Development of Enantioselective Organocatalytic Technologies for the Alpha-functionalization of Aldehydes and Ketones

Thesis by

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In Partial Fulfillment of the Requirements for the

Degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2008

(Defended April 18, 2008)

To Dad
for all your love, support and encouragement that enabled me to achieve my dreams

and

Tony
pour toute la joie et le bonheur que tu apportes à ma vie qui font passer les jours avec douceur, et qui rend possible la poursuite de tous les désires de mon coeur

Acknowledgements

When I look back at the series of events that led to this day, I can't help but remember a few people who went out of their way, even defied their own superiors to help me succeed, and without whom I would not have reached this day. I am forever indebted to Mr. Ron Kramer, my junior high school history and civics teacher, who spent hours and hours with me after school, teaching me on his own time, to make up for several weeks of absences due to illness. He not only gave freely of his time to ensure I would maintain my good grades, he then fought against the school district so that I would not have to repeat the grade level due to the extent of my absence. His passion and skill for teaching is, without doubt, the best I have ever seen. Throughout the years he has remained an inspiration to me, and I will always remember him with the greatest esteem. I also owe a debt of gratitude to Mr. Steve Sayers and Mr. Jerry Bogard, my high school math teachers, for giving me the benefit of the doubt and cutting me slack when I needed it most. They risked their own jobs by doing so, and I am very grateful for the extraordinary kindness they showed me. I would also like to express much appreciation to Prof. Nancy Levinger, who during my undergraduate years in college and thereafter, has been an advocate for me and whose encouragement led me to pursue loftier goals than I otherwise would have had the courage to pursue. To Mr. Kramer, Mr. Sayers, Mr. Bogard, and Prof. Levinger, your kindness has not been forgotten.

Prior to graduate school, I had the privilege of working under some wonderful advisors who have contributed to the direction and success of my career. I am thankful to my research advisors while at Colorado State University, Prof. Steven Strauss and Prof. Frank Stermitz, who kindled my enthusiasm for chemical research and enabled me to obtain valuable laboratory skills that made much of my future endeavors possible. Had it not been for the silent direction of Dr. James Tata and the strong support and encouragement of Dr. Subha Raghavan, Dr. Kevin Chapman and Dr. Emma Parmee at Merck Research Laboratories, my choice of graduate school advisor and the course of my career may have been very different. I am grateful to all of them for their support.

It's very likely that my interest in science was acquired from my dad, a biologist who probably would have been a chemist had he not wanted to get paid to walk around in lakes and rivers (and fly fish after work). His strong support, guidance, and encouragement made it possible for me to pursue and achieve my dreams. Thanks Dad. The rest of my family initially didn't want me to pursue chemistry, and the toxic chemicals I work with continues to give my mom anxiety, but they have all been supportive nonetheless of my career choice. I need to thank my mom for her love and support and always admonishing me to take care of my health, and believe it or not Mom, I was paying attention. I'm also grateful for all the many effortless conversations my twin sister, Danni, provided when I was too tired to contribute to the conversation, which gave me the company I needed and made these graduate school years easier. Of course, graduate school would not have been nearly as pleasant had I not been able to share half of it with my husband, Tony. I was really concerned that working in the same lab for so many hours each day would be detrimental to our marriage. Dave mused that he would place Tony in Arcadia (when we

were still in Pasadena at Caltech), and promised to always keep us at opposite ends of the lab. Dave kept his promise but decided to add Tony to my project at the time. Yet, because Tony almost never leaves his hood (anyone who has worked next to him will understand what I mean), it honestly feels as though I saw less of him than I did when we were working in two separate buildings at Merck. Tony is one-of-a-kind, and I'm so honored that he chose me for his wife.

During my tenure as a graduate student in the MacMillan lab, I have had the pleasure of working with many brilliant young scientists. I am especially grateful to Dr. Young Chen for his insightful suggestions and scientific discussions that truly impacted my graduate school experience. Similarly, Dr. Hahn Kim and Rob Knowles have often been willing to lend their time to offer prudent advice and scientific knowledge, for which I am very thankful. I owe a debt of gratitude to Dr. Nikki Goodwin and Dr. Young Chen for helping me type NMR data and calculate J-values (certainly the most tedious and dreadful part of writing a paper) so that I could submit one of my papers for publication on schedule. I especially want to thank those who donated their time for proofreading this dissertation: Casey Jones, Diane Carrera, Connie Lee, and Dr. Maud Reiter. Although there are too many to thank individually by name, I would like to express much appreciation to all who gave of their time to assist me with editing and proofreading manuscripts over the past few years. I would like to thank my former bay-mate, Dr. Roxanne Kunz, and all my past and current coworkers for making graduate school an enjoyable experience. I truly hope that the comaraderie of the MacMillan lab will continue for years to come.

I would like to thank my thesis committee members, Profs. Dennis Dougherty, Douglas Rees, and David Tirrell for their willingness to serve on my committee and their invaluable time that was required of them to do so.

Lastly and most importantly, I would like to express deep appreciation to my doctoral research advisor, Professor David MacMillan, for his unparalleled mentorship these past five years. Besides providing an exciting educational work environment, he has showed true concern, extraordinary generosity, and utmost fairness towards me which has made graduate school a pleasant experience and for which I will always be very grateful. He is a superb academic advisor, and I could not be more pleased with my decision to work for him.

Abstract

The development of an expeditious and room-temperature conversion of aliphatic aldehydes to chiral terminal epoxides is described. α-Chloroaldehydes were prepared via asymmetric enamine catalysis with an imidazolidinone catalyst followed by *in situ* reduction and cyclization to generate the terminal epoxide. Epoxides with a variety of aliphatic groups and functionalities were produced in 75 minutes with good yields and excellent selectivities.

The catalytic enantioselective direct α-fluorination of aldehydes and ketones is also reported. α-Fluoroaldehydes were conveniently prepared via enamine catalysis with an imidazolidinone catalyst and *N*-fluorobenzenesulfonimide (NFSI) as an electrophilic fluorine source. The method tolerated a wide variety of aldehyde substrates and functional groups. Catalyst loadings as low as 1 mol% generated the fluorinated products in good yield and excellent enantioselectivity. Additionally, various catalyst architectures were studied to apply the α-fluorination reaction to ketone substrates. Cinchona alkaloid-derived catalysts were found to successfully facilitate the α-fluorination of ketones in high yields and excellent enantioselectivities.

Also presented is the advent of SOMO catalysis, a new mode of organocatalytic activation based on the catalytic generation of radical cations. A secondary amine catalyst reacts with an aldehyde to transiently generate an enamine that, in turn, undergoes a single-electron oxidation to yield a stabilized radical cation that is subject to enantiofacial discrimination. While the parent enamine reacts only with electrophiles, the radical cation combines with SOMO nucleophiles at the same reacting center, thereby enabling a diverse range of previously unknown asymmetric transformations. As a first example and proof of principle, the development of the direct and enantioselective α-allylation of aldehydes using SOMO catalysis is described.

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List of Abbreviations

AcOH	acetic acid
AIBN	2,2’-azo-bis(isobutyronitrile)
BINAP	2,2'-Bis(diphenylphosphino)-1'1-binaphthyl
BOC	*tert*-butyl carbamate
Bn	benzyl
Bz	benzoyl
CA	cinchonine amine
CAN	ceric ammonium nitrate
CDA	cinchonidine amine
dba	dibenzilideneacetone
DBSI	dibenzenesulfonimide
DCA	dichloroacetic acid
DHQA	dihydroquinine amine
DHQDA	dihydroquinidine amine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMS	dimethylsulfide
DNBA	dinitrobenzoic acid
DTBP	di-*tert*-butyl pyridine
ee	enantiomeric excess
EI	electron impact

ES	electrospray
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
F-TEDA	1-Chloromethyl-4-Fluoro-1,4-Diazoniabicyclo [2.2.2]Octane Bis-(Tetrafluoroborate)
GLC	gas liquid chromatography
$HClO_4$	perchloric acid
h	hour
$HClO_4$	perchloric acid
HCN	hydrocyanic acid
HOMO	highest occupied molecular orbital
HMDS	bis(trimethylsilyl)amide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
IPA	isopropyl alcohol
***i*-Pr**	isopropyl
IR	infrared
LUMO	lowest unoccupied molecular orbital
Me	methyl
MeOH	methanol
min	minutes
MsOH	methanesulfonic acid

NaOEt	sodium ethoxide
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
NFSI	N-fluorobenzene sulfonimide
OEt	ethoxy
OMe	methoxy
PMB	*para*-methoxybenzyl
Ph	phenyl
***p*-TSA**	*para*-toluenesulfonic acid
QA	quinine amine
QDA	quinidine amine
SFC	supercritical fluid chromatography
SOMO	singly occupied molecular orbital
TADDOL	*trans*-a,a'-(dimethyl-1,3-dioxolane-4,5
TBAF	tetrabutylammonium fluoride
TCA	trichloroacetic acid
TEA	triethyl amine
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_r	retention time
vol	volume

Chapter 1

Asymmetric Organocatalysis: New Modes of Chemical Activation

Introduction

The chemical substances that make up living organisms are predominantly chiral and often exist as single enantiomers in the body. For example, mammalian proteins are composed exclusively of L-amino acids and carbohydrates of D-sugars. Mammals are unable to metabolize the L-enantiomer of sugars except via intestinal bacteria, which has made the sugars prospects for reduced-calorie substitutes.[1] Intestinal bacteria are incapable of L-glucose metabolism, which results in the sugar's powerful laxative qualities.[2] Enzymes and receptors that control biological pathways are highly substrate specific and often will not recognize stereoisomers of their targets. During the early years of pharmaceutical development, the importance of this biological phenomenon was not appreciated and due to the lack of methods for generating pure stereocenters, pharmaceuticals were produced and tested only in racemic forms. However, racemic drug formulations contain a 50-50 mixture of two similar, yet distinct compounds that often act very differently within the body, the tragic consequences of thalidomide being the most infamous example. Thalidomide was prescribed to pregnant mothers as an anti-emetic for morning sickness between 1957 and 1961 and caused well over 10,000 cases

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[1] Livesey, G.; Brown, J. C. *J. Nutr.* **1995**, *125*, 3020.

[2] Raymer, G. S.; Hartman, D. E.; Rowe, W. A.; Werkman, R. F.; Koch, K. L. *Gastrointest. Endosc.* **2003**, *58*, 30.

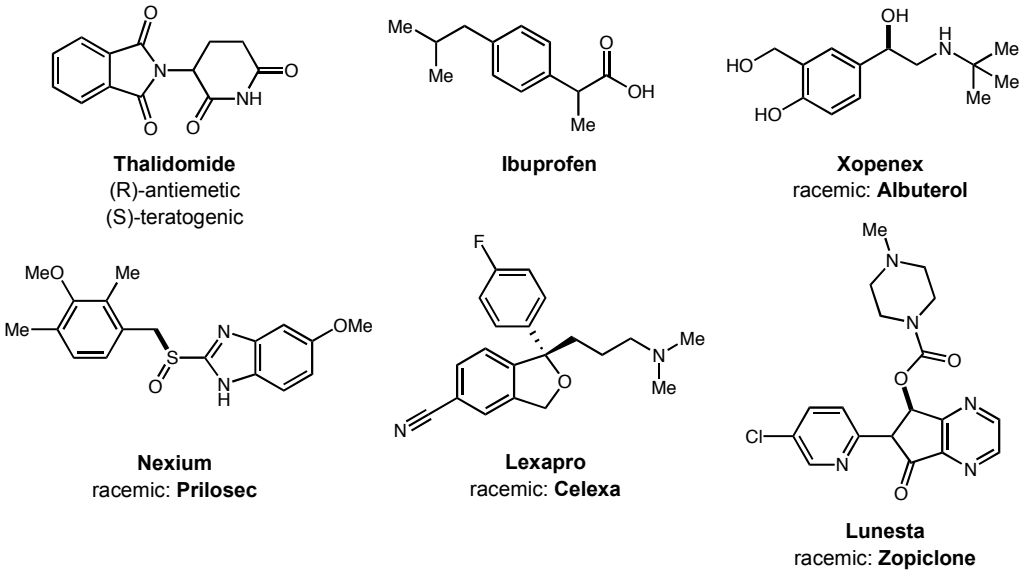

Figure 1. Pharmaceuticals marketed as racemic mixtures. Many were later marketed in the enantiopure form when generics of the racemic drug became available.

of birth defects.[3] It was later discovered that only the (S)-enantiomer of the drug is teratogenic. Since that time, numerous racemic drug formulations have been marketed worldwide. Due to required rigorous safety testing, drugs with toxic enantiomers like thalidomide no longer reach the consumer. However, many racemic formulations have been marketed in which one enantiomer is inactive, in essence doubling the minimum effective dose. History has shown that all pharmaceuticals have some degree of undesirable side effects, a risk that could be significantly reduced by removal of the unwanted enantiomer to provide a generally safer drug. For this reason, the development of new methods for inducing asymmetric transformations has been a focal point of extensive research in the chemical field over the last several decades.

[3] Bren, L. Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History. *FDA Consumer–U.S. Food and Drug Admin.* **2001**, *35*, *No. 2*.

Asymmetric Catalysis

Of the known methods for generating enantiomerically pure stereocenters from achiral starting materials, asymmetric catalysis is the most desirable for both cost and environmental reasons as a single chiral catalyst that is used in very small quantities can induce the production of large quantities of enantio-enriched material. Additionally, catalysts are often reusable, resulting in a significant reduction in the amount of waste produced during the process compared to a stoichiometric reaction. In order for an asymmetric catalyst to successfully induce chirality in the final desired product, the reaction rate of the uncatalyzed process must be significantly slower than the catalyzed reaction. To achieve this, a catalyst must sufficiently activate one or more of the chemical reagents, attaining essentially new reactivity.

Over the years, chemists have invented a plethora of asymmetric catalytic reactions, yet most have been generated using relatively few chemical activation modes, such as metal-insertion, atom transfer, and Lewis acid catalysis.[4] The importance of the discovery of these early activation modes on the field of chemical synthesis was demonstrated by the 2001 Nobel Prize in Chemistry being awarded to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless for their "work on chirally catalyzed hydrogenation reactions" and "chirally catalyzed oxidation reactions."[5]

Until recently, the field of asymmetric catalysis was predominated by chiral transition metal catalysts. These metallic catalysts induce chirality via their enantiopure

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[4] (a) *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999. (b) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994. (c) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

[5] (a) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998. (b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (c) Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.

ligands, which are often expensive and difficult to synthesize. The metals themselves are typically expensive and unstable to air and water in the atmosphere, which requires special handling and storage capabilities. In addition, these catalysts are often difficult to isolate for reuse and their toxicity makes them especially undesirable in pharmaceutical manufacturing processes. Luckily, these catalysts are typically highly efficient, such that only extremely small quantities are required for the synthesis of large amounts of desired material.

An alternative to metal catalysis that went almost completely unexplored until ten years ago is the field of organocatalysis, where the catalyst is itself an organic molecule. Organic molecules have the advantage of being insensitive to air and moisture, which makes handling them easier and the reactions performed with them more reproducible. The first organocatalyzed reaction was reported in 1912 by Bredig and Fiske, who found that cinchona alkaloids significantly accelerated the addition of HCN to benzaldehyde.[6] Since then, isolated examples of organocatalyzed reactions have been reported, but their general applicability to a wide range of organic transformations has only recently been realized. For example, in 1971 Eder, Sauer and Wiechert discovered that the amino acid L-proline is capable of catalyzing asymmetric intramolecular aldol reactions.[7] The reaction was not explored further for nearly thirty years, until Barbas et al. reported the proline-catalyzed intermolecular aldol condensation between ketones and aldehydes.[8] This sparked research efforts towards utilizing the enamine intermediate as an enolate

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[6] Bredig, G.; Fiske, W. S. *Biochem Z.* **1912**, 7.

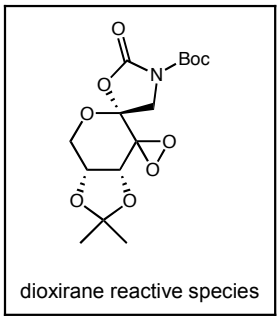
[7] (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem. Int. Ed.* **1971**, *10,* 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

[8] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

surrogate, leading to many new asymmetric transformations, and the process became known as "enamine catalysis."

Organocatalytic Modes of Activation

In the last ten years, the field of organocatalysis has exploded from a few isolated reactions in the literature to a thriving new field of chemical research encompassing a broad range of useful reactions and unprecedented reactivities.[9] In many respects, organic catalysts have been able to accomplish many of the same reactions and emulate many of the modes of reagent activation as metal catalysts. More importantly, organic catalysts have also enabled new chemical reactivities that were historically unattainable with metal catalysts. For example, emulating the atom transfer capabilities of transition metal catalysts (Figure 2), the ketone-catalyzed epoxidation and aziridination reactions developed by Shi (equation 1),[10] Denmark,[11] and Yang[12] were among the first organocatalytic reactions to be widely used in organic synthesis community.



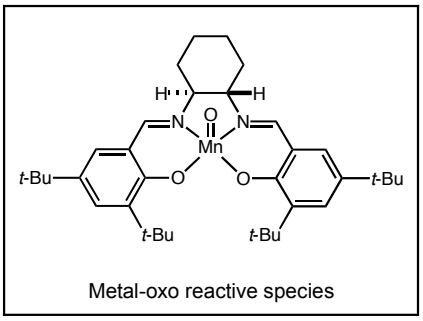


Figure 2. Reactive species of the atom transfer reactions catalyzed by Shi's chiral fructose-derived ketone catalyst and Jacobsen's manganese salen catalyst.

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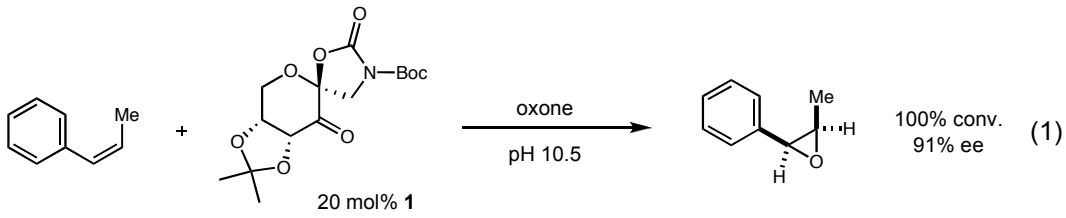
[9] *Asymmetric Organocatalysis*, Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005.

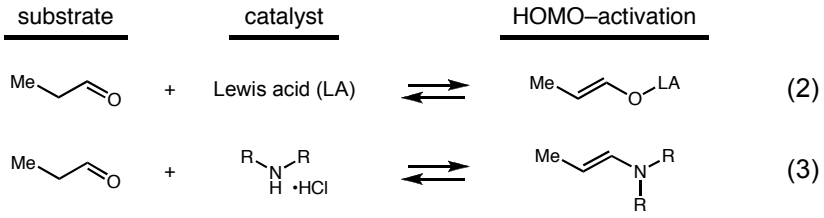
[10] (a) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Tian, H. Q.; She, X. G.; Shu, L.-H.; Yu, H. W.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (c) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794.

[11] Denmark, S. E.; Wu, Z. C. *Synlett* **1999**, 847.

[12] Yang, D.; Wong, M. K.; Wang, X. C.; Tang, Y. C. *J. Am. Chem. Soc.* **1998**, *120*, 6611.



Likewise, the traditional Lewis acid-catalyzed highest occupied molecular orbital (HOMO)-raising activation of carbonyls to form nucleophilic metal enolates is successfully mimicked by the reversible condensation of a secondary amine with a ketone or aldehyde, which tautomerizes to form a nucleophilic enamine (equations 2 and 3). In addition to aldol reactions, this strategy has been successfully employed for many enantioselective transformations including Mannich-type reactions and α-heteroatom functionalization of ketones and aldehydes.[13]



Similar activation is achieved by ammonium enolates,[14] which can be formed via nucleophilic addition of a tertiary amine to ketenes, α,β-unsaturated carbonyls, and α-halogenated carbonyls (Figure 3a-c), or via deprotonation with an ammonium base as in phase-transfer catalyzed reactions (Figure 3d).[15] Addition of N-heterocyclic carbenes to aldehydes generates a nucleophile of umpolung reactivity, enabling nucleophilic additions to the carbonyl carbon and enabling reactions such as the catalytic asymmetric

[13] Mukerjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[14] Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596.

[15] Maruoka, K.; Ooi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

benzoin condensation and Stetter reaction (Figure 3e).[16] All of these HOMO-raising activation modes have now been applied to many different asymmetric transformations with great success.

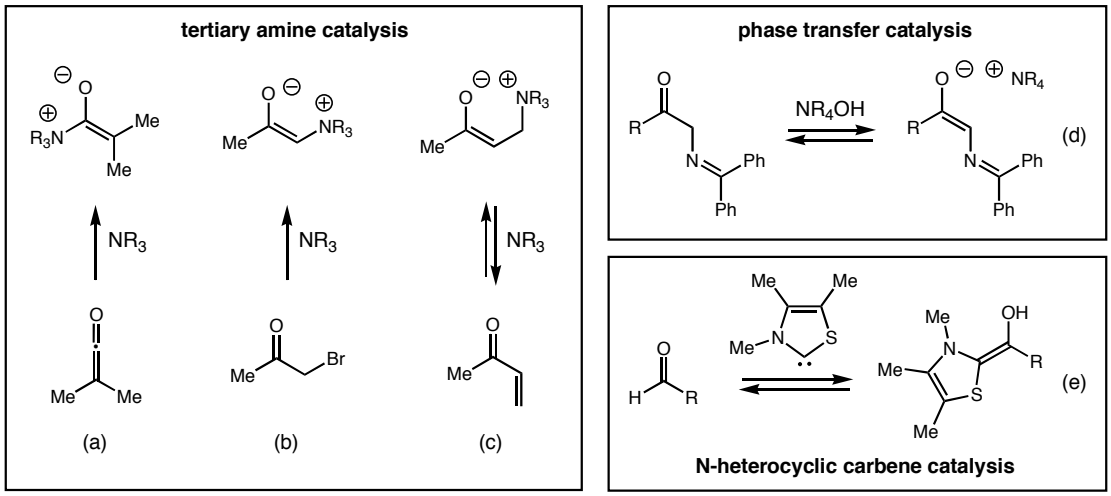
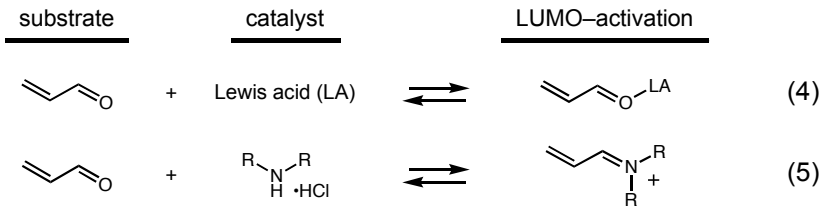


Figure 3. Organocatalytic modes of HOMO-raising activation.

In contrast to the HOMO-raising modes of activation that generate activated nucleophiles, our lab simultaneously envisioned emulating the Lewis acid activation of electrophiles via the reversible condensation of a secondary amine catalyst with α,β-unsaturated aldehydes and ketones to form activated iminium species (equations 4 and 5). This lowest unoccupied molecular orbital (LUMO)-lowering activation mode, termed "iminium catalysis," proved broadly useful for the invention of many new organocatalytic reactions such as cycloadditions, Friedel Crafts alkylations, and



[16] (a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

heteroatom conjugate additions.[17] Various other forms of LUMO-lowering activation of electrophiles have now come to fruition, such as H-Bonding and Brønsted acid catalysis[18] in which coordination of a hydrogen atom enhances a reagent's electrophilicity, and Lewis base catalysis,[19] in which the catalyst binds to a silicon atom, causing it to become a strong Lewis acid (Figure 4).

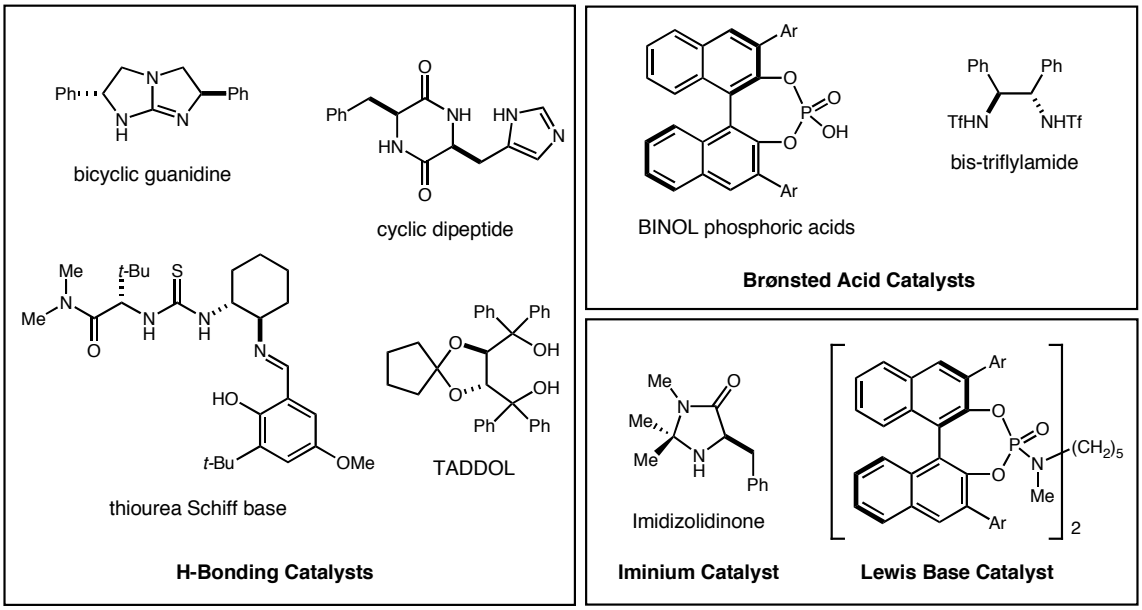


Figure 4. Organocatalysts used in LUMO-lowering activation of electrophiles.

Summary of Thesis Research

The following chapters describe applications of the HOMO-raising activation of enamine catalysis and the subsequent development of a new mode of organocatalytic activation, SOMO-catalysis. Chapter 2 discusses the development of a rapid and enantioselective one-pot conversion of aliphatic aldehydes to terminal epoxides using the

[17] Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

[18] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

[19] Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

organocatalyzed α-chlorination of aldehydes as a chiral synthon intermediate. Chapter 3 details the development of the enantioselective α-fluorination of aldehydes using chiral imidizolidinone catalysts and electrophilic fluorinating agents. Chapter 4 reports advancements towards the asymmetric α-fluorination of ketones by the identification of a suitable catalyst class. Chapter 5 chronicles the invention of SOMO-catalysis, from concept to implementation, as a new mode of organocatalytic activation that enables an entirely new variety of catalytic asymmetric transformations and details the development of the enantioselective SOMO-catalyzed α-allylation of aldehydes as a proof of principle.

Chapter 2

Direct and Enantioselective Conversion of Aliphatic Aldehydes to Terminal Epoxides

Introduction

Epoxides constitute one of the most powerful synthons in synthetic organic chemistry. Their ability to react with a wide range of nucleophiles stereospecifically to generate alcohol stereocenters has made epoxides a common intermediate in both organic synthesis[1] and nature.[2] Over the past few decades, a host of catalytic methodologies have been developed towards the asymmetric construction of epoxides[3] and excellent selectivities have been achieved for a broad range of substrates including allylic alcohols,[4] α,β-unsaturated carbonyls,[5] and styrene derivatives.[6] However, at the time of this work, there were surprisingly few methods for the catalytic enantioselective construction of terminal aliphatic epoxides. For the past ten years, the state of the art for

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1 (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996; pp 293–315. (b) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH; Weinheim, 2003; pp 137–159.

2 Stryer, L. *Biochemistry*; W. H. Freeman and Company; New York, 1995; pp 695.

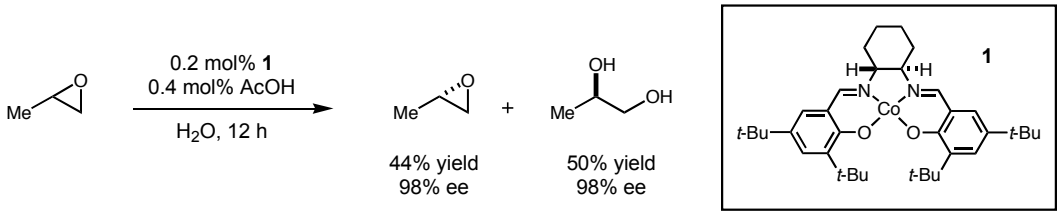
3 Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer; Berlin, 1999; Vol. 2.

4 (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

5 Berkessel, A. in *Asymmetric Synthesis: the Essentials*; Christmann, M.; Braese, S., Eds.; Wiley-VCH; Weinheim, 2007; pp 176–180.

6 See reference 3 and (a) Rose, E.; Ren Q.-Z.; Andrioletti, B. *Chem. Eur. J.* **2004**, *10*, 224. (b) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794. (c) Bulman Page, P. C.; Buckley, B. R.; Blacker, A. J. *Org. Lett.* **2004**, *6*, 1543.

directly obtaining terminal epoxides in an enantioenriched form has been the cobalt(III)-salen catalyzed kinetic resolution developed by Jacobsen (equation 1).[7] With catalyst loadings as low as 0.2 mol%, epoxides can be obtained in exceedingly high enantioselectivities (98-99% ee) and isolated yields up to 46%.



(1)

Alternatively, Shi and coworkers have developed a two-step process for generating terminal epoxides via the ketone-catalyzed asymmetric epoxidation of vinylsilanes, which may be secondarily treated with tetrabutylammonium fluoride (TBAF) to reveal the terminal epoxide (equation 2).[8] Excellent selectivities (up to 92% ee) in good-to-moderate yields were obtained but required catalyst loadings of 65 mol%. Subsequent to this work, Shi reported a single example of a direct enantioselective epoxidation of a terminal aliphatic olefin, vinylcyclohexanone, which was converted to the terminal epoxide in 93% yield and 71% ee (equation 3).[9] However, this was the only aliphatic terminal epoxide the authors reported.[10]

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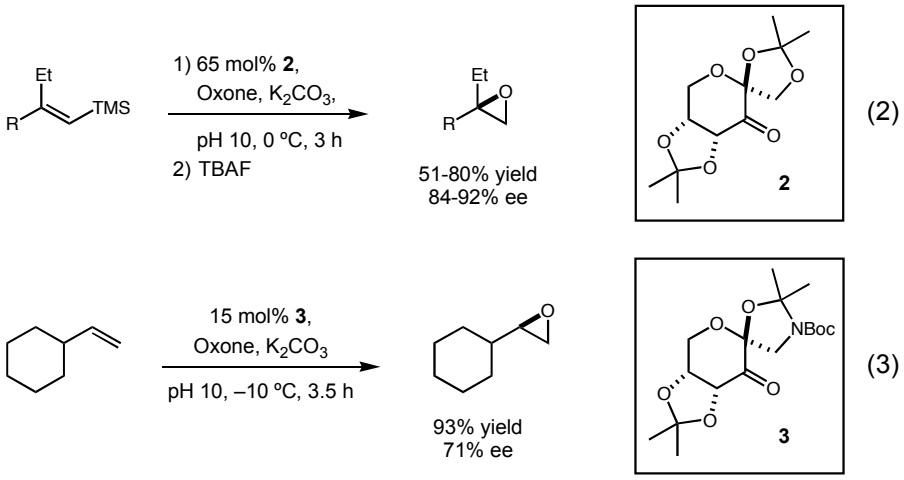
[7] (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. (c) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron Asymmetry* **2003**, *14*, 1407.

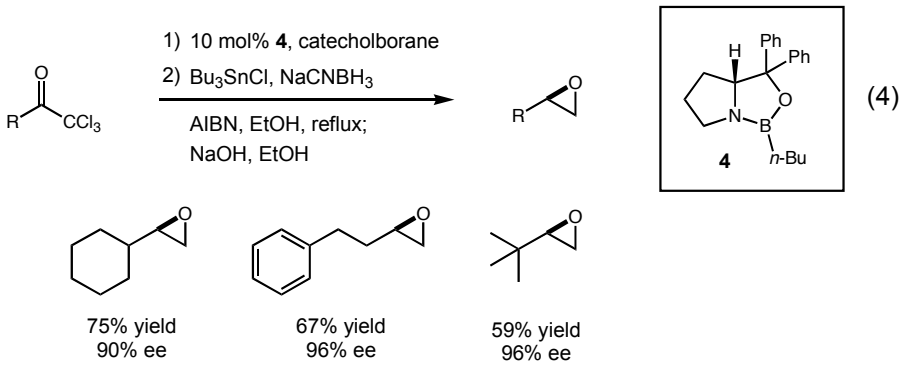
[8] Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675.

[9] (a) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435. (b) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929.

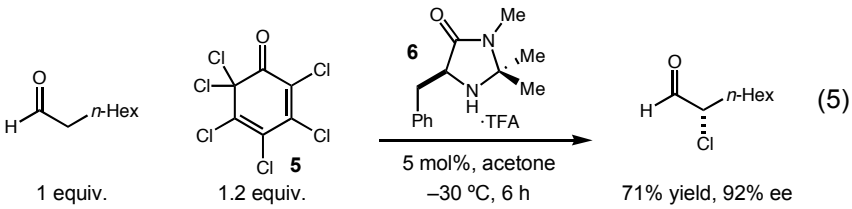
[10] Asymmetric epoxidation of terminal aliphatic olefins catalyzed by transition metals has recently been accomplished: (a) Calladon, M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G. *J. Am. Chem. Soc.* **2006**, *128*, 14006. (b) Sawada, Y.; Matsumoto, K.; Katsuki, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4559.



An alternative strategy for preparing unfunctionalized terminal epoxides is the base-induced cyclization of chiral halohydrins. Corey and Helal developed a two-step process for the asymmetric synthesis of chiral halohydrins with subsequent cyclization to the oxirane under basic conditions (equation 4).[11] The authors employed a catalytic oxazaborilidine reduction of trichloromethyl ketones to generate chiral trichlorohydrins that were subsequently dechlorinated under tin-mediated conditions to the chlorohydrin. After base-induced cyclization, three aliphatic terminal epoxides were prepared using this three-step, two-pot process in good-to-moderate yield (59–75% yield) and excellent stereoselectivity (90–96% ee).



[11] Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1993**, *34*, 5227.



Recently, our lab developed a direct organocatalytic α-chlorination of aldehydes using 5 mol% of imidazolidinone catalyst **6** and hexachlorocyclohexadieneone **5** as the chlorine source (equation 5).[12] Like Corey's trichloromethyl carbinols, we also saw our chiral chloroaldehydes as potential intermediates for the synthesis of important chiral synthons. While most asymmetric processes are capable of synthesizing a single structure class, we envisioned the α-chloroaldehyde to be a modular platform from which a variety of asymmetric motifs could be constructed *in situ* (Figure 1). We felt that the catalytic production of α-chloroaldehydes as intermediates during the synthesis of chiral motifs would be a viable alternative to the development of separate methodologies for each structure class. In this manner, a variety of important chiral synthons could be produced from simple achiral aldehydes in a single transformation simply by changing the reaction conditions of the second step.

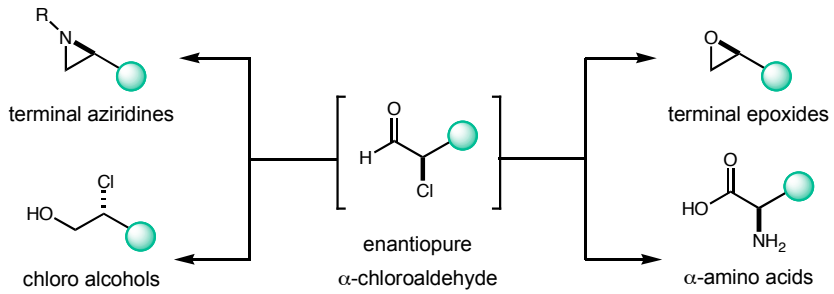


Figure 1. The α-chloroaldehyde as a platform for chiral structural diversity.

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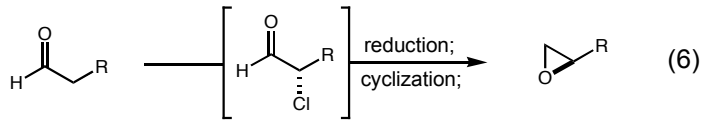
[12] (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (b) Simultaneously developed by: Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.

Initial Strategy

Initially, our efforts towards the asymmetric conversion of simple achiral aldehydes into valuable chiral structural classes began with the synthesis of terminal aliphatic epoxides. We envisioned that terminal epoxides might be accessed by a rapid three-step single transformation comprising a simple aldehyde reduction followed by base-induced cyclization, and that these chemical steps could be performed *in situ* without epimerization of the α-chloroaldehyde intermediate (equation 6) or the need for laborious chemical isolations and purifications.



Initially, we pursued a procedure using our published reaction conditions for the α-chlorination using catalyst **6** at sub-ambient temperatures. However, the optimal reaction medium for the α-chlorination is acetone, which itself can react with sodium borohydride ($NaBH_4$) and other reducing agents used to convert the α-chloroaldehyde to the corresponding chlorohydrin. As shown in Table 1,[13] acetone and chloroform ($CHCl_3$) are both optimal solvents for the α-chlorination reaction (entries 5–6) but both are unsuitable solvents for subsequent hydride reduction and basic conditions required for oxirane formation. Dichloromethane (CH_2Cl_2) provides slightly lower conversion and enantioselectivity than acetone and $CHCl_3$ (entry 4); however, its compatibility with the conditions for subsequent epoxide formation led us to select it as the reaction medium.

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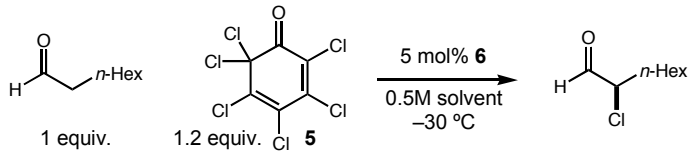
[13] Reproduced from: *Iminium and Enamine Activation: Methods for Enantioselective Organocatalysis.* Brown, S. P., Ph.D. Thesis: California Institute of Technology, Pasadena, CA, 2005.

Table 1. Survey of Solvents with Catalyst **6**[13]

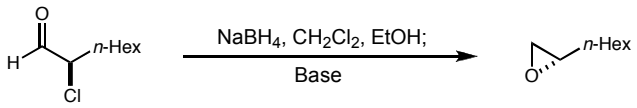


entry	solvent	time (h)	% conversion[a]	% ee[b]
1	EtOAc	12	93	87
2	THF	18	56	89
3	toluene	18	83	89
4	CH_2Cl_2	8	86	90
5	$CHCl_3$	8	91	92
6	acetone	7	93	92

(a) Conversion determined by GLC analysis relative to an internal standard (benzyl methyl ether). (b) Enantiomeric excess determined by GLC analysis (Bodman G-TA).

Next, a sampling of bases for affecting the epoxidation from the halohydrin was studied to determine conditions that could be successfully applied *in situ* after a $NaBH_4$ reduction (Table 2). A 50% solution of potassium hydroxide (KOH) was found to give the highest levels of conversion (entry 1) and a time study of the reduction and cyclization steps found that they were each completed in 30 min at ambient temperature. Longer cyclization reaction times resulted in reduced conversions due to unwanted epoxide opening and diol formation. While adequate levels of conversion to the desired terminal

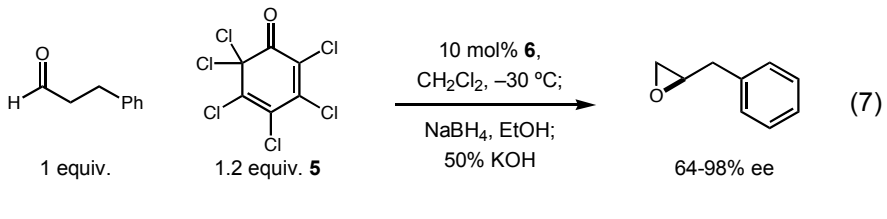
Table 2. Comparison of Bases for Oxirane Formation



entry	base	% conversion[a]
1	50% aq. KOH	89
2	50% aq. NaOH	81
3	25% NaOMe in MeOH	59
4	21% NaOEt in EtOH	71

(a) Conversion determined by GLC analysis with tridecane as an internal standard.

epoxide from the chloroaldehyde intermediate could now be achieved, the α-chlorinations were necessarily conducted at or below –30 ºC to obtain adequate levels of enantioselectivity; at warmer temperatures catalyst **6** readily epimerizes the α-chloro stereocenter, and complete racemization occurs in only a few hours.[13] However, the necessary warming of the reactions during the reduction of the chloroaldehyde to the chlorohydrin resulted in a decrease in enantioselectivity. To maintain high levels of selectivity during the reduction step, it was necessary to use pre-cooled ethanol (EtOH) and the reactions were slowly warmed to 0 ºC over a period of an hour to maintain the desired enantiopurities of the final epoxides. After base-induced oxirane formation, aqueous workup and purification, terminal epoxides were isolated in good yields and high selectivities. While enantioselectivities for the octanal-derived oxirane were consistently high at 90% ee, expansion of the substrate scope to include a variety of functionalized oxiranes led to difficulties with reproducibility and often inconsistent results (equations 7 and 8).



Improved Strategy

During the course of this work, graduate student Sean Brown began work on developing a new imidazolidinone catalyst that would be capable of maintaining high levels of enantioselectivity while being less apt to epimerize products after their formation. It was proposed that increasing the steric bulk of the catalyst would decrease the nucleophilicity of the amine, thereby reducing the propensity to reform enamine with the α-chloroaldehyde product. Catalyst **7** was developed as a pseudo C_2-symmetric catalyst in which the nitrogen lone pair is less accessible due to the bulky *tert*-butyl group (Figure 2).

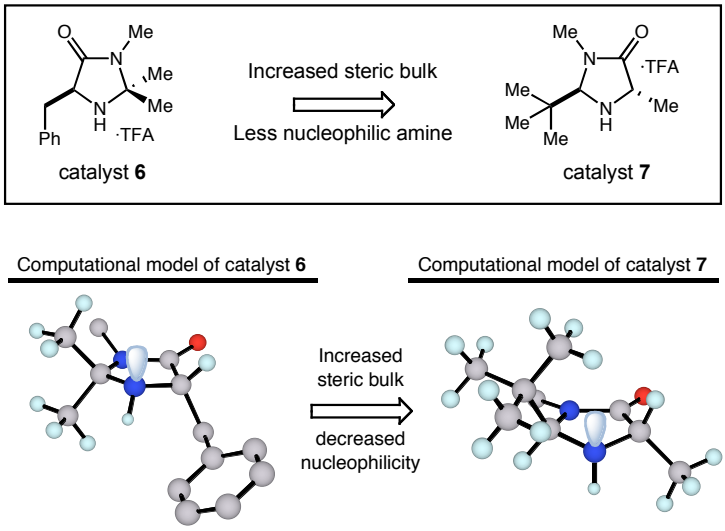


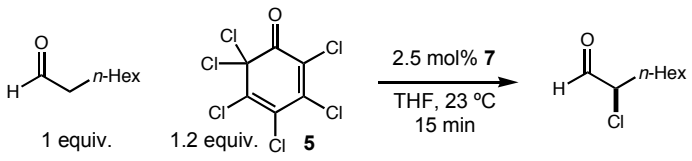
Figure 2. 3D models showing increased coverage of the nitrogen lone pair in catalyst **7** compared to catalyst **6**.

Notably, catalyst **7** was found to successfully affect the α-chlorination of aldehydes with excellent enantioselectivities, at ambient temperature.[13] In addition, the α-chloro stereocenter was stable for at least 2 hours at room temperature in the presence of catalyst **7**, as opposed to the rapid epimerization observed with catalyst **6**. Additionally, optimal solvents for the α-chlorination reaction with catalyst **6** were acetone and $CHCl_3$; however,

neither solvent is compatible with the single transformation procedure for terminal epoxides and a less optimal solvent providing lower enantioselectivities was chosen for the three-step process. In contrast, reactions using catalyst **7** were found to work exceedingly well in tetrahydrofuran (THF), diethyl ether (Et_2O), and ethyl acetate (EtOAc).[13]

In order to reduce the overall time needed for the three-step construction of terminal epoxides, the effect of concentration on the α-chlorination was evaluated and showed that complete conversion to the α-chloroaldehyde was obtained in 15 minutes using only 2.5 mol% of catalyst **7** without affecting the enantioselectivity of the reaction (Table 3). Notably, the use of catalyst **7** in THF achieved 96% ee for octanal, as opposed to 89% ee with catalyst **6** in THF and 90% ee in CH_2Cl_2. Also, since the reaction was now performed at ambient temperature, the reduction step could now be conducted in only 30 minutes as the slow warming process was no longer necessary to prevent epimerization. Using these new conditions, reaction times were reduced to a 15 minute α-chlorination, 30 minute $NaBH_4$, reduction and 30 minute cyclization for a total overall reaction time of 75 minutes.

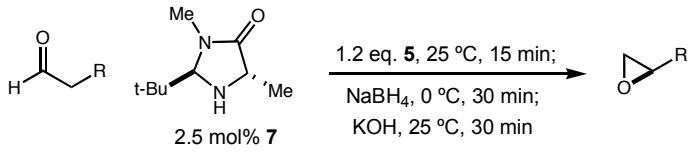
Table 3. Effect of Concentration using Catalyst **7**

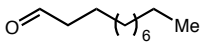
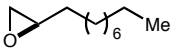
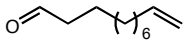
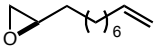
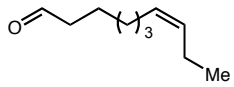
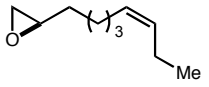
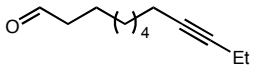
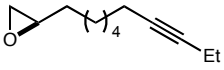
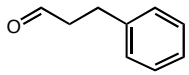
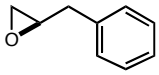
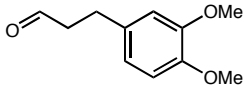
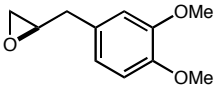
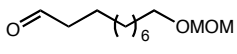
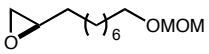
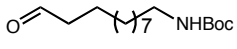
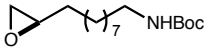
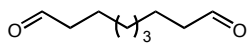
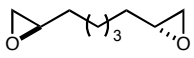
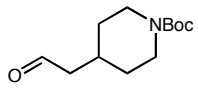
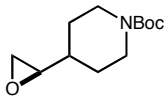
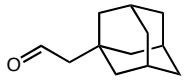
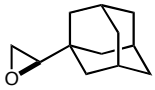


entry	concentration	% conversion[a]	% ee[b]
1	0.5 M	82	96
2	0.75 M	89	96
3	1 M	93	96
4	1.5 M	96	96
5	2 M	97	96
6	2.5 M	97	96

(a) Conversion determined by GLC analysis relative to an internal standard (benzyl methyl ether). (b) Enantiomeric excess determined by GLC analysis (Bodman Γ-TA).

Table 4. Enantioenriched Terminal Epoxides: Substrate Scope



entry	reactant	product	% yield	% ee
1			83	94
2			82	92
3			78	94
4			76	95
5			77	93
6			96[a]	94
7			75	93
8			83	95
9			81	>99[b]
10			86[a]	96
11			50[c]	89

(a) Total reaction time of 90 min. (b) 10:1 dr. (c) α-Chlorination using 20 mol% catalyst **6**, –40 ºC for 12 hr.

Finally, reactions were performed using a variety of structurally diverse aldehydes to determine the generality of this new protocol. As shown in Table 4, the reaction was found to be general for a broad range of functionalities including protected amines (entries 8 and 10), labile ethers (entry 7), and alkynes (entry 4). Sterically hindered substrates were also provided in excellent selectivities (entries 10 and 11), although the adamantyl substrate was a poor substrate for catalyst **7** and the initial protocol using catalyst **6** was used to provide the desired adamantyl epoxide. A bis-terminal epoxide was successfully synthesized using this new method in high yield and excellent selectivity (entry 9) and aromatic substrates were also obtained, with no evidence of electrophilic aromatic substitution on even highly electron-rich benzene rings (entries 5–6). Notably, while the generation of olefinic epoxides using typical olefin epoxidation methods is difficult to achieve due to regioselectivity requirements, such substrates are easily prepared using this new technology, which showed no evidence of olefin isomerization under the reaction conditions (entries 2 and 3).

Conclusion

In summary, the rapid enantioselective synthesis of chiral terminal epoxides from simple achiral aldehydes in a single transformation has been accomplished, providing the first example of the α-chloroaldehyde intermediate as a valuable chiral synthon. The use of a *trans*-imidazolidinone catalyst enabled the asymmetric chlorination of aldehydes at ambient temperatures in only fifteen minutes without product epimerization and allowed the development of a rapid, 75-minute one-pot protocol for constructing terminal aliphatic

epoxides. Using this new protocol, terminal epoxides containing a wide variety of functionalities including olefins, alkynes, and aromatic rings were easily prepared in good yields and excellent enantioselectivities.[14]

[14] Recently and subsequent to the completion of this work, a three-step synthesis of *trans*-epoxides was reported employing chlorohydrins as intermediates: Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083.

Supporting Information

General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego.[15] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on EMD Silica Gel 60 230-400 mesh or Iatrobeads 6RS–8060 according to the method of Still.[16] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching, ceric ammonium molybdate, or anisaldehyde stain. High performance liquid chromatography (HPLC) and gas liquid chromatography (GLC) assays to determine enantiometric excess were developed using racemic samples.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard 6850 Series gas chromatograph equipped

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[15] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd edition; Pergamon Press; Oxford, 1988.

[16] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex Γ-TA (30 m 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 Series chromatograph using a Chiralcel®OD-H, Chiralcel®OJ or Chiralpak®AD column (25 cm, 5 cm guard), as noted.

Starting Materials

10-(Methoxymethoxy)decanol: To a flask containing 1,10-decanediol (5.00 g, 28.7 mmol) and diisopropylethylamine (6.00 mL, 17.2 mmol) in CH_2Cl_2 (30 mL) was slowly added chloromethyl methyl ether (1.09 ml, 14.3 mmol) at 0 °C. The solution was warmed to room temperature and stirred for 12 h. The reaction was then treated with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3 × 100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (20–40% EtOAc/hexanes) to provide 10-(methoxymethoxy)decan-1-ol. IR (film) 3435, 2929, 2855, 2360, 1466, 1385, 1214, 1148, 1112, 1045, 920.5, 722.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (s, 2H, C**H**$_2$OMe), 3.62 (t, 2H, J = 6.7 Hz, C**H**$_2$OH), 3.50 (t, 2H, J = 6.7 Hz, CH_2C**H**$_2$O), 3.35 (s, 3H, C**H**$_3$), 1.65–1.21 (m, 16H, (C**H**$_2$)$_8$$CH_2$OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.35, 67.85, 55.05, 32.76, 29.70, 29.49, 29.47, 29.37, 26.16, 25.69; HRMS (FAB+) exact mass calculated for ($C_{12}H_{25}O_3$) $[(M+H)-H_2]^+$ requires m/z 217.1804, found m/z 217.1796.

10-(Methoxymethoxy)decanal: To a flask containing 10-(methoxymethoxy)decan-1-ol (1.46 g, 6.70 mmol) in CH_2Cl_2 (7.0 mL) was added TEMPO (105 mg, 0.670 mmol) followed by iodobenzene diacetate (2.36 g, 7.30 mmol). The reaction was stirred for 1 h and then diluted with CH_2Cl_2 (50 mL). Saturated aqueous solution of $Na_2S_2O_3$ (50 mL) was added and extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (75 mL) and brine (75 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (15% EtOAc/hexanes) to provide the title compound. IR (film) 2929, 2856, 2718, 2360, 1726, 1466, 1389, 1214, 1147, 1111, 1044, 919.3, 723.1, 668.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, 1H, J = 1.9 Hz, C**H**O), 4.62 (s, 2H, C**H**$_2$OMe), 3.51 (t, 2H, J = 6.6 Hz, CH_2C**H**$_2$O), 3.36 (s, 3H, C**H**$_3$), 2.42 (dt, 2H, J = 1.9, 7.2 Hz C**H**$_2$CHO), 1.68–1.54 (m, 4H, C**H**$_2CH_2$CHO, C**H**$_2CH_2$O), 1.40–1.24 (m, 10H, (C**H**$_2$)$_5CH_2CH_2$O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 96.34, 67.79, 55.02, 43.84, 29.67, 29.29, 29.23, 29.08, 26.13, 22.01; HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{24}O_3$) requires m/z 216.1726, found m/z 216.1716.

Dodec-9-ynal: To a flask containing dodec-9-yn-1-ol (4.56 g, 25.0 mmol) in CH_2Cl_2 (25 mL) was added TEMPO (390 mg, 2.50 mmol) followed by iodobenzene diacetate (8.86 g, 27.5 mmol). The reaction was stirred 1 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5% Et_2O/pentanes) to

provide the title compound. IR (CH_2Cl_2) 3052, 2978, 2937, 2859, 1710, 1435, 1266, 896.4, 747.2, 735.7, 705.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, 1H, *J* = 1.9 Hz, C**H**O), 2.42 (dt, 2H, *J* = 1.9, 7.2 Hz, C$\mathbf{H_2}$CHO), 2.20–2.09 (m, 4H, $CH_2C\mathbf{H_2}CC$, $C\mathbf{H_2}CH_3$), 1.68–1.26 (m, 10H, $(C\mathbf{H_2})_\mathbf{5}CH_2CHO$), 1.11 (t, 3H, *J* = 7.1 Hz, C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 81.64, 79.33, 43.82, 28.99, 28.96, 28.81, 28.53, 21.97, 18.63, 14.32, 12.35; HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{20}O$) requires *m/z* 180.1514, found *m/z* 180.1507.

***tert*-Butyl 10-Formyldecylcarbamate:** To a flask containing 11-*tert*-butoxycarbonylamino-undecanoic acid (3.60 g, 12.0 mmol) in CH_2Cl_2 (120 mL) was added N,O-dimethylhydroxylamine hydrochloride (1.30 g, 13.2 mmol) followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.30 g, 12.0 mmol), 4-dimethylaminopyridine (59.0 mg, 0.480 mmol), and diisopropylethylamine (2.30 mL, 13.2 mmol). The reaction was stirred 12 h and then diluted with CH_2Cl_2 (300 mL). The reaction was washed with water (2 × 100 mL), saturated aqueous citric acid solution (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to obtain an oily residue. THF (60 mL) was added and the solution cooled to 0 °C. $LiAlH_4$ (1.03 g, 27.1 mmol) was added in portions and stirred 2 h. 20% aqueous citric acid solution was added slowly (300 mL) and stirred vigorously for 30 min. The reaction was diluted with 20% aqueous citric acid solution (200 mL) and extracted with Et_2O (3 × 150 mL). The combined organics were washed with saturated $NaHCO_3$ solution (150 mL), brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo* to obtain the title compound. IR (film) 3374, 2978, 2918, 2850, 2361, 1720, 1681, 1517, 1463, 1390, 1366, 1250, 1172,

1042, 864.5, 783.1, 725.0, 666.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, 1H, *J* = 1.9 Hz, C**H**O), 4.54 (s, 1H, N**H**), 3.13 (q, 2H, *J* = 6.7 Hz, C$\mathbf{H_2}$NH), 2.45 (dt, 2H, *J* = 1.9, 7.4 Hz, C$\mathbf{H_2}$CHO), 1.76–1.22 (m, 25H, (C$\mathbf{H_2}$)$_8$CH$_2$CHO, C(C$\mathbf{H_3}$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 155.9, 78.91, 43.83, 40.56, 30.01, 29.38, 29.24, 29.18, 29.07, 28.37, 26.71, 22.00; HRMS (CI+) exact mass calculated for $[M+\bullet]^+$ ($C_{16}H_{31}NO_3$) requires *m/z* 285.2304, found *m/z* 285.2312.

Nonanedial: To a flask containing nonane-1,9-diol (2.40 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added TEMPO (351 mg, 2.25 mmol) followed by iodobenzene diacetate (10.15 g, 31.5 mmol). The reaction was stirred for 2 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (20–40% Et_2O/pentanes) to provide the title compound, which was identical to the known literature compound.[17]

***tert*-Butyl 4-(formylmethyl)piperidine-1-carboxylate:** To a flask containing *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (4.40 g, 19.2 mmol) in CH_2Cl_2 (20 mL) was added TEMPO (300 mg, 1.92 mmol) followed by iodobenzene diacetate (6.80 g, 21.1 mmol). The reaction was stirred 3 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3

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[17] Roels, J.; Metz, P. *Syn. Lett.* **2001**, *6*, 789.

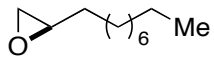
× 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (40–70% Et_2O/pentanes) to provide the title compound, which was identical to the reported literature compound.[18] ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 154.7, 79.37, 50.31, 43.68, 31.86, 30.63, 28.39.

Terminal Epoxides

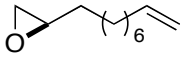
General Procedure for Epoxide Formation: To a 10 mL round-bottom flask equipped with a magnetic stir bar and charged with (2*R*,5*S*)-2-*tert*-butyl-5-methyl-3-methylimidazolidin-4-one **7** (8.6 mg, 0.05 mmol) and THF (0.8 mL) was added TFA (5.8 mg, 0.05 mmol) followed by 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one **5** (722 mg, 2.4 mmol). The aldehyde substrate (2.0 mmol) was added and the reaction mixture stirred 15 min. The reaction was cooled to 0 °C and diluted with 0.4 mL THF and 0.8 mL EtOH. $NaBH_4$ (189 mg, 5.0 mmol) was added and after 5 min the resulting suspension warmed to 25 °C and stirred an additional 25 min. 50% aqueous KOH solution (5 mL) was added and stirred vigorously for 30 min, drawing the organic phase completely into the aqueous phase. The cloudy suspension was allowed to separate and 10 mL of H_2O was added. The solution was extracted 3 times with Et_2O (10 mL) and the combined organics dried over Na_2SO_4. Filtration was followed by concentration *in vacuo* to afford a yellow oil that was then purified by forced flow chromatography to afford the

[18] Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Heterocycles* **2001**, *54*, 747.

title compounds. The enantioselectivity was determined either by chiral GLC analysis, or chiral HPLC analysis after epoxide opening with naphthalene-2-thiol.

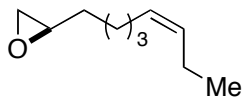


(*R*)-2-Nonyloxirane (Table 4, entry 1): Prepared according to the general procedure from undecanal (206 μL, 1.0 mmol) to afford a yellow oil. Purification on silica gel (5% Et_2O/pentanes) afforded (*R*)-2-nonyloxirane as a colorless liquid (142 mg, 83% yield, 94% ee). IR (film) 3043, 2956, 2926, 2855, 1466, 1410, 1378, 1259, 1129, 916.4, 836.9, 722.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.93–2.87 (m, 1H, OC**H**CH_2), δ 2.74 (dd, 1H, *J* = 4.1, 5.1 Hz, OCHC**H**$_2$), δ 2.46 (dd, 1H, *J* = 2.8, 5.0 Hz, OCHC**H**$_2$), δ 1.57–1.20 (m, 16H, (C**H**$_2$)$_8$$CH_3$), δ 0.88 (t, *J* = 7.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.40, 47.12, 32.49, 31.87, 29.55, 29.50, 29.44, 29.29, 25.96, 22.66, 14.09; HRMS (CI+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{23}O$) requires *m/z* 171.1749, found *m/z* 171.1746. $[\alpha]_D$ = +5.88 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 1-naphthyl-2-hydroxyundecane derivative (Chiralcel®OD-H Isocratic 5% IPA/hexanes). t_R(minor) = 11.9 min. t_R(major) = 14.2 min.



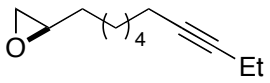
(*R*)-2-(Non-8-enyl)oxirane (Table 4, entry 2): Prepared according to the general procedure from undec-10-enal (416 μL, 2.00 mmol) to afford a yellow oil. Purification on silica gel (5% Et_2O/pentanes) afforded (*R*)-2-(non-8-enyl)oxirane as a colorless liquid

(277 mg, 82% yield, 92% ee). IR (film) 3584, 3077, 3044, 2977, 2928, 2856, 1641, 1465, 1411, 1259, 994.3, 909.8, 836.4, 665.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, 1H, *J* = 6.7, 10.1, 17.3 Hz, $CH_2C\mathbf{H}=CH_2$), δ 5.03–4.96 (m, 1H, $CH=C\mathbf{H}_2$), δ 4.96–4.91 (m, 1H, $CH=C\mathbf{H}_2$), δ 2.93–2.87 (m, 1H, $OC\mathbf{H}CH_2$), δ 2.74 (dd, 1H, *J* = 2.9, 5.1 Hz, $OCHC\mathbf{H}_2$), δ 2.46 (dd, 1H, *J* = 2.9, 5.1 Hz, $OCHC\mathbf{H}_2$), δ 2.07–2.00 (m, 2H, $C\mathbf{H_2}CH=CH_2$), δ 1.56–1.31 (m, 12H, $OCH(C\mathbf{H_2})_6$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 114.1, 52.33, 47.06, 33.74, 32.45, 29.35, 28.97, 28.84, 25.92; HRMS (CI+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}O$) requires *m/z* 169.1592, found *m/z* 169.1596. $[\alpha]_D$ = +7.12 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 1-naphthyl-2-hydroxyundec-10-ene derivative (Chiralcel®OD-H Isocratic 5% IPA/hexanes). t_R(minor) = 14.1 min. t_R(major) = 17.5 min.

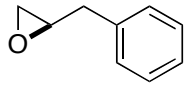


(*R*)-2-((*Z*)-Oct-5-enyl)oxirane (Table 4, entry 3): Prepared according to the general procedure from (*Z*)-dec-7-enal (366 μL, 2.00 mmol) to afford a yellow oil. Purification on silica gel (5% Et_2O/pentanes) afforded (*R*)-2-((*Z*)-oct-5-enyl)oxirane as a colorless liquid (240 mg, 78% yield, 94% ee). IR (film) 3369, 2932, 2861, 2360, 1461, 1413, 1373, 1260, 1137, 1066, 968.3, 915.0, 833.4, 668.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42–5.27 (m, 2H, $C\mathbf{H}=C\mathbf{H}Et$), δ 2.93–2.87 (m, 1H, $OC\mathbf{H}CH_2$), δ 2.75 (dd, 1H, *J* = 4.0, 5.1 Hz, $OCHC\mathbf{H}_2$), δ 2.46 (dd, 1H, *J* = 2.9, 5.1 Hz, $OCHC\mathbf{H}_2$), δ 2.08–1.99 (m, 4H, $C\mathbf{H_2}CH=CHC\mathbf{H_2}$), δ 1.58–1.35 (m, 6H, $OCH(C\mathbf{H_2})_3$), δ 0.95 (t, *J* = 7.4 Hz, 3H, $C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 128.8, 52.31, 47.11, 32.38, 29.51, 26.94, 25.56,

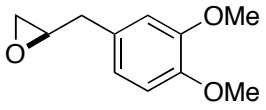
20.50, 14.35; HRMS (CI+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{19}O$) requires *m/z* 155.1436, found *m/z* 155.1430. $[\alpha]_D$ = +7.95 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 1-naphthyl-2-hydroxyoct-5-ene derivative (Chiralcel®OD-H Isocratic 2% IPA/hexanes). t_R(minor) = 30.2 min. t_R(major) = 43.7 min.



(*R*)-2-(Dec-7-ynyl)oxirane (Table 4, entry 4): Prepared according to the general procedure from dodec-9-ynal (405 μL, 2.00 mmol) to afford a yellow oil. Purification on silica gel (5-10% Et_2O/pentanes) afforded (*R*)-2-(dec-7-ynyl)oxirane as a colorless liquid (275 mg, 76% yield, 95% ee). IR (film) 3044, 2975, 2934, 2858, 1462, 1410, 1320, 1260, 1131, 1063, 916.6, 834.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.93–2.87 (m, 1H, OC**H**CH_2), δ 2.74 (dd, 1H, *J* = 4.0, 5.1 Hz, OCHC**H**$_2$), δ 2.46 (dd, 1H, *J* = 2.7, 5.1 Hz, OCHC**H**$_2$), δ 2.20–2.11 (m, 4H, C**H**$_2$CCC**H**$_2$), δ 1.59–1.30 (m, 10H, OCH(C**H**$_2$)$_5$), δ 1.11 (t, *J* = 7.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.68, 79.38, 52.35, 47.13, 32.41, 28.96, 28.93, 28.69, 25.84, 18.65, 14.36, 12.39; HRMS (CI+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{21}O$) requires *m/z* 181.1592, found *m/z* 181.1589. $[\alpha]_D$ = +6.97 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 1-naphthyl-2-hydroxydodec-9-yne derivative (Chiralcel®OD-H Isocratic 5% IPA/hexanes). t_R(minor) = 31.9 min. t_R(major) = 47.0 min.



(*R*)-2-Benzyloxirane (Table 4, entry 5): Prepared according to the general procedure from hydrocinnamaldehyde (263 μL, 2.00 mmol) to afford a yellow oil. Purification on silica gel (5–8% Et_2O/pentanes) afforded (*R*)-2-benzyloxirane as a colorless liquid (207 mg, 77% yield, 93% ee) that matched literature data.[19] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5H, Ph), δ 3.19–3.14 (m, 1H, OC**H**CH_2), δ 2.94 (dd, 1H, *J* = 5.6, 14.7 Hz, C**H**$_2$Ph), δ 2.86–2.79 (m, 2H, OC**H**$_2$CHC**H**$_2$Ph), δ 2.56 (dd, 1H, *J* = 2.7, 4.8 Hz, OCHC**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 129.0, 128.5, 126.6, 52.42, 46.86, 38.75; HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_9H_{10}O$) requires *m/z* 134.0732, found *m/z* 134.0734. $[\alpha]_D$ = +16.7 (c = 1.0, EtOH). Reported rotation for (*S*)-benzyl oxirane $[\alpha]_D$ = -17.3 (c = 1.94, EtOH). Enantiopurity was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (70 °C isotherm); (*R*) isomer t_r = 52.4 min and (*S*) isomer t_r = 57.4 min.



(*R*)-2-(3,4-Dimethoxybenzyl)oxirane (Table 4, entry 6): The catalyst **7** (17.0 mg, 0.100 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one **5** (361 mg, 1.20 mmol) in THF (2.0 mL) and TFA (11.4 mg, 0.100 mmol) was treated with 3-(3,4-dimethoxyphenyl)propanal (194 mg, 1.00 mmol) and stirred at rt for 30 min. The

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[19] Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.

reaction was cooled to 0 °C and diluted with EtOH (1.3 mL). $NaBH_4$ (95.0 mg, 2.50 mmol) was added and after 5 min the reaction was warmed to rt and stirred an additional 25 min. 50% aqueous KOH solution (6.0 mL) was added and the stirred vigorously for 30 min. 12 mL of H_2O was added and the solution extracted with Et_2O (3 × 12 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification on Iatrobeads (20–60% Et_2O/Pentanes) afforded (*R*)-2-(3,4-dimethoxybenzyl)oxirane as a colorless oil (186 mg, 96% yield, 94% ee) which matched literature data.[20] IR (film) 2996, 2936, 2836, 1608, 1590, 1517, 1464, 1420, 1335, 1262, 1237, 1157, 1141, 1028, 969.9, 833.6, 765.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84–6.77 (m, 3H, Ph), δ 3.88 (s, 3H, PhOC**H**$_3$), δ 3.87 (s, 3H, PhOC**H**$_3$), δ 3.17–3.11 (m, 1H, OC**H**CH_2), δ 2.83–2.78 (m, 3H, C**H**$_2$Ph, OCHC**H**$_2$), δ 2.54 (dd, 1H, J = 2.7, 4.5 Hz, OCHC**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.90, 147.81, 129.73, 120.90, 112.25, 111.25, 55.90, 55.84, 52.58, 46.77, 38.27; HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{11}H_{14}O_3$) requires m/z 194.0943, found m/z 194.0946. $[\alpha]_D$ = +9.2 (c = 1.0, $CHCl_3$). Reported rotation $[\alpha]_D$ = +9.7 (c = 0.5, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis (Chiralcel®OD-H Isocratic 4% IPA/hexanes). t_R(major) = 27.1 min. t_R(minor) = 32.1 min.

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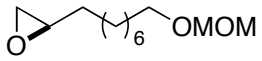
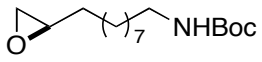
[20] Gooding, O. W.; Bansal, R. P. *Synth. Commun.* **1995**, *25*, 1155.

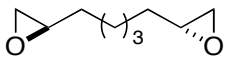


(*R*)-2-(8-(Methoxymethoxy)octyl)oxirane (Table 4, entry 7): Prepared according to the general procedure from 10-(methoxymethoxy)decanal (433 mg, 2.00 mmol) to afford a yellow oil. Purification on Iatrobeads (5–30% Et_2O/pentanes) afforded (*R*)-2-(8-(methoxymethoxy)octyl)oxirane as a colorless liquid (326 mg, 75% yield, 93% ee). IR (film) 3044, 2930, 2857, 1467, 1410, 1386, 1260, 1214, 1149, 1111, 1046, 918.6, 834.6, 723.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (d, 2H, *J* = 0.8 Hz, OC**H**$_2$O), δ 3.52 (t, 2H, *J* = 6.4 Hz, CH_2C**H**$_2$O), δ 3.36 (d, 3H, *J* = 0.8 Hz, OC**H**$_3$), δ 2.93–2.87 (m, 1H, OC**H**CH_2), δ 2.74 (dd, 1H, *J* = 4.8, 4.5 Hz, OCHC**H**$_2$), δ 2.46 (dd, 1H, *J* = 2.7, 5.1 Hz, OCHC**H**$_2$), δ 1.63–1.32 (m, 14H, OCH(C**H**$_2$)$_7$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.39, 67.84, 55.08, 52.36, 47.11, 32.47, 29.72, 29.47, 29.36, 29.31, 26.17, 25.94; HRMS (CI+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{25}O_3$) requires *m/z* 217.1804, found *m/z* 217.1798. $[\alpha]_D$ = +5.97 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 1-naphthyl-2-hydroxy-8-(methoxymethoxy)octane derivative (Chiralpak®AD Isocratic 2% IPA/hexanes). t_R(minor) = 71.4 min. t_R(major) = 75.7 min.



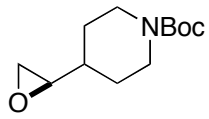
(*R*)-*tert*-Butyl 9-(oxiran-2-yl)nonylcarbamate (Table 4, entry 8): The catalyst **7** (4.30 mg, 25.0 μmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one **5** (361 mg, 1.20 mmol) in THF (1.0 mL) and TFA (2.90 mg, 25.0 μmol) was treated with *tert*-butyl 10-formyldecylcarbamate (286 mg, 1.00 mmol) and stirred at rt for 15 min. The reaction was cooled to 0 °C and diluted with THF (0.50 mL) and EtOH (1.0 mL). $NaBH_4$ (95.0

mg, 2.50 mmol) was added and after 5 min the reaction was warmed to rt and stirred an additional 25 min. 50% aqueous KOH solution (5.0 mL) was added and the stirred vigorously for 30 min. 10 mL of H_2O was added and the solution extracted with Et_2O (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil. Purification on Iatrobeads (20–50% Et_2O/pentanes) afforded (*R*)-*tert*-butyl 9-(oxiran-2-yl)nonylcarbamate as a colorless oil (237 mg, 83% yield, 95% ee). IR (film) 3358, 3045, 2977, 2929, 2856, 2361, 1715, 1523, 1456, 1391, 1366, 1250, 1174, 1042, 996.4, 916.0, 835.6, 781.1, 722.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.50 (s, 1H, N**H**), δ 3.09 (app. q, 2H, *J* = 6.7 Hz, C**H**$_2$NH), δ 2.93–2.87 (m, 1H, OC**H**CH_2), δ 2.74 (dd, 1H, *J* = 4.0, 5.1 Hz, OCHC**H**$_2$), δ 2.46 (dd, 1H, *J* = 2.7, 5.1 Hz, OCHC**H**$_2$), δ 1.57–1.34 (m, 16H, OCH(C**H**$_2$)$_8$), δ 1.28 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 78.92, 52.33, 47.06, 40.57, 32.43, 30.01, 29.37, 29.34, 29.19, 28.39, 26.72, 25.90; HRMS (CI+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{32}NO_3$) requires *m/z* 286.2382, found *m/z* 286.2372. $[\alpha]_D$ = +4.0 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 1-naphthyl-2-hydroxyundecane derivative (Chiralcel®OJ Isocratic 10% IPA/hexanes). t_R(major) = 36.6 min. t_R(minor) = 41.4 min.



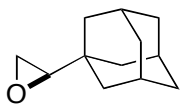
(*R*)-2-(5-(Oxiran-2-yl)pentyl)oxirane (Table 4, entry 9): The catalyst **7** (8.60 mg, 50.0 μmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one **5** (722 mg, 2.40 mmol) in THF (0.80 mL) and TFA (5.8 mg, 50.0 μmol) was treated with nonanedial (174

μL, 1.00 mmol) and stirred at rt for 15 min. The reaction was cooled to 0 °C and diluted with THF (0.40 mL) and EtOH (0.80 mL). $NaBH_4$ (132 mg, 3.50 mmol) was added and after 5 min the reaction was warmed to rt and stirred an additional 25 min. 50% aqueous KOH solution (5.0 mL) was added and the stirred vigorously for 30 min. 10 mL of H_2O was added and the solution extracted with Et_2O (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil. Purification on Iatrobeads (15–40% Et_2O/pentanes) afforded (*R*)-2-(5-(oxiran-2-yl)pentyl)oxirane as a colorless liquid (126 mg, 81% yield, >99% ee, 10:1 dr). IR (film) 3046, 2982, 2932, 2859, 1483, 1464, 1410, 1260, 1132, 915.8, 837.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.93–2.87 (m, 2H, OC**H**CH_2), δ 2.74 (dd, 2H, *J* = 4.0, 4.8 Hz, OCHC**H**$_2$), δ 2.46 (dd, 2H, *J* = 2.9, 5.1 Hz, OCHC**H**$_2$), δ 1.58–1.34 (m, 10H, OCH(C**H**$_2$)$_5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.29, 47.08, 32.33, 29.19, 25.89; HRMS (CI+) exact mass calculated for ($C_9H_{17}O_2$) $[M+H]^+$ requires *m/z* 157.1229, found *m/z* 157.1227. $[\alpha]_D$ = +18.1 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 1,9-dinaphthyl-2,8-dihydroxynonane derivative (Chiralcel®OD-H Isocratic 10% EtOH/hexanes). t_R(minor) = 33.2 min. t_R(diastereomer) = 39.4 min t_R(major) = 44.9 min.



(*R*)-*tert*-Butyl 4-(oxiran-2-yl)piperidine-1-carboxylate (Table 4, entry 10): The catalyst **7** (17.0 mg, 0.100 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one **5** (361 mg, 1.20 mmol) in THF (2.0 mL) and TFA (11.4 mg, 0.100 mmol) was treated with *tert*-butyl 4-(formylmethyl)piperidine-1-carboxylate (227 mg, 1.00 mmol) and stirred at

rt for 30 min. The reaction was cooled to 0 °C and diluted with EtOH (1.3 mL). $NaBH_4$ (95.0 mg, 2.50 mmol) was added and after 5 min the reaction was warmed to rt and stirred an additional 25 min. 50% aqueous KOH solution (6.0 mL) was added and the stirred vigorously for 30 min. 12 mL of H_2O was added and the solution extracted with Et_2O (3 × 12 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil. Purification on Iatrobeads (20–50% Et_2O/pentanes) afforded (*R*)-*tert*-butyl 4-(oxiran-2-yl)piperidine-1-carboxylate as a colorless oil (195 mg, 86% yield, 96% ee). IR (film) 2975, 2930, 2954, 1693, 1480, 1450, 1421, 1366, 1283, 1254, 1231, 1164, 1094, 1008, 976.7, 929.2, 872.4, 834.0, 809.9, 769.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (d, 2H, *J* = 12.0 Hz, N(C**H**$_2$)$_2$), δ 2.78–2.60 (m, 4H, N(C**H**$_2$)$_2$, OC**H**C**H**$_2$), δ 2.55 (dd, 1H, *J* = 4.0, 3.3 Hz, OCHC**H**$_2$), δ 1.85–1.75 (m, 1H, C**H**(CH$_2$)$_2$), δ 1.63–1.57 (m, 2H, CH(C**H**$_2$)$_2$), δ 1.45 (s, 9H, C(C**H**$_3$)$_3$), δ 1.42–1.22 (m, 2H, CH(C**H**$_2$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.76, 79.43, 77.20, 55.62, 45.81, 38.75, 28.68, 28.43, 27.81; HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{21}NO_3$) requires *m/z* 227.1521, found *m/z* 157.1516. $[\alpha]_D$ = +1.23 (c = 1.0, EtOH). Enantiopurity was determined by chiral HPLC analysis of the 1-naphthyl-2-hydroxypiperidine derivative (Chiralcel®OD-H Isocratic 5% IPA/hexanes). t_R(major) = 34.6 min. t_R(minor) = 39.8 min.



(*R*)-Tricyclo[3.3.1.1^{0,0}]dec-1-yl-oxirane (Table 4, entry 11): To a flask containing (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **6** (66 mg, 0.2 mmol) and

2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one **5** (361 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) at –40 °C was added tricyclo[3.3.1.$1^{0,0}$]dec-1-yl-acetaldehyde (169 μL, 1.00 mmol) and stirred for 24 h. The flask was cooled to –78 ºC and diluted with cooled CH_2Cl_2 (4 mL) and EtOH (4 mL). $NaBH_4$ (95 mg, 2.5 mmol) was added and the reaction allowed to warm slowly to rt. After stirring 25 min at rt, 50% KOH solution (20 mL) was added and then stirred vigorously 6 hr. 20 mL of H_2O was added and the solution extracted with Et_2O (3 × 20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil. Purification on silica gel (5% Et_2O/Pentanes) afforded (*R*)-Tricyclo[3.3.1.$1^{0,0}$]dec-1-yl-oxirane as a colorless oil (90 mg, 50%, 89% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (dd, 1H, *J* = 3.2, 4.5 Hz, OC**H**CH_2), δ 2.60 (dd, 2H, *J* = 4.0, 5.0 Hz, OCHC**H$_2$**), δ 2.02–1.95 (m, 3H), δ 1.77–1.51 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.48, 42.99, 38.40, 37.01, 32.20, 27.99; HRMS (EI) exact mass calculated for ($C_{12}H_{18}O$) requires *m/z* 178.1358, found *m/z* 178.1362. $[\alpha]_D$ = -9.42 (c = 1.0, EtOH). The enantiomeric ratio of the epoxide was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (100 °C isotherm, 1 mL/min); (*S*) isomer t_r = 44.4 min and (*R*) isomer t_r = 46.4 min.

Chapter 3

Enantioselective Organocatalytic Direct α-Fluorination of Aldehydes*

Introduction

In the previous chapter, the utility of an asymmetric α-chloroaldehyde as an intermediate in the formation of valuable chiral synthons was discussed. Using the enamine catalysis platform, we felt that other halogen stereocenters such as bromine, iodine, and fluorine could be envisioned as well. We were particularly interested in the possibility of forming fluorine stereocenters due to the lack of direct methods for creating them and their pharmaceutical importance.[1] A key goal of drug design is to prevent rapid degradation and excretion due to unwanted metabolism. While many metabolites are rendered inactive, some may have adverse biological activity making the parent drug unsuitable for human use. Due to its high metabolic stability, the carbon-fluorine bond is widely used as a surrogate for carbon-hydrogen bonds as a method for circumventing unwanted metabolism.[2] Additionally, fluorine atoms provide improved lipohilicity and

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* A patent and communication of this work has been published: (a) Beeson, T. D.; MacMillan, D. W. C. Enantioselective alpha-Fluorination of Aldehydes Using Chiral Organic Catalysts. U.S. Patent 7,265,249, September 4, 2007. (b) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.

[1] Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*, **2004**, *5*, 637.

[2] Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

bioavailability of pharmaceuticals in the body due to their electron-withdrawing effect on nearby heteroatoms whose basicities hinder membrane permeability.[3]

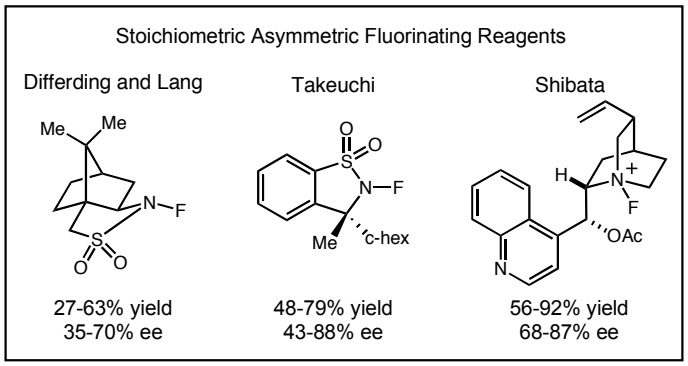

Figure 1. Examples of chiral stoichiometric fluorinating reagents reported in the literature.

It was therefore surprising that at the time of this work, most enantioselective methods for creating asymmetric C-F bonds required the use of stoichiometric amounts of chiral fluorinating agents[4] (Figure 1) and the few known catalytic methods had focused exclusively on highly enolizable substrates such as β-ketoesters and malonates.[5] The first transition metal-catalyzed fluorinations reported by Togni and coworkers using titanium TADDOL complexes[6] had been further developed by Sodeoka using palladium BINAP complexes[7] (equation 1) and Cahard using copper oxazolines[8] to achieve high levels of

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[3] (a) Avdeef, A. *Curr. Top. Med. Chem.* **2001**, *1*, 277. (b) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem.* **2007**, *2*, 1100.

[4] (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087. (b) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708. (c) Cahard, D.; Audouard, C.; Plaquevent, J. C.; Roques, N.; *Org. Lett.* **2000**, *2*, 3699. (d) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728. (e) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001.

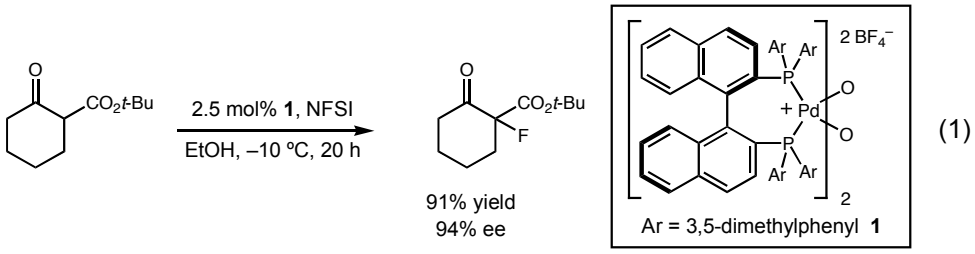
[5] (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (b) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065.

[6] (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (b) Togni, A.; Mezzetti, A.; Barthazy, P.; Becker, C.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Sanna, M. *Chimia* **2001**, *55*, 801.

[7] (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530.

[8] Ma, J. A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007.

enantioselectivity for a variety of cyclic and acyclic β-ketoesters. At the same time, Kim and Park demonstrated that phase-transfer catalysis using quaternized cinchona alkaloid derivatives could also effectively induce high levels of enantiocontrol for the fluorination of β-ketoesters (equation 2).[9]



The Enamine Approach to α-Fluorinations

Since catalytic asymmetric fluorinations were limited to highly enolizable substrates that were structurally precluded from product epimerization, we felt that a direct catalytic asymmetric α-fluorination of aldehydes would be a valuable addition to the current methods for generating fluorine stereocenters. Initial studies in our lab performed by postdoctoral fellow Young-Kwan Kim involved the use of 20 mol% of L-proline (Figure 2) as a catalyst and *N*-fluorobenzenesulfonimide (NFSI) as the electrophilic fluorine source (equation 3). Unfortunately, proline was ineffective as a catalyst for the fluorination reaction and very poor conversions were obtained.

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[9] Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545.

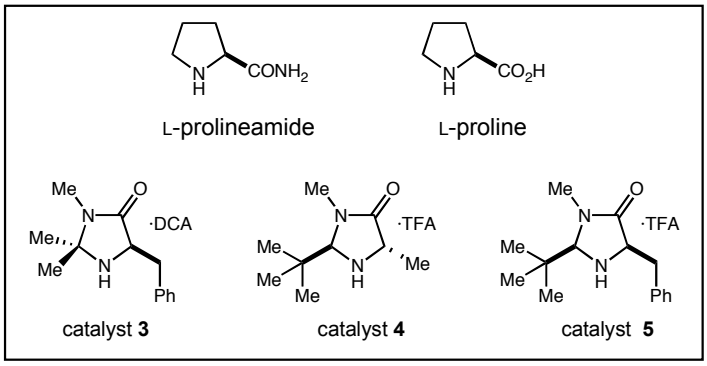
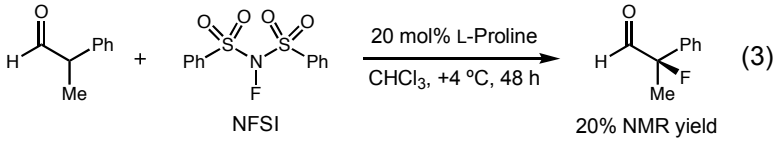
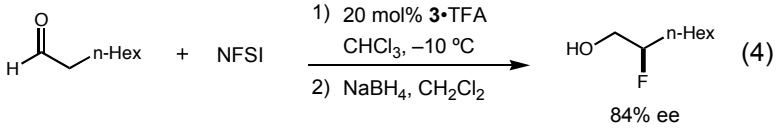


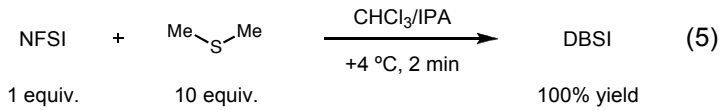
Figure 2. Catalysts for the enantioselective α-fluorination of aldehydes

Subsequently, graduate student Michael Brochu showed that our lab's first-generation imidazolidinone catalyst **3** (Figure 2) could achieve good levels of enantioselectivity (equation 4); however, attempts to isolate the α-fluoroaldehyde products from the residual NFSI were hindered by tedious separations and significant product decomposition. To complicate matters further, attempts at in situ reduction of the sensitive α-fluoroaldehydes were unsuccessful unless all NFSI and its acidic byproduct, dibenzenesulfonimide (DBSI) were first removed, which was accomplished only with difficulty and not reproducibly. For these reasons, it was first necessary to develop a method for the consumption of excess NFSI in the reaction and subsequent removal of the DBSI byproduct.





Interestingly, a report by Umemoto and coworkers in 1986 showed that *N*-fluoropyridinium triflates are able to α-fluorinate sulfides at room temperature.[10] Based on this report, we speculated that if NFSI was capable of reacting with sulfides in the same manner, a volatile sulfide such as dimethylsulfide (DMS) could be used to transform any remaining fluorinating agent into the DBSI byproduct and the resultant fluorosulfide could simply be removed by evaporation. Gratifyingly, when DMS was added to a suspension of NFSI at +4 ºC, an instantaneous exothermic reaction occurred and the NFSI was completely consumed (equation 5). However, the addition of DMS to the α-fluorination reaction in the presence of imidazolidinone catalyst resulted in rapid epimerization of the fluorine stereocenter. On the other hand, it was observed that addition of DMS after removal of the catalyst by filtration had no effect on the stability of the fluoro stereocenter and product enantioselectivities remained stable over 24 hours.



(5)

This observed stereocenter stability led us to wonder whether washing the reactions with a mildly basic sodium bicarbonate solution could remove the acidic DBSI byproduct without epimerizing or decomposing the α-fluoroaldehyde products. Subsequent experiments showed that the α-fluoro stereocenter was indeed stable to the mildly basic conditions, and DBSI could be almost quantitatively removed with two or more bicarbonate washes.

With a successful method for removing excess reagents and reaction byproducts in hand, we began to optimize the reaction conditions by investigating the effect of solvents.

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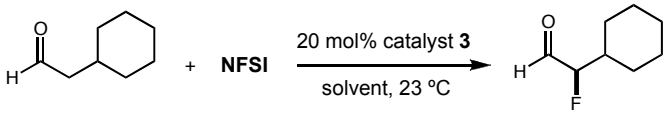
[10] Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3625.

As shown in Table 1, solvents such as toluene, CH_2Cl_2, and $CHCl_3$ provided moderate enantioselectivites (entries 1–4), while THF and acetone achieved the highest levels of selectivity (entries 8 and 10). In all cases except isopropanol (IPA), rapid consumption of the α-fluoroaldehyde product to the α,α-difluoroaldehyde was observed, resulting in low conversions of the desired mono-fluorinated product.

Table 1. Survey of Solvents for Aldehyde α-Fluorination



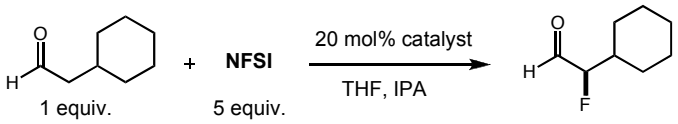
entry	solvent	equiv. NFSI	time (min)	% conv.[a]	% ee[b]
1	Toluene	5	30	46	55
2	CH_3CN	5	30	56	93
3	CH_2Cl_2	5	30	42	62
4	$CHCl_3$	5	60	58	80
5	$CHCl_3$/10% IPA	5	60	70	96
6	$CHCl_3$/10% IPA	3	60	68	91
7	$CHCl_3$/10% IPA	1.2	60	59	82
8	Acetone	5	20	78	96
9	Acetone/10% IPA	5	60	85	97
10	THF	5	5	56	97
11	THF/10% IPA	5	30	75	98
12	IPA	5	360	60	92

(a) Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). (b) Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

Interestingly, when 10% of IPA was added, difluoroaldehyde production was significantly slowed and enantioselectivities were enhanced (entries 5, 9, 11), presumably due to facile addition of IPA to the highly electrophilic carbonyl of the fluoroaldehyde, forming a hemi-acetal that serves as a protecting group to prevent the product from re-

reacting with the catalyst.[11] The excess of NFSI was also lowered to suppress difluoroaldehyde formation; however, reduced overall conversions and significantly lower enantioselectivities were obtained (entries 5–7). Notably, when the reaction temperature was lowered, significant increases in reaction efficiency were observed at +4 ºC (Table 2, entry 9) and at –10 ºC, complete inhibition of difluoroaldehyde formation was obtained (Table 2, entry 10).

Table 2. Effect of Catalyst and Temperature on the α-Fluorination



entry	catalyst	Temp. (°C)	time	% conversion[a]	% ee[b]
1	L-proline	+23	4 h	76	26
2	L-prolineamide	+23	10 h	46	20
3	**5**	+23	15 min	97	63
3	**4**	+23	7 h	91	94
4	**3**•TfOH	+23	4 h	22	87
5	**3**•HCl	+23	4 h	25	41
6	**3**•TFA	+23	15 min	71	97
7	**3**•TCA	+23	15 min	70	90
8	**3**	+23	30 min	78	98
9	**3**	+4	6 h	97	98
10	**3**	–10	8 h	98	98

(a) Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). (b) Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

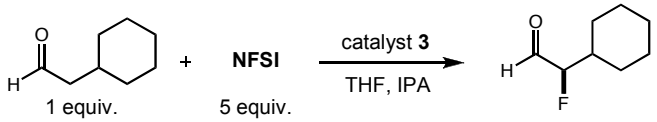
Further, using the optimized solvent conditions we compared catalyst **3** with imidazolidinone catalysts **4** and **5**, as well as L-proline and L-prolineamide (Table 2). While L-proline yielded reasonable levels of conversion under the new reaction conditions, the stereoselectivity remained low (entry 1). Catalyst **5** reacted very rapidly to excellent

[11] Other additives such as ethanol, methanol, and water had the same effect but required much longer reaction times and resulted in slightly lower enantioselectivities.

levels of conversion but yielded only moderate selectivity at this temperature (entry 3). While good levels of conversion and selectivity were achieved with catalyst **4** (entry 4), prolonged reaction times were required. Although imidazolidinone catalysts **4** and **5** could both be applied in this fluorination protocol, we pursued further optimization with catalyst **3** due to its low cost and ease of synthesis.

Subsequently, various co-catalysts were also analyzed. As shown in Table 2, dichloroacetic acid (DCA) and trifluoroacetic acid (TFA) salts of catalyst **3** were optimal for both reaction efficiency and enantioselectivity (entries 4–8). Additionally, catalyst loadings were evaluated to determine if lesser amounts of catalyst would reduce the preponderance for difluorination and allow reactions to be performed at ambient temperature (Table 3). Notably, catalyst loadings as low as 1 mol% achieved excellent levels of enantioselectivity and conversion. However, even with only 1 mol% of catalyst, difluorination was never fully inhibited at room temperature and conversions slowly decreased with time.

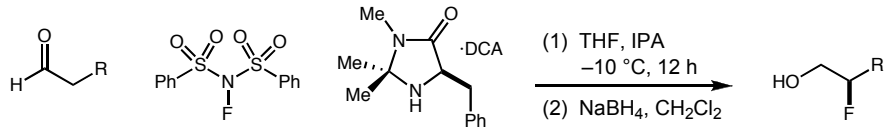
Table 3. Effect of Catalyst Loading on the α-Fluorination



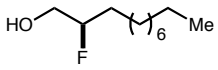
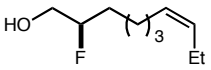
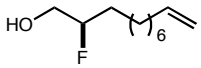
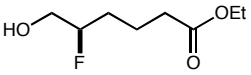
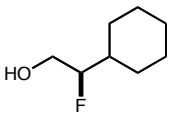
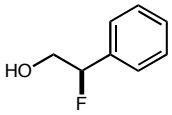
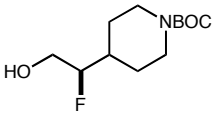
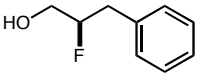
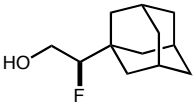
entry	mol% catalyst	Temp °C	time	% conv.[a]	% ee[b]
1	20	+23	30 min	74	98
2	20	–10	8 h	98	98
3	10	+23	1 h	77	98
4	10	+4	8 h	97	98
5	5	+23	3 h	79	98
6	5	+4	25 h	95	98
7	2.5	+23	6 h	77	98
8	1	+23	24 h	83	98

(a) Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). (b) Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

Table 4. Enantioselective α-Fluorination: Substrate Scope



1 equiv. 5 equiv. 20 mol% **3** product

entry	product	% yield	% ee[a]	entry	product	% yield	% ee[a]
1		70	94	3		81	94
2		79	94	4		77	91
entry	product	% yield	% ee[a]	entry	product	% yield	% ee[a]
5		96	99	7		55	99
6		85	98	8		78	96
				9		82	98

(a) Entries 1–4, 6 and 9 enantiomeric excess determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel® OJ). Entries 5, 7 and 8 enantiomeric excess determined by chiral GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc).

Lastly, the generality of the reaction was studied and a variety of aldehyde substrates were chosen to determine the effect of sterics and functional group compatibility. As shown in Table 4, olefinic aldehydes were successfully α-fluorinated without isomerization of the double bond configuration (entries 2–3). Although NFSI is susceptible to electrophilic aromatic substitution,[12] aromatic substrates were also obtained in good yields with excellent enantioselectivities (entries 7–8). The acid-labile *tert*-butoxycarbonyl

[12] Differding, E.; Ofner, H. *Synlett* **1991**, 187.

(BOC) nitrogen protecting group was also unaffected by the acidic reaction conditions (entry 6). Surprisingly, there was no difference in reaction times between substrates of differing steric demands (entries 5–9), with even the highly hindered adamantyl acetaldehyde reacting in 12 hours to give excellent results for the α-fluoroaldehyde product (entry 9).

Conclusion

In summary, development of the direct and enantioselective α-fluorination of aldehydes has been described using an inexpensive and easily prepared imidazolidinone catalyst and NFSI as the fluorinating source.[13,14] The mild reaction conditions have allowed the α-fluorination of a wide variety of structures and functionalities, including those of high steric demand and catalyst loadings as low as 1 mol% were capable of inducing high yields and enantioselectivities. It is our hope that this new methodology for creating fluorine stereocenters will open the door for practitioners of pharmaceutical synthesis to pursue structural diversifications that have until now been inaccessible.

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[13] After submission of this work for publication, the following papers appeared in the literature also describing the enantioselective organocatalyzed α-fluorination of aldehydes: (a) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991. (b) Marigo, M.; Fielenbach, D. I.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (c) Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706.

[14] For reviews on recent advances in the field of asymmetric fluorination see: (a) Brunet, V. A.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1179. (b) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469. (c) Pihko, P. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 544. (d) Prakash, G. K. S.; Beier, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2172. (e) Bobbio, C.; Gouberneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065.

Supporting Information

General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego.[15] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on EMD Silica Gel 60 230-400 mesh or Davisil® Silica Gel 200-425 mesh according to the method of Still.[16] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching using potassium permanganate stain. High performance liquid chromatography (HPLC) and gas liquid chromatography (GLC) assays to determine enantiometric excess were developed using racemic samples.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Varian Mercury 300 (300 MHz, 75 MHz and 282 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C and ^{19}F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass

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[15] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd edition; Pergamon Press; Oxford, 1988.

[16] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Spectral Facility. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard 6850 Series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 Series chromatograph using a Chiralcel® OJ column (25 cm, 5 cm guard) as noted.

General Procedure for the α-Fluorination of Aldehydes: To a 25 mL round-bottom flask equipped with a magnetic stir bar and charged with **1** (*R*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt (139 mg, 0.400 mmol) and *N*-fluorobenzenesulfonimide (3.15 g, 10.0 mmol) was added THF (9.0 mL) and IPA (1.0 mL). The mixture was stirred at rt until homogeneous then cooled to –10 °C. The aldehyde substrate (2.0 mmol) was added and the reaction mixture stirred 12 h. The reaction was cooled to –78 ºC, diluted with 10 mL Et_2O and filtered through a pad of Davisil® Silica Gel, eluting with Et_2O. Me_2S (5.0 mL) was added forming a white precipitate. The resulting mixture was washed with sat. $NaHCO_3$ (3 × 150 mL) and brine (1 × 150 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (12 mL) and EtOH (8 mL), and $NaBH_4$ (189 mg, 5.0 mmol) was added. After 30 min the reaction was cooled to 0 ºC and sat. NH_4Cl (150 mL) was added. The mixture was warmed to rt and stirred vigorously 1 h. The cloudy suspension was allowed to separate and 75 mL of CH_2Cl_2 was added. The solution was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organics washed with sat. $NaHCO_3$ (3 × 150 mL) and brine (1 × 150 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Purification of the resulting oil by forced flow chromatography afforded the title compounds. The enantioselectivity was determined either by chiral GLC analysis, or chiral HPLC analysis after acylation of the alcohol with 2-naphthoylchloride.

Starting Materials

Ethyl 5-formylpentanoate: To a flask containing ethyl 6-hydroxyhexanoate (4.07 mL, 25.0 mmol) in CH_2Cl_2 (25 mL) was added TEMPO (391 mg, 2.50 mmol) followed by iodobenzene diacetate (8.86 g, 27.5 mmol). The reaction was stirred 2 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (20-40% Et_2O/pentanes) to provide the title compound, which was identical to the reported literature compound.[17]

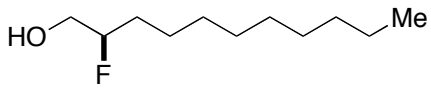
***tert*-Butyl 4-(formylmethyl)piperidine-1-carboxylate:** To a flask containing *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (4.4 g, 19.2 mmol) in CH_2Cl_2 (20 mL) was added TEMPO (300 mg, 1.92 mmol) followed by iodobenzene diacetate (6.8 g, 21.1 mmol). The reaction was stirred 3 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150

[17] Taber, D. F.; Teng, D. *J. Org. Chem.* **2002**, *67*, 1607.

mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (40–70% Et_2O/pentanes) to provide the title compound, which was identical to the reported literature compound.[18] ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 154.7, 79.4, 50.3, 43.7, 31.9, 30.6, 28.4.

Adamantylacetaldehyde: To a flask containing 2-adamantyl-1-ethanol (5 g, 27.7 mmol) in CH_2Cl_2 (28 mL) was added TEMPO (433 mg, 2.77 mmol) followed by iodobenzene diacetate (9.8 g, 30.5 mmol). The reaction was stirred 1 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5% Et_2O/pentanes) to provide the title compound, which was identical to the reported literature compound.[19]

α-Fluoro Alcohols



(*R*)-2-Fluoro-1-undecanol (Table 4, entry 1): Prepared according to the general procedure from undecanal (411 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (10–50% Et_2O/Pentanes) afforded (*R*)-2-fluoro-1-undecanol as a colorless solid

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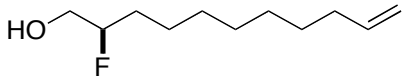
[18] Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Heterocycles* **2001**, *54*, 747.

[19] Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.

(261 mg, 70% yield, 94% ee). IR (film) 3271 3171, 2954, 2914, 2848, 1470, 1071, 842.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$). δ 4.56 (dm, *J* = 46.8 Hz, 1H, FC**H**), δ 3.59–3.77 (m, 2H, OC$\mathbf{H_2}$), δ 1.89 (s, 1H, -O**H**), 1.20–1.78 (m, 16H, (C$\mathbf{H_2}$)$_\mathbf{8}$), δ 0.88 (t, *J* = 6.9 Hz, 3H, C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 96.3 (d, *J* = 166.3 Hz), 65.1 (d, *J* = 21.3 Hz), 31.9, 30.9 (d, *J* = 20.3 Hz), 29.5, 29.4 (d, *J* = 3 Hz), 29.3, 24.9, 24.9, 22.7, 14.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –189.6 (m). HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{11}H_{22}FO$) requires *m/z* 189.1655, found *m/z* 189.1660. $[\alpha]_D$ = 7.6 (c = 1.0, $CHCl_3$).[20] Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 3% IPA/Hexanes). t_R(major) = 11.4 min. t_R(minor) = 15.0 min.



(*R*)-2-Fluoroundec-10-en-1-ol (Table 4, entry 2): Prepared according to the general procedure from undec-10-enal (416 μL, 2.00 mmol) to afford a colorless oil. Purification on Davisil® silica gel (10–20% EtOAc/Pentanes) afforded (*R*)-2-fluoroundec-10-en-1-ol as a colorless solid (296 mg, 79% yield, 94% ee). IR (film) 3214, 2918, 2848, 1641, 1460, 1348, 1073, 990.7, 914.2, 837.8, 806.0, 757.8, 724.4, 668.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$). δ 5.74–5.87 (m, 1H, $CH_2C\mathbf{H}=CH_2$), δ 4.90–5.03 (m, 2H, $CH_2CH=C\mathbf{H_2}$), δ 4.57 (dm, 1H, *J* = 50.7 Hz, FC**H**); δ 3.60–3.80 (m, 2H, OC$\mathbf{H_2}$), δ 2.03 (q, 2H, *J* = 14.1, and 7.5 Hz, C$\mathbf{H_2}$CH=CH_2), δ 1.83 (t, 1H, *J* = 6.6 Hz, -O**H**), δ 1.26–1.76 (m, 12H, FCH(C$\mathbf{H_2}$)$_\mathbf{6}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 139.1, 114.2, 94.8 (d, *J* = 166.5 Hz), 65.1 (d, *J* = 21.8 Hz), 31.7, 30.9 (d, *J* = 20.0 Hz), 29.3, 29.3, 29.0, 28.8, 24.9 (d, *J* =

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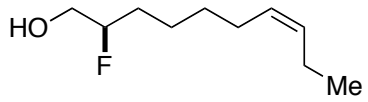
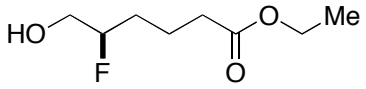
[20] $[\alpha]_D$ = -8.6 (c = 2.0, Et_2O) for (*S*)-2-fluoro-1-decanol and $[\alpha]_D$ = -7.2 (c = 2.0, Et_2O) for (*S*)-2-fluoro-1-dodecanol. Nohira, H.; Kamei, M.; Nakamura, S.; Yoshinaga, K.; Kai, M. JPN Patent 62093248, **1987**.

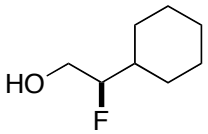
3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –189.6 (m). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{11}H_{21}FO$) requires *m/z* 188.1576, found *m/z* 188.1575. $[\alpha]_D$ = 8.1 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 3% IPA/Hexanes). t_R(major) = 15.7 min. t_R(minor) = 22.7 min.



(*R*)-(*Z*)-2-Fluorodec-7-en-1-ol (Table 4, entry 3): Prepared according to the general procedure from (*Z*)-dec-7-enal (366 μL, 2.00 mmol) to afford a yellow oil. Purification on silica gel (5–20% EtOAc/Pentanes) afforded (*R*)-(*Z*)-2-fluorodec-7-en-1-ol as a pale yellow liquid (283 mg, 81% yield, 94% ee). IR (film) 3369, 3006, 2935, 2861, 1462, 1376, 1172, 1056, 843.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26–5.42 (m, 2H, $CH_2C\mathbf{H}=\mathbf{H}CCH_2$), δ 4.56 (dm, 1H, *J* = 50.5 Hz, FC**H**), δ 3.62–3.76 (m, 2H, O$\mathbf{CH_2}$), δ 1.98–2.10 (m, 4H, $\mathbf{CH_2}CH=HC\mathbf{CH_2}$), δ 1.89 (t, 1H, *J* = 6.4 Hz, -O**H**), δ 1.32–1.74 (m, 6H, $CFH(\mathbf{CH_2})_3$), δ 0.95 (t, 3H, *J* = 7.4 Hz, $C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 132.0, 128.7, 94.7 (d, *J* = 166.5 Hz), 65.1 (d, *J* = 21.3 Hz), 30.9 (d, *J* = 20.0 Hz), 29.5, 26.8, 24.5 (d, *J* = 5.0 Hz), 20.5, 14.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –189.6 (m). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{10}H_{19}FO$) requires *m/z* 174.1420, found *m/z* 174.1421. $[\alpha]_D$ = 5.6 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 0.5% IPA/Hexanes). t_R(major) = 32.2 min. t_R(minor) = 51.9 min.

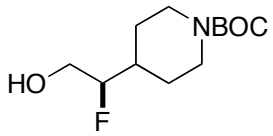


(*R*)-Ethyl 5-fluoro-6-hydroxyhexanoate (Table 4, entry 4): Prepared according to the general procedure from ethyl 5-formylpentanoate (319 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (20–40% EtOAc/Pentanes) afforded (*R*)-ethyl 5-fluoro-6-hydroxyhexanoate as a colorless liquid (274 mg, 77% yield, 91% ee). IR (film) 3436, 2942, 1733, 1453, 1376, 1165, 1096, 1065, 1035, 849.9, 772.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (dm, 1H, *J* = 49.4, FC**H**), δ 4.12 (q, 2H, *J* = 7.2 Hz, $CO_2C\mathbf{H_2}$), δ 3.60–3.78 (m, 2H, $OC\mathbf{H_2}$), δ 2.34 (t, 2H, *J* = 7.0 Hz, $C\mathbf{H_2}CO_2$), δ 2.04 (s, 1H, -O**H**), δ 1.50–1.88 (m, 4H, $CFH(C\mathbf{H_2})_2$), δ 1.24 (t, 3H, *J* = 7.2 Hz, $C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.3, 94.2 (d, *J* = 167.3 Hz), 64.8 (d, *J* = 21.7 Hz), 60.4, 33.8, 30.2 (d, *J* = 20.6 Hz), 20.4 (d, *J* = 5.0 Hz), 14.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –190.3 (m). HRMS (EI+) exact mass calculated for $[M+H]^+$ ($C_8H_{16}FO_3$) requires *m/z* 179.1084, found *m/z* 179.1083. $[\alpha]_D$ = 5.1 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 10% EtOH/Hexanes). t_R(major) = 47.7 min. t_R(minor) = 68.7 min.



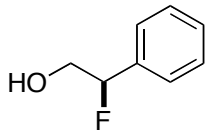
(*R*)-2-Cyclohexyl-2-fluoro-1-ethanol (Table 4, entry 5): Prepared according to the general procedure from 2-cyclohexyl-1-ethanol (291 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (10–50% Et_2O/Pentanes) afforded (*R*)-2-cyclohexyl-2-fluoro-1-ethanol as a colorless liquid (282 mg, 96% yield, 99% ee). IR

(film) 3369, 2928, 2854, 1450, 1091, 1074, 1058, 1024, 977.7, 891.8, 858.9, 837.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (dm, 1H, *J* = 49.2 Hz, FC**H**), δ 3.68–3.81 (m, 2H, OC$\mathbf{H_2}$), δ 1.83–1.94 (m, 2H, C$\mathbf{H_2}$), δ 1.56–1.84 (m, 5H, (C$\mathbf{H_2}$)$_2$ and O**H**), δ 0.99–1.34 (m, 5H, (C$\mathbf{H_2}$)$_2$ and CFHC**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 98.4 (d, *J* = 168.3 Hz), 63.2 (d, *J* = 26.2 Hz), 30.2 (d, *J* = 19.1 Hz), 28.1 (dd, *J* = 22.7, 6.0 Hz), 26.1, 25.7 (d, *J* = 12.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –194.7 (m). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_8H_{15}FO$) requires *m/z* 146.1107, found *m/z* 146.1101. $[\alpha]_D$ = –0.26 (c = 1.0, EtOH). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (100 °C isotherm); (*R*) isomer t_r = 79.9 min and (*S*) isomer t_r = 88.8 min.



(*R*)-*tert*-Butyl 4-(1-fluoro-2-hydroxyethyl)piperidine-1-carboxylate (Table 4, entry 6): Prepared according to the general procedure from *tert*-butyl 4-(formylmethyl)piperidine-1-carboxylate (455 mg, 2.00 mmol) to afford a colorless oil. Purification on silica gel (25–50% EtOAc/Pentanes) afforded (*R*)-*tert*-Butyl 4-(1-fluoro-2-hydroxyethyl)piperidine-1-carboxylate as a colorless oil (422 mg, 85% yield, 98% ee). IR (film) 3430, 2930, 1692, 1671, 1427, 1365, 1283, 1241, 1170, 1084, 1040, 971.6, 940.0, 857.2, 770.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06–4.40 (m, 3H, N(C$\mathbf{H_a}$CH$_b$)$_2$, and FC**H**), δ 3.69–3.83 (m, 2H, OC$\mathbf{H_2}$), δ 2.68 (br m, 2H, N(CH$_a$C$\mathbf{H_b}$)$_2$), δ 2.01 (t, 1H, *J* = 6.0 Hz, -O**H**), δ 1.80–1.87 (m, 2H, (C$\mathbf{H_a}$CH$_b$CH$_2$)$_2$N), δ 1.51–1.67 (m, 1H, CHFC**H**), δ 1.44 (s, 9H, (C$\mathbf{H_3}$)$_3$), δ 1.22–1.32 (m, 2H, (CH$_a$C$\mathbf{H_b}$CH$_2$)$_2$N); ^{13}C NMR (75 MHz,

$CDCl_3$) δ: 154.7, 97.3 (d, *J* = 170.0 Hz), 79.5, 62.8 (d, *J* = 22.0 Hz), 60.4, 37.1 (d, *J* = 19.7 Hz), 28.4, 27.3, 27.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –194.5 (bs). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{22}FNO_3$) requires *m/z* 247.1584, found *m/z* 247.1587. $[\alpha]_D$ = 3.0 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 10% EtOH/Hexanes). t_R(major) = 28.3 min. t_R(minor) = 41.1 min.



(*R*)-2-Fluoro-2-phenyl-1-ethanol (Table 4, entry 7): Prepared according to the general procedure from phenylacetaldehyde (234 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (10–50% Et_2O/Pentanes) afforded (*R*)-2-fluoro-2-phenyl-1-ethanol as a colorless liquid (152 mg, 54% yield, 99% ee), which matched literature data.[21] IR (film) 3369, 1496, 1454, 1078, 1043, 877.9, 834.2, 757.3, 698.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.41 (m, 5H, $C_6\mathbf{H_5}$), δ 5.57 (ddd, 1H, *J* = 48.9, 7.7, and 5.2 Hz, FC**H**), δ 3.73–4.01 (m, 2H, OC$\mathbf{H_2}$), δ 2.18 (dd, 1H, -O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.3 (d, *J* = 19.6 Hz), 128.8 (d, *J* = 2.0 Hz), 128.6, 125.7 (d, *J* = 6.9 Hz), 94.8 (d, *J* = 170.9 Hz), 66.6 (d, *J* = 24.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –187.0 (ddd, *J* = 12.8, 7.6, 4.5 Hz). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ (C_8H_9FO) requires *m/z* 140.0637, found *m/z* 140.0636. $[\alpha]_D$ = 47.9 (c = 1.0, $CHCl_3$). Reported rotation for the *S*-

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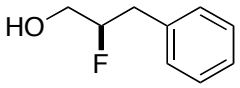
[21] Watanabe, S.; Fujita, T.; Usui, Y. *J. Fluorine Chem.* **1986**, *31*, 247.

enantiomer $[\alpha]_D = -52.5$ (c = 1.1, $CHCl_3$).[22] Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (110 °C isotherm); (*R*) isomer t_r = 57.1 min and (*S*) isomer t_r = 59.4 min.



(*R*)-2-Fluoro-3-phenyl-1-propanol (Table 4, entry 8): Prepared according to the general procedure from hydrocinnamaldehyde (263 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (10–40% Et_2O/Pentanes) afforded (*R*)-2-fluoro-3-phenyl-1-propanol as a colorless liquid (218 mg, 71% yield, 96% ee), which matched literature data.[23] IR (film) 3369, 3029, 2932, 1497, 1455, 1052, 904.3, 835.6, 745.7, 700.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.36 (m, 5H, $C_6\mathbf{H_5}$), δ 4.78 (dm, 1H, *J* = 48.6 Hz, FC**H**), δ 3.60–3.85 (m, 2H, OC$\mathbf{H_2}$), δ 2.87–3.10 (m, 2H, PhC$\mathbf{H_2}$), δ 1.97 (t, 1H, *J* = 6.1 Hz, -O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.3 (d, *J* = 6.0 Hz), 129.3, 128.6, 126.8, 95.6 (d, *J* = 170.6 Hz), 64.1 (d, *J* = 21.3 Hz), 37.4 (d, *J* = 20.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –187.6 (m). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_9H_{11}FO$) requires *m/z* 154.0794, found *m/z* 194.0797. $[\alpha]_D = 16.7$ (c = 1.0, $CHCl_3$). Reported rotation for the *S*-enantiomer $[\alpha]_D = -17.6$ (c = 1.7, $CHCl_3$).[23] Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C isotherm); (*R*) isomer t_r = 76.1 min and (*S*) isomer t_r = 84.3 min.

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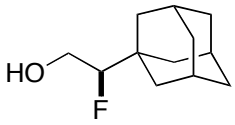
[22] Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153.

[23] Takeuchi, Y.; Nagata, K.; Koizumi, T. *J. Org. Chem.* **1989**, *54*, 5453.



(*R*)-2-Adamantyl-2-fluoro-1-ethanol (Table 4, entry 9): Prepared according to the general procedure from adamantylacetaldehyde (334 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (5–20% EtOAc/Pentanes) afforded (*R*)-2-adamantyl-2-fluoro-1-ethanol as a colorless solid (326 mg, 82% yield, 98% ee). IR (film) 3306, 2903, 2850, 1451, 1348, 1087, 1058, 1028, 989.3, 859.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (ddd, 1H, *J* = 49.7, 7.8, and 5.1 Hz, FC**H**), δ 3.62–3.88 (m, 2H, OC$\mathbf{H_2}$), δ 1.99 (s, 3H, C**H**$(CH_2)_3$) δ 1.54–1.84 (m, 13H, -O**H**, (C$\mathbf{H_2}$)$_6$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 101.8 (d, *J* = 170.3 Hz), 61.3 (d, *J* = 22.3 Hz), 37.7 (d, *J* = 4.1 Hz), 36.9, 35.4 (d, *J* = 19.6 Hz), 27.9 (*J* = 0.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –203.1 (ddd, *J* = 48.5, 34.2, 17.2 Hz). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{19}FO$) requires *m/z* 198.1420, found *m/z* 198.1417. $[\alpha]_D$ = –9.5 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 3% IPA/Hexanes). t_R(major) = 20.8 min. t_R(minor) = 26.5 min.

Chapter 4

Enantioselective Organocatalytic Direct α-Fluorination of Ketones

Introduction

In the previous chapter, the development of the enantioselective enamine-catalyzed α-fluorination of aldehydes was discussed. Due to the importance of fluorine stereocenters and the scarcity of direct methods for creating them, we subsequently sought to expand on this valuable methodology to include the α-fluorination of ketones. As mentioned in the previous chapter, the majority of direct asymmetric fluorination methods have focused (with the exception of the enamine-catalyzed aldehyde fluorination) on highly enolizable substrates such as β-ketoesters that are precluded from product epimerization.[1] Asymmetric construction of epimerizable α-fluoroketone stereocenters has only been accomplished with low yields and selectivities, or by multi-step syntheses. For example, a two-step procedure for preparing chiral α-fluoroketones introduced by Haufe and coworkers explored the possibility of desymmetrizing meso epoxides by catalytic asymmetric ring opening using a fluoride source, subsequent

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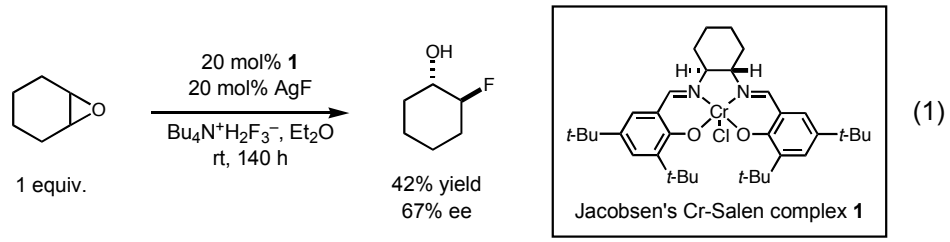
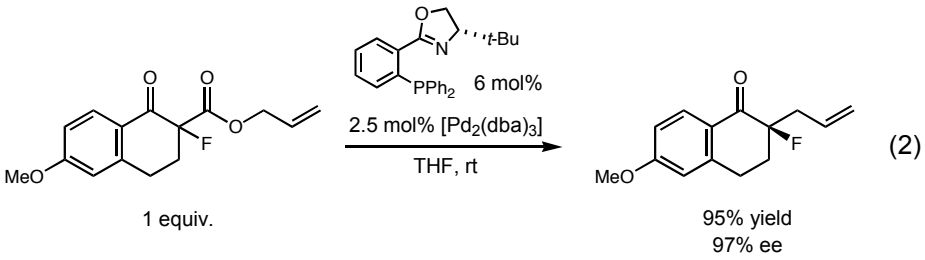
[1] (a) Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* **2000**, *112*, 4530. (b) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709. (c) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (d) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545. (e) Hamashima, Y.; Yagi, K.; Takao, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225. (f) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007. (g) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett.* **2004**, 1703.

oxidation of which would yield the desired fluoroketones.[2] Using catalytic quantities of Jacobsen's chromium salen complex **1**, the fluorohydrin was obtained in 42% yield and 67% ee (equation 1). Higher conversions could be obtained but required stoichiometric amounts of the chromium complex.



(1)



(2)

Additionally, Nakamura et al. showed that racemic α-fluoro-β-ketoesters could undergo enantioselective decarboxylative allylation to generate α-allyl-α-fluoroketones in high yield and enantiomeric excess (equation 2).[3] However, as with most methodologies that produce α-fluoro stereocenters, this method also generates a product that is precluded from post-epimerization.

Recently, Szori, Szöllosi, and Bartók reported an asymmetric hydrogenation of racemic 2-fluorocyclohexanone over a cinchona alkaloid-modified platinum-aluminum oxide catalyst.[4] As the reaction progressed, a kinetic resolution was observed and one

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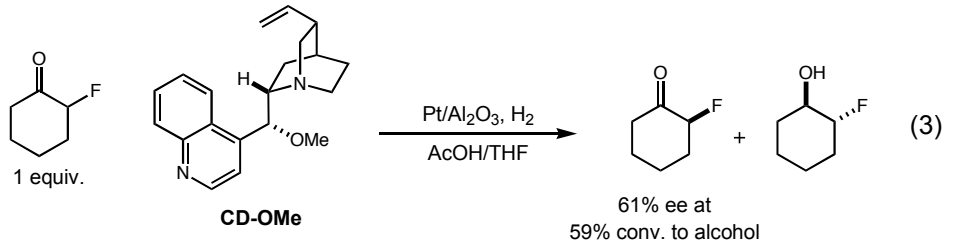
[2] (a) Haufe, G.; Bruns, S. *Adv. Synth. Catalysis* **2002**, *344*, 165. (b) Haufe, G.; Bruns, S.; Runge, M. *J. Fluorine Chem.* **2001**, *112*, 55.

[3] (a) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem. Int. Ed.* **2005**, *44*, 7248. (b) Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, 2824.

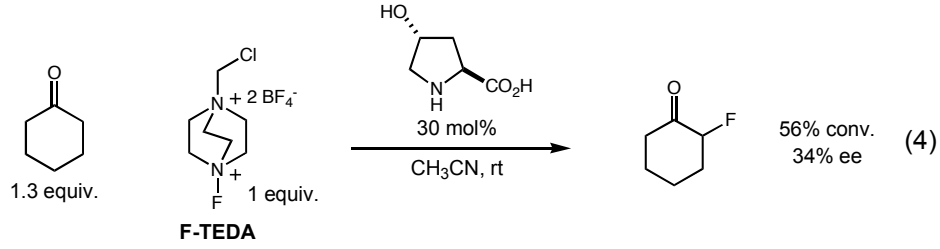
[4] Szori, K.; Szöllosi, G.; Bartók, M. *J. Catalysis* **2006**, *244*, 255.

enantiomer of the racemic starting material was accumulated in the reaction. Using methoxy-cinchonidine (CD-OMe), α-fluorocyclohexanone was observed at 61% ee when the reaction had reached 60% conversion (equation 3).



(3)

In an attempt to perform a direct α-fluorination of ketones using enamine activation, which had been successful with aldehydes, Enders and Hüttl studied α-fluorination of ketones using proline-based catalysts and F-TEDA as the fluorine source (equation 4).[5] Unfortunately, the best result obtained was 56% conversion and 34% ee for α-fluorocyclohexanone using 4-hydroxyproline as the catalyst. Enders has also demonstrated the asymmetric synthesis of fluoroketones using the SAMP/RAMP chiral auxiliaries to α-silate ketones enantioselectively, which can then be fluorinated diastereoselectively and desilated to generate the desired fluoroketones; however, this method requires a minimum of five synthetic steps.[6]



(4)

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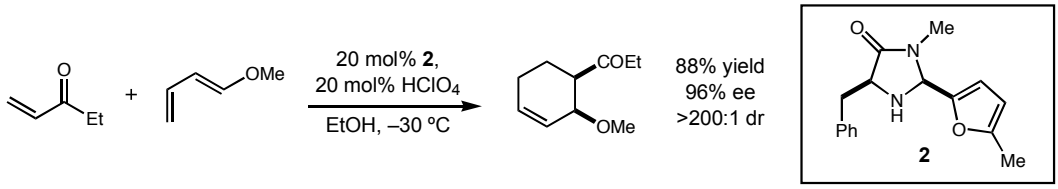
5 Enders, D.; Hüttl, M. R. M. *Synlett*, **2005**, 991.

6 Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, 2307.

α-Fluorination using Imidazolidinone Catalysts

Like Enders, we also felt that the enamine activation mode could potentially provide direct access to fluorinated ketones, and in contrast to other established methods for creating stereogenic fluorine centers, enamine catalysis should enable the induction of epimerizable stereocenters. Since our lab's class of imidazolidinone catalysts had been shown to perform readily as enamine catalysts and had already achieved high levels of stereoselectivities for the α-chlorination and α-fluorination of aldehydes, we felt that this class of catalyst might be able to overcome the reactivity and selectivity issues that Enders had faced with proline-based catalysts. Although the typical imidazolidinone catalysts that yield high reactivities with aldehydes had been shown to react very poorly with ketones, former graduate student Alan Northrup successfully developed a furanyl-imidazolidinone **2** that facilitated the first enantioselective ketone Diels-Alder reaction with excellent yields and stereoselectivities (equation 5).[7,8]



(5)

Employing catalyst **2** with our previously determined aldehyde fluorination reaction conditions and two equivalents of *N*-fluorobenzenesulfonimide (NFSI) as the fluorine source, we were delighted to find that 2-fluorocyclohexanone could be obtained in 85% conversion and 34% enantiomeric excess (ee) (equation 6). While this result was

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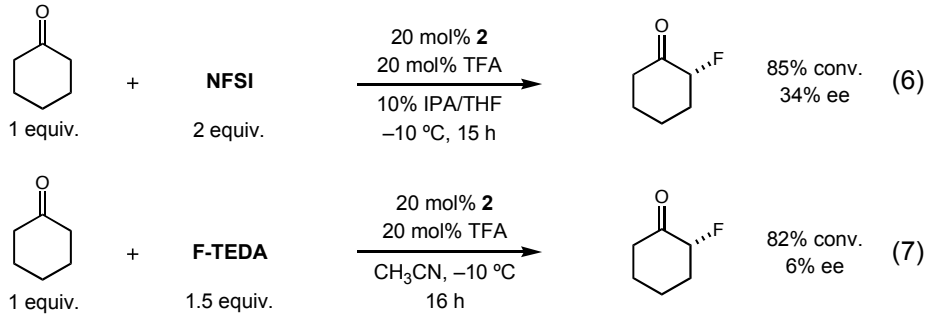
[7] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

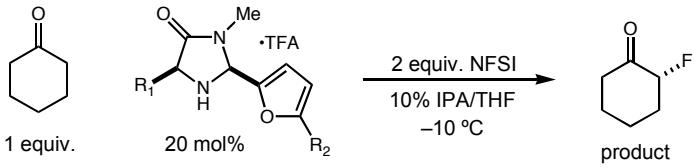
[8] Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.

very promising, the stereoselectivity was far from optimal. Interestingly, when F-TEDA was used as the fluorine source, high levels of conversion were also obtained but with no stereoselectivity (equation 7). This result is possible evidence for the transition state proposed for the aldehyde fluorination with NFSI in which the sulfonimide of the fluorinating agent is hydrogen-bonded to the enamine through a proton.



During the development of the aldehyde α-fluorination (chapter 3), it was noted that the reaction medium had a large impact on the outcome of the reaction. We therefore investigated the ketone fluorination in a variety of solvents, both with and without the addition of 10% isopropanol (IPA). However, the initial reaction conditions were determined to be optimal and we next focused our efforts on evaluating the effect of catalyst architecture. With the goal of developing a more broadly useful catalyst for the enamine and iminium-catalyzed functionalization of ketones, graduate student Anthony Mastracchio had prepared a number of imidazolidinone catalysts with modified catalyst **2** architectures. As shown in Table 1, all catalysts achieved excellent reactivity; however, no significant improvement in enantioselectivity was obtained for any of the catalysts studied. A variety of pyrrolidine-based catalyst architectures were also studied but poor conversions and very low selectivities were obtained. Subsequently, we turned our attention to a class of mono-substituted imidazolidinone catalysts (Figure 1), which had been demonstrated to induce high levels of selectivity for the transfer hydrogenation of

Table 1. Effect of Modifications to Catalyst **2** Architecture



entry	R_1	R_2	time (h)	% conversion[a]	% ee[b]
1	Ph	Me	10	80	34
2	Ph	CF_3	11	97	29
3	*p*-NO_2-Ph	Me	10	90	8
4	*p*-NO_2-Ph	CF_3	10	89	14
5	*p*-O*t*-Bu-Ph	CF_3	3	87	36
6	2-naphthyl	CF_3	10	91	27
7	1-naphthyl	CF_3	10	86	13
8	Ph, Ph	CF_3	20	62[c]	13

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc). (c) Reaction performed at +4 ºC.

aldehydes[9] and shown promise as a catalyst for enamine-catalyzed reactions of ketones.[10] As shown in Table 2, reactions performed with catalyst **3** achieved very high levels of enantioselectivity; however, the bulky *tert*-butyl group severely hindered the reaction efficiency and a maximum of 23% conversion was obtained. Notably, the *cis*-diphenyl-diamino catalyst **6** developed by Jørgensen and successfully used for the α-chlorination

[9] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

[10] Kim, Y.-K.; MacMillan, D. W. C. unpublished results.

and α-bromination of ketones[11] yielded both low conversion and selectivity in the fluorination reaction.

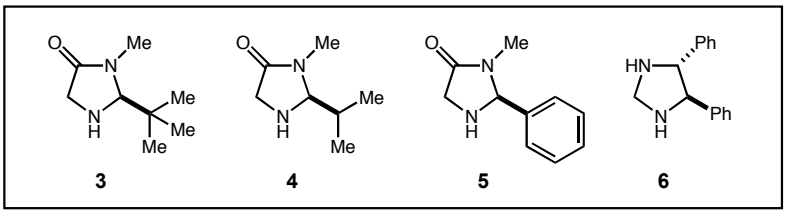
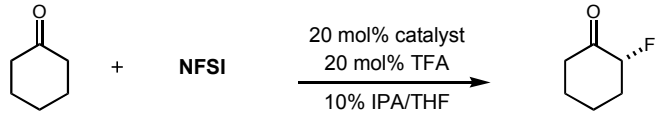


Figure 1. Structures of monosubstituted imidazolidinone catalysts and Jørgensen's *cis*-diphenyl-diamino catalyst.

Table 2. Mono-Substituted Imidazolidinone Catalysts



entry	catalyst	Temp (ºC)	time (h)	% conversion[a]	% ee[b]
1	**3**	+23	15	23[c]	73
2	**3**	+4	27	19[c,d]	87
3	**3**	–10	120	21[c,d]	87
4	**4**	+4	24	53	58
5	**4**	–10	24	35	64
6	**5**	–20	16	79	37
7	**5**	–40	16	45	45
8	**6**	+23	18	41[e]	25

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc). (c) Reactions using 20 mol% TCA instead of TFA. (d) Reactions performed without IPA. (e) Reactions using 20 mol% BzOH instead of TFA.

In an attempt to optimize the reaction efficiency using catalyst **3**, studies were conducted in which the solvent, alcohol additive, catalyst loading and concentration were varied. While increasing the reaction concentration from 0.125M to 1.0M did achieve

[11] (a) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5507. (b) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821.

conversions as high as 38%, the enantioselectivity decreased with increasing concentration. Using 10% IPA as an additive, product epimerization with time was quite noticeable and switching to ethanol or methanol significantly slowed the loss of stereoselectivity; unfortunately the maximum conversions achieved were identical to those using IPA. Variations in solvent and catalyst loading were also found to have no beneficial effect.

Cinchona Alkaloid Catalysts

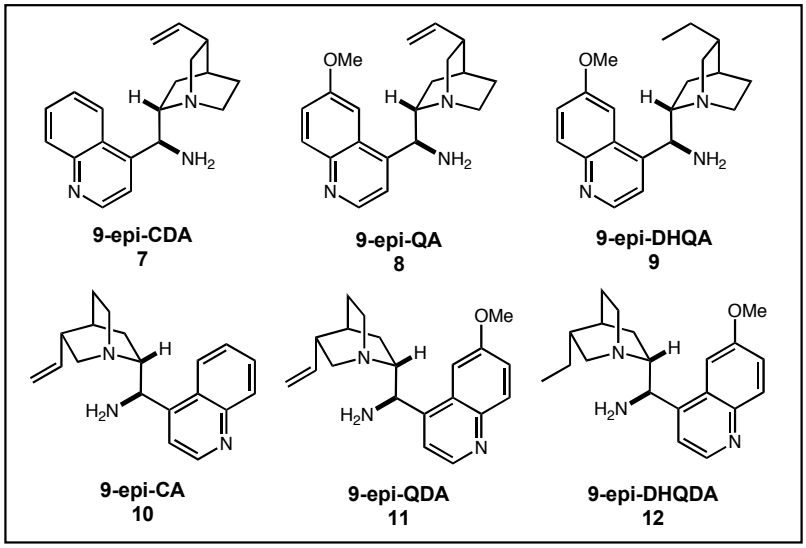
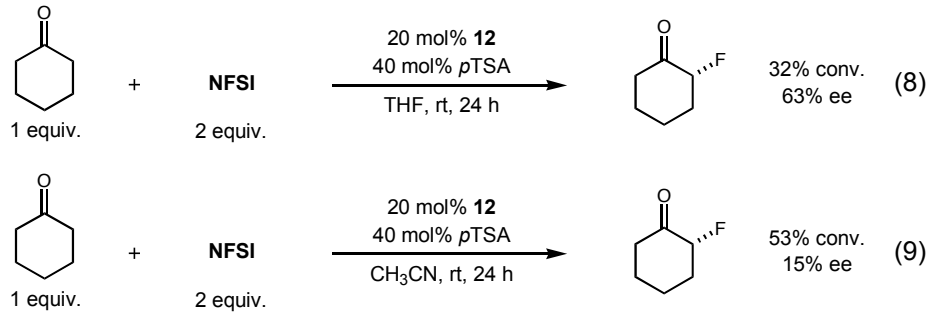


Figure 2. Structures of cinchona alkaloid-derived catalysts; CD=cinchonidine, Q=quinine, C=cinchonine, QD=quinidine DH=dihydro, A=amine.

Recently, McCooey and Connon introduced cinchona alkaloid-derived primary amine catalysts for the enamine-catalyzed addition of ketones to nitroolefins.[12] Since then a number of papers have been published demonstrating the broad usefulness of this

[12] McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.

class of catalysts for both enamine[13] and iminium catalysis.[14] We investigated this catalyst class in the α-fluorination of ketones and found that while the tris-HCl salt of 9-epi-DHQDA **12** resulted in no reaction, 20 mol% of the free-based catalyst with 40 mol% of *para*-toluenesulfonic acid (*p*TSA) as cocatalyst at ambient temperature achieved remarkably high enantioselectivity, albeit in low conversion (equation 8). Use of acetonitrile as solvent achieved much higher reaction efficiency; however, the stereoselectivity was very low (equation 9).



Interestingly, while reactions performed without cocatalyst yielded much lower conversions, the use of anywhere from 20 to 40 mol% of cocatalyst achieved identical results to those performed with 40 mol%. However, reactions performed with 60 mol% of cocatalyst resulted in precipitation of the catalyst and no reaction was observed. This led us to speculate that as the reaction progresses and an equivalent of acid is produced, the catalyst would eventually form a tris-salt and precipitate out of solution, leading to the reaction stalling at low conversion. To circumvent this problem, base additives were

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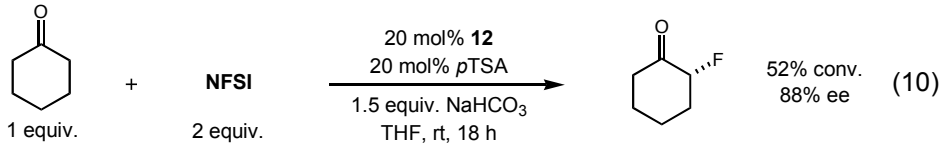
[13] Liu, T.-Y.; Cui, H.-L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 3671.

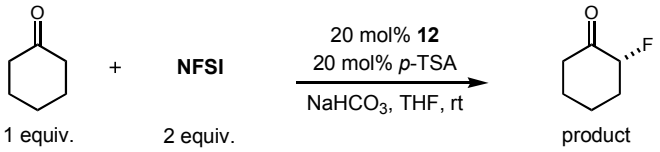
[14] (a) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem. Int. Ed.* **2007**, *46*, 389. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (c) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49. (d) Li, X.; Cun, L.; Lian, C.; Zhong, L.; Chen, Y.; Liao, J.; Zhu, J.; Deng, J. *Org. Biomol. Chem.* **2008**, *6*, 349.



(10)

investigated and to our delight, it was found that the addition of 1.5 equivalents of sodium bicarbonate ($NaHCO_3$) to the reaction mixture resulted in a significant increase in both conversion and enantioselectivity (equation 10). Other additives such as alcohols and molecular sieves, which had been used in literature procedures with cinchona-derived amine catalysts,[15] were not beneficial for the α-fluorination reaction.

Table 3. Effect of Concentration and Base



entry	conc. (M)	equiv. $NaHCO_3$	time (h)	% conversion[a]	% ee[b]
1	0.5	1.5	1	54	86
2	0.33	1	4	57	88
3	0.33	1.5	2	52	89
4	0.33	2	2	53	89
5	0.33	4	2	51	90
6	0.25	1.5	2	56	91
7	0.167	1.5	2	39	92
8	0.125	1.5	2	34	94

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc).

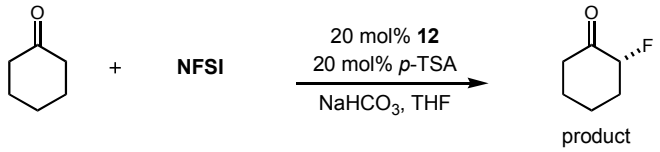
Subsequently, studies were performed to determine the effect of concentration and additional base additive (Table 3). Although increasing the amount of base used in the reaction resulted in slight increases in enantioselectivity (entry 5), conversions

[15] See reference 13.

remained unchanged. On the other hand, more dilute reaction conditions achieved significantly higher enantioselectivities (entry 8), but with lower reaction efficiency.

In all cases studied, it appeared that the reactions were stalling at about 50–60% maximum conversion, possibly due to tris-salt formation that was not being free-based by the excess $NaHCO_3$, or more likely, due to reaction of the catalyst with NFSI over time, generating either an unreactive or insoluble form of the catalyst. Notably, transfer fluorination from NFSI to cinchona alkaloids has been demonstrated in the literature and used for preparing cinchona-derived fluorinating agents.[16]

Table 4. Effect of Temperature and Stoichiometry



entry	equiv. ketone	Temp (ºC)	time (h)	% conversion[a]	% ee[b]
1	1	+23	2	53	85
2	1	+4	8	64	95
3	1	–10	24	71	94
4	1	–20	44	70	96
5	1.5	+4	8	72	96
6	1.5	–20	24	72	97
7	2	–20	24	88	97
8	3	+23	2	70	94

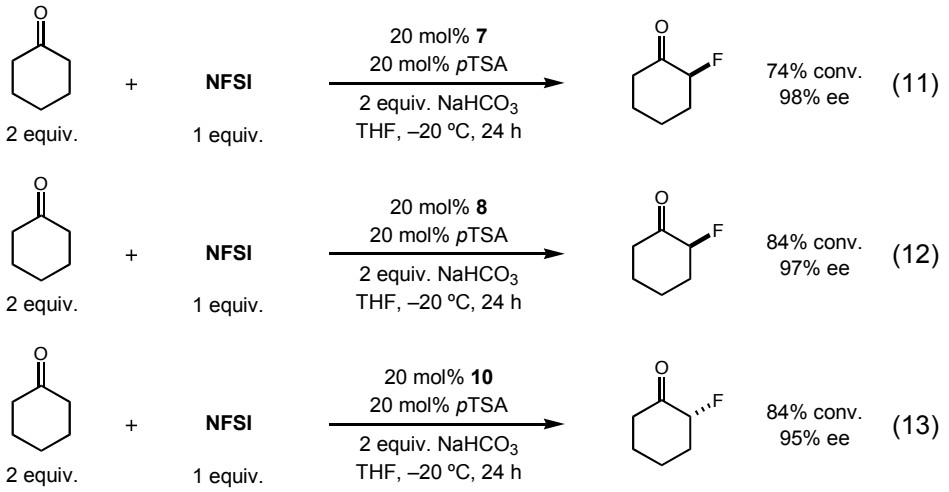
(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc).

In order to circumvent unwanted fluorination of the catalyst and since the highly concentrated reactions were found to be complete in only 1 hour (Table 3, entry 1), the reaction temperature was lowered and the stoichiometry of the reaction was altered so

[16] Baudequin, C.; Loubassou, J.-F.; Plaquevent, J.-C.; Cahard, D. *J. Fluorine Chem.* **2003**, *122*, 189.

that NFSI was used as the limiting reagent. As shown in Table 4, reactions performed at –20 ºC with excess of ketone achieved excellent levels of conversion and enantioselectivity (entry 7; 88% conv., 97% ee). Reactions using these conditions performed in DME, EtOAc, CH_3CN, and DMF demonstrated that the choice of THF as the reaction medium was optimal.[17]

With these optimized reaction conditions in hand, we next investigated the use of other cinchona alkaloid-derived catalysts to determine if equal levels of enantioselectivity and reactivity could be achieved for the opposite enantiomer of the product. Gratifyingly, reactions performed with catalysts **7** and **8** resulted in equally high enantioselectivities and good conversions to the desired (*S*)-2-fluorocyclohexanone (equations 11 and 12). Catalyst **10** resulted in slightly lower selectivities than those obtained with catalyst **12**, but maintained excellent reaction efficiency (equation 13).



Lastly, these reaction conditions have now been applied to a variety of cyclic ketone substrates. Postdoctoral fellow Dr. Piotr Kwiatkowski has successfully

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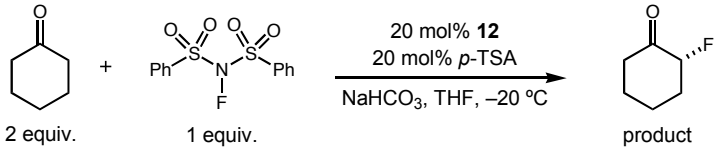
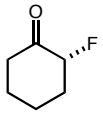
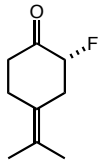
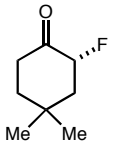
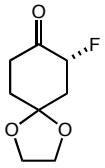
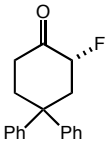
[17] Reactions performed using 1.5 equiv. ketone, 2 equiv. $NaHCO_3$ at –20 ºC for 24 h in DME: 68% conv., 96% ee; EtOAc: 63% conv., 90% ee; CH_3CN: 53% conv. 79% ee; DMF: 13% conv., 92% ee.

synthesized chiral 2-fluorocyclohexyl ketones in good yields and excellent enantioselectivities (Table 5). Further studies are being conducted by Dr. Kwiatkowski towards the fluorination of acyclic rings and heterocyclic ketones such as *N*-BOC-piperidone and 4-tetrahydropyranone, which react under the optimized reaction conditions with excellent enantioselectivities, but are currently difficult to isolate as they readily form hydrates and epimerize under standard chromatographic methods. Full details of the scope of this reaction will soon be reported.

Table 5. α-Fluorination of Ketone Substrates



entry	product	% yield[a]	% ee	entry	product	% yield	% ee
1		50[b] (88)	97	4		73 (79)	98
2		65[b] (95)	96	5		85 (90)	94
3		88	94				

(a) Isolated yields after silica gel chromatography. Yields in parentheses obtained by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Volatile products.

Conclusion

In summary, the development of the first highly enantioselective direct α-fluorination of ketones has been accomplished using cinchona alkaloid-derived catalysts. While traditional catalysts for the amine-catalyzed functionalization of ketones failed to provide desired levels of conversion and stereoselectivity, high yields with excellent enantioselectivities were obtained using 20 mol% of 9-Epi-DHQDA catalyst and NFSI as the fluorine source. This method provides epimerizable fluorine stereocenters using an organocatalyst that is easily prepared and using reaction conditions that are insensitive to both air and moisture, making it a valuable tool for practitioners of pharmaceutical and synthetic chemistry.

Supporting Information

General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego.[18] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on EMD Silica Gel 60 230-400 mesh or Davisil® Silica Gel 200-425 mesh according to the method of Still.[19] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching using potassium permanganate stain. High performance liquid chromatography (HPLC) and gas liquid chromatography (GLC) assays to determine enantiomeric excess were developed using racemic samples.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker Ultrashield™ Plus 500 (500 MHz, 125 MHz) and ^{19}F NMR spectra were recorded on Varian Mercury 300 (282 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C and ^{19}F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the

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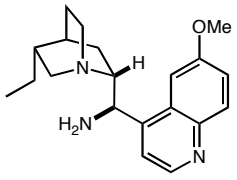
[18] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd edition; Pergamon Press; Oxford, 1988.

[19] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Princeton University Mass Spectral Facility. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard 6850 Series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 Series chromatograph using a Chiralcel® OJ column (25 cm, 5 cm guard) as noted.

Starting Materials



9-epi-DHQDA
12

9-Epi-DHQDA: The triple HCl salt was prepared from hydroquinidine according to the procedure of McCooey and Connon.[20] Isolation of the pure salt was accomplished by dissolving the residue (15 mmol scale reaction) in approx. 250 mL of MeOH while heating to 55 ºC. EtOAc was dripped into the hot solution until the first signs of a fine powder begin to form. The solution was cooled to rt, then placed in a –20 ºC freezer overnight. Care must be taken not to crash out the powder by adding additional EtOAc, which results in impure catalyst. The triple salt was free-based by partitioning between 1N NaOH and DCM, extracting 3 x with DCM, and drying over Na_2SO_4. 1.9g obtained, 29% yield.

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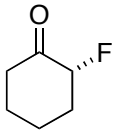
[20] McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.

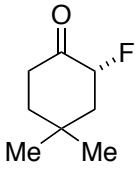
General Procedure for the α-Fluorination of Ketones: To a 10 mL round-bottom flask equipped with a magnetic stir bar and charged with 9-Epi-DHQDA (16 mg, 0.05 mmol), *p*-toluenesulfonic acid (9.5 mg, 0.05 mmol), *N*-fluorobenzenesulfonimide (79 mg, 0.25 mmol), and $NaHCO_3$ (42mg, 0.50 mmol) was added THF (1.0 mL) and the mixture was cooled to –20 °C. The mixture was stirred for 15 min to allow time for the catalyst to dissolve. Ketone (0.50 mmol) was added and the reaction mixture stirred at –20 ºC for 24 h. The reaction was filtered through a pad of silica gel, eluting with Et_2O and purified by silica gel chromatography. Purification of the resulting oil by forced flow chromatography afforded the title compounds. The enantioselectivity was determined either by chiral GLC analysis, chiral HPLC or SFC analysis. The GC yield was determined using methyl cyclohexane-carboxylate as an internal standard and calculated with a GC response factor.

α-Fluoro Ketones



(*R*)-2-Fluorocyclohexanone (Table 5, entry 1): Prepared according to the general procedure from cyclohexanone (259 μL, 2.50 mmol) to afford a colorless oil. Purification on silica gel (20–40% Et_2O/Pentanes) afforded (*S*)-2-fluorocyclohexanone as a colorless liquid (73 mg, 50% yield, 88% GC yield, 97% ee). IR (film) 2947, 2870, 1729, 1452, 1431, 1316, 1086, 1067, 951.5, 912.7, 879.7, 836.9, 743.2, 665.5 cm^{-1}; ^1H NMR (Varian 400 MHz, $CDCl_3$). δ 4.86 (dm, *J* = 49.0 Hz, 1H, FC**H**), δ 2.34–2.59 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.28–2.46 (m, 2H, O=CC$\mathbf{H}_2$, FCHC$\mathbf{H}_2$), δ 1.92–2.06 (m, 2H,

FCHCH$_2$C**H$_2$**), δ 1.78–1.92 (m, 1H, FCHC**H$_2$**), δ 1.60–1.78 (m, 2H, O=CCH$_2$C**H$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 205.9 (d, *J* = 14.8 Hz), 92.9 (d, *J* = 190.3 Hz), 40.4, 34.4 (d, *J* = 18.6 Hz), 27.1 (d, *J* = 1.0 Hz), 22.9 (d, *J* = 10.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –188.7 (dm, *J* = 48.4 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ (C_6H_9FO) requires *m/z* 116.0637, found *m/z* 116.0637. $[\alpha]_D$ = +44.0 (c = 0.68, C_6H_6).[21] Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 140 ºC, 30 min); (*S*) isomer t_r = 39.6 min and (*R*) isomer t_r = 41.2 min.



(*R*)-2-Fluoro-4,4-dimethylcyclohexanone (Table 5, entry 2): Prepared according to the general procedure from 4,4-dimethylcyclohexanone (66 mg, 0.50 mmol) to afford a colorless oil. Purification on silica gel (5–20% Et_2O/Pentanes) afforded (*S*)-2-Fluoro-4,4-dimethylcyclohexanone as colorless volatile crystals (24 mg, 65% yield, 95% GC yield, 96% ee). IR (film) 2595, 2933, 2866, 1727, 1474, 1424, 1366, 1316, 1179, 1129, 1115, 1083, 1048, 1016, 998, 911, 855, 732.1, 703.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$). δ 5.03 (dddd, *J* = 48.4, 12.5, 6.6, 0.8 Hz, 1H, FC**H**), δ 2.34–2.59 (m, 2H, O=CC**H$_2$**), δ 2.18 (dddd, *J* = 12.5, 6.8, 5.6, 3.2, 1H, FCHC**H$_2$**), δ 1.61–1.88 (m, 3H, FCHC**H$_2$**, O=CCH$_2$C**H$_2$**), 1.24 (s, 3H, C**H$_3$**), δ 1.10 (s, 3H, C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 206.3 (d, *J* = 13.4 Hz), 90.6 (d, *J* = 189.4 Hz), 46.3 (d, *J* = 15.7 Hz), 39.5 (d,

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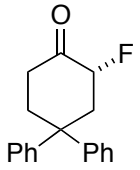
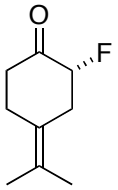
[21] (*R*)-2-Fluorocyclohexanone $[\alpha]_D$ = +54.8 (c = 0.68, C_6H_6): Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, 2307.

J = 1.0 Hz), 36.8, 32.5 (d, *J* = 10.0 Hz), 31.4, 25.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –193.9 (dm, *J* = 48.4 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_8H_{14}FO$) requires *m/z* 144.0950, found *m/z* 144.0950. $[\alpha]_D$ = +46.4 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min); (*S*) isomer t_r = 26.4 min and (*R*) isomer t_r = 28.3 min.

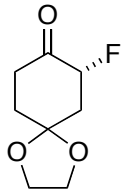


(*R*)-2-Fluoro-4,4-diphenylcyclohexanone (Table 5, entry 3): Prepared according to the general procedure from 4,4-diphenylcyclohexanone (252 mg, 1.04 mmol) to afford a colorless oil. Purification on silica gel (5–20% EtOAc/Petroleum ether) afforded (*S*)-2-Fluoro-4,4-diphenylcyclohexanone as a colorless solid (119 mg, 88% yield, 94% ee). IR (film) 3.59, 2960, 1738, 1599, 1496, 1447, 1072, 1033, 886.4, 841.1, 751.4, 700.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$). δ 7.56 (dd, *J* = 8.4, 1.2 Hz, 1H, **Ph**), δ 7.43–7.51 (m, 1H, **Ph**), δ 7.32–7.38 (m, 1H, **Ph**), δ 7.24–7.32 (m, 2H, **Ph**), δ 7.13–7.23 (m, 2H, **Ph**), δ 5.01 (ddd, *J* = 48.2, 12.8, 6.2 Hz, 1H, FC**H**), δ 3.28–3.54 (m, 1H, FCHC$\mathbf{H}_2$), δ 2.91–3.09 (m, 1H, FCHC$\mathbf{H}_2$), δ 2.51–2.66 (m, 2H, O=CCH_2C$\mathbf{H_2}$), δ 2.29–2.44 (m, 1H, O=CC$\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0 (d, *J* = 13.5 Hz), 147.3, 142.2, 129.6, 128.8, 127.3, 127.0, 126.8, 126.0, 90.5 (d, *J* = 190.3 Hz), 47.4 (d, *J* = 10.4 Hz), 43.5 (d, *J* = 18.2 Hz), 37.5, 37.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –192.5 (d, *J* = 49.0 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}FO$) requires *m/z* 268.1263,

found *m/z* 268.1262. $[\alpha]_D$ = +2.6 (c = 1.1, $CHCl_3$). Enantiopurity was determined by SFC analysis (Chiralcel®ADH 5-50% CH_3CN). t_R(minor) = 3.3 min. t_S(major) = 3.5 min.



(*R*)-2-Fluoro-4-(propan-2-ylidene)cyclohexanone (Table 5, entry 4): Prepared according to the general procedure from 4-(propan-2-ylidene)cyclohexanone (145 mg, 1.04 mmol) to afford a colorless oil. Purification on silica gel (10–20% Et_2O/Petroleum Ether) afforded (*S*)-2-Fluoro-4-(propan-2-ylidene)cyclohexanone as a colorless oil (57 mg, 73% yield, 79% GC yield, 98% ee). IR (film) 2987, 2915, 2859, 1734, 1450, 1429, 1376, 1105, 1070, 1026, 858.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$). δ 4.84 (ddd, *J* = 49.2, 11.8, 6.6 Hz, 1H, FC**H**), δ 3.14–3.37 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.73–2.90 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.45–2.64 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.26–2.43 (m, 2H, FCHC$\mathbf{H}_2$, O=CCH_2C$\mathbf{H}_2$), δ 2.13–2.26 (m, 1H, O=CCH_2C$\mathbf{H}_2$), 1.79 (s, 3H, C$\mathbf{H_3}$), δ 1.77 (s, 3H, C$\mathbf{H_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 205.8 (d, *J* = 14.0 Hz), 129.1, 123.1, 91.8 (d, *J* = 193.4 Hz), 39.4, 36.5 (d, *J* = 19.7 Hz), 28.6, 20.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –188.2 (dm, *J* = 49.3 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_9H_{14}FO$) requires *m/z* 156.0950, found *m/z* 156.0949. $[\alpha]_D$ = +1.8 (c = 0.58, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 140 ºC, 40 min); (*R*) isomer t_r = 45.8 min and (*S*) isomer t_r = 48.1 min.



(*R*)-2-Fluoro-1,4-dioxaspiro[4.5]decan-8-one (Table 5, entry 5): Prepared according to the general procedure from 1,4-dioxaspiro[4.5]decan-8-one (158 mg, 1.00 mmol) to afford a colorless oil. Purification on silica gel (10–30% EtOAc/Petroleum Ether) afforded (*S*)-2-Fluoro-1,4-dioxaspiro[4.5]decan-8-one as a colorless crystalline solid (74 mg, 85% yield, 90% GC yield, 94% ee). IR (film) 2962, 2938, 2904, 1737, 1443, 1424, 1372, 1353, 1310, 1244, 1146, 1123, 1089, 1047, 984.5, 950.9, 930.5, 844.8, 706.8 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$). δ 5.11 (dm, *J* = 48.3 Hz, 1H, FC**H**), δ 3.94–4.15 (m, 4H, (OC$\mathbf{H_2}$)$_2$), δ 2.58–2.70 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.37–2.58 (m, 2H, O=CC$\mathbf{H}_2$, FCHC$\mathbf{H}_2$), δ 2.08–2.26 (m, 1H, FCHC$\mathbf{H}_2$), δ 1.87–2.08 (m, 2H, O=CCH$_2$C$\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 204.6 (d, *J* = 14.3 Hz), 107.4 (d, *J* = 13.8 Hz), 90.2 (d, *J* = 191.2 Hz), 65.1 (d, *J* = 3.3 Hz), 41.7 (d, *J* = 17.6 Hz), 35.3, 34.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –194.1 (dm, *J* = 48.1 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_8H_{12}FO_3$) requires *m/z* 174.0692, found *m/z* 174.0692. $[\alpha]_D$ = +40.5 (c = 1.1, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 140 ºC, 40 min); (*R*) isomer t_r = 50.9 min and (*S*) isomer t_r = 52.1 min.

Chapter 5

SOMO Catalysis: A New Mode of Organocatalytic Activation*†

Introduction

Over the last four decades, the capacity to induce asymmetric transformations using enantioselective catalysts has remained a focal point for extensive research efforts in both industrial and academic settings. During this time, thousands of new asymmetric catalytic reactions have been invented, yet most are derived from a small number of long-established activation modes. Activation methods such as Lewis acid catalysis[1], metal-insertions[2], and hydrogen-bonding catalysis[3] have spawned countless reactions within each class, dramatically expanding the synthetic toolbox available to practitioners of chemical synthesis. Therefore, the design and implementation of novel catalytic activation modes that enable the invention of previously unknown transformations is a necessary objective for the continued advancement of the field of organic chemistry.

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* A report of this work has been published. Portions taken in part from: Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

† The work reported in this chapter was conducted by T. D. Beeson, with the exception of the aldehyde α-allylation substrate scope, which was conducted in cooperation with A. Mastracchio.

1 Yamamoto, H., Ed. *Lewis Acids in Organic Synthesis*; Wiley-VCH; New York, 2000.

2 (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 4th edition; Wiley-Interscience; Hoboken, NJ, 2005. (b) Noyori, R. in *Asymmetric Catalysis in Organic Synthesis*; Wiley-VCH; New York, 1994, pp 123–173. (c) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 2nd edition; Wiley-VCH; New York, 2000.

3 Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

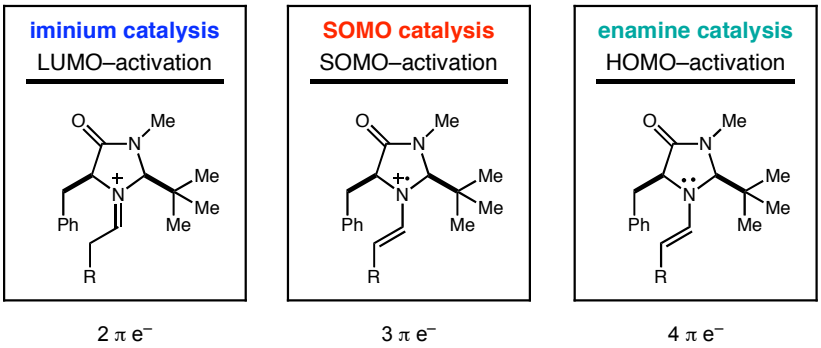
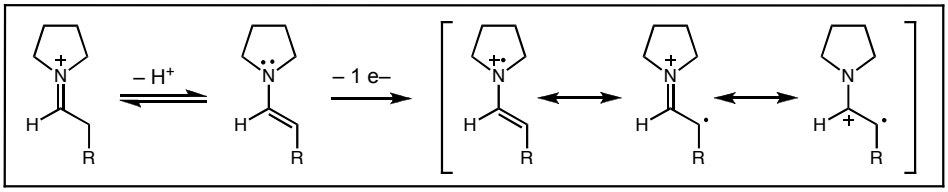


Figure 1. Singly occupied molecular orbital (SOMO) catalysis, a new activation mode that electronically bisects iminium and enamine catalysis.

The previous chapters have discussed both iminium and enamine catalysis, two activation modes that have enabled the discovery of more than sixty new asymmetric chemical reactions to date.[4] Although both have proved to be broadly useful strategies for the enantioselective functionalization of aldehydes and ketones, their expansion to include alkylations,[5] alkenylations, and arylations has been scarce or not yet come to fruition. Given that the π-systems of an iminium and an enamine differ by two electrons, we questioned whether it might be possible to access a new mode of catalytic activation by chemically intercepting the three-electron species that electronically bisects

Scheme 1. Formation of a reactive radical cation by enamine single-electron oxidation



enamine and iminium formation (Figure 1). Whereas enamines react specifically with electrophiles, we hypothesized that a one-electron oxidation of a transient enamine

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[4] (a) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79. (b) Erkkilä, A.; Majander, I.; Pihko, P. *Chem. Rev.* **2007**, *107*, 5416. (c) Mukerjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[5] The intramolecular enamine-catalyzed α-alkylation of aldehydes has been accomplished: Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

species should generate a three-π-electron radical cation that is activated toward a range of nucleophiles, thereby enabling a diverse range of previously unknown asymmetric transformations (Scheme 1).

Proof of Concept Validation

From the outset we recognized that the viability of this concept relied upon the meeting of two key requirements. First, the oxidation potential of the enamine would need to be sufficiently lower than its aldehyde and amine precursors such that a single-electron oxidant could chemoselectively oxidize the enamine in preference to the other species present. The first ionization potential of 1-(but-1-enyl)pyrrolidine[6] has been measured to be 1.56 eV lower than pyrrolidine[7] and 2.6 eV lower than butanal[7] (Figure 2). This data reveals the transient enamine component to be sufficiently more susceptible to oxidation than the accompanying reaction partners.

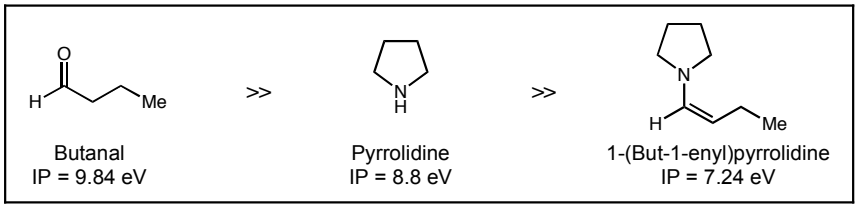

Figure 2. First ionization potentials of an enamine and its precursor aldehyde and amine.

Second, an amine catalyst class was needed that would enforce high levels of facial selectivity to the radical cation. We recognized that like enamines, the radical cation's 3-π-electron system is delocalized with the p-orbital of the nitrogen lone pair

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[6] The second ionization potential of 1-(but-1-enyl)pyrrolidine is 10.04 eV. Müller, K.; Previdoli, F.; Desilvesro, H. *Helv. Chim. Acta* **1981**, *64*, 2497.

[7] Lide, D. R., Ed., *Handbook of Chemistry and Physics*; 76th edition; CRC Press; New York, 1995; p 220.

(Scheme 1) and therefore, the orbitals should maintain a geometry nearly identical to that of its parent enamine. We were able to confirm this on the basis of density functional theory (DFT) calculations performed on the enamine and its radical cation formed between proprionaldehyde and imidazolidinone catalyst **1**. As shown in Figure 3,

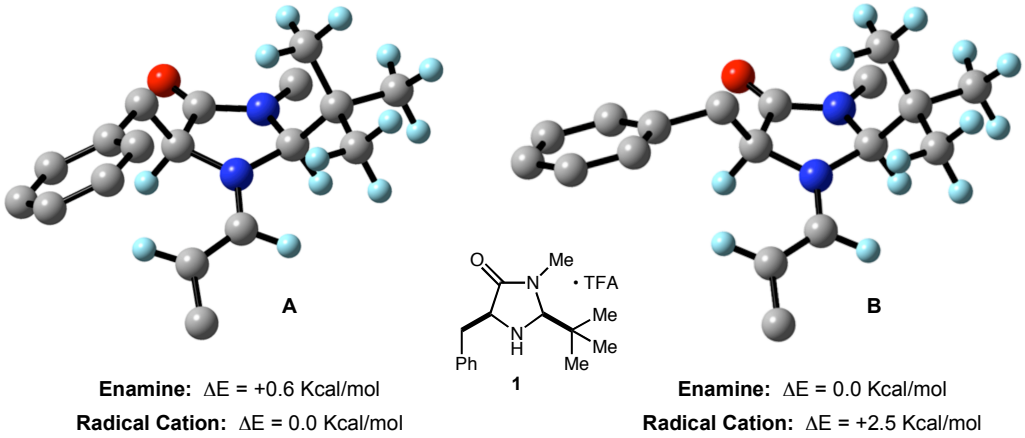

Figure 3. 3-D representations depicting the two lowest energy conformations for both the enantio-differentiated enamine and its radical cation formed between imidazolidinone catalyst **1** and propionaldehyde. Relative energies calculated using density functional theory (DFT).[8]

the two lowest energy conformations, **A** and **B**, display significant facial bias towards one face of the π-system. In conformation **B**, the benzene ring rests directly over the π-system and generates a highly effective facial bias, while in conformation **A**, it is rotated away from the π-system and the facial bias is slightly diminished. Interestingly, while the enamine has a slight preference for conformation **B** (ΔE = 0.6 Kcal/mol), the radical cation highly favors conformation **A** (ΔE = 2.5 Kcal/mol), presumably due to a type of "cation-π" interaction between the benzene ring and the delocalized radical cation of the π-system.

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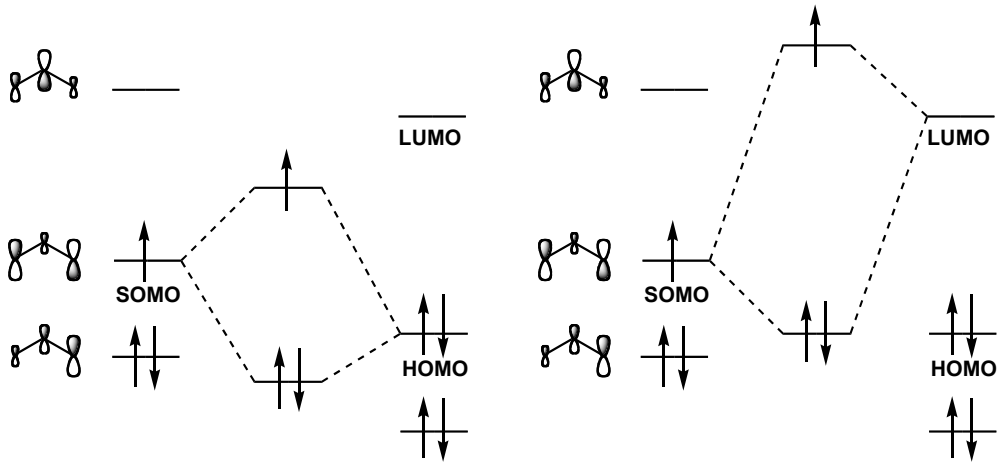
[8] Gaussian DFT calculations performed by Prof. Robert Pascal, Department of Chemistry, Princeton University. Calculations performed using B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d).

Scheme 2. The interaction of the SOMO of a radical with (a) HOMO and (b) LUMO orbitals[9]



(a) SOMO-HOMO (b) SOMO-LUMO

Since radical cations generated from the oxidation of enamines are stabilized due to delocalization of the radical with the π-system (Scheme 1), the singly occupied molecular orbital (SOMO) is relatively low in energy and prefers to interact with the highest occupied molecular orbital (HOMO) of nucleophiles rather than the lowest unoccupied molecular orbital (LUMO) of electrophiles (Scheme 2). Radical cations generated from pre-formed enamines have been shown to react with both unactivated olefins[10] and electron-rich olefins such as silylenolethers.[11] Therefore, as a first attempt at our proposed SOMO-catalyzed reaction, the intramolecular cyclization of cis-6-nonenal was studied using our second-generation imidazolidinone catalyst[12] **1** in the presence of a variety of oxidants. Both organic and metal-based oxidants were analyzed

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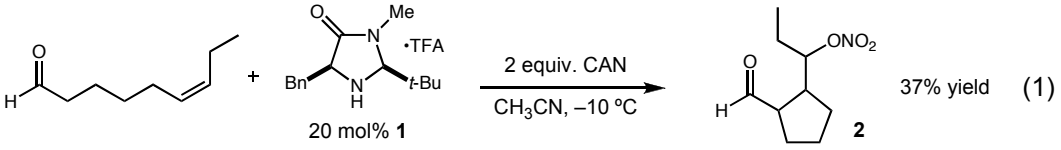
[9] Figure adapted from: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons, Ltd.; Chichester, 2000; p 183.

[10] Cossy, J.; Bouzide, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1218.

[11] Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099.

[12] Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.

and, to our delight, reactions performed with ceric ammonium nitrate (CAN) generated the 5-exo cyclized product **2** with subsequent trapping by a nitrate ligand (equation 1).



α-Allylation of Aldehydes

With this proof of concept in hand, we recognized the potential of this new activation mode to enable the invention of many new and useful enantioselective reactions. Radical cations have been shown to participate in many non-catalytic C–C, C–O, C–N, C–S and C–X (where X is a halogen) bond formations,[13] leading us to believe that SOMO catalysis might provide access to a diverse and powerful collection of previously unknown asymmetric reactions. One such reaction of intense interest within our group and others was the direct and enantioselective α-allylation of aldehydes, due to the established importance of allylation products as chiral synthons in chemical synthesis. While advancements in the α-allylation of other carbonyl species had been accomplished,[14] at the time of this work, there were no aldehyde α-allylation methods in existence.[15,16] In fact, direct allylic alkylations of dicarbonyl species had been established

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[13] Also see references 8 and 9. (a) Kirchgessner, M.; Sreenath, K.; Gopidas, K. R. *J. Org. Chem.* **2006**, *71*, 9849. (b) Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636. (c) Lee, H. B.; Sung, M. J.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 11322. (d) Renaud, P.; Sibi, M. P., Eds.; *Radicals in Organic Synthesis*; Wiley-VHC; Weinheim, 2001; Vol. 2, pp 144–205.

[14] Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103* 2921.

[15] Before publication of this work, a non-enantioselective α-allylation of aldehydes appeared in the literature: Ibrahem, I.; Córdova, J. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1952.

[16] After completion of this work, the following enantioselective α-allylation of aldehydes appeared in the literature: Mukerjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336.

but methods for the allylic alkylation of ketones have required covalent attachment of the allylating species for intramolecular alkylation[17] or preforming of the silylenol ether[18a] or metal enolate[18] to act as the reactive species.[19]

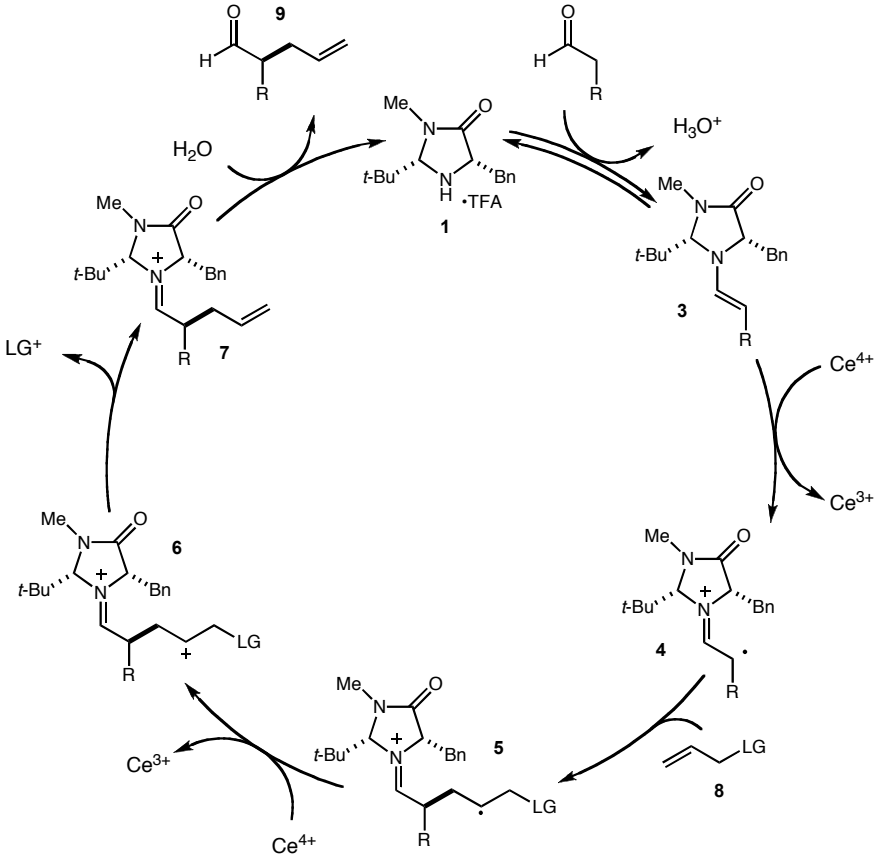

Figure 4. Proposed catalytic cycle of the SOMO-catalyzed aldehyde α-allylation reaction.

Mechanistically, we speculated that a transiently formed radical cation **4** could combine with an allyl π-nucleophile **8** with a facile leaving group to generate a secondary radical **5** (Figure 4). Upon further oxidation to the secondary carbocation **6**, the leaving

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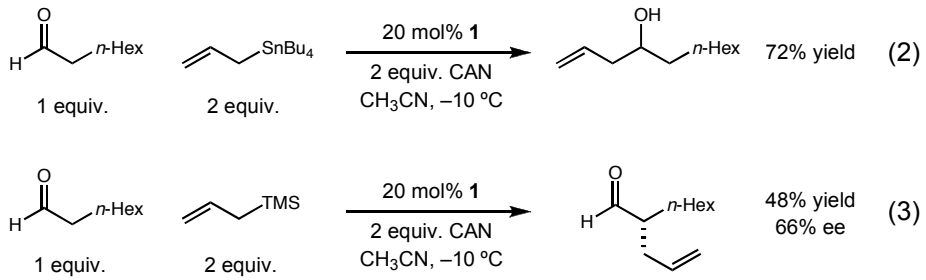
[17] (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (c) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180.

[18] Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62.

[19] Direct ketone allylic alkylation via in situ formation of lithium enolates has now been accomplished: (a) Braun, M.; Meier, T. *Synlett*, 2968. (b) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718.

group could eliminate to generate the α-allylated iminium species **7**, which upon hydrolysis would provide the desired α-allylated aldehyde **9** and regenerate the catalyst.

With this in mind, we first examined a variety of allylating reagents with the capacity to generate stabilized intermediates and/or leaving groups. Of the reagents studied, only allyltributylstannane and allyltrimethylsilane afforded the desired α-allylated aldehyde, however, allyltributylstannane predominantly reacted with the carbonyl of the starting material (equation 2). On the other hand, allyltrimethylsilane reacted solely with the transient enamine radical cation, and to our delight, generated the desired product in 66% ee and 48% yield (equation 3).



A broad survey of potential single–electron oxidants was conducted to ascertain whether CAN was the optimal oxidant for the SOMO-catalyzed α-allylation reaction, including hypervalent idodides, quinones and an assortment of transition metals. Since oxidation potentials can vary widely with the choice of solvent, oxidants were studied in both CH_3CN and methylene chloride (CH_2Cl_2). While certain iron and copper oxidants were shown to generate product in CH_3CN,[20] the reactions progressed with much lower efficiency than CAN and therefore, we chose to pursue further optimization of the CAN-mediated reaction.

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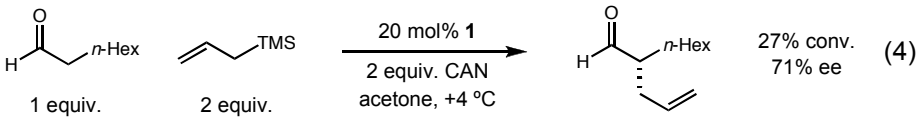
[20] Approximately 5% conversion was obtained with $Fe(NO_3)_3$, $Cu(NO_3)_2$, and $Cu(OTFA)_2$. 11% conversion was obtained with $Fe(Phen)_3(PF_6)_3$.

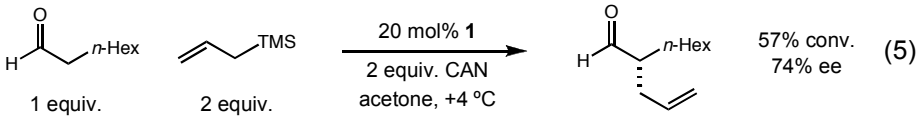
The first major achievement came after literature analysis suggested that the radical cation might be able to react with oxygen in the atmosphere,[21] competing with the allylsilane for product formation. Degassing the reaction mixture prior to addition of the starting aldehyde dramatically improved the conversion and at +4 ºC in CH_3CN, the conversion more than doubled from 23% to 53%. Reactions subsequently performed in acetone achieved higher enantioselectivities and also saw a dramatic increase in conversion upon oxygen exclusion (equations 4 and 5).

Reaction without degassing:



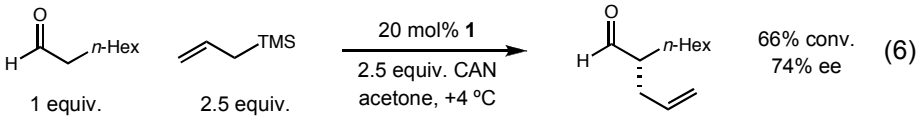
1 equiv. 2 equiv. (4)

Degassed reaction conditions:



1 equiv. 2 equiv. (5)

Additionally, as our understanding of the reaction mechanism dictated that a minimum of 2 moles of CAN were required per mole of aldehyde, we increased the relative stoichiometry of the reaction and determined that 2.5 equivalents of oxidant and allylsilane were optimal (equation 6). Additional amounts of oxidant prohibited efficient stirring of the reaction and provided lower overall yields.



1 equiv. 2.5 equiv. (6)

Next we studied the effect of temperature and concentration, hoping to obtain the needed improvement in enantiocontrol. As shown in Table 1, a slight increase in

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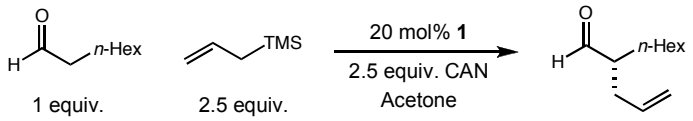
[21] Nair, V.; Rajan, R.; Mohana, K.; Sheeba, V. *Tetrahedron Lett.* **2003**, *44*, 4585.

selectivity was achieved at –20 ºC, with maximum conversions obtained at more dilute concentrations. At the same time, a variety of imidazolidinone catalyst architectures were studied, including geminally disubstituted and *trans*-oriented catalysts, however, catalyst **1** consistently yielded the best results. Acid co-catalysts of varying pKa values were also studied, and while a few of the acids achieved comparable conversions and enantioselectivities, they did not improve on the results already obtained with the trifluoroacetic acid (TFA) salt of catalyst **1**. Likewise, the electronic requirement of the trialkylsilane component was investigated with a variety of alkyl- and aryl-substituted allylsilanes, and allyltrimethylsilane was shown to be the preferable allylating reagent. Full details of these experiments can be found in Appendix A on page 115.

Table 1. Effect of Temperature and Concentration



1 equiv. 2.5 equiv.

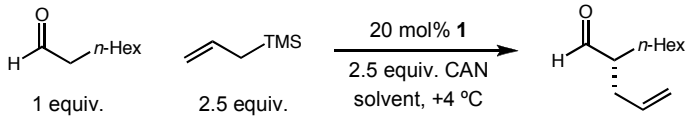
entry	Conc. (M)	Temp (ºC)	time (h)	% conversion[a]	% ee[b]
1	0.0625	+4	3	64	75
2	0.0625	–10	6	72	77
3	0.0625	–20	18	75	80
4	0.0833	–20	18	75	80
5	0.125	–20	18	67	80
6	0.167	–20	18	44	80
7	0.250	–20	18	48	80

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

Since we had achieved such a dramatic improvement in enantioselectivity when the reaction medium was changed from CH_3CN to acetone (66% ee versus 74% ee), additional solvents were studied to ascertain whether further improvements in selectivity could be attained. As shown in Table 2, reactions performed in ethyl acetate (EtOAc)

were similar to those in acetone while chloroform provided no desired product. Surprisingly, reactions performed in the etherial solvents tetrahydrofuran (THF) and dimethoxyethane (DME) attained significantly higher levels of enantioselectivity; however, the reaction efficiencies were much lower than those in other solvents.

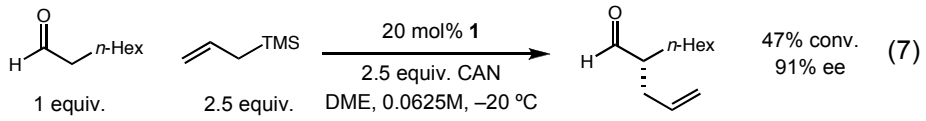
Table 2. Effect of Solvent on the α-Allylation Reaction



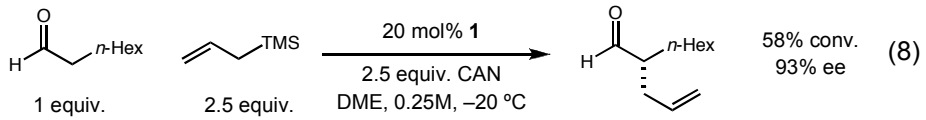
entry	solvent	time (h)	% conversion[a]	% ee[b]
1	CH_3CN	2	53	66
2	Acetone	3	66	74
3	EtOAc	13	44	73
4	$CHCl_3$	13	0	–
5	THF	6	19	82
6	DME	6	31	85

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

Nevertheless, further optimization of the reaction performed in DME demonstrated that excellent enantioselectivity and improved reaction efficiency could be achieved with lower reaction temperatures and higher concentrations (equations 7 and 8), a surprising result considering that lower concentrations were optimal for reactions performed in acetone. Although excellent enantioselectivities for the α-allylation reaction had been realized, reaction efficiencies remained inadequate and needed further optimization.

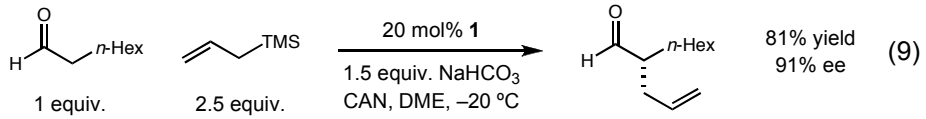


(7)



(8)

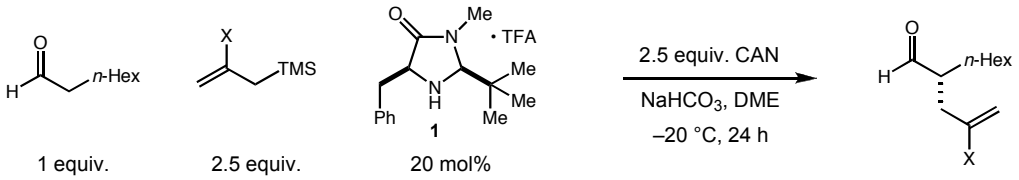
At this point in time, we began to question whether the large excess of allylsilane required in the reaction was possibly the result of acidic degradation induced by the silane cation or nitric acid formed during the reaction. For this reason, we studied a variety of base additives that could act as scavengers of these acidic byproducts. Of the bases studied, sodium bicarbonate ($NaHCO_3$), potassium bicarbonate ($KHCO_3$), and di-*tert*-buylpyridine (DTBP) provided the most improvement, with 1.5 equivalents of $NaHCO_3$ consistently achieving the best results. Gratifyingly, the α-allylation of octanal could now be accomplished in 81% yield and 91% ee (equation 9).



(9)

Furthermore, we explored the generality of the α-allylation reaction by investigating a variety of substituted allylsilanes and aldehydes containing common functionalities. As demonstrated in Table 3, an assortment of π-rich substituted allylsilanes readily participate as allylic alkylating reagents in this new catalytic protocol. Both methyl and phenyl 2-substituted allylsilanes reacted without loss in reaction efficiency or enantiocontrol (entries 1–2). Perhaps most striking is the electron-deficient acrylate substrate (entry 4), which reacted as effectively as the more π-rich substrates, likely due to its capacity to stabilize the subsequently formed radical through the captodative effect. The ester appendage acts effectively as an electron-withdrawing "captor," while the β-silicon serves in a "dative" capacity to donate electrons from the silicon-carbon σ-bond to the radical p-orbital.

Table 3. SOMO-Catalyzed Reactions with Substituted Allylsilanes



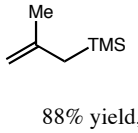
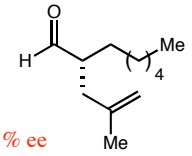
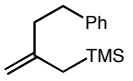
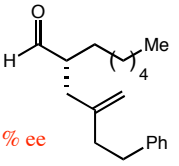
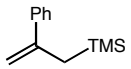
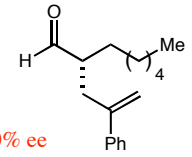
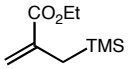
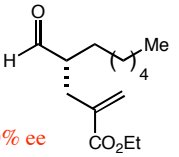
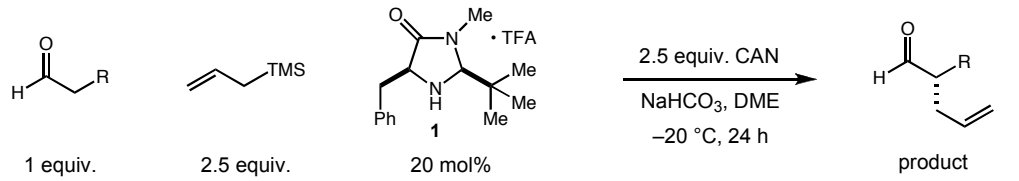
entry	allylsilane	product	entry	allylsilane	product
1			3		
	88% yield, 91% ee			77% yield, 88% ee	
2			4		
	87% yield, 90% ee			81% yield, 90% ee	

Table 4. SOMO-Catalyzed α-Allylation of Various Aldehydes



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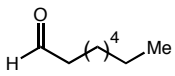
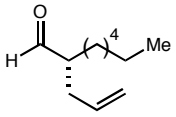
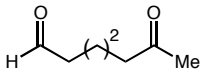
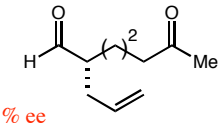
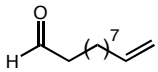
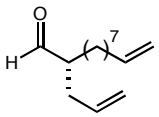
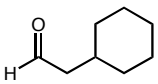
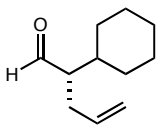
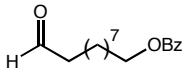
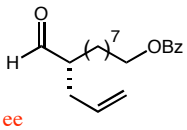
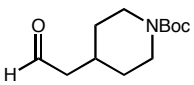
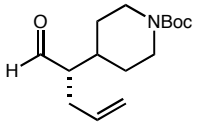
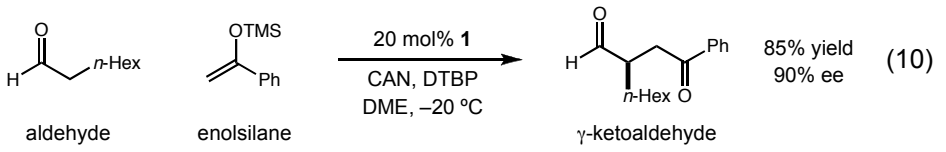
1			4		
	81% yield, 91% ee			72% yield, 87% ee	
2			5		
	75% yield, 92% ee			75% yield[a], 94% ee	
3			6		
	72% yield, 95% ee			70% yield, 93% ee	

(a) Yield determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate).

Additionally, aldehyde substrates with various functionalities including olefins, ketones, and esters, as well as protected alcohols and amines were well tolerated in the α-allylation reaction (Table 4, entries 1–4). We were very pleased to find that the more sterically demanding cyclohexyl and piperidine substrates reacted just as effectively, achieving good yields and excellent enantioselectivities (Table 4, entries 5–6).

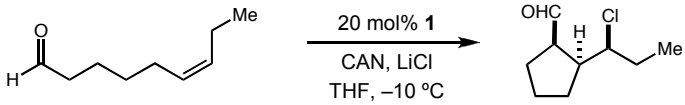
SOMO-Catalysis Applications

Over the last few years, the advent of SOMO-catalysis as a new activation mode has allowed our lab to rapidly invent many previously unknown catalytic and enantioselective transformations. For example, Drs. Jang and Hong showed that silylenol ethers were able to act efficiently as SOMO nucleophiles to produce enantiopure 1,4-dicarbonyls (equation 10), presumably through a similar mechanism as the α-allylation reaction in which a β-silyl radical intermediate at the carbonyl carbon undergoes oxidation to the carbocation, and subsequent silyl cation elimination.[22] Similarly, postdoctoral fellow Dr. Hahn Kim realized the potential of vinyl boronates to act as π-nucleophiles that could undergo radical combination alpha to the boronate (equation 11),



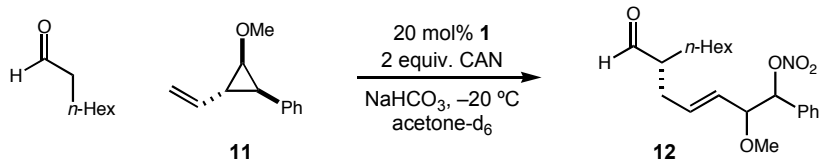
[22] Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004.

generating a beta-stabilized radical intermediate similar to that produced in the α-allylation reaction.[23] Interestingly, postdoctoral fellow Dr. Kate Ashton discovered that the intramolecular 5-exo-cyclization reaction of cis-6-nonenal could be terminated with a halogen nucleophile, out-competing the nitrate ligand, and generating three contiguous stereocenters (equation 12).[24] In addition, SOMO-catalyzed α-arylations[24] and α-carbo-oxidations[25] have also been accomplished, and to date, a total of fourteen new transformations have been invented in our lab using the SOMO-catalysis protocol.



(12)

Finally, a demonstration of the radical-based mechanism of SOMO-catalysis has been carried out using the radical clock **11** developed by Newcomb and coworkers to distinguish between radical and cationic pathways.[26] Exposing **11** to our SOMO-catalysis reaction conditions resulted in scission of the benzylic cyclopropyl bond followed by nitrate trapping to form **12**, which is in complete accord with a radical-based pathway (equation 13).



(13)

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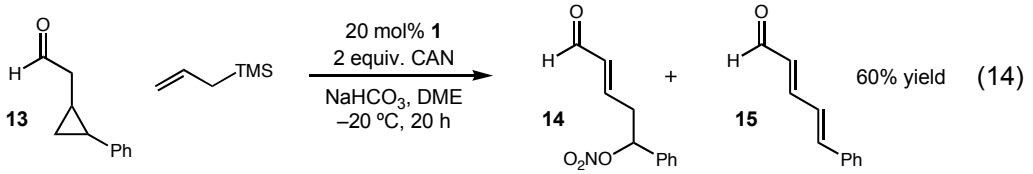
[23] Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398.

[24] Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

[25] Jones, C. M.; Graham, T. H.; MacMillan, D. W. C. in press.

[26] (a) Newcomb M.; Chestney, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 9753. (b) Le Tadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc. Perkin Trans.* **1996**, *2*, 1467.

In addition, graduate student Robert Knowles has shown that the cyclopropyl aldehyde **13** undergoes facile ring opening to generate the α,β-unsaturated aldehyde **14** with subsequent nitrate trapping (equation 14). The nitrated product rapidly eliminates nitric acid while standing at ambient temperature to form the fully conjugated diene **15**. Notably, there was no detection of any α-allylated cyclopropyl aldehyde in these experiments.



(14)

Conclusion

In summary, we have described a new mode of chemical activation based on the catalytic formation of chiral radical cations. While enamines react only with electrophiles, single-electron oxidation to the radical cation allows reactions with SOMO nucleophiles at the same reacting center and enabling a diverse range of previously unknown asymmetric transformations. This technology, termed SOMO-catalysis, has enabled the first enantioselective α-allylation of aldehydes through a radical mechanism with simple allylsilanes. Using this new platform of reactivity, several previously unknown asymmetric methodologies have been developed, demonstrating the value of SOMO-catalysis as a new activation mode for the field of organic chemistry.

Supporting Information

General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego.[27] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Iatrobeads 6RS–8060 according to the method of Still.[28] Filtration of reactions was performed using EMD Silica Gel 60 230-400 mesh. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching using anisaldehyde, ceric ammonium molybdenate, potassium permanganate or iodine stain. Supercritical fluid chromatography (SFC) and gas liquid chromatography (GLC) assays to determine enantiomeric excess were developed using racemic samples.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) unless otherwise noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H and ^{13}C NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of

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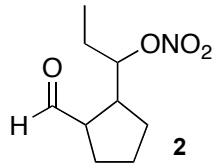
[27] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd edition; Pergamon Press; Oxford, 1988.
[28] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Technology Mass Spectral Facility unless otherwise noted. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard 6850 Series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column or Hewlett Packard HP-1 (30m x 0.32mm) column. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a variable-wavelength UV detector using a Chiralcel® OJH, ODH and Chiralpak®ADH column (25 cm) as noted (4.0 mL/min.). Optical rotations were recorded on a Jasco P-1010 Polarimeter.



2

1-(2-formylcyclopentyl)propyl nitrate 2 (equation 1): To an oven-dried 50 mL round-bottom flask equipped with a magnetic stir bar and charged with (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one trifluoroacetic acid salt **1** (72 mg, 0.20 mmol) and ceric ammonium nitrate (CAN) (1.10g, 2.0 mmol) was added acetonitrile (CH_3CN) (16 mL) and the mixture cooled to –10 ºC. *Cis*-6-nonenal (167 μL, 1.00 mmol) was added and the reaction stirred vigorously 24 h at –10 ºC, and then filtered through a pad of silica gel, eluting with ether (Et_2O). Purification on silica gel (5–50% Et_2O/Pentanes) afforded 1-(2-formylcyclopentyl)propyl nitrate as a mixture of two diastereomers. (75 mg, 37% yield). IR (film) 2962, 2876, 2815, 2719, 1719, 1616, 1459, 1386, 1269, 912.9, 852.2, 784.0, 753.7, 695.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for the major diastereomer δ 9.64 (d, J = 2.4 Hz, 1H, C**H**O), 4.99–5.05 (m, 1H, C**H**NO_3), 2.57–2.72 (m, 2H, C**H**C**H**CHO), 1.20–1.97 (m, 8H, CH(C$\mathbf{H_2})_3$, C$\mathbf{H_2}CH_3$), 0.99 (t, J = 7.5 Hz, 3H, C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, acetone-d_6) major diastereomer: δ 202.4, 88.1, 55.3, 41.9, 30.1, 27.4,

25.5, 25.3, 9.3. Minor diastereomer: δ 202.4, 87.1, 54.0, 41.6, 27.9, 27.6, 25.2, 25.0, 9.9. HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_9H_{16}NO_4$) requires *m/z* 201.1001, found *m/z* 201.1002.

General Procedure for the α-Allylation of Aldehydes:

To an oven-dried 25 mL round-bottom flask equipped with a magnetic stir bar and charged with (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one trifluoroacetic acid salt **1** (72 mg, 0.20 mmol), ceric ammonium nitrate (CAN) (1.37g, 2.5 mmol), and oven-dried sodium bicarbonate (126 mg, 1.5 mmol) was added dimethoxyethane[29] (DME) (4.0 mL). The suspension was cooled to –50 ºC and deoxygenated by stirring vigorously under vacuum for 3–5 min.[30] The mixture was back-filled with argon and degassed twice more. The allyltrimethylsilane substrate (2.5 mmol) was added followed by the aldehyde substrate (1.0 mmol). The reaction was warmed to -20 ºC and stirred for 24 h under an argon atmosphere. The reaction was then cooled to -50 ºC and quickly filtered through a pad of silica gel, eluting with Et_2O. The flask was washed with a minimal amount of DME to transfer any remaining yellow solid to the silica pad. The filtrate was concentrated *in vacuo* and purified by forced flow chromatography to afford the title compounds. The enantioselectivity was determined either by chiral GLC analysis or chiral SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride.

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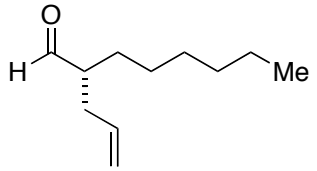
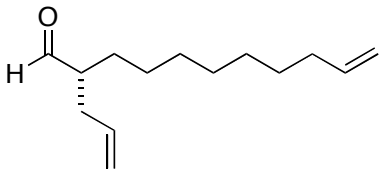
[29] Wet, non-distilled DME. Alternatively, 0.3 equiv. H_2O can be added to dry DME.

[30] The method of freeze-pump thaw, when used to deoxygenate the reaction mixture, showed less consistent results and lower yields, possibly due to the heterogeneity of the reactions.

α-Allyl Aldehydes

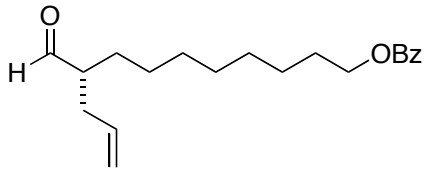


(*R*)-2-Allyloctanal (Table 4, entry 1): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) to afford a yellow oil. Purification on Iatrobeads (2–10% Et_2O/Pentanes) afforded (*R*)-2-allyloctanal as a colorless oil (137 mg, 81% yield, 91% ee). IR (film) 3075, 2928, 2858, 2703, 1728, 1708, 1641, 1458, 992.6, 915.5, 724.0 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.4 Hz, 1H, C**H**O), 5.69–5.84 (m, 1H, C**H**=CH_2), 4.97–5.10 (m, 2H, CH=C**H**$_2$), 2.30–2.46 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 2.17–2.28 (m, 1H, CHC**H**$_2$CH), δ 1.38–1.72 (dm, 2H, C**H**$_2$(CH_2)$_4$), 1.20–1.38 (m, 8H, CH_2(C**H**$_2$)$_4$), 0.87 (t, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 136.4, 116.9, 51.7, 33.5, 32.2, 29.9, 28.8, 27.4, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{11}H_{20}O$) requires *m/z* 168.1514, found *m/z* 168.1508. $[\alpha]_D$ = +12.7 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 23.2 min and (*R*) isomer t_r = 23.8 min.



(*R*)-2-Allyl-undec-10-enal (Table 4, entry 2): Prepared according to the general procedure from undecylenic aldehyde (200 μL, 1.00 mmol) to afford a yellow oil.

Purification on Iatrobeads (2–10% Et_2O/Pentanes) afforded (*R*)-2-allyl-undec-10-enal as a colorless oil (156 mg, 75% yield, 92% ee). IR (film) 3077, 2927, 2855, 2704, 1728, 1641, 1441, 993.1, 912.1, 721.4 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.2 Hz, 1H, C**H**O), 5.69–5.86 (m, 2H, $CHCH_2C\mathbf{H}{=}CH_\mathbf{2}$, $CH_2CH_2C\mathbf{H}{=}CH_2$), 4.86–5.10 (m, 4H, $CHCH_2CH{=}C\mathbf{H_2}$, $CH_2CH_2CH{=}C\mathbf{H_2}$), 2.30–2.46 (m, 2H, $CHC\mathbf{H}_2CH$, C**H**CHO), 2.17–2.28 (m, 1H, $CHC\mathbf{H}_2CH$), 1.98–2.06 (m, 2H, $CH_2C\mathbf{H_2}CH{=}CH_2$), 1.20–1.72 (m, 12H, $CH(C\mathbf{H_2})_\mathbf{6}$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 139.7, 136.5, 116.9, 114.6, 51.7, 34.4, 33.5, 29.9, 29.6, 29.5, 28.8, 27.5. HRMS (FAB+) exact mass calculated for $[M+\bullet]^+$ ($C_{14}H_{24}O$) requires *m/z* 208.1827, found *m/z* 208.1822. $[\alpha]_D$ = +12.1 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride. (Chiralcel®OJH 5% Isocratic MeCN). t_S(minor) = 3.9 min. t_R(major) = 4.4 min.



(*R*)-9-Formyldodec-11-enyl benzoate (Table 4, entry 3): Prepared according to the general procedure from 9-formylnonyl benzoate (138 mg, 0.5 mmol) to afford a yellow oil. Purification on Iatrobeads (10–50% Et_2O/Pentanes) afforded (*R*)-9-formyldodec-11-enyl benzoate as a colorless oil (114 mg, 72% yield, 95% ee). IR (film) 3077, 2927, 2855, 2704, 1728, 1641, 1441, 993.1, 912.1, 721.4 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.1 Hz, 1H, C**H**O), 7.99–8.04 (m, 2H, Ph), 7.59–7.66 (m, 1H, Ph), 7.47–7.54 (m, 2H, Ph), 5.69–5.84 (m, 1H, $C\mathbf{H}{=}CH_\mathbf{2}$), 4.97–5.10 (m, 2H, $CH{=}C\mathbf{H_2}$),

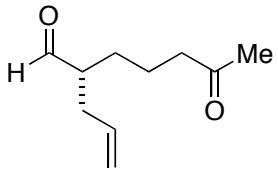
4.30 (t, J = 6.5 Hz, 2H, C**H**$_2$OBz), 2.30–2.46 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 2.17–2.28 (m, 1H, CHC**H**$_2$CH), 1.20–1.82 (m, 14H, (C**H**$_2$)$_7$CH$_2$OBz); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 166.6, 136.5, 133.7, 131.4, 130.0, 129.3, 116.9, 65.4, 51.7, 33.5, 30.2, 29.9, 29.8, 29.3, 28.8, 27.4, 26.6. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{20}H_{28}O_3$) requires m/z 316.2039, found m/z 316.2041. $[\alpha]_D$ = +5.8 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after acetal formation with (*R,R)*-pentadiol of both (*R*)-9-formyldodec-11-enyl benzoate and (*S*)-9-formyldodec-11-enyl benzoate, separately. (Chiralcel®ODH 5–10% MeCN). (*R,R,S*) isomer t_r = 6.2 min and (*R,R,R*) isomer t_r = 6.9 min.

9-Formylnonyl Benzoate: A solution of 10-hydroxydecyl benzoate (2.9 g, 10.4 mmol) in dichloromethane (DCM) (40 mL) was cooled to 0 ºC and pyridinium chlorochromate (PCC) was added (3.4 g, 15.6 mmol). The reaction was warmed to ambient temperature and stirred for 4 h. The reaction was filtered through Florisil®, washed with Et_2O, and concentrated in vacuo. Purification by forced flow chromatography (30% Et_2O/Pentanes) afforded the title compound (1.58 g, 55% yield). IR (film) 2922, 2851, 1714, 1451, 1386, 1309, 1269, 1173, 1105, 1070, 1024, 708 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.77 (t, J = 1.83 Hz, 1H, C**H**O), 8.04–8.06 (m, 2H, *ortho*-phenyl), 7.54–7.58 (m, 1H, *para*-phenyl), 7.43–7.46 (m, 2H, *meta*-phenyl), 4.32 (t, J = 6.78 Hz, 2H, C**H**$_2$OC(O)Ph), 2.34–2.44 (m, 2H, C**H**$_2$CHO), 1.75–1.79 (m, 2H, C**H**$_2$CH$_2$OC(O)Ph), 1.62–1.65 (m, 2H, C**H**$_2$CH$_2$CHO), 1.33–1.47 (m, 10H, CH$_2$(C**H**$_2$)$_5$CH$_2$); ^{13}C NMR (125 MHz, acetone-d_6) δ 202.9, 166.7, 133.8, 131.5, 130.1,

129.4, 64.6, 44.3, 34.2, 30.1, 30.0, 29.9, 26.8, 25.7, 22.7. HRMS (EI+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}O_3$) requires *m/z* 277.1804, found *m/z* 277.1795.

10-Hydroxydecyl benzoate: To a solution of 1,10-decanediol (5.0 g, 28.7 mmol) in 100 mL of tetrahydrofuran (THF) was added triethylamine (TEA) (4.8 mL, 34.4 mmol) and the reaction mixture was cooled to 0 ºC. Benzoyl chloride (1.7 mL, 14.3 mmol) was slowly added and the reaction mixture was stirred at 0 ºC for 45 min, then at ambient temperature overnight. The reaction was concentrated in vacuo until 15 mL of solvent remained, then filtered and washed with Et_2O. The filtrate was concentrated in vacuo and filtered a second time, and the filtrate purified by forced flow chromatography (30–100% Et_2O/Pentanes) (2.91 g, 73% yield). IR (film) 3362, 2922, 2851, 1717, 1451, 1383, 1312, 1269, 1173, 1110, 1067, 1024, 706 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.04 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H, *ortho*-phenyl), 7.62–7.66 (m, 1H, *para*-phenyl), 7.50–7.55 (m, 2H, *meta*-phenyl), 4.32 (t, *J* = 6.8 Hz, 2H, C**H**$_2$OC(O)Ph), 3.51–3.55 (m, 2H, C**H**$_2$OH), 3.38–3.44 (m, 1H, O**H**), 1.75–1.82 (m, 2H, C**H**$_2$CH$_2$OC(O)Ph), 1.31–1.54 (m, 14H, (C**H**$_2$)$_7$CH$_2$OH; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 133.0, 130.7, 129.7, 128.5, 65.3, 63.3, 33.0, 29.7, 29.6, 29.6, 29.4, 28.9 26.2, 25.9. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{17}H_{26}O_3$) requires *m/z* 278.1882, found *m/z* 278.1879.[31]

[31] Mass spectra obtained from the Princeton University Mass Spectral Facility.



(*R*)-2-Allyl-6-oxoheptanal (Table 4, entry 4): Prepared according to the general procedure from 6-oxoheptanal[32] (128 mg, 1.0 mmol) to afford a yellow oil. Purification on Iatrobeads (20–60% Et_2O/Pentanes) afforded (*R*)-2-allyl-6-oxoheptanal as a colorless oil (121 mg, 72% yield, 87% ee). IR (film) 3418, 3079, 2931, 2862, 2720, 1718, 1642, 1416, 1361, 1164, 996.4, 919.5, 725.7 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.60 (d, *J* = 2.1 Hz, 1H, C**H**O), 5.69–5.84 (m, 1H, C**H**=CH_2), 4.97–5.11 (m, 2H, CH=C$\mathbf{H_2}$), 2.46 (t, *J* = 6.9 Hz, 2H, C$\mathbf{H_2}$OCH_3), 2.32–2.44 (m, 2H, CHC$\mathbf{H_2}$CH, C**H**CHO), 2.18–2.28 (m, 1H, CHC$\mathbf{H_2}$CH), 2.06 (s, 3H, C$\mathbf{H_3}$), 1.39–1.68 (m, 4H, CH(C$\mathbf{H_2}$)$_\mathbf{2}$); ^{13}C NMR (75 MHz, acetone-d_6) δ 207.6, 204.6, 136.3, 117.0, 51.6, 43.4, 33.4, 29.6, 28.1, 21.6. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{10}H_{16}O_2$) requires *m/z* 168.1150, found *m/z* 168.1149. $[\alpha]_D$ = –8.0 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC analysis after acetal formation with (*R,R)*-pentadiol of both (*R*)-2-allyl-6-oxoheptanal and (*S*)-2-allyl-6-oxoheptanal, separately. Varian Chirasil-Dex-CB (25M x 0.25mm) column (115 ^{0}C isotherm); (*R,R,R*) isomer t_r = 93.5 min and (*R,R,S*) isomer t_r = 96.6 min.

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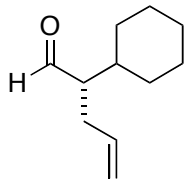
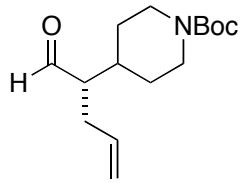
[32] Hong, B.-C.; Chen, F.-L.; Chen, S.-H.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2005**, *7*, 557.



(*S*)-2-Cyclohexylpent-4-enal (Table 4, entry 5): Prepared according to the general procedure from 2-cyclohexylacetaldehyde (15.6 mg, 0.125 mmol) and methyl cyclohexanecarboxylate (19.9 mg, 0.140 mmol) as an internal standard (75% GC yield, 94% ee). Purification on Iatrobeads for characterization (10–50% Et_2O/Pentanes) afforded (*S*)-2-cyclohexylpent-4-enal as a volatile colorless oil containing Et_2O. IR (film) 3078, 2927, 2854, 2706, 1726, 1642, 1449, 994.1, 914.8, 851.6 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.62 (d, *J* = 2.7 Hz, 1H, C**H**O), 5.68–5.81 (m, 1H, C**H**=CH_2), 4.94–5.08 (m, 2H, CH=C**H**$_2$), 2.36–2.47 (m, 1H, CHC**H**$_2$CH), 2.16–2.30 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 1.60–1.78 and 1.02–1.33 (m, 11H, cyclohexyl); ^{13}C NMR (75 MHz, acetone-d_6) δ 205.0, 137.1, 116.5, 57.4, 38.4, 31.1, 30.8, 30.6, 27.0, 27.0, 26.8. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{11}H_{18}O$) requires *m/z* 166.1358, found *m/z* 166.1361. $[\alpha]_D$ = +33.9 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 36.3 min and (*R*) isomer t_r = 37.7 min.



***tert*-Butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate (Table 4, entry 6):** Prepared according to the general procedure from *tert*-butyl 4-(formylmethyl)piperidine-1-carboxylate[33] (114 mg, 0.5 mmol) to afford a yellow oil. Purification on Iatrobeads (25–50% Et_2O/Pentanes) afforded *tert*-butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate as a colorless oil (94 mg, 70% yield, 93% ee). IR (film) 2977, 2932, 2854, 2713, 1726, 1692, 1423, 1366, 1281, 1249, 1172, 918.0, 866.6, 769.3 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.65 (d, *J* = 2.7 Hz, 1H, C**H**O), 5.69–5.84 (m, 1H, C**H**=CH_2), 4.98–5.10 (m, 2H, CH=C$\mathbf{H_2}$), 4.08 (bs, 2H, (C$\mathbf{H_a}H_b)_2$NBoc), 2.67 (bs, 2H, ($CH_a\mathbf{H_b}$)$_2$NBoc), 2.24–2.46 (m, 3H, CHC$\mathbf{H_2}$CH, C**H**CHO), 1.84–1.98 (m, 1H, C**H**CHCHO), 1.58–1.72 (m, 2H, (C$\mathbf{H_a}H_bCH_2)_2$NBoc), 1.41 (s, 9H, (C$\mathbf{H_3}$)$_3$), 1.13–1.31 (m, 2H, ($CH_a\mathbf{H_b}CH_2)_2$NBoc); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 154.8, 136.7, 116.9, 79.1, 56.5, 36.5, 30.8, 28.4. HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{15}H_{24}NO_3$) requires *m/z* 266.1756, found *m/z* 266.1762. $[\alpha]_D$ = +7.8 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride. (Chiralcel®ODH 5–50% MeCN). t_R(major) = 5.9 min. t_S(minor) = 6.2 min.

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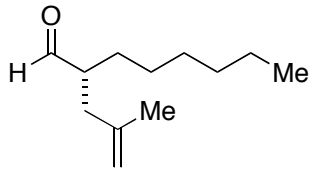
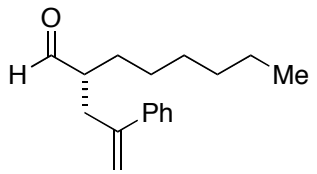
[33] Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Heterocycles*, **2001**, *54*, 747.

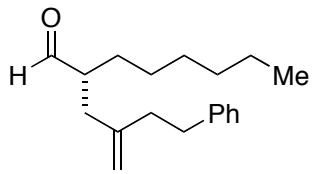


(*R*)-2-(2-Methylallyl)octanal (Table 3, entry 1): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and methallyltrimethylsilane (440μL, 2.50 mmol) to afford a yellow oil. Purification on Iatrobeads (2–10% Et_2O/Pentanes) afforded (*R*)-2-(2-methylallyl)octanal as a colorless oil (160 mg, 88% yield, 91% ee). IR (film) 3075, 2929, 2857, 2703, 1729, 1651, 1456, 1377, 892.5, 724.0 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.56 (d, *J* = 2.7 Hz, 1H, C**H**O), 4.74–4.77 (m, 1H, C=C**H**$_a$H$_b$), 4.70–4.72 (m, 1H, C=CH$_a$**H**$_b$), 2.35–2.52 (m, 2H, CHC**H**$_2$C=, C**H**CHO), 2.10–2.16 (m, 1H, CHC**H**$_2$C=), 1.70 (s, 3H, CC**H**$_3$), 1.40–1.66 (dm, 2H, C**H**$_2$(CH$_2$)$_4$), 1.22–1.34 (m, 8H, CH$_2$(C**H**$_2$)$_4$), 0.86 (t, *J* = 6.6 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.9, 143.7, 112.6, 50.1, 37.7, 32.3, 29.3, 27.5, 23.1, 22.3, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{22}O$) requires *m/z* 182.1671, found *m/z* 182.1663. $[\alpha]_D$ = +14.5 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 35.4 min and (*R*) isomer t_r = 36.1 min.



(*R*)-2-(2-Phenylallyl)octanal (Table 3, entry 2): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and trimethyl(2-

phenylallyl)silane:[34] (476 mg, 2.50 mmol) to afford a yellow oil. Purification on Iatrobeads (3–30% Et_2O/Pentanes) afforded (*R*)-2-(2-phenylallyl)octanal as a colorless oil (213 mg, 87% yield, 90% ee). IR (film) 3082, 3057, 3025, 2955, 2929, 2857, 2710, 1727, 1628, 1600, 1574, 1495, 1456, 1378, 1303, 1076, 1028, 900.6, 778.7, 705.8 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.58 (d, *J* = 2.7 Hz, 1H, C**H**O), 7.12–7.30 (m, 5H, **Ph**), 5.32 (d, *J* = 1.3 Hz, 1H, C=C**H**$_a$H$_b$), 5.13 (q, *J* = 1.3 Hz, 1H, C=CH$_a$**H**$_b$), 2.96 (ddd, *J* = 14.6 Hz, 7.4 Hz, 1.3 Hz, 1H, CHOCHC**H**$_a$H$_b$), 2.63 (ddd, *J* = 14.6 Hz, 6.9 Hz, 1.1 Hz, 1H, CHOCHCH$_a$**H**$_b$), 2.31–2.42 (m, 1H, C**H**CHO), 1.42–1.68 (m, 2H, CH_2(C**H**$_2$)$_4$), 1.18–1.34 (m, 8H, CH_2(C**H**$_2$)$_4$), 0.84 (t, *J* = 7.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.5, 147.0, 141.3, 129.2, 128.4, 127.0, 114.7, 50.4, 35.2, 32.2, 29.9, 29.0, 27.2, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{17}H_{24}O$) requires *m/z* 244.1827, found *m/z* 244.1837. $[\alpha]_D$ = +13.4 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol. (Chiralcel®OJH 2–5% IPA). t_R(major) = 5.2 min. t_S(minor) = 6.1 min.



(*R*)-2-Hexyl-4-phenethyl-pent-4-enal (Table 3, entry 3): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and trimethyl(2-methylene-4-phenylbutyl)silane[35] (546 mg, 2.50 mmol) to afford a yellow oil. Purification on

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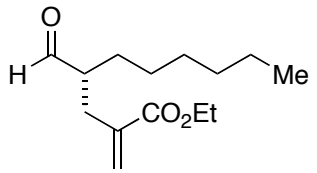
[34] Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.

[35] Clark, J. S.; Dossetter, A. G.; Wong, Y. S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. *J. Org. Chem*, **2004**, *69*, 3886.

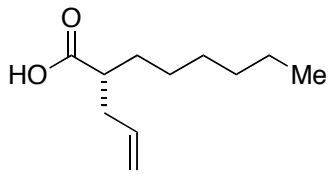
Iatrobeads (3–30% Et_2O/Pentanes) afforded (*R*)-2-hexyl-4-phenethyl-pent-4-enal as a colorless oil (209 mg, 77% yield, 88% ee). IR (film) 3085, 3027, 2955, 2929, 2857, 2708, 1727, 1645, 1604, 1496, 1454, 1077, 1031, 895.9, 747.2, 698.7 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.57 (d, *J* = 2.9 Hz, 1H, C**H**O), 7.13–7.30 (m, 5H, **Ph**), 4.84 (app. d, *J* = 1.3 Hz, 1H, C=C**H**$_a$H$_b$), 4.79 (app. d, *J* = 1.1 Hz, 1H, C=CH$_a$**H**$_b$), 2.76 (dd, *J* = 8.2 Hz, 8.0 Hz, 2H, C**H**$_2$Ph), 2.14–2.57 (m, 5H, C**H**CHO, CHC**H**$_2$C=C, C**H**$_2$CH$_2$Ph), 1.38–1.68 (dm, 2H, C**H**$_2$(CH$_2$)$_4$), 1.20–1.38 (m, 8H, CH$_2$(C**H**$_2$)$_4$), 0.86 (t, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.9, 147.2, 142.7, 129.1, 129.0, 126.5, 112.0, 50.2, 38.3, 36.1, 34.8, 32.3, 29.4, 27.5, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{19}H_{28}O$) requires *m/z* 272.2140, found *m/z* 272.2129. $[\alpha]_D$ = +11.6 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride. (Chiralpak®ADH 2–25% IPA). t_S(minor) = 7.4 min. t_R(major) = 7.8 min.



(*R*)-Ethyl 4-formyl-2-methylenedecanoate (Table 3, entry 4): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) to afford a yellow oil. Purification on Iatrobeads (10–50% Et_2O/Pentanes) afforded (*R*)-ethyl 4-formyl-2-methylenedecanoate as a colorless oil (194 mg, 81% yield, 90% ee). IR (film) 2930, 2858, 2712, 1720, 1630, 1466, 1370, 1302, 1185, 1153, 1027, 948.7, 854.3, 818.8, 724.7 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.58 (d, *J* = 2.7 Hz, 1H, C**H**O), 6.16 (d, *J* = 1.3

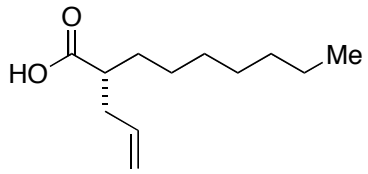
Hz, 1H, C=C**H**$_a$H$_b$), 5.66 (d, *J* = 1.3 Hz, 1H, C=CH$_a$**H**$_b$), 4.16 (q, *J* = 7.2 Hz, 2H, OCH$_2$CH$_3$), 2.64–2.73 (m, 1H, C**H**$_a$H$_b$C=CH$_2$), 2.47–2.58 (m, 1H, C**H**CHO), 2.37–2.45 (m, 1H, CH$_a$**H**$_b$C=CH$_2$), 1.38–1.72 (dm, 2H, C**H**$_2$(CH$_2$)$_4$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.22–1.36 (m, 8H, CH$_2$(C**H**$_2$)$_4$), 0.86 (t, *J* = 6.6 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d$_6$) δ 204.3, 166.9, 139.2, 126.9, 61.1, 51.2, 32.2, 31.8, 29.9, 29.2, 27.4, 23.1, 14.3, 14.2. HRMS (EI+) exact mass calculated for [M-H]$^+$ (C$_{14}$H$_{23}$O$_3$) requires *m/z* 239.1647, found *m/z* 239.1659. $[\alpha]_D$ = +13.0 (c = 1.0, CHCl$_3$). Enantiopurity was determined by achiral GLC after acetal formation with (*R,R*)-pentanediol and (*S,S*)-pentanediol, separately. Hewlett Packard HP-1 (30 m x 0.32 mm) column (140 °C isotherm); (*R,R,R*) and (*S,S,S)* isomer t_r = 91.5 min and (*R,R,S*) and (*S,S,R)* isomer t_r = 93.7 min.

Determination of Absolute Stereochemistry



(*R*)-2-Allyloctanoic acid: To a flask containing (*R*)-2-allyloctanal (45 mg, 0.267 mmol, 91% ee) and dissolved in *tert*-butanol (800 μL) and water (300 μL) at 0 ºC was added sodium dihydrogenphosphate hydrate (9.2 mg, 0.067 mmol) followed by 2-methyl-2-butene (124 μL, 1.17 mmol). Separately, sodium chlorite (42 mg, 0.374 mmol) was dissolved in water (500 μL) and cooled to 0 ºC, and the solution added to the aldehyde solution. The reaction was allowed to warm to ambient temperature over 4 h. Saturated sodium sulfite (1.00 mL) was added and stirred vigorously 5 min. The reaction was

acidified to pH~2, extracted with Et_2O (3 x 25 mL), and dried over Na_2SO_4. Purification by forced flow chromatography on Iatrobeads (5–50% Et_2O/Pentanes) afforded a colorless oil (31 mg, 63% yield), which corresponded to the reported literature compound.[36] $[\alpha]_D$ = +12.7 (c = 1.0, EtOH), Lit. (*S*)-2-allyloctanoic acid $[\alpha]_D$ = –11.1 (c = 1.0, EtOH).



(*R*)-2-Allylnonanoic acid: Prepared according to the oxidation procedure for (*R*)-2-allyloctanoic acid from (*R*)-2-allylnonanal[37] (45 mg, 0.250 mmol, 91% ee). Purification by forced flow chromatography on Iatrobeads (5–50% Et_2O/Pentanes) afforded a colorless oil (37 mg, 76% yield). Spectral data for the title compound matched the reported literature compound.[38] $[\alpha]_D$ = +5.99 (c = 1.0, $CHCl_3$), Lit. (*S*)-2-allylnonanoic acid $[\alpha]_D$ = –8.1 (c = 2.78, $CHCl_3$).

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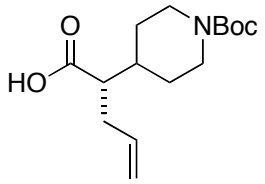
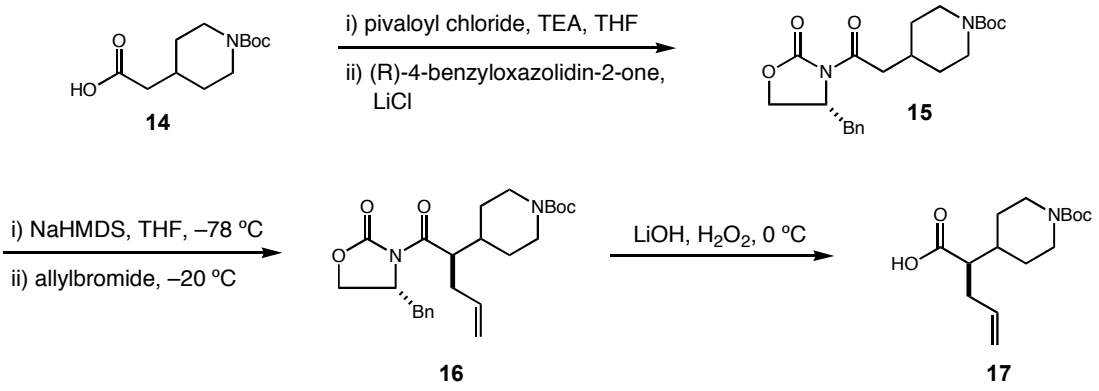
[36] Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423.

[37] (*R*)-2-Allylnonanal was prepared according to the general procedure from nonanal (132 mg, 73% yield, 91% ee).

[38] Expósito, A.; Fernández-Suárez, M.; Iglesias, T.; Muñoz, L.; Riguera, R. *J. Org. Chem.* **2001**, *66*, 4206.



(*S*)-2-(1-*tert*-Butoxycarbonyl)piperidin-4-yl)pent-4-enoic acid: Prepared according to the oxidation procedure for (*R*)-2-allyloctanoic acid from *tert*-butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate (52 mg, 0.194 mmol, 93% ee). The reaction was extracted with EtOAc (3 x 25 mL) in place of Et_2O (40 mg, 73% yield). IR (film) 3073, 2977, 2934, 2861, 1733, 1659, 1428, 1367, 1282, 1249, 1167, 1138, 993.8, 916.7, 866.4, 766.3 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 5.74–5.85 (m, 1H, C**H**=CH_2), 4.96–5.10 (m, 2H, CH=C$\mathbf{H_2}$), 4.08 (bs, 2H, (C$\mathbf{H_a}H_b)_2$NBoc), 2.67 (bs, 2H, ($CH_a\mathbf{H_b}$)$_2$NBoc), 2.24–2.38 (m, 3H, CHC$\mathbf{H_2}$CH, C**H**CHO), 1.58–1.80 (m, 3H, (C$\mathbf{H_a}H_bCH_2)_2$NBoc, C**H**CHCHO), 1.41 (s, 9H, (C$\mathbf{H_3}$)$_3$), 1.10–1.32 (m, 2H, ($CH_a\mathbf{H_b}CH_2)_2$NBoc); ^{13}C NMR (Bruker Avance II 500, APT experiment, 125 MHz, acetone-d_6) δ 176.2, 155.8, 137.8, 117.6, 80.1, 52.1, 39.6, 35.1, 31.4, 29.4. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{26}NO_4$) requires *m/z* 284.1862, found *m/z* 284.1872. $[\alpha]_D$ = +12.23 (c = 1.0, EtOH).



(*R*)-2-(1-*tert*-Butoxycarbonyl)piperidin-4-yl)pent-4-enoic acid: *tert*-Butyl 4-(formylmethyl)piperidine-1-carboxylate[31] (500 mg, 2.2 mmol) was converted to the corresponding carboxylic acid **14** using the procedure described for (*R)*-2-allyloctanoic acid (473 mg, 88% yield).

The carboxylic acid **14** was converted to the 4-[2-((*R*)-4-benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester **15** in like manner as described by Fuwa et al.[39] The carboxylic acid **14** (217 mg, 0.89 mmol) was dissolved in dry THF (7.0 mL) and TEA (248 μL, 1.78 mmol) and cooled to –78 ºC. Pivaloyl chloride (132 μL, 1.07 mmol) was added and the reaction was gradually warmed to 0 ºC over 90 min. (*R*)-4-benzyloxazolidin-2-one (158 mg, 0.89 mmol) was added followed by lithium chloride (113 mg, 2.67 mmol) and the reaction was warmed to ambient temperature and stirred overnight. The reaction was diluted with ethyl acetate (EtOAc) (25 mL) and washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by forced flow chromatography (silica gel, 10–50% EtOAc/Hexanes) afforded **15** (215 mg, 60% yield).

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[39] Fuwa, H.; Okamura, Y.; Natsugari, H. *Tetrahedron* **2004**, *60*, 5341.

Allylation of **15** was performed in like manner to Evans et al.[40] **15** (172 mg, 0.427 mmol) was dissolved in THF (4 mL) and cooled to –78 ºC. $NaN(SiMe_3)_2$ (641 μL, 0.64 mmol) was added and the reaction was stirred for 1 h. Allylbromide (145 μL, 1.71 mmol) was then added and the reaction was warmed to –20 ºC over 6 h. A saturated NH_4Cl solution (5 mL) was added and the reaction stirred overnight. The reaction was diluted with EtOAc (25 mL) and washed with saturated aqueous NH4Cl (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by forced flow chromatography (silica gel, 5–50% EtOAc/hexanes) afforded 4-[(*R*)-1-((*R*)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-but-3-enyl]-piperidine-1-carboxylic acid *tert*-butyl ester **16** (60 mg, 32% yield).

The allylated oxazolidinone **16** was converted to the title compound **17** in like manner to the method of Stončius, et al.[41] **16** (40 mg, 0.09 mmol) was dissolved in THF (1 mL) and cooled to 0 ºC. H_2O_2 (30% aqueous, 44 μL, 0.39 mmol) was added dropwise followed by a solution of LiOH hydrate (8.4 mg, 0.20 mmol) in water (500 μL). Stirring was continued at 0 ºC for 3 h. Saturated Na_2SO_3 (500 μL) and saturated $NaHCO_3$ (500 μL) aqueous solutions were added and the mixture stirred vigorously allowing to warm to ambient temperature overnight. The reaction was acidified with 1N HCl to pH~2, and extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the title compound **17** (20 mg, 80% yield). Spectral data was identical to the (*S*)-enantiomer synthesized above. $[\alpha]_D = -11.07$ (c = 1.0, EtOH).

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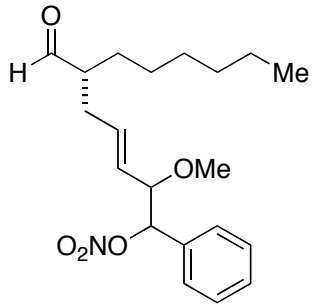
[40] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

[41] Stončius, A.; Nahrwold, M.; Sewald N. *Synthesis* **2005**, *11*, 1829.

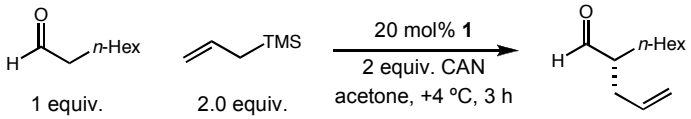


2-((*E*)-4-methoxy-5-nitrooxy-5-phenylpent-2-enyl)octanal: Prepared according to the general procedure, in acetone-d_6 with water (18mg, 1.0 mmol), from octanal (78 μl, 0.5 mmol) and (*trans, trans*-2-methoxy-3-phenylcyclopropyl)ethylene[26] to afford a yellow oil. Purification on Iatrobeads (5-50% Et_2O/Pentanes) afforded 2-((*E*)-4-methoxy-5-nitrooxy-5-phenylpent-2-enyl)octanal as a colorless oil. The product obtained is a 2:1:1:0.5 mixture of diastereomers. Data reported for the major diastereomer only. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.59 (d, 1H, *J* = 2.4 Hz, C**H**O), 7.26–7.44 (m, 5H, Ph), 5.94 (d, 1H, *J* = 5.2, Hz, C**H**ONO_2), 5.66–5.73 (m, 1H, C**H**=CH), 5.35–5.42 (m, 1H, C**H**=CH), 4.04–4.09 (m, 1H, C**H**-OMe), 3.21 (s, 3H, OC**H**$_3$), 2.36–2.46 (m, 3H, C**H**CHO, C**H**$_2$CH=CH), 1.29–1.66 (m, 10H, (C**H**$_2$)$_5$CH$_3$) 0.87–0.89 (m, 3H, C**H**$_3$); ^{13}C NMR (150 MHz, acetone-d_6) δ 205.3, 135.9, 130.29, 130.0, 129.7, 129.4, 129.1, 87.5, 83.9, 57.2, 52.3, 34.7, 32.8, 32.5, 30.0, 28.0, 23.8, 14.9.

Appendix A

Additional Tables and Figures

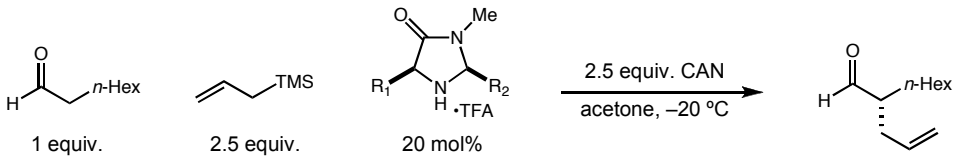
Table 5. Effect of Co-catalyst on the α-Allylation Reaction

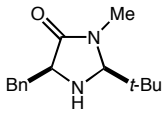
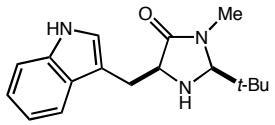
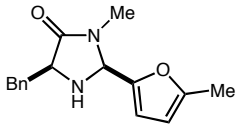
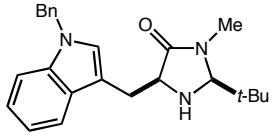
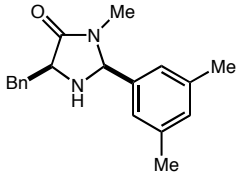
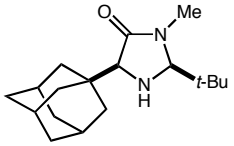


entry	Co-catalyst	pKa	% conversion[a]	% ee[b]
1	TfOH	–14	50	56
2	$HClO_4$	–10	49	75
3	HCl	–6.1	36	74
4	MsOH	–2.6	44	74
5	pTSA	–1.3	47	74
6	TFA	0.52	46	74
7	DCA	1.4	42	74
8	AcOH	4.8	40	74
9	4-NO_2-Phenol	7.1	40	75

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

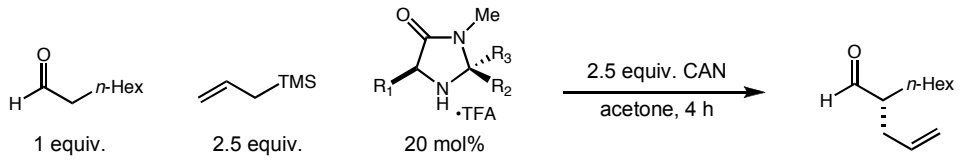
Table 6. Effect of Catalyst Architecture on the α-Allylation Reaction



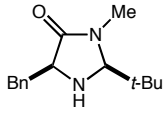
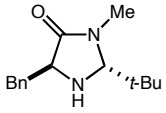
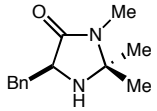
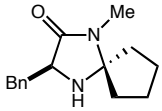
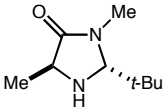
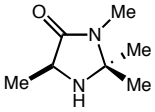
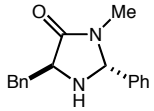
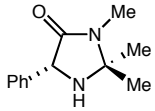
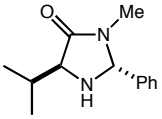
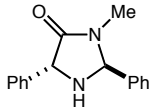
entry	catalyst	results[a]	entry	catalyst	results[a]
1		69% conv. 80% ee	6		26% conv. 38% ee
2		56% conv. 21% ee	7		23% conv. 46% ee
3		34% conv. 13% ee	8		54% conv. 78% ee

(a) After 18 h. Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

Table 7. Effect of Catalyst Architecture on the α-Allylation Reaction

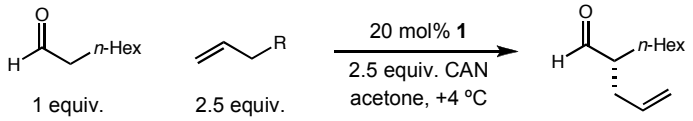


1 equiv. 2.5 equiv. 20 mol%

entry[a]	catalyst	+23 ºC	+4 ºC	entry[a]	catalyst	+23 ºC	+4 ºC
1		32% conv. 68% ee	58% conv. 74% ee	6		7% conv. 64% ee	6% conv. 81% ee
2		5% conv. 69% ee	6% conv. 84% ee	7		4% conv. 56% ee	3% conv. 81% ee
3		12% conv. 76% ee	13% conv. 82% ee	8		23% conv. 65% ee	17% conv. 71% ee
4			31% conv. 61% ee	9			10% conv. 44% ee
5			15% conv. 61% ee	10			10% conv. 43% ee

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB). (b) After 4 h.

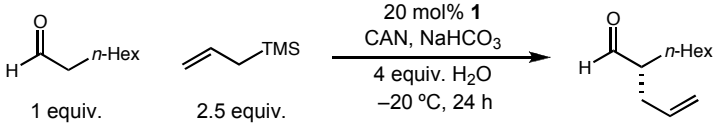
Table 8. Steric and Electronic Effects of the Allylsilane Component



entry	R	% conversion[a]	% ee[b]
1	$SiMe_3$	64	74
2	$SiMe_2Cl$	3	11
3	$SiMe_2CH_2Cl$	26	71
4	$SiMe_2$*p*-OMePh	58	71
5	Si(*i*-Pr)$_3$	trace	–
6	$SiPh_3$	12	37
7	$SiCl_3$	0	–
8	Si(OMe)$_3$	5	54
9	Si(OEt)$_3$	23	86

(a) After 2 h. Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

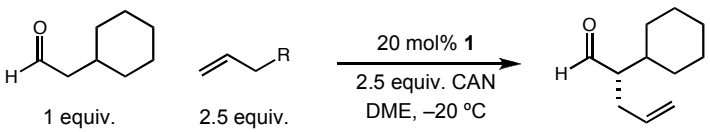
Table 9. Effect of Solvent with Water on the α-Allylation Reaction



entry	solvent (0.25M)	% conversion[a]	% ee[b]
1	DME	64	93
2	THF	80	83
3	Et_2O	23	86
4	EtOAc	53	82
5	DCM	32	66
6	$CHCl_3$	18	70
7	DMF	6	69

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

Table 10. Effect of Base Additive on the α-Allylation Reaction



1 equiv. 2.5 equiv.

entry	base	equiv.	% conversion[a]	% ee[b]
1	None	–	27	90
2	$NaHCO_3$	1.5	75	94
3	$NaHCO_3$	3.0	50	93
4	DTBP	1.5	36	92
5	DTBP	3.0	37	92

(a) After 24 h. Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).