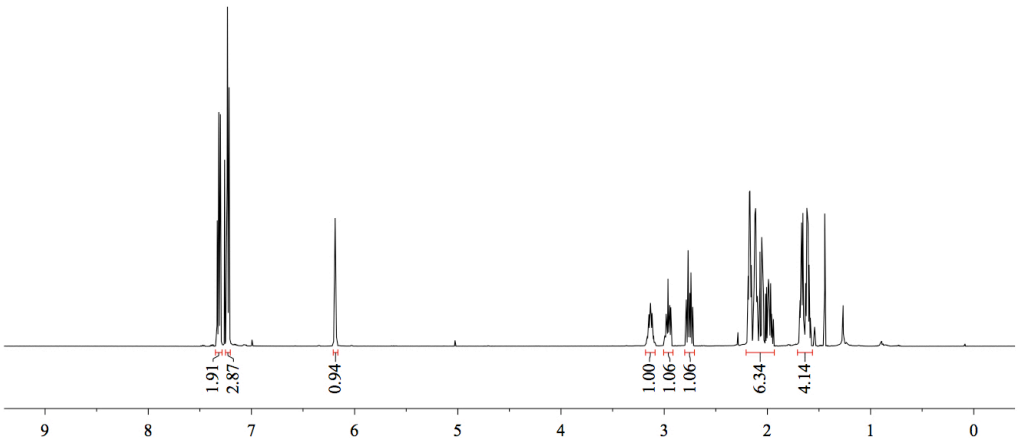


Table 5.3, Entry 10
($CDCl_3$, 500 MHz)



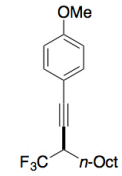


Table 5.4, Entry 1
($CDCl_3$, 500 MHz)

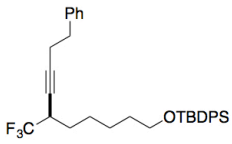


Table 5.4, Entry 2
($CDCl_3$, 500 MHz)

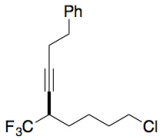
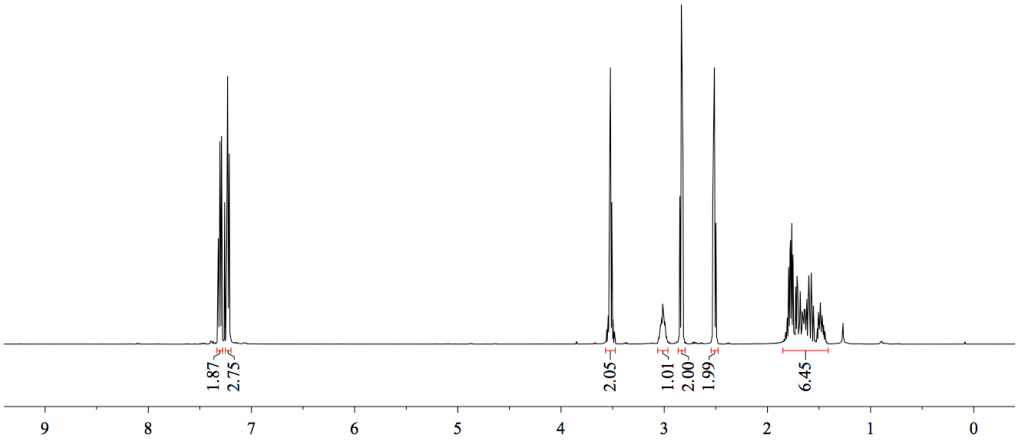


Table 5.4, Entry 3
($CDCl_3$, 500 MHz)



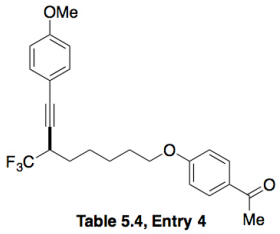


Table 5.4, Entry 4
($CDCl_3$, 500 MHz)

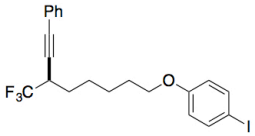
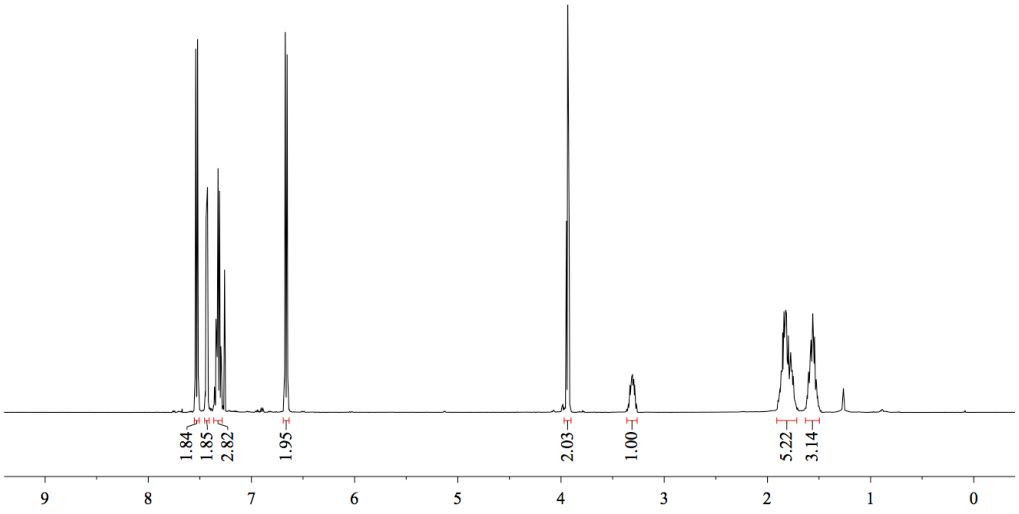


Table 5.4, Entry 5
($CDCl_3$, 500 MHz)



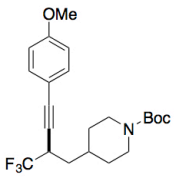


Table 5.4, Entry 6
($CDCl_3$, 500 MHz)

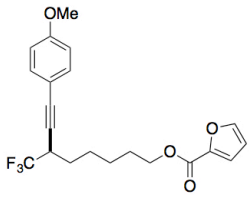
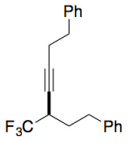
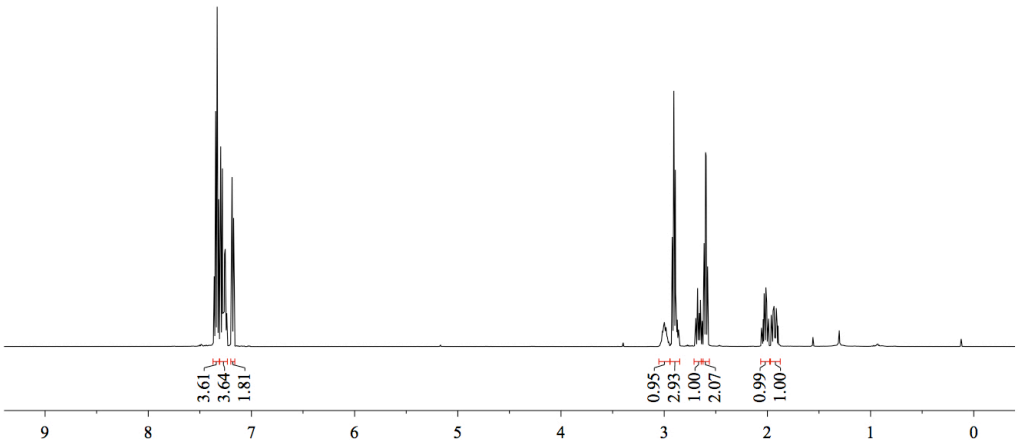
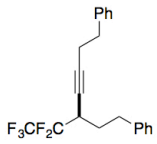


Table 5.4, Entry 7
($CDCl_3$, 500 MHz)

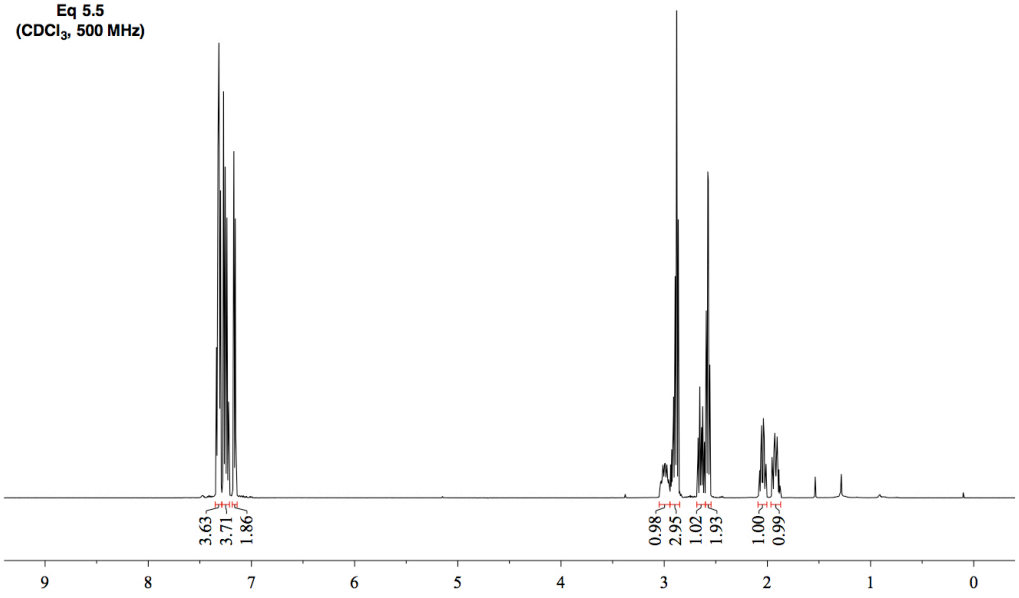


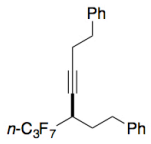
Eq 5.3
($CDCl_3$, 500 MHz)



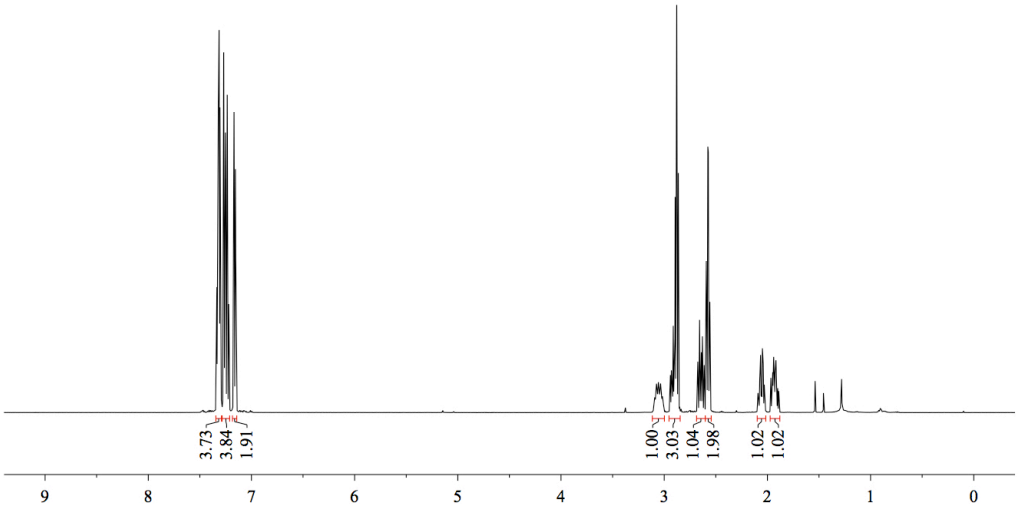


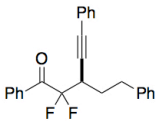
Eq 5.5
($CDCl_3$, 500 MHz)



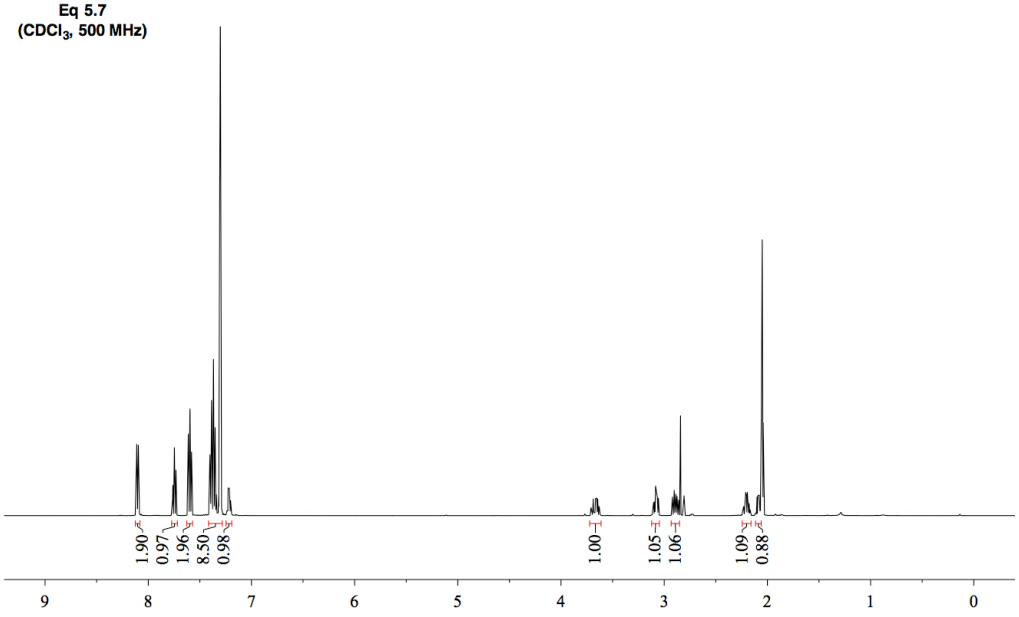


Eq 5.6
($CDCl_3$, 500 MHz)





Eq 5.7
($CDCl_3$, 500 MHz)



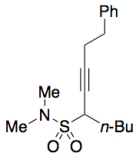


Table 5.5, Entry 1
($CDCl_3$, 500 MHz)

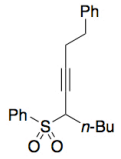
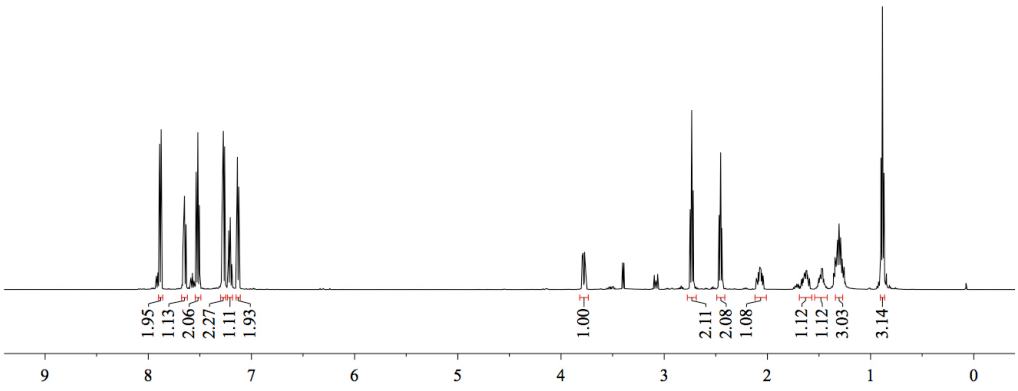


Table 5.5, Entry 2
($CDCl_3$, 500 MHz)



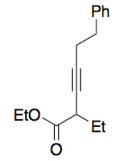
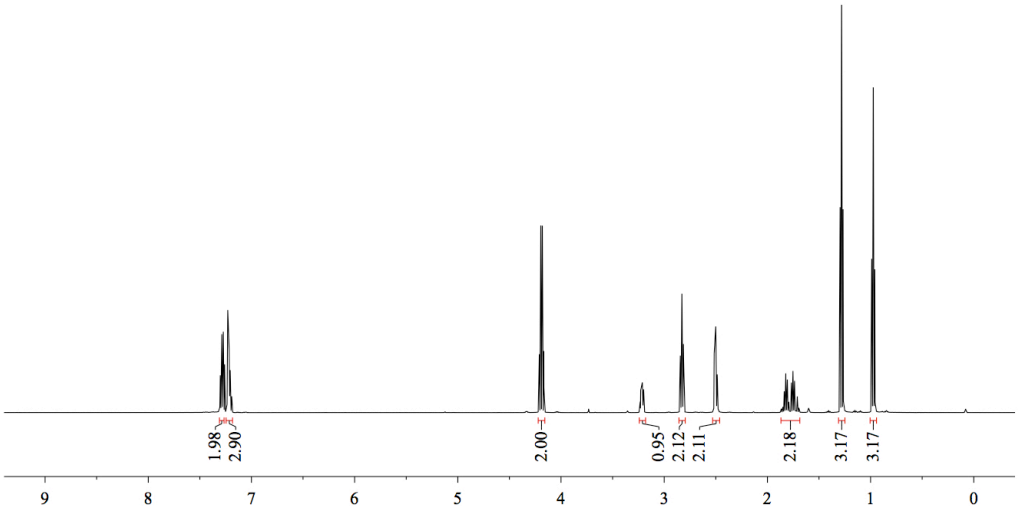


Table 5.5, Entry 3
($CDCl_3$, 500 MHz)



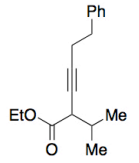


Table 5.5, Entry 4
($CDCl_3$, 500 MHz)

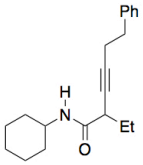
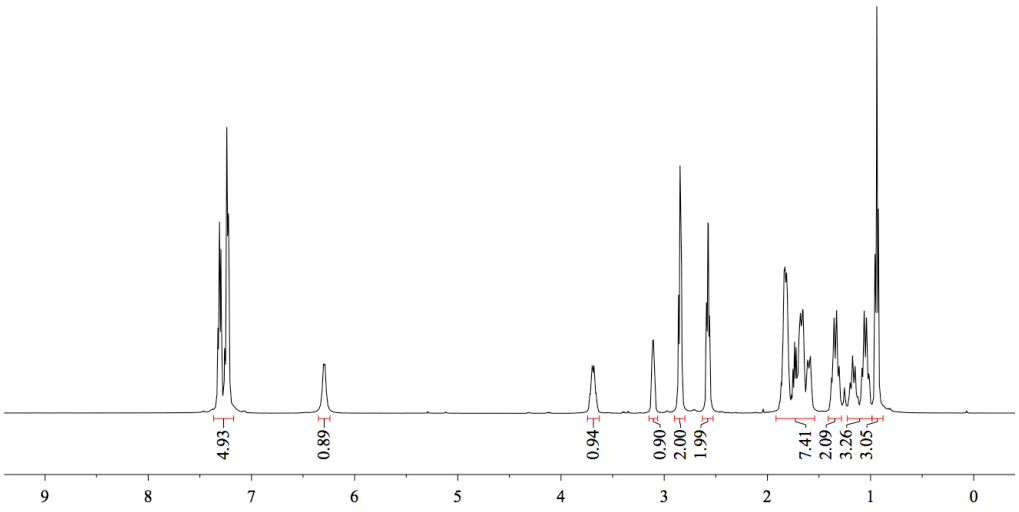


Table 5.5, Entry 5
($CDCl_3$, 500 MHz)



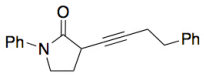
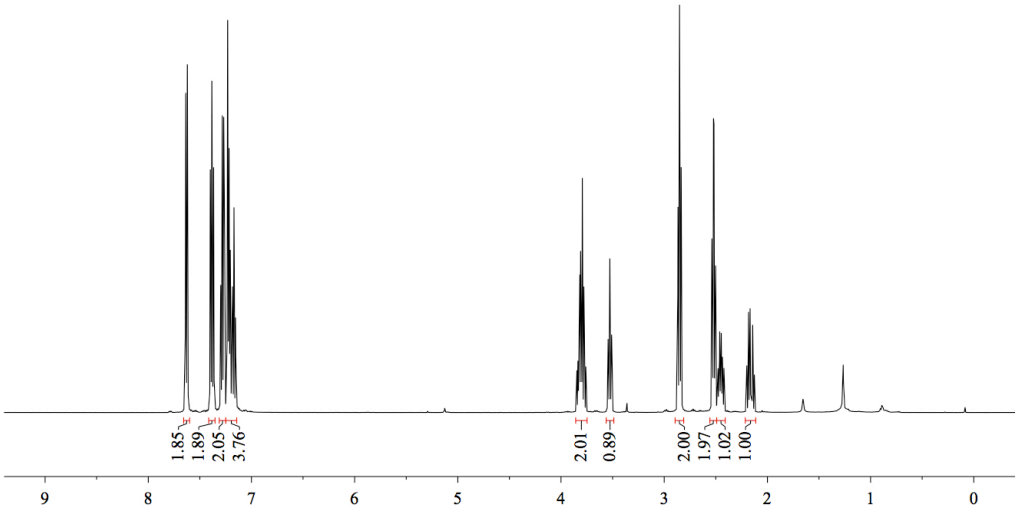


Table 5.5, Entry 6
($CDCl_3$, 500 MHz)



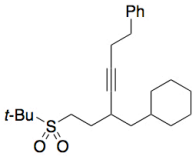


Table 5.5, Entry 7
($CDCl_3$, 500 MHz)

5.7 Notes and References

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