Copper and Nickel Catalysis for the Construction of Novel C–N and C–C Bonds

Thesis by

Carson D. Matier

In Partial Fulfillment of the Requirements for
the Degree of
Doctor of Philosophy in Chemistry

CALIFORNIA INSTITUTE OF TECHNOLOGY
Pasadena, California

2019

(Defended May 6th, 2019)

Carson D. Matier

ORCID: 0000-0002-1618-7944

ACKNOWLEDGEMENTS

Graduate school is hard, like really hard. No one makes it through this journey alone. I have been lucky to share this experience with many people, and for that I owe my PhD, in part, to them.

First I must thank my advisor, Prof. Greg Fu. After discussing organic chemistry with him as part of a graduate course in my first months at Caltech, I knew I wanted to be as smart as him. Nearly five years after he let me join his group I am still a long way off from that goal, but his guidance and support have led me to become an independent researcher with confidence (and hopefully competence) in my ability to study chemistry. Thank you, Greg, this has been an experience I will never forget.

I must also thank Prof. Jonas Peters. Though I was not a joint student, much of my graduate research was in collaboration with his group. He has provided great insights into my research. The other two members of my committee are Prof. Sarah Reisman, my committee chair, and Prof. Brian Stoltz. I thank them for contributions to my research and development.

I would not be in graduate school at all if it was not for my undergraduate research advisor, Prof. Fred West at the University of Alberta (my alma mater). He gave me my first opportunity at chemical research and inspired me to apply to Caltech. I will be forever grateful for everything you have done for me. I thank Prof. Ratmir Derda (University of Alberta) and Prof. Jeffrey Stryker (University of Alberta) for their invaluable letters of support in my graduate school applications. I must also thank Prof. Dennis Hall (University of Alberta), Dr. Christine Brzezowski (University of Alberta), and Dr. Les Rawluk (Grande Prairie Regional College) for their inspiring chemistry lectures.

I was lucky in my undergrad to receive guidance from a number of talented researchers and great people. Dr. Olivier Soueidan, thank you for guiding me through my first research experience. Dr. Yonghoon Kwon, thank you for your encouragement, fostering my indepedance and all those coffees. Dr. Alexander Belovodskiy, you are a true friend and a great baymate. You were a constant source of support throughout my PhD.

The facilities and support staff at Caltech are truly some of the best people around. I must acknowledge Dr. David Vander Velde from the NMR facility, Dr. Paul Oyala from the

EPR facility, Dr. Mona Shahgoli and Naseem Torian from the MS facility, Dr. Scott Virgil from the Caltech Center for Catalysis and Chemical Synthesis, and Dr. Michael Takase and Lawrence Henling from the X-ray Crystallography Facility. Julianne Just, you are our group's true MVP. I would also like to thank Joe Drew, Alison Ross, Lynne Martinez, and Agnes Tong for their help through my PhD.

I have had the great fortune of overlapping with a number of talented researchers during my time in the Fu group that I would like to acknowledge:

Saaket Agrawal, Dr. Joe Ahn, Arianna Ayonon, Dr. Shoshana Bachman, Dr. Agnieszka Bartoszewicz, Dr. Suzanne Batiste, Dr. Zhichao Cao, Dr. Caiyou Chen, Hyungdo Cho, Prof. Huan Cong, Dr. Jaika Dörfler, Dylan Freas, Bradley Gorsline, Gregory Harlow, Dr. Haohua Huo, Dr. Stefan Jungbauer, Dr. Quirin Kainz, Prof. Marcin Kalek, William Kayitare, James Lawniczak, Dr. Yufan Liang, Dr. Yusuke Masuda, Dr. Xin Mu, Dr. Socrates Munoz, Holt Sakai, Prof. Nathan Schley, Dr. Jens Schmidt, Joseph Schneider, Dr. Jonas Schwaben, Dr. Gregg Schwarzwalder, Dr. Martin Slusarczyk, Dr. Hidehiro Suematsu, Dr. Zhaobin Wang, Dr. Felicia Weber, Dr. Zepeng Yang, Dr. Haolin Yin, Dr. Daniel Ziegler, Dr. Yasushi Yoshida, Wendy Zhang, and Dr. Wei Zhao.

I would like to specifically acknowledge my collaborators to whom I owe so much to—teamwork makes the dream work. Dr. Agnieszka Bartoszewicz, Dr. Quirin Kainz, Dr. Jonas Schwaben, Dylan Freas, Joseph Schneider, and Dr. Gregg Schwarzwalder have contributed greatly to the work contained herein.

Friends are the support system that really keep you going during graduate school. I have to acknowledge my friends that have been there through the tough times, and celebrated with during the best times. Though thousands of miles away back in Canada, Garrison Fast, Richard Larson, Leo MacDonald, and Thomas Ridgeway have remained good friends while I have been abroad. Within the lab, Dr. Joe Ahn, Arianna Ayonon, Dr. Shoshana Bachman, Dr. Suzanne Batiste, Dr. Jaika Dörfler, Dylan Freas, Bradley Gorsline, Dr. Xin Mu, Dr. Jens Schmidt, Dr. Jonas Schwaben, Dr. Gregg Schwarzwalder, Dr. Felicia Weber, Dr. Haolin Yin, Dr. Daniel Ziegler, Wendy Zhang, and Dr. Wei Zhao have either been instrumental in scientific discussions or dear friends, and often both. Outside of the lab I have had many thought-provoking discussions or good times with a number of people, including, but not

limited to: Dr. Alex Chapman, Dr. Kangway Chuang, Nick Fastuca, Ramsey Garrett, Dr. Jase Gehring, Dr. Maddi Kieffer, Dr. Steven Loskot, Skyler Mendoza, Dr. David Miller, David Schuman, Prof. Suzie Stevenson, Dr. Haoxuan Wang, Prof. Eric Welin, Prof. Julian West, Dr. William Wolf, Annie Wong, and Austin Wright.

Wherever life takes us, Alice Rose Wong, I want you to know you have been the most important person throughout my graduate studies. Your passion, intelligence, and humor inspire me every day to not only be a better chemist, but a better person. Thank you, for everything.

Finally, I have to thank my family. I would like to acknowledge my grandparents, uncles, cousins, in-laws, and numerous nephews and nieces. My sister, Mandy Pollock, and my brothers, Tyler and Justin Matier, are so important to me and you each inspire me in your own way. To my mom and dad, Donna and Dwayne Matier, I want you to know how proud I am to be your son—you are the best people. Thank you all for your love and support.

ABSTRACT

First-row transition-metals such as nickel and copper have revolutionized cross-coupling chemistry. Their propensity to form radical intermediates from alkyl electrophiles has greatly expanded the scope of traditional cross-coupling reactions. Alkyl radicals can be recaptured by a chiral transition-metal catalyst allowing for enantioselective bond formation. In general, alkyl radicals rapidly epimerize, and thus both enantiomers of a racemic mixture of an alkyl electrophile can be processed into the same enantiomer of product, rendering the overall process enantioconvergent. Herein, the development of basic bond constructions and the development of asymmetric reactions leveraging alkyl radical intermediates for carbon-nitrogen and carbon-carbon bond formations are discussed. Reaction development is the primary focus of this work, though mechanistic insights discovered along the way are also detailed within.

Chapter 2 describes the development of an enantioconvergent alkylation of amine nucleophiles with alkyl electrophiles. Carbazole and indole derivatives are employed as nucleophiles to undergo copper-catalyzed cross-coupling with tertiary α-chloroamide electrophiles under visible light irradiation. Reaction optimization, scope of reactivity, inorganic synthesis, and mechanistic insights are described within.

Chapter 3 details the development of a non-asymmetric copper-catalyzed alkylation of aliphatic amines with unactivated alkyl electrophiles under visible light irradiation. The development of a novel catalytic system to circumvent the issues with the photophysical properties of aliphatic amine-copper complexes is discussed. Scope of reactivity and mechanistic investigations are detailed within. Additionally, our efforts to develop an asymmetric variant of this reaction are enclosed.

Chapter 4 discusses the development of a copper-catalyzed alkylation of N-heterocycles with α-halolactams in the absence of light. The scope of the reactivity is detailed within. Mechanistic studies contained in this section suggest a unique and interesting reaction pathway—one that does not proceed through a radical intermediate.

Chapter 5 presents a novel class of organosilane electrophiles employed in an enantioconvergent nickel-catalyzed cross-coupling reaction. Here, the development of the reaction, scope of reactivity, and initial mechanistic insights are discussed.

PUBLISHED CONTENT AND CONTRIBUTIONS

This dissertation contains materials adapted with permission from the following publications:

1. Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C–N Cross-Couplings Induced by Visible Light. *Science* **2016,** *351*, 681–684. doi: 10.1126/science.aad8313

C. D. M. participated in determining scope of reactivity, inorganic synthesis and reactivity, X-ray diffraction studies, additive effects studies, stereochemical studies, and preparation of the manuscript.

2. Matier, C. D. ; Schwaben, J. ; Peters, J. C. ; Fu, G. C. Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *J. Am. Chem. Soc.* **2017**, *139*, 17707−17710. doi: 10.1021/jacs.7b09582

C. D. M. participated in conceiving the project, optimization, determining scope of reactivity, additive effects studies, product derivatization, ESI-MS experiments, EPR studies, and preparation of the manuscript.

3. Schwarzwalder, G. M.‡; Matier, C. D.‡; Fu, G. C. Enantioconvergent Cross-Coupling of Alkyl Electrophiles: The Catalytic Asymmetric Synthesis of Organosilanes. *Angew. Chem. Int. Ed.* **2019**, *58*, 3571–3574. doi: 10.1002/anie.201814208

C. D. M. participated in optimization, determining scope of reactivity, additive effects studies, product derivatization, ESI-MS experiments, EPR studies, stereochemical studies, X-ray diffraction studies, and preparation of the manuscript. ‡Authors contributed equally to this work.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

{^{1}H}	proton-decoupled
{^{31}P}	phosphorus-decoupled
^{1}H	proton
^{13}C	carbon-13
2-Me-THF	2-methyl-tetrahydrofuran
^{31}P	phosphorus-31
Å	angstrom(s)
Ac	acetyl
APCI	atmospheric pressure chemical ionization
Aq	aqueous
Ar	aryl group
ATR	attenuated total reflection
Boc	*tert*-butoxycarbonyl
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
br	broad
BTPP	*tert*-butylimino-tri(pyrrolidino)phosphorane
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
c	concentration
°C	degrees Celsius
calcd	calculated
cat.	catalyst
c.f.	consult or compare to (Latin: confer)
CFL	compact fluorescent light
cm^{-1}	wavenumber(s)
conc.	concentrated
Cy	cyclohexyl
d	doublet
DCM	dichloromethane
DMA	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane

DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
e	electron
ee	enantiomeric excess
E	trans (entgegen) olefin geometry
E2	bimolecular elimination
e.g.	for example (Latin: exempli gratia)
EI	electron impact
EPR	electron paramagnetic resonance
eq	equation
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
FAB	fast-atom bombardment
FT	Fourier transform
g	gram(s)
GC	gas chromatography
GHz	gigahertz
h	hour(s)
n-Hex	hexyl or *norm*-hexyl group
HMDS	hexamethyldisilamide or hexamethyldisilazide
HPLC	high performance liquid chromatography
HR	high-resolution
hv	light
Hz	hertz
i.e.	that is (Latin: id est)
IPA	isopropanol
IR	infrared spectroscopy
J	coupling constant
K	Kelvin or equilibrium constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
kJ	kilojoule(s)

L	liter or neutral ligand
L*	chiral neutral ligand
LC	liquid chromatography
LED	light-emitting diode
LR	low-resolution
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
µ	micro
max	maximum
Me	methyl
MeOH	methanol
Mes	mesityl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole
mol	mole(s)
MS	mass spectrometry
m/z	mass-to-charge ratio
N	normal or molar
n	generic number
naph	naphthyl
nm	nanometer(s)
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
P orb	P orbital
pdt	product
n-pent	pentyl or *norm*-pentyl
Ph	phenyl
PhMe	toluene
ppm	parts per million
Pr	propyl
i-Pr	*iso*-propyl
n-Pr	propyl or *norm*-propyl

i-PrOH	isopropanol
py	pyridine
q	quartet
R	alkyl group
R	rectus
rac	racemic
ref	reference
Rf	retention factor
rpm	revolutions per minute
rt	room temperature (or r.t.)
s	singlet or seconds
S	sinister
sat.	saturated
SET	single electron transfer
SFC	supercritical fluid chromatography
S_H2	homolytic substitution
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet or time
TBS	*tert*-butyldimethylsilyl
temp	temperature
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetamide
THF	tetrahydrofuran
TLC	thin-layer chromatography
T.M.	transition-metal
TMS	trimethylsilyl
tol	tolyl
t_r	retention time
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
vis	visible
W	watt
X	anionic ligand or halide
xs	excess
XRD	X-ray diffraction
Z	cis (zusammen) olefin geometry

*	excited state
[α]	specific rotation
μL	microliter
μW	microwave irradiation

Chapter 1

INTRODUCTION

1.1. Cross-Couplings with Radical Intermediates

First-row transition-metals, such as iron, manganese, cobalt, copper, and nickel are exciting starting points for the design of new transition-metal catalyzed reactions. Not only are they generally inexpensive due to their high earth-abundance, they often exhibit low toxicity compared to noble metals (e.g., ruthenium, rhodium, palladium, iridium). Moreover, their propensity to undergo single-electron transfer events allows access to interesting chemical transformations. For example, whereas palladium has a tendency to undergo two-electron chemistry with alkyl and aryl halides, first-row transition-metals like nickel and copper can readily undergo single-electron transfer to an alkyl or aryl halide, generating highly reactive radical intermediates under unusually mild conditions (i.e., room temperature or lower) (Figure 1.1).[1,2] In the case of secondary or tertiary alkyl halides, both enantiomers of electrophile can generate a common alkyl radical intermediate after single-electron transfer. If a chiral catalyst is employed, stereoselective bond formation could occur. Thus, such a system portends itself to enantioconvergent processes—where both enantiomers of a racemic mixture of electrophile are processed into a single enantiomer of product.

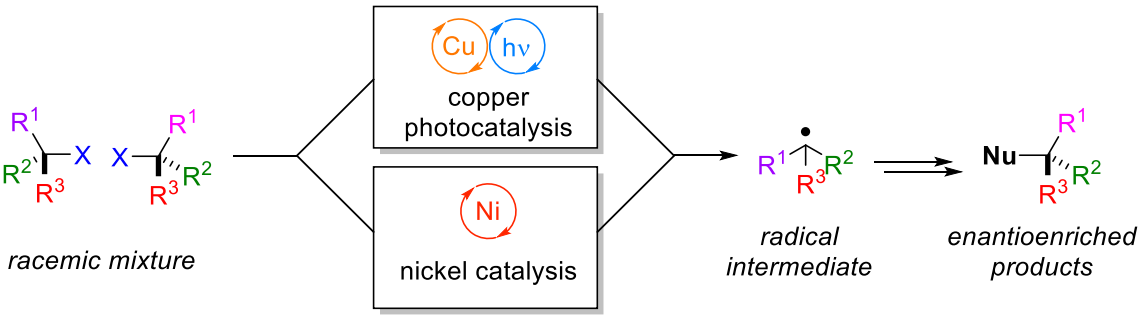


Figure 1.1. Copper and nickel catalysis can generate radical intermediates that can be recaptured by the metal catalyst to form enantioenriched bonds.

Using transition-metals like nickel and copper to generate alkyl radical intermediates can allow one to circumvent issues with classical methods for nucleophilic substitution reactions of alkyl electrophiles.[1–3] For example, S_N1 reactions have a number of inherent limitations (Figure 1.2): substrates are usually limited to tertiary electrophiles; competing elimination and rearrangement side-reactions of carbocation intermediates can occur; Lewis or Brønsted acids are often required for ionization and can quench the nucleophilic partner; and this reaction manifold can rarely be employed in an enantioconvergent fashion.[4]

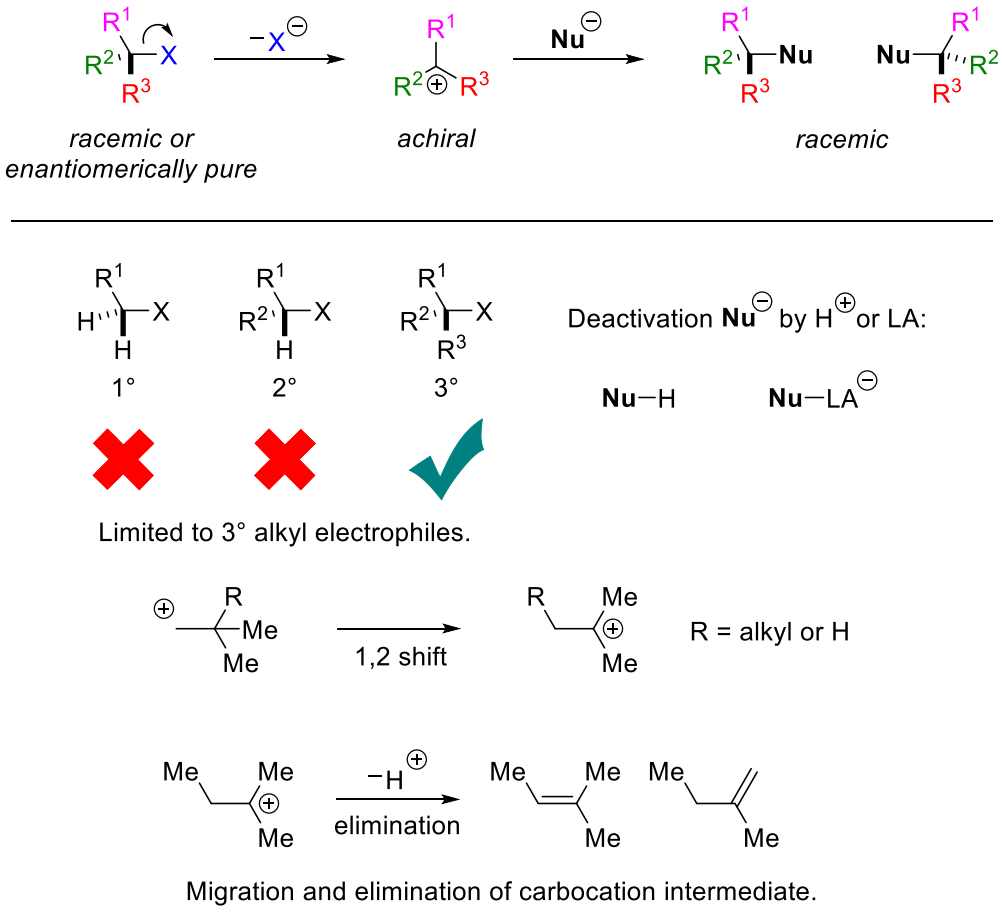


Figure 1.2. S_N1 reaction and the associated limitations.

There are also various limitations to S_N2 reactions of alkyl halide electrophiles (Figure 1.3):[1–3] substrates are generally limited to unhindered primary or activated secondary

electrophiles; strong nucleophiles or the addition of a strong base is generally required, which can result in an E2 reaction with the electrophile; amine nucleophiles can readily undergo overalkylation; and, because this process is stereoinvertive, one enantiomer of electrophile can only be converted into the opposite enantiomer of product.

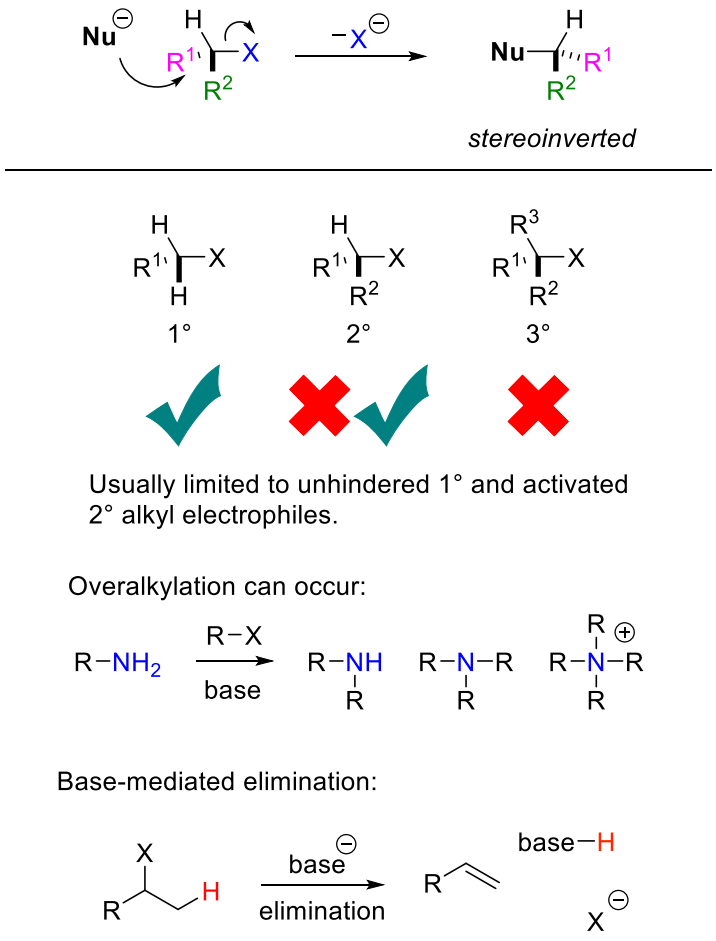


Figure 1.3. S_N2 reaction and the associated limitations.

A radical approach can avoid many of these limitations.[1,2] For example, in contrast to its carbocation counterpart, alkyl radicals do not readily undergo 1,2-alkyl or 1,2-hydride rearrangements.[5] Substitution reactions of alkyl electrophiles via radical intermediates are known as S_H2 (homolytic substitution) reactions. However, the likelihood of an S_H2 reaction occurring largely depends on the nucleophilic component. The generated alkyl radical must be able to react via atom transfer or addition into a π system with the nucleophile.[5] As a

result, first-row nucleophiles with lone pairs (e.g., amines, alcohols, etc.) and saturated carbon nucleophiles are not amenable to this reactivity.

Transition-metal catalysis has been essential in expanding nucleophilic substitution reactions to aryl, alkenyl, and alkynyl electrophiles with various nucleophilic coupling partners.[6] Typically, these transformations proceed through a common cycle of oxidative addition, transmetallation, and reductive elimination (Figure 1.4). Oxidative addition has been successful for a number of C_{sp2}–X and C_{sp}–X electrophiles; however, the analogous reaction with C_{sp3}–X electrophiles is limited due to steric interactions with 2° and 3° electrophiles and competing β-hydride elimination of alkylmetal intermediates.[1,2]

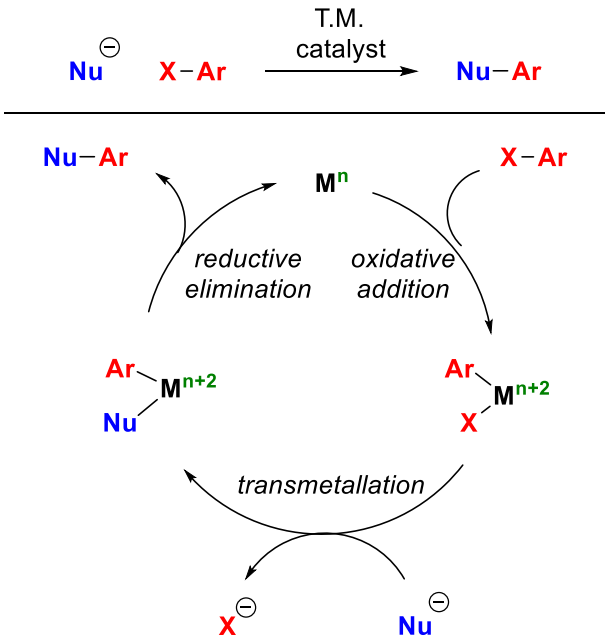


Figure 1.4. General outline of a transition-metal catalyzed cross-coupling reaction of an aryl electrophile with a generic nucleophilic via two-electron oxidative addition.

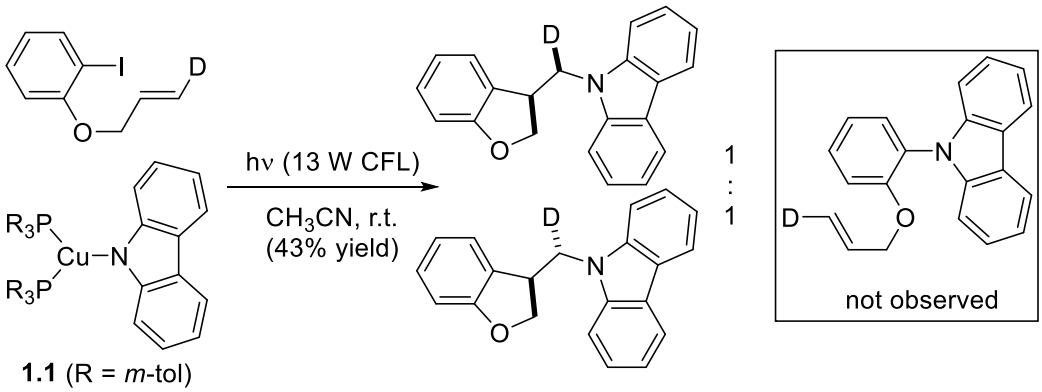
Fortunately, there are alternatives to the two-electron oxidative addition pathway that allow the net oxidative addition of alkyl electrophiles.[7] Transition-metals can undergo two-step oxidative addition by first generating an alkyl radical (through halide atom abstraction, single electron transfer, or a related process) followed by recombination of the radical and

transition-metal catalyst to effect the oxidative addition product.[8] By exploiting the propensity of certain transition-metals (i.e., nickel and copper) to undergo this reactivity, the scope of nucleophilic substitution reactions has been greatly expanded (Figure 1.1).[1,2] Transition-metal catalysis proceeding through radical intermediates is a powerful tool in synthetic chemistry and is largely the focus of the chemistry discussed within this thesis.

1.2. Photoinduced Copper Catalysis

Copper is privileged in its ability construct C–N bonds.[9] However, high catalyst loadings and elevated reaction temperatures of many copper-catalyzed reactions have continued to be significant drawbacks—advancements in ligand design over the years have begun to address these issues. Alternatively, light used in conjunction with copper catalysis has opened to door to accessing high energy intermediates under milder conditions. Photoredox catalysis has been intensively studied and is commonly featured in new cross-coupling reactions. Most reports involve catalyst systems based on ruthenium and iridium photocatalysts, though copper photocatalysts have recently garnered significant attention.[10]

Previously, the Peters group had studied luminescent copper species and their ability to partake in photoinduced electron transfer events.[11] Together the Fu and Peters have leveraged these photoluminescent properties to probe mechanistic questions regarding the Ullmann coupling.[12] They found copper(I)-amide complex **1.1** could mediate the formation of C–N bonds under UV light irradiation (eq 1.1).[12] Mechanistic studies determined that the reaction proceeds through a radical intermediate derived from the electrophile.



(1.1)

Since this initial study, the Fu and Peters groups have demonstrated a wide array of nucleophilic coupling partners able to undergo cross-coupling with both aryl and alkyl halide electrophiles via radical intermediates using copper photocatalysis (Figure 1.5).[13] Additionally, this reaction manifold has even been extended to the asymmetric variant and will be discussed in Chapter 2 (eq 1.2).[13g] Ongoing studies in the Fu and Peters groups are largely focused on studying the mechanisms of these reactions, expanding the scope of reactivity and developing new asymmetric transformations.

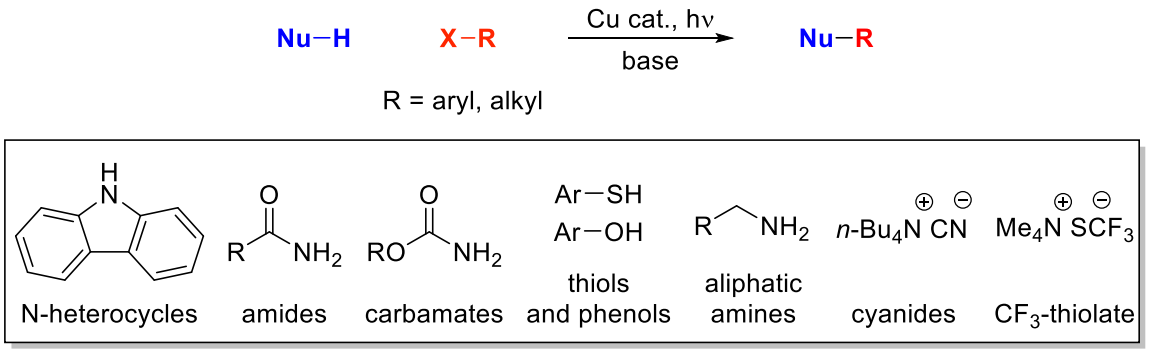
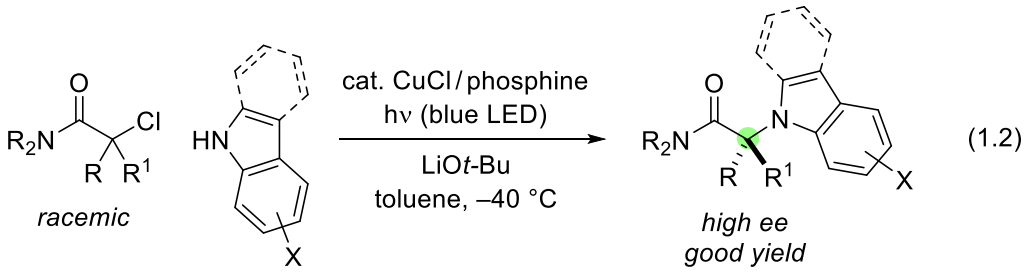


Figure 1.5. Nucleophiles used in copper-catalyzed alkylation and arylation cross-coupling reactions that are induced by light irradiation.



(1.2)

Because initial studies were conducted under UV light irradiation, photoinduced C–X bond homolysis could not be ruled out as means to generate radical intermediates.[12] However, recently developed photoinduced copper-catalyzed reactions, such as those discussed within Chapters 2 and 3, have been performed under visible light irradiation.[13g,13j–m] Visible light is highly attractive, as it is lower in energy than UV light and therefore safer to work with and allows for greater functional group tolerance. Under such

conditions, C–X bond homolysis has not been shown to be possible. The Fu and Peters groups have shown that copper complex **1.3**, used to catalyze the alkylation of carbamates under visible light irradiation (eq 1.3), can undergo photoexcitation and have its excited state quenched by an alkyl bromide—likely through a single electron transfer event.[13l]

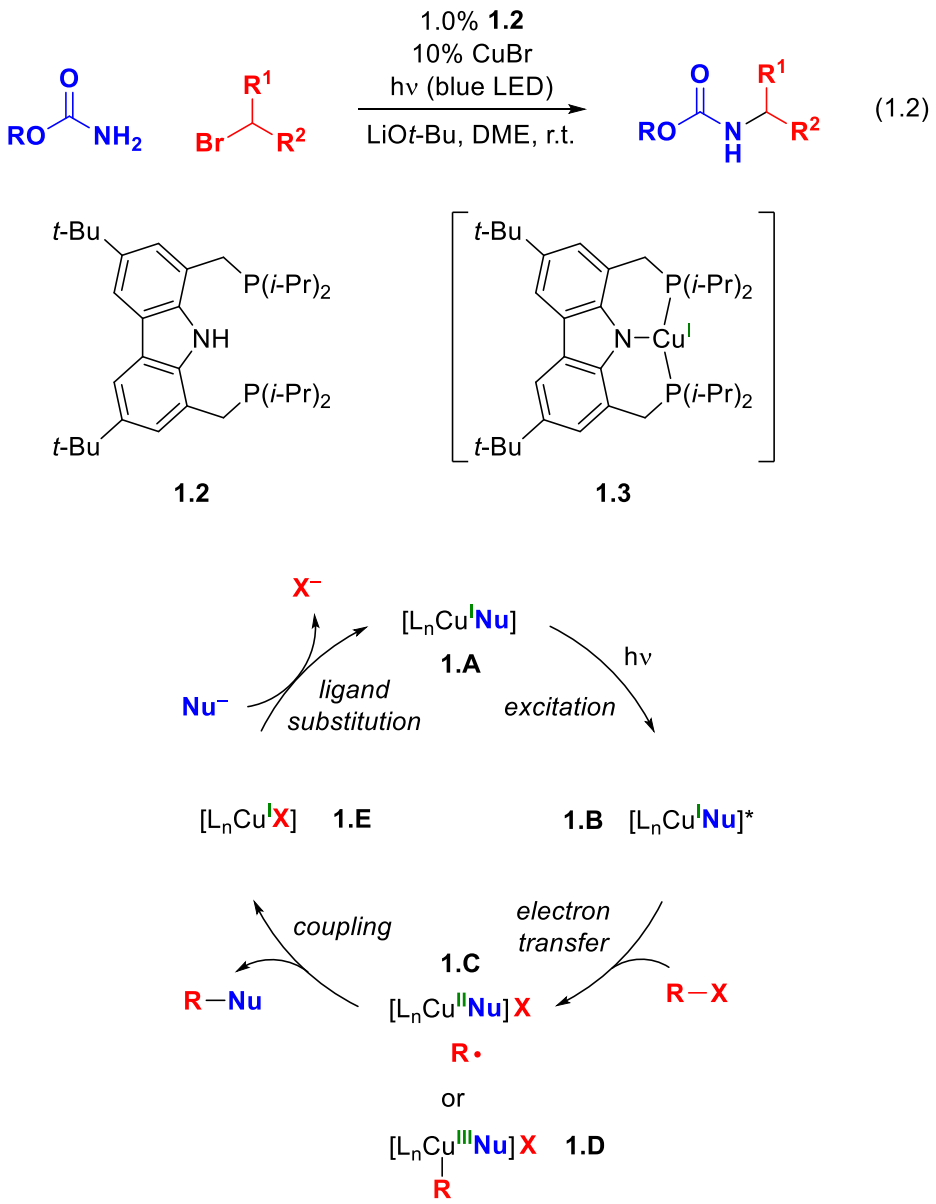


Figure 1.6. Outline of one of the possible pathways for photoinduced, copper-catalyzed cross-coupling reactions.

Based on previous studies by the Fu and Peters groups, a general mechanism (outlined in Figure 1.6) can be considered where a copper(I)-nucleophile complex (**1.A**) can undergo photoexcitation to **1.B**. **1.B** could then undergo single electron transfer to the electrophile generating a radical intermediate (**R•**) and copper(II) species **1.C**. It is not clear whether product is formed through recombination of **R•** and **1.C** to form copper(III) species **1.D** or rather directly reacts with the nucleophilic component of **1.C** and releases copper(I) species **1.E**. Mechanistic studies in the Fu and Peters are ongoing to elucidate this process.

Copper photocatalysis continues to be a powerful tool to construct new bonds, shows great promise for asymmetric reaction development and is rich in mechanistic details to uncover. This thesis will be primarily focused on the development of C–N bond forming reactions using copper and light and mechanistic studies of those transformations. Chapter 2 will discuss the first asymmetric alkylation of an amine using a copper catalyst under visible light irradiation (eq 1.2). Chapter 3 will discuss the development of a novel catalytic system capable of coupling aliphatic amines to unactivated secondary alkyl halides under visible light irradiation. Efforts to translate this reaction to the asymmetric variant will also be discussed. Chapter 4 will disclose a unique asymmetric, copper-catalyzed reaction to form C–N bonds, however, in the absence of light.

1.3. Nickel Catalysis

While copper photocatalysis has been an enabling tool for C_{sp3}–heteroatom bond formation, nickel catalysis is particularly adept at carbon-carbon bond formation. Traditionally, carbon-carbon bond formation has been dominated by palladium catalysis, but has been largely limited to C_{sp2}–C_{sp2} bond formation.[2] Efforts have been made to extend this reactivity to alkyl-alkyl bond constructions, but often facile β-hydride elimination of alkylmetal species has been limiting.[2] However, in recent years there have been tremendous efforts to catalyze the formation of C_{sp3}–C_{sp3} (alkyl-alkyl) bonds with alkyl electrophiles and organometallic nucleophiles. Particularly, there is great interest in constructing these bond

enantioselectively due to the growing interest in accessing chiral molecules in the pharmaceutical industry.[14]

A number of transition-metals (e.g., copper, palladium, manganese, iron) have been successful in catalyzing alkyl-alkyl cross-coupling reactions.[1,2] However, nickel has been a standout in its versatility and ability to catalyzed enantioselective reactions with secondary and tertiary alkyl electrophiles.[12,14,15] Initial mechanistic studies of nickel-catalyzed alkyl-alkyl cross-coupling systems describe the formation of radicals intermediates derived from alkyl electrophiles, suggesting a different mechanism from that outlined in Figure 1.4.[16–19] As mentioned earlier, the formation of alkyl radicals can lend themselves to enantioconvergent processes. There are likely unique mechanistic nuances to each combination of ligand, electrophile and nucleophile, but many of the reaction developed by the Fu group likely follow a mechanism proposed through studies done by the Fu group for the nickel-catalyzed Negishi arylations of propargylic bromides (Figure 1.7).[19] Here, nickel(I) species **1.F** can abstract a halide from the electrophile generating a radical intermediate and nickel(II) species **1.G**. Transmetallation could then occur to generate nickel(II)-alkyl **1.H**. Upon capturing the radical intermediate, nickel(III) species **1.I** can then reductively eliminate to form product and regenerate **1.F**.

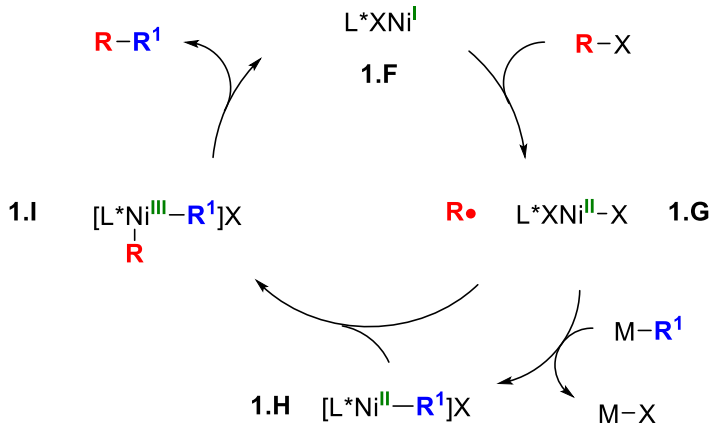


Figure 1.7. General outline for nickel-catalyzed reactions proceeding through a radical intermediate.

The Fu group has been very interested in enantioconvergent nickel-catalyzed alkyl-alkyl cross-couplings for a number of years. Various catalyst systems have been developed to target enantioconvergence through different approaches (Figure 1.8). A racemic electrophile can couple with an achiral organometallic nucleophile to access enantioenriched products. Conversely, a racemic nucleophile can react with an achiral alkyl electrophile to achieve a similar outcome. Coupling a racemic electrophile and a racemic nucleophile while controlling the stereochemical outcome of both stereocenters would be the ultimate goal for nickel-catalyzed alkyl-alkyl cross-couplings.

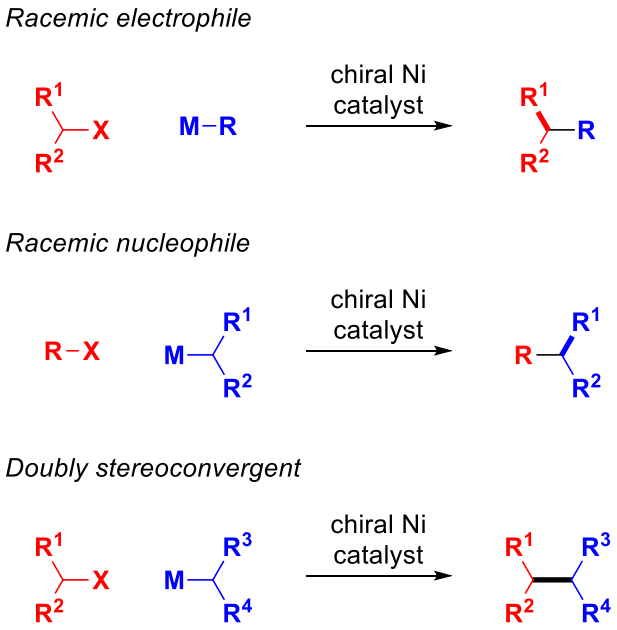


Figure 1.8. Reaction paradigms of nickel-catalyzed alkyl-alkyl cross-couplings.

Discussed within Chapter 5 of this thesis is the development of a nickel-catalyzed reaction utilizing a racemic electrophile and an achiral nucleophile (Figure 1.8, top). This paradigm is the most well-studied in the Fu group.[20] In general, a racemic alkyl electrophile requires a pendant directing group or a π system directly adjacent to the halide for high enantioselectivity (Figure 1.9). However, recent work has shown that α-trifluoromethyl[20t] and α-silyl[20x] electrophiles are capable of undergoing cross-coupling with high enantioselectivities. In the case of enantioconvergent arylations of α-trifluoromethyl alkyl

halides, it is unclear whether the stereoselectivity is due to the trifluoromethyl group acting as a directing group or as an electron-withdrawing group. However, α-halosilanes are unactivated alkyl electrophiles, as substitution of a carbon with a silicon does not significantly stabilize an adjacent radical.[21] To our knowledge, the coupling of α-halosilanes with alkylzinc reagents is the first example of an enantioconvergent nickel-catalyzed cross-coupling reaction with an electrophile lacking both a directing and an activating group. This transformation will be discussed in Chapter 5.

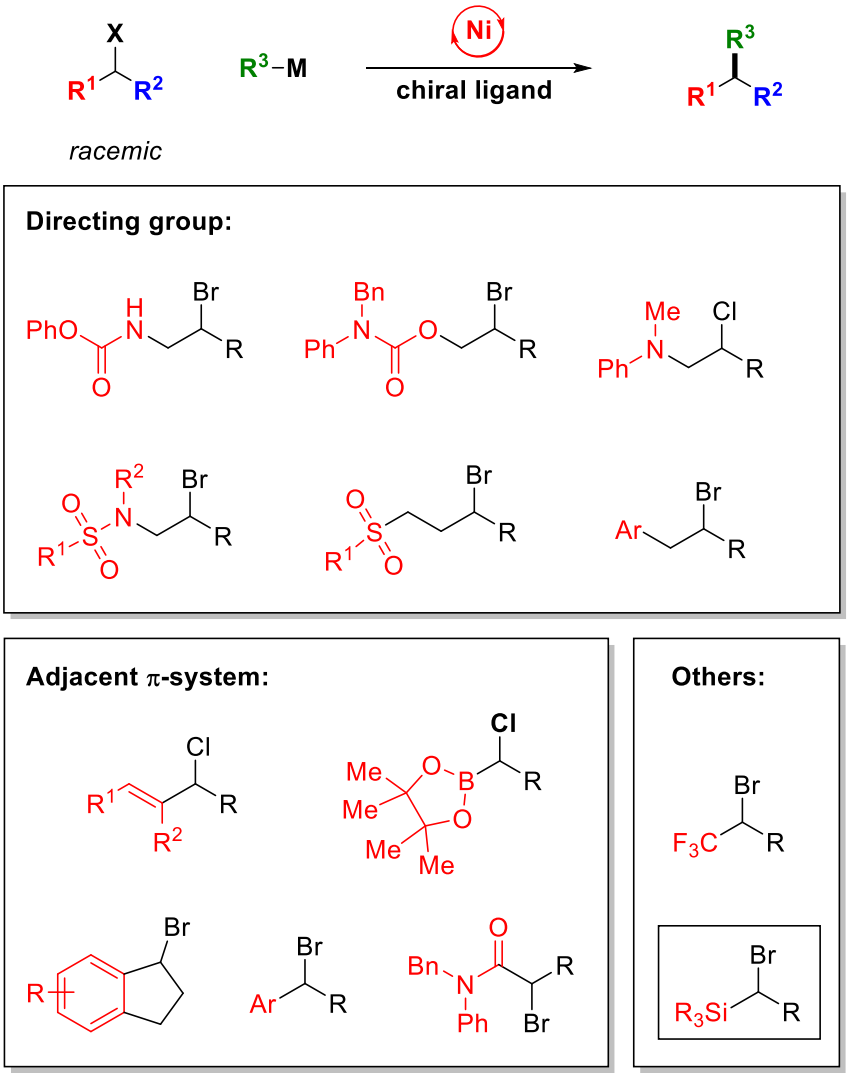


Figure 1.9. Various classes of racemic electrophiles used in nickel-catalyzed alkyl-alkyl cross-couplings.

1.4. Notes and References

1. Fu, G. C. *ACS Cent. Sci.*, **2017**, *3*, 692−700.
2. Choi, J.; Fu, G. C. *Science*, **2017**, *356*, 152–160.
3. Hartshorn, S. R. *Aliphatic Nucleophilic Substitution*; Cambridge University Press: London, 1973.
4. For a recent example of an enantioconvergent S_N1 reaction, see: Wendlandt, A. E.; Vangal, P.; Jacobsen, E. N. *Nature*, **2018**, *556*, 447–451.
5. *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C.; Studer, A., Eds.; John Wiley & Sons, Chichester, U.K., 2012; Vols. 1 and 2.
6. *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A.; Brase, S.; Oestreich, M., Eds.; Wiley¨−VCH: Weinheim, Germany, 2014.
7. Labinger, J. A. *Organometallics* **2015**, *34*, 4784−4795.
8. Jahn, U. *Top. Curr. Chem.* **2011**, *320*, 323−452.
9. Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. *Angew. Chem. Int. Ed*. **2017**, *56*, 16136–16179.
10. For recent reviews, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev*. **2013**, *113*, 5322–5363. (b) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176. (c) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 0052. (d) Paria, S.; Reiser, O. *ChemCatChem.* **2014**, *6*, 2477–2483.
11. (a) Harkins, S. B.; Peters, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 2030–2031. (b) Mankad, N. P.; Rivard, E.; Harkins, S. B.; Peters, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16032–16033. (c) Miller, A. J. M.; Dempsey, J. L.; Peters, J. C. *Inorg. Chem.* **2007**, *46*, 7244–7246. (d) Harkins, S. B.; Mankad, N. P.; Miller, A. J. M.; Szilagyi, R. K.; Peters, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 3478–3485. (e) Mankad, N. P.; Harkins, S. B.; Antholine, W. E.; Peters, J. C. *Inorg. Chem.* **2009**, *48*, 7026–7032. (f) Lotito, K. J.; Peters, J. C. *Chem. Comm.* **2010**, *46*, 3690–3692. (g) Deaton, J.; Switalski, S.; Kondakov, D.; Young, R.; Pawlik, T.; Giesen, D.; Harkins, S.; Miller, A.; Mickenberg, S.; Peters, J. C. *J. Am. Chem.* Soc. **2010**, *132*, 9499–9508.
12. Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647–651.

13. (a) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129–5133. (b) Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 9548–9552. (c) Ziegler, D. T.; Choi, J.; Muñoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 13107–13112. (d) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162–2167. (e) Tan, Y.; Muñoz-Molina, J. M.; Fu, G. C.; Peters, J. C. *Chem. Sci.* **2014**, *5*, 2831–2835. (f) Ratani, T. S.; Bachman, S.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2015**, *137*, 13902–13907. (g) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016,** *351*, 681–684. (h) Johnson, M. W.; Hannoun, K., I.; Tan, Y.; Fu, G. C.; Peters, J. C. *Chem. Sci.*, **2016**, *7*, 4091–4100. (i) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.*, **2017**, 1*39*, 12716–12723. (j) Zhao, W.; Wurz, R. P.; Peters, J. P.; Fu, G. C. *J. Am. Chem. Soc.*, **2017**, 1*39*, 12153–12156. (k) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.*, **2017**, *139*, 17707–17710. (l) Ahn, J. M.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.*, **2017**, *139*, 18101–18106. (m) He, J.; Chen, C.; Fu, G. C.; Peters, J. C. *ACS Catal.*, **2018**, 8, 11741–11748.

14. Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587–9652.

15. Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 8347–8349.

16. Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175−13183.

17. Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192−16197.

18. Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. *J. Am. Chem. Soc.* **2013**, *135*, 12004−12012.

19. Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588−16593.

20. (a) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 4594–4595. (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (c) Saito, B.; Fu, G. C. *J. Am. Chem. Soc*. **2008**, *130*, 6694–6695. (d) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc*. **2008**, *130*, 12645–12647. (e) Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem. Int. Ed*. **2009**, *48*, 154–156. (f) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266. (g) Lou, S.;

Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 5010–5011. (h) Lundin, P.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029. (i) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909. (j) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157. (k) Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966–2999. (l) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794–5797. (m) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105. (n) Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006. (o) Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288–16291. (p) Cong, H.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 3788–3791. (q) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520–552. (r) Lee, S. Y.; Neufeind, S.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 8899–8902. (s) Choi, J.; Martín-Gago, P.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 12161–12165. (t) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015,** *137*, 9523–9526. (u) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. *Science*, **2016**, *354*, 1265–1269. (v) Mu, X.; Shibata, Y.; Makida, Y.; Fu, G. C. *Angew. Chem. Int. Ed.*, **2017**, *56*, 5821–5824. (w) Wang, Z.; Yin, H.; Fu, G. C. *Nature*, **2018**, *563*, 379–383. (x) Schwarzwalder, G. M.; Matier, C. D.; Fu, G. C. *Angew. Chem. Int. Ed.*, **2019**, *58*, 3571–3574.

21. Doncaster, A. M.; Walsh, R. *J. Chem. Soc., Faraday Trans. 1* **1976**, *72*, 2908–2916.

Chapter 2

ASYMMETRIC COPPER-CATALYZED C−N CROSS-COUPLINGS INDUCED BY VISIBLE LIGHT

Adapted in part with permission from:

Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C–N Cross-Couplings Induced by Visible Light. *Science* **2016,** *351*, 681–684. doi: 10.1126/science.aad8313

2.1. Introduction

Photochemistry can furnish reactive intermediates that would otherwise be difficult to access under synthetically useful conditions. Its application in organic synthesis has therefore expanded rapidly during the past decades,[1] most recently in the context of enantioselective photoredox catalysis with transition metals.[2–4] With several recent noteworthy exceptions, each of which involves the α-functionalization of carbonyl compounds by a chiral iridium catalyst,[5–7] the metal-catalyzed methods require two catalysts, a transition metal complex that undergoes photoexcitation and serves as a site for redox chemistry, as well as a separate chiral catalyst that effects enantioselective bond formation. Transition metal-free asymmetric photoredox catalysis has also been reported.[8,9]

We have been interested in photocatalytic approaches to the construction of C–N bonds,[10] given the high value of amines in fields ranging from biology to chemistry to materials science.[11] Whereas initial efforts to develop transition metal-catalyzed C–N cross-coupling reactions focused on the use of aryl and alkenyl halides as the electrophilic coupling partner,[12,13] during the past few years, alkyl halides that are not suitable substrates for classic S_N2 reactions have emerged as useful coupling partners under the combined action of light and copper catalysis.[14,15] To date progress has not yet been reported in the development of

an asymmetric variant of these reactions, and the use of copper as a photoredox catalyst[16] is uncommon by comparison with precious metals such as iridium and ruthenium. Here we describe a copper-catalyzed enantioconvergent cross-coupling of racemic tertiary alkyl halides that is induced by visible light, a process that lies at the intersection of several important dimensions of modern chemical catalysis (Figure 2.1A).

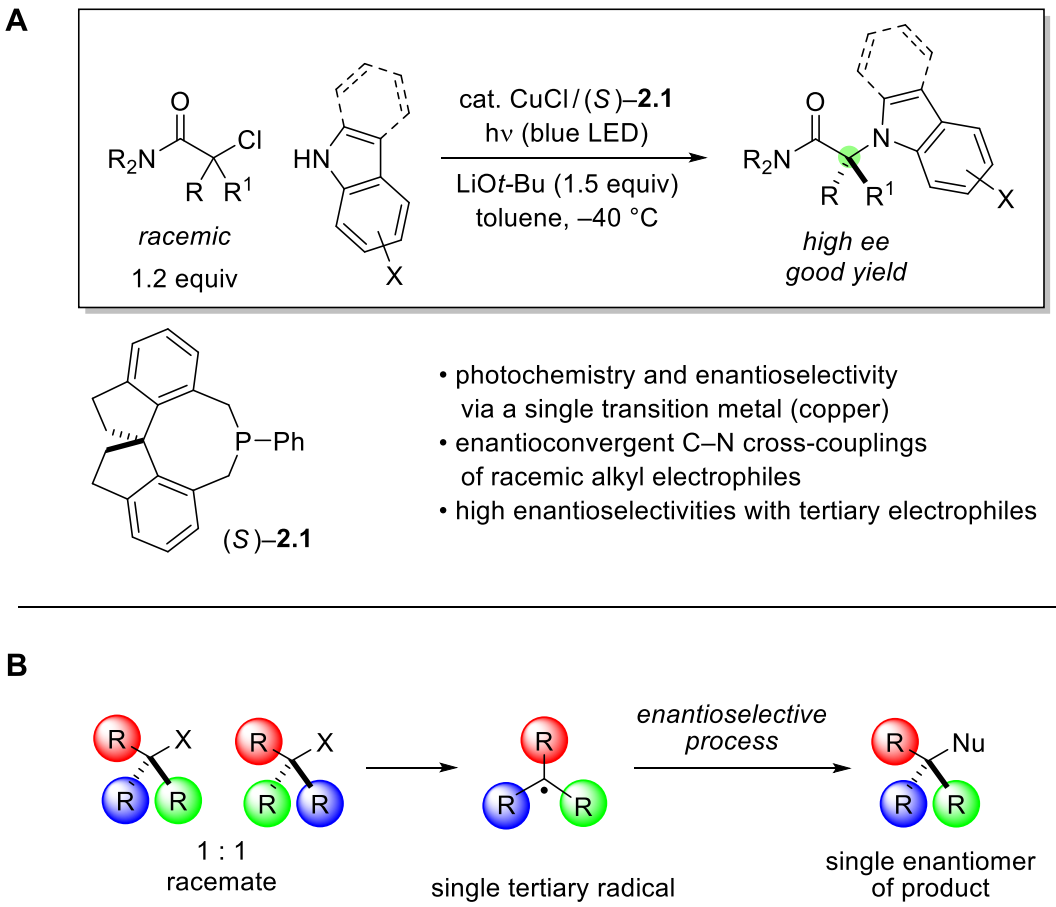


Figure 2.1. A photocatalytic approach to the asymmetric synthesis of amines. (**A**) Asymmetric copper-catalyzed C–N cross-couplings induced by visible light. (**B**) Outline of a strategy for the enantioconvergent cross-coupling of a racemic tertiary alkyl halide via a radical intermediate.

Although considerable advances have recently been reported in the development of enantioconvergent cross-couplings of racemic secondary alkyl electrophiles with carbon

nucleophiles to form C–C bonds,[17–19] no highly effective methods have yet been described for tertiary alkyl halides, which require differentiation by the catalyst of three distinct carbon substituents in order to furnish high enantioselectivity. Indeed, in the field of asymmetric synthesis as a whole, highly stereoselective reactions of tertiary electrophiles are relatively uncommon, despite the fact that fully substituted carbons are a common motif in organic molecules.[20] We anticipated that the radical mechanism that we have postulated for C–X bond cleavage in the presence of copper and light (vide infra)[14,15] might enable us to surmount this challenge, because a single, comparatively stable tertiary radical could be formed from a racemic mixture of electrophiles (Figure 2.1B).

Another issue was whether common chiral ligands such as phosphines would even bind to copper, much less induce high enantioselectivity in the C–N bond-forming process, in the presence of a much more abundant nucleophilic coupling partner. Indeed, the previously described methods for photoinduced, copper-catalyzed N-alkylation had employed CuI as a pre-catalyst with no added ligand.[14,15]

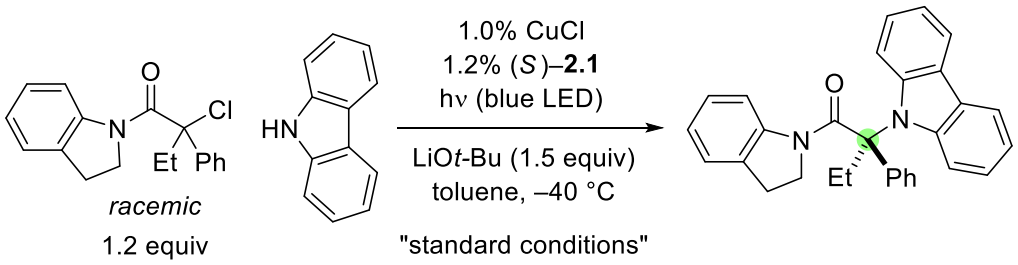
2.2. Results and Discussion

2.2.1. Optimization

As a model coupling process, we examined the reaction of carbazole, a heterocycle that occurs in bioactive molecules, including N-*tert*-alkyl-substituted compounds,[21,22] with an α-halocarbonyl compound, a class of electrophiles that has not previously been employed in photoinduced, copper-catalyzed cross-couplings. Upon investigating a range of reaction parameters, we discovered that irradiation of the cross-coupling partners at –40 °C for 16 hours in the presence of CuCl, a chiral phosphine (**2.1**), and a Brønsted base provides the desired product in 95% yield and 95% enantiomeric excess (ee) (Table 2.1, entry 1). In contrast to our earlier studies of photoinduced, copper-catalyzed N-alkylations, this process operates under visible light from a blue LED (rather than an ultraviolet source) and at relatively low catalyst loading (1.0 mol% rather than 10 mol%); a catalyst loading of 0.25 mol% led to only a modest loss in yield and no erosion in ee (entry 2: ~300 turnovers;

previously, the highest turnover number for a photoinduced, copper-catalyzed N-alkylation was ~9).[14,15]

Table 2.1. Asymmetric copper-catalyzed C–N cross-couplings induced by visible light: Effect of reaction parameters.



entry	change from the "standard conditions"	yield (%)[a]	ee (%)
1	**none**	**95**	**95**
2	CuCl (0.25 mol%), (*S*)–**2.1** (0.30 mol%)	77	95
3	no CuCl	<1	–
4	no hν	<1	–
5	no (*S*)–**2.1**	3	0
6	added water (0.10 equiv)	83	94

[a]Yields were determined through analysis by ^{1}H NMR spectroscopy (average of two experiments).

Control experiments established that copper (Table 2.1, entry 3; the alkyl halide is recovered quantitatively) and light (entry 4) are necessary to achieve C–N bond formation under these conditions. Furthermore, essentially no C–N coupling (<1%) occurs when the tertiary alkyl chloride, carbazole, and LiO*t*-Bu are heated at 80 °C in toluene for 16 hours. Our concern that a phosphine (e.g., **2.1**) might not bind effectively to copper in the presence of a stoichiometric quantity of the nucleophile appears to be unfounded, as evidenced by our observation of high enantiomeric excess in the C–N coupling (entry 1) and of enhanced rate in the presence of the ligand (ligand-accelerated catalysis[23]: entry 1 vs. entry 5). From a practical point of view, it is worth noting that CuCl and the chiral phosphine are commercially available and that the process is not highly moisture-sensitive (entry 6).

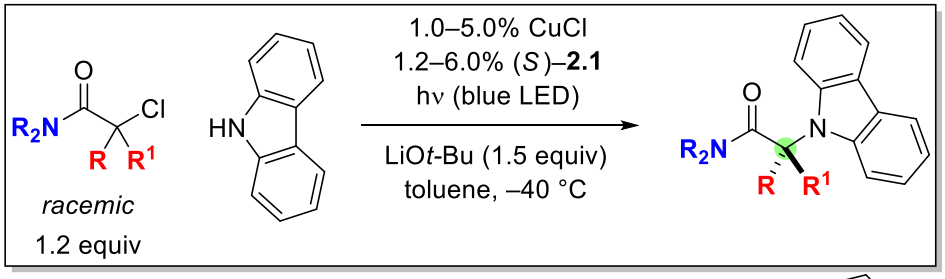
2.2.2. Scope of Reactivity

We have examined the scope of this photoinduced, copper-catalyzed method for enantioconvergent N-alkylation by racemic tertiary alkyl halides (Figure 2.2). For couplings of carbazole with N-acylindoline-derived electrophiles, good to excellent yields and enantioselectivities are observed with a range of substituents in the α position of the electrophile (entries 1–6). In the case of α,α-dialkyl-substituted electrophiles (entries 5 and 6), the catalyst selectively discriminates between two alkyl groups, including a methyl and an isobutyl group (entry 6), to furnish high ee.

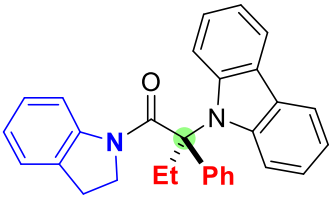
To gain insight into the compatibility of various functional groups with these conditions for enantioconvergent C–N cross-couplings of tertiary alkyl halides, we have examined the impact of additives (1.0 equivalent) on the course of the coupling process depicted in Figure 2.2, entry 1. We determined that an unactivated secondary alkyl bromide (cyclohexyl bromide), a ketone (2-nonanone), a secondary alcohol (5-nonanol), an ester (methyl octanoate), an alkene (*cis*- or *trans*-5-decene), an alkyne (5-decyne), and a nitrile (valeronitrile) have no adverse impact on the yield/enantioselectivity and can be recovered intact at the end of the cross-coupling, whereas a primary amine (3-phenylpropylamine) and an aldehyde (octanal) impede N-alkylation.

The introduction of an electron-donating or an electron-withdrawing substituent onto the indoline does not compromise the efficiency of the cross-coupling (Figure 2.2, entries 7 and 8). If desired, N-acylindolines can be transformed into primary alcohols or carboxylic acids.[24] A variety of other α-haloamides are also suitable electrophilic cross-coupling partners (entries 9–11), including a Weinreb amide (entry 11), which is important in synthesis because it serves as a useful precursor to ketones.[25]

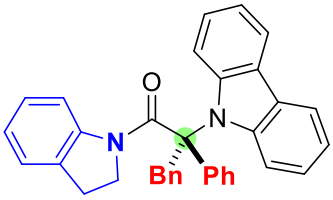
With respect to the nucleophilic coupling partner, substituted carbazoles are also suitable substrates (Figure 2.3, entries 1–5); the enantioconvergent C–N cross-coupling can be conducted on a gram-scale with a similar outcome (entry 2: 1.29 g of product, 94% yield, 94% ee). Indoles can also be employed as nucleophiles in these photoinduced, copper-



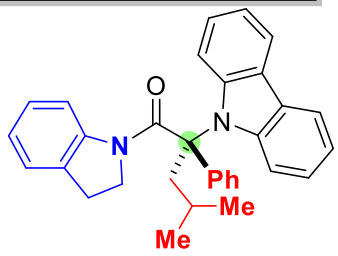
Variation of the α substituents:



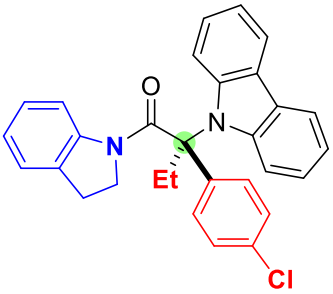
entry 1: 90% yield, **94% ee**



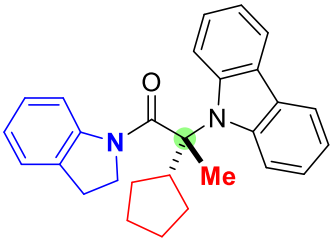
entry 2: 77% yield, **94% ee**



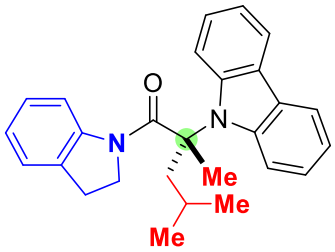
entry 3: 82% yield, **99% ee**



entry 4: 85% yield, **92% ee**

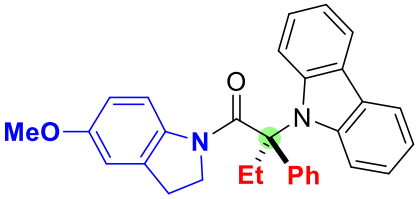


entry 5: 84% yield, **98% ee**

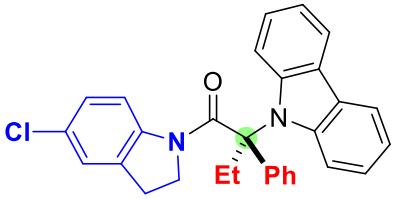


entry 6: 90% yield, **87% ee**

Electronic effects of the amide group:

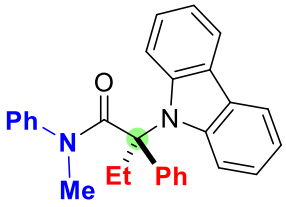


entry 7: 92% yield, **92% ee**

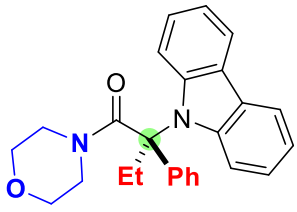


entry 8: 90% yield, **96% ee**

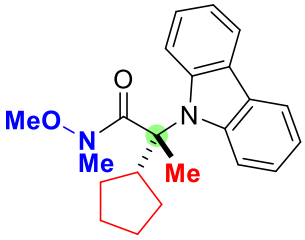
Variation of the amide:



entry 9: 79% yield, **94% ee**



entry 10: 74% yield, **90% ee**



entry 11: 73% yield, **95% ee**

Figure 2.2. Scope with respect to the electrophile (yields determined after purification).

catalyzed couplings, furnishing the desired product with good yield and enantioselectivity (entries 6–9). Because indoles are common subunits in bioactive compounds,[26] and natural products with a tertiary N-alkyl substituent are known,[27,28] these represent a useful addition to the limited nitrogen nucleophiles compatible with metal-catalyzed C–N alkylations.[14,15]

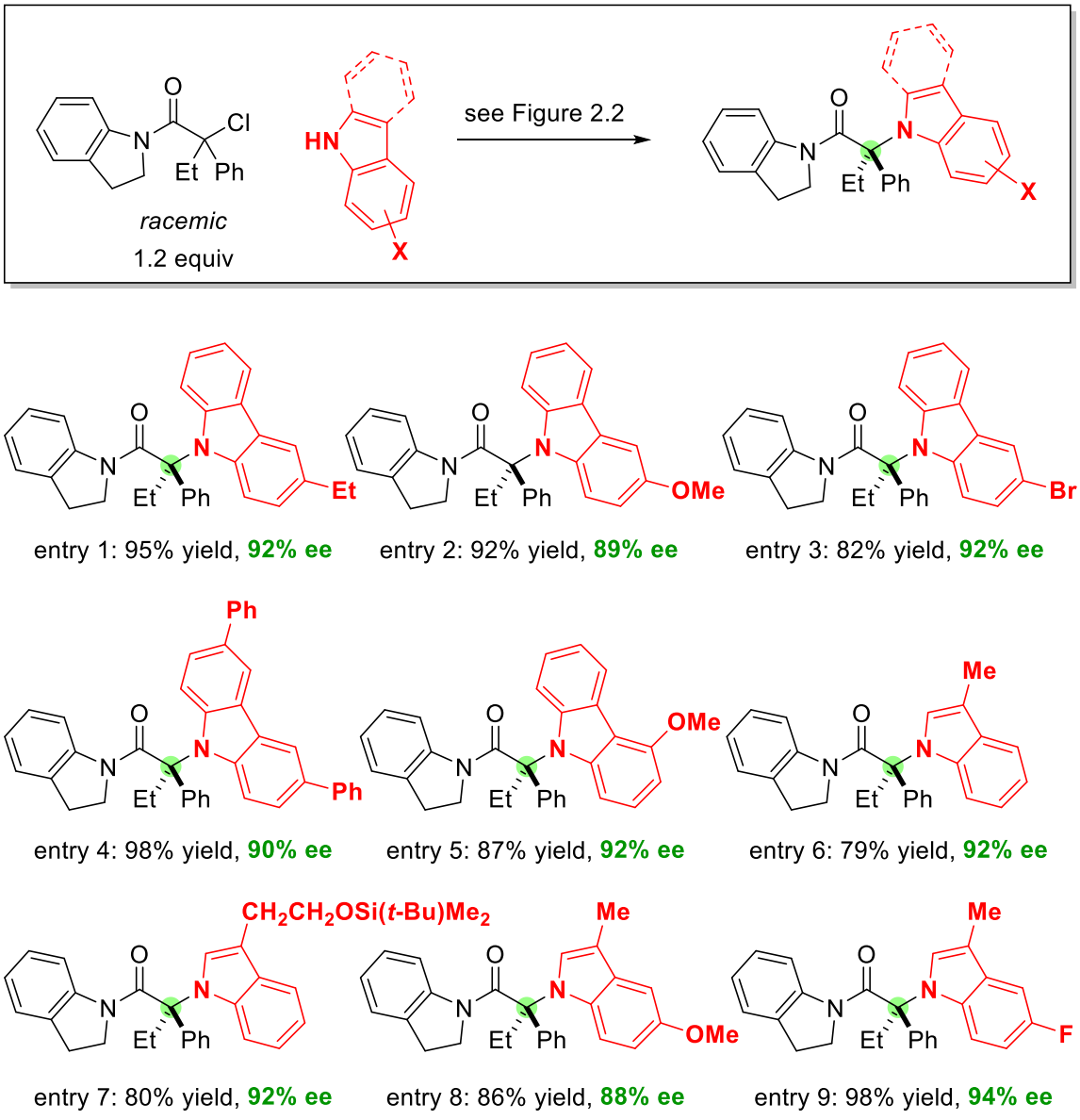
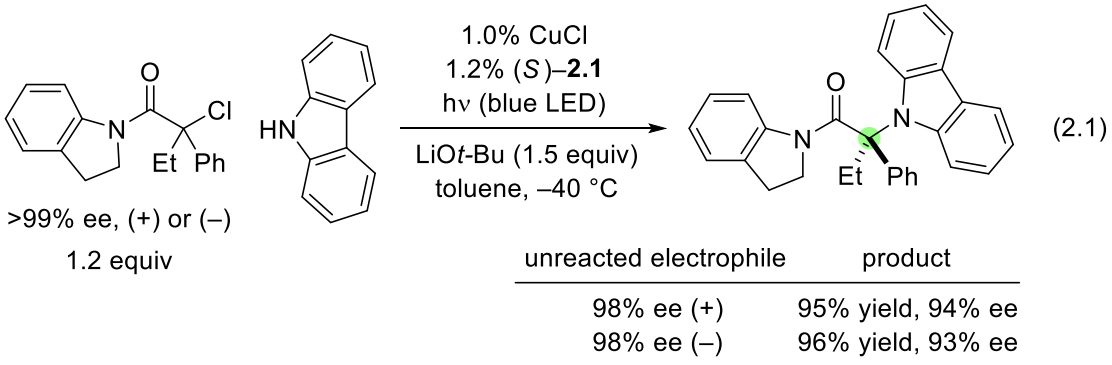


Figure 2.3. Scope with respect to the nucleophile (yields determined after purification).

2.2.3. Mechanistic Insights

Because we are able to obtain the cross-coupling product in high yield and ee when using only 1.2 equivalents of a racemic electrophile, it is evident that both enantiomers of the electrophile can be transformed under the reaction conditions into a particular enantiomer of the product (enantioconvergence), although not necessarily at identical rates (kinetic resolution[29]). To gain insight into whether a kinetic resolution was occurring, we measured the ee of the unreacted tertiary alkyl halide at the end of the cross-coupling depicted in Figure 2.2, entry 1. Our observation that the recovered electrophile is racemic suggests either that the enantiomeric substrates are reacting at essentially identical rates (i.e., no kinetic resolution) or that in situ racemization of the electrophile is occurring. Through the use of enantiopure alkyl halides, we established that virtually no racemization takes place under the reaction conditions (eq 2.1). These couplings with enantiopure electrophiles further establish that the chiral ligand very effectively controls the absolute configuration of the product, regardless of the stereochemistry of the starting electrophile, and that C–Cl bond cleavage is essentially irreversible.



An outline of a possible mechanism for photoinduced, copper-catalyzed C–N couplings of alkyl halides is illustrated in Figure 2.4.[14,15] Irradiation of a copper–nucleophile complex (**2.A**) could lead to an excited-state adduct (**2.B**) that would then engage in electron transfer with the alkyl halide (R–X) to generate an alkyl radical; next, Nu–R bond formation could occur through an inner-sphere pathway involving a copper–nucleophile complex (**2.C**). In contrast to most asymmetric photoredox reactions catalyzed by transition metals,[2–4]

a single metal (copper) appears to be responsible for both the photochemistry and the enantioselective bond-forming process. The binding of the nucleophile to copper in situ to form a copper complex that can serve as a photoreductant is important in this outline.

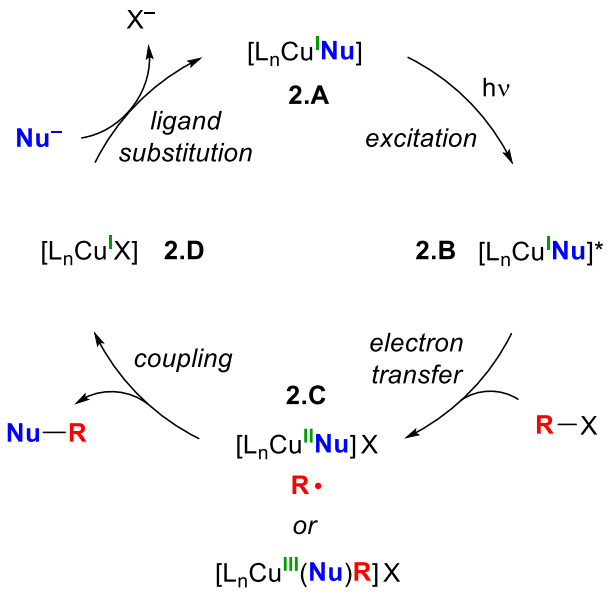


Figure 2.4. Outline of a possible pathway for photoinduced, copper-catalyzed C–N cross-couplings of alkyl halides.

We have synthesized and crystallographically characterized a copper complex that includes the chiral phosphine and the carbazolide nucleophile, ((*R*)–**2.1**)$_2$Cu(carbazolide) (**2.2**; Figure 2.5A). The three ligands are arranged in a trigonal planar geometry around copper. When complex **2.2** (1.0 mol%) is employed in place of CuCl/**2.1** under our standard reaction conditions, the yield and the ee of the C–N cross-coupling product are essentially unchanged (92% yield, 94% ee; cf. Figure 2.2, entry 1: 95% yield, 95% ee). Furthermore, irradiation of complex **2.2** in the presence of a stoichiometric amount of a racemic tertiary alkyl halide leads to C–N bond formation in good yield and with enantioselectivity that is comparable to the catalyzed process (Figure 2.5B; cf. Figure 2.2, entry 1: 95% ee); no coupling occurs in the absence of light. Collectively, these observations are consistent with the suggestion that complex **2.2**, or a copper/carbazolide/**2.1** species that can be derived from **2.2**, is a plausible intermediate in the catalytic cycle.

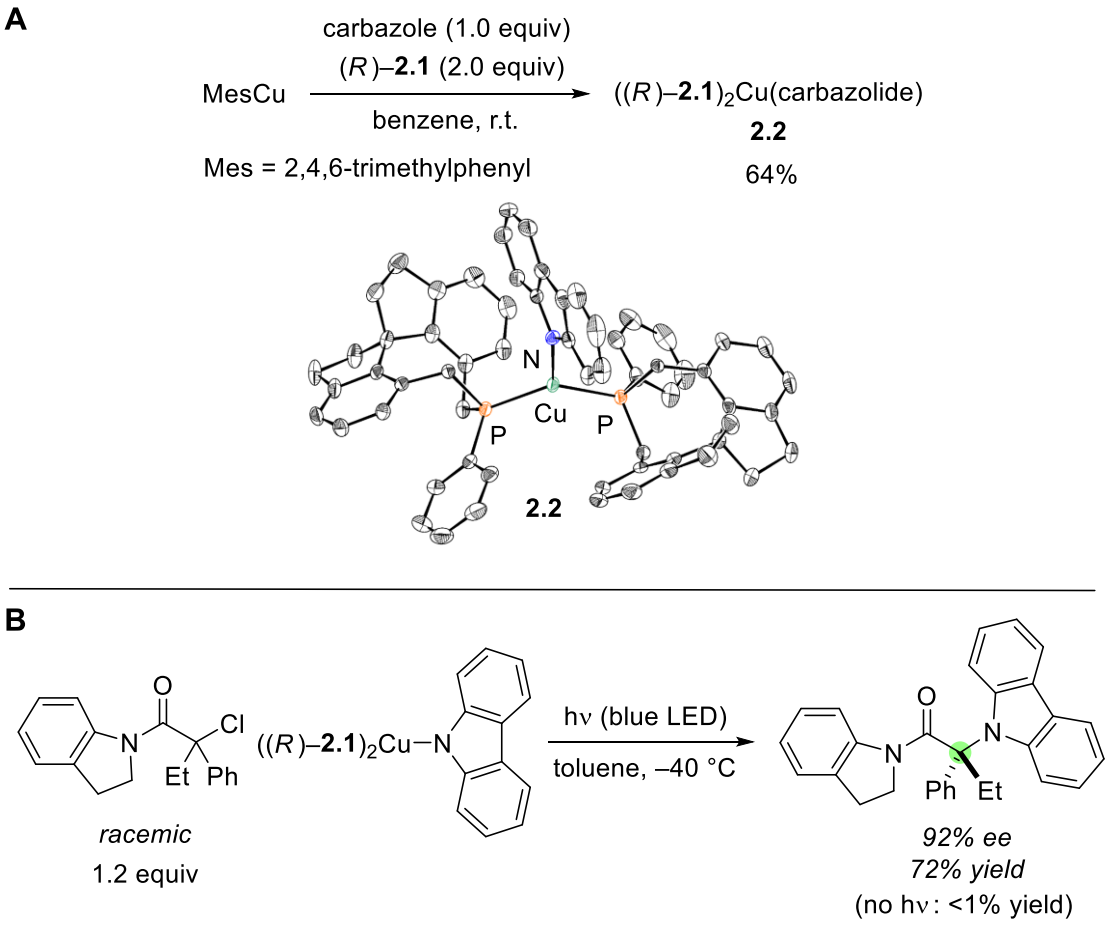


Figure 2.5. (**A**) Synthesis and structural characterization of ((*R*)−**2.1**)$_2$Cu(carbazolide) (thermal ellipsoids drawn at 50% probability and H atoms omitted for clarity). (**B**) Stoichiometric cross-coupling reaction with isolated ((*R*)−**2.1**)$_2$Cu(carbazolide).

2.3 Conclusions

Whereas enantioconvergent metal-catalyzed cross-couplings of racemic secondary alkyl halides have recently emerged as powerful tools for C–C bond construction, there has been little progress in corresponding C–heteroatom bond-forming processes or in the use of tertiary alkyl halides as coupling partners. Herein, we have established that, with the aid of visible light, a copper-based chiral catalyst derived from commercially available components can achieve enantioconvergent C–N cross-coupling reactions of racemic tertiary alkyl chlorides with good to excellent enantioselectivity. In contrast to nearly all metal-catalyzed

asymmetric photoredox methods described to date, which employ separate catalysts to effect redox chemistry and bond formation, in this method a single catalyst is responsible for the photochemistry and for the enantioselective bond construction. This work stands at a previously unexplored intersection of asymmetric synthesis, catalysis with Earth-abundant metals, photoinduced processes, and cross-coupling reactions of alkyl electrophiles, each of which represents an important current theme in chemical synthesis. We anticipate that our observations comprise the initial advances in a fertile area of asymmetric catalysis: the enantioconvergent synthesis of secondary and tertiary C–heteroatom bonds through photoinduced transition metal-catalyzed couplings of alkyl halides.

2.4. Experimental Section

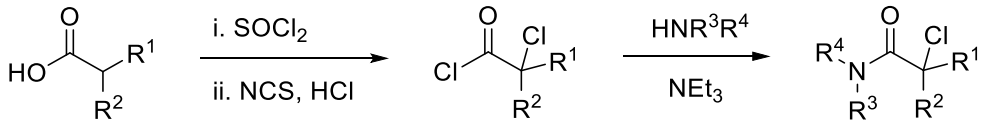
2.4.1. General Information

All manipulations of air-sensitive materials were carried out in oven-dried glassware using standard Schlenk or glovebox techniques under an N_2 atmosphere. Unless otherwise noted, chemicals were purchased from commercial suppliers and used as received. CH_2Cl_2, THF, and toluene were purified and dried using a solvent-purification system that contained activated alumina. Indoline (Aldrich), NEt_3 (EMD), $SOCl_2$ (Alfa), and SO_2Cl_2 (Acros) were distilled prior to use. Carbazole (Aldrich) and 3-methyl-indole (Aldrich) were recrystallized. Ligand (*S*)–**2.1** was purchased from Strem (>99.9% ee) and used without further purification. Ligand (*R*)–**2.1** was purchased from Strem (>98.6% ee) and was purified on preparative HPLC in the P-oxide form using a Daicel CHIRALPAK® AD column (80% *i*-PrOH/hexanes, 10.0 mL/min; (*S*)–**2.1** oxide: 8.6 min, (*R*)–**2.1** oxide: 24.6 min). The enantiopure ligand (>99.9% ee) was then obtained by reduction in analogy to a reported procedure.[30] ^1H and ^{13}C NMR data were collected on a Bruker 400 MHz or a Varian 500 MHz spectrometer at ambient temperature unless otherwise noted. 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). ATR-IR measurements were carried out on a Thermo Scientific Nicolet iS5 FT-IR spectrometer

equipped with an iD5 ATR accessory. Blue LED lamps (32W; Kessil H150 Blue) were used to irradiate the reaction mixtures.

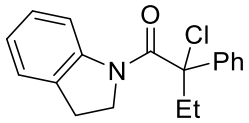
2.4.2 Preparation of Electrophiles

These procedures have not been optimized.



Representative Procedure A for the Synthesis of α-Chloro Amides: This is based on previously published procedures.[31,32] The carboxylic acid (25 mmol) was dissolved in $SOCl_2$ (7.25 mL, 100 mmol), and the resulting solution was heated at reflux at 80 °C for 30 min with vigorous stirring ($CaCl_2$ drying tube). The mixture was allowed to cool to r.t., and then *N*-chlorosuccinimide (8.34 g, 63 mmol), $SOCl_2$ (5 mL), and HCl (concentrated; 4 drops) were added. The resulting mixture was heated at 90 °C for 2.5 h. The mixture was then allowed to cool to r.t., the precipitate was removed by filtration, and the solvent was removed by evaporation. The resulting liquid residue was distilled into an ice-cooled flask.

Next, triethylamine (4.2 mL, 30 mmol) and the α-chloro acid chloride were added dropwise to a solution of a secondary amine (20 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The stirring was continued at 0 °C for 15 min and then at r.t. for 3 h. Next, an aqueous solution of HCl (1 M; 50 mL) was added, and the organic layer was separated. The organic phase was washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum.



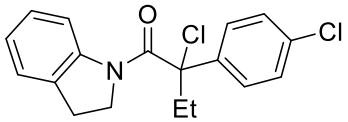
2-Chloro-1-(indolin-1-yl)-2-phenylbutan-1-one. The title compound was prepared from 2-phenylbutyric acid and indoline following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless solid (88% yield over 2 steps). The enantiomers of the title compound can be separated by preparative HPLC on a Daicel CHIRALPAK® AD column (3% *i*-PrOH/ hexanes, 10 mL/min, internal diameter 20 mm, column length 250 mm, particle size 5 µm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.42 – 7.28 (m, 3H), 7.28 – 7.19 (m, 1H), 7.14 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.05 (td, *J* = 7.4, 1.1 Hz, 1H), 4.17 (ddd, *J* = 10.9, 9.6, 6.5 Hz, 1H), 3.06 (ddd, *J* = 11.0, 9.7, 6.6 Hz, 1H), 2.93 (ddd, *J* = 16.1, 9.5, 6.7 Hz, 1H), 2.73 (ddd, *J* = 15.9, 9.6, 6.6 Hz, 1H), 2.53 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.30 (dq, *J* = 14.5, 7.2 Hz, 1H), 0.86 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 144.0, 139.0, 131.7, 128.7 (2C), 128.1, 127.5, 126.0 (2C), 124.6, 124.5, 118.3, 76.6, 49.2, 37.8, 28.8, 8.8;

FT-IR (ATR) 2965, 1656, 1477, 1460, 1445, 1120, 861, 761, 751, 697 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{18}H_{19}ClNO$: 300.1150, found: 300.1140.



2-Chloro-2-(4-chlorophenyl)-1-(indolin-1-yl)butan-1-one. The title compound was prepared from 2-(4-chlorophenyl)butanoic acid and indoline following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless solid (34% yield over 2 steps).

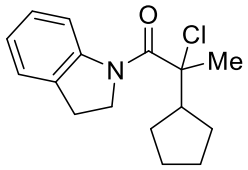
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.1 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.38 – 7.32 (m, 2H), 7.27 – 7.19 (m, 1H), 7.15 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.06 (td, *J* = 7.4, 1.1 Hz, 1H), 4.17 (ddd, *J* = 10.9, 9.6, 6.6 Hz, 1H), 3.10 (ddd, *J* = 10.9, 9.7, 6.5 Hz, 1H), 2.95 (ddd, *J* = 16.0,

9.6, 6.5 Hz, 1H), 2.77 (ddd, *J* = 15.9, 9.7, 6.6 Hz, 1H), 2.51 (dq, *J* = 14.5, 7.2 Hz, 1H), 2.26 (dq, *J* = 14.5, 7.2 Hz, 1H), 0.86 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 143.8, 137.8, 134.1, 131.6, 129.0 (2C), 127.6, 127.4 (2C), 127.3, 124.6, 118.3, 75.9, 49.3, 37.7, 28.8, 8.7;

FT-IR (ATR) 2973, 2935, 1649, 1477, 1384, 1334, 1092, 1012, 816, 759 cm^{-1};

HRMS (ESI) *m/z* $(M–Cl)^+$ calcd for $C_{18}H_{17}ClNO$: 298.0993, found: 298.0990.



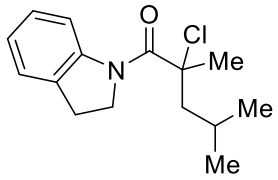
2-Chloro-2-cyclopentyl-1-(indolin-1-yl)propan-1-one. The title compound was prepared from 2-cyclopentylpropanoic acid and indoline following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless solid (32% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.21 (m, 1H), 7.26 (tq, *J* = 6.8, 0.9 Hz, 2H), 7.11 (td, *J* = 7.3, 1.1 Hz, 1H), 4.62 (ddd, *J* = 10.8, 8.8, 6.6 Hz, 1H), 4.50 (ddd, *J* = 10.8, 9.0, 7.7 Hz, 1H), 3.27 – 3.10 (m, 2H), 2.99 – 2.86 (m, 1H), 2.01 (ddtt, *J* = 12.6, 8.9, 6.1, 3.6 Hz, 1H), 1.85 (s, 3H), 1.81 – 1.47 (m, 7H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 144.4, 131.6, 127.4, 124.5, 124.4, 118.7, 74.4, 50.6, 48.4, 29.5, 28.9, 28.1, 26.2, 25.9, 25.4;

FT-IR (ATR) 2939, 2861, 1637, 1595, 1479, 1386, 1369, 1333, 1265, 1067, 904, 751, 712, 690 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{16}H_{21}ClNO$: 278.1306, found: 278.1311.



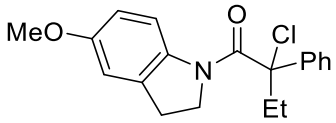
2-Chloro-1-(indolin-1-yl)-2,4-dimethylpentan-1-one. The title compound was prepared from 2,4-dimethylpentanoic acid and indoline following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless solid (37% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.17 (m, 1H), 7.26 (ddt, *J* = 7.9, 6.8, 0.9 Hz, 2H), 7.11 (td, *J* = 7.3, 1.1 Hz, 1H), 4.76 (ddd, *J* = 10.7, 9.2, 6.2 Hz, 1H), 4.31 (ddd, *J* = 10.7, 9.3, 7.4 Hz, 1H), 3.30 – 3.08 (m, 2H), 2.25 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.13 (dd, *J* = 14.4, 5.3 Hz, 1H), 1.96 (s, 3H), 1.93 – 1.82 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 144.2, 131.6, 127.5, 124.5, 124.4, 118.6, 70.3, 50.4, 50.0, 29.8, 29.4, 25.9, 24.6, 23.3;

FT-IR (ATR) 2963, 2870, 1635, 1596, 1476, 1393, 1377, 1259, 1171, 1068, 889, 750 672 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{15}H_{21}ClNO$: 266.1306, found: 266.1309.



2-Chloro-1-(5-methoxyindolin-1-yl)-2-phenylbutan-1-one. The title compound was prepared from 2-phenylbutyric acid and 5-methoxyindoline following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless solid (76% yield over 2 steps).

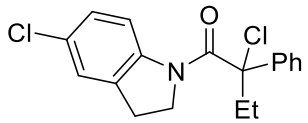
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.9 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.40 – 7.34 (m, 2H), 7.35 – 7.28 (m, 1H), 6.76 (ddt, *J* = 8.9, 2.8, 0.8 Hz, 1H), 6.70 (ddd, *J* = 2.5, 1.4, 0.9 Hz, 1H), 4.15 (ddd, *J* = 11.0, 9.6, 6.4 Hz, 1H), 3.78 (s, 3H), 3.05 (ddd, *J* = 11.0, 9.6, 6.6 Hz, 1H),

2.95 – 2.85 (m, 1H), 2.75 – 2.65 (m, 1H), 2.53 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.29 (dq, *J* = 14.4, 7.2 Hz, 1H), 0.86 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 156.9, 139.2, 137.6, 133.3, 128.7 (2C), 128.0, 126.0 (2 C), 118.9, 111.9, 110.8, 76.5, 55.8, 49.3, 37.7, 29.0, 8.8;

FT-IR (ATR) 2933, 2833, 1640, 1594, 1485, 1385, 1267, 1191, 1032, 859, 841, 752, 699 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{19}H_{21}ClNO_2$: 330.1255, found: 330.1250.



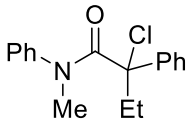
2-Chloro-1-(5-chloroindolin-1-yl)-2-phenylbutan-1-one. The title compound was prepared from 2-phenylbutyric acid and 5-chloroindoline following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless solid (76% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.7 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.40 – 7.35 (m, 2H), 7.35 – 7.30 (m, 1H), 7.19 (ddt, *J* = 8.7, 2.3, 0.8 Hz, 1H), 7.09 (dt, *J* = 2.2, 1.1 Hz, 1H), 4.18 (ddd, *J* = 11.0, 9.7, 6.5 Hz, 1H), 3.06 (ddd, *J* = 11.0, 9.7, 6.7 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.76 – 2.66 (m, 1H), 2.51 (dq, *J* = 14.5, 7.2 Hz, 1H), 2.28 (dq, *J* = 14.5, 7.2 Hz, 1H), 0.86 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 142.7, 138.8, 133.5, 129.4, 128.8 (2 C), 128.2, 127.4, 125.9 (2 C), 124.7, 119.1, 76.4, 49.3, 37.7, 28.6, 8.7;

FT-IR (ATR) 2972, 2931, 1657, 1468, 1374, 1329, 1169, 862, 836, 753, 699 cm^{-1};

HRMS (ESI) *m/z* $(M–Cl)^+$ calcd for $C_{18}H_{17}ClNO$: 298.0993, found: 298.0980.



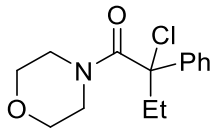
2-Chloro-*N*-methyl-*N*,2-diphenylbutanamide. The title compound was prepared from 2-phenylbutyric acid and *N*-methylaniline following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless oil (72% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 6.62 (m, 10H), 3.11 (br s, 3H), 2.46 (dt, *J* = 14.5, 7.1 Hz, 1H), 2.24 (dq, *J* = 14.5, 7.2 Hz, 1H), 0.75 (br s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 139.8, 128.5 (5 C), 127.6 (2 C), 127.1, 125.7 (2 C), 75.6, 40.9, 37.9, 8.6;

FT-IR (ATR) 2975, 2937, 1652, 1594, 1492, 1445, 1363, 1273, 748, 695 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{17}H_{19}ClNO$: 288.1150, found: 288.1162.



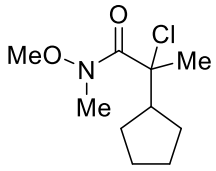
2-Chloro-1-morpholino-2-phenylbutan-1-one. The title compound was prepared from 2-phenylbutyric acid and morpholine following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished as colorless oil (78% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.14 (m, 5H), 3.65 – 2.45 (m, 4H), 3.33 – 3.15 (m, 2H), 3.00 – 2.75 (m, 2H), 2.26 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.07 (dq, *J* = 14.4, 7.2 Hz, 1H), 0.67 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 139.7, 128.7 (2 C), 128.1, 125.6 (2 C), 74.8, 66.8, 65.8, 47.8, 43.7, 38.1, 8.8;

FT-IR (ATR) 2972, 2920, 2857, 1644, 1443, 1425, 1270, 1237, 1111, 970, 864, 852, 750, 700 cm^{-1};

HRMS (ESI) *m/z* $(M–Cl)^+$ calcd for $C_{14}H_{18}NO_2$: 232.1338, found: 232.1346.



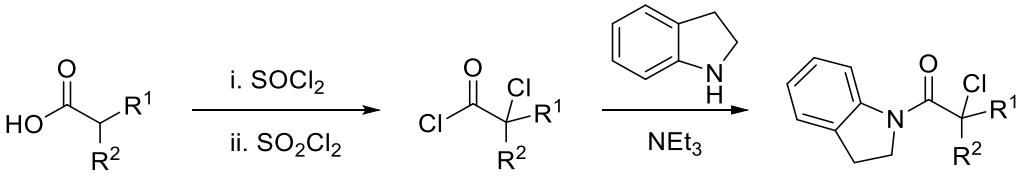
2-Chloro-2-cyclopentyl-*N*-methoxy-*N*-methylpropanamide. The title compound was prepared from 2-cyclopentylpropanoic acid and *N*,*O*-dimethylhydroxylamine·HCl following procedure A. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless oil (31% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.23 (s, 3H), 2.93 – 2.82 (m, 1H), 1.87 – 1.78 (m, 1H), 1.72 (s, 3H), 1.69 – 1.48 (m, 6H), 1.48 – 1.32 (m, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 73.1, 60.8, 47.5, 34.4, 28.6, 28.0, 26.1, 25.9, 24.9;

FT-IR (ATR) 2950, 2869, 1653, 1456, 1377, 1198, 998, 733, 642 cm^{-1};

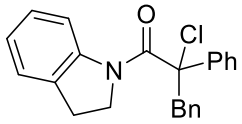
HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{10}H_{19}ClNO_2$: 220.1099, found: 220.1099.



Representative Procedure B for the Synthesis of α-Chloro Amides: This is based on previously published procedures.[31,33] The carboxylic acid (5.0 mmol) was dissolved in $SOCl_2$ (1.5 mL, 20 mmol), and the resulting solution was heated at reflux for 30 min with vigorous stirring ($CaCl_2$ drying tube). SO_2Cl_2 (4.1 g, 50 mmol) was added via a dropping funnel over 2 h at 85 °C, and then the mixture was heated at reflux for an additional 24 h. Next, the reaction mixture was allowed to cool to r.t., and the excess $SOCl_2$ and SO_2Cl_2 were removed by distillation.

Next, triethylamine (1.04 mL, 7.5 mmol) and the α-chloro acid chloride were added dropwise to a solution of indoline (560 µL, 5.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The stirring was continued at 0 °C for 15 min and then at r.t. for 3 h. Next, an aqueous solution of HCl (1 M; 20 mL) was added, and the organic layer was separated. The organic phase

was washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum.



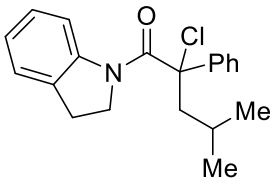
2-Chloro-1-(indolin-1-yl)-2,3-diphenylpropan-1-one. The title compound was prepared from 2-chloro-2,3-diphenylpropanoyl chloride following procedure B. The product was purified by flash chromatography on silica gel (0% → 10% Et_2O/hexanes), which furnished a colorless solid (60% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.1 Hz, 1H), 7.33 – 7.25 (m, 4H), 7.23 – 7.16 (m, 2H), 7.17 – 7.12 (m, 2H), 7.11 – 7.03 (m, 3H), 6.74 – 6.66 (m, 2H), 4.15 (ddd, *J* = 10.9, 9.6, 6.3 Hz, 1H), 3.78 (d, *J* = 14.1 Hz, 1H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.05 (ddd, *J* = 10.9, 9.6, 6.9 Hz, 1H), 2.94 (ddd, *J* = 16.2, 9.5, 6.8 Hz, 1H), 2.73 (ddd, *J* = 15.9, 9.6, 6.3 Hz, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 144.0, 138.2, 135.1, 131.9 (2 C), 131.7, 128.5 (2 C), 128.3, 127.6, 127.3 (2 C), 126.8, 126.4 (2 C), 124.63, 124.60, 118.4, 75.0, 49.9, 49.3, 28.8;

FT-IR (ATR) 3026, 1648, 1478, 1384, 1338, 1261, 953, 756, 699, 633 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{23}H_{21}ClNO$: 362.1312, found: 362.1306.



2-Chloro-1-(indolin-1-yl)-4-methyl-2-phenylpentan-1-one. The title compound was prepared from 4-methyl-2-phenylpentanoic acid following procedure B. The product was purified by flash chromatography on silica gel (0% → 8% Et_2O/hexanes), which furnished a colorless solid (52% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.2 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.40 – 7.29 (m, 3H), 7.26 – 7.19 (m, 1H), 7.17 – 7.09 (m, 1H), 7.04 (td, *J* = 7.4, 1.1 Hz, 1H), 4.16 (ddd, *J* = 10.8, 9.5, 6.3 Hz, 1H), 3.03 (ddd, *J* = 10.7, 9.6, 6.8 Hz, 1H), 2.93 (ddd, *J* = 16.1, 9.6, 6.7 Hz, 1H), 2.72 (ddd, *J* = 15.8, 9.6, 6.3 Hz, 1H), 2.50 – 2.37 (m, 1H), 2.33 – 2.22 (m, 1H), 1.72 (pdd, *J* = 6.7, 5.4, 4.5 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.50 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 144.1, 139.2, 131.6, 128.8 (2 C), 128.2, 127.5, 126.1 (2 C), 124.6, 124.4, 118.4, 75.9, 52.7, 49.2, 28.8, 24.9, 24.4, 24.3;

FT-IR (ATR) 2956, 2868, 1656, 1599, 1479, 1387, 1338, 1266, 754, 701 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{23}ClNO$: 328.1463, found: 328.1471.

2.4.3. Asymmetric Photoinduced, Copper-Catalyzed C−N Cross-Coupling

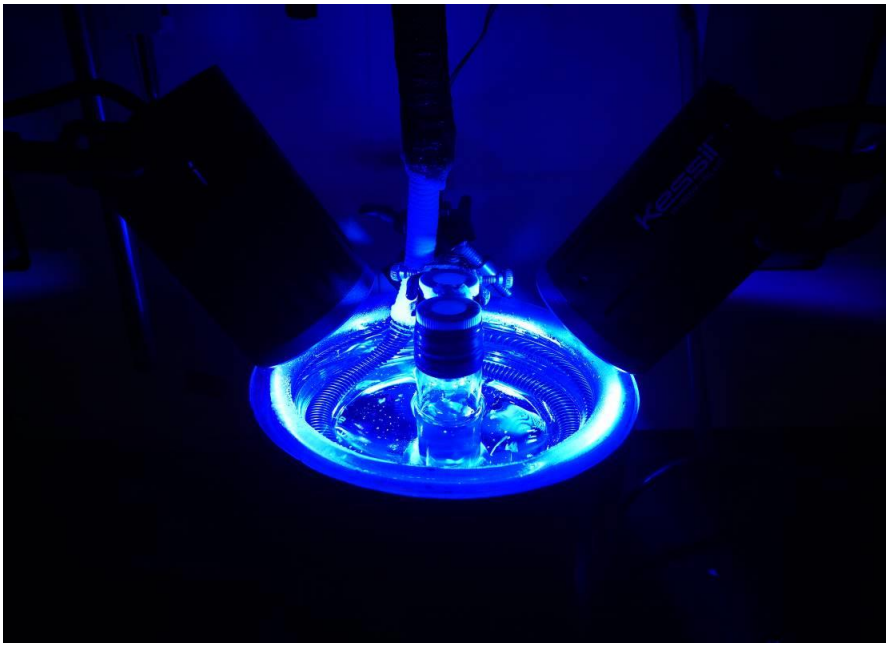
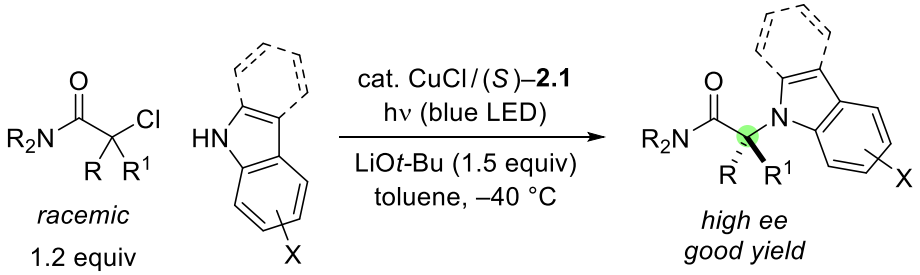


Figure 2.6. Picture of the reaction setup, running two reactions in parallel.

General Procedure A and General Procedure B can be used interchangeably.



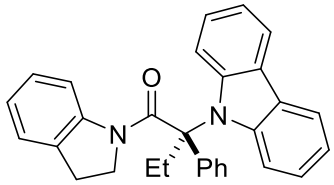
General Procedure A (Glovebox-Free). A stock solution of the catalyst was prepared by vigorously stirring CuCl (4.9 mg, 0.050 mmol) and (*S*)–**2.1** (21.3 mg, 0.060 mmol) in toluene (10.0 mL) at 60 °C for 30 min under a nitrogen atmosphere. An oven-dried 40 mL vial equipped with a magnetic stir bar was capped with a PTFE-lined septum cap, cooled under vacuum, and then backfilled with nitrogen. The carbazole or indole nucleophile (0.50 mmol) and LiO*t*-Bu (60.0 mg, 0.75 mmol) were added to the vial, and then the vial was placed under vacuum and refilled with nitrogen (three cycles). Next, toluene (17 mL) was added, and the resulting mixture was stirred for 5 min. Then, the catalyst (1.0 mL of the stock solution) was added, and the reaction mixture was stirred at r.t. for 20 min. The alkyl chloride (0.60 mmol) was added to an oven-dried 4 mL vial, the vial was capped, and then it was evacuated and backfilled with nitrogen (three cycles). Toluene (2.0 mL) was added, and the resulting solution was transferred to the reaction mixture via syringe. The reaction mixture was degassed by applying three freeze-pump-thaw cycles. The reaction vial was backfilled with nitrogen, detached from the Schlenk line, and the holes in the septum were covered with grease. The vial was placed ~5 cm from two 32W blue LED lamps, and the reaction mixture was irradiated at –40 °C for 16 h under a nitrogen atmosphere. Next, the mixture was passed through a short plug of silica (eluant: Et_2O; monitored by TLC), and the resulting solution was concentrated under vacuum and purified by flash chromatography (hexanes/Et_2O).

A second run was performed using (*R*)–**2.1**.

General Procedure B (Glovebox). In a nitrogen-filled glovebox, a stock solution of the catalyst was prepared by vigorously stirring CuCl (4.9 mg, 0.050 mmol) and (*S*)–**2.1** (21.3 mg, 0.060 mmol) in toluene (10.0 mL) for 30 min; gentle heating by a heat gun facilitated

the dissolution of the components. The carbazole or indole nucleophile (0.50 mmol) and LiO*t*-Bu (60.0 mg, 0.75 mmol) were added to a 40 mL vial, followed by a stir bar and toluene (17 mL). The mixture was stirred for 5 min, and then the stock solution of the catalyst (1.0 mL) was added, and stirring was continued for 20 min. The alkyl chloride (0.60 mmol) was dissolved in toluene (2.0 mL) and added to the reaction mixture. The vial was sealed with a PTFE-lined septum cap, the joint was wrapped with electrical tape, and the vial was taken out of the glovebox. The vial was placed ~5 cm from two 32W blue LED lamps, and the reaction mixture was irradiated at –40 °C for 16 h under a nitrogen atmosphere. Next, the mixture was passed through a short plug of silica (eluant: Et_2O; monitored by TLC), and the resulting solution was concentrated under vacuum and purified by flash chromatography (hexanes/Et_2O).

A second run was performed using (*R*)–**2.1**.



(*S*)-2-(Carbazol-9-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one (Figure 2.2, entry 1). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 193 mg (90% yield), 94% ee. Second run: 196 mg (91% yield), 93% ee.
X-ray quality crystals were obtained by slow evaporation of solvent from a saturated solution in hexanes of a sample synthesized with (*S*)–**2.1**.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (5% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 6.2 min (minor), 7.7 min (major).

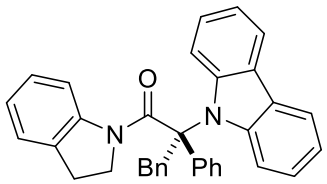
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dt, *J* = 8.2, 0.7 Hz, 1H), 8.14 – 8.11 (m, 2H), 7.60 – 7.56 (m, 2H), 7.36 – 7.31 (m, 3H), 7.27 – 7.18 (m, 7H), 7.10 – 7.02 (m, 2H), 3.76 (ddd, *J* = 10.8, 9.3, 4.0 Hz, 1H), 3.24 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.11 (dt, *J* = 10.8, 9.3 Hz, 1H), 2.92 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.57 (ddd, *J* = 15.5, 9.2, 4.0 Hz, 1H), 0.69 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 144.0, 141.3, 137.9, 131.9, 128.8, 128.0, 127.9, 127.4, 125.6, 124.6, 124.5, 124.3, 120.1, 120.0, 119.1, 113.6, 74.2, 49.3, 32.3, 29.4, 10.5;

FT-IR (ATR) 2933, 1647, 1595, 1476, 1445, 1374, 1334, 1315, 1261, 1178, 1027, 748, 723 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{30}H_{27}N_2O$: 431.2118, found: 431.2112;

$[\alpha]^{25}_D$ (94% ee) = –27.1° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(Carbazol-9-yl)-1-(indolin-1-yl)-2,3-diphenylpropan-1-one (Figure 2.2, entry 2). The title compound was synthesized according to General Procedure B from carbazole (66.9 mg, 0.40 mmol) and 2-chloro-1-(indolin-1-yl)-2,3-diphenylpropan-1-one (173.7 mg, 0.48 mmol). The product was purified by flash chromatography (0% → 10% Et_2O/hexanes). Colorless solid. First run: 149 mg (76% yield), 96% ee. Second run: 154 mg (78% yield), 91% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 7.6 min (minor), 13.9 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dt, *J* = 8.2, 0.8 Hz, 1H), 8.11 – 8.03 (m, 2H), 7.77 – 7.68 (m, 2H), 7.46 – 7.35 (m, 3H), 7.33 – 7.27 (m, 1H), 7.18 (t, *J* = 7.4 Hz, 2H), 7.13 – 7.04 (m, 4H), 6.97 (s, 2H), 6.80 (dt, *J* = 8.7, 4.3 Hz, 1H), 6.69 (d, *J* = 4.3 Hz, 4H), 4.80 (d, *J* =

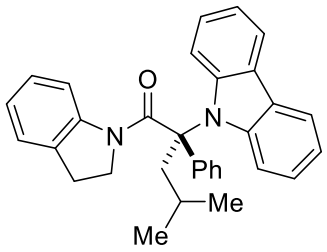
13.5 Hz, 1H), 4.01 (d, *J* = 13.5 Hz, 1H), 3.77 (ddd, *J* = 10.7, 7.8, 5.0 Hz, 1H), 3.32 (dt, *J* = 10.7, 9.3 Hz, 1H), 2.59 – 2.46 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 144.1, 141.0, 136.5, 135.7, 131.8, 131.0, 128.9, 128.0, 127.8, 127.3, 127.0, 126.4, 124.9, 124.5, 124.3, 124.1, 119.65, 119.56, 119.0, 113.8, 74.9, 49.5, 42.6, 29.3;

FT-IR (ATR) 2955, 1652, 1596, 1540, 1476, 1455, 1375, 1335, 1314, 1211, 1031, 748, 723 cm^{-1};

HRMS (FAB) *m/z* $(M+H)^+$ calcd for $C_{35}H_{29}N_2O$: 493.2280, found: 493.2280;

$[\alpha]^{25}_D$ (96% ee) = +46.8° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).

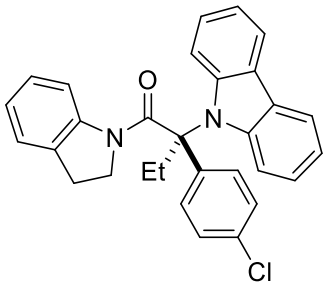


(*S*)-2-(Carbazol-9-yl)-1-(indolin-1-yl)-4-methyl-2-phenylpentan-1-one (Figure 2.2, entry 3). The title compound was synthesized according to General Procedure B from carbazole (66.9 mg, 0.40 mmol) and 2-chloro-1-(indolin-1-yl)-4-methyl-2-phenylpentan-1-one (157.4 mg, 0.48 mmol). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 150 mg (82% yield), 99% ee. Second run: 149 mg (81% yield), 99% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 0.7 mL/min); retention times for compound obtained using (*S*)–**2.1**: 6.5 min (minor), 7.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.1 Hz, 1H), 8.17 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.72 – 7.63 (m, 2H), 7.55 – 7.14 (m, 10H), 7.13 – 7.03 (m, 2H), 3.82 (ddd, *J* = 10.8, 9.2, 3.4 Hz, 1H), 3.22 (dd, *J* = 14.2, 3.7 Hz, 1H), 3.05 (q, *J* = 9.9 Hz, 1H), 2.81 (dd, *J* = 14.1, 5.9 Hz, 1H), 2.65 (dt, *J* = 15.3, 9.5 Hz, 1H), 2.55 (ddd, *J* = 15.4, 9.1, 3.4 Hz, 1H), 1.80 (dqd, *J* = 13.1, 6.6, 3.7 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.22 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 144.0, 140.9, 138.1, 131.8, 128.7, 127.7, 127.6, 127.3, 125.3, 124.4, 124.3, 124.2, 120.0, 119.8, 119.0, 74.2, 49.4, 47.0, 29.3, 25.3, 25.0, 23.5;
FT-IR (ATR) 2955, 1652, 1595, 1489, 1446, 1375, 1313, 1211, 1163, 748, 724 cm^{-1};
HRMS (FAB) *m/z* $(M+H)^+$ calcd for $C_{32}H_{31}N_2O$: 459.2431, found: 459.2435;
$[\alpha]^{25}_D$ (99% ee) = –36.7° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).

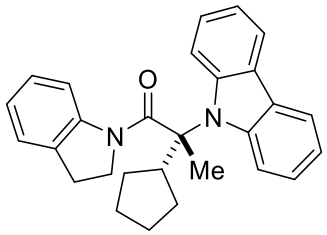


(*S*)–2-(Carbazol-9-yl)-2-(4-chlorophenyl)-1-(indolin-1-yl)butan-1-one (Figure 2.2, entry 4). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-2-(4-chlorophenyl)-1-(indolin-1-yl)butan-1-one (200.5 mg, 0.60 mmol). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 196 mg (84% yield), 95% ee. Second run: 200 mg (86% yield), 90% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 7.4 min (minor), 9.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dt, *J* = 8.1, 0.8 Hz, 1H), 8.17 (dd, *J* = 7.1, 2.7 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.35 – 7.31 (m, 2H), 7.31 – 7.23 (m, 7H), 7.14 – 7.06 (m, 2H), 3.85 (ddd, *J* = 10.6, 9.4, 3.7 Hz, 1H), 3.25 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.03 – 2.91 (m, 2H), 2.81 – 2.68 (m, 1H), 2.59 (ddd, *J* = 15.6, 9.2, 3.7 Hz, 1H), 0.81 (t, *J* = 7.2 Hz, 3H);
^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 143.8, 140.9, 137.2, 133.7, 131.6, 130.0, 128.0, 127.4, 125.8, 124.6, 124.4, 124.2, 120.12, 120.08, 118.9, 113.3, 73.7, 49.1, 32.2, 29.2, 10.4;
FT-IR (ATR) 2957, 1650, 1598, 1476, 1446, 1370, 1209, 1091, 838, 747, 721 cm^{-1};
HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{30}H_{26}ClN_2O$: 465.1728, found: 465.1726;

$[\alpha]^{25}_{D}$ (95% ee) = –69.9° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*R*)-2-(Carbazol-9-yl)-2-cyclopentyl-1-(indolin-1-yl)propan-1-one (Figure 2.2, entry 5). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-2-cyclopentyl-1-(indolin-1-yl)propan-1-one (166.7 mg, 0.60 mmol). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). White solid. First run: 169 mg (83% yield), 97% ee. Second run: 172 mg (84% yield), 98% ee.

X-ray quality crystals were obtained by slow diffusion of pentane into a saturated solution in benzene of a sample synthesized with (*S*)−**2.1**.

The ee was determined by HPLC on a Daicel CHIRALPAK® IB column (1% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)−**2.1**: 6.2 min (major), 7.0 min (minor).

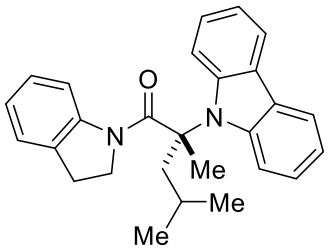
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 – 8.45 (m, 1H), 8.21 – 8.08 (m, 2H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.32 (q, *J* = 6.3 Hz, 2H), 7.29 – 7.20 (m, 2H), 7.09 – 7.01 (m, 2H), 3.81 (ddd, *J* = 10.9, 9.7, 4.0 Hz, 1H), 3.61 – 3.50 (m, 1H), 2.90 – 2.79 (m, 1H), 2.50 – 2.46 (m, 1H), 2.45 (s, 3H), 2.43 – 2.30 (m, 2H), 1.81 – 1.63 (m, 3H), 1.48 (d, *J* = 3.3 Hz, 1H), 1.42 – 1.30 (m, 2H), 0.91 – 0.82 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 144.0, 140.7, 139.7, 131.2, 127.3, 126.1, 124.3, 124.1, 123.7, 120.5, 119.7, 119.4, 118.1, 112.5, 111.7, 69.8, 47.7, 47.6, 29.1, 28.9, 27.7, 26.3, 24.1, 19.9.

FT-IR (ATR) 2959, 1645, 1595, 1476, 1443, 1391, 1375, 1314, 1222, 747, 726 cm^{-1};

HRMS (FAB) *m/z* $(M+H)^+$ calcd for $C_{28}H_{29}N_2O$: 409.2280, found: 409.2297;

$[\alpha]^{25}_{D}$ (97% ee) = +289° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*R*)-2-(Carbazol-9-yl)-1-(indolin-1-yl)-2,4-dimethylpentan-1-one (Figure 2.2, entry 6). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2,4-dimethylpentan-1-one (159.5 mg, 0.60 mmol). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 181 mg (91% yield), 89% ee. Second run: 179 mg (90% yield), 85% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® OD column (5% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 5.3 min (major), 9.5 min (minor).

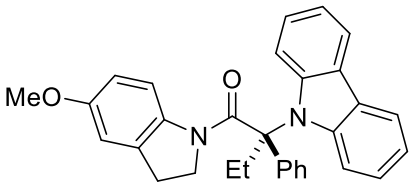
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 8.2, 0.9 Hz, 1H), 8.16 – 8.02 (m, 2H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.47 – 7.37 (m, 1H), 7.37 – 7.30 (m, 1H), 7.29 – 7.17 (m, 3H), 7.05 – 6.96 (m, 2H), 3.54 (d, *J* = 11.9 Hz, 1H), 2.89 – 2.72 (m, 2H), 2.50 (ddd, *J* = 15.0, 9.5, 4.1 Hz, 1H), 2.37 (dd, *J* = 14.4, 4.2 Hz, 5H), 1.68 (hd, *J* = 6.6, 4.2 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.27 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 143.9, 140.7, 139.8, 131.1, 127.3, 126.2, 124.3, 124.1, 123.7, 120.5, 119.9, 119.7, 119.5, 118.1, 111.9, 111.8, 67.8, 47.4, 45.8, 28.9, 25.6, 24.4, 23.8;

FT-IR (ATR) 2954, 1640, 1595, 1477, 1454, 1375, 1316, 1220, 1075, 750, 723 cm^{-1};

HRMS (FAB) *m/z* $(M+H)^+$ calcd for $C_{27}H_{29}N_2O$: 397.2280, found: 397.2270;

$[\alpha]^{25}_D$ (89% ee) = +202° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(Carbazol-9-yl)-1-(5-methoxyindolin-1-yl)-2-phenylbutan-1-one (Figure 2.2, entry 7). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-1-(5-methoxyindolin-1-yl)-2-phenylbutan-1-one (197.9 mg, 0.60 mmol). The product was purified by flash chromatography (0% → 15% Et_2O/hexanes). Colorless solid. First run: 213 mg (94% yield), 92% ee. Second run: 208 mg (90% yield), 92% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (5% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 10.2 min (minor), 14.1 min (major).

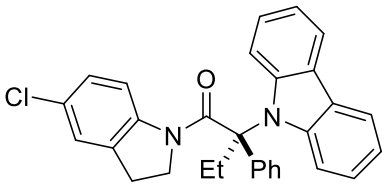
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.9 Hz, 1H), 8.21 – 8.13 (m, 2H), 7.66 – 7.60 (m, 2H), 7.42 – 7.33 (m, 3H), 7.31 – 7.09 (m, 6H), 6.82 (ddd, *J* = 8.7, 2.1, 1.3 Hz, 1H), 6.70 (dd, *J* = 2.6, 1.2 Hz, 1H), 3.82 (s, 4H), 3.30 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.14 (dt, *J* = 10.8, 9.2 Hz, 1H), 2.95 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.67 (dtt, *J* = 15.6, 9.2, 1.1 Hz, 1H), 2.57 (ddd, *J* = 15.6, 9.2, 3.9 Hz, 1H), 0.73 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 156.9, 141.2, 137.9, 137.4, 133.4, 128.7, 127.9, 127.7, 125.5, 124.2, 120.0, 119.8, 119.6, 113.6, 111.7, 110.6, 73.9, 55.6, 49.4, 32.1, 29.4, 10.4;

FT-IR (ATR) 2927, 1642, 1594, 1488, 1445, 1374, 1297, 1181, 1031, 861, 748, 724 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{31}H_{29}N_2O_2$: 461.2224, found: 461.2220;

$[\alpha]^{25}_D$ (92% ee) = –27.5° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(Carbazol-9-yl)-1-(5-chloroindolin-1-yl)-2-phenylbutan-1-one (Figure 2.2, entry 8). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-1-(5-chloroindolin-1-yl)-2-phenylbutan-1-one (200.5 mg, 0.60 mmol). The product was purified by flash chromatography (0% → 10% Et_2O/hexanes). Colorless solid. First run: 213 mg (91% yield), 96% ee. Second run: 206 mg (89% yield), 96% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 9.1 min (minor), 11.6 min (major).

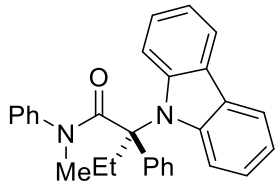
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.7 Hz, 1H), 8.21 – 8.14 (m, 2H), 7.66 – 7.59 (m, 2H), 7.43 – 7.34 (m, 3H), 7.33 – 7.11 (m, 7H), 7.08 (dt, *J* = 2.3, 1.2 Hz, 1H), 3.82 (ddd, *J* = 10.8, 9.4, 4.1 Hz, 1H), 3.29 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.15 (dt, *J* = 10.9, 9.3 Hz, 1H), 2.97 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.67 (dtt, *J* = 15.7, 9.3, 1.1 Hz, 1H), 2.58 (ddd, *J* = 15.7, 9.3, 4.1 Hz, 1H), 0.75 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 142.5, 141.0, 137.6, 133.7, 129.5, 128.7, 128.0, 127.9, 127.3, 125.6, 124.5, 124.2, 120.1, 120.0, 119.8, 113.2, 74.0, 49.4, 32.1, 29.0, 10.4;

FT-IR (ATR) 2936, 1652, 1593, 1465, 1444, 1367, 1315, 1210, 1164, 819, 748, 723 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{30}H_{26}ClN_2O$: 465.1728, found: 465.1725;

$[\alpha]^{25}_D$ (96% ee) = –16.4° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(Carbazol-9-yl)-*N*-methyl-*N*,2-diphenylbutanamide (Figure 2.2, entry 9). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-*N*-methyl-*N*,2-diphenylbutanamide (172.7 mg, 0.60 mmol). 3.0 mL of the stock solution of the catalyst were used (3.0 mol% CuCl). The product was purified by flash chromatography (0% → 10% Et_2O/hexanes). Colorless solid. First run: 162 mg (78% yield), 94% ee. Second run: 168 mg (80% yield), 93% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (5% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 6.5 min (major), 9.6 min (minor).

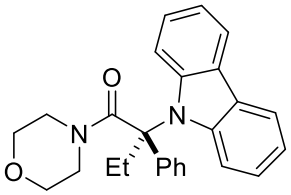
^{1}H NMR (500 MHz, d_6-DMSO, 80 °C) δ 8.12 (dd, *J* = 7.3, 1.6 Hz, 2H), 7.49 – 7.41 (m, 2H), 7.30 (d, *J* = 6.8 Hz, 3H), 7.23 – 7.13 (m, 4H), 7.12 – 6.90 (m, 5H), 6.59 (s, 2H), 2.99 (s, 3H), 2.92 – 2.78 (m, 2H), 0.74 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, d_6-DMSO, 80 °C) δ 170.5, 144.4, 141.1, 140.5, 129.1, 128.8, 128.2, 128.1, 127.1, 126.8, 125.6, 124.2, 120.1, 119.7, 113.6, 73.8, 41.3, 32.2, 10.3;

FT-IR (ATR) 2936, 1651, 1593, 1473, 1445, 1367, 1315, 1213, 750, 723, 698 cm^{-1};

HRMS (FAB) *m/z* $(M)^{+\bullet}$ calcd for $C_{29}H_{26}N_2O$: 418.2045, found: 418.2048;

$[\alpha]^{25}_D$ (94% ee) = +10.0° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(Carbazol-9-yl)-1-morpholino-2-phenylbutan-1-one (Figure 2.2, entry 10). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-1-morpholino-2-phenylbutan-1-one (160.7 mg, 0.60 mmol). The

product was purified by flash chromatography (0% → 30% Et_2O/hexanes). Colorless solid. First run: 145 mg (73% yield), 90% ee. Second run: 149 mg (75% yield), 90% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (3% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 15.4 min (minor), 22.9 min (major).

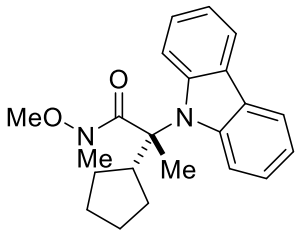
^{1}H NMR (500 MHz, d_6-DMSO, 80 °C) δ 8.20 (dd, *J* = 7.4, 1.2 Hz, 2H), 7.47 (dd, *J* = 7.7, 2.1 Hz, 2H), 7.41 – 7.33 (m, 3H), 7.30 (ddd, *J* = 8.6, 7.1, 1.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 3.37 – 3.22 (m, 4H), 3.09 – 2.84 (m, 6H), 0.66 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, d_6-DMSO, 80 °C) δ 168.9, 140.9, 139.9, 128.6, 128.3, 128.1, 125.9, 124.2, 120.5, 120.2, 113.9, 73.4, 65.6, 45.6, 32.0, 10.4;

FT-IR (ATR) 2923, 2855, 1635, 1592, 1475, 1417, 1315, 1269, 1228, 1112, 750, 717 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{26}H_{27}N_2O_2$: 399.2067, found: 399.2068;

$[\alpha]^{25}_D$ (90% ee) = +44.2° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*R*)-2-(Carbazol-9-yl)-2-cyclopentyl-*N*-methoxy-*N*-methylpropanamide (Figure 2.2, entry 11). The title compound was synthesized according to General Procedure A from carbazole (83.6 mg, 0.50 mmol) and 2-chloro-2-cyclopentyl-*N*-methoxy-*N*-methylpropanamide (131.8 mg, 0.60 mmol). 5.0 mL of the stock solution of the catalyst were used (5.0 mol% CuCl). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Sticky white solid. First run: 127 mg (73% yield), 95% ee. Second run: 127 mg (73% yield), 95% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 0.7 mL/min); retention times for compound obtained using (*S*)–**2.1**: 8.2 min (minor), 9.1 min (major).

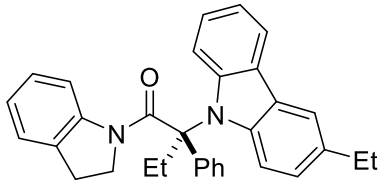
^{1}H NMR (500 MHz, d_6-DMSO, 80 °C) δ 8.22 – 8.08 (m, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.37 (ddd, *J* = 8.8, 7.2, 1.5 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 2H), 3.38 (dt, *J* = 10.6, 7.5 Hz, 1H), 2.97 (s, 3H), 2.52 (s, 3H), 2.27 (s, 3H), 2.14 – 2.00 (m, 1H), 1.60 – 1.52 (m, 3H), 1.43 (dt, *J* = 15.4, 5.6 Hz, 1H), 1.33 – 1.18 (m, 2H), 0.75 – 0.62 (m, 1H);

^{13}C NMR (126 MHz, d_6-DMSO, 80 °C) δ 173.5, 140.6, 126.1, 123.6, 120.3, 119.4, 112.7, 69.0, 59.4, 46.7, 33.9, 28.9, 27.2, 26.1, 24.4, 19.1.

FT-IR (ATR) 2939, 2865, 1644, 1592, 1473, 1445, 1372, 1317, 1223, 996, 741, 723 cm^{-1};

HRMS (ESI) *m/z* $(M)^+$ calcd for $C_{22}H_{26}N_2O_2$: 350.1994, found: 350.1987;

$[\alpha]^{25}_D$ (95% ee) = +172° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(3-Ethyl-carbazol-9-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one (Figure 2.3, entry 1). The title compound was synthesized according to General Procedure A from 3-ethylcarbazole (97.6 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 215 mg (94% yield), 93% ee. Second run: 219 mg (96% yield), 92% ee.

Gram-scale reaction: A solution of the catalyst was prepared by vigorously stirring CuCl (3.0 mg, 30 μmol) and (*S*)–**2.1** (12.8 mg, 36 μmol) in toluene (7.2 mL) at 60 °C for 30 min under nitrogen. An oven-dried 250 mL round-bottom flask equipped with a stir bar was capped with a septum, cooled under vacuum, and then backfilled with nitrogen. 3-Ethylcarbazole (586 mg, 3.0 mmol) and Li*Ot*-Bu (360 mg, 4.5 mmol) were added to the flask, which was then placed under vacuum and refilled with nitrogen (three cycles). Then,

toluene (100 mL) was added, and the mixture was stirred for 5 min. Next, the solution of catalyst was added, with the aid of toluene (0.8 mL), and the resulting mixture was stirred at r.t. for 20 min. 2-Chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (1.08 g, 3.6 mmol) was added to an oven-dried 20 mL vial, the vial was capped, and then it was evacuated and backfilled with nitrogen (three cycles). Toluene (12 mL) was added, and the solution was transferred via syringe to the reaction mixture. The mixture was degassed by applying three freeze-pump-thaw cycles. The reaction vial was backfilled with nitrogen and then detached from the Schlenk line, and the holes in the septum were covered by grease. The flask was placed ~5 cm from three 32W blue LED lamps, and the reaction mixture was irradiated at −40 °C for 16 h under a nitrogen atmosphere. Next, the mixture was passed through a short plug of silica (eluent: Et_2O; monitored by TLC). The resulting solution was concentrated under vacuum, and the residue was purified by flash chromatography (0% → 6% Et_2O/hexanes), which furnished 1.29 g (94% yield, 94% ee) of a colorless powder.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)−**2.1**: 7.1 min (minor), 9.1 min (major).

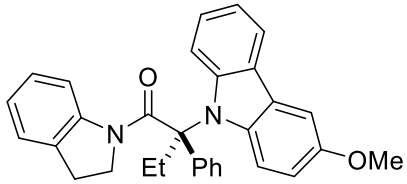
^{1}H NMR (500 MHz, d_6-DMSO, 80 °C) δ 8.24 (d, J = 8.1 Hz, 1H), 8.20 – 8.15 (m, 1H), 8.06 – 8.00 (m, 1H), 7.58 – 7.52 (m, 2H), 7.41 – 7.30 (m, 3H), 7.22 – 7.05 (m, 7H), 7.02 (td, J = 7.4, 1.1 Hz, 1H), 3.65 (ddd, J = 10.9, 9.4, 5.2 Hz, 1H), 3.12 (dt, J = 14.4, 7.1 Hz, 1H), 3.08 (d, J = 1.7 Hz, 1H), 3.07 – 3.03 (m, 1H), 3.03 – 2.97 (m, 1H), 2.79 – 2.71 (m, 2H), 2.70 – 2.54 (m, 2H), 1.28 (t, J = 7.6 Hz, 3H), 0.73 (t, J = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, d_6-DMSO, 80 °C) δ 169.1, 144.2, 141.4, 139.6, 139.3, 135.7, 132.1, 128.8, 128.4, 128.2, 127.3, 126.2, 125.8, 124.9, 124.6, 124.3, 124.1, 120.5, 120.0, 119.2, 118.4, 113.3, 113.2, 74.0, 49.2, 31.8, 29.0, 28.2, 16.1, 10.5;

FT-IR (ATR) 2960, 1649, 1597, 1477, 1452, 1370, 1213, 875, 748, 717 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{32}H_{31}N_2O$: 459.2431, found: 459.2445;

$[\alpha]^{25}_D$ (93% ee) = –23.2° (c = 0.50, $CHCl_3$, obtained with (*S*)−**2.1**).



(*S*)-1-(Indolin-1-yl)-2-(3-methoxy-carbazol-9-yl)-2-phenylbutan-1-one (Figure 2.3, entry 2). The title compound was synthesized according to General Procedure A from 3-methoxy-carbazole (98.6 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). 3.0 mL of the stock solution of the catalyst were used (3.0 mol% CuCl). The product was purified by flash chromatography (0% → 12% Et_2O/hexanes). Colorless solid. First run: 221 mg (96% yield), 90% ee. Second run: 204 mg (89% yield), 88% ee.

The ee was determined by HPLC on a Daicel CHIRALCEL® OD column (2% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 9.2 min (major), 12.4 min (minor).

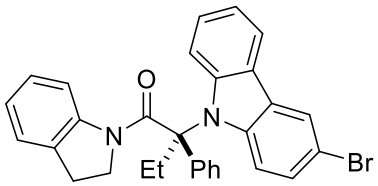
^{1}H NMR (500 MHz, d_6-DMSO, 80 °C) δ 8.24 (d, *J* = 8.2 Hz, 1H), 8.22 – 8.17 (m, 1H), 7.76 (d, *J* = 2.7 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.41 – 7.31 (m, 3H), 7.23 – 7.11 (m, 5H), 7.09 – 6.98 (m, 2H), 6.87 (dd, *J* = 9.2, 2.7 Hz, 1H), 3.86 (s, 3H), 3.66 (ddd, *J* = 10.9, 9.4, 5.1 Hz, 1H), 3.13 (dt, *J* = 14.1, 7.2 Hz, 1H), 3.06 – 2.96 (m, 2H), 2.73 – 2.54 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, d_6-DMSO, 80 °C) δ 169.2, 154.2, 144.2, 141.7, 139.3, 135.9, 132.1, 128.8, 128.4, 128.2, 127.3, 126.0, 125.01, 124.95, 124.7, 124.1, 120.8, 119.7, 118.4, 114.8, 114.1, 113.3, 104.0, 74.0, 56.2, 49.2, 31.8, 29.0, 10.5;

FT-IR (ATR) 2935, 1674, 1597, 1477, 1455, 1374, 1320, 1291, 1200, 1173, 1032, 750, 717, 699 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{31}H_{29}N_2O_2$: 461.2224, found: 461.2225;

$[\alpha]^{25}_D$ (90% ee) = –22.0° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(3-Bromo-carbazol-9-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one (Figure 2.3, entry 3). The title compound was synthesized according to General Procedure A from 3-bromo-carbazole (123.1 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). 3.0 mL of the stock solution of the catalyst were used (3.0 mol% CuCl). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 203 mg (80% yield), 93% ee. Second run: 210 mg (83% yield), 91% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 0.7 mL/min); retention times for compound obtained using (*S*)–**2.1**: 11.1 min (minor), 13.0 min (major).

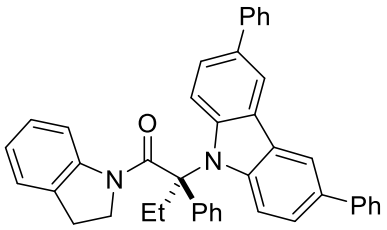
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.1 Hz, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 8.14 – 8.08 (m, 1H), 7.65 – 7.56 (m, 2H), 7.43 – 7.36 (m, 3H), 7.36 – 7.20 (m, 5H), 7.17 – 6.98 (m, 3H), 3.76 (ddd, *J* = 10.8, 9.2, 4.1 Hz, 1H), 3.27 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.15 (dt, *J* = 10.7, 9.2 Hz, 1H), 2.93 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.73 (dt, *J* = 15.4, 9.2 Hz, 1H), 2.64 (ddd, *J* = 15.5, 9.3, 4.1 Hz, 1H), 0.72 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 143.7, 141.5, 139.8, 137.4, 131.7, 128.7, 128.6, 128.1, 128.0, 127.4, 126.3, 126.1, 124.7, 124.4, 123.1, 122.7, 120.3, 120.2, 120.0, 119.9, 118.9, 112.9, 74.2, 49.2, 32.2, 29.3, 10.3;

FT-IR (ATR) 2935, 1648, 1597, 1476, 1441, 1262, 1213, 1030, 868, 722, 700 cm^{-1};

HRMS (ESI) *m/z* $(M)^+$ calcd for $C_{30}H_{25}{}^{81}BrN_2O$: 510.1130, found: 510.1136;

$[\alpha]^{25}_D$ (93% ee) = –17.7° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(3,6-Diphenyl-carbazol-9-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one (Figure 2.3, entry 4). The title compound was synthesized according to General Procedure A from 3,6-diphenyl-carbazole (159.7 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). The product was purified by flash chromatography (0% → 10% Et_2O/hexanes). Colorless solid. First run: 286 mg (98% yield), 91% ee. Second run: 288 mg (99% yield), 88% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 10.5 min (major), 11.7 min (minor).

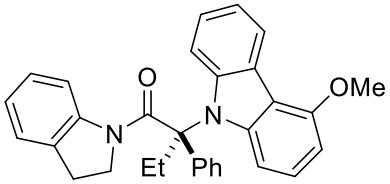
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 – 8.45 (m, 3H), 7.82 – 7.75 (m, 4H), 7.73 – 7.68 (m, 2H), 7.59 – 7.49 (m, 6H), 7.49 – 7.38 (m, 5H), 7.38 – 7.19 (m, 3H), 7.19 – 7.09 (m, 2H), 3.91 (ddd, *J* = 10.8, 9.3, 4.0 Hz, 1H), 3.35 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.26 (dt, *J* = 10.7, 9.2 Hz, 1H), 3.04 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.84 – 2.73 (m, 1H), 2.68 (ddd, *J* = 15.5, 9.3, 4.0 Hz, 1H), 0.83 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 143.9, 141.3, 141.1, 137.7, 133.3, 131.8, 128.9, 128.8, 128.04, 127.99, 127.4, 127.2, 126.8, 125.1, 125.0, 124.6, 124.5, 119.0, 118.3, 113.8, 74.2, 49.3, 32.4, 29.3, 10.5;

FT-IR (ATR) 2935, 1651, 1598, 1474, 1457, 1374, 1264, 1216, 1078, 878, 756, 695 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{42}H_{35}N_2O$: 583.2744, found: 583.2748;

$[\alpha]^{25}_D$ (91% ee) = –20.8° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-1-(indolin-1-yl)-2-(4-methoxy-carbazol-9-yl)-2-phenylbutan-1-one (Figure 2.3, entry 5). The title compound was synthesized according to General Procedure A from 4-methoxy-carbazole (98.6 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). 3.0 mL of the stock solution of the catalyst were used (3.0 mol% CuCl). The product was purified by flash chromatography (0% → 10% Et_2O/hexanes). Colorless solid. First run: 196 mg (85% yield), 93% ee. Second run: 206 mg (89% yield), 92% ee.

The ee was determined by HPLC on a Daicel CHIRALCEL® OD column (1% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 6.8 min (major), 9.0 min (minor).

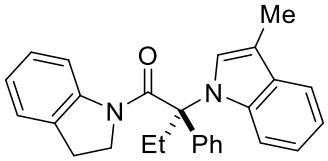
^{1}H NMR (500 MHz, d_6-DMSO, 100 °C) δ 8.42 – 8.32 (m, 1H), 8.24 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.30 (m, 3H), 7.23 – 7.14 (m, 5H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.81 (dd, *J* = 10.8, 8.2 Hz, 2H), 4.07 (d, *J* = 1.3 Hz, 3H), 3.63 (td, *J* = 10.0, 5.2 Hz, 1H), 3.23 – 3.01 (m, 3H), 2.62 (dtd, *J* = 25.4, 15.7, 15.3, 7.1 Hz, 2H), 0.77 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, d_6-DMSO, 100 °C) δ 169.2, 156.4, 144.2, 142.6, 140.5, 139.4, 132.1, 128.8, 128.3, 128.2, 127.3, 126.7, 124.90, 124.88, 124.6, 123.5, 123.3, 120.2, 118.4, 113.3, 113.0, 106.4, 102.1, 74.3, 56.0, 49.2, 31.9, 29.0, 10.5;

FT-IR (ATR) 2932, 1648, 1595, 1476, 1434, 1374, 1258, 1113, 1027, 749, 718 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{31}H_{29}N_2O_2$: 461.2224, found: 461.2225;

$[\alpha]^{25}_D$ (93% ee) = –27.6° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-1-(Indolin-1-yl)-2-(3-methyl-indol-1-yl)-2-phenylbutan-1-one (Figure 2.3, entry 6). The title compound was synthesized according to General Procedure A from 3-methyl-indole (65.5 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). 5.0 mL of the stock solution of the catalyst were used (5.0 mol% CuCl). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 155 mg (79% yield), 92% ee. Second run: 156 mg (79% yield), 92% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® AD column (1% *i*-PrOH/hexanes, 0.7 mL/min); retention times for compound obtained using (*S*)–**2.1**: 8.9 min (minor), 10.0 min (major).

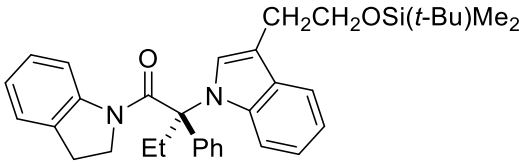
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.61 (ddd, *J* = 7.7, 1.6, 0.7 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.48 – 7.37 (m, 3H), 7.35 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.28 (tdd, *J* = 8.2, 1.5, 0.8 Hz, 1H), 7.21 (q, *J* = 1.1 Hz, 1H), 7.17 – 7.10 (m, 3H), 7.10 – 7.05 (m, 1H), 3.27 – 3.14 (m, 2H), 2.97 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.84 – 2.76 (m, 2H), 2.66 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.38 (d, *J* = 1.1 Hz, 3H), 0.77 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 143.9, 137.5, 136.2, 131.4, 130.0, 128.6, 128.3, 128.0, 127.4, 124.7, 124.4, 124.3, 122.0, 119.4, 119.1, 118.4, 112.9, 111.0, 73.1, 48.4, 33.4, 28.8, 9.9, 9.8;

FT-IR (ATR) 2933, 1651, 1598, 1477, 1455, 1381, 1262, 1182, 1019, 739, 702 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{27}H_{27}N_2O$: 395.2118, found: 395.2120;

$[\alpha]^{25}_D$ (92% ee) = –17.9° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(3-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-indol-1-yl)-1-(indolin-1-yl)-2-phenyl-butan-1-one (Figure 2.3, entry 7). The title compound was synthesized according to General Procedure A from 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-indole[34] (*35*) (137.7 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). 5.0 mL of the stock solution of the catalyst were used (5.0 mol% CuCl). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 215 mg (80% yield), 92% ee. Second run: 214 mg (79% yield), 92% ee.

The ee was determined by HPLC on a Daicel CHIRALPAK® IB column (0.5% *i*-PrOH/hexanes, 0.7 mL/min); retention times for compound obtained using (*S*)–**2.1**: 8.0 min (minor), 8.5 min (major).

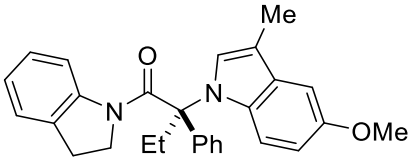
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.2 Hz, 1H), 7.65 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.49 – 7.34 (m, 4H), 7.33 – 7.25 (m, 2H), 7.18 – 7.04 (m, 4H), 3.93 (dd, *J* = 7.5, 6.1 Hz, 2H), 3.29 – 3.09 (m, 2H), 3.07 – 2.93 (m, 3H), 2.79 (t, *J* = 8.1 Hz, 2H), 2.65 (dq, *J* = 14.3, 7.2 Hz, 1H), 0.93 (d, *J* = 1.1 Hz, 9H), 0.79 (td, *J* = 7.2, 1.1 Hz, 3H), 0.09 (d, *J* = 1.1 Hz, 6H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 143.8, 137.4, 136.1, 131.4, 129.5, 128.6, 128.3, 128.0, 127.4, 125.1, 124.3, 124.3, 122.0, 119.5, 119.2, 118.5, 113.0, 112.7, 73.1, 63.7, 48.4, 33.4, 28.9, 28.8, 26.0, 18.3, 10.0, –5.2, –5.3;

FT-IR (ATR) 2927, 2854, 1653, 1600, 1478, 1456, 1387, 1256, 1180, 1073, 831, 757 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{34}H_{43}N_2O_2Si$: 539.3088, found: 539.3091;

$[\alpha]^{25}_D$ (92% ee) = –4.1° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-1-(Indolin-1-yl)-2-(5-methoxy-3-methyl-indol-1-yl)-2-phenylbutan-1-one (Figure 2.3, entry 8). The title compound was synthesized according to General Procedure A from 5-methoxy-3-methyl-indole[35] (*36*) (74.6 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). 5.0 mL of the stock solution of the catalyst were used (5.0 mol% CuCl). The product was purified by flash chromatography (0% → 11% Et_2O/hexanes). Colorless solid. First run: 182 mg (86% yield), 88% ee. Second run: 184 mg (87% yield), 88% ee.

The ee was determined by HPLC on a Daicel CHIRALCEL® OD column (2% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 6.8 min (minor), 7.7 min (major).

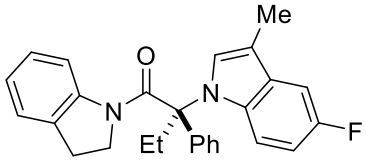
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.46 – 7.35 (m, 3H), 7.28 (dddd, *J* = 8.2, 6.6, 1.6, 0.8 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.18 (d, *J* = 1.3 Hz, 1H), 7.14 (ddt, *J* = 6.5, 1.6, 0.7 Hz, 1H), 7.07 (td, *J* = 7.4, 1.1 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.76 (dd, *J* = 9.0, 2.6 Hz, 1H), 3.89 (s, 3H), 3.23 (q, *J* = 8.2 Hz, 2H), 2.91 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.81 (td, *J* = 8.0, 3.1 Hz, 2H), 2.65 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.34 (d, *J* = 1.0 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 153.9, 143.9, 137.7, 131.41, 131.38, 130.5, 128.5, 128.3, 128.0, 127.4, 125.4, 124.4, 124.3, 118.4, 113.7, 111.8, 110.5, 100.8, 73.1, 55.7, 48.4, 33.5, 28.8, 9.89, 9.87;

FT-IR (ATR) 2934, 1661, 1598, 1477, 1456, 1376, 1262, 1241, 1218, 1078, 1060, 754 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{28}H_{29}N_2O_2$: 425.2222, found: 425.2224;

$[\alpha]^{25}_D$ (88% ee) = –15.5° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).



(*S*)-2-(5-Fluoro-3-methyl-indol-1-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one (Figure 2.3, entry 9). The title compound was synthesized according to General Procedure A from 5-fluoro-3-methyl-indole (74.6 mg, 0.50 mmol) and 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (179.9 mg, 0.60 mmol). 5.0 mL of the stock solution of the catalyst were used (5.0 mol% CuCl). The product was purified by flash chromatography (0% → 7% Et_2O/hexanes). Colorless solid. First run: 201 mg (98% yield), 94% ee. Second run: 201 mg (97% yield), 94% ee.

X-ray quality crystals were obtained by slow diffusion of pentane into a saturated solution in benzene of a sample synthesized with (*S*)–**2.1**.

The ee was determined by HPLC on a Daicel CHIRALCEL® OD column (2% *i*-PrOH/hexanes, 1.0 mL/min); retention times for compound obtained using (*S*)–**2.1**: 7.1 min (minor), 8.6 min (major).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 – 8.39 (m, 1H), 7.56 – 7.48 (m, 2H), 7.48 – 7.36 (m, 3H), 7.29 – 7.21 (m, 4H), 7.15 (ddq, *J* = 7.4, 1.7, 1.0 Hz, 1H), 7.08 (td, *J* = 7.4, 1.1 Hz, 1H), 6.85 (td, *J* = 9.1, 2.6 Hz, 1H), 3.20 (q, *J* = 7.7 Hz, 2H), 2.93 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.84 – 2.77 (m, 2H), 2.64 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.34 (d, *J* = 1.1 Hz, 3H), 0.77 (t, *J* = 7.2 Hz, 3H);

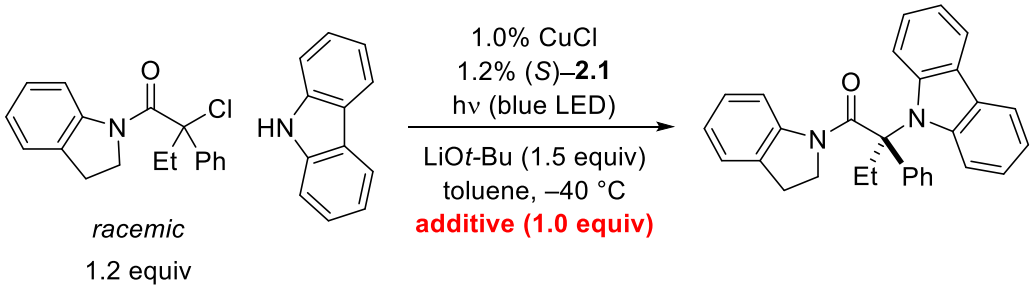
^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 157.7 (d, *J* = 235.8 Hz), 143.8, 137.4, 132.7, 131.3, 130.5 (d, *J* = 9.3 Hz), 128.5, 128.4, 128.1, 127.4, 126.3, 124.43, 124.41, 118.4, 113.5 (d, *J* = 9.2 Hz), 111.0 (d, *J* = 4.7 Hz), 110.4 (d, *J* = 25.8 Hz), 104.0 (d, *J* = 22.9 Hz), 73.1, 48.4, 33.4, 28.8, 9.9, 9.8;

FT-IR (ATR) 2935, 1650, 1598, 1454, 1377, 1263, 1190, 917, 849, 754, 699 cm^{-1};

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{27}H_{26}FN_2O$: 413.2024, found: 413.2023;

$[\alpha]^{25}_D$ (94% ee) = –14.3° (c = 0.50, $CHCl_3$, obtained with (*S*)–**2.1**).

2.4.4. Additive Effects

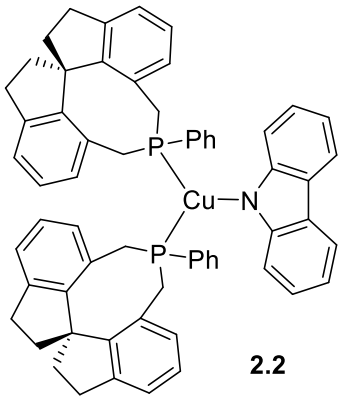


In a nitrogen-filled glovebox, a stock solution of the catalyst was prepared by vigorously stirring CuCl (1.0 mg, 0.010 mmol) and (*S*)–**2.1** (4.3 mg, 0.012 mmol) in toluene (2.0 mL) for 30 min, with warming by a heat gun. Carbazole (16.7 mg, 0.10 mmol), LiO*t*-Bu (12.0 mg, 0.15 mmol), a stir bar, and toluene (2.8 mL) were added to a 4 mL vial. The resulting mixture was stirred for 5 min, and then the stock solution of the catalyst (200 µL) was added, and stirring was continued for 20 min. 2-Chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (1.0 mL aliquot of a 0.12 M stock solution; 36.0 mg, 0.12 mmol) and then the additive (0.10 mmol) were added to the reaction mixture, and then the vial was sealed with a PTFE-lined septum cap, taken out of the glovebox, placed ~5 cm from two 32W blue LED lamps, and irradiated at −40 °C for 16 h under a nitrogen atmosphere. Next, the mixture was allowed to warm to r.t., and dibenzyl ether (19 µL; 0.10 mmol) was added as an internal standard. A portion (~ 1.5 mL) of the reaction mixture was passed through a short silica plug to remove traces of copper. The recovery of the additive was determined by GC analysis, and the yield of the product was determined by ^{1}H NMR analysis, both using dibenzyl ether as an internal standard. After purification by preparative TLC (17% EtOAc/hexanes), the ee was determined by HPLC on a Daicel CHIRALPAK® AD column (5% *i*-PrOH/hexanes, 1.0 mL/min); retention times: 6.2 min (minor), 7.7 min (major).

Table 2.2. Effect of additives (1.0 equiv) on cross-couplings (average of two experiments).

entry	additive	yield (%)	ee (%)	recovered additive (%)
1	cyclohexyl bromide	95	94	90
2	2-nonanone	92	94	96
3	5-nonanol	90	94	99
4	methyl octanoate	92	94	98
5	*cis*-5-decene	96	95	>99
6	*trans*-5-decene	98	95	>99
7	5-decyne	97	94	>99
8	valeronitrile	94	94	80
9	3-phenylpropylamine	7	28	87
10	*N*-methyl-2-phenylethylamine	12	86	89
11	*n*-octanal	40	90	4

2.4.5. Synthesis and Reactivity of ((*R*)−2.1)$_2$Cu(carbazolide).



2.2

Preparation of Complex 2.2. In a nitrogen-filled glovebox, an oven-dried 4 mL amber-glass vial was charged with carbazole (16.7 mg, 0.10 mmol), a stir bar, and a solution of mesitylcopper (18.2 mg, 0.10 mmol) in benzene (400 μL). The mixture was stirred for 10 min, and then a solution of (*R*)−**2.1** (70.8 mg, 0.20 mmol) in benzene (600 μL) was added. The resulting reaction mixture was stirred for 6 h, and then pentane (2.0 mL) was added dropwise. This mixture was stirred for 1 h, during which time a white precipitate formed.

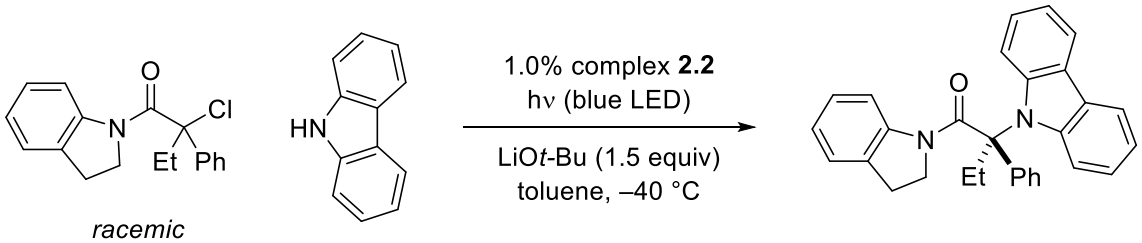
The white precipitate was filtered, rinsed with pentane (5 mL), and dried to give 64 mg (64% yield) of the desired product as a white powder.

X-ray quality crystals were obtained by slow evaporation of solvent from a saturated solution in a mixture of benzene/ether/pentane.

^{1}H NMR (400 MHz, C_6D_6) δ 8.74 – 8.41 (m, 2H), 7.41 (p, *J* = 6.6 Hz, 4H), 7.11 (t, *J* = 7.5 Hz, 4H), 7.01 – 6.80 (m, 10H), 6.74 (d, *J* = 7.6 Hz, 2H), 6.65 (t, *J* = 7.5 Hz, 2H), 5.65 (d, *J* = 7.7 Hz, 2H), 3.56 (d, *J* = 14.3 Hz, 2H), 3.27 (s, 2H), 2.91 – 2.53 (m, 12H), 2.16 – 1.78 (m, 8H), 1.30 – 1.15 (m, 2H), 0.95 (t, *J* = 6.9 Hz, 2H);

^{13}C NMR (101 MHz, C_6D_6) δ 151.0, 147.6, 147.0, 143.1, 142.5, 132.3, 129.8, 129.6, 129.5, 128.8, 128.6, 128.3, 126.2, 125.6, 123.5, 123.2, 123.1, 120.2, 115.0, 114.4, 61.4, 38.3, 37.6, 30.6, 30.4, 30.1, 25.0;

^{31}P NMR (162 MHz, C_6D_6) δ –13.9.

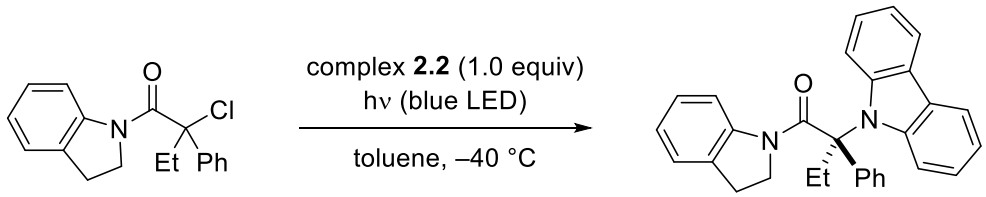


racemic
1.2 equiv

Use of Complex 2.2 as a Catalyst. In a nitrogen-filled glovebox, a stock solution of catalyst was prepared by vigorously stirring complex **2.2** (1.9 mg, 2.0 μmol) in toluene (400 μL) for 30 min. Carbazole (16.7 mg, 0.10 mmol) and LiO*t*-Bu (12.0 mg, 0.15 mmol) were added to a 4 mL vial, followed by a stir bar and toluene (2.8 mL). The mixture was stirred for 5 min, and then the stock solution of complex **2.2** (200 μL) was added, and the resulting mixture was stirred for 20 min. 2-Chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (1.0 mL aliquot of a 0.12 M solution in toluene; 36.0 mg, 0.12 mmol) was added to the reaction mixture, and then the vial was sealed with a PTFE-lined septum cap and taken out of the glovebox. The vial was placed ~5 cm from two 32W blue LED lamps, and the reaction mixture was irradiated at −40 °C for 16 h under a nitrogen atmosphere. Dibenzyl ether (19 μL, 0.10 mmol) was

added as an internal standard, and the yield was determined through analysis by ^{1}H NMR spectroscopy. (*R*)-2-(Carbazol-9-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one was produced in 92% yield and 94% ee.

After purification by preparative TLC (17% EtOAc/hexanes), the ee was determined by HPLC on a Daicel CHIRALPAK® AD column (5% *i*-PrOH/hexanes, 1.0 mL/min); retention times: 6.2 min (major), 7.7 min (minor).



racemic
1.2 equiv

Stoichiometric Reaction of Complex 2.2 in the Stoichiometric Reaction. In a nitrogen-filled glovebox, complex **2.2** (23.5 mg, 0.025 mmol), a stir bar, and toluene (3.0 mL) were added in turn to a 4 mL vial. The mixture was stirred for 5 min, and then 2-chloro-1-(indolin-1-yl)-2-phenylbutan-1-one (1.0 mL aliquot of a 0.030 M solution in toluene; 9.0 mg, 0.030 mmol) was added. The vial was sealed with a PTFE-lined septum cap and then taken out of the glovebox. The vial was placed ~5 cm from two 32W blue LED lamps, and the reaction mixture was irradiated at −40 °C for 16 h under a nitrogen atmosphere. Dibenzyl ether (19 µL, 0.10 mmol) was added as an internal standard, and the yield was determined through analysis by ^{1}H NMR spectroscopy. (*R*)-2-(Carbazol-9-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one was produced in 72% yield and 92% ee.

After purification by preparative TLC (17% EtOAc/hexanes), the ee was determined by HPLC on a Daicel CHIRALPAK® AD column (5% *i*-PrOH/hexanes, 1.0 mL/min); retention times: 6.2 min (major), 7.7 min (minor).

2.4.6. Determination of Absolute Stereochemistry

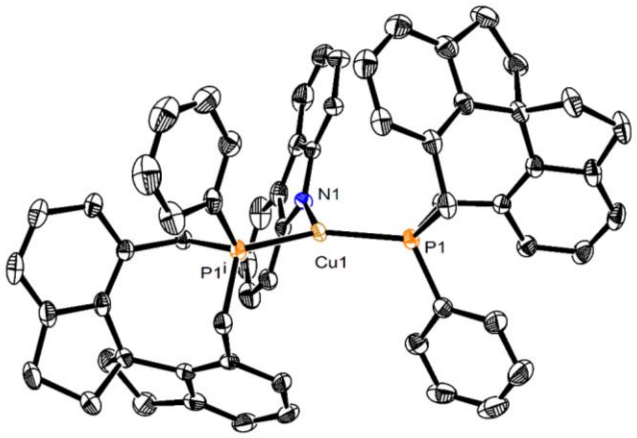


Figure 2.7. Complex **2.2**; structure determined by x-ray diffraction.

Complex 2.2. X-ray quality crystals were obtained by slow evaporation of solvent from a saturated solution of a sample in a mixture of benzene/ether/pentane. A crystal of $C_{62}H_{54}CuNP_2$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Photon CMOS diffractometer with filtered Mo-Kα radiation at a temperature of 100 K. Using Olex2[36], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package[37] using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

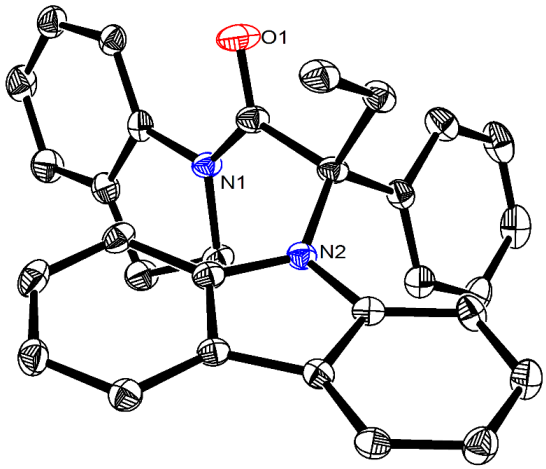


Figure 2.8. Figure 2.2, entry 1; structure determined by x-ray diffraction. One of two molecules in the asymmetric unit is shown.

(*S*)-2-(Carbazol-9-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one (Figure 2.2, entry 1). X-ray quality crystals were obtained by slow evaporation of solvent from a saturated solution in hexanes of a sample synthesized with (*S*)−**2.1**. A crystal of $C_{30}H_{26}N_2O$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Photon diffractometer with filtered Cu-Kα radiation at a temperature of 100 K. Using Olex2[36], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package[37] using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

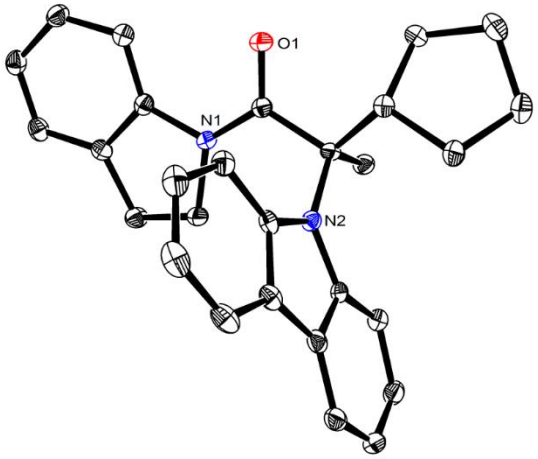


Figure 2.9. Figure 2.2, Entry 5; structure determined by x-ray diffraction. One of two molecules in the asymmetric unit is shown.

(*R*)-2-(Carbazol-9-yl)-2-cyclopentyl-1-(indolin-1-yl)propan-1-one (Figure 2.2, entry 5). X-ray quality crystals were obtained by slow diffusion of pentane into a saturated solution in benzene of a sample synthesized with (*S*)–**2.1**. A crystal of $C_{28}H_{28}N_2O$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Photon CMOS diffractometer with filtered Cu-Kα radiation at a temperature of 100 K. Using Olex2[36], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package[37] using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

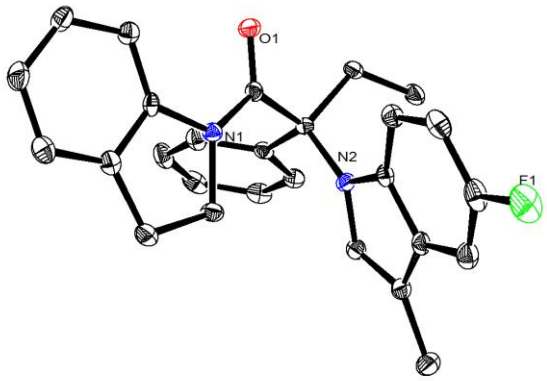


Figure 2.10. Figure 2.3, entry 9; structure determined by x-ray diffraction. One of two molecules in the asymmetric unit is shown.

(*S*)-2-(5-Fluoro-3-methyl-indol-1-yl)-1-(indolin-1-yl)-2-phenylbutan-1-one (Figure 2.3, entry 9). X-ray quality crystals were obtained by slow diffusion of pentane into a saturated solution in benzene of a sample synthesized with (*S*)–**2.1**. A crystal of $C_{27}H_{25}FN_2O$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Photon diffractometer with filtered Cu-Kα radiation at a temperature of 100 K. Using Olex2[36], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package[37] using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

2.5. Notes and References

1. *Photochemically-Generated Intermediates in Synthesis*; Albini, A.; Fagnoni, M. Eds.; Wiley: Hoboken, NJ, 2013.
2. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363.
3. Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. *Angew. Chem. Int. Ed*. **2015**, *54*, 3872–3890.

4. Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176.

5. Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Rose, R.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100–103.

6. Huo, H.; Wang, C.; Harms, K.; Meggers, E. *J. Am. Chem. Soc*. **2015**, *137*, 9551–9554.

7. Wang, C.; Zheng, Y.; Huo, H.; Rose, P.; Zhang, L.; Harms, K.; Hilt, G.; Meggers, E. *Chem. Eur. J*. **2015**, *21*, 7355–7359.

8. Bauer, A.; Westkämper, F.; Grimme, S.; Bach, T. *Nature* **2005**, *436*, 1139–1140.

9. Nicewicz, D. A.; Nguyen, T. M.; *ACS Catal.* **2014**, *4*, 355–360.

10. Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science*, **2012**, *338*, 647–651.

11. *Amines: Synthesis, Properties and Applications*; Lawrence, S. A. Cambridge Univ. Press: Cambridge, UK, 2004.

12. Jiang, L.; Buchwald, S. L. in *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A.; Diederich, F.; Eds. Wiley–VCH: Weinheim, Germany, 2004, *2*, 699–760.

13. Hartwig, J. F.; Shekhar, S.; Shen, Q.; Barrios-Landeros, F. in *Chemistry of Anilines*, Rappoport, Z.; Ed. Wiley: New York, 2007, *1*, 455–536.

14. Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed*. **2013**, *52*, 5129–5133.

15. Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc*. **2014**, *136*, 2162–2167.

16. Paria, S.; Reiser, O. *ChemCatChem* **2014**, *6*, 2477–2483.

17. Fischer, C.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 4594–4595.

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

19. Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc*. **2015**, *137*, 7128–7134.

20. Quasdorf, K. W.; Overman, L. W. *Nature* **2014**, *516*, 181–191.

21. Schuster, C.; Konstanze, J.-G. K.; Schnitzler, H.; Hesse, R.; Jager, A.; Schmidt, A. W.; Knölker, H.-J. *J. Org. Chem*. **2015**, *80*, 5666–5673.

22. Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193–3328.

23. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059–1070.

24. Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc*. **2010**, *132*, 11027–11029.

25. Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707–3738.
26. *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*; Gribble, G. W.; Ed., Springer: Heidelberg, Germany, 2010.
27. Vallakati, R.; May, J. A. *J. Am. Chem. Soc*. **2012**, *134*, 6936–6939.
28. Schmitt, E. K.; Riwanto, M.; Sambandamurthy, V.; Roggo, S.; Miault, C.; Zwingelstein, C.; Krastel, P.; Noble, C.; Beer, D.; Rao, S. P.; Au, M.; Niyomrattanakit, P.; Lim, V.; Zheng, J.; Jeffery, D.; Pethe, K.; Camacho, L. R. *Angew. Chem. Int. Ed*. **2011**, *50*, 5889–5891.
29. Pellissier, H. in *Separation of Enantiomers*, Todd, M.; Ed. Wiley–VCH: Weinheim, Germany, 2014, 75–122.
30. Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 3803–3806.
31. Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157.
32. Harpp, D. N.; Bao, L. Q.; Black, R. A.; Smith, R. A.; Gleason, J. G. *Tetrahedron Lett.* **1974**, *15*, 3235–3238.
33. Schwenk, E.; Papa, D. *J. Am. Chem. Soc*. **1948**, *70*, 3626–3627.
34. Du, Y.; Huang, H.-Y.; Liu, H.; Ruan, Y.-P.; Huang, P.-Q. *Synlett* **2011**, 565–568.
35. Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3250–3254.
36. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339–341.
37. Sheldrick, G. M. *Acta Crystallogr. A* **2008**, *64*, 112–122.

C h a p t e r 3

COPPER-CATALYZED ALKYLATION OF ALIPHATIC AMINES INDUCED BY VISIBLE LIGHT

Adapted in part with permission from:

Matier, C. D. ; Schwaben, J. ; Peters, J. C. ; Fu, G. C. Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *J. Am. Chem. Soc.* **2017**, *139*, 17707−17710. doi: 10.1021/jacs.7b09582

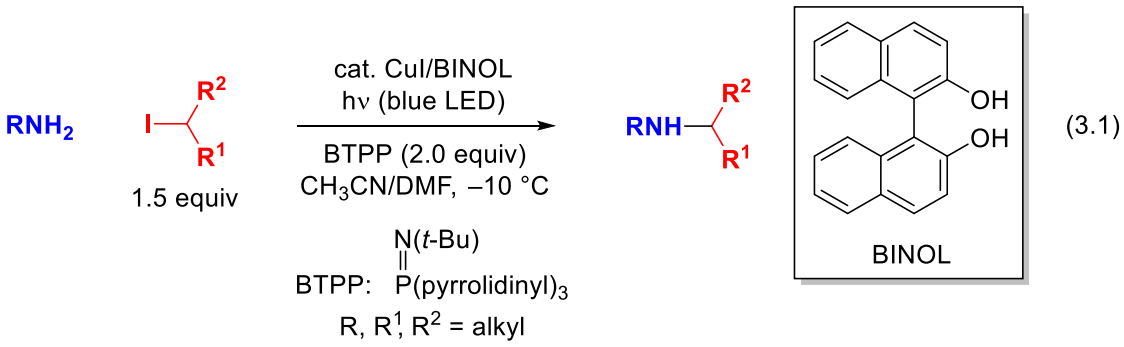
3.1. Introduction

Because amines are a privileged functional group in bioactive molecules,[1] the development of more versatile methods for their synthesis is an important objective.[2] Whereas the alkylation of an amine by an alkyl halide via an S_N2 pathway is a classic transformation, at the same time the process represents an ongoing challenge in synthesis.[3] Thus, rather than the desired C–N bond formation, undesired pathways such as E2 reactions and over-alkylation often intervene. Furthermore, because S_N2 reactions are sensitive to steric effects, unactivated secondary and tertiary alkyl halides oftentimes do not serve as useful electrophilic partners. Due in part to these limitations, an array of methods other than the substitution reaction of an amine with an alkyl halide have been developed in order to selectively and efficiently introduce an alkyl group to an amine.[2]

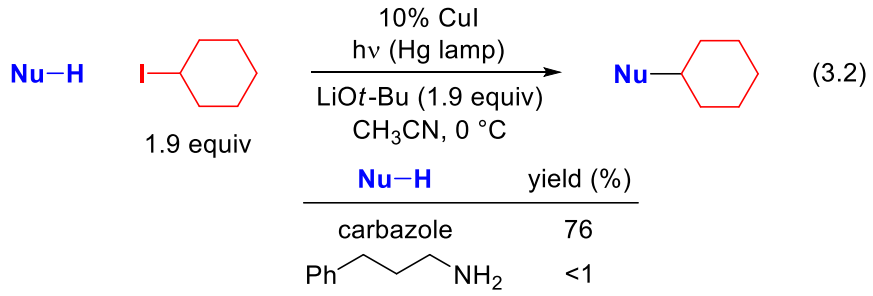
Whereas transition-metal catalysis has been pursued very extensively to address the challenge of effecting substitution reactions of *aryl* halides by nitrogen nucleophiles,[4] until recently there were essentially no systematic investigations of corresponding metal-catalyzed substitution reactions of *alkyl* halides.[5] During the past few years, this deficiency has begun to be addressed, including through our work on photoinduced, copper-catalyzed processes (carbazoles, carboxamides, and indoles as nucleophiles)[6,7] and a study by Hartwig on palladium-catalyzed reactions (benzophenone imines as nucleophiles).[8]

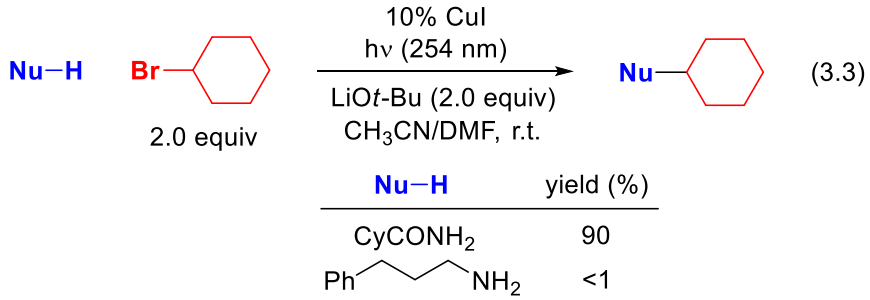
Nevertheless, to date a general method for transition-metal-catalyzed substitution of an alkyl halide by an aliphatic amine, which can be regarded as the prototypical nitrogen nucleophile, has not been described. In this study, we report a photoinduced, copper-catalyzed process that achieves the selective mono-alkylation of an array of aliphatic amines with unactivated secondary alkyl halides under mild conditions (–10 °C; eq 3.1).

In earlier work, we have described a variety of coupling reactions of nucleophiles with organic (aryl, alkenyl, alkynyl, and alkyl) electrophiles that are induced by light and catalyzed by copper;[6,9] an outline of one of the possible pathways for such processes is provided in Figure 3.1.[10,11] To date, all of our reported couplings have employed nucleophiles wherein the nucleophilic site is part of a π system (N: carbazole, indole, and imidazole; S: aryl thiol; O: phenol; C: cyanide). On the other hand, our initial efforts to utilize nucleophiles that lack this feature were unsuccessful. For example, under conditions in which carbazole[6a] and cyclohexanecarboxamide[6b] undergo alkylation by an unactivated secondary halide in good yield, the corresponding alkylation of a primary aliphatic amine does not proceed (eq 3.2 and eq 3.3). Having the nucleophilic site incorporated within a π system might be important for any of a variety of reasons, including determining the viability of the initial photoexcitation (**3.A** → **3.B** in Figure 3.1)[12] and/or of electron transfer from that excited state to the electrophile to generate a copper(II) complex (**3.B** → **3.C**).[13]

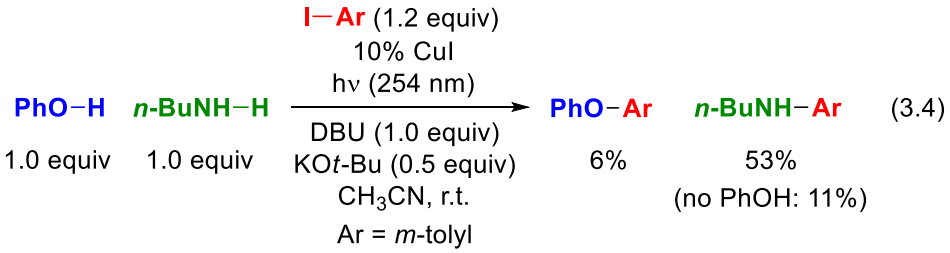


(3.1)





While examining the functional-group compatibility of a method that we had developed for photoinduced, copper-catalyzed arylations of phenols,[9d] we discovered that the presence of 1.0 equiv of an aliphatic amine additive unexpectedly leads to predominant N-arylation of the aliphatic amine, rather than O-arylation of the phenol (eq 3.4; in the absence of *n*-BuNH$_2$: 80% yield of PhO–Ar).



One of the possible pathways by which phenol might enable the photoinduced, copper-catalyzed cross-coupling of an aliphatic amine is depicted in Figure 3.2. Thus, photoexcitation of a copper(I)–phenoxide complex (**3.E** → **3.F**) and then electron transfer to an electrophile (R–X) affords a copper(II)–phenoxide (**3.G**) and an organic radical (R•). Ligand exchange of the copper(II)–phenoxide with an amine (NH_2R) leads to a copper(II)–amido (**3.H**)[14] that engages in C–N bond formation with the organic radical to furnish the

cross-coupling product (R–NHR) and a copper(I) complex (**3.I**).[15] Ligand substitution then regenerates a copper(I)–phenoxide complex (**3.E**).

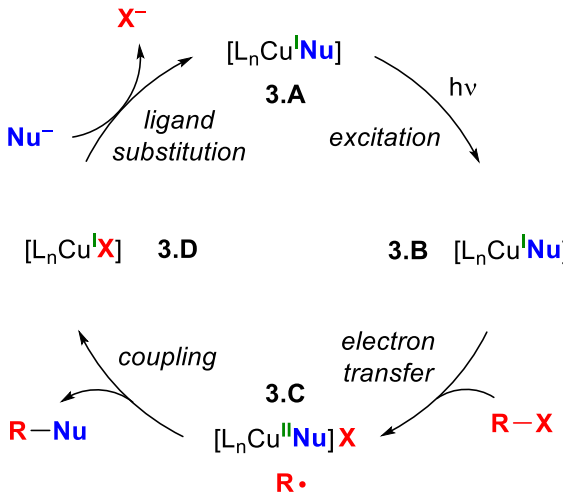


Figure 3.1. Outline of one of the possible pathways for photoinduced, copper-catalyzed coupling reactions.

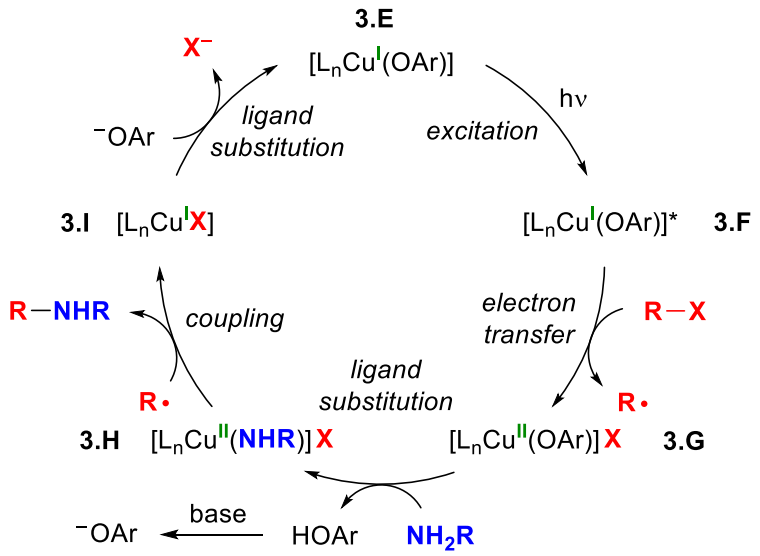


Figure 3.2. Simplified outline of one of the possible pathways for the photoinduced, copper-catalyzed coupling of an aliphatic amine in the presence of a phenol.

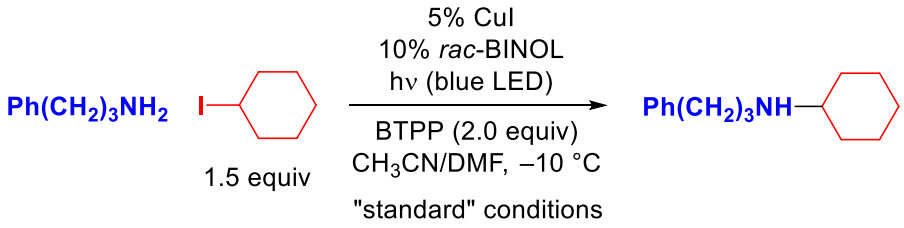
3.2. Results and Discussion

3.2.1. Optimization

Given the paucity of systematic studies of metal-catalyzed substitution reactions of unactivated alkyl halides by aliphatic amines, we attempted to exploit our initial observation (eq 3.4) to devise a photoinduced, copper-catalyzed process that would address this deficiency. Indeed, building on this lead result, we have been able to develop a method that achieves the selective mono-alkylation of a primary aliphatic amine by an unactivated secondary alkyl halide under mild conditions (–10 °C) in good yield (92%).

Control reactions establish that essentially none of the coupling product is generated in the absence of CuI, *rac*-BINOL, light, or BTPP (Table 3.1, entries 2−6). A variety of copper(I) and copper(II) sources furnish a good yield of the desired secondary amine, whereas copper nanopowder does not (entries 7–11). N-Alkylation proceeds less efficiently in the presence of less BINOL (entries 12 and 13) and when BINOL is replaced with related ligands (entries 14 and 15). The use of other Brønsted bases (entries 16 and 17), a smaller excess of electrophile or BTPP (entries 18 and 19), or a lower catalyst loading (entry 20; no further reaction after 24 h) also leads to significantly lower yields. Under our standard conditions, other cyclohexyl electrophiles (bromide, chloride, and tosylate) do not serve as suitable coupling partners (entries 21–23). Cross-coupling does occur in the presence of a small amount of air or water, although less effectively (entries 24 and 25).

Table 3.1. Photoinduced, copper-catalyzed coupling of an aliphatic amine with an unactivated secondary alkyl iodide: Effect of reaction parameters.



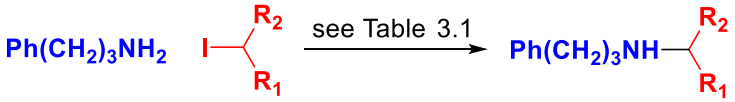
entry	variation from the "standard" conditions	yield (%)[a]
1	none	92
2	no CuI	<1
3	no *rac*-BINOL	<1
4	no hν	<1
5	no BTPP	<1
6	no CuI, no *rac*-BINOL, no light	<1
7	CuBr, instead of CuI	84
8	CuCl, instead of CuI	86
9	$CuBr_2$, instead of CuI	81
10	$Cu(OTf)_2$, instead of CuI	82
11	copper nanopowder, instead of CuI	<1
12	6% *rac*-BINOL	70
13	4% *rac*-BINOL	48
14	2-naphthol, instead of *rac*-BINOL	14
15	*rac*-BINOL dimethyl ether, instead of *rac*-BINOL	<1
16	1,1,3,3-tetramethylguanidine, instead of BTPP	50
17	LiO*t*-Bu, instead of BTPP	14
18	1.2 equiv CyI	62
19	1.0 equiv BTPP	62
20	2.5% CuI, 5% *rac*-BINOL	54
21	CyBr, instead of CyI	<1
22	CyCl, instead of CyI	<1
23	CyOTs, instead of CyI	<1
24	under air (capped vial)	39
25	0.1 equiv H_2O added	78

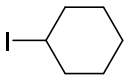
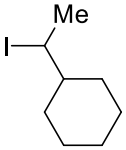
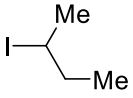
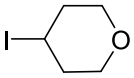
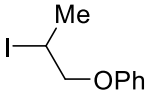
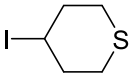
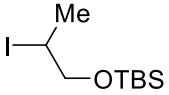
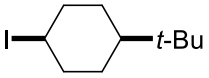
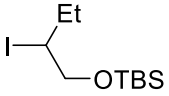
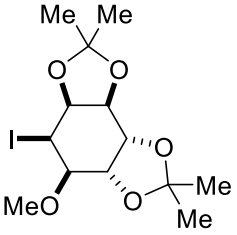
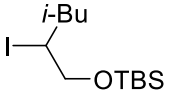
[a] Yields were determined via ^{1}H NMR analysis versus an internal standard (average of two experiments).

3.2.2. Scope of Reactivity

An array of unactivated secondary alkyl iodides, both cyclic and acyclic, serve as suitable electrophiles in this photoinduced, copper-catalyzed mono-alkylation of aliphatic amines (Table 5.2).[16] The efficiency of the coupling is sensitive to steric effects, with more hindered electrophiles furnishing more modest yields (entries 6 and 7). Saturated oxygen and sulfur heterocycles are compatible with the reaction conditions (entries 8 and 9), and C–N bond formation can be achieved with excellent diastereoselectivity (entries 11 and 12; >20:1). In a gram-scale reaction, the alkylation illustrated in entry 1 proceeds in good yield with 10% CuI/20% BINOL (1.32 g, 81%).

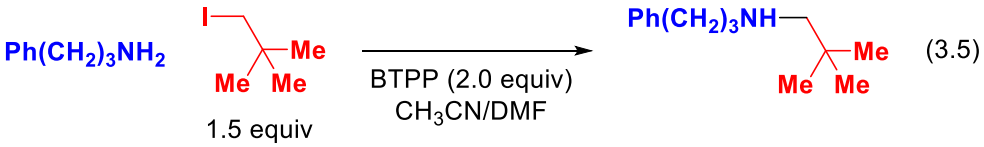
Table 3.2. Scope with respect to the electrophile.



entry	electrophile	yield (%)[a]	entry	electrophile	yield (%)[a]
1		80	7[b]		41
2		70	8		82
3		65	9[b]		56
4		74	10[c]		54
5		55	11[d]		61
6		34			

[a] Yields of purified product (average of two experiments). [b] Catalyst loading: 10% CuI, 20% *rac*-BINOL. [c] Starting material: cis/trans = 5/1; product: trans/cis >20/1.[d] Starting material: β/α >20/1; product: α/β >20/1.

Although many unactivated primary alkyl halides can serve as useful electrophiles in S_N2 reactions, neopentyl halides typically are rather poor substrates.[17] Nevertheless, the combination of a CuI/BINOL catalyst and blue-LED irradiation enables the alkylation of an aliphatic amine by neopentyl iodide in good yield at –10 °C (eq 3.5). In contrast, a simple S_N2 reaction proceeds very slowly even at 100 °C, and the addition of CuI/BINOL is not beneficial (eq 3.5).



(3.5)

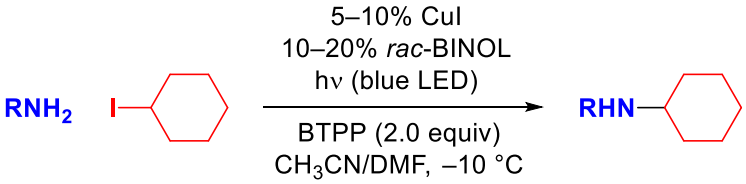
conditions	yield (%)
10% CuI, 20% *rac*-BINOL, hν (blue LED), –10 °C	70
–10 °C	<1
100 °C	4
10% CuI, 20% *rac*-BINOL, 100 °C	4

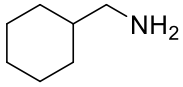
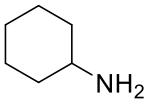
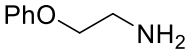
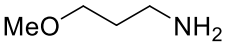
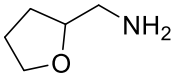
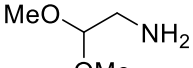
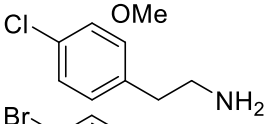
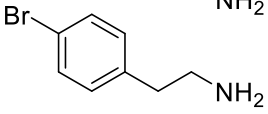
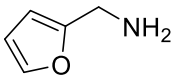
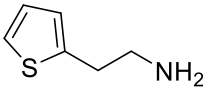
We have also examined the scope of this photoinduced, copper-catalyzed N-alkylation with respect to the nucleophile (Table 3.3). Thus, the efficiency of C–N bond formation does not appear to be highly sensitive to the steric demand of the aliphatic amine (entries 1 and 2). The method is compatible with a variety of functional groups, including an ether, an acetal, an aryl chloride, an aryl bromide, a furan, and a thiophene (entries 3–10).

Through an additive study, we have further assessed the functional-group compatibility of this method. For the coupling illustrated in entry 1 of Table 3.2, the addition of 1.0 equiv of an alcohol (5-nonanol), an alkyne (5-decyne), an ester (methyl octanoate), a ketone (2-nonanone), a cis olefin (*cis*-5-decene), and a trans olefin (*trans*-5-decene) has little impact on N-alkylation (>75% yield), and the additive is virtually unaffected (>90% recovery). On the other hand, the addition of a nitroalkane (nitrocyclopentane) or an aldehyde (cyclohexanecarboxaldehyde) impede coupling (<5% and 51% yield, respectively).

If desired, N-protection of the secondary amine can be effected in situ in good yield. For example, upon completion of the alkylation illustrated in entry 1 of Table 3.2, direct trifluoroacetylation followed by purification provides the TFA-protected amine in 86% yield. Similarly, a 73% yield of the purified carbamate can be obtained after in situ protection with Boc_2O.

Table 3.3. Scope with respect to the nucleophile.

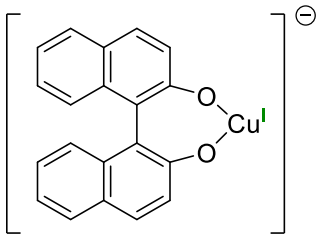


entry	nucleophile	yield (%)[a]
1		83
2		71
3		61
4[b]		84
5		60
6[b]		75
7		64
8		52
9		54
10		80

[a] Yields of purified product (average of two experiments).
[b] Isolated as the trifluoroacetamide derivative.

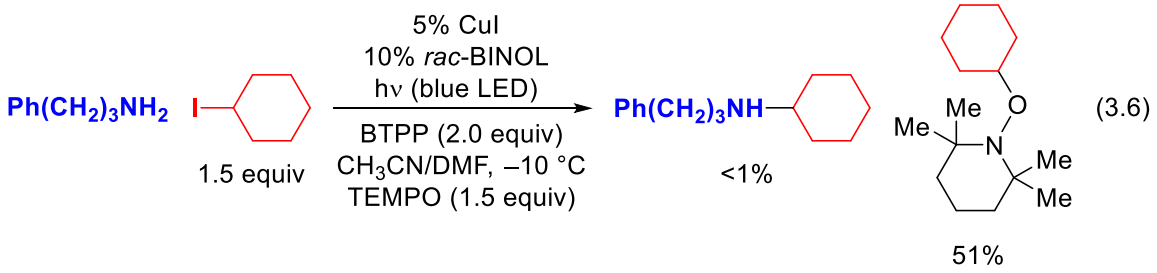
3.2.3. Mechanistic Insights

Although reaction development is the primary focus of this investigation, we have also carried out preliminary mechanistic studies; as mentioned earlier, one of the possible pathways for this process is outlined in Figure 3.2. With regard to the identity of the primary photoreductant, ESI–MS of a reaction mixture after partial conversion reveals the presence of copper(I)–binaphtholate complex **3.E'**; alternatively, deprotonated BINOL itself could also fill this role.[18,19] The illustrated mechanism includes d^9 copper(II) complexes as intermediates, and we have indeed detected such species via EPR spectroscopy by sampling a catalyzed coupling at partial conversion; at least two copper(II) species are evident (hyperfine coupling to copper), which together account for ~60% of the total copper that is present in the reaction mixture.



3.E'

According to the pathway depicted in Figure 3.2, C–N bond formation occurs through out-of-cage coupling of an organic radical (R•) with a copper(II)–amido complex.[15] Consistent with this hypothesis, the addition of TEMPO (1.5 equiv) to a reaction mixture leads to the formation of a TEMPO adduct (eq 3.6).



(3.6)

3.3. Conclusions

In summary, we have determined that the combination of visible light and a copper catalyst provides the first general method for the transition-metal-catalyzed alkylation of aliphatic amines by unactivated secondary alkyl halides. This process addresses some of the deficiencies of the classic S_N2 approach, including its need for reactive electrophiles and its propensity for over-alkylation. With respect to our efforts to expand photoinduced, copper-catalyzed coupling reactions, this represents our first success with nucleophiles wherein the nucleophilic site is not part of a π system. With our optimized method, C–N bond formation proceeds without significant over-alkylation (<1%) under mild conditions (–10 °C) in the presence of a variety of functional groups, upon irradiation by blue-LED lamps of a catalyst derived from commercially available components. A preliminary mechanistic study is consistent with the formation of an alkyl radical that engages in out-of-cage C–N bond formation. Our future work will focus on expanding photoinduced, copper-catalyzed couplings to other classes of non-conjugated nucleophiles, as well as on elucidating the mechanisms of these processes.

3.4. Development of an Asymmetric Variant

Translating the alkylation of aliphatic amines into an asymmetric variant is an interesting and important challenge, as it would allow for the formation of α-chiral amines from easily available racemic alkyl halides. α-Chiral amines are a particularly important class of molecules, as they are featured in many bioactive molecules, ligands, and natural products. This chiral functional group plays a role to impart unique and medically relevant biological activity in a variety of organic small molecules (Figure 3.3). For example, tamsulosin (Flomax™) is used to treat enlarged prostates and sertraline (Zoloft™) is used as an antidepressant. Due to the privileged bioactivity of α-chiral amines, there has been intense focus on reaction development to access these products in high ee.[20,21] Despite the vast and impressive contributions to this field, to the best of our knowledge there has only been one report of an asymmetric alkylation of an amine with an alkyl halide electrophile (see Chapter 2).[6c] However, that reaction is limited by the utility of *N*-alkylated indoles and carbazoles.

Ideally, a transformation that could couple a simple alkyl amine (e.g., 3-phenylpropylamine) and a racemic mixture of an unactivated alkyl halide with high enantioconvergence would be highly desirable. To this end, the reactivity discussed earlier in this chapter has been employed in an attempt to achieve such a transformation by leveraging the axial chirality of BINOL ligands and copper photocatalysis.

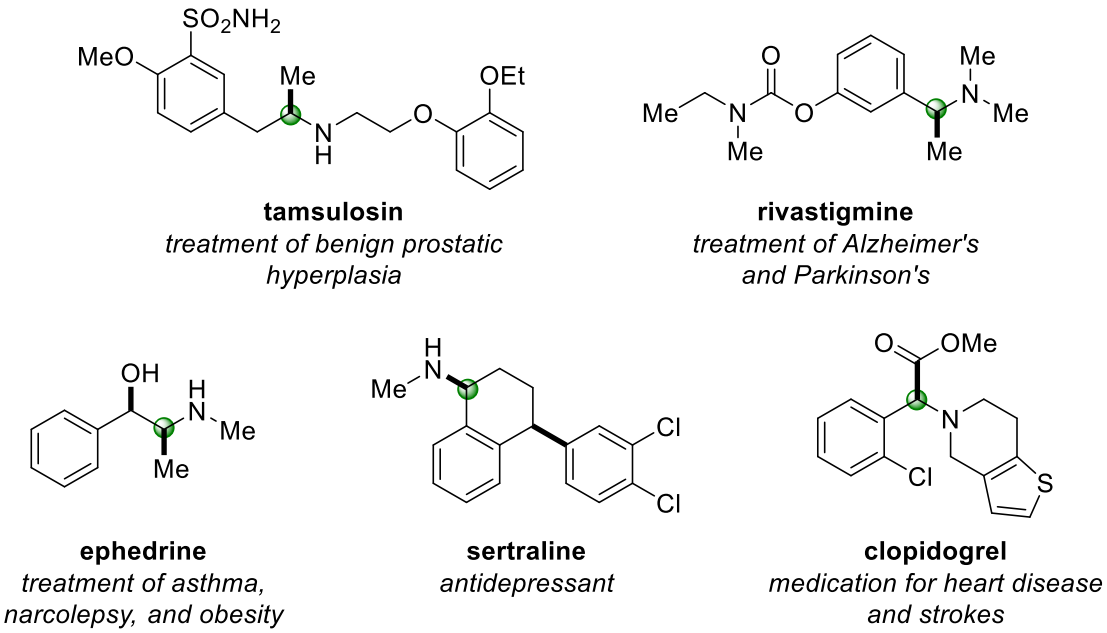
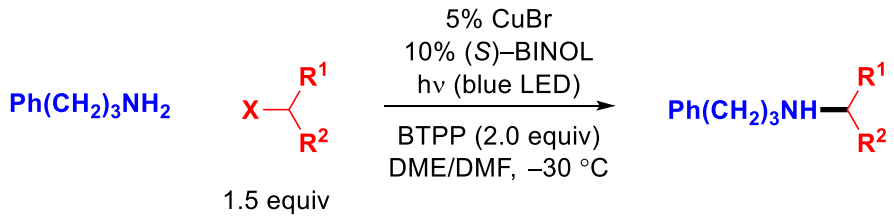


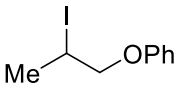
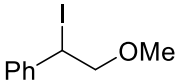
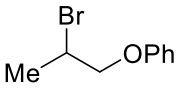
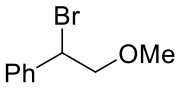
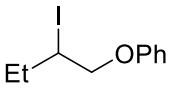
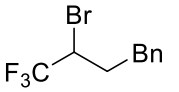
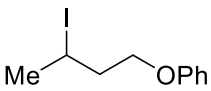
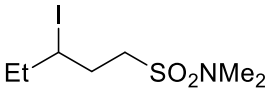
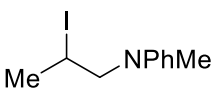
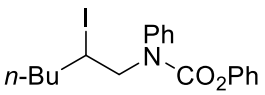
Figure 3.3. Selected examples of α-chiral amines show diverse and important biological activity.

Initial optimization aimed at achieving enantioinduction focused on identifying a promising yet general class of alkyl electrophile. Minor modifications to the conditions shown in Table 3.1 enabled an acyclic secondary alkyl iodide that was previously applicable in the racemic variant (Table 3.2, entry 3) to undergo cross-coupling with 3-phenylpropylamine with modest ee (Table 3.4, entry 1; 50% yield, 28% ee). Control reactions (not shown) confirmed the reaction required a copper catalyst, BINOL, and light. This initial result was encouraging that we may able achieve enantioconvergent amine alkylation under straightforward conditions with commercially available reagents using copper photocatalysis. However, due to the yield and low ee, a kinetic resolution of the

electrophile has not been ruled out. Other classes of electrophiles were assessed under these conditions (Table 3.4). While alkyl bromides are not amenable (entries 2, 7, and 8), some variations to the alkyl iodide are tolerated, although they result in either a loss in yield, ee, or both. The catalytic system is sensitive to sterics, as increasing steric bulk on either side of the iodide results in lower yield and ee (entries 3 and 4). Using different directing groups such as a Lewis basic tertiary amine (entry 5), sulfonamide (entry 9), or carbamate (entry 10) resulted in racemic product, or no product at all. Using a benzylic iodide did result in a high yield of product, but with little ee (entry 6),

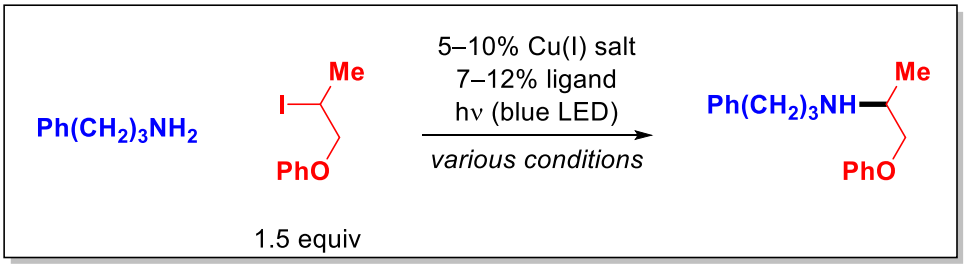
Table 3.4. Copper-catalyzed asymmetric alkylation of aliphatic amines: initial conditions and substrate identification.



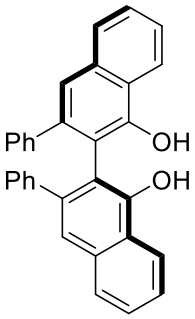
entry	electrophile	yield (%)[a]	ee (%)[b]	entry	electrophile	yield (%)[a]	ee (%)[b]
1		50	28	6[c]		88	<5
2		<5	–	7[c]		no pdt	–
3		33	12	8[c]		no pdt	–
4		29	10	9[c]		no pdt	–
5[c]		54	<5	10[c]		no pdt	–

[a]Yield determined by ^{1}H NMR analysis versus an internal standard. [b]ee determined by SFC analysis. [c]Performed with 10% CuBr and 15% (*S*)–BINOL.

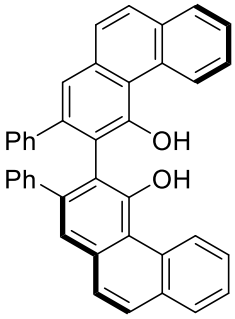
Optimization efforts then turned towards the identification of a more suitable ligand system. Various 3,3'-disusbtituted BINOL's and other aromatic diols were assessed (Figure 3.4A). While none of the ligands tested were able to improve ee's, enantioenriched product was still obtained. Further testing of additional BINOL derivatives, including 6,'6-



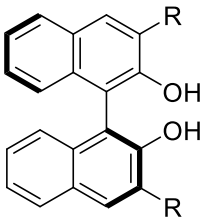
A



(*R*)–**3.1**
49% yield, **21% ee**

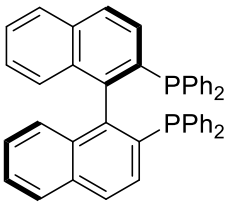


(*R*)–**3.2**
88% yield, **16% ee**

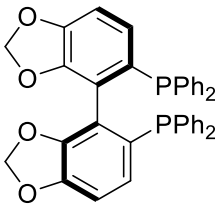


(*S*)–**3.3**	1-naph	4% yield	–
(*S*)–**3.4**	$SiPh_3$	13% yield	**<5% ee**
(*S*)–**3.5**	(3,5-CF_3)-Ph	77% yield	**20% ee**

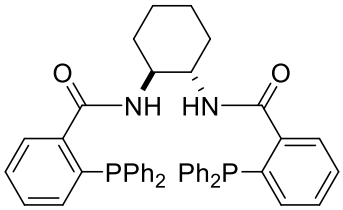
B



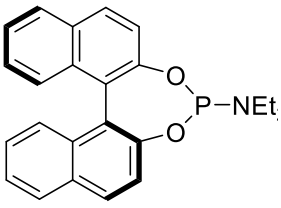
(*R*)–**3.6**
74% yield, **<5% ee**



(*R*)–**3.7**
7% yield, –



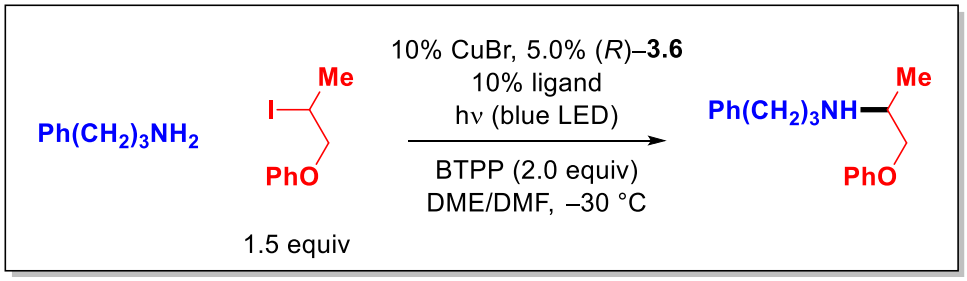
(*R*)–**3.8**
6% yield, –

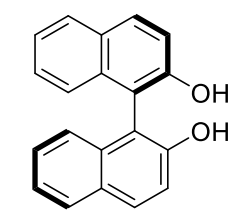


(*R*)–**3.9**
39% yield, **6% ee**

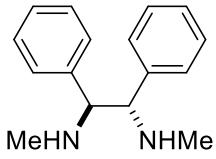
Figure 3.4. Selected examples of ligand screened for enantioinduction in the copper-catalyzed asymmetric alkylation of aliphatic amines. (**A**) Diol-based ligands. (**B**) Phosphine-based ligands.

disubstituted variants, should be carried out in the future.[22] Phosphine ligands, which had proven competent with ongoing projects the Fu group, were also tested (Figure 3.4B). Representative examples shown did not result in enantioenriched cross-coupling product, though (*R*)–**3.6** resulted in high yields. Possibly, Cu/**3.6** could serve as a photocatalyst to generate alkyl radicals, and a second Cu/ligand combination could construct the bond enantioselectively.

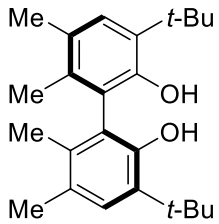




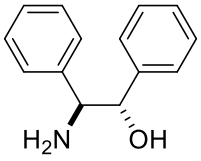
(*R*)–BINOL
46% yield, **24% ee**



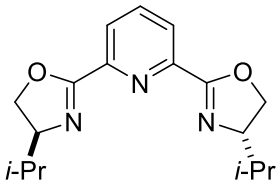
(*S,S*)–**3.10**
13% yield, **20% ee**



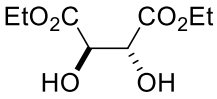
(*S*)–**3.11**
27% yield, **<5% ee**



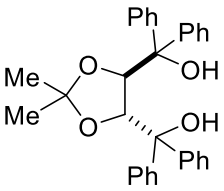
(*S,S*)–**3.12**
81% yield, **<5% ee**



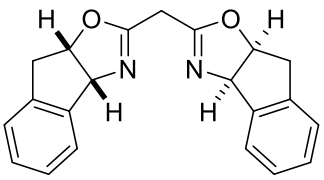
(*S,S*)–**3.13**
62% yield, **<5% ee**



(*S,S*)–**3.14**
18% yield, **<5% ee**



(*R,R*)–**3.15**
73% yield, 0% ee

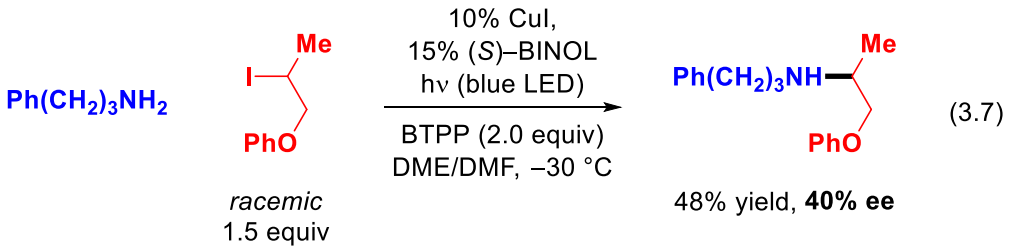


(*R,S,R,S*)–**3.16**
no product

Figure 3.5. Ligand screened for enantioinduction in the copper-catalyzed asymmetric alkylation of aliphatic amines using a copper/phosphine photocatalyst.

To this end, a number of ligands were screened in the presence of a catalytic amount of (*R*)–**3.6** (Figure 3.5). Interestingly, product with ee was obtained with two ligands. (*R*)–BINOL again achieved product in good yield and modest ee, but there appeared to be no advantage over using BINOL on its own. On the other hand, (*S*,*S*)–**3.10** was able to form product in 13% yield and 20% ee. This is particularly interesting because a copper/(*S*,*S*)–**3.10** complex should lack the photophysical properties required to undergo photoexcitation under visible light irradiation. This result suggests cooperative mechanism where a copper/(*R*)–**3.6** complex may be serving a photocatalyst and a separate copper/(*S*,*S*)–**3.10** complex may be serving as a bond-forming catalyst.. Further screening of this ligand class (1,2-diaryl-1,2-ethylenediamines) may prove to be a fruitful avenue for further optimization.

Further parameterization was performed extensively. Metal-to-ligand ratio, stoichiometry, temperature, solvent, base, additive, light source, copper precatalyst, and catalyst loading were all modified to some degree and ultimately resulted in minor modifications to the conditions with limited improved in ee (eq 3.7). As mentioned earlier, variation of the ligand system may be the most promising path forward. Specifically, BINOL derivatives and a copper/phosphine/diamine system have shown some potential for further optimization. A final note from Dante for those seeking to finish developing this reaction: *Lasciate ogne speranza, voi ch'entrate*, for once the reaction is optimized you will still have to purify the products.



(3.7)

3.5. Experimental Section

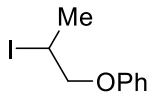
3.5.1. General Information

All manipulations of air-sensitive materials were carried out in oven-dried glassware under an N_2 atmosphere using standard Schlenk or glovebox techniques. 3-Phenylpropylamine (Alfa Aesar), cyclohexanemethylamine (Acros), cyclohexylamine (Sigma-Aldrich), 2-phenoxyethylamine (Alfa Aesar), 3-methoxypropylamine (Sigma-Aldrich), tetrahydrofurfurylamine (Sigma-Aldrich), 2,2-dimethoxyethylamine (Sigma-Aldrich), and 4-chlorophenethylamine (Acros), 4-bromophenethylamine (Oakwood), furfurylamine (Sigma-Aldrich), and thiophene-2-ethylamine (Oakwood) were distilled prior to use. Et_2O, CH_2Cl_2, and CH_3CN were purified and dried using a solvent-purification system that contained activated alumina under argon. CuI (99.999% trace metal basis, Sigma-Aldrich), *rac*-BINOL (Oakwood), BTPP (*tert*-butylimino-tri(pyrrolidino)phosphorane, Sigma-Aldrich), DMF (anhydrous, 99.8%, Sigma-Aldrich), iodocyclohexane (Oakwood), 4-iodotetrahydro-2*H*-pyran (Combi-Blocks), 1-iodo-2-2-dimethylpropane (Sigma-Aldrich), 1,3,5-trimethoxybenzene (≥99%, Sigma-Aldrich), and tetradecane (≥99%, Sigma-Aldrich) were used as received. ^{1}H, ^{13}C, and ^{31}P NMR data were collected on a Bruker 400 MHz or a Varian 500 MHz spectrometer at ambient temperature unless otherwise noted. FT-IR measurements were carried out on a Thermo Scientific Nicolet iS5 FT-IR spectrometer equipped with an iD5 ATR accessory. HRMS and LRMS were acquired using an Agilent 6850 GC, a JEOL JMS-600H MS in fast atom bombardment (FAB) ionization mode, or an Agilent 6200 Series TOF MS with an Agilent G1978A Multimode source in electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) mode. GC analyses were obtained on an Agilent 6890N GC. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle) or using basic alumina (Brockmann I, particle size 50-200 μm, Acros). Blue LED lamps (34 W; Kessil H150-Blue) were used to irradiate the reaction mixtures.

3.5.2. Preparation of Electrophiles

The yields have not been optimized.

General Procedure A.[23,24] PPh_3 (1.50 equiv) and imidazole (1.50 equiv) were dissolved in CH_2Cl_2 (~0.3 m), and the resulting solution was cooled to 0 °C. At this temperature, iodine (1.50 equiv) was added slowly in portions, and the resulting mixture was stirred for 10 min. Next, the alcohol (1.00 equiv) was added, and the resulting mixture was allowed to warm to room temperature and stirred overnight. Then, the reaction mixture was poured into hexanes (~3 times the volume of the reaction mixture) and filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel to afford the pure product.



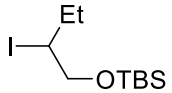
(2-Iodopropoxy)benzene. The title compound was synthesized according to General Procedure A from 1-phenoxypropan-2-ol (1.50 g, 9.86 mmol), PPh_3 (3.88 g, 14.8 mmol), imidazole (1.00 g, 14.8 mmol), and iodine (3.75 g, 14.8 mmol). The product was purified by flash chromatography with silica gel (95:5 → 80:20 hexanes/Et_2O). Colorless liquid; 1.64 g (63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 2H), 6.99 (td, *J* = 7.3, 1.1 Hz, 1H), 6.91 (dd, *J* = 7.7, 1.1 Hz, 2H), 4.46 – 4.30 (m, 1H), 4.25 (dd, *J* = 10.0, 5.5 Hz, 1H), 4.05 (dd, *J* = 10.0, 7.8 Hz, 1H), 2.01 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 129.7, 121.5, 114.9, 74.9, 24.9, 22.4.

FT-IR (neat) 3039, 2970, 2921, 2867, 1598, 1587, 1495, 1455, 1381, 1300, 1240, 1172, 1138, 1104, 1076, 1050, 1030, 1014, 994, 882, 815, 753, 691, 630 cm^{-1}.

HRMS (FAB) *m/z* $(M)^+$ calcd for $C_9H_{11}IO$: 261.9855, found: 261.9842.



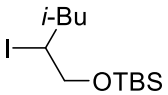
***tert*-Butyl(2-iodobutoxy)dimethylsilane.** The title compound was synthesized according to General Procedure A from 1-((*tert*-butyldimethylsilyl)oxy)butan-2-ol[25] (3.00 g, 14.2 mmol), PPh_3 (5.60 g, 21.4 mmol), imidazole (1.45 g, 21.4 mmol), and iodine (5.42 g, 21.4 mmol). The product was purified by flash chromatography with silica gel (95:5 → 80:20 hexanes/Et_2O). Colorless liquid; 2.66 g (60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 – 3.99 (m, 1H), 3.88 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.74 (dd, *J* = 10.6, 7.9 Hz, 1H), 2.01 – 1.84 (m, 1H), 1.81 – 1.63 (m, 1H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 68.7, 40.5, 29.2, 26.0, 18.5, 14.0, –5.1, –5.2.

FT-IR (neat) 2956, 2929, 2884, 2857, 1471, 1462, 1254, 1137, 1103, 1078, 838, 814, 777 cm^{-1}.

HRMS (FAB) *m/z* $(M+H-H_2)^+$ calcd for $C_{10}H_{22}IOSi$: 313.0485, found: 313.0484.



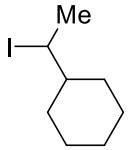
***tert*-Butyl((2-iodo-4-methylpentyl)oxy)dimethylsilane.** The title compound was synthesized according to General Procedure A from 1-((*tert*-butyldimethylsilyl)oxy)-4-methylpentan-2-ol (2.00 g, 8.3 mmol), PPh_3 (3.3 g, 12.5 mmol), imidazole (0.85 g, 12.5 mmol), and iodine (3.2 g, 12.5 mmol). The product was purified by flash chromatography with silica gel (hexanes). Colorless liquid; 1.82 g (64% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 – 4.04 (m, 1H), 3.88 (dd, *J* = 10.7, 5.4 Hz, 1H), 3.73 (dd, *J* = 10.6, 7.2 Hz, 1H), 1.92 – 1.77 (m, 1H), 1.78 – 1.64 (m, 1H), 1.61 – 1.51 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.08 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 69.6, 45.3, 37.1, 28.3, 26.0, 23.3, 21.0, 18.5, –5.0, –5.1.

FT-IR (neat) 2955, 2928, 2857, 1470, 1386, 1253, 1140, 1121, 1085, 1035, 1005, 834, 811, 775, 668 cm^{-1}.

HRMS (FAB) *m/z* $(M+H)^+$ calcd for $C_{12}H_{28}IOSi$: 343.0949, found: 343.0952.



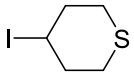
(1-Iodoethyl)cyclohexane. The title compound was synthesized according to General Procedure A from 1-cyclohexylethan-1-ol[26] (3.38 g, 25.6 mmol), PPh_3 (10.1 g, 38.4 mmol), imidazole (2.61 g, 38.4 mmol), and iodine (9.7 g, 38.4 mmol). The product was purified by flash chromatography with silica gel (hexanes). Colorless liquid; 2.13 g (35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (qd, *J* = 7.0, 3.9 Hz, 1H), 1.90 (d, *J* = 7.0 Hz, 3H), 1.88 – 1.80 (m, 1H), 1.80 – 1.69 (m, 3H), 1.69 – 1.59 (m, 1H), 1.37 – 1.21 (m, 2H), 1.21 – 0.92 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 46.7, 40.5, 32.1, 31.6, 26.4, 26.1, 26.0.

FT-IR (neat) 2981, 2925, 2852, 1448, 1377, 1295, 1236, 1196, 1164, 1145 cm^{-1}.

HRMS (GC) *m/z* $(M)^+$ calcd for $C_8H_{15}I$: 238.0219, found: 238.0194.



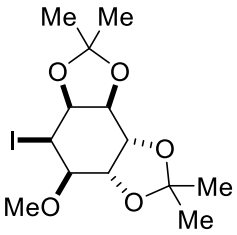
4-Iodotetrahydro-2*H*-thiopyran. The title compound was synthesized according to General Procedure A from tetrahydro-2*H*-thiopyran-4-ol[27] (2.00g, 16.9 mmol), PPh_3 (6.66 g, 25.4 mmol), imidazole (1.73 g, 25.4 mmol), and iodine (6.4 g, 25.4 mmol). The product was purified by flash chromatography with silica gel (hexanes). Colorless liquid; 1.80 g (47% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 – 4.40 (m, 1H), 2.90 – 2.74 (m, 2H), 2.65 – 2.45 (m, 2H), 2.40 – 2.15 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 38.8, 31.0, 28.1.

FT-IR (neat) 2909, 2820, 1441, 1423, 1349, 1268, 1238, 1211, 1200, 1124, 990, 943, 905, 816, 671, 643 cm^{-1}.

HRMS (FAB) *m/z* $(M)^+$ calcd for C_5H_9IS: 227.9470, found: 227.9450.



(3a*S*,4*R*,5*R*,5a*S*,8a*R*,8b*S*)-4-Iodo-5-methoxy-2,2,7,7-tetramethylhexahydrobenzo[1,2-d:3,4-d']bis([1,3]dioxole). According to a literature procedure,[28] PPh_3 (1.39 g, 5.30 mmol) and imidazole (0.36 g, 5.30 mmol) were suspended in toluene (12 mL) at room temperature. Then, iodine (1.35 g, 5.30 mmol) was added slowly in portions, and the resulting mixture was stirred for 10 min. Next, 1,2:5,6-di-O-isopropylidene-D-chiro-inositol (1.00 g, 3.54 mmol) was added, and the resulting mixture was refluxed overnight. Then, the reaction mixture was allowed to cool to room temperature and poured into a mixture of CH_2Cl_2 (25 mL) and a saturated solution of $NaHCO_3$ (25 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the residue was purified by flash chromatography with silica gel (2:1 hexanes/EtOAc). Crystalline solid; 1.19 g (89% yield, dr >20:1).

3.5.3. Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light

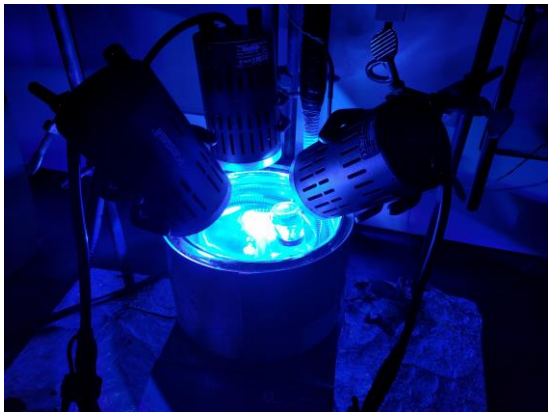
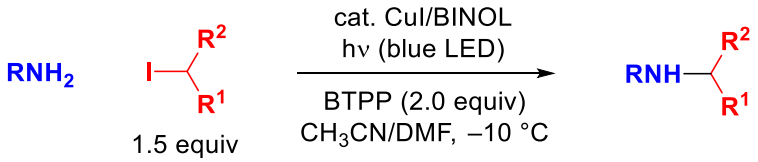


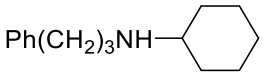
Figure 3.6. Photograph of the reaction setup for the copper-catalyzed alkylation of aliphatic amines induced by visible light.



General Procedure. CuI (6.7 mg, 0.035 mmol), *rac*-BINOL (20.1 mg, 0.070 mmol), and a stir bar were added to an oven-dried 20 mL vial. The vial was sealed with a septum cap, and then it was evacuated and backfilled with nitrogen (three cycles). DMF (1.0 mL), CH_3CN (4.0 mL), and BTPP (428 μL, 1.40 mmol) were added in turn. The mixture was stirred for 5 min, in order to dissolve the BTPP. Next, the amine (0.70 mmol) was added, followed by the alkyl iodide (1.05 mmol). The septum cap was covered with vacuum grease, the vial was detached from the Schlenk line, and the puncture holes were covered with vacuum grease. The vial was then placed, freely moving, in an isopropanol bath cooled to −10 °C by an immersion cooler. The reaction mixture was stirred at −10 °C for 5 min, and then it was irradiated with three 34 W Kessil blue LED lamps, placed ~5 cm away, for 24 h. After the reaction was complete, the reaction mixture was transferred to a 250 mL round-bottom flask with the aid of CH_2Cl_2. Next, basic alumina was added to the flask, and then the solvent was removed by rotary evaporation and then placement under high vacuum, at which time a free-flowing powder was obtained. Products were visualized with a $KMnO_4$ stain on silica-gel TLC plates using solvent systems composed of hexane/EtOAc/7 N NH_3 in MeOH; traces of DMF and NEt_3 (used in purification) are usually visible after staining.

Protection as the Trifluoroacetamide Derivative. This procedure was used in two instances (Table 3.3, entries 4 and 6) to facilitate isolation and purification (volatility). After the reaction was complete, the grease was wiped from the septum cap, and the vial was placed under a positive pressure of nitrogen on a Schlenk line and allowed to warm to room temperature. Pyridine (310 μL, 3.85 mmol) and then trifluoroacetic anhydride (495 μL, 3.50 mmol) were added. After 10 min, the nitrogen inlet was removed, and the reaction mixture was stirred at room temperature for 3 h. Next, the reaction mixture was transferred to a 250 mL round-bottom flask with the aid of CH_2Cl_2, silica gel was added to the flask, and

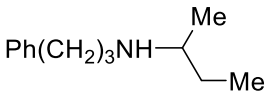
then the solvent was removed by rotary evaporation and then placed under high vacuum, at which time a free-flowing powder was obtained.



***N*-(3-Phenylpropyl)cyclohexanamine (Table 3.2, entry 1).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol). The product was purified by flash chromatography with basic alumina (8:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 122 mg (80% yield). Second run: 123 mg (80% yield).

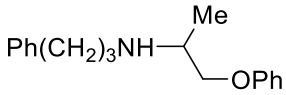
Gram Scale Reaction. CuI (143 mg, 0.750 mmol), *rac*-BINOL (429 mg, 1.50 mmol), and a cross-shaped stir bar were added to an oven-dried 100 mL round-bottom flask. The flask was sealed with a septum and then evacuated and backfilled with nitrogen (on a Schlenk line; three cycles). DMF (11.0 mL), CH_3CN (44.0 mL), and BTPP (4.59 mL, 15.0 mmol) were added in turn. The mixture was allowed to stir for 10 min, to solubilize the BTPP. Then, 3-phenylpropylamine (1.07 mL, 7.5 mmol) was added, followed by iodocyclohexane (1.46 mL, 11.3 mmol). The septum was covered with vacuum grease, the flask was detached from the Schlenk line, and the puncture holes were covered with vacuum grease. The flask was then fixed in an isopropanol bath cooled to −10 °C with an immersion cooler. The reaction mixture was stirred at −10 °C for 10 min, and then it was irradiated with four 34 W Kessil blue LED lamps, placed ~5 cm away, for 40 h. After the reaction was complete, the reaction mixture was transferred to a 500 mL round-bottom flask with the aid of CH_2Cl_2. Next, basic alumina was added to the flask, and then the solvent was removed by rotary evaporation and then placement under high vacuum, at which time a free-flowing powder was obtained. The residue was partially purified by flash chromatography with basic alumina (8:1:0.01 hexanes/EtOAc/NEt_3). The residue was then transferred to a 50 mL flask, concentrated, and placed under high vacuum for 4 h to remove traces of DMF. The residue was then purified by twice distilling with a Büchi Kugelrohr distillation apparatus (190 °C at 750 mTorr). Pale yellow oil; 1.32 g (81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.21 (d, *J* = 7.0 Hz, 3H), 2.73 – 2.62 (m, 4H), 2.41 (tt, *J* = 10.5, 3.7 Hz, 1H), 1.93 – 1.79 (m, 4H), 1.79 – 1.69 (m, 2H), 1.69 – 1.59 (m, 1H), 1.47 (s, 1H), 1.32 – 1.13 (m, 3H), 1.12 – 1.01 (m, 2H). The ^{1}H NMR spectrum matches the spectrum reported in the literature.[29]



***N*-(3-Phenylpropyl)butan-2-amine (Table 3.2, entry 2).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and 2-iodobutane (124 μL, 1.05 mmol). The product was purified by flash chromatography with basic alumina (8:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 91 mg (68% yield). Second run: 95 mg (71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 2.73 – 2.51 (m, 5H), 1.90 – 1.79 (m, 2H), 1.56 – 1.44 (m, 2H), 1.38 – 1.25 (m, 1H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H). The ^{1}H NMR spectrum matches the spectrum reported in the literature.[30]



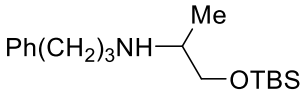
***N*-(1-Phenoxypropan-2-yl)-3-phenylpropan-1-amine (Table 3.2, entry 3).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and (2-iodopropoxy)benzene (276 mg, 1.05 mmol). The product was purified by flash chromatography with basic alumina (first column: 8:1:0.01 hexanes/EtOAc/NEt_3; second column: 3:1:0.01 hexanes/EtOAc/NEt_3 → 100% EtOAc). Pale yellow oil. First run: 126 mg (67% yield). Second run: 119 mg (63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 4H), 7.23 – 7.09 (m, 3H), 7.03 – 6.81 (m, 3H), 3.87 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.82 (dd, *J* = 9.1, 6.8 Hz, 1H), 3.15 – 3.03 (m, 1H), 2.80 – 2.59 (m, 4H), 1.95 – 1.71 (m, 2H), 1.56 (s, 1H), 1.15 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 142.2, 129.6, 128.42, 128.35, 125.9, 120.9, 114.7, 72.0, 52.5, 46.8, 33.8, 32.1, 17.6.

FR-IR (neat) 3026, 2925, 2858, 1599, 1586, 1495, 1454, 1371, 1337, 1299, 1170, 1078, 1036, 1001, 881, 813, 750, 711 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{18}H_{24}NO$: 270.1852, found: 270.1852.



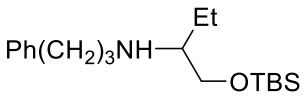
***N*-(1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-3-phenylpropan-1-amine (Table 3.2, entry 4).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and *tert*-butyl(2-iodopropoxy)dimethylsilane[31,32] (316 mg, 1.05 mmol). The product was purified by flash chromatography with basic alumina (8:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 157 mg (72% yield). Second run: 164 mg (76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.25 – 7.16 (m, 3H), 3.59 – 3.38 (m, 2H), 2.80 – 2.65 (m, 4H), 2.59 (ddd, *J* = 11.2, 7.8, 6.6 Hz, 1H), 1.85 (qdd, *J* = 7.9, 6.4, 4.8 Hz, 2H), 1.63 (s, 1H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.92 (s, 9H), 0.08 (d, *J* = 1.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 128.5, 128.5, 125.9, 67.5, 54.8, 46.9, 33.8, 32.2, 26.1, 18.4, 17.0, –5.2, –5.3.

FT-IR (neat) 3026, 2954, 2928, 2856, 1496, 1471, 1462, 1454, 1388, 1361, 1251, 1089, 1030, 1006, 842, 814, 774, 744, 697, 667 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{18}H_{34}NOSi$: 308.2404, found: 308.2398.



1-((*tert*-Butyldimethylsilyl)oxy)-*N*-(3-phenylpropyl)butan-2-amine (Table 3.2, entry 5). The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and *tert*-butyl(2-iodobutoxy)dimethylsilane

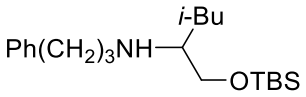
(331 mg, 1.05 mmol). The product was purified by flash chromatography with basic alumina (8:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 127 mg (56% yield). Second run: 121 mg (54% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.18 (m, 3H), 3.70 – 3.41 (m, 2H), 2.78 – 2.56 (m, 4H), 2.56 – 2.47 (m, 1H), 1.90 – 1.76 (m, 2H), 1.57 (s, 1H), 1.52 – 1.32 (m, 2H), 0.92 (d, *J* = 2.0 Hz, 12H), 0.08 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 128.5, 128.4, 125.8, 64.7, 60.8, 46.9, 33.8, 32.3, 26.1, 24.1, 18.4, 10.5, –5.2, –5.3.

FT-IR (neat) 3027, 2955, 2928, 2856, 1496, 1471, 1462, 1388, 1361, 1251, 1088, 1006, 938, 884, 813, 774, 743, 697, 668 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{19}H_{36}NOSi$: 322.2561, found: 322.2567.



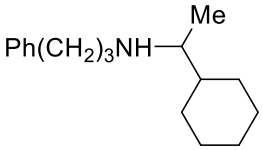
1-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-*N*-(3-phenylpropyl)pentan-2-amine (Table 3.2, entry 6). The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and *tert*-butyl((2-iodo-4-methylpentyl)oxy)dimethyl-silane (361 mg, 1.05 mmol). The product was purified by flash chromatography with basic alumina (10:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 86 mg (35% yield). Second run: 33 mg (33% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.21 – 7.14 (m, 3H), 3.59 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.42 (dd, *J* = 10.0, 6.5 Hz, 1H), 2.75 – 2.44 (m, 5H), 1.86 – 1.75 (m, 2H), 1.71 – 1.55 (m, 1H), 1.48 (s, 1H), 1.30 – 1.12 (m, 2H), 1.01 – 0.74 (m, 15H), 0.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 128.5, 128.4, 125.8, 65.2, 57.3, 46.8, 41.2, 33.8, 32.3, 26.1, 25.2, 23.4, 23.0, 18.4, –5.2, –5.3.

FT-IR (neat) 3027, 2953, 2927, 2856, 1496, 1471, 1384, 1361, 1251, 1087, 1006, 936, 834, 812, 774, 743, 697, 668 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{21}H_{40}NOSi$: 350.2874, found: 350.2874.



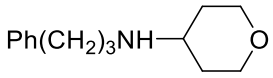
***N*-(1-Cyclohexylethyl)-3-phenylpropan-1-amine (Table 3.2, entry 7).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and (1-iodoethyl)cyclohexane (251 mg, 1.05 mmol). Catalyst loading: 10% CuI and 20% *rac*-BINOL. The product was purified by flash chromatography with basic alumina (10:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 72 mg (42% yield). Second run: 69 mg (40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H), 7.14 – 7.07 (m, 3H), 2.66 – 2.54 (m, 3H), 2.47 (dt, *J* = 11.4, 7.2 Hz, 1H), 2.34 (qd, *J* = 6.5, 5.0 Hz, 1H), 1.77 – 1.63 (m, 4H), 1.63 – 1.54 (m, 3H), 1.29 – 0.97 (m, 5H), 0.96 – 0.83 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 128.5, 128.4, 125.8, 57.9, 47.2, 43.0, 33.9, 32.2, 30.1, 28.1, 26.9, 26.8, 26.6, 16.9.

FT-IR (neat) 3062, 3026, 2923, 2851, 1603, 1496, 1450, 1371, 1156, 1030, 745, 698 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{17}H_{28}N$: 246.2216, found: 246.2218.



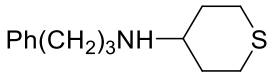
***N*-(3-Phenylpropyl)tetrahydro-2*H*-pyran-4-amine (Table 3.2, entry 8).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and 4-iodotetrahydro-2*H*-pyran (224 mg, 1.05 mmol). The product was purified by flash chromatography with basic alumina (3:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 129 mg (84% yield). Second run: 123 mg (80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.21 (dtd, *J* = 8.4, 3.3, 2.8, 1.8 Hz, 3H), 4.09 – 3.90 (m, 2H), 3.40 (td, *J* = 11.7, 2.2 Hz, 2H), 2.81 – 2.46 (m, 5H), 1.98 – 1.78 (m, 4H), 1.52 – 1.11 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 128.37, 128.36, 125.9, 67.0, 54.2, 46.1, 34.0, 33.8, 32.1.

FT-IR (neat) 3061, 2932, 2842, 1603, 1495, 1466, 1453, 1365, 1234, 1143, 1093, 1010, 981, 865, 817, 745, 712, 625 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{14}H_{22}NO$: 220.1696, found: 220.1695.



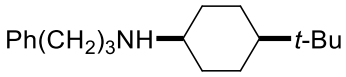
***N*-(3-Phenylpropyl)tetrahydro-2*H*-thiopyran-4-amine (Table 3.2, entry 9).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and 4-iodotetrahydro-2*H*-thiopyran (240 mg, 1.05 mmol). Catalyst loading: 10% CuI and 20% *rac*-BINOL. The product was purified by flash chromatography with basic alumina (5:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 91 mg (55% yield). Second run: 93 mg (56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.21 (ddt, *J* = 8.1, 3.4, 1.5 Hz, 3H), 2.79 – 2.56 (m, 8H), 2.45 (tt, *J* = 10.3, 3.4 Hz, 1H), 2.20 – 2.11 (m, 2H), 1.83 (dtd, *J* = 9.0, 7.6, 6.6 Hz, 2H), 1.51 (dtd, *J* = 13.1, 10.2, 4.7 Hz, 2H), 0.91 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 128.38, 128.35, 125.9, 56.2, 46.3, 34.9, 33.8, 32.2, 27.8.

FT-IR (neat) 3052, 3018, 2903, 2850, 1606, 1493, 1450, 1423, 1338, 1272, 1218, 1200, 1124, 998, 948, 915, 815, 671 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{14}H_{22}NS$: 236.1467, found: 236.1465.



(1*R,4*R**)-4-(*tert*-Butyl)-*N*-(3-phenylpropyl)cyclohexan-1-amine (Table 3.2, entry 10).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and 1-(*tert*-butyl)-4-iodocyclohexane[33] (cis/trans 5:1; 281 mg, 1.05 mmol). The product was purified by flash chromatography with basic

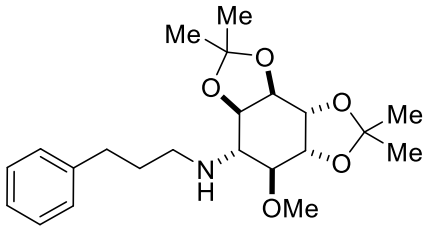
alumina (8:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 97 mg (51% yield, dr >20:1). Second run: 107 mg (56% yield, dr >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 2.68 (ddd, *J* = 7.9, 6.8, 2.7 Hz, 4H), 2.39 – 2.29 (m, 1H), 2.01 – 1.92 (m, 2H), 1.90 – 1.66 (m, 5H), 1.10 – 0.98 (m, 5H), 0.86 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 128.5, 128.4, 125.9, 57.4, 48.0, 46.9, 34.2, 34.0, 32.5, 32.3, 27.8, 26.3.

FT-IR (neat) 3026, 2938, 2858, 1452, 1364, 745, 699 cm^{-1}.

HRMS (FAB) *m/z* $(M)^+$ calcd for $C_{19}H_{31}N$: 273.2457, found: 273.2467.



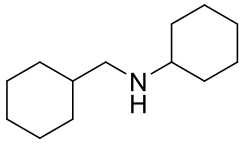
(3a*R*,4*S*,5*S*,5a*R*,8a*R*,8b*R*)-5-Methoxy-2,2,7,7-tetramethyl-*N*-(3-phenylpropyl)hexahydro-benzo[1,2-*d*:3,4-*d*']bis([1,3]dioxole)-4-amine (Table 3.2, entry 11). The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (161 μL, 0.70 mmol) and (3a*S*,4*R*,5*R*,5a*S*,8a*R*,8b*S*)-4-iodo-5-methoxy-2,2,7,7-tetramethylhexahydrobenzo[1,2-*d*:3,4-*d*']bis([1,3]dioxole) (α/β >20:1; 269 mg, 0.70 mmol). Catalyst loading: 10% CuI and 20% *rac*-BINOL; reaction time: 48 h. The product was purified by flash chromatography with basic alumina (10:1:0.01 → 5:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 170 mg (62% yield, dr >20:1). Second run: 165 mg (60% yield, dr >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 4.26 – 4.16 (m, 2H), 4.16 – 4.06 (m, 2H), 3.55 (s, 3H), 3.22 (dd, *J* = 11.7, 6.3 Hz, 1H), 2.93 – 2.84 (m, 1H), 2.78 – 2.63 (m, 4H), 1.98 (s, 1H), 1.91 – 1.80 (m, 2H), 1.53 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 128.5, 128.4, 125.8, 110.0, 109.9, 80.3, 80.2, 80.0, 77.6, 77.2, 59.4, 59.0, 47.6, 33.7, 32.1, 28.0, 27.9, 25.5, 25.4.

FT-IR (neat) 3328, 2986, 2934, 1603, 1496, 1454, 1380, 1370, 1245, 1214, 1160, 1110, 1090, 976 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{22}H_{34}NO_5$: 392.2431, found: 392.2441.



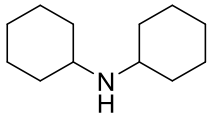
***N*-(Cyclohexylmethyl)cyclohexanamine (Table 3.3, entry 1).** The title compound was synthesized according to the General Procedure from cyclohexanemethylamine (91 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol) using 10% CuI (13.3 mg, 0.070 mmol) and 20% *rac*-BINOL (40.1 mg, 0.140 mmol). The product was purified by flash chromatography with basic alumina (12:1:0.01 → 6:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 112 mg (82% yield). Second run: 115 mg (84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (d, *J* = 6.7 Hz, 2H), 2.42 – 2.32 (m, 1H), 1.94 – 1.83 (m, 2H), 1.78 – 1.59 (m, 8H), 1.49 – 1.37 (m, 1H), 1.31 – 1.00 (m, 9H), 0.97 – 0.83 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.9, 53.8, 38.2, 33.7, 31.6, 26.7, 26.2, 26.1, 25.2.

FT-IR (neat) 2922, 2851, 1448, 1129 cm^{-1}.

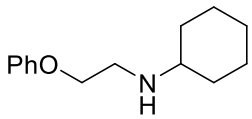
HRMS (FAB) *m/z* $(M+H)^+$ calcd for $C_{13}H_{26}N$: 196.2065, found: 196.2067.



Dicyclohexylamine (Table 3.3, entry 2). The title compound was synthesized according to the General Procedure from cyclohexylamine (80 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol) using 10% CuI (13.3 mg, 0.070 mmol) and 20% *rac*-BINOL (40.1 mg, 0.140 mmol). The product was purified by flash chromatography with basic alumina

(15:1:0.01 → 6:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 93 mg (73% yield). Second run: 88 mg (69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (tt, *J* = 10.6, 3.8 Hz, 2H), 1.87 (ddt, *J* = 15.1, 6.3, 2.8 Hz, 4H), 1.80 – 1.67 (m, 4H), 1.62 (dpd, *J* = 12.1, 3.3, 1.5 Hz, 2H), 1.32 – 1.10 (m, 6H), 1.09 – 0.97 (m, 4H), 0.86 (s, 1H). The ^{1}H NMR spectrum matches the spectrum reported in the literature.[34]



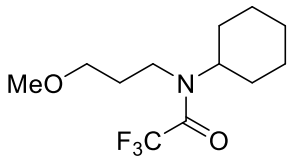
***N*-(2-Phenoxyethyl)cyclohexanamine (Table 3.3, entry 3).** The title compound was synthesized according to the General Procedure from 2-phenoxyethylamine (92 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol) using 10% CuI (13.3 mg, 0.070 mmol) and 20% *rac*-BINOL (40.1 mg, 0.140 mmol). The product was purified by flash chromatography with basic alumina (first column: 8:1:0.01 hexanes/EtOAc/NEt_3; second column: 3:1:0.01 → 0:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 94 mg (61% yield). Second run: 94 mg (61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 2H), 7.01 – 6.90 (m, 3H), 4.09 (t, *J* = 5.3 Hz, 2H), 3.05 (t, *J* = 5.3 Hz, 2H), 2.51 (tt, *J* = 10.5, 3.8 Hz, 1H), 2.00 – 1.90 (m, 2H), 1.85 – 1.73 (m, 2H), 1.70 – 1.61 (m, 1H), 1.58 (s, 1H), 1.34 – 1.08 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 129.6, 120.9, 114.7, 67.7, 56.8, 46.1, 33.7, 26.3, 25.2.

FT-IR (neat) 2924, 2851, 1599, 1587, 1496, 1458, 1242, 1171, 1135, 1079, 1042, 883, 800, 751, 690 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{14}H_{22}NO$: 220.1696, found: 220.1693.



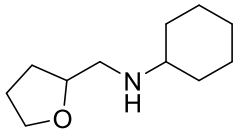
***N*-Cyclohexyl-2,2,2-trifluoro-*N*-(3-methoxypropyl)acetamide (Table 3.3, entry 4).** The title compound was synthesized according to the General Procedure from 3-methoxypropylamine (76 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol) using 10% CuI (13.3 mg, 0.070 mmol) and 20% *rac*-BINOL (40.1 mg, 0.140 mmol). The reaction mixture was then subjected to in situ protection. The product was purified by flash chromatography with silica gel (95:5 → 80:20 hexanes/EtOAc). Pale yellow oil. First run: 151 mg (81% yield). Second run: 163 mg (87% yield).

^{1}H NMR (500 MHz, d_6-DMSO, 130 °C) δ 3.77 – 3.65 (m, 1H), 3.41 (s, 4H), 3.28 (d, *J* = 4.8 Hz, 3H), 1.83 (q, *J* = 6.8 Hz, 4H), 1.77 – 1.59 (m, 5H), 1.42 – 1.27 (m, 2H), 1.19 (td, *J* = 12.6, 5.9 Hz, 1H).

^{13}C NMR (126 MHz, d_6-DMSO, 130 °C) δ 156.2 (q, *J* = 34.6 Hz), 117.1 (q, *J* = 288.7 Hz), 70.1, 58.4, 58.2, 41.9, 30.8, 29.6, 25.8, 25.1.

FT-IR (neat) 2934, 2860, 1682, 1447, 1257, 1207, 1184, 1117, 1030, 998, 896, 758, 705 cm^{-1}.

HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{12}H_{21}F_3NO_2$: 268.1519, found: 268.1503.



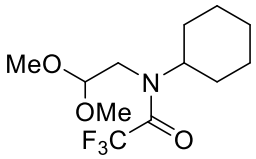
***N*-((Tetrahydrofuran-2-yl)methyl)cyclohexanamine (Table 3.3, entry 5).** The title compound was synthesized according to the General Procedure from tetrahydrofurfurylamine (72 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol) using 10% CuI (13.3 mg, 0.070 mmol) and 20% *rac*-BINOL (40.1 mg, 0.140 mmol). The product was purified by flash chromatography with basic alumina (3:1:0.01 → 1:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 77 mg (60% yield). Second run: 76 mg (59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (dtd, *J* = 7.7, 6.9, 3.7 Hz, 1H), 3.86 (dt, *J* = 8.3, 6.6 Hz, 1H), 3.76 (dt, *J* = 8.2, 6.8 Hz, 1H), 2.75 (dd, *J* = 11.7, 3.8 Hz, 1H), 2.64 (dd, *J* = 11.8, 8.1 Hz, 1H), 2.43 (tt, *J* = 10.4, 3.8 Hz, 1H), 2.01 – 1.86 (m, 5H), 1.74 (dt, *J* = 13.2, 3.9 Hz, 2H), 1.65 – 1.48 (m, 3H), 1.30 – 1.06 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 78.6, 67.8, 57.0, 51.7, 33.6, 33.5, 29.4, 26.2, 25.7, 25.09, 25.07.

FT-IR (neat) 2923, 2851, 1673, 1449, 1368, 1258, 1183, 1139, 1068, 1018, 919, 889, 843, 788, 742 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{11}H_{22}NO$: 184.1696, found: 184.1698.



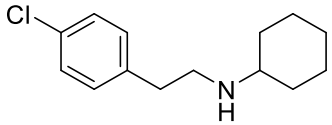
***N*-Cyclohexyl-*N*-(2,2-dimethoxyethyl)-2,2,2-trifluoroacetamide (Table 3.3, entry 6).** The title compound was synthesized according to the General Procedure from 2,2-dimethoxyethylamine (76 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol) using 10% CuI (13.3 mg, 0.070 mmol) and 20% *rac*-BINOL (40.1 mg, 0.140 mmol). The reaction mixture was then subjected to in situ protection. The product was purified by flash chromatography with silica gel (95:5 → 80:20 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 147 mg (74% yield). Second run: 150 mg (76% yield).

^{1}H NMR (500 MHz, d_6-DMSO, 100 °C) δ 4.56 (t, *J* = 4.9 Hz, 1H), 3.64 (p, *J* = 7.5 Hz, 1H), 3.43 (d, *J* = 5.0 Hz, 2H), 3.35 (d, *J* = 2.0 Hz, 6H), 1.81 (d, *J* = 13.5 Hz, 2H), 1.77 – 1.66 (m, 4H), 1.61 (dt, *J* = 13.2, 3.2 Hz, 1H), 1.34 – 1.23 (m, 2H), 1.15 (ddt, *J* = 16.3, 12.9, 6.5 Hz, 1H).

^{13}C NMR (126 MHz, d_6-DMSO, 100 °C) δ 156.7 (d, *J* = 34.3 Hz), 117.0 (d, *J* = 289.1 Hz), 102.9, 58.7, 55.2, 47.0, 30.9, 25.9, 25.1.

FT-IR (neat) 2936, 2858, 1684, 1447, 1257, 1211, 1187, 1137, 1122, 1077, 1032, 981, 896, 809, 759, 711 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{12}H_{21}F_3NO_3$: 284.1468, found: 284.1494.



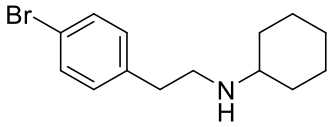
***N*-(4-Chlorophenethyl)cyclohexanamine (Table 3.3, entry 7).** The title compound was synthesized according to the General Procedure from 4-chlorophenethylamine (98 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol) using 10% CuI (13.3 mg, 0.070 mmol) and 20% *rac*-BINOL (40.1 mg, 0.140 mmol). The product was purified by flash chromatography with basic alumina (3:1:0.01 → 1:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 102 mg (61% yield). Second run: 111 mg (67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.18 – 7.13 (m, 2H), 2.97 – 2.74 (m, 4H), 2.44 (tt, *J* = 10.5, 3.8 Hz, 1H), 1.93 – 1.81 (m, 2H), 1.79 – 1.68 (m, 2H), 1.67 – 1.57 (m, 1H), 1.32 – 1.03 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 131.8, 130.0, 128.5, 56.8, 48.1, 36.0, 33.6, 26.1, 25.1.

FT-IR (neat) 2924, 2851, 1491, 1448, 1406, 1363, 1347, 1125, 1091, 1015, 889, 834, 809, 714, 667, 630 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{14}H_{21}ClN$: 238.1357, found: 238.1352.



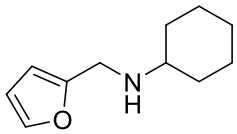
***N*-(4-Bromophenethyl)cyclohexanamine (Table 3.3, entry 8).** The title compound was synthesized according to the General Procedure from 4-bromophenethylamine (109 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol). The product was purified by flash chromatography with basic alumina (3:1:0.01 → 1:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 103 mg (52% yield). Second run: 104 mg (53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 7.16 – 7.07 (m, 2H), 2.97 – 2.86 (m, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.43 (tt, *J* = 10.5, 3.8 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.73 (dt, *J* = 13.4, 3.7 Hz, 2H), 1.66 – 1.59 (m, 1H), 1.36 – 1.12 (m, 4H), 1.11 – 1.00 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 131.5, 130.4, 119.9, 56.7, 48.0, 36.1, 33.6, 26.1, 25.1.

FT-IR (neat) 2930, 2853, 1488, 1449, 1127, 1072, 1011, 808 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{14}H_{21}{}^{79}BrN$: 282.0852, found: 282.0849.



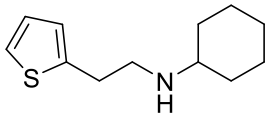
***N*-(Furan-2-ylmethyl)cyclohexanamine (Table 3.3, entry 9).** The title compound was synthesized according to the General Procedure from furfurylamine (72 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol). The product was purified by flash chromatography with basic alumina (6:1:0.01 → 1:2:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 64 mg (55% yield). Second run: 64 mg (52% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.17 – 6.10 (m, 1H), 3.80 (d, *J* = 0.7 Hz, 2H), 2.44 (tt, *J* = 10.4, 3.8 Hz, 1H), 1.94 – 1.82 (m, 2H), 1.76 – 1.67 (m, 2H), 1.64 – 1.54 (m, 1H), 1.40 (s, 1H), 1.29 – 1.07 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 141.6, 110.1, 106.5, 55.8, 43.4, 33.4, 26.1, 25.0.

FT-IR (neat) 2924, 2852, 1505, 1449, 1370, 1345, 1147, 1117, 1074, 1010, 919, 885, 803, 727 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{11}H_{18}NO$: 180.1383, found: 180.1382.



***N*-(2-(Thiophen-2-yl)ethyl)cyclohexanamine (Table 3.3, entry 10).** The title compound was synthesized according to the General Procedure from thiophene-2-ethylamine (82 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol) using 10% CuI (13.3 mg, 0.070 mmol) and 20% *rac*-BINOL (40.1 mg, 0.140 mmol). The product was purified by flash chromatography with basic alumina (6:1:0.01 → 1:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 117 mg (80% yield). Second run: 117 mg (80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.84 (dt, *J* = 3.5, 1.1 Hz, 1H), 3.06 – 2.87 (m, 4H), 2.44 (tt, *J* = 10.5, 3.8 Hz, 1H), 1.91 – 1.81 (m, 2H), 1.76 – 1.67 (m, 2H), 1.66 – 1.57 (m, 1H), 1.28 – 1.01 (m, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 126.8, 124.9, 123.5, 56.6, 48.3, 33.6, 30.8, 26.2, 25.1.
FT-IR (neat) 2923, 2850, 1447, 1364, 1258, 1126, 1041, 889, 848, 820, 689 cm^{-1}.
HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{12}H_{20}NS$: 210.1311, found: 210.1310.

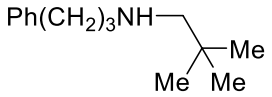
3.5.4. Reactions with Neopentyl Iodide

In a nitrogen-filled glovebox, an oven-dried 4 mL vial was charged with a stir bar and, when applicable, CuI (3.8 mg, 0.020 mmol) and *rac*-BINOL (11.5 mg, 0.0400 mmol). DMF (0.3 mL), CH_3CN (1.1 mL), and BTPP (122 μL, 0.400 mmol) were added in turn. The reaction mixture was allowed to stir for 5 min, to solubilize the BTPP. Then, 3-phenylpropylamine (28.5 μL, 0.200 mmol) was added, followed by neopentyl iodide (40 μL, 0.30 mmol). The vial was immediately sealed with a PTFE-lined vial cap and then removed from the glovebox.

Entries 1 and 2: The vial was placed upside-down in a fixed position in an isopropanol bath cooled to −10 °C with an immersion cooler. The reaction mixture was stirred at −10 °C for 5 min, and then, if applicable, it was irradiated with a single 34 W Kessil blue LED lamp from ~3 cm away for 24 h.

Entries 3 and 4: The vial was placed in a 100 °C oil bath for 24 h.

^{1}H NMR analysis. A 20 mL vial was charged with a known amount of 1,3,5-trimethoxybenzene. The reaction vessel was uncapped, diluted with CH_2Cl_2 (~2 mL), recapped, and shaken. Then, the mixture was passed through a plug of basic alumina into the 20 mL vial containing the internal standard. The reaction vessel was washed three times with EtOAc (~4 mL), and the washings were passed through a plug of basic alumina into the 20 mL vial. The filtered reaction mixture was concentrated and then placed under high vacuum for 2 h in order to remove most of the DMF.



2,2-Dimethyl-*N*-(3-phenylpropyl)propan-1-amine. The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and 1-iodo-2,2-dimethylpropane (140 μL, 1.05 mmol). Catalyst loading: 10% CuI and 20% *rac*-BINOL; reaction time: 48 h. The product was purified by flash chromatography with basic alumina (8:1:0.01 hexanes/EtOAc/NEt_3). Pale yellow oil. First run: 101 mg (70% yield). Second run: 99 mg (69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.26 – 7.17 (m, 3H), 2.74 – 2.62 (m, 4H), 2.36 (s, 2H), 1.91 – 1.79 (m, 2H), 0.93 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 128.5, 128.4, 125.8, 62.5, 50.6, 33.8, 31.8, 31.5, 28.0.

FT-IR (neat) 3026, 2949, 2863, 2809, 1496, 1463, 1453, 1361, 1125, 1030, 907, 742, 710 cm^{-1}.

HRMS (ESI/APCI) *m/z* $(M+H)^+$ calcd for $C_{14}H_{24}N$: 206.1903, found: 206.1896.

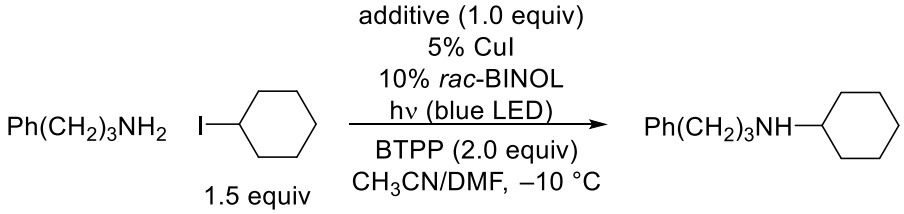
3.5.5. TEMPO Trapping Experiment

In a nitrogen-filled glovebox, an oven-dried 4 mL vial was charged with CuI (1.9 mg, 0.010 mmol), *rac*-BINOL (5.7 mg, 0.020 mmol), and a stir bar. DMF (0.3 mL), CH_3CN (1.1 mL), and BTPP (122 μL, 0.400 mmol) were added in turn. The reaction mixture was allowed to stir for 5 min, to solubilize the BTPP. Then, 3-phenylpropylamine (28.5 μL, 0.200 mmol) was added, followed by iodocyclohexane (39.0 μL, 0.302 mmol) and TEMPO (47 mg, 0.30 mmol). Next, the vial was immediately sealed with a PTFE-lined vial cap, removed from the glovebox, and placed upside-down in a fixed position in an isopropanol bath cooled to −10 °C with an immersion cooler. After stirring for 5 min at −10 °C, the reaction mixture was irradiated with a single 34 W Kessil blue LED lamp, placed ~3 cm away, for 24 h. The experiment was run four times: twice for GC analysis (to determine the yield of the TEMPO adduct) and twice for ^{1}H NMR analysis (to determine the yield of the product).

GC analysis. Tetradecane (52.0 μL, 0.200 mmol) was added to the reaction mixture, and then the mixture was diluted with CH_2Cl_2 (~2 mL). An aliquot (~200 μL) of the reaction mixture was passed through a plug of silica gel, followed by EtOAc (~1 mL). The filtrate was then analyzed by GC.

^{1}H NMR analysis. A 20 mL vial was charged with a known amount of 1,3,5-trimethoxybenzene. The reaction vessel was uncapped, diluted with CH_2Cl_2 (~2 mL), recapped, and shaken. Then, the mixture was passed through a plug of basic alumina into the 20 mL vial containing the internal standard. The reaction vessel was washed three times with EtOAc (~4 mL), and the washings were passed through a plug of basic alumina into the 20 mL vial. The filtered reaction mixture was concentrated and then placed under high vacuum for 2 h in order to remove most of the DMF.

3.5.6. Additive Effects



In a nitrogen-filled glovebox, an oven-dried 4 mL vial was charged with CuI (1.9 mg, 0.010 mmol), *rac*-BINOL (5.7 mg, 0.020 mmol), and a stir bar. DMF (0.3 mL), CH_3CN (1.1 mL), and BTPP (122 μL, 0.400 mmol) were added in turn. The reaction mixture was allowed to stir for 5 min, to solubilize the BTPP. Then, 3-phenylpropylamine (28.5 μL, 0.200 mmol) was added, followed by iodocyclohexane (39.0 μL, 0.302 mmol) and the additive (0.200 mmol). Next, the vial was immediately sealed with a PTFE-lined vial cap, removed from the glovebox, and placed upside-down in a fixed position in an isopropanol bath cooled to −10 °C with an immersion cooler. After stirring for 5 min at −10 °C, the reaction mixture was irradiated with a single 34 W Kessil blue LED lamp, placed ~3 cm away, for 24 h. For each additive, four reactions were run: two for GC analysis (to determine

the amount of additive remaining) and two for ^{1}H NMR analysis (to determine the yield of the product).

GC analysis. Tetradecane (52.0 μL, 0.200 mmol) was added to the reaction mixture, and then the mixture was diluted with CH_2Cl_2 (~2 mL). An aliquot (~200 μL) of the reaction mixture was passed through a plug of silica gel, followed by EtOAc (~1 mL). The filtrate was then analyzed by GC.

^{1}H NMR analysis. A 20 mL vial was charged with a known amount of 1,3,5-trimethoxybenzene. The reaction vessel was uncapped, diluted with CH_2Cl_2 (~2 mL), recapped, and shaken. Then, the mixture was passed through a plug of basic alumina into the 20 mL vial containing the internal standard. The reaction vessel was washed three times with EtOAc (~4 mL), and the washings were passed through a plug of basic alumina into the 20 mL vial. The filtered reaction mixture was concentrated and then placed under high vacuum for 2 h in order to remove most of the DMF.

Table 3.5. Effect of additives (average of two experiments).

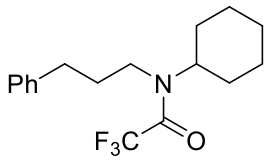
Entry	Additive	Remaining Additive (%)	Yield (%)
1	*cis*-5-decene	97	92
2	*trans*-5-decene	95	92
3	5-nonanol	92	90
4	5-decyne	97	87
5	methyl octanoate	98	84
6	2-nonanone	>99	78
7	iodobenzene	61	100
8	N-methylpyrrolidone	99	90
9	pyridine	88	66
10	cyclohexanecarboxaldehyde	44	51
11	nitrocyclopentane	–	<1

3.5.7. N-Protection of the Amine

The yields have not been optimized.

Table 3.6. N-Protection of the amine.

Entry	Protecting Group	Yield (%)
1	Trifluoroacetamide	86
2	Boc	73
3	Troc	68
4	Tosyl	64
5	Nosyl	56



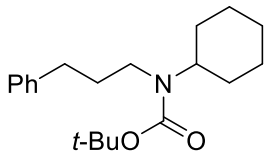
***N*-Cyclohexyl-2,2,2-trifluoro-*N*-(3-phenylpropyl)acetamide (Table 3.6, entry 1).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol). After the N-alkylation was complete, the reaction mixture was allowed to warm to room temperature. Next, pyridine (310 μL, 3.87 mmol) and TFAA (500 μL, 3.51 mmol) were added, and the resulting mixture was stirred at room temperature for 5 h. Then, the reaction mixture was transferred to a 250 mL round-bottom flask with the aid of CH_2Cl_2, silica gel was added to the flask, and the solvent was removed by rotary evaporation. The product was purified by flash chromatography with silica gel (90:10 → 50:50 hexanes/Et_2O). Colorless oil. First run: 188 mg (86% yield). Second run: 189 mg (86% yield).

^{1}H NMR (500 MHz, d_6-DMSO, 130 °C) δ 7.29 (t, *J* = 7.7 Hz, 2H), 7.25 – 7.16 (m, 3H), 3.70 (td, *J* = 11.6, 5.4 Hz, 1H), 3.43 – 3.27 (m, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.91 (t, *J* = 7.8 Hz, 2H), 1.81 (dt, *J* = 13.4, 3.5 Hz, 2H), 1.75 – 1.50 (m, 5H), 1.38 – 1.26 (m, 2H), 1.21 – 1.08 (m, 1H).

^{13}C NMR (126 MHz, d_6-DMSO, 130 °C) δ 156.1 (q, *J* = 34.3 Hz), 141.5, 128.7, 128.6, 126.2, 117.1 (q, *J* = 288.8 Hz), 58.3, 44.1, 33.1, 30.8, 25.8, 25.1.

FT-IR (neat) 2935, 2859, 1679, 1497, 1453, 1257, 1207, 1181, 1132, 1084, 1030, 996, 896, 749, 698 cm^{-1}.

LRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{17}H_{23}F_3NO$: 314.2, found: 314.1.



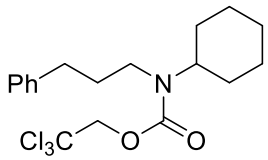
***tert*-Butyl cyclohexyl(3-phenylpropyl)carbamate (Table 3.6, entry 2).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol). After the N-alkylation was complete, the reaction mixture was allowed to warm to room temperature. Next, Boc_2O (764 mg, 3.50 mmol) and 4-DMAP (86 mg, 0.70 mmol) were added, and the resulting mixture was stirred at room temperature for 24 h. Then, the reaction mixture was transferred to a 250 mL round-bottom flask with the aid of CH_2Cl_2, silica gel was added to the flask, and the solvent was removed by rotary evaporation. The product was purified by flash chromatography with silica gel (95:5 → 50:50 hexanes/Et_2O). Colorless oil. First run: 162 mg (73% yield). Second run: 161 mg (73% yield).

^{1}H NMR (500 MHz, d_6-DMSO, 70 °C) δ 7.27 (dd, *J* = 7.9, 7.1 Hz, 2H), 7.22 – 7.13 (m, 3H), 3.60 (s, 1H), 3.11 – 3.04 (m, 2H), 2.56 (t, *J* = 7.7 Hz, 2H), 1.82 – 1.69 (m, 4H), 1.65 – 1.54 (m, 3H), 1.48 – 1.39 (m, 2H), 1.38 (s, 9H), 1.24 (qt, *J* = 13.1, 3.6 Hz, 2H), 1.04 (qt, *J* = 13.0, 3.7 Hz, 1H).

^{13}C NMR (126 MHz, d_6-DMSO, 70 °C) δ 154.9, 142.2, 128.65, 128.57, 126.1, 78.6, 56.0, 43.4, 33.3, 32.3, 31.2, 28.6, 26.2, 25.6.

FT-IR (neat) 2973, 2930, 2856, 1720, 1687, 1497, 1453, 1410, 1390, 1364, 1298, 1273, 1254, 1159, 1101, 1076, 908, 894, 869, 774, 749, 698 cm^{-1}.

HRMS (FAB) *m/z* $(M+H)^+$ calcd for $C_{20}H_{32}NO_2$: 318.2433, found: 318.2433.



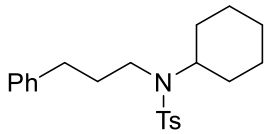
2,2,2-Trichloroethyl cyclohexyl(3-phenylpropyl)carbamate (Table 3.6, entry 3). The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol). After the N-alkylation was complete, the reaction mixture was allowed to warm to room temperature. Next, pyridine (310 μL, 3.87 mmol) and TrocCl (742 mg, 3.50 mmol) were added, and the resulting mixture was stirred at room temperature for 24 h. Then, the reaction mixture was transferred to a 250 mL round-bottom flask with the aid of CH_2Cl_2, silica gel was added to the flask, and the solvent was removed by rotary evaporation. The product was purified by flash chromatography with silica gel (95:5 → 50:50 hexanes/Et_2O). Pale yellow oil. First run: 193 mg (70% yield). Second run: 180 mg (65% yield).

^{1}H NMR (500 MHz, d_6-DMSO, 100 °C) δ 7.30 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 4.82 (s, 2H), 3.69 (tt, *J* = 12.0, 3.8 Hz, 1H), 3.26 (ddd, *J* = 9.6, 6.8, 1.6 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.89 (t, *J* = 7.6 Hz, 2H), 1.80 – 1.67 (m, 4H), 1.64 – 1.49 (m, 3H), 1.36 – 1.22 (m, 2H), 1.10 (ddt, *J* = 16.8, 13.1, 6.5 Hz, 1H).

^{13}C NMR (126 MHz, d_6-DMSO, 100 °C) δ 153.9, 142.0, 128.65, 128.57, 126.1, 96.8, 74.8, 57.4, 44.3, 33.2, 31.7, 31.0, 26.1, 25.4.

FT-IR (neat) 2931, 2855, 1712, 1471, 1452, 1418, 1297, 1242, 1168, 1119, 1058, 761, 750, 719, 699 cm^{-1}.

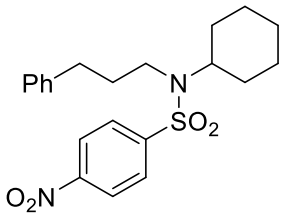
LRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{18}H_{25}Cl_3NO_2$: 392.1, found: 392.1.



***N*-Cyclohexyl-4-methyl-*N*-(3-phenylpropyl)benzenesulfonamide (Table 3.6, entry 4).** The title compound was synthesized according to the General Procedure from 3-

phenylpropylamine (99 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol). After the N-alkylation was complete, the reaction mixture was allowed to warm to room temperature. Next, CH_2Cl_2 (5 mL), aqueous NaOH (2 N, 2.5 mL), and TsCl (666 mg, 3.50 mmol) were added, and the resulting mixture was stirred at room temperature for 18 h. Then, the reaction mixture was transferred to a 250 mL round-bottom flask with the aid of CH_2Cl_2, silica gel was added to the flask, and the solvent was removed by rotary evaporation. The product was purified by flash chromatography with silica gel (100:0 → 75:25 hexanes/EtOAc). White solid. First run: 163 mg (63% yield). Second run: 167 mg (64% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 2H), 7.31 – 7.24 (m, 4H), 7.22 – 7.16 (m, 3H), 3.61 (tt, *J* = 11.3, 3.5 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.41 (s, 3H), 2.08 – 1.90 (m, 2H), 1.70 (d, *J* = 8.7 Hz, 2H), 1.63 – 1.51 (m, 4H), 1.36 – 1.16 (m, 4H). The ^{1}H NMR spectrum matches the spectrum reported in the literature.[35]



***N*-Cyclohexyl-4-nitro-*N*-(3-phenylpropyl)benzenesulfonamide (Table 3.6, entry 5).** The title compound was synthesized according to the General Procedure from 3-phenylpropylamine (99 μL, 0.70 mmol) and iodocyclohexane (136 μL, 1.05 mmol). After the N-alkylation was complete, the reaction mixture was allowed to warm to room temperature. Next, CH_2Cl_2 (5 mL), NEt_3 (540 μL, 3.87 mmol), and 4-nitrobenzenesulfonyl chloride (708 mg, 3.50 mmol) were added, and the resulting mixture was stirred at room temperature for 18 h. Then, the reaction mixture was transferred to a 250 mL round-bottom flask with the aid of CH_2Cl_2, silica gel was added to the flask, and the solvent was removed by rotary evaporation. The product was purified by flash chromatography with silica gel (100:0 → 75:25 hexanes/EtOAc). White solid. First run: 154 mg (55% yield). Second run: 158 mg (56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.28 (m, 2H), 7.98 – 7.89 (m, 2H), 7.33 – 7.28 (m, 2H), 7.24 – 7.15 (m, 3H), 3.74 – 3.55 (m, 1H), 3.20 – 3.08 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.07 – 1.93 (m, 2H), 1.82 – 1.71 (m, 2H), 1.60 (d, *J* = 15.6 Hz, 4H), 1.26 (q, *J* = 10.5, 9.3 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 147.5, 141.0, 128.6, 128.5, 128.1, 126.3, 124.4, 58.7, 43.8, 33.21, 33.16, 32.0, 26.1, 25.3.

FT-IR (neat) 2932, 2858, 1603, 1524, 1495, 1469, 1451, 1340, 1322, 1306, 1280, 1211, 1169, 1153, 1121, 1086, 1055, 1029, 1013, 982, 896, 821, 750, 742, 733, 700, 615 cm^{-1}.

LRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{21}H_{27}N_2O_4S$: 403.2, found: 403.1.

3.5.8. Data on S_N2 Reactions

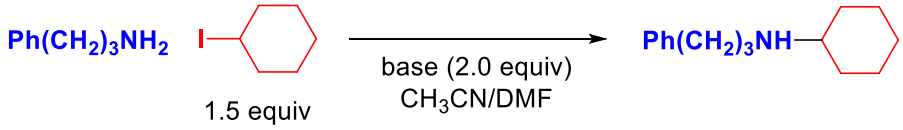
In a nitrogen-filled glovebox, an oven-dried 4 mL vial was charged with base (when LiOtBu or KH was used as base; 0.400 mmol) and a stir bar. DMF (0.3 mL), CH_3CN (1.1 mL), and base (when BTPP was used as base; 0.400 mmol) were added in turn. The reaction mixture was allowed to stir for 5 min to solubilize the base. Then, 3-phenylpropylamine (28.5 µL, 0.200 mmol) was added, followed by iodocyclohexane (39.0 µL, 0.302 mmol). The base-free reactions used an excess of 3-phenylpropylamine (57.0 µL, 0.401 mmol) relative to iodocyclohexane (26.0 µL, 0.201 mmol). Next, the vial was immediately sealed with a PTFE-lined vial cap, removed from the glovebox, and stirred at the indicated temperature for 24 h. For each reaction at each temperature, four reactions were run: two for GC analysis (to determine the amount of remaining electrophile) and two for 1 H NMR analysis (to determine the yield of the product).

GC analysis. Tetradecane (52.0 µL, 0.200 mmol) was added to the reaction mixture, and then the mixture was diluted with CH_2Cl_2 (~2 mL). An aliquot (~200 µL) of the reaction mixture was passed through a plug of silica gel, followed by EtOAc (~1 mL). The filtrate was then analyzed by GC.

^{1}H NMR analysis. A 20 mL vial was charged with a known amount of 1,3,5-trimethoxybenzene. The reaction vessel was uncapped, diluted with CH_2Cl_2 (~2 mL), recapped, and shaken. Then, the mixture was passed through a plug of basic alumina into the

20 mL vial containing the internal standard. The reaction vessel was washed three times with EtOAc (~4 mL), and the washings were passed through a plug of basic alumina into the 20 mL vial. The filtered reaction mixture was concentrated and then placed under high vacuum for 2 h in order to remove most of the DMF.

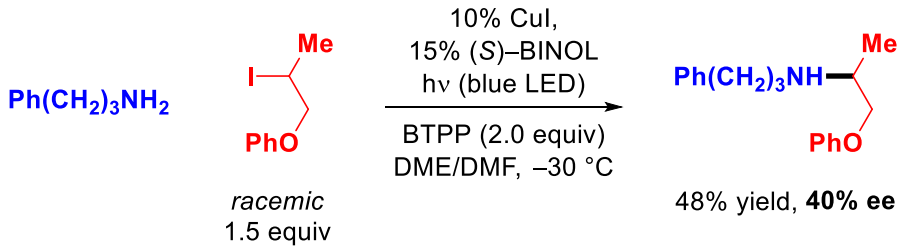
Table 3.7. Reactivity of substrates under metal- and light-free conditions to assess the viability of an S_N2 reaction.



base	temp. (°C)	yield (%)[a]	remaining electrophile (%)[b]
BTPP	rt	0	74
	50	<1	18
	80	6	0
LiO*t*-Bu	rt	0	48
	50	0	4
	80	0	0
KH	rt	0	2
	50	0	2
	80	0	1
none[c]	rt	0	94
	50	4	55
	80	3	<1

[a]The yield was determined through analysis via ^{1}H NMR spectroscopy, versus an internal standard (average of two experiments). [b]The amount of unreacted electrophile was determined through GC analysis versus an internal standard (average of two experiments). [c]Ratio of nucleophile-to-electrophile: 2:1

3.5.9. Asymmetric Reaction Procedure and Analysis



In a nitrogen-filled glovebox, an oven-dried 4 mL vial was charged with CuI (3.8 mg, 0.020 mmol), (*S*)−BINOL (8.9 mg, 0.030 mmol) and a stir bar. DME (0.70 mL), DMF (0.70 mL), then BTPP (122 µL, 0.400 mmol) were added and the reaction mixture was allowed to stir for 10 min to homogenize the reaction mixture. At this point the reaction mixture should appear yellow-orange and homogenous. Then, 3-phenylpropylamine (28.5 µL, 0.200 mmol) was added, followed by (2-iodopropoxy)benzene (79 mg ≈ 49 µL, 0.30 mmol). Next, the vial was immediately sealed with a PTFE-lined vial cap, removed from the glovebox, and placed upside-down in a fixed position in an isopropanol bath cooled to −30 °C with an immersion cooler. After stirring for 5 min at −30 °C, the reaction mixture was irradiated with 34 W Kessil blue LED lamps (one lamp per four reactions), placed ~3 cm away, for 24 h.

Dibenzyl ether (20.0 µL, 0.105 mmol) was added to the reaction mixture, and then the mixture was diluted with CH_2Cl_2 (~2 mL) and left to stir for 5 mins to warm to r.t. The entire reaction mixture was passed through a plug of basic alumina into a 20 mL vial. The reaction vial was then washed with ca. 2 mL CH_2Cl_2 and passed through the same alumina plug into the same 20 mL vial; this was repeated an additional three times. The filtered reaction mixture was concentrated to 1−2 mL and a ca. 0.5 mL aliquot was used to determine yield by ^{1}H NMR analysis versus the dibenzyl ether internal standard. To the remaining concentrate, ca. 10 mL of CH_2Cl_2 was added, followed by NEt_3 (~60 µL, ~0.44 mmol), TsCl (~77 mg, ~0.40 mmol) and a stir bar. The mixture was stirred at r.t. for 4 h, then the reaction mixture was concentrated. After purification by preparative TLC (1:4 EtOAc/hexanes, Rf ≈ 0.5), the ee was determined via SFC on a CHIRALPAK AD-H column (15% *i*-PrOH in

supercritical CO_2, 3.5 mL/min) with t_r = 8.3 min (major (*S*,)–BINOL), 9.2 min (major (*R*)–BINOL).

3.6. Notes and References

1. For example, see: *Alkaloids: A Treasury of Poisons and Medicines*; Funayama, S.; Cordell, G. A., Eds.; Academic Press: Waltham, MA, 2014.
2. For leading references, see: (a) Lawrence, S. A. *Amines: Synthesis, Properties, and Applications*; Cambridge University Press: Cambridge, U.K., 2004. (b) Yang, Q.; Wang, Q.; Yu, Z. *Chem. Soc. Rev.* **2015**, *44*, 2305−2329. (c) Schafer, L. L.; Yim, J. C.-H.; Yonson, N. In *Metal-Catalyzed Cross-Coupling Reactions and More*; De Meijere, A., Bräse, S., Oestreich, M., Eds.; Wiley–VCH: Weinheim, Germany, 2014. (d) Margaretha, P. In *Science of Synthesis, Knowledge Updates*; Georg Thieme Verlag: Hamburg, Germany, 2010; pp 405–442.
3. For leading references, see: Marvin, C. C. In *Comprehensive Organic Synthesis*; Knochel, P., Molander, G. A., Eds.; Elsevier: Amsterdam, 2015; Vol. 6, pp 34–99.
4. For reviews and leading references, see: (a) Jiang, Y.; Ma, D. In *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; John Wiley & Sons: Hoboken, NJ, 2014; pp 3–40. (b) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564−12649. (c) Hartwig, J. F.; Shekhar, S.; Shen, Q.; Barrios−Landeros, F. In *Chemistry of Anilines*; Rapaport, Z., Ed.; John Wiley & Sons: New York, 2007; Vol. 1, pp 455−536.
5. For early examples of reactions of unactivated alkyl electrophiles (all are primary alkyl bromides) that proceed in the presence of a sub-stoichiometric quantity of a transition metal, see: (a) Aydin, A.; Kaya, I. *Electrochimica Acta* **2012**, *65*, 104–114 (165 °C). (b) Tu, X.; Fu, X.; Jiang, Q.; Liu, Z; Chen, G. *Dyes and Pigments* **2011**, *88*, 39–43 (80 °C). (c) Kozuka, M.; Tsuchida, T.; Mitani, M. *Tetrahedron Lett.* **2005**, *46*, 4527–4530 (83 °C).
6. (a) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129–5133. (b) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J.

C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162–2167. (c) For activated tertiary alkyl halides, see: Kainz, Q. M.; Matier, C. M.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681–684.

7. For examples of work by others on photoinduced, copper-catalyzed couplings (not with alkyl electrophiles), see: (a) Paria, S.; Reiser, O. *ChemCatChem* **2014**, *6*, 2477−2483. (b) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034–9037. (c) Sagadevan, A.; Hwang, K. C. *Adv. Synth. Catal.* **2012**, *354*, 3421−3427.
8. Peacock, D. M.; Roos, C. B.; Hartwig, J. F. *ACS Cent. Sci.* **2016**, *2*, 647–652.
9. (a) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647–651. (b) Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 9548–9552. (c) Ziegler, D. T.; Choi, J.; Munoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 13107–13112. (d) Tan, Y.; Munoz-Molina, J. M.; Fu, G. C.; Peters, J. C. *Chem. Sci.* **2014**, *5*, 2831–2835. (e) Ratani, T. S.; Bachman, S.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2015**, *137*, 13902–13907.
10. For mechanistic studies, see: (a) Johnson, M. W.; Hannoun, K. I.; Tan, Y.; Fu, G. C.; Peters, J. C. *Chem. Sci.* **2016**, *7*, 4091–4100. (b) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc*. **2017**, *139*, 12716–12723.
11. For leading references on photoredox catalysis, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev*. **2013**, *113*, 5322−5363. (b) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev*. **2016**, *116*, 10035−10074.
12. For example, see: (a) Lotito, K. J.; Peters, J. C. *Chem. Commun.* **2010**, *46*, 3690–3692. (b) Miller, A. J. M.; Dempsey, J. L.; Peters, J. C. *Inorg. Chem.* **2007**, *46*, 7244–7246.
13. For examples of studies that show a role for the π system of the nucleophile in the electronic structure of copper(I) and copper(II) intermediates in photoinduced cross-couplings, see ref 10.
14. For ease of discussion, the transformation of **3.G** → **3.H** in Figure 3.2 is drawn as a simple ligand exchange, whereas our data (e.g., out-of-cage C–N bond formation (vide infra)) point to a more complex pathway.
15. In the case of a photoinduced, copper-catalyzed decarboxylative coupling, we have recently described evidence for out-of-cage C–N coupling after ligand exchange: Zhao,

W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc*. **2017**, *139*, 12153–12156. See also ref 10b.

16. Notes: (a) For all N-alkylations that are illustrated in Tables 3.2 and 3.3, essentially no over-alkylation is observed (<1%). (b) Preliminary observations: this process can be conducted under flow conditions; an unactivated tertiary alkyl halide is not a suitable electrophile; in a light-on/light-off experiment, alkylation stops when irradiation stops, and alkylation resumes when irradiation resumes.
17. Relative to Me–X, neopentyl–X is typically 3.3 x 10^{-7} less reactive in S_N2 reactions. For example, see Table 11.5 in: Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006.
18. (a) Upon irradiation at 350 nm, 2-naphtholate has been reported to serve as a photoreductant of aryl and alkyl halides. For example, see: Argüello, J. E.; Peñeñory, A. B. *J. Org. Chem.* **2003**, *68*, 2362−2368. Legros, B.; Vandereecken, P.; Soumillion, J. P. *J. Phys. Chem.* **1991**, *95*, 4752−4761. (b) We have observed that deprotonated BINOL can serve as a photoreductant of iodocyclohexane upon irradiation with a blue LED lamp.
19. For an example of a photoinduced, copper-catalyzed coupling wherein both a copper-bound and a copper-free nucleophile (carbazolide) appear to serve as photoreductants, see ref 10b.
20. *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed; Wiley-VCH: Bremen, Germany, 2010.
21. *Stereoselective Formation of Amines*; Li, W.; Zhang, X., Eds.; Springer: Heidelberg, Germany, 2014.
22. Accessing BINOL derivatives is time-consuming and annoying. These factors limited this author's motivation to do additional screening on such compounds.
23. Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun*. **1979**, 978−980.
24. Dang, H.; Cox, N.; Lalic, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 752−756.
25. Gharpure, S. J.; Shukla, M. K.; Vijayasree, U. *Org. Lett.* **2009**, *11*, 5466−5469.
26. Fernholz, E.; Schloeder, D.; Liu, K. K.-C.; Bradshaw, C. W.; Huang, H.; Janda, K.; Lerner, R. A.; Wong, C-H. *J. Org. Chem*. **1992**, *57*, 4756–4761.

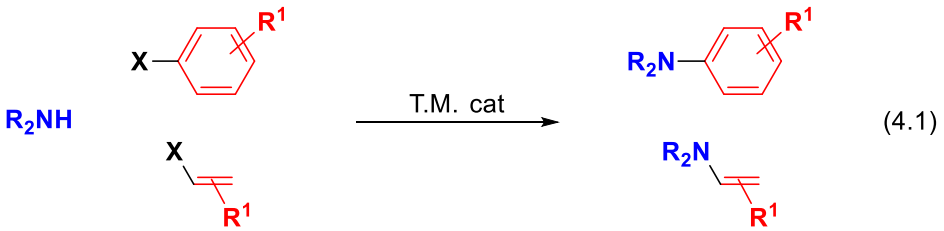
27. van Walree, C. A.; Lutz, M.; Spek, A. L.; Jenneskens, L. W.; Havenith, R. W. A. *J. Mol. Struct.* **2013**, *1036*, 115–120.
28. Paulsen, H.; von Deyn, W.; Roeben, W. *Liebigs Ann. Chem.* **1984**, 433–449.
29. Zhang, T.; Zhang, Y.; Zhang, W.; Luo, M. *Adv. Synth. Catal.* **2013**, *355*, 2775–2780.
30. Beak, P.; Basu, K. C.; Li, J. J. *J. Org. Chem.* **1999**, *64*, 5218–5223.
31. Perali, R. S.; Mandava, S.; Chunduri, V. R. *Tetrahedron Lett.* **2011**, *52*, 3045–3047.
32. Qureshi, Z.; Schlundt, W.; Lautens, M. *Synthesis* **2015**, *47*, 2446–2456.
33. Seel, S.; Dagousset, G.; Thaler, T.; Frischmuth, A.; Karaghiosoff, K.; Zipse, H.; Knochel, P. *Chem. Eur. J.* **2013**, *19*, 4614–4622.
34. Vázquez, A. J.; Rodriguez, C.; Nudelman, N. S. *Synth. Commun.* **2009**, *39*, 3958–3972.
35. Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. J. Am. Chem. Soc. 2009, 131, 1766−1774.

Chapter 4

ASYMMETRIC COPPER-CATALYZED ALKYLATION OF N-HETEROCYCLES UNDER LIGHT-FREE CONDITIONS

4.1 Introduction

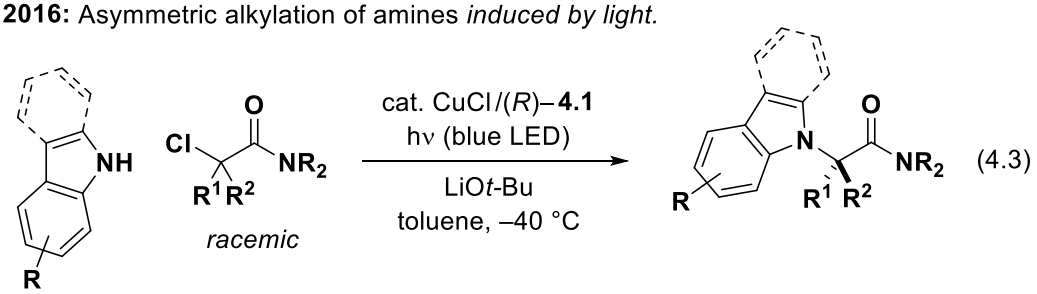
Amines can be found in a myriad of natural products, pharmaceuticals, agrochemicals, and polymers.[1] Their prevalence and importance in the chemical world has been underscored by the wide range of methods to access these compounds, notably, through the formation of carbon-nitrogen bonds. In particular, the stereocontrolled synthesis of α-chiral amines is of high value, due their ubiquity in biological systems and among medicinally relevant compounds.[1] The majority of methods to access α-chiral amines rely on the application of unsaturated prochiral precursors.[2] The most prominent approaches belonging to this group are additions into or reductions of imines and enamides[3] and hydroaminations[4] of olefins. There are only a handful of asymmetric methods that directly construct the bond between a nitrogen and a saturated alkyl moiety, and those are almost exclusively limited to processes involving C–H activation.[5]



Transition-metal catalysis has been a powerful tool for the construction of carbon-nitrogen bonds. However, in contrast to the well-established approaches to construct C_{sp2}–N bonds between aryl and alkenyl halides with amines,[6] the analogous C_{sp3}–N bond formation

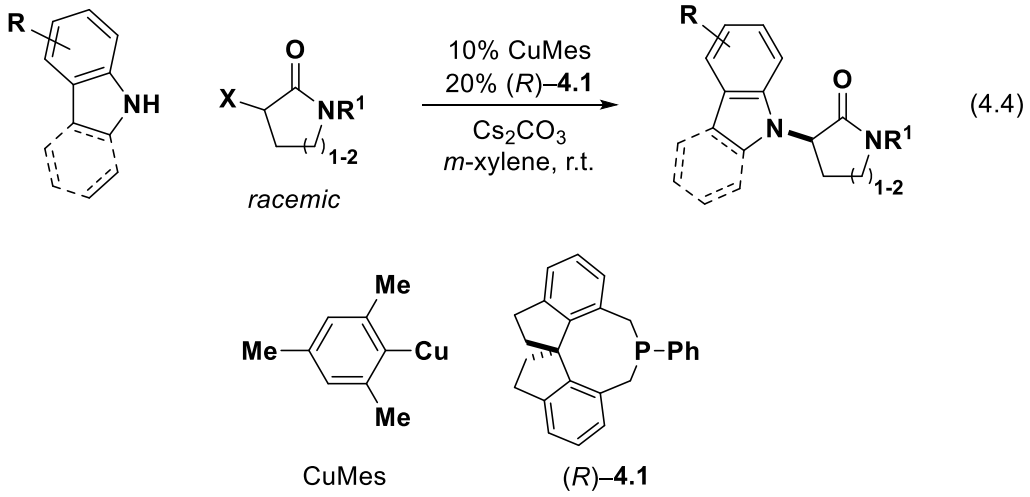
with alkyl halides is underdeveloped (eq 4.1).[7] Recent progress has been made with transition-metal catalysis to overcome the limitations often associated with C_{sp3}–N cross-coupling reactions; namely, base-mediated E2 reactions of electrophiles and β-hydride elimination of alkylmetal intermediates.[8] To this end, our group has reported a series of photoinduced copper-catalyzed coupling reactions of amine nucleophiles with alkyl halide electrophiles (eq 4.2).[9] Notably, our group has recently demonstrated that even stereoconvergent transition-metal catalyzed alkylation of amines can be achieved using copper photocatalysis (eq 4.3).[10]

2016: Asymmetric alkylation of amines *induced by light.*



(4.3)

This work: Asymmetric alkylation of amines *without light.*



(4.4)

Herein, we describe the development of a cross-coupling reaction between nitrogen-containing heterocycles and racemic α-halolactams catalyzed by a chiral copper catalyst in the *absence of light* (eq 4.4). This is in contrast to our previous copper-catalyzed stereoconvergent amine alkylation, where visible light irradiation was essential for bond

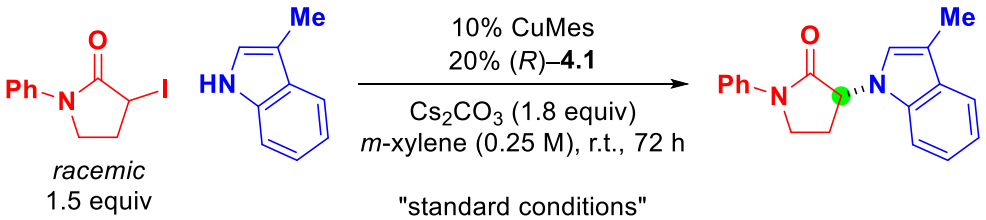
fomation.[10] In light of the paucity of methods to form C_{sp3}–N bonds stereoconvergently, developing conceptually distinct methods is of high practical value, as this may lead to additional strategies to access chiral amines. Moreover, the reaction illustrated in eq 4.4 delivers α-aminolactams, which are common motifs in many bioactive molecules.[11]

4.2. Results and Discussion

4.2.1. Optimization

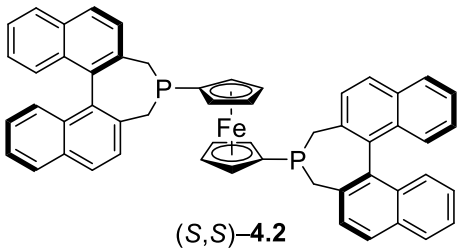
We began investigations toward the asymmetric cross-coupling between *N*-phenyl-3-iodopyrrolidin-2-one and 3-methylindole building on our previous conditions for other photoinduced copper-catalyzed reactions.[9,10] However, we established that superior results could be achieved in the absence of UV or visible light irradiation. Under the optimized conditions shown in Table 4.1, coupling proceeds in high yield and high ee (entry 1; 84% yield, and 87% ee). Control reactions established mesitylcopper(I), phosphine **4.1**, and cesium carbonate are all essential components of the reaction (entries 2−5).[12] Mesitylcopper is superior to the other catalyst precursors, likely due to its solubility in *m*-xylene (entries 6−8). Only **4.1** provides exceptional yield and ee compared to other related phosphines ligands (entries 9−11).[13] Lowering the catalyst loading or altering the ligand-to-metal ratio is deleterious to the reaction (entries 13 and 14). This transformation is particularly sensitive to the solubility and strength of the base additive (entries 15−18). At an elevated temperature (entry 19; 35°C), product is formed quantitatively without any asymmetric induction. Conversely, at a lower temperature (entry 20; 10°C), fewer turnovers are observed. A key factor for product formation and stereocontrol is that cesium carbonate is sparingly soluble in *m*-xylene under the optimized conditions (i.e., at higher temperatures, too much base is present in solution and racemizes product and at lower temperatures not enough base is available to turn over the catalytic cycle). On the other hand, this factor is likely the cause of extended reaction times (72 h) and of the requirement of using base in excess (entry 18). Other modifications to reaction conditions, such as concentration or electrophile stoichiometry result to lower yields or ee's (entries 21−24). Finally, it was found that the reaction is not highly sensitive to either air or water (entries 25 and 26).

Table 4.1. Effect of reaction parameters.

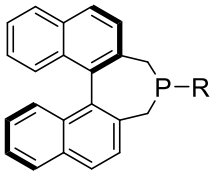


entry	change from the "standard conditions"	yield (%)*a*	ee (%)*b*
1	none	84	87
2	no CuMes	13	23
3	no CuMes, no (*R*)–**4.1**	8	<1
4	no Cs_2CO_3	10	91
5	no (*R*)–**4.1**	55	<1
6	Cu nanoparticles instead of CuMes	62	<1
7	CuI instead of CuMes	51	91
8	$Cu(OTf)_2$ instead of CuMes	79	38
9	(*S*,*S*)–**4.2** instead of of (*R*)–**4.1**	17	–13
10	(*R*)–**4.3** instead of of (*R*)–**4.1**	38	–32
11	(*R*)–**4.4** instead of of (*R*)–**4.1**	53	–35
12	toluene instead of *m*-xylene	82	83
13	5/10% CuMes/(*R*)–**4.1** instead of 10/20%	64	82
14	14% (*R*)–**4.1** instead of 20%	76	68
15	$CsOH{\cdot}H_2O$ instead of Cs_2CO_3	37	42
16	K_2CO_3 instead of Cs_2CO_3	13	92
17	LiO*t*-Bu instead of Cs_2CO_3	29	<1
18	1.2 equiv Cs_2CO_3 instead of 1.8 equiv	61	90
19	35 °C instead of r.t.	99	<1
20	10 °C instead of r.t.	63	86
21	0.15 M instead of 0.25 M	85	85
22	0.30 M instead of 0.25 M	86	87
23	0.50 M instead of 0.25 M	94	82
24	1.0 equiv of electrophile instead of 1.5 equiv	87	76
25	under air in a capped vial	67	83
26	0.1 equiv of water	74	85

[a]Determined by ^{1}H NMR spectroscopy with the use an internal standard (average of two experiments). [b]A negative ee value denotes the formation of the opposite enantiomer of the product.



(*S*,*S*)–**4.2**

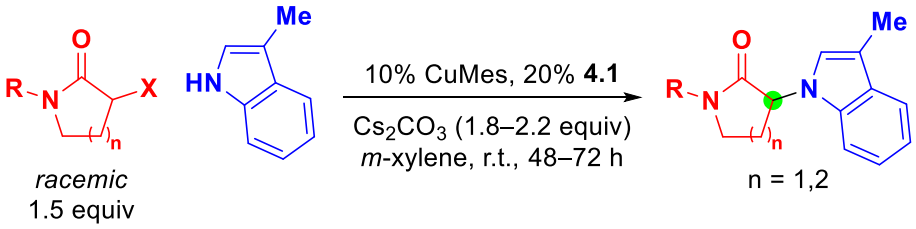


R = Ph, (*R*)–**4.3**
R = *i*-Pr, (*R*)–**4.4**

4.2.2. Scope of Reactivity

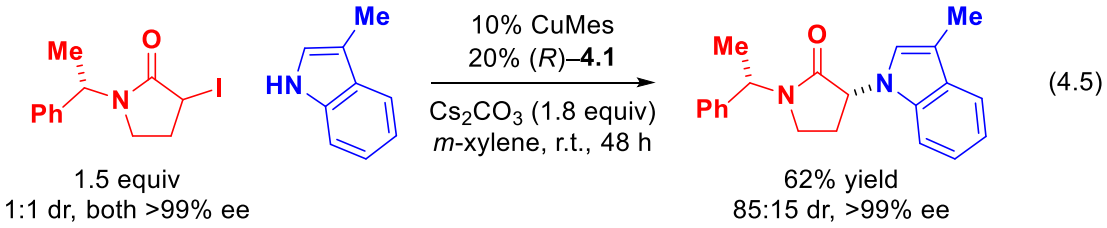
With the optimized reaction conditions in hand, we explored the scope of this asymmetric copper-catalyzed C–N cross-coupling with respect to the electrophile (Table 4.2). Both iodide and bromide-containing 5-memebered lactam electrophiles are capable of undergoing cross-coupling, however the latter needs to be used in a larger excess in order to achieve high yield of the isolated product (entries 1–3). A variety of *N*-substituted 3-iodopyrrolidin-2-ones can be transformed into the corresponding products in good yields and good ee's. The substituent at the amide position (R in Table 4.2) does not have a significant impact on the reactivity and stereoselectivity and it can be either aryl or alkyl (entries 1–7). The reaction also works for 6-membered lactams (entries 8 and 9).[14]

Table 4.2. Scope with respect to α-halolactams.

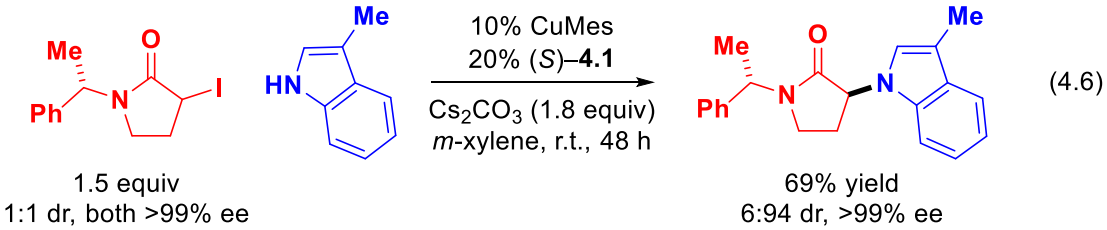


entry	R	X	n	yield (%)[a]	ee (%)
1	Ph	I	1	73	88
2	Ph	Br	1	60	88
3[b]	Ph	Br	1	85	87
4	4-(OMe)C_6H_4	I	1	78	91
5	4-$CF_3C_6H_4$	I	1	73	90
6	Bn	I	1	72	90
7	Ph-$(CH_2)_3$	I	1	80	82
8	Ph	I	2	88	80
9	4-(OMe)C_6H_4	I	2	74	88

[a]Yield of purified product (average of two experiments). [b]2.0 equiv of the electrophile were used.



(4.5)



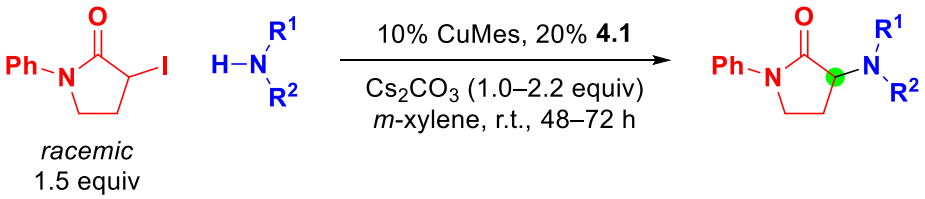
(4.6)

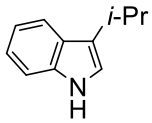
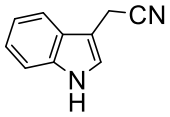
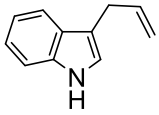
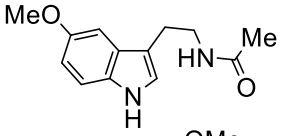
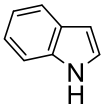
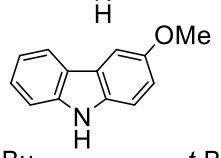
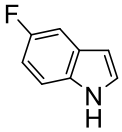
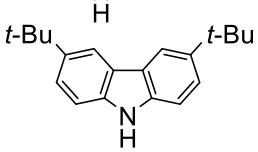
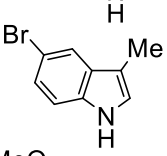
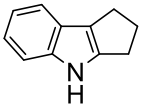
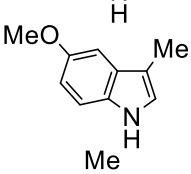
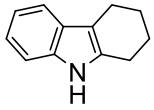
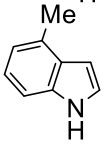
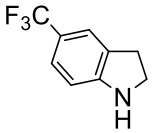
We have also examined reactions with an electrophile containing an additional chiral center with a predefined configuration adjacent to the amide nitrogen. When a 1:1 mixture of enantiopure diastereomers of this electrophile was subjected to the reaction conditions using opposite enantiomers of **4.1**, different diastereomers of the product were formed with high selectivity in each case (eq 4.5 and 4.6). These results demonstrate that the stereoselectivity of the reaction is predominantly controlled by chiral catalyst.

Next, we turned our attention to the exploration of the scope with respect to the nucleophilic coupling partner (Table 4.3). Indole, indoline, and carbazole derivatives can be used in this reaction to achieve the desired C–N coupled products. Indoles with a *C*3 substituent typically perform well under these conditions (entries 1, 2, 5, and 6), while indoles lacking this kind of substitution afford reduced yields due to competing C–C coupling at that position (entries 3, 4, and 7). Bulkier nucleophiles tend to give higher ee's, likely due to their ability to inherently improve enantioselectivity and impede racemization of the products (entries 10–13). An array of functional groups, such as nitriles, halides, ethers, alkenes, and secondary amides are tolerated under these conditions. Moreover, a non-aromatic amine, indoline, can also be employed as the substrate in the C–N coupling, giving the product in high enantioselectivity (entry 13). On a gram scale, the reaction depicted in entry 10 proceeds in 85% yield (1.06 g of isolated product) and 92% ee. In addition,

essentially all of (*R*)–**4.1** can be recovered after the oxidation to the corresponding phosphine oxide (see Experimental Section).

Table 4.3. Scope with respect to N-heterocycles.



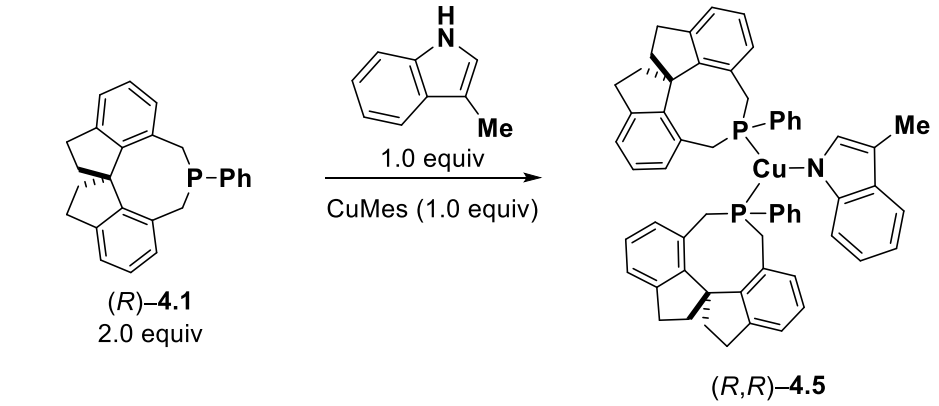
entry	HNR_2	yield (%)[a]	ee (%)	entry	HNR_2	yield (%)[a]	ee (%)
1		84	90	8		54	87
2		94	87	9		56	84
3		53	83	10		82	96
4		53	84	11		80	94
5		70	88	12		66	96
6		84	90	13		69	98
7		58	91	14		64	88

[a]Yield of purified product (average of two experiments).

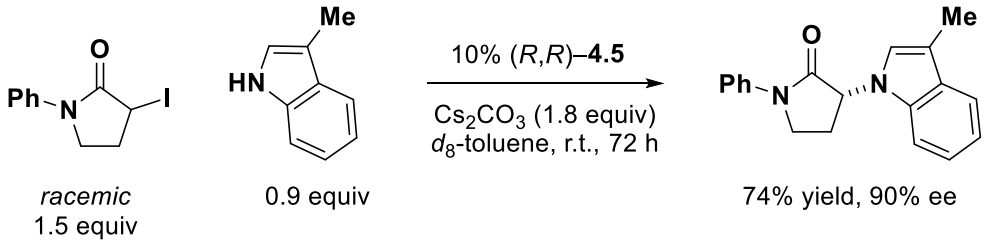
4.2.3. Mechanistic Insights

To gain insight into the mechanism of this transformation we conducted time-course experiments following the reactions of both iodide- and bromide-containing electrophiles (Table 4.2, entries 1 and 2). It was observed that the ee of the unreacted alkyl bromide increases throughout the reaction, indicating this electrophile undergoes a kinetic resolution (see Figure 4.4 in Experimental Section). This explains the necessity of using a higher excess of α-bromolactam to achieve high yields, since with only 1.5 equiv of this electrophile, the theoretical amount of product is limited to 75% (Table 4.2, entry 2 vs. 3). On the other hand, it is clear that both enantiomers of the alkyl iodide are being converted into the major enantiomer of product based on the yield and ee. These results indicate alkyl iodide electrophiles are undergoing a stereoconvergent reaction with this catalyst system. Our observation that the alkyl iodide illustrated in Table 4.2, entry 1 undergoes an initial increase in ee which is then is racemized over the course of the reaction suggests a dynamic kinetic resolution process is operative (see Figure 4.6 in Experimental Section). Likely, racemization of the α-iodolactam occurs via a facile S_N2 exchange of the iodide in the α position as iodide salts are generated over the course of the reaction.

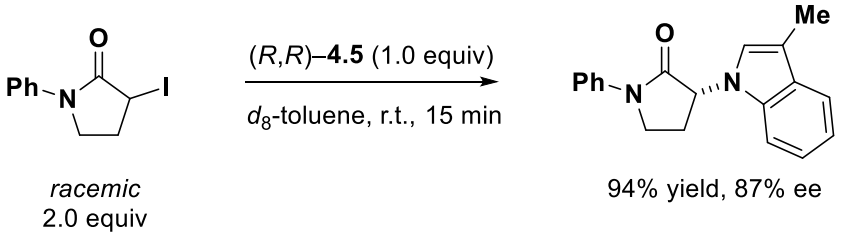
In an effort to identify catalytic species in this reaction, we were able to synthesize and crystallographically characterize a bis-**4.1**-ligated copper(I) species (eq 4.7). When (*R*,*R*)−**4.5** is used catalytically in place of the copper catalyst and ligand (eq 4.8), cross-coupling between 3-methylindole and 3-iodo-1-phenylpyrrolidin-2-one occurs in similar yield and ee to the unmodified conditions (74% yield, 90% ee; c.f. Table 4.1, entry 1: 84% yield, 87% ee). When a stoichiometric amount of (*R*,*R*)−**4.5** reacts with 3-iodo-1-phenylpyrrolidin-2-one, the C–N coupling product is again formed in similar yield and ee (eq 4.9; 94% yield, 87% ee). In addition, we have examined the dependence of the ee of the product on the ee of the chiral ligand. For both 3-bromo- and 3-iodo-1-phenylpyrrolidin-2-ones, the reactions exhibit a slight positive non-linear effect (see Figure 4.7 in Experimental Section). These results suggest (*R*,*R*)−**4.5** is likely an intermediate in the catalytic cycle.



(4.7)



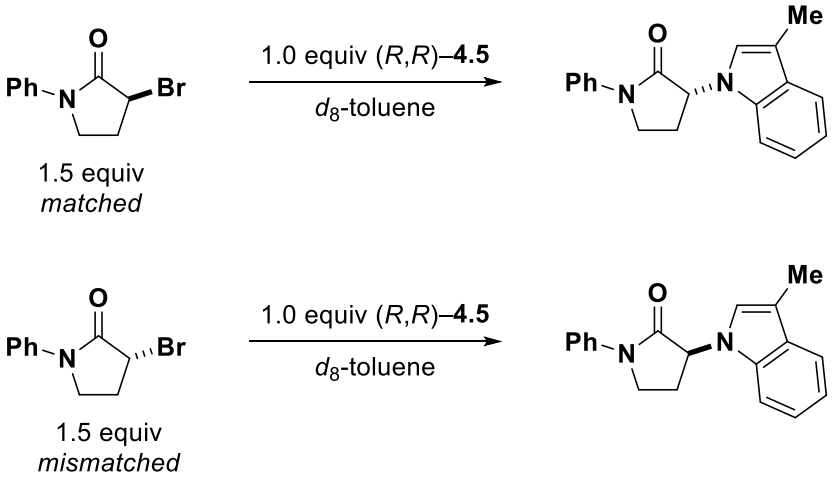
(4.8)



(4.9)

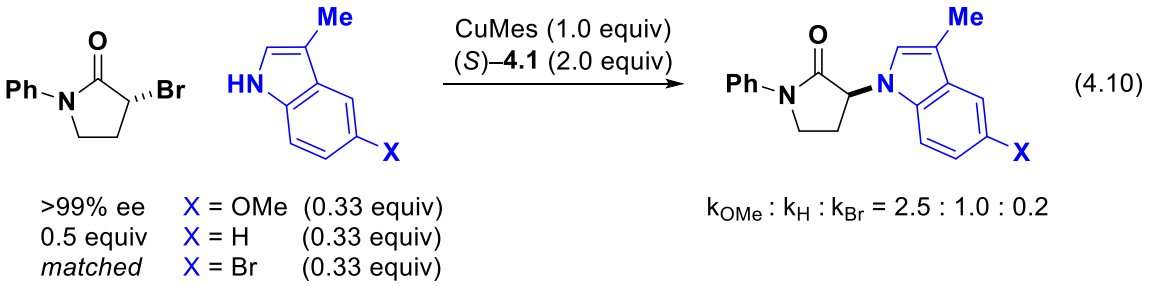
To gain insight into the C–N bond-forming step, separate enantiomers of 3-bromo-1-phenylpyrrolidin-2-one were reacted with complex (*R*,*R*)–**4.5**.[15] For either enantiomer of alkyl bromide, a stereospecific inversion of the configuration at the α position was observed (Table 4.4; absolute configuration of the electrophiles and the products were unambiguously determined by x-ray crystallography). These finding are consistent with reports by Kambe and Liu who have shown inversion of configuration in copper-catalyzed Kumada couplings of alkyl halides and tosylates.[16] These experiments also show that opposite enantiomers of α-bromolactam indeed react at different rates with (*R*,*R*)–**4.5**. In addition, intermolecular competition experiments determined the relative rates of three electronically distinct 5-substituted 3-methylindoles, which indicated that electron-rich nucleophiles react faster than electron-poor nucleophiles (eq 4.10).[17,18]

Table 4.4. Stereochemical course of the stoichiometric C–N coupling.



	matched		*mismatched*	
time	yield (%)[a]	ee (%)	yield (%)[a]	ee (%)
20 min	57	>99	5	> –99
1 h	86	>99	13	> –99
4h	96	>99	27	> –99

[a]Determined by ^{1}H NMR Spectroscopy with the use of an interal standard.



(4.10)

>99% ee X = OMe (0.33 equiv)
0.5 equiv X = H (0.33 equiv)
matched X = Br (0.33 equiv)

$k_{OMe} : k_H : k_{Br} = 2.5 : 1.0 : 0.2$

Based on these results, we propose two possible catalytic cycles for the copper-catalyzed asymmetric C–N coupling illustrated in Figure 4.1. Copper(I) amide complex **4.5** (represented as **4.A**) could preferentially react with one enantiomer of the electrophile resulting in a kinetic resolution. In the case of α-iodolactams, a dynamic kinetic resolution via in situ racemization at the α position renders the reaction stereoconvergent. There are two possible pathways in which the C–N bond formation may occur, both of them complying with our experimental findings. The reaction may proceed through an enantioselective S_N2

reaction between **4.A** and the electrophile, leading directly to the product with inverted configuration and releasing **4.B** (Figure 4.1A). On the other hand, a stepwise oxidative addition/reductive elimination sequence may operate with the involvement of copper(III) intermediates such as **4.C** (Figure 4.1B). The overall stereospecific inversion (Table 4.4)

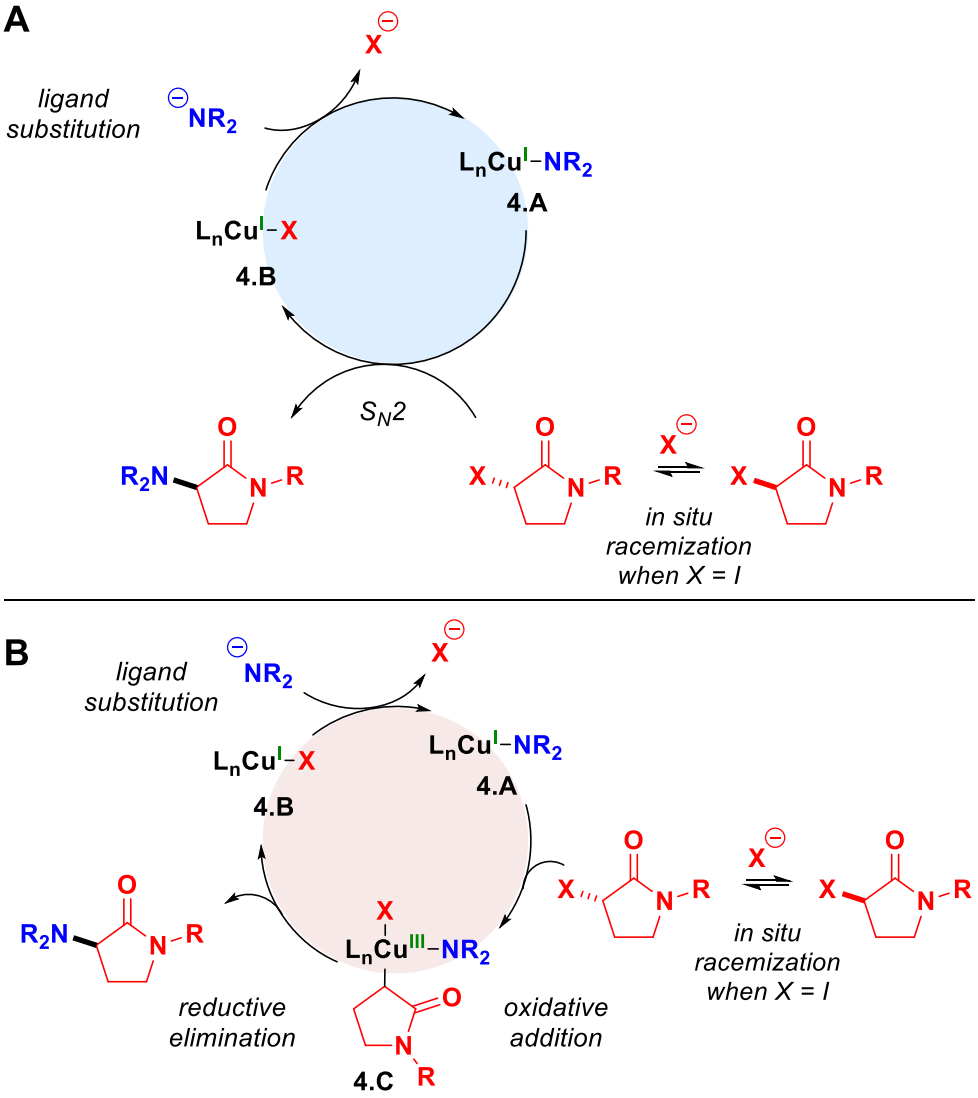


Figure 4.1. (**A**) Outline of a proposed mechanism involving an enantioselective S_N2 reaction. Bottom: (**B**) Outline of a proposed mechanism involving an enantioselective oxidative addition/reductive elimination pathway.

implies that oxidative addition proceeds in an enantioselective S_N2 manner and subsequently, the stereochemical configuration of the alkyl moiety remains intact. Alternatively, an enantioselective concerted oxidative addition could occur where the stereochemistry at the α position inverted through an *O*-bound copper(III) enolate.[19] For either the direct S_N2 or oxidative addition/reductive elimination pathway, the copper(I)-amide complex bearing a more electron-rich nucleophile is expected to react faster, however in the latter case only if oxidative addition is slower than reductive elimination. Both catalytic cycles are closed by a ligand substitution of copper halide complex **4.B**, releasing halide salts that can racemize the electrophile when X = I.

4.3 Conclusions

We have developed an asymmetric stereoconvergent C–N cross-coupling of α-halolactams and heterocyclic amines using copper catalysis under light-free condition. This work is complementary to photoinduced copper-catalyzed alkylations previously reported by our group. This method constitutes a straightforward entry to biologically important amino acid analogs in an enantioenriched form. Mechanistic investigations disclose that racemic alkyl iodide electrophiles undergo a dynamic kinetic resolution rendering the reaction stereoconvergent whereas alkyl bromides undergo a simple kinetic resolution. During the bond formation, a stereospecific inversion of the configuration at the α carbon takes place. Additionally, a bis-phosphine ligated copper(I)-amide complex has been identified as a likely catalytic species. Future work will be focused on adopting this reactivity to a broader class of nucleophiles.

4.4. Experimental Section

4.4.1. General Information

SITCP ligands [(*R*)– or (*S*)–**4.1**] and mesitylcopper were purchased from Strem Chemicals. Cesium carbonate (99.995%) and α-hydroxy-γ-butyrolactone were purchased from Acros Organics. *m*-Xylene (anhydrous, ≥99%) and 2,4-dibromobutyryl chloride were

purchased from Sigma-Aldrich. Indole, indoline and carbazole derivatives were purchased from Sigma-Aldrich, AK Scientific, Oakwood Chemicals, or AstaTech. Unless otherwise noted, all materials were purchased from commercial suppliers and used as received. Silicycle *Silia*Flash® P60 Silica gel (particle size 40–63 nm) was used for flash chromatography. Biotage® KP-C18-HS support gel (particle size 30–90 μm) was used for reverse-phase flash chromatography. Preparative thin-layer chromatography (TLC) was performed on EDM/Merck TLC Silica gel 60 F_{254} pre-coated plates (0.25 mm). ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Ascend 400 (at 400 MHz, 101 MHz and 162 MHz, respectively), with $CHCl_3$ (^{1}H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.0) as internal references relative to Me_4Si external reference and with 85% H_3PO_4 (^{31}P) external reference. ^{13}C NMR spectra of phosphorus-containing compounds were recorded on a Varian Inova 600 (at 151 MHz) using ^{1}H and ^{31}P decoupling. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent.) IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured on a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI) mode and JEOL MSRoute JMS-600H mass spectrometer using fast atom bombardment (FAB). Analytical HPLC analyses were carried out using an Agilent 1100 Series system with Daicel CHIRALPAK® columns (internal diameter 4.6 mm, column length 25.0 cm, particle size 5 μm). Analytical SFC was performed with a Thar SFC supercritical CO_2 analytical chromatography system with CHIRALPAK® columns (internal diameter 10 mm, column length 25.0 cm, particle size 5 μm). Microwave-assisted syntheses were performed on a Biotage® Initiator 2.5 microwave reactor. Preparative HPLC separations were carried out using an Agilent 1100 Series system with a Daicel CHIRALPAK® IC column (internal diameter 2.0 cm, column length 25.0 cm, particle size 5 μm).

4.4.2. Preparation of Electrophiles

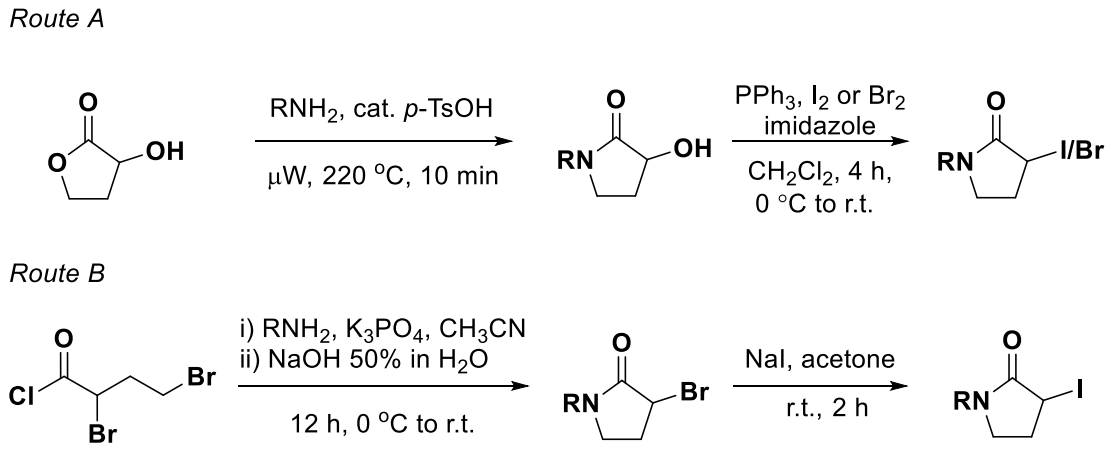
General Procedures for the Synthesis of α-Iodo-γ-Lactams and α-Bromo-γ-Lactams.

The yields have not been optimized.

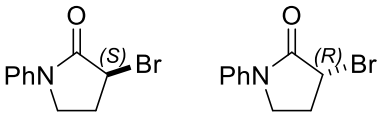
Route A: α-Iodo-γ-lactams and α-bromo-γ-lactams were synthesized from α-hydroxy-γ-butyrolactone γ-lactone in a two-step sequence (Scheme 4.1). In the first step, α-hydroxy-γ-butyrolactone (10.0 mmol), amine (12.0 mmol, 1.2 equiv.) and *p*-toluenesulfonic acid (1.0 mmol, 10 mol%) were placed in a 10 mL microwave vial and stirred for 10 minutes at 220 °C in a microwave reaction. Crude reaction mixture was dissolved in 200 mL of dichloromethane and washed with 5 M HCl solution, followed by saturated $NaHCO_3$ solution and brine. Organic layers were combined, dried over magnesium sulfate, and concentrated to give α-hydroxy-γ-lactam, which was used without further purification in the subsequent step. In the second step triphenylphosphine (13.0 mmol, 1.3 equiv.) was dissolved in 100 mL of dichloromethane. Resulting solution was cooled down to 0 °C and iodine or bromine (12.0 mmol, 1.2 equiv.) was added. After 10 minutes of stirring, imidazole (13.0 mmol, 1.3 equiv.) and α-hydroxy-γ-lactam (10.0 mmol) were added. Reaction mixture was slowly warmed up to room temperature and stirred for 4 hours. Reaction mixture was washed with water and the organic layer was dried over magnesium sulfate, concentrated and crude product was purified by column chromatography using hexanes: diethyl ether solvent system.

Route B: In the first step of the reaction, 2,4-dibromobutyryl chloride (10.0 mmol) was added slowly to a suspension of amine (10.0 mmol, 1.0 equiv.) and potassium phosphate tribasic (5.0 mmol, 0.5 equiv.) in 50 mL of acetonitrile at 0 °C. Reaction was stirred for 1 hour, then 2 mL of 50% NaOH solution was added and stirred overnight. Crude reaction mixture was filtered, solid was washed with 100 mL of dichloromethane and combined filtrate was concentrated. Residue was purified by column chromatography using hexanes: diethyl ether solvent system. In the next step, α-bromo-γ-lactam (10.0 mmol) was subjected to a suspension of NaI (15.0 mmol, 1.5 equiv.) in 50 mL of acetone. After 2 hours, reaction

was concentrated and residue was purified by column chromatography using hexanes: diethyl ether solvent system.



Scheme 4.1. Synthesis of α-halo-γ-lactam electrophiles.

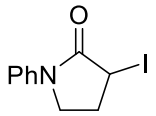


(*3S*)-*3*-Bromo-1-phenylpyrrolidin-2-one and **(*3R*)-*3*-Bromo-1-phenylpyrrolidin-2-one**. The racemic mixture of the title products was prepared similarly to the procedure described in literature[20] (Route B, Scheme 4.1). Pure enantiomers of title compound were obtained from the racemate by separation on preparative Diacel CHIRALPAK® IC column; 45% *i*-PrOH in hexanes, 10.0 mL/min flow-rate; retention times: 24.9 min (*S*-enantiomer), 32.8 min (*R*-enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.61 (m, 2H), 7.50 – 7.34 (m, 2H), 7.27 – 7.18 (m, 1H), 4.62 (dd, *J* = 7.0, 2.8 Hz, 1H), 4.09 (ddd, *J* = 9.8, 7.9, 6.6 Hz, 1H), 3.86 (ddd, *J* = 10.1, 7.8, 2.6 Hz, 1H), 2.88 – 2.61 (m, 1H), 2.49 (ddt, *J* = 14.3, 6.6, 2.7 Hz, 1H).

(*S*)-enantiomer $[\alpha]^{25}_D$ (100% ee): 117.4° (c = 1.0, $CHCl_3$)

(*R*)-enantiomer $[\alpha]^{25}_D$ (100% ee): –118.5° (c = 1.0, $CHCl_3$)



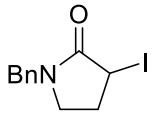
3-Iodo-1-phenylpyrrolidin-2-one. The compound was prepared according to the general procedure (Route B, Scheme 4.1, second step) from *3*-bromo-1-phenylpyrrolidin-2-one. After purification by flash chromatography (30→60% Et_2O in hexanes) the title compound was isolated as a white solid in 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.55 (m, 2H), 7.55 – 7.35 (m, 2H), 7.26 – 7.13 (m, 1H), 4.75 (dd, *J* = 7.1, 2.0 Hz, 1H), 3.97 (ddd, *J* = 9.9, 8.7, 6.3 Hz, 1H), 3.77 (ddd, *J* = 9.8, 7.7, 1.9 Hz, 1H), 2.83 – 2.52 (m, 1H), 2.41 (ddt, *J* = 14.4, 6.2, 1.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 139.1, 129.0, 125.3, 120.00, 47.3, 31.4, 20.9.

FT-IR: 2946, 1694, 1597, 1494, 1476, 1393, 1300, 1224, 1116, 1035, 875, 762 cm^{-1}.

HRMS: *m/z* 287.9878 ($[M+H]^+$, $C_{10}H_{11}INO^+$ calcd. 287.9885).



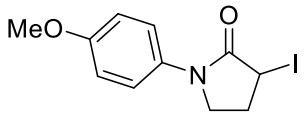
1-Benzyl-3-iodopyrrolidin-2-one. The compound was prepared according to the general procedure (Route A, Scheme 4.1) from α-hydroxy-γ-butyrolactone and benzyl amine. After purification by flash chromatography (30→90% Et_2O in hexanes) the title compound was isolated as yellow oil in 51% yield over 2 steps. ^{1}H NMR data of the intermediate α-hydroxy-γ-lactam was identical to previously reported data.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.09 (m, 5H), 4.60 (dd, *J* = 7.3, 1.9 Hz, 1H), 4.53 (d, *J* = 14.7 Hz, 1H), 4.39 (d, *J* = 14.7 Hz, 1H), 3.28 (ddd, *J* = 10.2, 8.4, 6.3 Hz, 1H), 3.11 (ddd, *J* = 9.9, 7.8, 1.8 Hz, 1H), 2.55 – 2.38 (m, 1H), 2.24 (ddt, *J* = 14.5, 6.4, 1.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 135.7, 128.8, 128.1, 127.8, 47.3, 45.2, 31.7, 19.8.

FT-IR: 3026, 2916, 1690, 1494, 1423, 1358, 1306, 1267, 1125, 1082, 1028, 878, 751 cm^{-1}.

HRMS: *m/z* 302.0045 ($[M+H]^+$, $C_{11}H_{13}INO^+$ calcd. 302.0042).



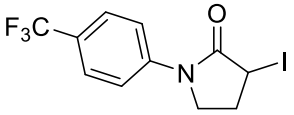
3-Iodo-1-(4-methoxyphenyl)pyrrolidin-2-one. The compound was prepared according to the general procedure (Route B, Scheme 4.1) from 2,4-dibromobutyryl chloride and *p*-anisidine. After purification by flash chromatography (30→70% Et_2O in hexanes) the title compound was isolated as a white solid in 48% yield over 2 steps. ^1H NMR data of the intermediate *3*-bromo-1-phenylpyrrolidin-2-one was identical to previously reported data.[22]

^1H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.37 (m, 2H), 7.01 – 6.84 (m, 2H), 4.71 (dd, *J* = 7.1, 2.0 Hz, 1H), 3.89 (ddd, *J* = 10.0, 8.7, 6.2 Hz, 1H), 3.81 (s, 3H), 3.69 (ddd, *J* = 9.8, 7.7, 1.9 Hz, 1H), 2.75 – 2.49 (m, 1H), 2.37 (ddt, *J* = 14.5, 6.3, 1.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 157.1, 132.3, 121.8, 114.2, 55.5, 47.8, 31.5, 21.1.

FT-IR: 2915, 1698, 1512, 1463, 1395, 1369, 1290, 1248, 1178, 1099, 1031, 828, 740 cm^{-1}.

HRMS: *m/z* 317.9985 ($[M+H]^+$, $C_{11}H_{13}INO_2^+$ calcd. 317.9991).



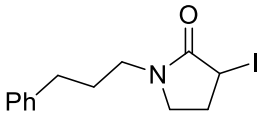
3-Iodo-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one. The compound was prepared according to the general procedure (Route B, Scheme 4.1) from 2,4-dibromobutyryl chloride and 4-(trifluoromethyl)aniline. After purification by flash chromatography (20→50% Et_2O in hexanes) the title compound was isolated as a yellow solid in 53% yield over 2 steps. ^1H NMR data of the intermediate *3*-trifluoro-1-phenylpyrrolidin-2-one was identical to previously reported data.[20]

^1H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.73 (m, 2H), 7.77 – 7.55 (m, 2H), 4.77 (dd, *J* = 7.0, 2.1 Hz, 1H), 4.00 (td, *J* = 9.3, 6.3 Hz, 1H), 3.81 (ddd, *J* = 9.8, 7.7, 1.9 Hz, 1H), 2.87 – 2.48 (m, 1H), 2.43 (ddt, *J* = 14.5, 6.3, 2.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 142.5, 126.7 (q, *J* = 32.8 Hz), 126.2 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 271.6 Hz), 119.4, 47.0, 31.1, 20.0.

FT-IR: 2883, 1703, 1614, 1520, 1479, 1428, 1390, 1320, 1303, 1224, 1120, 1069, 1018, 879, 839 cm^{-1}.

HRMS: *m/z* 355.9756 ($[M+H]^+$, $C_{11}H_{10}F_3INO^+$ calcd. 355.9759).



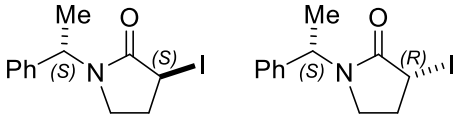
3-Iodo-1-(3-phenylpropyl)pyrrolidin-2-one. The compound was prepared according to the general procedure (Route A, Scheme 4.1, second step) from 3-hydroxy-1-(3-phenylpropyl)pyrrolidin-2-one. After purification by flash chromatography (40→80% Et_2O in hexanes) the title compound was isolated as yellow oil in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.09 (m, 5H), 4.54 (dd, *J* = 7.1, 1.8 Hz, 1H), 3.51 – 3.39 (m, 2H), 3.29 (dt, *J* = 13.8, 7.1 Hz, 1H), 3.20 (ddd, *J* = 9.8, 7.7, 1.7 Hz, 1H), 2.80 – 2.55 (m, 2H), 2.52 – 2.31 (m, 1H), 2.26 (ddt, *J* = 14.4, 6.3, 1.8 Hz, 1H), 1.93 (p, *J* = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 141.3, 128.5, 128.3, 126.1, 45.7, 43.0, 33.0, 31.8, 28.6, 20.2.

FT-IR: 3056, 2929, 1691, 1590, 1483, 1435, 1308, 1279, 1194, 1118, 1070, 1028, 997, 880, 754, 722 cm^{-1}.

HRMS: *m/z* 330.0354 ($[M+H]^+$, $C_{13}H_{17}INO^+$ calcd. 330.0355).



Diastereomers are not assigned to either set of the following data. They are formed in a 1:1 mixture and were used as such in eq 4.5 and eq 4.6. However, they can be separated by column chromatography.

3-Iodo-1-(1-phenylethyl)pyrrolidin-2-one (diastereomer I). The compound was prepared according to the general procedure (Route A, Scheme 4.1) from α-hydroxy-γ-butyrolactone and (*S*)-1-phenylethylamine. After purification by flash chromatography (30→80% Et_2O in hexanes) the title compound was isolated as white solid in 27% yield over 2 steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.29 (m, 5H), 5.46 (q, *J* = 7.1 Hz, 1H), 4.59 (dd, *J* = 6.8, 1.8 Hz, 1H), 3.53 – 3.17 (m, 1H), 3.05 – 2.72 (m, 1H), 2.42 – 2.06 (m, 2H), 1.55 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 139.7, 128.6, 127.7, 127.1, 50.0, 41.0, 31.7, 20.9, 14.8.

FT-IR: 3025, 2969, 2934, 1670, 1478, 1440, 1425, 1344, 1309, 1282, 1227, 1178, 1129, 1053, 784, 701 cm^{-1}.

$[\alpha]^{25}_D$ (100% ee): –109.8° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 316.0196 ($[M+H]^+$, $C_{12}H_{15}INO^+$ calcd. 316.0198).

3-Iodo-1-(1-phenylethyl)pyrrolidin-2-one (diastereomer II). The compound was prepared according to the general procedure (Route A, Scheme 4.1) from α-hydroxy-γ-lactone and (*S*)-1-phenylethanamine. After purification by flash chromatography (30→80% Et_2O in hexanes) the title compound was isolated as white solid in 29% yield over 2 steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.29 (m, 5H), 5.50 (q, *J* = 7.1 Hz, 1H), 4.61 (dd, *J* = 7.2, 1.9 Hz, 1H), 3.22 – 3.09 (m, 1H), 3.00 – 2.84 (m, 1H), 2.62 – 2.38 (m, 1H), 2.20 (ddt, *J* = 14.4, 6.3, 1.8 Hz, 1H), 1.60 (d, *J* = 7.1 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 139.1, 128.7, 127.7, 127.1, 49.5, 41.0, 31.7, 20.6, 16.2.

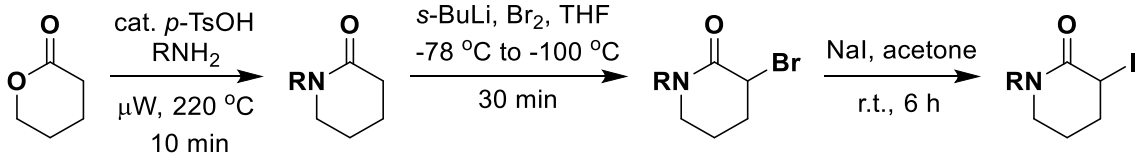
FT-IR: 3027, 2982, 2875, 1673, 1485, 1449, 1419, 1346, 1305, 1277, 1223, 1178, 1117, 877, 699, 657 cm^{-1}.

$[\alpha]^{25}_D$ (100% ee): –139.6° (c = 1.0, $CHCl_3$).

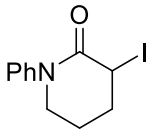
HRMS: *m/z* 316.0189 ($[M+H]^+$, $C_{12}H_{15}INO^+$ calcd. 316.0198).

General Procedure for the Synthesis of α-Iodo-δ-Lactams. α-Iodo-δ-lactams were synthesized from δ-lactone in a three-step sequence (Scheme 4.2). The yields have not been optimized. In the first step δ-lactone (10.0 mmol), amine (12.0 mmol, 1.2 equiv.) and *p*-

toluenesulfonic acid (1.0 mmol, 10 mol%) were placed in a 10 mL microwave vial and stirred for 10 minutes at 220 °C in a microwave reactor. Crude reaction mixture was dissolved in 200 mL of dichloromethane and washed with 5 M HCl solution, followed by saturated $NaHCO_3$ solution and brine. Organic layers were combined, dried over magnesium sulfate, and concentrated. Residue was purified by column chromatography using hexanes: diethyl ether solvent system to give δ-lactam. In the second step, δ-lactam (10.0 mmol) dissolved in 200 mL of THF was cooled down to −78 °C. Next, 11.0 mL of *s*-BuLi (1.0 M in hexanes) was added. Reaction was stirred for 30 minutes then temperature was decreased to −100 °C and bromine (10.0 mmol, 1.0 equiv.) was added drop-wise over 2 minutes. Reaction was immediately quenched (at −100 °C) with 10 mL of water. Reaction mixture was slowly warmed up to rt, washed with aqueous solution of sodium thiosulfate then ammonium chloride. Organic layers were combined and dried over magnesium sulfate, concentrated and residue was purified by column chromatography using hexanes: diethyl ether solvent system. In the next step α-bromo- δ-lactam (10.0 mmol) was subjected to a suspension of NaI (15.0 mmol, 1.0 equiv.) in 50 mL of acetone. After 2 hours reaction was concentrated and residue was purified by column chromatography using hexanes:Et_2O solvent system.



Scheme 4.2. Synthesis of α-iodo-δ-lactam electrophiles.



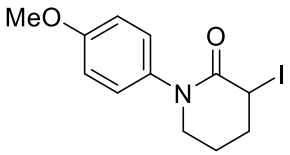
3-Iodo-1-phenylpiperidin-2-one. The compound was prepared according to the general procedure (Scheme 4.2) from δ-lactone and aniline. In the first step 1-phenylpiperidin-2-one was obtained in 58% yield. In the second step, after purification by flash chromatography (50→90% Et_2O in hexanes), 3-bromo-1-phenylpiperidin-2-one[23] was obtained in 53% yield. After purification from the last step by flash chromatography (50→90% Et_2O in hexanes), the title product was obtained in 92% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.37 (m, 2H), 7.31 – 7.24 (m, 3H), 5.00 (ddd, J = 4.7, 3.2, 1.4 Hz, 1H), 3.94 (ddd, J = 12.1, 10.9, 5.0 Hz, 1H), 3.76 (dddd, J = 12.2, 5.7, 3.3, 1.4 Hz, 1H), 2.60 – 2.40 (m, 1H), 2.42 – 2.29 (m, 1H), 2.32 – 2.17 (m, 1H), 2.05 – 1.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 142.9, 129.1, 127.0, 125.6, 51.2, 32.74, 23.5, 21.0.

FT-IR: 2946, 1651, 1595, 1492, 1417, 1346, 1310, 1240, 1173, 763 cm^{-1}.

HRMS: *m/z* 302.0051 ($[M+H]^+$, $C_{11}H_{13}INO^+$ calcd. 302.0042).



3-Iodo-1-(4-methoxyphenyl)piperidin-2-one. The compound was prepared according to the general procedure (Scheme 4.2, third step) from 3-bromo-1-(4-methoxyphenyl)piperidin-2-one. After purification by flash chromatography (50→100% Et_2O in hexanes), the title product was obtained in 71% yield as a white solid.

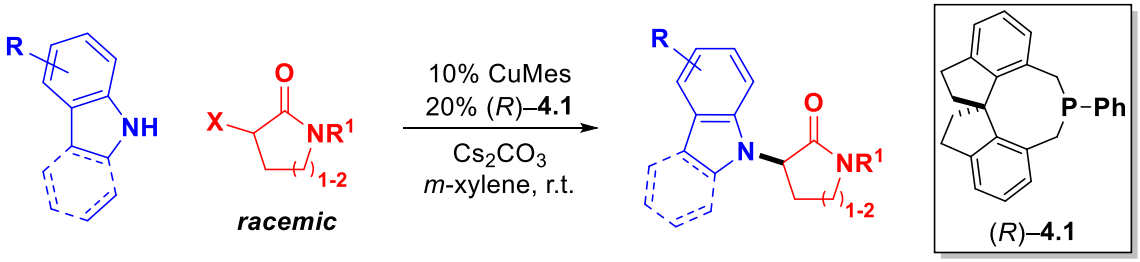
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.10 (m, 2H), 7.03 – 6.78 (m, 2H), 4.99 (ddd, *J* = 4.7, 3.1, 1.4 Hz, 1H), 3.89 (ddd, *J* = 12.3, 10.9, 5.0 Hz, 1H), 3.83 (s, 3H), 3.76 – 3.67 (m, 1H), 2.55 – 2.39 (m, 1H), 2.39 – 2.29 (m, 1H), 2.29 – 2.14 (m, 1H), 2.07 – 1.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 158.2, 135.7, 126.8, 114.4, 55.5, 51.5, 32.7, 23.6, 21.0.

FT-IR: 2953, 2833, 1651, 1605, 1510, 1440, 1345, 1317, 1298, 1241, 1173, 1148, 1032, 830 cm^{-1}.

HRMS: *m/z* 332.0160 ([M+H]$^+$, $C_{12}H_{15}INO_2^+$ calcd. 332.0147).

4.4.3. Copper-Catalyzed Asymmetric C_{sp3}–N Couplings



General Procedure for Asymmetric Copper-Catalyzed C_{sp3}–N couplings. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with nucleophile (0.250 mmol) and solution of mesitylcopper[24] (4.6 mg, 0.025 mmol) in 500 μL and a stir bar were added and the vial was closed with a screw cap. After stirring for 10 min, solution of (*R*)–**4.1**[25] [(*R*)–**4.1**] ligand (17.7 mg, 0.050 mmol) in 500 μL of *m*-xylene was added and the vial was recapped. After stirring for additional 10 min, α-iodolactam (108.0 mg, 0.375 mmol) was added. After the reaction mixture became homogenous (ca. 5 min), Cs_2CO_3[26] (147.0 mg, 0.45 mmol) was added. The vial was recapped and wrapped entirely with electrical tape to prevent access of light. The reaction vessel was removed from the glovebox and the reaction mixture was stirred vigorously (1500 rpm; adequate stirring is necessary to achieve full conversion) at 23-26 °C (exact reaction temperature is indicated below, exceeding 26 °C leads to lowered ee; see below for the description of an experimental setup used to maintain the reaction temperature). After the time indicated below, the crude reaction mixture was directly transferred to the top of a chromatography column. The reaction vial was additionally consecutively washed with toluene (2 mL) and dichloromethane (1 mL) and the washings were also applied on the column. The product was purified by column chromatography using solvent system given below.

To avoid overheating the reaction mixture by the stir-plate, while ensuring efficient stirring, following experimental setup was used: the reaction vessel was suspended 3 mm

over the stir-plate, and a small fan was placed 40 cm above the reaction vessel (Figure 4.2). The temperature was controlled with a thermometer placed next to the vial.

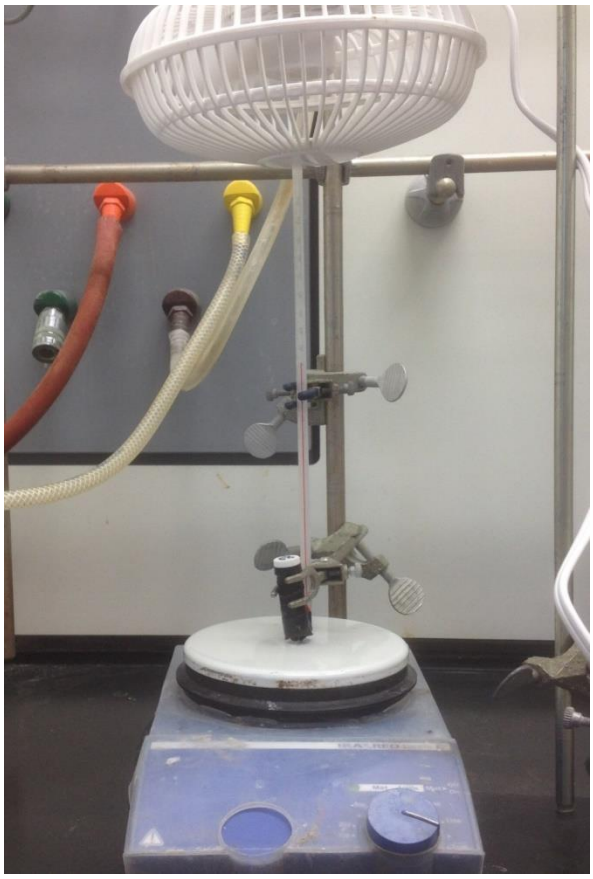
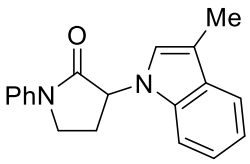


Figure 4.2. Reaction setup of copper-catalyzed asymmetric C–N coupling.



3-(3-Methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (Table 4.2, entries 1–3). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3

(147 mg, 0.45 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (20→50% Et_2O in hexanes) and reverse phase chromatography (0→60% MeOH in H_2O) the title compound was isolated as a white solid in 72% yield (52 mg) and 86% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 74% yield (54 mg) and 89% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 22.5 min (minor), 26.5 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.67 (m, 2H), 7.62-7.60 (m, 1H), 7.53 – 7.35 (m, 2H), 7.30- 7.27 (m, 1H), 7.27 – 7.21 (m, 2H), 7.16 (m, 1H), 6.97 (q, *J* = 1.1 Hz, 1H), 5.31 (dd, *J* = 10.1, 8.7 Hz, 1H), 4.06 – 3.96 (m, 2H), 2.88 – 2.74 (m, 1H), 2.53 – 2.37 (m, 1H), 2.36 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 139.1, 136.4, 129.3, 129.1, 125.2, 123.4, 121.9, 119.8, 119.4, 119.3, 112.4, 109.1, 57.9, 45.0, 26.5, 9.7.

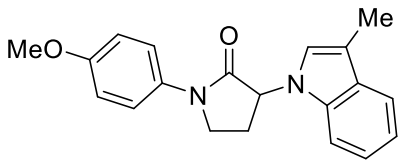
FT-IR: 3045, 2915, 1704, 1598, 1500, 1462, 1394, 1370, 1307, 1237, 1199, 758, 739, 691 cm^{-1}.

$[\alpha]^{25}_D$ (86% ee): –53.8° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 291.1492 ($[M+H]^+$, $C_{19}H_{19}N_2O^+$ calcd. 291.1497).

The title compound was also prepared with 3-bromo-1-phenylpyrrolidin-2-one (90.0 mg, 0.375 mmol) was isolated in 58% yield (42 mg) and 88% ee with (*R*)−**4.1** and in 63% yield (46 mg) and 87% ee with (*S*)−**4.1**

The title compound was also prepared with 3-bromo-1-phenylpyrrolidin-2-one (120 mg, 0.50 mmol) was isolated in 83% yield (60 mg) and 88% ee with (*R*)−**4.1** and in 87% yield (63 mg) and 86% ee with (*S*)−**4.1**.



1-(4-Methoxyphenyl)-3-(3-methyl-1*H*-indol-1-yl)pyrrolidin-2-one (Table 4.2, entry 4). The compound was prepared according to the General Procedure from 3-iodo-1-(4-

methoxyphenyl)pyrrolidin-2-one (119 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 2.2 equiv. of Cs_2CO_3 (179 mg, 0.55 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (20→80% Et_2O in hexanes) and reverse phase chromatography (0→70% MeOH in H_2O) the title compound was isolated as a white solid in 83% yield (66 mg) and 90% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 72% yield (58 mg) and 92% ee. HPLC analysis of the product: Diacel CHIRALPAK® IA column; 30% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 27.3 min (minor), 31.4 min (major).

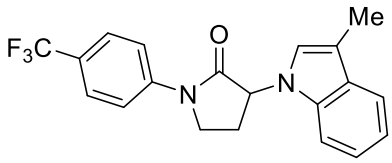
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.58 (m, 3H), 7.37 – 7.11 (m, 3H), 7.03 – 6.91 (m, 3H), 5.27 (dd, *J* = 9.9, 8.7 Hz, 1H), 4.02 – 3.89 (m, 2H), 3.85 (s, 3H), 2.85 – 2.69 (m, 1H), 2.47 – 2.29 (m, 1H), 2.36 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 157.0, 136.4, 132.3, 129.3, 123.4, 121.8, 121.5, 119.3, 119.2, 114.2, 112.1, 109.1, 57.7, 55.5, 45.3, 26.5, 9.7.

FT-IR: 3049, 2915, 1697, 1512, 1463, 1395, 1290, 1249, 1179, 1032, 828, 740 cm^{-1}.

$[\alpha]^{25}_D$ (90% ee): –59.8° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 321.1598 ($[M+H]^+$, $C_{20}H_{21}N_2O_2^+$ calcd. 321.1603).



3-(3-Methyl-1*H*-indol-1-yl)-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (Table 4.2, entry 5). The compound was prepared according to the General Procedure from 3-iodo-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (133 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (20→60% Et_2O in hexanes) and reverse phase chromatography (0→80% MeOH in H_2O) the title compound was isolated as a white solid in 75% yield (67 mg) and 90% ee. The second run was performed with (*S*)−**4.1**. The product

was isolated as a white solid in 71% yield (64 mg) and 91% ee. HPLC analysis of the product: Diacel CHIRALPAK® IA column; 20% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 16.7 min (major), 23.3 min (minor).

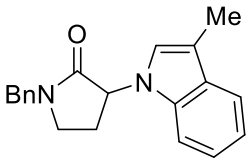
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.87 (m, 2H), 7.75 – 7.66 (m, 2H), 7.66 – 7.59 (m, 1H), 7.34 – 7.13 (m, 2H), 6.95 (q, *J* = 1.1 Hz, 1H), 5.33 (dd, *J* = 10.4, 8.8 Hz, 1H), 4.11 – 3.97 (m, 2H), 2.91 – 2.78 (m, 1H), 2.56 – 2.42 (m, 1H), 2.36 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 141.9, 136.4, 129.3, 126.3, 123.1, 122.0, 119.5, 119.4, 119.2, 112.4, 109.0, 57.8, 44.7, 26.2, 9.7 (2 carbons signals are overlapping).

FT-IR: 2920, 1712, 1614, 1520, 1463, 1389, 1322, 1237, 1197, 1165, 1120, 1069, 1015, 840, 740 cm^{-1}.

$[\alpha]^{25}_D$ (90% ee): –39.8° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 359.1371 ($[M+H]^+$, $C_{20}H_{18}F_3N_2O^+$ calcd. 359.1371).



1-Benzyl-3-(3-methyl-1*H*-indol-1-yl)pyrrolidin-2-one (Table 4.2, entry 6). The compound was prepared according to the General Procedure from 1-benzyl-3-iodopyrrolidin-2-one (113 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 2.2 equiv. of Cs_2CO_3 (179 mg, 0.55 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (20→80% Et_2O in hexanes) and reverse phase chromatography (0→100% MeOH in H_2O) the title compound was isolated as a white solid in 76% yield (58 mg) and 90% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 67% yield (51 mg) and 90% ee. HPLC analysis of the product: Diacel CHIRALPAK® IA column; hexanes:2-propanol/50:50, 1.0 mL/min flow-rate; retention times: 7.9 min (minor), 9.7 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 1H), 7.48 – 7.27 (m, 5H), 7.27 – 7.09 (m, 3H), 6.90 (q, *J* = 1.1 Hz, 1H), 5.16 (t, *J* = 9.1 Hz, 1H), 4.71 (d, *J* = 14.5 Hz, 1H), 4.55 (d, *J*

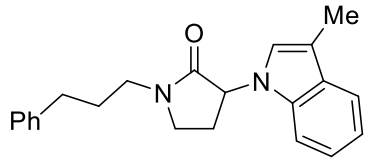
= 14.5 Hz, 1H), 3.50 – 3.29 (m, 2H), 2.69 – 2.55 (m, 1H), 2.36 (d, *J* = 1.1 Hz, 3H), 2.17 (~dq, *J* = 13.2, 8.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 136.4, 135.9, 129.3, 128.9, 128.5, 128.0, 123.4, 121.7, 119.3, 119.1, 112.0, 109.1, 56.8, 47.5, 43.3, 26.5, 9.7.

FT-IR: 3028, 2917, 1697, 1494, 1461, 1439, 1357, 1289, 1256, 1233, 739, 700cm^{-1}.

$[\alpha]^{25}_D$ (90% ee): –4.2° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 305.1650 ($[M+H]^+$, $C_{20}H_{21}N_2O^+$ calcd. 305.1654).



3-(3-Methyl-1*H*-indol-1-yl)-1-(3-phenylpropyl)pyrrolidin-2-one (Table 4.2, entry 7). The compound was prepared according to the General Procedure from 3-iodo-1-(3-phenylpropyl)pyrrolidin-2-one (123 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 2.2 equiv. of Cs_2CO_3 (180 mg, 0.55 mmol). The reaction was run for 48 hours at 23-25 °C. After purification by flash chromatography (35→100% Et_2O in hexanes) and reverse phase chromatography (0→70% MeOH in H_2O) the title compound was isolated as yellow oil in 85% yield (71 mg) and 83% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as yellow oil in 76% yield (63 mg) and 81% ee. HPLC analysis of the product: Diacel CHIRALPAK® IA column; 50% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 12.5 min (minor), 13.6 min (major).

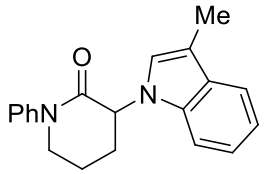
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.56 (m, 1H), 7.45 – 7.33 (m, 2H), 7.33 – 7.20 (m, 5H), 7.21 – 7.10 (m, 1H), 6.89 (q, *J* = 1.1 Hz, 1H), 5.05 (t, *J* = 9.1 Hz, 1H), 3.59 – 3.37 (m, 4H), 2.83 – 2.69 (m, 2H), 2.67 – 2.51 (m, 1H), 2.37 (d, *J* = 1.2 Hz, 3H), 2.23 – 2.06 (m, 1H), 2.09 – 1.91 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 141.2, 136.5, 129.3, 128.6, 128.4, 126.2, 123.4, 121.7, 119.3, 119.1, 111.9, 109.1, 56.8, 43.9, 43.2, 33.3, 28.8, 26.8, 9.8.

FT-IR: 3053, 3025, 2926, 2859, 1698, 1494, 1462, 1386, 1368, 1292, 1233, 1199, 739, 700 cm^{-1}.

$[\alpha]^{25}_D$ (83% ee): –42.0° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 333.1965 ($[M+H]^+$, $C_{22}H_{25}N_2O^+$ calcd. 333.1967).



3-(3-methyl-1*H*-indol-1-yl)-1-phenylpiperidin-2-one (Table 4.2, entry 8). The compound was prepared according to the General Procedure from 1-phenyl-3-iodopiperidin-2-one (113 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 48 hours at 23-25 °C. After purification by flash chromatography (20→80% Et_2O in hexanes) and reverse phase chromatography (0→70% MeOH in H_2O) the title compound was isolated as a white solid in 89% yield (68 mg) and 80% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 86% yield (65 mg) and 80% ee. HPLC analysis of the product: Diacel CHIRALPAK® AD column; 30% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 13.7 min (major), 16.9 min (minor).

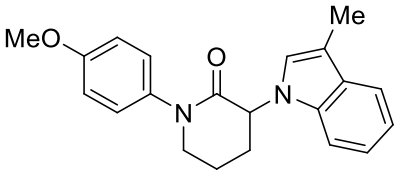
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 1H), 7.49 – 7.41 (m, 2H), 7.41 – 7.35 (m, 2H), 7.35 – 7.31 (m, 2H), 7.26 – 7.18 (m, 1H), 7.16 – 7.08 (m, 1H), 6.96 (q, J = 1.2 Hz, 1H), 5.17 (t, *J* = 8.2 Hz, 1H), 4.12 – 3.92 (m, 1H), 3.90 – 3.76 (m, 1H), 2.51 – 2.42 (m, 2H), 2.37 (d, *J* = 1.1 Hz, 3H), 2.30 – 2.11 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 142.6, 136.5, 129.13, 129.09, 126.9, 125.9, 124.0, 121.6, 119.2, 118.9, 111.3, 109.2, 56.7, 51.5, 28.8, 21.9, 9.7.

FT-IR: 3049, 2916, 2861, 1660, 1594, 1493, 1462, 1422, 1351, 1327, 1224, 1190, 759, 737, 694 cm^{-1}.

$[\alpha]^{25}_D$ (80% ee): –3.2° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 305.1649 ($[M+H]^+$, $C_{20}H_{21}N_2O^+$ calcd. 305.1654).



1-(4-Methoxyphenyl)-3-(3-methyl-1*H*-indol-1-yl)piperidin-2-one (Table 4.2, entry 9). The compound was prepared according to the General Procedure from 1-(4-methoxyphenyl)-3-iodopiperidin-2-one (124 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 2.2 equiv. of Cs_2CO_3 (179 mg, 0.55 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (0→10% MeOH in CH_2Cl_2) and reverse phase chromatography (0→50% MeOH in H_2O) the title compound was isolated as a white solid in 78% yield (66 mg) and 89% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 69% yield (58 mg) and 87% ee. HPLC analysis of the product: Diacel CHIRALPAK® IA column; 50% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 10.6 min (major), 15.7 min (minor).

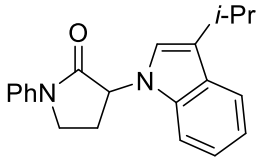
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.40 – 7.20 (m, 4H), 7.14 (d, *J* = 1.0 Hz, 1H), 7.04 – 6.88 (m, 3H), 5.12 (t, *J* = 8.1 Hz, 1H), 3.94 – 3.84 (m, 1H), 3.81 (s, 3H), 3.81 – 3.71 (m, 1H), 2.47 – 2.38 (m, 2H), 2.36 (d, *J* = 1.1 Hz, 3H), 2.23 – 2.10 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 158.2, 136.5, 135.6, 129.1, 127.1, 124.1, 121.6, 119.2, 118.9, 114.4, 111.1, 109.3, 56.7, 55.5, 51.9, 28.8, 21.9, 9.8.

FT-IR: 3046, 2933, 2835, 1660, 1607, 1510, 1462, 1326, 1296, 1240, 1189, 1032, 829, 738 cm^{-1}.

$[\alpha]^{25}_D$ (89% ee): –1.8° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 335.1755 ($[M+H]^+$, $C_{21}H_{23}N_2O_2^+$ calcd. 335.1760).



3-(3-Isopropyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 1). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 3-isopropyl-1*H*-indole (39.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (35% Et_2O in hexanes) and reverse phase chromatography (0→75% MeOH in H_2O) the title compound was isolated as a white solid in 82% yield (65 mg) and 89% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 86% yield (68 mg) and 91% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 9.5 min (minor), 12.3 min (major).

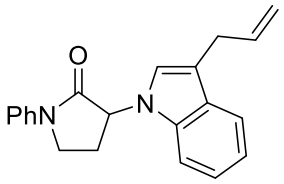
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.73 (m, 2H), 7.74 – 7.63 (m, 1H), 7.50 – 7.42 (m, 2H), 7.34 – 7.19 (m, 3H), 7.18 – 7.09 (m, 1H), 6.94 (d, *J* = 0.9 Hz, 1H), 5.31 (dd, *J* = 10.3, 8.8 Hz, 1H), 4.40 – 3.59 (m, 2H), 3.24 (hd, *J* = 6.8, 0.9 Hz, 1H), 2.80 (dddd, *J* = 13.0, 8.8, 5.6, 3.4 Hz, 1H), 2.44 (ddt, *J* = 13.0, 10.3, 9.2 Hz, 1H), 1.39 (d, *J* = 6.8, 3H),1.37 (d, *J* = 6.8, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 139.1, 136.7, 129.1, 128.0, 125.3, 124.2, 121.8, 121.2, 119.9, 119.8, 119.1, 109.3, 58.0, 45.0, 26.3, 25.6, 23.30, 23.26.

FT-IR: 3046, 2958, 2868, 1706, 1598, 1495, 1462, 1395, 1307, 1226, 1198, 758, 739, 690 cm^{-1}.

$[\alpha]^{25}_D$ (89% ee): –50.8° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 319.1805 ($[M+H]^+$, $C_{21}H_{23}N_2O^+$ calcd. 319.1810).



3-(3-Allyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 2). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 3-allyl-1*H*-indole (39.3 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 72 hours at 23-24 °C. After purification by flash chromatography (35% Et_2O in hexanes) and reverse phase chromatography (0→75% MeOH in H_2O) the title compound was isolated as yellow oil in 89% yield (70 mg) and 87% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as yellow oil in 98% yield (78 mg) and 87% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 14.5 min (minor), 17.0 min (major).

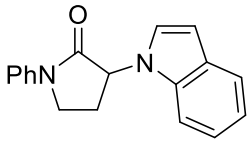
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H), 7.64 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.32 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.28 – 7.20 (m, 2H), 7.15 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.99 (s, 1H), 6.10 (ddt, *J* = 16.6, 10.0, 6.5 Hz, 1H), 5.32 (dd, *J* = 10.2, 8.7 Hz, 1H), 5.20 (dq, *J* = 17.0, 1.7 Hz, 1H), 5.14 – 5.06 (m, 1H), 4.02 (dd, *J* = 9.2, 4.6 Hz, 2H), 3.55 (dq, *J* = 6.5, 1.4 Hz, 2H), 2.81 (ddt, *J* = 13.2, 8.9, 4.5 Hz, 1H), 2.44 (ddt, *J* = 13.0, 10.3, 9.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 139.1, 137.2, 136.6, 129.1, 128.5, 125.3, 123.6, 122.0, 119.8, 119.6, 119.4, 115.4, 114.8, 109.4, 58.0, 44.9, 30.0, 26.3.

FT-IR: 3057, 2923, 1704, 1638, 1598, 1500, 1462, 1395, 1308, 1225, 1177, 1113, 995, 912, 758, 740 cm^{-1}.

$[\alpha]^{25}_D$ (87% ee): –53.0° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 317.1647 ($[M+H]^+$, $C_{21}H_{21}N_2O^+$ calcd. 317.1654).



3-(1*H*-Indol-1-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 3). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and indole (29.3 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 72 h at 25-26 °C. After purification by flash chromatography (35→60% Et_2O in hexanes) the title compound was isolated as a white solid in 54% yield (37 mg) and 83% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 49% yield (34 mg) and 83% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 28.4 min (minor), 35.1 min (major).

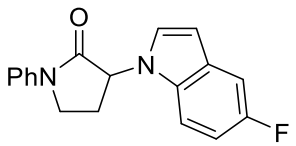
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.73 (m, 2H), 7.73 – 7.65 (m, 1H), 7.55 – 7.40 (m, 2H), 7.37 – 7.33 (m, 1H), 7.29 – 7.21 (m, 2H), 7.21 – 7.12 (m, 2H), 6.63 (d, *J* = 3.2 Hz, 1H), 5.33 (dd, *J* = 10.1, 8.7 Hz, 1H), 4.19 – 3.85 (m, 2H), 2.98 – 2.63 (m, 1H), 2.45 (dq, *J* = 12.9, 8.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 139.0, 136.0, 129.1, 129.0, 126.1, 125.3, 121.9, 121.3, 119.9, 119.8, 109.4, 102.9, 58.2, 45.0, 26.4.

FT-IR: 3048, 2952, 1701, 1597, 1496, 1480, 1460, 1396, 1310, 1226, 1199, 759, 741, 690 cm^{-1}.

$[\alpha]^{25}_D$ (83% ee): –55.0° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 277.1339 ($[M+H]^+$, $C_{18}H_{17}N_2O^+$ calcd. 277.1341).



3-(5-Fluoro-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 4). The compound was prepared according to the General Procedure from 3-iodo-1-

phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 5-fluoro-1*H*-indole (33.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 72 hours at 25-26 °C. After purification by flash chromatography (30→65% Et_2O in hexanes) the title compound was isolated as a white solid in 52% yield (38 mg) and 83% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 54% yield (35 mg) and 84% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 14.6 min (minor), 18.6 min (major).

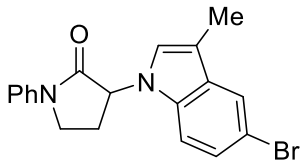
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.67 (m, 2H), 7.59 – 7.40 (m, 2H), 7.38 – 7.11 (m, 4H), 7.07 – 6.90 (m, 1H), 6.57 (d, *J* = 3.3, 1H), 5.29 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.20 – 3.83 (m, 2H), 2.92 – 2.70 (m, 1H), 2.56 – 2.35 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 158.1 (d, *J* = 234.8 Hz), 138.9, 132.6, 129.4 (d, *J* = 10.2 Hz), 129.1, 127.7, 125.4, 119.8, 110.3(d, *J* = 26.4 Hz), 110.0 (d, *J* = 9.7 Hz), 106.1(d, *J* = 23.3 Hz), 102.9 (d, *J* = 4.7 Hz), 58.4, 45.0, 26.4.

FT-IR: 3065, 2923, 1704, 1597, 1495, 1482, 1449, 1399, 1309, 1222, 1117, 949, 758, 690 cm^{-1}.

$[\alpha]^{25}_D$ (83% ee): –33.7° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 295.1241 ($[M+H]^+$, $C_{18}H_{16}FN_2O^+$ calcd. 295.1247).



3-(5-Bromo-3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 5). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 5-bromo-3-methyl-1*H*-indole (52.2 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 48 hours at 24-25 °C. After purification by flash chromatography (25→75% Et_2O in hexanes) the title compound was

isolated as a white solid in 74% yield (68 mg) and 87% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 65% yield (60 mg) and 90% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 15.3 min (minor), 17.1 min (major).

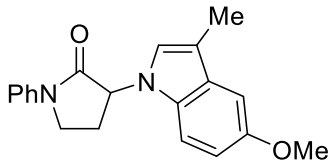
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 3H), 7.58 – 7.38 (m, 2H), 7.38 – 7.20 (m, 2H), 7.20 – 7.12 (m, 1H), 6.96 (q, *J* = 1.2 Hz, 1H), 5.21 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.13 – 3.86 (m, 2H), 2.89 – 2.67 (m, 1H), 2.55 – 2.33 (m, 1H), 2.31 (d, *J* = 1.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 138.9, 135.1, 131.0, 129.1, 125.4, 124.7, 124.6, 122.0, 119.8, 112.6, 111.8, 110.7, 58.0, 44.9, 26.3, 9.6.

FT-IR: 2917, 1700, 1598, 1494, 1458, 1394, 1307, 1225, 1199, 786, 758, 691 cm^{-1}.

$[\alpha]^{25}_D$ (87% ee): –22.9° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 369.0593 ($[M+H]^+$, $C_{19}H_{18}BrN_2O^+$ calcd. 369.0603).



3-(5-Methoxy-3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 6). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 5-methoxy-3-methyl-1*H*-indole (40.0 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 2.2 equiv. of Cs_2CO_3 (180 mg, 0.55 mmol). The reaction was run for 72 hours at 24-25 °C. After purification by flash chromatography (25→85% Et_2O in hexanes) the title compound was isolated as a white solid in 86% yield (69 mg) and 91% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 83% yield (66 mg) and 90% ee. HPLC analysis of the product: Diacel CHIRALPAK® IA column; 50% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 10.0 min (minor), 31.0 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.68 (m, 2H), 7.59 – 7.37 (m, 2H), 7.28 – 7.21 (m, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.95 (d, *J* = 1.2 Hz, 1H), 6.90 (dd, *J*

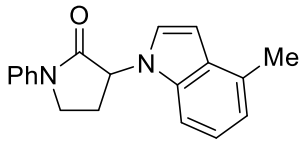
= 8.8, 2.5 Hz, 1H), 5.22 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.04 – 3.94 (m, 2H), 3.90 (s, 3H), 2.89 – 2.64 (m, 1H), 2.52 – 2.33 (m, 1H), 2.33 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 154.0, 139.1, 131.6, 129.7, 129.1, 125.2, 124.2, 119.8, 112.0, 111.6, 109.9, 101.3, 58.1, 56.0, 45.0, 26.4, 9.8.

FT-IR: 2933, 1704, 1597, 1487, 1457, 1395, 1309, 1244, 1221, 1100, 1047, 759 cm^{-1}.

$[\alpha]^{25}_D$ (90% ee): –74.8° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 321.1592 ($[M+H]^+$, $C_{20}H_{21}N_2O_2^+$ calcd. 321.1603).



3-(4-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 7). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 4-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 48 hours at 23-25 °C. After purification by flash chromatography (0→60% Et_2O in hexanes) the title compound was isolated as a white solid in 59% yield (43 mg) and 91% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 58% yield (42 mg) and 91% ee. HPLC analysis of the product: Diacel CHIRALPAK® IB column; 20% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 4.5min (minor), 5.1 min (major).

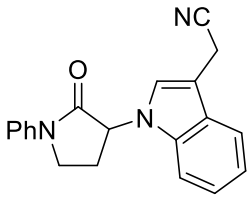
^{1}H NMR (400 MHz, CDCl3) δ 7.81 – 7.74 (m, 2H), 7.49 – 7.42 (m, 2H), 7.27 – 7.11 (m, 4H), 6.99 – 6.93 (m, 1H), 6.64 (dd, J = 3.3, 0.8 Hz, 1H), 5.34 (dd, *J* = 10.1, 8.7 Hz, 1H), 4.09 – 3.98 (m, 2H), 2.88 – 2.79 (m, 1H), 2.59 (s, 3H), 2.53 – 2.41 (m, 1H).

^{13}C NMR (101 MHz, CDCl3) δ 169.5, 139.0, 135.7, 130.8, 129.1, 128.8, 125.4, 125.3, 122.1, 120.2, 119.8, 107.0, 101.4, 58.3, 45.0, 26.5, 18.7.

FT-IR: 3045, 2917, 1703, 1598, 1492, 1458, 1397, 1307, 1226, 749, 690 cm^{-1}.

$[\alpha]^{25}_D$ (91% ee): –3.2° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 291.1487 ($[M+H]^+$, $C_{19}H_{19}N_2O^+$ calcd. 291.1497).



2-(1-(2-Oxo-1-phenylpyrrolidin-3-yl)-1*H*-indol-3-yl)acetonitrile (Table 4.3, entry 8). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 2-(1*H*-indol-3-yl)acetonitrile (39.0 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.0 equiv. of Cs_2CO_3 (81.5 mg, 0.25 mmol). The reaction was run for 48 hours at 23-25 °C. After purification by flash chromatography (50→100% Et_2O in hexanes) the title compound was isolated as yellow oil in 55% yield (43 mg) and 86% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as yellow oil in 52% yield (41 mg) and 88% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 50% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 15.4 min (minor), 48.1 min (major).

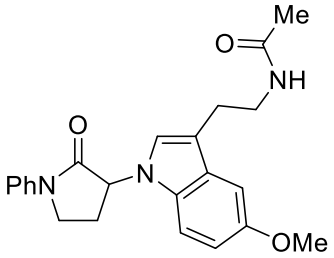
^{1}H NMR (400 MHz, CDCl3) δ 7.79 – 7.70 (m, 2H), 7.65 – 7.59 (m, 1H), 7.51 – 7.42 (m, 2H), 7.39 – 7.20 (m, 5H), 5.33 (dd, *J* = 10.4, 8.7 Hz, 1H), 4.11 – 3.94 (m, 2H), 3.86 (d, *J* = 1.1 Hz, 2H), 2.95 – 2.72 (m, 1H), 2.59 – 2.30 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 138.8, 136.5, 129.1, 127.0, 125.5, 124.6, 122.9, 120.5, 119.9, 118.7, 118.1, 109.8, 105.0, 58.1, 45.0, 26.5, 14.5.

FT-IR: 3050, 2922, 2248, 1700, 1597, 1495, 1464, 1398, 1307, 1226, 1205, 1178, 742, 692 cm^{-1}.

$[\alpha]^{25}_D$ (86% ee): –44.1° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 316.1443 ($[M+H]^+$, $C_{20}H_{18}N_3O^+$ calcd. 316.1450).



***N*-(2-(5-Methoxy-1-(2-oxo-1-phenylpyrrolidin-3-yl)-1*H*-indol-3-yl)ethyl)acetamide (Table 4.3, entry 9)**. The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and *N*-acetyl-5-methoxytryptamine (58.1 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 2.2 equiv. of Cs_2CO_3 (179 mg, 0.55 mmol). The reaction was run for 72 hours at 25-26 °C. After purification by flash chromatography (0→15% MeOH in CH_2Cl_2) and reverse phase chromatography (0→70% MeOH in H_2O) the title compound was isolated as a white solid in 57% yield (56 mg) and 86% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 54% yield (53 mg) and 83% ee. SFC analysis of the product: Diacel CHIRALPAK® IC column; 50% MeOH in CO_2, 3.0 mL/min flow-rate; retention times: 5.1 min (minor), 5.9 min (major).

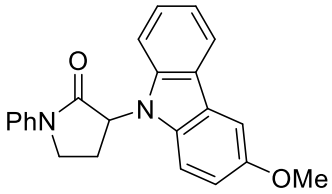
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.68 (m, 2H), 7.54 – 7.41 (m, 2H), 7.28 – 7.18 (m, 2H), 7.10 – 7.06 (d, *J* = 2.4 Hz, 1H), 7.00 (s, 1H), 6.91 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.66 (br s, 1H), 5.24 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.11 – 3.93 (m, 2H), 3.88 (s, 3H), 3.76 – 3.46 (m, 2H), 3.11 – 2.87 (m, 2H), 2.88 – 2.76 (m, 1H), 2.52 – 2.37 (m, 1H), 1.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.6, 154.3, 138.9, 131.7, 129.1, 128.9, 125.4, 124.7, 119.8, 112.9, 112.4, 110.3, 101.1, 58.3, 56.0, 45.0, 39.7, 26.4, 25.3, 23.4.

FT-IR: 3305, 3065, 2934, 1703, 1651, 1597, 1548, 1485, 1452, 1396, 1307, 1223, 1176, 1030, 760, 692 cm^{-1}.

$[\alpha]^{25}_D$ (86% ee): –29.2° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 392.1973 ($[M+H]^+$, $C_{23}H_{26}N_3O_3^+$ calcd. 392.1974).



3-(3-Methoxy-9*H*-carbazol-9-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 10). The title compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 3-methoxy-9*H*-carbazole (49.3 mg, 0.25 mmol), using (*R*)−**4.1**, and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 60 h at 23-25 °C. After purification by flash chromatography (25→80% Et_2O in hexanes) the title compound was obtained as a white solid in 79% yield (70 mg) and 96% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 84% yield (75 mg) and 97% ee. HPLC analysis of the product: Diacel CHIRALPAK® IA column; 50% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 13.6 min (minor), 41.6 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.06 (m, 1H), 7.87 – 7.76 (m, 2H), 7.63 (d, *J* = 2.5 Hz, 1H), 7.57 – 7.39 (m, 3H), 7.37 – 7.18 (m, 4H), 7.08 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.54 (dd, *J* = 10.8, 9.3 Hz, 1H), 4.32 – 3.97 (m, 2H), 3.95 (s, 3H), 2.74 – 2.52 (m, 2H).

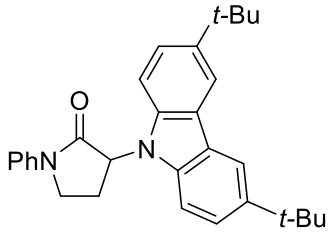
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 154.1, 139.2, 129.1, 125.8, 125.3, 124.2, 123.6, 120.5, 119.7, 119.2, 114.8, 110.0, 109.3, 103.7, 56.2, 56.2, 44.9, 23.3. (2 carbons are missing due to overlap)

FT-IR: 3049, 2952, 2831, 1704, 1597, 1490, 1462, 1405, 1306, 1201, 1081, 1032, 744, 689 cm^{-1}.

$[\alpha]^{25}_D$ (96% ee): –88.8° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 357.1598 ($[M+H]^+$, $C_{23}H_{21}N_2O_2^+$ calcd. 357.1603).

Gram-scale Reaction. The title compound was prepared as above from 3-iodo-1-phenylpyrrolidin-2-one (1.51 g, 5.25 mmol) and 3-methoxy-9*H*-carbazole (690 mg, 3.50 mmol), using (*S*)−**4.1**, and 2.5 equiv. of Cs_2CO_3 (2.85 g, 8.75 mmol). The reaction was run for 90 h at 23-25 °C. The product was isolated as a white solid in 85% yield (1.06 g) and 92% ee. See Section 4.4.4 for details of **4.1** recovery.



3-(3,6-Di-tert-butyl-9*H*-carbazol-9-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 12). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 3,6-di-tert-butyl-9*H*-carbazole (69.9 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (0→50% Et_2O in hexanes) and reverse phase chromatography (0→80% MeOH in H_2O) the title compound was isolated as a white solid in 79% yield (87 mg) and 94% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 81% yield (89 mg) and 95% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 15% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 15.4 min (minor), 48.1 min (major).

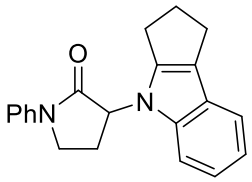
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (m 0.6 Hz, 2H), 7.87 – 7.79 (m, 2H), 7.56 – 7.42 (m, 4H), 7.33 – 7.17 (m, 3H), 5.58 (dd, *J* = 10.5, 9.6 Hz, 1H), 4.12 – 4.02 (m, 2H), 2.73 – 2.63 (m, 1H), 1.48 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 142.4, 139.3, 129.1, 125.2, 123.5, 119.8, 116.6, 56.1, 44.9, 34.7, 32.0, 23.4 (3 carbons are missing due to overlap).

FT-IR: 3046, 2959, 1708, 1598, 1491, 1477, 1404, 1392, 1362, 1308, 1262, 1167, 804, 757, 691 cm^{-1}.

$[\alpha]^{25}_D$ (94% ee): –84.2° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 439.2743 ($[M+H]^+$, $C_{30}H_{35}N_2O^+$ calcd. 439.2749).



3-(2,3-Dihydrocyclopenta[*b*]indol-4(1*H*)-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 12). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 1,2,3,4-tetrahydrocyclopenta[*b*]indole (39.3 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (25→55% Et_2O in hexanes) and reverse phase chromatography (0→75% MeOH in H_2O) the title compound was isolated as a white solid in 67% yield (53 mg) and 97% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 64% yield (51 mg) and 96% ee. HPLC analysis of the product: Diacel CHIRALPAK® IB column; 20% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 22.4 min (minor), 40.6min (major).

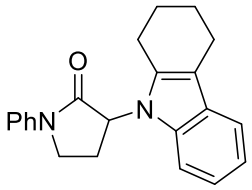
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.66 (m, 2H), 7.64 – 7.39 (m, 3H), 7.36 – 7.19 (m, 2H), 7.19 – 7.06 (m, 2H), 5.26 (dd, *J* = 10.4, 8.9 Hz, 1H), 3.95 (m, 2H), 3.05 – 2.78 (m, 4H), 2.71 (m, 1H), 2.58 (m 2H), 2.39 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 144.9, 141.0, 139.2, 129.1, 125.2, 125.1, 120.4, 120.1, 119.8, 119.5, 119.0, 109.5, 57.1, 44.9, 28.6, 26.1, 26.0, 24.4.

FT-IR: 3045, 2951, 2850, 1706, 1597, 1495, 1456, 1402, 1375, 1307, 738, 690 cm^{-1}.

$[\alpha]^{25}_D$ (97% ee): –86.2° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 317.1648 ($[M+H]^+$, $C_{21}H_{21}N_2O^+$ calcd. 317.1654).



3-(3,4-Dihydro-1*H*-carbazol-9(2*H*)-yl)-1-phenylpyrrolidin-2-one (Table 4.3, entry 13). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 2,3,4,9-tetrahydro-1*H*-carbazole (42.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). The reaction was run for 72 hours at 23-25 °C. After purification by flash chromatography (0→5% MeOH in CH_2Cl_2) and reverse phase chromatography (0→100% MeOH in H_2O) the title compound was isolated as a white solid in 72% yield (59 mg) and 98% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 66% yield (55 mg) and 97% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 35% i-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 14.5 min (minor), 27.9 min (major).

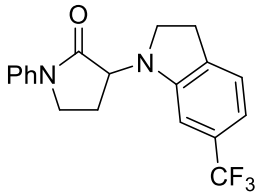
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.72 (m, 2H), 7.55 – 7.40 (m, 3H), 7.28 – 7.21 (m, 1H), 7.21 – 7.07 (m, 3H), 5.25 (s, 1H), 4.22 – 3.84 (m, 2H), 3.07 – 2.70 (m, 4H), 2.71 – 2.42 (m, 2H), 22.17 – 1.73 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 139.2, 129.1, 125.2, 121.0, 119.8, 119.2, 118.3, 56.0, 44.8, 23.3, 23.0, 21.1 (7 carbons are missing due to overlap).

FT-IR: 3046, 2929, 2838, 1705, 1597, 1495, 1464, 1401, 1375, 1309, 1226, 758, 738, 692 cm^{-1}.

$[\alpha]^{25}_D$ (98% ee): –94.2° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 331.1806 ($[M+H]^+$, $C_{22}H_{23}N_2O^+$ calcd. 331.1810).



1-Phenyl-3-(6-(trifluoromethyl)indolin-1-yl)pyrrolidin-2-one (Table 4.3, entry 14). The compound was prepared according to the General Procedure from 3-iodo-1-phenylpyrrolidin-2-one (108 mg, 0.375 mmol) and 6-(trifluoromethyl)indoline (46.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.5 equiv. of Cs_2CO_3 (122 mg, 0.375 mmol). The reaction was run for 48 hours at 25-26 °C. After purification by flash chromatography (10→100% Et_2O in hexanes) and reverse phase chromatography (0→75% MeOH in H_2O) the title compound was isolated as a white solid in 69% yield (60 mg) and 86% ee. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 59% yield (51 mg) and 90% ee. HPLC analysis of the product: Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times: 7.9 min (minor), 10.1 min (major).

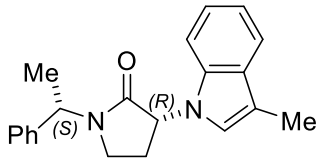
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 2H), 7.47 – 7.32 (m, 2H), 7.25 – 7.18 (m, 1H), 7.18 – 7.12 (m, 1H), 7.00 – 6.87 (m, 1H), 6.72 – 6.64 (m, 1H), 4.63 (dd, *J* = 10.5, 8.6 Hz, 1H), 4.12 – 3.79 (m, 2H), 3.79 – 3.49 (m, 2H), 3.24 – 3.00 (m, 2H), 2.63 – 2.37 (m, 1H), 2.39 – 2.11 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 151.2, 139.1, 133.9, 129.8 (q, *J* = 31.5 Hz), 129.0, 125.1, 124.6, 124.6 (q, *J* = 272.1 Hz), 119.7, 115.2 (q, *J* = 4.2 Hz), 103.1 (q, *J* = 3.9 Hz), 58.4, 48.5, 45.0, 28.2, 20.8.

FT-IR: 3045, 2954, 2853, 1698, 1614, 1598, 1497, 1450, 1402, 1316, 1286, 1160, 1115, 1059, 760, 691 cm^{-1}.

$[\alpha]^{25}_D$ (86% ee): –11.5° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 347.1365 ($[M+H]^+$, $C_{19}H_{18}F_3N_2O^+$ calcd. 347.1371).



(3*R*)-3-(3-Methyl-1*H*-indol-1-yl)-1-((1*S*)-1-phenylethyl)pyrrolidin-2-one. The compound was prepared according to the General Procedure from 3-iodo-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (118 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25 mmol), using 10 mol% of mesitylcopper and 20 mol% of (*R*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). After purification by flash chromatography (20→60% Et_2O in hexanes) and reverse phase chromatography (0→90% MeOH in H_2O) the title compound was isolated as a white solid in 64% yield (51 mg) and 15:85 dr and again in 61% yield (49 mg) and 15:85 dr. The second run was performed with (*S*)−**4.1**. The product was isolated as a white solid in 68% yield (54 mg) and 94:6 dr and again in 70% yield (56 mg) and 94:6 dr.

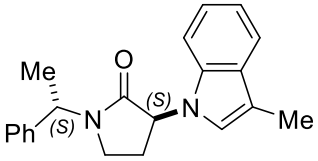
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 1H), 7.45 – 7.30 (m, 5H), 7.27 – 7.18 (m, 2H), 7.18 – 7.10 (m, 1H), 6.89 (t, *J* = 1.1 Hz, 1H), 5.69 (q, *J* = 7.1 Hz, 1H), 5.10 (t, *J* = 8.9 Hz, 1H), 3.63 – 3.37 (m, 1H), 3.06 (dt, *J* = 10.0, 7.8 Hz, 1H), 2.62 – 2.44 (m, 1H), 2.35 (d, *J* = 1.1 Hz, 3H), 2.23 – 2.08 (m, 1H), 1.71 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 139.6, 136.5, 129.4, 128.8, 128.0, 127.4, 123.5, 121.8, 119.3, 119.2, 111.8, 109.3, 57.3, 50.2, 39.4, 26.5, 16.3, 9.8.

FT-IR: 3050, 2974, 1695, 1490, 1457, 1424, 1283, 1234, 1014, 778, 739cm^{-1}.

$[\alpha]^{25}_D$ (100% ee): –171.0° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 319.1807 ($[M+H]^+$, $C_{21}H_{23}N_2O^+$ calcd. 319.1810).



(3*S*)-3-(3-Methyl-1*H*-indol-1-yl)-1-((1*S*)-1-phenylethyl)pyrrolidin-2-one. The compound was prepared according to the General Procedure from 3-iodo-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (118 mg, 0.375 mmol) and 3-methyl-1*H*-indole (32.8 mg, 0.25

mmol), using 10 mol% of mesitylcopper and 20 mol% of (*S*)−**4.1** and 1.8 equiv. of Cs_2CO_3 (147 mg, 0.45 mmol). After purification by flash chromatography (20→60% Et_2O in hexanes) and reverse phase chromatography (0→90% MeOH in H_2O). The product was isolated as a white solid in 68% yield (54 mg) and 94:6 dr and again in 70% yield (56 mg) and 94:6 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.52 (m, 1H), 7.52 – 7.41 (m, 4H), 7.41 – 7.32 (m, 1H), 7.22 – 7.08 (m, 3H), 6.82 (d, *J* = 1.2 Hz, 1H), 5.68 (q, *J* = 7.1 Hz, 1H), 5.16 (t, *J* = 9.1 Hz, 1H), 3.53 – 3.41 (m, 1H), 3.26 – 3.12 (m, 1H), 2.65 – 2.55 (m, 1H), 2.32 (d, *J* = 1.1 Hz, 3H), 2.17 – 2.00 (m, 1H), 1.64 (d, *J* = 7.2 Hz, 3H).

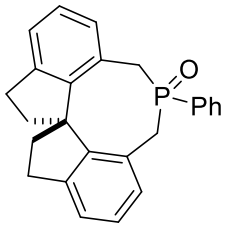
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 139.6, 136.3, 129.3, 128.8, 127.9, 127.2, 123.5, 121.7, 119.3, 119.1, 111.8, 109.2, 57.3, 49.9, 39.1, 26.5, 16.1, 9.7.

FT-IR: 3050, 2976, 1693, 1494, 1462, 1428, 1353, 1285, 1219, 1015, 781, 739 cm^{-1}.

$[\alpha]^{25}_D$ (100% ee): –175° (c = 1.0, $CHCl_3$).

HRMS: *m/z* 319.1804 ($[M+H]^+$, $C_{21}H_{23}N_2O^+$ calcd. 319.1810).

4.4.4. 4.1 Recovery



Recovery of (*S*)−4.1 Oxide. After column chromatography of the gram-scale reaction, fraction suspected to contain **4.1** and **4.1** oxide were collected and concentrated. Care was taken to avoid fractions containing remaining electrophile. Residue was dissolved in 20 mL of MeOH and cooled to °C. Next, 200 μL of H_2O_2 was added. Reaction mixture was warmed to room temperature and stirred for 1 hour then concentrated. Residue was purified by flash chromatography (0→15% MeOH in Et_2O) to afford (*S*)−**4.1** oxide a yellow solid in 94% recovery (243 mg).

^{1}H {^{31}P} NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.46 (m, 1H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.26 – 7.14 (m, 4H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.24 (d, *J* = 7.5 Hz, 1H), 3.81 (d, *J* = 13.8 Hz, 1H), 3.65 (d, *J* = 13.9 Hz, 1H), 3.08 (ddd, *J* = 17.7, 11.5, 6.7 Hz, 2H), 2.94 (ddd, *J* = 15.9, 10.8, 8.2 Hz, 2H), 2.81 (ddd, *J* = 28.2, 13.8, 1.7 Hz, 2H), 2.33 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.25 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.00 (dtdd, *J* = 36.4, 11.9, 7.3, 3.1 Hz, 2H).

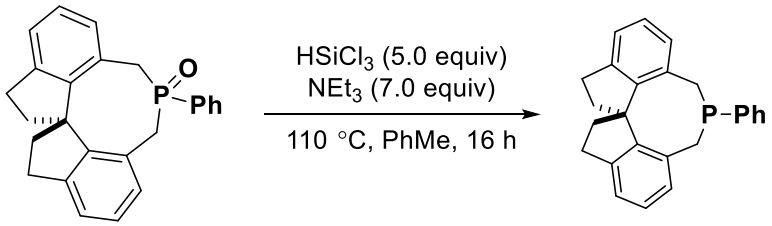
^{13}C NMR (101 MHz, $CDCl_3$) δ.

^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 35.65

FT-IR: 3054, 2945, 2850, 1703, 1591, 1468, 1452, 1435, 1405, 1306, 1257, 1223, 1213, 1177, 1106, 1061, 848, 822, 804, 752 cm^{-1}.

$[\alpha]^{25}_{D}$ (100% ee): –39.8° (c = 1.0, $CHCl_3$).

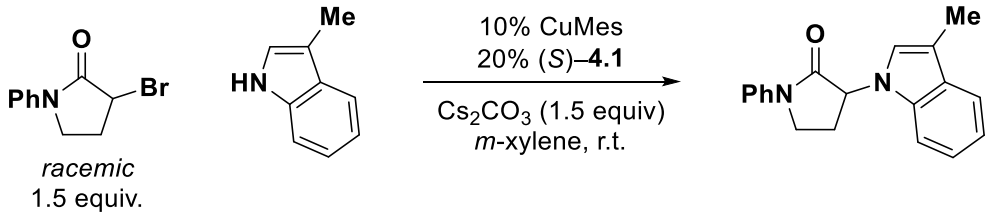
HRMS: *m/z* 371.1567 ($[M+H]^+$, $C_{25}H_{24}PO^+$ calcd. 371.1565).



Recycling of (*S*)−4.1. Reduction of **4.1** oxide has been adapted from a previously reported literature procedure.[27] In a nitrogen-atmosphere glovebox, (*S*)−**4.1** oxide was dissolved in toluene (0.03 M) in a sealed flask then triethylamine (7.0 equiv.) was added. Trichlorosilane (5.0 equiv.) was then added dropwise to the reaction mixture. Reaction mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere outside of the glovebox. To quench the reaction a degassed KOH solution (5.0 M in water) was added dropwise to the reaction mixture inside of a nitrogen-atmosphere glovebox. The flask was resealed with septum and needle vent prior to addition of KOH solution to prevent over-pressurization of the flask. After stirring for 20 minutes, the organic layer was separated by pipette extraction and benzene was used to extract the aqueous phase. The organic layers we collected and concentrated. Residue was dissolved in benzene and filtered through a silicia gel-filled

pipette using benzene to wash the product through. The filtrate was concentrated and isolated as a white solid. ^{1}H NMR data was identical to previously reported data.[28]

4.4.5. Mechanistic Studies



Enantiomeric Excess of Product and α-Bromo-γ-Lactam Electrophile During the Course of the Reaction. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with 3-methyl-1*H*-indole (0.20 mmol) and solution of mesitylcopper (3.6 mg, 0.02 mmol) in 200 μL of *m*-xylene. A stir bar was added and the vial was closed with a screw cap. After stirring for 10 minutes, a solution of (*S*)–**4.1** (14.1 mg, 0.04 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 26.6 mg, 0.10 mmol) in 680 μL of *m*-xylene was added and the vial was recapped. After stirring for additional 10 minutes, α-bromo-γ-lactam (72.0 mg, 0.30 mmol) was added. When the reaction mixture became homogenous (ca. 5 minutes), cesium carbonate (97.7 mg, 0.30 mmol) was added. The vial was recapped and wrapped entirely with electrical tape to prevent access of light. The reaction mixture was stirred vigorously at 24 °C in the glovebox. Aliquots were taken from reaction mixture at different reaction times and were immediately quenched by dilution with 2 mL of dichloromethane followed by filtration. The composition of each sample was determined by ^{1}H NMR analysis. Pure samples of product and electrophile were obtained by preparative TLC (silica gel, 40→60% Et_2O in hexanes). The ee's were determined by HPLC Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times for product: 22.5 min (major), 26.5 min (minor); retention times for electrophile 12.8 min (major) and 17.0 min (minor).

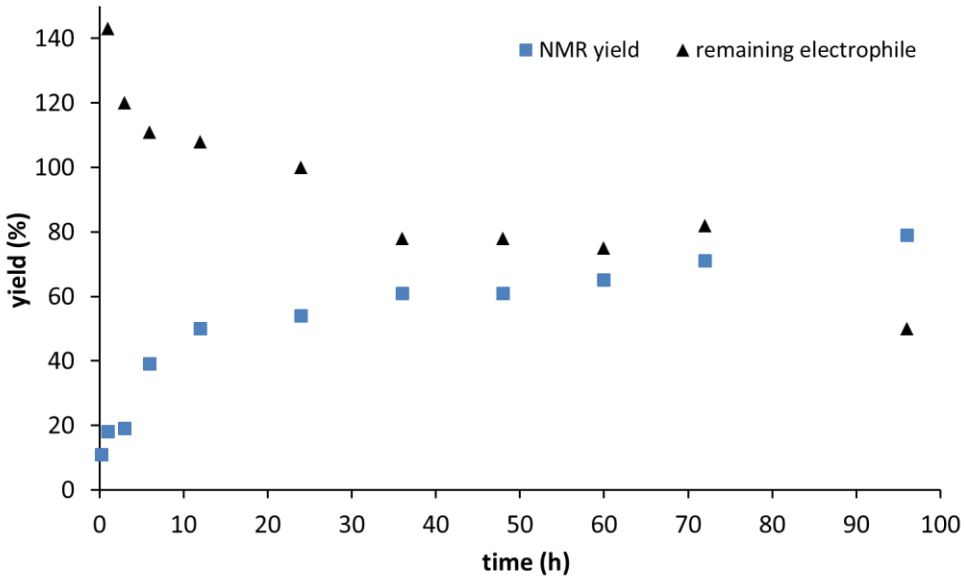


Figure 4.3. ^{1}H NMR yield and remaining electrophile as a function of time.

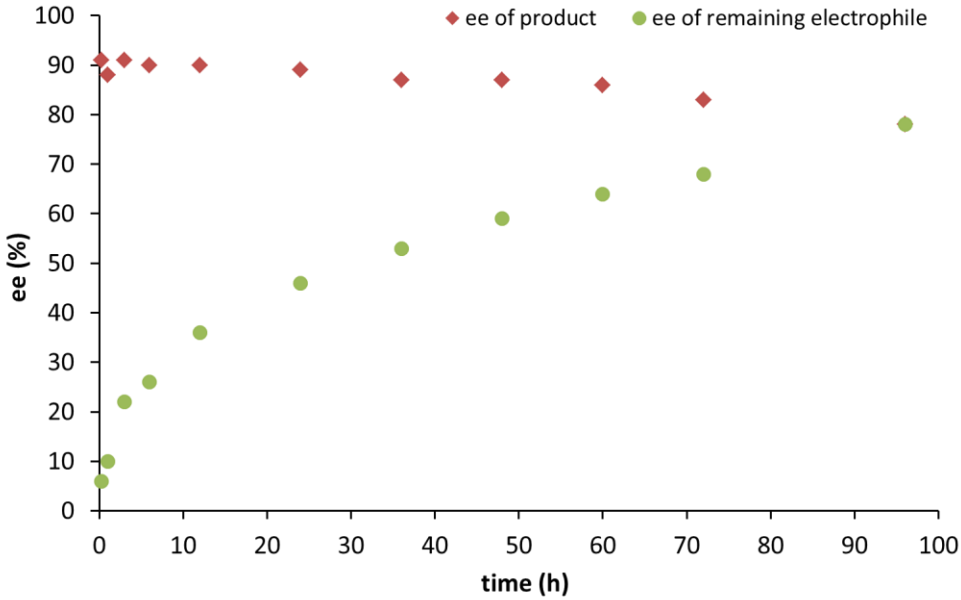
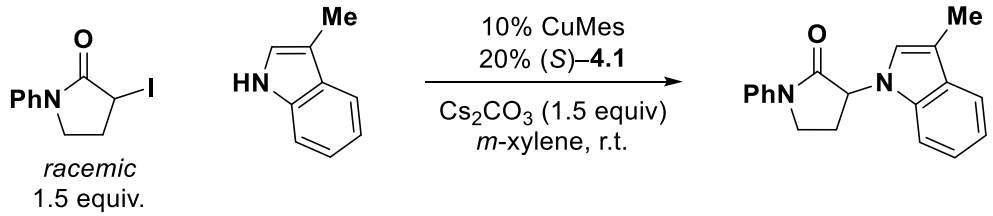


Figure 4.4. Enantiomeric excess of product and remaining electrophile as a function of time.



Enantiomeric Excess of Product and α-Iodo-γ-Lactam Electrophile During the Course of the Reaction. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with 3-methyl-1*H*-indole (0.20 mmol) and solution of mesitylcopper (3.6 mg, 0.02 mmol) in 200 μL of *m*-xylene. A stir bar was added and the vial was closed with a screw cap. After stirring for 10 minutes, a solution of (*S*)–**4.1** (14.1 mg, 0.04 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 26.6 mg, 0.10 mmol) in 680 μL of *m*-xylene was added and the vial was recapped. After stirring for additional 10 minutes, α-iodo-γ-lactam (86.1 mg, 0.30 mmol) was added. When the reaction mixture became homogenous (ca. 5 minutes), cesium carbonate (97.7 mg, 0.30 mmol) was added. The vial was recapped and wrapped entirely with electrical tape to prevent access of light. The reaction mixture was stirred vigorously at 24 °C in the glovebox. Aliquots were taken from reaction mixture at different reaction times and were immediately quenched by dilution with 2 mL of dichloromethane followed by filtration. The composition of each sample was determined by ^{1}H NMR analysis. Pure samples of product and electrophile were obtained by preparative TLC (silica gel, 40→60% Et_2O in hexanes). The ee's were determined by HPLC Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times for product: 22.5 min (major), 26.5 min (minor); retention times for electrophile 13.9 min (major) and 15.0 min (minor).

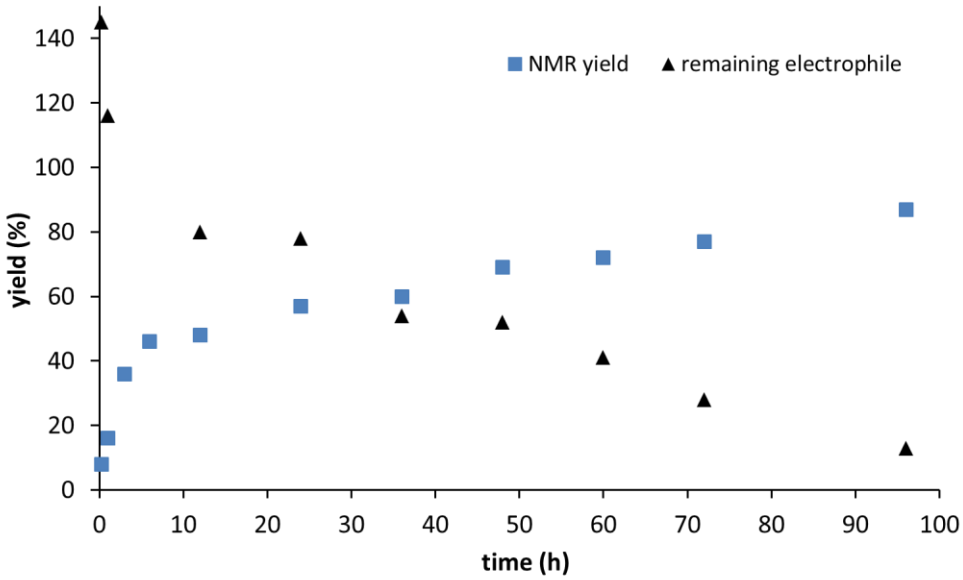


Figure 4.5. ^{1}H NMR yield of and remaining electrophile as a function of time.

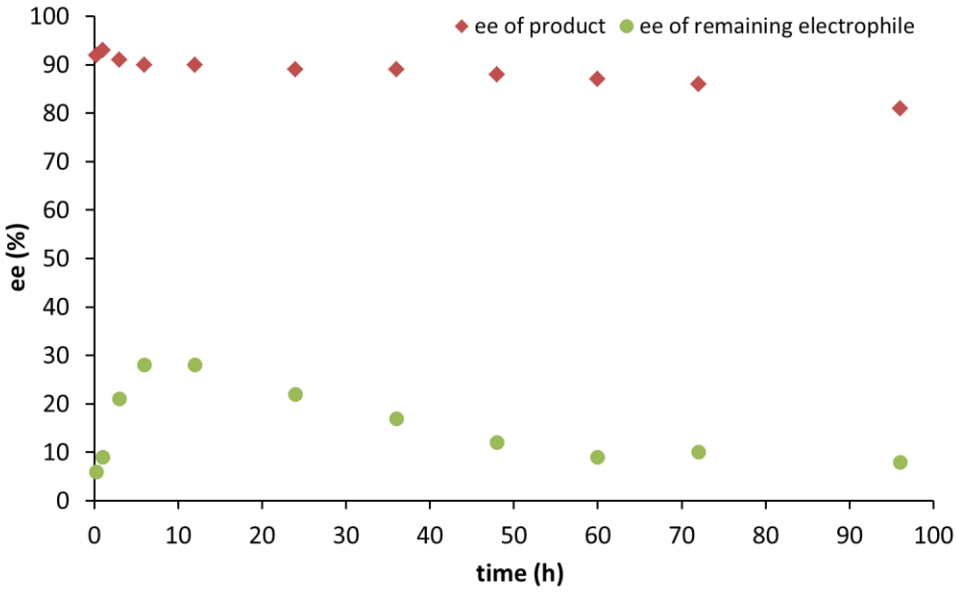
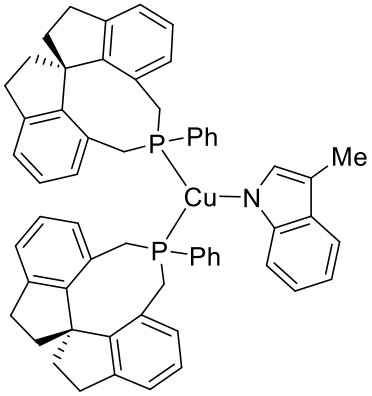


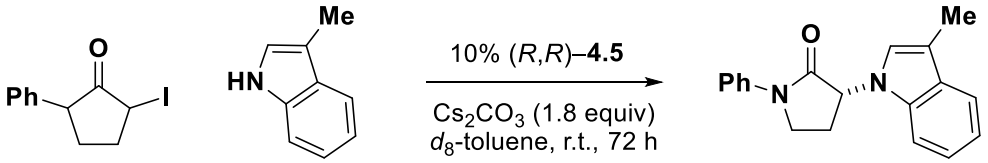
Figure 4.6. Enantiomeric excess of product and remaining electrophileas a function of time.



Preparation of (*R*,*R*)−4.5 Complex. In a nitrogen-atmosphere glovebox**,** an oven-dried 4 mL amber-glass vial was charged with 3-methyl-1*H*-indole (16.4 mg, 0.125 mmol), a stir bar, and a solution of mesitylcopper (22.8 mg, 0.125 mmol) in 500 μL of benzene. After stirring for 10 minutes, a solution of (*R*)−**4.1** (88.5 mg, 0.25 mmol) in 1.5 mL of benzene was added. After stirring for 16 hours, the reaction was concentrated to ca. 0.25 mL and added 2.0 mL of pentane was added dropwise. After stirring for 1 hour, a white precipitate of crude complex was filtered, rinsed with 5 mL of pentane, and dried to give 65% yield (73 mg) of product as a white powder. X-Ray quality crystals were obtained by slow evaporation of solvent from a saturated solution of sample in a benzene/ether/pentane mixture.

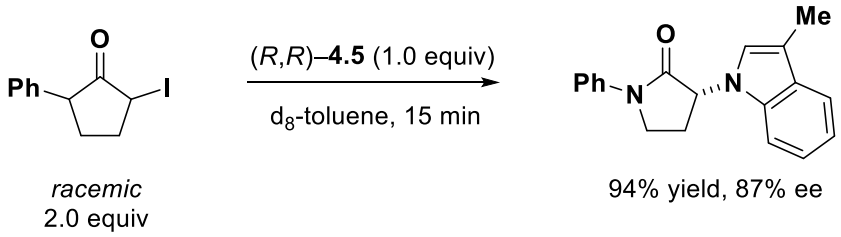
^{1}H NMR (400 MHz, C_6D_6) δ 8.01 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.27 (m, 1H), 7.15 – 6.79 (m, 21H), 6.65 (t, *J* = 7.5 Hz, 2H), 5.70 (d, *J* = 7.5 Hz, 2H), 3.32 (d, *J* = 14.0 Hz, 2H), 3.24 (t, *J* = 11.1 Hz, 2H), 2.88 (d, *J* = 12.0 Hz, 2H), 2.78 – 2.66 (m, 4H), 2.70 (s, 3H), 2.63 – 2.51 (m, 4H), 2.38 (d, *J* = 14.0 Hz, 2H), 1.94 (ddd, *J* = 24.8, 12.2, 6.5 Hz, 4H), 1.87 – 1.69 (m, 4H).

^{13}C NMR (101 MHz, C_6D_6) δ 147.6 , 147.4 , 147.1 , 142.9 , 142.6 , 135.8, 132.9 (d, *J* = 13.3 Hz), 132.1 (d, *J* = 15.3 Hz), 131.2 , 130.5 , 129.9 , 129.6 , 128.8, 128.6 , 126.3 , 123.2 (d, *J* = 20.3 Hz), 117.8 (d, *J* = 19.4 Hz), 115.7 (d, *J* = 19.4 Hz), 108.1 , 61.4 , 38.0 (d, *J* = 47.9 Hz?), 30.6 , 30.2 (d, *J* = 17.6 Hz), 25.3 (d, *J* = 7.4 Hz), 10.7.



Catalytic Competence of (*R,R*)–4.5. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with 3-methyl-1*H*-indole (0.09 mmol), a stir bar, and a solution of (*R,R*)–**4.5** (9.0 mg, 0.01 mmol) in 200 μL of d_8-toluene, then the vial was closed with a screw cap. After stirring for 10 minutes, α-iodo-γ-lactam (43.1 mg, 0.15 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 9.8 mg, 0.037 mmol) were added. After the reaction mixture became homogenous (ca. 5 minutes), cesium carbonate (58.7 mg, 0.18 mmol) was added. The vial was recapped and wrapped entirely with electrical tape to prevent access of light. The reaction mixture was stirred vigorously at 24 °C in the glovebox. After 72 hours, the crude reaction mixture was filtered through a syringe filter. An aliquot of 50 μL of filtrate was used for ^{1}H NMR analysis. Pure sample of product and remaining electrophile were obtained by preparative TLC (silica gel, 40% Et_2O in hexanes). The ee was determined by HPLC Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times for product: 22.5 min (minor), 26.5 min (major); retention times for electrophile 13.9 min (minor) and 15.0 min (major).

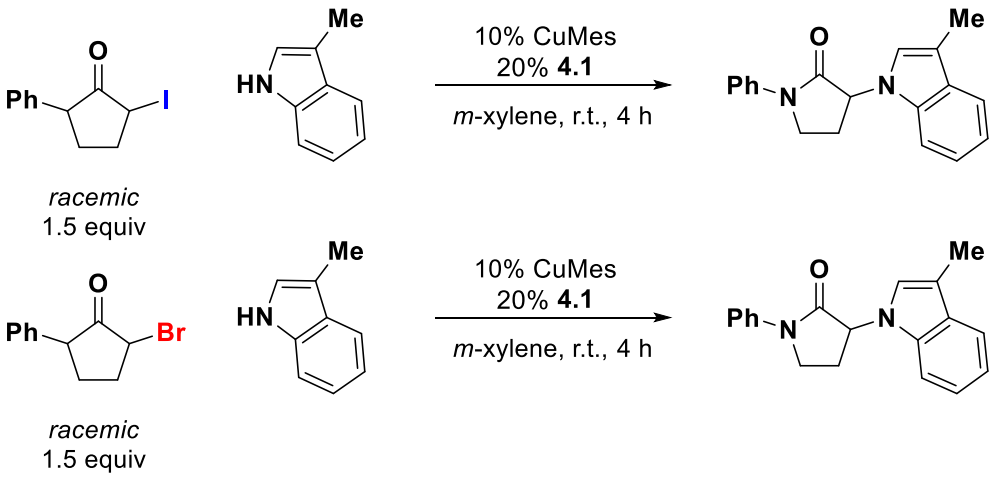
The above reaction was done in duplicate giving; *run 1*: 73% yield and 90% ee of product, 3% ee of remaining electrophile; *run 2*: 75% yield and 90% ee, 3% ee of remaining electrophile.



Stoichiometric Competence of (*R,R*)−4.5. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with (*R,R*)−**4.5** (9.0 mg, 0.01 mmol), a stir bar and a solution of α-iodo-γ-lactam (5.7 mg, 0.02 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 4.8 mg, 0.018 mmol) in 150 μL of d_8-toluene then the vial was closed with a screw cap. Reaction mixture was stirred vigorously for 15 minutes at 24 °C in the glovebox. After this, the crude reaction mixture was removed from the glovebox, diluted with 2 mL of d_1-chloroform and filtered through a syringe filter. An aliquot of 50 μL of filtrate was used for ^{1}H NMR analysis. Pure sample of product and remaining electrophile were obtained by preparative TLC (silica gel, 40% Et_2O in hexanes). The ee was determined by HPLC Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times for product: 22.5 min (minor), 26.5 min (major); retention times for electrophile 13.9 min (minor) and 15.0 min (major). ^{1}H NMR and HPLC analysis showed 94% yield, 87% product ee and 68% ee of remaining starting material.

Inversion of Configuration at α-Center. In a nitrogen-atmosphere glovebox, two parallel reactions were prepared. Two oven-dried 4 mL amber-glass vials were charged with (*R,R*)−**4.5** (9.0 mg, 0.01 mmol), a stir bar. A solution of (*S*)-α-bromo-γ-lactam (3.6 mg, 0.015 mmol) and internal standard(4,4′-di-tert-butylbiphenyl, 3.9 mg, 0.015 mmol) in 150 μL of d_8-toluene was added to the first vial and a solution of (*R*)-α-bromo-γ-lactam (3.6 mg, 0.015 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 3.9 mg, 0.015 mmol) in 150 μL of d_8-toluene was added to the second vial. Vials were closed with a screw cap. Reaction mixtures were stirred vigorously for 4 hours at 24 °C in glovebox. Aliquots were taken from reaction mixtures at different reaction times and were immediately quenched by dilution with

2 mL of dichloromethane and filtered through a syringe filter. The composition of each sample was determined by ^{1}H NMR analysis. Pure samples of product and electrophile were obtained by preparative TLC (silica gel, 40% Et_2O in hexanes). Their ee's were determined by HPLC Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times for: (*S*)-product 22.5 min, (*R*)-product 26.5 min; retention times for (*S*)-electrophile 12.8 min and (*S*)-electrophile 17.0 min. See Table 4.4 for results.



Non-linear Effects: General Procedure. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with a 50 μL aliquot containing 3-methyl-1*H*-indole (0.05 mmol), mesitylcopper (0.005 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 0.011 mmol) in *m*-xylene taken from a stock solution. A 100 μL aliquot containing **4.1** of known ee (0.01 mmol) in *m*-xylene was taken from a stock solution was then added. The vial was charged with a stir bar and stirred for 10 minutes. After this time, a solution α-iodo-γ-lactam or α-bromo-γ-lactam (0.075 mmol) in 150 μL of *m*-xylene was added. The vial was recapped and wrapped entirely with electrical tape to prevent access of light. The reaction mixture was stirred vigorously for 4 hours at 24 °C in glovebox. After this time, the crude reaction mixture was removed from the glovebox, diluted with 2 mL of d_1-chloroform, and filtered through syringe filter. An aliquot of 50 μL of filtrate was used for ^{1}H NMR analysis. Pure sample of product was obtained by preparative TLC (silica gel, 40% Et_2O in hexanes).

The ee was determined by HPLC Diacel CHIRALPAK® IC column; 35% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times for product: 22.5 min (minor), 26.5 min (major). This study was performed with 24 parallel reactions containing different ee's of **4.1** and α-iodo-γ-lactam (12 reactions) or α-bromo-γ-lactam (12 reactions). The precise ee of **4.1** in each reaction was determined by HPLC Diacel CHIRALPAK® AD column; 40% *i*-PrOH in hexanes, 1.0 mL/min flow-rate; retention times for: (*S*)−**4.1** 5.0 min, (*R*)−**4.1** 15.4 min.

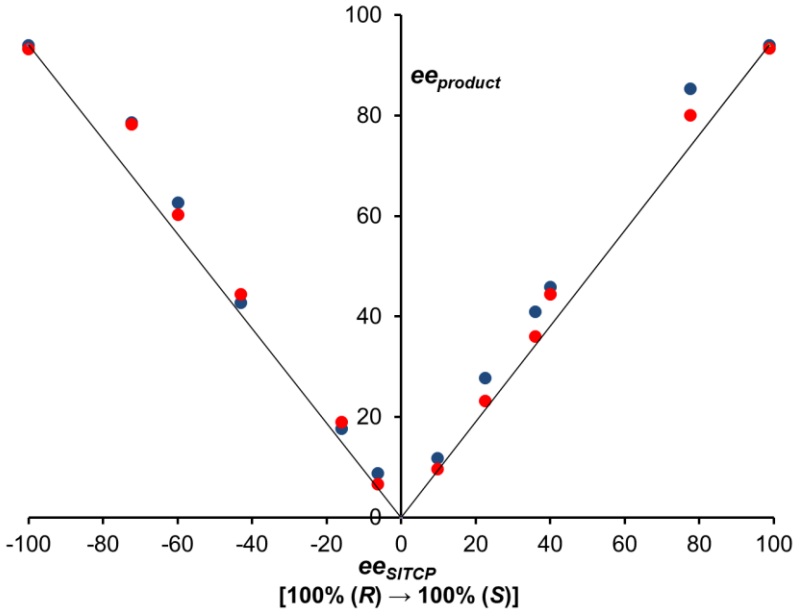
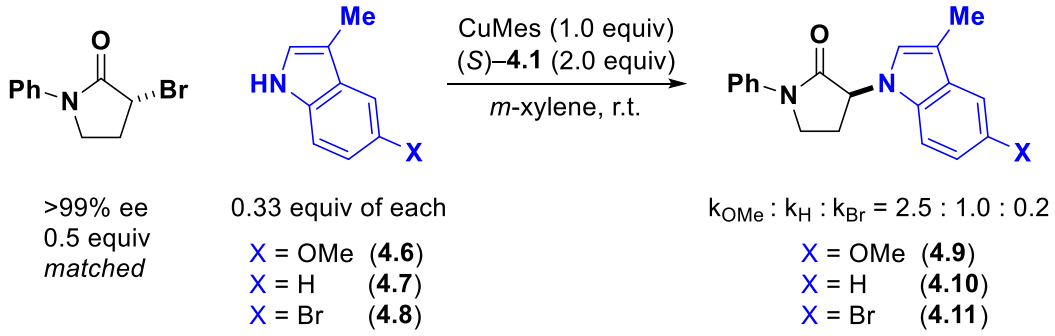


Figure 4.7. Non-linear effects study: a) Blue Plot: dependence of ee of product on ee of **4.1** in reaction with racemic α-iodo-γ-lactam, b) Red Plot: dependence of ee of product on ee of **4.1** in reaction with racemic α-bromo-γ-lactam. Yield of all reactions in this study were 9−10%.



Stoichiometric Competition Studies I. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with 3-methyl-1*H*-indole (1.1 mg, 0.0083 mmol), 5-bromo-3-methyl-1*H*-indole (1.7 mg, 0.0083 mmol), 5-methoxy-3-methyl-1*H*-indole (1.3 mg, 0.0083 mmol), a stir bar and a solution of mesitylcopper (4.6 mg, 0.025 mmol) in 200 µL *m*-xylene then closed with a screw cap. After stirring for 10 minutes, a solution of (*S*)−**4.1** (17.7 mg, 0.05 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 4.4 mg, 0.017 mmol) in 200 µL of *m*-xylene was added and the vial was recapped. After stirring for additional 10 minutes, (*R*)-α-bromo-γ-lactam (3.0 mg, 0.0125 mmol) was added and the vial was recapped and wrapped entirely with electrical tape to prevent access of light. Reaction mixture was stirred vigorously at 24 °C in the glovebox. Aliquots were taken from reaction mixture at different reaction times and were immediately quenched by dilution with 2 mL of dichloromethane and filtered through a syringe filter. The composition of each sample was determined by LCMS and ^{1}H NMR analysis. Quantitative analysis was done from integrating signals from an Agilent 1290 UHPLC-LCMS (5→95% acetonitrile in H_2O) at 280 nm; retentions times: 5-methoxy-3-methyl-1*H*-indole (**4.6**) 3.5 min, 3-methyl-1*H*-indole (**4.7**) 3.8 min, 5-bromo-3-methyl-1H-indole (**4.8**) 5.0 min, (S)-3-(5-methoxy-3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.9**) 5.3 min, (*S*)-3-(3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.10**) 5.5 min, (*S*)-3-(5-bromo-3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.11**) 6.3 min, 4,4′-di-tert-butylbiphenyl (**IS**) 9.1 min. Selectivity was determined by relative rates (k_X/k_H) calculated using the relationship described by Ingold and Shaw shown below.[29] $c_{H(t=0)}$ is initial conc. of 3-methyl-1*H*-indole and c_H is conc. of 3-methyl-1*H*-indole at a given time. c_x and $c_{x(t=0)}$ denote conc. of 5-substituted-3-methyl-1*H*-indole.

$$\frac{k_X}{k_H} = \frac{\ln\left(\frac{c_X}{c_{X(t=0)}}\right)}{\ln\left(\frac{c_H}{c_{H(t=0)}}\right)}$$

Table 4.5. Integral areas of LC-MS analysis.

	LC-MS Area % (UV at 280 nm)						
Time (min)	**4.6**	**4.7**	**4.8**	**4.9**	**4.10**	**4.11**	**IS**
0	24.92	21.37	16.91	n/a	n/a	n/a	36.80
5	7.95	13.35	14.7	19.30	8.70	1.18	34.84
10	10.04	15.00	15.61	15.72	6.64	0.72	36.29
15	3.70	9.60	13.2	24.7	13.03	1.50	34.28
20	4.23	10.1	13.45	24.18	12.31	1.48	34.25
30	7.68	13.12	15.53	19.42	8.47	1.00	34.80
24 h	1.25	5.86	12.96	28.86	18.10	3.43	29.54

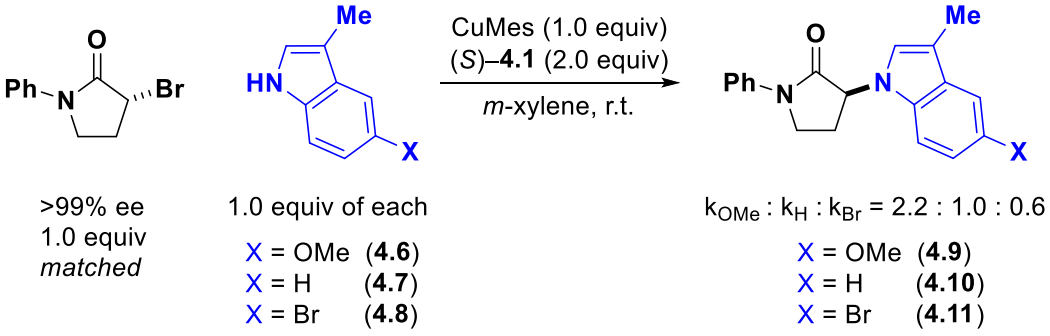
Table 4.6. Integral areas of LC-MS analysis divided by integral of the internal standard.

	LC-MS Area/IS (UV at 280 nm)					
Time (min)	**4.6**	**4.7**	**4.8**	**4.9**	**4.10**	**4.11**
0	0.68	0.58	0.46	n/a	n/a	n/a
5	0.28	0.41	0.43	0.43	0.18	0.03
10	0.23	0.38	0.42	0.55	0.25	0.02
15	0.11	0.28	0.39	0.72	0.38	0.04
20	0.12	0.29	0.39	0.71	0.36	0.04
30	0.22	0.38	0.45	0.56	0.24	0.03
24 h	0.04	0.20	0.44	0.98	0.61	0.12

Table 4.7. Relative rates for 5-substituted 3-methylindole nucleophiles.

Time (min)	$\ln\left(\frac{c_{OMe}}{c_{OMe(t=0)}}\right)$	$\ln\left(\frac{c_{H}}{c_{H(t=0)}}\right)$	$\ln\left(\frac{c_{Br}}{c_{Br(t=0)}}\right)$	$\frac{k_{OMe}}{k_{H}}$	$\frac{k_{Br}}{k_{H}}$
0	0.62	0.23	0.03	2.70	0.12
5	0.90	0.34	0.07	2.63	0.19
10	1.09	0.42	0.09	2.62	0.21
15	1.84	0.73	0.18	2.52	0.24
20	1.70	0.68	0.16	2.51	0.23
30	1.12	0.43	0.03	2.60	0.07
24 h	2.77	1.07	0.05	2.58	0.04

k_{Br}/k_H = 0.23 k_{OMe}/k_H = 2.54



>99% ee
1.0 equiv
matched

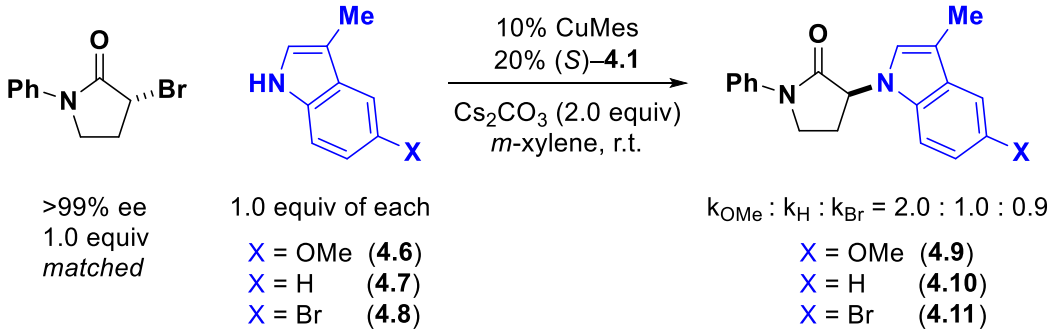
1.0 equiv of each
X = OMe (**4.6**)
X = H (**4.7**)
X = Br (**4.8**)

$k_{OMe} : k_H : k_{Br}$ = 2.2 : 1.0 : 0.6
X = OMe (**4.9**)
X = H (**4.10**)
X = Br (**4.11**)

Stoichiometric Competition Studies II. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with 3-methyl-1*H*-indole (3.3 mg, 0.025 mmol), 5-bromo-3-methyl-1*H*-indole (5.2 mg, 0.025 mmol), 5-methoxy-3-methyl-1*H*-indole (4.2 mg, 0.025 mmol), a stir bar and a solution of mesitylcopper (4.6 mg, 0.025 mmol) in 200 μL *m*-xylene then closed with a screw cap. After stirring for 10 minutes, a solution of (*S*)–**4.1** (17.7 mg, 0.05 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 4.4 mg, 0.017 mmol) in 200 μL of *m*-xylene was added and the vial was recapped. After stirring for additional 10

minutes, (*R*)-α-bromo-γ-lactam (6.0 mg, 0.025 mmol) in 600 μL of *m*-xylene was added and the vial was recapped and wrapped entirely with electrical tape to prevent access of light. Reaction mixture was stirred vigorously at 24 °C in the glovebox. Aliquots were taken from reaction mixture at different reaction times and were immediately quenched by dilution with 2 mL of dichloromethane and filtered through a syringe filter. The composition of each sample was determined by LCMS and ^{1}H NMR analysis. Quantitative analysis was done from integrating signals from Agilent 1290 UHPLC-LCMS (5→95% acetonitrile in H_2O) at 280 nm; retentions times: 5-methoxy-3-methyl-1*H*-indole (**4.6**) 3.5 min, 3-methyl-1*H*-indole (**4.7**) 3.8 min, 5-bromo-3-methyl-1H-indole (**4.8**) 5.0 min, (S)-3-(5-methoxy-3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.9**) 5.3 min, (*S*)-3-(3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.10**) 5.5 min, (*S*)-3-(5-bromo-3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.11**) 6.3 min, 4,4′-di-tert-butylbiphenyl (**IS**) 9.1 min.

k_{OMe}/k_H = 2.16 k_{Br}/k_H = 0.59

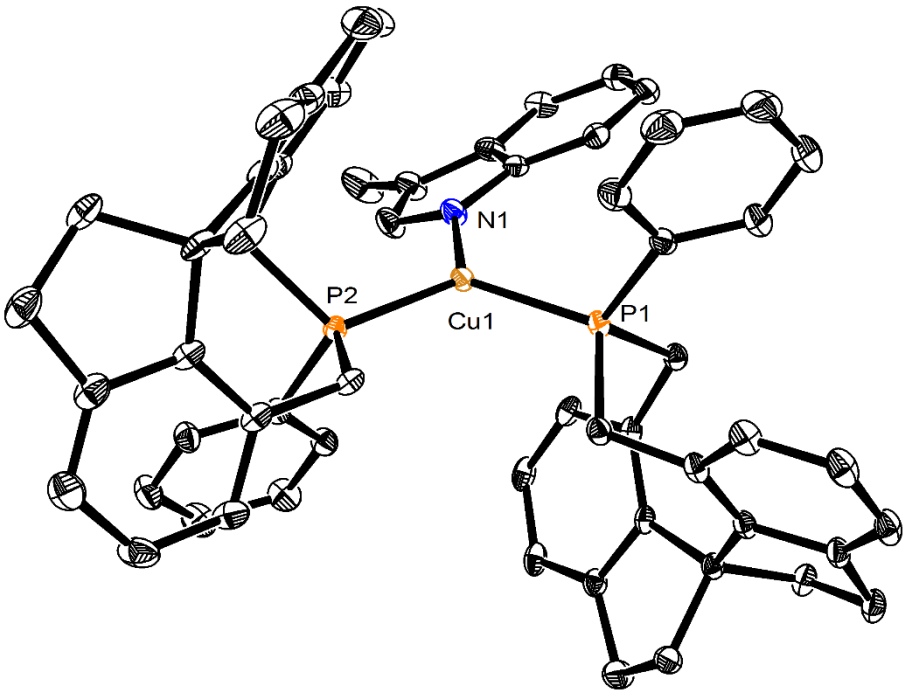


Catalytic Competition Studies. In a nitrogen-atmosphere glovebox, an oven-dried 4 mL amber-glass vial was charged with 3-methyl-1*H*-indole (6.6 mg, 0.05 mmol), 5-bromo-3-methyl-1*H*-indole (10.4 mg, 0.05 mmol), 5-methoxy-3-methyl-1*H*-indole (8.4 mg, 0.05 mmol), a stir bar and a solution of mesitylcopper (0.9 mg, 0.005 mmol) in 200 μL of *m*-xylene then closed with a screw cap. After stirring for 10 minutes, a solution of (*S*)–**4.1** (3.5 mg, 0.01 mmol) and internal standard (4,4′-di-tert-butylbiphenyl, 6.8 mg, 0.026 mmol) in 200 μL of *m*-xylene was added and the vial was recapped. After stirring for additional 10

minutes, (*R*)-α-bromo-γ-lactam (12.0 mg, 0.05 mmol) in 600 μL of *m*-xylene was added. After stirring for 4 minutes, cesium carbonate (32.6 mg, 0.10 mmol) was added and the vial was recapped and wrapped entirely with electrical tape to prevent access of light. Reaction mixture was stirred vigorously at 24 °C in the glovebox. Aliquots were taken from reaction mixture at different reaction times and were immediately quenched by dilution with 2 mL of dichloromethane and filtered through a syringe filter. The composition of each sample was determined by LCMS and ^{1}H NMR analysis. Quantitative analysis was done from integrating signals from Agilent 1290 UHPLC-LCMS (5→95% acetonitrile in H_2O) at 280 nm; retentions times: 5-methoxy-3-methyl-1*H*-indole (**4.6**) 3.5 min, 3-methyl-1*H*-indole (**4.7**) 3.8 min, 5-bromo-3-methyl-1H-indole (**4.8**) 5.0 min, (S)-3-(5-methoxy-3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.9**) 5.3 min, (*S*)-3-(3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.10**) 5.5 min, (*S*)-3-(5-bromo-3-methyl-1*H*-indol-1-yl)-1-phenylpyrrolidin-2-one (**4.11**) 6.3 min, 4,4′-di-tert-butylbiphenyl (**IS**) 9.1 min.

$$\mathbf{k_{OMe}/k_H = 2.03 \qquad k_{Br}/k_H = 0.88}$$

4.4.6. Determination of Absolute Stereochemistry



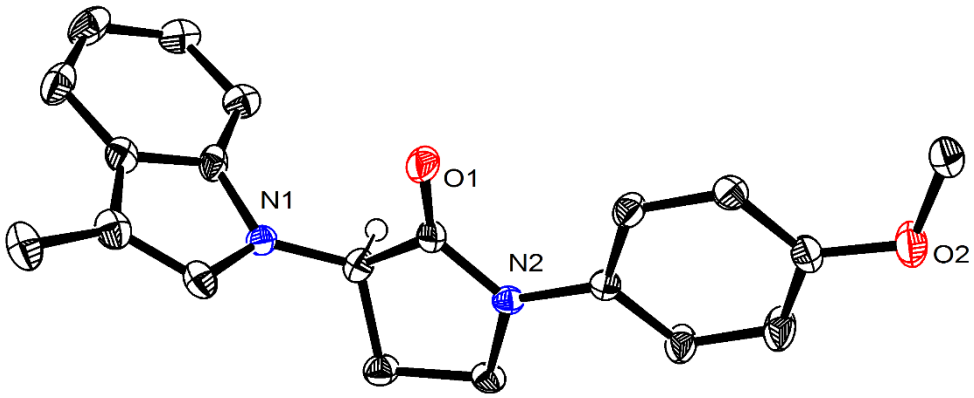
(*R*,*R*)−4.5. A suitable crystal for X-ray crystallography was grown by slow evaporation of solvent from a saturated solution of sample in a benzene/pentane mixture.

Disordered solvent omitted for clarity

Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON 100 CMOS detector with Mo K_α radiation (λ = 0.71073 Å) from an IμS micro-source for the structure of compound P15143. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2014 using established refinement techniques.[30] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times

the *U* value of the atoms they are linked to (1.5 times for methyl groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3-distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters.

(*R*,*R*)–**4.5** crystallizes in the tetragonal space group $P4_3$ with one molecule in the asymmetric unit along with half a molecule of pentane. The pentane molecule is located near a crystallographic 4_3-screw axis. It was modeled as a disorder with two unique components in addition to the components generated by the 4_3-screw axis.

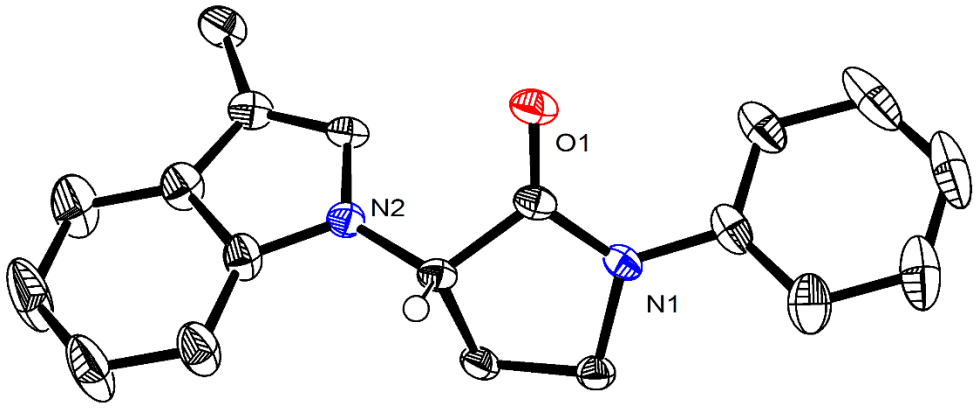


One of two molecules in the asymmetric unit shown

(3*R*)-1-(4-Methoxyphenyl)-3-(3-methyl-1*H*-indol-1-yl)pyrrolidin-2-one. A suitable crystal for X-ray crystallography was grown by vapor diffusion with diethyl ether and hexane.

A crystal of $C_{20}H_{20}N_2O_2$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Photon diffractometer with filtered Cu-Kα radiation at a temperature of 100 K. Using Olex2[31], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement

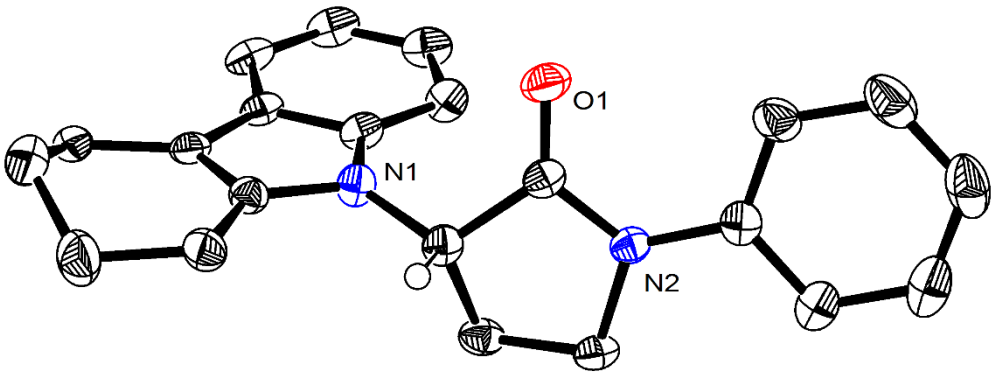
package[30] using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.



(3*S*)-3-(3-Methyl-1H-indol-1-yl)-1-phenylpyrrolidin-2-one. A suitable crystal for X-ray crystallography was grown by vapor diffusion with diethyl ether and hexane.

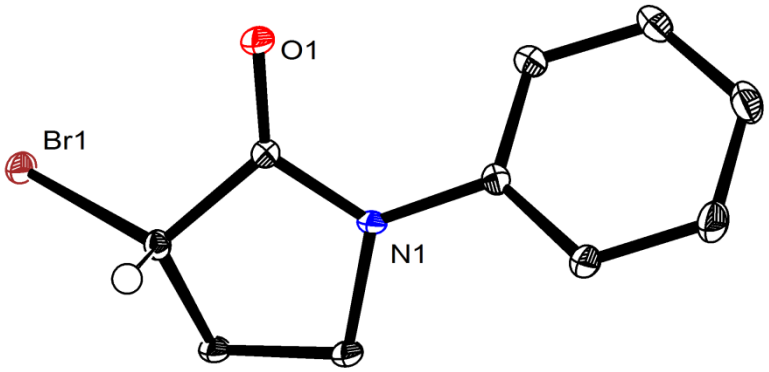
The more-ordered of two molecules in the asymmetric unit shown

A crystal of $C_{19}H_{18}N_2O$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Photon diffractometer with filtered Cu-Kα radiation at a temperature of 100 K. Using Olex2[31], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package[30] using Least Squares minimization. All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3-distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters. The absolute stereochemistry was determined on the basis of the absolute structure parameter.



(3*S*)-3-(3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)-1-phenylpyrrolidin-2-one. A suitable crystal for X-ray crystallography was grown by vapor diffusion with diethyl ether and hexane.

A crystal of $C_{22}H_{22}N_2O$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Photon diffractometer with filtered Cu-Kα radiation at a temperature of 100 K. Using Olex2[31], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package[30] using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.



(3*S*)-3-Bromo-1-phenylpyrrolidin-2-one. A suitable crystal for X-ray crystallography was grown by vapor diffusion with isopropanol and hexane.

A crystal of $C_{10}H_{10}BrNO$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker APEX2 diffractometer with filtered Mo-Kα radiation at a temperature of 100 K. Using Olex2[31], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package[30] using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

4.5. Notes and References

1. (a) *Amines: Synthesis, Properties and Applications*, S. A. Lawrence, Ed.; Cambridge University Press: Cambridge, 2004; (b) Ricci, A. in *Amino Group Chemistry. From Synthesis to the Life Sciences*, Ricci, A. Ed.; Wiley-VCH: Weinheim, 2008.
2. *Chiral Amine Synthesis*; Nugent, T. C. Ed.; Wiley–VCH: Weinheim, 2010.
3. For recent reviews of asymmetric reductions of imines and enamides, see: (a) Nugent, T. C.; Mohamed, E.-S. *Adv. Synth. Catal.* **2010**, *352*, 753–819. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704. (c) Xie, J.-H.; Zhu, S.-F.;

Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713–1760. (d) Wang, C.; Xiao, J. *Top. Curr. Chem.* **2013**, *343*, 261−282.

4. For recent reviews of asymmetric hydroaminations, see: (a) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596–2697. (b) Soradova, Z.; Sebesta, R. *ChemCatChem* **2016**, *8*, 1–9. (c) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 48–57.
5. For recent reviews of asymmetric C−H aminations, see: (a) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926–1936. (b) Lebel, H.; Trudel, C.; Spitz, C. *Chem. Commun.* **2012**, *48*, 7799–7801. (c) Gephart, R. T.; Warren, T. H. *Organometallics* **2012**, *31*, 7728–7752. (d) Zheng, C.; You, S.-L. *RSC Adv.* **2014**, *4*, 6173–6214. (e) Park, Y.; Kim, Y.; Chang, C. *Chem. Rev.* **2017**, *117*, 9247–9301.
6. For recent reviews of transition-metal catalyzed cross-couplings reactions to form C_{sp2}−N bonds, see: (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *2*, 27–50. (b) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, *2011*, 829–856. (c) Beletskaya, I. P.; Cheprakov, A. V. *Organometallics* **2012**, *31*, 7753–7808 (d) Bariwal, J.; Eycken, E. V. der. *Chem. Soc. Rev.* **2013**, *42*, 9283–9303. (e) Casitas, A.; Ribas, X. *Chem. Sci.* **2013**, *4*, 2301. (e) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525–3550. (f) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564–12649.
7. For early examples of reactions of unactivated alkyl electrophiles (all are primary alkyl bromides) that proceed in the presence of a substoichiometric quantity of a transition metal, see: (a) Kozuka, M.; Tsuchida, T.; Mitani, M. *Tetrahedron Lett.* **2005**, *46*, 4527−4530. (b) Tu, X.; Fu, X.; Jiang, Q.; Liu, Z.; Chen, G. *Dyes Pigm.* **2011**, *88*, 39−43. (c) Aydin, A.; Kaya, I. *Electrochim. Acta* **2012**, *65*, 104−114.
8. For examples of transition-metal catalyzed reactions between amines and alkyl electrophiles, see: (a) Peacock, D. M.; Roos, C. B.; Hartwig, J. F. *ACS Cent. Sci.* **2016**, *2*, 647−652. (b) Liang, Y.; Zhang, X.; MacMillan, D. W. C. *Nature* **2018**, *559*, 83–88. (c) Mao, R.; Balon, J.; Hu, X. *Angew. Chem. Int. Ed.* **2018**, *57*, 9501–9504.
9. For examples of photoinduced copper-catalyzed alkylation of amines from our group, see: (a) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647–651. (b)

Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129–5133. (c) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162–2167. (d) Zhao, W.; Wurz, R. P.; Peters, J. P.; Fu, G. C. *J. Am. Chem. Soc.*, **2017**, 1*39*, 12153–12156. (e) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.*, **2017**, *139*, 17707–17710. (f) Ahn, J. M.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.*, **2017**, *139*, 18101–18106.

10. Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016,** *351*, 681–684.
11. (a) Thorsett, E. D.; Harris, E. E.; Aster, S. D.; Peterson, E. R.; Snyder, J. P.; Springer, J. P.; Hirshfield, J.; Tristram, E. W.; Patchett, A. A. *J. Med. Chem.* **1986**, *29*, 251−260. (b) Semple, J. E.; Rowley, D. C.; Brunck, T. K.; Ha-Uong, T.; Minami, N. K.; Owens, T. D.; Tamura, S. Y.; Goldman, E. A.; Siev, D. V.; Ardecky, R. J.; Carpenter, S. H.; Ge, Y.; Richard, B. M.; Nolan, T. G.; Håkanson, K.; Tulinsky, A.; Nutt, R. F.; Ripka, W. C. *J. Med. Chem.* **1996**, *39*, 4531−4536. (c) Tamura, S. Y.; Goldman, E. A.; Brunck, T. K.; Ripka, W. C.; Edward Semple, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 331−336. (d) Bell, I. M.; Gallicchio, S. N.; Abrams, M.; Beese, L. S.; Beshore, D. C.; Bhimnathwala, H.; Bogusky, M. J.; Buser, C. A.; Culberson, J. C.; Davide, J.; Ellis-Hutchings, M.; Fernandes, C.; Gibbs, J. B.; Graham, S. L.; Hamilton, K. A.; Hartman, G. D.; Heimbrook, D. C.; Homnick, C. F.; Huber, H. E.; Huff, J. R.; Kassahun, K.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Lynch, Joseph J.; Robinson, R.; Rodrigues, A. D.; Taylor, J. S.; Walsh, E. S.; Williams, T. M.; Zartman, C. B. *J. Med. Chem.* **2002**, *45*, 2388−2409. (e) Kemp, J. A.; Leeson, P. D. *Trends Pharmacol. Sci.* **1993**, *14*, 20−25.
12. It was found in the absence of a copper catalyst the electrophile reacts with (*R*)−**4.1** in *m*-xylene at room temperature to form a 1:1 mixture of diastereomers of the corresponding phosphonium salt. A similar salt could not be detected by ^{31}P NMR analysis in an unmodified reaction mixture (Table 4.1, entry 1). When the isolated phosphonium salt (mixture of diastereomers) was used in place of the electrophile in the C–N cross-coupling (without catalyst), no product formation was observed.

13. (a) Phosphine **4.1** is commercially available from Strem Chemicals. (b) For the original synthesis of **4.1** see: Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*, 2333−2335.
14. (a) Under the optimized conditions, 5-membered lactams containing chloride, tosylate, and mesylate leaving groups did not undergo conversion, while the one with nonaflate provided high yield but low ee. (b) 3-Iodopyrrolidin-2-ones with bulkier R groups, such as 2,6-diisopropylphenyl and 2,4,6-trimethylphenyl, afforded low yields. (c) 3-Iodo-4,4-dimethyl-1-phenylpyrrolidin-2-one and acyclic α-iodoamides gave low yields (<5%). (d) 7-Membered α-iodolactam gave predominantly the elimination product.
15. To avoid complications with the racemization of the starting material, 3-bromo-1-phenylpyrrolidin-2-one was used in these experiments.
16. (a) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 2086−2089. (b) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124−11127.
17. To avoid additional complications with the kinetic resolution and the racemization of the starting material, an enantiopure matched 3-bromo-1-phenylpyrrolidin-2-one was used in these experiments. For the details of the calculation of the relative rates, see the supporting information.
18. In a catalytic competition reaction with these three differently 5-substituted 3-methylindoles a similar selectivity trend was observed. This result suggests that the selectivity in the catalytic reaction is predominantly governed by the intrinsic relative reactivities of the complexes of type **4.5**, and not by the relative rates of the deprotonation of the nucleophiles or the relative stability of these complexes. Due to the heterogeneity of the reaction mixture, we have not been able to perform meaningful kinetics studies.
19. Huang, Z.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 1028 –1032.
20. Lin, X.; Chen, W.; Qiu, Z.; Guo, L.; Zhu, W.; Li, W.; Wang, Z.; Zhang, W.; Zhang, Z.; Rong, Y.; Zhang, M.; Yu, L.; Zhong, S.; Zhao, R.; Wu, X.; Wong, J. C.; Tang, G., *J. Med. Chem.* **2015,** *58*, 2809−2820.
21. Kamal, A.; Ramana, K. V.; Ramana, A. V.; Babu, A. H *Tetrahedron: Asymmetry* **2003**, *14*, 2587−2594.

22. Sedlák, M.; Hanusek, J.; Macháček, V.; Hejtmánková, L. *J. Heterocyc. Chem.* **2002**, 39, 1105−1107.

23. Okawara, T.; Matsuda, T.; Furukawa, M. *Chem. Pharm. Bull.* **1982,** *30*, 1225−1233.

24. Mesitylcopper was prepared using procedure described previously in literature: Tsuda, T.; Yazawa, T.; Watanabe, K.; Fujii, T.; Saegusa, T. *J. Org. Chem.* **1981,** *46*, 192−194.

25. (*R*)-SITCP [(*R*)−**4.1**] and (*S*)-SITCP [(*S*)−**4.1**] were purchased from Strem Chemicals.

26. Cs_2CO_3 used in all experiments was of 99.995% purity.

27. Wu, H.-C.; Yu, J.-Q.; Spencer, J. B. *Org. Lett.* **2004**, *6*, 4675−4678.

28. Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*, 2333−2335.

29. (a) Ingold, C. K.; Shaw, F. R. *J. Chem. Soc.* **1927,** 2918−2926. (b) Yau, H. M.; Croft, A. K.; Harper, J. B. *Chem. Comm.* **2012,** *48*, 8937−8939.

30. Sheldrick, G. M. *Acta. Crystallogr. A.* **2008**, *64*, 112.

31. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. J *Appl Crystallogr.* **2009**, *42*, 339.

Chapter 5

ENANTIOCONVERGENT CROSS-COUPLINGS OF ALKYL ELECTROPHILES: THE CATALYTIC ASYMMETRIC SYNTHESIS OF ORGANOSILANES

Adapted with permission from:

Schwarzwalder, G. M.‡; Matier, C. D.‡; Fu, G. C. Enantioconvergent Cross-Coupling of Alkyl Electrophiles: The Catalytic Asymmetric Synthesis of Organosilanes. *Angew. Chem. Int. Ed.* **2019**, *58*, 3571–3574. doi: 10.1002/anie.201814208

5.1 Introduction

Significant progress has been described in the development of methods for the synthesis of carbon–carbon bonds through enantioconvergent substitution reactions of racemic alkyl electrophiles with carbon nucleophiles.[1–3] To date, high enantioselectivity has only been observed in cross-couplings wherein the electrophile bears either a directing group (**5.I**) or a p/π orbital proximal to the leaving group (**5.II**) (Figure 5.1).[4]

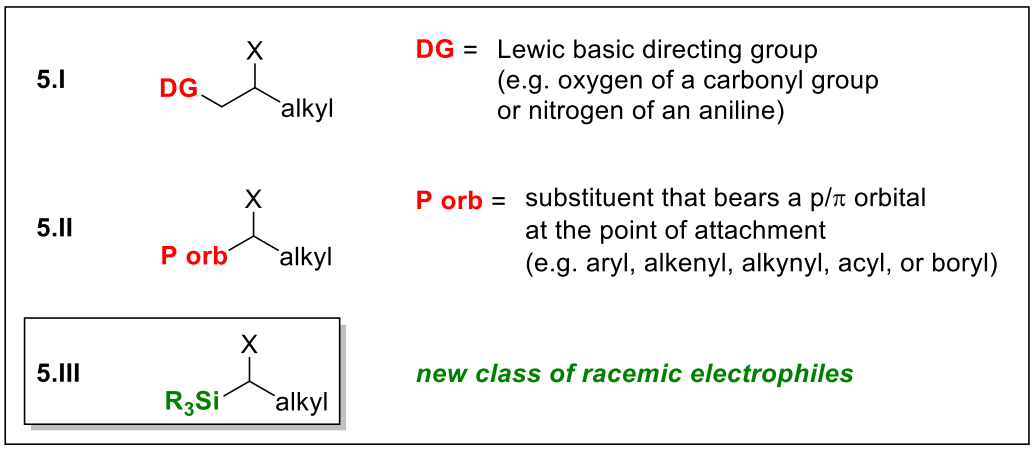
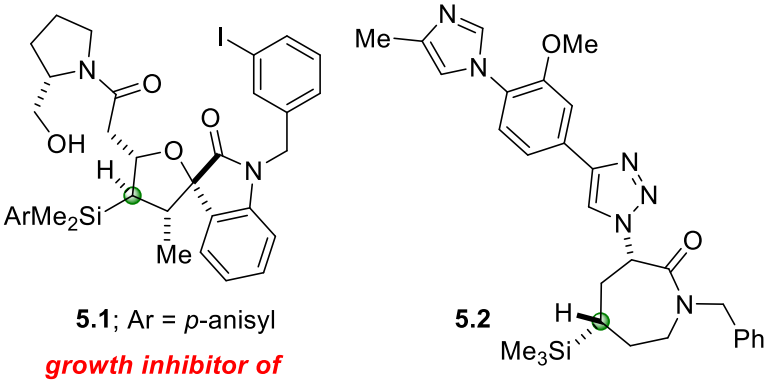
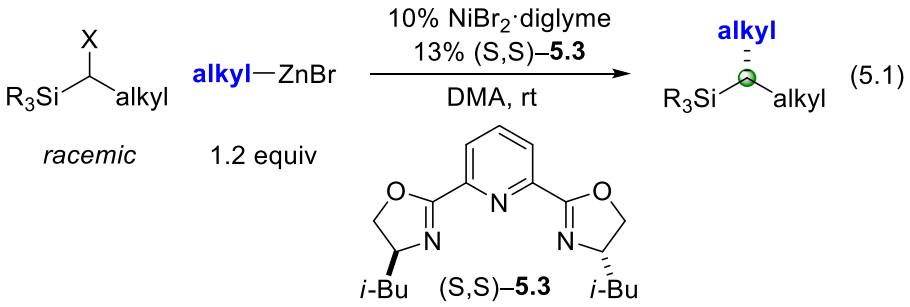


Figure 5.1. Background: Racemic electrophiles used in enantioconvergent cross-couplings. **5.I** and **5.II**: Prior work. **5.III**: This study.

We have been interested in expanding the scope of enantioconvergent cross-couplings to include electrophiles that lack either of the features illustrated in **5.I** and **5.II** (Figure 5.1). An example of such an electrophile is α-halosilane **5.III**,[5,6] enantioconvergent cross-coupling of which would provide chiral organosilanes. Chiral organosilanes (e.g., **5.1**[7] and **5.2**[8]) are of interest in fields such as medicinal chemistry, since replacement of carbon with silicon can lead to improved pharmacological properties (e.g., enhanced lipophilicity and potency) without element-specific toxicity due to the presence of silicon;[9] to date, there are limited methods for the direct catalytic asymmetric synthesis of such organosilanes.[10,11] In this report, we establish that a chiral nickel catalyst can achieve the asymmetric synthesis of organosilanes via the cross-coupling of racemic α-halosilanes with alkylzinc reagents under simple and mild conditions (eq 5.1), thereby demonstrating that enantioconvergent cross-couplings are possible with electrophiles that lack both a directing group and a proximal p/π orbital (Figure 5.1).

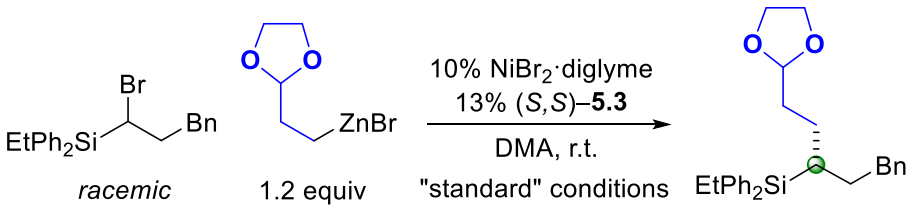




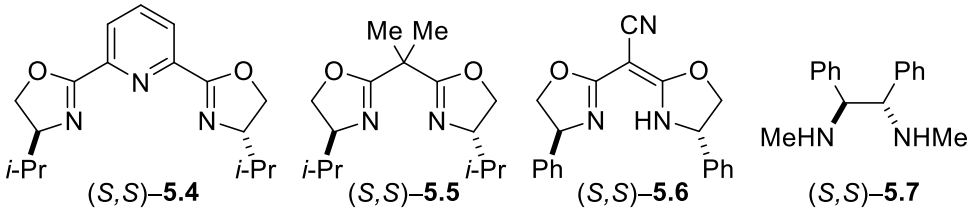
5.2 Results and Discussion

5.2.1. Optimization

Table 5.1. Effect of reaction parameters.



entry	variation from the "standard" conditions	yield (%)[a]	ee (%)
1	none	78	92
2	no $NiBr_2$·diglyme	<1	–
3	no (*S,S*)–**5.3**	16	–
4	under air (capped vial)	12	88
5	H_2O (0.05 equiv) added	38	90
6	(*S,S*)–**5.4**, instead of (*S,S*)–**5.3**	55	74
7	(*S,S*)–**5.5**, instead of (*S,S*)–**5.3**	30	<5
8	(*S,S*)–**5.6**, instead of (*S,S*)–**5.3**	8	<5
9	(*S,S*)–**5.7**, instead of (*S,S*)–**5.3**	<1	–
10	alkyl–I, instead of alkyl –Br	61	88
11	alkyl–Cl, instead of alkyl–Br	<1	–
12	5% $NiBr_2$·diglyme, 6.5% (*S,S*)–**5.3**	62	92

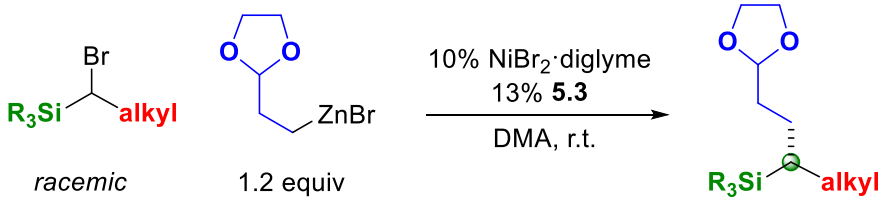


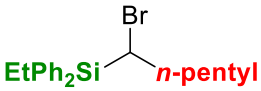
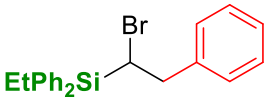
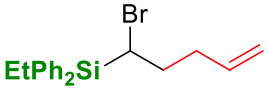
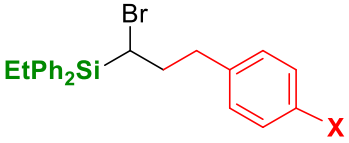
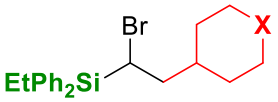
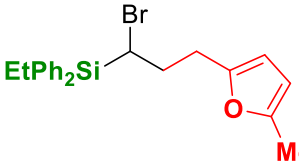
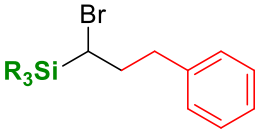
[a]Yield was determined via GC analysis versus an internal standard (average of two experiments).

Upon examining a range of reaction parameters, we determined that $NiBr_2$·diglyme and a chiral pybox ligand (**5.3**) can accomplish the enantioconvergent Negishi cross-coupling illustrated in Table 1 in good yield and high ee (78% yield, 92% ee; entry 1). In the absence of $NiBr_2$·diglyme, virtually no carbon–carbon bond formation is observed (entry 2), whereas in the absence of ligand **5.3**, the coupling proceeds in low yield (entry 3). When the reaction

is run under an atmosphere of air or in the presence of water, formation of product is inefficient, although the ee is good (entries 4 and 5). Other ligands, including representative examples of classes of ligands that have been useful in other nickel-catalyzed enantioconvergent cross-couplings,[1] are less effective than ligand **5.3** (entries 6–9).

Table 5.2. Scope with respect to the electrophile.



entry	electrophile		ee (%)	yield (%)[a]
1			90	64
2			94	65
3			91	54
4		X = H	93	74
5		OMe	92	86
6		Cl	91	55
7		X = CH_2	90	59
8		O	91	68
9		NBoc	90	68
10			90	72
11		R_3Si = $SiMePh_2$	85	80
12		$SiMe_3$	85	80
13		$SiEt_3$	90	50
14		Si(*t*-Bu)Me_2	84	25

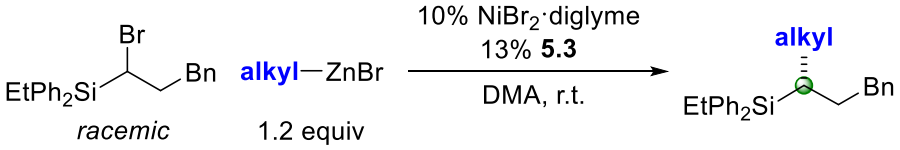
[a] Yield of purified product (average of two experiments).

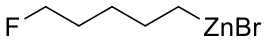
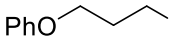
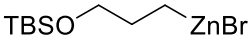
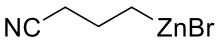
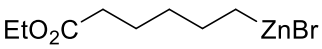
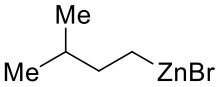
Although the corresponding alkyl iodide cross-couples with fairly good yield and ee under these conditions (entry 10), use of the alkyl chloride leads to essentially no carbon–carbon bond formation (entry 11). A lower catalyst loading can be employed with only a small loss in yield and no loss in enantioselectivity (entry 12).

5.2.2. Scope of Reactivity

α-Bromosilanes that bear a variety of functional groups serve as suitable electrophiles in these nickel-catalyzed enantioconvergent cross-couplings (Table 5.2). Thus, an alkene, ether, or an aryl chloride, as well as a saturated or an unsaturated oxygen or nitrogen heterocycle, can be present, with little impact on ee. Although branching in the α position of the alkyl group of the electrophile inhibits cross-coupling, branching in the β position is tolerated (entries 7–9). The enantioconvergent coupling proceeds with an array of substituents on silicon, with lower yields observed as the steric demand of the electrophile increases (entries 11–14).[12]

Table 5.3. Scope with respect to the nucleophile.



entry	alkyl—ZnBr	ee (%)	yield (%)[a]
1		87	56
2		88	80
3		88	69
4		87	50
5		87	59
6		91	66

[a] Yield of purified product (average of two experiments).

Organozinc reagents that include various functional groups, such as an alkyl fluoride, an ether, a nitrile, and an ester, can be employed as nucleophiles in these nickel-catalyzed enantioconvergent cross-couplings (entries 1–5 of Table 5.3). The cross-coupling is sensitive to steric effects–while branching at the γ position is tolerated (entry 6), little carbon–carbon bond formation occurs if there is branching at the α or the β position. On a gram scale, the coupling illustrated in entry 2 proceeds in 88% ee and 89% yield (1.66 g of product).[13]

5.2.3. Mechanistic Insights

Our working hypothesis is that this process may be following a pathway analogous to that elucidated for nickel/pybox-catalyzed enantioconvergent Negishi arylations of propargylic halides, wherein nickel complex **5.C** is the predominant resting state of nickel during catalysis, and complexes **5.A**, **5.B**, and **5.D** do not accumulate (Figure 5.2).[14] Consistent with this suggestion, ESI–MS analysis of a cross-coupling (the model reaction in Table 5.1) at partial conversion reveals a strong signal at m/z = 488.2, consistent with the

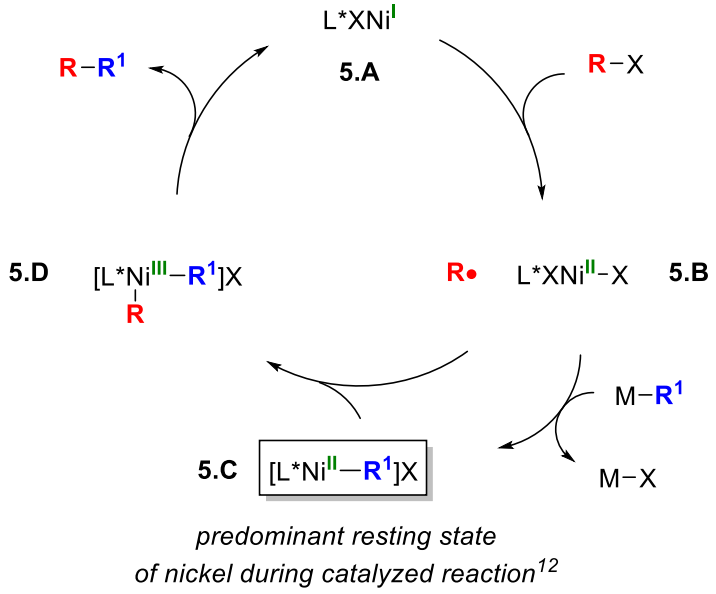
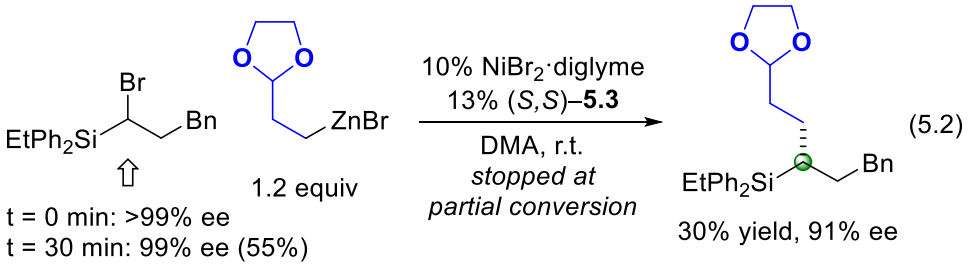


Figure 5.2. Outline of a possible mechanism.

presence of $[L^*Ni–R^1]^+$ (**5.C** in Figure 5.2; L* = **5.3**; R^1 = 2-(1,3-dioxolan-2-yl)ethyl; exact mass: 488.2). Similarly, the EPR spectrum of a reaction at partial conversion indicates that odd-electron nickel intermediates such as **5.A** or **5.D** do not accumulate to a significant (>2%) extent.

An enantioenriched α-bromosilane does not racemize under the standard conditions (eq 5.2),[15,16] indicating that C–Br bond cleavage is irreversible and that the chiral catalyst is processing both enantiomers of the electrophile in the stereoconvergent coupling of a racemic electrophile (no dynamic kinetic resolution). When an enantioconvergent cross-coupling of a racemic electrophile is stopped at partial conversion, the unreacted electrophile is still racemic, indicating that the chiral catalyst is not discriminating between the enantiomeric electrophiles (no kinetic resolution).[17]



5.3. Conclusions

Thus, we have expanded the scope of enantioconvergent cross-couplings beyond electrophiles that bear a directing group or a p/π orbital proximal to the leaving group. Specifically, we have determined that a chiral nickel/pybox catalyst can achieve stereoconvergent cross-couplings of racemic α-bromosilanes with alkylzinc reagents under simple and mild conditions to afford enantioenriched organosilanes, a useful family of target compounds. Our mechanistic observations indicate that the chiral catalyst reacts with both enantiomers of the electrophile, without kinetic resolution, to provide the enantioenriched product via irreversible C–Br bond cleavage. This work sets the stage for substantial enlargement of the range of racemic electrophiles that can be employed in enantioconvergent cross-couplings, free of the need for a directing group or p/π conjugation.

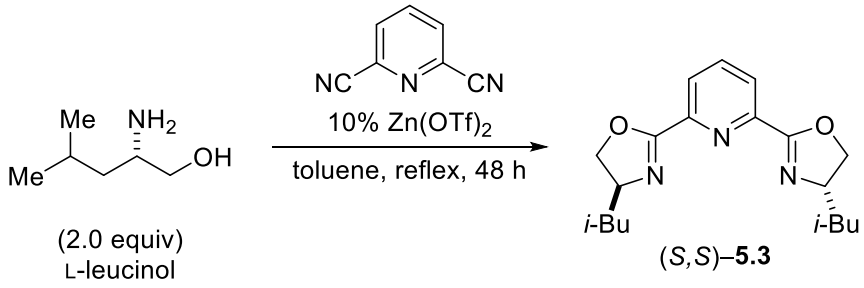
5.4. Experimental Section

5.4.1 General Information

All manipulations of air-sensitive materials were carried out in oven-dried glassware under an Ar or N_2 atmosphere using standard Schlenk or glovebox techniques. Glovebox manipulations were carried out under N_2 atmosphere. THF and CH_2Cl_2 were purified and dried using a solvent purification system that contained activated alumina under argon. Unless otherwise noted, all commercially available reagents were used as received, including $NiBr_2$•diglyme (Sigma-Aldrich) and DMA (anhydrous, 99.8%, Sigma-Aldrich). ^1H and ^{13}C NMR data were collected on a Bruker 400 MHz, a Varian 300 MHz, or a Varian 500 MHz spectrometer at ambient temperature unless otherwise noted and are reported in terms of chemical shift (δ ppm) relative to residual $CHCl_3$ (δ 7.26 ppm, ^1H NMR; δ 77.36 ppm, ^{13}C NMR). Data for NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br = broad. IR spectra were obtained on a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). HR-MS were acquired by the Caltech Mass Spectral Facility using a JEOL JMS-600H MS in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or using a Waters LCT Premier XE TOF MS in electrospray ionization (ESI+) mode. LC-MS were obtained on an Agilent 5975C GC/MSD System in electron ionization (EI+) mode. Optical rotations were measured on a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm) using a 100 mm pathlength cell. Analytical SFC was performed on a Mettler SFC supercritical CO_2 analytical chromatography system utilizing CHIRALPAK (AD-H, IC-3) or CHIRALCEL (OD-H, OJ) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Preparative SFC was performed on a JASCO SFC supercritical CO_2 preparative chromatography system utilizing a CHIRALPAK AD-H column (10 mm x 250 cm) obtained from Daicel Chemical Industries, Ltd. GC analyses were obtained on an Agilent 6890N GC. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle). Thin-layer chromatography (TLC) and preparatory TLC was performed using Merck silica gel 60 F_{254} pre-coated plates (0.25 mm)

and visualized by UV fluorescence quenching and $KMnO_4$ staining. X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker APEX-II CCD diffractometer. ESI–MS experiments were conducted by direct injection using a Thermo Scientific LTQ linear ion trap mass spectrometer. X-band EPR measurements were collected with a Bruker EMX spectrometer. EPR simulation was conducted using EasySpin.[18]

5.4.2. Preparation of (*R*,*R*)− or (*S*,*S*)−5.3.

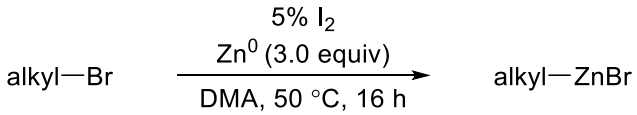


2,6-Bis(isobutyl-2-oxazolin-2-yl)pyridine. The title compound was prepared by a literature known procedure from D- or L-lecuinol (1.0 g, 8.6 mmol).[19] Isolated 0.78 g (51% yield) of white, flaky solid after recrystallization from heptane.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 7.8 Hz, 2H), 7.85 (dd, J = 8.2, 7.5 Hz, 1H), 4.61 (dd, J = 9.5, 8.1 Hz, 2H), 4.48 – 4.33 (m, 2H), 4.09 (t, J = 8.2 Hz, 2H), 1.86 (dq, J = 13.3, 6.7 Hz, 2H), 1.73 (dt, J = 13.5, 6.8 Hz, 2H), 1.39 (dt, J = 13.3, 7.2 Hz, 2H), 0.97 (t, J = 6.3 Hz, 12H).

This data corresponds to the literature reported spectrum.[19]

5.4.3. Preparation of Nucleophiles

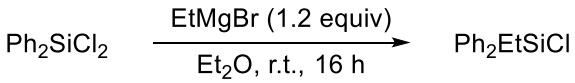


Preparation of Alkylzinc Reagents. An oven-dried 40 mL vial was charged with Zn^0 powder (3.0 equiv) and a cross-shaped stir bar. The vial was then sealed with a pierceable septum cap and placed under vacuum on a Schlenk line. The vial was then heated with a heat gun for ca. 4 mins and then allowed to cool to room temperature under vacuum. The Schlenk line was turned to static and the reaction vial was fitted with an Ar-filled balloon. The Schlenk line was then opened to allow argon to purge through the system for 15 mins. Next, the Schlenk line was removed and anhydrous DMA was added (total volume of DMA should be 1.0 mL per 1.0 mmol of alkyl bromide, including solvent used in the next step). To a stirring suspension of Zn^0 powder was added a solution of I_2 (0.050 equiv in 1.0 mL DMA) and the mixture was allowed to stir until the yellow color dissipated. Then, alkyl bromide (1.0 equiv) was added, vacuum grease was applied to the outside of the septum to avoid leakage, and the reaction mixture was warmed to 50 °C and stirred for 16 h. After cooling to room temperature, the Ar-filled balloon is removed and the crude reaction mixture was brought into an N_2 atmosphere glovebox. The suspension was passed through syringe filters to remove residual zinc powder. The alkylzinc bromide solution can be titrated with a known amount of I_2 in 1.0 mL THF.

Note: The alkylzinc bromide solutions can become viscous. Filtering first through a 1-micron syringe filter and then a 0.45-micron syringe filter makes filtration easier. Often, the 0.45-micron syringe filters become clogged, therefore 2-3 may be required. The appearance of alkylzinc bromide solutions can range from nearly colorless to dark red or dark green solutions. Ideal alkylzinc bromide concentrations should range from 0.70 M to 1.0 M.

4.2.4. Preparation of Electrophiles

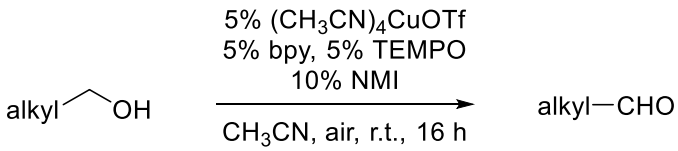
The yields have not been optimized.



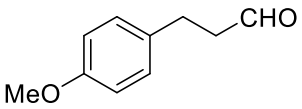
Chloro(ethyl)diphenylsilane. The title compound was prepared by a literature known procedure from dichlorodiphenylsilane (52.6 mL, 250 mmol).[20] Isolated 19.4 g (31% yield) of colorless oil after vacuum distillation.

LR-MS (EI+) m/z $[M]^{+\bullet}$ calcd for $C_{14}H_{16}ClSi$: 246.1, found: 246.1, 219.1, 217.1, 183.1.

This data corresponds to the literature reported mass spectrum.[20]



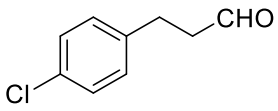
Preparation of aldehyde precursors. Aldehydes that were not commercially available were prepared from a literature known procedure.[21]



3-(4-Methoxyphenyl)propanal. The title compound was prepared from 3-(4-methoxyphenyl)propan-1-ol (2.5 mL, 15 mmol). The title compound was purified by flash chromatography with silica gel (10% EtOAc in hexanes). Isolated 2.3 g (92% yield) of colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, J = 1.4 Hz, 1H), 7.16 – 7.06 (m, 2H), 6.89 – 6.77 (m, 2H), 3.78 (d, J = 0.7 Hz, 3H), 2.91 (t, J = 7.3 Hz, 2H), 2.80 – 2.69 (m, 2H).

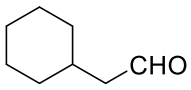
This data corresponds to the literature reported spectrum.[22]



3-(4-Chlorophenyl)propanal. The title compound was prepared from 3-(4-chlorophenyl)propan-1-ol (3.4 g, 20 mmol). The title compound was purified by flash chromatography with silica gel (5 → 10% EtOAc in hexanes). Isolated 2.5 g (74% yield) of pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, J = 1.3 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.16 – 7.08 (m, 2H), 3.00 – 2.88 (m, 2H), 2.84 – 2.68 (m, 2H).

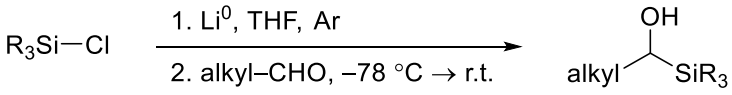
This data corresponds to the literature reported spectrum.[23]



2-Cyclohexylacetaldehyde. The title compound was prepared from 2-cyclohexylethan-1-ol (4.2 mL, 30 mmol). The title compound was then nominally pure after workup and used without further purification in **General Procedure A**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, J = 2.4 Hz, 1H), 2.29 (dd, J = 6.8, 2.3 Hz, 2H), 1.99 – 1.79 (m, 1H), 1.77 – 1.59 (m, 5H), 1.38 – 0.92 (m, 5H).

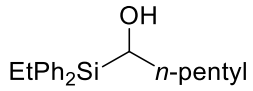
This data corresponds to the literature reported spectrum.[24]



General Procedure A: Preparation of α-Hydroxysilanes. *Procedure for substrates containing at least one aryl substituents on the silyl group.* A flame-dried round bottom flask was charged with a glass-covered magnetic stirring bar, Li^0 metal pellets (2.3 equiv), and

R_3SiCl (*if solid*) and then sealed with a rubber septum cap. The flask was then evacuated and backfilled with an Ar-filled balloon three times. THF (1.0 M with respect to R_3SiCl) was then added followed by R_3SiCl (*if liquid*) as a steady stream. The resulting mixture was stirred for 16 h at room temperature (note: after ca. 20 mins of stirring, the reaction mixture will rapidly turn dark green or brown).

A solution of aldehyde (0.75 equiv) was prepared in THF (0.38 M with respect to aldehyde) in a flame-dried round bottom flask under N_2 atmosphere. The resulting solution was cooled to −78 °C and the previously generated lithiathed silane solution was then added dropwise. The reaction mixture was then warmed to room temperature and stirred for 16 h. The mixture was quenched with saturated NH_4Cl solution (1.0 mL per 1.0 mmol of R_3SiCl) and extracted with EtOAc three times. Organic phases were collected, dried with $MgSO_4$, filtered, concentrated and the resulting α-hydroxysilane was purified with flash chromatography. α-Hydroxysilane can be monitored via TLC using $KMnO_4$ stain.



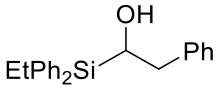
1-(Ethyldiphenylsilyl)hexan-1-ol. The title compound was synthesized according to **General Procedure A** from *n*-hexanal (0.83 mL, 6.8 mmol) and chloro(ethyl)diphenylsilane (2.2 g, 9.0 mmol). The product was purified by flash chromatography with silica gel (2 → 5% EtOAc in hexanes). Isolated 1.6 g (76% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.53 (m, 4H), 7.47–7.31 (m, 6H), 3.98 (dd, J = 9.4, 3.2 Hz, 1H), 1.66–1.52 (m, 3H), 1.38–1.11 (m, 8H), 1.06 (t, J = 7.8 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.7, 134.1, 133.9, 129.8, 129.7, 128.17, 128.16, 64.2, 33.8, 31.8, 26.9, 22.9, 14.3, 7.8, 3.1;

FT-IR (thin flim) 3368, 3070, 2962, 1428, 1261, 1094, 1030, 863 cm^{-1};

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{20}H_{27}OSi$: 311.1831, found: 311.1835.



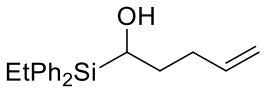
1-(Ethyldiphenylsilyl)-2-phenylethan-1-ol. The title compound was synthesized according to **General Procedure A** from 2-phenylacetaldehyde (0.60 mL, 5.1 mmol) and chloro(ethyl)diphenylsilane (1.7 g, 6.8 mmol). The product was purified by flash chromatography with silica gel (0 → 6% EtOAc in hexanes). Isolated 0.41 g (36% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 4H), 7.44 – 7.37 (m, 6H), 7.33 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 4.16 (dd, J = 12.0, 2.7 Hz, 1H), 2.93 (dd, J = 14.0, 2.7 Hz, 1H), 2.76 (dd, J = 14.0, 11.9 Hz, 1H), 1.53 (s, 1H), 1.27 – 1.17 (m, 2H), 1.08 (t, J = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 135.29, 135.85, 134.6, 134.01, 133.97, 129.93, 129.91, 129.4, 128.9, 128.31, 128.28, 128.25, 126.8, 65.4, 40.3, 7.9, 3.2.

FT-IR (thin flim) 3546, 3068, 2913, 1454, 1428, 1260, 1111, 1012, 856 cm^{-1};

HR-MS (FAB+) m/z $[M+H]^+$ calcd for $C_{22}H_{25}OSi$: 333.1675, found: 333.1646.



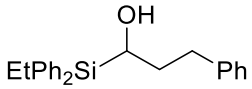
1-(Ethyldiphenylsilyl)pent-4-en-1-ol. The title compound was synthesized according to **General Procedure A** from pent-4-enal (0.50 mL, 5.1 mmol) and chloro(ethyl)diphenylsilane (1.7 g, 6.8 mmol). The product was purified by flash chromatography with silica gel (2 → 4% EtOAc in hexanes). Isolated 0.42 g (27% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.65 – 7.54 (m, 4H), 7.47 – 7.33 (m, 6H), 5.95 – 5.73 (m, 1H), 5.04 (dq, J = 17.1, 1.7 Hz, 1H), 4.98 (ddt, J = 10.1, 2.1, 1.2 Hz, 1H), 4.07 – 3.94 (m, 1H), 2.44 – 2.25 (m, 1H), 2.15 (dtdd, J = 14.5, 7.4, 2.6, 1.3 Hz, 1H), 1.77 – 1.66 (m, 2H), 1.30 – 1.10 (m, 3H), 1.05 (t, J = 7.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 135.9, 135.8, 135.0, 134.0, 133.9, 129.92, 129.89j, 128.3, 115.5, 63.7, 33.1, 31.7, 7.9, 3.1;

FT-IR (thin flim) 3436, 3069, 2958, 1428, 1261, 1111, 1011, 912 cm^{-1};

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{19}H_{23}OSi$: 295.1518, found: 295.1515.



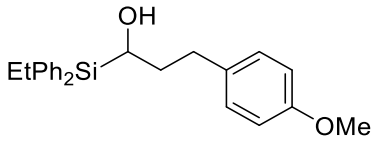
1-(Ethyldiphenylsilyl)-3-phenylpropan-1-ol. The title compound was synthesized according to **General Procedure A** from 3-phenylpropanal (0.99 mL g, 7.5 mmol) and chloro(ethyl)diphenylsilane (2.5 g, 10 mmol). The product was purified by flash chromatography with silica gel (5 → 10% EtOAc in hexanes). Isolated 1.2 g (46% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 4H), 7.46 – 7.33 (m, 6H), 7.31 – 7.25 (m, 2H), 7.22 – 7.13 (m, 3H), 3.99 (ddd, J = 9.8, 5.3, 3.9 Hz, 1H), 2.94 (ddd, J = 14.1, 8.6, 5.8 Hz, 1H), 2.66 (ddd, J = 13.6, 8.7, 7.3 Hz, 1H), 2.00 – 1.84 (m, 2H), 1.19 – 1.10 (m, 3H),1.03 (t, J = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 135.85, 135.79, 133.84, 133.76, 130.0, 129.9, 128.9, 128.7, 128.3, 128.3, 126.1, 63.6, 35.8, 33.6, 7.8, 3.1.

FT-IR (thin flim) 3568, 3447, 3067, 2954, 1602, 1496, 1454, 1428, 1379, 1232, 1190, 1111, 1027, 955, 914 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{23}H_{25}OSi$: 345.1669, found: 345.1668.



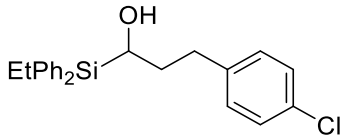
1-(Ethyldiphenylsilyl)-3-(4-methoxyphenyl)propan-1-ol. The title compound was synthesized according to **General Procedure A** from 3-(4-methoxyphenyl)propanal (1.1 g, 6.8 mmol) and chloro(ethyl)diphenylsilane (2.2 g, 9.0 mmol). The product was purified by flash chromatography with silica gel (5 → 15% EtOAc in hexanes). Isolated 2.2 g (87% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.51 (m, 4H), 7.45–7.33 (m, 6H), 7.11–7.04 (m, 2H), 6.85–6.79 (m, 2H), 3.97 (dt, J = 9.8, 4.9 Hz, 1H), 3.79 (s, 3H), 2.87 (ddd, J = 13.9, 8.2, 6.1 Hz, 1H), 2.61 (dt, J = 13.8, 8.2 Hz, 1H), 1.94–1.83 (m, 2H), 1.20–1.11 (m, 2H), 1.02 (t, J = 7.7 Hz, 3H). Alcohol proton not observed.

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 135.8, 135.7, 134.2, 133.8, 133.7, 129.83, 129.81, 129.7, 128.22, 128.21, 114.0, 63.4, 55.5, 35.8, 32.5, 7.8, 3.0.

FT-IR (thin flim) 3448, 3068, 2954, 1611, 1517, 1458, 1427, 1300, 1246, 1177, 1110, 1035, 808 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{24}H_{27}SiO_2$: 375.1780, found: 375.17890.



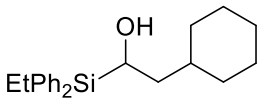
3-(4-Chlorophenyl)-1-(ethyldiphenylsilyl)propan-1-ol. The title compound was synthesized according to **General Procedure A** from 3-(4-chlorophenyl)propanal (1.1 g, 6.8 mmol) and chloro(ethyl)diphenylsilane (2.2 g, 9.0 mmol). The product was purified by flash chromatography with silica gel (5 → 7% EtOAc in hexanes). Isolated 1.1 g (44% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.51 (m, 4H), 7.43–7.33 (m, 6H), 7.23 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 3.94 (q, J = 6.3 Hz, 1H), 2.90 (dt, J = 14.0, 7.1 Hz, 1H), 2.64 (dt, J = 14.0, 8.4 Hz, 1H), 1.93–1.82 (m, 2H), 1.19–1.12 (m, 3H), 1.02 (t, J = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 135.71, 135.66, 133.6, 133.5, 131.7, 130.2, 129.93, 129.91, 128.7, 128.28, 128.27, 63.2, 35.5, 32.7, 7.7, 3.0.

FT-IR (thin flim) 3434, 3068, 2956, 1492, 1428, 1260, 1111, 1092, 1015, 808 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{23}H_{24}ClOSi$: 379.1285, found: 379.1288.



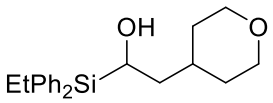
2-Cyclohexyl-1-(ethyldiphenylsilyl)ethan-1-ol. The title compound was synthesized according to **General Procedure A** from 2-cyclohexylacetaldehyde (0.82 g, 6.5 mmol) and chloro(ethyl)diphenylsilane (2.14 g, 8.66 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Isolated 2.24 g (>99% yield, nominally pure) of a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.51 (m, 4H), 7.46–7.31 (m, 6H), 4.15 (ddd, J = 11.4, 5.6, 2.2 Hz, 1H), 1.90 (d, J = 12.5 Hz, 1H), 1.78–1.45 (m, 7H), 1.42–1.34 (m, 1H), 1.23–1.11 (m, 4H), 1.08–0.99 (m, 5H), 0.83–0.68 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.7, 134.0, 133.9, 129.74, 129.71, 128.2, 128.1, 60.8, 41.4, 34.9, 34.1, 32.1, 26.9, 26.7, 26.4, 7.7, 3.0.

FT-IR (thin flim) 3445, 3069, 2913, 1427, 1236, 1189, 1110, 1013, 872 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+$ calcd for $C_{22}H_{31}OSi$: 339.2144, found: 339.2153.



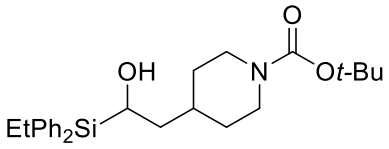
1-(Ethyldiphenylsilyl)-2-(tetrahydro-2*H*-pyran-4-yl)ethan-1-ol. The title compound was synthesized according to **General Procedure A** from 2-(tetrahydro-2*H*-pyran-4-yl)acetaldehyde (0.87 g, 6.75 mmol) and chloro(ethyl)diphenylsilane (2.22 g, 9.00 mmol). The product was purified by flash chromatography with silica gel (20 → 40% EtOAc in hexanes). Isolated 1.55 g (67% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.54 (m, 4H), 7.44–7.34 (m, 6H), 4.14 (ddd, J = 12.0, 5.8, 2.4 Hz, 1H), 3.96 (ddd, J = 11.3, 4.3, 1.6 Hz, 1H), 3.91 (ddd, J = 11.3, 4.5, 1.6 Hz, 2H), 3.36 (tdd, J = 11.7, 7.8, 2.2 Hz, 2H), 1.89–1.73 (m, 2H), 1.63–1.56 (m, 1H), 1.54–1.46 (m, 1H), 1.41 (ddd, J = 14.4, 9.7, 2.3 Hz, 1H), 1.36–1.28 (m, 1H), 1.20–1.13 (m, 2H), 1.05 (t, J = 7.7 Hz, 3H), 1.00 (d, J = 6.0 Hz, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.63, 135.57, 133.6, 133.4, 129.83, 129.80, 128.184, 128.176, 68.24, 68.18, 60.2, 40.7, 34.3, 32.0, 31.5, 7.6, 2.8.

FT-IR (thin flim) 3436, 3068, 2913, 1724, 1428, 1386, 1300, 1261, 1190, 1110, 1013, 872 cm^{-1};

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{21}H_{27}O_2Si$: 339.1780, found: 339.1774.



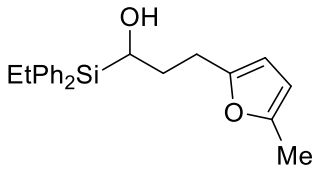
***Tert*-butyl 4-(2-(ethyldiphenylsilyl)-2-hydroxyethyl)piperidine-1-carboxylate.** The title compound was synthesized according to **General Procedure A** from *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (1.53 g, 6.75 mmol) and chloro(ethyl)diphenylsilane (2.22 g, 9.00 mmol). The product was purified by flash chromatography with silica gel (20 → 30% EtOAc in hexanes). Isolated 2.40 g (81% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.53 (m, 4H), 7.46–7.32 (m, 6H), 4.12 (ddd, J = 12.0, 5.8, 2.2 Hz, 1H), 4.08 (br s, 2H), 2.66 (t, J = 10.6 Hz, 2H), 1.84 (d, J = 12.5 Hz, 1H), 1.79–1.67 (m, 1H), 1.64–1.50 (m, 2H), 1.44 (s, 9H), 1.39 (ddd, J = 14.4, 9.8, 2.2 Hz, 1H), 1.21–1.08 (m, 3H), 1.04 (t, J = 7.6 Hz, 3H), 1.07–1.01 (m, 1H), 1.01–0.95 (m, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 135.7, 135.6, 133.6, 133.5, 129.92, 129.89, 128.3, 79.4, 60.6, 44.2 (br), 40.4, 33.5, 32.6, 31.1, 28.7, 7.7, 2.9;

FT-IR (thin flim) 3447, 3069, 2916, 1694, 1668, 1428, 1366, 1279, 1246, 1167, 1111, 1011, 974, 974, 869 cm^{-1};

HR-MS (FAB+) m/z $[M+H]^+$ calcd for $C_{26}H_{38}NSiO_3$: 440.2621, found: 440.2632.



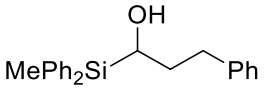
1-(Ethyldiphenylsilyl)-3-(5-methylfuran-2-yl)propan-1-ol. The title compound was synthesized according to **General Procedure A** from 3-(5-methylfuran-2-yl)propanal (0.95 mL, 7.1 mmol) and chloro(ethyl)diphenylsilane (2.4 g, 9.5 mmol). The product was purified by flash chromatography with silica gel (5 → 10% EtOAc in hexanes). Isolated 1.9 g (77% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.51 (m, 4H), 7.48–7.30 (m, 6H), 5.88–5.80 (m, 2H), 3.98 (dd, J = 11.5, 2.6 Hz, 1H), 2.85 (ddd, J = 13.6, 8.2, 5.2 Hz, 1H), 2.69 (dt, J = 15.5, 7.8 Hz, 1H), 2.27 (s, 3H), 2.03–1.92 (m, 1H), 1.91–1.78 (m, 1H), 1.44 (s, br, 1H), 1.23–1.13 (m, 2H), 1.04 (t, J = 7.8 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 150.6, 135.73, 135.67, 133.73, 133.67, 129.82, 129.79, 128.19, 128.18, 106.1, 106.0, 63.3, 32.4, 25.7, 13.8, 7.7, 3.0;

FT-IR (thin flim) 3293, 3070, 2959, 1590, 1458, 1428, 1261, 1118, 1012, 829 cm^{-1};

HR-MS (FAB+) m/z $[M+H]^+$ calcd for $C_{22}H_{27}O_2Si$: 351.1780, found: 351.1782.



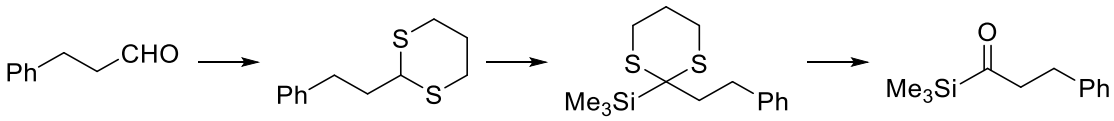
1-(Methyldiphenylsilyl)-3-phenylpropan-1-ol. The title compound was synthesized according to **General Procedure A** from 3-phenylpropanal (1.4 mL, 11 mmol) and chloro(methyl)diphenylsilane (2.4 mL, 14 mmol). The product was purified by flash chromatography with silica gel (5 → 10% EtOAc in hexanes). Isolated 2.1 g (73% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 4H), 7.46 – 7.32 (m, 6H), 7.31 – 7.25 (m, 2H), 7.22 – 7.14 (m, 3H), 3.93 (dd, J = 8.9, 5.3 Hz, 1H), 2.95 (ddd, J = 14.1, 8.5, 6.4 Hz, 1H), 2.66 (dt, J = 13.6, 8.1 Hz, 1H), 2.02 – 1.85 (m, 2H), 1.19 (s, 1H), 0.61 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 135.4, 135.3, 135.1, 134.8, 130.0, 129.96, 128.9, 128.7, 128.37, 128.36, 126.1, 64.2, 35.5, 33.6, -6.4.

FT-IR (thin flim) 3566, 3443, 3068, 2924, 1602, 1496, 1454, 1428,1253, 1112, 1028, 914 cm^{-1};

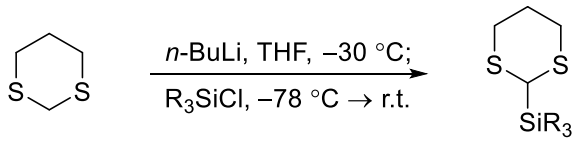
HR-MS (FAB+) m/z $[M+H]^+$ calcd for $C_{22}H_{25}OSi$: 333.1675, found: 333.1680.



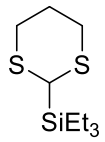
3-Phenyl-1-(trimethylsilyl)propan-1-one. The title compound was synthesized according to a literature procedure from 3-phenylpropanal (6.6 mL, 50 mmol). Isolated 1.8 g (18% yield over 3 steps) of a pale yellow oil.[25]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 2.98 – 2.76 (m, 4H), 0.19 (d, J = 0.7 Hz, 9H).

This data corresponds to the literature reported spectrum.[25]



General Procedure B: **Preparation of α-Dithiane Silanes.** *Procedure for substrates lacking aryl substituents on the silyl group.* α-Dithiane silanes were prepared from a literature known procedure.[26]



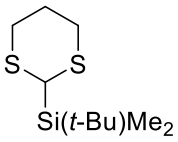
(1,3-Dithian-2-yl)triethylsilane. The title compound was synthesized according to **General Procedure B** from chlorotriethylsilane (16.8 mL, 100 mmol). The product was purified by high vacuum distillation. Isolated 16.9 g (87% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 1H), 2.94 – 2.83 (m, 2H), 2.78 – 2.66 (m, 2H), 2.18 – 1.95 (m, 2H), 1.01 (t, J = 7.9 Hz, 9H), 0.70 (q, J = 7.9, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 32.5, 31.8, 26.8, 7.8, 2.5.

FT-IR (thin flim) 2951, 2875, 1458, 1420, 1260, 1240, 1163, 1084, 1019, 778 cm^{-1};

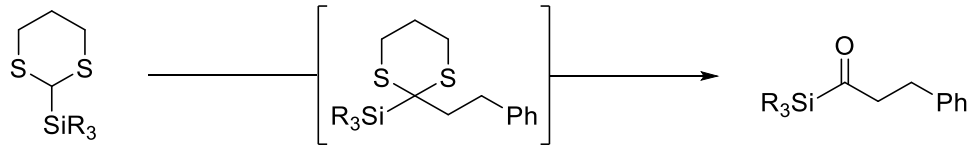
HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{10}H_{21}S_2Si$: 233.0854, found: 233.0846.



***Tert*-butyl(1,3-dithian-2-yl)dimethylsilane.** The title compound was synthesized according to **General Procedure B** from *tert*-butyl(chloro)dimethylsilane (15.1 g, 100 mmol). The product was purified by high vacuum distillation. Isolated 16.2 g (83 yield) of a pale purple oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 1H), 2.98 – 2.76 (m, 2H), 2.69 (ddd, J = 14.0, 4.1, 3.1 Hz, 2H), 2.17 – 1.90 (m, 2H), 0.96 (d, J = 0.6 Hz, 9H), 0.10 (d, J = 0.5 Hz, 6H).

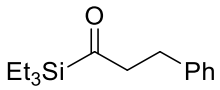
This data corresponds to the literature reported spectrum.[27]



General Procedure C: Preparation of Acyl Silanes. *Procedure for substrates lacking aryl substituents on the silyl group.* The alkylation of α-dithiane silanes was done according to a

literature known procedure.[28] In a flame-dried round bottom flask, *n*-BuLi (1.05 equiv) was added dropwise to a stirring solution of α-dithiane silane (1.00 equiv) in THF (0.4 M with respect to α-dithiane silane) at room temperature under N_2 atmosphere. The solution was then stirred for 10 mins at room temperature and then cooled to −40 °C. Then, (2-bromoethyl)benzene (1.10 equiv) was added dropwise. The reaction mixture was then warmed to room temperature and left to stir for an additional 2 h. The reaction was then quenched with saturated NH_4Cl solution, extracted with Et_2O three times, and the organic phases were collected, dried with $MgSO_4$, filtered and concentrated. The crude material was then used in the next step without further purification.

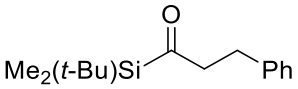
The deprotection of α-alkyl-α-dithiane silanes was done according to a literature known prodcedure.[25] In a round bottom flask, crude α-alkyl-α-dithiane silane was dissolved in a 4:1 mixture of THF/H_2O (0.9 M with respect to α-dithiane silane). The solution was cooled to 0 °C, and $CaCO_3$ (15.6 equiv) was added followed by I_2 (12.0 equiv), which was added in portions. The reaction was warmed to room temperature and stirred for 16 h. The reaction was quench by added Et_2O (15 mL per mmol of α-dithiane silane) and saturated $Na_2S_2O_3$ solution. The biphasic mixture was filtered through Celite and placed in a separatory funnel (note: if iodine color still remains, wash with additional saturated $Na_2S_2O_3$ solution). The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated. The acyl silane can be used in **General Procedure D** without further purification.



3-Phenyl-1-(triethylsilyl)propan-1-one. The title compound was synthesized according to **General Procedure C** from (1,3-dithian-2-yl)triethylsilane (2.2 g, 9.2 mmol). The product was purified by flash chromatography with silica gel (0 → 3% EtOAc in hexanes). Isolated 1.1 g (48% yield over two steps) of colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.22 – 7.13 (m, 3H), 2.95 – 2.76 (m, 4H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.73 (q, *J* = 7.9 Hz, 6H).

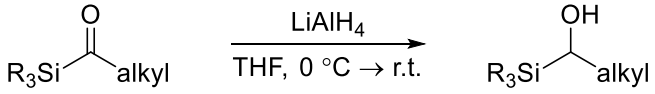
This data corresponds to the literature reported spectrum.[29]



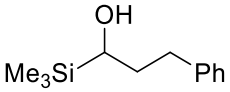
1-(*Tert*-butyldimethylsilyl)-3-phenylpropan-1-one. The title compound was synthesized according to **General Procedure C** from *tert*-butyl(1,3-dithian-2-yl)dimethylsilane (4.0 g, 17.1 mmol). The product was purified by flash chromatography with silica gel (0 → 2% EtOAc in hexanes). Isolated 4.25 g (>99% yield of nominally pure material over two steps) of white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 2H), 7.30 – 7.20 (m, 3H), 3.07 – 2.78 (m, 4H), 0.99 (s, 9H), 0.25 (s, 6H).

This data corresponds to the literature reported spectrum.[30]



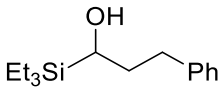
General Procedure D: Reduction of Acyl Silanes. *Procedure for substrates lacking aryl substituents on the silyl group.* In a round bottom flask with charged with a stir bar, slowly dissolve $LiAlH_4$ (4.9 equiv) in THF (ca. 40 mL per mmol of acyl silane) at 0 °C and stir for 10 mins. Dissolve acyl silane in THF (ca. 1.5 mL per mmol of acyl silane) and add with a gentle, steady stream to the $LiAlH_4$ solution at 0 °C. Warm the reaction mixture to room temperature and stir for 3 h. The reaction was then quenched and worked up using the Feiser method.



3-Phenyl-1-(trimethylsilyl)propan-1-ol. The title compound was synthesized according to **General Procedure D** from 3-phenyl-1-(trimethylsilyl)propan-1-one (1.8 g, 8.9 mmol). The product was purified by flash chromatography with silica gel (5 → 10% EtOAc in hexanes). Isolated 1.8 g (92% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 3.39 – 3.29 (m, 1H), 2.99 – 2.87 (m, 1H), 2.71 – 2.61 (m, 1H), 1.91 – 1.74 (m, 2H), 1.11 (s, 1H), 0.05 (s, 9H).

This data corresponds to the literature reported spectrum.[31]



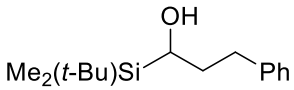
3-Phenyl-1-(triethylsilyl)propan-1-ol. The title compound was synthesized according to **General Procedure D** from 3-phenyl-1-(triethylsilyl)propan-1-one (1.1 g, 4.4 mmol). The product was purified by flash chromatography with silica gel (5% EtOAc in hexanes). Isolated 0.82 g (75% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.24 – 7.12 (m, 3H), 3.51 (dd, J = 11.2, 2.9 Hz, 1H), 2.96 (ddd, J = 13.7, 9.8, 5.0 Hz, 1H), 2.66 (tdd, J = 13.6, 8.7, 6.9 Hz, 1H), 1.96 – 1.75 (m, 2H), 1.50 (s, 1H), 1.03 – 0.93 (m, 9H), 0.68 – 0.49 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 126.83, 126.77, 124.1, 62.5, 34.3, 31.9, 5.9, 0.0.

FT-IR (thin flim) 3448, 3026, 2953, 1708, 1604, 1496, 1455, 1415, 1260, 1239, 1018, 912 cm^{-1};

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{15}H_{25}OSi$: 249.1675, found: 249.1679.

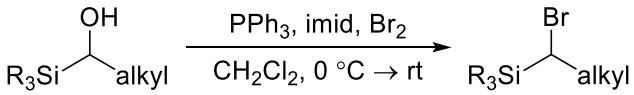


1-(*Tert*-butyldimethylsilyl)-3-phenylpropan-1-ol. The title compound was synthesized according to **General Procedure D** from 1-(*tert*-butyldimethylsilyl)-3-phenylpropan-1-one (3.5 g, 14 mmol). The product was purified by flash chromatography with silica gel (0 → 15% EtOAc in hexanes). Isolated 2.4 g (67% yield) of colorless oil.

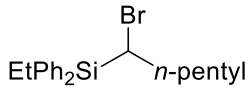
^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.34 – 7.27 (m, 2H), 7.25 – 7.15 (m, 3H), 3.53 (dd, J = 9.8, 4.2 Hz, 1H), 2.96 (ddd, J = 13.6, 9.0, 6.0 Hz, 1H), 2.65 (ddd, J = 13.5, 8.9, 7.2 Hz, 1H), 1.96 – 1.77 (m, 2H), 1.08 (s, 1H), 0.94 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 128.82, 128.77, 126.2, 64.4, 36.7, 33.8, 27.4, 17.1, -7.2, -8.2.

FT-IR (thin flim) 3467, 3027, 2954, 1604, 1496, 1471, 1362, 1255, 1024, 914, 832 cm^{-1}; HR-MS (FAB+) m/z $[M+H]^+$–H_2 calcd for $C_{15}H_{25}OSi$: 249.1675, found: 249.1673.



General Procedure E: Preparation of α-Bromosilanes. PPh_3 (1.50 equiv) and imidazole (1.50 equiv) were dissolved in CH_2Cl_2, and the resulting solution was cooled to 0 °C. At this temperature, I_2 (1.50 equiv) was added in portions, and the resulting mixture was stirred for 10 min. Next, α-hydroxysilane (1.00 equiv) was added, and the resulting mixture was allowed to warm to room temperature and stirred overnight. Then, the reaction mixture was quenched with H_2O. The product was extracted with EtOAc, dried with Na_2SO4, filtered, and concentrated. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel to afford the pure product.



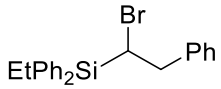
(1-Bromohexyl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 1-(ethyldiphenylsilyl)hexan-1-ol (1.6 g, 5.1 mmol). The product was purified by flash chromatography with silica gel (2 → 5% EtOAc in hexanes). Isolated 1.5 g (76% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.54 (m, 4H), 7.49–7.34 (m, 6H), 3.81 (dd, J = 11.9, 2.7 Hz, 1H), 1.94–1.81 (m, 1H), 1.79–1.62 (m, 2H), 1.47–1.35 (m, 1H), 1.35–1.22 (m, 5H), 1.22–1.12 (m, 1H), 1.04 (t, J = 7.8 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 135.8, 133.5, 133.0, 130.0, 129.9, 128.1, 128.0, 41.2, 33.6, 31.1, 29.1, 22.8, 14.3, 7.6, 4.4.

FT-IR (thin flim) 3070, 2959, 1458, 1428, 1261, 1106, 1029, 802 cm^{-1}.

HR-MS (FAB+) m/z $[M]^{+\bullet}$ calcd for $C_{20}H_{27}Si^{79}Br$: 374.1065, found: 374.1060.



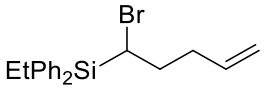
(1-Bromo-2-phenylethyl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 1-(ethyldiphenylsilyl)-2-phenylethan-1-ol (0.70 g, 2.1 mmol). The product was purified by flash chromatography with silica gel (20% $CHCl_3$ in hexanes). Isolated 0.64 g (76% yield) of colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.60 (m, 4H), 7.52 – 7.38 (m, 6H), 7.32 – 7.21 (m, 3H), 7.20 – 7.15 (m, 2H), 3.98 (dd, J = 12.3, 2.7 Hz, 1H), 3.36 (dd, J = 15.2, 2.6 Hz, 1H), 2.86 (dd, J = 15.1, 12.3 Hz, 1H), 1.41 – 1.19 (m, 2H), 1.13 – 0.99 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 136.1, 135.9, 133.2, 132.7, 130.3, 130.2, 129.1, 128.6, 128.4, 128.3, 126.9, 40.9, 40.0, 7.7, 4.6.

FT-IR (thin flim) 3068, 2962, 1588, 1496, 1454, 1427, 1261, 1105, 1030, 801 cm^{-1}.

HR-MS (FAB+) m/z $[M]^{+\bullet}$ calcd for $C_{22}H_{23}Si^{79}Br$: 394.0752, found: 394.0762.



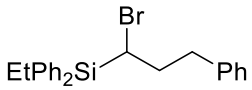
(1-Bromopent-4-en-1-yl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 1-(ethyldiphenylsilyl)pent-4-en-1-ol (1.1 g, 3.6 mmol). The product was purified by flash chromatography with silica gel (5 → 20% $CHCl_3$ in hexanes). Isolated 0.87 g (68% yield) of colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.55 (m, 4H), 7.48 – 7.35 (m, 6H), 5.72 (dddd, J = 17.1, 10.1, 7.7, 5.9 Hz, 1H), 5.11 – 4.98 (m, 2H), 3.83 (dd, J = 12.3, 2.5 Hz, 1H), 2.49 – 2.33 (m, 1H), 2.27 – 2.15 (m, 1H), 2.01 – 1.89 (m, 1H), 1.80 (dddd, J = 14.9, 12.3, 7.8, 4.5 Hz, 1H), 1.36 – 1.19 (m, 2H), 1.07 – 0.98 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 136.1, 135.9, 133.4, 132.9, 130.13, 130.08, 128.24, 128.18, 116.5, 40.0, 33.2, 32.8, 7.6, 4.5.

FT-IR (thin flim) 3070, 2961, 1640, 1589, 1488, 1428, 1261, 1110, 1028, 916, 803 cm^{-1}.

HR-MS (FAB+) m/z $[M]^{+\bullet}$ calcd for $C_{19}H_{23}Si^{79}Br$: 358.0752, found: 358.0746.



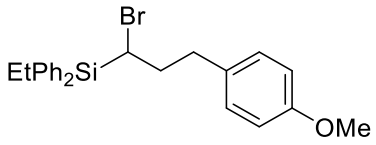
(1-Bromo-3-phenylpropyl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 1-(ethyldiphenylsilyl)-3-phenylpropan-1-ol (1.2 g, 3.5 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Isolated 1.1 g (75% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 2H), 7.49 – 7.26 (m, 10H), 7.25 – 7.19 (m, 1H), 7.18 – 7.11 (m, 2H), 3.72 (dd, J = 12.2, 2.2 Hz, 1H), 3.00 (ddd, J = 13.8, 7.9, 4.3 Hz, 1H), 2.73 (dt, J = 13.6, 8.1 Hz, 1H), 2.24 – 2.11 (m, 1H), 2.01 (dddd, J = 15.0, 12.1, 7.8, 4.3 Hz, 1H), 1.31 – 1.16 (m, 2H), 1.03 – 0.88 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 135.7, 135.5, 133.0, 132.4, 129.8, 129.7, 128.8, 128.4, 127.87, 127.86, 126.1, 39.3, 35.1, 34.7, 7.2, 4.2.

FT-IR (thin flim) 3069, 2961, 1589, 1496, 1454, 1428, 1261, 1110, 802 cm^{-1}.

HR-MS (FAB+) m/z $[M-C_2H_5]^{+\bullet}$ calcd for $C_{21}H_{20}Si^{79}Br$: 379.0518, found: 379.0504.



(1-Bromo-3-(4-methoxyphenyl)propyl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 1-(ethyldiphenylsilyl)-3-(4-methoxyphenyl)propan-1-ol (2.2 g, 5.8 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Isolated 1.7 g (65% yield) of colorless oil.

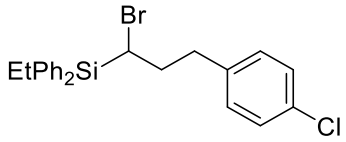
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.58 (m, 2H), 7.55–7.49 (m, 2H), 7.49–7.34 (m, 6H), 7.17–7.08 (m, 2H), 6.93–6.85 (m, 2H), 3.84 (s, 3H), 3.77 (dd, J = 12.1, 2.3 Hz, 1H), 2.97

(ddd, J = 13.6, 7.4, 4.3 Hz, 1H), 2.74 (dt, J = 13.8, 8.2 Hz, 1H), 2.19 (dtd, J = 15.1, 7.8, 2.2 Hz, 1H), 2.03 (dddd, J = 15.0, 12.0, 7.6, 4.3 Hz, 1H), 1.39–1.24 (m, 2H), 1.03 (t, J = 7.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 135.9, 135.7, 133.2, 133.0, 132.6, 130.00, 129.95, 129.9, 128.1, 128.0, 114.0, 55.4, 39.5, 35.5, 33.9, 7.5, 4.4.

FT-IR (thin flim) 3070, 2955, 1611, 1512, 1428, 1301, 1427, 1177, 1111, 1037, 807 cm^{-1}.

HR-MS (FAB+) m/z $[M]^{+\bullet}$ calcd for $C_{23}H_{29}Si_2{}^{81}Br$: 440.0991, found: 440.0997.



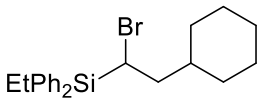
(1-Bromo-3-(4-chlorophenyl)propyl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 3-(4-chlorophenyl)-1-(ethyldiphenylsilyl)propan-1-ol (1.1 g, 3.0 mmol). The product was purified by flash chromatography with silica gel (5 → 10% EtOAc in hexanes). Isolated 0.63 g (48% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.54 (m, 2H), 7.49–7.32 (m, 8H), 7.26 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 3.67 (dd, J = 12.2, 2.3 Hz, 1H), 2.95 (ddd, J = 13.7, 7.6, 4.2 Hz, 1H), 2.72 (dt, J = 13.8, 8.0 Hz, 1H), 2.13 (dddd, J = 15.1, 8.6, 7.7, 2.2 Hz, 1H), 1.99 (dddd, J = 15.1, 12.1, 7.6, 4.3 Hz, 1H), 1.31–1.21 (m, 2H), 0.99 (t, J = 7.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 135.9, 135.7, 133.1, 132.5, 132.1, 130.4, 130.1, 130.0, 128.8, 128.14, 128.12, 39.2, 35.1, 34.2, 7.5, 4.3.

FT-IR (thin flim) 3069, 2955, 1589, 1492, 1428, 1262, 1218, 1152, 1112, 1015, 998, 956, 843, 812 cm^{-1}.

HR-MS (FAB+) m/z $[M–Br]^{+\bullet}$ calcd for $C_{23}H_{24}ClSi$: 363.1336, found: 363.1333.



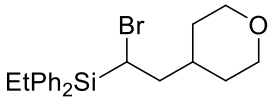
(1-Bromo-2-cyclohexylethyl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 2-cyclohexyl-1-(ethyldiphenylsilyl)ethan-1-ol (2.2 g, 6.6 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Isolated 1.6 g (59% yield) of colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.48 (m, 4H), 7.45–7.33 (m, 6H), 3.96 (dd, J = 12.4, 2.1 Hz, 1H), 1.92 (d, J = 12.5 Hz, 1H), 1.78–1.59 (m, 5H), 1.59–1.47 (m, 1H),1.33–1.07 (m, 6H), 1.02 (t, J = 7.8 Hz, 3H), 0.93–0.80 (m, 1H), 0.71 (qd, J = 12.4, 3.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 135.8, 133.5, 132.9, 130.0, 129.9, 128.1, 128.0, 40.9, 37.8, 35.7, 34.3, 31.2, 26.8, 26.5, 26.2, 7.5, 4.4.

FT-IR (thin flim) 3069, 2923, 1589, 1488, 1448, 1428, 1261, 1110, 1029, 803 cm^{-1}.

HR-MS (EI+) m/z $[M]^{+\bullet}$ calcd for $C_{22}H_{29}Si^{79}Br$: 400.1222, found: 400.1251.



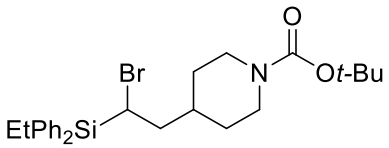
(1-Bromo-2-(tetrahydro-2*H*-pyran-4-yl)ethyl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 1-(ethyldiphenylsilyl)-2-(tetrahydro-2*H*-pyran-4-yl)ethan-1-ol (1.6 g, 4.6 mmol). The product was purified by flash chromatography with silica gel (3 → 5% EtOAc in hexanes). Isolated 1.3 g (68% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.53 (m, 4H), 7.48–7.34 (m, 6H), 3.98 (dd, J = 11.4, 4.2 Hz, 1H), 3.92 (dd, J = 12.9, 2.3 Hz, 1H), 3.89 (dd, J = 11.4, 4.4 Hz, 1H), 3.38 (dtd, J = 16.8, 11.9, 2.3 Hz, 2H), 1.99–1.85 (m, 1H), 1.84–1.70 (m, 2H), 1.62 (ddd, J = 15.0, 10.0, 2.4 Hz, 1H), 1.49–1.40 (m, 1H), 1.34–1.18 (m, 3H), 1.11 (td, J = 12.1, 4.5 Hz, 1H), 1.02 (t, J = 7.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 135.8, 133.2, 132.6, 130.1, 130.0, 128.2, 128.1, 68.2, 68.1, 40.3, 36.7, 33.7, 33.2, 31.2, 7.5, 4.4.

FT-IR (thin flim) 3070, 2929, 1428, 1190, 1111, 1012, 849 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{21}H_{26}OSi^{79}Br$: 401.0936, found: 401.0918.



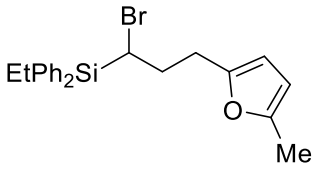
***Tert*-butyl 4-(2-bromo-2-(ethyldiphenylsilyl)ethyl)piperidine-1-carboxylate.** The title compound was synthesized according to **General Procedure E** from *tert*-butyl 4-(2-(ethyldiphenylsilyl)-2-hydroxyethyl)piperidine-1-carboxylate (2.4 g, 5.5 mmol). The product was purified by flash chromatography with silica gel (3 → 7% EtOAc in hexanes). Isolated 2.0 g (74% yield) of colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.53 (m, 4H), 7.48–7.36 (m, 6H), 4.13 (br s, 1H), 4.04 (br s, 1H), 3.92 (dd, J = 12.8, 2.1 Hz, 1H), 2.69 (q, J = 11.5 Hz, 2H), 1.95–1.73 (m, 3H), 1.60 (ddd, J = 14.8, 9.7, 2.2 Hz, 1H), 1.55–1.47 (m, 1H), 1.45 (s, 9H), 1.32–1.24 (m, 2H), 1.16–1.06 (m, 1H), 1.03 (t, J = 7.9 Hz, 3H), 0.96–0.89 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 135.9, 135.7, 133.1, 132.5, 130.1, 130.0, 128.2, 128.1, 79.5, 43.9 (br), 40.0, 37.0, 34.3, 32.9, 30.2, 28.7, 7.5, 4.3. Two carbon signals are overlapping (α-amino methylenes, 43.9 ppm).

FT-IR (thin flim) 3070, 2931, 1694, 1428, 1365, 1261, 1162, 1111, 1026, 865 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{26}H_{35}NO_2Si^{79}Br$: 500.1620, found: 500.1618.



(1-Bromo-3-(5-methylfuran-2-yl)propyl)(ethyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 1-(ethyldiphenylsilyl)-3-(5-methylfuran-2-yl)propan-1-ol (1.9 g, 5.5 mmol). The product was purified by flash

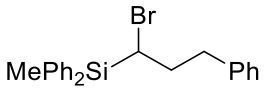
chromatography with silica gel (0 → 5% EtOAc in hexanes). Isolated 1.1 g (50% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.55 (m, 2H), 7.55–7.48 (m, 2H), 7.48–7.30 (m, 6H), 5.94–5.80 (m, 2H), 3.76 (dd, J = 12.4, 2.0 Hz, 1H), 2.90 (ddd, J = 15.1, 7.0, 4.5 Hz, 1H), 2.77 (ddd, J = 15.7, 8.6, 7.4 Hz, 1H), 2.31–2.20 (m, 1H), 2.26 (s, 3H), 1.92 (dddd, J = 15.1, 12.4, 7.1, 4.2 Hz, 1H), 1.31–1.24 (m, 2H), 0.99 (t, J = 7.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 150.9, 136.0, 135.8, 133.2, 132.6, 130.05, 129.96, 128.10, 128.08, 107.0, 106.1, 39.4, 32.3, 27.4, 13.8, 7.4, 4.4.

FT-IR (thin flim) 3070, 2960, 1568, 1428, 1261, 1109, 1020, 800 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^{+\bullet}$ calcd for $C_{22}H_{25}OSi^{79}Br$: 412.0858, found: 412.0840.



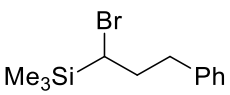
(1-Bromo-3-phenylpropyl)(methyl)diphenylsilane. The title compound was synthesized according to **General Procedure E** from 1-(methyldiphenylsilyl)-3-phenylpropan-1-ol (1.0 g, 3.7 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Isolated 1.0 g (70% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.55 – 7.48 (m, 4H), 7.46 – 7.27 (m, 8H), 7.24 – 7.17 (m, 1H), 7.17 – 7.10 (m, 2H), 3.68 (dd, J = 11.8, 2.7 Hz, 1H), 3.01 (ddd, J = 12.9, 8.0, 4.4 Hz, 1H), 2.77 – 2.69 (m, 1H), 2.23 – 1.97 (m, 2H), 0.71 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 135.4, 135.3, 134.6, 134.33, 134.28, 130.13, 130.07, 129.1, 128.8, 128.3, 128.2, 128.1, 126.4, 40.7, 35.4, 35.1, -5.2.

FT-IR (thin flim) 3069, 2962, 1603, 1589, 1496, 1454, 1428, 1260, 1113, 1029, 998 cm^{-1}.

HR-MS (FAB+) m/z $[M-C_6H_6]^{+\bullet}$ calcd for $C_{16}H_{17}Si^{79}Br$: 316.0283, found: 316.0296.



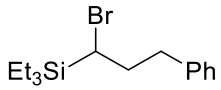
(1-Bromo-3-phenylpropyl)trimethylsilane. The title compound was synthesized according to **General Procedure E** from 3-phenyl-1-(trimethylsilyl)propan-1-ol (1.7 g, 7.9 mmol). The product was purified by flash chromatography with silica gel (0 → 1% EtOAc in hexanes). Isolated 1.8 g (84% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.27 – 7.20 (m, 3H), 3.23 (dd, J = 11.5, 3.3 Hz, 1H), 3.08 (ddd, J = 13.3, 8.4, 4.7 Hz, 1H), 2.76 (ddd, J = 13.6, 8.7, 7.6 Hz, 1H), 2.17 – 1.94 (m, 2H), 0.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 129.0, 128.8, 126.3, 44.6, 35.54, 35.46, –2.7.

FT-IR (thin flim) 3027, 2955, 1604, 1496, 1454, 1250, 1110, 1075, 1030, 867, 840 cm^{-1}.

HR-MS (EI+) m/z $[M]^{+\bullet}$ calcd for $C_{12}H_{19}Si^{79}Br$: 270.0439, found: 270.0419.



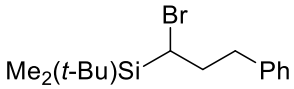
(1-Bromo-3-phenylpropyl)triethylsilane. The title compound was synthesized according to **General Procedure E** from 3-phenyl-1-(triethylsilyl)propan-1-ol (3.1 g, 12 mmol). The product was purified by flash chromatography with silica gel (0 → 2% EtOAc in hexanes). Isolated 2.7 g (70% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 3.37 – 3.27 (m, 1H), 3.07 (ddd, J = 13.3, 7.3, 5.5 Hz, 1H), 2.71 (dt, J = 13.6, 8.1 Hz, 1H), 2.14 – 1.98 (m, 2H), 0.96 (t, J = 7.9 Hz, 9H), 0.68 (q, J = 7.4, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 129.0, 128.8, 126.3, 42.1, 35.9, 35.7, 7.8, 2.9.

FT-IR (thin flim) 3027, 2955, 1604, 1496, 1454, 1415, 1260, 1096, 1019, 804 cm^{-1};

HR-MS (FAB+) m/z $[M]^{+\bullet}$ calcd for $C_{15}H_{25}Si^{79}Br$: 312.0909, found: 312.0918.

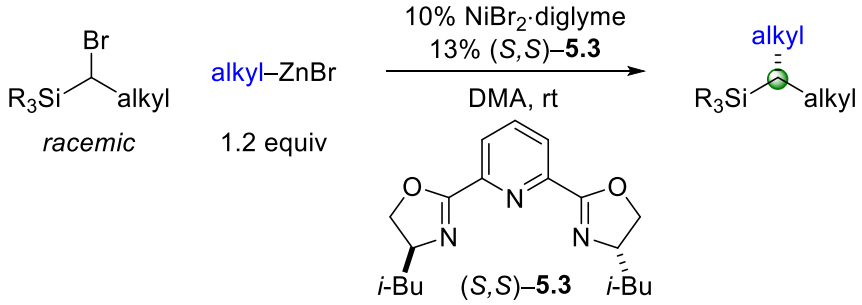


(1-Bromo-3-phenylpropyl)(*tert*-butyl)dimethylsilane. The title compound was synthesized according to **General Procedure E** from 1-(*tert*-butyldimethylsilyl)-3-

phenylpropan-1-ol (2.00 g, 8.00 mmol). The product was purified by flash chromatography with silica gel (0 → 1% EtOAc in hexanes). Isolated 1.94 g (77% yield) of colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.25 – 7.18 (m, 3H), 3.34 (dd, J = 11.8, 2.8 Hz, 1H), 3.07 (ddd, J = 13.3, 8.5, 4.5 Hz, 1H), 2.74 (ddd, J = 13.5, 8.7, 7.6 Hz, 1H), 2.22 – 1.96 (m, 2H), 0.93 (s, 9H), 0.13 (s, 1H), 0.07 (s, 1H).

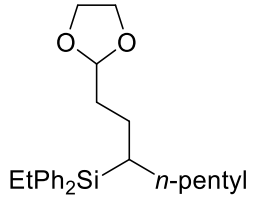
5.4.5. Nickel-Catalyzed Alkyl-Alkyl Cross-Couplings



General Procedure. An oven-dried 4-mL vial was charged with α-bromosilane (0.500 mmol), then $NiBr_2$•diglyme (15.4 mg, 0.0500 mmol), then (*R*,*R*)– or (*S*,*S*)–**5.3** (21.4 mg, 0.0650 mmol). Next, an oven-dried stirbar was added and the reaction vial was capped with a pierceable septum-cap and sealed with electrical tape. The reaction vial was placed under high vacuum on a Schlenk line for 10 mins. The Schlenk line was turned to static and the reaction vial was fitted with an Ar-filled balloon. The Schlenk line was then opened to allow argon to purge through the system for 15 mins. Next, the Schlenk line was removed and anhydrous DMA (2.1 mL) was added. The reaction mixture was then allowed to stir for 15 min, after which it appears as a cloudy orange solution. Significant oxygen contamination will cause the reaction mixture to appear nearly colorless; we do not recommend proceeding if the reaction mixture is not orange. Then alkylzinc bromide solution (0.600 mmol; concentration of alkylzinc bromide solutions between 0.70 M and 1.00 M are recommended) was added as a gentle stream turning the reaction mixture a dark red-black/brown color. Significant oxygen contamination will usually cause the reaction mixture to appear bright

red. Vacuum grease was then liberally applied to the top of the septum-cap, the argon balloon was removed, and the vacuum grease was gently pressed onto of the cap to avoid leakage. The reaction was then stirred for 20 hours at room temperature at ca. 800 rpm. The reaction mixture then then directly transferred to a silica gel column for purification without any additional workup.

Note: Our research lab uses N_2 in our Schlenk system; N_2 attached to the Schlenk system is turned off for the duration of the reaction setup. We have found an N_2 atmosphere leads to lower and less reproducible yields.



(1-(1,3-Dioxolan-2-yl)octan-3-yl)(ethyl)diphenylsilane (Table 5.2, entry 1). The title compound was synthesized according to the General Procedure from (1-bromohexyl)(ethyl)diphenylsilane (188 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 3% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 122 mg (62% yield), + 90% ee; (*R*,*R*)–**5.3**: 133 mg (67% yield), – 91% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (5% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 3.2 min (major (*S*,*S*)–**5.3**), 3.7 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.47 (m, 4H), 7.42–7.29 (m, 6H), 4.73 (t, J = 4.5 Hz, 1H), 3.97–3.85 (m, 2H), 3.85–3.75 (m, 2H), 1.79–1.65 (m, 2H), 1.65–1.50 (m, 2H), 1.49–1.38 (m, 1H), 1.38–1.25 (m, 3H), 1.25–1.13 (m, 5H), 1.13–1.06 (m, 2H), 0.96 (t, J = 7.7 Hz, 3H), 0.82 (t, J = 6.9 Hz, 3H).

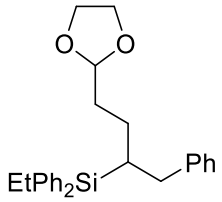
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.70, 135.68, 135.6, 129.22, 129.21, 127.89, 127.88, 105.0, 65.01, 64.99, 34.1, 32.4, 30.0, 29.5, 24.5, 23.0, 22.8, 14.3, 7.9, 4.5.

FT-IR (thin flim) 3068, 2953, 2929, 2973, 1456, 1428, 1140, 1109, 1036, 1036, 944 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{25}H_{35}O_2Si$: 395.2406, found: 395.2392.

$[\alpha]^{23}_D$ = – 0.8 (c = 0.725, $CHCl_3$); + 90% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 0.1 (c = 0.670, $CHCl_3$); – 91% ee from (*R*,*R*)–**5.3**.



(4-(1,3-Dioxolan-2-yl)-1-phenylbutan-2-yl)(ethyl)diphenylsilane (Table 5.2, entry 2). The title compound was synthesized according to the General Procedure from (1-bromo-2-phenylethyl)(ethyl)diphenylsilane (198 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (10 → 15% EtOAc in hexanes). Colorless waxy solid.

(*S*,*S*)–**5.3**: 136 mg (65% yield), + 93% ee; (*R*,*R*)–**5.3**: 135 mg (65% yield), – 94% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC-3 column (2% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 13.6 min (major (*S*,*S*)–**5.3**), 16.2 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 4H), 7.43 – 7.34 (m, 6H), 7.25 – 7.20 (m, 2H), 7.17 – 7.12 (m, 3H), 4.59 (t, J = 4.6 Hz, 1H), 3.87 – 3.77 (m, 2H), 3.77 – 3.68 (m, 2H), 2.93 (dd, J = 14.1, 3.9 Hz, 1H), 2.46 (dd, J = 14.1, 10.1 Hz, 1H), 1.76 – 1.62 (m, 2H), 1.50 – 1.39 (m, 3H), 1.06 (q, J = 7.3 Hz, 2H), 0.93 (t, J = 7.6 Hz, 3H).

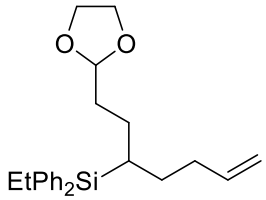
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 135.50, 135.46, 135.0, 134.9, 129.2, 128.78, 128.77, 128.2, 127.80, 127.79, 125.7, 104.7, 64.7, 64.6, 36.4, 33.6, 25.1, 24.0, 7.6, 4.3.

FT-IR (thin flim) 3023, 2952, 2874, 1601, 1495, 1493, 1427, 1134, 1108, 1030, 944 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{27}H_{31}O_2Si$: 415.2093, found: 415.2073.

$[\alpha]^{23}_D$ = – 1.4 (c = 0.495, $CHCl_3$); + 93% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 0.8 (c = 0.490, $CHCl_3$); – 94% ee from (*R*,*R*)–**5.3**.



(1-(1,3-Dioxolan-2-yl)hept-6-en-3-yl)(ethyl)diphenylsilane (Table 5.2, entry 3). The title compound was synthesized according to the General Procedure from (1-bromopent-4-en-1-yl)(ethyl)diphenylsilane (180 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (5% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 100 mg (53% yield), – 90% ee; (*R*,*R*)–**5.3**: 104 mg (55% yield), + 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (7% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 7.0 min (major (*S*,*S*)–**5.3**), 3.5 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.48 (m, 4H), 7.42 – 7.31 (m, 6H), 5.71 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 4.98 – 4.86 (m, 2H), 4.74 (t, J = 4.5 Hz, 1H), 3.96 – 3.84 (m, 2H), 3.87 – 3.74 (m, 2H), 2.16 – 2.04 (m, 1H), 2.03 – 1.92 (m, 1H), 1.79 – 1.63 (m, 3H), 1.62 – 1.53 (m, 1H), 1.51 – 1.37 (m, 2H), 1.37 – 1.29 (m, 1H), 1.12 (q, J = 7.8 Hz, 2H), 0.96 (t, J = 7.7 Hz, 3H).

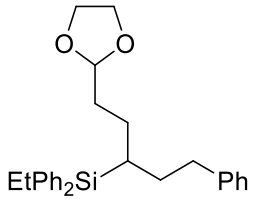
^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 135.59, 135.55, 135.4, 135.3, 129.22, 129.20, 127.85, 127.84, 114.7, 104.9, 64.93, 64.90, 33.9, 33.6, 29.4, 24.1, 22.2, 7.8, 4.3.

FT-IR (thin flim) 3069, 2952, 2925, 2875, 1427, 1415, 1139, 1108, 1038, 998, 911 cm^{-1}.

HR-MS (ESI+) m/z $[M+Na]^+$ calcd for $C_{24}H_{32}O_2SiNa$: 403.2069, found: 403.2066.

$[\alpha]^{23}_D$ = + 4.0 (c = 0.715, $CHCl_3$); – 90% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = – 4.1 (c = 0.620, $CHCl_3$); + 92% ee from (*R*,*R*)–**5.3**.



(1-(1,3-Dioxolan-2-yl)-5-phenylpentan-3-yl)(ethyl)diphenylsilane (Table 5.2, entry 4). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)(ethyl)diphenylsilane (205 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 163 mg (76% yield), – 94% ee; (*R*,*R*)–**5.3**: 153 mg (71% yield), + 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (35% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 6.8 min (major (*S*,*S*)–**5.3**), 4.4 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.44 (m, 4H), 7.42–7.29 (m, 6H), 7.26–7.20 (m, 2H), 7.16 (tt, J = 7.3, 1.3 Hz, 1H), 7.05 (d, J = 7.5 Hz, 2H), 4.76 (t, J = 4.6 Hz, 1H), 3.98–3.87 (m, 2H), 3.87–3.77 (m, 2H), 2.64 (ddd, J = 13.5, 10.6, 5.0 Hz, 1H), 2.48 (ddd, J = 13.5, 10.6, 6.4 Hz, 1H), 1.89 (dddd, J = 14.0, 10.7, 6.4, 4.4 Hz, 1H), 1.84–1.68 (m, 2H), 1.68–1.47 (m, 3H), 1.37 (tt, J = 7.9, 4.4 Hz, 1H), 1.17–1.08 (m, 2H), 0.95 (t, J = 7.7 Hz, 3H).

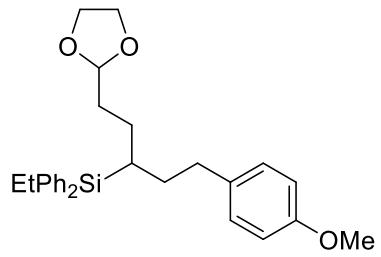
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 135.7, 135.6, 135.5, 135.3, 129.4, 129.3, 128.7, 128.5, 127.98, 127.95, 125.9, 104.9, 65.04, 65.01, 35.9, 33.9, 32.2, 24.2, 22.5, 7.9, 4.4.

FT-IR (thin flim) 3068, 3023, 2950, 2874, 1602, 1495, 1454, 1427, 1133, 1108, 1030, 944 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{28}H_{33}O_2Si$: 429.2250, found: 429.2257.

$[\alpha]^{23}_D$ = + 7.5 (c = 0.540, $CHCl_3$); – 94% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = – 6.9 (c = 0.530, $CHCl_3$); + 92% ee from (*R*,*R*)–**5.3**.



(1-(1,3-Dioxolan-2-yl)-5-(4-methoxyphenyl)pentan-3-yl)(ethyl)diphenylsilane (Table 5.2, entry 5). The title compound was synthesized according to the General Procedure from (1-bromo-3-(4-methoxyphenyl)propyl)(ethyl)diphenylsilane (220 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 199 mg (86% yield), – 90% ee; (*R*,*R*)–**5.3**: 199 mg (86% yield), + 93% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (40% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 8.1 min (major (*S*,*S*)–**5.3**), 4.5 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.45 (m, 4H), 7.42–7.30 (m, 6H), 6.97 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 4.76 (t, J = 4.6 Hz, 1H), 3.97–3.87 (m, 2H), 3.87–3.79 (m, 2H), 3.78 (s, 3H), 2.59 (ddd, J = 13.7, 10.5, 5.0 Hz, 1H), 2.44 (ddd, J = 13.7, 10.5, 6.4 Hz, 1H), 1.92–1.68 (m, 3H), 1.66–1.49 (m, 3H), 1.36 (ddd, J = 11.8, 7.6, 4.3 Hz, 1H), 1.17–1.08 (m, 2H), 0.96 (t, J = 7.7 Hz, 3H).

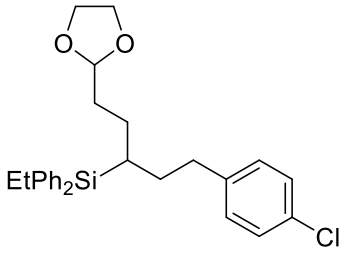
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 135.7, 135.6, 135.5, 135.4, 134.9, 129.6, 129.33, 129.29, 128.0, 127.9, 113.9, 104.9, 65.04, 65.01, 55.5, 34.9, 33.9, 32.4, 24.2, 22.4, 7.9, 4.4.

FT-IR (thin flim) 3068, 2951, 2875, 1611, 1512, 1458, 1300, 1246, 1177, 1133, 1109, 1037, 945, 821 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{29}H_{35}O_3Si$: 459.2356, found: 459.2345.

$[\alpha]^{23}_D$ = + 11.9 (c = 0.520, $CHCl_3$); – 90% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = – 11.7 (c = 0.605, $CHCl_3$); + 93% ee from (*R*,*R*)–**5.3**.



(1-(4-Chlorophenyl)-5-(1,3-dioxolan-2-yl)pentan-3-yl)(ethyl)diphenylsilane (Table 5.2, entry 6). The title compound was synthesized according to the General Procedure from (1-bromo-3-(4-chlorophenyl)propyl)(ethyl)diphenylsilane (222 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 116 mg (50% yield), – 90% ee; (*R*,*R*)–**5.3**: 140 mg (60% yield), + 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (35% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 10.7 min (major (*S*,*S*)–**5.3**), 4.8 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.44 (m, 4H), 7.43–7.29 (m, 6H), 7.20 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 8.3 Hz, 2H), 4.76 (t, J = 4.6 Hz, 1H), 3.98–3.87 (m, 2H), 3.87–3.77 (m, 2H), 2.60 (ddd, J = 13.7, 10.3, 5.1 Hz, 1H), 2.45 (ddd, J = 13.7, 10.3, 6.6 Hz, 1H), 1.92–1.67 (m, 3H), 1.66–1.46 (m, 3H), 1.34 (ddt, J = 8.7, 7.6, 4.5 Hz, 1H), 1.16–1.08 (m, 2H), 0.96 (t, J = 7.8 Hz, 3H).

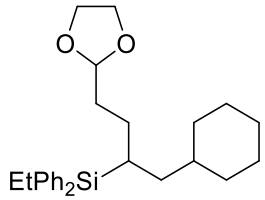
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 135.7, 135.6, 135.4, 135.2, 131.5, 130.0, 129.42, 129.38, 128.5, 128.02, 128.00, 104.8, 65.1, 65.0, 35.1, 33.9, 32.2, 24.2, 22.4, 7.9, 4.4.

FT-IR (thin flim) 3068, 2950, 2874, 1491, 1427, 1134, 1108, 1037, 1014, 808 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{28}H_{32}O_2SiCl$: 463.1860, found: 463.1869.

$[\alpha]^{23}_D$ = + 14.8 (c = 0.470, $CHCl_3$); – 90% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = – 15.7 (c = 0.600, $CHCl_3$); + 92% ee from (*R*,*R*)–**5.3**.



(1-Cyclohexyl-4-(1,3-dioxolan-2-yl)butan-2-yl)(ethyl)diphenylsilane (Table 5.2, entry 7). The title compound was synthesized according to the General Procedure from (1-bromo-2-cyclohexylethyl)(ethyl)diphenylsilane (201 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 3% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 132 mg (62% yield), + 90% ee; (*R*,*R*)–**5.3**: 119 mg (56% yield), – 91% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (5% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 4.7 min (major (*S*,*S*)–**5.3**), 5.6 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.49 (m, 4H), 7.42–7.31 (m, 6H), 4.71 (t, J = 4.6 Hz, 1H), 3.95–3.85 (m, 2H), 3.85–3.75 (m, 2H), 1.78 (d, J = 13.0 Hz, 1H), 1.74–1.53 (m, 7H), 1.48–1.32 (m, 3H), 1.30–1.07 (m, 7H), 0.96 (t, J = 7.7 Hz, 3H), 0.88–0.64 (m, 2H).

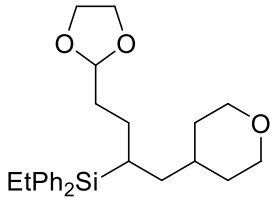
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.74, 135.67, 135.66, 135.6, 129.22, 129.19, 127.88, 127.86, 105.0, 65.0, 38.2, 36.4, 34.6, 34.0, 32.9, 26.9, 26.65, 26.57, 24.9, 19.3, 7.9, 4.4. Two carbon signals are overlapping (dioxolanyl methylenes, 65.0 ppm).

FT-IR (thin flim) 3068, 2922, 2851, 1448, 1428, 1260, 1229, 1131, 1108, 1033, 945 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{27}H_{37}O_2Si$: 421.2563, found: 421.2576.

$[\alpha]^{23}_D$ = – 4.1 (c = 0.485, $CHCl_3$); + 90% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 3.8 (c = 0.600, $CHCl_3$); – 91% ee from (*R*,*R*)–**5.3**.



(4-(1,3-Dioxolan-2-yl)-1-(tetrahydro-2*H*-pyran-4-yl)butan-2-yl)(ethyl)diphenylsilane (Table 5.2, entry 8). The title compound was synthesized according to the General Procedure from (1-bromo-2-(tetrahydro-2*H*-pyran-4-yl)ethyl)(ethyl)diphenylsilane (202 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (5 → 15% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 136 mg (64% yield), – 91% ee; (*R*,*R*)–**5.3**: 150 mg (71% yield), + 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (10% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 23.6 min (major (*S*,*S*)–**5.3**), 3.4 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.47 (m, 4H), 7.42–7.30 (m, 6H), 4.71 (t, J = 4.6 Hz, 1H), 3.96–3.74 (m, 6H), 3.25 (tdd, J = 11.4, 9.3, 2.2 Hz, 2H), 1.78–1.52 (m, 4H), 1.51–1.36 (m, 5H), 1.30–1.15 (m, 2H), 1.14–1.03 (m, 3H), 0.95 (t, J = 7.7 Hz, 3H).

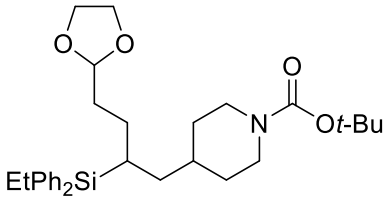
^{13}C NMR (101 MHz $CDCl_3$) δ 135.7, 135.6, 135.4, 135.2, 129.39, 129.36, 127.98, 127.97, 104.9, 68.33, 68.30, 65.024, 65.016, 37.7, 34.2, 34.0, 33.8, 32.8, 24.8, 19.0, 7.9, 4.3.

FT-IR (thin flim) 3069, 2928, 2876, 1427, 1236, 1131, 1108, 1091, 1015, 982 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+$ calcd for $C_{26}H_{37}O_3Si$: 425.2512, found: 425.2527.

$[\alpha]^{23}_D$ = – 4.8 (c = 0.525, $CHCl_3$); – 91% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 5.6 (c = 0.610, $CHCl_3$); + 92% ee from (*R*,*R*)–**5.3**.



***Tert*-butyl 4-(4-(1,3-dioxolan-2-yl)-2-(ethyldiphenylsilyl)butyl)piperidine-1-carboxylate (Table 5.2, entry 9).** The title compound was synthesized according to the General Procedure from *tert*-butyl 4-(2-bromo-2-(ethyldiphenylsilyl)ethyl)piperidine-1-carboxylatediphenylsilane (251 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (5 → 15% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 178 mg (68% yield), – 90% ee; (*R*,*R*)–**5.3**: 180 mg (69% yield), + 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-H column (10% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 4.6 min (major (*S*,*S*)–**5.3**), 3.9 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (500 MHz, d_6-DMSO, 75 °C) δ 6.98 – 6.88 (m, 4H), 6.85 – 6.75 (m, 7H), 4.16 – 3.96 (m, 1H), 3.23 – 3.07 (m, 4H), 2.02 – 1.88 (m, 4H), 1.10 – 1.01 (m, 2H), 1.00 – 0.74 (m, 16H), 0.69 – 0.59 (m, 1H), 0.53 (q, J = 8.0, 2.5 Hz, 2H), 0.37 (t, J = 7.6 Hz, 3H), 0.32 – 0.13 (m, 2H)

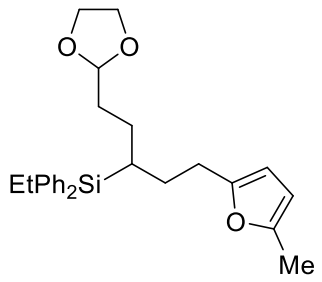
^{13}C NMR (126 MHz, d_6-DMSO, 75 °C) δ 154.5, 135.7, 135.63, 135.56, 135.50, 129.68, 129.66, 128.34, 128.33, 104.4, 79.0, 64.75, 64.72, 44.2 (br), 37.5, 34.9, 33.9, 33.1, 32.0, 28.8, 25.2, 19.8, 8.1, 4.0. Two carbon signals are overlapping (α-amino methylenes, 44.2 ppm).

FT-IR (thin flim) 3069, 2929, 2875, 1693, 1427, 1365, 1281, 1241, 1169, 1109, 1033, 947 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+$–H_2 calcd for $C_{31}H_{44}O_4NSi$: 522.3040, found: 522.3051.

$[\alpha]^{23}_D$ = + 8.2 (c = 0.555, $CHCl_3$); – 90% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = – 9.2 (c = 0.520, $CHCl_3$); + 90% ee from (*R*,*R*)–**5.3**.



(1-(1,3-Dioxolan-2-yl)-5-(5-methylfuran-2-yl)pentan-3-yl)(ethyl)diphenylsilane (Table 5.2, entry 10). The title compound was synthesized according to the General Procedure from (1-bromo-3-(5-methylfuran-2-yl)propyl)(ethyl)diphenylsilane (207 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Pale yellow oil.

(*S*,*S*)–**5.3**: 152 mg (70% yield), – 89% ee; (*R*,*R*)–**5.3**: 158 mg (73% yield), + 91% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (15% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 11.6 min (major (*S*,*S*)–**5.3**), 8.1 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.45 (m, 4H), 7.41–7.30 (m, 6H), 5.82 (dd, J = 3.0, 1.0 Hz, 1H), 5.76 (d, J = 3.0 Hz, 1H), 4.73 (t, J = 4.6 Hz, 1H), 3.95–3.85 (m, 2H), 3.85–3.75 (m, 2H), 2.60 (ddd, J = 14.7, 9.3, 5.4 Hz, 1H), 2.50 (ddd, J = 15.8, 8.7, 7.2 Hz, 1H), 2.24 (d, J = 0.6 Hz, 3H), 1.93 (dddd, J = 13.8, 9.3, 7.0, 4.3 Hz, 1H), 1.80–1.56 (m, 4H), 1.52–1.40 (m, 1H), 1.34 (ddt, J = 8.4, 7.2, 4.3 Hz, 1H), 1.11 (q, J = 7.8 Hz, 2H), 0.94 (t, J = 7.8 Hz, 3H).

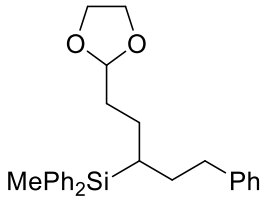
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 150.4, 135.7, 135.6, 135.4, 135.3, 129.4, 129.3, 127.97, 125.95, 105.9, 105.8, 104.9, 65.03, 65.00, 33.9, 28.6, 27.8, 24.1, 21.9, 13.8, 7.9, 4.4.

FT-IR (thin flim) 3068, 2951, 2875, 1568, 1427, 1218, 1134, 1108, 1021, 943 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{27}H_{33}O_3Si$: 433.2199, found: 433.2181.

$[\alpha]^{23}_D$ = – 3.8 (c = 0.575, $CHCl_3$); – 89% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 0.3 (c = 0.510, $CHCl_3$); + 91% ee from (*R*,*R*)–**5.3**.



(1-(1,3-Dioxolan-2-yl)-5-phenylpentan-3-yl)(methyl)diphenylsilane (Table 5.2, entry 11). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)(methyl)diphenylsilane (198 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 7% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 163 mg (78% yield), – 86% ee; (*R*,*R*)–**5.3**: 170 mg (82% yield), + 84% ee.

HPLC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (15% *i*-PrOH in hexane, 3.5 mL/min) with t_r = 8.7 min (major (*S*,*S*)–**5.3**), 4.4 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.47 (m, 4H), 7.43 – 7.30 (m, 6H), 7.26 – 7.21 (m, 2H), 7.20 – 7.13 (m, 1H), 7.07 – 6.98 (m, 2H), 4.76 (t, J = 4.3 Hz, 1H), 4.00 – 3.87 (m, 2H), 3.86 – 3.75 (m, 2H), 2.64 (ddd, J = 13.4, 10.5, 5.2 Hz, 1H), 2.47 (ddd, J = 13.4, 10.5, 6.3 Hz, 1H), 1.95 – 1.57 (m, 6H), 1.35 (tt, J = 7.2, 4.7 Hz, 1H), 0.61 (s, 3H).

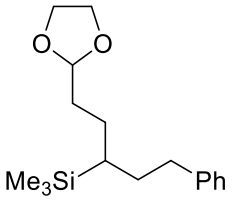
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 137.0, 136.8, 135.02, 134.95, 129.35, 129.32, 128.7, 128.4, 128.03, 128.02, 125.9, 104.9, 65.01, 64.99, 35.7, 33.7, 32.2, 24.2, 23.4, -5.1.

FT-IR (thin flim) 3067, 3023, 2924, 2858, 1602, 1495, 1454, 1427, 1252, 1133, 1110, 1038, 944, 873 cm^{-1}.

HR-MS (ESI+) m/z $[M+H]^+–H_2$ calcd for $C_{27}H_{31}O_2Si$: 415.2093, found: 415.2083;

$[\alpha]^{23}_D$ = – 5.3 (c = 0.530, $CHCl_3$); – 86% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 6.3 (c = 0.675, $CHCl_3$); + 84% ee from (*R*,*R*)–**5.3**.



(1-(1,3-Dioxolan-2-yl)-5-phenylpentan-3-yl)trimethylsilane (Table 5.2, entry 12). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)trimethylsilane (137 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 2% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 114 mg (78% yield), + 86% ee; (*R*,*R*)–**5.3**: 121 mg (83% yield), – 84% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-H column (2% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 2.5 min (major (*S*,*S*)–**5.3**), 2.8 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 4.84 (t, J = 4.7 Hz, 1H), 4.03 – 3.94 (m, 2H), 3.92 – 3.81 (m, 2H), 2.70 (ddd, J = 13.5, 10.9, 5.3 Hz, 1H), 2.56 (ddd, J = 13.5, 10.9, 6.0 Hz, 1H), 1.82 – 1.45 (m, 6H), 0.67 (tt, J = 7.4, 5.1 Hz, 1H), 0.03 (s, 9H).

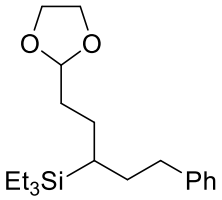
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 128.6, 128.5, 125.9, 105.1, 65.08, 65.06, 35.7, 33.5, 32.0, 25.5, 24.0, -1.9.

FT-IR (thin flim) 3026, 2950, 2859, 1603, 1496, 1454, 1407, 1248, 1135, 1092, 1040, 944, 855, 834 cm^{-1}.

HR-MS (ESI+) m/z $[M+H]^+–H_2$ calcd for $C_{17}H_{27}O_2Si$: 291.1780, found: 291.1782.

$[\alpha]^{23}_D$ = – 6.7 (c = 0.680, $CHCl_3$); + 86% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 7.8 (c = 0.725, $CHCl_3$); – 84% ee from (*R*,*R*)–**5.3**.



(1-(1,3-Dioxolan-2-yl)-5-phenylpentan-3-yl)triethylsilane (Table 5.2, entry 13). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)triethylsilane (157 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 5% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 77 mg (46% yield), + 92% ee; (*R*,*R*)–**5.3**: 92 mg (55% yield), – 89% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (1% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 6.1 min (major (*S*,*S*)–**5.3**), 7.3 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 7.21 – 7.12 (m, 3H), 4.83 (t, J = 4.7 Hz, 1H), 4.07 – 3.92 (m, 2H), 3.91 – 3.79 (m, 2H), 2.71 (ddd, J = 13.4, 11.0, 5.1 Hz, 1H), 2.54 (ddd, J = 13.4, 10.9, 5.9 Hz, 1H), 1.84 – 1.44 (m, 6H), 0.94 (t, J = 7.9 Hz, 9H), 0.80 – 0.76 (m, 1H), 0.58 (q, J = 8.1 Hz, 6H).

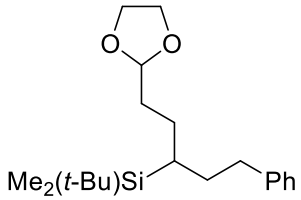
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 128.6, 128.5, 125.9, 105.1, 65.11, 65.08, 36.1, 34.0, 32.3, 24.2, 22.7, 8.0, 3.1.

FT-IR (thin flim) 3026, 2951, 2910, 2874, 1496, 1454, 1413, 1238, 11i37, 1092, 1040, 1016, 944, 872 cm^{-1}.

HR-MS (ESI+) m/z $[M+H]^+–H_2$ calcd for $C_{20}H_{33}O_2Si$: 333.2250, found: 333.2250.

$[\alpha]^{23}_D$ = – 7.0 (c = 0.490, $CHCl_3$); + 92% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 8.1 (c = 0.530, $CHCl_3$); – 89% ee from (*R*,*R*)–**5.3**.



(1-(1,3-Dioxolan-2-yl)-5-phenylpentan-3-yl)(*tert*-butyl)dimethylsilane (Table 5.2, entry 14). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)(*tert*-butyl)dimethylsilane (157 mg, 0.500 mmol) and (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 2% EtOAc in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 46 mg (27% yield), + 84% ee; (*R*,*R*)–**5.3**: 39 mg (23% yield), – 85% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (1% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 3.4 min (major (*S*,*S*)–**5.3**), 3.8 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.22 – 7.15 (m, 3H), 4.84 (t, J = 4.4 Hz, 1H), 4.04 – 3.94 (m, 2H), 3.92 – 3.80 (m, 2H), 2.71 (ddd, J = 13.4, 11.1, 5.0 Hz, 1H), 2.54 (ddd, J = 13.5, 11.0, 5.9 Hz, 1H), 1.89 – 1.47 (m, 6H), 0.89 (s, 9H), 0.87 – 0.81 (m, 1H), -0.01 (s, 6H).

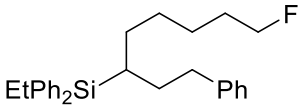
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 128.6, 128.5, 125.9, 105.1, 65.11, 65.08, 35.6, 33.4, 32.4, 27.5, 24.2, 22.4, 17.7, -6.0. Two carbon signals are overlapping (silyl methyls, -6.0 ppm).

FT-IR (thin flim) 3026, 2953, 2928, 2856, 1496, 1471, 1409, 1362, 1250, 1138, 1040, 941, 837, 806 cm^{-1}.

HR-MS (ESI+) m/z $[M+H]^+–H_2$ calcd for $C_{20}H_{33}O_2Si$: 333.2250, found: 333.2235.

$[\alpha]^{23}_D$ = – 5.5 (c = 0.740, $CHCl_3$); + 84% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 5.9 (c = 0.565, $CHCl_3$); – 85% ee from (*R*,*R*)–**5.3**.



Ethyl(8-fluoro-1-phenyloctan-3-yl)diphenylsilane (Table 5.3, entry 1). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)(ethyl)diphenylsilane (205 mg, 0.500 mmol) and (5-fluoropentyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 25% CH_2Cl_2 in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 125 mg (58% yield), – 87% ee; (*R*,*R*)–**5.3**: 118 mg (55% yield), + 87% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (20% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 6.8 min (major (*S*,*S*)–**5.3**), 5.5 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.46 (m, 4H), 7.43 – 7.31 (m, 6H), 7.28 – 7.22 (m, 2H), 7.20 – 7.14 (m, 1H), 7.09 – 7.02 (m, 2H), 4.38 (dt, J = 47.3, 6.2 Hz, 2H), 2.64 (ddd, J = 13.4, 10.6, 5.2 Hz, 1H), 2.50 (ddd, J = 13.4, 10.4, 6.3 Hz, 1H), 1.90 (dddd, J = 13.8, 10.6, 6.3, 4.3 Hz, 1H), 1.71 – 1.56 (m, 4H), 1.47 – 1.22 (m, 6H), 1.12 (q, J = 7.8 Hz, 2H), 0.97 (t, J = 7.7 Hz, 3H).

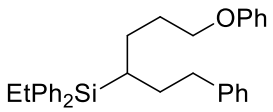
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 135.45, 135.42, 135.40, 134.9, 129.09, 129.07, 128.5, 128.3, 127.74, 127.72, 125.7, 84.2 (d, J = 164.1 Hz), 35.9, 32.2, 30.3 (d, J = 19.4 Hz), 29.8, 29.1, 25.5 (d, J = 5.5 Hz), 22.4, 7.7, 4.3.

FT-IR (thin flim) 3024, 2932, 2857, 1455, 1428, 1108, 1010 cm^{-1}.

HR-MS (ESI+) m/z $[M+Na]^+$ calcd for $C_{28}H_{35}SiFNa$: 441.2390, found: 441.2390.

$[\alpha]^{23}_D$ = + 8.1 (c = 0.695, $CHCl_3$); – 87% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = – 9.2 (c = 0.675, $CHCl_3$); + 87% ee from (*R*,*R*)–**5.3**.



Ethyl(6-phenoxy-1-phenylhexan-3-yl)diphenylsilane (Table 5.3, entry 2). The title compound was synthesized according to the General Procedure from (1-bromo-3-

phenylpropyl)(ethyl)diphenylsilane (205 mg, 0.500 mmol) and (3-phenoxypropyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel: column #1 (0 → 2% EtOAc in hexanes); column #2 (20 → 40% CH_2Cl_2 in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 193 mg (83% yield), + 87% ee; (*R*,*R*)–**5.3**: 182 mg (78% yield), – 89% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OD-H column (30% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 3.0 min (major (*S*,*S*)–**5.3**), 3.8 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.47 (m, 4H), 7.44–7.32 (m, 6H), 7.31–7.22 (m, 4H), 7.17 (tt, J = 7.3, 1.3 Hz, 1H), 7.10–7.03 (m, 2H), 6.94 (tt, J = 7.3, 1.0 Hz, 1H), 6.90–6.83 (m, 2H), 3.94–3.81 (m, 2H), 2.66 (ddd, J = 13.6, 10.6, 5.2 Hz, 1H), 2.52 (ddd, J = 13.6, 10.4, 6.4 Hz, 1H), 2.00–1.49 (m, 6H), 1.41 (tt, J = 7.7, 4.4 Hz, 1H), 1.20–1.10 (m, 2H), 0.97 (t, J = 7.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 142.8, 135.7, 135.6, 135.5, 135.4, 129.6, 129.4, 129.3, 128.7, 128.5, 128.00, 127.98, 125.9, 120.7, 114.7, 67.9, 35.9, 32.3, 29.2, 26.3, 22.3, 7.9, 4.4.

FT-IR (thin flim) 3067, 3024, 2930, 2873, 1600, 1586, 1496, 1469, 1427, 1301, 1244, 1172, 1108, 1080, 1030 cm^{-1}.

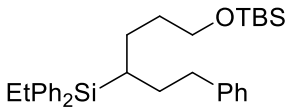
HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{32}H_{35}OSi$: 463.2457, found: 463.2457.

$[\alpha]^{23}_D$ = – 0.6 (c = 0.595, $CHCl_3$); + 87% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = + 0.6 (c = 0.510, $CHCl_3$); – 89% ee from (*R*,*R*)–**5.3**.

Gram-Scale Reaction. An oven-dried 20-mL vial was charged with (1-bromo-3-phenylpropyl)(ethyl)diphenylsilane (1.64 g, 4.00 mmol), then $NiBr_2$•diglyme (123 mg, 0.400 mmol), then (*S*,*S*)–**5.3** (171 mg, 0.520 mmol). Next, an oven-dried stirbar was added and the reaction vial was capped with a pierceable septum-cap and sealed with electrical tape. The reaction vial was placed under high vacuum on a Schlenk line for 10 mins. The Schlenk line was turned to static and the reaction vial was fitted with an Ar-filled balloon. The Schlenk line was then opened to allow argon to purge through the system for 15 mins. Next, the Schlenk line was removed and anhydrous DMA (8.8 mL) was added (reaction is at a higher concentration on the gram-scale, c = 0.45 M). The reaction mixture was then allowed to stir for 15 min, after which it appeared as a cloudy orange solution. Then (3-phenoxypropyl)zinc

bromide (4.80 mmol) solution was added as a gentle stream, turning the reaction mixture a dark red-black/brown color. Vacuum grease was then liberally applied to the top of the septum-cap, the argon balloon was removed, and the vacuum grease was gently pressed onto of the cap to avoid leakage. The reaction was then stirred for 20 hours at room temperature at ca. 800 rpm. The reaction mixture was then purified by flash chromatography with silica gel: column #1 (0 → 2% EtOAc in hexanes); column #2 (20 → 40% CH_2Cl_2 in hexanes). Isolated 1.66 g (89% yield), + 88% ee, of colorless oil.



***Tert*-butyl((4-(ethyldiphenylsilyl)-6-phenylhexyl)oxy)dimethylsilane (Table 5.3, entry 3).** The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)(ethyl)diphenylsilane (205 mg, 0.500 mmol) and (3-((*tert*-butyldimethylsilyl)oxy)propyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 20% CH_2Cl_2 in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 164 mg (65% yield), – 87% ee; (*R*,*R*)–**5.3**: 182 mg (73% yield), + 88% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (10% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 3.4 min (major (*S*,*S*)–**5.3**), 2.3 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.45 (m, 4H), 7.41–7.30 (m, 6H), 7.27–7.21 (m, 2H), 7.20–7.13 (m, 1H), 7.08–7.02 (m, 2H), 3.54 (t, J = 6.0 Hz, 2H), 2.64 (ddd, J = 13.3, 10.8, 5.1 Hz, 1H), 2.49 (13.3, 10.5, 6.4 Hz, 1H), 1.89 (dddd, J = 14.0, 10.7, 6.4, 4.3 Hz, 1H), 1.76–1.56 (m, 3H), 1.53–1.39 (m, 2H), 1.39–1.31 (m, 1H), 1.12 (q, J = 7.8 Hz, 2H), 0.96 (t, J = 7.8 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H).

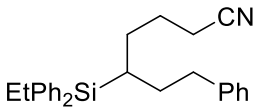
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 135.70, 135.68, 135.64, 135.60, 129.3, 129.2, 128.7, 128.5, 127.94, 127.93, 125.8, 63.6, 36.0, 33.0, 32.4, 26.23, 26.22, 22.5, 18.6, 7.9, 4.5, -5.00, -5.02.

FT-IR (thin flim) 3068, 3025, 2953, 2929, 2856, 1462, 1427, 1386, 1255, 1107, 1008, 953, 836 cm^{-1}.

HR-MS (ESI+) m/z $[M+Na]^+$ calcd for $C_{32}H_{46}OSi_2Na$: 525.2985, found: 525.2969.

$[\alpha]^{23}_D$ = + 7.2 (c = 0.755, $CHCl_3$); – 87% ee from (*S,S*)–**5.3**.

$[\alpha]^{23}_D$ = – 6.4 (c = 0.635, $CHCl_3$); + 88% ee from (*R,R*)–**5.3**.



5-(Ethyldiphenylsilyl)-7-phenylheptanenitrile (Table 5.3, entry 4). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)(ethyl)diphenylsilane (205 mg, 0.500 mmol) and (3-cyanopropyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (3 → 5% EtOAc in hexanes. Colorless oil.

(*S,S*)–**5.3**: 108 mg (54% yield), + 88% ee; (*R,R*)–**5.3**: 93 mg (47% yield), – 86% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (45% MeOH in supercritical CO_2, 3.5 mL/min) with t_r = 7.2 min (major (*S,S*)–**5.3**), 19.7 min (major (*R,R*)–**5.3**).

^{1}H NMR (400 MHz, CDCl3) δ 7.58–7.45 (m, 4H), 7.45–7.31 (m, 6H), 7.29–7.23 (m, 2H), 7.22–7.14 (m, 1H), 7.11–7.02 (m, 2H), 2.63 (ddd, J = 13.7, 10.1, 5.4 Hz, 1H), 2.51 (ddd, J = 13.7, 10.1, 6.6 Hz, 1H), 2.28–2.12 (m, 2H), 1.93 (dddd, J = 14.2, 10.6, 6.6, 4.4 Hz, 1H), 1.80–1.71 (m, 1H), 1.70–1.58 (m, 2H), 1.58–1.47 (m, 2H), 1.38–1.28 (m, 1H), 1.13 (q, J = 7.8 Hz, 2H), 0.97 (t, J = 7.7 Hz, 3H).

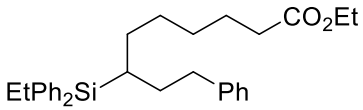
^{13}C NMR (101 MHz, CDCl3) δ 142.4, 135.6, 135.53, 134.95, 134.9, 129.57, 129.55, 128.7, 128.6, 128.14, 128.11, 126.1, 119.9, 35.8, 32.0, 29.5, 25.4, 22.3, 17.6, 7.9, 4.3.

FT-IR (thin flim) 3067, 3024, 2931, 2873, 2244, 1454, 1427, 1108, 1010 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{27}H_{30}NSi$: 396.2148, found: 396.2142.

$[\alpha]^{23}_D$ = + 10.6 (c = 0.485, $CHCl_3$); + 88% ee from (*S,S*)–**5.3**.

$[\alpha]^{23}_D$ = – 10.8 (c = 0.485, $CHCl_3$); – 86% ee from (*R,R*)–**5.3**.



Ethyl 7-(ethyldiphenylsilyl)-9-phenylnonanoate (Table 5.3, entry 5). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)(ethyl)diphenylsilane (205 mg, 0.500 mmol) and (6-ethoxy-6-oxohexyl)zinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel: column #1 (0 → 5% EtOAc in hexanes); column #2 (30 → 60% CH_2Cl_2 in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 142 mg (60% yield), – 88% ee; (*R*,*R*)–**5.3**: 136 mg (58% yield), + 86% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (20% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 13.9 min (major (*S*,*S*)–**5.3**), 9.5 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 4H), 7.41 – 7.30 (m, 6H), 7.27 – 7.22 (m, 2H), 7.20 – 7.13 (m, 1H), 7.08 – 7.03 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.62 (ddd, J = 13.4, 10.6, 5.1 Hz, 1H), 2.48 (ddd, J = 13.5, 10.4, 6.3 Hz, 1H), 2.23 (t, J = 7.6 Hz, 2H), 1.88 (dddd, J = 13.7, 10.5, 6.3, 4.2 Hz, 1H), 1.67 – 1.51 (m, 4H), 1.44 – 1.19 (m, 9H), 1.11 (q, J = 7.4 Hz, 2H), 0.95 (t, J = 7.7 Hz, 3H).

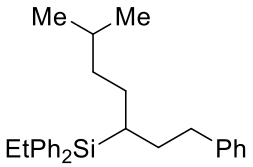
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 142.8, 135.61, 135.54, 135.52, 129.19, 129.16, 128.6, 128.4, 127.84, 127.82, 125.8, 60.3, 36.0, 34.5, 32.3, 29.9, 29.6, 29.3, 25.0, 22.6, 14.4, 7.8, 4.4. Two carbon signals are overlapping (aryl carbons, unidentifiable).

FT-IR (thin flim) 3068, 3024, 2930, 2856, 1735, 1454, 1427, 1373, 1180, 1108, 1030 cm^{-1}.

HR-MS (FAB+) m/z $[M+H]^+–H_2$ calcd for $C_{31}H_{39}O_2Si$: 471.2719, found: 471.2732.

$[\alpha]^{23}_D$ = + 4.5 (c = 0.525, $CHCl_3$); – 88% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = – 4.9 (c = 0.595, $CHCl_3$); + 86% ee from (*R*,*R*)–**5.3**.



Ethyl(6-methyl-1-phenylheptan-3-yl)diphenylsilane (Table 5.3, entry 6). The title compound was synthesized according to the General Procedure from (1-bromo-3-phenylpropyl)(ethyl)diphenylsilane (205 mg, 0.500 mmol) and isopentylzinc bromide (0.600 mmol). The product was purified by flash chromatography with silica gel (0 → 5% CH_2Cl_2 in hexanes). Colorless oil.

(*S*,*S*)–**5.3**: 129 mg (65% yield), + 91% ee; (*R*,*R*)–**5.3**: 132 mg (66% yield), – 91% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ column (15% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 3.5 min (major (*S*,*S*)–**5.3**), 5.1 min (major (*R*,*R*)–**5.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.45 (m, 4H), 7.41–7.30 (m, 6H), 7.27–7.21 (m, 2H), 7.16 (tt, J = 7.3, 1.3 Hz, 1H), 7.09–7.03 (m, 2H), 2.63 (ddd, J = 13.5, 10.7, 5.0 Hz, 1H), 2.48 (ddd, J = 13.5, 10.5, 6.3 Hz, 1H), 1.88 (dddd, J = 14.0, 10.6, 6.4, 4.3 Hz, 1H), 1.71–1.56 (m, 2H), 1.50–1.33 (m, 2H), 1.33–1.20 (m, 2H), 1.19–1.06 (m, 3H), 0.96 (t, J = 7.8 Hz, 3H), 0.81 (t, J = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 135.85, 135.76, 135.7, 135.6, 129.24, 129.22, 128.7, 128.4, 127.90, 127.89, 125.8, 39.1, 36.1, 32.5, 28.6, 27.7, 23.0, 22.9, 22.7, 8.0, 4.5.

FT-IR (thin flim) 3068, 3025, 2953, 2925, 2872, 1496, 1458, 1427, 1108, 1010 cm^{-1}.

HR-MS (ESI+) m/z $[M+H]^+–H_2$ calcd for $C_{28}H_{35}Si$: 399.2508, found: 399.2499.

$[\alpha]^{23}_D$ = + 10.6 (c = 0.600, $CHCl_3$); + 91% ee from (*S*,*S*)–**5.3**.

$[\alpha]^{23}_D$ = – 11.5 (c = 0.600, $CHCl_3$); – 91% ee from (*R*,*R*)–**5.3**.

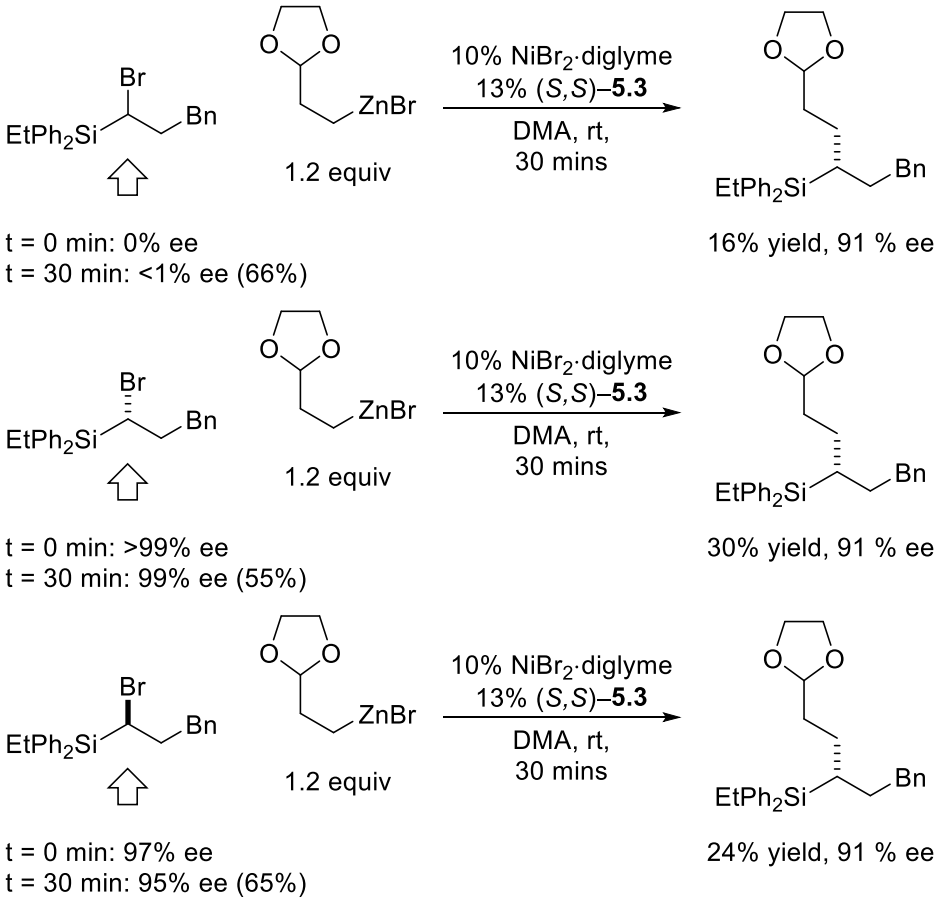
5.4.6. Enantioenriched Electrophile Experiments

Procedure for Enantioenriched Electrophile Experiments. (1-Bromo-3-phenylpropyl)(ethyl)diphenylsilane was separated via preparative-scale SFC on a CHIRALPAK AD-H column (2% *i*-PrOH, 4.0 mL/min) with t_r = 3.9 min, 5.0 min. In a N_2

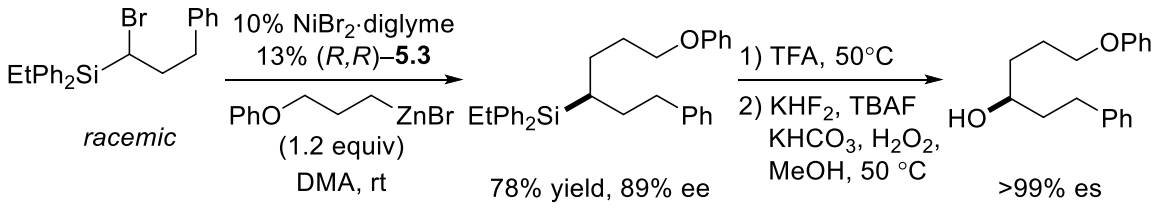
atmosphere glovebox, an oven-dried 4-mL vial was charged with *rac*-, (+)-, or (−)-(1-bromo-3-phenylpropyl)(ethyl)diphenylsilane (29 mg, 0.070 mmol), then $NiBr_2$•diglyme (2.5 mg, 0.0070 mmol), then (*S*,*S*)−**5.3** (3.0 mg, 0.0091 mmol). Next, an oven-dried stirbar was added followed by anhydrous DMA (0.3 mL), and the reaction was stirred for 10 mins. Then, (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide (0.084 mmol) was added, the vial was capped and removed from the glovebox. The vial cap was sealed with electrical tape and allowed to stir at room temperature for 30 mins. After 30 mins, EtOH (0.20 mL) was added and allowed to stir for 10 mins to quench the reaction. Then tetradecane (internal standard for GC analysis, 20 μL), hexanes (0.50 mL), and Et_2O (2.0 mL) were added. The mixture was then passed through a short silica plug into a test tube, flushing with Et_2O. An aliquot of the filtrate was taken for GC analysis. The remaining filtrate was the concentrated and ca. 2 mL of H_2O and ca. 1 mL of 1:1 hexanes/Et_2O mixture were added and the test tube was capped and thoroughly shaken. The organic layer was extracted and placed on a preparative TLC plate to separate starting electrophile and product (eluent 50:1 hexanes/Et_2O, electrophile: $r_f \sim 0.6$; product: $r_f \sim 0.2$).

SFC analysis of remaining electrophile: The ee was determined via SFC on a CHIRALCEL OJ column (3% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 4.6 min, 5.6 min.

SFC analysis of product: The ee was determined via SFC on a CHIRALCEL OJ column 35% *i*-PrOH in supercritical CO_2, 3.5 mL/min) with t_r = 6.8 min (major (*S*,*S*)–**5.3**), 4.4 min (minor (*S*,*S*)–**5.3**).

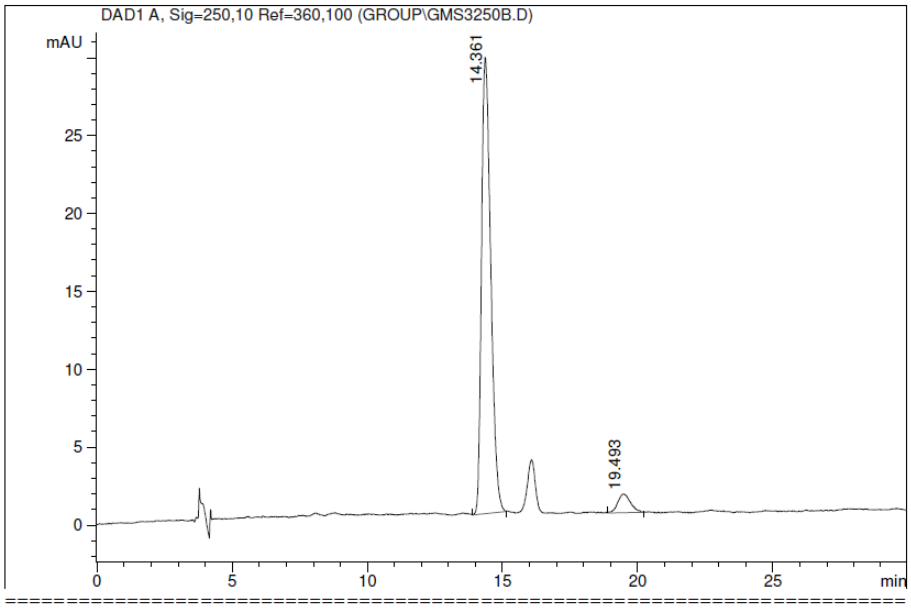


5.4.7. Determination of Absolute Stereochemistry



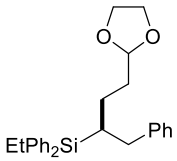
The absolute configuration of (*R*)-ethyl(6-phenoxy-1-phenylhexan-3-yl)diphenylsilane (Table 5.3, entry 2) was determined after an enantiospecific Fleming-Tamao oxidation[32] to yield (*R*)-6-phenoxy-1-phenylhexan-3-ol. The absolute configuration of this molecule has previously been determined by single crystal x-ray diffraction.[33] Comparison of HPLC data determined absolute configuration. HPLC analysis: The ee was

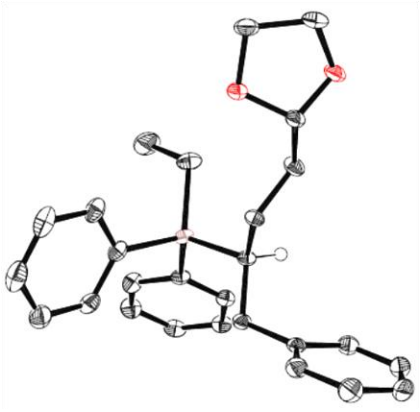
determined via HPLC on a CHIRALPAK AS-H column (3% *i*-PrOH in hexanes, 1.0 mL/min) with t_r = 19.5 min (major (*S*,*S*)–**5.3**), 14.4 min (major (*R*,*R*)–**5.3**).



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	14.361	0.396	696.396	94.715
2	19.493	0.543	38.859	5.285





(*S*)-(4-(1,3-dioxolan-2-yl)-1-phenylbutan-2-yl)(ethyl)diphenylsilane (Table 5.2, entry 2). Single crystals were obtained with (S,S)–**5.3** after slow evaporation from Et_2O. The

crystal was kept at 99.95 K during data collection. Using Olex2[34], the structure was solved with the XT[35] structure solution program using intrinsic phasing and refined with the ShelXL[36] refinement package using least squares minimization.

5.5. Notes and References

1. (a) Choi, J.; Fu, G. C. *Science* **2017**, 356, eaaf7230; (b) Fu, G. C. *ACS Cent. Sci.* **2017**, *3*, 692–700.
2. For related reviews, see: (a) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. *Chem. Rev.* **2017**, *117*, 4528–4561; (b) Iwasaki, T.; Kambe, N. *Top. Curr. Chem.* **2016**, *374*, 1–36; (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587–9652; (d) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
3. For examples of applications to the synthesis of natural products, see: (a) Schmidt, T.; Kirschning, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 1063–1066; *Angew. Chem.* **2012**, *124*, 1087–1091; (b) Yamada, R.; Adachi, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 6067–6070; *Angew. Chem.* **2016**, *128*, 6171–6174.
4. In the case of enantioconvergent arylations of α-trifluoromethyl alkyl halides, it is unclear whether the stereoselectivity is due to the trifluoromethyl group acting as a directing group or as an electron-withdrawing group: Liang, Y.; Fu, G. C. *J. Am. Chem. Soc*. **2015**, *137*, 9523–9526.
5. We consider generic α-halosilanes to be unactivated alkyl electrophiles, as substitution of a carbon with a silicon does not significantly stabilize an adjacent radical. For example, the bond-dissociation energies for the C–H bonds of Me_3**C**CH_2–H (417±5 kJ/mol) and Me_3**Si**CH_2–H (415±5 kJ/mol) are essentially identical: Doncaster, A. M.; Walsh, R. *J. Chem. Soc., Faraday Trans. 1* **1976**, *72*, 2908–2916.
6. The Reisman laboratory has recently described a powerful method for the synthesis of enantioenriched α-aryl allylsilanes through the reductive alkenyl–alkyl cross-coupling of alkenyl halides with activated α-aryl-α-halosilanes (benzylic electrophiles): Hofstra, J. L.; Cherney, A. H.; Ordner, C. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2018**, *140*,

139−142. For a pioneering umpolung variant of this reaction, see: Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962−4963.

7. Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020–1021.
8. Fischer, C.; Zultanski, S. L.; Zhou, H.; Methot, J. L.; Shah, S.; Nuthall, H.; Hughes, B. L.; Smotrov, N.; Hill, A.; Szewczak, A. A.; Moxham, C. M.; Bays, N.; Middleton, R. E.; Munoz, B.; Shearman, M. S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3140–3146.
9. For reviews, see: (a) Ramesh, R.; Reddy, D. S. *J. Med. Chem.* **2018**, *61*, 3779–3798; (b) Fujii, S.; Hasimoto, Y. *Future Med. Chem.* **2017**, *9*, 485–505; (c) Tacke, R.; Dörrich, S. *Top. Med. Chem.* **2014**, *17*, 29–60.
10. For examples of early studies of the catalytic asymmetric synthesis of related chiral silanes (two alkyl substituents on the stereogenic carbon that bears silicon), see: (a) 1,4-addition to α,β-unsaturated carbonyl compounds: Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5579–5581; (b) hydrosilylation of olefins: Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887–9888.
11. For recent examples of (and leading references to) the catalytic asymmetric synthesis of related chiral silanes (two alkyl substituents on the stereogenic carbon that bears silicon), see: (a) hydrosilylation of olefins: Cheng, B.; Liu, W.; Lu, Z. *J. Am. Chem. Soc.* **2018**, *140*, 5014–5017; (b) hydrogenation of vinylsilanes: Wang, A.; Bernasconi, M.; Pfaltz, A. *Adv. Synth. Catal.* **2017**, *359*, 2523–2529.
12. Notes: (a) For entries 12–14 of Table 5.2, we observe enantioselectivities that are comparable to the other examples described in this study, indicating that an aryl substituent on silicon is not essential for enantioselectivity and that the aryl substituent is not likely serving as a directing group. (b) For the electrophile illustrated in entry 12 of Table 5.2, when Si is replaced with C, essentially no cross-coupling is observed under our standard conditions.
13. When PhZnBr in THF is employed as the nucleophile, under otherwise identical conditions, essentially no cross-coupling is observed.
14. Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc*. **2014**, *136*, 16588–16593.

15. Consistent with the hypothesis that an organic radical is an intermediate in these nickel-catalyzed cross-couplings, the model reaction (Table 5.1) does not proceed (<1% yield) in the presence of TEMPO (0.4 equiv).
16. For an example of isomerization of the electrophile in a nickel-catalyzed enantioconvergent cross-coupling of an alkyl halide, see: Mu, X.; Shibata, Y.; Makida, Y.; Fu, G. C. *Angew. Chem. Int. Ed*. **2017**, *56*, 5821–5824; *Angew. Chem.* **2017**, *129*, 5915–5918.
17. For an example of kinetic resolution of the electrophile in a nickel-catalyzed enantioconvergent cross-coupling of a racemic alkyl halide, see: Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc*. **2010**, *132*, 11027–11029.
18. Stoll, S.; Schweiger, A. *J. Magn. Reson.* **2006**, *178*, 42–55.
19. Espelt, L. R.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452**–**2455.
20. Kwak, Y.-W.; Lee, K.-K. *J. Organomet. Chem.* **1997**, *542*, 219–225.
21. Hoover, J. M.; Stahl, S. S. *Org. Synth.* **2013**, *90*, 240–250.
22. Condon, S.; Dupre, D.; Nedelec, J. Y. *Org. Lett*. **2003**, *5*, 4701–4703.
23. Goosen, A.; Marais, C. F.; McCleland, C. W.; Rinaldi, F. C. J. *Chem. Soc., Perkin Trans. 2* **1995**, 1227–1236.
24. Valente, C.; Organ, M. G. *Chem. Eur. J.* **2008**, *14*, 8239–8245.
25. Decostanzi, M.; Van Der Lee, A.; Campagne, J.-M.; Leclerc, E. *Adv. Synth. Catal.* **2015**, *357*, 3091–3097.
26. Winter, P.; Hiller, W.; Christmann, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3396–3400.
27. Scheller, M. E.; Frei, B. *Helv. Chem. Acta.* **1984**, *67*, 1734–1747.
28. Smith, A. B.; Xian, M.; Kim, W.-S.; Kim, D.-S. *J. Am. Chem. Soc.* **2006**, *128*, 12368–12369.
29. Reddy, G. R.; Reddy, J. S.; Das, S.; Roisnel, T.; Yadav, J. S.; Chandrasekhar, S.; Gree, R. *Org. Lett.* **2013**, *15*, 1524–1527.
30. Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609–5617.
31. Goddard, J.-P.; Le Gall, T.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1455–1456.

32. Suginome, M.; Iwanami, T.; Ohmori, Y.; Matsumoto, A.; Ito, Y. *Chem. Eur. J.* **2005**, *11*, 2954−2965.

33. Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. *Science*, **2016**, *354*, 1265−1269.

34. Dolomanov, O.V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339−341.

35. Sheldrick, G.M. *Acta. Cryst.* **2015**, *A71*, 3−8.

36. Sheldrick, G.M. *Acta. Cryst.* **2015**, *C71*, 3−8.