Development of Iminium–Activation Technologies and the Total Syntheses of (+)–Frondosin B

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To 엄마 and 아빠

&

Rob

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Abstract

The enantioselective imidazolidinone-catalyzed epoxidation of α,β-unsaturated aldehydes has been accomplished via a novel 1,4-heteroconjugate addition reaction using hypervalent iodine reagents. Development of an "internal syringe pump" protocol for the slow release of iodosobenzene from an iminoiodinane source provides high levels of reaction efficiency and enantiomeric control in the asymmetric epoxidation of electron-deficient olefins. Fundamental to our studies were ^{15}N NMR experiments that elucidated the oxidation pathways that lead to catalyst depletion, thereby providing a mechanistic rational for the utilization of iminoiodinanes, which circumvent these catalyst depletion pathways.

We further established iminium catalysis as a valuable strategy for asymmetric synthesis in an organocatalytic addition of trifluoro(organo)borates and boronic acids to α,β-unsaturated aldehydes. Inspired by the Petasis reaction and guided by rational mechanistic considerations, we discovered a new mode of reactivity for organoboronates and a metal-free "coupling" procedure for enantioselective C–C bond construction. From a practical standpoint, this methodology stands to benefit from the structural diversity and wide commercial availability of several hundred organoboron reagents accessible to organic chemists. Furthermore, the low toxicity and the air and moisture stability of potassium organotrifluoroborates reagents make this powerful new organocatalytic process operationally trivial.

A five-step total synthesis of (+)-frondosin B highlights the stereoselective construction of a natural product target using an organocatalytic conjugate addition of a trilfluoro(organoboronate) reagent. This key step unambiguously established the absolute configuration of the frondosin B to be the (*R*)-enantiomer and led to the reassignment of naturally occurring frondosin B, thus resolving an existing discrepancy in the literature. To date, this work represents the most effective synthesis of frondosin B, which is accessible in only five steps and in a 32% overall yield.

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Abbreviations

Ac_2O	acetic anhydride
AcOH	acetic acid
BOC	*tert*-butyl carbamate
Bn	benzyl
Bz	benzoyl
CMHP	cumene hydrogen peroxide
CAN	cyanoacetic acid
DCA	dichloroacetic acid
DCE	1,2-dichloroethane
DMA	*N*,*N*-dimethylacetonide
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	Dimethylsulfoxide
DNBA	dinitrobenzoic acid
ee	enantiomeric excess
EtOAc	ethyl acetate
GC	gas liquid chromatography
$HClO_4$	perchloric acid
hr	hour
HOMO	highest occupied molecular orbital
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
IC_{50}	concentration necessary for 50% inhibition
IPA	isopropyl alcohol

LUMO	lowest unoccupied molecular orbital
***m*-CPBA**	3-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
min	minutes
MS	molecular sieves
NsNIPh	[(4-nitrobenzene sulfonylimino)iodo]benzene
NMR	nuclear magnetic resonance
Nu	nucleophile
PhIO	iodosobenzene
***p*-TSA**	*para*-toluenesulfonic acid
PMB	*para*-methoxybenzyl
RCM	ring-closing metathesis
SAR	structure-activity relationship
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydrogen peroxide
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
TPAP	tetrapropylammonium perruthenate
UHP	urea hydrogen peroxide
vol	volume

Chapter 1

Enantioselective LUMO–Lowering Organocatalysis

I. Introduction

Asymmetric catalysis poses a fundamental challenge to synthetic chemists to emulate nature in the synthesis of single-enantiomer products. It is this challenge that is central to the thriving field of asymmetric catalysis, which has arrived at the forefront of chemical research in modern organic chemistry.[1] In accord with the ever-increasing demand for "atom economic" processes,[2] single-enantiomer building blocks, and complex medicinal agents from the pharmaceutical and fine chemical industries, [3] the development of new chiral catalyst systems and asymmetric transformations have advanced at an astounding rate over the last 30 years.[4]

Defined by the early successes in metal-catalyzed redox reactions, the establishment of chiral transition metal and Lewis-acid catalysts produced rich and multifaceted platforms for the invention, discovery, and development of enantioselective

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1. This is evidenced by the 2001 Nobel Prize in Chemistry, which was awarded for "work on chirally catalyzed hydrogenation reactions" and also "chirally catalyzed oxidation reactions." (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.

2. Trost, B. M. *Angew.Chem., Int. Ed. Engl.* **1995**, *34*, 259.

3. (a) Collins, A. N.; Sheldrake, G. N.; Crosby, J. *Chirality in Industry*; Wiley: New York, 1997; Vol. 2. (b) *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker: New York, 1999.

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. (d) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Wienheim, 2004.

transformations.[3,5] As the two primary avenues for enantioselective synthesis were either by metal catalysts and biocatalysts (i.e., enzymes), only a few examples in the literature recognized the potential for small organic molecules to directly function as catalysts. This was surprising considering the advantages—small organic molecules are usually more robust, less expensive, readily available, and can be applied in less demanding reaction conditions. Moreover, the absence of a transition metal species eliminates issues associated with toxicity and trace metal contamination in industrial processes.

Only over the last decade has the use of organic molecules as catalysts emerged as a major concept in asymmetric catalysis and into a thriving field of general methods and reactivities with wide applicability.[6] With historical roots that date back as early as 1912, the first enantioselective organocatalytic reaction was carried out by Bredig and Fiske, having employed alkaloids for the addition of hydrogen cyanide to benzaldehyde to obtain modest optical yields (≤ 10% ee).[7] Unfortunately, this work remained fallow for nearly fifty years until Pracejus saw the use of alkaloids (such as *O*-acetylquinine, **1**) to catalyze the addition of methanol into phenylmethylketene with remarkable selectivity (74% ee, *eq. 1*).[8] The next major breakthrough was made in 1971 with the discovery of the Hajos-Parrish-Eder-Sauer-Wiechert reaction in which L-proline (**2**) catalyzed the intramolecular aldol condensation and cyclodehydration of an achiral trione to a bicyclic

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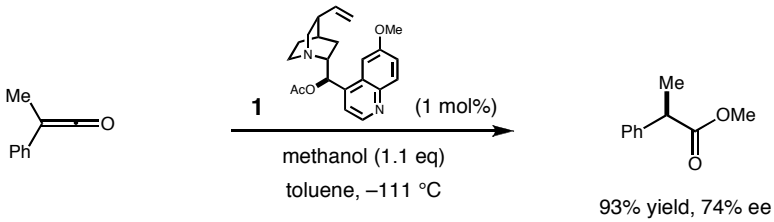
5. (a) Foote, C. S., Ed. *Acc. Chem. Res.* **2000**, *33* (Special Issue), 323. (b) Maruoka, K., Ed. *Tetrahedron* **2001**, *57* (Symposium-in-print), 805. (c) Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC: Tokyo, 1996. (d) Narasaka, K. *Synthesis* **1991**, 1. (e) Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3101.

6. (a) *Asymmetric Organocatalysis*, Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005. (b) Houk, K. N., List. B., Eds. *Acc. Chem. Res.* **2004**, *37* (Special Issue), 487. (c) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (d) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8.

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

8. (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9. (b) Pracejus, H.; Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195.



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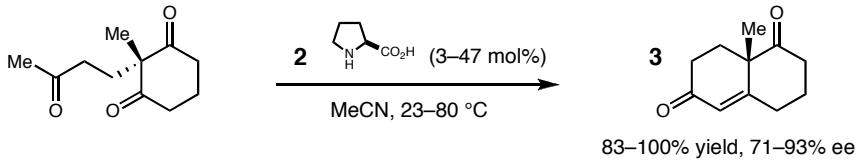
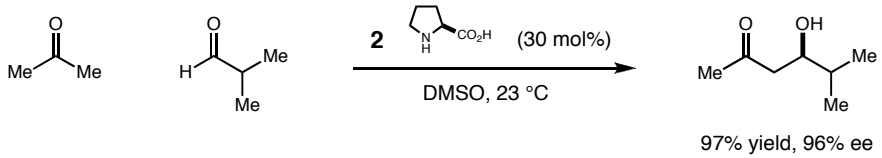


(2)

diketone **3** (also known as the Wieland-Miescher ketone)[9] with high enantioselectivities (71–93% ee, *eq. 2*).[10]

As isolated examples of specific catalysts mitigating single transformations appeared in the 1960s through the 1980s, the value of organocatalytic chemistry was largely unrealized until List and co-workers demonstrated a highly enantioselective intermolecular aldol reaction using L-proline as an organocatalyst in 2000 (96% ee, *eq. 3*). This and other recent seminal works (*vide infra*) had set the stage for an exponential



(3)

growth of research in the field of organocatalysis as evidenced by the increasing number of publications that have been put forth by the greater chemical community over the last several years (*Figure 1*).

9. Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215.

10. (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.

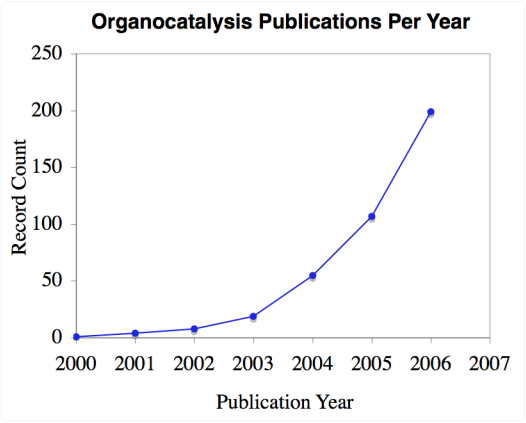


Figure 1. Publication rate of articles on the topic of organocatalysis.[11]

In fact, the field of organocatalysis has now flourished to include a wide variety of catalysts that are applicable to a range of chemical transformations with general activation mechanisms through Lewis acidic, Lewis basic, hydrogen-bonding interactions, etc. Some notable organocatalysts that have been landmarks in their discoveries and are representative of a class of catalysts are shown in Figure 2. Phase-transfer catalysts, such as the Cinchona-derived phase-transfer catalyst **4** first developed at Merck,[12] have been further explored by Corey[13] and later developed by Maruoka for enantioselective α-alkylations, as well as aldol and Michael reactions.[14] Chiral ketone catalysts (**5**) independently developed by Shi, Yang, and Denmark[15] function via *in situ*

11. ISI Web of Knowledge℠ database. http://portal.isiknowledge.com/portal.cgi (accessed April 2007). Search string in Web of Science® was the phrase "organocatalysis" as found in article titles, keywords, and abstracts.

12. Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *118*, 446.

13. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

14. (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) Ooi, T.; Maruoka, K., *Acc. Chem. Res.* **2004**, *37*, 526. (c) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (d) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002,** *41*, 4542. (e) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.*, **2003**, *125*, 2054. (f) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022.

15. (a) Curci, R.; Fiorentino, M.; Serio, M. R. *Chem. Commun.* **1984**, 155. (b) Curci, R.; Daccolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831. (c) Denmark, S. E.; Wu, Z. C.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (d) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587. (e) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. (f) Adam, W.; Zhao, C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. (g) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng,

formation of chiral dioxiranes used in the epoxidation of olefins. Lewis base catalysts operate through covalent activation of a substrate and can be represented by L-proline (**2**) and the amino acid-derived imidazolidinone catalyst (**7**) introduced by MacMillan and co-workers.[16] These catalysts have enabled excellent enantioselectivities to be attained in cycloadditions and α– and β–functionalizations of aldehydes and ketones.[17] Additionally, there are the planar chiral DMAP catalysts (**6**) developed by Fu et al.[18] that

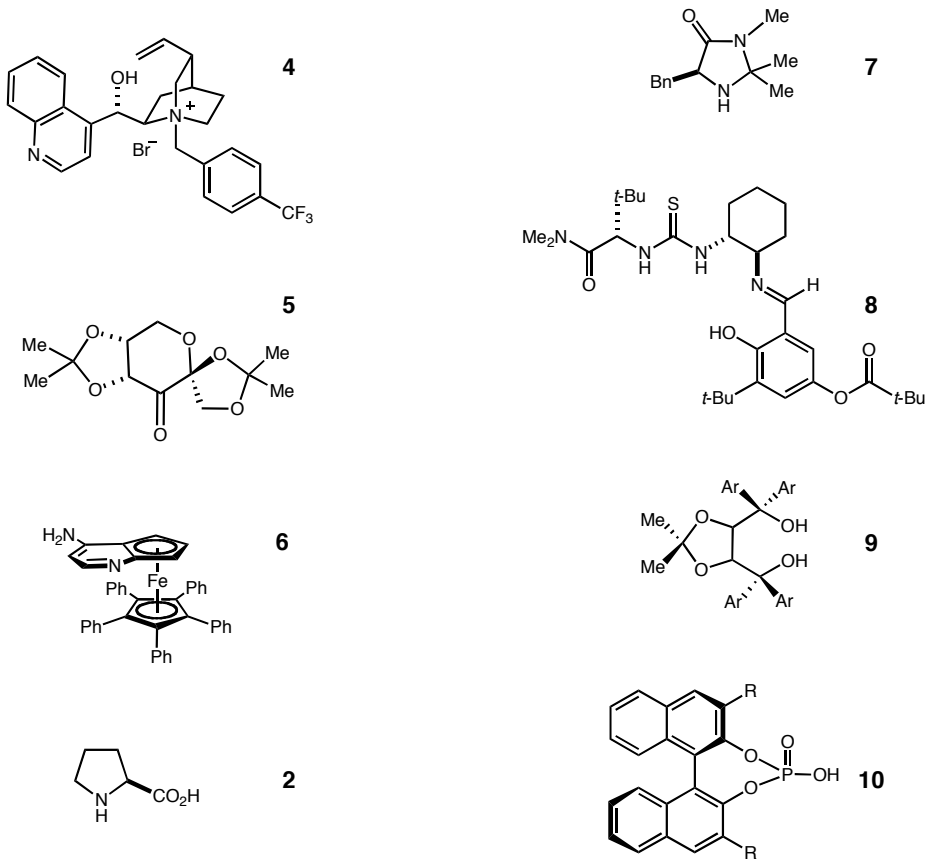


Figure 2. Some established organocatalysts.

J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (h) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

16. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

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

18. Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794.

participate in acyl-transfer reactions for kinetic resolutions and desymmetrizations. Seminal contributions have been made by Jacobsen and co-workers[19] in the use of hydrogen bonds to activate organocatalytic reactions using chiral thiourea catalysts (**8**), which successfully catalyze asymmetric Strecker, Mannich, hydrophosphonylation, and Pictet- Spengler reactions.[20] This mode of activation also mitigates the hydrogen-bond promoted hetero-Diels-Alder reaction by the chiral diol (**9**, R = 1-naphthyl) developed by Rawal and co-workers.[21] Stronger Brønsted acid catalysts based on the phosphoric acid motif (**10**, R = aryl)[22] have been developed by Akiyama[23] and Terada[24] as efficient catalysts.

The collective research over the last several years reflects an exciting and impressive advancement in the field of asymmetric catalysts. With many catalysts that perform many transformations, the ultimate goal in the field has been towards catalyst systems that achieve a "privileged" status,[25] in which one asymmetric catalyst promotes more than one mechanistically distinct asymmetric reaction. Although there are several recent examples of catalysts that demonstrate more sophisticated utility, future research is focused on broadening reaction scope and the design of more powerful and farther-reaching catalysts.

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22. Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.

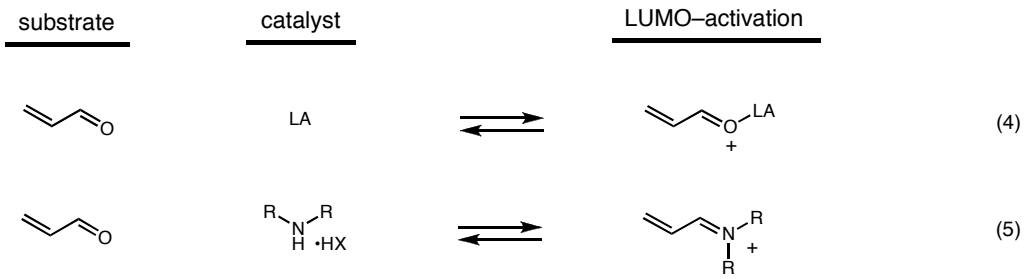
23. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem.* **2004**, *116*, 1592.

24. Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, *5356*.

25. Yoon, T. P; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

II. Iminium–Activation Approach to Enantioselective Organocatalysis

Iminium-activation is a discreet mode of catalytic activation within the field of asymmetric organocatalysis that has borne impressive development since its introduction in 2000. With the disclosure of the first organocatalytic Diels-Alder reaction, the MacMillan group had established the conceptual foundations for iminium-activation catalysis, wherein secondary amines play a key role in the activation of carbonyl compounds.[26,27] In analogy to Lewis acid catalysis, chiral amines emulate the equilibrium dynamics and π-orbital electronics[28] that are inherent to Lewis acid catalysis (*eq. 4*) through the reversible formation of iminium ions with α,β-unsaturated aldehydes



(*eq. 5*). Thus, iminium formation provides the mechanistic basis for enantioselective amine catalysis of cycloaddition and conjugate addition processes via LUMO-lowering substrate activation.[15]

Imidazolidinone catalysts (*Figure 3*) have proved to be successful chiral secondary amine organocatalysts with demonstrated utility in over 40 discrete transformations with high levels of enantiocontrol (≥ 90% ee).[25] Derived from an amino

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26. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

27. Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

28. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: Chichester, 1976; pp 161–165.

acid (L-phenylalanine) and readily available starting materials,[29] these catalysts (**11**, **12**, *Figure 3*) are exceedingly robust and straightforward in preparation, storage and implementation.[30] The imidazolidinone framework is defines the chiral environment of the reactive iminium-ion intermediate responsible for enantioinduction.

first-generation imidazolidone catalyst

second-generation imidazolidone catalyst

Figure 3. MacMillan first- and second-generation imidazolidinone catalysts

Transition state topology of the activated catalyst-substrate iminium complex (**MM3**-**13**) is defined by the *s-trans* geometry around the C=C bond and the chiral environment provided by the *C*-2 and *C*-5 catalyst substituents (*Figure 4*). This geometry is enforced by the non-bonding interactions imposed by the *tert*-butyl group and is further stabilized by an intramolecular π-stacking interaction between a *C*-2 *tert*-butyl group and the phenyl ring of the *C*-5 benzyl substituent of the catalyst (**12**).[31] Enantiofacial discrimination of the iminium π-system favors the open *Re*-face for reaction, thus imparting the absolute sense of enantioinduction in the resulting transformation.[32]

This platform of reactivity, established on the basic principles of LUMO-lowering activation and non-bonding interactions in the iminium ion intermediate, has been

29. Notably, catalysts **11** and **12** are both commercially available from Sigma-Aldrich.

30. These catalysts are relatively insensitive to air and moisture and tolerant to long-term benchtop storage.

31. NOE experiments support this interaction, see: Park, J. Y. Development of an Enantioselective Organocatalytic Michael Addition using Unactivated Nucleophiles. M.S. Thesis, California Institute of Technology, Pasadena, CA, 2002.

32. Notably, this model is in agreement with all observed cases thus far.

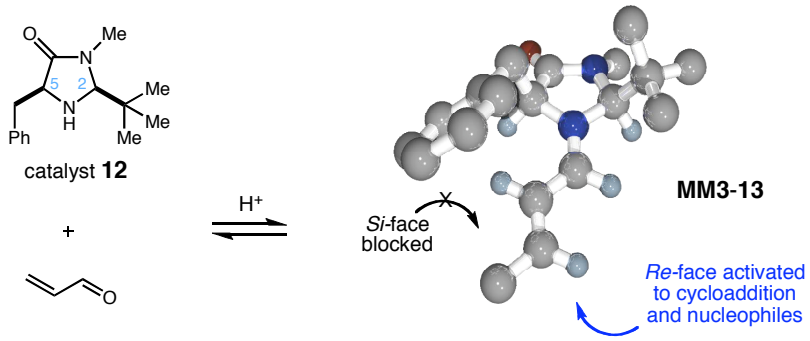

Figure 4. Rationale for catalyst-controlled enantioselectivity.

successfully applied to enantioselective transformations such as cycloadditions,[33] Friedel-Crafts alkylations,[34] Mukaiyama-Michael additions,[35] hydrogenations,[36] heteroconjugate additions,[37] cyclopropanations,[38] and cascade reactions.[39]

III. Summary of Thesis Research

The following chapters detail efforts towards further establishing iminium catalysis as a viable strategy for organocatalysis with the development of new

33. (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. J. Am. Chem. Soc. 2000, 122, 4243. (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (d) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.

34. (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894 (d) Brown, S. P; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

35. Borths, C. J. Investigations in Enantioselective Catalysis. Development of Novel Asymmetric Organocatalytic Reactions. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 2004.

36. (a) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2005**, *127*, 32. (b) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.

37. Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.

38. Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.

39. (a) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (b) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, *10*, 1477.

methodologies. Chapter 2 discusses the development of an enantioselective imidazolidinone-catalyzed epoxidation of α,β-unsaturated aldehydes via a novel 1,4-heteroconjugate addition reaction using hypervalent iodine reagents. Chapter 3 details the organocatalytic addition of trifluoro(organo)borates and boronic acids to α,β-unsaturated aldehydes as a metal-free "coupling" procedure for enantioselective C–C bond construction. Chapter 4 describes a five-step total synthesis of (+)-frondosin B highlighting the utility of the organocatalytic conjugate addition of a trilfluoro(organoboronate) reagent.

Chapter 2

The Imidazolidinone-Catalyzed Epoxidation of α,β-Unsaturated Aldehydes*

I. Introduction

In 2001, a Nobel prize was awarded to Sharpless "for his work on chirally catalyzed oxidation reactions," in recognition that the asymmetric catalytic epoxidation reaction stands as one of the most significant transformations in synthetic chemistry.[1] Enantioenriched epoxides in and of themselves are of fundamental importance to organic chemistry due to their capacity to transfer stereochemical information with complete specificity to provide two vicinal carbon stereocenters upon reaction with a wide variety of nucleophiles. As such, they are preeminent sp^3 carbon-electrophiles and powerfully versatile synthetic intermediates in the construction of complex enantiorich structures and natural product targets.

The first highly enantioselective epoxidation of olefins (≥ 90% ee) was achieved by Sharpless through the use of a titanium-tartrate complex for the oxidation of allylic alcohols (*eq. 1*).[2] Prior to this report in 1980, the highest enantioselective excess obtained

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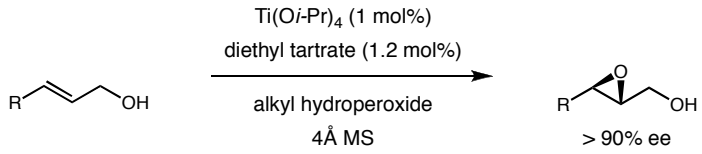
* For a full article of this work, see: Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, *62*, 11413.

1. Sharpless was awarded ½ the Nobel prize in 2001, see: Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.

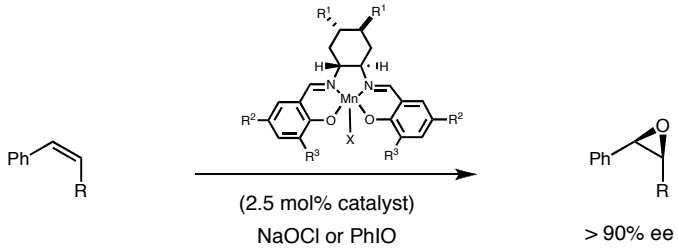
2. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

was 35%.[3] With the advent of this catalytic asymmetric epoxidation reaction ensued an ever-increasing demand for a generalized catalytic oxidation process that enabled efficient and predictable access to enantioenriched oxiranes.[4] Subsequently, significant efforts to expand the scope of catalytic epoxidations have been directed towards the development of methods that were broadly applicable to other olefinic classes.



(1)

A decade later, Jacobsen[5] and Katsuki[6] made seminal contributions that advanced the scope of catalytic enantioselective epoxidations to include unfunctionalized *cis*-alkenes. Devised to mimic biological oxidation systems,[7] these [Mn^{III}(salen)] catalysts effectively promoted stereospecific electrophilic metal oxo-transfer to olefinic substrates in the presence of a stoichiometric oxidant (*eq. 2*; Jacobsen: R^1 = H, R^2 = R^3 = *t*-Bu, X = Cl; Katsuki: R^1 = Ph, R^2 = H, R^3 = $CH(CH_2CH_3)Ph$, X = PF_6). Though cyclic and acyclic di-



(2)

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3. Kagan, H. B.; Mimoun, H.; Mark, C.; Schurig, V. *Angew. Chem. Int. Ed.* **1979**, *18*, 485.

4. Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991; vol. 7, p. 389.

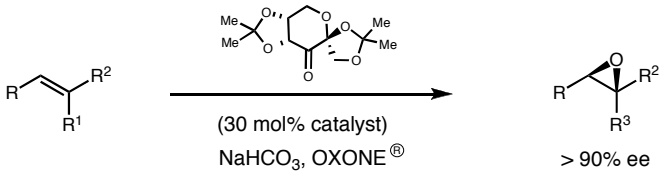
5. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

6. Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.

7. (a) McMurry, T. J.; Groves, J. T. In *Cytochrome P-450: Structure, Mechanism, and Biochemistry*, Ortiz de Montellano, P. R., Ed.; Plenum Publishing: New York, 1986; Chapter 1. (b) Holland, H. L. *Organic Synthesis with Oxidative Enzymes*; VCH Publishers: New York, 1992. (c) Allain, E. J.; Hager, L. P.; Deng, L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 4415.

and trisubstituted *cis*-olefins proved to be excellent substrates for the metallosalen-catalyzed epoxidation, unfunctionalized simple *trans*-olefins remained elusive.

A complimentary approach to the more established method of oxyfunctionalization via organometallic agents was a novel and elegant organocatalytic strategy. The emergence of organic-based chiral dioxirane catalysts came about in 1984,[8] and since then moderately successful stoichiometric and catalytic examples have been developed.[9] Significant progress was achieved independently by Yang (using a C_2-symmetric, cyclic binaphthalenyl ketone catalyst)[10] and Shi (using a fructose-derived ketone catalyst, *eq. 3*)[11] in the discovery of a highly enantioselective epoxidation of simple *trans*- and trisubstituted olefins. These dioxirane-mediated oxidations were important in bridging a substantial gap in existing asymmetric epoxidation methodologies with respect to substrate scope.



(3)

Though newly developed epoxidation methodologies came to encompass several olefin classes, there remained a limited applicability towards electron-deficient olefins. Due to the predominant focus on electrophilic oxidations, these technologies were not applicable towards enones and enals. Existing strategies for electron-deficient olefins were

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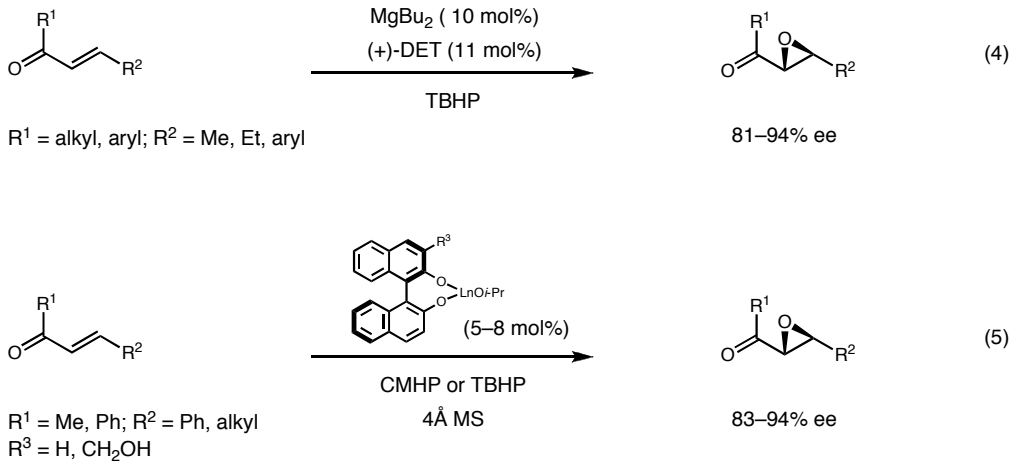
8. Curci, R.; Fiorentino, M.; Serio, M. R. *Chem. Commun.* **1984**, 155.

9. (a) Curci, R.; Daccolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831. (b) Denmark, S. E.; Wu, Z. C.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (c) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587. (d) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. (d) Adam, W.; Zhao, C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995.

10. Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491.

11. Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

variants of the Weitz-Scheffer[12] epoxidation, wherein a nucleophilic chiral peroxide adds to an enone, or more specifically to a chalcogen substrate. This strategy of hydroperoxide



delivery via a homogeneous chiral metal complex has been adopted and developed by Enders[13] in a stoichiometric manner (using diethylzinc, oxygen, and *N*-methylephedrine) and in a catalytic approach by Jackson (*eq. 4*)[14] and Shibasaki (*eq. 5*).[15] Alternatively, asymmetric phase transfer agents have been used to transport a reactive oxo-species from the basic aqueous phase into the organic phase of the olefin substrate; this is epitomized in the works of Roberts,[16] in using a modified Juliá-Colonna polyamino acid procedure,[17] in iminium salts,[18] and in the cinchona alkaloid-derived salts of Lygo[19] and

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12. Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 2327.

13. (a) Enders, D.; Zhu, J. Q.; Raabe, G. *Angew. Chem. Int. Ed.* **1996**, *35*, 1725. (b) Enders, D.; Zhu, J. Q.; Kramps, L. *Liebigs Ann. Chem.* **1997**, 1101.

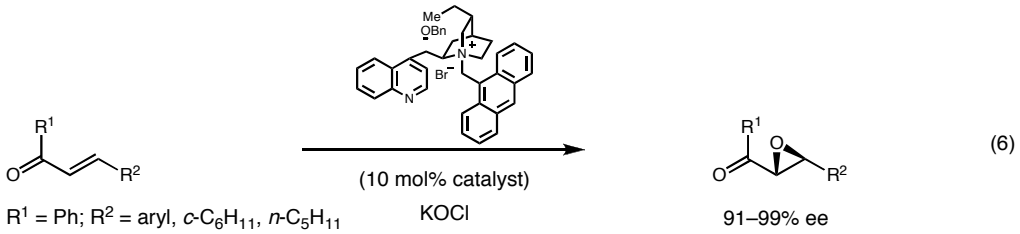
14. Elston, C. L.; Jackson, R. F. W.; MacDonald, S. J. F.; Murray, P. J. *Angew. Chem. Int. Ed.* **1997**, *36*, 410.

15. Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329.

16. Dhanda, A.; Drauz, K.-H.; Geller, T. P; Roberts, S. M. *Chirality* **2000**, *12*, 313.

17. (a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem. Int. Ed.* **1980**, *19*, 929. (b) Julia, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317.

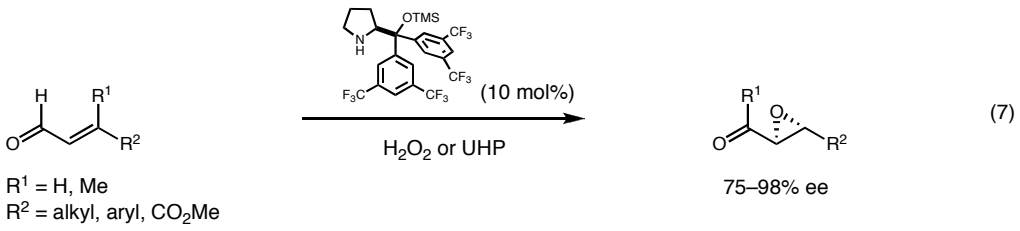
18. (a) Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-H.; Yang, D. *Org. Lett.* **2001**, *3*, 2587. (b) Page, P. C. B.; Rassias, D.; Barros, D.; Ardakani, A.; Buckley, B.; Bethell, D.; Smith, T. A. D.; Slawin, A. M. Z. *J. Org. Chem.* **2001**, *66*, 6926



(6)

Corey (*eq. 6*).[20] Though these described methodologies successfully address the epoxidation of some electron-deficient alkenes, they are generally limited to s-*cis*-chalogens and have yet to include the full range of electron-deficient alkene substrates such as s-*trans*-enones, unsaturated amides, esters, aldehydes, and nitrile systems.

More recently, in 2005, Jørgensen and co-workers[21] forayed into the open realm of enal olefin epoxidations by demonstrating the asymmetric organocatalytic epoxidation of α,β-unsaturated aldehydes using iminium catalysis (*eq. 7*).[22] In these elegant studies, a variety of enals rapidly underwent asymmetric epoxidation using hydrogen peroxide or urea hydrogen peroxide as the stoichiometric oxidant in the presence of a proline-derived, bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl] pyrrolidine) catalyst.



(7)

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19. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599. (b) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289.

20. Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.

21. (a) Marigo, M.; Franzen, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964. (b) Zhuang, W.; Marigo, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3883. (c) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928.

22. This work was published subsequent to our own epoxidation studies, which were initiated in 2002 and later published: Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, *62*, 11413.

II. A Mechanism-Based Organocatalytic Epoxidation Strategy

In 2002, we initiated studies to develop a novel organocatalytic methodology for the asymmetric epoxidation of α,β-unsaturated aldehydes based upon the activation principle of iminium catalysis (*vide* Chapter 1) with the goal of providing rapid access to enantioenriched 1,2-*trans*-formyl epoxides, an ambiphilic class of electrophile of known value in chemical synthesis.[23] Having demonstrated the capacity of chiral amines to function as asymmetric catalysts, and building on previous successes in cycloadditions and 1,4-conjugate additions,[19] there was strong precedence for the mechanism-based design of an organocatalytic epoxidation reaction. It was envisaged that a nucleophilic oxygen, incorporated with a suitable leaving group, could add with enantiofacial selectivity to an iminium-activated complex formed from the condensation an α,β-unsaturated aldehyde with an amine catalyst (*Figure 1*). Subsequent enamine formation, followed by

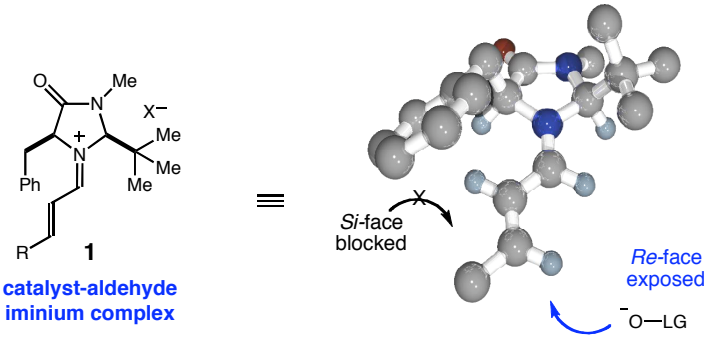

Figure 1. Rational of catalyst-controlled enantioselectivity utilizing a MM3-2 model of the catalyst-aldehyde iminium complex

intramolecular trapping of the pendent electrophilic oxygen with concomitant expulsion of the oxygen-tethered leaving group (LG), would then produce an oxirane (*Figure 2*). The

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23. Antoniotti, S.; Dunach, E. *Synthesis* **2003**, *18*, 2753.

feasibility of this proposed catalytic cycle is then contingent on judicious selection of an ambiphilic oxygen source that must dually function as a viable nucleophile for the conjugate addition step and then be suitably electrophilic (via incorporation of an electronegative nucleofuge with high leaving group ability) to enable intramolecular

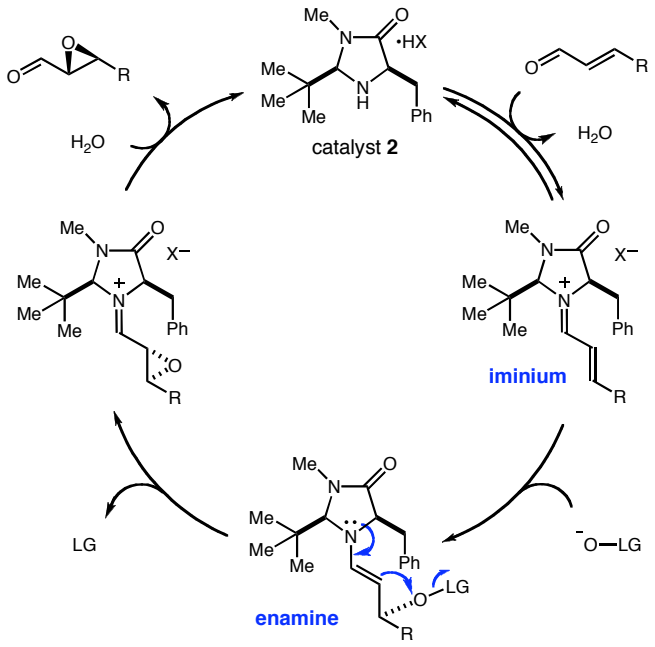
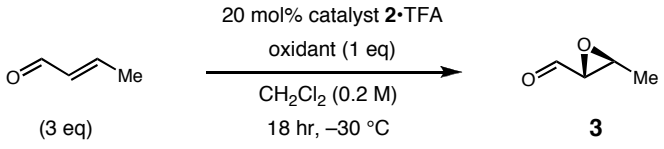


Figure 2. Proposed organocatalytic cycle for oxirane formation and the generation of an α,β-epoxy aldehyde

enamine cyclization and oxirane formation. As such, preliminary investigations were focused on defining potential oxygen sources that would participate in the requisite 1,4-heteroconjugate addition and enamine cyclization sequence of reactions. Initial experiments were carried out under a standard system consisting of crotonaldehyde and a variety of commercially available oxidants in the presence of catalyst **2**·TFA (*Table 1*). The first candidate chosen was pyridinium *N*-oxide, given that it bears a relatively good leaving group and the oxygen of the N–O ylide is known to nucleophilically add to

Michael-acceptors.[24] Gratifyingly, pyridinium *N*-oxide gave the desired 2,3-epoxy-crotonaldehyde product (**3**) in 12% yield at room temperature. However, the observed reaction was completely suppressed when conducted at subambient temperatures (*entry 1*). It was immediately apparent that the amine by-product (pyridine) inhibited the organocatalytic cycle via proton abstraction from the requisite acid co-catalyst. Consequently, this placed a theoretical limit on this reaction based on the acid co-catalyst loading. Notably, other commercially available *N*-oxides were evaluated (such as triethyl amine *N*-oxide, *N*-methyl-*N*-morpholine oxide, 4-nitro, and 4-methoxy pyridinium *N*-oxide) and were found to be less productive reagents.

Table 1. Initial Survey of Oxygen Sources for Epoxidation



entry	oxidant	% conversion[a]	% ee[b]
1	pyridine *N*-oxide	NR	--
2	*m*-CPBA	34	73
3	*t*-BuOOH[c]	35	69
4	H_2O_2[d]	9	59
5	OXONE®	NR	--
6	NaOCl[e]	9	0
7	PhIO	43	72

[a] Conversion determined by GC relative to methyl benzyl ether. [b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA). [c] Used as 5 M solution in decane. [d] Used as a 50% solution in water. [e] Used as a 30% solution in water.

Peroxides were next examined in the epoxidation reaction and were found to readily provide **3** (*Table 1, entries 2–4*). Evaluation of *m*-CPBA under identical reaction

24. Katritzky, A. R. *Quart. Rev., Chem. Soc.* **1956**, *10*, 395.

conditions produced encouraging levels of selectivity (73% ee, *entry 2*); however, studies to define the utility of this reagent (by modification of reaction parameters such as solvent and temperature) resulted in little improvement in overall enantiocontrol. The use of peroxides, such as *tert*-butyl hydrogen and hydrogen peroxide also furnished the desired oxirane with notable enantioselectivities (69% and 59% ee, *entries 3* and *4*). However, attempts to extend these reactions to less reactive substrates (such as cinnamaldehyde) unfortunately resulted in substantial levels of catalyst *N*-oxidation and therefore, these reagents were not further pursued. Other simple oxidants were also found to be unviable reagents for this process (*Table 1, entries 5* and *6*). Notably, at ambient temperature OXONE® gave the desired transformation to **3** in 55% conversion and 13% ee, however upon cooling showed no reactivity (*entry 5*). Additionally, NaOCl demonstrated some reactivity but yielded racemic product at 23 °C and also at –30 °C (*entry 6*).

Having exhausted the possibility of using a more conventional oxidant, we next considered the use of hypervalent λ^3-iodanes as potential oxidants for this organocatalytic epoxidation reaction. With well-known involvement in alkene epoxidations, one of the most important oxygen transfer agents in metal-oxo-mediated oxy-functionalization is iodosobenzene.[25] Though, the oxidative properties of these reagents are predominantly attributed to the electrophilic nature of the hypervalent iodine, there are a few precedented cases, where the oxygen in iodosobenzene is reported to possess sufficient

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25. For excellent reviews on hypervalent iodine, see: (a) Stang, P. *Chem. Rev.* **1996**, *96*, 1123. (b) Wirth, T.; Ochiai, M.; Varvgolis, A.; Zhdankin, V. V.; Koser, G. F.; Tohma, H.; Kita, Y. *Topics in Current Chemistry: Hypervalent Iodine Chemistry–Modern Developments in Organic Synthesis*; Springer-Verlag, Berlin, 2002; vol. 224, pp. 1–248. (c) Varvoglis, A. *Hypervalent Iodine Chemistry in Organic Synthesis*; Academic Press: London. 1997; pp. 1–223.

ylide character to participate in nucleophilic addition.[26] From the outset, we hypothesized that the remarkable lability of the phenyliodonio moiety (which is ~10^6 times better leaving group ability than triflate)[25b] would enable rapid oxirane ring formation and thereby minimize the intervention of a reversible oxo-conjugate addition (an equilibrium process that would diminish kinetic enantiocontrol). Another attractive feature of this reagent is the presence of a phenyl ring, which could serve as a handle for electronic modification and potentially serve as a key point of interaction with the benzyl group of the catalyst-complex (**1**) that could enhance the selectivity of the enantiodetermining step. Moreover, we presumed that the oxidation byproduct, iodobenzene, would have no deleterious impact on the organocatalytic cycle (*Figure 2*). To our immediate delight, we were indeed validated when application of iodosobenzene in the proposed 1,4-heteroconjugate addition afforded **3** with a 43% conversion and an encouraging level of enantiocontrol (72% ee, *Table 1*, *entry 7*).

To gain insight into this initial result with iodosobenzene, the reaction parameters of the crotonaldehyde epoxidation were thoroughly examined. A survey of reaction media (*Table 2*) revealed that solvents with high dielectric constants typically enabled higher efficiencies (87–41% conversion, *entries 1–3*) while lower dielectric systems provided higher levels of asymmetric induction (64–82% ee, *entries 4–9*). Balancing this apparent dichotomy, dichloromethane (80% ee, *entry 4*) and chloroform (82% ee, *entry 7*) demonstrated useful efficiencies while maintaining optimal enantioselectivity. On this

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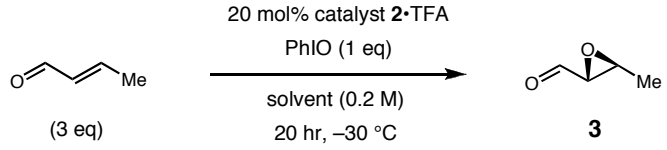
26. For an example of a 1,4-addition with iodosobenzene, see: (a) Pettus, L. P; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2001**, *3*, 905. For examples of nucleophilic attack by the oxygen of iodosobenzene, see: (a) Ono, T.; Henderson, P. *Tetrahedron Lett.* **2002**, *43*, 7961. (c) Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 686. (d) Zefirov, N.S.; Kozhushkov, S. I.; Zhdankin, V. V.; Safronov, S. O. *Zh. Org. Khim.* **1989**, 25, 1109.

basis, these halogenated solvents were selected as optimal reaction media for the epoxidation reaction. It is also noteworthy that a reaction carried out in dry THF and in

Table 2. Effect of Solvent on the Epoxidation Reaction with Iodosobenzene

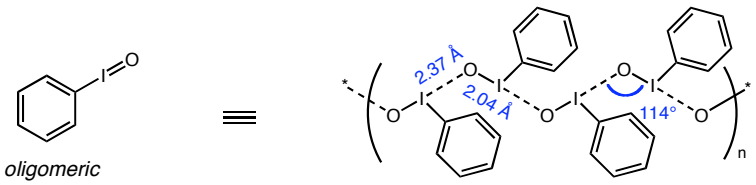


entry	solvent	ε[a]	% conversion[b]	% ee[c]
1	DMF (10% H_2O)	--	87	25
2	MeCN	37	55	33
3	acetone	21	41	42
4	CH_2Cl_2	8.9	50	80
5	THF	7.5	14	76
6	THF (10% H_2O)	--	12	75
7	chloroform	4.8	45	82
8	ether	4.3	29	63
9	toluene	2.4	63	64

[a] *CRC Handbook of Chemistry and Physics*, 81st ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 2000. [b] Conversion determined by GC relative to tridecane. [c] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).

the presence of 10% water (entries *5* and *6*) irrespectively had similar levels of conversion and enantioselectivity, which suggests that water is a non-detrimental factor in this reaction.

Heterogeneity remained an issue in these solvent studies, because iodosobenzene exists as a oligomer in most organic solvents (*eq. 8*).[25a] Though, soluble in alcohols (such as trifluoroethanol and methanol) iodosobenzene is only moderately soluable in water, DMF, DMSO, and nitromethane. Efforts to identify homogenous reaction conditions using mixed alcohol and pure alcohol solvent systems, unfortunately produced complex reaction profiles that were plagued with indiscriminant acetal formation as an unavoidable side product. To alleviate issues with insolubility, the reaction was found to

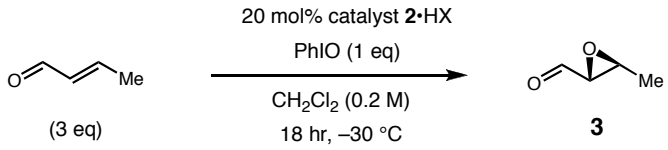


(8)

perform best under more dilute conditions (≥ 0.5 M) to better solubilize iodosobenzene in the reaction.

The impact of the Brønsted acid co-catalyst component on this organocatalytic epoxidation was next examined. As revealed in Table 3, an apparent correlation was observed between reaction conversion and enantiocontrol to the pK_a of the acid co-catalyst.

Table 3. Effect of Acid co-Catalyst on the Epoxidation Reaction using Iodosobenzene



entry	HX	pK_a[a]	% conversion[b]	% ee[c]
1	TfOH	–14	74	87
2	$HClO_4$	–10	68	88
3	*p*-TSA	–2.6	50	76
4	TFA	–0.3	42	72
5	DCA	1.3	27	72
6	CNA	2.5	27	69

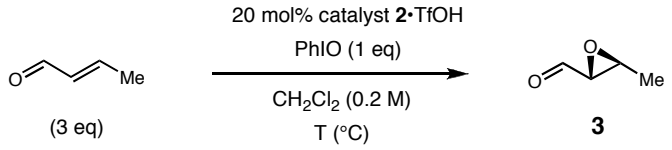
[a] Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley & Sons: New York, 2001. [b] Conversion determined by GC relative to benzyl ether. [c] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).

More specifically, stronger acids, such as TfOH and $HClO_4$, provided the epoxide adduct with enhanced selectivities and conversions (pK_a –14 to –10, 74–68% conversion, 87–88% ee, *entries 1* and *2*), while acids with higher pK_a resulted in poorer conversions (pK_a 1.3 to 2.5, 27% conversion, 69–72% ee, *entries 5* and *6*). This trend can be rationalized on the basis that the stronger acid co-catalyst enables a higher equilibrium content of the catalyst

substrate iminium adduct (**1**), which is observable by ^{1}H NMR. In the case of TfOH, the equilibrium lies entirely in favor of the iminium species **1**, thus the rate of the addition-cyclization sequence is subsequently accelerated. Moreover, the observed enantioselectivity appears to track with the reaction efficiency according to traditional requirements for the catalyst-controlled pathway to kinetically out-compete the non-catalyzed (racemic) process. As a result, the more acidic co-catalysts were deemed optimal for this reaction and further optimization studies were carried out with TfOH and $HClO_4$.

The influence of temperature on this epoxidation protocol was next investigated (*Table 4*). An apparent trend of improving enantioselectivity was realized upon lowering the reaction temperature. More surprisingly, however, was the corresponding increase in reaction efficiency with the same temperature trend. Subsequent studies (*vide infra*) have

Table 4. Effect of Temperature on Reaction Efficiency and Selectivities



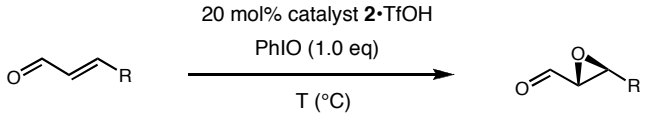
entry	T (°C)	time (hr)	% conversion[a]	% ee[b]
1	–20	15	49	83
2	–30	20	74	87
3	–40	15	98	89
4	–50	15	100	93

[a] Conversion determined by GC relative to benzyl ether. [b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).

revealed that lower temperatures are essential to avoid detrimental catalyst oxidation pathways. Additionally, it is possible that lower temperatures are necessary to preclude substrate decomposition pathways that may arise from the presence of a two-fold excess of aldehyde.

Having established optimal epoxidation conditions, we next examined the scope of the olefin component in the organocatalytic oxirane formation. As revealed in Table 5, α,β-unsaturated aldehydes that incorporate alkyl group substituents are susceptible to iodosobenzene epoxidation with good efficiency and enantioselectivities (80–93% ee, *entries 1–3*). However, substrates that form more stabilized iminium species with catalyst **2** (such as cinnamaldehyde, *entry 5*) demonstrated diminished conversion and lower levels of asymmetric induction. At this juncture, it was hypothesized that a catalytic cycle wherein the 1,4-oxygen addition step is rate determining would be consistent with these findings. Moreover, we rationalized that implementation of a more nucleophilic iodosobenzene source should therefore provide an increase in both reaction rate and enantioselectivity. To this end, we initiated additional studies aimed at increasing the reactivity of iodosobenzene and further evaluating the reactivity profile of iodosobenzene reagents for this organocatalytic transform.

Table 5. Organocatalytic Epoxidations with Iodosobenzene: Initial Studies



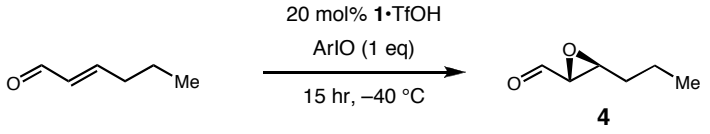
entry	R	T (°C)	time (hr)	% yield	% ee[a]
1	Me[b]	–50	10	100[d]	93
2	*n*-Pr[b]	–50	15	93[e]	88
3	*i*-Pr[c]	–40	15	86[e]	80
4	Ph[c]	–40	15	78[f]	73
5	CO_2Me	–50	15	45	85

[a] Enantiomeric excesses were determined by chiral GC analysis (Chiraldex G-TA). [b] 3 eq of starting aldehyde in CH_2Cl_2 (0.075 M). [c] 1 eq of aldehyde in $CHCl_3$ (0.25 M). [d] Yield based on NMR analysis using benzyl ether as a standard. [e] Yield based on isolation of corresponding epoxy alcohol. [f] Stereochemical determination via correlation to literature, see supporting information.

III. Alternative Iodosobenzene Sources

The substituent effects of iodosobenzene have been studied by Basolo with respect to the aptitude of oxygen transfer to metals relative to electronic modification on the phenyl ring.[27] In their studies, the IR stretching frequencies of the I–O bond on iodosobenzene with electron-donating groups on the phenyl ring resulted in higher frequencies (longer and more polarized I–O bond) relative to electron-withdrawing groups which gave lower frequencies (shorter and less polarized I–O bond). Therefore, IR data predicts that electron-donating substituents enhance the nucleophilicity of the oxygen in iodosobenzene. With this in mind, we prepared a variety of electronically differentiated substituted iodosobenzenes with *p*-Me, *o*-Me, *o*-Cl, *p*-NO_2 on the benzene ring.[28] To our great surprise, all other functionalized iodosobenzenes gave much poorer yielding results relative to unfunctionalized iodosobenzene.

As *p*-Me iodosobenzene was synthesized with the expectation of being a more nucleophilic version of iodosobenzene, it was unforseen that a test epoxidation reaction with hexenal would be much lower yielding than the analogous reaction with iodosobenzene (Ar = *p*-MePh, 21% yield, *eq. 9*). This highly unexpected result prompted a ^{1}H NMR investigation of this reaction (*eq. 10*) wherein each component of the reaction was



Ar = Ph: 93% yield, 88% ee
Ar = *p*-MePh: 21% yield, 85% ee (9)

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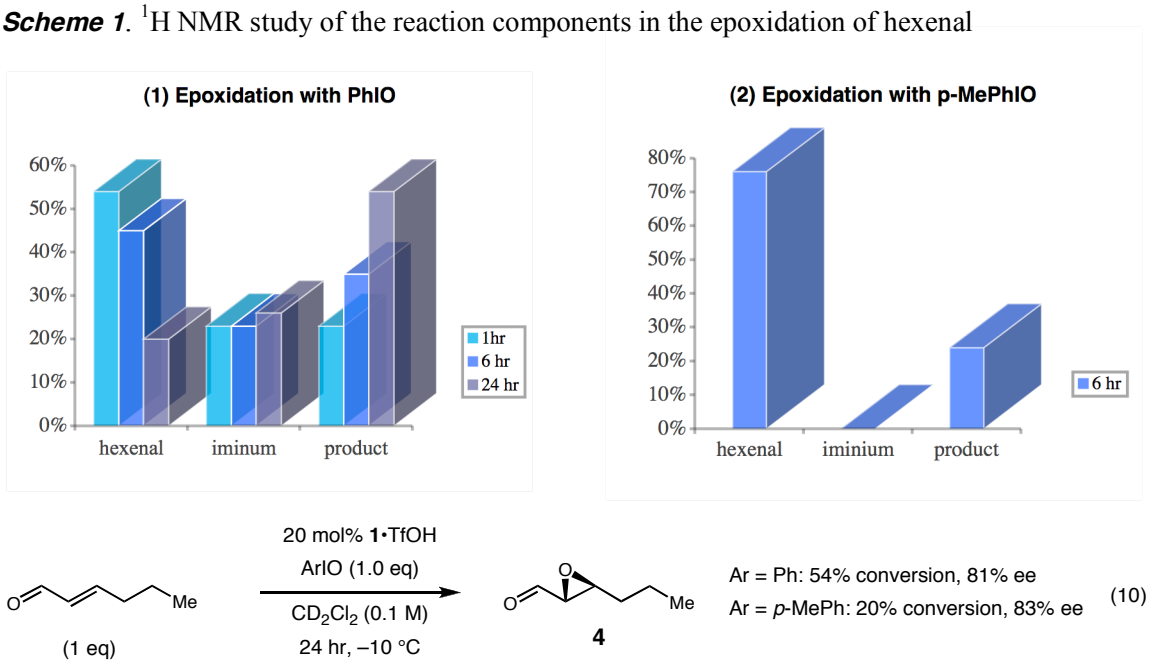
27. (a) Harden, G. J. *J. Chem. Soc., Perkins Trans. 2* **1995**, 1883. (b) Gao, Y.; Jiao. X.; Fan, W.; Shen, J.-K.; Shiu, Q.; Basolo, F. *J. Coord. Chem.* **1993**, *29*, 349.

28. All iodosobenzene substrates were prepared using a modified procedure outlined in Sawaguchi, M.; Aruba, S.; Hara, S. *Synthesis* **2002**, *13*, 1802, using an appropriately functionalized iodobenzene starting material.

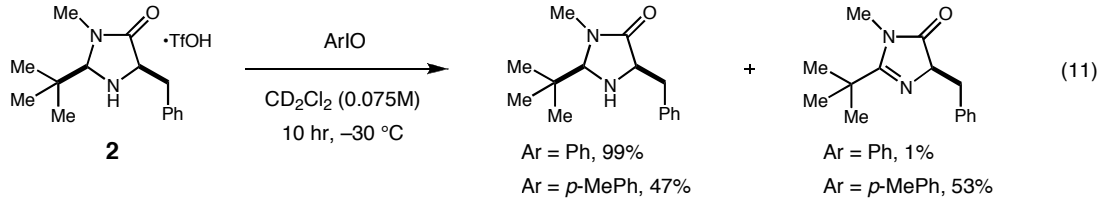
followed over the course of 24 hours (using modified reaction conditions tailored to this ^{1}H NMR study in order to conduct the reaction at a higher temperature and lower overall concentration). The NMR profile of the crude reaction of hexenal with iodosobenzene demonstrated good progression (54% conversion, 81% ee) and a persistent level of reactive iminium (20%, *graph 1*, *Scheme 1*) over 24 hours. In contrast, the reaction of hexanal with

Scheme 1. ^{1}H NMR study of the reaction components in the epoxidation of hexenal



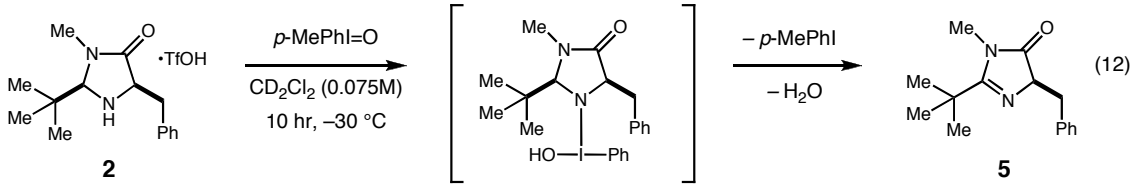
p-Me iodosobenzene after 24 hours did not advance beyond 20% conversion (and 83% ee) to epoxide **4**. In fact, the reaction was complete after only 6 hours since additional progression to product was not possible due to the absence of reactive iminium complex (0%, *graph 2*, *Scheme 1*).

With focus on potential catalyst and oxidant interactions, additional ^{1}H NMR studies were undertaken with *p*-Me iodosobenzene and catalyst **2** in the absence of an aldehyde substrate. It was revealed that a rapid depletive imidazolidinone oxidation pathway compromised the integrity of the catalyst (Ar = *p*-MePh, *eq. 11*). Intriguingly, a



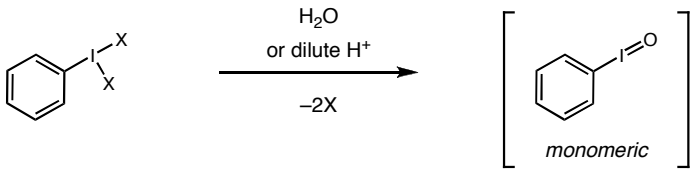
(11)

slower variant of the same catalyst decomposition pathway was observed using iodosobenzene as the reaction oxidant (Ar = Ph, *eq. 10*) to a much lesser extent. We surmised that the increased nucleophilicity of the oxygen in the *p*-Me iodosobenzene, consequently lead to increased electrophilicity of the iodine, making the system more susceptible to attack by the catalyst free amine (*eq. 12*); Thus, the ensuing reductive β-elimination gives rise to the observed oxidation product, imine **5**.



(12)

At this stage, we presumed that the diminished enantioselectivities observed in the cinnamaldehyde epoxidation case (*Table 5*, *entry 4*) could be attributed to the intervention of a catalyst oxidation pathway that is competitive with the iminium-catalyzed addition-cyclization step. With respect to the relative capacities of iodosobenzene and *p*-Me iodosobenzene to function as catalyst oxidants, we have determined that the tolyl-derived system is more soluble under the reaction conditions than its polymeric phenyl iodide counterpart. As a result, the relative concentration of *p*-Me iodosobenzene in solution was found to be much higher, a scenario that dramatically increases the rate of catalyst oxidation and leads to greatly diminished conversions with this iodane. On this basis, we began to focus upon identifying alternative sources of hypervalent iodine, which could be

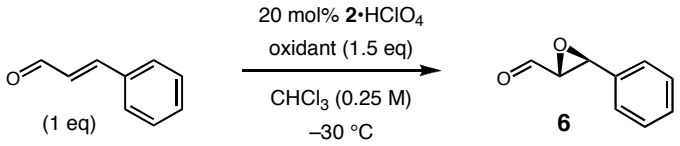


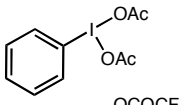
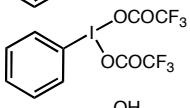
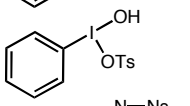
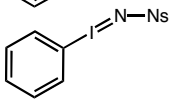
(13)

employed to slowly generate reactive iodosobenzene monomer *in situ*, and in doing so function as a type of "internal syringe pump" (*eq. 13*). In this manner, we hoped the imidazolidinone **2** would be partitioned exclusively towards iminium formation with the aldehyde substrate and thereby avoid catalyst oxidation.

We next examined a range of hypervalent λ^3-iodane sources that we expected would slowly release iodosobenzene monomer when subjected to water or mildly acidic conditions in accessing an equilibrium content of iodosobenzene (*Table 6*). These studies were specifically performed with cinnamaldehyde with the anticipation that an improvement in enantioselectivity with this substrate would be observed as compared to an

Table 6. Alternative Iodosobenzene Sources



entry	oxidant	additive	% conversion[a]	% ee[b]
1		water	68	84
2		water	10	71
3[c]		water	7	76
4		water	71	80
		1M AcOH	100	92

[a] Conversion determined by ^{1}H NMR analysis using methyl benzyl ether as a standard. [b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA). [c] Koser's salt = [(hydroxy)(tosyloxy)iodo]benzene.

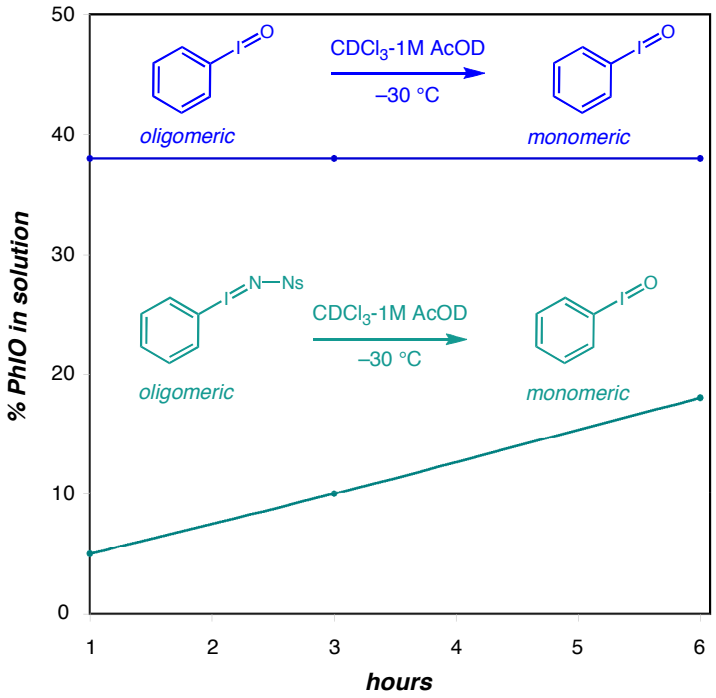
analogous experiment with iodosobenzene (73% ee, *Table 5*, *entry 4*). As revealed in Table 6, the use of commercially available diacetoxy iodosobenzene in the presence of water did indeed provide the desired epoxide with enhanced levels of enantiocontrol (84% ee*, entry 1*); however, bis(trifluoroacetoxy) iodosobenzene and Koser's salt provided the oxirane **6** with poor efficiency (7–10% yield, *entries 2* and *3*). Given that hypervalent I–N systems have been established to be less stable than the corresponding I–O class of reagents,[25a] we next examined the use of iminoiodanes as potential iodosobenzene surrogates in the presence of water or acid. To our great delight, exposure of cinnamaldehyde to [(nosylimino)iodo]benzene (NsNIPh) in the presence of catalyst **2** and 1M acetic acid (20 vol% to facilitate the hydrolysis of the sulfonamide) did indeed furnish epoxide **6** with excellent levels of conversion and enantiocontrol (100% conversion, 92% ee, *entry 4*). It is noteworthy that arylsulfonylimino(aryl)iodanes are stable, easily storable compounds[25a] that we have determined will function as controlled release iodosobenzene oxidants in the presence of dilute acid (*vide infra*).

IV. NMR Studies on the Mechanism of the Internal Syringe Pump Effect

In an attempt to gain further insight into the inherent advantages of using NsNIPh in comparison to iodosobenzene in this organocatalytic epoxidation, various NMR studies were undertaken to examine: (1) the controlled release of monomeric iodosobenzene from NsNIPh and (2) the subsequent effect of the monomeric iodosobenzene concentration on the rate of imidazolidinone catalyst oxidation.

A low-temperature ^{1}H NMR study (–30 °C) was performed to investigate the conversion of NsNIPh to monomeric iodosobenzene in the presence of deuterated chloroform and 1M acetic acid (AcOD).[29] As revealed in Figure 3, the iminoiodane (NsNIPh) does indeed undergo slow hydrolysis to provide a steady increase in the concentration of monomeric iodosobenzene over the course of six hours. It is important to note that constant concentrations of diacetoxy iodosobenzene (5%) and hemi-hydrolyzed

Figure 3. The solution content of monomeric iodosobenzene from NsNIPh as monitored by NMR



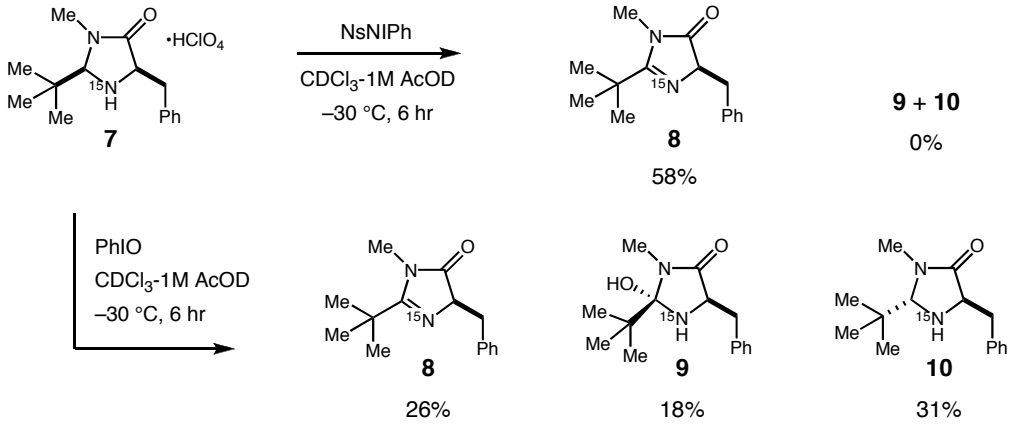
nosyliodosobenzene (1%) were also present in the reaction solution. In contrast, when the analogous ^{1}H NMR experiment was performed with oligomeric iodosobenzene, we observed the immediate formation of a relatively high concentration of iodosobenzene monomer (38%) that remained constant over the course of this six-hour study. Again, a

29. Concentrations of iodosobenzene species were calculated relative to benzyl methyl ether (internal standard) and determined after removal of oligomeric iodosobenzene by filtration through celite.

minimal concentration of diacetoxy iodosobenzene (2%) was also detected in this experiment. These ^{1}H NMR studies clearly demonstrate that the proposed slow release of monomeric iodosobenzene from NsNIPh ("internal syringe pump" effect) is not only feasible, but likely operational.

We next turned to ^{15}N NMR studies to examine the mode of catalyst depletion and to investigate the role of monomeric iodosobenzene concentration on catalyst depletion (via a variety of presumed amine oxidation pathways). In this context, we first investigated the use of ^{15}N isotopically-labeled imidazolidinone **7** as a catalyst for the epoxidation of cinnamaldehyde using: (a) NsNIPh and (b) oligomeric iodosobenzene as the respective reaction oxidants (*Scheme 2*). It should be noted that in both cases, reaction efficiencies and enantioselectivities were observed that were within the experimental error of the corresponding results observed with a catalyst having a natural abundance of nitrogen. With respect to catalyst depletion, we observed striking differences in both the rate and nature of imidazolidinone decomposition as a function of these two oxidants and the relevant iodosobenzene monomer concentration. As illustrated in Scheme 2, the use of

Scheme 2. Mode of catalyst degradation when utilizing NsNIPh or PhIO as observed by ^{15}N NMR



oligomeric iodosobenzene leads to the formation of three catalyst-derived amines over the course of the reaction, namely imine **8**, aminol **9**, and the corresponding trans catalyst isomer **10**. In contrast, the analogous reaction that employs NsNIPh leads only to the formation of the corresponding imine **8**. It should be noted that isolation and separate resubjection of catalyst derivatives **8**, **9**, and **10** to the outlined epoxidation conditions has confirmed that each of these amine species is catalytically inactive. More important, however, is that the rate of catalyst consumption appears to be a function of the source of

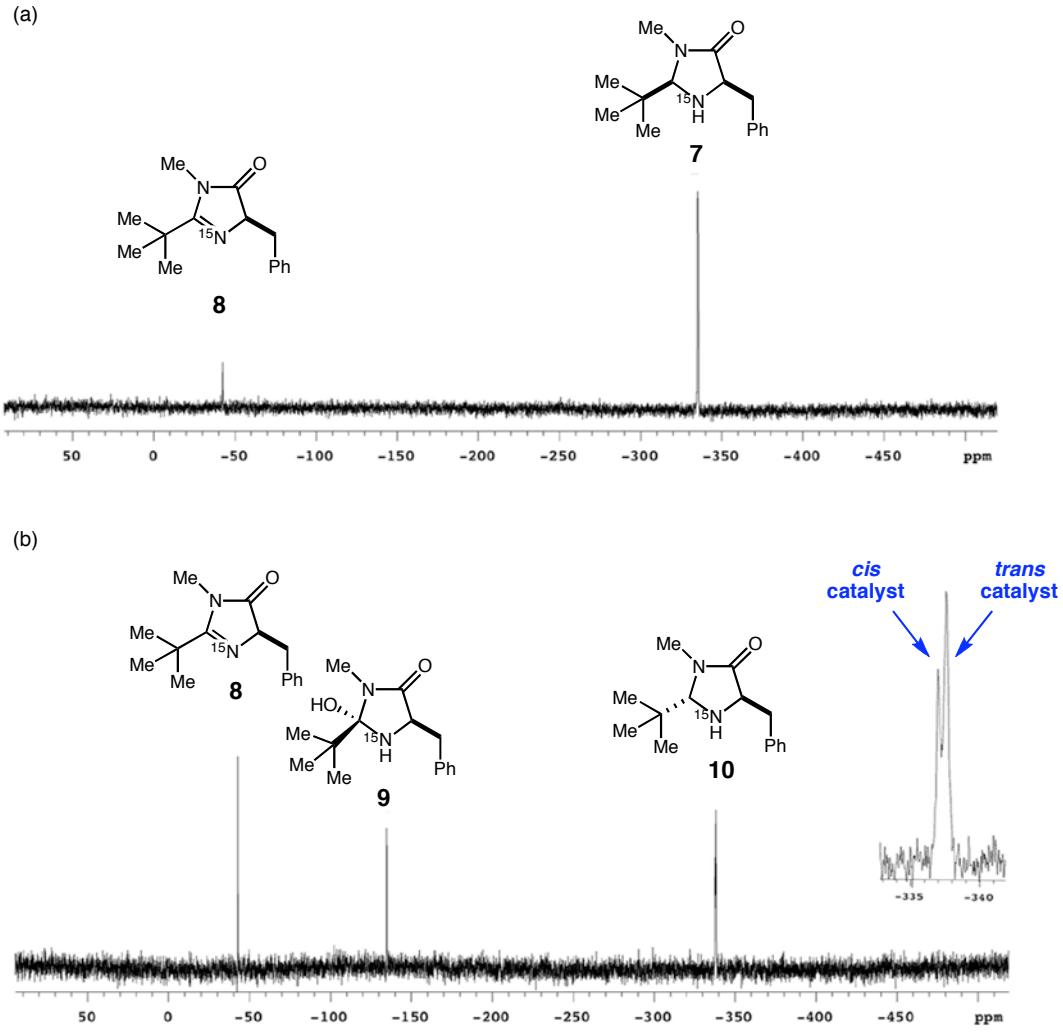


Figure 4. ^{15}N-VT NMR experiments of the ^{15}N-labeled catalyst (**7**) at –30 °C showing the catalyst species that are present using iodosobenzene after (a) 20 min and (b) 6 hr

monomeric iodosobenzene. As revealed in Figures 4 and 5, real time ^{15}N NMR studies performed on a low temperature epoxidation reaction with oligomeric iodosobenzene clearly demonstrates that the formation of imine **8** occurs within the first 20 minutes of the reaction protocol (*Figure 4(a)*). Moreover, after six hours there is almost complete conversion of the catalyst to amine derivatives **8**, **9**, and **10** (*Figure 4(b)*). We presume that these secondary oxidized catalysts species originate from imine **8**, which gives rise to the

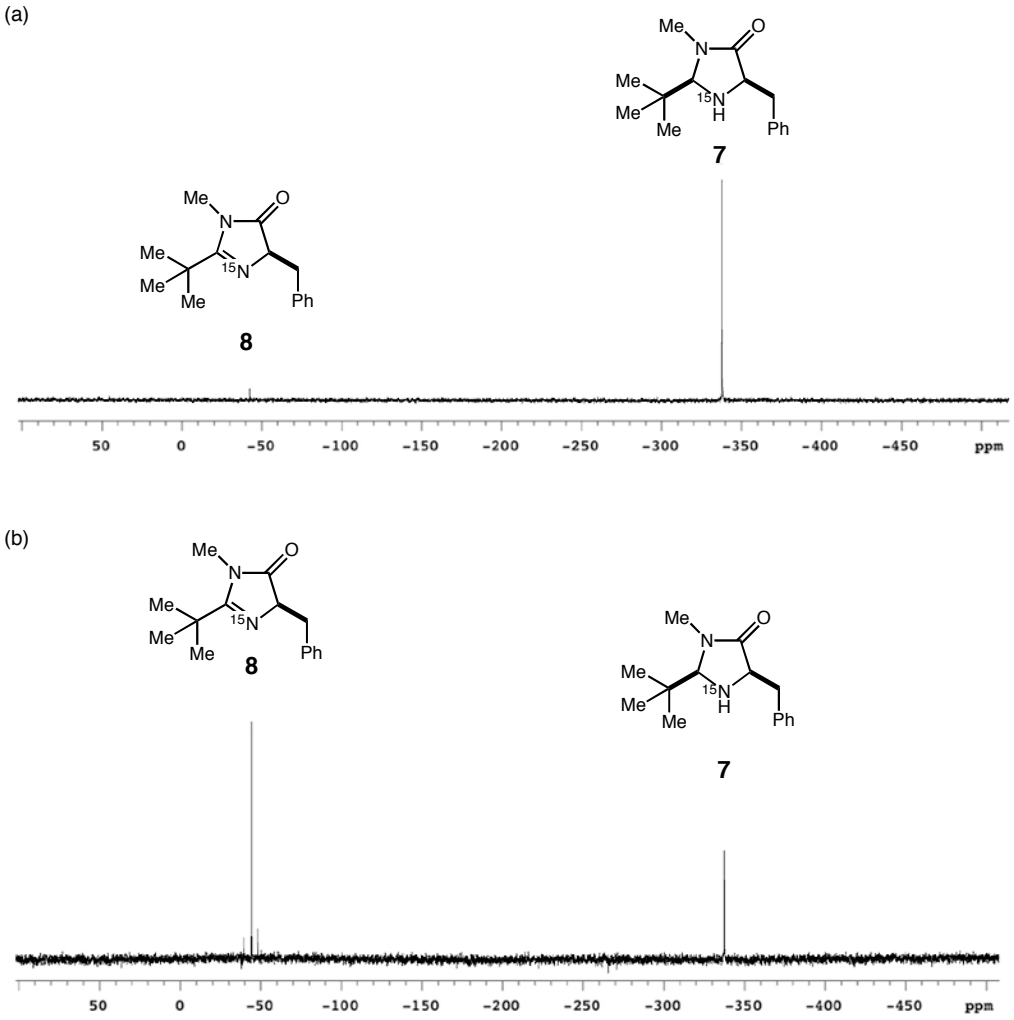


Figure 5. ^{15}N-VT NMR experiments of the ^{15}N-labeled catalyst (**7**) at –30 °C showing the catalyst species that are present using [(nosylimino)iodo]benzene after (a) 20 min and (b) 6 hr

hydroxy addition product **9**[30] and the isomerized *trans*-catalyst (**10**) by way of a non-selective addition and elimination of water. In contrast, the use of the slow release oxidant NsNIPh results in minimal catalyst oxidation after 20 minutes (*Figure 5(a)*), and only imine adduct **8** is formed in observable quantities after six hours (*Figure 5(b)*). Notably, significant quantities of the active catalyst **7** remain after six hours when NsNIPh is employed, highlighting that the "internal syringe pump" concept is key to achieving useful levels of catalyst efficiency within this epoxidation protocol.

V. Organocatalytic Epoxidation Substrate Scope

Having developed optimal epoxidation conditions, we sought to extend this methodology to other α,β-unsaturated aldehydes. As revealed in Table 7, a variety of enal olefins can be successfully utilized with both high levels of reactivity and enantiomeric control in the presence of NsNIPh. Most impressively, the cinnamaldehyde epoxidation reaction that had previously been 78% yield and 73% ee (*entry 4*) with iodosobenzene is now dramatically improved to excellent levels, 92% yield and 92% ee (*entry 7*). Electronic variation on the phenyl ring reveals that electronic electron-poor (*entry 8*) and electron-rich (*entry 9*) substitution is well tolerated. Exploring systems with alkyl substituents (*entries 1–3*) with varying steric demand shows good reactivity in the range of 72–88% and selectivities in the range of 88–93% ee. Examples of compatible functional groups for this

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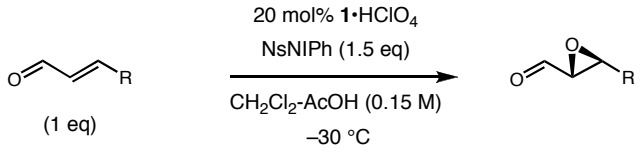
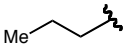
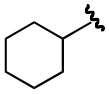
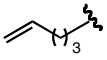
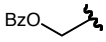
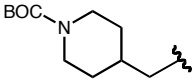
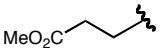
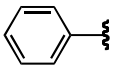
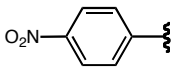
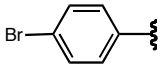
30. α-Oxidation by iodosobenzene is known to occur in the presence of acid or halogen salts, see: (a) Huang, W.-J.; Singh, O. V.; Chen, C.-H.; Choiu, S.-Y.; Lee, S.-S. *Helv. Chim. Acta* **2002**, *85*, 1069. (b) Tohma, H.; Maegawa, T.; Takizawa, Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328. (c) Ueno, M.; Nabana, T.; Togo, H. *J. Org. Chem.* **2003**, *68*, 6424. (d) Sohmiya, H.; Kimura, T.; Fujita, M.; Ando, T. *Tetrahedron* **1998**, *54*, 13737.

reaction manifold include esters (*entry 6*) and heterocyclic substituted amines (*entry 5*), provided that amine is protected with an electron-withdrawing protecting group. Additionally, unactivated olefins (*entry 4*) remain unoxidized under these reaction conditions in this chemoselective epoxidation by iodosobenzene. It should be noted that when a substrate is significantly electron-withdrawing (CH_2OBz, *entry 5*) the system is overly active to 1,4-addition and the nosyl-protected aziridine product can be formed

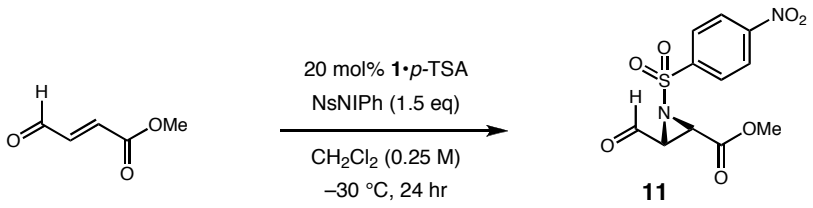
Table 7. Enantioselective Organocatalyzed Epoxidation: Scope



entry	R	time (hr)	% yield[a]	% ee[b]
1	Me	10	88[c]	93
2		15	72	88
3		13	77	92
4		16	95[d]	92
5		15	89[e]	85
6		11	86	87
7		12	86	90
8		12	92[d]	92
9		6	89[d]	97
10		8	93[d]	93

[a] Products are a single diastereomers, except in entry 1 (dr = 1:7). [b] Enantiomeric excess determined by chiral GC and SFC analysis. [c] Yield determined by NMR analysis. [d] $CHCl_3$ was used as solvent. [e] Iodosobenzene was used as the oxidant at –40 °C.

competitively when NsNIPh is used as the oxidant (1:1.6 aziridine:epoxide). In the extreme case, where the olefin is doubly activated (R = CO_2Me, *eq. 14*) the aziridine is the



(14)

major product when the reaction is conducted with the exclusion of a dilute acid (1M AcOH) to minimize the hydrolysis of the NsNIPh to iodosobenzene. Further efforts to optimize this reaction for the exclusive formation of the aziridine product have not been successful due to the unavoidable hydrolysis of NsNIPh in this organocatalytic reaction.[31]

IV. Conclusion

In summary, we have further established iminium catalysis as a valuable strategy for asymmetric synthesis in the context of an enantioselective enal epoxidation protocol. This new organocatalytic reaction allows for the enantioselective formation of oxiranes from a wide array of electronically and sterically diverse α,β-unsaturated aldehydes. Fundamental to these studies has been the recognition that hypervalent iodine reagents are suitable oxidants for organocatalytic epoxidations using imidazolidinone catalyst **1**. Optimal levels of reaction efficiency and enantiocontrol have been accomplished using an "internal syringe pump" protocol wherein the slow release of monomeric iodosobenzene

31. Since our report of this result, other organocatalytic aziridination methodologies have been reported: (a) Vesely, J.; Ibrahem, I.; Zhao, G. L.; Rios, R.; Cordova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778. (b) Armstrong, A.; Baxter, C. A.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Org. Lett.* **2007**, *9*, 351.

from an *in situ* iminoiodane source is accomplished using a mild acid. NMR studies (^{15}N) have revealed that this slow, *in situ* production of monomeric iodosobenzene from NsNIPh is central to alleviating losses in catalytic efficiency arising from a variety of imidazolidinone oxidation pathways.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[32] Iodosobenzene reagents were synthesized and iodometrically titrated for purity prior to use.[33] All solvents were purified according to the method of Grubbs.[34] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile compounds. Chromatographic purification of products was accomplished using force-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still,[35] and, where noted, Iatrobeads 6RS-8060 was used in place of silica gel. 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, anisaldehyde, $KMnO_4$, or ninhydrin stain.

^1H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz or 75 MHz) or an Inova 500 (500MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H 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. Data for ^{13}C NMR are reported in terms of chemical shift. ^{15}N NMR spectra were externally referenced to 7M nitromethane in

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32. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon Press: Oxford, 1988.

33. (a) Saltzman, H.; Sharefkin, J. G. *Org. Synth.* **1973**, *5*, 658. (b) Simàndi, L. I.; Nèmeth, S.; Besenyei, G. *Tetrahedron Lett.* **1993**, *34*, 6105.

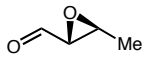
34. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518.

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

deuterated chloroform and are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 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 Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with split-mode capillary injection system and flame ionization detectors using Bodman Chiraldex Γ-TA and Varian Chirasil-Dex-CB (30 m x 0.25 mm) columns. High pressure liquid chromatography (HPLC) was preformed on a Hewlett-Packard 1100 series chromatograph using a Chiralcel OD-H column (25 cm) and OD guard (5 cm) as noted. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a variable-wavelength UV detector using a Chiralpak AD-H column (25 cm) and AD guard (5 cm).

General epoxidation procedure A (using iodosobenzene): A solution of the trifluoromethanesulfonic acid salt of (*2R*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (0.2 eq) in dichloromethane (0.075M) is prepared in a scintillation vial equipped with a magnetic stir bar at –50 or –40 °C (as noted) for 10 minutes. The aldehyde (3 eq) and iodosobenzene (1 eq) are added to form a light yellow suspension and the reaction is stirred at constant temperature for 10–15 hours until no further reaction progression is observed. The cold reaction is filtered through celite, washed with ether and concentrated *in vacuo*. The resulting residue is purified by column chromatography (solvents noted) to provide the title compounds.

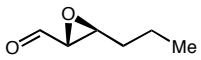
General epoxidation procedure B (using NsNIPh): A scintillation vial equipped with a magnetic stir bar was charged with perchloric acid (70 wt%, 0.2 eq), dichloromethane and 20 vol% of 1M AcOH (0.15 M) and (*2R*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (0.2 eq) and allowed to stir for ten minutes at –30 °C. The aldehyde (1 eq) and [(nosylimino)iodo]benzene (1.5 eq) are added to form a light yellow suspension in an icy solution, which is stirred at constant temperature for 6–16 hours until complete consumption of the starting material is observed. The cold reaction is quenched by adding pH 7 buffer, filtration through celite, and extraction with ether (2 x 4 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* and the resulting residue is purified by column chromatography (solvents as noted) to provide the title compounds.



((2*R*, 3*S*)-3-Methyl-oxirane-2-carbaldehyde (3). Prepared according to general epoxidation procedure A using crotonaldehyde (296 μL, 3.57 mmol) in CD_2Cl_2 at –50 °C with benzyl ether as an internal standard to establish NMR yield, after filtration through silica gel. The title compound was obtained in a 100% NMR yield and 93% ee.

Also prepared according to general epoxidation procedure B with crotonaldehyde (296 μL, 3.57 mmol) in CD_2Cl_2 and mesitylene as an internal standard to establish NMR yield. After filtration through silica gel, the title compound was obtained in an 88% NMR yield and 93% ee. Material for characterization was obtained by flash chromatography (Iatrobeads, 20% ether in pentane). IR (film) 3416, 2965, 2929, 1443, 1380, 1124, 871 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.00 (d, 1H, *J* = 6.0 Hz, C**H**O), 3.30 (qd, 1H, *J* = 2.1, 5.1 Hz, C**H** oxirane), 3.08 (dd, 1H, *J* = 2.1, 6.3 Hz, C**H** oxirane), 1.42 (d, 3H, *J* = 5.1 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 60.23, 53.06, 17.06; HRMS (EI+) exact mass

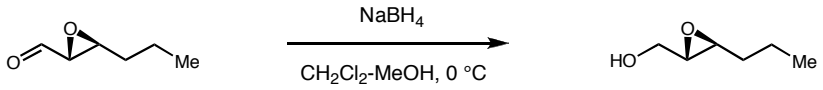
calculated for $[M]^+$ ($C_4H_6O_2$) requires *m*/*z* 86.03678, found *m*/*z* 86.03649; $[\alpha]_D$= +47.9 (c = 2.7, $CHCl_3$). The enantiomeric purity was determined on the alcohol product, which is prepared by a $NaBH_4$ reduction, and analyzed by GLC analysis using a Bodman Γ-TA column (40 °C isotherm, 12 psi); (2*S*, 3*R*) isomer t_r = 57.1 min, (2*S*, 3*R*) isomer t_r = 58.7 min.



(2*R*, 3*S*)-3-Propyloxirane-2-carbaldehyde (4). Prepared according to general epoxidation procedure A using (*E*)-hex-2-enal (591 μL, 5.09 mmol) at –50°C. After stirring for 15 hrs, this reaction was filtered through silica, washed with dichloromethane (30 mL), and cooled to 0 °C. Reduction to the alcohol was performed on the crude reaction solution by adding ethanol (1 mL) and $NaBH_4$ (770 mg, 20.4 mmol). The reaction was quenched with a saturated solution of Rochelle's salt (30 mL) on completion as judged by TLC. The alcohol product was extracted with dichloromethane (3 x 30 mL) and concentrated *in vacuo* at 0 °C, before purifying by flash chromatography (silica gel, 50% ether in pentane) to afford the title compound as a clear, colorless oil in 93% yield (182 mg, 1.57 mmol), 88 % ee.

Also prepared according to general epoxidation procedure B using (*E*)-hex-2-enal (234 mL, 2.0 mmol) to afford the title compound as a clear, colorless oil (162 mg, 72% yield, 88% ee) after chromatography (silica gel, 30% to 70% ether in pentanes, linear gradient). IR (film) 2962, 2935, 2875, 1731, 1671, 1534, 1458, 1378, 1350, 1125, 1092, 1044, 915.1, 737.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (d, 1H, *J* = 6.3 Hz, C**H**O), 3.23 (td, 1H, *J* = 2.1, 5.1, 7.8 Hz, C**H** oxirane), 3.13 (dd, 1H, *J* = 1.8, 6.3 Hz, C**H** oxirane),

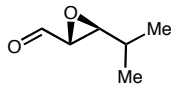
1.69–1.50 (m, 4H, C**H**$_2$C**H**$_2$), 0.98 (t, 3H, *J* = 7.2 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 59.34, 56.83, 33.39, 19.39, 13.98; HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_6H_9O_2$) requires *m*/*z* 113.0603, found *m*/*z* 113.0602; $[\alpha]_D$= +11.4 (c = 2.38, $CHCl_3$). The enantiomeric purity was determined by GLC using a Bodman Γ-TA column (70 °C isotherm, 15 psi, flow = 1.3 mL/min); (2*S*, 3*R*) isomer t_r = 8.87 min, (2*R*, 3*S*) isomer t_r = 9.79 min.



Determination of the absolute stereochemistry of (2*R*, 3*S*)-3-Propyloxirane-2-carbaldehyde by correlation to ((2*R*, 3*R*)-3-propyloxiran-2-yl)methanol.[36] Reduction of the aldehyde to the alcohol by $NaBH_4$ (2.6 mmol) in dichloromethane (5.0 mL) with catalytic ethanol (0.2 mL) was performed at 0 °C. The reduction was quenched by a saturated solution of Rochelle's salt (5.0 mL) and extracted with ether (2.0 x 5 mL) and concentrated *in vacuo* at 0 °C, before purifying by flash chromatography (silica gel, 50% ether in pentanes) to afford alcohol as a clear, colorless oil. IR (film) 2922, 1700, 1521, 1458, 1020, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (ddd, 1H, *J* = 2.4, 5.1, 12.3 Hz, C**H**OH), 3.67 (ddd, 1H, *J* = 4.5, 7.8, 12.6 Hz, C**H**OH), 3.02–2.94 (m, 2H, C**H** oxirane), 1.65–1.47 (m, 4H, C**H**$_2$C**H**$_2$), 1.03 (t, 3H, *J* = 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.86, 58.70, 55.96, 33.54, 19.21, 13.84; HRMS (EI^+) exact mass calculated for $[M+H]^+$ ($C_6H_{13}O_2$) requires *m*/*z* 117.0916, found *m*/*z* 117.0917; $[\alpha]_D$= –13.2 (c = 0.42, $CHCl_3$). ^{1}H

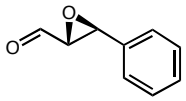
36. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamume, H.; Sharpless, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Hill, J. G.; Sharpless, B. M.; Exon, C. M.; Regenye, R. *Org. Synth.* **1984**, *63*, 66.

NMR matched the reported values and the literature $[\alpha]_D$= –46.3 (c = 3.87, $CHCl_3$). This enantiomerically enriched compound is also commercially available from Sigma-Aldrich.



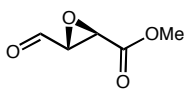
((2*R*, 3*S*)-3-Isopropyloxiran-2-yl)methanol (***Table 5*, *entry 3*).** Prepared according to general epoxidation procedure A using (*E*)-4-methylpent-2-enal (592 μL, 5.09 mmol) and iodosobenzene (1.52 g, 6.92 mmol) in dichloromethane (18.3 mL) at –40 °C. After stirring for 15 hrs, this reaction was filtered through silica gel, washed with dichloromethane (50 mL) and cooled to 0 °C. Reduction to the alcohol was performed on the crude reaction solution by adding ethanol (1.0 mL) and $NaBH_4$ (770 mg, 20.4 mmol). The reaction was quenched with a saturated solution of Rochelle's salt (30 mL) on completion as judged by TLC. The alcohol product was extracted with dichloromethane (3.0 x 30 mL) and concentrated *in vacuo* at 0 °C, before purifying by flash chromatography (silica gel, 30% to 50% ether in pentanes, linear gradient) to afford the title compound as a clear, colorless oil in 86% yield (505 mg, 4.35 mmol), 80 % ee. IR (film) 2963, 2930, 1459, 1067, 895.1, 669.3 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (ddd, 1H, *J* = 2.4, 5.7, 12.3 Hz, C**H**OH), 3.70 (ddd, 1H, *J* = 4.2, 7.2, 12.3 Hz, C**H**OH), 3.02 (dt, 1H, *J* = 3.0, 3.9 Hz, C**H** oxirane), 2.81 (dd, 1H, *J* = 2.4, 6.9 Hz, C**H** oxirane), 1.70–1.59 (m, 1H, C**H**Me_2), 1.08 (d, 3H, *J* = 6.6 Hz, C$\mathbf{H}_3$), 1.02 (d, 3H, *J* = 6.9 Hz, C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.86, 61.14, 57.36, 30.07, 19.02, 18.37; HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_6H_{11}O_2$) requires *m*/*z* 115.0759, found *m*/*z* 115.0702; $[\alpha]_D$= –14.0 (c = 0.74, $CHCl_3$). The enantiomeric purity was on the crude alcohol product determined by GLC analysis using a

Bodman Γ-TA column (60 °C isotherm, 12 psi); (2*S*, 3*R*) isomer t_r = 12.8, (2*R*, 3*S*) isomer t_r = 16.2 min.

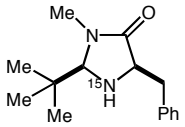


(2*R*, 3*S*)-3-Phenyloxirane-2-carbaldehyde (6). Prepared using general epoxidation procedure A using cinnamaldehyde (159 μL, 1.26 mmol) and iodosobenzene (378 mg, 1.72 mmol) in dichloromethane (5.04 mL) at –40 °C. Flash chromatography (silica gel, 30% ether in pentane) afforded the title compound as a clear, light yellow oil in a 71% yield (133 mg, 0.90 mmol), 78 % ee.

Prepared according to general epoxidation procedure B using cinnamaldehyde (94.4 μL, 0.75 mmol) using 1M AcOH (0.75 mL) and chloroform (3.0 mL). Flash chromatography (silica gel, 30% ether in pentane) afforded the title compound as a clear, light yellow oil (101 mg, 92% yield, 92% ee). IR (film) 1726, 1460, 1137, 990.8, 754.3, 697.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, 1H, *J* = 6.0 Hz, C**H**O), 7.39–7.28 (m, 5 H, aryl **H)**, 4.17 (d, 1H, *J* = 2.1 Hz, C**H** oxirane), 3.45 (dd, 1H, *J* = 2.1, 6.0 Hz, C**H** oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 129.4, 129.0, 125.9, 63.2, 56.9; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_9H_8O_2$) requires *m*/*z* 148.0524, found *m*/*z* 148.0522; $[\alpha]_D$= +35.8 (c = 0.76, $CHCl_3$). The enantiomeric purity was determined by GLC analysis using a Bodman G-TA column (90 °C isotherm, 15 psi, flow = 1.0 mL/min); (2*S*, 3*R*) isomer t_r = 29.9 min, (2*R*, 3*S*) isomer t_r = 33.1 min.



Methyl 3-((2*R*, 3*S*)-3-formyloxiran-2-yl)propanoate (***Table 5*, *entry 5*).** Prepared according to general epoxidation procedure B using (*E*)-methyl 5-formylpent-4-enoate[37] (142 mg, 1.0 mol) to afford the title compound as a clear, colorless oil (137 mg, 86% yield, 90% ee) after flash chromatography (silica gel, 40% ether in pentanes). IR (film) 1731, 1438, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, 1H, *J* = 6.3 Hz, C**H**O), 3.72 (s, 3H, $CO_2C\mathbf{H}_3$), 3.38–3.34 (m, 1H, C**H** oxirane), 3.20 (dd, 1H, *J* = 2.0, 6.0 Hz, C**H** oxirane), 2.52 (t, 2H, *J* = 6.9 Hz, $C\mathbf{H}_2CO_2Me$), 2.15–1.88 (m, 2H, $C\mathbf{H}_2CH_2CO_2Me$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 151.1, 59.29, 55.81, 52.16, 30.11, 26.66; HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_7H_9O_4$) requires *m*/*z* 157.0501, found *m*/*z* 157.0501; $[\alpha]_D$= +27.3 (c = 1.25, $CHCl_3$). The enantiomeric purity was determined by GLC using a Chirasil-DEX CB column (90 °C isotherm, 15 psi, flow = 1.0 mL/min); (2*R*, 3*S*) isomer t_r = 60.62 min, (2*S*, 3*R*) isomer t_r = 62.23 min.



^{15}N-labeled (2*R*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (**7**)**.** D-phenylalanine (98% ^{15}N-labeled, 3g, 18.05 mmol) in a three-neck 100 mL round-bottom flask equipped with a reflux condenser and magnetic stirrer is suspended in methanol (36 mL) under an Ar atmosphere. Thionyl chloride (3.3 mL, 45.1 mmol) is added dropwise and the reaction becomes homogenous upon exotherm and evolution of gas. The reaction is refluxed for 12 hours and then cooled to room temperature and partitioned with aqueous $NaHCO_3$ (30 mL) and ethyl acetate (2.0 x 30 mL). The separated organic layers are

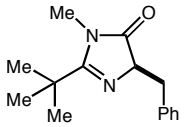
37. Kukovinets, O. S.; Kasradze, V. G.; Chernukha, E. V.; Odinokov, V. N.; Dolidze, A. V.; Galin, F. Z.; Spirikhin, L. B.; Abdullin, M. I.; Tolstikov, G. A. *Russ. J. Org. Chem.* **1999**, *35*, 1156.

combined, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue is purified on a short plug of silica gel and washed with ethyl acetate (20 mL) to yield ^{15}N-labeled (*R*)-methyl 2-amino-3-phenylpropanoate as a clear oil (3.22 g, quantitative yield).

The methyl ester (3.2 g, 18.1 mmol) and methylamine (8M in ethanol, 10 mL) in a 25 mL round-bottom flask are magnetically stirred at room temperature for 12 hours under an Ar atmosphere. The reaction is diluted with 0.5M HCl (20 mL) and partitioned by ethyl acetate (2.0 x 20 mL). The separated organic layers are combined, dried over Na_2SO_4, and concentrated *in vacuo* to give ^{15}N-labeled (*R*)-2-amino-*N*-methyl-3-phenylpropanamide as a clear oil (3.2 g, quantitative yield).

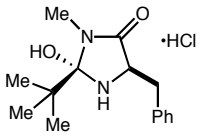
To a dry, three-necked 100 mL round-bottom flask equipped with a reflux condenser, Dean-Stark trap, and magnetic stir bar is added $FeCl_3$ (586 mg, 3.6 mmol) under a N_2 atmosphere. A solution of the amide (3.2 g, 18.1 mmol) and pivaldehyde (2.1 mL, 18.1 mmol) in toluene (36 mL) is added by cannula addition to the flask containing $FeCl_3$. The reaction is refluxed for 12 hours under an Ar atmosphere and cooled to room temperature before dilution with brine (50 mL) and partitioning with ethyl acetate (2.0 x 30 mL). The separated organic layers are combined, dried over Na_2SO_4 and concentrated *in vacuo* to give a brown oil. ^{1}H NMR shows a *cis* : *trans* ratio of 1.2 to 1.0. The desired *cis*-isomer is purified from the *trans*-isomer by flash chromatography (silica gel, 50% ethyl acetate in hexanes) to yield the title compound as a yellow crystalline solid (2.13 g, 48% yield). IR (film) 3338, 2958, 1700, 1395, 1101, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H, aryl **H**), 4.07 (s, 1H, *N*, *N*-acetal **H**), 3.72-3.71 (br m, 1H, α-amide **H**), 3.17 (dt, 1H, J = 3.8, 13.5 Hz, benzyl **H**), 2.95 (ddd, 1H, J = 2.5, 8.0, 13.5 Hz, benzyl **H**), 2.30 (s, 3H, *N*-C**H**$_3$), 1.76 (br s, 1H, N**H**), 0.85 (s, 3H, C(C**H**$_3$)$_3$); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 175.46, 142.90, 138.06, 129.78, 128.76, 126.82, 82.65 (d, J_{15N-C} = 3.02 Hz), 59.58 (d, J_{15N-C} = 3.64 Hz), 38.43 (d, J_{15N-C} = 2.39 Hz), 35.19 (d, J_{15N-C} = 1.76 Hz), 25.51 (d, J_{15N-C} = 1.13 Hz); ^{15}N NMR (50 MHz, $CDCl_3$) δ –337.08; ^{15}N NMR (50 MHz, $CDCl_3$-1M AcOH) for the $HClO_4$ salt of the title compound, δ –336.35; HRMS (FAB+) exact mass calculated for $[M]^+$ ($C_{15}H_{22}N^{15}NO$) requires *m*/*z* 247.1703, found *m*/*z* 247.1726; $[\alpha]_D$= –46.4 (c = 1.10, $CHCl_3$).



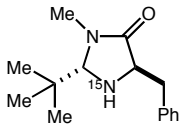
(*R*)-2-*tert*-butyl-4-benzyl-1-methyl-1*H*-imidazol-5(4*H*)-one (**5**)**.** A scintillation vial equipped a stir bar is charged with dichloromethane (5 mL), iodobenzene diacetate (403 mg, 1.25 mmol) and activated 3Å molecular sieves (500 mg). After 10 minutes, ((2*R*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (61.6 mg, 0.25 mmol) is added to the vial and the reaction is stirred for 3 hours at room temperature. The reaction is filtered through celite, concentrated *in vacuo* and purified by flash chromatography (Iatrobeads, 50% ether in pentanes) to yield the title compound as a clear oil (51.9 mg, 85% yield). It should be noted that the crude reaction (as observed by NMR) initially produces the acetate addition product of the imine, which upon workup and purification causes elimination of the acetate to yield the imine product. IR (film) 2961, 1706, 1636, 1495, 1425, 1395, 1366, 1232, 701, 665 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.12, 165.44, 135.72, 130.99, 129.58, 128.72, 126.98, 91.85, 36.76, 31.26, 26.34; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_{15}H_{20}N_2O$) requires *m*/*z* 244.1576, found *m*/*z* 244.1586; $[\alpha]_D$= –76.3 (c = 1.22, $CHCl_3$).

The title compound was additionally synthesized using ^{15}N-labeled ((2*R*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one using the above procedure to yield **8**. ^{15}N NMR (50 MHz, $CDCl_3$-1M AcOD) δ –40.78.

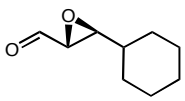


(5*R*)-2-*tert*-butyl-5-benzyl-2-hydroxy-3-methylimidazolidin-4-one HCl salt (9). A scintillation vial equipped with a stir bar is charged with dichloromethane (5 mL) and 1M AcOH (1ML), iodosobenzene (161Mg, 0.5 mmol), and ((2*R*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (61.6 mg, 0.25 mmol). The reaction is stirred for 2 hours at room temperature before filtration and concentration *in vacuo*. Purification was by flash chromatography (silica gel, 40% ethyl acetate in hexanes) and the isolated residue is dissolved in HCl (2M in ether, 125 mL) and dichloromethane (12.5 mL) and cooled to –70 °C to facilitate precipitation. The precipitate is filtered and washed with cold ether and dried under reduced pressure to yield the title compound as a white solid (18 mg, 24% yield). IR (KBr) 2961, 1780, 1657, 1495, 1253, 706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H, aryl **H**), 4.79 (dd, 1H, *J* = 3.0, 5.4 Hz, α-amide **H**), 4.00 (dd, 1H, *J* = 5.4, 13.8 Hz, benzyl **H**), 3.35 (dd, 1H, *J* = 3.0, 13.5 Hz, benzyl **H**), 3.09 (s, 3H, *N*-C**H**$_3$), 1.29 (s, 3H, C(C**H**$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.98, 175.16, 132.28, 130.27, 129.19, 128.59, 128.17, 61.052, 35.91, 35.86, 29.10, 28.54, 26.62; HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}N_2O_2$) requires *m*/*z* 261.1603, found *m*/*z* 261.1605; $[\alpha]_D$= +4.2 (c = 1.24, $CHCl_3$).

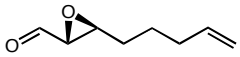
The title compound was additionally synthesized using ^{15}N-labeled ((2*R*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one using the above procedure to yield the HCl salt. Notably, this compound was hydrolyzed using 0.5M NH_4OH to the corresponding free base prior to use in the ^{15}N NMR studies. ^{15}N NMR (50 MHz, $CDCl_3$-1M AcOD) δ –133.20.



^{15}N-labeled ((2*S*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (10). The title compound is prepared and isolated from the procedure for ^{15}N-labeled (2*R*, 5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one as a yellow crystalline solid (1.57 g, 35% yield). IR (film) 3306, 2953, 1684, 1394, 1096, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H, aryl **H**), 3.85–3.83 (br m, 1H, α-amide **H**), 3.81 (t, 1H, *J* = 1.5 Hz, *N*, *N*-acetal **H**), 3.11 (dt, 1H, *J* = 3.6, 14.1 Hz, benzyl **H**), 2.89 (ddd, 1H, *J* = 2.7, 6.9, 14.1 Hz, benzyl **H**), 2.89 (s, 3H, *N*-C**H**$_3$), 1.86 (br s, 1H, N**H**), 0.90 (s, 3H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.53, 137.68, 129.70, 128.74, 126.89, 83.62 (d, J_{15N-C} = 3.02 Hz), 59.71 (d, J_{15N-C} = 4.08 Hz), 38.77, 37.93, 31.54, 25.57; ^{15}N NMR (50 MHz, $CDCl_3$) δ –337.68; HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}N^{15}NO$) requires *m*/*z* 248.1781, found *m*/*z* 247.1790; $[\alpha]_D$= –60.0 (c = 1.13, $CHCl_3$).



(2*R*, 3*S*)-3-Cyclohexyloxirane-2-carbaldehyde (*Table 7, entry 3*). Prepared according to general epoxidation procedure B using 3-cyclohexylacrylaldehyde[38] (147 mg, 1.06 mmol) to afford the title compound as a clear, colorless oil (124 mg, 77% yield, 92% ee) after flash chromatography (silica gel, 20% ether in pentanes with 1% Et_3N). IR (film) 2928, 2853, 1730, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, 1H, *J* = 6.0 Hz, C**H**O), 3.17 (dd, 1H, *J* = 1.8, 6.3 Hz, C**H** oxirane), 3.02 (dd, 1H, *J* = 2.1, 6.6 Hz, C**H** oxirane), 1.85–1.66 (m, 5H), 1.41–1.30 (m, 1H), 1.26-1.05 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 61.05, 58.28, 39.51, 29.72, 28.91, 26.24, 25.68, 25.60; HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_9H_{13}O_2$) requires *m*/*z* 153.0916, found *m*/*z* 153.0910; $[\alpha]_D$= +75.6 (c = 1.02, $CHCl_3$). The enantiomeric purity was determined by GLC using a Varian Chirasil-Dex-CB column (80 °C isotherm, 15 psi, flow = 1.0 mL/min); (2*S*, 3*R*) isomer t_r = 42.07 min, (2*R*, 3*S*) isomer t_r = 46.87 min.



(2*R*, 3*S*)-3-(pent-4-enyl)oxirane-2-carbaldehyde (*Table 7, entry 4*). Prepared according to general epoxidation procedure B using 3-(*E*)-octa-2,7-dienal[39] (270 mg, 2.18 mol) to afford the title compound as a clear, colorless oil (292 mg, 95% yield, 92% ee) after flash chromatography (silica gel, 20% ether in pentanes). IR (film) 1729, 1440, 1148, 993.1, 914.4, 849.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, 1H, *J* = 6.3 Hz, C**H**O), 5.82-5.69 (m, 1H, C**H**=CH_2), 5.04-4.94 (m, 2H, CH=C**H**$_2$), 3.11 (dd, 1H, *J* = 1.8, 6.3 Hz, C**H** oxirane), 3.23-3.19 (m, 1H, C**H** oxirane), 2.10 (q, 2H, *J* = 6.9 Hz, C**H**$_2$), 1.71-1.52 (m,

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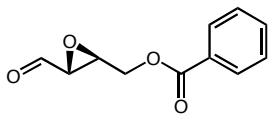
38. Martin, S. F.; Garrison, P. J. *Tetrahedron Lett.* **1977**, *44*, 3875.

39. Singh, O. V.; Han, H. *Org. Lett.* **2004**, *6*, 3067.

4H, C**H**$_2$-C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 61.05, 58.28, 39.51, 29.72, 28.91, 26.24, 25.68, 25.60; HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_8H_{11}O_2$) requires *m*/*z* 139.0760, found *m*/*z* 139.0759; $[\alpha]_D$= +48.8 (c = 1.10, $CHCl_3$). The enantiomeric purity was determined by GLC using a Chirasil-DEX CB column (80 °C isotherm, 15 psi, flow = 1.0 mL/min); (2*R*, 3*S*) isomer t_r = 21.75 min, (2*S*, 3*R*) isomer t_r = 22.27 min.



((2*R*, 3*S*)-3-formyloxiran-2-yl)methyl benzoate (***Table 7*, *entry 5*).** Prepared according to general epoxidation procedure A using (*E*)-3-formylallyl benzoate[40] (104 mg, 0.55 mol) to afford the title compound as a clear, colorless oil (101Mg, 89% yield, 85% ee) after flash chromatography (silica gel, 20% ethyl acetate in hexanes). IR (film) 3447, 1723, 1273, 1111, 710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (d, 1H, *J* = 6.3 Hz, C**H**O), 8.08–8.04 (m, 2H, aryl **H**), 7.63–7.57 (m, 1H, aryl **H**), 7.49–7.44 (m, 2H, aryl **H**), 4.75 (dd, 1H, *J* = 3.0, 12.6 Hz, C**H**$_2$), 4.34 (dd, 1H, *J* = 5.4, 12.6 Hz, C**H**$_2$), 3.68 (m, 1H, C**H** oxirane), 3.44 (dd, 1H, *J* = 2.1, 6.3 Hz, C**H** oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.01, 166.15, 133.72, 129.97, 129.35, 128.73, 63.13, 56.73, 54.0; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_{11}H_{10}O_4$) requires *m*/*z* 206.0579, found *m*/*z* 206.0581; $[\alpha]_D$= +16.0 (c = 1.12, $CHCl_3$). The enantiomeric purity was determined by SFC using a Chiralpak AD-H column (5% to 50% ethanol in hexanes, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); (2*R*, 3*S*) isomer t_r = 4.19 min, (2*S*, 3*R*) isomer t_r = 4.96 min.

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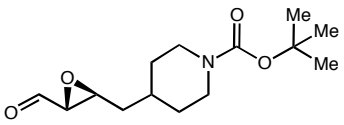
40. Guziec, F. S.; Luzzio, F. A. *J. Org. Chem.* **1982**, *47*, 1787.



***tert*-Butyl 4-(((2*R*, 3*S*)-3-formyloxiran-2-yl)methyl)piperdine-1-carboxylate (*Table 7*, *entry 6*).** A solution of *tert*-butyl 4-((*E*)-3-methoxycarbonyl)allyl)piperdine-1-carboxylate[41] (1.8 g, 6.68 mmol) in ether (60 mL) in a 100 mL round-bottom flask equipped with a magnetic stir bar was cooled to –78 °C. DIBAL (1M in hexanes, 13.4 mL) was added dropwise to the flask and the reaction is stirred at constant temperature for 15 minutes before warming to 0 °C. After 3 hours, the reaction is quenched by the addition of a saturated solution of Rochelle's salt (30 mL) and is stirred at room temperature until the biphasic solution no longer effervesces and both layers become clear. The organic layer is extracted, dried, and concentrated *in vacuo*. The resulting oil is purified by flash chromatography (silica gel, 20% ethyl acetate in hexanes) to yield *tert*-butyl 4-((*E*)-3-hydroxybut-2-enyl))piperdine-1-carboxylate as a clear oil (1.1 g, 61% yield). IR (film) 3436, 2915, 1669, 1429, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65–5.62 (m, 2H, C**H**=C**H**), 4.08 (t, 2H, α-hydroxy C$\mathbf{H}_2$), 4.03 (br s, 1H, O**H**), 3.20 (br t, 2H, J = 12.0 Hz, piperdine C$\mathbf{H}_2$), 1.98 (t, 2H, J = 6.0 Hz, CH=CH-C$\mathbf{H}_2$), 1.65 (br s, 1H, piperdine C$\mathbf{H}_2$), 1.60 (br s, 1H, piperdine C$\mathbf{H}_2$), 1.40 (s, 9H, C(C$\mathbf{H}_3$)$_3$), 1.27 (m, 1H, piperdine C$\mathbf{H}_2$), 1.07 (ddd, 2H, J = 4.2, 12.0, 24.6 Hz, piperdine C$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.10, 130.99, 130.69, 79.45, 63.80, 39.42, 36.31, 32.09, 43.92, 39.42, 36.31, 32.09, 31.14, 28.67; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_{14}H_{25}NO_3$) requires *m*/*z* 255.1834, found *m*/*z* 255.1837.

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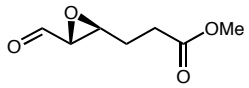
41. Orlek, B.S. *Syn. Lett.* **1993**, *10*, 758.

In a scintillation vial equipped with a magnetic stir bar is a solution of *tert*-Butyl 4-((*E*)-3-hydroxybut-2-enyl))piperdine-1-carboxylate (198 mg, 0.78 mmol), *N*-methylmorpholine *N*-oxide (96 mg, 0.82 mmol) and activated 3Å molecular sieves (150 mg) in dichloromethane (4 mL) at room temperature. After 5 minutes, tetrapropylammonium perruthenate (14 mg, 0.04 mmol) is added in one portion. The reaction is complete after 30 minutes and is filtered through a pad of celite, concentrated *in vacuo*, and purified by flash chromatography (silica gel, 20% acetone in pentanes) to yield *tert*-butyl 4-((*E*)-3-formylallyl)piperidine-1-carboxylate as a light yellow oil (160 mg, 80% yield). IR (film) 2929, 1691, 1417, 1365, 1240, 1163, 976, 866, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, 1H, *J* = 8.1 Hz, C**H**O), 6.78 (dt, 1H, *J* = 7.2, 15.9 Hz, CH=C**H**), 6.01 (ddd, 1H, *J* = 1.2, 2.7, 9.0 Hz, CHO-C**H**=CH), 3.20 (br d, 2H, *J* = 11.1 Hz, piperidine C**H**$_2$), 2.66 (br t, 2H, *J* = 12.0 Hz, piperidine C**H**$_2$), 2.24 (t, 2H, *J* = 7.5 Hz, piperidine C**H**$_2$), 1.67 (br s, 1H, piperidine C**H**$_2$), 1.64 (br s, 1H, piperdine C**H**$_2$), 1.39 (s, 9H, C(C**H**$_3$)$_3$), 1.07 (ddd, 2H, *J* = 3.0, 13.8, 25.8 Hz, piperdine C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.90, 156.20, 154.95, 134.64, 79.62, 43.92, 39.76, 35.73, 32.08, 28.62; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_{14}H_{23}NO_3$) requires *m*/*z* 253.1678, found *m*/*z* 253.1671.

The title compound was prepared according to general epoxidation procedure B using *tert*-butyl 4-((*E*)-3-formylallyl)piperidine-1-carboxylate (156 mg, 0.62 mmol) to afford the title compound as a clear, yellow oil (134 mg, 86% yield, 87% ee) after flash chromatography (silica gel, 25% ethyl acetate in hexanes). IR (film) 3436, 2915, 2361, 1678, 1413, 1164, 852 cm^{-1}; ^{1}H NMR (300 MHz. $CDCl_3$) δ 8.99 (d, 1H, *J* = 18.0 Hz, C**H**O), 4.08 (br d, 2H, *J* = 10.5 Hz, piperdine C**H**$_2$), 3.26–3.21 (m, 1H, C**H** oxirane), 3.09

(dd, 1H, *J* = 1.8, 6.3 Hz, C**H** oxirane), 3.72–3.63 (m, 2H, piperdine C**H**$_2$), 1.72-1.61 (m, 3H, piperdine C**H**$_2$), 1.42 (s, 9H, C(C**H**$_3$)$_3$), 1.21–1.15 (m, 2H, piperdine C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.36, 151.03, 79.63, 59.29, 55.27, 43.92, 38.31, 34.44, 32.38, 32.03, 28.64; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_{14}H_{23}NO_4$) requires *m*/*z* 269.1627, found *m*/*z* 269.1628; $[\alpha]_D$= +30.9 (c = 0.95, $CHCl_3$). The enantiomeric purity was determined by SFC analysis using a Chiralpak AD-H column (5% to 50% ethanol in hexanes, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); (2*R*, 3*S*) isomer t_r = 6.97 min, (2*S*, 3*R*) isomer t_r = 7.74 min.



Methyl 3-((2*S*,3*R*)-3-formyloxiran-2-yl)propanoate (*Table 7*, *entry 7*). Prepared according to general epoxidation procedure B using (*E*)-methyl 6-oxohex-4-enoate[42] (142 mg, 1.0 mmol) using 1M AcOH (1.33 mL) and dichloromethane (5.34 mL). Flash chromatography (silica gel, 60% ether in hexanes with 10% dichloromethane) afforded the title compound as a light yellow oil (137 mg, 86% yield, 90% ee). IR (film) 1731, 1438, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, 1H, *J* = 6.3 Hz, C**H**O), 3.72 (s, 3H, OC**H**$_3$**)**, 3.38–3.34 (m, 1H, C**H** oxirane), 3.19 (dd, 1H, *J* = 2.1, 6.0 Hz, C**H** oxirane), 2.52 (t, 2H, *J* = 6.9 Hz, α-C**H**$_2$), 2.15–1.88 (m, 2H, β-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 151.1, 59.29, 55.81, 52.16, 30.11, 26.66; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_7H_9O_4$) requires *m*/*z* 158.0501, found *m*/*z* 157.0502; $[\alpha]_D$= +27.3 (c = 1.25, $CHCl_3$).

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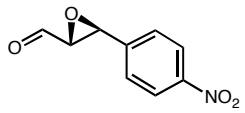
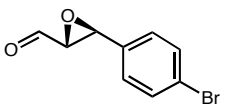
42. (a) Dygos, J. H.; Adamek, J. P.; Babiak, K. A.; Behling, J. R.; Medich, J. R.; Ng, J. S.; Wieczork, J. J. *J. Org. Chem.* **1991**, *56*, 2549. (b) Kukovinets, O. S.; Kasradze, V. G.; Chernukha, E. V.; Odinokov, V. N.; Dolidze, A. V.; Galin, F. Z.; Spirikhin, L. B.; Abdullin, M. I.; Tolstikov, G. A. *Zh. Org. Khim.* **1999**, *35*, 1156. (c) Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Gleason, J. G. *J. Med. Chem.* **1985**, *28*, 1847.

The enantiomeric purity was determined by GLC analysis using a Chirasil-DEX CB column (90 °C isotherm, 15 psi, flow = 1.0 mL/min); (2*R*, 3*S*) isomer t_r = 60.6 min, (2*S*, 3*R*) isomer t_r = 62.2 min.

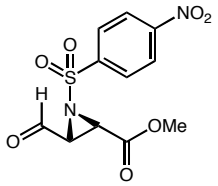


(2*S*, 3*R*)-3-(4-Nitrophenyl)oxirane-2-carbaldehyde (***Table 7*, *entry 9*).** Prepared according to general epoxidation procedure B using 4-nitrocinnamaldehyde (138 mg, 0.75 mmol) using 1M AcOH (0.75 mL) and chloroform (3.0 mL). Flash chromatography (silica gel, 40% ether in hexanes with 2% NEt_3) afforded the title compound as a light yellow solid (154 mg, 89% yield, 97% ee). IR (film) 1727, 1605, 1520, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (d, 1H, *J* = 6.0 Hz, C**H**O), 8.21 (dd, 2H, *J* = 2.4, 9.1 Hz, aryl **H)**, 7.46 (dd, 2H, *J* = 2.4, 9.1 Hz, aryl **H**), 4.26 (d, 1H, *J* = 1.8 Hz, C**H** oxirane), 3.41 (dd, 1H, *J* = 1.8, 5.7 Hz, C**H** oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 141.2, 126.3, 123.8, 62.5, 55.3; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_9H_7NO_4$) requires *m*/*z* 193.0375, found *m*/*z* 193.0374; $[\alpha]_D$= –13.0 (c = 1.18, $CHCl_3$). The enantiomeric purity was determined by GLC analysis using a Chirasil-DEX CB column (120 °C ramp 5 °C/min to 145 °C, 15 psi, flow = 1.0 mL/min); (2*R*, 3*S*) isomer t_r = 74.8 min, (2*S*, 3*R*) isomer t_r = 75.9 min.



(2*S*, 3*R*)-3-(4-Bromophenyl)oxirane-2-carbaldehyde (***Table 7*, *entry 10*).** Prepared according to general epoxidation procedure B using 4-bromocinnamaldehyde

(158 mg, 0.75 mmol) using 1M AcOH (0.75 mL) and chloroform (3.0 mL). Flash chromatography (silica gel, 30% ether in pentane with 2% NEt_3) afforded the title compound as a clear oil (158 mg, 93% yield, 93% ee). IR (film) 1727, 1490, 1070, 1011, 824.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, 1H, *J* = 6.0 Hz, C**H**O), 7.48 (d, 2 H, *J* = 9.0 Hz, aryl **H)**, 7.14 (d, 2H, *J* = 9.0 Hz, aryl **H**), 4.11 (d, 1H, *J* = 1.8 Hz, C**H** oxirane), 3.37 (dd, 1H, *J* = 1.7, 6.2 Hz, C**H** oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 132.2, 127.5, 62.92, 56.28; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_9H_7O_2Br$) requires *m*/*z* 225.9629, found *m*/*z* 225.9626; $[\alpha]_D$= –10.5 (c = 0.945, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis of the alcohol using a Chiralpak AD column (5% ethanol in hexanes, flow = 1.0 mL/min); (2*R*, 3*S*) isomer t_r = 33.7 min, (2*S*, 3*R*) isomer t_r = 36.9 min.



(2*S*,3*S*)-methyl 3-formyl-1-(4-nitrophenylsulfonyl)aziridine-2-carboxylate (11). Prepared according to general epoxidation procedure B using (*E*)-methyl 4-oxobut-2-enoate (170 mg, 1.5 mmol) in dichloromethane (3.0 mL, in the absence of 1M AcOH) and using *p*-TSA as the acid co-catalyst. After 24 hours, the reaction was quenched with pH 7 buffer (5.0 mL), filtered through celite, and washed with chloroform (3 x 5.0 mL). The reaction conversion and ratio of epoxide to aziridine was determined by ^1H NMR of this crude reaction mixture to be 1:4 (63% conversion to the aziridine product, 90% ee). Purification was achieved in three steps: (1) column chromatography (silica gel, 65% ether in pentane), then (2) $NaBH_4$ reduction of the collected impure fractions containing product,

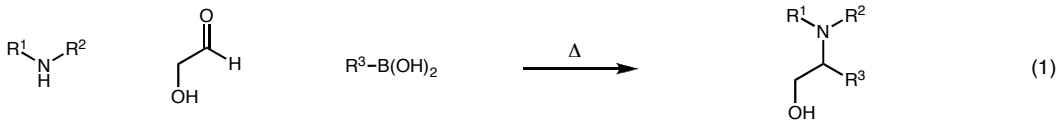
and (3) prep TLC (20% ethyl acetate in hexanes) to afford the alcohol of the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41–8.39 (m, 2H, aryl **H**), 8.20–8.17 (m, 2 H, aryl **H)**, 4.28 (dd, 1H, *J* = 3.0, 13.5 Hz, HOC**H**$_2$), 4.12 (dd, 1H, *J* = 7.5, 13.5 Hz, HOC**H**$_2$), 3.75 (s, 3H, CO_2C**H**$_3$), 3.66 (d, 1H, *J* = 7.3 Hz, C**H** aziridine), 3.47 (m, 1H, C**H** aziridine); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 145.1, 129.0, 124.7, 59.98, 53.38, 50.65, 41.87; HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{13}N_2O_7S$) requires *m*/*z* 317.0443, found *m*/*z* 317.0437. The enantiomeric purity was determined by HPLC analysis of the benzoyl functionalized alcohol using a Chiralcel OD-H column (10% ethanol in hexanes, flow = 1.0 mL/min); (2*R*, 3*R*) isomer t_r = 30.1 min, (2*S*, 3*S*) isomer t_r = 35.3 min.

Chapter 3

Organocatalytic Addition of Organoboron Reagents

I. Introduction

The Petasis multicomponent reaction provides a powerful and convenient method for the one-pot synthesis of unnatural amino acid derivatives from the union of three simple components—an amine, an aldehyde and an organoboronic acid (*eq. 1*).[1] Over the last decade the Petasis reaction has met considerable success as a powerful synthetic tool, particularly in regard to the construction of combinatorial libraries.[2] However,



(1)

$R^1 = R^2$ = alkyl; R^3 = alkenyl, aryl, heteroaryl

allylic or benzylic amines

despite the wide appeal of the Petasis reaction as a mild method for the preparation of allylic or benzylic amines, there has been limited research devoted to the development of stereoselective variants. Thus far, diastereoselective methodologies have employed either homochiral aldehydes or amines as reaction components, such that the source of

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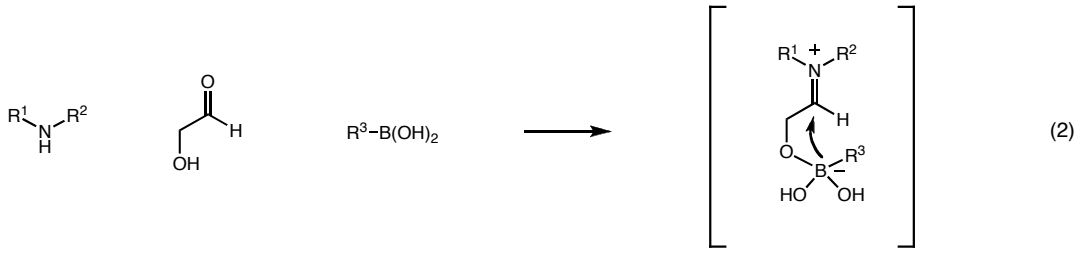
1. (a) Petasis, N. A.; Akritopoulou I. *Tetrahedron Lett.* **1993**, *34*, 583. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

2. (a) Gravel, M.; Thompson, K. A.; Zak, M.; Berube, C.; Hall, D. G. *J. Org. Chem.* **2002**, *67*, 3. (b) Pulici, M.; Cervi, G.; Martina, K.; Quartieri, F. *Comb. Chem. High Throughput Screen* **2003**, *6*, 693.

chiral induction is incorporated in the final product.[3] Unfortunately, the alternative approach of employing chiral boronic esters has met relative nonsuccess.[4] As of yet, there has been no enantioselective or catalytic variants of this important multicomponent coupling reaction.[5]

Aside from the Petasis boronic acid-Mannich reaction, carbon–carbon bond forming reactions using organoboron reagents still remain predominantly transition metal-mediated processes.[6] Though it is evident from the Petasis reaction that boronic acids are indeed capable nucleophiles, there has been minimal progress in the development of reactions to advance this observed mode of reactivity.[7] In part, this is due to the fact that the mechanism of the Petasis reaction remains relatively ambiguous. It is hypothesized that the nucleophilicity of the boronic acid is manifested upon complexation to an α-hydroxy



(2)

3. (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, 120, 11798. (b) Harwood, L. M.; Currie, G. S.; Drew, M. G. B.; Luke, R. W. A. *Chem. Commun.* **1996**, 1953.

4. (a) Koolmeister, T.; Sodergren, M.; Scobie, M. *Tetrahedron Lett.* **2002**, *43*, 5969. (b) Southwood, T. J.; Curry, M. C.; Hutton, C. A. *Tetrahedron* **2006**, *62*, 236.

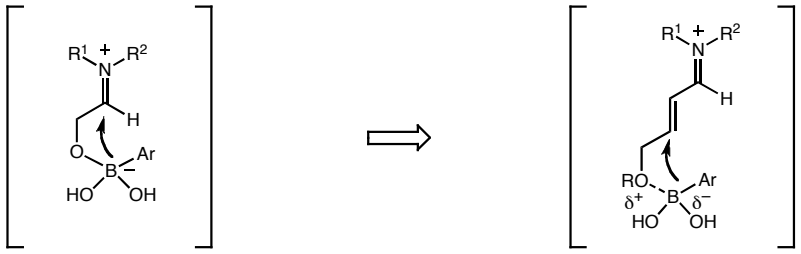
5. This excludes results from our laboratories in which an enantioselective, organocatalytic Petasis reaction has been discovered: Ni, Y.; Warkentin, A. *unpublished results.*

6. (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (e) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (f) Suzuki, A. *Proc. Jpn. Acad., Ser. B* **2004**, *80*, 359. (h) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (g) For a review of rhodium-catalyzed 1,4-additions, see: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829 and Hayashi, T. *Synlett* **2001**, *SI*, 879.

7. (a) Tremblay-Morin, J. P.; Raeppel, S.; Gaudette, F. *Tetrahedron Lett.* **2004**, *45*, 3471. (b) For a recently developed methodology utilizing metal-free boronic ester addition reactions, see: Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244 and Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2007**, *ASAP.*

donor group to form an electron-rich ate-complex (*eq. 2*), which then reacts with the iminium ion by an intramolecular addition.[8] This hypothesis is substantiated by the fact that aldehydes containing only α- or *ortho*-activating groups participate in this reaction.

On the basis of this mechanism, we postulated that the advancement of this concept towards an iminium-activated π-system would enable the development of a vinylogous addition (*eq. 3*), wherein the amine component of the reaction would gain the capacity to



(3)

function as a catalyst. This modification of the standard Petasis reaction offers the potential for a chiral amine to catalyze an enantioselective addition of organoboron reagents.

II. An Organocatalytic Strategy for the Addition of Boronic Acids

Inspired by the Petasis reaction, we initiated studies to develop an organocatalytic methodology for the asymmetric conjugate addition of boronic acids to α,β-unsaturated aldehydes based upon the activation principle of iminium catalysis (*vide* Chapter 1). Having established chiral secondary amines as enantioselective LUMO-lowering catalysts,[9] we sought to develop the first asymmetric, organocatalytic 1,4-addition of activated

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8. (a) Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567. (b) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063. (c) Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023.

9. Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta*, **2006**, *39*, 79.

organoboronate nucleophiles to α,β-unsaturated aldehydes for the incorporation of simple olefins and heteroaromatics in a broad platform of β-functionalization.

In our initial design plan, we focused on replicating the *in situ* formation of a tetra-coordinate boronate complex (from the Petasis reaction, *eq. 3*) by employing an aldehyde appropriately functionalized with an α-heteroatom adjacent to the reaction site (**2**, *Figure 1*). We envisioned the condensation of aldehyde **2** with imidazolidinone catalyst **1** would generate iminium adduct **3**, wherein the pendent ether tether would engage the boronic acid

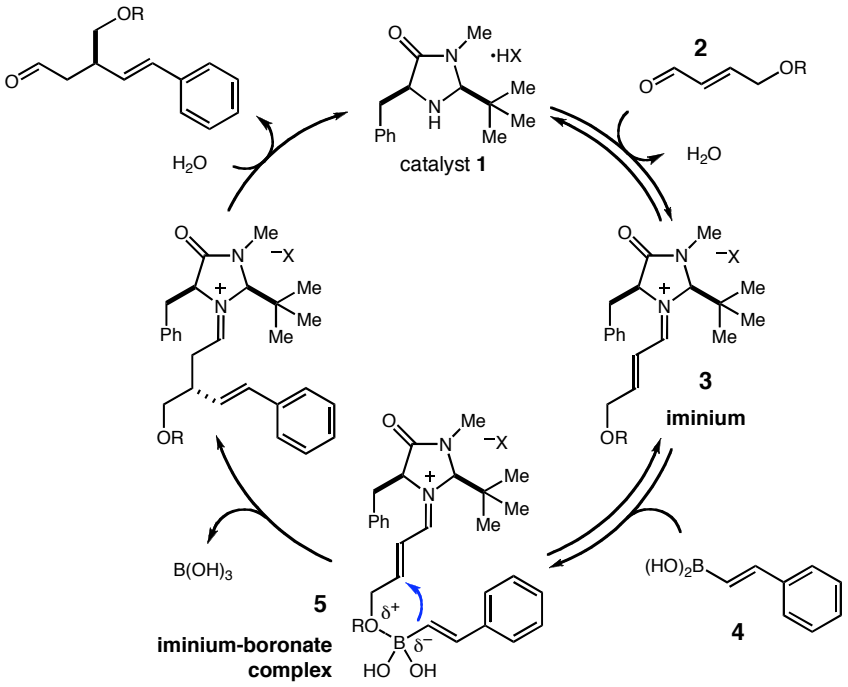
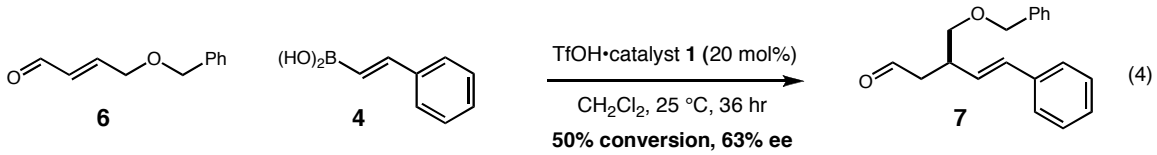


Figure 1. Proposed catalytic cycle and formation of an activated iminum-boronate complex (**5**)

(**4**) to form an activated boronate species (**5**). Subsequently, the activated iminium-boronate complex (**5**) initiates an intramolecular vinyl transfer into the iminium π-system giving rise to a newly formed β-carbon stereocenter. Enantioinduction in this key bond-forming event results from a *Re*-face addition to complex **5** due to the stereochemical environment created by catalyst architecture, which shields the *Si*-face from nucleophilic

attack. Hydrolysis of the resultant adduct would release the enantioenriched product and concomitantly regenerate the secondary amine catalyst **1**, thereby completing the catalytic cycle.

To our great delight, when we prepared a benzyl ether functionalized aldehyde substrate (**6**) to react with boronic acid **4**, we obtained the desired adduct **7** (50% conversion, 63% ee, *eq. 4*) in the presence of imidazolidinone catalyst **1**. Importantly, this



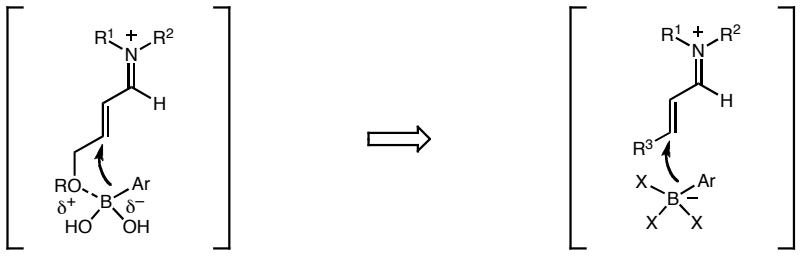
(4)

initial result validated our hypothesis—activated boronic acids can indeed function as competent nucleophiles. We sought to further substantiate our hypothesis by defining the key features of this reaction. First, we verified that there was no detectable background reaction in the absence of the secondary amine catalyst **1** (after 48 hours of reaction time at ambient temperature). Along with the fact that proline-derived catalysts were non-functional in this reaction,[10] we concluded that iminium-activation was indeed a prerequisite for reactivity. Secondly, it was determined that this reaction was exclusive to aldehyde substrates functionalized with a pendant heteroatom to engage the boronic acid in a complexation event (and thus form the active ate-complex **5**) in order to activate the system towards addition. This was made apparent when enal substrates lacking oxy-functionalization, such as crotonaldehyde and cinnamaldehyde, were found to be completely unreactive to **4** under identical reaction conditions. Thus, we presumed formation of the doubly activated iminium-boronate complex (**5**) was requisite for product

10. Proline is typically a poor catalyst for iminium-activated processes, see: Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.

formation.

Having defined the requirements for reactivity, namely the iminium-activation of the aldehyde substrate and the activation of the boronic acid the boronate, we considered the extension of these concepts towards an intermolecular reaction. Circumvention of the required intramolecular activation of the boronic acid (via the formation of **5**) would open the possibility for an activated iminium species to react directly with a boronate (*eq. 5*).



(5)

More importantly, an intermolecular reaction offers potential for greater variation in the enal substrate by eliminating the structural requirement of an ether tether. Thus, replacement of the boronic acid by a boronate would expand this methodology to include simple α,β-unsaturated aldehydes. To this end, we sought to investigate boronate species that could participate in this organocatalytic conjugate addition reaction.

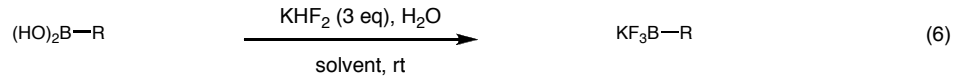
III. Organotrifluoroborate Salts

In recent years, there have been great advancements in the application of organotrifluoroborate salts to new methodologies.[11] This stems from the highly desirable

11. For excellent reviews on potassium organotrifluoroborates, see: (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta.* **2005**, *38*, 49. (b) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, *22*, 4313. (c) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623.

features that are characteristic of these organoboron reagents, e.g., (1) greater nucleophilicity than their boronic acid or ester counterparts;[12] (2) high functional group compatibility; (3) commercial availability and straightforward preparation; (4) low toxicity; and (5) impressive stability to air and moisture.

In 1995, Vedejs and co-workers first described a convenient procedure for the preparation of potassium trifluoroborate salts from the corresponding boronic acid (*eq. 6*).[13]



(6)

This discovery vastly simplified the previously known multi-step method for the preparation of these compounds and subsequently made a significant impact in the development of chemistries associated with these compounds.[14,15]

Recently, trifluoroborate salts have found major application as a surrogate to boronic acids in transmetallation reactions in transition metal-mediated methodologies. In this regard, organotrifluoroborate salts are widely employed as coupling partners in Suzuki cross-coupling reactions and are generally more reactive than the corresponding boronic acids (*eq. 7*). Impressively, examples of aryl-, alkynyl-, alkenyl-, and alkyltrifluoroborates as successful coupling partners to a variety of aryl and vinyl bromides using palladium(II)

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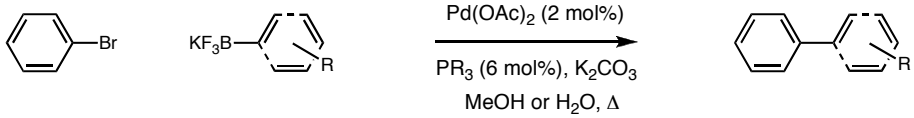
12. Unlike trivalent boron substituents, trifluoroborate is an electron-donating substituent, see: Frohn, H.-J.; Franke, H.; Fritzen, P.; Bardin, V. V. *J. Organomet. Chem.* **2000**, *598*, 127.

13. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.

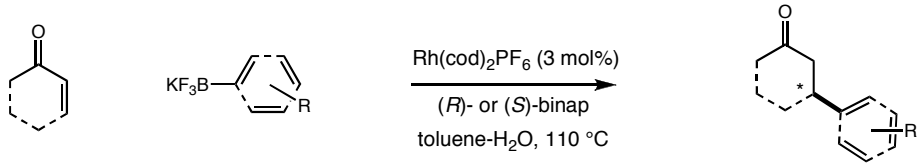
14. Initially, organotrifluoroborate salts were prepared from the reaction of organodihaloboranes with aqueous KF. These highly unstable dihalo(organo)boranes were generally generated *in situ* from organostanane precursors.

15. Organotrifluoroborate salts are commercially available or readily synthesized from the corresponding boronic acids or esters, see: (a) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2005**, *70*, 3950. (b) Molander, G. A.; Fumagalli, T. *J. Org. Chem.* **2006**, *71*, 5743. (c) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020. (d) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.

catalysts have been demonstrated.[16] Another major application of trifluoroborate salts has been in rhodium(I)-catalyzed conjugate addition reactions to electron-deficient olefins (*eq. 8*).[17] As these reactions are amenable to modification by asymmetric ligand systems,



(7)



(8)

enantioselective 1,4-additions have been achieved with enones and α,β-unsaturated amides for the efficient construction of β-chiral stereocenters.

Trifluoro(organo)borates are also utilized as mild nucleophiles in Lewis acid-mediated methodologies. For example the allylation of aldehydes has been achieved with potassium allyl- and crotyltrifluoroborates in the presence of a various Lewis acids to afford valuable homoallylic alcohol products (*eq. 9*).[18] Likewise, homoallylic amines were prepared in the allylation of aliphatic, aromatic and heterocyclic *N*-tosylamines (*eq. 10*).[19] Additionally, potassium trifluoro(organoborate) salts have been employed as successful nucleophiles in an extension of the Petasis boronic-Mannich reaction to yield the desired

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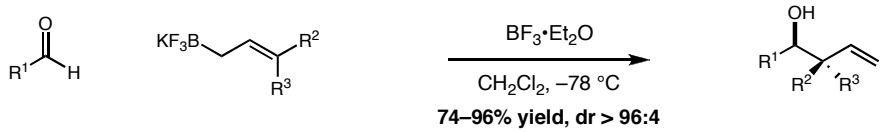
16. (a) For the first Suzuki-Miyaura reaction involving organotrifluoroborate salts, see: Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P *Tetrahedron Lett.* **1997**, *38*, 4393. (b) For subsequent applications, see: Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *ASAP*.

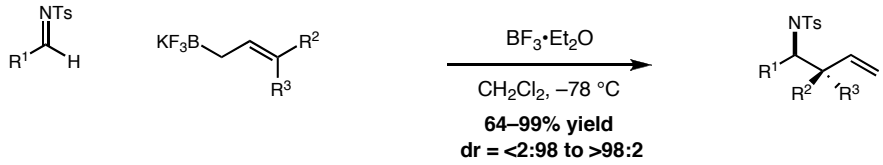
17. (a) Pucheault, M.; Darses, S.; Genêt, J.-P. *Tetrahedron* **2002**, *43*, 6155. (b) Pucheault, M.; Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2002**, 3552. (c) For a review of 1,4- and 1,2-additions by BF_3K salts, see ref. 11c. (d) For a review of rhodium-catalyzed conjugate additions, see: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

18. (a) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis*, **2000**, 990. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289.

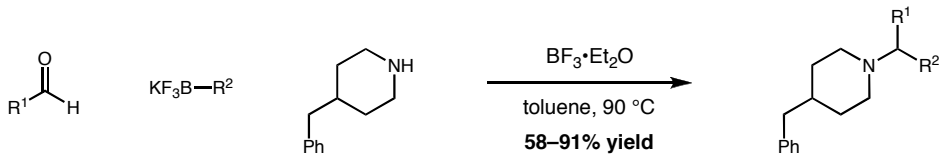
19. (a) Solin, N.; Wallner, O. A.; Szabó, J. K. *Org. Lett.* **2005**, *7*, 689. (b) Wallner, O. A.; Szabó, J. K. *Chem.—Eur. J.* **2006**, *12*, 6976.



(9)



(10)



(11)

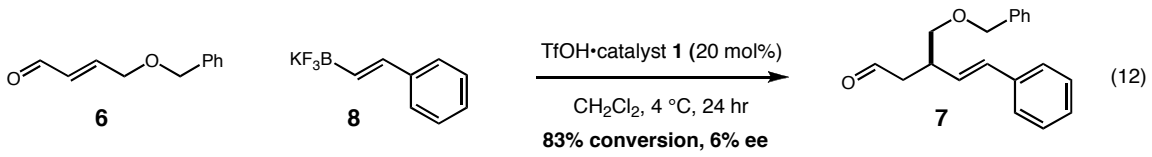
coupled products (*eq. 11*).[20]

In short, potassium trifluoro(organo)borate salts have recently emerged as highly stable and reactive alternatives to organoboronic acids and esters. As such, they have found considerable application as effective organometallic reagents in numerous carbon–carbon bond forming methodologies.

IV. The Imidazolidinone-Catalyzed Addition of Organotrifluoroboronate Salts

Having demonstrated that organoboronates (generated *in situ*) were competent nucleophiles in an organocatalytic conjugate addition reaction (*eq. 4*), we recognized that an ate-complex could directly participate in an intermolecular reaction (*eq. 5*). In this context, we sought to employ potassium trifluoro(organo)borate salts, which preexist in the desired oxidation state. By employing a preformed ate-complex, such as potassium

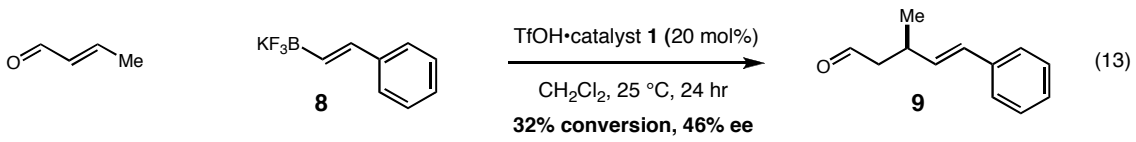
20. (a) Schlienger, N.; Ryce, M. R.; Hansen, T. K. *Tetrahedron Lett.* **2000**, *41*, 1303. (b) Billard, T; Langlois, B. R. *J. Org. Chem.* **2002**, *67*, 997. (c) Trembley-Morin, J.-P.; Raeppel, S.; Gaudette, F. *Tetrahedron Lett.* **2004**, *45*, 3471. (d) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729.



(12)

styryltrifluoroborate (**8**) in a reaction with aldehyde **6** at 4 °C, we witnessed exceptional reactivity, albeit with low enantioselectivity (83% conversion, 6% ee, *eq. 12*). Nevertheless, we were encouraged by the increased levels of reactivity observed when the trifluoroborate salt was used in place of the boronic acid (*eq. 4*).

To test the premise that the boronate salt reacts via an intermolecular process, we next attempted the 1,4-addition reaction with an unfunctionalized aldehyde substrate (such as crotonaldehyde) that could not proceed via an intramolecular pathway. To our delight, exposure of crotonaldehyde to **8** resulted in the formation of the desired adduct (**9**) in moderate yield and enantioselectivity (32% conversion, 46% ee, *eq. 13*).[21] Notably, the



(13)

analogous reaction with styrylboronic acid and crotonaldehyde was found to be completely unreactive. These results implicated that a greater potential scope for this methodology was possible with the use of potassium trifluoroborate salts—by elimination of the structural requirement of an ether tether in the enal substrate, simple α,β-unsaturated aldehydes (like crotonaldehyde) are viable substrates.

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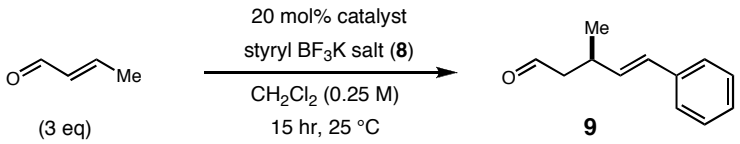
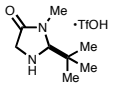
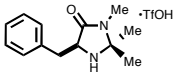
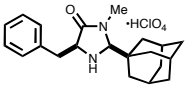
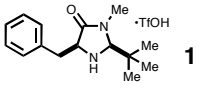
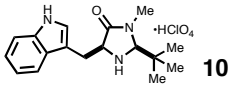
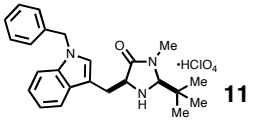
21. There was also no background reaction in the absence of the imidazolidinone catalyst **1**. Additionally, the reaction performed with catalytic $BF_3 \cdot OEt_2$ (in place of TfOH·catalyst **1**) did not yield the desired product (**9**).

Efforts were next focused on obtaining higher levels of reaction efficiency. As low levels of enantioselectivity were observed in our initial experiments, we sought to directly impact the enantiodiscriminating step of this reaction by modification of catalyst structure. Being that a number of catalyst architectures have been established within our group, a survey of these catalysts was carried out in Table 1. An apparent trend was observed

Table 1. Survey of Imidazolidinone Catalysts for the Organocatalytic Conjugate Addition



entry	catalyst	% conversion[a]	% ee[b]
1		22	13
2		5.3	27
3		53	38
4	 **1**	32	46
5	 **10**	38	54
6	 **11**	42	56

[a] Conversion determined by ^{1}H NMR relative to methyl benzyl ether. [b] Enantiomeric excess determined by chiral SFC analysis (Chiracel OD-H) on the corresponding purified alcohol product.

between the enantioselectivity of the reaction (13–56% ee, *entries 1–6*) and the relative steric bulk of the catalyst substituents. Specifically, tryptophan-derived catalysts (54–56% ee, *entries 5* and *6*) were more selective than the phenylalanine-based catalysts (27–46% ee, *entries 2–4*). This trend can be rationalized on comparison of the MM3 force-field

calculations of the catalyst-substrate iminium complexes (**MM3-12** and **MM3-13**) for catalyst **1** and **10** (*Figure 2*). The increased enantiofacial discrimination achieved using catalyst **10** results from the introduction of the indole shielding group in **MM3-13**[22]. Since indoles are known to have a more negative electrostatic potential surface (32.6 kcal/mol)

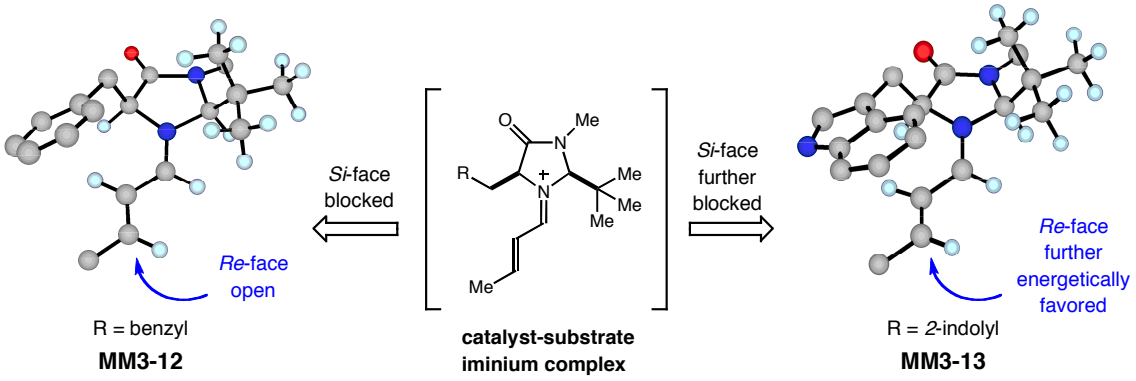


Figure 2. MM3 structures of iminium complexes of crotonaldehyde and catalysts **1** and **10**

than that of benzene (27.1 kcal/mol), the tryptophan-derived catalyst **10** has a more favorable electrostatic interaction with the iminium π-system relative to catalyst **1**.[23] This increased cation-π stabilization in iminium complex **MM3-13** provides a greater population of the blocked π-face confirmation and thus leads to more selective reaction. As catalyst **11** demonstrated the highest levels of enantioselectivity (56% ee, *entry 6*), it was chosen as the optimal catalyst for this transformation and was used in all subsequent studies.

Further optimization of the catalyst system was accomplished by studying the impact of the Brønsted acid co-catalyst. As shown in Table 2, it was immediately apparent

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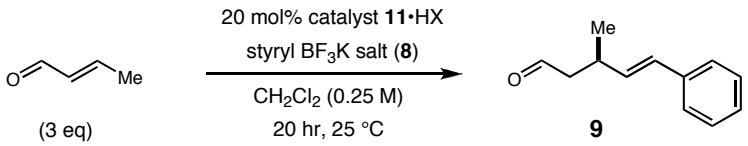
22. Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci. USA*, **2004**, *101*, 5482.

23. (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303. (b) Gallivan, J. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 9459 (c) For relevant calculations on iminium intermediate **MM3-12**, see: Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558.

that co-catalysts with lower pK_a values ($pK_a < -2$, *entries 1–4*) were required for this transformation. More specifically, stronger acids provided the desired product **9** with higher conversions (27–40% conversion, *entries 1–4*) while weaker acids yielded poorer results (1–3% conversion, *entries 5–7*). This was rationalized on the following basis: (1) that stronger acid co-catalysts enable a higher equilibrium content of the catalyst-substrate iminium adduct and (2) the more electronegative character of the conjugate base of the co-catalyst results in a more reactive iminium-ion intermediate.[24] Thus, the combination of these two factors resulted in more productive reactions when stronger acids, such as triflic acid (TfOH) and hydrochloric acid (HCl) were employed. Since the reaction performed with HCl exhibited a slight improvement in the conversion (40% conversion, *entry 3*),

Table 2. Impact of the Acid Co-Catalyst on the Organocatalytic Conjugate Addition



entry	HX	pK_a[a]	% conversion[b]	% ee[c]
1	TfOH	–14	38	54
2	$HClO_4$	–10	33	54
3	HCl	–8.0	40	51
4	*p*-TSA	–2.0	27	50
5	TFA	–0.3	3	--
6	DCA	1.3	1	--
7	2,4-DNBA	3.4	3	--

[a] Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley & Sons: New York, 2001. [b] Conversion determined by GC relative to tridecane. [c] Enantiomeric excess determined by chiral SFC analysis (Chiracel OD-H) on the corresponding purified alcohol product.

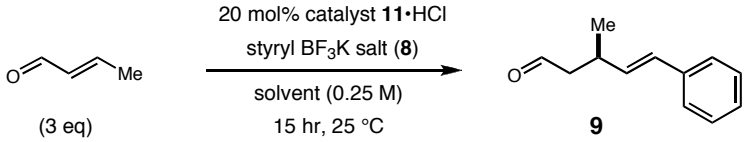
24. ^{1}H NMR studies using more electronegative counterions result in a downfield chemical shift in the iminium proton, which could be suggestive of a more activated system, see: Mayr, H.; Ofial, A. R.; Würthwein, E.-U.; Aust, N. C. *J. Am. Chem. Soc.* **1997**, *119*, 12727.

further optimization studies were conducted with this acid co-catalyst.

A variety of solvents were next evaluated for the organocatalytic conjugate addition reaction. As evident from Table 3, there was no empirical correlation between the dielectric constant of the reaction media and the extent of product formation. However, it was apparent that dichloromethane provided higher conversions albeit with moderate enantiodiscrimination (40% conversion, 51% ee, *entry 4*). Contrastingly, the reaction conducted in 1,2-dimethoxyethane (DME) demonstrated substantially higher levels of induction but with low levels of product formation (17% conversion, 83% ee, *entry 6*). Though the reaction was moderately functional in most examined solvents, we focused on DME as the optimal solvent, having provided higher levels of enantioinduction.

To address concerns pertaining to reaction efficiency, NMR studies were

Table 3. Solvent Effect on the Imidazolidinone-Catalyzed Addition of Organotrifluoroborate Salts



entry	solvent	ε[a]	% conversion[b]	% ee[c]
1	DMF	38	4.0	--
2	MeCN	37	11	65
3	acetone	21	16	72
4	CH_2Cl_2	9.1	40	51
5	THF	7.5	14	72
6	DME	7.1	17	83
7	EtOAc	6.0	21	74
8	ether	4.3	3.2	--
9	toluene	2.4	13	63

[a] *CRC Handbook of Chemistry and Physics*, 81st ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 2000. [b] Conversion determined by GC relative to tridecane. [c] Enantiomeric excess determined by chiral SFC analysis (Chiracel OD-H) on the corresponding purified alcohol product.

undertaken to identify potential issues impeding reaction progression. We chose to conduct ^{11}B NMR experiments on the basis of boron chemical shifts being distinctive and highly dependent on the nature of the complexing ligands.[25] Monitoring the crude reaction of crotonaldehyde with **8** over the course of 36 hours, we observed three peaks by ^{11}B NMR: (1) unreacted starting material **8** (δ 3.1), (2) boron trifluoride (BF_3) (δ –0.8), and (3) an unidentified boron complex (δ 28.1).[26] Presumably, interaction of the BF_3 byproduct from the conjugate addition reaction with water or the Lewis basic nitrogen of the catalyst gave rise to the unknown boron complex.[27] Thus, catalyst inhibition by the reaction byproduct was identified as a probable cause for the observed low reaction efficiency. We hypothesized removal of this byproduct would lead to increased reaction.

With the aim of improving reaction efficiency, we explored a variety of Lewis basic additives to sequester the BF_3 byproduct from the conjugate addition reaction. As revealed in Table 4, water and simple alcohols were ineffective additives that did not have any marked affect on the reaction (11–12% conversion, 78% ee, *entries 2–4*). Similarly, the addition of a buffered tertiary amine salt lead to slightly lower reaction efficiencies (10% conversion, 73% ee, *entry 5*). As fluoride anions are also considered Lewis bases, a variety of fluorine sources were examined (*entries 6–10*). Prototypical fluoride anion sources, such as TBAF and KF, were found to be detrimental to the reaction resulting in lower levels of conversion (0–10% conversion, *entries 8–10*). In these cases, we presumed that the basicity of the fluoride anion interfered with the catalytic cycle via proton abstraction

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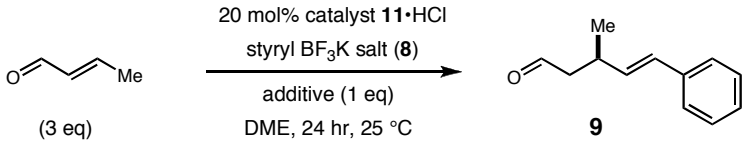
25. (a) Siedle, A. R. *Annu. Rep. NMR Spectrosc.* **1988**, *20*, 205. (b) Wrackmeyer, B. *Annu. Rep. NMR Spectrosc.* **1988**, *20*, 61.

26. ^{11}B NMR experiments were carried out in CH_2Cl_2 and were externally referenced to $BF_3{\cdot}Et_2O$ (δ 0.00).

27. Typically, the chemical shift associated with $BF_2{\cdot}L$ (L = N, O) complexes is expected to be 17–30.

Table 4. Evaluation of Reaction Additives



entry	additive	% conversion[a]	% ee[b]
1	none	17	83
2	water	12	78
3	*i*-PrOH	11	78
4	catechol	16	79
5	Et_3N•HCl	10	73
6	HF[c]	36[d]	76
7	cyanuric acid	25	73
8	KHF_2	5.7	81
9	KF	10	78
10	TBAF[e]	0	--

[a] Conversion determined by GC relative to tridecane. [b] Enantiomeric excess determined by chiral SFC analysis (Chiracel OD-H) on the corresponding purified alcohol product. [c] Used as 48 wt% solution in H_2O. [d] Reaction was complete after 12 hr. [e] Used as 1M solution in THF.

from the acid co-catalyst. In contrast, the use of acidic sources of fluorine,[28] such as hydrofluoric acid (HF) and cyanuric acid,[29] led to improved reaction progression (25–36% conversion, *entries 6* and *7*). More significantly, employing HF accelerated the rate of reaction such that maximum conversion was obtained after 12 hours at ambient temperature.[30]

Intrigued by the increased rate of reaction observed in the presence of HF, we were motivated to conduct ^{19}F NMR studies to further probe this result (*Table 4*, *entry 6*). In a

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28. pK_a (HF) = 3.2 and pK_a (cyanuric acid) = 6.8 (Koppenol, W. H.; Moreno, J. J.; Pryor, W. A.; Ischiropoulos, H.; Beckman, J. S. *Chem. Res. Toxicol.* **1992**, *5*, 834.)

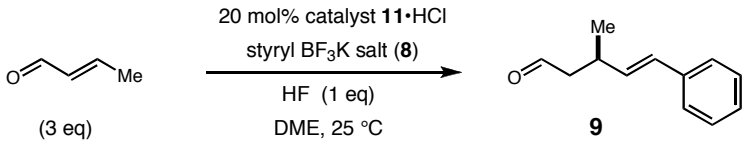
29. Cyanuric acid has been demonstrated to be a capable fluorine source, see: Hara, S.; Shudoh, H.; Ishimura, S.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2403, and Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 487.

30. Notably, additional equivalents of HF did not yield any added rate acceleration or increase in conversion.

crude reaction monitored by ^{19}F NMR, we observed the formation of potassium tetrafluoroborate salt (BF_4K) as the reaction byproduct.[31] This validated our hypothesis that a reaction additive could indeed sequester the BF_3 generated from the conjugate addition reaction (in this case by formation of an inert BF_4K salt).[32] Thus, HF successfully moderates BF_3 inhibition and subsequently increases the rate and efficiency of the reaction.

We next investigated the impact of concentration on the organocatalytic conjugate addition. As revealed in Table 5, the influence of concentration proved to have a profound effect on the reaction rate and overall efficiency. As the reaction was typically conducted

Table 5. Effect of Concentration on the Organocatalytic Conjugate Addition



entry	concentration	t (hr)	% conversion[a]	% ee[b]
1	0.05 M	20	12	75
2	0.125 M	20	26	76
3	0.25 M	12	36	76
4	0.5 M	6	78	76
5	1.0 M	3	100	76

[a] Conversion determined by GC relative to tridecane. [b] Enantiomeric excess determined by chiral SFC analysis (Chiracel OD-H) on the corresponding purified alcohol product.

at 0.25M (*entry 3*) in our previous studies, lower concentrations were relatively poorer yielding (12–26% conversion, 0.05–0.125M, *entries 1* and *2*). Conversely, a reaction conducted at a concentration of 1.0M demonstrated quantitative conversion to **9** in only

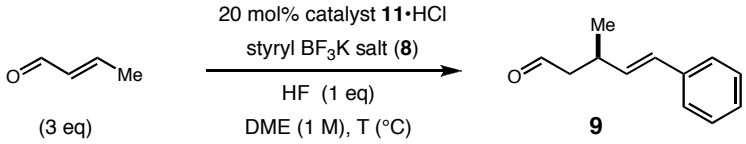
31. ^{19}F NMR experiments were carried out in d_6-acetone (to obtain an homogeneous reaction) and externally referenced to $HF_{(aq)}$ (δ –204.0). Authentic BF_4K was found to have a chemical shift of δ –167.6 whereas synthetic BF_4K from a crude reaction sample had a chemical shift of δ –167.5.

32. Notably, as the reaction progresses (in DME) the precipitation of BF_4K is observed.

three hours at room temperature (100% conversion, 76% ee, *entry 5*). Based on these results, further optimization studies were carried out at higher reaction concentrations.

Having attained high levels of reaction efficiency, temperature studies were undertaken with the aim of improving the selectivity of the reaction (*Table 6*). As expected, the enantioselectivity was found to be temperature dependent, with lower reaction temperatures favoring a more selective process. However, this trend was limited

Table 6. Temperature dependence on the Organocatalytic Conjugate Addition Reaction



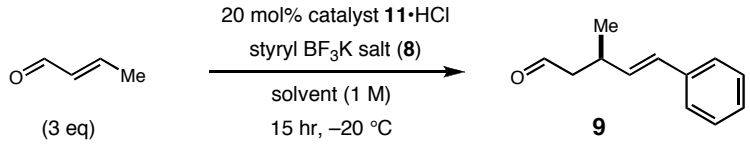
entry	temperature (°C)	t (hr)	% conversion[a]	% ee[b]
1	+25	3	100	76
2	+4	5	100	79
3	–20	20	100	87
4	–40	20	6.0	88

[a] Conversion determined by GC relative to tridecane. [b] Enantiomeric excess determined by chiral SFC analysis (Chiracel OD-H) on the corresponding purified alcohol product.

to temperatures above –40 °C, as the reaction was inhibited at lower temperatures due to issues from insolubility (6% conversion, 88% ee, *entry 4*). The optimum temperature for this reaction was determined to be –20 °C, which demonstrated high levels of enantioselection while maintaining excellent reaction efficiency (100% conversion, 87% ee, *entry 3*).

At this juncture, optimal reaction conditions were defined for the organocatalytic conjugate addition reaction. However, an additional solvent screen was conducted to determine the compatibility of optimized conditions with solvents other than DME (*Table 7*). We were pleased to discover that the reaction was tolerant to multiple solvent systems

Table 7. Secondary Solvent Evaluation for the Organocatalytic Conjugate Addition Reaction



entry	solvent	% conversion[a]	% ee[b]
1	MeCN	28	64
2	CH_2Cl_2	100	72
3	EtOAc	92	78
4	toluene	100	87
5	DME	100	87

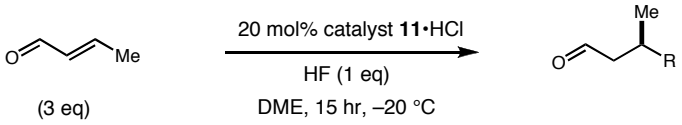
[a] Conversion determined by GC relative to tridecane. [b] Enantiomeric excess determined by chiral SFC analysis (Chiracel OD-H) on the corresponding purified alcohol product.

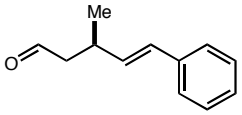
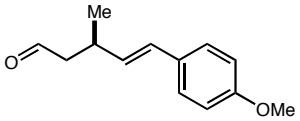
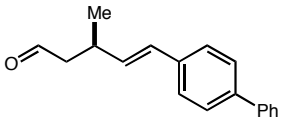
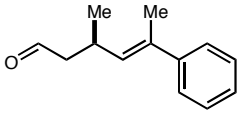
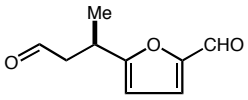
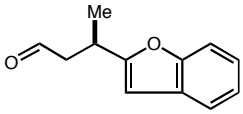
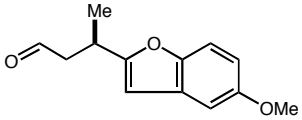
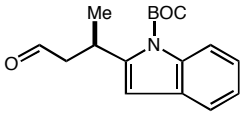
(92–100% conversion, *entries 2–4*), though the selectivity of the reaction remained highest in DME (87% ee, *entry 5*). Alternatively, DME could be interchangeably used with toluene, as both solvents produced identical results (87% ee, *entry 4*).

V. Scope of the Organocatalytic Conjugate Addition of Trifluoroborate Salts

With optimized reaction parameters in hand, the scope of the organo(trifluoro)borate salt addition with crotonaldehyde was examined (*Table 8*). Styryltrifluoroborate salts, with varied substitution on the benzene ring, were successful reaction partners in the generation of allylic methyl stereocenters (96–91% yield, 87–95% ee, *entries 1–3*). α-Methyl substitution on the styryl nucleophile was well tolerated (84% yield, 82% ee, *entry 4*), though notably, the analogous reaction conducted with a β-methyl styryl nucleophile was found to be completely unreactive. Unfortunately, the reaction was found to be specific to styryltrifluoroborate salts, as attempts to employ other alkenyl

Table 8. Variation of the Nucleophile: The Scope of the Potassium Trifluoroborate Salt



entry	product	time (h)	% yield[a]	% ee[b]
1		24	96	87
2		20	70[c]	88
3		24	91[c]	95
4		24	84[d]	82
5		24	85	95
6		20	90	97
7		24	94	92
8		24	79[e]	91

[a] Absolute stereochemistry assigned by chemical correlation and crystal structure. [b] Enantiomeric excess determined by chiral SFC analysis. [c] Reaction was conducted at –40 °C. [d] Reaction was conducted at –50 °C. [e] 40 mol% catalyst was used.

systems met with no success.[33] Other trifluoroborate salts with alkyl,[34] alkynyl,[35] allylic,[36] and phenyl[37]functionalities were found to be unsuitable reaction partners.

Heteroaromatic systems were amenable to this chemistry.[38] Extension of this reaction to include heteroaromatic frameworks showcases the powerful versatility of this methodology, which simultaneously introduces a benzylic stereocenter and gives rapid entry into a new structural architecture (*Table 8*, *entries 5–8*). In this regard, furanyl[39] (*entry 5*) and benzofuranyl substrates (85–94% yield, 92–95% ee, *entries 6* and *7*) were found to be excellent in this reaction. Moreover, as a result of functionalization to the potassium trifluoroborate salt, we are able to alter the typical Friedel-Crafts reactivity of an indole[40] by a site-specific activation of the 2′-carbon. Thus, we were able to achieve alkylation at the 2′-position of a BOC-protected indole over an unsubstituted 3′-position with complete regioselective control and in high enantioselectivity (79% yield, 91% ee, *entry 8*).[41]

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33. Attempted alkenyl substrates: potassium (*E*)-3-phenylprop-1-enyl-, (*E*)-2-cyclohexyl-, (*E*)-pent-1-enyl-, (*E*)-non-1-enyl-, 2-methylprop-1-enyl-, 1-phenylvinyl-, cyclopentenyl-, (*E*)-3-chloroprop-1-enyl-, (*E*)-3-(ethanoyloxy)prop-1-enyltrifluoroborate salts.

34. e.g., Potassium isopropyltrifluoroborate salt

35. e.g., Potassium 3,3-dimethylbut-1-ynyltrifluoroborate salt

36. Exposure of a potassium allyltrifluoroborate salt to reaction conditions resulted in a non-selective 1,2-addition to the aldehyde.

37. Attempted aryl substrates: potassium *p*-tolyl-, 4-methoxyphenyl-, 2-methoxyphenyl-, 2,4,6-trimethoxyphenyl-, benzo[*d*][1,3]dioxol-5-yltrifluoroborate salts.

38. Systems that demonstrated no reaction with crotonaldehyde were: potassium 1-benzyl-1*H*-pyrazol-4-yl-, 3,5-dimethylisoxazol-4-yl, 5-methylthiophen-2-yl-, benzo[*b*]thiophen-2-yl-, 2-phenyloxazol-5-yl-, benzo[*d*]oxazol-2-yl-, quinolin-3-yltrifluoroborate salts.

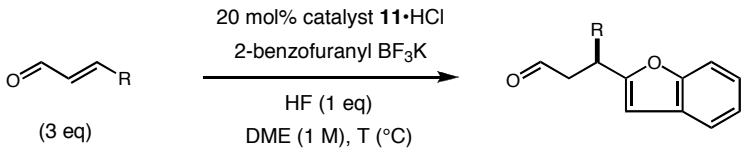
39. Notably, the reaction with potassium 2-furanyltrifluoroborate salt resulted in bis-alkylation.

40. (a) Lei, F.; Chen Y.-J.; Yong, S.; Liu, L.; Wang, D. *Synlett* **2003**, *8*, 1160. (b) *vide* ref. 22.

41. Notably, the analogous reaction with the potassium 1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yltrifluoroborate salt was plagued by competitive protodeborylation.

The vast potential of structural motifs accessible from differentially functionalized organotrifluoroborates and aldehyde substrates offers a versatile and modular approach in the rapid assembly of molecular complexity. A survey of the electrophilic component of the reaction encompassed a representative scope of α,β-unsaturated aldehydes (*Table 9*) inclusive of both alkyl (90–97% yield, 93–97% ee, *entries 1* and *2*) and aryl substituents

Table 9. Scope of the Electrophile



entry	R	T (°C)	% yield	% ee[a]
1	Me	–20	90	97
2	*n*-Pr	4	97	93
3	MeO_2C	–20	93	88
4	$BzOCH_2$[b]	–20	75	89
5	*p*-NO_2Ph	25	69	92

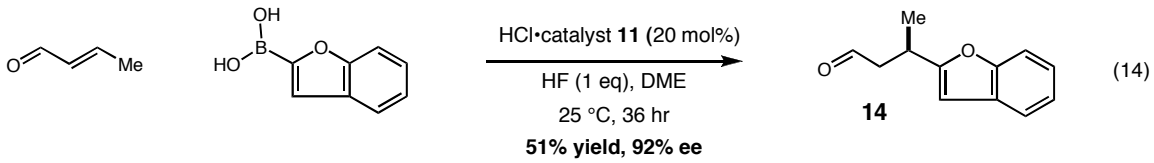
[a] Enantiomeric excess determined by chiral SFC analysis. [b] Bz = 4-NO_2PhC(O).

(69% yield, 92% ee, *entry 5*).[42] Additionally, significant variation of aldehyde functionality from a methyl ester group (93% yield, 88% ee, *entry 3*) to a pendent, protected alcohol (75% yield, 89% ee, *entry 4*)[43] was well tolerated. Notably, the optimal reaction temperature of the reaction was modulated with the reactivity of aldehyde substrate such that less reactive substrates were conducted at higher temperatures.

42. Without the activation of the system by the *p*-NO_2 group, cinnamaldehyde was significantly less reactive, only progressing to approximately 20% conversion.

43. Without the activation of the system by the *p*-NO_2 group, (*E*)-4-oxobut-2-enyl benzoate was significantly less reactive providing the desired product in 50% conversion and 76% ee at room temperature.

On the basis of these results, we considered the direct addition of boronic acids via an *in situ* formation of a boronate species through the introduction of an activating additive. This notion was validated when in the presence of hydrofluoric acid (*eq. 14*), we achieved



(14)

the addition of a boronic acid to crotonaldehyde to yield the corresponding adduct, **14** (51% yield, 92% ee).[44] This result demonstrates the extension of this methodology towards unfunctionalized aldehyde substrates that would otherwise be unreactive toward boronic acids (*vide supra*).

V. Conclusion

In summary, we have further established iminium catalysis as a valuable strategy for asymmetric synthesis in the context of the first example of organocatalytic addition of trifluoro(organo)borates and boronic acids to α,β-unsaturated aldehydes. We envision this new mode of reactivity for organotrifluoroborates will prove invaluable as a robust metal-free "coupling" procedure for enantioselective C–C bond construction. From a practical standpoint, this methodology stands to benefit from the structural diversity and wide commercial availability of several hundred organoboron reagents accessible to organic chemists. Furthermore, the low toxicity and the air and moisture stability of potassium

44. The analogous reaction of crotonaldehyde and an unfunctionalized benzofuran (under identical conditions noted in eq. 14) did not yield **14**.

organotrifluoroborates reagents make this powerful new organocatalytic process operationally trivial.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[45] All solvents were purified according to the method of Grubbs.[46] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile compounds. Potassium trifluoroborate salts were synthesized from commercially available boronic acids or esters using a modified Molander procedure.[47] Chromatographic purification of products was accomplished using force-flow chromatography on Silicycle silica gel according to the method of Still[48] and where noted, Iatrobeads 6RS-8060 was used in place of silica gel. Thin-layer chromatography (TLC) was performed on Silicycle 250 mm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching and anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz or 75 MHz), Mercury 400 (400 MHz or 100 MHz), or an Inova 500 (500MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals (note: $CDCl_3$ referenced at δ 7.24). Data for ^{1}H 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. Data for ^{13}C NMR are reported in terms of

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45. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon Press: Oxford, 1988.

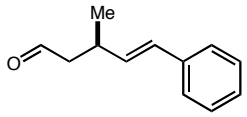
46. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics,* **1996**, *15*, 1518.

47. (a) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (b) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867. Note: The cited procedures were found to be more efficient when reaction slurries were sonicated.

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

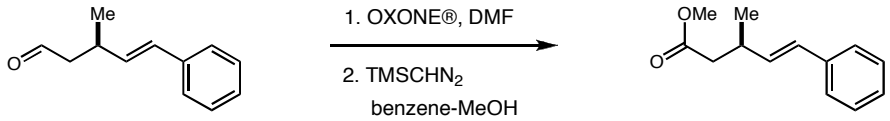
chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral Facility and the Princeton Mass Spectroscopy Facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with split-mode capillary injection system and flame ionization detectors using Bodman Chiraldex γ-TA (30 m x 0.25 mm) column. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a diode array UV detector (λ = 214–258 nm) using a chiral column (25 cm) and guard column (5 cm) as noted for each compound.

General procedure: To a plastic vial (Wheaton HDPE) was added HF (48 wt%, 1.0 eq) followed by 1,2-dimethoxyethane (DME) (1M, relative to aldehyde) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (0.2 eq) and HCl (0.2 eq) and was then cooled to temperature (as noted). The reaction was started with the addition of the aldehyde (3.0 eq) to the DME solution immediately followed by the addition of the trifluoroborate salt (1.0 eq). The reaction was stirred at temperature (for approximately 20–24 hr, as noted) and was often worked-up by an aqueous quench, which was then partitioned with dichloromethane, chloroform, or ether, as noted. The combined organic layers are dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was then purified by column chromatography (conditions noted) to yield the desired product.



***(3R,4E)*-3-methyl-5-phenylpent-4-enal (7).** Prepared according to the general procedure using crotonaldehyde and potassium *trans*-styryltrifluoroborate salt. To a plastic vial was added HF (48 wt%, 7.00 mg, 0.167 mmol) followed by DME (500 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (12.5 mg, 0.033 mmol) and HCl (4N in dioxane, 8.30 μL, 0.033 mmol) and was then cooled to –20 °C. Crotonaldehyde (58.0 μL, 0.50 mmol) was charged to the DME solution followed by the addition of potassium 2-benzofuranyltrifluoroborate salt (37.3 mg, 0.167 mmol). The reaction was stirred at –20 °C for 24 hours, quenched with 1M HCl (1.0 mL) and was stirred with chloroform (1.5 mL) for 30 minutes. The organic layer was extracted with CH_2Cl_2 (2 x 2.0 mL), dried over Na_2SO_4, filtered through celite (ether wash) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 20% ether in pentanes) yielded the title compound as clear oil (27.9 mg, 96% yield, 87% ee). IR (film) 2962, 1718, 965.0, 747.0, 692.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, 1H, J = 2.1 Hz, C**H**O), 7.34–7.19 (m, 5H, aryl **H**), 6.42 (dd, 1H, J = 0.6, 15.9 Hz, C**H**=CH), 6.14 (dd, 1H, J = 7.5, 15.9 Hz, CH=C**H**), 2.94 (m, 1H, C**H**CH_3), 2.50 (ddd, 2H, J = 2.1, 6.9, 16.5 Hz, C$\mathbf{H}_2$), 1.16 (d, 3H, C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.33, 134.16, 129.32, 128.76, 127.50, 126.33, 50.60, 32.08, 20.65; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{12}H_{14}O$) requires m/z 174.1045, found m/z 174.1051; $[\alpha]_D$= –49.1 (c = 0.45, $CHCl_3$). The enantiomeric excess was determined on the alcohol product, which was prepared by a $NaBH_4$ reduction and analyzed by SFC analysis using a Chiralcel OD-H column (5% to

35% IPA, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 4.75 min, (*R*) isomer t_r = 5.35 min.



Determination of the absolute stereochemistry of (*3R,4E*)-3-methyl-5-phenylpent-4-enal by correlation to methyl [1-((*E*)-styryl)ethyl]acetate. Aldehyde **7** (22.0 mg, 0.126 mmol) was subjected to oxidation[49] using Oxone® (77.6 mg, 0.126 mmol) in DMF (1.26 mL) to quantitatively produce the corresponding acid (24.0 mg, 0.126 mmol). Subsequently, the acid was esterified using TMS diazomethane (2M in hexane, 130 μL) in a solution of 25% methanol in benzene (1.0 mL) at room temperature. Purification was accomplished via chromatography (prep TLC, 20% ether in pentanes) and yielded (*3R,4E*)-methyl 3-methyl-5-phenylpent-4-enoate in 34% isolated yield. ^{1}H NMR and ^{13}C NMR (500 MHz, CCl_4 with TMS internal reference) spectral data matched literature values.[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.18 (m, 5H, aryl **H**), 6.38 (d, 1H, *J* = 15.6 Hz, CH=C**H**), 6.12 (dd, 1H, *J* = 7.6, 15.9 Hz, C**H**=CH), 6.14 (dd, 1H, *J* = 7.5, 16.0 Hz, CH=C**H**), 3.65 (s, 3H, OC**H**$_3$), 2.84 (septet, 1H, *J* = 7.2 Hz, C**H**CH$_2$), 2.39 (ddd, 2H, *J* = 7.2, 14.4, 21.6 Hz, C**H**$_2$) 1.13 (d, 3H, *J* = 6.4 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 134.4, 129.1, 128.7, 127.4, 126.3, 51.74, 41.73, 34.22, 20.42; $[\alpha]_D$= –57.8 (c = 0.502, CCl_4).

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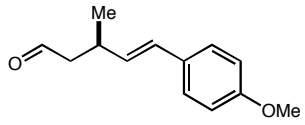
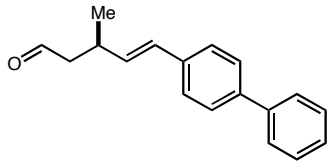
49. Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

50. Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723 (reported $[\alpha]_D$= –49.2 (c = 1.3, CCl_4) for a product that was 79% ee).



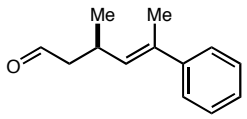
(*3R*,*4E*)-5-(4-methoxyphenyl)-3-methylpent-4-enal (**Table 8, entry 2**)**.** Prepared according to the general procedure using crotonaldehyde and potassium *trans*-2-(4-methoxyphenyl)trifluoroborate salt. To a plastic vial was added HF (48 wt%, 3.5 mg, 0.083 mmol) followed by DME (250 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (6.25 mg, 0.017 mmol) and HCl (4N in dioxane, 4.2 μL, 0.017 mmol) and was then cooled to –40 °C. Crotonaldehyde (21.0 μL, 0.25 mmol) was charged to the DME solution followed by the addition of potassium *trans*-2-(4-methoxyphenyl)trifluoroborate salt (20.0 mg, 0.083 mmol). The reaction was stirred at –40 °C for 20 hours, quenched with 1M HCl (1.0 mL) and was stirred with chloroform (1.5 mL) for 30 minutes. The organic layer was extracted with CH_2Cl_2 (2 x 2.0 mL), dried over Na_2SO_4, filtered through celite (ether wash) and concentrated *in vacuo*. Purification by chromatography (prep TLC, 10% ether in pentanes) yielded the title compound as clear oil (13.9 mg, 70% yield, 88% ee). IR (film) 2954, 1720, 1605, 1510, 1243, 1174, 1030, 964.8, 804.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, 1H, *J* = 2.1 Hz, C**H**O), 7.27 (d, 2H, *J* = 8.4 Hz, aryl **H**), 6.84 (d, 2H, *J* = 9.0 Hz, aryl **H**), 6.36 (d, 1H, *J* = 15.9 Hz, CH=C**H**), 6.01 (dd, 1H, *J* = 7.5, 15.9 Hz, C**H**=CH), 3.80 (s, 3H, OC$\mathbf{H}_3$), 2.93 (m, 1H, C**H**CH_2), 2.50 (ddd, 2H, *J* = 2.1, 7.2, 16.2 Hz, C$\mathbf{H}_2$), 1.17 (d, 3H, *J* = 6.6 Hz, C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.54, 159.17, 132.01, 130.11, 128.68, 127.44, 114.15, 55.51, 50.73, 32.11, 20.79; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{13}H_{16}O_2$) requires *m*/*z* 204.1150, found *m*/*z* 204.1150; $[\alpha]_D$= –44.0 (c = 1.26, $CHCl_3$). The enantiomeric excess

was determined by SFC analysis using a Chiralpak AS-H column (5% to 10% MeCN, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 4.03 min, (*R*) isomer t_r = 4.68 min.



(*3R*,*4E*)-5-(4-biphenyl)-3-methylpent-4-enal (**Table 8, entry 3**). Prepared according to the general procedure using crotonaldehyde and potassium *trans*-2-(biphenyl)trifluoroborate salt. To a plastic vial was added HF (48 wt%, 6.3 mg, 0.15 mmol) followed by DME (450 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (11.3 mg, 0.03 mmol) and HCl (4N in dioxane, 7.5 μL, 0.03 mmol) and was then cooled to –40 °C. Crotonaldehyde (37.5 μL, 0.45 mmol) was charged to the DME solution followed by the addition of potassium *trans*-2-(4-biphenyl)trifluoroborate salt (42.9 mg, 0.15 mmol). The reaction was stirred at –40 °C for 24 hours and was directly subjected to purification by flash chromatography (Iatrobeads, 1% acetone and 5% ether in pentanes) to yield the title compound as light, yellow solid (20.6 mg, 91% yield, 95% ee). IR (film) 2924, 2854, 1724, 972.3, 761.7, 694.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, 1H, *J* = 2.0 Hz, C**H**O), 7.58–7.52 (m, 4H, aryl **H**), 7.43–7.39 (m, 4H, aryl **H**), 7.33–7.24 (m, 1H, aryl **H**), 6.44 (d, 1H, *J* = 16.0 Hz, CH=C**H**), 6.19 (dd, 1H, *J* = 7.5, 16.0 Hz, C**H**=CH), 2.97 (septet, 2H, *J* = 7.0 Hz, C**H**CH_2), 2.52 (ddd, 2H, *J* = 2.0, 7.0, 16.5 Hz, C$\mathbf{H}_2$), 1.18 (d, 3H, *J* = 7.0 Hz, C$\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.21, 140.95, 140.31, 136.41, 134.34, 128.99, 128.93,

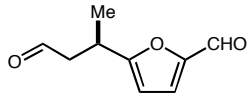
127.46, 127.12, 126.77, 50.65, 32.15, 29.92, 20.67; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{13}H_{16}O_2$) requires *m*/*z* 250.1358, found *m*/*z* 250.1349; $[\alpha]_D$= –13.6 (c = 1.29, $CHCl_3$). The enantiomeric excess was determined by SFC analysis using a Chiralcel OJ-H column (5% to 15% MeCN, 2%/min gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 2.97 min, (*R*) isomer t_r = 3.23 min.



(*3R*,*4E*)-3-methyl-5-phenylhex-4-enal (**Table 8, entry 4**)**.** Prepared according to the general procedure using crotonaldehyde and potassium (*E*)-(2-phenylprop-1-enyl) trifluoroborate salt.[51] To a plastic vial was added HF (48 wt%, 3.5 mg, 0.083 mmol) followed by DME (250 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (6.25 mg, 0.017 mmol) and HCl (4N in dioxane, 4.2 μL, 0.017 mmol) and was then cooled to –20 °C. Crotonaldehyde (21.0 μL, 0.25 mmol) was charged to the DME solution followed by the addition of potassium (*E*)-(2-phenylprop-1-enyl) trifluoroborate salt (18.7 mg, 0.083 mmol). The reaction was stirred at –50 °C for 24 hours, quenched with 1M HCl (1.0 mL) and was stirred with dichloromethane (1.5 mL) for 30 minutes. The organic layer was extracted with dichloromethane (2 x 2.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% ethyl acetate in hexanes) yielded the title

51. (a) Prepared via synthesis of the corresponding boronic ester using a literature procedure, see: Coapes, R. B.; Souza, F. E. S.; Thomas, R. L.; Hall, J. J.; Marder, T. B. *Chem. Commun.* **2003**, 614. (b) Petasis N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1997**, 606.

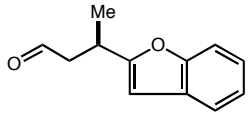
compound as a clear, light yellow oil (13.1 mg, 84% yield, 82% ee). This is a known compound that has previously been synthesized as a racemate.[52] Notably, all spectroscopic data are in accord with literature values. IR (film) 2961, 1724, 1444, 758.0, 697.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, 1H, *J* = 2.1 Hz, C**H**O), 7.38–7.22 (m, 5H, aryl **H**), 5.58 (dd, 1H, *J* = 1.5, 9.6 Hz, C=C**H**), 3.16 (m, 1H, C**H**CH_3), 2.46 (dd, 2H, *J* = 2.1, 7.2 Hz, C**H**$_2$), 2.08 (d, 3H, *J* = 1.2 Hz, C**H**$_3$), 1.17 (d, 3H, *J* = 6.6 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.83, 132.61, 128.41, 127.05, 125.95, 51.25, 28.62, 20.93, 16.12; HRMS (EI+) exact mass calculated for [$M^{+\bullet}$] ($C_{13}H_{16}O$) requires *m*/*z* 188.1201, found *m*/*z* 188.1197; $[\alpha]_D$= –70.1 (c = 0.96, $CHCl_3$). The enantiomeric excess was determined on the alcohol product, which was prepared by a $NaBH_4$ reduction and analyzed by SFC analysis using a Chiralpak AD-H column (0% to 10% IPA, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 5.79 min, (*R*) isomer t_r = 6.32 min.



(*3R*)-5-(4-oxobutan-2-yl)furan-2-carbaldehyde (**Table 8, entry 5**). Prepared according to the general procedure using crotonaldehyde and potassium 2-(5-formylfuran-2-yl) trifluoroborate salt. To a plastic vial was added HF (48 wt%, 3.5 mg, 0.083 mmol) followed by DME (250 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (6.25 mg, 0.017 mmol) and HCl (4N in dioxane, 4.2 μL, 0.017 mmol) and was then cooled to –20 °C. Crotonaldehyde (21.0 μL, 0.25

52. Nasveschuk, C. G.; Rovis, T. *Org. Lett.* **2005**, *7*, 2173.

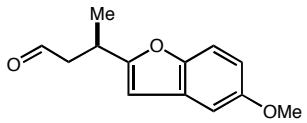
mmol) was charged to the DME solution followed by the addition of potassium 2-(5-formylfuran-2-yl) trifluoroborate salt (20.0 mg, 0.083 mmol). The reaction was stirred at –20 °C for 20 hours, quenched with 1M HCl (1.0 mL) and was stirred with ether (1.5 mL) for 30 minutes. The organic layer was extracted with ether (2 x 2.0 mL), dried over Na_2SO_4, filtered through celite (ether wash) and concentrated *in vacuo* (ice-water bath). Purification by flash chromatography (silica gel, 10% ether in pentanes) yielded the title compound as a clear, light yellow oil (11.7 mg, 85% yield, 95% ee). IR (film) 1719, 1670, 1513, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, 1H, *J* = 1.5 Hz, C**H**O), 9.51 (s, 1H, furyl C**H**O), 7.17 (d, 1H, *J* = 3.6 Hz, aryl **H**), 6.30 (dd, 1H, *J* = 0.9, 3.6 Hz, aryl **H**), 3.53 (m, 1H, C**H**CH_3), 2.81 (ddd, 2H, *J* = 1.5, 7.2, 17.7 Hz, C$\mathbf{H}_2$), 1.35 (d, 3H, *J* = 7.2 Hz, C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.53, 177.45, 152.56, 123.72, 108.38, 49.08, 28.55, 19.07; HRMS (EI+) exact mass calculated for [$M^{+\bullet}$] ($C_9H_{10}O_3$) requires *m/z* 166.0630, found *m/z* 166.0629; $[\alpha]_D$= –1.09 (c = 1.17, $CHCl_3$). The enantiomeric excess was determined by SFC analysis using a Chiralpak AS-H column (5% to 10% MeCN, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 2.73 min, (*R*) isomer t_r = 3.63 min.



***(3R)*-3-(benzofuran-2-yl)butanal (Table 8, entry 6).** Prepared according to the general procedure using crotonaldehyde and potassium 2-benzofuranyltrifluoroborate salt.[53] To a plastic vial was added HF (48 wt%, 6.25 mg, 0.167 mmol) followed by DME

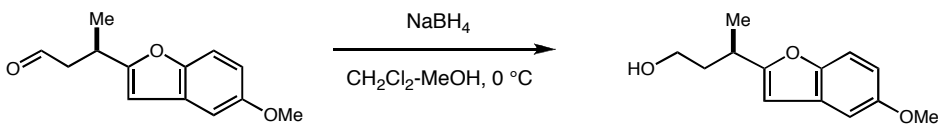
53. Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757.

(450 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (11.3 mg, 0.033 mmol) and HCl (4N in dioxane, 7.50 μL, 0.033 mmol) and was then cooled to –20 °C. Crotonaldehyde (37.3 μL, 0.45 mmol) was charged to the DME solution followed by the addition of potassium 2-benzofuranyltrifluoroborate salt (33.6 mg, 0.150 mmol). The reaction was stirred at –20 °C for 23 hours and then flushed though a silica gel plug (wash with 30% ether in pentanes). Concentration *in vacuo* (ice-water bath) provided the title compound as clear oil (25.5 mg, 90% yield, 97% ee). IR (film) 1722, 1454, 1253, 1168, 750.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H, C**H**O), 7.54–7.43 (m, 2H, aryl **H**), 7.29–7.19 (m, 2H, aryl **H**), 6.45 (t, 1H, *J* = 0.9 Hz, 3'-benzofuranyl **H**), 3.61 (m, 1H, C**H**CH_3), 2.85 (dd, 2H, *J* = 1.8, 17.1 Hz, C$\mathbf{H}_2$), 1.45 (d, 3H, *J* = 6.6 Hz, C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.06, 161.47, 154.81, 128.68, 123.81, 122.81, 120.75, 111.07, 101.58, 49.06, 28.38, 19.04; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{12}H_{12}O_2$) requires *m*/*z* 188.0837, found *m*/*z* 188.0844; $[\alpha]_D$= –17.1 (c = 1.22, $CHCl_3$). The enantiomeric excess was determined on the alcohol product, which was prepared by a $NaBH_4$ reduction and analyzed by SFC analysis using a Chiralpak AS-H column (5% to 50% methanol, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 2.17 min, (*R*) isomer t_r = 2.40 min.

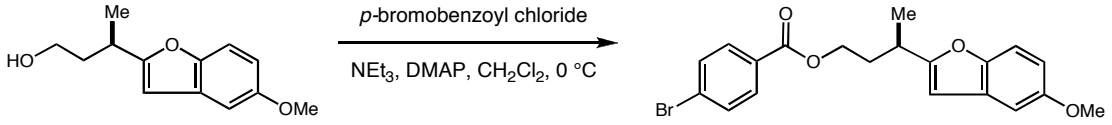


***(3R)*-3-(5-methoxybenzofuran-2-yl)butanal (Table 8, entry 7).** Prepared according to the general procedure using crotonaldehyde and potassium 2-(5-methoxybenzofuranyl)trifluoroborate salt. To a plastic vial was added HF (48 wt%, 6.25

mg, 0.15 mmol) followed by DME (450 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (10.9 mg, 0.03 mmol) and HCl (4N in dioxane, 7.5 μL, 0.03 mmol) and was then cooled to –20 °C. Crotonaldehyde (37.5 μL, 0.45 mmol) was charged to the DME solution followed by the addition of potassium 2-(5-methoxybenzofuranyl)trifluoroborate salt (42.4 mg, 0.15 mmol). The reaction was stirred at –20 °C for 24 hours, quenched with 1M HCl (1.0 mL) and was stirred with chloroform (1.5 mL) for 30 minutes. The organic layer was extracted with chloroform (2 x 2.0 mL), dried over Na_2SO_4, filtered through celite (ether wash) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 15% ether in pentanes) yielded the title compound as clear oil (30.7 mg, 94% yield, 92% ee). IR (film) 1724, 1475, 1205, 1030 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 9.78 (t, 1H, *J* = 1.5 Hz, C**H**O), 7.29 (d, 1H, *J* = 8.4 Hz, aryl **H**), 6.98 (d, 1H, *J* = 2.4 Hz, aryl **H**), 6.81 (dd, 1H, *J* = 2.4, 9.0 Hz, aryl **H**), 6.38 (d, 1H, *J* = 0.9 Hz), 3.01 (s, 3H, OC**H**$_3$), 3.54 (m, 1H, C**H**CH_3), 2.79 (ddd, 2H, *J* = 1.5, 6.6, 17.4 Hz, C**H**$_2$), 1.39 (d, 3H, *J* = 0.9 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.32, 163.07, 156.46, 150.05, 129.72, 112.37, 111.60, 103.72, 101.93, 56.29, 49.30, 28.78, 19.18; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{13}H_{14}O_3$) requires *m*/*z* 218.0943, found *m*/*z* 218.0944; $[\alpha]_D$= –8.51 (c = 1.29, $CHCl_3$). The enantiomeric excess was determined by SFC using a Chiracel OJ-H column (5% to 10% MeCN, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 5.17 min, (*R*) isomer t_r = 5.61 min.



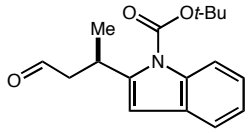
Determination of the absolute stereochemistry of (*3R*)-3-(5-methoxybenzofuran-2-yl)butanal by correlation to (*3R*)-3-(5-methoxybenzofuran-2-yl)butan-1-ol. To a stirring solution of the aldehyde (25 mg, 0.11 mmol) in CH_2Cl_2 (2.0 mL) and ethanol (20 μL) at 0 °C was added $NaBH_4$ (13 mg, 0.34 mmol). The reaction was quenched after 5 minutes by a saturated solution of Rochelle's salt (2.0 mL). The organic was then extracted with ether (2 x 3.0 mL) and concentrated *in vacuo* to yield a clear oil (quantitative yield) with spectroscopic data matching literature values.[54] IR (film) 3306 (br), 2922, 1458, 1201, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 1H, *J* = 8.7 Hz, aryl **H**), 6.94 (d, 1H, *J* = 2.7 Hz, aryl **H**), 6.79 (dd, 1H, *J* = 2.7, 8.7 Hz, aryl **H**), 6.33 (s, 1H, aryl **H**), 3.81 (s, 3H, OC**H**$_3$), 3.69 (m, 2H, C**H**$_2$CH$_2$), 3.11 (m, 1H, C**H**CH$_3$), 2.06–1.95 (m, 1H, C**H**$_2$OH), 1.91–1.79 (m, 1H, C**H**$_2$OH), 1.57 (br s, 1H, O**H**), 1.34 (d, 3H, *J* = 7.2 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.11, 155.98, 149.73, 129.48, 111.81, 111.38, 103.45, 101.40, 60.97, 56.16, 38.53, 30.56, 19.38; HRMS (EI+) exact mass calculated for [M+1] ($C_{13}H_{16}O_3$) requires *m/z* 220.1100, found *m/z* 220.1089; $[\alpha]_D$= –46.2 (c = 0.83, $CHCl_3$).[39] The enantiomeric excess was determined by SFC analysis using a Chiralcel OJ-H column (5% to 10% methanol, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 5.71 min, (*R*) isomer t_r = 6.56 min.



Determination of the absolute stereochemistry of (*3R*)-3-(5-methoxybenzofuran-2-yl)butanal by obtaining a crystal structure of (*3R*)-3-(5-

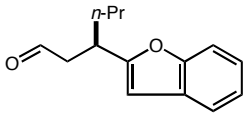
54. Hughes, C. C.; Trauner, D. *Tetrahedron*, **2004**, *60*, 9675 (reported $[\alpha]_D$= –33.0 (c = 1.00, $CHCl_3$) for a product that was 91% ee).

methoxybenzofuran-2-yl)butyl 4-bromobenzoate (*vide infra*). Esterification of (*3R*)-3-(5-methoxybenzofuran-2-yl)butan-1-ol (22 mg, 0.10 mmol) proceeded in a solution of CH_2Cl_2 (1.0 mL) to which NEt_3 (21 μL, 0.15 mmol) and DMAP (1.2 mg, 0.01 mmol) were added. The solution was then cooled to 0 °C and *p*-bromobenzoyl chloride (24 mg, 0.11 mmol) was added. The ice bath was removed and after 30 minutes at room temperature, 0.5 M HCl (2.0 mL) was added to quench the reaction. The organic layer was dried with Na_2SO_4, triturated with diethyl ether, filtered (to remove salt impurities), and concentrated *in vacuo* to yield a yellow solid (34 mg, 85% yield). IR (film) 2929, 1719, 1591, 1477, 1271, 1205, 1102, 1012, 756.3 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 2H, *J* = 8.4 Hz, aryl **H**), 7.47 (d, 2H, *J* = 8.4 Hz, aryl **H**), 7.22 (s, 1H, aryl **H**), 6.89 (d, 1H, *J* = 2.8 Hz, aryl **H**), 6.77 (dd, 1H, *J* = 2.8, 9.2 Hz, aryl **H**), 6.32 (s, 1H, aryl **H**), 4.33 (m, 2H, C**H**$_2$OC(O)), 3.78 (s, 3H, OC**H**$_3$), 3.11 (m, 1H, CH_3C**H**), 2.25–2.01 (m, 2H, C**H**$_2$), 1.37 (t, 3H, *J* = 7.2 Hz, CHC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.95, 163.18, 155.97, 149.75, 131.76, 131.17, 129.40, 129.18, 128.11, 111.85, 111.32, 103.42, 101.62, 63.41, 56.10, 34.32m 31.20, 19.23; HRMS (EI+) exact mass calculated for [$M^{+\bullet}$] ($C_{20}H_{19}BrO_4$) requires *m*/*z* 402.0467, found *m*/*z* 402.0481; $[\alpha]_D$= –52.7 (c = 1.02, $CHCl_3$).

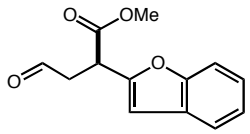


(*3R*)-*tert*-butyl 2-(4-oxobutan-2-yl)-1*H*-indole-1-carboxylate (**Table 8, entry 8).** Prepared according to the general procedure using crotonaldehyde and potassium 2-(*tert*-butyl 1*H*-indole-1-carboxylate)trifluoroborate salt. To a plastic vial was added HF (48 wt%, 3.5 mg, 0.083 mmol) followed by DME (250 μL) and a magnetic stir bar. The

catalyst and acid co-catalyst were charged to the vial with the addition of (*2S,5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (12.4 mg, 0.033 mmol) and HCl (4N in dioxane, 8.3 μL, 0.033 mmol) and was then cooled to –20 °C. Crotonaldehyde (21.0 μL, 0.25 mmol) was charged to the DME solution followed by the addition of potassium 2-(*tert*-butyl 1*H*-indole-1-carboxylate)trifluoroborate salt (26.9 mg, 0.083 mmol). The reaction was stirred at –20 °C for 24 hours and quenched with 1M HCl (1.0 mL) and was stirred with chloroform (1.5 mL) for 30 minutes. The organic layer was extracted with chloroform (2 x 2.0 mL), dried over Na_2SO_4, filtered through celite (ether wash) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% ether in pentanes) yielded the title compound as light yellow oil (19.0 mg, 79% yield, 91% ee). IR (film) 1728, 1455, 1370, 1327, 1157, 747.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, 1H, *J* = 1.8 Hz, C**H**O), 8.03 (dt, 1H, *J* = 0.6, 7.8 Hz, aryl **H**), 7.45 (m, 1H, aryl **H**), 7.26–7.15 (m, 2H, aryl **H**), 6.40 (t, 1H, *J* = 0.9 Hz, aryl **H**), 4.24 (m, 1H, C**H**CH_3), 2.57 (dd, 1H, C**H**$_2$), 2.89 (1H, dd, *J* = 1.8, 5.4 Hz, C**H**$_2$), 1.37 (t, 3H, *J* = 6.9 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.95, 150.69, 145.80, 129.22, 123.96, 123.00, 120.28, 115.94, 106.42, 84.47, 50.80, 28.45, 28.02, 21.06; HRMS (EI+) exact mass calculated for [$M^{+\bullet}$] ($C_{17}H_{21}NO_3$) requires *m/z* 287.1521, found *m/z* 287.1533; $[\alpha]_D$= –6.1 (c = 0.6, $CHCl_3$). The enantiomeric excess was determined by SFC analysis using a Chiralcel OD-H column (5% to 50% MeCN, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 2.51 min, (*R*) isomer t_r = 2.97 min.

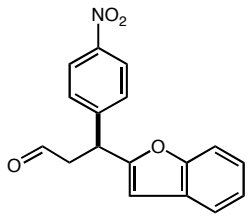


(*3R*)-3-(benzofuran-2-yl) hexanal (Table 9, entry 2). Prepared according to the general procedure using hexenal and potassium 2-benzofuranyltrifluoroborate salt. To a plastic vial was added HF (48 wt%, 7.00 mg, 0.167 mmol) followed by DME (500 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (12.5 mg, 0.033 mmol) and HCl (4N in dioxane, 8.30 μL, 0.033 mmol) and was then cooled to 4 °C. Hexenal (58.0 μL, 0.50 mmol) was charged to the DME solution followed by the addition of potassium 2-benzofuranyltrifluoroborate salt (37.3 mg, 0.167 mmol). The reaction was stirred at 4 °C for 12 hours and quenched with a saturated solution of Rochelle's salt (1.0 mL) and was partitioned with dichloromethane (2 x 1.5 mL). The combined organic layers are dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (silica gel, 10% ether in pentanes) to yield the title compound as clear oil (34.9 mg, 97% yield, 93% ee). IR (film) 2959, 2932, 2873, 1725, 1456, 1253, 751.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, C**H**O), 7.49–7.38 (m, 2H, aryl **H**), 7.24–7.14 (m, 2H, aryl **H**), 6.42 (s, 1H, 3'-benzofuranyl **H**), 3.48–3.39 (m, 1H, $CH_2C\mathbf{H}CH_2$), 2.80 (ddd, 2H, J = 1.8, 7.5, 17.1 Hz, α-C$\mathbf{H}_2$), 1.85–1.58 (m, 2H, C$\mathbf{H}_2$), 1.37–1.24 (m, 2H, C$\mathbf{H}_2$), 0.89 (t, 3H, J = 6.9 Hz, C$\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.31, 147.98, 132.55, 123.73, 122.82, 120.73, 111.12, 102.85, 67.13, 47.70, 35.97, 33.69, 20.48, 14.07; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{14}H_{16}O_2$) requires m/z 216.1150, found m/z 216.1142; $[\alpha]_D$= –7.3 (c = 1.05, $CHCl_3$). The enantiomeric excess was determined on the alcohol product, which was prepared by a $NaBH_4$ reduction and analyzed by SFC using a Chiralpak AS-H column (5% to 25% IPA, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 3.18 min, (*R*) isomer t_r = 3.36 min.



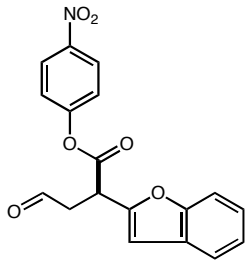
(*3R*)-methyl 2-(benzofuran-2-yl)-3-formylpropanoate (Table 9, entry 3). Prepared according to the general procedure using (*E*)-methyl 3-formylacrylate and potassium 2-benzofuranyltrifluoroborate salt. To a plastic vial was added HF (48 wt%, 7.00 mg, 0.167 mmol) followed by DME (500 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (12.5 mg, 0.033 mmol) and HCl (4N in dioxane, 8.30 μL, 0.033 mmol) and was then cooled to –20 °C. (*E*)-Methyl 3-formylacrylate (58.0 μL, 0.50 mmol) was charged to the DME solution followed by the addition of potassium 2-benzofuranyltrifluoroborate salt (37.3 mg, 0.167 mmol). The reaction was stirred at –20 °C for 18 hours, quenched with 1M HCl (1.0 mL) and was stirred in chloroform (1.5 mL) for 30 minutes. The organic layer was extracted with chloroform (2 x 2.0 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (silica gel, 25% ether in pentanes) to yield the title compound as clear oil (36.0 mg, 93% yield, 88% ee). IR (film) 1736, 1720, 1453, 1168, 750.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H, C**H**O), 7.52–7.40 (m, 2H, aryl **H**), 7.28–7.17 (m, 2H, aryl **H**), 6.58 (s, 1H, 3'-benzofuranyl **H**), 4.42 (dd, 1H, *J* = 5.1, 9.0 Hz, C**H**CH_2), 3.73 (s, 3H, OC**H**$_3$), 3.45 (ddd, 1H, *J* = 0.6, 9.0, 18.6 Hz, C**H**$_2$), 3.02 (ddd, 1H, *J* = 0.6, 5.1, 18.6 Hz, C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.82, 191.57, 147.97, 132.45, 128.33, 124.52, 123.18, 121.14, 111.42, 104.62, 53.120, 44.37, 39.39; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{13}H_{12}O_4$) requires *m*/*z* 232.0736, found *m*/*z* 232.0728; $[\alpha]_D$= –95.0 (c = 0.8, $CHCl_3$). The enantiomeric excess was determined on the diol product, which is prepared

by reduction of the ester and aldehyde (21.5 mg, 0.093 mmol) in THF (1.0 mL) using $LiAlH_4$ (1M in THF, 200 μL, 0.2 mmol) at –60 °C. SFC analysis was performed using a Chiralpak AD-H column (5% to 15% methanol, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 10.23 min, (*R*) isomer t_r = 10.80 min.



(*3S*)-3-(Benzofuran-2-yl)-3-(4-nitrophenyl)propanal (Table 9, entry 4). Prepared according to the general procedure using *p*-nitrocinnamaldehyde and potassium 2-benzofuranyltrifluoroborate salt. To a plastic vial was added HF (48 wt%, 3.50 mg, 0.083 mmol) followed by DME (250 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (6.26 mg, 0.017 mmol) and HCl (4N in dioxane, 4.20 μL, 0.017 mmol). *p*-Nitrocinnamaldehye (44.3 mg, 0.250 mmol) was charged to the DME solution followed by the addition of potassium 2-benzofuranyltrifluoroborate salt (18.7 mg, 0.083 mmol). The reaction was stirred at ambient temperature for 24 hours, quenched with a saturated solution of Rochelle's salt (1.0 mL) and was then partitioned with dichloromethane (2 x 1.5 mL). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by chromatography (prep TLC, 25% dichloromethane in benzene) to yield the title compound as a light yellow oil (16.9 mg, 69% yield, 92% ee). IR (film) 1724, 1519, 1454, 1347, 1254, 752.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H, C**H**O), 8.19 (d, 2H, *J* = 8.4

Hz, aryl **H**), 7.53–7.39 (m, 4H, aryl **H**), 7.28–7.18 (m, 2H, aryl **H**), 6.50 (s, 1H, 3'-benzofuranyl **H**), 4.90 (t, 1H, J = 7.2 Hz, $CH_2C\mathbf{H}$), 3.32 (dd, 2H, J = 6.9, 17.7 Hz, $C\mathbf{H}_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.65, 157.20, 147.99, 129.13, 124.55, 124.30, 123.25, 121.11, 111.32, 104.11, 47.82, 39.16; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{17}H_{13}NO_4$) requires m/z 295.0845, found m/z 295.0853; $[\alpha]_D$= 48.7 (c = 1.0, $CHCl_3$). The enantiomeric excess was determined on the alcohol product, which was prepared by a $NaBH_4$ reduction and analyzed by SFC using a Chiralpak AS-H column (5% to 25% methanol, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 6.93 min, (*R*) isomer t_r = 7.22 min.



(*3S*)-2-(benzofuran-2-yl)-3-formylpropyl 4-nitrobenzoate (**Table 9, entry 5).** Prepared according to the general procedure using (*E*)-3-formylallyl 4-nitrobenzoate and potassium 2-benzofuranyltrifluoroborate salt. To a plastic vial was added HF (48 wt%, 2.1 mg, 0.05 mmol) followed by DME (150 μL) and a magnetic stir bar. The catalyst and acid co-catalyst were charged to the vial with the addition of (*2S*,*5S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (7.51 mg, 0.02 mmol) and HCl (4N in dioxane, 5.0 μL, 0.02 mmol). (*E*)-3-Formylallyl 4-nitrobenzoate (35.3 mg, 0.15 mmol) was charged to the DME solution followed by the addition of potassium 2-benzofuranyltrifluoroborate salt (11.2 mg, 0.05 mmol). The reaction was stirred at –20 °C for 23 hours, quenched with 1M HCl (1.0 mL) and was stirred with chloroform (1.5 mL)

for 30 minutes. The organic layer was extracted with chloroform (2 x 2.0 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified by chromatography (prep TLC, 40% dichloromethane in benzene) to yield the title compound as a yellow oil (13.3 mg, 75% yield, 89% ee). IR (film) 1725, 1526, 1348, 1272, 1120, 1103, 752.6, 718.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (t, 1H, *J* = 1.2 Hz, C**H**O), 8.19 (dd, 4H, *J* = 2.1, 39.9 Hz, aryl **H**), 7.45 (dd, 2H, *J* = 7.5, 27.6 Hz, aryl **H**), 7.28–7.17 (m, 2H, aryl **H**), 6.57 (s, 1H, 3'-benzofuranyl **H**), 4.66 (dd, 2H, *J* = 6.3, 10.8 Hz, C**H**$_2$OBz), 4.07–3.98 (m, 1H, C**H**CH_2), 3.04 (ddd, 2H, *J* = 1.2, 6.6, 18.0 Hz, CHC**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.20, 164.53, 156.03, 135.21, 130.98, 128.29, 124.44, 123.85 121.08, 111.25, 104.05, 66.47, 44.23, 33.31; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{19}H_{15}NO_6$) requires *m*/*z* 353.0899, found *m*/*z* 353.0885; $[\alpha]_D$= +6.29 (c = 1.06, $CHCl_3$). The enantiomeric excess was determined on the alcohol product, which was prepared by a $NaBH_4$ reduction and analyzed by SFC using a Chiralpak AD-H column (30% to 50% methanol, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 5.78 min, (*R*) isomer t_r = 6.34 min.

Crystal Structure Analysis of:

(*3R*)-4-Bromobenzoic Acid-3-(5-Methoxybenzofuran-2-yl)butyl Ester (DWCM003)

For Investigator: Sandra Lee
Advisor: David W. C. MacMillan

By Douglas M. Ho

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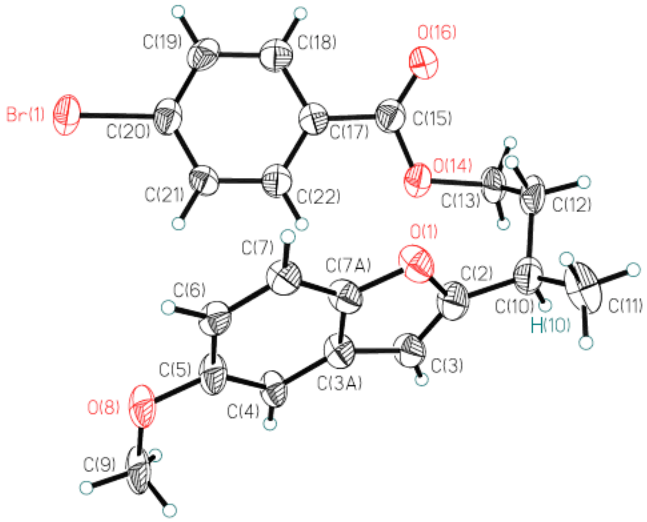

(*3R*)-4-Bromobenzoic Acid-3-(5-Methoxybenzofuran-2-yl)butyl Ester (DWCM003)

Experimental

Evaporation of a carbon disulfide solution of the compound yielded a yellow oil. Upon standing at room temperature for a number of hours, the oil crystallized into colorless bundles of intergrown plates. A fragment approximately 0.03 mm x 0.08 mm x 0.25 mm in size was cut from one of the plates, mounted on a glass fiber with silicone grease and transferred to a Nonius KappaCCD diffractometer equipped with an MSC X-stream cryosystem and Mo Kα radiation (λ = 0.71073 Å). Fourteen hundred and forty frames of data were collected at 200(2) K with an ω oscillation range of 0.5°/frame, and an exposure time of 60 s/deg.[55] A total of 7927 reflections (θ_{max} = 22.46°) were indexed, integrated and corrected for Lorentz and polarization effects using *DENZO-SMN* and *SCALEPACK*.[56] The crystal did not exhibit any usable data beyond that θ_{max} value. Therefore, a standard 0.76961 Å (θ_{max} = 27.5°) data set was not warranted or pursued. Gaussian and ψ-scan absorption corrected data sets were also examined but did not lead to improved refinement results and were therefore not pursued further as well. Data reduction yielded 2296 unique reflections (R_{int} = 0.066) of which 1735 had $I > 2\sigma(I)$. Postrefinement of the unit cell parameters gave a = 5.8677(3) Å, b = 7.3771(5) Å, c = 20.8583(14) Å, α = 90°, β = 97.998(4)°, γ = 90°, and V = 894.1(1) Å^3. Axial photographs and systematic absences were consistent with the compound having crystallized in one of two possible monoclinic space groups, i.e., $P2_1$ or $P2_1/m$. The observed mean $|E^2-1|$ value was 0.948 (versus the expectation values of 0.968 and 0.736

55. *COLLECT*.; Nonius BV: Delft, The Netherlands, 1998.

56. Otwinowski, Z.; Minor, W. In *Methods in Enzymology*; Carter, C. W., Sweet, R. M., Eds.; MacMomolecular Crystallography, Part A; Academic Press: New York, 1997; pp 307–326.

for centric and noncentric data, respectively). Nevertheless, the chiral space group $P2_1$ (No. 4) was selected since the compound was indicated to be optically pure.

The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using *SHELXTL*.[57] The asymmetric unit was found to contain only a single molecule of (*3R*)-4-bromobenzoic acid-3-(5-methoxybenzofuran-2-yl)butyl ester. All of the nonhydrogen atoms were refined with anisotropic displacement coefficients. The hydrogen atoms were assigned isotropic displacement coefficients $U(\mathrm{H}) = 1.2U(\mathrm{C})$ or $1.5U(\mathrm{C_{methyl}})$, and their coordinates were allowed to ride on their respective carbons. The sample was also found to be twinned with the volume fractions of the twin components being 0.9774(6) and 0.0226(6). Convergence of this single molecule model gave $wR(F^2) = 0.1141$ for 2296 unique reflections of which 1735 had $I > 2\sigma(I)$, 227 parameters and 199 restraints. This model, however, gave atoms exhibiting large thermal vibrations, and was therefore abandoned in favor of a two-site whole molecule disorder model. Initial occupancy refinement tests yielded site occupancy factors of 0.45(4) and 0.55(4) for the atoms of the two sites indicating that each site was half-occupied within the errors of the experiment. A whole molecule disorder model consisting of two exactly half-occupied molecules was therefore selected. Distance, similarity and common plane restraints were employed due to the close proximity of the two half molecules. The weighting scheme employed was $w = 1/[\sigma^2(F_o^2) + 0.1541P]$ where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to $R(F) = 0.0483$, $wR(F^2) = 0.0910$, and $S = 1.224$ for 1735 reflections with $I > 2\sigma(I)$, and $R(F) = 0.0741$, $wR(F^2) = 0.1017$, and $S = 1.142$ for 2296 unique reflections, 451 parameters and 724 restraints. The maximum $|\Delta/\sigma|$ in the final cycle of least-squares

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57. Sheldrick, G. M. *SHELXTL*, version 5.04; Siemens Analytical X-ray Instruments, Inc.: Madison, WI, 1996.

was 0.001, and the residual peaks on the final difference-Fourier map ranged from –0.256 to 0.354 eÅ^{-3}. The *R*-factor ratio between the $wR(F^2)$ values for the single molecule model and the whole molecule disorder model is R = 0.1141/0.1017 = 1.12 while $R_{224,2069,0.005}$ = 1.07, i.e., $R > R_{224,2069,0.005}$.[58] Hence, the notion that the model without whole molecule disorder might be preferable is convincingly rejected at the 0.005 level. Scattering factors were taken from the International Tables for Crystallography, Volume C.[59]

The Flack parameter refined to 0.04(2) [vs. the expectation values of 0 for the correct hand and 1 for the wrong hand] indicating that the coordinates below are for the correct hand of the molecule and that the absolute configuration at the chiral carbon is unequivocally *R* (IUPAC Numbering: Wanted = (*3R*), Found = (*3R*); Crystallographic Atom Numbering: Wanted = (*10R*/*10'R*), Found = (*10R*/*10'R*)).[60] Due to the complexity of the molecule, the IUPAC butyl *C*-3 atom is given the crystallographic label *C*-10 in the atoms list below. (The *C*-10' atom listed below corresponds to the chiral atom in the second molecule of the two-site whole molecule disorder model employed.)

For comparison, a refinement of the inverted molecule having the wrong absolute structure, i.e., (*3S*), gave $R(F)$ = 0.0696, $wR(F^2)$ = 0.1670, and S = 1.129 for 1735 reflections with $I > 2\sigma(I)$, and $R(F)$ = 0.0949, $wR(F^2)$ = 0.1858, and S = 1.052 for 2296 unique reflections, 451 parameters, and 724 restraints for the whole molecule disorder model. The Flack parameter based on the wrong absolute structure was 0.95(3). Based

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58. Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.

59. Maslen, E. N.; Fox, A. G.; O'Keefe, M. A. *International Tables for Crystallography: Mathematical, Physical and Chemical Tables*; Wilson, A. J. C., Ed.; Kluwer: Dordrecht, The Netherlands, 1992; Vol. C, pp 476–516.

60. Flack, H. D. *Acta Crystallogr. Sect. A* **1983**, *39*, 876.

on these $wR(F^2)$ and Flack values, the (*3S*) isomer is soundly rejected.

Table 1. Crystal data

$C_{20}H_{19}BrO_4$	$Z = 2$
$M_r = 403.26$	$D_x = 1.498$ Mg m^{-3}
Monoclinic, $P2_1$ (No. 4)	Mo $K\alpha$ radiation
$a = 5.8677$ (3) Å	Cell parameters from 7927 reflections
$b = 7.3771$ (5) Å	$\theta = 1.97–22.46°$
$c = 20.8583$ (14) Å	$\mu = 2.32$ mm^{-1}
$\beta = 97.998$ (4)°	$T = 200$ (2) K
$V = 894.1$ (1) Å^3	Plate, Colorless

Table 2. Data collection

Nonius KappaCCD diffractomer	1735 reflections with $I > 2\sigma(I)$
ω scans; 1440 0.5° rotations	$R_{int} = 0.066$
Absorption correction: none	$\theta_{max} = 22.46°$
	$h = -6 \rightarrow 6$
7927 measured reflections	$k = -7 \rightarrow 7$
2296 independent reflections	$l = -22 \rightarrow 22$

Table 3. Refinement

Refinement on F^2	H atoms constrained to parent site
$R[F^2 > 2\sigma(F^2)] = 0.0483$ (obs data)	2296 unique reflections
$wR(F^2) = 0.0910$ (obs data)	451 parameters
$S = 1.224$ (obs data)	724 restraints
$R[F^2 > 2\sigma(F^2)] = 0.0741$ (uniq data)	$\lvert\Delta/\sigma\rvert_{max} = 0.001$
$wR(F^2) = 0.1017$ (uniq data)	$\Delta\rho_{max} = 0.354$ e Å^{-1}

S = 1.142 (uniq data)	$\Delta\rho_{min}$ = -0.256 e Å^{-1}
Flack parameter: 0.038 (15)	Extinction correction: none
Absolute structure[60]	Calculated weights $w = 1/[\sigma^2(F_o^2) + 0.154$ where $P = (F_o^2 + 2F_c^2)/3$

Table 4. Atomic site parameters for dwcm003f

	x	*y*	*z*	*U*
Br1	-0.1992 (9)	0.8493	0.0767 (3)	0.0563 (13)
O1	0.5174 (14)	0.2757 (12)	0.3126 (5)	0.039 (2)
C2	0.7373 (17)	0.3442 (11)	0.3350 (5)	0.043 (3)
C3	0.8475 (15)	0.3863 (12)	0.2851 (5)	0.041 (3)
H3	0.9986	0.4350	0.2882	0.049
C3A	0.7002 (15)	0.3461 (10)	0.2259 (5)	0.032 (3)
C4	0.7143 (17)	0.3591 (12)	0.1597 (5)	0.033 (3)
H4	0.8492	0.4047	0.1449	0.039
C5	0.5301 (18)	0.3048 (12)	0.1170 (5)	0.039 (3)
C6	0.3296 (17)	0.2371 (13)	0.1375 (5)	0.033 (3)
H6	0.2042	0.2003	0.1064	0.039
C7	0.3131 (16)	0.2233 (14)	0.2031 (6)	0.035 (3)
H7	0.1780	0.1776	0.2178	0.042
C7A	0.4998 (15)	0.2785 (11)	0.2463 (5)	0.034 (2)
O8	0.5136 (20)	0.3079 (14)	0.0504 (5)	0.041 (3)
C9	0.7208 (24)	0.3394 (23)	0.0232 (6)	0.049 (4)
H9A	0.6869	0.3385	-0.0241	0.074
H9B	0.8326	0.2439	0.0375	0.074
H9C	0.7850	0.4575	0.0378	0.074
C10	0.7945 (20)	0.3537 (14)	0.4060 (5)	0.043 (3)
H10	0.9547	0.4025	0.4156	0.051
C11	0.7942 (32)	0.1714 (18)	0.4365 (6)	0.050 (4)
H11A	0.8329	0.1834	0.4836	0.075

H11B	0.9083	0.0940	0.4199	0.075
H11C	0.6412	0.1169	0.4263	0.075
C12	0.6356 (26)	0.4817 (19)	0.4395 (6)	0.046 (4)
H12A	0.4738	0.4422	0.4279	0.055
H12B	0.6757	0.4709	0.4870	0.055
C13	0.6563 (22)	0.6770 (18)	0.4202 (6)	0.041 (4)
H13A	0.5965	0.7557	0.4526	0.049
H13B	0.8206	0.7072	0.4200	0.049
O14	0.5282 (18)	0.7132 (15)	0.3560 (5)	0.046 (3)
C15	0.3100 (19)	0.7738 (12)	0.3535 (5)	0.041 (3)
O16	0.2201 (23)	0.8108 (20)	0.4005 (5)	0.054 (4)
C17	0.1954 (17)	0.7883 (11)	0.2855 (5)	0.032 (3)
C18	-0.0240 (18)	0.8709 (13)	0.2751 (5)	0.040 (3)
H18	-0.0920	0.9144	0.3109	0.048
C19	-0.1399 (16)	0.8885 (11)	0.2130 (5)	0.039 (3)
H19	-0.2874	0.9440	0.2059	0.047
C20	-0.0392 (15)	0.8246 (7)	0.1614 (4)	0.041 (3)
C21	0.1767 (15)	0.7427 (11)	0.1705 (5)	0.033 (3)
H21	0.2436	0.6994	0.1345	0.040
C22	0.2923 (17)	0.7252 (13)	0.2325 (5)	0.038 (3)
H22	0.4397	0.6695	0.2391	0.045
Br1'	-0.1809 (10)	0.9272 (11)	0.0755 (3)	0.0726 (15)
O1'	0.5261 (14)	0.3606 (12)	0.3134 (5)	0.042 (3)
C2'	0.7441 (16)	0.4309 (11)	0.3363 (5)	0.041 (3)
C3'	0.8558 (15)	0.4738 (13)	0.2866 (5)	0.040 (4)
H3'	1.0062	0.5237	0.2900	0.048
C3A'	0.7102 (14)	0.4318 (10)	0.2272 (5)	0.039 (3)
C4'	0.7269 (15)	0.4447 (13)	0.1611 (5)	0.033 (4)
H4'	0.8618	0.4914	0.1467	0.039
C5'	0.5443 (17)	0.3885 (12)	0.1181 (5)	0.046 (3)
C6'	0.3443 (17)	0.3195 (14)	0.1379 (5)	0.041 (5)

H6'	0.2205	0.2816	0.1066	0.049
C7'	0.3253 (17)	0.3058 (14)	0.2037 (6)	0.040 (3)
H7'	0.1902	0.2590	0.2180	0.047
C7A'	0.5104 (15)	0.3628 (11)	0.2471 (5)	0.039 (3)
O8'	0.5322 (19)	0.3919 (15)	0.0515 (5)	0.049 (3)
C9'	0.7420 (24)	0.4290 (24)	0.0260 (6)	0.046 (4)
H9A'	0.7126	0.4279	-0.0214	0.069
H9B'	0.8564	0.3361	0.0410	0.069
H9C'	0.8004	0.5484	0.0410	0.069
C10'	0.8007 (20)	0.4419 (14)	0.4073 (5)	0.046 (3)
H10'	0.9612	0.4898	0.4170	0.055
C11'	0.7986 (37)	0.2589 (20)	0.4377 (7)	0.074 (6)
H11D	0.8368	0.2703	0.4848	0.111
H11E	0.9125	0.1811	0.4210	0.111
H11F	0.6453	0.2051	0.4272	0.111
C12'	0.6431 (24)	0.5697 (19)	0.4409 (6)	0.047 (4)
H12C	0.4815	0.5293	0.4299	0.056
H12D	0.6849	0.5593	0.4884	0.056
C13'	0.6596 (23)	0.7647 (20)	0.4219 (6)	0.050 (4)
H13C	0.5968	0.8420	0.4540	0.060
H13D	0.8234	0.7973	0.4222	0.060
O14'	0.5337 (19)	0.8008 (14)	0.3575 (5)	0.049 (3)
C15'	0.3155 (19)	0.8615 (12)	0.3539 (5)	0.050 (3)
O16'	0.2219 (24)	0.9006 (19)	0.4000 (5)	0.074 (5)
C17'	0.2047 (18)	0.8735 (11)	0.2853 (5)	0.037 (3)
C18'	-0.0179 (17)	0.9502 (15)	0.2740 (5)	0.041 (3)
H18'	-0.0900	0.9912	0.3093	0.050
C19'	-0.1310 (16)	0.9655 (15)	0.2116 (4)	0.044 (3)
H19'	-0.2807	1.0169	0.2038	0.052
C20'	-0.0239 (15)	0.9052 (11)	0.1605 (5)	0.043 (3)
C21'	0.1951 (16)	0.8294 (13)	0.1707 (5)	0.041 (3)

H21'	0.2662	0.7886	0.1351	0.050
C22'	0.3081 (16)	0.8140 (13)	0.2331 (5)	0.035 (3)
H22'	0.4578	0.7624	0.2403	0.042

Table 5. Anisotropic atomic displacement parameters for dwcm003f

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br1	0.0435 (14)	0.087 (4)	0.035 (2)	0.000 (2)	-0.0086 (12)	0.006 (2)
O1	0.038 (4)	0.047 (6)	0.032 (4)	-0.016 (4)	0.002 (3)	-0.013 (5)
C2	0.038 (5)	0.053 (8)	0.035 (4)	-0.007 (6)	-0.008 (4)	-0.009 (6)
C3	0.030 (4)	0.057 (9)	0.033 (4)	-0.008 (6)	-0.003 (4)	-0.015 (8)
C3A	0.028 (4)	0.034 (6)	0.032 (4)	-0.016 (5)	-0.001 (4)	-0.007 (5)
C4	0.032 (5)	0.038 (9)	0.026 (5)	-0.015 (7)	-0.003 (4)	-0.005 (7)
C5	0.034 (5)	0.050 (8)	0.031 (5)	-0.016 (5)	-0.008 (4)	0.000 (5)
C6	0.026 (5)	0.033 (10)	0.036 (5)	-0.007 (5)	-0.003 (4)	-0.008 (6)
C7	0.029 (4)	0.038 (7)	0.037 (4)	-0.011 (4)	0.003 (4)	-0.006 (5)
C7A	0.033 (4)	0.038 (6)	0.032 (4)	-0.012 (4)	0.004 (3)	-0.012 (5)
O8	0.036 (4)	0.054 (7)	0.029 (4)	-0.018 (5)	-0.010 (4)	-0.003 (5)
C9	0.042 (6)	0.072 (11)	0.028 (6)	-0.024 (7)	-0.014 (5)	0.000 (7)
C10	0.041 (5)	0.051 (8)	0.034 (5)	0.000 (7)	-0.002 (4)	0.008 (7)
C11	0.084 (9)	0.032 (9)	0.033 (7)	-0.026 (9)	0.002 (7)	-0.010 (7)
C12	0.047 (6)	0.059 (9)	0.026 (5)	0.003 (6)	-0.014 (5)	-0.003 (6)
C13	0.043 (5)	0.052 (9)	0.024 (6)	-0.003 (7)	-0.008 (5)	-0.006 (7)
O14	0.036 (4)	0.066 (8)	0.033 (4)	0.004 (5)	-0.002 (3)	0.008 (5)
C15	0.036 (5)	0.049 (8)	0.039 (5)	-0.005 (6)	0.004 (4)	0.010 (6)
O16	0.043 (6)	0.087 (11)	0.031 (5)	0.012 (6)	0.005 (5)	0.007 (6)
C17	0.025 (4)	0.037 (8)	0.033 (4)	-0.017 (5)	0.002 (4)	0.001 (5)
C18	0.033 (4)	0.044 (8)	0.043 (5)	-0.009 (6)	0.006 (4)	0.004 (7)
C19	0.025 (4)	0.044 (8)	0.047 (4)	-0.008 (6)	0.000 (4)	0.003 (6)
C20	0.035 (5)	0.051 (8)	0.034 (5)	-0.012 (5)	0.001 (4)	0.015 (6)

C21	0.032 (4)	0.040 (8)	0.030 (4)	-0.007 (5)	0.011 (4)	0.011 (6)
C22	0.030 (5)	0.047 (8)	0.035 (5)	-0.010 (5)	0.004 (4)	0.008 (6)
Br1'	0.053 (2)	0.122 (4)	0.040 (2)	-0.006 (2)	-0.0018 (13)	-0.001 (3)
O1'	0.034 (3)	0.070 (7)	0.025 (3)	-0.012 (5)	0.010 (3)	-0.014 (6)
C2'	0.031 (5)	0.060 (9)	0.031 (4)	-0.006 (6)	0.004 (4)	-0.014 (6)
C3'	0.033 (5)	0.061 (10)	0.027 (5)	-0.006 (6)	0.005 (4)	-0.017 (6)
C3A'	0.027 (4)	0.062 (8)	0.028 (4)	-0.016 (5)	0.008 (4)	-0.011 (6)
C4'	0.015 (5)	0.056 (11)	0.028 (5)	-0.006 (6)	0.006 (4)	-0.006 (7)
C5'	0.028 (5)	0.083 (9)	0.030 (4)	-0.020 (6)	0.012 (4)	-0.006 (7)
C6'	0.024 (5)	0.062 (14)	0.035 (5)	-0.011 (6)	-0.004 (4)	-0.011 (6)
C7'	0.031 (4)	0.060 (8)	0.031 (4)	-0.014 (5)	0.015 (4)	-0.013 (5)
C7A'	0.030 (3)	0.065 (7)	0.025 (3)	-0.014 (5)	0.012 (3)	-0.011 (5)
O8'	0.031 (4)	0.085 (9)	0.031 (4)	-0.024 (6)	0.007 (3)	-0.004 (6)
C9'	0.045 (6)	0.065 (10)	0.030 (6)	-0.028 (7)	0.016 (5)	-0.002 (7)
C10'	0.041 (5)	0.066 (9)	0.030 (5)	0.005 (6)	0.004 (4)	-0.005 (6)
C11'	0.120 (12)	0.060 (11)	0.041 (8)	0.000 (13)	0.007 (10)	-0.016 (8)
C12'	0.040 (6)	0.075 (10)	0.029 (6)	0.001 (8)	0.014 (5)	-0.003 (6)
C13'	0.043 (5)	0.078 (9)	0.028 (6)	0.007 (7)	0.003 (4)	0.000 (7)
O14'	0.038 (4)	0.080 (9)	0.031 (4)	0.005 (5)	0.006 (3)	-0.002 (5)
C15'	0.035 (4)	0.077 (9)	0.038 (4)	0.004 (7)	0.007 (4)	0.001 (7)
O16'	0.047 (6)	0.137 (15)	0.038 (5)	0.015 (9)	0.012 (5)	-0.014 (9)
C17'	0.028 (4)	0.052 (7)	0.033 (4)	-0.015 (6)	0.007 (3)	0.003 (6)
C18'	0.034 (5)	0.058 (9)	0.035 (5)	-0.005 (6)	0.016 (4)	0.005 (6)
C19'	0.028 (5)	0.055 (8)	0.047 (5)	-0.009 (5)	0.002 (4)	0.009 (6)
C20'	0.041 (5)	0.054 (7)	0.034 (4)	-0.006 (6)	0.002 (4)	0.005 (6)
C21'	0.042 (4)	0.052 (9)	0.031 (4)	-0.011 (5)	0.008 (4)	0.009 (6)
C22'	0.023 (4)	0.046 (9)	0.037 (4)	-0.014 (5)	0.007 (4)	0.005 (5)

Table 6. Geometric parameters (Å, °) for dwcm003f

Br1—C20	1.890 (7)	Br1'—C20'	1.889 (7)
O1—C7A	1.374 (7)	O1'—C7A'	1.374 (7)
O1—C2	1.404 (7)	O1'—C2'	1.401 (7)
C2—C3	1.337 (8)	C2'—C3'	1.340 (8)
C2—C10	1.473 (8)	C2'—C10'	1.474 (8)
C3—C3A	1.437 (8)	C3'—C3A'	1.437 (8)
C3A—C7A	1.397 (7)	C3A'—C7A'	1.393 (7)
C3A—C4	1.397 (8)	C3A'—C4'	1.398 (7)
C4—C5	1.362 (8)	C4'—C5'	1.363 (8)
C5—O8	1.379 (7)	C5'—O8'	1.380 (7)
C5—C6	1.399 (8)	C5'—C6'	1.394 (8)
C6—C7	1.390 (8)	C6'—C7'	1.395 (8)
C7—C7A	1.379 (8)	C7'—C7A'	1.379 (8)
O8—C9	1.430 (7)	O8'—C9'	1.434 (7)
C10—C11	1.488 (12)	C10'—C11'	1.492 (12)
C10—C12	1.558 (11)	C10'—C12'	1.554 (11)
C12—C13	1.506 (13)	C12'—C13'	1.499 (13)
C13—O14	1.466 (8)	C13'—O14'	1.463 (8)
O14—C15	1.350 (8)	O14'—C15'	1.348 (7)
C15—O16	1.209 (7)	C15'—O16'	1.207 (7)
C15—C17	1.486 (8)	C15'—C17'	1.489 (8)
C17—C22	1.391 (9)	C17'—C22'	1.390 (9)
C17—C18	1.413 (8)	C17'—C18'	1.413 (8)
C18—C19	1.383 (8)	C18'—C19'	1.381 (8)
C19—C20	1.381 (8)	C19'—C20'	1.382 (8)
C20—C21	1.392 (8)	C20'—C21'	1.391 (8)
C21—C22	1.380 (9)	C21'—C22'	1.381 (9)

C7A—O1—C2	105.5 (5)	C7A'—O1'—C2'	105.6 (5)
C3—C2—O1	110.3 (5)	C3'—C2'—O1'	110.2 (5)
C3—C2—C10	134.8 (7)	C3'—C2'—C10'	134.3 (6)
O1—C2—C10	114.9 (6)	O1'—C2'—C10'	115.5 (6)
C2—C3—C3A	108.8 (5)	C2'—C3'—C3A'	108.7 (5)
C7A—C3A—C4	119.6 (6)	C7A'—C3A'—C4'	119.7 (5)
C7A—C3A—C3	104.1 (5)	C7A'—C3A'—C3'	104.3 (5)
C4—C3A—C3	136.3 (6)	C4'—C3A'—C3'	136.0 (6)
C5—C4—C3A	118.4 (6)	C5'—C4'—C3A'	118.1 (6)
C4—C5—O8	126.3 (6)	C4'—C5'—O8'	125.7 (6)
C4—C5—C6	122.0 (6)	C4'—C5'—C6'	122.2 (6)
O8—C5—C6	111.7 (6)	O8'—C5'—C6'	112.2 (6)
C7—C6—C5	120.3 (6)	C5'—C6'—C7'	120.3 (6)
C7A—C7—C6	117.6 (6)	C7A'—C7'—C6'	117.3 (6)
O1—C7A—C7	126.5 (6)	O1'—C7A'—C7'	126.4 (6)
O1—C7A—C3A	111.3 (5)	O1'—C7A'—C3A'	111.3 (5)
C7—C7A—C3A	122.2 (6)	C7'—C7A'—C3A'	122.3 (6)
C5—O8—C9	117.2 (6)	C5'—O8'—C9'	116.7 (6)
C2—C10—C11	111.9 (6)	C2'—C10'—C11'	111.3 (7)
C2—C10—C12	114.3 (6)	C2'—C10'—C12'	114.9 (6)
C11—C10—C12	108.6 (8)	C11'—C10'—C12'	108.5 (8)
C13—C12—C10	112.7 (8)	C13'—C12'—C10'	113.5 (8)
O14—C13—C12	111.6 (8)	O14'—C13'—C12'	112.0 (9)
C15—O14—C13	117.3 (7)	C15'—O14'—C13'	117.8 (7)
O16—C15—O14	124.2 (7)	O16'—C15'—O14'	124.6 (7)
O16—C15—C17	124.6 (7)	O16'—C15'—C17'	124.4 (7)
O14—C15—C17	111.2 (6)	O14'—C15'—C17'	111.0 (6)
C22—C17—C18	119.1 (6)	C22'—C17'—C18'	119.3 (6)
C22—C17—C15	123.5 (6)	C22'—C17'—C15'	123.7 (6)
C18—C17—C15	117.4 (6)	C18'—C17'—C15'	117.1 (6)
C19—C18—C17	120.2 (6)	C19'—C18'—C17'	120.2 (6)

C20—C19—C18	119.4 (6)	C18'—C19'—C20'	119.3 (6)
C19—C20—C21	121.4 (6)	C19'—C20'—C21'	121.5 (6)
C19—C20—Br1	119.0 (5)	C19'—C20'—Br1'	118.7 (5)
C21—C20—Br1	119.6 (6)	C21'—C20'—Br1'	119.8 (6)
C22—C21—C20	119.2 (6)	C22'—C21'—C20'	119.3 (7)
C21—C22—C17	120.7 (6)	C21'—C22'—C17'	120.6 (6)

Computer programs

Data collection: COLLECT.[55] Cell refinement: DENZO-SMN.[55] Data reduction: DENZO-SMN.[55] Program(s) used to solve structure: Siemens SHELXTL.[57] Program(s) used to refine structure: Siemens SHELXTL.[57] Molecular graphics: Siemens SHELXTL.[57] Software used to prepare material for publication: Siemens SHELXTL,[57] publCIF,[61] printCIF for Word.[62]

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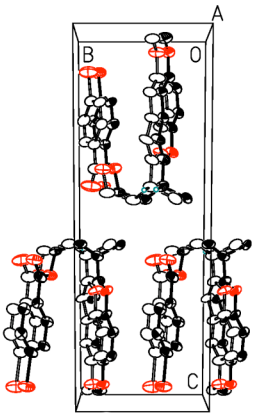
61. Westrip, S. P. *publCIF*, version 1.0c; International Union of Crystallography, Abbey Square: Chester, U. K., 2006.

62. *prinfCIF for word*; International Union of Crystallography, Abbey Square: Chester, U. K., 2005.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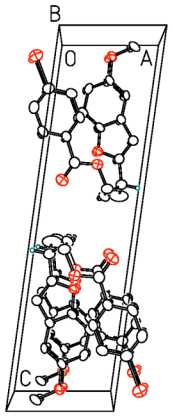
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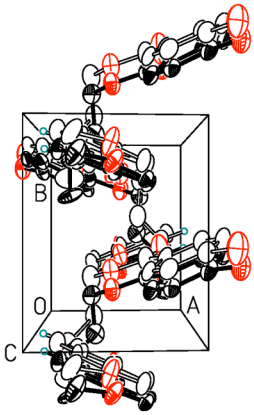
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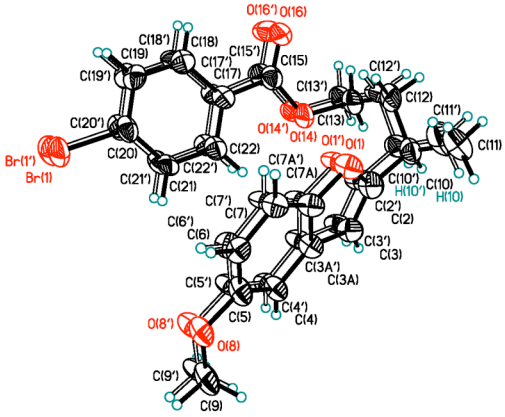
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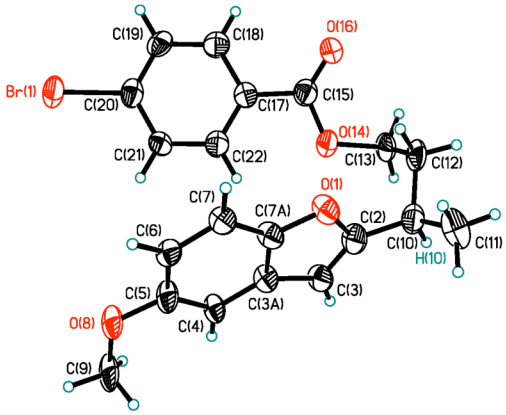
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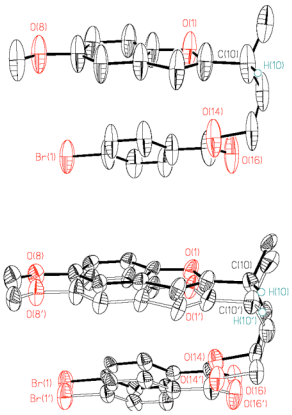
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O(14')
O(15)
Br(1')
O(16')

Chapter 4

Total Synthesis of (+)-Frondosin B

I. Introduction

Members of the frondosins, part of the sesquiterpene class of natural products (*Figure 1*) were first isolated by Freyer and co-workers from the marine sponge *Dysidea frondosa* off the waters of Pohnpei in the Federated States of Micronesia.[1] Significantly, each of the frondosins exhibit inhibition of interleukin-8 (IL-8) receptors and protein kinase C (PKC) with IC_{50} values in the low micromolar range as found in preliminary *in vitro* biological investigations.[1b,2] As pro-inflammatory cytokines (such as IL-8) act as a chemoattractant to promote the accumulation and activation of neutrophils, the resulting increase of monocyte superoxide anion production has been implicated in autoimmune disorders such as psoriasis, rheumatoid arthritis, osteoarthritis and many lung diseases.[3] It is also known that this neutrophil-activating peptide plays an important role in tumor

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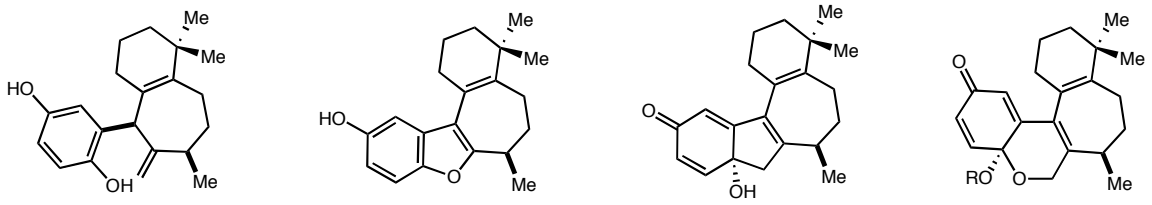
1. (a) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron*, **1997**, *53*, 5047. (b) For an independent claim for the discovery of frondosins A and D, see: Hallock, Y. F.; Cardellina, J. H.; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153.

2. Additionally, frondosins A and D were shown to demonstrate moderate HIV-inhibitory activity: Lane, B. R.; Lore, K.; Bock, P. J.; Andersson, J.; Coffey, M. J.; Strieter, R. M.; Markovitz, D. M. *J. Virol.* **2001**, *75*, 8195.

3. (a) Seitz, M.; Dewald, B.; Gerber, N.; Baggiolini, M. *J. Clin. Invest.* **1991**, 87, 463. (b) Miller, E. J.; Cohen, A. B.; Nagao, D.; Griffith, R. J.; Maunder, R. J.; Martin, T. R.; Weiner-Kronish, J. P. Sticherling, M.; Christophers, E.; Matthay, M. *Am. Rev. Respir. Dis.* **1992**, 146, 247.



frondosin	IL-8 Rα	IL-8 Rβ	PKC-α
A	3.4	3.2	1.8
B	9.6	11	4.8
C	84	26	21
D	98	11	26
E	64	37	31

Figure 1. The frondosin family of marine natural products and their biological activity (IC_{50} = μM)

progression and metastasis in several human cancers.[4] Thus, IL-8 receptor antagonists represent a promising lead compound for the development of novel anti-inflammatory agents and cancer therapies.

The frondosins possess a novel sesquiterpenoid skeleton that bear an incidental resemblance to one another with a unifying structural feature that consists of a central bicyclo[5.4.0] ring system appended to variously permuted hydroquinone moieties.[5] Their relative structural features were determined by extensive NMR experiments with supportive IR and mass spectral data. One major difference in this family of compounds was found in the optical rotations of the isolated species, which revealed that all the

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4. (a) Brat, D. J.; Bellail, A. C.; Van Meir, E. G. *Neuro-Oncology* **2005**, *7*, 122. (b) Zhu, Y. M.; Webster, S. J.; Flower, D.; Woll, P. J. *Br. J. Cancer* **2004**, *91*, 1970. (c) Yuan, A.; Chen, J. J.; Yao, P. L.; Yang, P. C. *Front Biosci.* **2005**, 853.

5. For a review of marine sesquiterpenes and quinones, see: Capon, R. J. In *Studies in Natural Products Chemistry*; Rahman, A,U., Ed.; Elsevier: New York, 1995; Vol. 15, p 289.

frondosins (except for B) exist in both enantiomeric forms in nature. Notably, the relative stereochemistries of the frondosins were established primarily through NMR studies, though the absolute configurations were not initially assigned.

II. Previous Synthetic Efforts towards Frondosin B

The frondosins have inspired a number of research groups to pursue their total syntheses given their interesting chemical architecture and pharmacological activity. To date, only frondosin B has been synthetically made, whilst the syntheses of frondosins A[6] and C[7] remain works in progress.

The first total synthesis of frondosin B was reported by Danishefsky and co-workers.[8] In this initial racemic synthesis, a number of strategies were implemented from which there came two successful programs. Both retrosynthetic plans were convergent on a common tricyclic cycloheptanone intermediate (*Figure 2(b)*) that then diverged in regards to installation of the final cyclohexene ring (ring A, *Figure 2(a)*). Construction of tricyclic intermediate **1** occurred via initial formation of a known acetyl benzofuran[9] and subsequent elaboration by a Wittig four-carbon homologation and an intramolecular Friedel-Crafts acylation to form the central B-ring (*Figure 2 (a)*). Formation of the final A-ring occurred by functionalization of the ketone precursor towards either a homoprenyl group for an acid-

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6. Hu, Y.; Trost, B. M. *Abstr. Pap. Am. Chem. Soc.* **2006**, *231*, 2.

7. (a) Martinez, I.; Alford, P. E.; Ovaska, T. V. *Org. Lett.* **2005**, *7*, 1133. (b) Li, X.; Kyne, R. E.; Ovaska, T. V. *Org. Lett.* **2006**, *8*, 5153.

8. Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761.

9. Landelle, H.; Godard, A. M.; Laduree, D.; Chenu, E.; Robba, M. *Chem. Pharm. Bull.* **1991**, *39*, 3057.

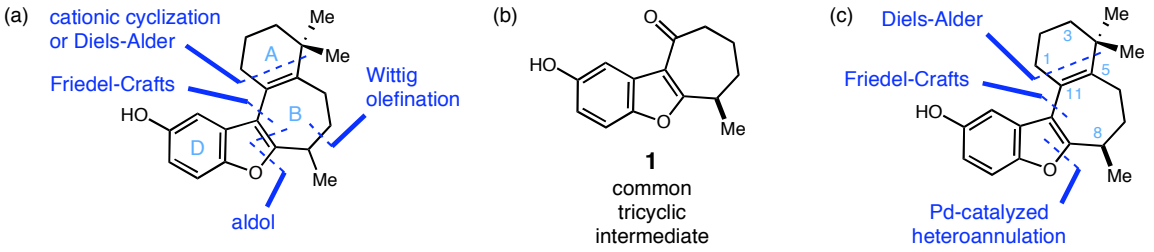

Figure 2. Danishefsky's strategies for the (a) racemic and (c) enantiospecific synthesis of frondosin B via (b) a common synthetic intermediate

induced cyclization or into a diene to participate in a Diels-Alder reaction. Having completed two full racemic syntheses of frondosin B, efforts were then shifted towards the enantiospecific preparation of the natural product.

In their third total synthesis, Danishefsky and co-workers aimed to determine the absolute configuration of the naturally occurring enantiomer of frondosin B by correlation to their enantiomerically-defined synthetic product.[10] On the basis of their previous experiences, a modified strategy was adopted to include the construction of the benzofuran from a chiral precursor (*Figure 2(c)*). Central to this new approach was the introduction of the *C*-8 methyl stereocenter of known absolute configuration by way of a Sharpless asymmetric epoxidation, which would ultimately converge to the same tricyclic intermediate (**1**) from the racemic route (*Figure 2(b)*).

As shown in Scheme 1, the synthesis of (+)-frondosin B commenced with the epoxidation of a known allylic alcohol (**2**)[11] to provide the corresponding (*S*,*S*)-epoxy alcohol product **3**. Regiospecific opening of the epoxide via C-methylation serves as a method for introducing the *C*-8 methyl stereocenter with *R* configuration in product **4**.

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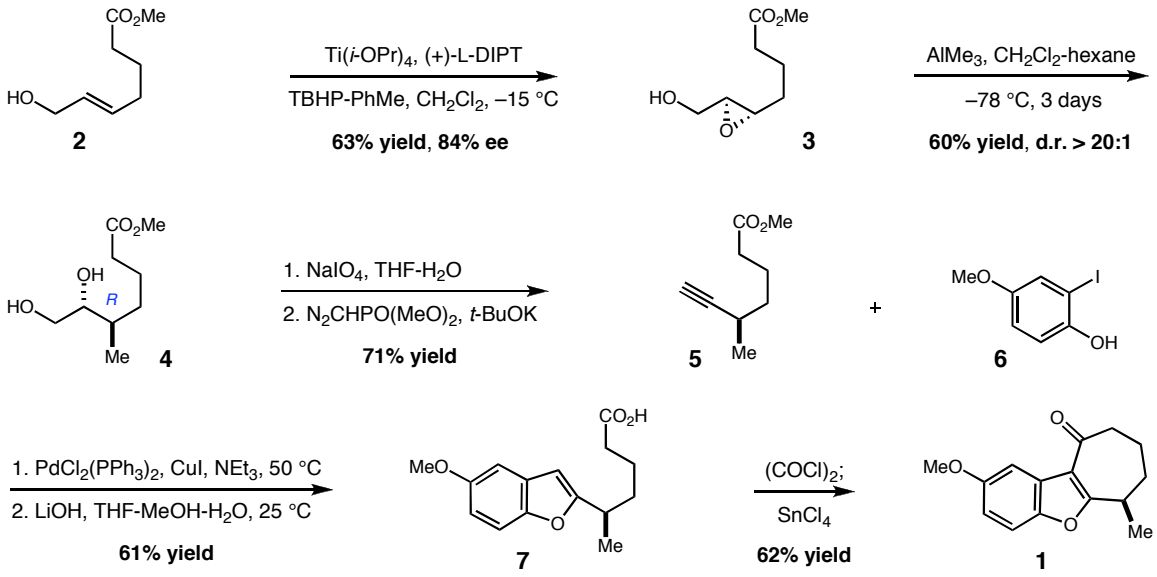
10. Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878.

11. Patterson, J. W. *Synthesis* **1985**, 337.

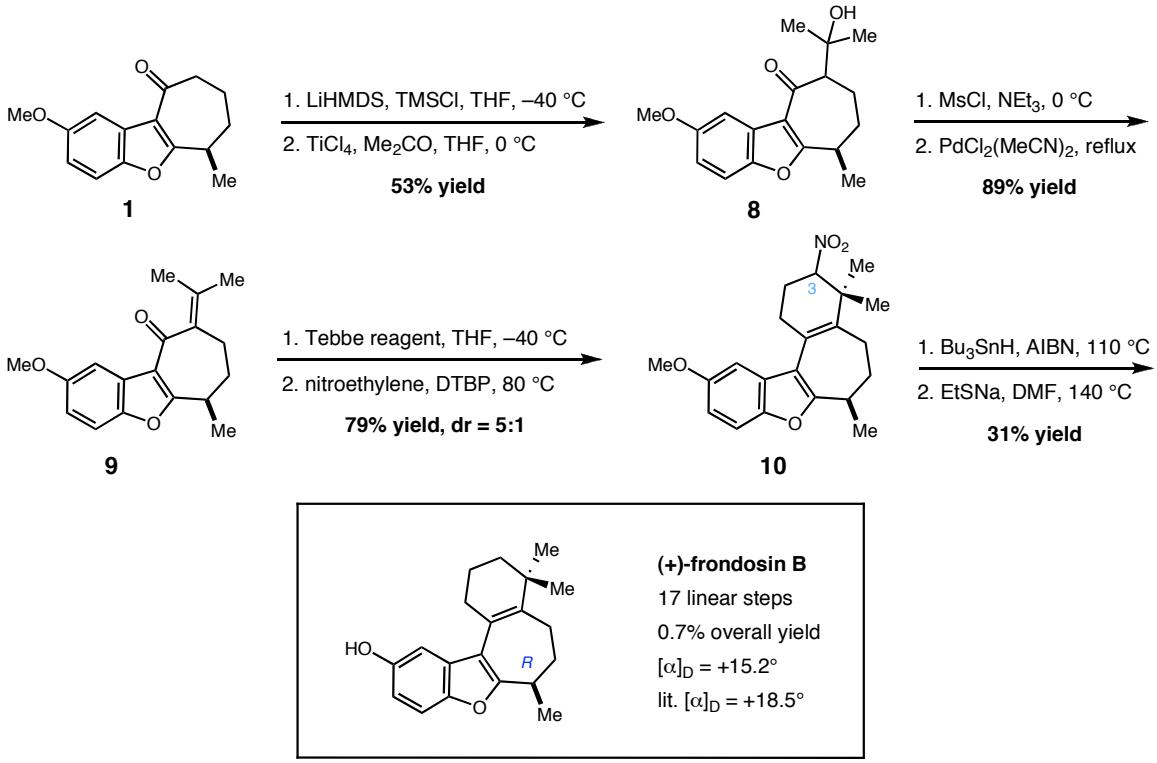
Scheme 1. Danishefsky's construction of the *C*-8 methyl stereocenter and the benzofuran moiety



Oxidative cleavage of diol **4** provides an aldehyde intermediate, which upon treatment with Gilbert reagent, smoothly leads to formation of terminal alkyne **5**. Subsequent construction of the benzofuran framework was accomplished in a one-pot procedure via a palladium-catalyzed Sonogashira coupling reaction of alkyne **5** and 2-iodo-4-methoxyphenol (**6**) with successive heteroannulation. Saponification of the resulting ester yields carboxylic acid **7**, which is activated as an acyl chloride to then participate in an intramolecular Friedel-Crafts acylation to form the central cycloheptenone ring. At this point, this asymmetric synthesis then intersects the previous racemic route towards frondosin B.

Completion of the synthesis then proceeded by installation of the final ring of frondosin B via a Diels-Alder cyclization (*Scheme 2*). To prepare the diene component for the Diels-Alder reaction, the cycloheptenone intermediate **1** was subjected first to a Mukaiyama reaction with acetone and then a dehydration-methylenation sequence. Reaction with nitroethylene afforded the A-ring in a 5:1 mixture of nitro stereoisomers (**10**) at *C*-3. Final unmasking of this cycloadduct (by denitration and *O*-demethylation)

Scheme 2. Danishefsky's synthesis and structural assignment of (+)-frondosin B.



produced a product that unambiguously matched all spectroscopic data for the reported natural product. Thus, in this 17-linear-step natural product synthesis of frondosin B, Danishefsky and co-workers established the absolute configuration of the secondary methyl stereocenter at *C*-8 to be of *R* configuration. [12]

Closely following Danishefsky's report, Trauner and co-workers disclosed an asymmetric total synthesis of frondosin B.[13] Their synthetic strategy (*Figure 3*) utilizes a similar approach for the construction of the benzofuran core but uniquely features a palladium-mediated coupling reaction to forge the central cycloheptadiene ring. Installation of the key *C*-8 stereocenter is again established via a Sharpless epoxidation

12. Beginning from 2-propyn-1-ol, Danshefsky's synthesis was 17 linear steps with an overall yield of 0.7%

13. Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569.

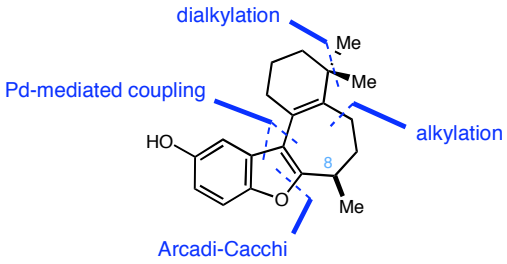
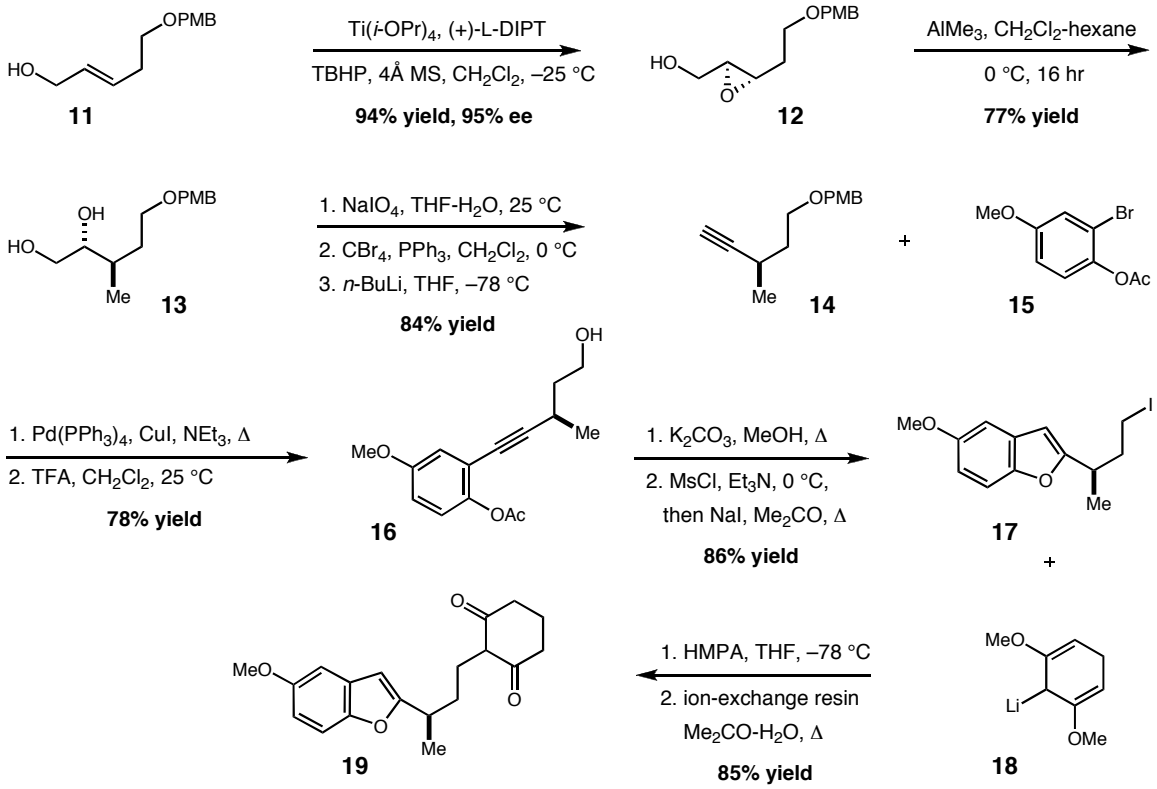


Figure 3. Trauner's strategy for the asymmetric synthesis of frondosin B

reaction with the intention of generating the *R*-configured natural product.

As shown in Scheme 3, Trauner's synthesis begins with the establishment of the asymmetric stereocenter by way of a Sharpless epoxidation and subsequent epoxide-opening reaction with a methylating reagent to yield **13**. Following a literature procedure, the known *R*-configured alkyne **14** was obtained in a straightforward manner via periodate

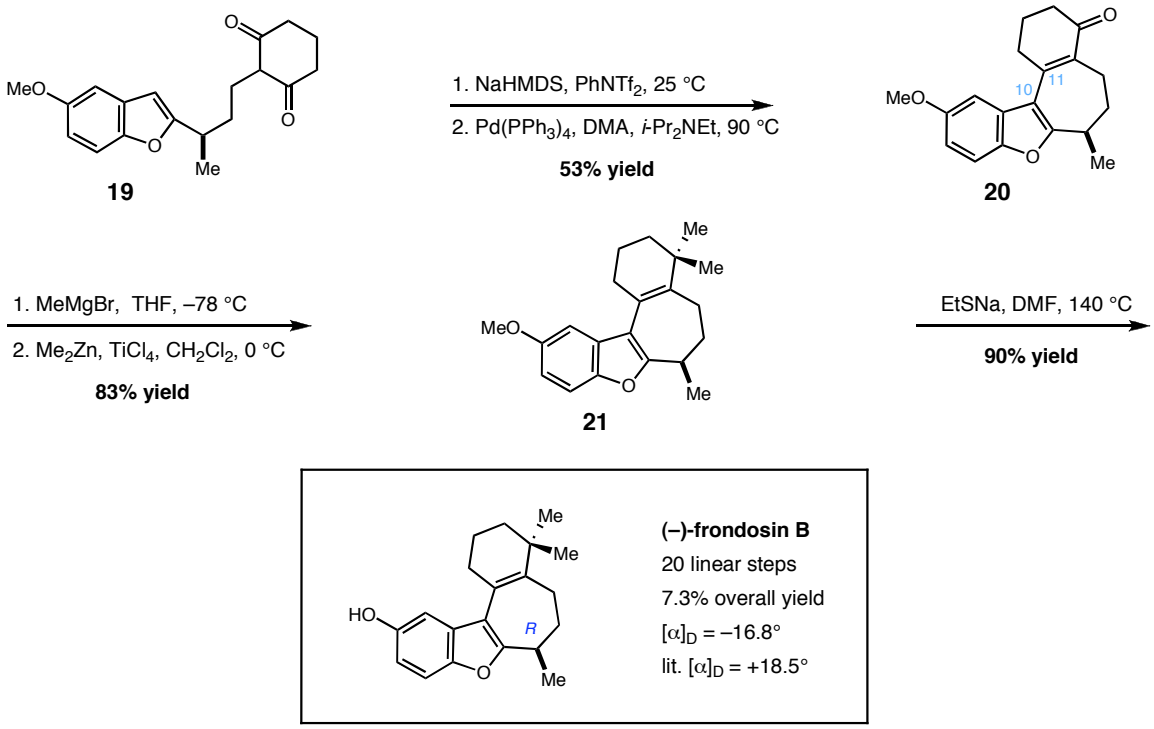
Scheme 3. Trauner's installation of the *C*-8 methyl stereocenter and key intermediate



cleavage of diol **13** and a Corey-Fuchs reaction with subsequent dehalogenation by a strong base.[14] Next, the benzofuran core was assembled in a three-step sequence that commenced with: (1) a Sonogashira coupling reaction, (2) followed by an acidic deprotection of the primary alcohol (to yield **16**), and (3) saponification of the phenolic acetate to initiate the Acardi-Cacchi cyclization reaction.[15] Conversion of the primary alcohol to iodide **17** sets the scene for an alkylation event with dimethoxylithiocyclohexadiene (**18**) to install the A-ring of frondosin B.

The key step of the synthesis was achieved via conversion of dione **19** to an enol triflate, which undergoes oxidative insertion with Pd(0), resulting in an intramolecular

Scheme 4. Trauner's key cyclization step and completion of the natural product

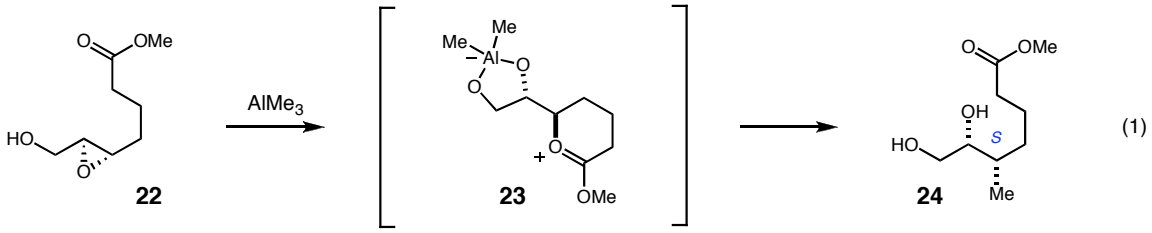


14. Murai, A.; Oka, T. *Tetrahedron* **1998**, *54*, 1.

15. Acardi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Martinelli, F. *J. Org. Chem* **1996**, *61*, 9280.

Heck reaction to forge the C10-C11 bond (**20**, *Scheme 4*). The synthesis was then concluded with a known dialkylation procedure[16] to install the *gem*-dimethyl group in **21**, followed by Danishefsky's deprotection protocol to yield frondosin B.[17] However, it was found that this synthetic material did not match the optical rotation of Danishefsky's *R*-configured product nor that of the naturally occurring product.

To reconcile this discrepancy, Trauner put forth a mechanistic supposition that Danishefsky and co-workers had unintentionally inverted the *C*-8 stereocenter and had instead synthesized the (*S*)-enantiomer of frondosin B.[18] It was proposed that the *C*-8 methyl stereocenter in Danishefsky's starting chiral building block (**24**) was unintentionally carried through the synthesis as the *S*-isomer because the nucleophilic opening of epoxy alcohol **22** proceeded by an unnoticed double inversion (*eq. 1*).[19] Though Trauner and co-workers employed an analogous methodology for setting their *C*-8 methyl stereocenter,



(1)

they assert that their epoxy alcohol substrate **11** lacks the ester functionality that was responsible for the neighboring group participation observed in the Danishefsky case (*Scheme 3*). On this basis, the original stereochemical assignment of naturally occurring frondosin B was reassigned by Trauner to have an absolute configuration of *S*.

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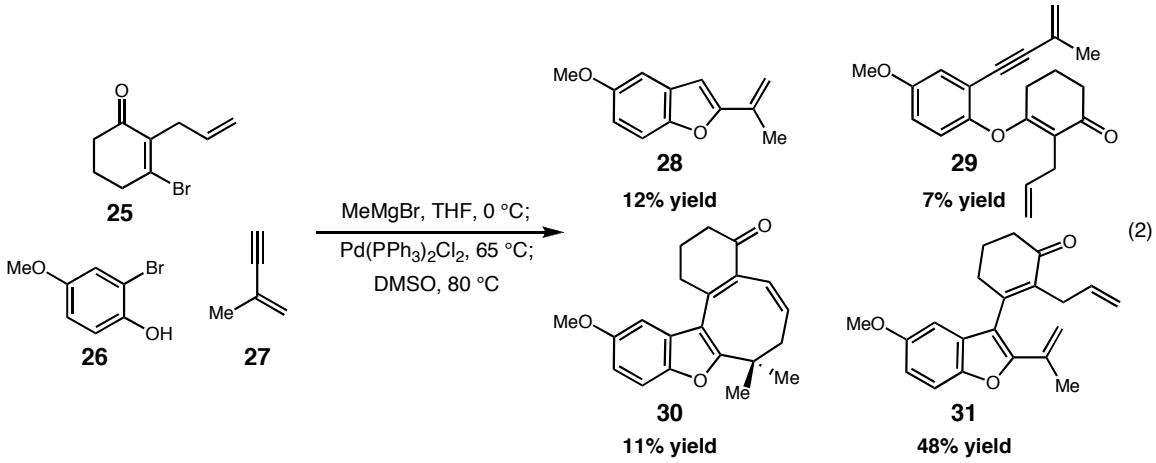
16. Reetz, M. T.; Westermann, J.; Steinbach, R. *J. Chem. Soc. Chem. Commun.* **1981**, 237.

17. Beginning from propane-1,3-diol, Trauner's synthesis was 20 linear steps with an overall yield of 7.3%

18. Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675.

19. This type of neighboring group participation by an ester is not unprecedented, see: Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.

The most recent synthesis of frondosin B has been executed by Flynn and co-workers in 2004.[20] In contrast to the other approaches to frondosin B, the primary focus in this strategy was to enable rapid and divergent access to analogs in order to aid SAR studies. To this end, a one-pot three-component coupling reaction was devised to build the racemic core of frondosin B in six steps from commercially available starting materials (*eq. 2*). In their key step, aryl bromide **26** is first subjected to deprotonation and then a



palladium-mediated coupling with 3-methylbutenyne (**27**) to yield an intermediary *o*-alkylnylphenolate. Successive addition of allyl-cyclohexadione **25** at elevated temperatures then instigates a heteroannulation and coupling reaction to give the benzofuran product **31** in 48% yield. Impressively, the desired compound is isolated as the major product (from a complex reaction mixture comprised of **28**, **29**, **30**, and **31**) in a key step that simultaneously forges four new bonds. The tetracyclic core is then completed via ring-closing metathesis (RCM) to form **32** (*Scheme 5*). Upon performing a selective hydrogenation of the central cycloheptatriene ring, the synthesis then converges onto Trauner's penultimate intermediate (±)-**21** in his synthesis of frondosin B. After a

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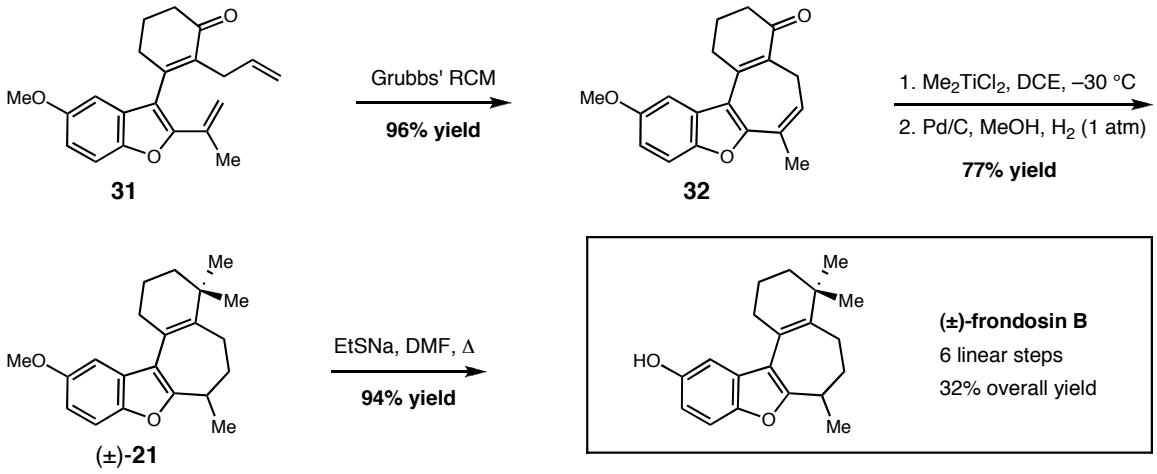
20. Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457.

Scheme 5. Flynn's completed synthesis of (±)-frondosin B



straightforward dialkylation and deprotection sequence, Flynn and co-workers complete an expedient synthesis of the racemic natural product.

III. Synthesis of (+)-Frondosin B

We were inspired to undertake an asymmetric synthesis of frondosin B on the basis of its intriguing structural features and notable biological activity. Additionally, we sought to unambiguously determine the absolute configuration of the *C*-8 methyl stereocenter and thereby resolve the current dissension in the literature.

Our synthetic strategy focused on addressing the key structural elements of frondosin B, namely the 2,3-disubstitued benzofuran moiety fused to a norsesquiterpenoid framework and the *C*-8 methyl stereocenter (*Figure 4*). Though frondosin B features only a single stereocenter, it inarguably remains a synthetic challenge in light of the previous strategies that used indirect means to introduce the enantio-defined methyl stereocenter. Thus, we envisioned our key disconnect to be across the C8-C9 bond, which will be forged

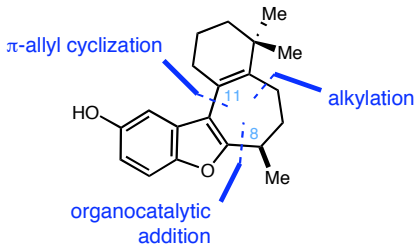


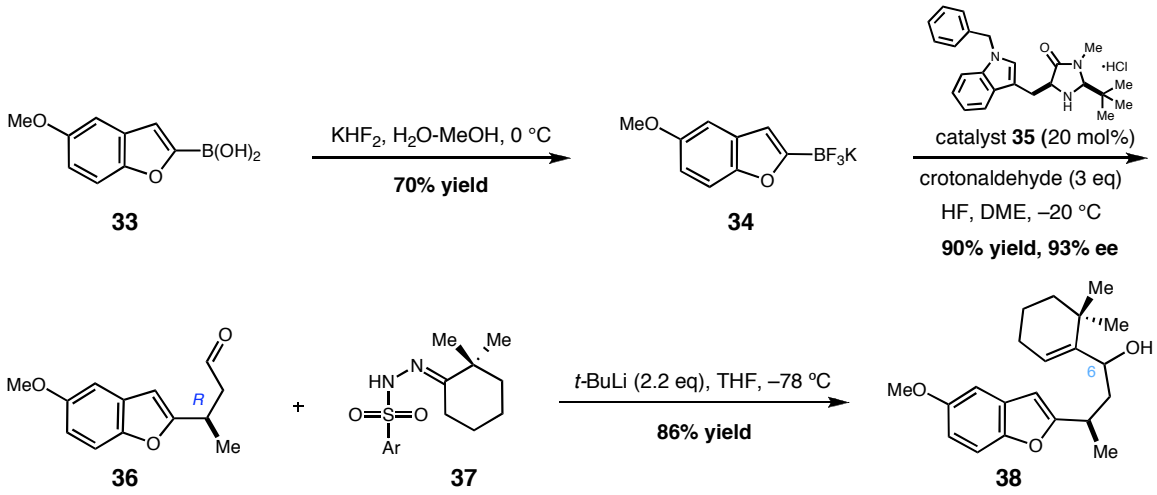
Figure 4. MacMillan's retrosynthesis of frondosin B.

by an enantioselective organocatalytic conjugate addition reaction (*vide* Chapter 3) that will concomitantly install the *C*-8 methyl stereocenter and establish the benzofuran structure. Like our predecessors, the other main retrosynthetic disconnection will be cleavage of the C10-C11 bond, which we hoped to establish via a metal-mediated π-allyl cyclization or alternatively an S_N2' reaction. The final A-ring will then be incorporated through an alkylation event with a cyclohexene ring already functionalized with the geminal methyl group in position. In this manner, a concise and convergent approach was designed to synthesize frondosin B.

Our synthetic endeavors commenced by the initial establishment of all requisite carbons in the natural product. As shown in Scheme 6, we began with the synthesis of the potassium trifluoroborate salt of 5-methoxybenzofuran (**34**), which was prepared from the commercially available boronic acid **33** using a modified Molander procedure.[21] The enantioselective organocatalytic conjugate addition was then carried out with **34** and excess crotonaldehyde in the presence of a chiral secondary amine catalyst **35** to efficiently install the *C*-8 stereocenter (**36**, 90% yield, 93% ee). Importantly, we were able to directly access the *R*-configured methyl stereocenter in a catalyst-controlled fashion (such that the opposite

21. (a) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, 68, 4302. (b) Molander, G. A.; Petrillo, D. E.; Landzberg, N. R.; Rohanna, J. C.; Biolatto, B. Synlett **2005**, 1763.

Scheme 6. Establishing the carbon framework of frondosin B



catalyst enantiomer provides the *S*-configured product).[22] Elaboration of the resultant aldehyde functionality was achieved by a Shapiro reaction with known hydrazone **37** (Ar = 2, 4, 6-triisopropylbenzene)[23] to afford allylic alcohol **38** as 1:1 mixture of diastereomers at *C*-6.[24] Thus, the carbon framework of frondosin B was concisely established in three linear steps.

With the carbon skeleton and *C*-8 stereocenter of frondosin B in place, the completion of its total synthesis required an intramolecular cyclization to construct the central B-ring. As the Shapiro reaction product **38** could be readily functionalized to an allylic acetate, we felt that subsequent formation of a metal π-allyl species might be susceptible to attack by the electron-rich benzofuran moiety (*Figure 5*). We anticipated this unprecedented intramolecular cyclization might take place at the less hindered site *C*-11 (*reaction a*, *Figure 5*) to generate the desired seven-membered ring adduct **39**. We felt

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22. The absolute configuration of intermediate **36** was unambiguously assigned as *R* on the basis of an X-ray crystal structure (*vide* Chapter 3) when employing (*S*,*S*)-catalyst **35**.

23. Pazos, Y.; Iglesias, B.; de Lera, A. L. *J. Org. Chem.* **2001**, *66*, 8483.

24. (a) Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L.; Capuano, L. A. *Tetrahedron Lett.* **1975**, 1811. (b) Shapiro, R. H. *Org. React.* **1976**, *23*, 405.

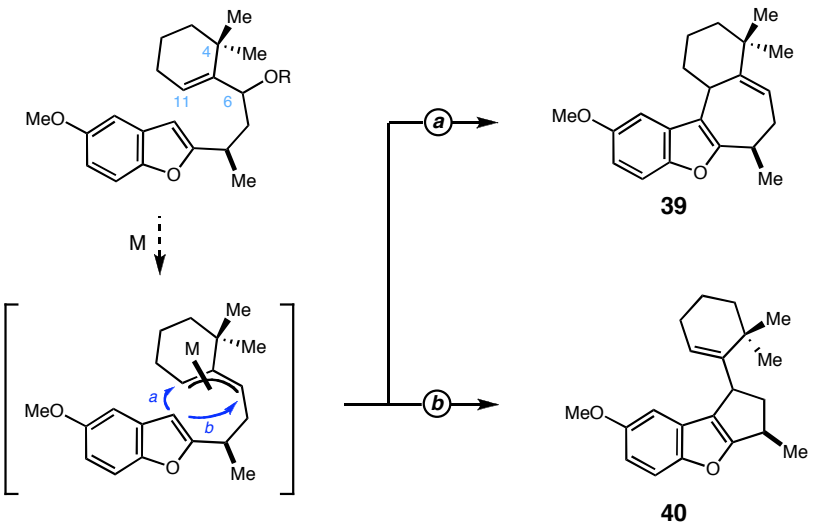

Figure 5. Potential regioselectivity issue in the proposed intramolecular cyclization

that the alternative, formation of a five-membered ring product (**40**) arising from addition to the *C*-6 position (*reaction b*, *Figure 5*), would be sufficiently disfavored due to the proximity of the adjacent *gem*-dimethyl substituents at *C*-4. Additionally, we hoped that the resultant C5-C6 olefin in **39** from the cyclization would migrate into the more thermodynamically favored position (between C5-C11) as part of this single-pot operation.

Along with Dr. Maud Reiter in our group, we sought to investigate this critical cyclization step. Our initial foray into π-allyl chemistry relied on palladium-mediated methods due to the vast number of successful examples that are known in the literature.[25,26] Experiments were set up with a cyclization precursor prepared via functionalization of allylic alcohol **38** to an acetate and also a methyl carbonate—both functionalities are

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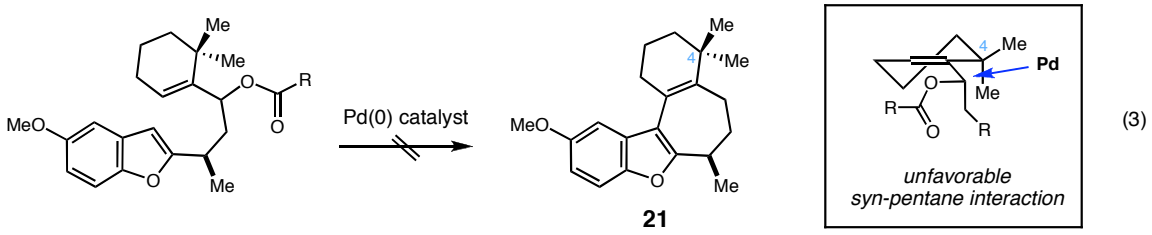
25. (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (d) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. (e) Trost, B. M. *Adv. Chem. Ser.* **1992**, 463.

26. (a) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 2nd ed.; Wiley & Sons: West Sussex, 2004; Chapter 4. (b) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999; Chapter 9.

known to react with palladium species to provide η^3-allyl complexes.[26] To our great surprise, our exploratory reactions using a variety of palladium(0) reagents and ligands, under a variety of reaction conditions (solvents and temperatures), all resulted in recovery of starting material (R = Me, OMe, *eq. 3*).[27] We surmised that formation of the η^3-



(3)

allylpalladium complex was inhibited by the adjacent geminal methyl groups, which impeded displacement of the leaving group due to an unfavorable *syn*-pentane interaction (*eq. 3*).

At this juncture, we reconsidered our palladium-mediated cyclization strategy due to our inability to access the requisite π-allyl intermediate. Because of the sterically demanding environment of the reaction site, it was apparent that the initial coordination to the C=C bond by palladium(0) and subsequent extrusion of the leaving group was not possible (*eq. 4(a)*).[28c] In contrast to this mechanism of oxidative addition by palladium, it is known that Group VI transition metals such as molybdenum and tungsten react though a different mechanistic manifold to form the π-allyl metal complex.[28] Since these metals are relatively more Lewis-acidic in character, association of the metal to an allylic substrate occurs first with the Lewis-basic carbonyl oxygen of the leaving group, which is then

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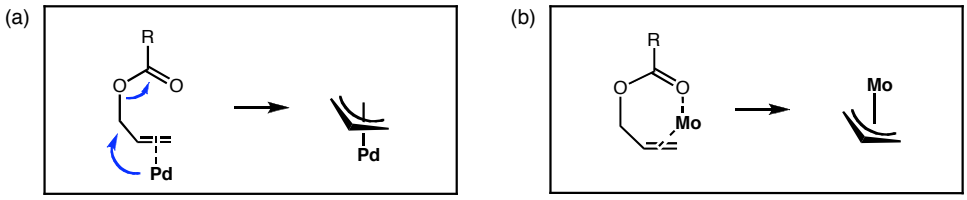
27. Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.

28. (a) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159. (b) Hughes, D. L.; Krska, S. W.; Reamer, R. A.; Mathre, D. J.; Sun, Y. In *Methodologies in Asymmetric Catalysis*; American Chemical Society: Washington, DC 2004; Vol. 880, pp 131–144. (c) Malkov, A. V.; Braxendale, I. R.; Dvorak, D.; Mansfield, D. J.; Kocovsky, P. *J. Org. Chem.* **1999**, *64*, 2737.



(4)

followed by coordination to the C=C bond (*eq. 4(b)*).[28b] Thus, we hypothesized that a molybdenum-mediated reaction could potentially avoid the prohibitive non-bonding interactions that were encountered in the palladium system and thereby give rise to the desired η^3-allylmolybdenum complex.

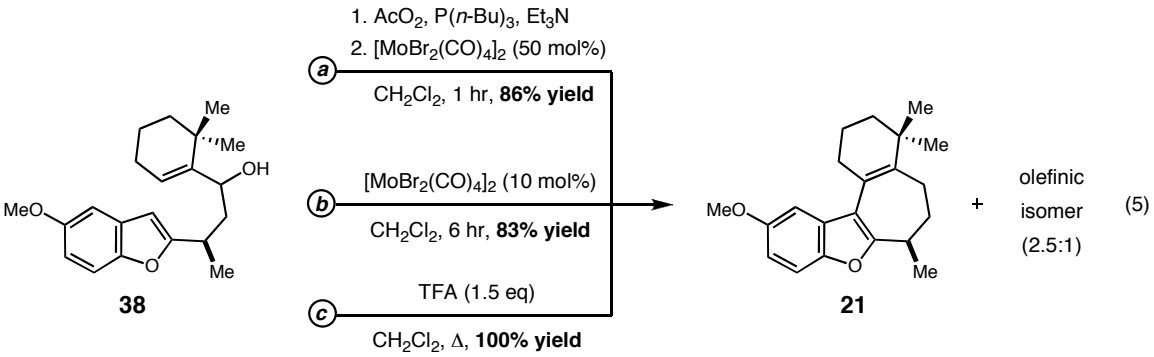
Armed with a new strategy for the proposed cyclization reaction, we prepared a molybdenum(II) catalyst known to be highly reactive in allylic substitution reactions,[28c] namely the dibromomolybdenum tetracarbonyl dimer.[29] Impressively, exposure of the acetyl derivative of **38** to this molybdenum catalyst (*reaction a*, *eq. 5*) resulted in an 86% yield (over two steps) of cycloheptadiene **21** as a single regioisomeric product. Additionally, the olefin had indeed migrated into conjugation and to the desired tetrasubstituted-position (C5-C11) as it is in the natural product. Though notably, an inseparable olefinic isomer was also obtained as part of this reaction mixture.[30] Delighted by this successful cyclization, we were encouraged to attempt a more ambitious direct cyclization of **38** (being that allylic alcohols have been shown to be reactive precursors to

29. Experimental evidence in reference 28c has suggested that Mo(II) is the reactive species in allylic substitution reactions and is thus supposed to be a more active catalyst relative to Mo(0) reagents.

30. Danishefsky (in reference 10) noted that **21** readily forms a 2.5:1 thermodynamic ratio with an olefin isomer (C=C between C1-C11) under acidic conditions.

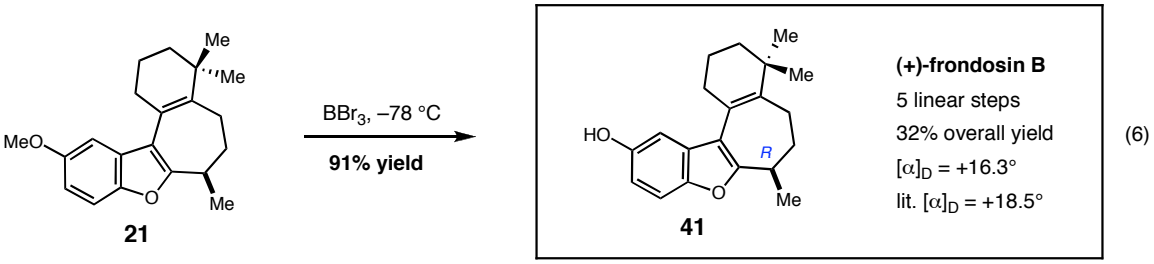
metal π-allyl complexes).[31] We were extremely pleased when subjection of **38** to the molybdenum catalyst efficiently provided the cyclized product **21** (*reaction b*, *eq. 5*).

Having also considered a potential S_N2' reaction to forge this C10-C11 bond, we additionally explored a number of non-metal catalyzed alternatives. We were pleased to discover that organic acids were indeed capable of effecting the desired transformation,



though Lewis acids (i.e., $BF_3{\cdot}OEt_2$) were found to be unreactive. Using optimal conditions, a TFA-promoted reaction (*reaction c, eq. 5*) yielded complete conversion to the cyclized product **21**, however again as a mixture of olefinic products.[30]

Completion of the synthesis was achieved upon a final *O*-demethylation to reveal the natural product (**41**, *eq. 6*). All spectroscopic aspects of this prepared material matched



that of the frondosin B, including the magnitude and absolute sense of optical rotation. Because the sign of the optical rotation matches that of Danishefsky's synthetic product as

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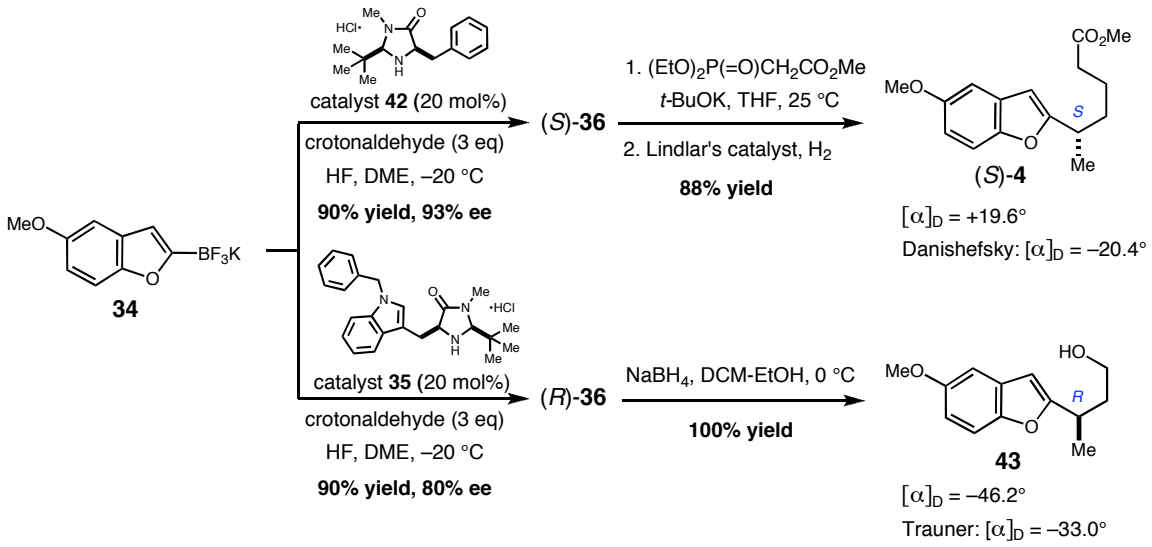
31. (a) Stary, I.; Stara, I. G.; Kocovsky, P. *Tetrahedron* **1994**, *50*, 529. (b) Dubs, C.; Yamamoto, T.; Inagaki, A.; Akita, M. *Chem. Commun.* **2006**, 1962. (c) Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* **2004**, 1200.

well as that of the natural frondosin B, we can confidently conclude naturally occurring frondosin B to exist as the *R*-enantiomer, having established the *C*-8 methyl stereocenter as being *R*-configured in our synthesis. Thus, we can assume Trauner's reassignment of natural frondosin B as the *S*-enantiomer to be invalid.

IV. Resolution of the Absolute Configuration of (+)-Frondosin B

Subsequent to the synthesis of frondosin B, we undertook an investigation to determine the origin of the differing enantiomeric *C*-8 methyl stereocenters in the Danishefsky and Trauner syntheses. Our analysis of the situation began with Trauner's supposition that Danishefsky and co-workers had synthesized an *S*-configured *C*-8 stereocenter. To test Trauner's hypothesis, we sought to intercept an advanced intermediate in Danishefsky's synthesis of frondosin B and determine its absolute configuration. As shown in Scheme 7, we prepared Danishefsky's benzofuran intermediate using our (*R*,*R*)-chiral imidazolidinone catalyst (**42**) to access the *S*-configured product **4**. However, this compound had the opposite sense of rotation to that of Danishefsky's intermediate. Therefore, we can conclude that Trauner's assertion that Danishefsky synthesized the *S*-configured natural product was incorrect. To complete our study, we also synthesized Trauner's intermediate **11** in order to validate the configuration of the methyl stereocenter in their synthesis (*Scheme 7*). Using the (*S*,*S*) catalyst **35**, we could obtain an *R*-configured product **43** that matched Trauner's intermediate in all spectroscopic aspects. Thus, we conclude that both groups indeed had synthesized *R*-configured intermediates.

Scheme 7. Interception of Danishefsky's (**4**) and Trauner's (**43**) synthetic intermediates

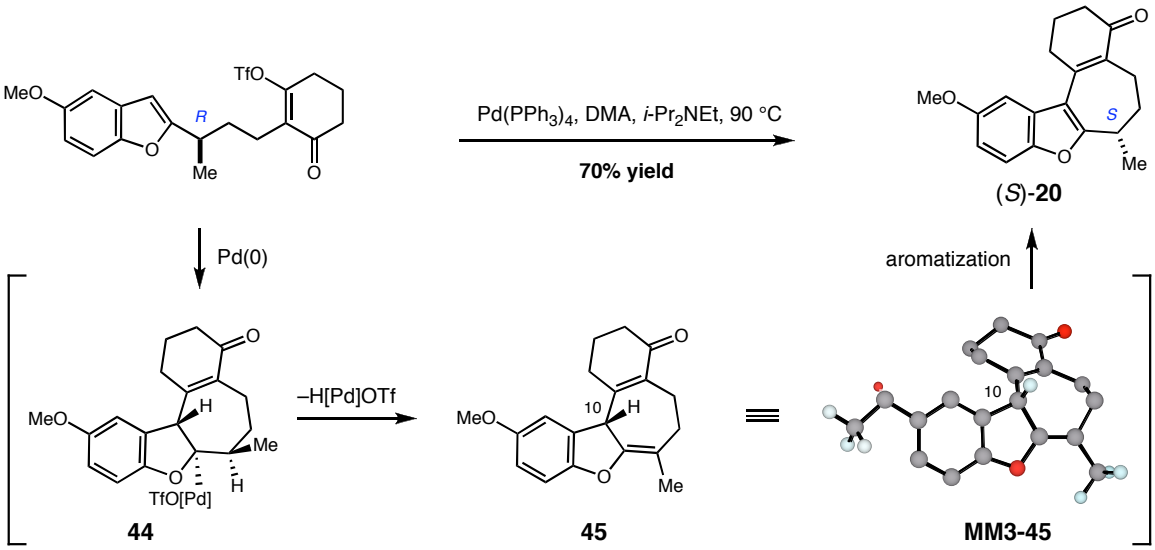


We then examined Trauner's synthesis to pinpoint a possible mode in which the *C*-8 stereocenter could have undergone an inversion of configuration. Having verified that their advanced intermediate was in fact *R*-configured, we retraced their subsequent steps. The penultimate Heck-cyclization reaction was identified as a potential culprit. In this key step, Trauner and co-workers propose that the reaction proceeds via a cationic palladium species and not through the standard Heck mechanism.[32] He rules out this mechanistic pathway based on the fact that racemization of the stereocenter at *C*-8 was not observed.[13] However, we assert that this mechanism can not be ruled out on the basis of their argument. In their cyclization step (*Scheme 8*), we propose that the Heck mechanism is indeed operational and results in the concomitant formation of two intermediary stereocenters at

32. Standard Heck reactions are said to involve oxidative insertion, migratory insertion, and β-hydride elimination (*vide* reference 26b).

the newly formed ring juncture. *Syn*-elimination of this hydridopalladium species (**44**) provides enol ether **45,** which retains a single stereocenter at *C*-10. According to Trauner,

Scheme 8. Hypothesized mechanism of inversion in Trauner's synthesis of frondosin B



rearomatization ofenol ether **45** would assuredly form a racemic product. However, we assert that enol ether **45** can only be protonated from its convex face (as is apparent from **MM3-45**) to yield an *S*-configured *C*-8 methyl stereocenter. Thus, we show a convincing method by which Trauner synthesized the opposite enantiomer of the natural product.

V. Conclusion

In summary, an efficient five-step total synthesis of (+)-frondosin B has been described. This work highlights the use of organocatalysis in the stereoselective construction of a natural product target. An enantioselective, organocatalytic conjugate addition reaction played a critical role in setting the *C*-8 methyl stereocenter and was key in the establishment of the absolute configuration of the natural product as *R*. Thus, by

correlation we were able to confidently reassign naturally occurring (+)-frondosin B to exist as the (*R*)-enantiomer. And in doing so, we were able to resolve a discrepancy in the literature that purported the natural product to exist as the (*S*)-enantiomer. We also demonstrated a novel intramolecular cyclization strategy that proved to be numerously successful in yielding the completed tetracyclic framework of frondosin B. To date, this work represents the most effective synthesis of frondosin B, which can now be accessed in five steps and a 32% overall yield.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[33] All solvents were purified according to the method of Grubbs.[34] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile compounds. Potassium tri(fluoro)borate salts were synthesized from commercially available boronic acids or esters using a modified Molander procedure.[35] Chromatographic purification of products was accomplished using force-flow chromatography on Silicycle silica gel according to the method of Still[36] and where noted, Iatrobeads 6RS-8060 was used in place of silica gel. Thin-layer chromatography (TLC) was performed on Silicycle 250 mm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching and anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz or 75 MHz), Mercury 400 (400 MHz or 100 MHz), or an Inova 500 (500MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals (note: $CDCl_3$ referenced at δ 7.24). Data for ^{1}H 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. Data for ^{13}C NMR are reported in terms of

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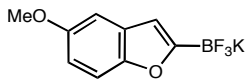
33. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon Press: Oxford, 1988.

34. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics,* **1996**, *15*, 1518.

35. (a) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (b) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867. Note: The cited procedures were found to be more efficient when reaction slurries were sonicated.

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

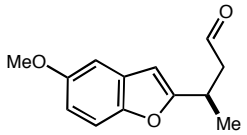
chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral Facility and the Princeton Mass Spectroscopy Facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with split-mode capillary injection system and flame ionization detectors using Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a diode array UV detector (λ = 214–258 nm) using a chiral column (25 cm) and guard column (5 cm) as noted for each compound.



Potassium 2-(5-methoxybenzofuranyl)trifluoroborate salt (34). 2-(5-methoxybenzofuranyl)trifluoroborate. Prepared according to a modified procedure from Molander and co-workers.[37] Commercially available 2-(5-methoxybenzofuranyl) boronic acid (**33**, 1.75 g, 9.0 mmol) was dissolved in anhydrous methanol (25 mL). Finely ground potassium hydrogenfluoride (2.44 g, 31 mmol) was added and the resulting suspension was sonicated for 5 minutes before being cooled down to 0 °C. Cold H_2O (8 mL) was added drop-wise over 45 min via syringe pump and resulted in the gradual formation of a thick slurry. The resulting suspension was stirred at ambient temperature for 2 hours and then concentrated *in vacuo*, azeotroped with methanol (5 x 10 mL), and

37. (a) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (b) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.

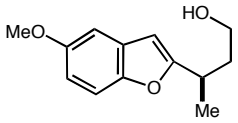
dried under high vacuum to remove all traces of moisture. The resulting free-flowing white solid was then dissolved in hot acetone and filtered. The filtrate was cooled to room temperature and concentrated *in vacuo*. Ethyl ether was added to titurate the product to produce a white powder that was filtered and dried under high vacuum (1.60 g, 70 % yield). IR (solid) 1560 1467, 1450, 1206, 1153, 1134, 967.5, 937.3, 902.0, 848.9, 799.9, 753.9 cm^{-1}. ^{1}H NMR (d_6-acetone, 400 MHz) δ 7.18 (d, 1H, *J* = 8.7 Hz, aryl **H**), 6.92 (d, 1H, *J* = 2.4 Hz, aryl **H**), 6.64 (dd, 1H, *J* = 8.7, 2.4 Hz, aryl **H**), 6.45 (s, 1H, aryl **H**), 3.54 (s, 3H, C**H**$_3$); ^{13}C NMR (d_6-acetone, 125 MHz) δ 155.5, 151.5, 130.5, 110.7, 110.2, 107.6, 102.9, 55.3; ^{19}F NMR (d_6-acetone, 282 MHz) δ –143.1 (br d, *J* = 44 Hz). HRMS (TOF ES) exact mass calculated for $[M]^{+\bullet}$ ($C_9H_7BF_3O_3$) requires *m*/*z* 215.0491, found *m*/*z* 215.0462.



***(R)*-3-(5-methoxybenzofuran-2-yl)butanal (36).**[38] To a plastic vial (Wheaton HDPE) is added HF (48 wt%, 6.25 mg, 0.15 mmol) followed by 1,2-dimethoxyethane (DME) (450 μL) and a magnetic stir bar. The catalyst and acid co-catalyst are charged to the vial with the addition of (2*S*,5*S*)-2-*tert*-butyl-5-((1-benzyl-1*H*-indol-3-yl)methyl)-3-methylimidazolidin-4-one (10.9 mg, 0.03 mmol) and HCl (4N in dioxane, 7.5 μL, 0.03 mmol) and is then cooled to –20 °C. The reaction is started with the addition of crotonaldehyde (37.5 μL, 0.45 mmol) to the DME solution followed by the addition of

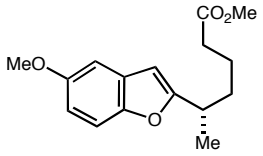
38. For stereochemical proofs for the title compound, see supporting information in Chapter 3 (p. 92).

potassium 2-(5-methoxybenzofuranyl)trifluoroborate (42.4 mg, 0.15 mmol). The reaction is stirred at –20 °C for 24 hours and quenched with 1M HCl (1.0 mL) and is stirred with chloroform (1.5 mL) for 30 minutes. The organic layer is extracted with chloroform (2 x 2.0 mL), dried over Na_2SO_4, filtered through celite (ether wash) and concentrated *in vacuo*. Purification by chromatography (silica gel, 15% ether in pentanes) yields the title compound as clear oil (30.7 mg, 94% yield, 92% ee). IR (film) 1724, 1475, 1205, 1030 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 9.78 (t, 1H, *J* = 1.5 Hz, C**H**O), 7.29 (d, 1H, *J* = 8.4 Hz, aryl **H**), 6.98 (d, 1H, *J* = 2.4 Hz, aryl **H**), 6.81 (dd, 1H, *J* = 2.4, 9.0 Hz, aryl **H**), 6.38 (d, 1H, *J* = 0.9 Hz), 3.01 (s, 3H, OC**H**$_3$), 3.54 (m, 1H, C**H**CH_3), 2.79 (ddd, 2H, *J* = 1.5, 6.6, 17.4 Hz, C**H**$_2$), 1.39 (d, 3H, *J* = 0.9 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.32, 163.07, 156.46, 150.05, 129.72, 112.37, 111.60, 103.72, 101.93, 56.29, 49.30, 28.78, 19.18; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{13}H_{14}O_3$) requires *m/z* 218.0943, found *m/z* 218.0944; $[\alpha]_D$= –8.51 (c = 1.29, $CHCl_3$). The enantiomeric excess was determined by SFC using a Chiracel OJ-H column (5% to 10% MeCN, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 5.17 min, (*R*) isomer t_r = 5.61 min.



(*3R*)-3-(5-methoxybenzofuran-2-yl)butan-1-ol. To a stirring solution of aldehyde **36** (25 mg, 0.11 mmol) in CH_2Cl_2 (2.0 mL) and ethanol (20 μL) at 0 °C was added $NaBH_4$ (13 mg, 0.34 mmol). The reaction was quenched after 5 minutes by a saturated solution of Rochelle's salt (2.0 mL). The organic layer was then extracted with ether (2 x 3.0 mL) and

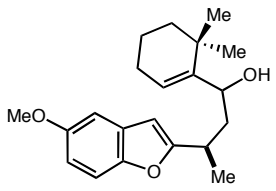
concentrated *in vacuo* to yield a clear oil (quantitative yield) with spectroscopic data matching literature values.[39] IR (film) 3306 (br), 2922, 1458, 1201, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 1H, *J* = 8.7 Hz, aryl **H**), 6.94 (d, 1H, *J* = 2.7 Hz, aryl **H**), 6.79 (dd, 1H, *J* = 2.7, 8.7 Hz, aryl **H**), 6.33 (s, 1H, aryl **H**), 3.81 (s, 3H, OC**H**$_3$), 3.69 (m, 2H, C**H**$_2$CH$_2$), 3.11 (m, 1H, C**H**CH$_3$), 2.06–1.95 (m, 1H, C**H**$_2$OH), 1.91–1.79 (m, 1H, C**H**$_2$OH), 1.57 (br s, 1H, O**H**), 1.34 (d, 3H, *J* = 7.2 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.11, 155.98, 149.73, 129.48, 111.81, 111.38, 103.45, 101.40, 60.97, 56.16, 38.53, 30.56, 19.38; HRMS (EI+) exact mass calculated for [M+1] ($C_{13}H_{16}O_3$) requires *m*/*z* 220.1100, found *m*/*z* 220.1089; $[\alpha]_D$= –46.2 (c = 0.83, $CHCl_3$).[39] The enantiomeric excess was determined by SFC analysis using a Chiralcel OJ-H column (5% to 10% methanol, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 5.71 min, (*R*) isomer t_r = 6.56 min.



(*S*)-methyl-5-(5-methoxybenzofuran-2-yl)-hexanoate. To a suspension of potassium *tert*-butoxide (30.6 mg, 0.273 mmol, 1.3 eq.) in dry THF (3.0 mL) at 0 °C was added methyldiethylphosphonoacetate (53.3 μL, 0.294 mmol, 1.4 mmol) portionwise. The resulting reaction mixture was allowed to warm up to room temperature and stirred for an additional 15 min, before adding a solution of (*S*)-3-(5-methoxybenzofuran-2-yl)butanal (45 mg, 0.21 mmol) in THF (2.0 mL). Upon stirring for 12 hours, the reaction

39. Hughes, C. C.; Trauner, D. *Tetrahedron*, **2004**, *60*, 9675 (reported $[\alpha]_D$= –33.0 (c = 1.00, $CHCl_3$) for a product that was 91% ee).

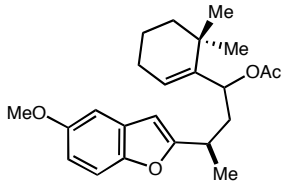
was diluted with diethyl ether (2.0 mL) and then quenched by the slow addition of H_2O (1.0 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give the crude product (50 mg), which was used in the next step without further purification. Crude (*S,E*)-methyl-(5-methoxybenzofuran-2-yl)-hexanoate (40 mg, 0.145 mmol) was dissolved in methanol (3.0 mL) and Lindlar's catalyst (15.5 mg, 0.07 mmol, 5 mol%) were added to a flame-dried flask. The system flushed with hydrogen and the mixture was stirred for 12 hours at room temperature. The reaction was then diluted with methanol and filtered through Celite to remove palladium. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica gel, 10% ether in pentanes) to give the title compound (40 mg, 0.145 mmol) in 88% yield over the two steps. IR (film) 1735, 1475, 1205, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, 1H, *J* = 9.0 Hz, aryl **H**), 6.96 (d, 1H, *J* = 2.7 Hz, aryl **H**), 6.80 (dd, 1H, *J* = 2.7, 9.0 Hz, aryl **H**), 6.32 (s, 1H, aryl **H**), 3.83 (s, 3H, OC**H**$_3$), 3.66 (s, 3H, $CO_2C\mathbf{H}_3$), 2.92 (m, 1H, C**H**CH_3), 2.32 (t, 2H, *J* = 7.0 Hz, C$\mathbf{H}_2CO_2$Me; 1.80 (m, 1H, C$\mathbf{H}_2CH_2CO_2$Me), 1.66 (m, 3H, $CHCH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.32 (d, 3H, *J* = 7.0 Hz, CHC**H**$_3$), ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 164.3, 155.9, 149.7, 129.6, 111.7, 111.4, 103.5, 101.3, 56.2, 51.7, 35.0, 34.2, 33.7, 22.8, 19.2; $[\alpha]_D$= + 19.6 (c = 0.10, $CHCl_3$).



(3*R*)-1-(6,6-dimethylcyclohex-1-enyl)-3-(5-methoxybenzofuran-2-yl)butan-1-ol (38). 2,4,6-triisopropylbenzenesulfonyl hydrazone[40] (0.32 g, 0.78 mmol) was dissolved in anhydrous THF (1.5 mL) and cooled to –78 °C. *tert*-Butyl lithium (1.3 mL, 1.3 M in hexanes, 1.72 mmol) was added drop-wise over 15 min during which time the reaction solution turned yellow and then dark orange. The reaction was aged for 30 min at –78 °C and then at 0 °C for 15 min, upon which $N_{2(g)}$ evolution was observed. Upon cooling the system to –78 °C, aldehyde **36** (0.29 g, 1.32 mmol, 1.0 mL THF solution) was added via cannula to the reaction. The resulting reaction mixture was then stirred at 0 °C for 1 hour and at room temperature for 3 additional hours before being quenched by the addition of $NH_4Cl_{(aq)}$ (5.0 mL). The organic layer was extracted with chloroform (3 x 10 mL), dried over Na_2SO_4, filtered through celite (ether wash) and concentrated *in vacuo*. Purification by chromatography (silica gel, 10% ethyl acetate in hexanes) yielded the title compound as yellow oil in a 1:1 mixture of diastereomers (dia 1 + 2, 0.22 g, 86% yield). IR (film) 3475, 1617, 1475, 1205, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, 1H, *J* = 8.8 Hz, aryl **H,** dia 1), 7.23 (d, 1H, *J* = 8.8 Hz, aryl **H,** dia 2), 6.93 (d, 1H, *J* = 2.8 Hz, aryl **H,** dia 1), 6.92 (d, 1H, *J* = 2.8 Hz, aryl **H,** dia 2), 6.78 (dt, 1H, *J* = 2.8, 8.8 Hz, aryl **H**, dia 1+2), 6.35 (s, 1H, aryl **H**, dia 1), 6.30 (s, 1H, aryl **H**, dia 2), 5.82 (t, 1H, *J* = 4.0 Hz, C=C**H**, dia 1), 5.80 (t, 1H, *J* = 4.0 Hz, C=C**H**, dia 2), 4.26 (dd, 1H, *J* = 2.8, 10 Hz, C**H**OH, dia 1), 4.02 (dd, 1H, *J* = 2.8, 10 Hz, C**H**OH, dia 2), 3.80 (s, 3H, OC$\mathbf{H_3}$, dia 1), 3.79 (s, 3H, OC$\mathbf{H_3}$, dia 2), 3.18 (m, 1H, C**H**CH_3, dia 1 + 2), 2.08 (ddd, 1H, *J* = 4.4, 9.2, 13.6 Hz CHOHC$\mathbf{H_2}$, dia 1), 1.98 (t, 2H, *J* = 2.4 Hz, C=CC$\mathbf{H_2}$, dia 1+2), 1.91 (ddd, 1H, *J* = 2.8, 10.0, 13.6 Hz, CHOHC$\mathbf{H_2}$, dia 2), 1.76 (ddd, 1H, *J* = 4.8, 10, 13.4 Hz, CHOHC$\mathbf{H_2}$, dia 2), 1.65 (ddd, 1H,

40. Pazos, Y.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **2001**, *66*, 8483.

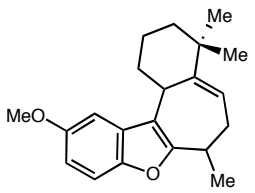
J = 2.8, 9.2, 13.6 Hz, CHOHC**H**$_2$, dia 1), 1.55 (m, 2H, C=CCH$_2$C**H**$_2$, dia 1 + 2) 1.40 (m, 2H, C(CH$_3$)$_2$C**H**$_2$, dia 1 + 2), 1.32 (d, 3H, *J* = 6.9 Hz, CHC**H**$_3$, dia 1), 1.31 (d, 3H, *J* = 6.9 Hz, CHCH$_3$, dia 2), 1.08 (s, 3H, C(C**H**$_3$)$_2$, dia 1), 0.94 (s, 3H, C(C**H**$_3$)$_2$, dia 2), 0.93 (s, 3H, C(C**H**$_3$)$_2$, dia 1) 0.80 (s, 3H, C(C**H**$_3$)$_2$, dia 2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 164.2, 155.9, 149.8, 129.6, 129.5, 122.7, 122.4, 111.7, 111.6, 111.3, 103.5, 101.8, 100.8, 67.9, 67.1, 56.2, 44.9, 44.2, 39.8, 39.7, 34.0, 33.9, 31.6, 31.0, 28.6, 28.5, 28.3, 28.2, 26.0, 20.1, 19.3, 18.5; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{21}H_{28}O_3$) requires *m*/*z* 328.2038, found *m*/*z* 328.2043.



(3*R*)-1-(6,6-dimethylcyclohex-1-enyl)-3-(5-methoxybenzofuran-2-yl)butyl ethanoate. Prepared according to a procedure adapted from Vedejs et al.[41] To a round-bottom flask was charged 1-(6,6-dimethylcyclohex-1-eyl-)-3-(5-methoxybenzofuran-2-yl)butan-1-ol (0.115 g, 0.35 mmol), freshly distilled tributylphosphine (13 μL, 0.05 mmol), triethylamine (80 μL, 0.53 mmol), acetic anhydride (100 μL, 1.0 mmol), and anhydrous diethyl ether (13 mL). The resulting reaction mixture was refluxed for 30 hours, upon which the reaction was allowed to cool to room temperature and was quenched with addition of $NH_4Cl_{(aq)}$ (10 mL). The solution was partitioned with diethyl ether (3 x 10.0 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography (silica gel, 5% ethyl

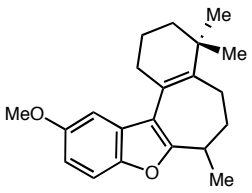
41. Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358.

acetate in hexanes) yielded the title compound as clear oil (dia 1 + 2, 130 mg, 0.35 mmol) in quantitative yield. IR (film) 1732, 1617, 1475, 1235, 1205, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, 1H, *J* = 9.0 Hz, aryl **H,** dia 1), 7.28 (d, 1H, *J* = 9.0 Hz, aryl **H,** dia 2), 6.96 (d, 1H, *J* = 2.5 Hz, aryl **H,** dia 1 + 2), 6.81 (dd, 1H, *J* = 2.5, 9.0 Hz, aryl **H**, dia 1 + 2), 6.34 (s, 1H, aryl **H**, dia 1), 6.33 (s, 1H, aryl **H**, dia 2), 5.80 (t, 1H, *J* = 4.0 Hz, C=C**H**, dia 1), 5.76 (t, 1H, *J* = 4.0 Hz, C=C**H**, dia 2), 5.48 (dd, 1H, *J* = 3.5, 9.5 Hz, C**H**OAc, dia 1), 5.26 (dd, 1H, *J* = 3.5, 9.5 Hz, C**H**OAc, dia 2), 3.83 (s, 3H, OC$\mathbf{H_3}$, dia 1+2), 2.92 (m, 1H, C**H**CH_3, dia 1 + 2), 2.24 (ddd, 1H, *J* = 4.4, 9.0, 15.0 Hz CHOHC$\mathbf{H_2}$, dia 1), 2.10 (ddd, 1H, *J* = 2.8, 9.0, 15.0 Hz, CHOHC$\mathbf{H_2}$, dia 2), 2.02 (t, 2H, *J* = 2.4 Hz, C=CC$\mathbf{H_2}$, dia 1 + 2), 1.76 (m, 4H, (C=O)C$\mathbf{H_3}$, CHOHC$\mathbf{H_2}$, dia 2), 1.80 (ddd, 1H, *J* = 2.8, 9.0, 15.0 Hz, CHOHC$\mathbf{H_2}$, dia 1), 1.55 (m, 2H, C=CCH_2C$\mathbf{H_2}$, dia 1+2) 1.42 (m, 2H, C$(CH_3)_2$C$\mathbf{H_2}$, dia 1 + 2), 1.35 (d, 3H, *J* = 7.0 Hz, CHC$\mathbf{H_3}$, dia 1+2), 1.08 (s, 3H, C(C$\mathbf{H_3}$)$_2$, dia 1), 0.98 (s, 3H, C(C$\mathbf{H_3}$)$_2$, dia 2), 0.97 (s, 3H, C(C$\mathbf{H_3}$)$_2$, dia 1) 0.90 (s, 3H, C(C$\mathbf{H_3}$)$_2$, dia 2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.3, 164.2, 163.3, 155.9, 149.8, 149.7, 145.0, 144.9, 129.6, 129.5, 124.5, 124.0, 111.8, 111.7, 111.3, 103.4, 101.9, 101.1, 70.9, 70.4, 56.1, 42.3, 42.0, 39.9, 39.8, 33.9, 33.8, 31.4, 31.3, 28.8, 28.7, 28.2, 26.0, 25.9, 21.6, 21.5, 19.7, 19.1; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{23}H_{30}O_4$) requires *m*/*z* 370.2144, found *m*/*z* 370.2136.

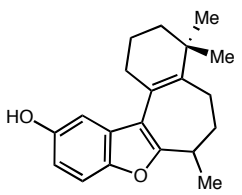


(*R*)-*O*-methyl frondosin B non-conjugated olefin isomer (39). To a round bottom flask was charged 1-(6,6-dimethylcyclohex-1-eyl-)-3-(5-methoxybenzofuran-2-

yl)butan-1-ol (33 mg, 0.088 mmol) and $[Mo(CO)_4(Br_2]_2$ (34 mg, 0.044 mmol). Freshly distilled and degassed dichloromethane (2.0 mL) was added and the reaction was stirred at —20 °C for 12 hours (and monitored by TLC). Upon reaction completion, diethyl ether (10 mL) was added and the solution was filtered through Fluorosil (ether wash) and was concentrated *in vacuo*. Purification by chromatography (silica gel, 5% ethyl acetate in hexanes) yielded the title compound as pale yellow oil (27 mg, 0.087 mmol) in 98% yield as a mixture of two diastereomers in an approximate 1:1 ratio (dia 1 + 2). IR (film) 1613, 1475, 1205, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, 1H, *J* = 8.8 Hz, aryl **H,** dia 1), 7.25 (d, 1H, *J* = 8.8 Hz, aryl **H,** dia 2), 6.87 (d, 1H, *J* = 3.0 Hz, aryl **H,** dia 1 + 2), 6.80 (dd, 1H, *J* = 2.5, 9.0 Hz, aryl **H**, dia 1), 6.78 (dd, 1H, *J* = 2.5, 9.0 Hz, aryl **H**, dia 2), 5.59 (dd, 1H, *J* = 4.4, 6.4 Hz, C=C**H**, dia 1), 5.55 (dd, 1H, *J* = 6.4, 7.6 Hz, C=C**H,** dia 2), 3.85 (s, 3H, OC$\mathbf{H_3}$, dia 1+2), 3.70 (m, 1H, C**H**C=C, dia 1), 3.68 (m, 1H, C**H**C=C, dia 2), 3.20 (dqd, 1H, *J* = 2.4, 7.2, 7.2 Hz, $CHCH_3$, dia 1), 3.14 (qd, 1H, *J* = 2.8, 7.2, 7.2 Hz, C**H**CH_3, dia 2), 2.55 (dqd, 1H, *J* = 2.2, 4.4, 16.4 Hz, $CHCH_3C\mathbf{H_2}$, dia 1), 2.41 (ddd, *J* = 2.4, 7.2, 16.4 Hz, $CHCH_3C\mathbf{H_2}$, dia 2), 2.42 (m, 2H, CHC$\mathbf{H_2}$), 1.86 (m, 1H $CHCH_2C\mathbf{H_2}$), 1.66 (m, 1H $CHCH_2C\mathbf{H_2}$), 1.58 (m, 2H, C$\mathbf{H_2}C(CH_3)_2$), 1.34 (d, 3H, *J* = 7.2 Hz, CHC$\mathbf{H_3}$, dia 1 + 2), 1.18 (s, 3H, $C(C\mathbf{H_3})_2$, dia 1 + 2), 1.14 (s, 3H, $C(C\mathbf{H_3})_2$, dia 1), 1.12 (s, 3H, $C(C\mathbf{H_3})_2$, dia 2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.53, 158.9, 155.7, 148.6, 148.3, 147.3, 131.2, 131.1, 117.3, 116.1, 115.6, 115.3, 111.3, 111.2, 110.7, 110.6, 102.4, 56.4, 43.1, 42.9, 39.2, 39.0, 36.9, 36.7, 35.8, 35.7, 34.9, 33.6, 33.1, 31.0, 30.8, 26.8, 26.6, 23.7, 23.6, 19.7, 18.4; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{21}H_{26}O_2$) requires *m*/*z* 310.1933, found *m*/*z* 310.1928.

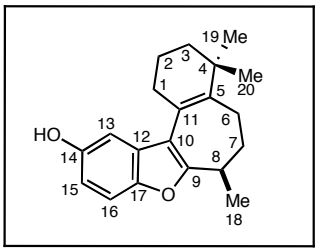


(*R*)-*O*-methyl frondosin B (**21**). A round bottom flask was charged with 1-(6,6-dimethylcyclohex-1-eyl-)-3-(5-methoxybenzofuran-2-yl)butan-1-ol (100 mg, 0.30 mmol) and $[Mo(CO)_4(Br_2]_2$ (22.4 mg, 0.03 mmol). Freshly distilled and degassed dichloromethane (2.0 mL) was added and the reaction was stirred at ambient temperature for 6 hours. The reaction mixture was diluted with diethyl ether and filtered through Fluorosil. The organic solvent was concentrated *in vacuo* and purification by chromatography (silica gel, 5% ethyl acetate in hexanes) yielded the title compound as pale yellow oil (77 mg, 0.25 mmol) in 83% yield, as a 2.5:1 mixture with its conjugated olefinic isomer. IR (film) 1613, 1475, 1205, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, 1H, *J* = 8.8 Hz, aryl **H**), 7.12 (d, 1H, *J* = 2.5 Hz, aryl **H**), 6.77 (dd, 1H, *J* = 8.8, 2.5 Hz, aryl **H**), 3.82 (s, 3H, OC**H**$_3$), 3.15 (q, 1H, *J* = 8.5 Hz, C**H**CH_3), 2.55 (t, 2H, *J* = 7.5 Hz, C=CC**H**$_2$), 2.15 (m, 1H, C**H**$_2$C=C), 2.11 (m, 1H, C**H**$_2$C=C), 2.08 (m, 1H, C=CCH_2C**H**$_2$), 1.82 (m, 1H, C=CCH_2C**H**$_2$), 160 (m, 4H, 1H, C**H**$_2$C**H**$_2$C$(CH_3)_2$), 1.32 (d, 3H, *J* = 8.5 Hz, CHC**H**$_3$), 1.06 (s, 3H, C(C**H**$_3)_2$), 1.02 (C(C**H**$_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 155.5, 149.3, 144.6, 129.5, 124.1, 116.9, 111.1, 111.0, 105.6, 56.3, 39.8, 39.0, 36.0, 34.9, 30.8, 29.2, 28.2, 26.3, 20.3, 20.0; HRMS (EI+) exact mass calculated for $[M]^{+\bullet}$ ($C_{21}H_{26}O_2$) requires *m*/*z* 310.1933, found *m*/*z* 310.1928.



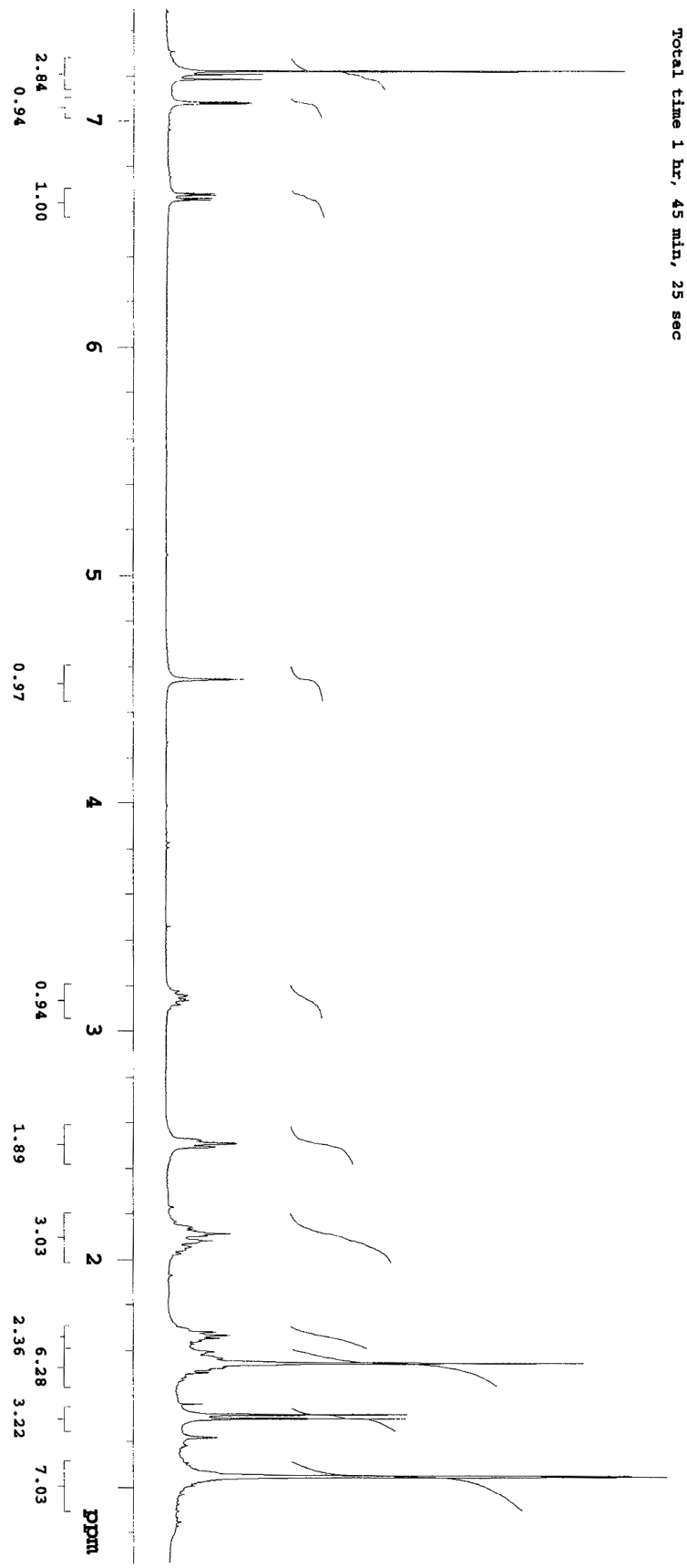
(*R*)-frondosin B (41). A solution of the mixture of (*R*)-*O*-methyl frondosin B and its olefinic conjugated isomer (125 mg, 0.40 mmol) in dichloromethane (2.0 mL) was cooled to –78 °C and treated with boron tribromide (1M in dichloromethane, 1.28 mL, 1.28 mmol). After being stirred at that temperature for 30 min, the solution was warmed to 0 °C and stirred at this temperature for a further hour. The reaction mixture was quenched with saturated solution of $NaHCO_3$ and partitioned with ethyl acetate (6.0 mL). The organic layer was washed with saturated solution of $NaHCO_3$ (6.0 mL) and then with brine (6.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography (silica gel, 5% ethyl acetate in hexanes) yielded the title compound as pale yellow oil (105 mg, 0.36 mmol) in 90% yield, as a 2.5:1 mixture with its conjugated olefinic isomer. The two isomers were separated by preparative HPLC. IR (film) 330, 2930, 1620, 1460, 1189 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21 (d, 1H, *J* = 8.8 Hz, aryl **H**), 7.09 (d, 1H, *J* = 2.5 Hz, aryl **H**), 6.67 (dd, 1H, *J* = 8.8, 2.5 Hz, aryl **H**), 4.51 (s, 1H, O**H**), 3.17 (q, 1H, *J* = 8.5 Hz, C**H**CH_3), 2.51 (t, 2H, *J* = 6.0 Hz, C=CC$\mathbf{H_2}$), 2.15 (m, 1H, C$\mathbf{H_2}$C=C), 2.11 (m, 1H, C$\mathbf{H_2}$C=C), 2.08 (m, 1H, C=CCH_2C$\mathbf{H_2}$), 1.82 (m, 1H, C=CCH_2C$\mathbf{H_2}$), 1.60 (m, 4H, 1H, C$\mathbf{H_2}$C$\mathbf{H_2}$C$(CH_3)_2$), 1.32 (d, 3H, *J* = 8.5 Hz, CHC$\mathbf{H_3}$), 1.05 (s, 6H, C(C$\mathbf{H_3}$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 150.7, 149.1, 144.4, 129.6, 123.7, 116.5, 111.3, 112.6, 111.1, 107.3, 39.5, 38.5, 36.6, 35.7, 34.7, 30.6, 29.7, 28.9, 26.1, 24.7, 20.0, 19.8; $[\alpha]_D$= + 16.3 (c = 0.12, MeOH).

Table 1. ^{1}H and ^{13}C NMR Data for Natural[1] and Synthetic (+)-Frondosin B[a]



position		natural frondosin B[b]		synthetic frondosin B[c]	
		^{13}C (δ)	^{1}H (δ), #H, m, J (Hz)	^{13}C (δ)	^{1}H (d), #H, m, J (Hz)
1		30.5	2.55, 2H,t, J = 5.9	30.55	2.54, 2H,t, J = 6.0
2		20.0	1.71, 2H, m	20.03	1.69, 2H, m
3		39.5	1.56, 2H, m	39.50	1.57, 2H, m
4		35.7	---	35.73	---
5		144.3	---	144.40	---
6		26.0	2.15, 1H, m 2.10, 1H, m	26.06	2.14, 1H, m 2.11, 1H, m
7		38.5	2.12, 1H, m 1.62, 1H, m	38.48	2.11, 1H, m 1.61, 1H, m
8		34.7	3.19, 1H, m	34.73	3.18, 1H, m
9		160.2	---	160.22	---
10		116.3	---	116.47	---
11		123.8	---	123.73	---
12		129.6	---	129.62	---
13		107.3	7.12, 1H, d, J = 2.5	107.27	7.11, 1H, d, J = 2.8
14		150.7	---	150.70	---
15		111.1	6.71, 1H, dd, J = 2.5, 8.7	111.07	6.70, 1H, dd, J = 2.8, 8.8
16		110.9	7.24, 1H, d, J = 8.7	110.91	7.23, 1H, d, J = 8.8
17		149.1	---	149.08	---
18		19.7	1.35, 3H, d, J = 7.0	19.78	1.34, 3H, d, J = 6.8
19		28.9	1.09, 3H, s	28.94	1.08, 3H, s
20		27.9	1.10, 3H, s	27.89	1.09, 3H, s
OH		---	4.77, 1H, br s	---	4.54, 1H, br s

[a]Spectra were measured in $CDCl_3$. [b] ^{1}H NMR (400 MHz); ^{13}C (100 MHz). [c] ^{1}H NMR (500 MHz); ^{13}C (125 MHz).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4
3
2
ppm
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0.94
1.00
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7.03

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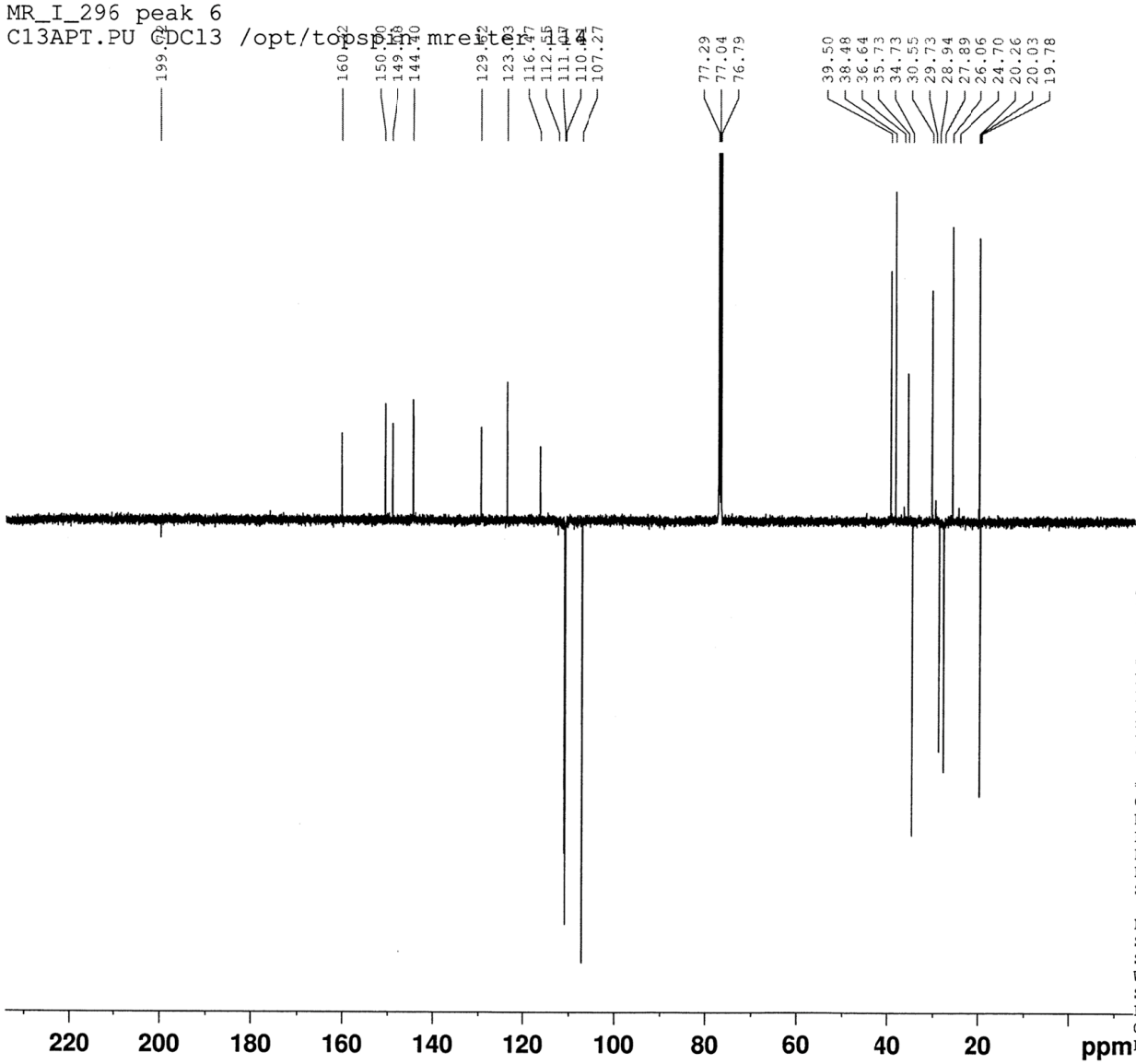

BRUKER

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PROCNO 1

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======== CHANNEL f2 ========
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