Studies on Organocatalytic Asymmetric Construction of Chiral Carbinols

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Abbreviations

α	observed optical rotation
Å	ångström
Ac	acetyl
Ar	aryl
aq	aqueous
br	broad (spectral)
Bu	butyl
Bn	benzyl
Bz	benzoyl
c	concentration
°C	degrees Celsius
calcd	calculated
cm	centimeter(s)
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
δ	chemical shift in perts per million downfield from tetramethylsilane
d	doublet (spectral)
d	day(s)
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
E	*entgegen* (means "opposite")
Ed(s).	editor(s)
ee	enantiomeric excess
ent	enantiomer
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrum
Hz	hertz (s^{-1})
i	iso
IR	infrared (spectral)
J	coupling constant (spectral)
m	multiplet (spectral)
M	molar (1 M = 1 mol dm^{-3})
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
mol	mole(s)
Mp.	melting point
MS 4A	molecular sieves 4Å
n	normal
nm	nanometer(s)
NMR	nuclear magnetic resonance
p	para
Ph	phenyl
ppm	parts per million (spectral)
Pr	propyl
q	quartet (spectral)
R_f	retention factor (TLC)
rt	room temperature (*ca*. 25 °C)
s	singlet (spectral)
t (*tert*)	tertiary
t	triplet (spectral)
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	4-methylbenzenesulfonyl
TLC	thin-layer chromatography
UV	ultraviolet
Vol.	volume(s)

General Introduction

The conformational analysis of saturated six-membered rings provides fruitful insights for the precise control of dynamic stereochemistry. Ever since Barton and Hassel established the foundation for the conformational analysis of these molecules in the 1950s,[1] it has been widely accepted that six-membered rings adopt unstrained chair-like conformations, on which the substituents are locate in either axial or equatorial positions. While sterically hindered substituents generally prefer to occupy equatorial positions to minimize unfavorable 1,3-diaxial interactions, small and electronegative substituents adjacent to the heteroatoms of six-membered heterocycles favor axial positions due to the anomeric effect (Figure 1).[2] Because such steric and stereoelectronic interactions are also crucial to the configurations of reaction intermediates or transition states, introduction of chair-like conformations in organic reactions is an efficient strategy for precise control of diastereoselectivity.[3] The integration of this methodology with enantioselective transformations would therefore be a powerful approach for asymmetric synthesis.

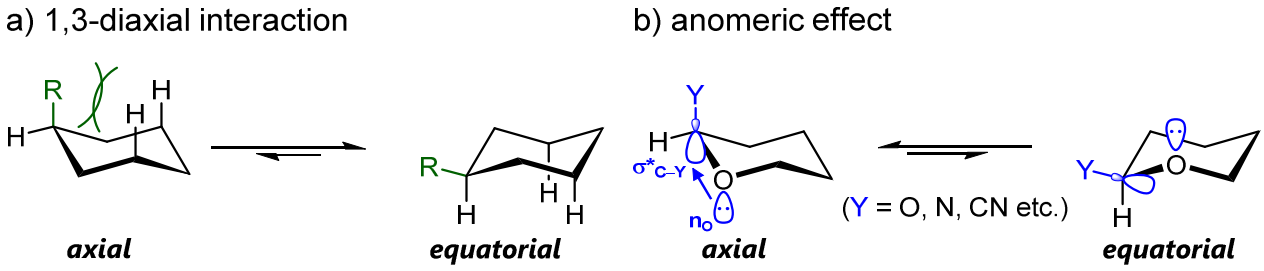


Figure 1. Steric and stereoelectronic effects on chair-like conformations of six-membered rings.

Based on this hypothesis, the author has pursued the development of stereoselective reactions that take advantage of the aforementioned features to control diastereoselectivity via the formation of a six-membered oxacycle in combination with enantioselective catalysis, thereby allowing for a rapid increase of molecular complexity and the construction of hitherto inaccessible chiral structures from achiral or racemic starting materials. In order to achieve asymmetric induction

while maintaining the high diastereoselectivity derived from the prefered chair-like conformation, the chiral catalysts must selectively activate the specific conformer leading to the desired stereoisomer of the product. Inspired by enzymatic catalysis that utilizes cooperative noncovalent interactions with specific sites of the substrates, the author envisioned that chiral organocatalysts that employ hydrogen bonding would be effective for these asymmetric reactions.[4,5] In particular, chiral organocatalysts bearing acidic and basic sites can activate the cyclization substrate via multiple hydrogen bonds,[6] which would allow for efficient six-membered ring-forming reactions with multiple stereogenic centers simultaneously constructed in highly enantio- and diastereoselective manners (Figure 2).

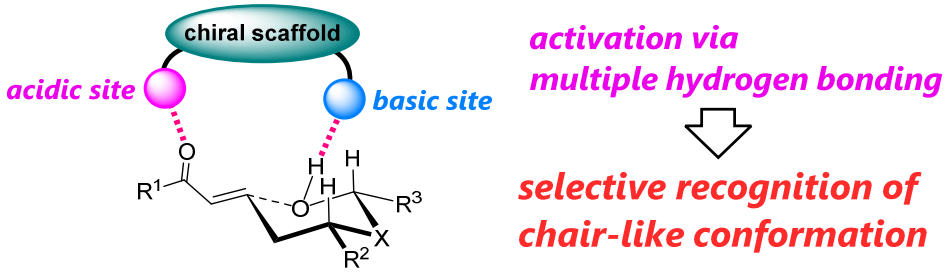


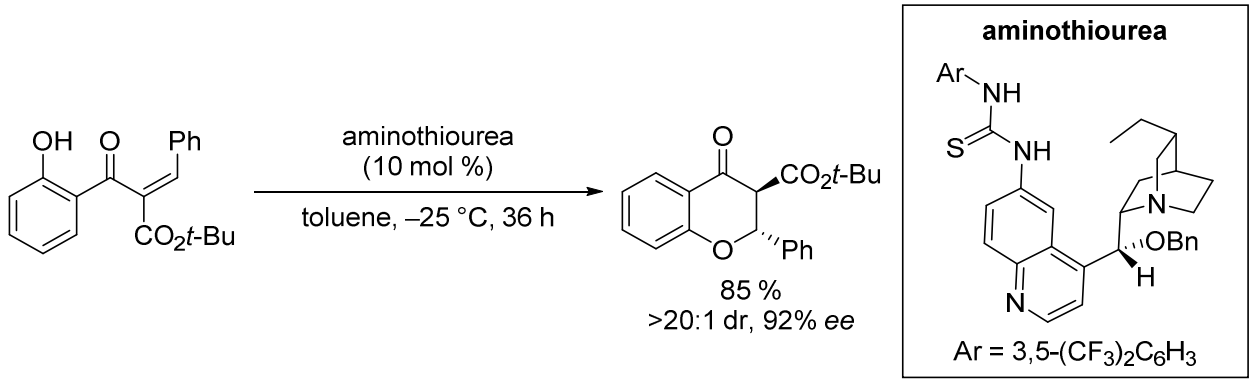
Figure 2. Asymmetric six-membered ring-forming reactions using chiral bifunctional organocatalysts.

A key concept throughout the author's research is the selective recognition of a six-membered chair-like conformation by bifunctional or dual-functional organocatalysts, thereby leading to highly enantio- and diastereoselective transformations. Moreover, as these reactions afford enantioenriched carbinols or their protected products bearing various functionalities, they can be utilized as useful chiral building blocks for the synthesis of biologically active compounds. Below is a perspective on the topics related to the author's research.

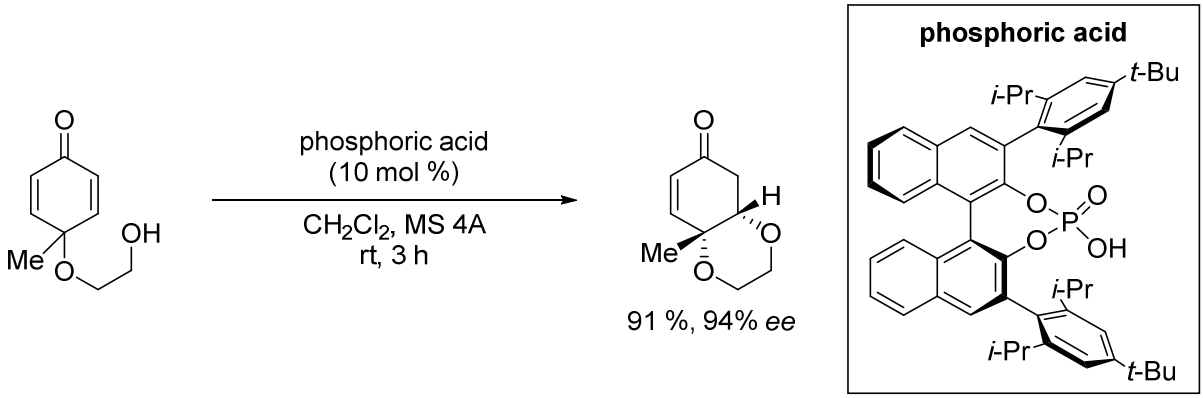
1. Enantioselective Intramolecular Oxy-Michael Addition Based on Multipoint Recognition via Hydrogen Bonding

The oxy-Michael addition reaction is useful for the introduction of an oxygen atom into the β-position of a carbonyl compound.[7] In particular, the asymmetric intramolecular oxy-Michael addition is a promising method for affording various pharmaceutically important chiral oxacyclic motifs. While a couple of general drawbacks, such as low nucleophilicity of the oxygen atom and difficulty in constructing a suitable chiral environment for asymmetric induction, have hampered development of the asymmetric oxy-Michael addition reaction, recent advances have demonstrated that the use of chiral organocatalysts with multiple hydrogen bonding is particularly effective for obtaining high enantioselectivity. In a seminal work, Scheidt reported the highly enantioselective intramolecular oxy-Michael addition of phenol derivatives in 2007 (Scheme 1).[8] Bifunctional aminothiourea catalysts based on cinchona alkaloid scaffolds provide chiral flavanone and chromanone derivatives in high yields with good to high enantioselectivies. In 2010, You revealed that chiral phosphoric acid catalysts, which possess both an acidic proton and a basic phosphoryl oxygen atom in the same functional group, enable the desymmetrization of cyclohexadienones via an asymmetric intramolecular oxy-Michael addition (Scheme 2).[9] Asano and Matsubara developed an asymmetric cycloetherification of ε- and ζ-hydroxy-α,β-unsaturated ketones mediated by bifunctional aminothiourea catalysts (Scheme 3).[10] They proposed that the thiourea and tertiary amine moieties of the catalyst simultaneously interact with the carbonyl oxygen and nucleophilic hydroxy group, respectively, of the substrate via hydrogen bonding. Such multipoint recognition enables the highly enantioselective intramolecular oxy-Michael addition, affording optically active tetrahydrofurans and tetrahydropyrans. This method was also applied to the asymmetric synthesis of chromans.[11]

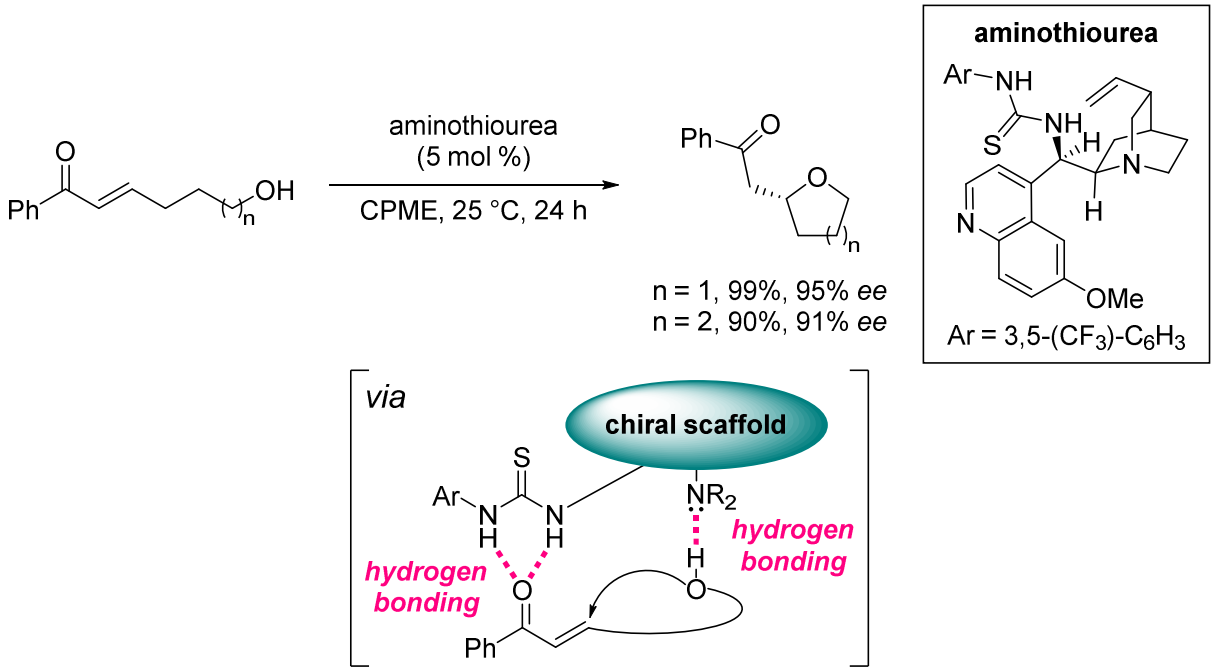
Scheme 1. Asymmetric Synthesis of Flavanone Derivatives Using Bifunctional Aminothiourea Catalysts



Scheme 2. Desymmetrization of Cyclohexadienones Using Chiral Phosphoric Acid Catalysts

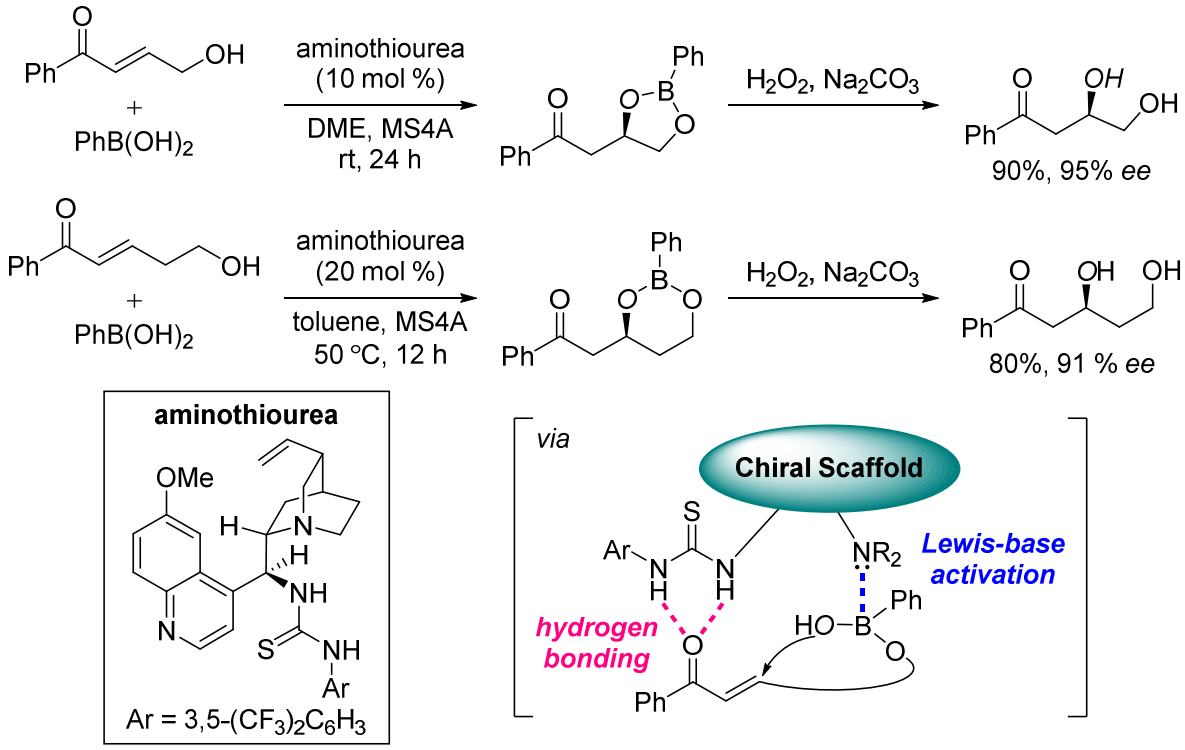


Scheme 3. Asymmetric Synthesis of Tetrahydrofurans and Tetrahydropyrans Using Bifunctional Aminothiourea Catalysts

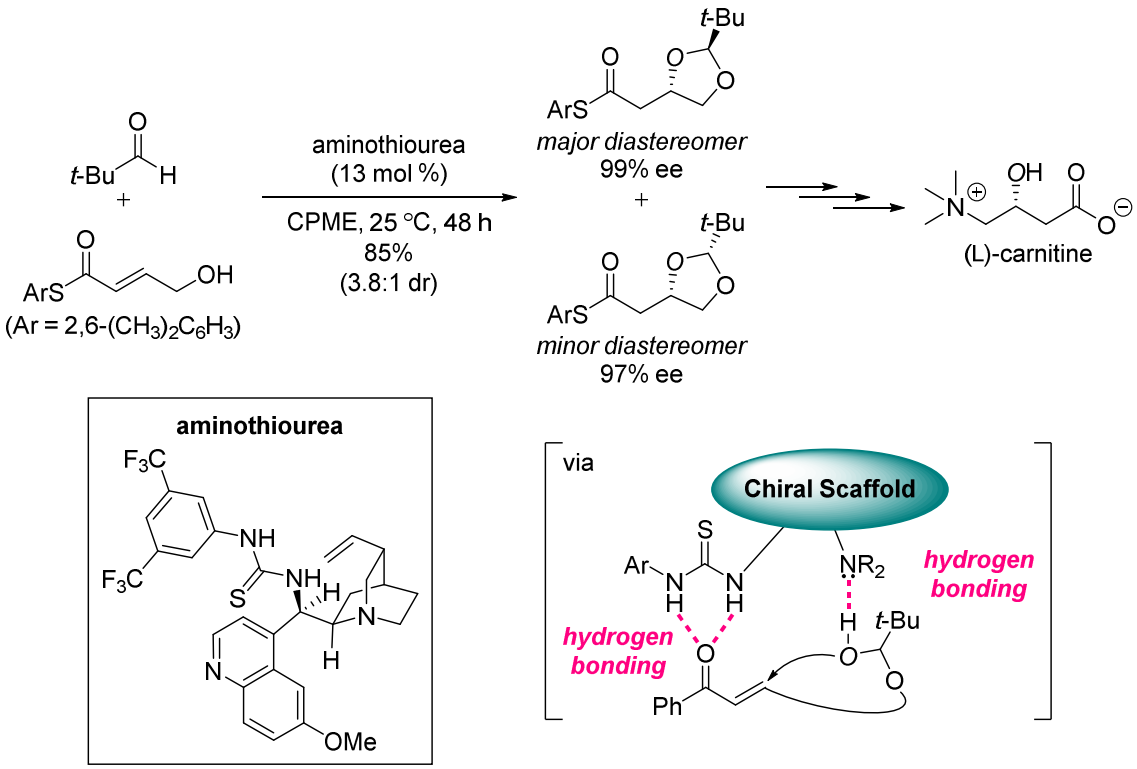


This method is also applicable to the asymmetric intramolecular oxy-Michael addition of in situ generated nucleophilic hydroxy groups. In 2008, Falck reported the asymmetric synthesis of cyclic boronates, which can be easily transformed into chiral 1,2- or 1,3-diol motifs, via the intramolecular oxy-Michael addition of in situ generated boronic acid hemiesters catalyzed by bifunctional aminothioureas (Scheme 4).[12] He proposed that multipoint interactions between the catalyst and substrate is crucial for high enantioselectivities, in which the tertiary amine moiety of the catalyst is proposed to play a role as a Lewis base coordinating to the boron atom of the boronic acid hemiester intermediate. Asano and Matsubara reported the asymmetric synthesis of five-membered cyclic acetals via a hemiacetal formation/intramolecular oxy-Michael addition cascade starting from γ-hydroxy-α,β-unsaturated carbonyl compounds and aldehydes (Scheme 5).[13,14] The synthetic utility of the obtained product was demonstrated by the further transformation into L-carnitine, a bioactive amino acid derivative.

Scheme 4. Asymmetric Synthesis of Cyclic Boronates Using Bifunctional Aminothiourea Catalysts



Scheme 5. Asymmetric Synthesis of Five-membered Cyclic Acetals Using Bifunctional Aminothiourea Catalysts



As described above, organocatalysis based on multipoint recognition via noncovalent interactions such as hydrogen bonding is a promising approach for asymmetric induction in intramolecular oxy-Michael additions. Therefore, the proper choice of such chiral organocatalysts should result in selective recognition of a specific chair-like conformation and thus enable the highly enantio- and diastereoselective construction of six-membered chiral oxacycles. This notion is the foundation for the development of novel synthetic methods throughout the author's research in this thesis.

2. Diastereoselective Construction of Chiral 1,3-Diol Motifs via Six-Membered Cyclic Acetal Formation

Chiral 1,3-diols are fundamental units of a variety of biologically active natural products and pharmaceuticals. The importance of these structures is exemplified by polyketides, which are one of the most representative classes of drug candidates (Figure 3).[15] These frameworks are also found in statins such as atorvastatin, a blockbuster lipid-lowering drug sold all over the world under the trade name Lipitor.[16]

As the development of efficient approaches to these compounds can contribute to the advance of pharmaceutical science, numerous methods for the stereoselective synthesis of chiral 1,3-diols have been developed.[17] Among them, the author has focused on a cascade transformation involving hemiacetalization and the subsequent intramolecular nucleophilic addition of a hydroxy group of the hemiacetal, affording 1,3-dioxanes as protected 1,3-diol motifs (Scheme 6). In this method, the stereoisomer of the 1,3-dioxane product with all the substituents in equatorial positions can be obtained preferentially due to the weaker unfavorable 1,3-diaxial interaction. A variety of related catalytic transformations have been reported to date, with some of the resulting products applied to the stereoselective syntheses of biologically active compounds.[18]

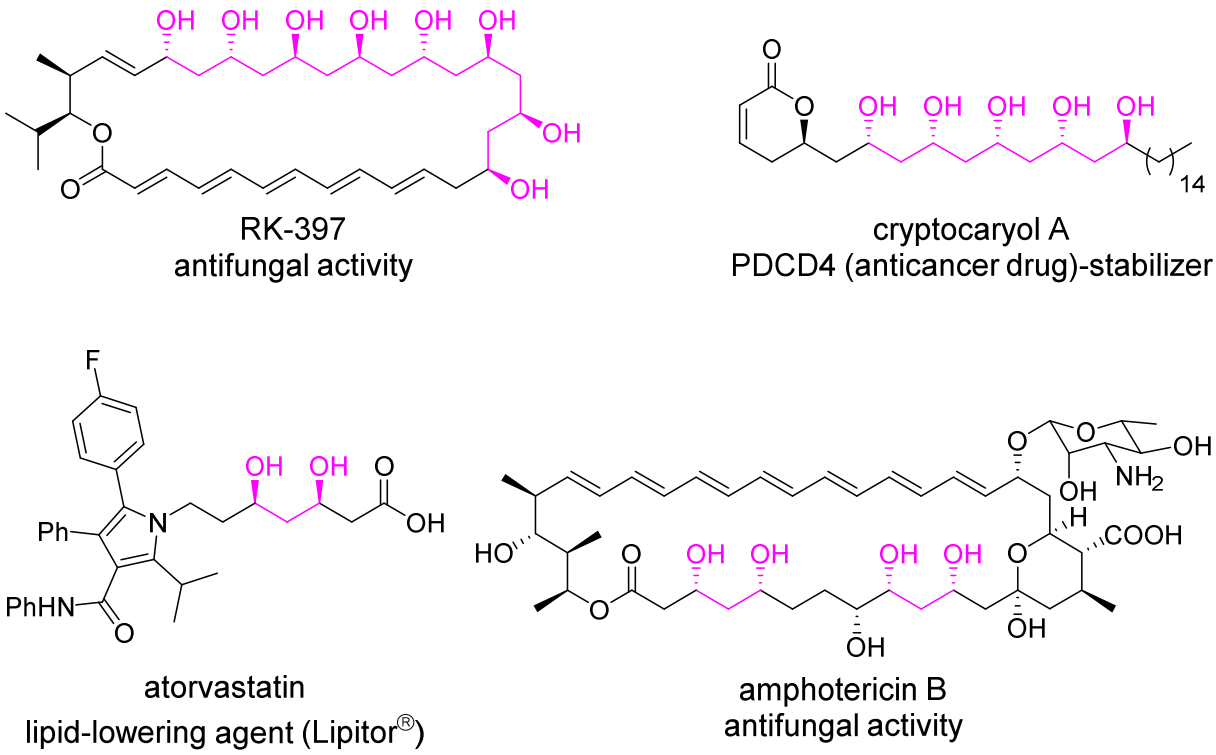
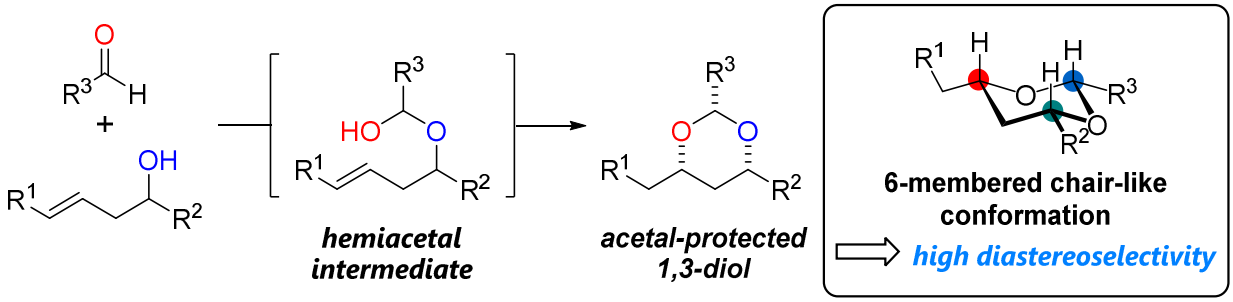


Figure 3. Selected examples of polyketides and statins bearing chiral 1,3-diols.

Scheme 6. Stereoselective Synthesis of 1,3-Dioxanes via Hemiacetal Formation

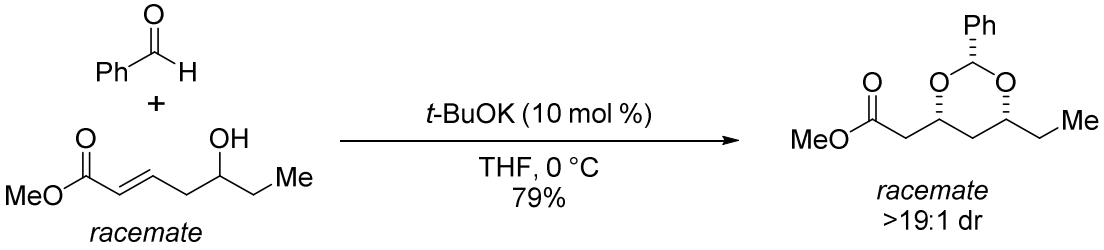


2.1. Hemiacetalization/Intramolecular Oxy-Michael Addition Cascade

The hemiacetalization/intramolecular oxy-Michael addition cascade reaction was pioneered by D. A. Evans and Prunet in 1993 (Scheme 7).[19] They established a base-catalyzed cascade reaction involving hemiacetalization and the subsequent intramolecular oxy-Michael addition

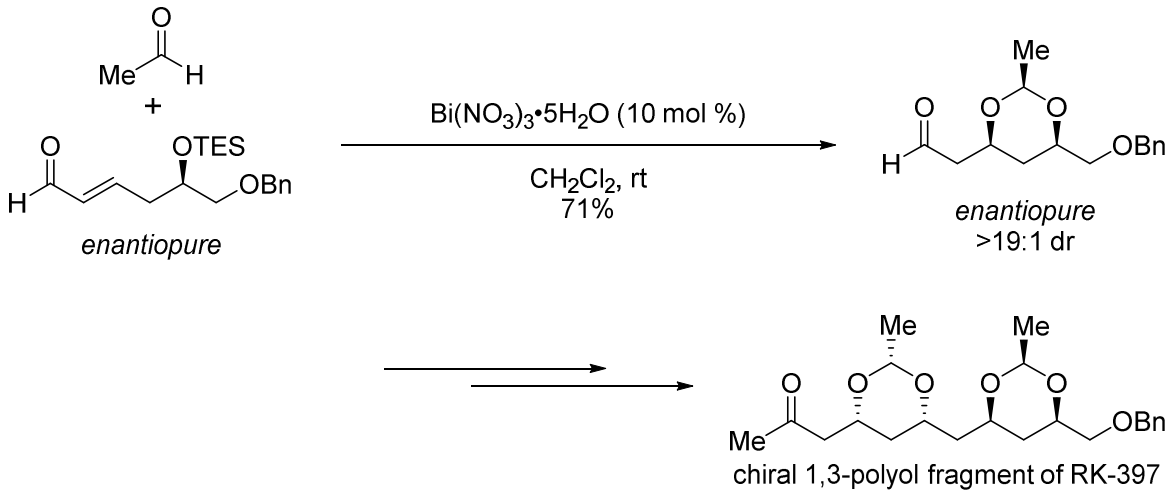
starting from δ-hydroxy-α,β-unsaturated compounds and benzaldehyde, affording *syn*-1,3-dioxanes in good yields with high diastereoselectivities. Several control experiments revealed that this reaction proceeds under thermodynamic control, predominantly affording a 1,3-dioxane with all-equatorial substituents. Prunet further explored the substrate scope for this type of reaction. Consequently, a wide range of Michael acceptors including α,β-unsaturated esters,[19] amides,[19] sulfones,[20] and sulfoxides,[21] can be used under similar reaction conditions.

Scheme 7. Base-catalyzed Diastereoselective Synthesis of *syn*-1,3-Dioxanes via Hemiacetalization/Oxy-Michael Addition Cascade



More recently, P. A. Evans succeeded in improving the utility of this transformation by replacing the strong base with an acidic bismuth (III) salt as the catalyst (Scheme 8).[22] Secondary alcohols bearing an α,β-unsaturated ketone or, even more synthetically useful, an α,β-unsaturated aldehyde, could be used under these mild conditions, exclusively affording the corresponding 1,3-dioxane with all-equatorial substituents. The synthetic utility of this reaction was demonstrated in an asymmetric synthesis of a 1,3-polyol fragment of RK-397, where the reaction was carried out using enantiomerically pure starting material. Owing to high diastereoselectivity and feasibility for subsequent transformations utilizing the remaining carbonyl moiety of the product, these methods have been broadly applied to stereoselective syntheses of complex molecules containing chiral 1,3-polyol structures.[23]

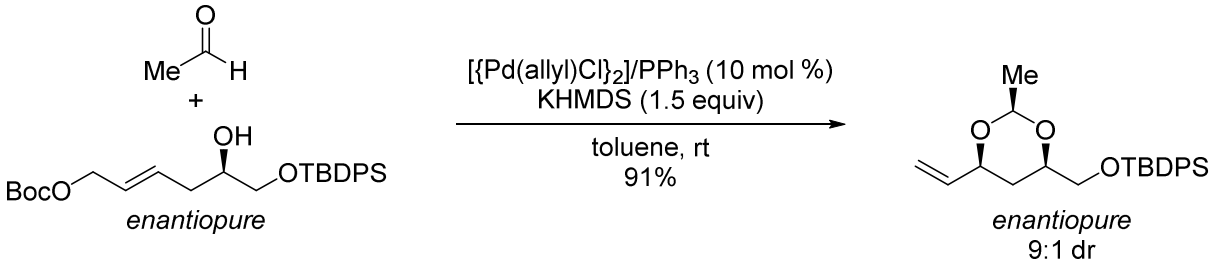
Scheme 8. Bismuth (III)-Catalyzed Diastereoselective Synthesis of *syn*-1,3-Dioxanes via Hemiacetalization/Oxy-Michael Addition Cascade



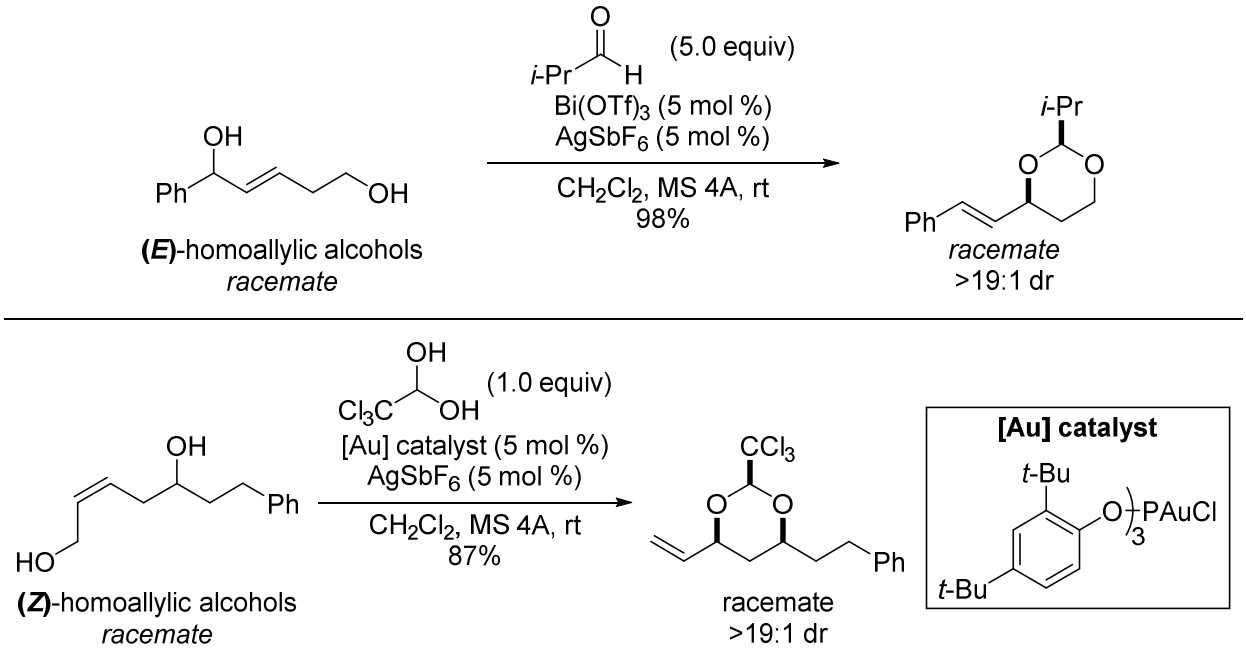
2.2. Hemiacetalization/Intramolecular Allylic Substitution Cascade

Transition-metal-catalyzed alkene activation is an alternative method for cyclization via C–O bond formation. In fact, successful six-membered ring formation via a hemiacetalization/allylic substitution cascade has been achieved using palladium,[24] bismuth,[25] and gold[25] as the transition metal catalysts (Schemes 9 and 10). These reactions afford the corresponding *syn*-1,3-dioxane products with good to high diastereoselectivities as a result of equilibration to the thermodynamically more stable isomer with all-equatorial substituents.

Scheme 9. Palladium-catalyzed Diastereoselective Synthesis of *syn*-1,3-Dioxanes via Hemiacetalization/Tsuji-Trost Reaction Cascade

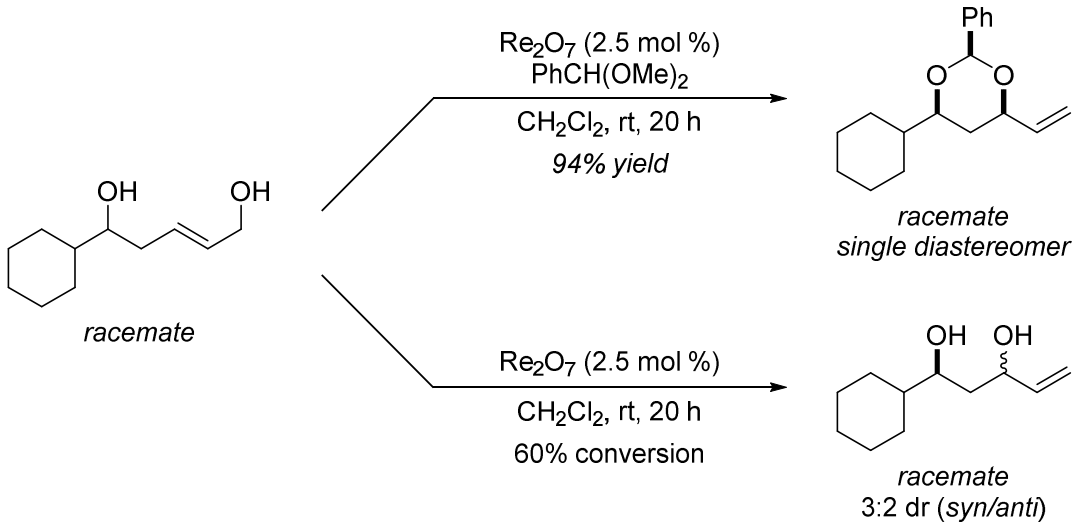


Scheme 10. Bismuth (III)- and Gold (I)-catalyzed Diastereoselective Synthesis of 1,3-Dioxanes via Hemiacetalization/Dehydrative Cyclization Cascade



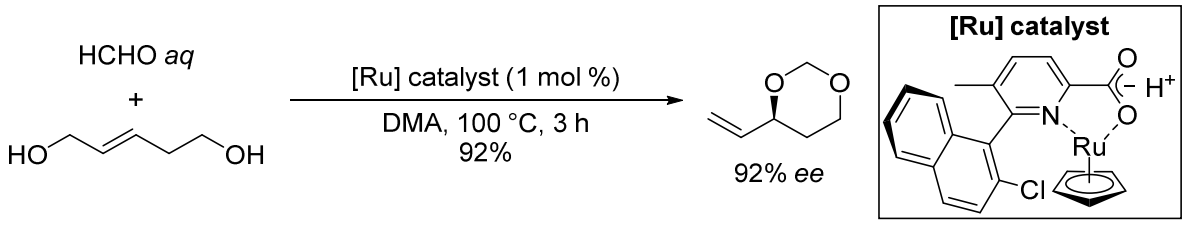
Meanwhile, Zakarian reported the rhenium-catalyzed synthesis of 1,3-dioxanes via transposition of allylic alcohols, which displays the significant advantage of six-membered ring formation on the regio- and diastereoselectivities of the reaction (Scheme 11).[26] When only allylic transposition takes place in the presence of Re_2O_7 as a catalyst, a 1,3-diol is obtained in moderate conversion with poor diastereoselectivity. However, trapping the in situ generated *syn*-1,3-diol via acetalization allows equilibration to the more stable stereoisomer of a six-membered ring, affording *syn*-1,3-dioxane as a single product in high yield.

Scheme 11. Rhenium-catalyzed Diastereoselective Synthesis of *syn*-1,3-Dioxanes via Allylic Transposition



The development of efficient methods such as the above-mentioned examples for constructing *syn*-1,3-diol motifs via six-membered acetal formation clearly indicates their significant utility for the stereoselective synthesis of biologically active compounds containing chiral 1,3-diol structures. However, despite various reports on diastereoselective methods, reports on an enantioselective approach have been limited. To the best of the author's knowledge, only one enantioselective example has been reported. In 2017, Kitamura reported that in the presence of a chiral ruthenium complex, a hemiacetalization/enantioselective allylic substitution cascade proceeds smoothly, affording a monosubstituted 1,3-dioxane with one chiral center constructed with high enantioselectivity (Scheme 12).[27] While this reaction is also applicable to enantioselective construction of other chiral modules, such as 1,2-diols and 1,2-/1,3-aminoalcohols, only one substrate shown in Scheme 12 was examined for chiral 1,3-dioxane synthesis, and the asymmetric construction of *syn*-1,3-diol motifs containing two chiral carbinols has not been reported.

Scheme 12. Chiral Ruthenium-catalyzed Enantioselective Synthesis of 1,3-Dioxane via Hemiacetalization/Enantioselective Dehydrative Cyclization Cascade



Thus, this research topic still has much room for improvement, and the development of methods for asymmetric induction in the diastereoselective formation of 1,3-diol structures bearing two chiral centers in particular is in high demand. To fill this void, the author investigated novel methods for the asymmetric construction of chiral 1,3-diol motifs via six-membered acetal formation. The progress of this research is described in Chapters through 4.

3. Kinetic Resolution of Chiral Tertiary Alcohols via Asymmetric Cyclization

Chiral tertiary alcohols are a class of important structures that exist in a wide variety of biologically active compounds (Figure 4). In addition, as they are composed of a stereogenic carbon center bearing four different substituents including a hydroxy group, they can be utilized as an efficient platform for accumulating multiple functionalities, as well as versatile chiral building blocks for the synthesis of functional molecules.

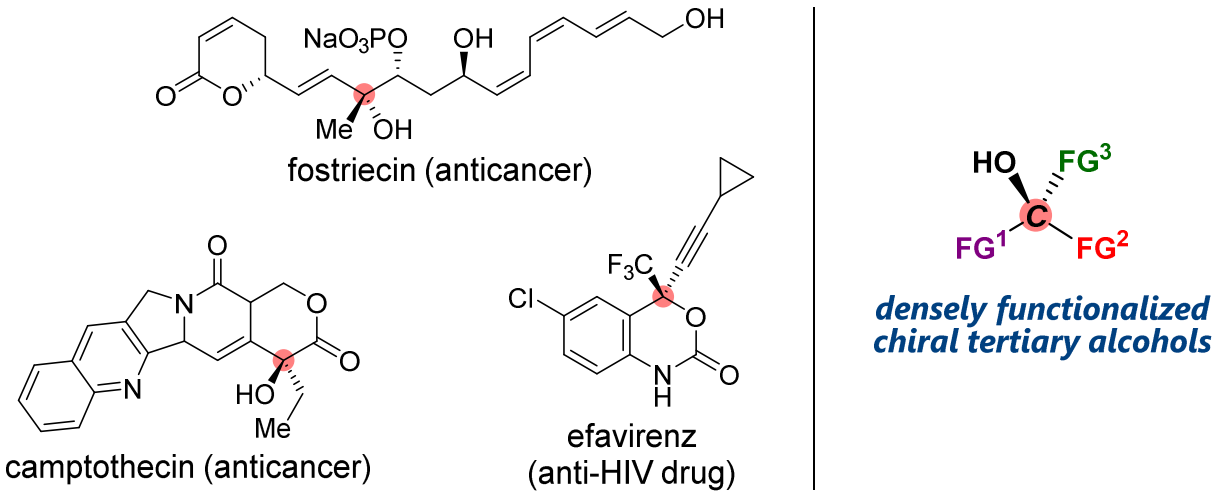
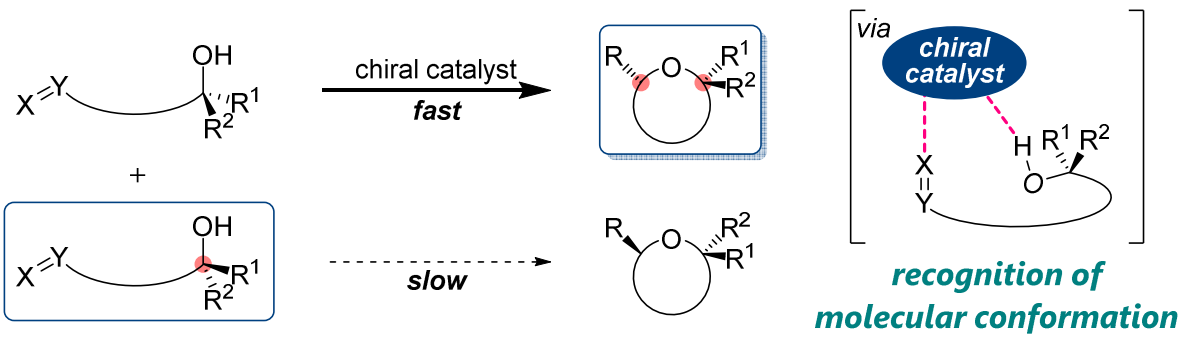


Figure 4. Biologically active compounds bearing chiral tertiary alcohols.

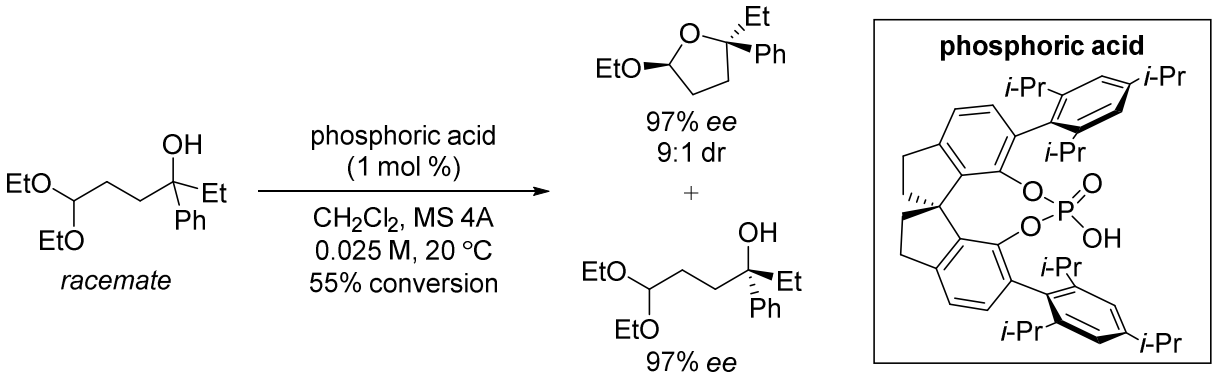
While the enantioselective addition of carbon nucleophiles to ketones has been actively investigated as one of the most straightforward methods for constructing chiral tertiary alcohols,[28] the kinetic resolution of racemic tertiary alcohols is a complementary method for the synthesis of densely functionalized chiral molecules.[29] The use of organocatalysts is an attractive approach for this because of their high functional group tolerance and thus the potential for the introduction of various functionalities into chiral tertiary alcohol substrates. Recent advances in organocatalytic kinetic resolution have expanded its applicability to a broad range of asymmetric transformations from various chiral substrates, some of which are generated in situ.[30] Among them, the author has focused on the asymmetric cyclization of chiral tertiary alcohols, where the catalysts can take advantage of noncovalent interactions for selective recognition of a specific molecular conformation (Scheme 13). In addition, this method provides optically active oxacycles bearing multiple stereogenic centers, one of which is fully substituted.

Scheme 13. Kinetic Resolution of Chiral Tertiary Alcohols via Asymmetric Cyclization

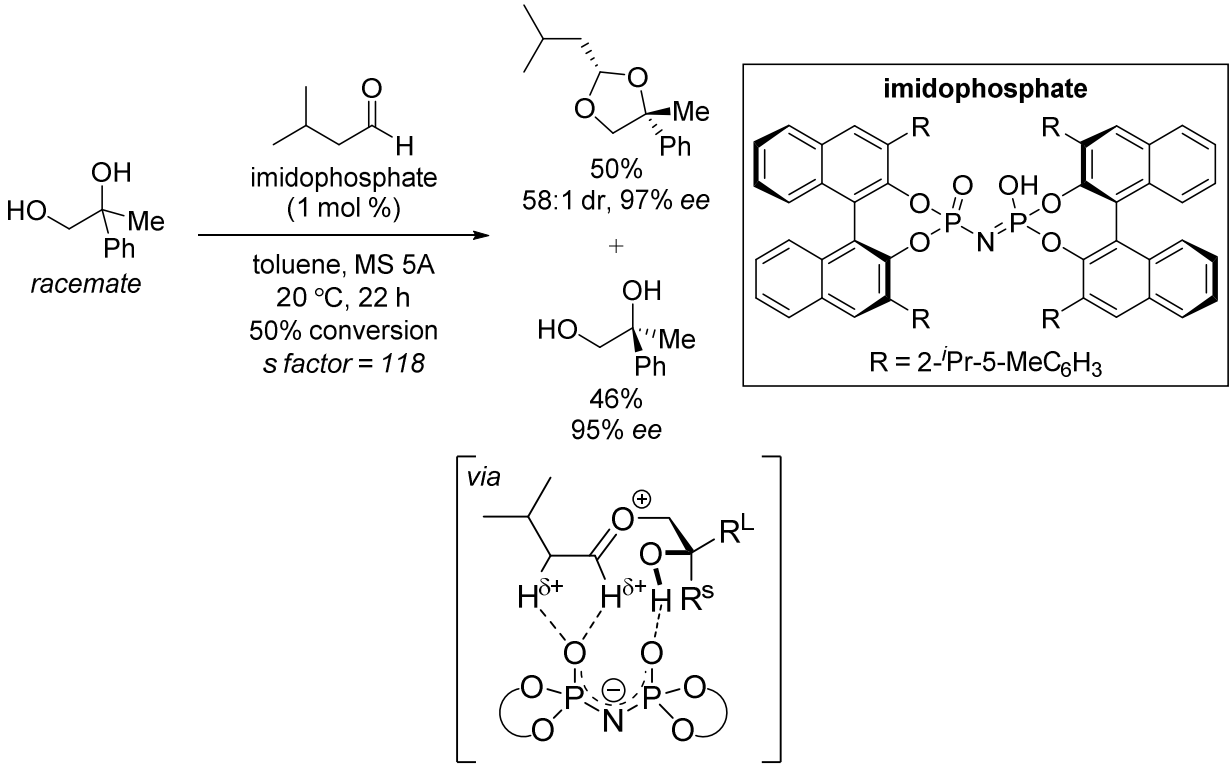


In 2010, List developed the kinetic resolution of homoaldols via asymmetric transacetalization (Scheme 14).[31] In the presence of a chiral phosphoric acid catalyst, both secondary and tertiary alcohols can be efficiently resolved, affording synthetically valuable chiral homoaldols with high enantioselectivities and chiral cyclic acetals with high enantio- and diastereoselectivities. He also reported the kinetic resolution of chiral diols using asymmetric acetalization by chiral imidodiphosphoric acid catalysts (Scheme 15).[32] Based on his previous studies,[33] the reaction is proposed to proceed via an oxocarbenium intermediate. The OH group at the tertiary alcohol may be hydrogen bonded to the chiral imidophosphate anion, while a C–H moiety of the oxocarbenium ion can additionally form hydrogen bonds with the anion to stabilize the transition state. More recently, kinetic resolution of chiral secondary and tertiary alcohols via asymmetric cycloetherification was developed by Asano and Matsubara (Scheme 16).[34] Initial experiments revealed that the use of bifunctional aminothioureas, a representative class of hydrogen-bonding catalysts, results in low stereoselectivities for this transformation. In contrast, chiral phosphoric acids, which also enable multipoint recognition of substrates via hydrogen bonding, give significantly better results. Several chiral tertiary alcohols bearing a pendant Michael acceptor can be obtained with moderate to high enantioselectivities after the kinetic resolution.

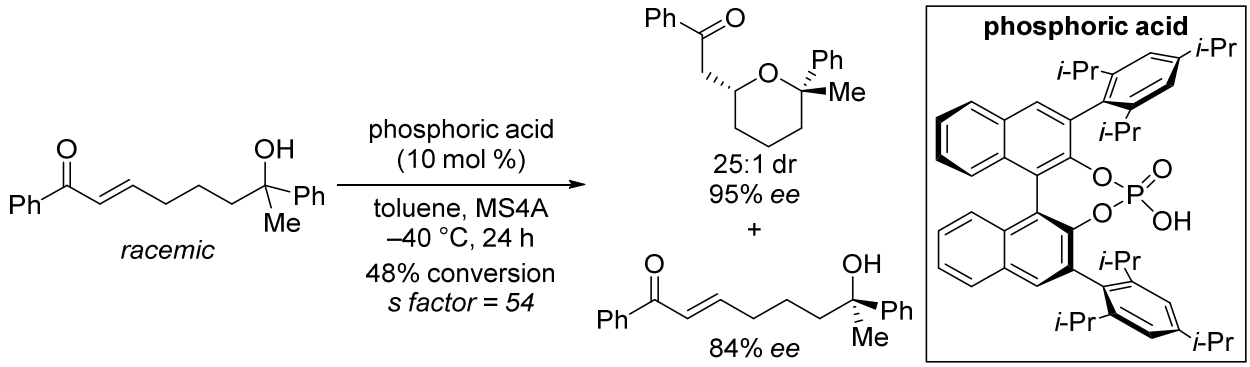
Scheme 14. Kinetic Resolution of Homoaldols via Asymmetric Transacetalization



Scheme 15. Kinetic Resolution of Diols via Asymmetric Transacetalization

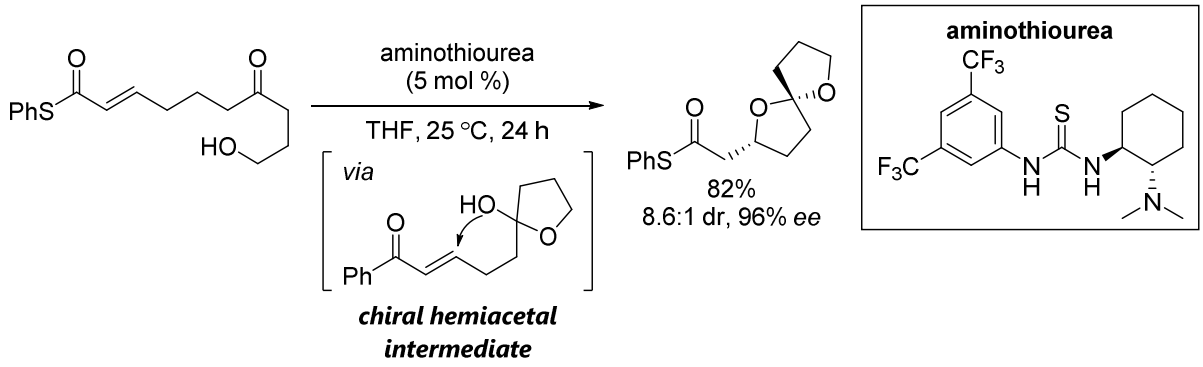


Scheme 16. Kinetic Resolution of Chiral Tertiary Alcohols via Organocatalytic Cycloetherification

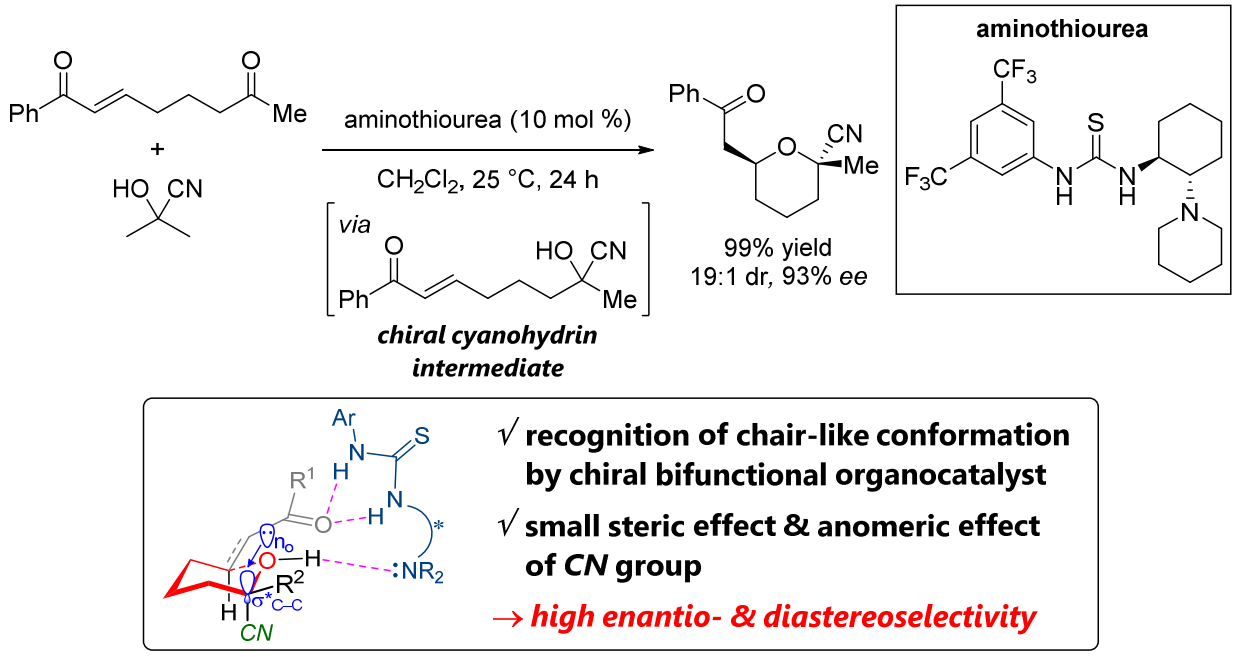


Asano and Matsubara succeeded in extending this methodology to the dynamic kinetic resolution of in situ generated chiral tertiary alcohols. Starting from dialkyl ketones bearing a pendant Michael acceptor and a hydroxy group as shown in Scheme 17, the reversible formation of hemiacetal intermediates as chiral tertiary alcohols and the subsequent kinetic resolution of these intermediates take place via organocatalytic intramolecular oxy-Michael addition.[35] This method provides a range of chiral spiroketal products in a highly enantio- and diastereoselective manner. More recently, they developed an efficient method for asymmetric synthesis of chiral tetrahydropyrans via dynamic kinetic resolution (Scheme 18).[36] In this method, the in situ formation of chiral tertiary alcohols is achieved by the reversible cyanation of ketones. The remarkably high stereoselectivities can be rationalized by the six-membered chair-like conformation of the chiral cyanohydrin intermediate, in which the cyano group is preferably located in the axial position due to its small steric size as well as a favorable anomeric effect. A chiral bifunctional aminothiourea catalyst selectively recognizes an intermediate with this conformation, leading to the formation of a six-membered oxacycle with the simultaneous construction of two stereogenic centers containing a tetrasubstituted chiral carbon.

Scheme 17. Dynamic Kinetic Resolution of in situ Generated Chiral Hemiacetals for Asymmetric Synthesis of Spiroketals



Scheme 18. Dynamic Kinetic Resolution of in situ Generated Chiral Cyanohydrins for Asymmetric Synthesis of Chiral Tetrahydropyrans



These examples suggest that organocatalytic kinetic resolution via highly stereoselective cyclization can be an alternative approach for the asymmetric synthesis of chiral tertiary alcohols or ethers that are difficult to achieve by conventional methods. Therefore, the author envisaged that this strategy could contribute to the development of a novel synthetic method to access chiral tertiary alcohols containing synthetically valuable tetrasubstituted chiral carbons. In chapter 5,

the author demonstrates the effectiveness of this strategy, focusing on the asymmetric construction of densely functionalized tetrasubstituted chiral carbons.

4. Thesis Overview

4.1. Asymmetric Construction of Chiral *syn*-1,3-Diol Motifs via Organocatalytic Six-membered Ring Formation (Chapters 1–4)

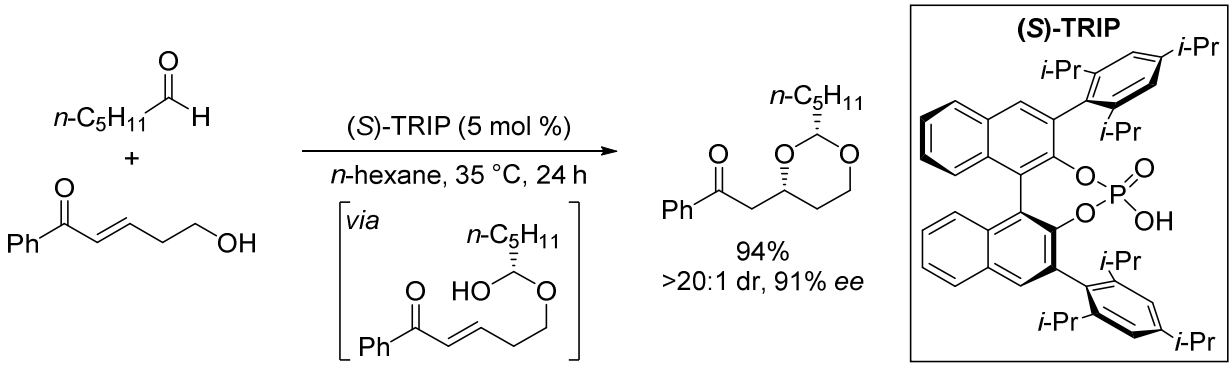
In order to develop asymmetric methods for the synthesis of chiral 1,3-diol motifs via six-membered cyclic acetal formation, the concept of multipoint recognition through hydrogen bonding by chiral organocatalysts is introduced (Chapter 1). Moreover, the diastereoselective reduction of the obtained products to form chiral 1,3,5-triol structures is also described (Chapter 2). The author further demonstrates that the asymmetric induction process developed in Chapter 1 can be applied to the kinetic resolution of chiral secondary alcohols (Chapter 3) and dynamic kinetic resolution of in situ generated chiral cyanohydrins (Chapter 4). Consequently, a variety of chiral 1,3-dioxanes are obtained in a highly stereoselective manner. These transformations suggest a novel strategy that facilitates the construction of a chiral 1,3-diol library for the advancement of pharmaceutical science.

4.1.1. Asymmetric Construction of 1,3-Dioxanes via a Hemiacetalization/Intramolecular Oxy-Michael Addition Cascade Using Chiral Phosphoric Acid Catalysts (Chapter 1)

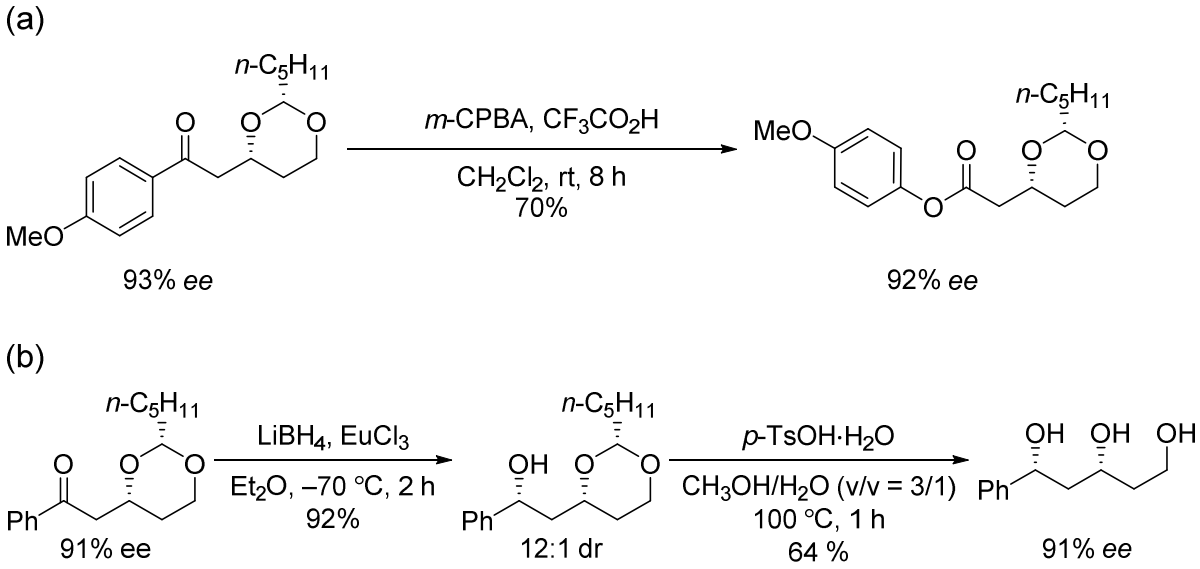
The author found that chiral phosphoric acids are suitable catalysts for enantioselective 1,3-dioxane construction via a hemiacetalization/intramolecular oxy-Michael addition cascade starting from δ-hydroxy-α,β-unsaturated ketones and aldehydes, affording optically active products with high enantioselectivities as well as good diastereoselectivities (Scheme 19).[37] In addition, the products were successfully transformed into optically active 1,3,5-triol motifs (Scheme 20).

These results indicate that the proposed method can provide useful chiral building blocks for the de novo synthesis of 1,3-polyol-containing biologically active compounds.

Scheme 19. Enantioselective 1,3-Dioxane Construction Catalyzed by Chiral Phosphoric Acids



Scheme 20. Transformations of 1,3-Dioxane Products

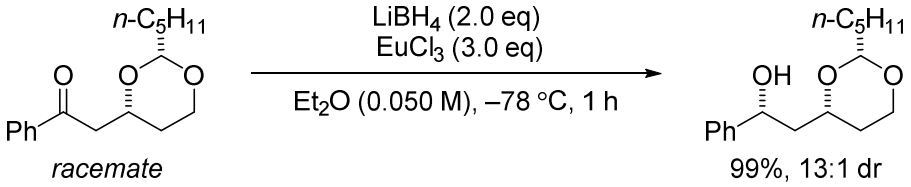


4.1.2. Diastereoselective Reduction of β-(1,3-Dioxan-4-yl)ketones (Chapter 2)

In spite of numerous reported methods for the diastereoselective reduction of carbonyl groups to afford 1,3-diol motifs, there is no method for the diastereoselective reduction of β-(1,3-dioxan-

4-yl)ketones, a useful precursor for chiral 1,3,5-triol structures. Therefore, the author optimized the conditions for the highly diastereoselective carbonyl reduction of these compounds. As a result, the use of lithium borohydride as a reducing agent in combination with europium(III) trichloride as an additive was found to exhibit high reactivity and diastereoselectivity (Scheme 21); the conditions were used for the optically active compound obtained in Chapter 1 (Scheme 20b).[38]

Scheme 21. Diastereoselective Reduction of β-(1,3-Dioxan-4-yl)ketones



4.1.3. Asymmetric *syn*-1,3-Dioxane Construction via Kinetic Resolution of Secondary Alcohols Using Chiral Phosphoric Acid Catalysts (Chapter 3)

Based on the results described in Chapter 1, the author further investigated the asymmetric synthesis of *syn*-1,3-dioxanes via kinetic resolution of secondary alcohols. As simultaneous stereocontrol of multiple chiral centers on the 1,3-dioxane ring is required for this transformation, the six-membered ring formation via a chair-like conformation with all equatorial substituents would be crucial for obtaining high diastereoselectivity (Figure 5). Moreover, a chiral phosphoric acid catalyst would make a pre-transition-state assembly with the matched enantiomer of the hemiacetal intermediate through multiple hydrogen bonds, where the catalyst would be distal to the chiral carbon of the secondary alcohol substrate, but proximal to the hemiacetal carbon. Thus, control of the chirality of the hemiacetal carbon in a six-membered chair-like conformation would lead to efficient kinetic resolution of secondary alcohols, which, when followed by an asymmetric intramolecular oxy-Michael addition, would afford optically active *syn*-1,3-dioxanes.

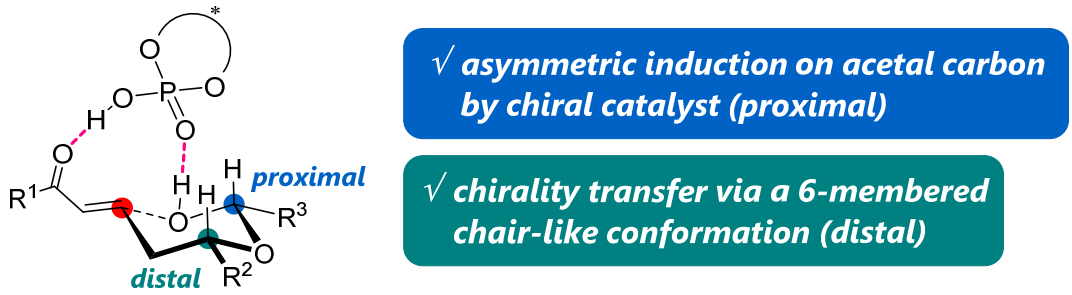
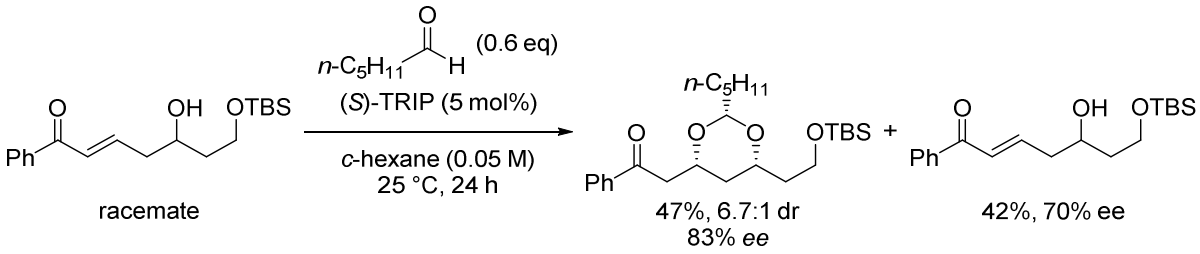


Figure 5. Proposed pre-transition-state assembly of intramolecular oxy-Michael addition using chiral phosphoric acid catalyst.

In fact, chiral phosphoric acid catalysts displayed good selectivities for the kinetic resolution of secondary alcohols via a hemiacetalization/intramolecular oxy-Michael addition cascade, affording the desired *syn*-1,3-dioxanes in high yields with high enantioselectivities as well as optically active secondary alcohols with good enantioselectivities (Scheme 22).[39] Results from the optimization studies suggest that the chiral phosphoric acid catalyst recognizes the chirality of the acetal carbon of the hemiacetal intermediate, which leads to efficient kinetic resolution of the secondary alcohols. The application of this method to an enantiodivergent synthesis as well as further elaborations of the obtained products demonstrate that the presented strategy offers an efficient asymmetric approach to access a series of chiral *syn*-1,3-diol motifs.

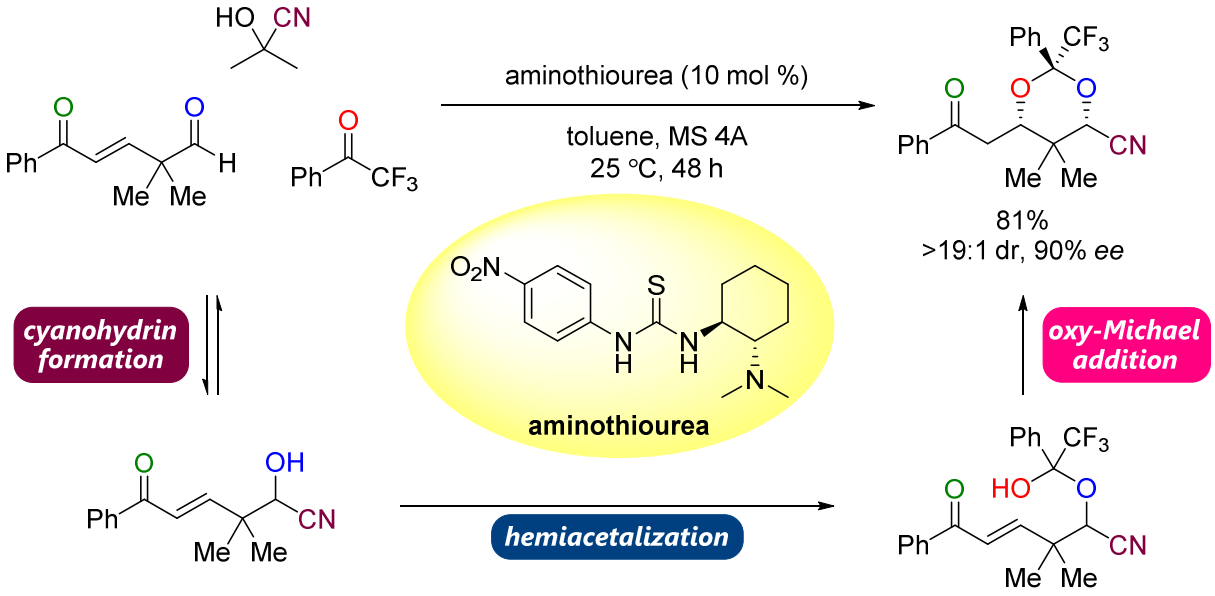
Scheme 22. Hemiacetalization/Intramolecular Oxy-Michael Addition Cascade via Kinetic Resolution of Secondary Alcohols



4.1.4. Enantio- and Diastereoselective Acetalization of δ-Oxoenones via Cyanohydrin Formation (Chapter 4)

The author then explored the application of this methodology to reactions of achiral substrates, with the goal of developing a method for the quantitative synthesis of chiral 1,3-diol motifs with the simultaneous construction of two stereogenic centers with high enantio- and diastereoselectivities. While such a method would be attractive in terms of the rapid increase in molecular complexity, to the best of the author's knowledge, there have been only a few asymmetric approaches, which provided chiral 1,3-diols in an *anti*-selective fashion.[40] Thus, the development of the complementary 1,3-*syn*-selective method in a single operation from achiral substrates is of great importance. Inspired by the previous study described in Scheme 18, the author designed a dynamic kinetic resolution process comprising a reaction sequence of reversible cyanohydrin formation, hemiacetalization, and intramolecular oxy-Michael addition (Scheme 23). The investigation of the reaction conditions revealed that the combination of bifunctional aminothiourea catalysts with a trifluoromethyl ketone as the acetalization reagent is crucial for promoting the desired reaction in a highly chemoselective manner. As a result, the desired chiral *syn*-1,3-dioxanes could be obtained in greater than 50% yields with high enantio- and diastereoselectivities.[41]

Scheme 23. Asymmetric Construction of Chiral *syn*-1,3-Dioxanes via Dynamic Kinetic Resolution of Chiral Cyanohydrins

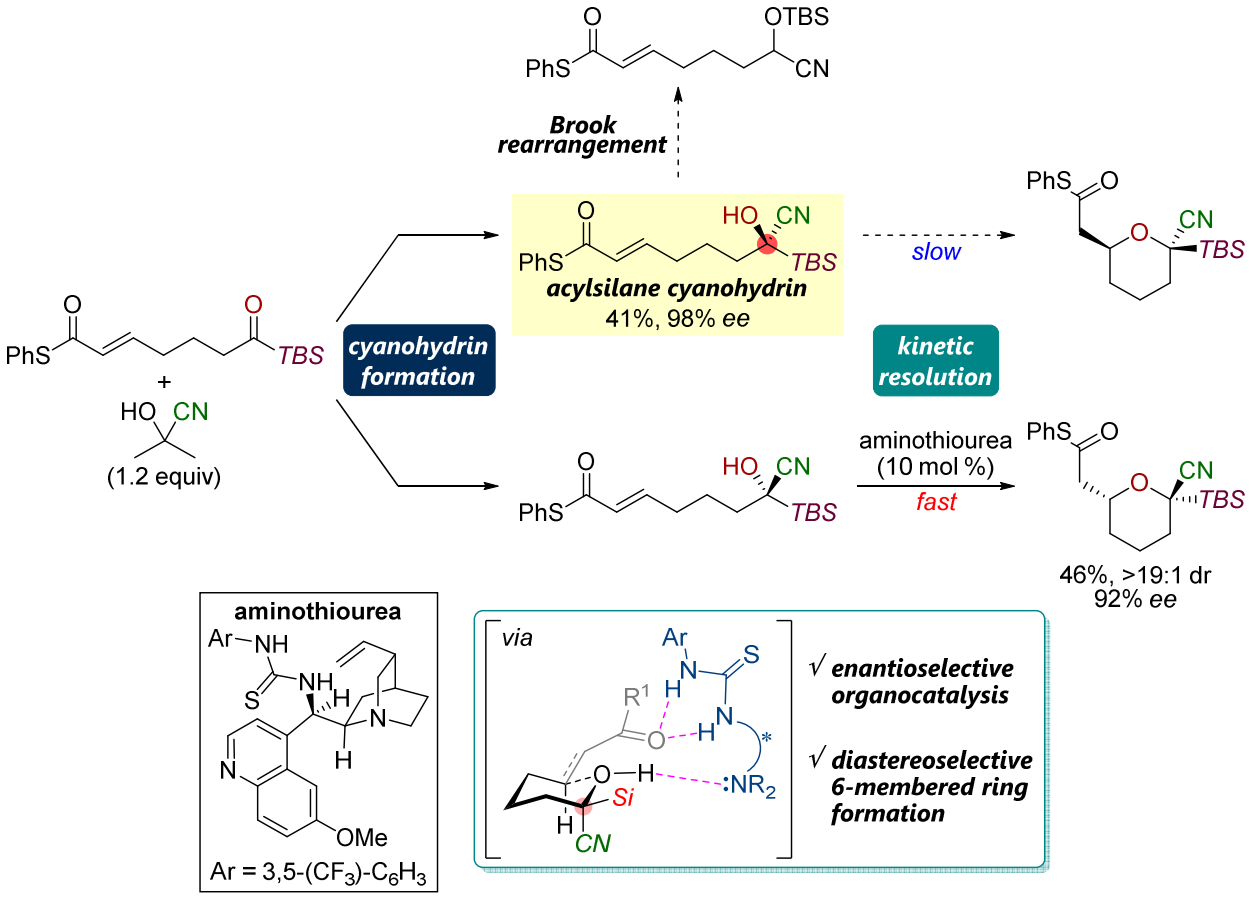


4.2. Kinetic Resolution of Acylsilane Cyanohydrins via Organocatalytic Cycloetherification (Chapter 5)

Having established the methods for asymmetric six-membered ring formation as described above, the author then focused his attention to applying this methodology involving kinetic resolution of chiral alcohols to the asymmetric synthesis of acyclic chiral tertiary alcohols. Therefore, the author decided to develop an asymmetric cyanation reaction for the synthesis of optically active cyanohydrins derived from acylsilanes. To the best of the author's knowledge, optically active acylsilane cyanohydrins have never been synthesized by a non-enzymatic process, and there remains a significant limitation in the substrate scope. Although the Brook rearrangement,[42] which easily takes place from the desired acylsilane cyanohydrins under basic conditions, was expected to be a competing side reaction, the author envisioned that the proposed method as shown in Scheme 24 would suppress the side reaction by taking advantage of in situ formation of the acylsilane cyanohydrins from more easily available acylsilanes under nearly

neutral conditions. Furthermore, the combination of enantioselective organocatalytic cycloetherification with diastereoselective six-membered ring formation would allow for efficient kinetic resolution of the in situ generated acylsilane cyanohydrins, achieving high enantioselectivities. In fact, a proper choice of bifunctional aminothiourea catalysts enabled the kinetic resolution while the Brook rearrangement was significantly suppressed.[43] Moreover, the obtained enantioenriched product could be further derivatized without loss of enantiomeric purity, indicating their potential as useful building blocks for the synthesis of chiral organosilanes. This organocatalytic method therefore offers a novel strategy to access densely-functionalized tetrasubstituted chiral carbons bearing silyl, cyano, and hydroxy groups.

Scheme 24. Asymmetric Cyanation of Acylsilanes via Organocatalytic Cycloetherification



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Instrumental and Materials

^{1}H and ^{13}C Nuclear magnetic resonance spectra were taken on a Varian UNITY INOVA 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer using tetramethylsilane as an internal standard for 1H NMR (δ = 0 ppm) and $CDCl_3$ as an internal standard for ^{13}C NMR (δ = 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F, 188 MHz) spectrometer with hexafluorobenzene as an internal standard (δ = 0 ppm). Mass spectra were recorded on a Thermo Scientific Exactive (ESI, APCI) spectrometers. High performance liquid chromatography (HPLC) was performed with a SHIMADZU Prominence. Infrared (IR) spectra were determined on a SHIMADZU IR Affinity-1 spectrometer. Melting points were determined using a YANAKO MP-500D. Optical rotations were measured on a HORIBA SEPA-200. X-ray data were taken on Bruker Smart APEX X-Ray diffractometer and Rigaku XtaLAB mini diffractometer and Rigaku R-AXIS RAPID diffractometer equipped with a CCD detector. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and/or such as an aqueous alkaline $KMnO_4$ solution followed by heating. Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Unless otherwise noted, commercially available reagents were used without purification.

Chapter 1

A Chiral Phosphoric Acid Catalyst for Asymmetric Construction of 1,3-Dioxanes

A novel method of enantioselective 1,3-dioxane construction via a hemiacetalization/ intramolecular oxy-Michael addition cascade by a chiral phosphoric acid catalyst was developed. The product was successfully transformed into an optically active 1,3-polyol motif, indicating that the proposed reaction can provide useful chiral building blocks for the de novo synthesis of polyketides.

Introduction

The oxy-Michael addition is one of most important methods for the introduction of oxygen into the β-position of carbonyl compounds.[1] In particular, stereoselective construction of 1,3-dioxanes via a hemiacetalization/intramolecular oxy-Michael addition cascade is a well-designed approach to synthesize stereodefined 1,3-diols found in polyketides, which are promising candidates for therapeutics (Scheme 1 and Fig. 1).[2,3] Indeed, such transformations have been utilized in the synthesis of a number of pharmacologically important molecules.[4] However, although several diastereoselective methods from chiral substrates under basic or acidic conditions have been reported,[5] enantioselective methods have remained largely unexamined thus far due to the lack of a useful strategy for asymmetric induction in the intramolecular oxy-Michael addition reaction.

Recently, Asano and Matsubara have developed an efficient methodology for enantioselective intramolecular oxy-Michael addition reactions by utilizing multipoint recognition through hydrogen bonding with bifunctional organocatalysts.[6–8] Intramolecular oxy-Michael additions from hemiacetal intermediates to afford 5-membered cyclic acetals, namely 1,3-dioxolanes, were conducted by using bifunctional aminothiourea catalysts. Such transformations, followed by deacetalization, proved to be efficient protocols for formal hydration to afford optically active polyols.[6b,c,f] However, as the aminothiourea catalysts do not have a sufficient activity to effect the construction of 6-membered 1,3-dioxanes, the author chose to focus on chiral phosphoric acids, because they have moderately higher acidity than thioureas and the following merits.[9] Firstly, the phosphoric acid catalysts possess both acidic and basic sites, allowing for multipoint recognition of a substrate through hydrogen bonding in the oxycyclization. In addition, such dual functionality provides double activation of a substrate for cyclization, thus leading to sufficient catalytic activity even without particularly high acidity, which is unsuitable in this transformation since the hemiacetal intermediates or the acetal products will be decomposed through the formation of oxocarbenium ions. Finally, an appropriate choice of substituents at the 3- and 3'-positions of

the catalysts enables their acidity and steric character to be finely tuned. Herein, the author demonstrates novel asymmetric 1,3-dioxane formation via a hemiacetalization/intramolecular oxy-Michael addition cascade using a chiral phosphoric acid catalyst.[10,11]

Scheme 1. 1,3-Dioxane Construction *via* Hemiacetalization/Intramolecular Oxy-Michael Addition Cascade

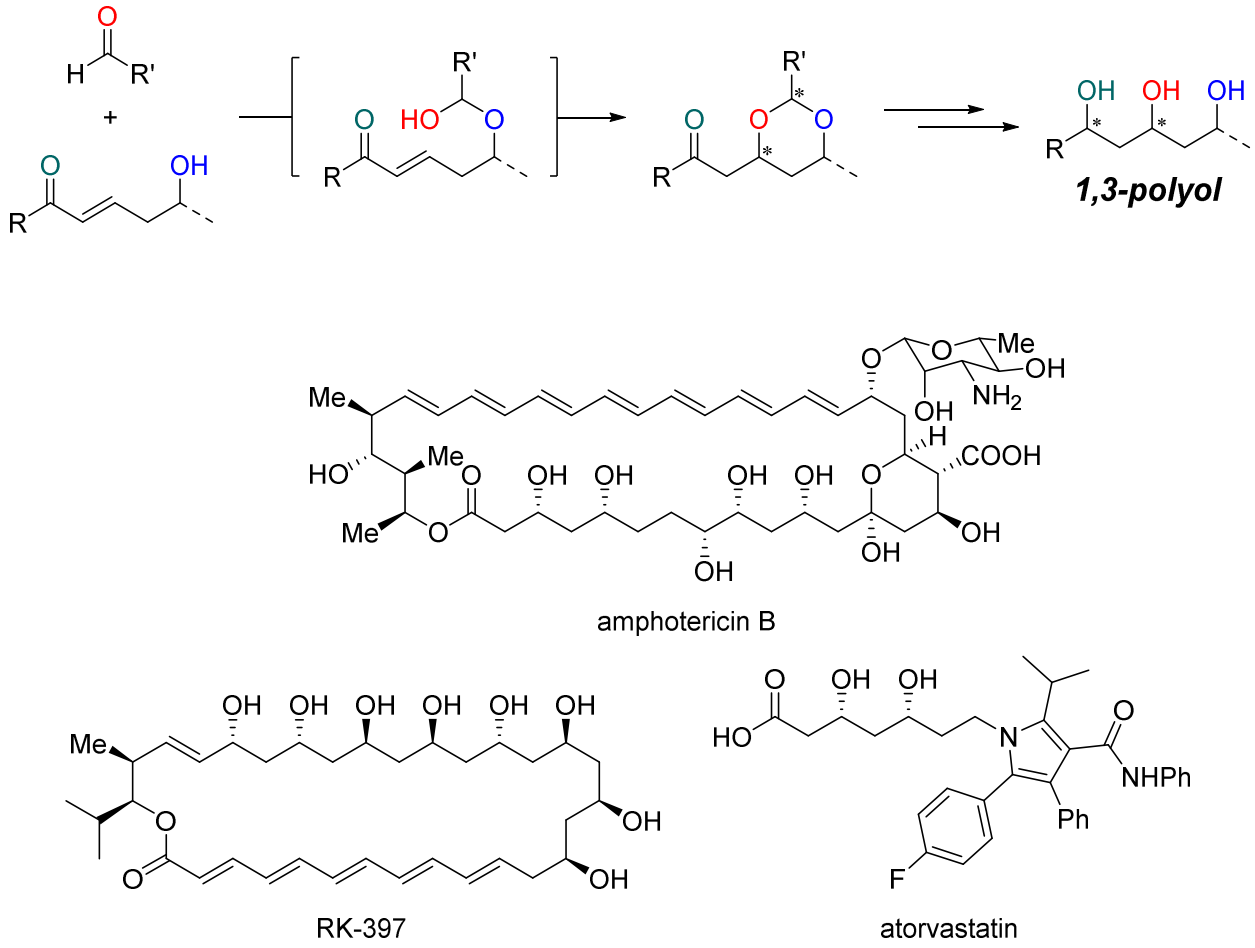
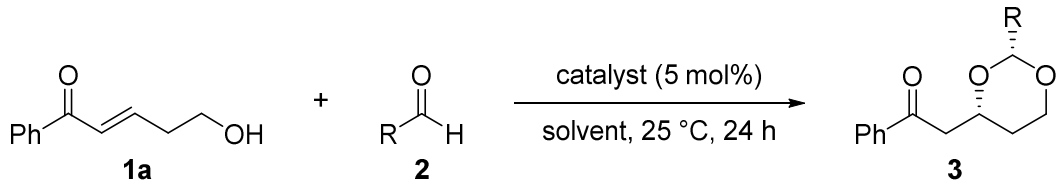


Figure 1. 1,3-Polyols in pharmaceutical compounds.

Results and Discussion

The author began by investigating the reaction between (*E*)-5-hydroxy-1-phenylpent-2-en-1-one (**1a**) and cyclohexanecarbaldehyde (**2a**) (Table 1) in the presence of 5 mol% of chiral phosphoric acid catalysts **4** (Fig. 2) in benzene at 25 °C. As expected, 1,3-dioxane product **3** was obtained enantioselectively as a single diastereomer (Table 1, entries 1–5), with (*S*)-TRIP (**4a**) proving to be the most promising among the various catalysts investigated (Table 1, entry 1). Using **4a** as a catalyst, reactions with other aldehydes **2** were also investigated (Table 1, entries 6–13). While the use of pivalaldehyde (**2d**) resulted in poor enantioselectivity, unbranched aliphatic aldehydes were shown to be efficient, with **2f** exhibiting the highest enantioselectivity (Table 1, entry 10). The use of benzaldehyde (**2i**) was also investigated, but failed to afford the desired reaction product (Table 1, entry 13). Subsequently, a range of reaction solvents were investigated (Table 1, entries 14–21), and it was found that less polar solvents gave improved yields and higher enantioselectivities (Table 1, entries 14–16). The enantioselectivity of the reaction was further improved by carrying out the reaction at lower concentrations in toluene at 35 °C (Table 1, entry 22).[13] In addition, the use of cyclohexane as a solvent also resulted in an enhanced yield, and only a slight loss of enantioselectivity was observed (Table 1, entry 23).

Table 1. Optimization of Conditions[a]



Entry	Catalyst	R (**2**)	Solvent	Yield (%)[b,c]	*ee* (%)
1	**4a**	Cy (**2a**)	benzene	56	80
2	**4b**	Cy (**2a**)	benzene	59	17
3	**4c**	Cy (**2a**)	benzene	21	–43

Table 1. (Continued)

4	**4d**	Cy (**2a**)	benzene	80	36
5	**4e**	Cy (**2a**)	benzene	52	5
6	**4a**	*i*-Pr (**2b**)	benzene	57	79
7	**4a**	*i*-Bu (**2c**)	benzene	64	71
8	**4a**	*t*-Bu (**2d**)	benzene	33	11
9	**4a**	Et (**2e**)	benzene	60	78
10	**4a**	*n*-C_5H_{11} (**2f**)	benzene	74	86
11	**4a**	*n*-C_9H_{19} (**2g**)	benzene	72	82
12	**4a**	$PhCH_2CH_2$	benzene	76	85
13	**4a**	Ph (**2i**)	benzene	<1	—
14	**4a**	*n*-C_5H_{11} (**2f**)	toluene	83	87
15	**4a**	*n*-C_5H_{11} (**2f**)	hexane	80	83
16	**4a**	*n*-C_5H_{11} (**2f**)	*c*-hexane	92	85
17	**4a**	*n*-C_5H_{11} (**2f**)	CH_2Cl_2	76	68
18	**4a**	*n*-C_5H_{11} (**2f**)	Et_2O	40	82
19	**4a**	*n*-C_5H_{11} (**2f**)	CPME[e]	18	86
20	**4a**	*n*-C_5H_{11} (**2f**)	EtOAc	29	81
21	**4a**	*n*-C_5H_{11} (**2f**)	CH_3CN	<5	58
22[d]	**4a**	*n*-C_5H_{11} (**2f**)	toluene	54	93
23[d]	**4a**	*n*-C_5H_{11} (**2f**)	*c*-hexane	94	91

[a]Reactions were run using **1a** (0.25 mmol), **2a** (0.25 mmol), and catalyst (0.025 mmol) in solvent (0.50 mL). [b]Isolated yields. [c]The diastereomeric ratio was ≥20:1 in all cases. [d]Reaction was run at 0 ºC. [e]Reaction was run using 1 mol % of **4a** (0.0025 mmol). [f]Reaction was run at –20 ºC.

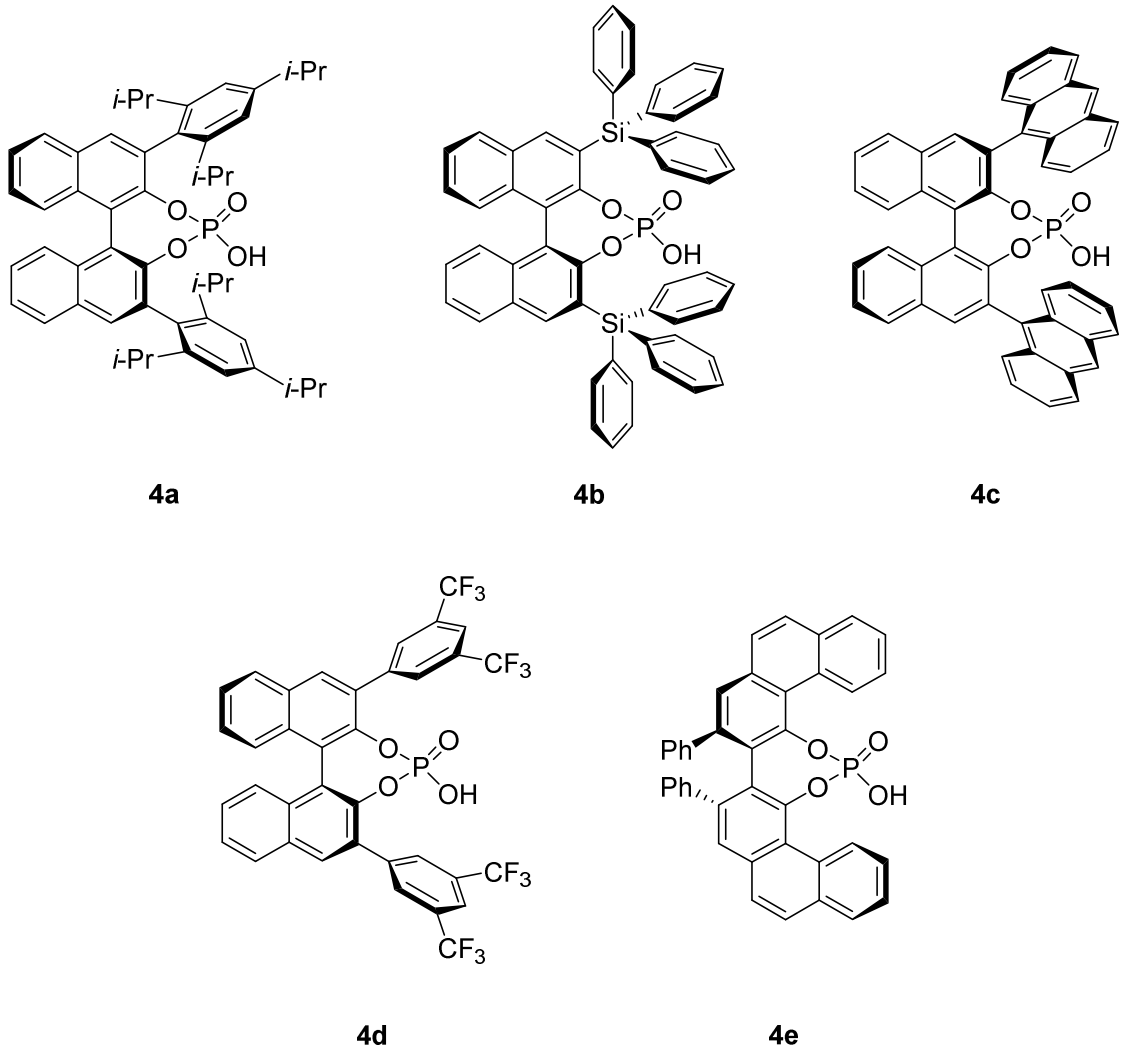
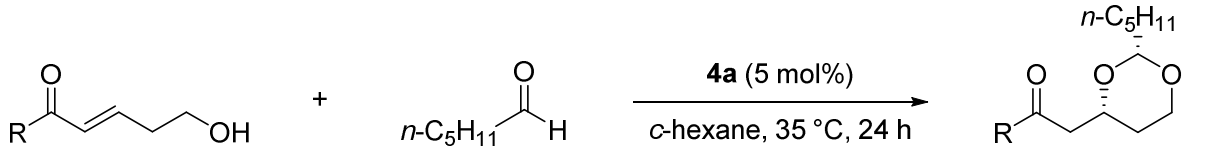


Figure 2. Chiral phosphoric acid catalysts.

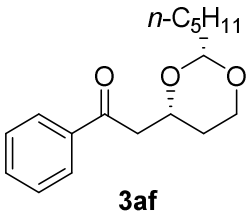
With the optimal conditions for the transformation established, the author explored the substrate scope for the reaction (Table 2). It was found that both electron-rich and electron-deficient enones gave high enantioselectivities (**3bf** and **3cf**). Substrates bearing 4-methylphenyl, 2-naphthyl, and 4-bromophenyl groups were also suitable, and afforded the corresponding 1,3-dioxanes in high yields and enantioselectivities (**3df**, **3ef**, and **3ff**). In addition, although the use of an aliphatic enone resulted in moderate enantioselectivity under the current conditions (**3gf**), better enantioselectivity was attained in the reaction of an alkenyl ketone (**3hf**), allowing further modifications such as regioselective hydration to approach higher polyols. Furthermore, although

no desired product could be obtained in the reaction from an α,β-unsaturated ester substrate, product **3bf** could be transformed into the corresponding ester **5** by means of Baeyer–Villiger oxidation using *m*-CPBA and TFA, without loss of optical purity (Scheme 2). This modification allows for further extension of this compound for the synthesis of longer polyketide structures through iterative manipulations of an established route,[4j,k,s] consisting of the reduction to the formyl group followed by allylation, olefin metathesis with acrylates, and another diastereoselective acetalization.[5a,b] The product can therefore be regarded as a useful chiral building block for polyketide synthesis. The absolute configuration of **3ef** was determined by X-ray crystallography, and the configurations of all other products were assigned analogously.

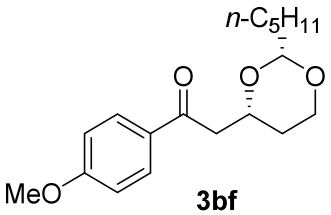
Table 2. Substrate Scope[a]



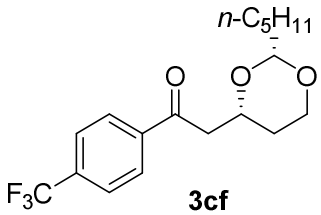
1 **2f** **3**



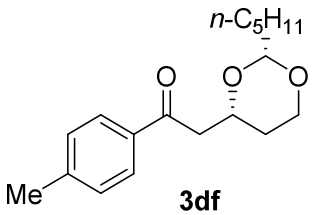
3af
94%
91% *ee*



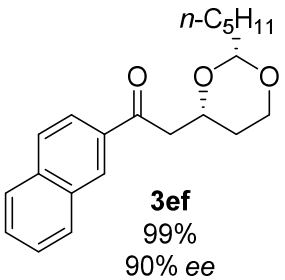
3bf
70%
93% *ee*



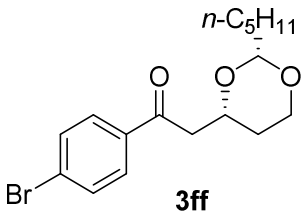
3cf
65%
89% *ee*



3df
75%
90% *ee*

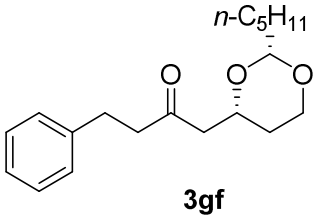


3ef
99%
90% *ee*

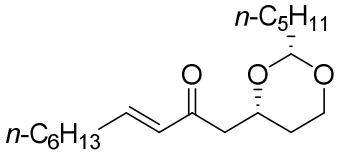


3ff
74%
90% *ee*

Table 2. (Continued)



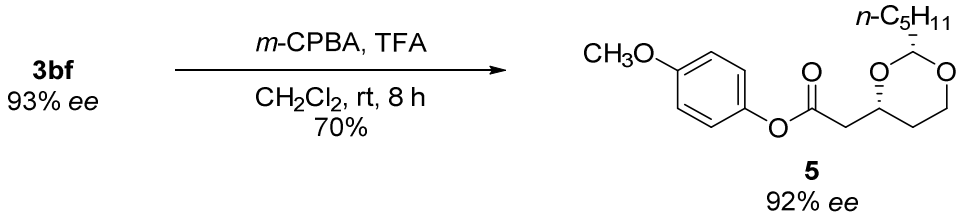
3gf
53%
63% *ee*



3hf
70%
78% *ee*

[a]Reactions were run using **1** (0.10 mmol), **2f** (0.20 mmol), and catalyst **4a** (0.0050 mmol) in cyclohexane (2.0 mL). Yields represent material isolated after silica gel column chromatography. The diastereomeric ratio was ≥20:1 in all cases.

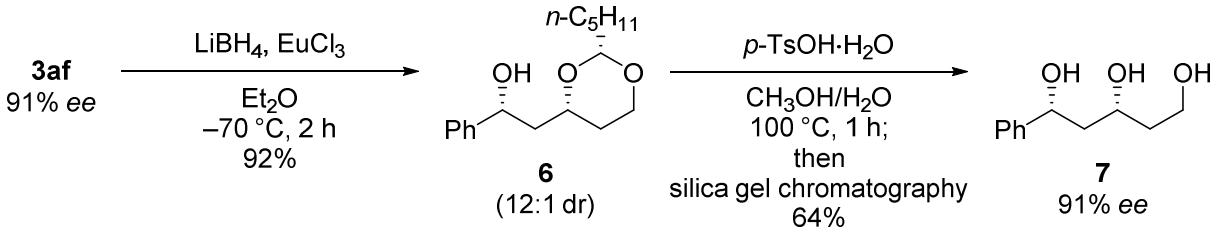
Scheme 2. Baeyer–Villiger Oxidation of 3bf



5
92% *ee*

The use of the obtained product in the asymmetric synthesis of a chiral 1,3,5-triol was then demonstrated. Reduction of **3af** with lithium borohydride in the presence of europium chloride afforded the corresponding alcohols in a 12:1 diastereomeric ratio, in which *syn*-isomer **6** was the major product.[13] Subsequent deacetalization of the diastereomer mixture, followed by isolation of the major diastereomer using flash silica gel column chromatography, gave chiral 1,3,5-triol **7** with high optical purity (Scheme 3).

Scheme 3. Synthesis of Chiral 1,3,5-Triol 7



Conclusion

In summary, the author has presented a novel enantioselective hemiacetalization/ intramolecular oxy-Michael addition cascade for the construction of 1,3-dioxanes, mediated by a chiral phosphoric acid catalyst. In addition, the utility of the products for the construction of stereodefined 1,3-polyol motifs was also demonstrated. These results indicate that the proposed methodology utilizing the dual functional organocatalyst opens a new avenue for the *de novo* synthesis of optically active polyketides.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification.

General procedure for asymmetric construction of 1,3-dioxane 3

To a 5-mL vial were added sequentially δ-hydroxy-α,β-unsaturated ketones **1** (0.10 mmol), cyclohexane (2.0 mL), aldehyde **2** (0.20 mmol) and phosphoric acid catalyst **4a** (0.005 mmol). The mixture was stirred in an oil bath maintained at 35 °C for 24 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **4a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel

column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent afforded the corresponding 1,3-dioxanes **3**.

Racemic compounds were prepared using HBF_4 or (±)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate as a catalyst.

General procedure for the preparation of δ-hydroxy-α,β-unsaturated ketones 1

To a solution of 1,3-propanediol (2.5 g, 33 mmol) in THF (80 mL) was added *n*-BuLi (20 mL, 1.63 M in hexane, 33 mmol) dropwise at 0 °C. After the mixture was stirred for 1 h, a solution of *tert*-butyldimethylsilyl chloride (4.5 g, 30 mmol) in THF (10 mL) was added, and the reaction was allowed to warm to ambient temperature. After being stirred for additional 23 h, the reaction was quenched with H_2O (10 mL), and the mixture was subsequently extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5/1) as an eluent gave 3-(*tert*-butyldimethylsilyloxy)-propan-1-ol as a colorless oil in 94% yield: CAS RN [73842-99-6]. ^{1}H NMR ($CDCl_3$) δ 3.84 (t, *J* = 5.0 Hz, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 1.78 (tt, *J* = 5.5, 5.0 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 63.0, 62.5, 34.2, 25.9, 18.2, –5.5.

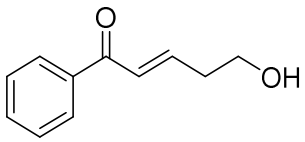
3-(*tert*-Butyldimethylsilyloxy) propan-1-ol (5.7 g, 30 mmol) was dissolved in EtOAc (100 mL, 0.30 M), and IBX (25 g, 90 mmol) was added. The resulting suspension was stirred vigorously in an oil bath maintained at 80 °C for 11 h. Subsequently, the reaction was cooled to ambient temperature and then filtered. The filter cake was washed with EtOAc, and the combined filtrates were concentrated to yield 3-(*tert*-butyldimethylsilyloxy)propanal as a colorless oil in 88 % yield, which was used for the next step without further purification: CAS RN [87184-81-4]. ^{1}H NMR ($CDCl_3$) δ 9.80 (t, *J* = 2,0 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.60 (dt, *J* = 6.0, 2.0 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 202.2, 57.4, 46.5, 25.7, 18.2, –5.5.

3-(*tert*-Butyldimethylsilyloxy)propanal (0.90 g, 4.8 mmol) and a stabilized ylide (5.26 mmol) were dissolved in THF (20 mL), and the solution was refluxed in an oil bath at 100 °C for hours.

After the solution was cooled to ambient temperature, solvents were removed in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 20/1) as an eluent gave the corresponding (*E*)-5-(*tert*-butyldimethylsilyloxy)pent-2-en-1-one. Subsequently, it was dissolved in CH_3CN (7.7 mL), and 46–48% aqueous HF (380 μL) was added to the solution. After being stirred for 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was subsequently extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave the corresponding δ-hydroxy-α,β-unsaturated ketone **1**.

Ylides commercially unavailable were prepared by the literature procedure.[14] The characterization results of **1** are as below.

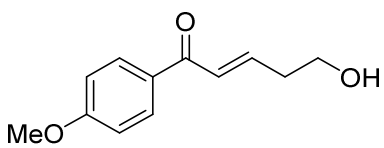
(*E*)-5-Hydroxy-1-phenylpent-2-en-1-one (1a): CAS RN [946523-96-2].



Colorless oil; 75% yield (for last 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.94 (m, 2H), 7.56 (m, 1H), 7.47 (m, 2H), 7.05 (dt, *J* = 15.0, 7.0 Hz, 1H), 7.00 (dt, *J* = 15.0, 1.0 Hz, 1H), 3.85 (t, *J* = 6.0 Hz, 2H), 2.60 (m, 2H), 1.61 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 190.5, 145.5, 137.7, 132.8, 128.6, 128.0, 61.1, 36.0.

(*E*)-5-Hydroxy-1-(4-methoxyphenyl)pent-2-en-1-one (1b): CAS RN [1005326-88-4].

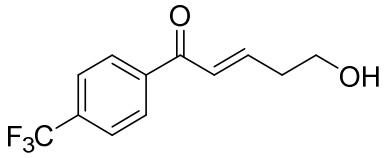


Colorless oil; 76% yield (for last 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.96–7.94 (m, 2H), 7.05–6.98 (m, 2H), 6.95–6.92 (m, 2H), 3.87 (s, 3H), 3.83

(t, J = 6.5 Hz, 2H), 2.58 (m, 2H), 1.88 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 188.8, 163.4, 144.5, 130.9, 130.5, 127.7, 113.8, 61.1, 55.4, 36.0.

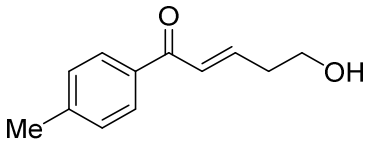
(*E*)-5-Hydroxy-1-(4-(trifluoromethyl)phenyl)pent-2-en-1-one (1c).



Pale yellow oil; 32% yield (for last 2 steps).

^{1}H NMR ($CDCl_3$) δ 8.02 (dd, J = 8.0, 1.0 Hz, 2H), 7.74 (dd, J = 8.0, 1.0 Hz, 2H), 7.10 (dt, J = 15.5, 7.0 Hz, 1H), 6.98 (dt, J = 15.5, 1.5 Hz, 1H), 3.87 (t, J = 6.0 Hz, 2H), 2.62 (m, 2H), 1.58 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 189.6, 147.1, 134.0 (q, J = 33.1 Hz), 128.8, 128.8, 126.1, 125.6 (q, J = 3.9 Hz), 123.6 (q, J = 272.6 Hz), 61.0, 36.0. ^{19}F NMR ($CDCl_3$) δ 98.7. TLC: R_f 0.38 (hexane/EtOAc = 1:1). IR (neat): 3381, 2937, 2888, 1672, 1624, 1616, 1411, 1326, 1229, 1169, 1128, 1068, 1016 cm^{-1}. HRMS Calcd for $C_{12}H_{10}F_3O_2$: $[M-H]^-$, 243.0638. Found: *m*/*z* 243.0640.

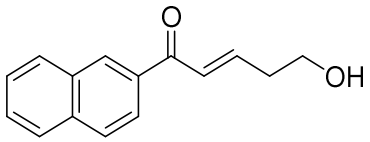
(*E*)-5-Hydroxy-1-(*p*-tolyl)pent-2-en-1-one (1d).



Pale yellow oil; 37% yield (for last 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.27 (m, 2H), 7.02 (m, 2H), 3.84 (dt, J = 6.5, 1.0 Hz, 2H), 2.59 (ddt, J = 7.0, 1.0, 6.5 Hz, 2H), 2.42 (s, 3H), 1.68 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 190.0, 144.9, 143.7, 135.1, 129.3, 128.7, 128.0, 61.1, 36.0, 21.6. TLC: R_f 0.25 (hexane/EtOAc = 1:1). IR (neat): 3421, 2923, 2883, 1669, 1617, 1605, 1350, 1289, 1182, 1040 cm^{-1}. HRMS Calcd for $C_{12}H_{15}O_2$: $[M+H]^+$, 191.1067. Found: *m*/*z* 191.1061.

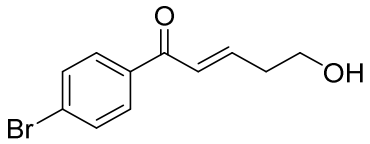
(*E*)-5-Hydroxy-1-(naphthalen-2-yl)pent-2-en-1-one (1e).



White solid; 46% yield (for last 2 steps).

^{1}H NMR ($CDCl_3$) δ 8.43 (s, 1H), 8.00 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.58 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.53 (ddd, *J* =8.0, 7.0, 1.0 Hz, 1H), 7.16 (d, *J* = 15.5 Hz, 1H), 7.11 (dt, *J* = 15.5, 5.5 Hz, 1H), 3.87 (t, *J* = 5.5 Hz, 2H), 2.63 (m 2H), 2.30 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 190.4, 145.7, 135.4, 134.9, 132.4, 130.1, 129.4, 128.4, 128.3, 127.8, 127.7, 126.7, 124.4, 61.0, 36.6. Mp. 69.7–70.5 °C. TLC: R_f 0.20 (hexane/EtOAc = 1:1). IR (KBr): 3283, 3270, 3267, 3055, 2892, 1665, 1620, 1610, 1460, 1424, 1370, 1292, 1289, 1193, 1125, 1067, 1044, 1012, 970 cm^{-1}. HRMS Calcd for $C_{15}H_{15}O_2$: $[M+H]^+$, 227.1067. Found: *m*/*z* 227.1059.

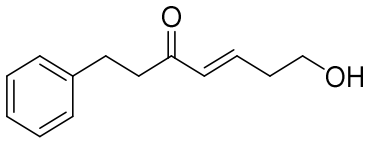
(*E*)-1-(4-Bromophenyl)-5-hydroxypent-2-en-1-one (1f).



Pale yellow oil; 23% yield (for last 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2H), 7.60 (m, 2H), 7.07 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.95 (dt, *J* = 15.5, 1.5 Hz, 1H), 3.85 (t, *J* = 6.0 Hz, 2H), 2.60 (ddt, *J* = 7.0, 1.0, 6.0 Hz, 2H), 1.60 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 189.3, 146.2, 136.3, 131.9, 130.1, 127.9, 127.4, 61.0, 36.0. TLC: R_f 0.22 (hexane/EtOAc = 1:1). IR (neat): 3431, 3089, 3061, 2933, 2883, 1715, 1662, 1622, 1586, 1566, 1484, 1397, 1350, 1288, 1225, 1178, 1105, 1072, 1039, 1009, 976, 823, 665 cm^{-1}. HRMS Calcd for $C_{11}H_{12}BrO_2$: $[M+H]^+$, 255.0015. Found: *m*/*z* 255.0008.

(*E*)-7-Hydroxy-1-phenylhept-4-en-3-one (1g).



Pale yellow oil; 42% yield (for last 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 6.81 (dt, *J* = 16.0, 7.0 Hz, 1H), 6.19 (dt, *J* = 16.0, 1.5 Hz, 1H), 3.77 (t, *J* = 6.0 Hz, 2H), 2.94 (m, 2H), 2.89 (m, 2H), 2.47 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 199.3, 143.4, 141.2, 132.3, 128.5, 128.4, 126.1, 61.0, 41.7, 35.6, 30.0. TLC: R_f 0.20 (hexane/EtOAc = 1:1). IR (neat): 3416, 3062, 3027, 2928, 2887, 1691, 1660, 1624, 1604, 1497, 1453, 1369, 1047, 700 cm^{-1}. HRMS Calcd for $C_{13}H_{17}O_2$: $[M+H]^+$, 205.1223. Found: *m*/*z* 205.1223.

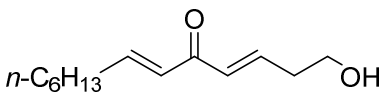
Procedure for preparation of 1h[15]

To a stirred mixture of diisopropylamine (10.1 g, 100 mmol) in Et_2O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (7.7 mL, 100 mmol). The reaction mixture was stirred at 0 °C for additional 5 min, and the newly formed crystals were filtered. The filter cake was washed with Et_2O, and the combined filtrates were concentrated in vacuo to afford pure diisopropylammoium 2,2,2-trifluoroacetate as a white solid in 85 % yield. Next, to a mixture of 3-decen-2-one (3.1 g, 20 mmol) and paraformaldehyde (1.2 g, 40 mmol) in dry THF (20 mL) was added diisopropylammoium 2,2,2-trifluoroacetate (4.3 g, 20 mmol) and trifluoroacetic acid (0.31 mL, 4.0 mmol). The reaction mixture was stirred under reflux for 2 h, and then cooled down to ambient temperature, and the second addition of paraformaldehyde (1.2 g, 40 mmol) was performed. The reaction mixture was stirred under reflux for additional 6 h. The reaction mixture was cooled down to ambient temperature and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 20/1) as an eluent gave undeca-1,4-dien-3-one as a pale yellow oil in 31 % yield; CAS RN [52353-97-6] ^{1}H NMR ($CDCl_3$) δ 6.95 (dt,

J = 15.5, 7.0 Hz, 1H), 6.61 (dd, *J* = 16.5, 10.5 Hz, 1H), 6.36 (dt, *J* = 15.5, 1.0 Hz, 1H), 6.28 (dd, *J* = 16.5, 1.0 Hz, 1H), 5.81 (dd, *J* = 10.5, 1.0 Hz, 1H), 2.25 (m, 2H), 1.48 (m, 2H), 1.35–1.25 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 190.1, 149.5, 135.1, 128.6, 128.4, 33.0, 31.8, 29.1, 28.3, 22.8, 14.3.

Hoveyda–Grubbs catalyst 2nd generation (47 mg, 0.076 mmol) was placed in a 30 mL round-bottom flask inside a glovebox. The flask was taken outside the glovebox and immediately filled with argon gas. Pure CH_2Cl_2 (5 mL), a solution of undeca-1,4-dien-3-one (1.3 g, 7.6 mmol) in CH_2Cl_2 (5 mL), and a solution of 3-buten-1-ol (0.11 g, 1.5 mmol) in CH_2Cl_2 (5 mL) were sequentially added to the flask. After the resulting mixture was stirred at ambient temperature for 10 h, the solvent was removed in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave (3*E*,6*E*)-1-hydroxytrideca-3,6-dien-5-one (**1h**) in 70 % yield.

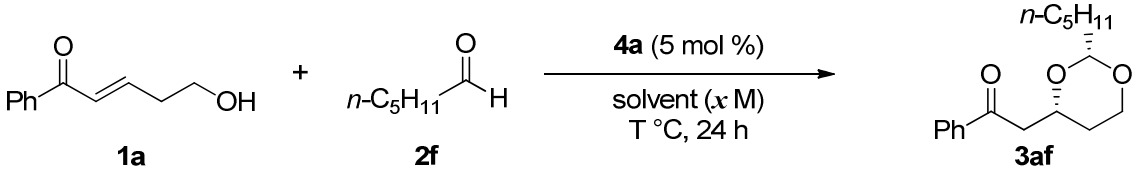
(3*E*,6*E*)-1-Hydroxytrideca-3,6-dien-5-one (1h)



^{1}H NMR ($CDCl_3$) δ 6.93 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.89 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.45 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.32 (dt, *J* = 15.5, 1.5 Hz, 1H), 3.80 (dt, *J* = 5.5, 6.0 Hz, 2H), 2.51 (m 2H), 2.24 (m, 2H), 1.47 (m, 2H), 1.35–1.24 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 189.3, 148.7, 143.4, 130.6, 128.6, 61.1, 35.8, 32.7, 31.6, 28.9, 28.1, 22.5, 14.1. TLC: R_f 0.29 (hexane/EtOAc = 1:1). IR (neat): 3417, 2956, 2928, 2858, 1667, 1636, 1614, 1466, 1457, 1420, 1351, 1305, 1293, 1212, 1050, 980 cm^{-1}. HRMS Calcd for $C_{13}H_{23}O_2$: $[M+H]^+$, 211.1693. Found: *m*/*z* 211.1690.

All aldehydes **2** listed in this manuscript were commercially available.

Table 3. Screening of Reaction Conditions[a]



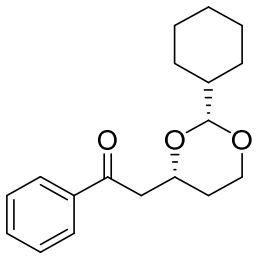
1a **2f** **3af**

entry	solvent	T (°C)	*x* (M)	yield (%)[b,c]	*ee* (%)
1	benzene	25	0.50	74	86
2	toluene	25	0.50	83	87
3	hexane	25	0.50	80	83
4	*c*-hexane	25	0.50	92	85
5	EtOAc	25	0.50	29	81
6	MeCN	25	0.50	<5	58
7	CH_2Cl_2	25	0.50	76	68
8	Et_2O	25	0.50	40	82
9	CPME[d]	25	0.50	18	86
10[e]	toluene	25	0.50	40	84
11	toluene	0	0.50	22	81
12	toluene	10	0.50	62	81
13	toluene	20	0.50	80	85
14	toluene	35	0.50	81	86
15	toluene	40	0.50	87	85
16	toluene	50	0.50	76	86
17	toluene	35	0.125	63	90
18	toluene	35	0.050	38	93
19	*c*-hexane	35	0.050	75	90
20[f]	*c*-hexane	35	0.050	94	91

[a]Reactions were run using **1a** (0.1 mmol), **2f** (0.12 mmol), and **4a** (0.0050 mmol) in the solvent (0.2 0mL). [b]The diastereomeric ratio was ≥20:1 in all cases. [c]Isolated yields. [d]CPME = cyclopentyl methyl ether. [e]Reaction was run using 5Å molecular sieves (50 mg). [f]Reactions were run using **1a** (0.10 mmol), **2f** (0.20 mmol), and the catalyst **4a** (0.0050 mmol) in *c*-hexane (2.0 mL).

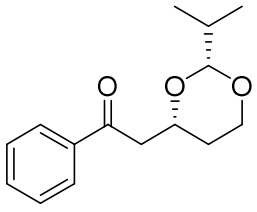
Characterization Data of Products

2-(2-Cyclohexyl-1,3-dioxan-4-yl)-1-phenylethanone (3aa).



Yield: 56%, ≥20:1 dr, 80% *ee*, white solid. $[\alpha]_D^{23}$ +5.5 (*c* 0.40, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 4.28 (d, *J* = 5.5 Hz, 1H), 4.26 (m, 1H), 4.12 (ddd, *J* = 11.5, 4.5, 1.0 Hz, 1H), 3.78 (ddd, *J* = 12.0, 12.0, 3.0 Hz, 1H), 3.37 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.99 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.76–1.64 (m, 6H), 1.61 (m, 1H), 1.47 (m, 1H), 1.22–1.05 (m, 3H), 1.01 (dd, *J* = 12.5, 3.5 Hz, 1H), 0.96 (dd, *J* = 12.5, 3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 198.0, 137.2, 133.2, 128.5, 128.3, 105.2, 73.2, 66.5, 44.9, 42.4, 31.7, 27.4, 27.3, 26.4, 25.77, 25.75. Mp. 60.5–61.4 °C. TLC: R_f 0.59 (hexane/EtOAc = 3:1). IR (KBr): 2928, 2850, 1686, 1595, 1451, 1378, 1249, 1142, 1098, 1071, 965, 754, 689 cm^{-1}. HRMS Calcd for $C_{18}H_{25}O_3$: $[M+H]^+$, 289.1798. Found: *m*/*z* 289.1791. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.5 min, t_{major} = 12.3 min.

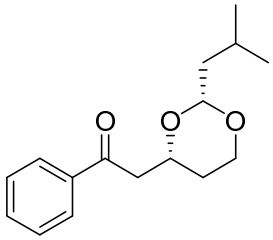
2-(2-Isopropyl-1,3-dioxan-4-yl)-1-phenylethanone (3ab).



Yield: 57%, ≥20:1 dr, 79% *ee*, colorless oil. $[\alpha]_D^{23}$ +4.8 (*c* 0.27, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.98 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 4.27 (m, 1H), 4.26 (d, *J* = 5.5 Hz, 1H), 4.13 (ddd, *J* = 11.5, 4.5, 1.0 Hz, 1H), 3.79 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H), 3.39 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.98 (dd, *J* = 16.0, 6.0 Hz, 1H), 1.73(m, 2H), 1.63 (m, 1H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 198.1, 137.2, 133.2, 128.5, 128.3, 73.3, 66.4, 44.8, 32.8, 31.6, 17.1,

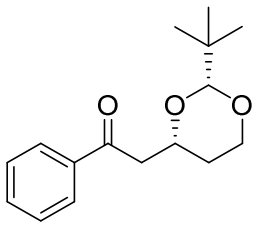
17.0. TLC: R_f 0.48 (hexane/EtOAc = 3:1). IR (neat): 2963, 2926, 2874, 2854, 1684, 1598, 1474, 1450, 1366, 1289, 1246, 1213, 1182, 1137, 1119, 1039, 986, 963, 753, 691 cm^{-1}. HRMS Calcd for $C_{15}H_{21}O_3$: $[M+H]^+$, 249.1485. Found: *m*/*z* 249.1476. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.5 min, t_{major} = 10.5 min.

2-(2-Isobutyl-1,3-dioxan-4-yl)-1-phenylethanone (3ac).



Yield: 64%, ≥20:1 dr, 71% *ee*, colorless oil. $[\alpha]_D^{23}$ +9.1 (*c* 0.33, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.52 (m, 2H), 4.61 (t, *J* = 5.5 Hz, 1H), 4.31 (m, 1H), 4.12 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H), 3.82 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H), 3.39 (dd, *J* = 16.5, 6.5 Hz, 1H), 3.01 (dd, *J* = 16.5, 6.5 Hz, 1H), 1.78–1.69 (m, 2H), 1.66 (m, 1H), 1.46 (m, 2H), 0.87 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 197.8, 137.1, 133.2, 128.6, 128.2, 73.1, 66.4, 44.8, 43.8, 31.5, 23.8, 22.8, 22.7. TLC: R_f 0.59 (hexane/EtOAc = 3:1). IR (neat): 2957, 2927, 2869, 2857, 1685, 1449, 1369, 1126, 979, 690 cm^{-1}. HRMS Calcd for $C_{16}H_{23}O_3$: $[M+H]^+$, 263.1642. Found: *m*/*z* 263.1632. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.5 min, t_{major} = 16.7 min.

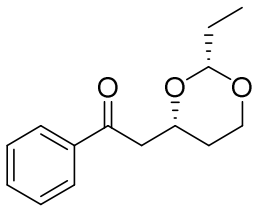
2-(2-*tert*-Butyl-1,3-dioxan-4-yl)-1-phenylethanone (3ad).



Yield: 33%, ≥20:1 dr, 11% *ee*, pale yellow oil. $[\alpha]_D^{23}$ –4.3 (*c* 0.40, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.99 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 4.23 (m, 1H), 4.12 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H),

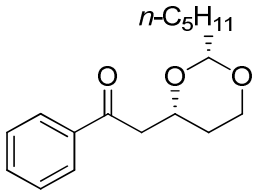
4.12 (s, 1H), 3.77 (dt, *J* = 11.5, 11.5, 3.0 Hz, 1H), 3.37 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.93 (dd, *J* = 16.0, 6.0 Hz, 1H), 1.71 (m, 1H), 1.60 (m, 1H), 0.82 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 198.6, 137.4, 133.1, 128.5, 128.4, 107.5, 73.6, 66.5, 44.9, 34.8, 31.6, 24.6. TLC: R_f 0.30 (hexane/EtOAc = 3:1). IR (neat): 2958, 2927, 2869, 2856, 1685, 1449, 1364, 1213, 1134, 1121, 1106, 1044, 982, 690 cm^{-1}. HRMS Calcd for $C_{16}H_{23}O_3$: $[M+H]^+$, 263.1642. Found: *m*/*z* 263.1642. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 11.2 min, t_{major} = 13.7 min.

2-(2-Ethyl-1,3-dioxan-4-yl)-1-phenylethanone (3ae).



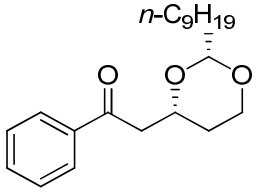
Yield: 60%, ≥20:1 dr, 78% *ee*, colorless oil. $[\alpha]_D^{23}$ +8.8 (*c* 0.24, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 4.52 (t, *J* = 5.5 Hz, 1H), 4.31 (m, 1H), 4.12 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.82 (ddd, *J* = 11.5, 11.5, 2.5 Hz, 1H), 3.39 (dd, *J* = 16.5, 6.0 Hz, 1H), 3.01 (dd, *J* = 16.5, 6.5 Hz, 1H), 1.74 (m, 1H), 1.67 (m, 1H), 1.61 (dq, *J* = 5.5, 7.5 Hz, 2H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.8, 137.1, 133.2, 128.6, 128.2, 103.2, 73.0, 66.4, 44.8, 31.5, 28.1, 8.3. TLC: R_f 0.56 (hexane/EtOAc = 3:1). IR (neat): 2969, 2933, 2855, 1685, 1375, 1369, 1136, 1099, 974, 691 cm^{-1}. HRMS Calcd for $C_{14}H_{19}O_3$: $[M+H]^+$, 235.1329. Found: *m*/*z* 235.1322. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 8.4 min, t_{major} = 13.3 min.

2-(2-Pentyl-1,3-dioxan-4-yl)-1-phenylethanone (3af).



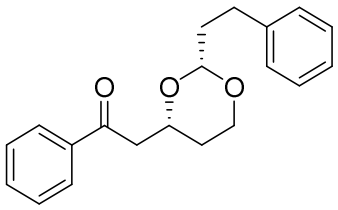
Yield: 94%, ≥20:1 dr, 91% *ee*, colorless oil. $[\alpha]_D^{23}$ +11.6 (*c* 0.62, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.57 (m, 1H), 7.52 (m, 2H), 4.57 (t, *J* = 5.0 Hz, 1H), 4.30 (m, 1H), 4.12 (ddd, *J* = 11.5, 4.5, 1.0 Hz, 1H), 3.81 (ddd, *J* = 11.5, 11.5, 2.5 Hz, 1H), 3.39 (dd, *J* = 16.5, 6.0 Hz, 1H), 3.01 (dd, *J* = 16.5, 6.5 Hz, 1H), 1.74 (m, 1H), 1.66 (m, 1H), 1.57 (m, 2H), 1.36–1.20 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.8, 137.0, 133.2, 128.6, 128.2, 102.3, 73.0, 66.4, 44.8, 35.0, 31.6, 31.5, 23.7, 22.5, 14.0. TLC: R_f 0.47 (hexane/EtOAc = 3:1). IR (neat): 2955, 2928, 2859, 1685, 1212, 1137, 1121, 1029, 990, 690, 668 cm^{-1}. HRMS Calcd for $C_{17}H_{25}O_3$: $[M+H]^+$, 277.1798. Found: *m*/*z* 277.1789. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 10.1 min, t_{minor} = 14.8 min.

2-(2-Nonyl-1,3-dioxan-4-yl)-1-phenylethanone (3ag).



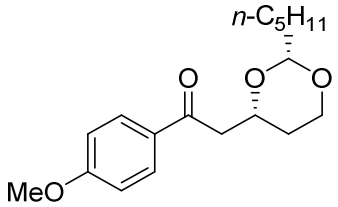
Yield: 72%, ≥20:1 dr, 82% *ee*, colorless oil. $[\alpha]_D^{23}$ +6.5 (*c* 0.23, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 4.57 (t, *J* = 5.5 Hz, 1H), 4.30 (m, 1H), 4.11 (ddd, *J* = 12.0, 5.0, 1.0 Hz, 1H), 3.81 (ddd, *J* = 12.0, 12.0, 3.0 Hz, 1H), 3.39 (dd, *J* = 11.5, 6.0 Hz, 1H), 3.00 (dd, *J* = 11.5, 6.5 Hz, 1H), 1.74 (m, 1H), 1.65 (m, 1H), 1.57 (m, 2H), 1.28 (m, 14H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.8, 137.1, 133.2, 128.6, 128.2, 102.3, 73.1, 66.4, 44.8, 35.1, 31.9, 31.5, 29.49, 29.48, 29.4, 29.3, 24.0, 22.3, 14.1. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (neat): 2954, 2925, 2855, 2368, 2321, 1688, 1653, 1124, 668 cm^{-1}. HRMS Calcd for $C_{21}H_{33}O_3$: $[M+H]^+$, 333.2424. Found: *m*/*z* 333.2410. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 8.5 min, t_{minor} = 12.3 min.

2-(2-Phenethyl-1,3-dioxan-4-yl)-1-phenylethanone (3ah).



Yield: 76%, ≥20:1 dr, 85% *ee*, colorless oil. $[\alpha]_D^{23}$ +21.0 (*c* 0.68, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.01 (m, 2H), 7.59 (m, 1H), 7.49 (m, 2H), 7.27 (m, 2H), 7.18 (m, 3H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.32 (m, 1H), 4.15 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.81 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H), 3.43 (dd, *J* = 16.5, 6.5 Hz, 1H), 3.02 (dd, *J* = 16.5, 6.0 Hz, 1H), 2.67 (t, *J* = 8.0 Hz, 2H), 1.91 (m, 2H), 1.79 (m, 1H), 1.67 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.8, 141.6, 137.2, 133.2, 128.6, 128.4, 128.3, 128.2, 125.7, 101.2, 73.2, 66.4, 44.8, 36.4, 31.5, 30.1. TLC: R_f 0.38 (hexane/EtOAc = 3:1). IR (neat): 3026, 2959, 2927, 2856, 2356, 1685, 1597, 1449, 1375, 1369, 1213, 1180, 1138, 1099, 1035, 751, 700, 691 cm^{-1}. HRMS Calcd for $C_{20}H_{23}O_3$: $[M+H]^+$, 311.1642. Found: *m*/*z* 311.1632. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.5 mL/min, λ = 254 nm, 40 °C): t_{major} = 16.0 min, t_{minor} = 21.2 min.

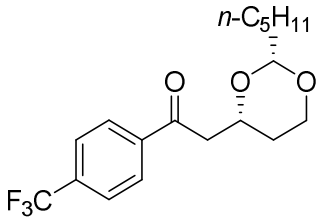
1-(4-Methoxyphenyl)-2-(2-pentyl-1,3-dioxan-4-yl)ethanone (3bf).



Yield: 70%, ≥20:1 dr, 93% *ee*, colorless oil. $[\alpha]_D^{23}$ +23.0 (*c* 2.18, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 6.93 (m, 2H), 4.56 (t, *J* = 5.5 Hz, 1H), 4.28 (m, 1H), 4.11 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.87 (s, 3H), 3.81 (ddd, *J* = 11.5, 11.5, 3.5 Hz, 1H), 3.34 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.96 (dd, *J* = 16.5, 6.5 Hz, 1H), 1.72 (m, 1H), 1.65 (m, 1H), 1.56 (m, 2H), 1.35–1.21 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 196.3, 163.6, 130.5, 130.2, 113.7, 102.3, 73.2, 66.4, 55.5, 44.5, 35.0, 31.62, 31.56, 23.7, 22.5, 14.0. TLC: R_f 0.29 (hexane/EtOAc = 3:1). IR (neat): 2955, 2929,

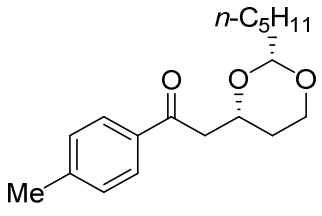
2859, 2364, 2346, 1675, 1601, 1507, 1261, 1172, 1136, 1121, 1032, 989 cm^{-1}. HRMS Calcd for $C_{18}H_{27}O_4$: $[M+H]^+$, 307.1904. Found: *m*/*z* 307.1892. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 13.7 min, t_{major} = 15.0 min.

2-(2-Pentyl-1,3-dioxan-4-yl)-1-(4-(trifluoromethyl)phenyl)ethanone (3cf).



Yield: 65%, ≥20:1 dr, 89% *ee*, colorless oil. $[\alpha]_D^{23}$ +5.4 (*c* 0.13, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.07 (m, 2H), 7.74 (m, 2H), 4.55 (t, *J* = 5.5 Hz, 1H), 4.29 (m, 1H), 4.13 (ddd, *J* = 12.0, 5.5, 1.5 Hz, 1H), 3.81 (ddd, *J* = 12.0, 12.0, 2.5 Hz, 1H), 3.41 (dd, *J* = 16.5, 7.0 Hz, 1H), 2.99 (dd, *J* = 16.5, 6.0 Hz, 1H), 1.76 (m, 1H), 1.65 (m, 1H), 1.55 (m, 2H), 1.33–1.19 (m, 6H), 0.84 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.1, 139.7, 134.4 (q, *J* = 32.7 Hz), 128.6, 125.6 (q, *J* = 3.9 Hz), 123.5 (q, *J* = 272.8 Hz), 102.3, 73.0, 66.3, 45.0, 34.9, 31.6, 31.4, 23.6, 22.5, 14.0. ^{19}F NMR (C_6F_6) δ 98.6. TLC: R_f 0.29 (hexane/EtOAc = 3:1). IR (neat): 2956, 1684, 1411, 1325, 1215, 1167, 1150, 1108, 1068, 974, 855, 821 cm^{-1}. HRMS Calcd for $C_{18}H_{23}F_3O_3Na$: $[M+Na]^+$, 367.1492. Found: *m*/*z* 367.1477. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 5.8 min, t_{minor} = 8.2 min.

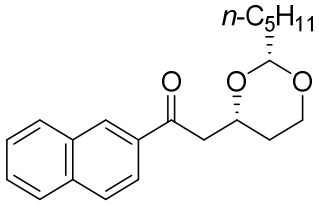
2-(2-Pentyl-1,3-dioxan-4-yl)-1-(*p*-tolyl)ethanone (3df).



Yield: 75%, ≥20:1 dr, 90% *ee*, pale yellow oil. $[\alpha]_D^{23}$ +12.9 (*c* 0.62, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.28 (m, 2H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.31 (m, 1H), 4.13 (ddd, *J* = 11.5, 5.0, 1.5

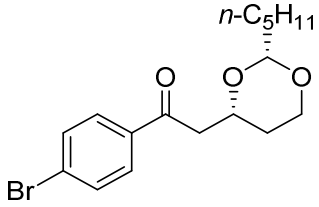
Hz, 1H), 3.82 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H), 3.37 (dd, *J* = 11.5, 6.0 Hz, 1H), 3.00 (dd, *J* = 11.5, 6.5 Hz, 1H), 2.43 (s, 3H), 1.74 (m, 1H), 1.66 (m, 1H), 1.58 (m, 2H), 1.38–1.21 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.2, 143.8, 134.3, 129.0, 128.1, 102.0, 72.9, 66.2, 44.4, 34.8, 31.4, 31.3, 23.4, 22.3, 21.4, 13.7. TLC: R_f 0.42 (hexane/EtOAc = 3:1). IR (neat): 2955, 2927, 2859, 2360, 2340, 1689, 1608, 1375, 1364, 1207, 1181, 1136, 1121, 1031, 995, 665 cm^{-1}. HRMS Calcd for $C_{18}H_{27}O_3$: $[M+H]^+$, 291.1955. Found: *m*/*z* 291.1944. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 13.1 min, t_{minor} = 20.0 min.

1-(Naphthalen-2-yl)-2-((2*R*,4*R*)-2-pentyl-1,3-dioxan-4-yl)ethanone (3ef).



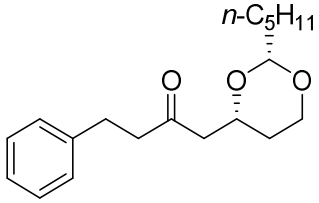
Yield: 99%, ≥20:1 dr, 90% *ee*, white solid. $[\alpha]_D^{23}$ +34.5 (*c* 0.80, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H), 8.03 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.58 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.56 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.59 (t, *J* = 5.5 Hz, 1H), 4.36 (m, 1H), 4.14 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.83 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H), 3.54 (dd, *J* = 16.5, 6.5 Hz, 1H), 3.13 (dd, *J* = 16.5, 6.5 Hz, 1H), 1.79 (m, 1H), 1.70 (m, 1H), 1.58 (m, 2H), 1.37–1.18 (m, 6H), 0.83 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.8, 135.6, 134.4, 132.4, 130.2, 129.6, 128.5, 128.4, 127.7, 126.8, 123.7, 102.3, 73.2, 66.4, 44.9, 35.0, 31.6, 31.5, 23.7, 22.5, 14.0. Mp. 58.5–59.2 °C. TLC: R_f 0.43 (hexane/EtOAc = 3:1). IR (neat): 2955, 2950, 2929, 2851, 1676, 1379, 1140, 1126, 1032, 864, 836, 757 cm^{-1}. HRMS Calcd for $C_{21}H_{27}O_3$: $[M+H]^+$, 327.1955. Found: *m*/*z* 327.1940. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 98.0/2.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 11.2 min, t_{minor} = 15.7 min.

1-(4-Bromophenyl)-2-(2-pentyl-1,3-dioxan-4-yl)ethanone (3ff).



Yield: 74%, ≥20:1 dr, 90% *ee*, colorless oil. $[\alpha]_D^{23}$ +15.1 (*c* 0.72, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.61 (m, 2H), 4.55 (t, *J* = 5.5 Hz, 1H), 4.27 (m, 1H), 4.12 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.80 (ddd, *J* = 11.5, 11.5, 2.5 Hz, 1H), 3.35 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.94 (dd, *J* = 16.5, 6.0 Hz, 1H), 1.74 (m, 1H), 1.64 (m, 1H), 1.55 (m, 2H), 1.35–1.19 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 196.9, 135.8, 131.9, 129.8, 128.5, 102.3, 73.0, 66.4, 44.7, 35.0, 31.6, 31.4, 23.6, 22.5, 14.0. TLC: R_f 0.43 (hexane/EtOAc = 3:1). IR (neat): 2956, 2927, 2859, 2368, 2331, 1689, 1586, 1136, 1122, 1072, 668 cm^{-1}. HRMS Calcd for $C_{17}H_{24}BrO_3$: $[M+H]^+$, 355.0903. Found: *m*/*z* 355.0888. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.9 min, t_{major} = 10.0 min.

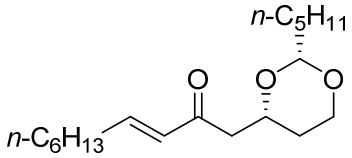
1-(2-Pentyl-1,3-dioxan-4-yl)-4-phenylbutan-2-one (3gf).



Yield: 53%, ≥20:1 dr, 63% *ee*, colorless oil. $[\alpha]_D^{23}$ –3.99 (*c* 0.43, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 7.21–7.16 (m, 3H), 4.50 (t, *J* = 5.5 Hz, 1H), 4.09 (m, 1H), 4.07 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.74 (ddd, *J* = 11.5, 11.5, 1.5 Hz, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.87–2.72 (m, 3H), 2.44 (dd, *J* = 16.0 Hz, 1H), 1.63 (m, 1H), 1.56 (m, 2H), 1.37–1.22 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 207.9, 140.9, 128.5, 128.3, 126.1, 102.2, 72.8, 66.3, 48.9, 45.5, 34.9, 31.6, 31.2, 29.4, 23.7, 22.5, 14.0. TLC: R_f 0.43 (hexane/EtOAc = 3:1). IR (neat): 2956, 2927, 2859, 2368, 2331, 1689, 1586, 1136, 1122, 1072, 668 cm^{-1}. HRMS Calcd for $C_{19}H_{28}O_3Na$: $[M+Na]^+$,

327.1931. Found: *m*/*z* 327.1924. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 95.0/5.0, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.3 min, t_{major} = 15.0 min.

(*E*)-1-(2-Pentyl-1,3-dioxan-4-yl)dec-3-en-2-one (3hf)

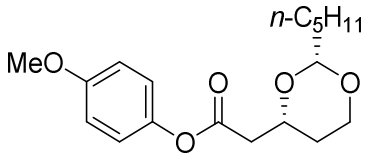


Yield: 70%, ≥20:1 dr, 78% *ee*, colorless oil. $[\alpha]_D^{23}$ +10.0 (*c* 0.56, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 6.85 (dt, *J* = 16.0, 7.0 Hz, 1H), 6.10 (dt, *J* = 16.0, 1.0 Hz, 1H), 4.52 (t, *J* = 5.0 Hz, 1H), 4.27 (m, 1H), 4.08 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H), 3.76 (ddd, *J* = 12.0, 12.0, 3.0 Hz, 1H), 2.93 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.59 (dd, *J* = 16.0 Hz, 6.5 Hz, 1H), 2.21 (m, 2H), 1.65 (m, 1H), 1.58–1.54 (m, 3H), 1.45 (m, 2H), 1.37–1.21 (m, 12H), 0.89–0.85 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 198.1, 148.7, 130.9, 102.2, 73.0, 66.4, 45.9, 35.0, 32.5, 31.64, 31.56, 31.4, 28.8, 28.0, 23.7, 22.5, 14.1, 14.0. TLC: R_f 0.28 (hexane/EtOAc = 10:1). IR (neat): 2956, 2858, 1693, 1669, 1628, 1624, 1466, 1459, 1378, 1367, 1137, 1124, 1030, 994, 976 cm^{-1}. HRMS Calcd for $C_{19}H_{35}O_3$: $[M+H]^+$, 311.2581. Found: *m*/*z* 311.2573. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 11.2 min, t_{minor} = 17.3 min.

Procedure for Baeyer–Villiger oxidation of 3bf [16]

The mixture of **3bf** (0.021 g, 0.070 mmol), *m*-CPBA (0.60 g, 0.35 mmol), and trifluoroacetic acid (0.003 mL, 0.04 mmol) in CH_2Cl_2 (0.6 mL) was stirred at ambient temperature for 8 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and subsequently extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave 4-methoxyphenyl 2-(2-pentyl-1,3-dioxan-4-yl)acetate (**5**).

4-Methoxyphenyl 2-(2-pentyl-1,3-dioxan-4-yl)acetate (5).



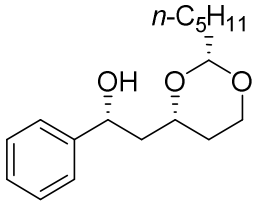
Yield: 70%, 92% *ee*, colorless oil. $[\alpha]_D^{23}$ –10.9 (*c* 0.43, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.00–6.98 (m, 2H), 6.89–6.87 (m, 2H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.20 (m, 1H), 4.14 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.80 (s, 3H), 3.80 (m, 1H), 2.83 (dd, *J* = 15.5, 8.0 Hz, 1H), 2.68 (dd, *J* = 15.5, 6.0 Hz, 1H), 1.79 (m, 1H), 1.64–1.58 (m, 3H), 1.39 (m, 2H), 1.34–1.24 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 169.8, 157.2, 144.0, 122.3, 114.4, 102.3, 73.0, 66.3, 55.6, 41.1, 35.0, 31.6, 31.0, 23.7, 22.6, 14.0. TLC: R_f 0.34 (hexane/EtOAc = 10:1). IR (neat): 2955, 2929, 2860, 2364, 2331, 1751, 1506, 1465, 1378, 1249, 1196, 1165, 1135, 1102, 1033 cm^{-1}. HRMS Calcd for $C_{18}H_{26}O_5Na$: $[M+Na]^+$, 345.1672. Found: *m*/*z* 345.1666. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 99.5/0.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 22.9 min, t_{minor} = 27.2 min.

Procedure for diastereoselective reduction of 3af

To a 30-mL round-bottom flask were added 2-(2-pentyl-1,3-dioxan-4-yl)-1- phenylethanone (**3af**, 0.076 g, 0.27 mmol), Et_2O (27.4 mL), and $EuCl_3$ (0.21 g, 0.82 mmol). After the mixture

was stirred under argon atmosphere at –78 °C for 0.5 h, $LiBH_4$ (0.012 g, 0.55 mmol) was added. The resulting mixture was additionally stirred at –78 °C for 2 h. The reaction was quenched with 3M aqueous NaOH, and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5/1) as an eluent gave 2-(2-pentyl-1,3-dioxan-4-yl)-1-phenylethanol (**6**).

2-(2-Pentyl-1,3-dioxan-4-yl)-1-phenylethanol (6).



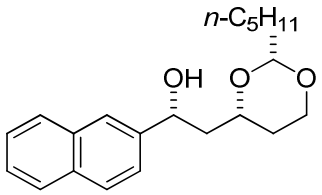
Yield: 92%, 12:1 dr, colorless oil. $[\alpha]_D^{23}$ +13.4 (*c* 0.90, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.37–7.32 (m, 4H), 7.27 (m, 1H), 4.97 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.58 (t, *J* = 5.0 Hz, 1H), 4.01 (ddd, *J* = 12.0, 5.0, 1.0 Hz, 1H), 3.92 (m, 1H), 3.76 (ddd, *J* = 12.0, 12.0, 2.5 Hz, 1H), 2.04 (m, 1H), 1.81–1.72 (m, 2H), 1.66–1.62 (m, 2H), 1.44–1.38 (m, 3H), 1.35–1.27 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 144.4, 128.6, 127.7, 126.0, 102.3, 74.1, 66.7, 45.4, 35.2, 31.9, 31.7, 24.0, 22.8, 14.3. TLC: R_f 0.37 (hexane/EtOAc = 3:1). IR (neat): 3462, 2953, 2925, 2858, 1465, 1378, 1364, 1139, 1087, 1028, 760, 700, 665 cm^{-1}. HRMS Calcd for $C_{17}H_{27}O_3$: $[M+H]^+$, 279.1955. Found: *m*/*z* 279.1945.

Procedure for diastereoselective reduction of 3ef

To a 20-mL round-bottom flask were added sequentially 1-(naphthalen-2-yl)-2-((2*R**,4*R**)-2-pentyl-1,3-dioxan-4-yl)ethanone (**3ef**, 0.033 g, 0.10 mmol), Et_2O (1.8 mL), and $EuCl_3$ (0.078 mg, 0.30 mmol). After the mixture was stirred under argon atmosphere at –78 °C for 0.5 h, a solution of $LiBH_4$ in Et_2O (0.2 mmol, 1.0 M, 0.2 mL) was added. The resulting mixture was additionally

stirred at –78 °C for 1 h. The reaction was quenched with 1M aqueous NaOH, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5/1) as an eluent gave (*R**)-1-(naphthalen-2-yl)-2-((2*R**,4*R**)-2-pentyl-1,3-dioxan-4-yl)ethanol (**dihydro-3ef**).

(*R)-1-(Naphthalen-2-yl)-2-((2*R**,4*R**)-2-pentyl-1,3-dioxan-4-yl)ethanol (dihydro-3ef)**.

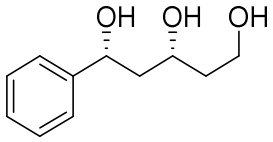


Yield: 99%, 11:1 dr, white solid. ^{1}H NMR ($CDCl_3$) δ 7.85–7.82 (m, 4H), 7.50–7.44 (m, 3H), 5.15 (dd, *J* = 9.0, 3.5 Hz, 1H), 4.60 (t, *J* = 5.5 Hz, 1H), 4.10 (ddd, *J* = 11.5, 5.0, 1.0 Hz, 1H), 3.96 (m, 1H), 3.75 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H), 3.68 (br s, 1H), 2.11 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.69–1.64(m, 2H), 1.47–1.41 (m, 3H), 1.38–1.30 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 141.5, 133.3, 132.9, 128.1, 128.0, 127.6, 126.0, 125.7, 124.4, 124.0, 102.1, 74.0, 66.5, 45.1, 35.0, 31.7, 31.5, 23.8, 22.5, 14.0. Mp. 78.0–78.8 °C. TLC: R_f 0.33 (hexane/EtOAc = 3:1). IR (KBr): 3482, 2955, 2937, 2931, 2910, 2871, 2851, 1424, 1365, 1165, 1139, 1086, 975.1, 862.2, 822.7, 758.1 cm^{-1}. HRMS Calcd for $C_{21}H_{28}O_3Na$: $[M+Na]^+$, 351.1931. Found: *m*/*z* 351.1918.

Procedure for deacetalizaton of 6

The mixture of **6** (diastereomer mixture, dr = 12:1, 0.059 g, 0.20 mmol) and *p*-TsOH·H_2O (0.040 g, 0.21 mmol) in CH_3OH (1.6 mL) and H_2O (0.5 mL) was stirred at 100 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/3) as an eluent gave 1-phenylpentane-1,3,5-triol (**7**).

1-Penylpentane-1,3,5-triol (7).



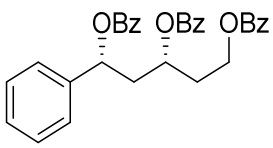
Yield: 64% (isolated yield of the major diastereomer), colorless oil. $[\alpha]_D^{23}$ +31.5 (*c* 0.72, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.38–7.34 (m, 4H), 7.29 (m, 1H), 5.00 (dd, *J* = 10.5, 2.5 Hz, 1H), 4.26 (m, 1H), 3.87 (m, 2H), 3.17 (br s, 3H), 1.97 (dt, *J* = 14.5, 10.5 Hz, 1H), 1.79–1.69 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 144.2, 128.6, 127.7, 125.6, 75.5, 73.0, 61.6, 45.4, 38.5. TLC: R_f 0.10 (hexane/EtOAc = 1:3). IR (neat): 3322, 3088, 3064, 3031, 2944, 2920, 1455, 1428, 1329, 1101, 1059, 1029, 1003, 759, 701, 673 cm^{-1}. HRMS Calcd for $C_{11}H_{17}O_3$: $[M+H]^+$, 197.1172. Found: *m*/*z* 197.1172.

The enantiomeric excess of **7** was determined by HPLC analysis after benzoylation.

Procedure for benzoylation of 7

To a solution of **7** (0.013 g, 0.068 mmol) in CH_2Cl_2 (0.3 mL) were added benzoyl chloride (0.024 mL, 0.20 mmol) and pyridine (0.027 mL, 0.33 mmol) at ambient temperature, and the mixture was stirred overnight. The resulting mixture was diluted with H_2O and subsequently extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave 1-phenylpentane-1,3,5-triyl tribenzoate.

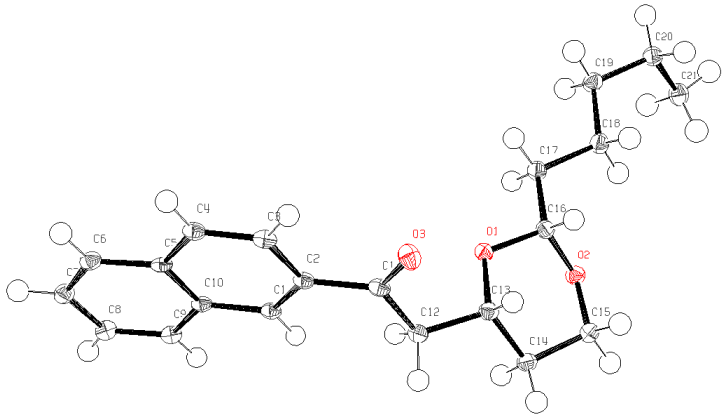
1-Phenylpentane-1,3,5-triyl tribenzoate.



Yield: 36%, 91% *ee*, colorless oil. $[\alpha]_D^{23}$ +1.21 (*c* 0.41, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 8.05–8.03 (m, 2H), 7.98–7.96 (m, 2H), 7.91–7.89 (m, 2H), 7.55–7.48 (m, 3H), 7.41–7.36 (m, 6H), 7.34–7.29

(m, 4H), 7.24 (m, 2H), 6.18 (t, J = 7.0 Hz, 1H), 5.40 (m 1H), 4.47 (m, 1H), 4.38 (m, 1H), 2.72 (m, 1H), 2.36–2.21 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 166.4, 165.8, 165.6, 139.7, 133.03, 133.02, 132.9, 129.94, 129.87, 129.64, 129.61, 129.5, 128.7, 128.33, 128.30, 128.2, 126.4, 73.7, 69.2, 61.1, 40.8, 33.1. TLC: R_f 0.39 (hexane/EtOAc = 3:1). IR (neat): 3090, 3064, 3034, 2964, 2926, 2854, 1706, 1602, 1585, 1492, 1452, 1315, 1265, 1177, 1110, 1098, 1070, 1026, 1002, 974, 805, 760, 707, 687 cm^{-1}. HRMS Calcd for $C_{32}H_{28}O_6Na$: $[M+Na]^+$, 531.1778. Found: m/z 531.1774. HPLC (Daicel Chiralpak IC, hexane/i-PrOH = 80.0/20.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 5.9 min, t_{minor} = 7.3 min.

ORTEP Drawing of 3ef



A. Crystal Data

Empirical Formula	$C_{21}H_{26}O_3$
Formula Weight	326.43
Crystal Color, Habit	Colorless, Needle
Crystal Dimensions	0.244 × 0.070 × 0.060 mm
Crystal System	Orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 5.7682(2) Å
	b = 7.7444(3) Å
	c = 39.9505(14) Å
	V = 1784.64(11) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.215 g/cm^3
F_{000}	704.00
μ(CuKα)	6.326 cm^{-1}

B. Intensity Measurements

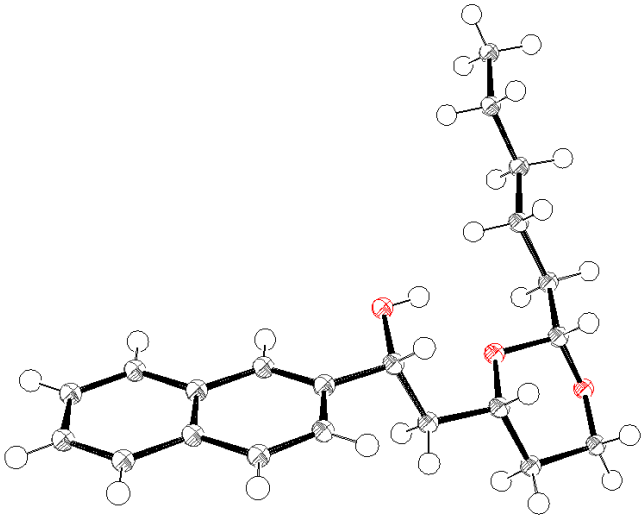
Diffractometer	R-AXIS RAPID
Radiation	CuKα (λ = 1.54187 Å)
	Multi-layer mirror monochromated
Voltage, Current	40kV, 30mA
Temperature	–180.0 °C
Detector Aperture	460.0 × 256.0 mm
Data Images	180 exposures
ω Oscillation Range (χ = 54.0, φ = 0.0)	80.0–260.0°
Exposure Rate	20.0 sec./°
ω Oscillation Range (χ = 54.0, φ = 90.0)	80.0–260.0°
Exposure Rate	20.0 sec./°
ω Oscillation Range (χ = 54.0, φ = 180.0)	80.0–260.0°
Exposure Rate	20.0 sec./°
ω Oscillation Range (χ = 54.0, φ = 270.0)	80.0–260.0°
Exposure Rate	20.0 sec./°
ω Oscillation Range (χ = 0.0, φ = 0.0)	80.0–260.0°
Exposure Rate	20.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2\theta_{max}$	136.4°
No. of Reflections Measured	Total: 20325
	Unique: 3254 (R_{int} = 0.0784)
	Parsons quotients (Flack x parameter): 1047
Corrections	Lorentz-polarization

	Absorption
	(trans. factors: 0.687–0.963)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS2013)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (F_0^2 - F_c^2)^2$
Least Squares Weights	$w = 1/\ [\ \sigma^2(F_0^2) + (0.1161 \cdot P)^2$ $+ 0.2777 \cdot P\ ]$ where $P = (Max(F_0^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	136.4°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	3254
No. Variables	217
Reflection/Parameter Ratio	15.00
Residuals: R1 (I>2.00σ(I))	0.0683
Residuals: R (All reflections)	0.0732
Residuals: wR2 (All reflections)	0.1857
Goodness of Fit Indicator	1.110
Flack parameter (Parsons' quotients = 1047)	0.0(2)
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.33 $e^-/Å^3$
Minimum peak in Final Diff. Map	–0.36 $e^-/Å^3$

ORTEP Drawing of dihydro-3ef



A. Crystal Data

Empirical Formula	$C_{21}H_{28}O_3$
Formula Weight	328.45
Crystal Color, Habit	Colorless, Prism
Crystal Dimensions	0.410 × 0.380 × 0.200 mm
Crystal System	Monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 28.83(4) Å
	b = 7.923(11) Å
	c = 7.876(11) Å
	ß = 89.14(2)°
	V = 1799(5) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.213 g/cm^3

F_{000}	712.00
μ(MoKα)	0.791 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å)
	graphite monochromated
Voltage, Current	50kV, 12mA
Temperature	20.0 °C
Detector Aperture	75 mm (diameter)
Data Images	1080 exposures
ω Oscillation Range	–60.0–120.0°
Exposure Rate	96.0 sec./°
Detector Swing Angle	30.50°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	96.0 sec./°
Detector Swing Angle	30.50°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	96.0 sec./°
Detector Swing Angle	30.50°
Detector Position	49.00 mm
Pixel Size	0.146 mm
$2\theta_{max}$	55.6°
No. of Reflections Measured	Total: 11513
	Unique: 3684 (R_{int} = 0.0874)
Corrections	Lorentz-polarization

	Absorption
	(trans. factors: 0.967–0.984)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (F_0^2 - F_c^2)^2$
Least Squares Weights	$w = 1/\ [\ \sigma^2(F_0^2) + (0.1000 \cdot P)^2$
	$+ 0.0000 \cdot P\ ]$
	where $P = (Max(F_0^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	55.6°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	3684
No. Variables	217
Reflection/Parameter Ratio	16.98
Residuals: R1 (I>2.00σ(I))	0.1052
Residuals: R (All reflections)	0.1523
Residuals: wR2 (All reflections)	0.2984
Goodness of Fit Indicator	1.270
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.33 $e^-/Å^3$
Minimum peak in Final Diff. Map	–0.35 $e^-/Å^3$

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Chapter 2

Diastereoselective Reduction of β-(1,3-Dioxan-4-yl)ketones

Stereoselective reduction of β-(1,3-dioxan-4-yl)ketones is an important step in the efficient synthesis of chiral 1,3-polyols, a typical structure of polyketides. In this study, the author carried out investigations to optimize the conditions for diastereoselective reduction.

Introduction

Optically active acetals are useful chiral auxiliaries for controlling the reaction at a proximal prochiral center.[1] Especially, the reduction of ketones bearing a chiral acetal, followed by deacetalization, is an efficient route to chiral polyols, which are prevalent in a wide range of natural products and bioactive agents (Figure 1). Indeed, Asano and Matsubara recently demonstrated the synthesis of a chiral 1,2,4-triol, a structure found in the antifungal agent, amphotericin B, from a ketone bearing the 1,3-dioxolane moiety. In this synthesis, highly diastereoselective reduction was accomplished using $LiAlH_4$ in the presence of LiI (Scheme 1).[2,3] In this context, a method for the synthesis of 1,3-polyols is in even greater demand, as they are found in a vast range of polyketides and are regarded as a valued structure in drug discovery.[4] However, previous studies on the reduction of β-(1,3-dioxan-4-yl)ketones, despite providing a useful template for the construction of a stereodefined 1,3-polyol motif, showed insufficient stereoselectivity (Scheme 2).[5] Therefore, the author optimized the diastereoselective reduction of β-(1,3-dioxan-4-yl)ketones.

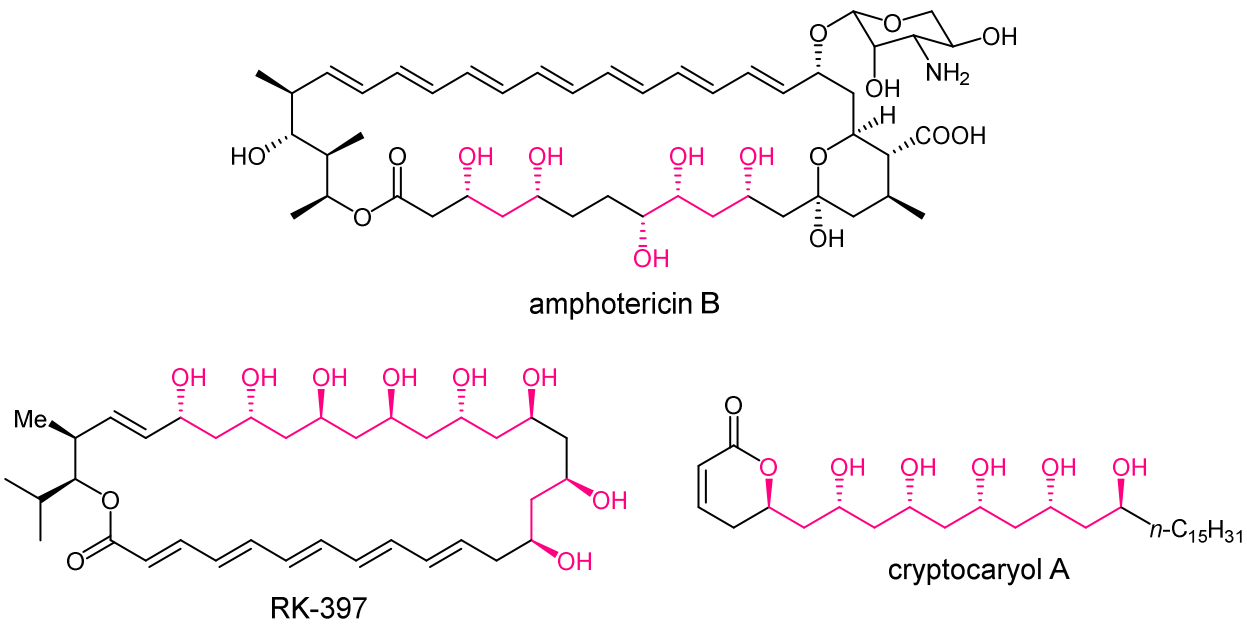
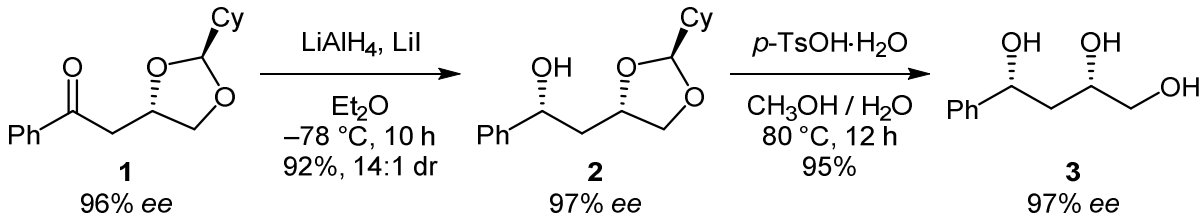
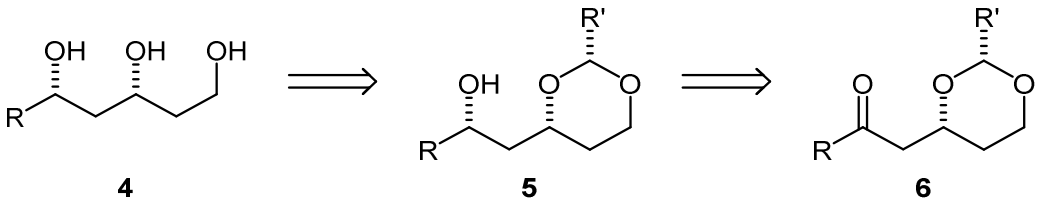


Figure 1. Chiral polyols in bioactive compounds.

Scheme 1. Synthesis of Chiral 1,2,4-Triol 3



Scheme 2. Retrosynthetic Analysis of 1,3,5-Triols

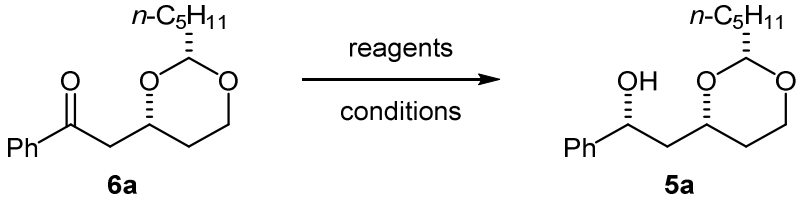


Results and Discussion

The author selected 2-((2*R**,4*R**)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethanone (**6a**) as the substrate for investigations (Table 1). Initially, the author used the reaction conditions from the previous report (Scheme 1); however, the stereoselectivity was much lower than the previous case (Table 1, entry 1). Although the addition of Lewis acid was found to be effective (Table 1, entries 1 and 2), these reagents lowered both the selectivity and reactivity when used with other solvents (Table 1, entries 3–5). Since the use of other Lewis acids with $LiAlH_4$ did not improve diastereoselectivity (Table 1, entry 6–14), other reducing agents were subsequently investigated (Table 1, entry 15–20); diastereoselectivity was improved on using $LiBH_4$ (Table 1, entry 20). The diastereoselectivity was further improved on using the Lewis acids with $LiBH_4$; Ti(O*i*-Pr)$_4$ resulted in better diastereoselectivity than LiI (Table 1, entry 21), and $EuCl_3$ was the most effective additive among those investigated (Table 1, entry 22). In order to establish a highly reproducible method, a solution of $LiBH_4$ in Et_2O prepared beforehand was used, and similarly good results

were obtained (Table 1, entry 23).

Table 1. Diastereoselective Reduction of 2-((2*R,4*R**)-2-Pentyl-1,3-Dioxan-4-yl)-1-Phenylethanone (4)**[a]



6a **5a**

Entry	Reagent	Condition	Conv. (%)[b]	dr[c]
1	$LiAlH_4$ (1 equiv), LiI (3 equiv)	Et_2O, –78 °C, 10 h	97	5.3:1
2	$LiAlH_4$ (1 equiv)	Et_2O, –78 °C, 10 h	90	2.7:1
3	$LiAlH_4$ (1 equiv), LiI (3 equiv)	THF, –78 °C, 10 h	49	1.6:1
4	$LiAlH_4$ (1 equiv), LiI (3 equiv)	CPME[d], –60 °C, 24 h	87	3.6:1
5	$LiAlH_4$ (1 equiv), LiI (3 equiv)	toluene, –78 °C, 14 h	<1	—
6	$LiAlH_4$ (1 equiv), $LiBF_4$ (3 equiv)	Et_2O, –78 °C, 5 h	94	2.7:1
7	$LiAlH_4$ (1 equiv), $ZnCl_2$ (3 equiv)	Et_2O, –78 °C, 10 h	73	1.7:1
8	$LiAlH_4$ (1 equiv), CuI (3 equiv)	Et_2O, –78 °C, 10 h	89	2.8:1
9	$LiAlH_4$ (1 equiv), $MgBr_2$ (3 equiv)	Et_2O, –78 °C, 10 h	83	1.6:1
10	$LiAlH_4$ (1 equiv), $MnCl_2$ (3 equiv)	Et_2O, –78 °C, 5 h	98	2.6:1
11	$LiAlH_4$ (1 equiv), $CaCl_2$ (3 equiv)	Et_2O, –78 °C, 5 h	96	2.4:1
12	$LiAlH_4$ (1 equiv), $LaCl_3$ (3 equiv)	Et_2O, –78 °C, 5 h	98	2.6:1

Table 1. (Continued)

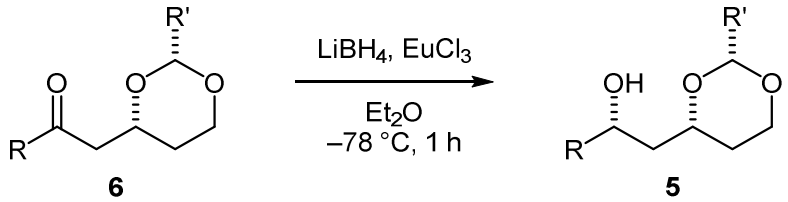
13	$LiAlH_4$ (1 equiv), $CeCl_3$ (3 equiv)	Et_2O, –78 °C, 5 h	47	2.3:1
14	$LiAlH_4$ (1 equiv), AgOTf (3 equiv)	Et_2O, –78 °C, 5 h	35	2.4:1
15	$NaBH_4$ (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	<1	—
16	$NaBH_4$ (2 equiv), LiI (3 equiv)	MeOH, –78 °C, 5 h	71	2.5:1
17	DIBAL (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	62	2.9:1
18	Red-Al® (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	98	2.1:1
19	L-Selectride® (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	96	2.0:1
20	$LiBH_4$ (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	59	7.3:1
21	$LiBH_4$ (2 equiv), $Ti(O\textit{i}\text{-}Pr)_4$ (3 equiv)	Et_2O, –78 °C, 5 h	99	10:1
22	$LiBH_4$ (2 equiv), $EuCl_3$ (3 equiv)	Et_2O, –78 °C, 5 h	99	15:1
23	$LiBH_4$ (2 equiv),[e] $EuCl_3$ (3 equiv)	Et_2O, –78 °C, 1 h	99	13:1

[a]Reactions were run using **6a** (0.10 mmol) and the reagents under the conditions in the solvent (0.050 M). [b]Conversions are determined by 1H NMR. [c]Diastereomeric ratios were determined by 1H NMR. [d]CPME = cyclopentyl methyl ether. [e]A solution of $LiBH_4$ in Et_2O (1.0 M) was used.

Subsequently, the effects of substituents on the acetal carbon were investigated under the optimized conditions (Table 2). A substrate containing the bulky isopropyl group was also tolerated, yielding the corresponding product quantitatively with high diastereoselectivity (Table 2, entry 2); however, the cyclohexyl group resulted in lower diastereoselectivity (Table 2, entry 3). An acetal bearing the phenylethyl group also exhibited high diastereoselectivity (Table 2, entry 4). On the other hand, a substrate with no substituent on the acetal carbon exhibited modest

diastereoselectivity, indicating that the presence of the substituent was important for high diastereoselectivity; the stereochemistry of the acetal carbon, which enables both substituents of the 1,3-dioxane to locate at the equatorial positions and stabilizes the conformation, also seems to help the effective coordination of the substrates to the Lewis acid (Table 2, entry 5). A substrate containing the 2-naphthyl ketone group also yielded the corresponding product in good diastereomeric ratio (Table 2, entry 6). The relative configurations of the major diastereomer **5f** were determined by X-ray analysis, and the configurations of all other examples were assigned analogously.

Table 2. Effects of Substituent on Acetal Carbon of 6[a]



6 **5**

Entry	R, R'	**5**	Conv. (%)[b]	dr[c]
1	Ph, *n*-C_5H_{11}	**5a**	99	13:1
2	Ph, *i*-Pr	**5b**	99	12:1
3	Ph, Cy	**5c**	89	7.1:1
4	Ph, $PhCH_2CH_2$	**5d**	99	11:1
5	Ph, H	**5e**	99	2.1:1
6[d]	2-naphthyl, *n*-C_5H_{11}	**5f**	99	11:1

[a]Reactions were run using **6** (0.10 mmol), $LiBH_4$ (0.10 mmol, 1 M solution in Et_2O), and $EuCl_3$ (0.30 mmol) in Et_2O (0.050 M). [b]Conversions are determined by 1H NMR. [c]Diastereomeric ratios were determined by 1H NMR. [d]Reaction was run using **6f** (0.30 mmol), $LiBH_4$ (0.30 mmol, 1 M solution in Et_2O), and $EuCl_3$ (0.90 mmol) for 2.5 h in Et_2O (0.050 M).

Conclusion

In summary, the author has accomplished highly diastereoselective reduction of β-(1,3-dioxan-4-yl)ketones using $LiBH_4$ in the presence of $EuCl_3$. The resulting product is a useful synthetic precursor to chiral polyols, which are found in a range of valuable bioactive compounds.

Experimental Section

Materials

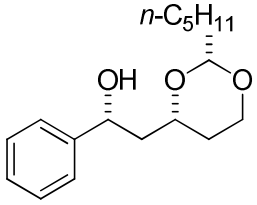
Unless otherwise noted, commercially available reagents were used without further purifications. Substrates **6** were prepared according to the procedure described in Experimental Section of Chapter 1.

General procedure for reduction of β-(1,3-dioxan-4-yl)ketones 6

To a 20-mL round-bottom flask, β-(1,3-dioxan-4-yl)ketone **6** (0.10 mmol), Et_2O (1.8 mL), and $EuCl_3$ (0.30 mmol) were sequentially added. After the mixture was stirred under argon atmosphere at –78 °C for 0.5 h, a solution of $LiBH_4$ in Et_2O (0.2 mmol, 1.0 M, 0.2 mL) was added. The resulting mixture was additionally stirred at –78 °C for 1 h. The reaction was quenched with 1M aqueous NaOH, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5/1) as an eluent gave the corresponding alcohols **5**.

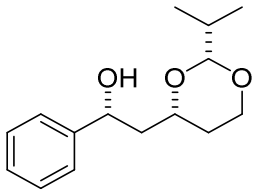
The characterization results of **5** are as below.

(*R)-2-((2*R**,4*R**)-2-Pentyl-1,3-dioxan-4-yl)-1-phenylethanol (5a)**.



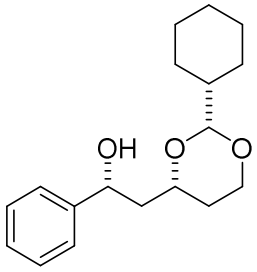
Yield: 99%, 13:1 dr, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.47–7.33 (m, 4H), 7.27 (m, 1H), 4.97 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.09 (ddd, *J* = 11.5, 5.0, 1.0 Hz, 1H), 3.92 (tt, *J* = 11.0, 2.5 Hz, 1H), 3.75 (ddt, *J* = 12.0, 2.5, 1.0 Hz, 1H), 2.04 (m, 1H), 1.80–1.72 (m, 2H), 1.67–1.62 (m, 2H), 1.44–1.38 (m, 3H), 1.35–1.27 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 144.4, 128.6, 127.7, 126.0, 102.3, 74.1, 66.7, 45.4, 35.2, 31.9, 31.7, 24.0, 22.8, 14.3. TLC: R_f 0.37 (hexane/EtOAc = 3:1). IR (neat): 3462, 2953, 2925, 2858, 1465, 1378, 1364, 1139, 1087, 1028, 760, 700, 665 cm^{-1}. HRMS Calcd for $C_{17}H_{27}O_3$: $[M+H]^+$, 279.1955. Found: *m*/*z* 279.1945.

(*R)-2-((2*R**,4*R**)-2-Isopropyl-1,3-dioxan-4-yl)-1-phenylethanol (5b)**.



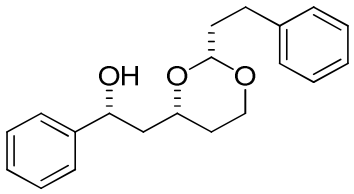
Yield: 99%, 12:1 dr, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.39–7.33 (m, 4H), δ 7.28–7.27 (m, 1H), δ 4.98 (dd, *J* = 9.5, 4.0 Hz, 1H), 4.31 (d, *J* = 5.0 Hz, 1H), 4.11 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.91 (tt, *J* = 11.0, 2.5 Hz, 1H), 3.74 (ddt, *J* = 12.0, 2.5, 1.0 Hz, 1H), 3.63 (d, *J* = 1.0 Hz, 1H), 2.02 (m, 1H), 1.88–1.70 (m, 3H), 1,40 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 144.1, 128.4, 127.4, 125.7, 105.6, 73.9, 66.5, 45.2, 32.7, 31.6, 17.3, 17.1. TLC: R_f 0.37 (hexane/EtOAc = 3:1). IR (neat): 3447, 3064, 3031, 2961, 2923, 2856, 1474, 1379, 1366, 1243, 1140, 1126, 1102, 1065, 1040, 986, 957, 919, 759, 701cm^{-1}. HRMS Calcd for $C_{15}H_{23}O_3$: $[M+H]^+$, 251.1642. Found: *m*/*z* 251.1632.

(*R)-2-((2*R**,4*R**)-2-Cyclohexanyl-1,3-dioxan-4-yl)-1-phenylethanol (5c)**.



Yield: 89%, 7.1:1 dr, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.38–7.33 (m, 4H), 7.27 (m, 1H), 4.98 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.31 (d, *J* = 5.5 Hz, 1H), 4.10 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.90 (tt, *J* = 10.5, 2.5 Hz, 1H), 3.73 (ddt, *J* = 11.5, 2.5, 0.5 Hz, 1H), 3.67 (br s,1H), 2.03 (m, 1H), 1.84–1.77 (m, 2H), 1.75–1.71 (m, 3H), 1.66 (m, 1H), 1.57 (m, 1H), 1.40 (m, 1H), 1.27–1.01 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 144.1, 128.4, 127.4, 125.7, 105.0, 73.9, 66.5, 45.1, 42.3, 31.7, 27.7, 27.4, 26.3, 25.7, 25.7. TLC: R_f 0.34 (hexane/EtOAc = 3:1). IR (neat): 3446, 3063, 3030, 2923, 2853, 1494, 1452, 1368, 1247, 1197, 1139, 1091, 1029, 1014, 959.6 cm^{-1}. HRMS Calcd for $C_{18}H_{27}O_3$: $[M+H]^+$, 291.1955. Found: *m*/*z* 291.1946.

(*R)-2-((2*R**,4*R**)-2-(2-Phenylethyl)-1,3-dioxan-4-yl)-1-phenylethanol (5d)**.

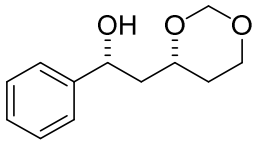


Yield: 99%, 11:1 dr, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.39–7.33 (m, 4H), 7.32–7.27 (m, 3H), 7.23–7.19 (m, 3H), 4.98 (dd, *J* = 9.5, 4.0 Hz, 1H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.12 (ddd, *J* = 11.5, 5.5 1.0 Hz, 1H), 3.90 (tt, *J* = 11.0, 2.5 Hz, 1H), 3.74 (dt, *J* = 12.5, 3.0 Hz, 1H), 3.49 (br s, 1H), 2.75 (t, *J* = 8.0 Hz, 2H), 2.07 (m, 1H), 2.01–1.96 (m, 2H), 1.83–1.74 (m, 2H), 1.42 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 144.1, 141.3, 128.4, 128.4, 127.5, 125.9, 125.7, 125.5, 101.0, 73.7, 66.4, 45.2, 36.3, 31.5, 30.2. TLC: R_f 0.25 (hexane/EtOAc = 3:1). IR (neat): 3439, 3062, 3027, 2954, 2860, 1497, 1455, 1430, 1379, 1139, 1087, 1068, 1031, 752, 700 cm^{-1}. HRMS Calcd for $C_{20}H_{25}O_3$: $[M+H]^+$, 313.1798. Found: *m*/*z* 313.1790.

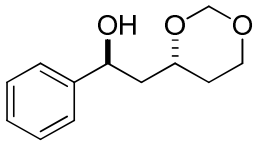
(*R)-2-((*R**)-1,3-Dioxan-4-yl)-1-phenylethanol (5e)**.

The diastereomers could not be separated.

Yield: 99%, 2.1:1 dr, white solid. Mp. 60.5–61.4 °C. TLC: R_f 0.15 (hexane/EtOAc = 3:1). IR (KBr): 3243, 3230, 2948, 2861, 1161, 1138, 1072, 1055, 1040, 1028, 1009, 997, 966 cm^{-1}. HRMS Calcd for $C_{12}H_{17}O_3$: $[M+H]^+$, 209.1172. Found: *m*/*z* 209.1165.

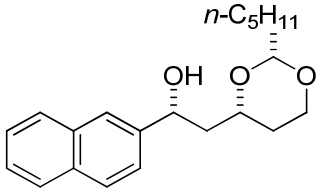


Major diastereomer: ^1H NMR ($CDCl_3$) δ 7.39–7.33 (m, 4H), 7.28 (m, 1H), 5.10 (m, 1H), 4.95 (dd, *J* = 9.0, 3.5 Hz, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 4.10 (m, 1H), 3.93–3.84 (m, 1H), 3.76–3.69 (m, 1H), 3.28 (d, *J* = 1.5 Hz, 1H), 2.07 (m, 1H), 2.04–1.58 (m, 2H), 1.44 (tt, *J* = 14.0, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 144.1, 128.4, 127.5, 125.8, 93.6, 73.5, 66.5, 45.2, 32.1.



Minor diastereomer: ^1H NMR ($CDCl_3$) δ 7.39–7.33 (m, 4H), 7.28 (m, 1H), 5.10 (m, 1H), 5.02 (quint, *J* = 4.5 Hz, 1H), 4.72 (d, *J* = 6.5 Hz, 1H), 4.09 (m, 1H), 3.93–3.84 (m, 1H), 3.76–3.69 (m, 1H), 2.72 (d, *J* = 4.5 Hz, 1H), 2.07 (m, 1H), 2.04–1.58 (m, 2H), 1.44 (tt, *J* = 14.0, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 144.1, 128.5, 127.4, 125.5, 93.7, 73.8, 66.2, 44.5, 31.8.

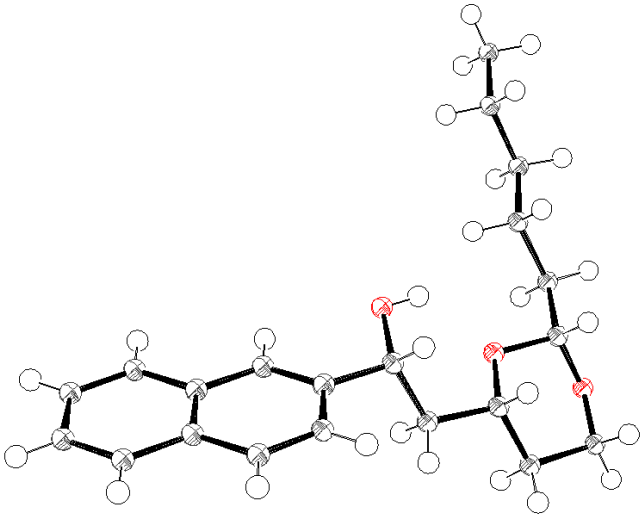
(*R)-1-(Naphthalen-2-yl)-2-((2*R**,4*R**)-2-pentyl-1,3-dioxan-4-yl)ethanol (5f)**.



Yield: 99%, 11:1 dr, white solid. ^1H NMR ($CDCl_3$) δ 7.85–7.82 (m, 4H), 7.50–7.44 (m, 3H), 5.15 (dd, *J* = 9.0, 3.5 Hz, 1H), 4.60 (t, *J* = 5.5 Hz, 1H), 4.10 (ddd, *J* = 11.5, 5.0, 1.0 Hz, 1H), 3.96 (tt, *J*

= 11.0, 2.5 Hz, 1H), 3.75 (dt, *J* = 12.5, 3.0 Hz, 1H), 3.68 (br s, 1H), 2.11 (m, 1H), 1.88 (dt, *J* = 15.0, 3.0 Hz, 1H), 1.78 (m, 1H), 1.69–1.64(m, 2H), 1.47–1.41 (m, 3H), 1.38–1.30 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 141.5, 133.3, 132.9, 128.1, 128.0, 127.6, 126.0, 125.7, 124.4, 124.0, 102.1, 74.0, 66.5, 45.1, 35.0, 31.7, 31.5, 23.8, 22.5, 14.0. Mp. 78.0–78.8 °C. TLC: R_f 0.33 (hexane/EtOAc = 3:1). IR (KBr): 3482, 2955, 2937, 2931, 2910, 2871, 2851, 1424, 1365, 1165, 1139, 1086, 975.1, 862.2, 822.7, 758.1 cm^{-1}. HRMS Calcd for $C_{21}H_{28}O_3Na$: $[M+Na]^+$, 351.1931. Found: *m*/*z* 351.1918.

ORTEP Drawing of 5f



A. Crystal Data

Empirical Formula	$C_{21}H_{28}O_3$
Formula Weight	328.45
Crystal Color, Habit	Colorless, Prism
Crystal Dimensions	0.410 × 0.380 × 0.200 mm
Crystal System	Monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 28.83(4) Å
	b = 7.923(11) Å
	c = 7.876(11) Å
	ß = 89.14(2)°
	V = 1799(5) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.213 g/cm^3

F_{000}	712.00
μ(MoKα)	0.791 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å)
	graphite monochromated
Voltage, Current	50kV, 12mA
Temperature	20.0 °C
Detector Aperture	75 mm (diameter)
Data Images	1080 exposures
ω Oscillation Range	–60.0–120.0°
Exposure Rate	96.0 sec./°
Detector Swing Angle	30.50°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	96.0 sec./°
Detector Swing Angle	30.50°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	96.0 sec./°
Detector Swing Angle	30.50°
Detector Position	49.00 mm
Pixel Size	0.146 mm
$2\theta_{max}$	55.6°
No. of Reflections Measured	Total: 11513
	Unique: 3684 (R_{int} = 0.0874)
Corrections	Lorentz-polarization

	Absorption
	(trans. factors: 0.967–0.984)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (F_0^2 - F_c^2)^2$
Least Squares Weights	$w = 1/\ [\ \sigma^2(F_0^2) + (0.1000 \cdot P)^2$ $+ 0.0000 \cdot P\ ]$ where $P = (Max(F_0^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	55.6°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	3684
No. Variables	217
Reflection/Parameter Ratio	16.98
Residuals: R1 (I>2.00σ(I))	0.1052
Residuals: R (All reflections)	0.1523
Residuals: wR2 (All reflections)	0.2984
Goodness of Fit Indicator	1.270
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.33 $e^-/Å^3$
Minimum peak in Final Diff. Map	–0.35 $e^-/Å^3$

References

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3. Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419.
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Chapter 3

Asymmetric *syn*-1,3-Dioxane Construction via Kinetic Resolution of Secondary Alcohols Using Chiral Phosphoric Acid Catalysts

In chapter 3, the author demonstrates a novel enantioselective hemiacetalization/ intramolecular oxy-Michael addition cascade for the synthesis of *syn*-1,3-diol frameworks via kinetic resolution of chiral secondary alcohols using chiral phosphoric acid catalysts. By utilizing the recovered optically active starting material, both enantiomers of the corresponding protected 1,3-diols could be obtained with high optical purities. In addition, the products with a carbonyl group were converted diastereoselectively to longer optically active 1,3-polyols, which are representative motifs in polyketides. Moreover, the organocatalytic approach presented in this study facilitates a library construction of useful chiral building blocks for the asymmetric synthesis of bioactive compounds.

Chapter 3

Introduction

Generally, 1,3-diols are fundamental building blocks of various functional molecules such as polyketides, which are representative bioactive compounds (Figure 1).[1,2] Thus, reliable methods for the stereoselective synthesis of 1,3-diol structures are crucial in drug discovery. In this context, an oxy-Michael addition is a useful approach to construct such frameworks.[3] In particular, intramolecular oxy-Michael addition of hemiacetals that are generated from chiral δ-hydroxy-α,β-unsaturated carbonyls and aldehydes, provides saturated six-membered cyclic acetals, namely 1,3-dioxanes. In this method, the relative stereochemistry can be controlled by favoring bulky substituents in equatorial positions in chair-like conformations. This leads to the effective formation of *syn*-1,3-diol units, which are useful in the synthesis of a number of pharmacologically important compounds.[4] Even though several diastereoselective protocols from optically active substrates have been developed so far,[5] there has been no report on enantioselective methods via kinetic resolution of racemic secondary alcohols to further facilitate the construction of such important chiral building blocks.

Asano and Matsubara recently reported on the development of organocatalytic asymmetric intramolecular hetero-Michael additions, some of which involve the in situ formation of hemiacetal intermediates.[6,7] In these methods, high enantioselectivities are obtained using multipoint recognition of substrates for organocatalytic cyclization.[8] Therefore, it is possible that the organocatalytic protocol is also effective for the enantioselective formation of *syn*-1,3-diol structures via intramolecular oxy-Michael addition. In the complex with a hemiacetal intermediate, the chiral catalyst is distal to the chiral carbon in the secondary alcohol substrate, but is proximal to the hemiacetal carbon (Scheme 1a). Thus, the control of the chirality of the hemiacetal carbon in a six-membered chair-like conformation would lead to the kinetic resolution of secondary alcohols followed by an asymmetric intramolecular oxy-Michael addition to form *syn*-1,3-diol frameworks. In this context, the author designed a hemiacetalization/oxy-Michael addition cascade through the kinetic resolution of the racemic δ-hydroxy-α,β-unsaturated ketone

(±)-**1** using chiral phosphoric acids (Scheme 1b).[9–11] In the process, product **3** serves as a precursor of chiral tetraols. The recovered optically active alcohol **1** can be transformed to the opposite enantiomer of the cyclic acetal (*ent*-**3**) which is an efficient enantiodivergent synthesis.

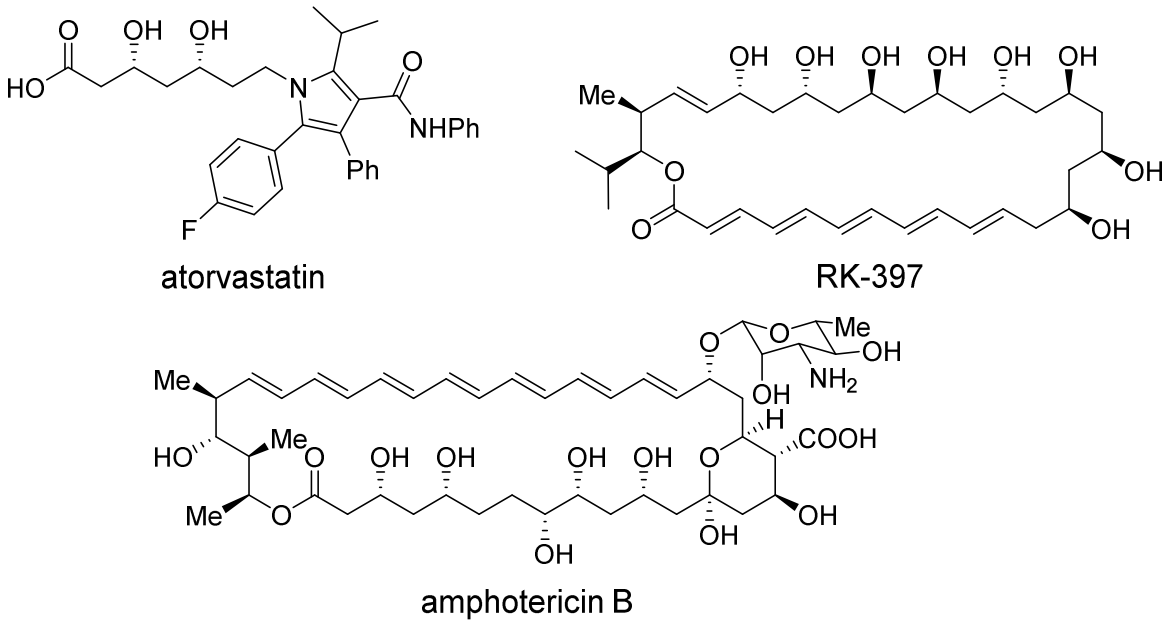
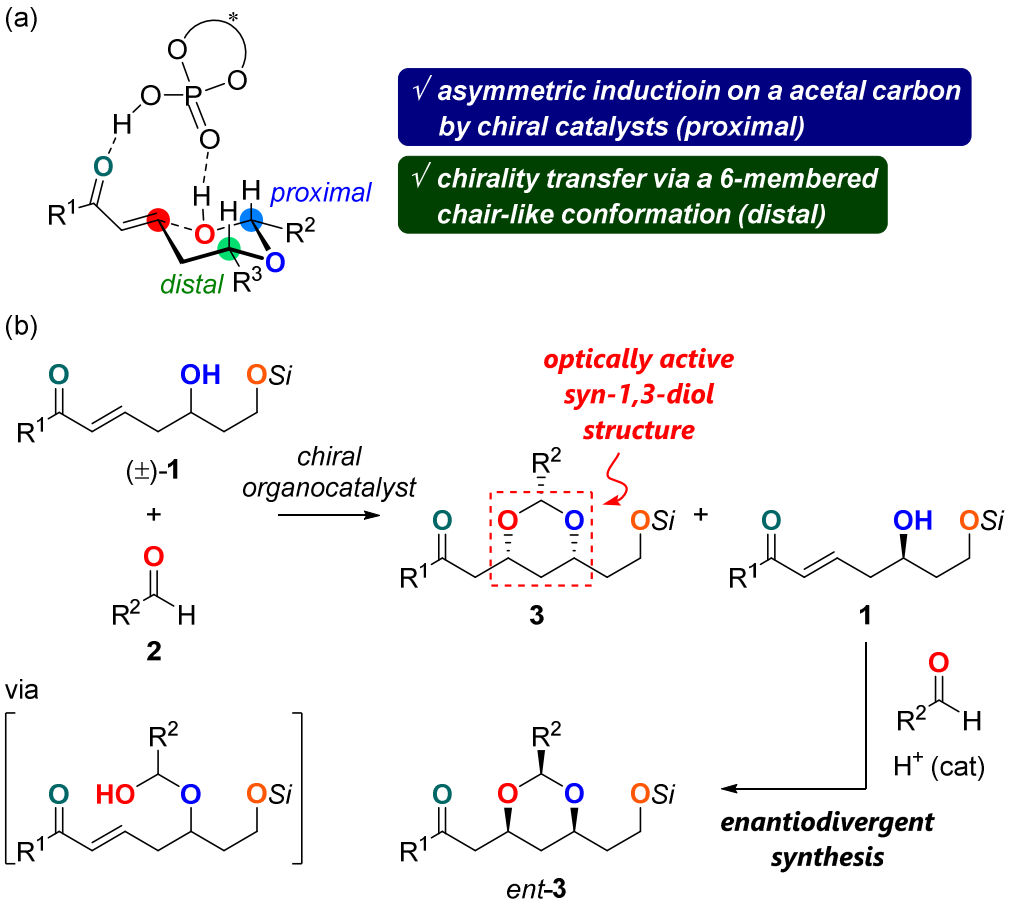


Figure 1. 1,3-Diols in pharmaceuticals.

Scheme 1. Hemiacetalization/Intramolecular Oxy-Michael Addition Cascade via Kinetic Resolution of Secondary Alcohols

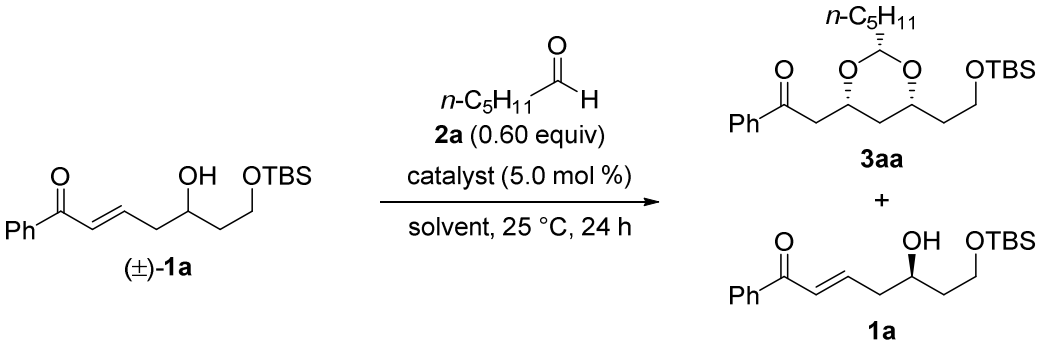


Results and Discussion

First, (±)-(*E*)-7-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-1-phenylhept-2-en-1-one ((±)-**1a**) and hexanal (**2a**) were reacted with 5 mol % of the chiral phosphoric acid catalysts **4** (Figure 2)[9] in cyclohexane at 25 °C (Table 1, entries 1–5). The catalyst screening revealed that **4a**[12] is a better catalyst in terms of both stereoselectivity and reactivity (Table 1, entry 1). Also, after performing screening studies using different aldehydes (see Experimental Section for details), hexanal (**2a**) was identified as the most suitable reagent. The use of a chiral hemiacetal carbon was found to

be essential for the reaction to run enantioselectively. When the reaction was carried out with paraformaldehyde and in the presence of **4a**, unreacted **1a** was recovered and the enantioselectivity was very poor (1% *ee*, see the Experimental Section for details). This result suggests that the asymmetric phosphoric acid catalyst recognized the chirality of the acetal carbon, which led to the kinetic resolution of (±)-**1a**. Furthermore, solvent screening showed that alkane solvents provided better reactivity (Table 1, entries 1 and 6–8). In terms of the yields of **3aa** and **1a** and their enantiomeric excesses, cyclohexane was found to be the most optimal solvent (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]

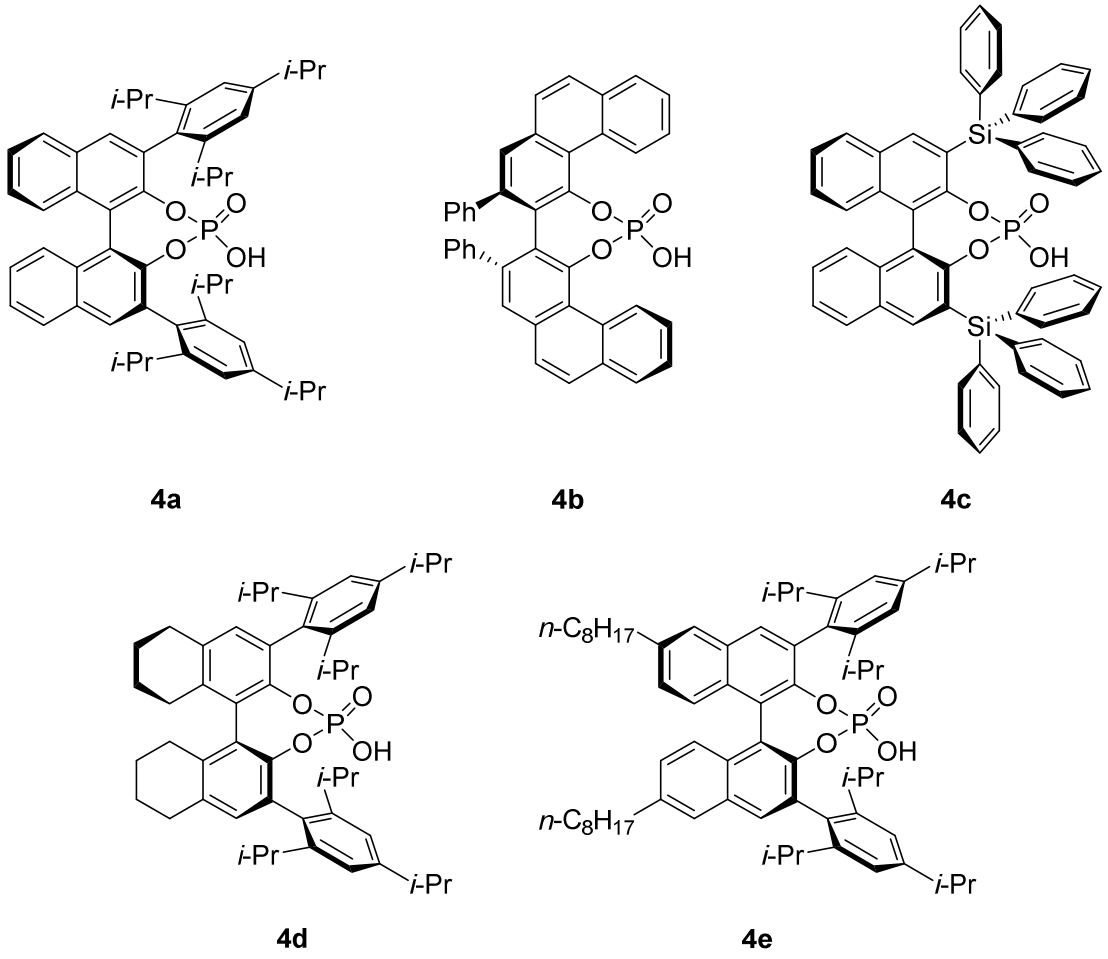


Entry	Catalyst	Solvent	Yield of **3a** (%)[b,c]	*ee* of **3a** (%)	Recovery of **1a** (%)[b]	*ee* of **1a** (%)
1	**4a**	*c*-hexane	47 (6.7:1)	83	42	73
2	**4b**	*c*-hexane	24 (2.3:1)	8	55	1
3	**4c**	*c*-hexane	11 (5.0:1)	9	34	5
4	**4d**	*c*-hexane	22 (3.3:1)	91	56	26
5	**4e**	*c*-hexane	34 (4.1:1)	89	60	43
6	**4a**	*n*-hexane	48 (5.9:1)	80	46	63
7	**4a**	*n*-pentane	56 (6.0:1)	76	53	74
			93			

Table 1. (Continued)

8	**4a**	*n*-heptane	47 (6.8:1)	80	50	62
9	**4a**	benzene	14 (5.9:1)	84	74	11
10	**4a**	Et_2O	<5	–	–	–
11	**4a**	CPME[d]	<5	–	–	–
12	**4a**	$CHCl_3$	<1	–	–	–

[a]Reactions were run using (±)-**1a** (0.20 mmol), **2a** (0.12 mmol), and the catalyst (0.010 mmol) in the solvent (4.0 mL). [b]Isolated yields. [c]Values in the parentheses are the diastereomeric ratios determined by ^{1}H NMR. [d]CPME = cyclopentyl methyl ether.



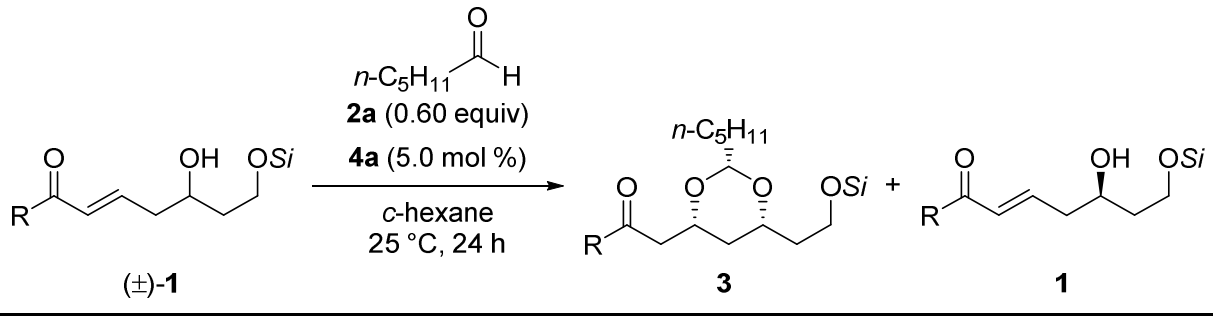
4a **4b** **4c**

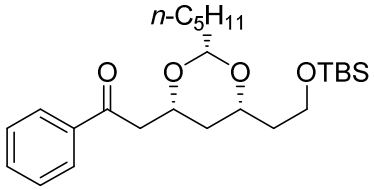
4d **4e**

Figure 2. Chiral phosphoric acid catalysts.

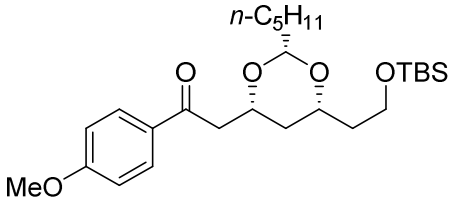
With the optimal conditions established, the author explored the substrate scope of the reaction (Table 2). A range of enones with various aryl, alkenyl, and aliphatic groups yielded the corresponding 1,3-dioxane products via efficient kinetic resolution. Aryl ketones **1b** and **1c**, bearing electron-donating and electron-withdrawing groups, exhibited good yields and stereoselectivities. Substrates **1d** and **1e**, with a *p*-bromophenyl group and 2-naphthyl group, respectively, were also applicable. In addition, the 1,3-dioxane **3fa** with an alkenyl moiety was investigated, because it allows for further modifications such as selective hydration to approach higher polyols. The product of the reaction with **1f** was obtained in good stereoselectivity, but the starting material **1f** was recovered in low yield. Furthermore, enone **1g** bearing an aliphatic group was successfully employed in the kinetic resolution. The absolute configurations of **3ba** were determined after its synthesys from a known compound, (*S*)-1-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-ol, by comparing the optical rotation.[13] The configurations of all other products were assigned analogously.

Table 2. Substrate Scope[a]



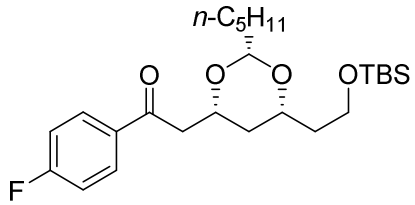


3aa: 47%, 6.7:1 dr, 83% *ee*
1a (recovery): 42%, 73% *ee*

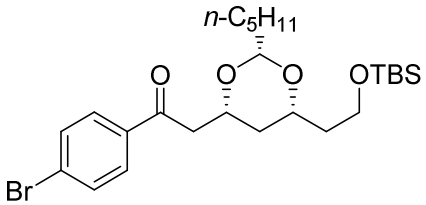


3ba: 52%, 6.2:1 dr, 82% *ee*
1b (recovery): 41%, 77% *ee*

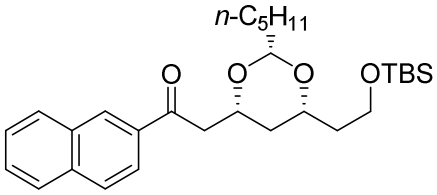
Table 2. (Continued)



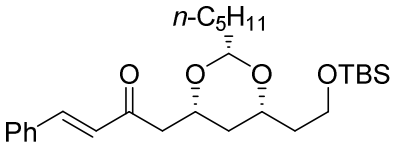
3ca: 51%, 10:1 dr, 85% *ee*
1c (recovery): 48%, 70% *ee*



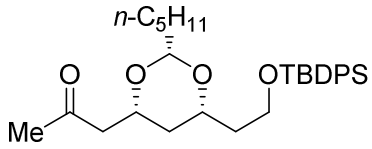
3da: 52%, 6.6:1 dr, 85% *ee*
1d (recovery): 43%, 75% *ee*



3ea: 51%, 10:1 dr, 80% *ee*
1e (recovery): 44%, 77% *ee*



3fa: 53%, 14:1 dr, 82% *ee*
1f (recovery): 21%, 74% *ee*

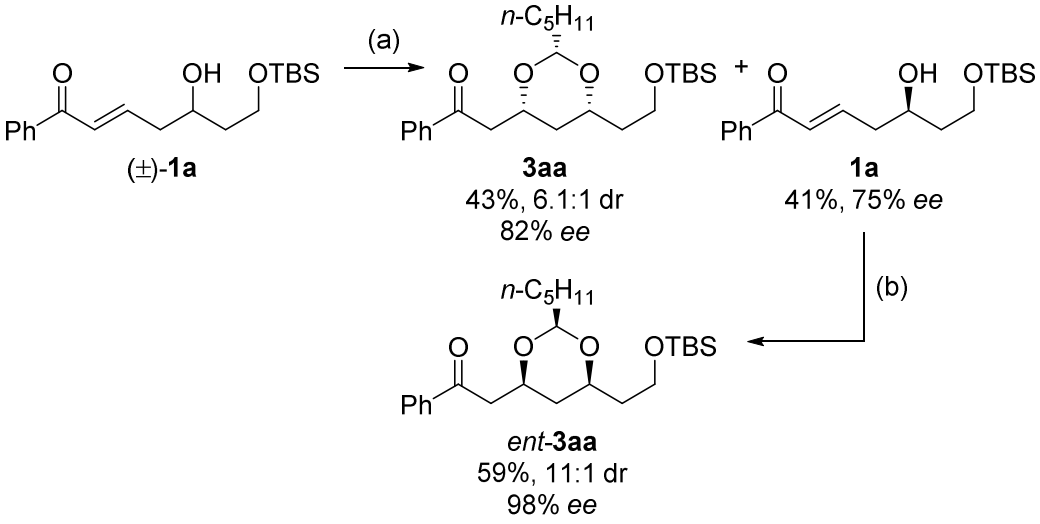


3ga: 46%, 10:1 dr, 71% *ee*
1g (recovery): 50%, 70% *ee*

[a]Reactions were run using (±)-**1** (0.20 mmol), **2a** (0.12 mmol), and **4a** (0.010 mmol) in cyclohexane (4.0 mL). Yields represent material isolated after silica gel column chromatography.

Due to the fact that kinetic resolution provides optically active starting materials as well, both enantiomers of the 1,3-dioxanes could be synthesized (Scheme 2). The kinetic resolution of (±)-**1a** using (*S*)-**4a** with 0.70 equivalents of **2a** provided **3aa** with optically active **1a** recovered. The subsequent treatment of the optically active **1a** with (*R*)-**4a** and 0.80 equivalents of **2a** gave *ent*-**3aa** with higher enantiomeric purity than **1a**. Therefore, this method offers a synthetic approach to both enantiomers of the 1,3-diol framework.

Scheme 2. Enantiodivergent Synthesis of 1,3-Dioxanes 3a



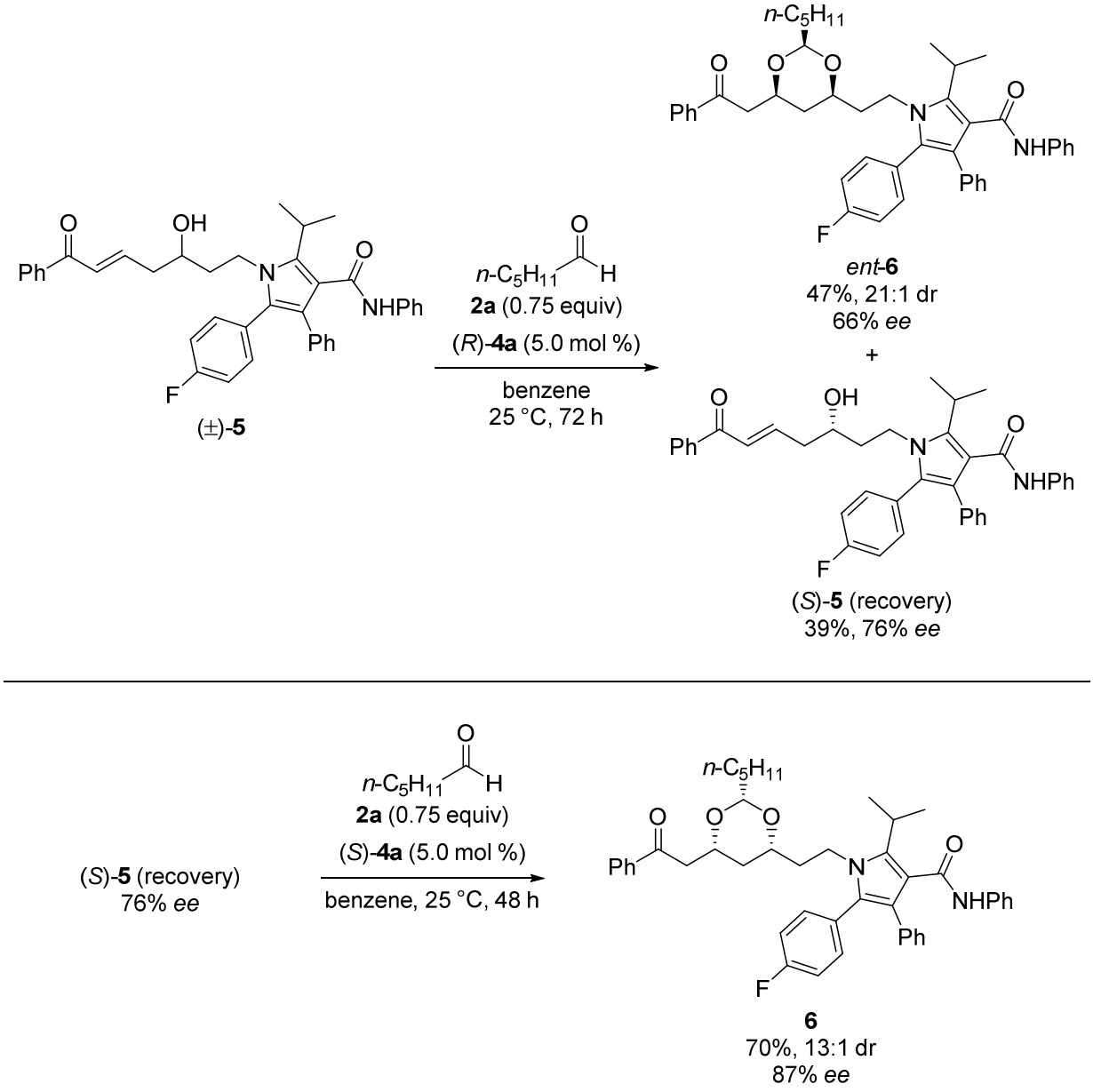
(a) **2a** (0.70 equiv), (*S*)-**4a** (5.0 mol %), cyclohexane (0.050 M), 25 °C, 24 h. (b) **2a** (0.80 equiv), (*R*)-**4a** (5.0 mol %), cyclohexane (0.050 M), 25 °C, 24 h.

In addition, this synthetic method was also useful for the construction of an optically active substructure of atorvastatin (Figure 1). This compound is a lipid-lowering agent and the key component in Lipitor, a representative top-selling pharmaceutical (Scheme 3).[14] The kinetic resolution of (±)-**5** using (*R*)-**4a** afforded the acetal product *ent*-**6** with optically active (*S*)-**5** recovered. Subsequently, the treatment of the recovered (*S*)-**5** with (*S*)-**4a** yielded the corresponding 1,3-dioxane **6**. The product contained absolute configurations that were consistent with atorvastatin and had a higher enantiomeric purity than (*S*)-**5**.

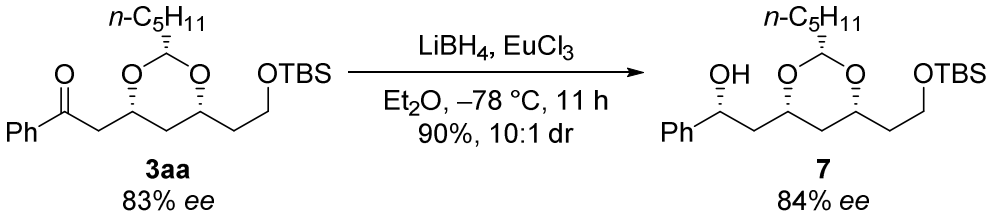
Several additional reactions were performed with some of the substrates used in the scope studies. The carbonyl group of **3aa** was reduced with lithium borohydride in the presence of europium chloride to afford the corresponding alcohol **7**, a protected 1,3,5,7-tetraol, in a 10:1 diastereomeric ratio (Scheme 4).[15] Moreover, the building block **3ga**, bearing a methylketone moiety, underwent an aldol reaction with an aldehyde in the presence of dicyclohexylboron triflate to extend the polyol chain while achieving high diastereoselectivity and maintaining the optical purity (Scheme 5).[16] These successful modifications demonstrated the utility of the products as

chiral building blocks in the asymmetric synthesis of 1,3-polyols, which are fundamental units in a range of polyketide pharmaceuticals.[1]

Scheme 3. Synthesis of Substructure in Atorvastatin



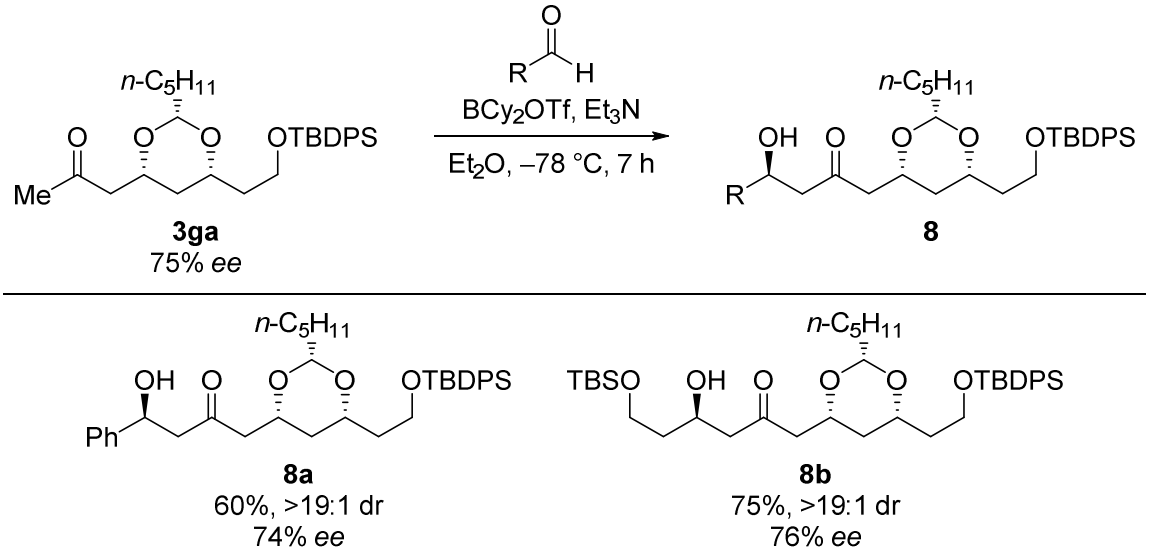
Scheme 4. Synthesis of Protected Chiral 1,3,5,7-Tetraol 7



3aa
83% *ee*

7
84% *ee*

Scheme 5. Diastereoselective Aldol Reactions of 3ga



3ga
75% *ee*

8

8a
60%, >19:1 dr
74% *ee*

8b
75%, >19:1 dr
76% *ee*

Conclusion

In summary, the author developed a novel hemiacetalization/intramolecular oxy-Michael addition cascade for the enantioselective synthesis of *syn*-1,3-dioxanes via kinetic resolution of racemic secondary alcohols using chiral phosphoric acid catalysts. The products contained optically active *syn*-1,3-diol frameworks, which are important substrates in the pharmaceutical industry. Subsequent utilization of the recovered starting material allowed for both enantiomers of the building blocks to be obtained in high optical purities. In addition, the diastereoselective

transformations of products with a carbonyl group led to the construction of optically active 1,3-polyol structures, which are characteristic motifs in polyketides. Thus, the presented organocatalytic approach supplies a library of synthetic modules for the asymmetric synthesis of bioactive compounds.

Experimental Section

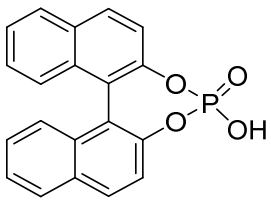
Materials

Unless otherwise noted, commercially available reagents were used without further purifications.

General procedure for asymmetric synthesis of 1,3-dioxanes 3 via kinetic resolution

To a solution of δ-hydroxy-α,β-unsaturated ketones (±)-**1** (0.20 mmol) in cyclohexane (4.0 mL) were added hexanal (**2a**, 15 μL, 0.12 mmol) and chiral phosphoric acid catalyst **4a** (7.5 mg, 0.010 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was diluted with hexane/EtOAc (v/v = 1:1), passed through a short silica gel pad, and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 15:1 to 3:1) as an eluent afforded the corresponding 1,3-dioxanes **3** and unreacted starting material **1**.

Racemic compounds were prepared using (±)-**4f** as a catalyst.



(±)-**4f**

Procedure for asymmetric synthesis of ent-3aa

To a solution of (±)-**1a** (0.10 g, 0.30 mmol) in cyclohexane (6.0 mL) were added hexanal (**2a**, 26 μL, 0.21 mmol) and chiral phosphoric acid catalyst (*S*)-**4a** (11 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was diluted with hexane/EtOAc (v/v = 1:1), passed through a short silica gel pad, and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 15:1 to 3:1) as an eluent afforded the corresponding 1,3-dioxane **3aa** (43% (56 mg), 82% *ee*) and **1a** (41% (41 mg), 75% *ee*).

Next, to a solution of the recovered **1a** (41 mg, 0.12 mmol) in cyclohexane (2.3 mL) were added hexanal (**2a**, 12 μL, 0.094 mmol) and chiral phosphoric acid catalyst (*R*)-**4a** (4.4 mg, 0.0059 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was diluted with hexane/EtOAc (v/v = 1:1), passed through a short silica gel pad, and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 15:1 to 3:1) as an eluent afforded the corresponding 1,3-dioxane *ent*-**3aa**.

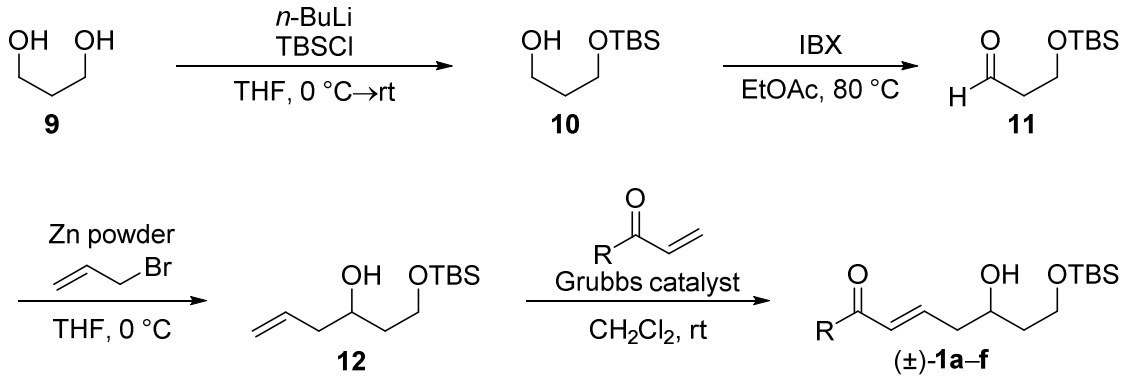
Procedure for asymmetric synthesis of 6

To a solution of (±)-**5** (0.18 g, 0.30 mmol) in benzene (3.0 mL) were added hexanal (**2a**, 28 μL, 0.23 mmol) and chiral phosphoric acid catalyst (*R*)-**4a** (11 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 72 h. The reaction mixture was diluted with hexane/EtOAc (v/v = 1:1), passed through a short silica gel pad, and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 1:1) as an eluent afforded *ent*-**6** (47% (89 mg), 66% *ee*) and (*S*)-**5** (39% (70 mg), 76% *ee*).

Next, to a solution of the recovered (*S*)-**5** (46 mg, 0.077 mmol) in benzene (0.15 mL) were added hexanal (**2a**, 6.6 μL, 0.054 mmol) and chiral phosphoric acid catalyst (*S*)-**4a** (2.9 mg, 0.0038 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C 48 h. The reaction mixture was diluted with hexane/EtOAc (v/v = 1:1), passed through a short silica gel pad, and

concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1 to 3:1) as an eluent afforded **6**.

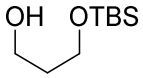
General procedure for the preparation of (±)-1a–f



Procedure for preparation of **10**

To a solution of 1,3-propanediol (**9**, 2.5 g, 33 mmol) in dry THF (80 mL) was added *n*-butyllithium (20 mL, 1.63 M in hexane, 33 mmol) dropwise at 0 °C. After the mixture was stirred for 1 h, *tert*-butyldimethylsilyl chloride (4.5 g, 30 mmol) in dry THF (10 mL) was added, and the reaction was allowed to warm to ambient temperature. After being stirred for additional 23 h, the reaction was quenched with H_2O (50 mL), and the mixture was subsequently extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1) as an eluent gave 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (**10**).

3-((*tert*-Butyldimethylsilyl)oxy)propan-1-ol (10): CAS RN [73842-99-6].



Colorless oil; 94% yield (5.9 g).

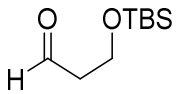
^{1}H NMR ($CDCl_3$) δ 3.84 (t, *J* = 5.0 Hz, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 1.78 (tt, *J* = 5.5, 5.0 Hz, 2H),

0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 63.0, 62.5, 34.2, 25.9, 18.2, –5.5.

Procedure for preparation of **11**

To a suspension of 2-iodoxybenzoic acid (25 g, 90 mmol) in dry EtOAc (60 mL) was added **10** (5.7 g, 30 mmol), and the mixture was stirred vigorously at 80 °C for 11 h. The reaction suspension was cooled to ambient temperature and then filtered. The filter cake was washed with EtOAc, and the combined filtrates were concentrated in vacuo to afford 3-((*tert*-butyldimethylsilyl)oxy)propanal (**11**), which was used for the next step without further purification.

3-((*tert*-Butyldimethylsilyl)oxy)propanal (11): CAS RN [87184-81-4].



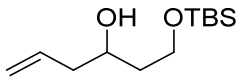
Colorless oil; 88 % yield (5.0 g).

^{1}H NMR ($CDCl_3$) δ 9.80 (t, J = 2.0 Hz, 1H), 3.99 (t, J = 6.0 Hz, 2H), 2.60 (dt, J = 6.0, 2.0 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 202.2, 57.4, 46.5, 25.7, 18.2, –5.5.

Procedure for preparation of **12**

To a suspension of zinc (2.6 g, 40 mmol) in dry THF (40 mL) were added **11** (3.8 g, 20 mmol) and allyl bromide (2.6 mL, 30 mmol), and the resulting mixture was cooled to 0 °C under argon atmosphere. After stirring for ca. 5 min, saturated aqueous NH_4Cl (1.0 mL) was added to the solution, and the mixture was stirred for additional 9 h. The reaction was quenched with an excess amount of saturated aqueous NH_4Cl, and the mixture was subsequently extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1) as an eluent gave 1-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-ol (**12**).

1-((*tert*-Butyldimethylsilyl)oxy)hex-5-en-3-ol (12): CAS RN [261633-45-8].



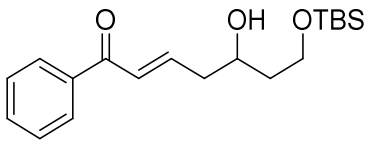
Colorless oil; 99% yield (4.6 g).

^{1}H NMR ($CDCl_3$) δ 5.85 (m, 1H), 5.13–5.07 (m, 2H), 3.92–3.88 (m, 2H), 3.81 (m, 1H), 3.41 (br s, 1H), 2.31–2.20 (m, 2H), 1.69–1.65 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 135.0, 117.3, 71.3, 62.6, 42.0, 37.7, 25.8, 18.1, –5.6.

Procedure for preparation of (±)-**1a**–(±)-**1e**

To a solution of **12** (1.2 g, 5.0 mmol) and α,β-unsaturated ketone (15 mmol) in dry CH_2Cl_2 (30 mL) was added Grubbs 2nd generation catalyst (0.21 g, 0.25 mmol). After being stirred for 12 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1) as an eluent gave the corresponding δ-hydroxy-α,β-unsaturated ketone (±)-**1**.

(*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-1-phenylhept-2-en-1-one ((±)-1a).

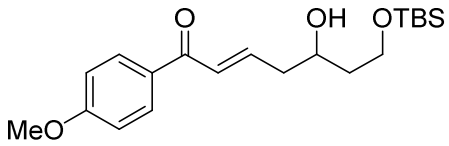


White solid; 50% yield.

^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 7.08 (dt, *J* = 15.5, 7.5 Hz, 1H), 6.96 (dt, *J* = 15.5, 1.5 Hz, 1H), 4.07 (m, 1H), 3.93 (dt, *J* = 10.5, 4.5 Hz, 1H), 3.84 (m, 1H), 3.67 (br s, 1H), 2.56 (dddd, *J* = 14.5, 7.5, 7.5, 1.0 Hz, 1H), 2.48 (dddd, *J* = 14.5, 7.5, 7.5, 1.0 Hz, 1H), 1.69 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 190.7, 145.7, 137.8, 132.6, 128.6, 128.5, 128.1, 71.2, 62.7, 40.8, 37.8, 25.8, 18.1, –5.6. TLC: R_f 0.20 (hexane/EtOAc = 3:1). Mp. 39.1–39.7 °C. IR (KBr): 3447, 1667, 1618, 1577, 1448, 1413, 1361, 1306, 1247, 1114, 1070, 998, 969,

923, 827 cm^{-1}. HRMS Calcd for $C_{19}H_{30}O_3SiNa$: $[M+Na]^+$, 357.1856. Found: *m*/*z* 357.1850. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.5 min, t_{major} = 13.9 min. $[\alpha]_D^{20}$ +38.1 (for **1a**, 73% *ee*, *c* 0.49, CH_2Cl_2).

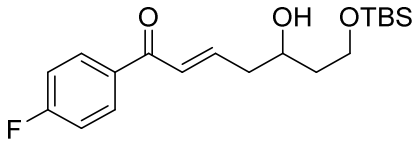
(*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-1-(4-methoxyphenyl)hept-2-en-1-one ((±)-1b).



Pale yellow oil; 80% yield.

^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.05 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.96 (m, 1H), 6.94 (m, 2H), 4.06 (m, 1H), 3.93 (dt, *J* = 10.0, 4.5 Hz, 1H), 3.87 (s, 3H), 3.83 (m, 1H), 3.65 (br s, 1H), 2.55 (m, 1H), 2.47 (m, 1H), 1.72 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 188.8, 163.3, 144.6, 130.9, 130.7, 127.8, 113.7, 71.2, 62.7, 55.4, 40.8, 37.8, 25.8, 18.1, –5.6. TLC: R_f 0.15 (hexane/EtOAc = 3:1). IR (neat): 3478, 1661, 1616, 1601, 1575, 1416, 1307, 1252, 1171, 1081, 1026 cm^{-1}. HRMS Calcd for $C_{20}H_{32}O_4SiNa$: $[M+Na]^+$, 387.1962. Found: *m*/*z* 387.1954. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 80.0/20.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.9 min, t_{major} = 7.4 min. $[\alpha]_D^{20}$ +6.4 (for **1b**, 77% *ee*, *c* 0.70, CH_2Cl_2).

(*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-1-(4-fluorophenyl)-5-hydroxyhept-2-en-1-one ((±)-1c).

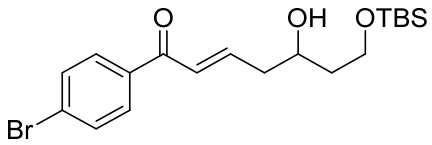


Brown solid; 56% yield.

^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.13 (m, 2H), 7.08 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.94 (dt, *J* = 15.0, 1.5 Hz, 1H), 4.07 (m, 1H), 3.93 (dt, *J* = 10.0, 4.5 Hz, 1H), 3.84 (m, 1H), 3.70 (br s, 1H), 2.55 (dddd, *J* = 14.5, 7.0, 7.0, 1.5 Hz, 1H), 2.47 (dddd, *J* = 14.5, 7.0, 7.0, 1.5 Hz, 1H), 1.72 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 189.0, 165.5 (d, *J* = 254.1 Hz), 146.0, 134.1, 131.2 (d, *J*

= 9.6 Hz), 127.6, 115.6 (d, J = 22.0 Hz), 71.2, 62.7, 40.8, 37.8, 25.8, 18.1, –5.6. ^{19}F NMR ($CDCl_3$) δ 55.9. TLC: R_f 0.30 (hexane/EtOAc = 3:1). Mp. 39.2–40.0 °C. IR (KBr): 3461, 1671, 1596, 1588, 1511, 1476, 1361, 1308, 1246, 1179, 1097, 1075, 1004 cm^{-1}. HRMS Calcd for $C_{19}H_{29}FO_3SiNa$: $[M+Na]^+$, 375.1762. Found: *m*/*z* 375.1755. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 80.0/20.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 2.8 min, t_{major} = 3.3 min. $[\alpha]_D^{20}$ +3.0 (for **1c**, 70% *ee*, *c* 0.79, CH_2Cl_2).

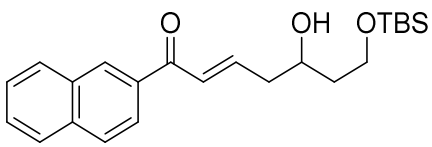
(*E*)-1-(4-Bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-5-hydroxyhept-2-en-1-one ((±)-1d).



Brown oil; 37% yield.

^{1}H NMR ($CDCl_3$) δ 7.79 (m, 2H), 7.60 (m, 2H), 7.09 (dt, J = 15.5, 7.5 Hz, 1H), 6.91 (dt, J = 15.5, 1.5 Hz, 1H), 4.07 (m, 1H), 3.93 (dt, J = 10.0, 4.5 Hz, 1H), 3.84 (m, 1H), 3.71 (br s, 1H), 2.55 (m, 1H), 2.47 (m, 1H), 1.72 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 189.5, 146.5, 136.5, 131.8, 130.1, 127.8, 127.5, 71.3, 62.8, 40.8, 37.7, 25.8, 18.1, –5.6. TLC: R_f 0.30 (hexane/EtOAc = 3:1). IR (neat): 3462, 1668, 1616, 1585, 1471, 1361, 1251, 1178, 1070, 1008 cm^{-1}. HRMS Calcd for $C_{19}H_{29}BrO_3SiNa$: $[M+Na]^+$, 435.0962. Found: *m*/*z* 435.0955. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 80.0/20.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.2 min, t_{major} = 4.2 min. $[\alpha]_D^{20}$ +3.2 (for **1d**, 75% *ee*, *c* 0.95, CH_2Cl_2).

(*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-1-(naphthalen-2-yl)hept-2-en-1-one ((±)-1e).



White solid; 60% yield.

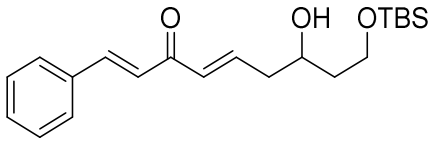
^{1}H NMR ($CDCl_3$) δ 8.46 (d, J = 1.0 Hz, 1H), 8.03 (dd, J = 8.0, 1.5 Hz, 1H), 7.97 (ddd, J = 8.0, 1.5,

1.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.60 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.16–7.14 (m, 2H), 4.11 (m, 1H), 3.95 (dt, *J* = 10.5, 4.5 Hz, 1H), 3.85 (m, 1H), 3.67 (br s, 1H), 2.60 (m, 1H), 2.53 (m, 1H), 1.75 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 190.4, 145.6, 135.5, 135.2, 132.5, 130.1, 129.5, 128.5, 128.3, 128.1, 127.8, 126.7, 124.6, 71.2, 62.7, 40.9, 37.9, 25.9, 18.1, –5.5. TLC: R_f 0.13 (hexane/EtOAc = 3:1). Mp. 68.2–69.2 °C. IR (KBr): 3456, 1667, 1629, 1606, 1472, 1369, 1306, 1257, 1193, 1109, 1075, 1061 cm^{-1}. HRMS Calcd for $C_{23}H_{32}O_3SiNa$: $[M+Na]^+$, 407.2013. Found: *m*/*z* 407.2005. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 80.0/20.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.3 min, t_{major} = 7.7 min. $[\alpha]_D^{20}$ +2.2 (for **1e**, 77% *ee*, *c* 0.81, CH_2Cl_2).

Procedure for preparation of (±)-**1f**

To a solution of **12** (0.28 g, 1.2 mmol) and (*E*)-1-phenylpenta-1,4-dien-3-one (0.76 g, 4.8 mmol) in dry CH_2Cl_2 (30 mL) was added Hoveyda-Grubbs 2nd generation catalyst (37 mg, 0.060 mmol). After being stirred for 12 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1) as an eluent gave (±)-**1f**.

(1*E*,4*E*)-9-((*tert*-Butyldimethylsilyl)oxy)-7-hydroxy-1-phenylnona-1,4-dien-3-one ((±)-1f).

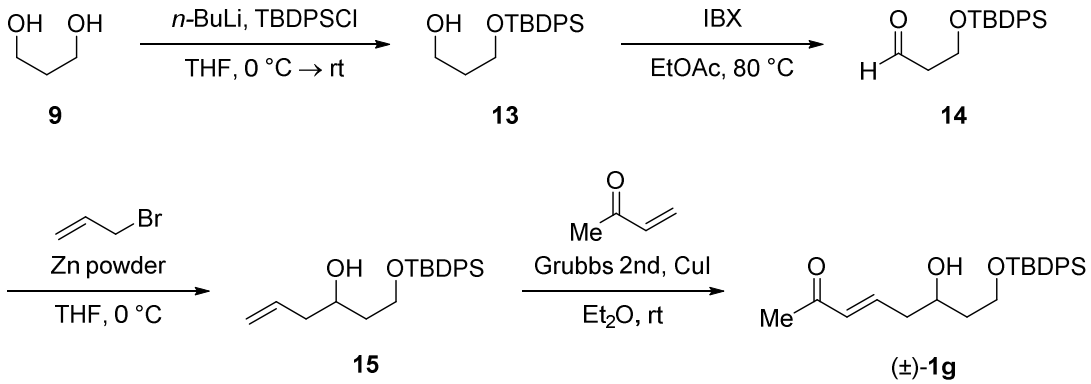


Brown oil; 81% yield.

^{1}H NMR ($CDCl_3$) δ 7.65 (d, *J* = 16.0 Hz, 1H), 7.56 (m, 2H), 7.41–7.35 (m, 3H), 7.04 (dt, *J* = 15.5, 7.0 Hz, 1H), 7.00 (d, *J* = 16.0 Hz, 1H), 6.50 (dt, *J* = 15.5, 1.5 Hz, 1H), 4.05 (m, 1H), 3.91 (m, 1H), 3.83 (m, 1H), 3.74 (br s, 1H), 2.54–2.42 (m, 2H), 1.69 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 189.0, 144.1, 143.2, 134.8, 131.5, 130.4, 128.9, 128.3, 124.5, 71.2, 62.7, 40.7,

37.8, 25.8, 18.1, –5.6. TLC: R_f 0.20 (hexane/EtOAc = 3:1). IR (neat): 3454, 1631, 1592, 1576, 1450, 1341, 1254, 1203, 1070 cm^{-1}. HRMS Calcd for $C_{21}H_{32}O_3SiNa$: $[M+Na]^+$, 383.2013. Found: *m*/*z* 383.2005. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 80.0/20.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.0 min, t_{major} = 5.7 min. $[\alpha]_D^{20}$ –18.8 (for **1f**, 74% *ee*, *c* 0.92, CH_2Cl_2).

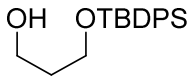
Procedure for preparation of (±)-1g



Procedure for preparation of **13**

To a solution of 1,3-propanediol (**9**, 2.7 g, 36 mmol) in dry THF (80 mL) was added *n*-butyllithium (22 mL, 1.63 M in hexane, 36 mmol) dropwise at 0 °C. After the mixture was stirred for 1 h, *tert*-butyldiphenylsilyl chloride (8.9 g, 32 mmol) in dry THF (10 mL) was added, and the reaction was allowed to warm to ambient temperature. After being stirred for additional 24 h, the reaction was quenched with H_2O (50 mL), and the mixture was subsequently extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1) as an eluent gave 3-((*tert*-butyldiphenylsilyl)oxy)propan-1-ol (**13**).

3-((*tert*-Butyldiphenylsilyl)oxy)propan-1-ol (13): CAS RN [127047-71-6].



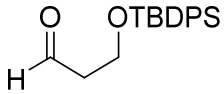
Colorless oil; 99% yield (11 g).

^{1}H NMR ($CDCl_3$) δ 7.71–7.69 (m, 4H), 7.47–7.40 (m, 6H), 3.87–3.85 (m, 4H), 2.53 (br s, 1H), 1.82 (tt, J = 5.5, 5.5 Hz, 2H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.5, 133.1, 129.8, 127.7, 63.3, 62.0, 34.1, 26.8, 19.0.

Procedure for preparation of **14**

To a suspension of 2-iodoxybenzoic acid (25 g, 90 mmol) in dry EtOAc (60 mL) was added **13** (9.6 g, 30 mmol), and the mixture was stirred vigorously at 80 °C for 7 h. The reaction suspension was cooled to ambient temperature and then filtered. The filter cake was washed with EtOAc, and the combined filtrates were concentrated in vacuo to afford 3-((*tert*-butyldiphenylsilyl)oxy)propanal (**14**), which was used for the next step without further purification.

3-((*tert*-Butyldiphenylsilyl)oxy)propanal (14): CAS RN [112897-03-7].



White solid; 96 % yield (9.0 g).

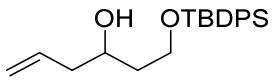
^{1}H NMR ($CDCl_3$) δ 9.82 (t, J = 2.0 Hz, 1H), 7.68–7.64 (m, 4H), 7.46–7.37 (m, 6H), 4.02 (t, J = 6.0 Hz, 2H), 2.61 (dt, J = 2.0, 6.0 Hz, 2H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 202.9, 135.5, 133.2, 129.8, 127.7, 58.2, 46.3, 26.7, 19.1.

Procedure for preparation of **15**

To a suspension of zinc (1.9 g, 29 mmol) in dry THF (30 mL) were added **14** (4.6 g, 15 mmol)

and allyl bromide (1.9 mL, 22 mmol), and the resulting mixture was cooled to 0 °C under argon atmosphere. After stirring for ca. 5 min, saturated aqueous NH_4Cl (1.0 mL) was added to the solution, and the mixture was stirred for additional 9 h. The reaction was quenched with an excess amount of saturated aqueous NH_4Cl, and the mixture was subsequently extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1) as an eluent gave 1-((*tert*-butyldiphenylsilyl)oxy)hex-5-en-3-ol (**15**).

1-((*tert*-Butyldiphenylsilyl)oxy)hex-5-en-3-ol (15): CAS RN [347189-30-4].



Yellow oil; 97% yield (5.2 g).

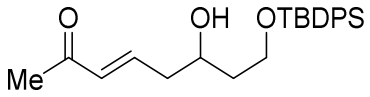
^{1}H NMR ($CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.35 (m, 6H), 5.85 (m, 1H), 5.13–5.08 (m, 2H), 3.97 (m, 1H), 3.90–3.81 (m, 2H), 3.28 (br s, 1H), 2.60–2.22 (m, 2H), 1.77–1.65 (m, 2H), 1.05 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 135.56, 135.55, 135.0, 134.8, 133.1, 133.0, 129.8, 127.8, 127.7, 117.4, 70.9, 63.3, 42.0, 37.9, 26.8, 19.0.

Procedure for preparation of (±)-**1g**

To a solution of **15** (2.8 g, 8.0 mmol) and but-3-en-2-one (2.0 mL, 24 mmol) in dry Et_2O (80 mL) was added Grubbs 2nd generation catalyst (0.21 g, 0.25 mmol) and CuI (76 mg, 0.40 mmol). After being stirred for 24 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1) as an eluent gave (*E*)-8-((*tert*-butyldiphenylsilyl)oxy)-6-hydroxyoct-3-en-2-one ((±)-**1g**).

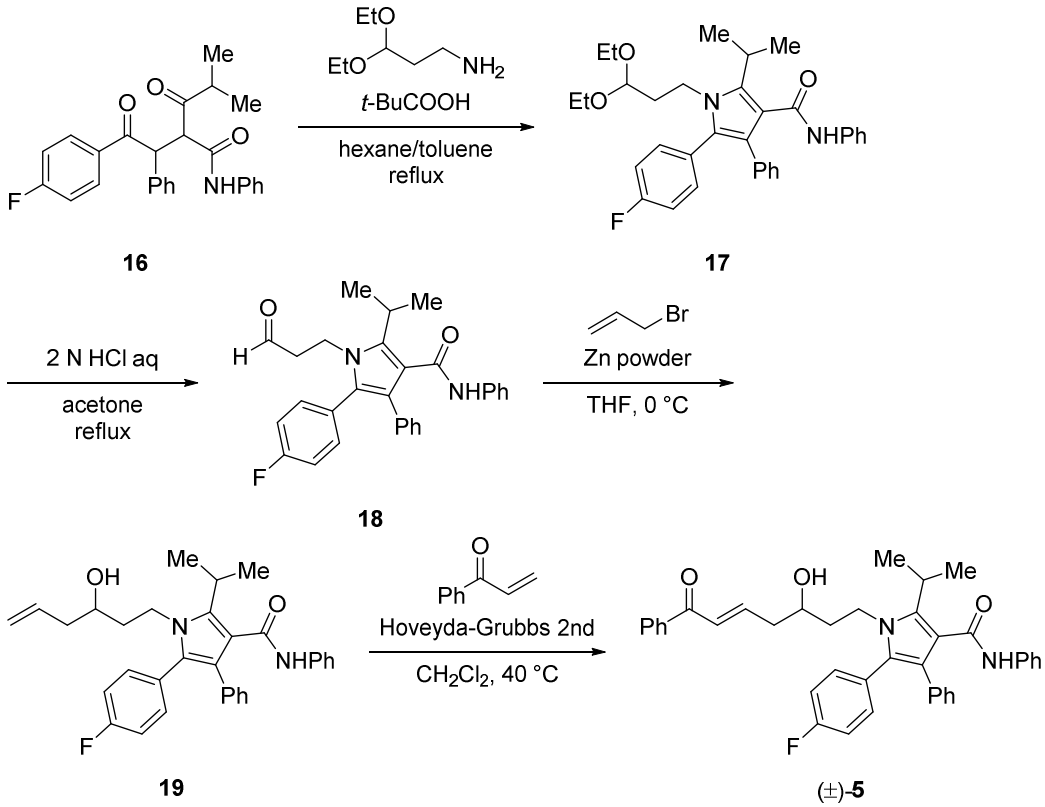
(*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-6-hydroxyoct-3-en-2-one ((±)-1g): CAS RN [1357931-11-3].



Colorless oil; 50% yield (1.6 g).

^{1}H NMR ($CDCl_3$) δ 7.68–7.67 (m, 4H), 7.47–7.38 (m, 6H), 6.88 (dt, J = 16.0, 7.0 Hz, 1H), 6.13 (d, J = 16.0 Hz, 1H), 4.09 (m, 1H), 3.87 (m ,2H), 3.65 (br s, 1H), 2.42 (m, 2H), 2.27 (s, 3H), 1.77 (m, 1H), 1.65 (m, 1H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 198.7, 144.6, 135.4, 133.2, 132.6, 129.9, 127.8, 70.8, 63.4, 40.4, 37.8, 26.72, 26.69, 18.9. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 11.6 min, t_{minor} = 12.8 min. $[\alpha]_D^{20}$ +5.3 (for **1g**, 70% *ee*, *c* 0.99, CH_2Cl_2).

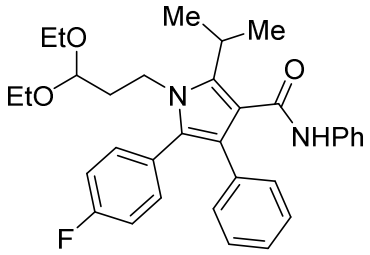
Procedure for preparation of (±)-5



Procedure for preparation of **17**[4w]

To a solution of **16** (2.2 g, 5.3 mmol) and 3,3-diethoxypropan-1-amine (1.3 g, 8.8mmol) in hexane/toluene (v/v = 9:1, 18 mL) was added pivalic acid (0.63 g, 6.2 mmol), and the mixture was heated to 110 °C using a Dean-Stark apparatus and stirred for 16 h under argon atmosphere. The mixture was cooled to ambient temperature and then filtered, and the resulting residue was washed with hexane. Purification by column chromatography using hexane/EtOAc (v/v = 5:1) as an eluent gave 1-(3,3-diethoxypropyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (**17**).

1-(3,3-Diethoxypropyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (17): CAS RN [125971-60-0].



Brown solid; 53%yield (1.5 g).

^{1}H NMR ($CDCl_3$) δ 7.22–7.15 (m, 9H), 7.06 (m, 2H), 7.02–6.97 (m, 3H), 6.85 (br s, 1H), 4.33 (t, *J* = 5.0 Hz, 1H), 3.97 (m ,2H), 3.61 (m, 1H), 3.44 (m, 2H), 3.29 (m, 2H), 1.83 (m, 2H), 1.53 (d, *J* = 7.5 Hz, 6H), 1.11 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 164.7, 162.3 (d, *J* = 248.3 Hz), 141.5, 138.3, 134.5, 133.2 (d, *J* = 7.7 Hz), 130.5, 128.8, 128.7, 128.3, 128.2, 126.6, 123.5, 121.7, 119.5, 115.4 (d, *J* = 22.1 Hz), 115.2, 100.4, 61.5, 40.2, 35.3, 26.0, 21.6, 15.1.

Procedure for preparation of **18**

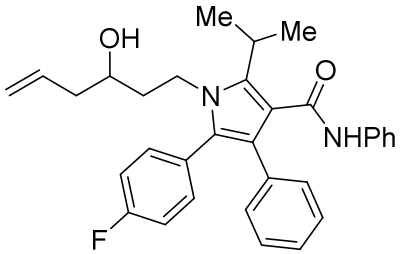
To a solution of **17** (1.5 g, 2.9 mmol) in acetone (20 mL) was added 2 M aqueous HCl (20 mL), and the mixture was heated to 65 °C and stirred for 2 h. After being cooled to ambient temperature, the mixture was concentrated in vacuo to remove acetone and subsequently extracted

with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give **18**, which was used for the next step without further purification.

Procedure for preparation of **19**

To a suspension of zinc (0.37 g, 5.7 mmol) in dry THF (6.0 mL) were added **18** (1.3 g, 2.9 mmol) and allyl bromide (0.37 mL, 4.3 mmol), and the resulting mixture was cooled to 0 °C under argon atmosphere. After stirring for 5 min, saturated aqueous NH_4Cl (0.30 mL) was added to the solution, and the mixture was stirred for additional 8 h. The reaction was quenched with an excess amount of saturated aqueous NH_4Cl, and the mixture was subsequently extracted with Et_2O (5.0 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1) as an eluent gave 5-(4-Fluorophenyl)-1-(3-hydroxyhex-5-en-1-yl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (**19**).

5-(4-Fluorophenyl)-1-(3-hydroxyhex-5-en-1-yl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (19): CAS RN [777093-40-0].



White solid; 85% yield (from **17**, 1.2 g).

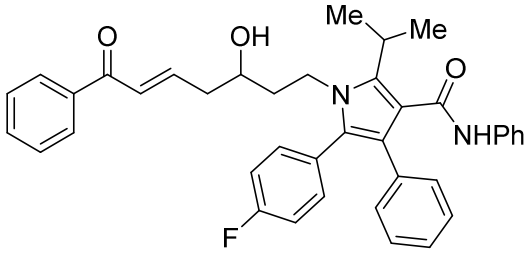
^{1}H NMR ($CDCl_3$) δ 7.23–7.14 (m, 9H), 7.06 (m, 2H), 7.03–6.97 (m, 3H), 6.85 (br s, 1H), 5.66 (m, 1H), 5.13–5.06 (m, 2H), 4.12 (m, 1H), 3.93 (m, 1H), 3.57 (m, 1H), 3.50 (m, 1H), 2.13 (m, 1H), 2.04 (m, 1H), 1.67 (m, 2H), 1.55 (d, J = 3.0 Hz, 3H), 1.53 (d, J = 3.0 Hz, 3H), 1.41 (d, J = 4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 164.7, 162.3 (d, J = 247.5 Hz), 141.5, 138.4, 134.6, 133.6, 133.2 (d, J = 7.7 Hz), 130.5, 128.8, 128,7, 128.3 (2C), 126.6, 123.5, 121.9, 119.6, 119.0, 115.4 (d, J = 21.1

Hz), 115.3, 68.2, 41.9, 41.6, 38.2, 26.1, 21.8, 21.6.

Procedure for preparation of (±)-**5**

To a solution of **19** (0.96 g, 1.9 mmol) and 1-phenylprop-2-en-1-one (1.3 g, 9.5 mmol) in dry CH_2Cl_2 (19 mL) was added Hoveyda-Grubbs 2nd generation catalyst (0.12 g, 0.19 mmol), and the mixture was stirred at 40 °C for 12 h. After being cooled to ambient temperature, the reaction mixture was concentrated in vacuo. Purification of the crude product by flush silica gel column chromatography using hexane/EtOAc (v/v = 3:1 to 1:1) as an eluent gave (*E*)-5-(4-fluorophenyl)-1-(3-hydroxy-7-oxo-7-phenylhept-5-en-1-yl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide ((±)-**5**).

(*E*)-5-(4-Fluorophenyl)-1-(3-hydroxy-7-oxo-7-phenylhept-5-en-1-yl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide ((±)-5).

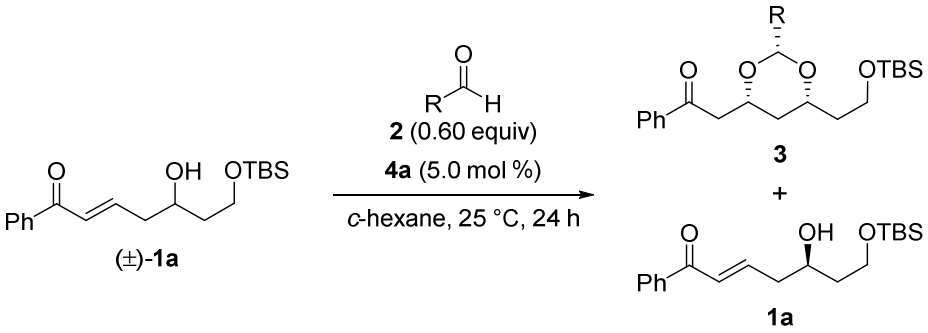


White solid; 75% yield (0.86 g).

^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 7.21–7.14 (m, 9H), 7.06 (m, 2H), 7.00–6.97 (m, 3H), 6.91 (m, 2H), 6.86 (br s, 1H), 4.16 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 3.97 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 3.66 (m, 1H), 3.56 (m, 1H), 2.35 (m, 2H), 1.73 (m, 2H), 1.66 (br s, 1H), 1.54 (d, *J* = 3.5 Hz, 3H), 1.53 (d, *J* = 3.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 190.0, 164.7, 162.2 (d, *J* = 248.4 Hz), 144.0, 141.4, 138.3, 137.4, 134.4, 133.1 (d, *J* = 8.5 Hz), 133.0, 130.4, 128.7, 128.6 (2C), 128.5 (2C), 128.3, 128.1 (2C), 126.6, 123.5, 121.9, 119.5, 115.5 (d, *J* = 21.1 Hz), 68.1, 41.4, 40.8, 38.5, 26.1, 21.8, 21.7. ^{19}F NMR ($CDCl_3$) δ 48.6. Mp. 128.5–129.3 °C. TLC: R_f 0.25 (hexane/EtOAc = 1:1). IR (KBr): 3411, 1665, 1590, 1496, 1434, 1345, 1307, 1170, 1157, 1094,

1022 cm^{-1}. HRMS Calcd for $C_{39}H_{37}FN_2O_3Na$: $[M+Na]^+$, 623.2680. Found: *m*/*z* 623.2674. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 80.0/20.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.0 min, t_{major} = 9.9 min. $[\alpha]_D^{20}$ +2.7 (for (*S*)-**5**, 76% *ee*, *c* 0.743, CH_2Cl_2).

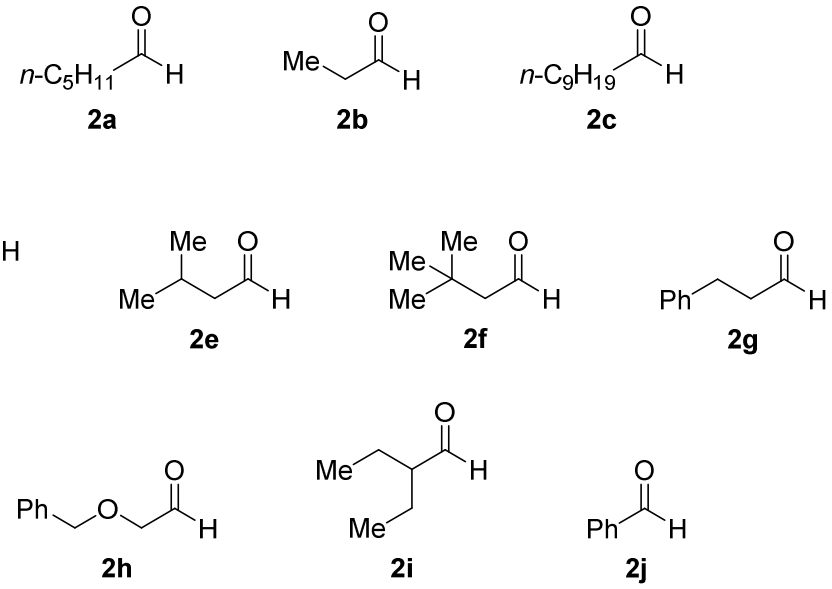
Table 3. Screening of Aldehydes[a]



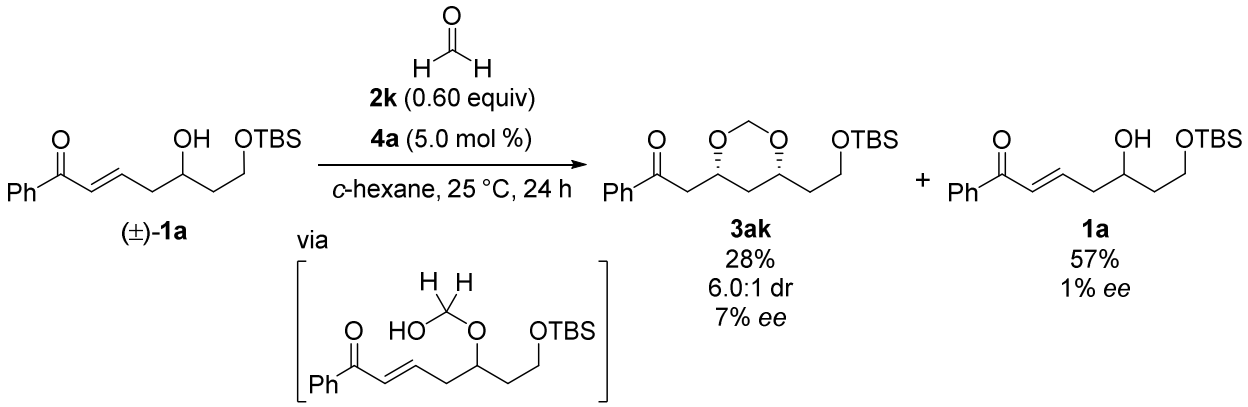
entry	aldehyde	yield of **3** (%)[b,c]	ee of **3** (%)	recovery of **1a** (%)[b]	ee of **1a** (%)
1	**2a**	47 (6.7:1)	83	42	73
2	**2b**	49 (5.4:1)	77	37	71
3	**2c**	24 (6.4:1)	88	48	26
4	**2d**	23 (6.0:1)	87	60	35
5	**2e**	30 (2.9:1)	81	58	33
6	**2f**	22 (3.2:1)	79	72	16
7	**2g**	41 (2.9:1)	79	37	69
8	**2h**	34 (8.5:1)	80	61	33
9	**2i**	6	–	–	–
10	**2j**	0	–	–	–

[a] Reactions were run using (±)-**1a** (0.20 mmol), **2** (0.12 mmol), and the catalyst (0.010 mmol) in the solvent (4.0 mL). [b] Isolated yields. [c] Values in the parentheses are the diastereomeric ratios determined by ^{1}H NMR (500 MHz) analyses of the crude products.

Table 3. (Continued)



Scheme 6. Reaction Using Paraformaldehyde (2k)



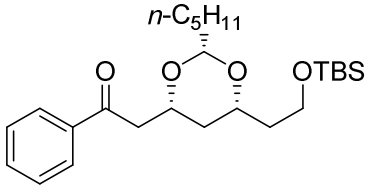
The reaction was performed using paraformaldehyde, which does not generate a chirality at the acetal carbon of the corresponding hemiacetal intermediate from **1a**. After 24 h, unreacted **1a** was recovered as an almost racemic form (1% *ee*). This result suggests that the asymmetric phosphoric acid catalyst **4a** recognized the chirality of the acetal carbon, which led to the kinetic resolution of (±)-**1a**.

Procedure

To a solution of (±)-**1a** (67 mg, 0.20 mmol) in cyclohexane (4.0 mL) were added paraformaldehyde (**2k**, 3.8 mg, 0.12 mmol) and **4a** (7.5 mg, 0.010 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was diluted with hexane/EtOAc (v/v = 1:1), passed through a short silica gel pad, and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 15:1 to 3:1) as an eluent afforded the corresponding 1,3-dioxanes **3ak** and unreacted starting material **1a**.

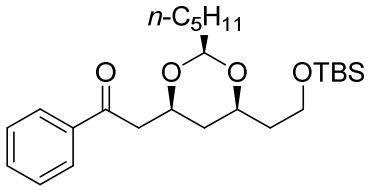
Characterization Data of Products

2-((2*R*,4*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethan-1-one (3aa).



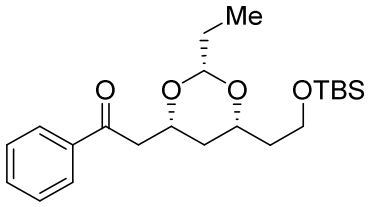
Yield: 47% (41 mg), 83% *ee*, 6.7:1 dr, colorless oil. $[\alpha]_D^{20}$ +16.3 (*c* 0.93, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 4.56 (t, *J* = 5.0 Hz, 1H), 4.30 (dddd, *J* = 13.0, 6.0, 6.0, 2.5 Hz, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 3.68 (m, 1H), 3.39 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.99 (dd, *J* = 16.0, 6.0 Hz, 1H), 1.76–1.64 (m, 3H), 1.59–1.55 (m, 2H), 1.39–1.20 (m, 7H), 0.89 (s, 9H), 0.85 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.9, 137.1, 133.2, 128.5, 128.2, 101.9, 72.8, 72.6, 58.7, 44.8, 38.9, 37.3, 34.9, 31.6, 25.9, 23.9, 22.5, 18.3, 14.0, –5.3. TLC: R_f 0.10 (hexane/EtOAc = 15:1). IR (neat): 2923, 2856, 1688, 1598, 1582, 1471, 1449, 1373, 1360, 1256, 1092 cm^{-1}. HRMS Calcd for $C_{25}H_{42}O_4SiNa$: $[M+Na]^+$, 457.2745. Found: *m*/*z* 457.2736. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.7 min, t_{major} = 6.9 min.

2-((2*S*,4*S*,6*S*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethan-1-one (*ent*-3aa).



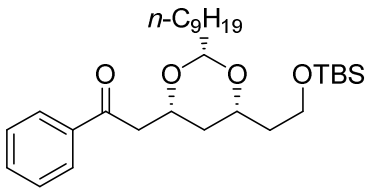
Yield: 59% (31 mg), 98% *ee*, 11:1 dr (for the last step), colorless oil. $[\alpha]_D^{20}$ –19.7 (*c* 0.95, CH_2Cl_2). HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 4.7 min, t_{minor} = 7.4 min.

2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-ethyl-1,3-dioxan-4-yl)-1-phenylethan-1-one (3ab).



Yield: 49% (38 mg), 77% *ee*, 5.4:1 dr, colorless oil. $[\alpha]_D^{20}$ +18.4 (*c* 0.97, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 4.50 (t, *J* = 5.5 Hz, 1H), 4.30 (dddd, *J* = 11.5, 6.5, 6.5, 2.5 Hz, 1H), 3.84 (m, 1H), 3.78 (m, 1H), 3.68 (m, 1H), 3.39 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.99 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.77–1.64 (m, 3H), 1.63–1.57 (m, 2H), 1.35 (m, 1H), 0.89 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.9, 137.1, 133.2, 128.6, 128.2, 102.7, 72.7, 72.6, 58.7, 44.7, 38.9, 37.3, 28.1, 25.9, 18.3, 8.6, –5.3. TLC: R_f 0.24 (hexane/EtOAc = 10:1). IR (neat): 2951, 2929, 2856, 1687, 1474, 1354, 1256, 972 cm^{-1}. HRMS Calcd for $C_{22}H_{36}O_4SiNa$: $[M+Na]^+$, 415.2275. Found: *m*/*z* 415.2268. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.5 min, t_{major} = 6.5 min.

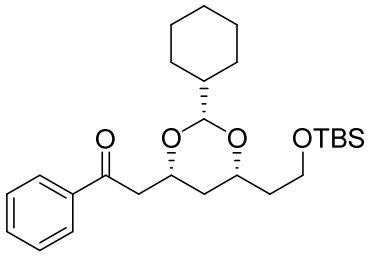
2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-nonyl-1,3-dioxan-4-yl)-1-phenylethan-1-one (3ac).



Yield: 24% (17 mg), 88% *ee*, 6.4:1 dr, colorless oil. $[\alpha]_D^{20}$ +22.1 (*c* 0.55, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 4.55 (t, *J* = 5.0 Hz, 1H), 4.29 (dddd, *J* = 11.0, 6.5, 6.5, 2.5 Hz, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 3.68 (m, 1H), 3.39 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.99 (dd, *J* = 16.5, 6.5 Hz, 1H), 1.75–1.66 (m, 3H), 1.60–1.55 (m, 2H), 1.39–1.23 (m, 15H), 0.89 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.9, 137.1, 133.2, 128.5,

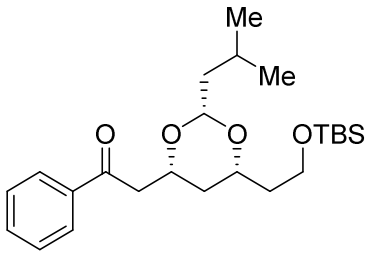
128.2, 101.9, 72.8, 72.6, 58.7, 44.7, 38.9, 37.3, 34.9, 31.9, 29.50, 29.48, 29.4, 29.3, 25.9, 24.2, 22.7, 18.3, 14.1, –5.3. TLC: R_f 0.30 (hexane/EtOAc = 10:1). IR (neat): 2954, 2953, 2856, 1690, 1449, 1352, 1256, 1094 cm^{-1}. HRMS Calcd for $C_{29}H_{50}O_4SiNa$: $[M+Na]^+$, 513.3371. Found: *m*/*z* 513.3368. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 95.0/5.0, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.5 min, t_{major} = 8.8 min.

2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-cyclohexyl-1,3-dioxan-4-yl)-1-phenylethan-1-one (3ad).



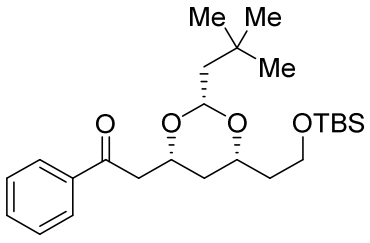
Yield: 23% (21 mg), 87% *ee*, 6.0:1 dr, colorless oil. $[\alpha]_D^{20}$ +15.9 (*c* 0.60, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 4.27–4.22 (m, 2H), 3.82–3.74 (m, 2H), 3.68 (m, 1H), 3.37 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.97 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.80 (m, 1H), 1.76–1.60 (m, 7H), 1.47 (m, 1H), 1.33 (m, 1H), 1.22–1.06 (m, 3H), 1.01–0.89 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 198.1, 137.2, 133.1, 128.5, 128.3, 104.7, 72.9, 72.5, 58.8, 44.8, 42.3, 39.0, 37.5, 27.6, 26.4, 25.9, 25.72, 25.69, 18.3, 1.00, –5.3. TLC: R_f 0.23 (hexane/EtOAc = 15:1). IR (neat): 2922, 2855, 1690, 1598, 1472, 1449, 1350, 1257, 1092 cm^{-1}. HRMS Calcd for $C_{26}H_{42}O_4SiNa$: $[M+Na]^+$, 469.2745. Found: *m*/*z* 469.2740. HPLC (Daicel Chiralpak IC, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.4 min, t_{major} = 5.0 min.

2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-isobutyl-1,3-dioxan-4-yl)-1-phenylethan-1-one (3ae).



Yield: 30% (25 mg), 81% *ee*, 2.9:1 dr, colorless oil. $[\alpha]_D^{20}$ +18.8 (*c* 0.49, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 4.62 (t, *J* = 5.5 Hz, 1H), 4.30 (dddd, *J* = 11.5, 6.5, 6.0, 2.5 Hz, 1H), 3.85 (m, 1H), 3.77 (m, 1H), 3.68 (m, 1H), 3.38 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.98 (dd, *J* = 16.5, 6.0 Hz, 1H), 1.78–1.64 (m, 4H), 1.47 (dd, *J* = 7.0, 5.5 Hz, 2H), 1.37 (m, 1H), 0.89 (s, 9H), 0.87 (d, *J* = 2.0 Hz, 6H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.9, 137.1, 133.2, 128.5, 128.2, 100.8, 72.8, 72.7, 58.7, 44.7, 43.6, 38.9, 37.3, 25.9, 23.9, 22.8, 18.3, –5.4. TLC: R_f 0.28 (hexane/EtOAc = 15:1). IR (neat): 2955, 2928, 2857, 1688, 1354, 1256, 1128, 1097 cm^{-1}. HRMS Calcd for $C_{24}H_{40}O_4SiNa$: $[M+Na]^+$, 443.2588. Found: *m*/*z* 443.2580. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.6 min, t_{major} = 5.6 min.

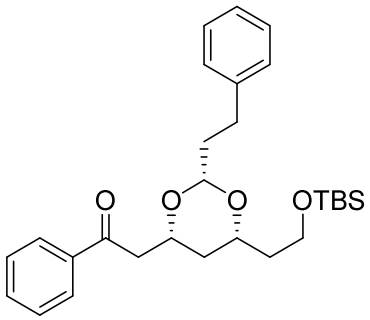
2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-neopentyl-1,3-dioxan-4-yl)-1-phenylethan-1-one (3af).



Yield: 22% (19 mg), 79% *ee*, 3.2:1 dr, colorless oil. $[\alpha]_D^{20}$ +16.3 (*c* 0.36, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 4.64 (t, *J* = 5.0 Hz, 1H), 4.32 (dddd, *J* = 11.0, 6.5, 6.0, 2.5 Hz, 1H), 3.85 (m, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.38 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.96 (dd, *J* = 16.5, 6.0 Hz, 1H), 1.74–1.64 (m, 3H), 1.51 (dd, *J* = 5.0, 2.0 Hz, 2H), 1.36 (m, 1H),

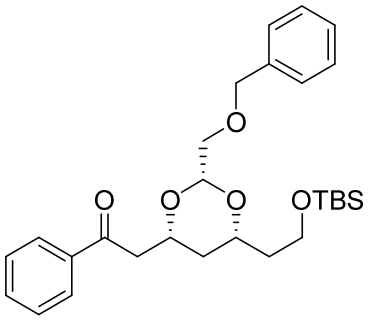
0.89–0.88 (m, 18H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 198.0, 137.1, 133.2, 128.5, 128.2, 100.7, 72.8, 72.7, 58.8, 48.0, 44.7, 38.9, 37.1, 30.0, 29.2, 25.9, 18.3, –5.3. TLC: R_f 0.26 (hexane/EtOAc = 15:1). IR (neat): 2954, 2858, 1688, 1472, 1449, 1378, 1363, 1252, 1213, 1142, 1097 cm^{-1}. HRMS Calcd for $C_{25}H_{42}O_4SiNa$: $[M+Na]^+$, 457.2745. Found: *m*/*z* 457.2735. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.4 min, t_{major} = 5.0 min.

2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-phenethyl-1,3-dioxan-4-yl)-1-phenylethan-1-one (3ag).



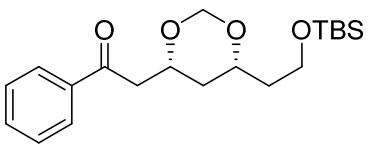
Yield: 41% (38 mg), 79% *ee*, 2.9:1 dr, colorless oil. $[\alpha]_D^{20}$ +21.8 (*c* 0.59, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.99 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 7.25 (m, 2H), 7.18–7.13 (m, 3H), 4.55 (t, *J* = 5.0 Hz, 1H), 4.28 (dddd, *J* = 11.0, 6.5, 6.0, 2.5 Hz, 1H), 3.83 (m, 1H), 3.78 (m, 1H), 3.70 (m, 1H), 3.41 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.98 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.65 (t, *J* = 8.0 Hz, 2H), 1.89 (m, 2H), 1.79–1.65 (m, 3H), 1.38 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.9, 141.7, 137.2, 133.2, 128.6, 128.4, 128.3, 125.7, 110.0, 100.8, 72.9, 72.8, 58.8, 44.7, 38.9, 37.3, 36.3, 30.2, 25.9, 18.3, –5.3. TLC: R_f 0.11 (hexane/EtOAc = 15:1). IR (neat): 2954, 2928, 2857, 1688, 1598, 1472, 1448, 1374, 1353, 1251, 1139, 1097, 1034 cm^{-1}. HRMS Calcd for $C_{28}H_{40}O_4SiNa$: $[M+Na]^+$, 491.2588. Found: *m*/*z* 491.2582. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.6 min, t_{major} = 14.4 min.

2-(2-((Benzyloxy)methyl)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1,3-dioxan-4-yl)-1-phenylethan-1-one (3ah).



Yield: 34% (33 mg), 80% *ee*, 8.5:1 dr, colorless oil. $[\alpha]_D^{20}$ +19.1 (*c* 0.68, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 7.34–7.25 (m, 5H), 4.83 (t, *J* = 4.5 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.36 (dddd, *J* = 11.5, 7.0, 5.5, 2.5 Hz, 1H), 3.90 (m, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.53 (dd, *J* = 13.0, 4.5 Hz, 1H), 3.51 (dd, *J* = 13.0, 4.5 Hz, 1H), 3.44 (dd, *J* = 16.5, 5.5 Hz, 1H), 3.04 (dd, *J* = 16.5, 7.0 Hz, 1H), 1.82–1.65 (m, 3H), 1.40 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.5, 138.0, 136.9, 133.3, 128.6, 128.3, 128.2, 127.8, 127.6, 100.0, 73.5, 73.0, 72.8, 71.3, 58.7, 44.6, 38.7, 37.2, 25.9, 18.3, –5.4. TLC: R_f 0.10 (hexane/EtOAc = 10:1). IR (neat): 2951, 2856, 1688, 1472, 1448, 1388, 1252, 1212, 1093 cm^{-1}. HRMS Calcd for $C_{28}H_{40}O_5SiNa$: $[M+Na]^+$, 507.2537. Found: *m*/*z* 507.2531. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.3 min, t_{major} = 7.7 min.

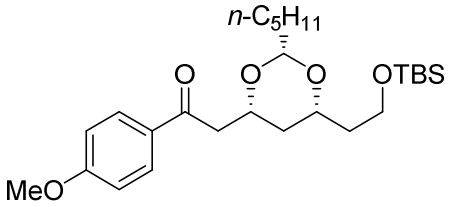
2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1,3-dioxan-4-yl)-1-phenylethan-1-one (3ak).



Yield: 28% (20 mg), 7% *ee*, 6.0:1 dr, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 5.06 (d, *J* = 6.0 Hz, 1H), 4.76 (d, *J* = 6.0 Hz, 1H), 4.30 (dddd, *J* = 11.0, 6.5, 6.0, 2.5 Hz, 1H), 3.83 (m, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.40 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.97 (dd, *J* = 16.5, 6.0 Hz, 1H), 1.78–1.65 (m, 3H), 1.53 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR

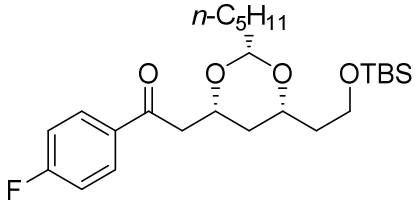
($CDCl_3$) δ 197.6, 136.9, 133.3, 128.6, 128.2, 93.5, 73.0, 72.8, 58.7, 44.5, 38.9, 37.8, 25.9, 18.3, –5.4. TLC: R_f 0.18 (hexane/EtOAc = 10:1). IR (neat): 2950, 2928, 2856, 1680, 1472, 1388, 1252, 1182, 1096, 1029 cm^{-1}. HRMS Calcd for $C_{20}H_{32}O_4SiNa$: $[M+Na]^+$, 387.1962. Found: *m*/*z* 387.1955. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.2 min, t_{major} = 9.7 min.

2-((2*R*,4*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-1-(4-methoxyphenyl)ethan-1-one (3ba).



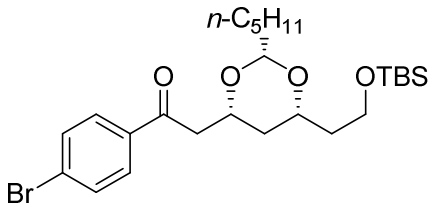
Yield: 52% (48 mg), 82% *ee*, 6.2:1 dr, yellow oil. $[\alpha]_D^{20}$ +19.8 (*c* 1.3, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.95 (m, 2H), 6.93 (m, 2H), 4.55 (t, *J* = 5.0 Hz, 1H), 4.26 (dddd, *J* = 11.5, 6.5, 6.5, 2.5 Hz, 1H), 3.87 (s, 3H), 3.83 (m, 1H), 3.76 (m, 1H), 3.68 (m, 1H), 3.33 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.93 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.76–1.63 (m, 3H), 1.59–1.55 (m, 2H), 1.37–1.21 (m, 7H), 0.89 (s, 9H), 0.85 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4, 163.6, 130.6, 130.4, 113.7, 101.9, 73.0, 72.7, 58.8, 55.5, 44.5, 38.9, 37.4, 34.9, 31.6, 26.0, 23.9, 22.5, 18.3, 14.0, –5.3. TLC: R_f 0.28 (hexane/EtOAc = 10:1). IR (neat): 2955, 2928, 2858, 1684, 1601, 1419, 1258, 1170, 1095, 1033 cm^{-1}. HRMS Calcd for $C_{26}H_{44}O_5SiNa$: $[M+Na]^+$, 487.2850. Found: *m*/*z* 487.2846. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 99.0/1.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.7 min, t_{major} = 7.2 min.

2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-1-(4-fluorophenyl)ethan-1-one (3ca).



Yield: 51% (46 mg), 85% *ee*, 10:1 dr, colorless oil. $[\alpha]_D^{20}$ +15.4 (*c* 0.93, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.99 (m, 2H), 7.12 (m, 2H), 4.54 (t, *J* = 5.0 Hz, 1H), 4.26 (dddd, *J* = 13.0, 6.5, 6.5, 2.0 Hz, 1H), 3.83 (m, 1H), 3.77 (m, 1H), 3.66 (m, 1H), 3.35 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.92 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.75–1.64 (m, 3H), 1.58–1.53 (m, 2H), 1.38–1.20 (m, 7H), 0.88 (s, 9H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4, 165.8 (d, *J* = 255.2 Hz), 133.6 (d, *J* = 2.9 Hz), 130.9 (d, *J* = 9.6 Hz), 115.6 (d, *J* = 21.1 Hz), 101.8, 72.8, 72.6, 58.7, 44.7, 38.8, 37.3, 34.9, 31.6, 25.9, 23.8, 22.5, 18.3, 14.0, –5.3. ^{19}F NMR ($CDCl_3$) δ 56.6. TLC: R_f 0.16 (hexane/EtOAc = 15:1). IR (neat): 2951, 2927, 2858, 1683, 1600, 1507, 1411, 1349, 1256, 1237, 1157, 1097 cm^{-1}. HRMS Calcd for $C_{25}H_{41}FO_4SiNa$: $[M+Na]^+$, 475.2650. Found: *m*/*z* 475.2644. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 98.0/2.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.2 min, t_{major} = 5.5 min.

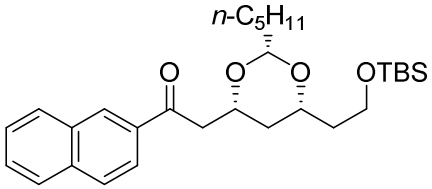
1-(4-Bromophenyl)-2-(6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)ethan-1-one (3da).



Yield: 52% (53 mg), 85% *ee*, 6.6:1 dr, colorless oil. $[\alpha]_D^{20}$ +16.4 (*c* 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 4.53 (t, *J* = 5.5 Hz, 1H), 4.25 (dddd, *J* = 13.0, 6.5, 6.5, 2.0 Hz, 1H), 3.83 (m, 1H), 3.76 (m, 1H), 3.67 (m, 1H), 3.34 (dd, *J* = 16.0, 6.5

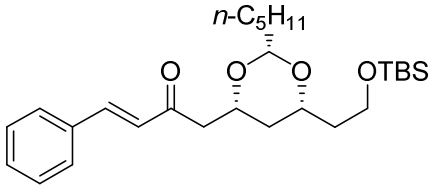
Hz, 1H), 2.91 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.75–1.63 (m, 3H), 1.57–1.53 (m, 2H), 1.38–1.19 (m, 7H), 0.88 (s, 9H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.0, 135.9, 131.8, 129.8, 128.4, 101.8, 72.8, 72.6, 58.9, 44.7, 38.8, 37.2, 34.9, 31.6, 25.9, 23.8, 22.5, 18.3, 14.0, –5.4. TLC: R_f 0.16 (hexane/EtOAc = 15:1). IR (neat): 2928, 2927, 2857, 1688, 1586, 1472, 1398, 1374, 1256, 1213, 1097 cm^{-1}. HRMS Calcd for $C_{25}H_{41}BrO_4SiNa$: $[M+Na]^+$, 535.1850. Found: *m*/*z* 535.1845. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.0 min, t_{major} = 5.0 min.

2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-1-(naphthalen-2-yl)ethan-1-one (3ea).



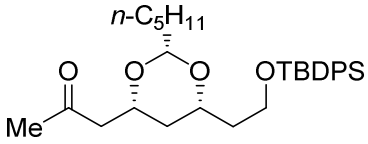
Yield: 51% (49 mg), 80% *ee*, 10:1 dr, colorless oil. $[\alpha]_D^{20}$ +25.7 (*c* 1.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.34 (d, *J* = 1.0 Hz, 1H), 8.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.62 (m, 1H), 7.55–7.50 (m, 2H), 7.25–7.19 (m, 2H), 4.58 (t, *J* = 5.0 Hz, 1H), 4.37 (dddd, *J* = 11.0, 6.5, 6.5, 2.0 Hz, 1H), 3.86–3.77 (m, 2H), 3.71 (m, 1H), 3.34 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.74 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.84–1.76 (m, 3H), 1.68 (m, 1H), 1.52–1.43 (m, 3H), 1.31 (m, 1H), 1.24–1.16 (m, 4H), 1.01 (s, 9H), 0.82 (t, *J* = 7.0 Hz, 3H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.9, 135.9, 135.3, 132.9, 130.4, 129.8, 128.6, 128.4, 128.3, 126.7, 124.3, 102.0, 73.2, 72.8, 59.2, 44.9, 39.5, 37.6, 35.5, 32.1, 26.2, 24.2, 23.0, 18.5, 14.2, –5.2. TLC: R_f 0.18 (hexane/EtOAc = 15:1). IR (neat): 2954, 2928, 2857, 1681, 1251, 1124, 1093 cm^{-1}. HRMS Calcd for $C_{29}H_{44}O_4SiNa$: $[M+Na]^+$, 507.2901. Found: *m*/*z* 507.2899. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.4 min, t_{major} = 6.0 min.

(*E*)-1-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-4-phenylbut-3-en-2-one (3fa).



Yield: 53% (49 mg), 82% *ee*, 14:1 dr, colorless oil. $[\alpha]_D^{20}$ +103.7 (*c* 0.27, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J* = 16.0 Hz, 1H), 7.54 (m, 2H), 7.41–7.39 (m, 3H), 6.77 (d, *J* = 16.0 Hz, 1H), 4.54 (t, *J* = 5.0 Hz, 1H), 4.18 (dddd, *J* = 11.5, 7.0, 6.0, 2.5 Hz, 1H), 3.85–3.75 (m, 2H), 3.68 (m, 1H), 3.06 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.70 (dd, *J* = 16.0, 6.0 Hz, 1H), 1.76–1.56 (m, 5H), 1.38–1.32 (m, 3H), 1.29–1.21 (m, 4H), 0.89 (s, 9H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 198.1, 143.4, 134.4, 130.6, 128.9, 128.3, 126.7, 101.8, 72.9, 72.6, 58.7, 46.7, 38.8, 37.2, 34.9, 31.6, 25.9, 23.9, 22.5, 18.3, 14.0, –5.3. TLC: R_f 0.23 (hexane/EtOAc = 10:1). IR (neat): 2954, 2928, 2857, 1653, 1610, 1472, 1252, 1139 cm^{-1}. HRMS Calcd for $C_{27}H_{44}O_4SiNa$: $[M+Na]^+$, 483.2901. Found: *m*/*z* 483.2896. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 9.8 min, t_{major} = 14 min.

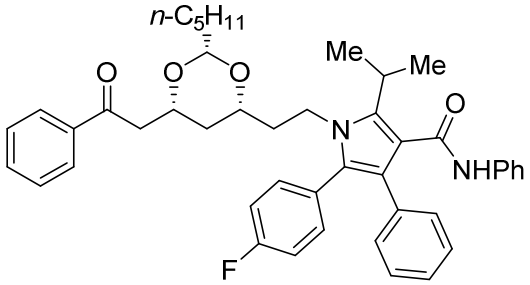
1-(6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)propan-2-one (3ga).



Yield: 46% (46 mg), 71% *ee*, 10:1 dr, colorless oil. $[\alpha]_D^{20}$ +6.1 (*c* 3.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.66–7.64 (m, 4H), 7.44–7.41 (m, 2H), 7.39–7.36 (m, 4H), 4.50 (t, *J* = 5.0 Hz, 1H), 4.06 (dddd, *J* = 11.5, 7.5, 5.0, 2.5 Hz, 1H), 3.90–3.82 (m, 2H), 3.71 (m, 1H), 2.75 (dd, *J* = 16.0, 7.5 Hz, 1H), 2.44 (dd, *J* = 16.0, 5.0 Hz, 1H), 2.19 (s, 3H), 1.80–1.67 (m, 2H), 1.57–1.53 (m, 3H), 1.37–1.23 (m, 7H), 1.04 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 207.0, 135.51, 135.50, 133.83, 133.77, 129.6 (2C), 127.60, 127.59, 101.8, 72.7, 72.5, 59.5, 49.5, 38.6, 36.9, 34.8, 31.6, 31.2, 26.8, 23.8, 22.5, 19.2, 14.0. TLC: R_f 0.13 (hexane/EtOAc = 10:1). IR (neat): 2955, 2931,

2859, 1719, 1428, 1113 cm^{-1}. HRMS Calcd for $C_{30}H_{44}O_4SiNa$: $[M+Na]^+$, 519.2901. Found: *m*/*z* 519.2898. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 98.0/2.0, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 9.2 min, t_{major} = 10.7 min.

5-(4-Fluorophenyl)-2-isopropyl-1-(2-(6-(2-oxo-2-phenylethyl)-2-pentyl-1,3-dioxan-4-yl)ethyl)-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (6).

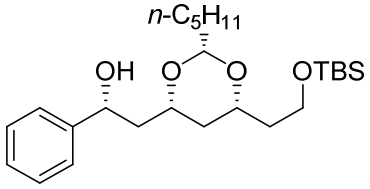


Yield: 70% (38 mg), 87% *ee*, 13:1 dr (for the last step), white solid. $[\alpha]_D^{20}$ +10.0 (*c* 1.1, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.94 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 7.21–7.14 (m, 9H), 7.06 (m, 2H), 7.00–6.97 (m, 3H), 6.87 (br s, 1H), 4.43 (t, *J* = 5.0 Hz, 1H), 4.19 (dddd, *J* = 12.5, 7.0, 5.5, 2.0 Hz, 1H), 4.11 (m, 1H), 3.93 (m, 1H), 3.58–3.49 (m, 2H), 3.35 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.97 (dd, *J* = 17.0, 7.0 Hz, 1H), 1.78–1.65 (m, 2H), 1.57–1.44 (m, 3H), 1.54 (d, *J* = 1.5 Hz, 3H), 1.52 (d, *J* = 1.5 Hz, 3H), 1.30–1.18 (m, 7H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.6, 164.7, 162.2 (d, *J* = 247.5 Hz), 141.4, 138.3, 136.8, 134.5, 133.3, 133.1 (d, *J* = 8.7 Hz), 130.4, 128.7, 128.63, 128.57, 128.3, 128.1 (2C), 126.5, 123.4, 121.8, 119.5, 115.4 (d, *J* = 21.1 Hz), 115.3, 101.7, 73.0, 72.5, 44.5, 40.7, 37.5, 36.6, 34.7, 31.6, 26.0, 23.6, 22.5, 21.8, 21.5, 14.0. ^{19}F NMR ($CDCl_3$) δ 48.1. Mp. 64.2–65.2 °C. TLC: R_f 0.28 (hexane/EtOAc = 3:1). IR (KBr): 3411, 3058, 1679, 1595, 1534, 1496, 1436, 1308, 1213, 1158, 1002 cm^{-1}. HRMS Calcd for $C_{45}H_{49}FN_2O_4Na$: $[M+Na]^+$, 723.3569. Found: *m*/*z* 723.3558. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 9.0 min, t_{major} = 9.8 min.

Procedure for synthesis of 7[15]

To a 30-mL round-bottom flask, **3aa** (83% *ee*, 60 mg, 0.14 mmol), Et_2O (14 mL), and $EuCl_3$ (0.12 g, 0.41 mmol) were sequentially added. After the mixture was stirred at –78 °C for 0.5 h under argon atmosphere, lithium borohydride (0.28 mL, 1.0 M in Et_2O, 0.28 mmol) was added. After the mixture was stirred at –78 °C for 2 h, lithium borohydride (0.28 mmol, 1.0 M in Et_2O, 0.28 mL) was further added to the reaction solution, and the resulting mixture was additionally stirred at –78 °C for 9 h. The reaction was quenched with 3.0 M aqueous NaOH, and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1 to 5:1) as an eluent gave 2-(6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethan-1-ol (**7**).

2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethan-1-ol (7).



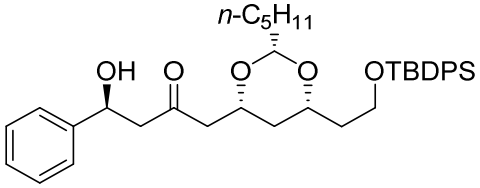
Yield: 90% (55 mg), 84% *ee*, 10:1 dr, colorless oil. $[\alpha]_D^{20}$ +15.0 (*c* 1.1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ 7.84–7.33 (m, 4H), 7.27 (m, 1H), 4.97 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.58 (t, *J* = 5.5 Hz, 1H), 3.92 (m, 1H), 3.83–3.74 (m, 2H), 3.71 (br s, 1H), 3.67 (m, 1H), 2.01 (ddd, *J* = 14.0, 10.0, 9.5 Hz, 1H), 1.77 (ddd, *J* = 14.0, 3.5, 3.0 Hz, 1H), 1.74–1.62 (m, 4H), 1.50 (ddd, *J* = 8.0, 2.5, 2.5 Hz, 1H), 1.44–1.38 (m, 3H), 1.37–1.28 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 144.2, 128.3, 127.4, 125.7, 101.6, 76.9, 73.9, 72.7, 58.6, 45.1, 38.7, 37.3, 34.9, 31.6, 25.9, 23.9, 22.5, 18.3, 14.0, –5.4. TLC: R_f 0.30 (hexane/EtOAc = 5:1). IR (neat): 2954, 2928, 2858, 1472, 1388, 1252, 1143, 1096, 1005 cm^{-1}. HRMS Calcd for $C_{25}H_{44}O_4SiNa$: $[M+Na]^+$, 459.2901. Found: *m*/*z* 459.2893. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 98.0/2.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.3 min, t_{major} = 6.9 min.

General Procedure for synthesis of 8[16a]

To a solution of dicyclohexylboron trifluoromethanesulfonate (0.13 g, 0.40 mmol) in Et_2O (1.5 mL) were added dropwise a solution of **3ga** (75% *ee*, 99 mg, 0.20 mmol) in Et_2O (0.50 mL) and a solution of triethylamine (61 mg, 0.60 mmol) in Et_2O (0.50 mL) at –78 °C under argon atmosphere. After the mixture was stirred at the same temperature for 2 h, a solution of aldehyde (0.40 mmol) in Et_2O (1.0 mL) was added dropwise. After being stirred at –78 °C for 9 h, pH 7.0 buffer (2.0 mL) and MeOH (2.0 mL) were added. 30% Aqueous H_2O_2 (2.0 mL) was then added slowly at –78 °C, and the resulting mixture was stirred at ambient temperature for 6 h. The mixture was extracted with CH_2Cl_2 (10 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1 to 5:1) as an eluent gave the corresponding aldol products **8**. The stereochemistry of the newly constructed chiral centers by these reactions was assigned analogously on the basis of the previous report.[16a]

1-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-4-hydroxy-4-phenylbutan-2-one (8a).

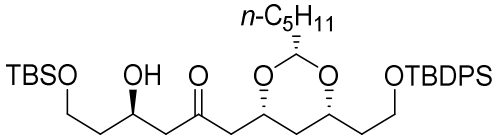


Yield: 60% (0.14 g), 74% *ee*, >19:1 dr, colorless oil. $[\alpha]_D^{20}$ –8.6 (*c* 1.8, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ 7.67–7.65 (m, 4H), 7.45–7.34 (m, 10H), 7.28 (m, 1H), 5,19 (ddd, *J* = 6.0, 3.0, 3.0 Hz, 1H), 4.50 (t, *J* = 5.5 Hz, 1H), 4.09 (dddd, *J* = 11.0, 8.0, 4.5, 2.0 Hz, 1H), 3.90–3.82 (m, 2H), 3.72 (m, 1H), 3.33 (d, *J* = 3.0 Hz, 1H), 2.89 (m, 2H), 2.77 (dd, *J* = 15.5, 8.0 Hz, 1H), 2.45 (dd, *J* = 15.5, 4.5 Hz, 1H), 1.80–1.68 (m, 2H), 1.57–1.50 (m, 3H), 1.37–1.23 (m, 7H), 1.06 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 209.4, 142.6, 135.51 (2C), 135.49, 133.8, 133.7, 129.6 (2C), 128.5, 127.61, 127.59, 125.6, 101.8, 72.7, 72.5, 69.7, 59.5, 52.7, 49.3, 38.6, 36.9, 34.8, 31.6, 26.8, 23.8, 22.5, 19.2, 14.0. TLC: R_f 0.10 (hexane/EtOAc = 15:1). IR (neat): 3450, 2955, 2931, 2858,

1700, 1428, 1374, 1107, 1029 cm^{-1}. HRMS Calcd for $C_{37}H_{50}O_5SiNa$: $[M+Na]^+$, 625.3320. Found: *m*/*z* 625.3314. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.8 min, t_{major} = 6.6 min.

6-((*tert*-Butyldimethylsilyl)oxy)-1-(6-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-4-hydroxyhexan-2-one (8b).

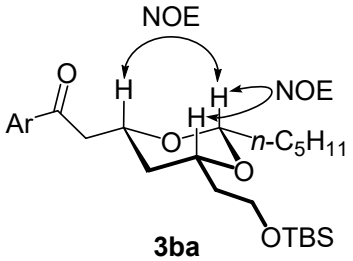


Yield: 75% (0.21 g), 76% *ee*, >19:1 dr, colorless oil. $[\alpha]_D^{20}$ –4.4 (*c* 0.32, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.66–7.64 (m, 4H), 7.43–7.40 (m, 2H), 7.39–7.35 (m, 4H), 4.48 (t, *J* = 5.5 Hz, 1H), 4.29 (m, 1H), 4.09 (dddd, *J* = 10.5, 8.0, 4.5, 2.0 Hz, 1H), 3.89–3.78 (m, 4H), 3.70 (m, 1H), 3.60 (br s, 1H), 2.77 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.64 (m, 2H), 2.44 (dd, *J* = 16.0, 4.5 Hz, 1H), 1.79–1.62 (m, 4H), 1.57–1.51 (m, 3H), 1.35–1.22 (m, 7H), 1.04 (s, 9H), 0.89 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 208.9, 135.53, 135.51, 133.9, 133.8, 129.6 (2C), 127.61, 127.60, 101.8, 72.7, 72.6, 67.0, 61.5, 59.5, 51.1, 49.4, 38.7, 38.3, 36.9, 34.8, 31.6, 26.9, 25.9, 23.8, 22.5, 19.2, 18.2, 14.0, –5.5. TLC: R_f 0.10 (hexane/EtOAc = 10:1). IR (neat): 3505, 2954, 2928, 2857, 1710, 1472, 1429, 1387, 1257, 1142, 1098 cm^{-1}. HRMS Calcd for $C_{39}H_{64}O_6Si_2Na$: $[M+Na]^+$, 707.4134. Found: *m*/*z* 707.4126. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 98.8/1.2, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 20.7 min, t_{major} = 23.1 min.

Determination of the Configurations of Products

(a) NOE experiment

The relative configurations of the 1,3-dioxane product **3ba** were determined by ^{1}H NMR analysis where NOE correlations between the acetal proton and the two methine protons were observed. The relative configurations of all other products **3** were assigned analogously.

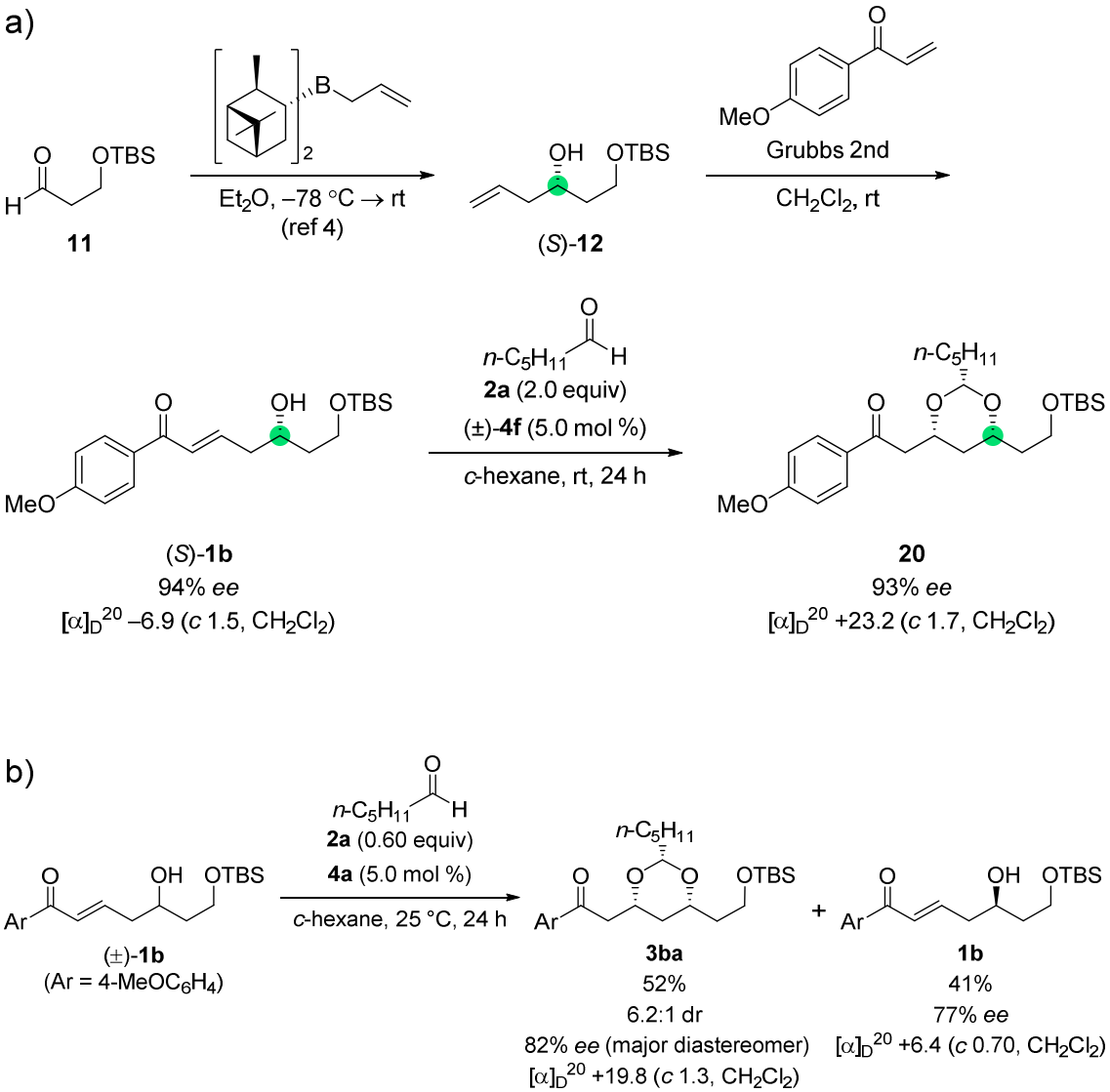


3ba
(major diastereomer)

(b) Comparison of optical rotations

In order to determine absolute configurations of the obtained products **3ba**, 2-((2*R*,4*R*,6*R*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-pentyl-1,3-dioxan-4-yl)-1-(4-methoxyphenyl)ethan-1-one (**20**) was synthesized by a known method[13] using Brown's asymmetric allylation of aldehyde **11** (Scheme 7a). Its optical rotation was compared with that of product **3ba** (Scheme 7b). These results indicated that their absolute configurations are identical. The absolute configurations of all other products **3** were assigned analogously.

Scheme 7. Asymmetric Synthesis of 20 and Comparison of Optical Rotations with 3ba



Procedure for synthesis of (*S*)-**12**[13]

To a solution of (–)-*B*-methoxydiisopinocampheylborane (11 g, 36 mmol) in dry Et_2O (0.12 L) was slowly added allylmagnesium bromide (45 mL, 0.63 M in Et_2O, 28 mmol) at –78 °C under argon atmosphere. The mixture was allowed to warm to ambient temperature and stirred for 1 h. The resulting white suspension was again cooled to –78 °C, and a solution of **11** (3.8 g, 20 mmol) in Et_2O (5.0 mL) was added dropwise. The mixture was stirred at the same temperature for 2 h, allowed to warm to ambient temperature, and stirred for additional 1 h. To the reaction solution were slowly added 2.5 M aqueous NaOH (30 mL) and 30% aqueous H_2O_2 (25 mL), and the resulting mixture was refluxed for 17 h. The reaction suspension was cooled to ambient temperature and extracted with Et_2O (50 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 20:1) as an eluent gave homoallylic alcohol (*S*)-**12** as a colorless oil in 77% yield.

Procedure for synthesis of (*S*)-**1b**

To a solution of (*S*)-**12** (1.5 g, 6.3 mmol) and 1-(4-methoxyphenyl)prop-2-en-1-one (4.1 g, 25 mmol) in dry CH_2Cl_2 (130 mL) was added Grubbs 2nd generation catalyst (0.32 g, 0.38 mmol). After being stirred for 72 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1 to 3:1) as an eluent gave (*S*)-**1b** (94% *ee*) as a pale yellow oil in 54% yield. $[\alpha]_D^{20}$ –6.9 (*c* 1.5, CH_2Cl_2). HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 80.0/20.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 5.0 min, t_{minor} = 8.3 min.

Procedure for synthesis of **20**

To a solution of (*S*)-**1b** (0.66 g, 1.8 mmol) in cyclohexane (3.6 mL) were added hexanal (**2a**, 0.45 mL, 3.6 mmol) and (±)-**4f** (31 mg, 0.090 mmol), and the resulting mixture was stirred at ambient temperature for 24 h. The reaction mixture was diluted with hexane/EtOAc (v/v = 1:1),

passed through a short silica gel pad, and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1 to 5:1) as an eluent afforded **20** (93% *ee*) as a yellow oil in 63% yield with >19:1 dr. $[\alpha]_D^{20}$ +23.2 (*c* 1.7, CH_2Cl_2). HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 99.0/1.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.7 min, t_{major} = 7.3 min.

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Chapter 4

Organocatalytic Enantio- and Diastereoselective Construction of *syn*-1,3-Diol Motifs via Dynamic Kinetic Resolution of In Situ Generated Chiral Cyanohydrins

An organocatalytic method for the asymmetric synthesis of *syn*-1,3-dioxanes as protected 1,3-diols via dynamic kinetic resolution of in situ generated chiral cyanohydrins has been developed. This method involves a reversible cyanohydrin formation/hemiacetalization/intramolecular oxy-Michael addition reaction cascade, affording a chiral *syn*-1,3-diol structure with simultaneous construction of two stereogenic centers. The use of trifluoromethyl ketones is crucial for the efficient three-component cascade reaction, and a chiral bifunctional organocatalyst imparts high enantio- and diastereoselectivities in the formation of the chiral *syn*-1,3-diol motifs.

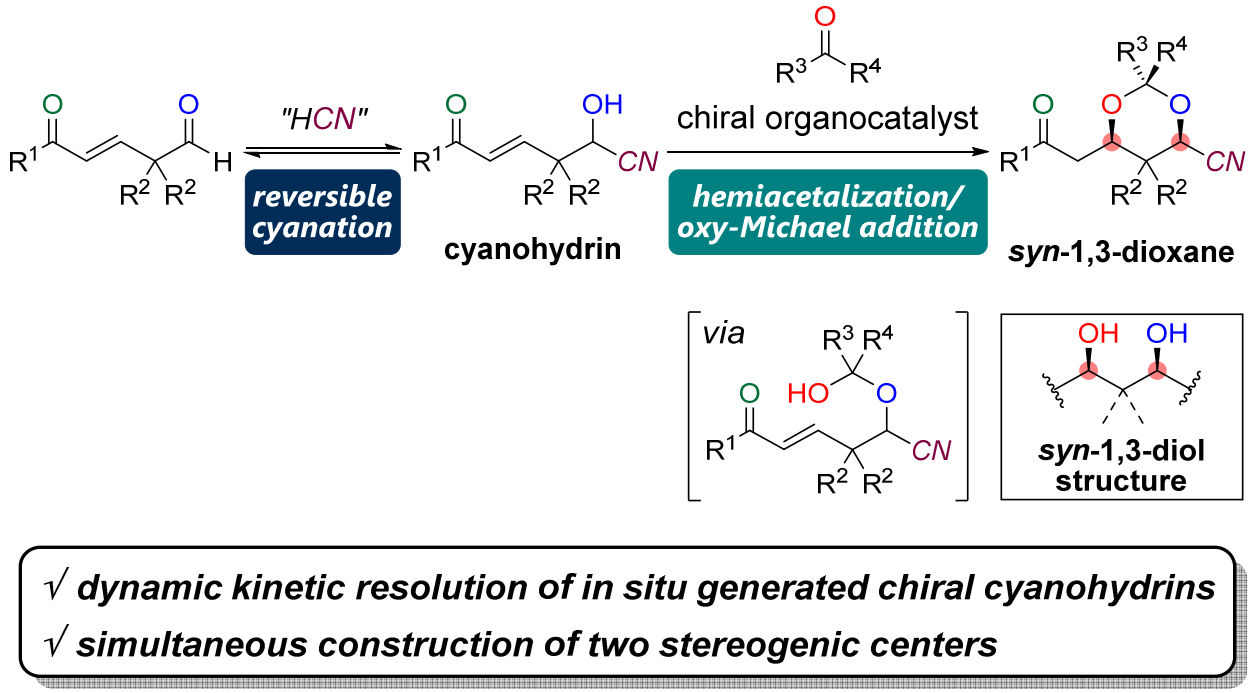
Introduction

Chiral 1,3-diols are ubiquitous structures found in biologically active natural products and pharmaceuticals, and therefore have received significant attention as attractive synthetic targets.[1] Because they contain two stereogenic centers, the development of synthetic methods with high stereocontrol is a challenging synthetic issue for these structures. In fact, tremendous efforts have been made to achieve rapid and precise access to stereodefined 1,3-diol motifs, and a number of stereoselective methods via multistep processes have been reported to date.[2] However, few efficient protocols involving the simultaneous construction of two stereogenic centers of chiral 1,3-diol motifs have been developed; in particular, a protocol affording *syn*-1,3-diol motifs from achiral substrates in a highly enantio- and diastereoselective manner has been unexploited as of yet.[3]

In the synthesis of chiral *syn*-1,3-diol motifs, a hemiacetalization/intramolecular oxy-Michael addition reaction cascade from chiral secondary alcohols is a reliable method to afford *syn*-1,3-dioxanes, and has been broadly applied to the stereoselective synthesis of complex molecules containing *syn*-1,3-diol structures.[4] Nevertheless, a catalytic asymmetric version of this approach has not been reported. Thus, asymmetric cyclization via kinetic resolution of racemic secondary alcohols should be developed. Moreover, in order to achieve a quantitative synthesis of enantioenriched *syn*-1,3-diol motifs based on this approach, dynamic kinetic resolution of chiral secondary alcohols would be desirable. The author previously developed an organocatalytic method for the asymmetric construction of 1,3-dioxanes from primary alcohols, which demonstrated the effectiveness of multipoint interaction by organocatalysts via hydrogen bonding for asymmetric induction in the intramolecular oxy-Michael addition of a hemiacetal intermediate.[5,6] Therefore, the author expected that combining an organocatalytic method with an alcohol racemization process would enable the asymmetric construction of *syn*-1,3-dioxanes via dynamic kinetic resolution of chiral secondary alcohols. Reversible cyanohydrin formation would be suitable for the racemization of chiral alcohols because this process takes place under mild reaction conditions, which is compatible with asymmetric organocatalysis of the subsequent

cyclization.[7] It is also notable that the resulting cyano group is a latent component that is convertible to various functionalities,[8,9] which would render the products useful building blocks containing chiral *syn*-1,3-diol structures. Herein, the author presents an organocatalytic method for the asymmetric synthesis of *syn*-1,3-dioxanes via dynamic kinetic resolution of in situ generated chiral cyanohydrins. This reaction cascade, involving reversible cyanohydrin formation/hemiacetalization/intramolecular oxy-Michael addition, enables the simultaneous construction of two stereogenic centers belonging to a *syn*-1,3-diol structure with high enantio- and diastereoselectivities (Scheme 1).

Scheme 1. Organocatalytic Asymmetric Synthesis of *syn*-1,3-Dioxanes via Dynamic Kinetic Resolution of Chiral Cyanohydrins



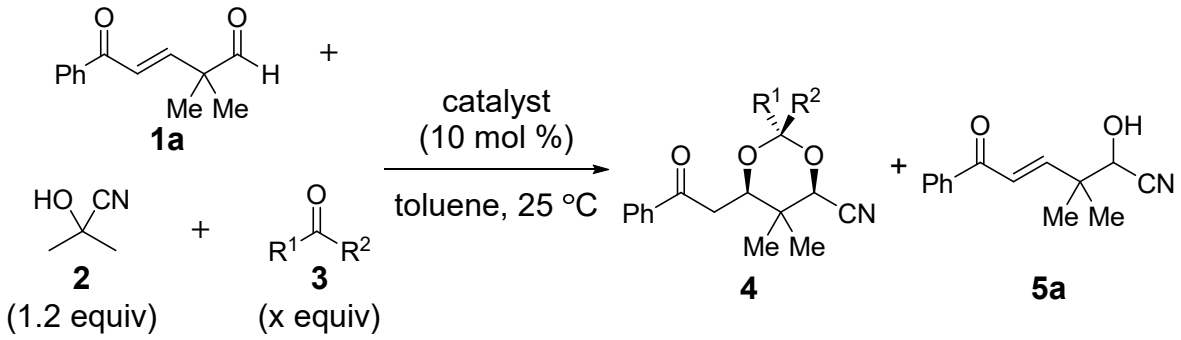
√ dynamic kinetic resolution of in situ generated chiral cyanohydrins
√ simultaneous construction of two stereogenic centers

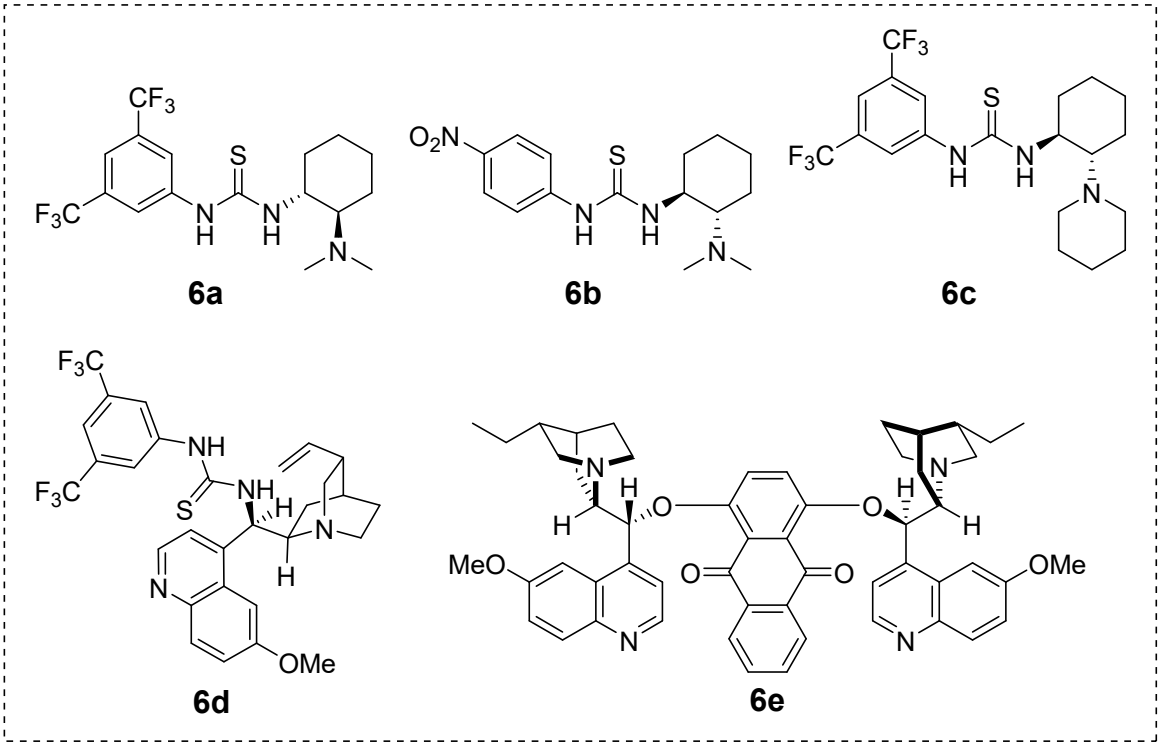
Results and Discussion

The reaction conditions were investigated using a δ-oxo-α,β-unsaturated ketone **1a**, acetone cyanohydrin (**2**), and ketone **3** (Figure 1). While the use of cyclohexanone (**3a**) resulted in the formation of cyanohydrin **5a** as the only product (Table 1, entry 1), the use of a trifluoromethyl ketone **3b** was found to be crucial for obtaining the desired *syn*-1,3-dioxane **4** (Table 1, entry 2). The catalyst screening revealed that bifunctional organocatalysts **6a** and **6b**, bearing thiourea and dimethylamino moieties on a chiral 1,2-cyclohexanediamine skeleton, showed promising results, affording the desired products with high stereoselectivities (Table 1, entries 2 and 3).[10] Differences in the catalyst structure largely influence both the catalytic activity and the enantioselectivity. While the use of aminothiourea catalyst **6c**, which bears a piperidine moiety as a tertiary amino group, decreased the enantioselectivity (Table 1, entry 4), use of cinchona alkaloid-derived bifunctional catalyst **6d** gave the product in lower yield (Table 1, entry 5). In contrast, chiral Lewis base catalyst **6e** predominantly gave cyanohydrin intermediate **5a** in almost racemic form, indicating that bifunctionality of the catalyst is essential for promoting the intramolecular oxy-Michael addition process (Table 1, entry 6). In the presence of catalyst **6b**, the use of 3.0 equivalents of cyanation reagent **2** significantly increased the yield (Table 1, entry 7). Other sources of hydrogen cyanide, such as the simultaneous use of trimethylsilyl cyanide and proton sources, resulted in decreased reactivities (Table 1, entries 8 and 9). Prolonged reaction time in the presence of molecular sieves (MS) slightly increased the yield and enantioselectivity (Table 1, entry 10). Moreover, a small amount of the remaining cyanohydrin intermediate **5a** was obtained in an almost racemic form, indicating that this reaction involves racemization of the chiral cyanohydrin. Subsequently, a range of other trifluoromethyl ketones (**3c**–**3f**) were investigated (Table 1, entries 11–14). Trifluoroacetophenone derivatives **3c** and **3d**, which bear electron-withdrawing groups at the para position of the aryl group, afforded the corresponding products **4** in high yields with slightly lower enantioselectivities (Table 1, entries 11 and 12). In contrast, the substitution of an electron-donating group at the same position resulted

in low yield with high enantioselectivity (Table 1, entry 13). Compared with aryl trifluoromethyl ketones, the use of hexafluoroacetone **3f** resulted in low reactivity and provided only cyanohydrin **5a**. These investigations identified **3b** as the most efficient reagent for both yield and enantioselectivity.

Table 1. Optimization of Reaction Conditions[a]





entry	catalyst	**3** (equiv)	yield of **4** (%)[b]	dr of **4**[b]	*ee* of **4** (%)	yield of **5a** (%)[b]
1	**6a**	**3a** (1.2)	<1	–	–	85
2	**6a**	**3b** (1.2)	43	11:1	–90	45
3	**6b**	**3b** (1.2)	42	>19:1	92	46
4	**6c**	**3b** (1.2)	33	>19:1	60	52
5	**6d**	**3b** (1.2)	9	11:1	91	67
6	**6e**	**3b** (1.2)	<5	–	–	97[c]
7	**6b**	**3b** (3.0)	80	>19:1	88	20
8[d]	**6b**	**3b** (3.0)	26	4.7:1	97	10
9[e]	**6b**	**3b** (3.0)	52	13:1	92	12
10[f]	**6b**	**3b** (3.0)	81	>19:1	90	19[c]
11[f]	**6b**	**3c** (3.0)	89	>19:1	84	11
12[f]	**6b**	**3d** (3.0)	79	>19:1	89	22
13[f]	**6b**	**3e** (3.0)	32	>19:1	92	68
14[f]	**6b**	**3f** (3.0)	<1	–	–	27

[a]Reactions were run using **1a** (0.15 mmol), **2** (0.18 mmol), **3**, and catalyst **6** (0.015 mmol) in toluene (0.30 mL) for 24 h. [b]Determined by ^{1}H NMR spectroscopy. [c]Cyanohydrin **5a** was recovered with <5% *ee*. [d]TMSCN (0.18 mmol) and *i*-PrOH (0.18 mmol) were used instead of **2**. [e]TMSCN (0.18 mmol) and H_2O (1.8 mmol) were used instead of **2**. [f]Reactions were run using MS 4A (50 mg) for 48 h.

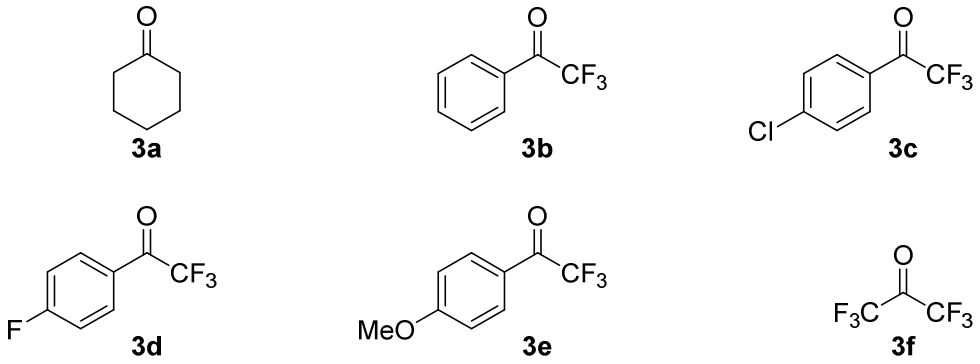
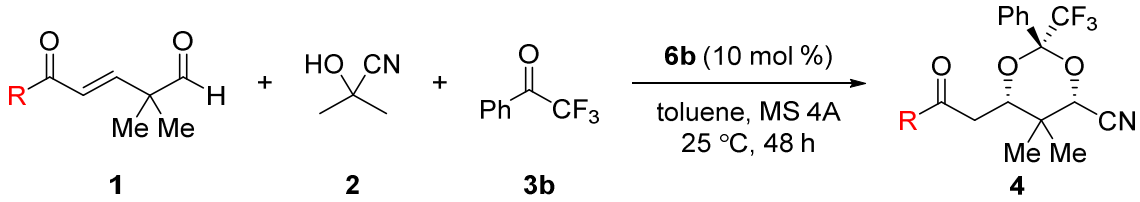


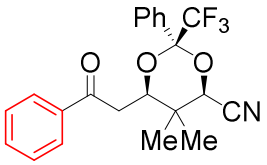
Figure 1. Ketones **3** investigated in the optimization study.

With the optimal conditions in hand, the author explored the substrate scope (Table 2). The reaction of an electron-rich enone afforded the corresponding *syn*-1,3-dioxane **4b** in high enantio- and diastereoselectivities, although the yield was slightly lower than for **4a**. In contrast, an electron-deficient enone resulted in the corresponding product **4c** in higher yield but with lower enantioselectivity. The reactions of substrates containing *p*-bromophenyl and *p*-biphenyl groups proceeded smoothly to give the corresponding products **4d** and **4e** in high yields with high stereoselectivities. The formation of *syn*-1,3-dioxanes bearing heteroaryl groups was then investigated. Product **4f** bearing a 2-thienyl group was successfully obtained in good yield with high enantio- and diastereoselectivities, and product **4g**, which bears a 3-pyridyl group, was also obtained in moderate yield with good stereoselectivity. Additionally, the reaction was found to be applicable to an aliphatic enone, providing optically active product **4h** bearing a terminal acetyl group. The absolute configurations of **4f** was determined by X-ray crystallography (see the Supporting Information for details), and the configurations of all other products were assigned analogously.

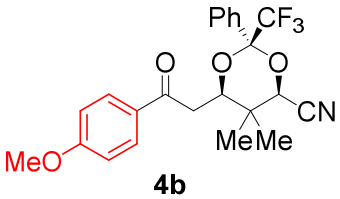
Table 2. Substrate Scope[a]



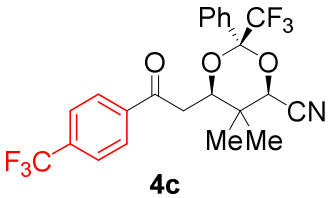
1 **2** **3b** **4**



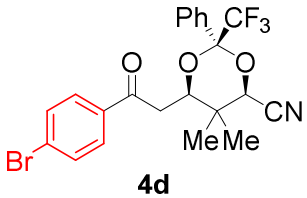
4a
81%
>19:1 dr
90% *ee*



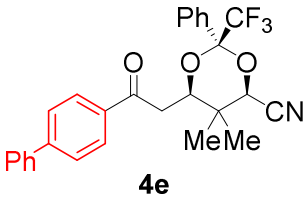
4b
68%
>19:1 dr
94% *ee*



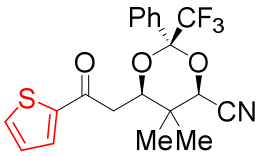
4c
84%
>19:1 dr
67% *ee*



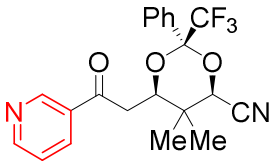
4d
85%
>19:1 dr
87% *ee*



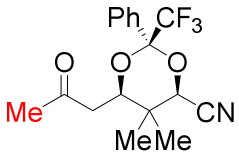
4e
79%
>19:1 dr
90% *ee*



4f
72%
>19:1 dr
92% *ee*



4g
43%
>19:1 dr
70% *ee*



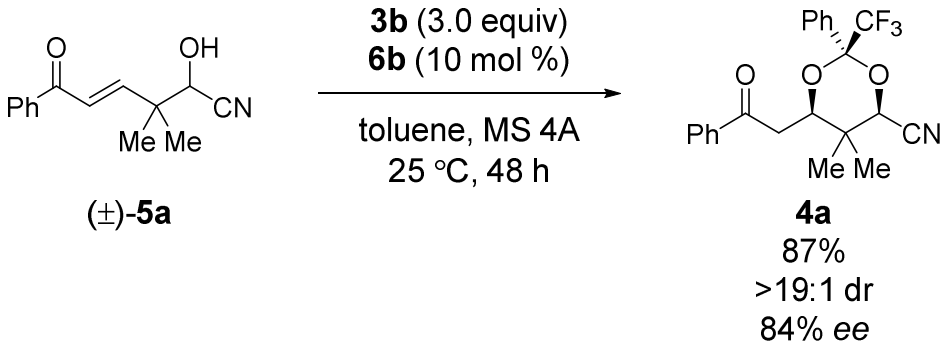
4h
73%
6.7:1 dr
75% *ee*

[a]Reactions were run using **1** (0.15 mmol), **2** (0.18 mmol), **3b** (0.45 mmol), and **6b** (0.015 mmol) in CH_2Cl_2 (0.30 mL). Yields are of material isolated after silica gel column chromatography.

Several experiments were conducted to obtain insight into the reaction mechanism. A series of NMR experiments indicated that, in the presence of catalyst **6b**, both substrate **1** and trifluoromethyl ketone **3b** react with **2** to form the corresponding cyanohydrins in a reversible

manner (See the Experimental Section for details). Moreover, the reaction was run using isolated racemic cyanohydrin **5a** as a substrate, affording the corresponding *syn*-1,3-dioxane **4a** in a yield significantly higher than 50% and with the same level of enantioselectivity as the reaction starting from **1a** (Scheme 2); therefore, the racemization via reversible cyanation proceeds smoothly to realize a dynamic kinetic resolution process. Although a reaction from the obtained product **4a** in the presence of catalyst **6b** indicated that the final ring-forming process via intramolecular oxy-Michael addition is also reversible, the retro-Michael addition pathway could be suppressed under the optimal reaction conditions by using an excess amount of acetone cyanohydrin **2** and ketone **3b** (See the Experimental Section for details).

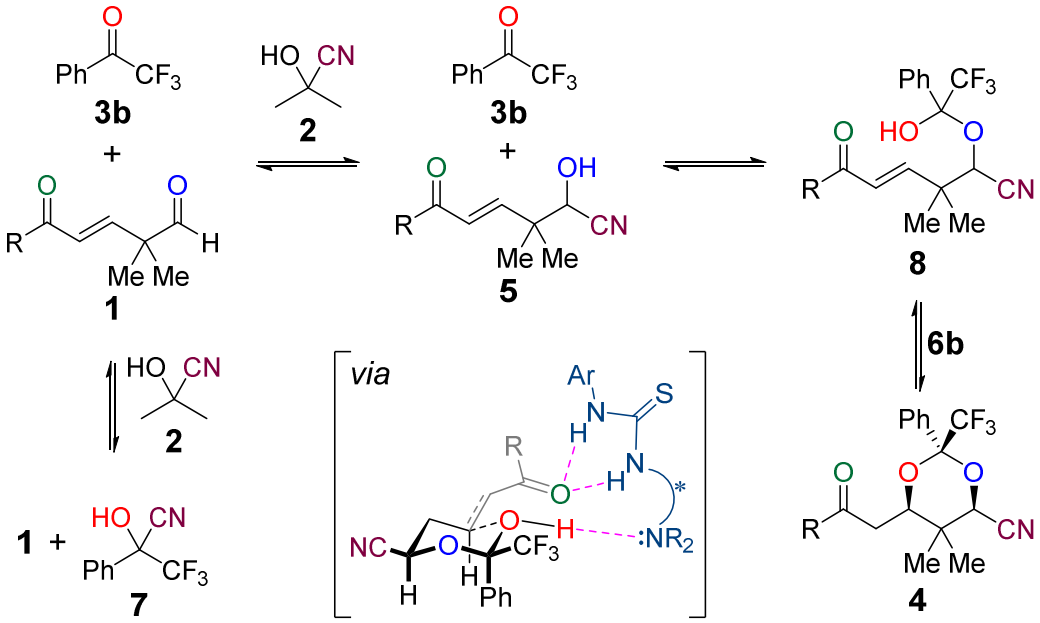
Scheme 2. Reaction from Racemic Cyanohydrin 5a



Based on these results, the author proposes the reaction mechanism shown in Scheme 3. The cyanation reagent **2** can react both with **1** and **3b** to form the corresponding cyanohydrins **5** and **7**, respectively. Even though the reaction of **2** with trifluoromethyl ketone **3b** would compete with the reaction of **2** with the formyl group of **1**, the resulting cyanohydrin **7** can take a backward pathway into the main catalytic process, which is confirmed by the aforementioned NMR experiments. Then another cyanohydrin **5**, which is reversibly generated from the substrate **1**, reacts with **3b** to form the corresponding hemiacetal intermediate **8**. In the subsequent six-membered ring-formation, chiral bifunctional organocatalyst **6b** selectively recognizes a specific chair-like conformation of **8** via multipoint interaction through hydrogen bonding; it enables the

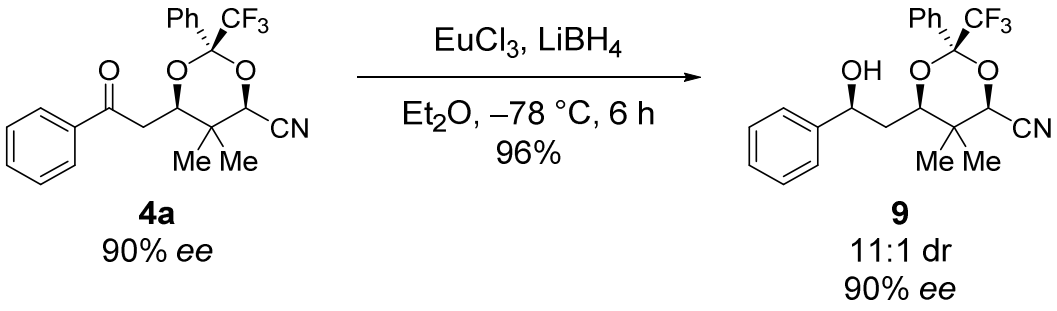
dynamic kinetic resolution of **5** and asymmetric oxy-Michael addition, thereby leading to the highly enantio- and diastereoselective formation of 1,3-dioxanes **4**.

Scheme 3. Proposed Reaction Mechanism



To demonstrate the utility of the obtained products, a diastereoselective reduction of **4a** was carried out (Scheme 4). The carbonyl moiety of **4a** was successfully reduced under the conditions the author previously reported,[11] affording the corresponding product **9** bearing a 1,3,5-triol motif in a highly diastereoselective manner without loss of optical purity. This result, as well as the synthetic utility of the cyano group, indicates that the obtained products have potential as useful building blocks for the synthesis of chiral 1,3-polyol compounds.

Scheme 4. Diastereoselective Reduction of 4a



4a
90% *ee*

9
11:1 dr
90% *ee*

Conclusion

In summary, the author has developed a novel method for the asymmetric synthesis of *syn*-1,3-dioxanes using bifunctional aminothiourea catalysts. This method involves reversible cyanohydrin formation for the racemization of chiral secondary alcohols, allowing for high-yielding access to optically active *syn*-1,3-diol motifs via dynamic kinetic resolution of the in situ generated chiral cyanohydrins. The use of trifluoromethyl ketones is key for achieving the efficient cascade reaction starting from three components, and a combination of enantioselective organocatalysis with diastereoselective six-membered ring formation enables the simultaneous stereocontrol of two stereogenic centers of the desired *syn*-1,3-diol structure.

Experimental Section

Materials

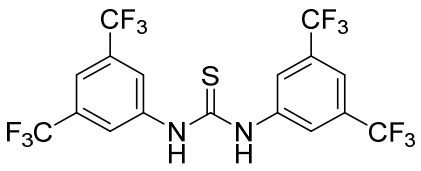
Unless otherwise noted, commercially available reagents were used without purification.

General procedure for asymmetric synthesis of 1,3-Dioxanes 4

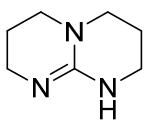
To a solution of δ-oxoenone **1** (0.15 mmol) in toluene (0.30 mL) were added acetone cyanohydrin (**2**, 16 μL, 0.18 mmol), 2,2,2-trifluoroacetophenone (**3b**, 61 μL, 0.45 mmol), molecular sieves 4 Å (50 mg) and bifunctional organocatalyst **6b** (4.8 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 48 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded the corresponding 1,3-dioxane **4**.

General procedure for synthesis of rac-4

To a solution of δ-oxoenone **1** (0.10 mmol) in toluene (0.30 mL) were added acetone cyanohydrin (**2**, 11 μL, 0.12 mmol), trifluoromethyl ketone **3** (0.30 mmol), achiral thiourea **10** (10 mg, 0.020 mmol), and achiral organic base catalyst **11** (2.8 mg, 0.020 mmol), and the resulting mixture was stirred at ambient temperature for 24 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded the corresponding racemic 1,3-dioxane *rac*-**4**.



10

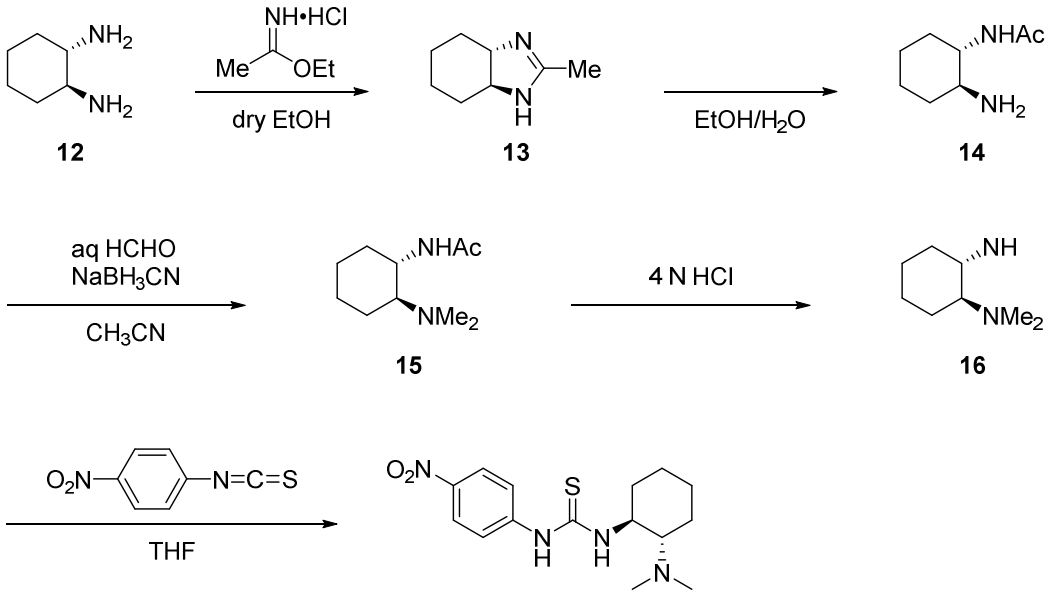


11

Procedure for synthesis of cyanohydrin rac-5a

To a solution of **1a** (100 mg, 0.50 mmol) in dichloromethane (1.0 mL) were added acetone cyanohydrin (**2**, 18.3 μL, 0.20 mmol) and triethylamine (21 μL, 0.15 mmol), and the resulting mixture was stirred at ambient temperature for 3.5 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1–1:1) as an eluent afforded the corresponding cyanohydrin **5a** in 99% yield.

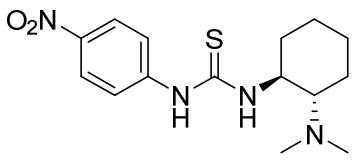
Procedure for preparation of bifunctional catalyst 6b



N,N-Disubstituted 1,2-diamine intermediate **16** was prepared by the literature procedure.[12] To a solution of ethyl acetimidate hydrochloride (2.5 g, 20 mmol) in dry EtOH (30 mL) was added (1*S*,2*S*)-cyclohexane-1,2-diamine (**12**, 1.1 g, 10 mmol) at 0 °C , and the resulting mixture was stirred overnight at room temperature. 1 N NaOH (7.5 mL) was added to the solution, and the mixture was extracted with 5% MeOH–CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford (3a*S*,7a*S*)-2-methyl-3a,4,5,6,7,7a-hexahydro-1H-

benzo[d]imidazole **13**, which was used for the next step without further purification. Next, the obtained compound **13** was dissolved in EtOH/H_2O (v/v = 1/1, 60 mL) and heated to reflux for 12 h. Evaporation of the solvent afforded *N*-((1*S*,2*S*)-2-aminocyclohexyl)acetamide **14**, which was used for the next step without further purification. Next, the obtained compound **14** and aqueous aldehyde (37% w/w, 4.1 g, 50 mmol) were combined in CH_3CN (60 mL), and the resulting mixture was stirred at room temperature for 30 min. $NaBH_3CN$ (6.4 g, 30 mmol) was added, and the solution was stirred for further 15 min. AcOH (3.0 mL) was added, and the solution was stirred for further 2 h. The reaction mixture was diluted with 2% MeOH–CH_2Cl_2, washed with 1 N NaOH, dried over Na_2SO_4, and concentrated in vacuo to afford *N*-((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)acetamide **15**, which was used for the next step without further purification. Next, the obtained compound **15** was heated to reflux in 4 N HCl. After cooling to ambient temperature, the reaction was made basic by addition of 4 N NaOH, and the mixture was extracted with 5% MeOH–CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford pure (1*S*,2*S*)-*N*,*N*-dimethylcyclohexane-1,2-diamine **16** as a colorless oil (700 mg, 5.0 mmol, 50 % for 4 steps).

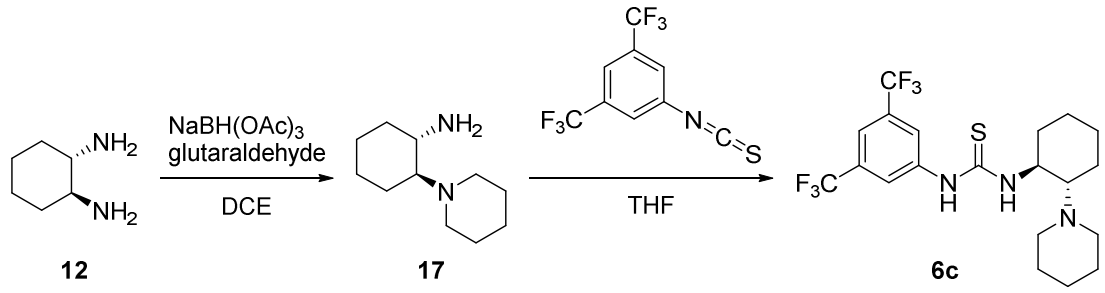
Bifunctional organocatalyst **6b** was synthesized from **16** by the literature procedure.[10b] To the solution of **16** (280 mg, 2.0 mmol) in THF (5.0 mL) was slowly added 4-nitrophenyl isothiocyanate (360 mg, 2.0 mmol) at 0 °C. The mixture was stirred overnight, and the solvents were removed in vacuo. Purification by flash silica gel column chromatography using $CHCl_3$/CH_3OH (v/v = 30:1 to 10:1) as an eluent gave bifunctional organocatalyst **6b**. The characterization results are as below.



6b. Yellow solid; 79% yield (for the last step, 0.50 g). $[\alpha]_D^{23}$ –56.4 (*c* 0.67, CH_2Cl_2). ^{1}H NMR (DMSO-d_6) δ 10.1 (br s, 1H), 8.28 (br s, 1H), 8.16 (dd, *J* = 8.5 Hz, 2H), 7.84 (dd, *J* = 8.5 Hz, 2H),

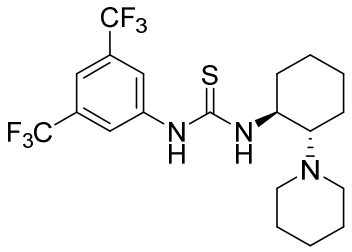
4.08 (m, 1H), 2.54 (m, 1H), 2.22 (m, 7H), 1.82 (m, 1H), 1.75 (m, 1H), 1.63 (m, 1H), 1.18 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 178.5, 146.7, 141.3, 124.8, 119.6, 65.1, 55.2, 37.6, 31.6, 24.7, 24.5, 21.2. Mp. 138.0–138.4 °C. IR (KBr): 3341, 3200, 2934, 2859, 1595, 1536, 1506, 1344, 1248, 1181, 1112, 1036 cm^{-1}. HRMS Calcd for $C_{15}H_{23}N_4O_2S$: $[M+H]^+$, 323.1536. Found: *m*/*z* 323.1541.

Procedure for preparation of bifunctional catalyst 6c



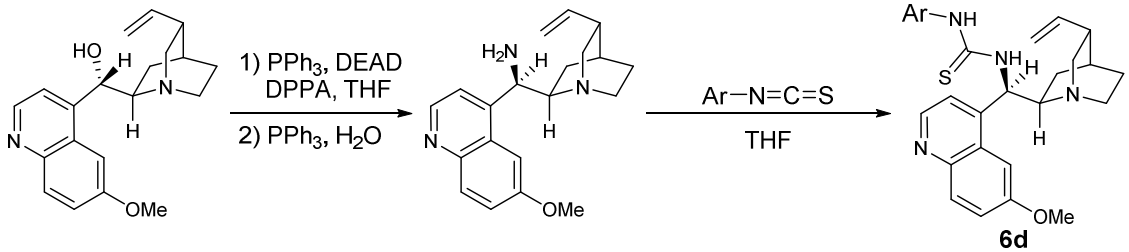
12 **17** **6c**

(1*S*,2*S*)-Cyclohexane-1,2-diamine (**12**, 1.1 g, 10 mmol) and $NaBH(OAc)_3$ (7.2 g, 34 mmol) were dissolved in 1,2-dichloroethane (60 mL), and the solution was cooled to 0 °C. To the resulting solution was added dropwise glutaraldehyde (ca. 50% in H_2O, 2.0 mL, 11 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature. After the resulting mixture was stirred for 3 h, 10% aqueous NaOH (40 mL) was added at 0 °C. The aqueous layers were separated and washed with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using $CHCl_3$/MeOH/Et_3N (v/v = 20:20:1) as an eluent gave (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine **17** (0.81 g, 4.5 mmol). Next, to the solution of **17** in THF (13 mL) was slowly added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.2 g, 4.5 mmol) at 0 °C. The mixture was stirred overnight, and the solvents were removed in vacuo. Purification by flash silica gel column chromatography using $CHCl_3$/CH_3OH (v/v = 20:1) as an eluent gave bifunctional organocatalyst **6c**. The characterization results are as below.



6c. White solid; 99% yield (for 2 steps, 0.44 g). $[\alpha]_D^{23}$ +1.72 (*c* 1.63, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 2H), 7.70 (s, 1H), 3.77 (br s, 1H), 2.64 (m, 3H), 2.39 (m, 3H), 1.94–1.73 (m, 5H), 1.70–1.42 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 181.4, 139.7, 132.7 (q, J = 33.9 Hz), 124.5, 122.9 (q, J = 272.8 Hz), 119.0, 68.8, 56.2, 49.5, 32.6, 26.3, 25.2, 24.4, 24.2, 23.4. Mp. 128.0–128.6 °C. IR (KBr): 3235, 3060, 2949, 2809, 1547, 1474, 1377, 1280, 1180, 1142, 1010, 969, 888, 706, 690 cm^{-1}. HRMS Calcd for $C_{20}H_{26}F_6N_3S$: $[M+H]^+$, 454.1746. Found: *m*/*z* 454.1737.

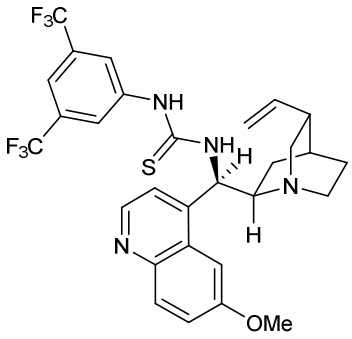
Procedure for preparation of bifunctional catalysts 6d



18 **19** **6d**
Ar = 3,5-$(CF_3)_2C_6H_3$

Bifunctional organocatalysts **6d** was prepared by the literature procedure.[13] Quinidine (**18**, 1.6 g, 5.0 mmol) and triphenylphosphine (1.6 g, 6.0 mmol) were dissolved in THF (25 mL), and the solution was cooled to 0 °C. Diethyl azodicarboxylate (1.0 g, 6.0 mmol) was subsequently added. To the resulting solution was added dropwise the solution of diphenyl phosphoryl azide (1.3 mL, 6.0 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to ambient temperature. After being stirred for 24 h, it was heated to 50 °C and stirred for 10 h. Triphenylphosphine (1.7 g, 6.5 mmol) was added again, and the mixture was stirred at 50 °C for additional 15 h. After the solution was cooled to ambient temperature, H_2O (0.5 mL) was added, and the solution was stirred for 24 h. The solvents were removed in vacuo, and the residue was

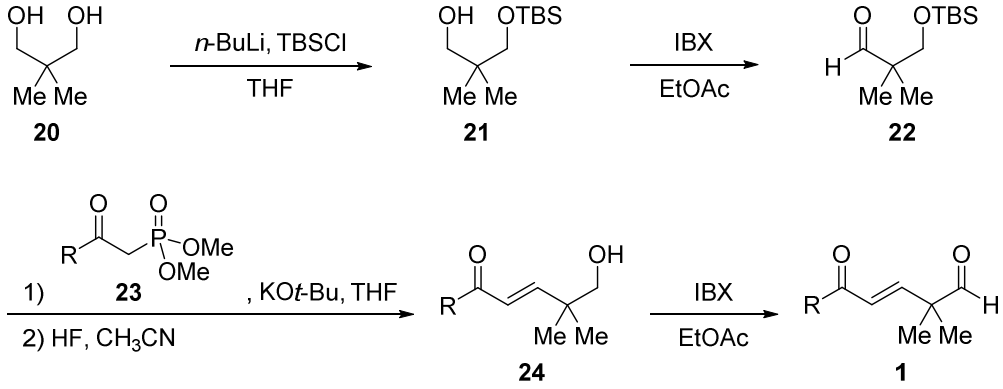
dissolved in CH_2Cl_2/10% aqueous HCl (25 mL/25 mL). The aqueous phase was separated and washed with CH_2Cl_2 (25 mL × 4). It was subsequently made alkaline with aqueous NH_3, and the aqueous layers were extracted with CH_2Cl_2 (25 mL × 4). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using EtOAc/CH_3OH (v/v = 9:1) then $CHCl_3$/CH_3OH (v/v = 4:1) as an eluent gave (9*R*)-9-amino-9-deoxyquinidine **19**. Next, to the solution of **19** in THF (6.0 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.0 equiv) in THF (4.0 mL) at ambient temperature. The mixture was stirred overnight, and the solvents were removed in vacuo. Purification by flash silica gel column chromatography using EtOAc/CH_3OH (v/v = 95:5–97.5:2.5) or EtOAc as an eluent gave **6d**. The characterization results are as below.



6d. White solid; 41% yield (for 2steps from **18**, 1.2 g). $[\alpha]_D^{23}$ +122.6 (*c* 1.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.65 (br s, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.86 (s, 2H), 7.67 (s, 1H), 7.59 (br s, 1H), 7.40 (d, *J* = 9.0 Hz, 1H), 7.23 (br s, 1H), 5.86 (br s, 2H), 5.19 (br s, 1H), 5.15 (d, *J* = 9.5 Hz, 1H), 3.97 (s, 3H), 3.22 (br s, 1H), 3.10 (br s, 1H), 3.03 (m, 2H), 2.94 (m, 1H), 2.38 (m, 1H), 1.70 (s, 1H), 1.61 (m, 2H), 1.27 (br s, 1H), 1.02 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 181.0, 158.1, 147.3, 144.7, 144.5, 140.1, 139.6, 132.5 (q, *J* = 33.6 Hz), 131.6, 128.0, 123.5, 122.9 (q, *J* = 273.0 Hz), 122.3, 118.7, 115.3, 101.7, 61.4, 55.6, 48.5, 47.1, 38.7, 27.1, 26.1, 25.0. Mp. 125.0–125.2 °C. IR (KBr): 3221, 2944, 2361, 1735, 1623, 1511, 1475, 1384, 1278, 1177, 1134, 1034, 959, 916, 884, 850, 826, 682 cm^{-1}. HRMS Calcd for $C_{29}H_{29}F_6N_4OS$: $[M+H]^+$, 595.1966. Found: *m*/*z* 595.1961.

Bifunctional organocatalysts **6a** and **6e** were commercially available and were used without purification.

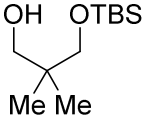
General procedure for preparation of 1



Procedure for preparation of **21**

To a solution of 2,2-dimethylpropane-1,3-diol (**20**, 5.2 g, 50 mmol) in dry THF (90 mL) was added *n*-butyllithium (34 mL, 1.63 M in *n*-hexane, 55 mmol) dropwise at 0 °C. After the mixture was stirred for 1 h, a solution of *tert*-butyldimethylsilyl chloride (7.5 g, 50 mmol) in dry THF (10 mL) was added, and the reaction was allowed to warm to ambient temperature. After being stirred for additional 18 h, the reaction was quenched with H_2O (50 mL), and the mixture was subsequently extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1) as an eluent gave 3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropan-1-ol (**21**).

3-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethylpropan-1-ol (21): CAS RN [127047-71-6].



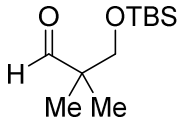
Colorless oil; 99% yield (11 g).

^{1}H NMR ($CDCl_3$) δ 3.47–3,46 (m, 4H), 2.86 (t, J = 5.5 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 6H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 73.0, 72.5, 36.6, 26.0, 21.7, 18.4, –5.3.

Procedure for preparation of **22**

To a suspension of 2-iodoxybenzoic acid (24 g, 86 mmol) in dry EtOAc (100 mL) was added **21** (4.8 g, 22 mmol) and the mixture was stirred vigorously at 80 °C for 6 h. The reaction suspension was cooled to ambient temperature and then filtered. The filter cake was washed with EtOAc, and the combined filtrates were concentrated in vacuo to yield 3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanal **22**, which was used for the next step without further purification.

3-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethylpropanal (22): CAS RN [144681-67-4].



Colorless oil; 70% yield (3.3 g).

^{1}H NMR ($CDCl_3$) δ 9.55 (s, 1H), 3.58 (s, 2H), 1.03 (s, 6H), 0.85 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 206.3, 68.6, 48.3, 26.0, 18.7, 18.4, –5.3.

General procedure for preparation of **24**

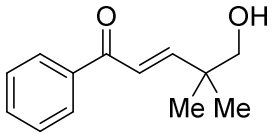
To a solution of *t*-BuOK (1.2 g, 10 mmol) in dry THF (25 mL) was added a solution of phosphonate **23** (10 mmol) in dry THF (5.0 mL) dropwise under argon atmosphere at 0 °C, and the mixture was stirred for 30 min. To this suspension was added a solution of aldehyde **22** (1.5 g, 6.9 mmol) in dry THF (5.0 mL) dropwise at 0 °C, and the mixture was allowed to warm to ambient temperature then heated to 70 °C. After being stirred for 12 h, the mixture was cooled to ambient

temperature, and saturated aqueous NH_4Cl (15 mL) was added to quench the reaction. The mixture was extracted with EtOAc (20 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 30:1) as an eluent gave the corresponding δ-siloxy-α,β-unsaturated ketone, some of which were eluted along with unreacted **22** and used as the mixture for the next step.

Next, to the solution of the obtained δ-siloxy-α,β-unsaturated ketone in CH_3CN (10 mL) was added 46% aqueous HF (0.98 mL, 23 mmol), and the mixture was stirred at ambient temperature for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1) as an eluent gave the corresponding δ-hydroxy-α,β-unsaturated ketone **24**.

Phosphonates **23** were prepared by the literature[14] except for dimethyl (2-oxopropyl)phosphonate, which is commercially available and used without any purification. The characterization results of **24** are as below.

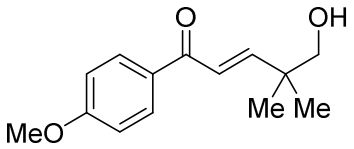
(*E*)-5-Hydroxy-4,4-dimethyl-1-phenylpent-2-en-1-one (24a).



Colorless oil; 64% yield (for 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2H), 7.56 (m, 1H), 7.49 (m, 2H), 7.03 (d, *J* = 16.0 Hz, 1H), 6.89 (d, *J* = 16.0 Hz, 1H), 3.50 (s, 2H), 1.84 (br s, 1H), 1.16 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 191.1, 155.4, 137.8, 132.8, 128.6, 128.5, 123.9, 71.0, 39.7, 23.2. TLC: R_f 0.15 (hexane/EtOAc = 3:1). IR (neat): 3434, 2962, 2930, 2870, 1668, 1616, 1579, 1448, 1301, 1225, 1048 cm^{-1}. HRMS Calcd for $C_{13}H_{16}O_2Na$: $[M+Na]^+$, 227.1043. Found: *m*/*z* 227.1043.

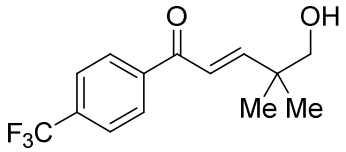
(*E*)-5-Hydroxy-1-(4-methoxyphenyl)-4,4-dimethylpent-2-en-1-one (24b).



Colorless oil; 20% yield (for 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.00 (d, *J* = 15.5 Hz, 1H), 6.95 (m, 2H), 6.90 (d, *J* = 15.5 Hz, 1H), 3.88 (s, 3H), 3.50 (d, *J* = 6.5 Hz, 2H), 1.70 (br s, 1H), 1.16 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 189.2, 163.4, 154.3, 130.9, 130.7, 123.7, 113.7, 71.0, 55.5, 39.6, 23.2. TLC: R_f 0.26 (hexane/EtOAc = 1:1). IR (neat): 3439, 2962, 2875, 1661, 1594, 1574, 1465, 1421, 1307, 1261, 1171, 1049 cm^{-1}. HRMS Calcd for $C_{14}H_{18}O_3Na$: $[M+Na]^+$, 257.1148. Found: *m*/*z* 257.1146.

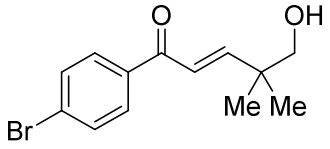
(*E*)-5-Hydroxy-4,4-dimethyl-1-(4-(trifluoromethyl)phenyl)pent-2-en-1-one (24c).



White solid; 26% yield (for 2 steps).

^{1}H NMR ($CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 16.0 Hz, 1H), 6.86 (d, *J* = 16.0 Hz, 1H), 3.53 (s, 2H), 1.59 (br s, 1H), 1.17 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 190.1, 156.9, 140.7, 134.0 (q, *J* = 32.5 Hz), 128.9, 125.6 (q, *J* = 3.8 Hz), 123.61, 123.59 (q, *J* = 273.2 Hz), 70.9, 39.8, 23.2. ^{19}F NMR ($CDCl_3$) δ 98.7. Mp. 49.0–49.8 °C. TLC: R_f 0.15 (hexane/EtOAc = 3:1). IR (KBr): 3293, 2969, 2934, 2873, 1670, 1614, 1474, 1411, 1324, 1223, 1168, 1129, 1069, 1013 cm^{-1}. HRMS Calcd for $C_{14}H_{16}F_3O_2$: $[M+H]^+$, 273.1097. Found: *m*/*z* 273.1098.

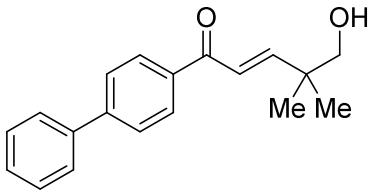
(*E*)-1-(4-Bromophenyl)-5-hydroxy-4,4-dimethylpent-2-en-1-one (24d).



Colorless oil; 23% yield (for 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 16.0 Hz, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 3.51 (s, 2H), 1.64 (br s, 1H), 1.16 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 189.8, 156.1, 136.5, 131.8, 130.1, 127.9, 123.4, 70.9, 39.7, 23.2. Mp. 65.0–66.0 °C. TLC: R_f 0.37 (hexane/EtOAc = 3:1). IR (KBr): 3441, 2960, 2873, 1666, 1610, 1587, 1465, 1394, 1332, 1302, 1218, 1181, 1070 cm^{-1}. HRMS Calcd for $C_{13}H_{15}BrO_2Na$: $[M+Na]^+$, 307.1207. Found: *m*/*z* 307.1208.

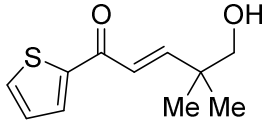
(*E*)-1-([1,1'-Biphenyl]-4-yl)-5-hydroxy-4,4-dimethylpent-2-en-1-one (24e).



Colorless oil; 41% yield (for 2 steps).

^{1}H NMR ($CDCl_3$) δ 8.03 (m, 2H), 7.70 (m, 2H), 7.64 (m, 2H), 7.48 (m, 2H), 7.42 (m, 1H), 7.07 (d, *J* = 16.0 Hz, 1H), 6.95 (d, *J* = 16.0 Hz, 1H), 3.53 (s, 2H), 1.57 (br s, 1H), 1.19 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 190.3, 155.2, 145.5, 139.9, 136.5, 129.2, 128.9, 128.2, 127.3, 127.2, 123.9, 71.0, 39.7, 23.3. Mp. 138.0–138.9 °C. TLC: R_f 0.15 (hexane/EtOAc = 3:1). IR (KBr): 3353, 2961, 2926, 2869, 1662, 1619, 1604, 1404, 1388, 1333, 1297, 1276, 1219, 1186, 1028 cm^{-1}. HRMS Calcd for $C_{19}H_{20}O_2Na$: $[M+Na]^+$, 303.1356. Found: *m*/*z* 303.1357.

(*E*)-5-Hydroxy-4,4-dimethyl-1-(thiophen-2-yl)pent-2-en-1-one (24f).

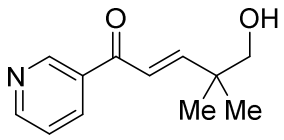


Colorless oil; 31% yield (for 2 steps).

^{1}H NMR ($CDCl_3$) δ 7.79 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.66 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.15 (dd, *J* = 5,0, 4.0 Hz, 1H), 7.08 (d, *J* = 16.0 Hz, 1H), 6.81 (d, *J* = 16.0 Hz, 1H), 3.51 (s, 2H), 1.64 (br s, 1H), 1.16

(s, 6H). ^{13}C NMR ($CDCl_3$) δ 182.4, 154.6, 145.1, 134.0, 132.1, 128.2, 123.5, 71.0, 39.6, 23.2. Mp. 60.5–61.4 °C. TLC: R_f 0.28 (hexane/EtOAc = 1:1). IR (KBr): 3249, 2958, 2927, 2864, 1645, 1597, 1516, 1407, 1354, 1324, 1309, 1241, 1225, 1060 cm^{-1}. HRMS Calcd for $C_{11}H_{14}O_2SNa$: $[M+Na]^+$, 233.0607. Found: *m*/*z* 233.0606.

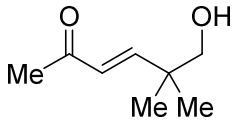
(*E*)-5-Hydroxy-4,4-dimethyl-1-(pyridin-3-yl)pent-2-en-1-one (24g).



Colorless oil; 41% yield (for 2 steps).

^{1}H NMR ($CDCl_3$) δ 9.13 (dd, *J* = 2.0, 1.0 Hz, 1H), 8.77 (dd, *J* = 5.0, 2.0 Hz, 1H), 8.21 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1H), 7.43 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 3.53 (s, 2H), 1,85 (br s, 1H), 1.17 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 189.6, 157.0, 153.1, 149.8, 136.1, 133.2, 123.7, 123.5, 70.9, 39.8, 23.2. Mp. 64.5–65.0 °C. TLC: R_f 0.31 (EtOAc). IR (KBr): 3277, 2977, 2958, 2924, 2864, 1669, 1609, 1588, 1420, 1302, 1233, 1191, 1064 cm^{-1}. HRMS Calcd for $C_{12}H_{16}N_1O_2$: $[M+H]^+$, 206.1176. Found: *m*/*z* 206.1176.

(*E*)-6-Hydroxy-5,5-dimethylhex-3-en-2-one (24h).



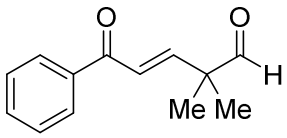
Colorless oil; 50% yield (for 2 steps).

^{1}H NMR ($CDCl_3$) δ 6.79 (d, *J* = 16.0 Hz, 1H), 6.08 (d, *J* = 16.0 Hz, 1H), 3.46 (s, 2H), 2.27 (s, 3H), 1.75 (br s, 1H), 1.09 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 199.1, 154.1, 129.0, 71.0, 39.2, 27.2, 23.2. TLC: R_f 0.20 (hexane/EtOAc = 1:1). IR (neat): 3432, 2964, 2931, 2871, 1673, 1624, 1363, 1264, 1054 cm^{-1}. HRMS Calcd for $C_8H_{14}O_2Na$: $[M+Na]^+$, 165.0886. Found: *m*/*z* 165.0884.

General procedure for preparation of **1**

To a suspension of 2-iodoxybenzoic acid (2.1 g, 7.5 mmol) in dry EtOAc (10 mL) was added δ-hydroxy-α,β-unsaturated ketone **24** (2.5 mmol) and the mixture was stirred vigorously at 80 °C for 6 h. The reaction suspension was cooled to ambient temperature and then filtered. The filter cake was washed with EtOAc, and the combined filtrates were concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1 to 5:1) as an eluent gave δ-oxo-α,β-unsaturated ketone **1**. The characterization results of **1** are as below.

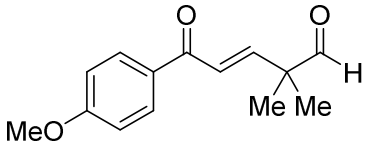
(*E*)-2,2-Dimethyl-5-oxo-5-phenylpent-3-enal (1a).



Colorless oil; 71% yield.

^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1H), 7.93 (m, 2H), 7.55 (m, 1H), 7.49 (m, 2H), 7.04 (d, J = 15.5 Hz, 1H), 6.91 (d, J = 15.5 Hz, 1H), 1.35 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 200.9, 190.2, 148.8, 137.4, 133.1, 128.7, 128.6, 125.6, 49.5, 21.3. TLC: R_f 0.26 (hexane/EtOAc = 10:1). IR (neat): 2973, 1726, 1672, 1616, 1580, 1448, 1333, 1301, 1221, 1018 cm^{-1}. HRMS Calcd for $C_{13}H_{14}O_2Na$: $[M+Na]^+$, 225.0886. Found: *m*/*z* 225.0885.

(*E*)-5-(4-Methoxyphenyl)-2,2-dimethyl-5-oxopent-3-enal (1b).

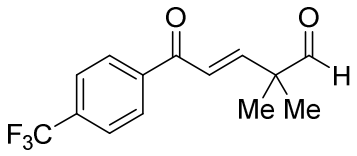


White solid; 89% yield.

^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1H), 7.95 (m, 2H), 7.01 (d, J = 16.0 Hz, 1H), 6.96 (m, 2H), 6.91 (d, J = 16.0 Hz, 1H), 3.88 (s, 3H), 1.34 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 201.0, 188.3, 163.6, 147.8, 131.0,

130.3, 125.3, 113.9, 55.5, 49.5, 21.3. Mp. 50.5–51.2 °C. TLC: R_f 0.23 (hexane/EtOAc = 3:1). IR (KBr): 2976, 2842, 1726, 1664, 1606, 1575, 1459, 1422, 1333, 1303, 1174, 1021 cm^{-1}. HRMS Calcd for $C_{14}H_{16}O_3Na$: $[M+Na]^+$, 255.0922. Found: *m*/*z* 255.0991.

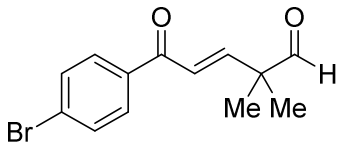
(*E*)-2,2-Dimethyl-5-oxo-5-(4-(trifluoromethyl)phenyl)pent-3-enal (1c).



White solid; 92% yield.

^1H NMR ($CDCl_3$) δ 9.53 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 16.0 Hz, 1H), 6.87 (d, *J* = 16.0 Hz, 1H), 1.36 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 200.7, 189.3, 150.3, 140.2, 134.2 (q, *J* = 32.5 Hz), 128.9, 125.7 (q, *J* = 3.8 Hz), 125.2, 123.5 (q, *J* = 273.3 Hz), 49.6, 21.3. ^{19}F NMR ($CDCl_3$) δ 98.6. Mp. 32.0–32.5 °C. TLC: R_f 0.21 (hexane/EtOAc = 5:1). IR (KBr): 2978, 1724, 1674, 1612, 1471, 1412, 1320, 1163, 1110, 1066 cm^{-1}. HRMS Calcd for $C_{14}H_{13}F_3O_2Na$: $[M+Na]^+$, 293.0760. Found: *m*/*z* 293.0760.

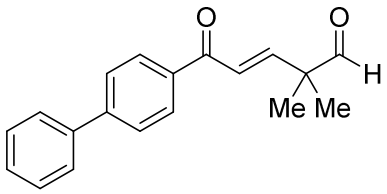
(*E*)-5-(4-Bromophenyl)-2,2-dimethyl-5-oxopent-3-enal (1d).



Colorless oil; 89% yield.

^1H NMR ($CDCl_3$) δ 9.52 (s, 1H), 7.79 (m, 2H), 7.63 (m, 2H), 7.05 (d, *J* = 16.0 Hz, 1H), 6.85 (d, *J* = 16.0 Hz, 1H), 1.35 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 200.8, 189.0, 149.4, 136.1, 132.0, 130.1, 128.3, 125.0, 49.6, 21.3. TLC: R_f 0.34 (hexane/EtOAc = 1:1). IR (neat): 2970, 1727, 1665, 1584, 1481, 1464, 1391, 1325, 1307, 1263, 1216, 1175, 1064, 1034 cm^{-1}. HRMS Calcd for $C_{13}H_{13}BrO_2Na$: $[M+Na]^+$, 304.9971. Found: *m*/*z* 304.9972.

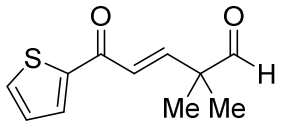
(*E*)-5-([1,1'-Biphenyl]-4-yl)-2,2-dimethyl-5-oxopent-3-enal (1e).



White solid; 83% yield.

^{1}H NMR ($CDCl_3$) δ 9.55 (s, 1H), 8.02 (m, 2H), 7.71 (m, 2H), 7.64 (m, 2H), 7.48 (m, 2H), 7.41 (m, 1H), 7.08 (d, J = 15.5 Hz, 1H), 6.96 (d, J = 15.5 Hz, 1H), 1.37 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 200.9, 190.0, 148.7, 145.8, 139.8, 136.1, 129.2, 129.0, 128.3, 127.29, 127.25, 125.5, 49.5, 21.3. Mp. 135.8–136. °C. TLC: R_f 0.18 (hexane/EtOAc = 15:1). IR (KBr): 2976, 2867, 1726, 1659, 1611, 1405, 1329, 1300, 1234, 1007 cm^{-1}. HRMS Calcd for $C_{19}H_{18}O_2Na$: $[M+Na]^+$, 301.1199. Found: *m*/*z* 301.1200.

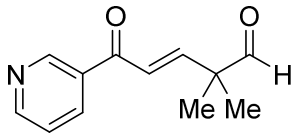
(*E*)-2,2-Dimethyl-5-oxo-5-(thiophen-2-yl)pent-3-enal (1f).



Colorless oil; 96% yield.

^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 7.78 (dd, J = 4.0, 1.0 Hz, 1H), 7.69 (dd, J = 5.0, 1.0 Hz, 1H), 7.17 (dd, J = 5,0, 4.0 Hz, 1H), 7.09 (d, J = 16.0 Hz, 1H), 6.81 (d, J = 16.0 Hz, 1H), 1.34 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 200.8, 181.6, 148.0, 144.7, 134.5, 132.3, 128.3, 125.1, 49.4, 21.3. TLC: R_f 0.53 (hexane/EtOAc = 1:1). IR (neat): 2973, 2807, 1728, 1657, 1607, 1517, 1414, 1354, 1300, 1236, 1063 cm^{-1}. HRMS Calcd for $C_{11}H_{12}O_2SNa$: $[M+Na]^+$, 231.0450. Found: *m*/*z* 231.0450.

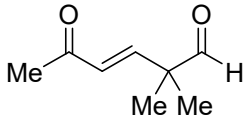
(*E*)-2,2-Dimethyl-5-oxo-5-(pyridin-3-yl)pent-3-enal (1g).



Colorless oil; 98% yield.

^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1H), 9.13 (dd, J = 2.5, 0.5 Hz, 1H), 8.80 (dd, J = 5.0, 1.5 Hz, 2H), 8.22 (ddd, J = 8.0, 2.5, 1.5 Hz, 1H), 7.45 (ddd, J = 8.0, 5.0, 0.5 Hz, 1H), 7.10 (d, J = 16.0 Hz, 1H), 6.88 (d, J = 16.0 Hz, 1H), 1.36 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 200.6, 188.8, 153.4, 150.2, 149.8, 136.0, 132.8, 125.0, 123.7, 49.6, 21.3. TLC: R_f 0.33 (EtOAc). IR (neat): 2974, 1727, 1634, 1616, 1586, 1420, 1340, 1301, 1232, 1051 cm^{-1}. HRMS Calcd for $C_{12}H_{14}N_1O_2$: $[M+H]^+$, 204.1019. Found: *m*/*z* 204.1018.

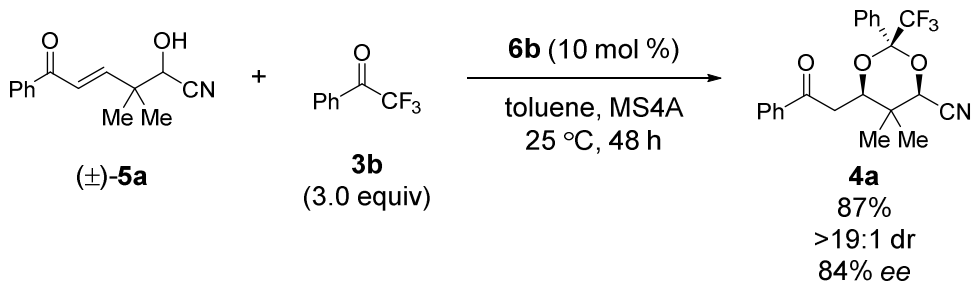
(*E*)-2,2-Dimethyl-5-oxohex-3-enal (1h).



Colorless oil; 74% yield.

^{1}H NMR ($CDCl_3$) δ 9.46 (s, 1H), 6.80 (d, J = 16.5 Hz, 1H), 6.12 (d, J = 16.5 Hz, 1H), 2.29 (s, 3H), 1.28 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 200.9, 198.0, 147.4, 130.7, 49.1, 27.3, 21.2. TLC: R_f 0.21 (hexane/EtOAc = 3:1). IR (neat): 2977, 1729, 1676, 1628, 1465, 1360, 1257, 1182 cm^{-1}. HRMS Calcd for $C_8H_{12}O_2Na$: $[M+Na]^+$, 163.0730. Found: *m*/*z* 163.0728.

Scheme 5. Reaction from Racemic (±)-**5a**

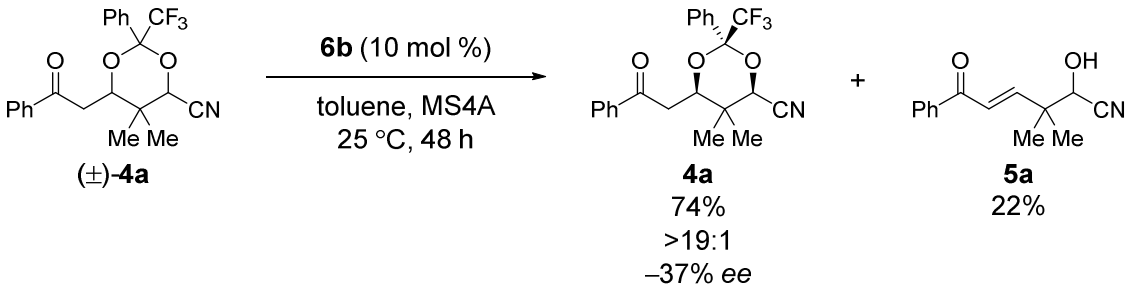


A reaction from racemic cyanohydrin (±)-**5a** with **3b** afforded 1,3-dioxane product **4a** in a yield significantly higher than 50% with the enantioselectivity comparable to the reaction starting from **1a**, indicating that the reaction proceeds via a dynamic kinetic resolution process.

Procedure

To a solution of racemic cyanohydrin (±)-**5a** (34 mg, 0.15 mmol) in toluene (0.30 mL) were added 2,2,2-trifluoroacetophenone (**3b**, 61 μL, 0.45 mmol), molecular sieves 4 Å (50 mg) and catalyst **6b** (4.8 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 48 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded **4a**.

Scheme 6. Reaction from (±)-**4a**

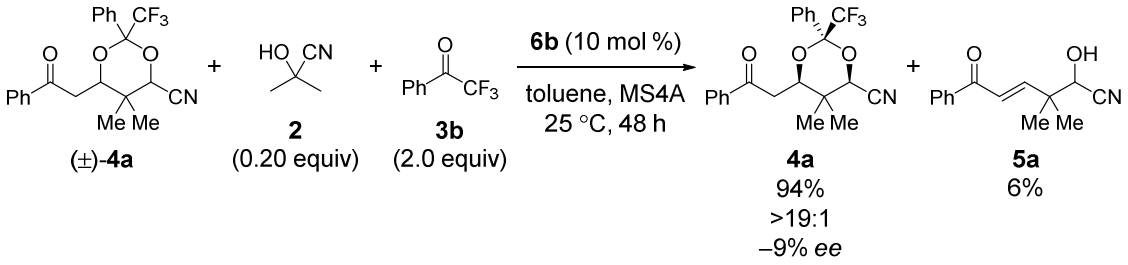


The subjection of racemic 1,3-dioxane (±)-**4a** to a solution containing catalyst **6b** for 48 h resulted in the formation of cyanohydrin **5a** along with 74% recovery of **4a**. These results indicate that the six-membered ring-forming process via oxy-Michael addition is reversible.

Procedure

To a solution of racemic 1,3-dioxane (±)-**4a** (48 mg, 0.12 mmol) in toluene (0.24 mL) was added catalyst **6b** (3.8 mg, 0.012 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 48 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded **5a** and unreacted **4a**.

Scheme 7. Reaction from (±)-**4a** in The Presence of Excess Amount of **2** and **3b**



A reaction from racemic 1,3-dioxane (±)-**4a** with **2** and **3b** was conducted under the conditions where the ratio of reaction components is identical with the optimal ones starting from δ-oxoenone **1a**. After 48 h, 94% of unreacted **4a** was obtained along with a small amount of **5a**. these results indicate that the presence of excess amounts of **2** and **3b** significantly suppressed the retro-Michael addition process from **4a**.

Procedure

To a solution of racemic 1,3-dioxane (±)-**4a** (61 mg, 0.15 mmol) in toluene (0.30 mL) were added acetone cyanohydrin (**2**, 2.7 μL, 0.030 mmol), 2,2,2-trifluoroacetophenone (**3b**, 41 μL, 0.30 mmol), molecular sieves 4 Å (50 mg) and catalyst **6b** (4.8 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 48 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded **5a** and unreacted **4a**.

NMR Experiments

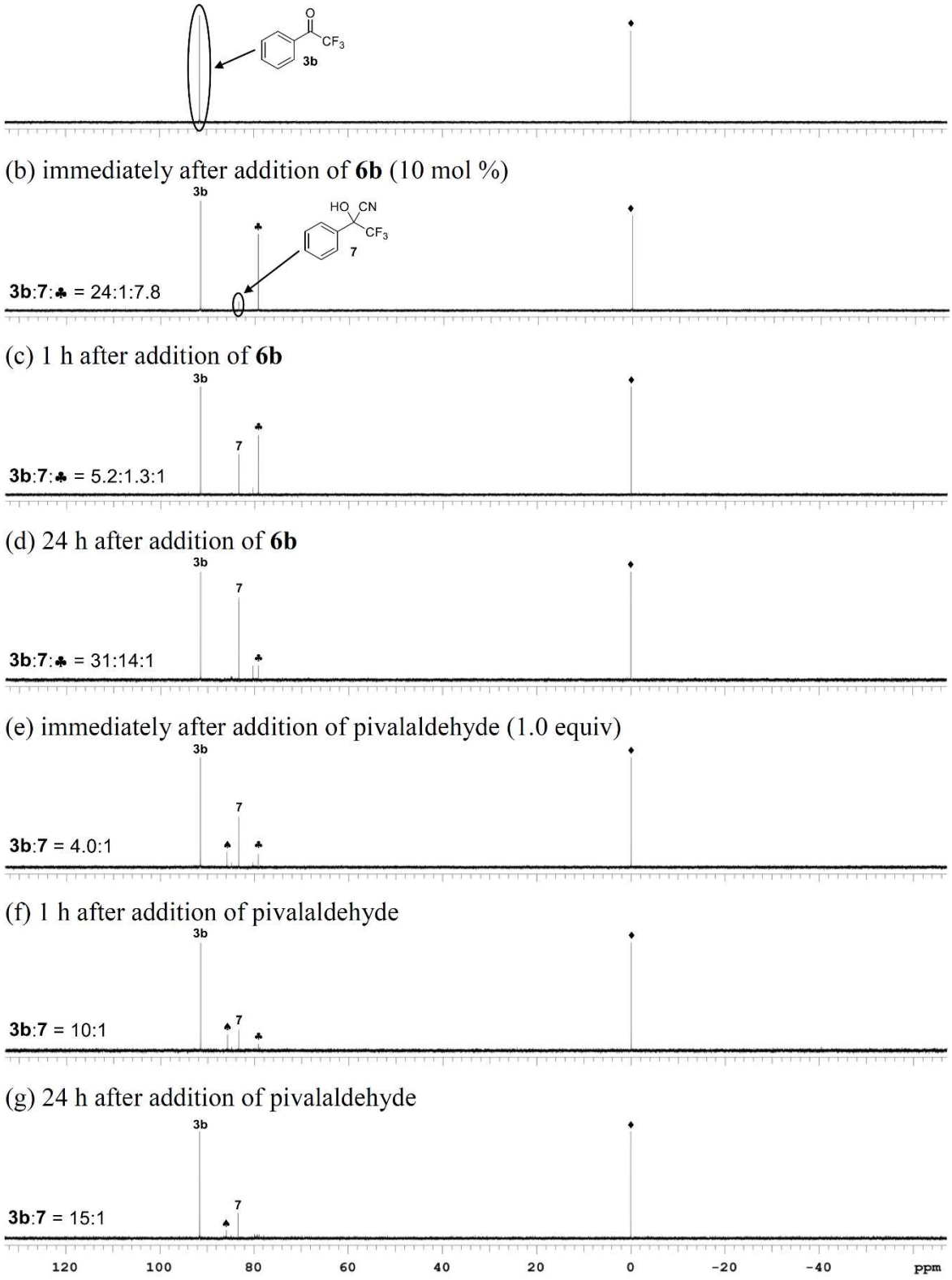


Figure 2. ^{19}F NMR (188 MHz, 0.30 M, C_6D_6, 20 °C) spectra of solutions including **2**, **3b**, **6b** and pivalaldehyde. Signals assigned with ♦ belongs to C_6F_6 as an internal standard.

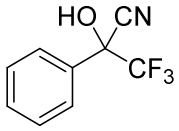
Results and Discussion

1. A ^{19}F NMR spectrum of a sample containing acetone cyanohydrin (**2**, 16 μL, 0.18 mmol), 2,2,2-trifluoroacetopheone (**3b**, 61 μL, 0.45 mmol), benzene-d_6 (0.50 mL) and hexafluorobenzene as an internal standard was taken at 20 °C, which gave only a signal derived from **3b** besides the one belonging to the internal standard assigned as ♦ (Figure 2a). This result indicates that **3b** do not react with **2** unless catalyst **6b** was added to the solution.
2. The addition of **6b** to the solution immediately gave additional two signals (Figure 2b). Among these two signals, the weaker one is derived from 3,3,3-trifluoro-2-hydroxy-2-phenylpropanenitrile (**7**), which is unambiguously identified by comparing with the spectrum of separately prepared **7**. The stronger one assigned with ♣ in Figure 2b is not identified, but probably derived from a hemiacetal generated from **2** and **3b**.
3. Several spectra of the sample was further taken during the course of the reaction at 25 °C (Figure 2c and d), which indicates that the amount of **7** in the solution overtakes that of unidentified species assigned with ♣. This reaction reached an equilibrium 24 hours after the addition of **6b**, where the ratio of signals **7**:♣ is 14:1 (Figure 2d).
4. The addition of pivalaldehyde as an analog of substrate **1** to the solution immediately gave an additional signal of unidentified species assigned with ♠ in Figure 2e. The ratio of **3b**:**7** gradually changed from 4.0:1 to 15:1 until the spectrum was taken 24 hours after the addition of pivalaldehyde (Figure 2e–g). These results indicate that, in the presence of **6b**, **7** reacts with pivalaldehyde to regenerate **3b** along with the formation of pivalaldehyde cyanohydrin, which is confirmed by ^{1}H NMR. Thus, the unidentified species assigned with ♠ might be a hemiacetal generated from **3b** and pivalaldehyde cyanohydrin.
5. A series of results indicate that **7** can be reversibly formed from **2** and **3b** under the optimal reaction conditions, and even though the formation of **7** would compete with the reaction of **2** with substrate **1** in the main catalytic process, **7** can be involved in the backward pathway to regenerate **2** and **3b** in a reasonable time scale.

Procedure for preparation of bifunctional 7[15]

To a solution of **3b** (87 μL, 1,0 mmol) in dry CH_2Cl_2 (1.0 mL) was added $TiCl_4$ (0.13 mL, 1.2 mmol) dropwise under argon atmosphere at 0 °C. after being stirred for 10 h at ambient temperature the reaction was quenched with H_2O (3.0 mL), and the mixture was subsequently extracted with CH_2Cl_2 (5.0 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give 3,3,3-trifluoro-2-hydroxy-2-phenylpropanenitrile (**7**).

3,3,3-Trifluoro-2-hydroxy-2-phenylpropanenitrile (7): CAS RN [93923-55-8].

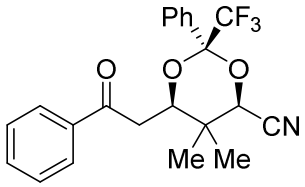


Colorless oil; 95% yield (0.19 g).

^{1}H NMR (C_6D_6) δ 7.45–7.44 (m, 2H), 6.97–6.89 (m, 3H), 3.13 (br s, 1H). ^{13}C NMR (C_6D_6) δ 131.1, 130.8, 128.9, 126.8, 122.2 (q, J = 285.7 Hz), 115.8, 74.2 (q, J = 33.5 Hz). ^{19}F NMR (C_6D_6) δ 83.3.

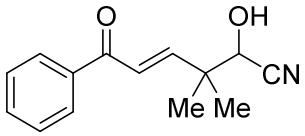
Characterization Data of Products

5,5-Dimethyl-6-(2-oxo-2-phenylethyl)-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4a).



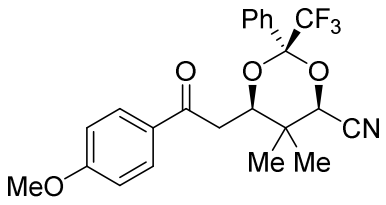
Yield: 81%, >19:1 dr, 90% *ee*, white solid. $[\alpha]_D^{20}$ –4.8 (*c* 1.56, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 2H), 7.63 (m, 1H), 7.59 (m, 2H), 7.55–7.51 (m, 5H), 4.43 (s, 1H), 4.32 (dd, *J* = 9.0, 1.5 Hz, 1H), 3.52 (dd, *J* = 17.0, 9.0 Hz, 1H), 2.88 (dd, *J* = 17.0, 1.5 Hz, 1H), 1.45 (s, 3H), 0.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 196.5, 136.8, 133.7, 130.8, 129.2, 128.8, 128.7, 128.6, 128.3, 120.8 (q, *J* = 284.8 Hz), 99.2 (q, *J* = 32.7 Hz), 74.8, 70.8, 38.5, 36.2, 20.6, 15.3. ^{19}F NMR ($CDCl_3$) δ 77.2. Mp. 144.0–144.6 °C. TLC: R_f 0.14 (hexane/EtOAc = 5:1). IR (KBr): 2969, 1685, 1451, 1325, 1301, 1192, 1116, 1066 cm^{-1}. HRMS Calcd for $C_{22}H_{20}F_3NO_3Na$: $[M+Na]^+$, 426.1287. Found: *m*/*z* 426.1303. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 9.2 min, t_{minor} = 9.9 min.

(*E*)-2-Hydroxy-3,3-dimethyl-6-oxo-6-phenylhex-4-enenitrile (5a).



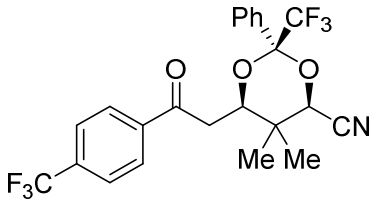
Yield: 99%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 7.04 (d, *J* = 16.0 Hz, 1H), 7.02 (d, *J* = 16.0 Hz, 1H), 4.38 (d, *J* = 6.5 Hz, 1H), 4.30 (br s, 1H), 1.34 (s, 3H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 191.3, 151.3, 137.2, 133.3, 128.72, 128.66, 125.6, 118.3, 68.9, 41.8, 22.8, 21.9. TLC: R_f 0.36 (hexane/EtOAc = 1:1). IR (neat): 3427, 2972, 1668, 1620, 1579, 1448, 1296, 1228, 1070 cm^{-1}. HRMS Calcd for $C_{14}H_{15}NO_2Na$: $[M+Na]^+$, 252.0995. Found: *m*/*z* 252.0993.

6-(2-(4-Methoxyphenyl)-2-oxoethyl)-5,5-dimethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4b).



Yield: 68%, >19:1 dr, 94% *ee*, white solid. $[\alpha]_D^{20}$ –23.8 (*c* 1.26, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.01 (m, 2H), 7.58–7.57 (m, 2H), 7.53–7.51 (m, 3H), 6.99 (m, 2H), 4.41 (s, 1H), 4.30 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.46 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.81 (dd, *J* = 16.5, 2.0 Hz, 1H), 1.44 (s, 3H), 0.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 194.9, 163.9, 130.8, 130.7, 129.9, 129.21, 129.15, 128.8, 120.8 (q, *J* = 284.8 Hz), 114.8, 113.9, 99.2 (q, *J* = 33.9 Hz), 75.0, 70.8, 55.5, 38.1, 36.2, 20.6, 15.2. ^{19}F NMR ($CDCl_3$) δ 77.2. Mp. 90.0–91.0 °C. TLC: R_f 0.18 (hexane/EtOAc = 3:1). IR (KBr): 2980, 2840, 1684, 1597, 1510, 1468, 1268, 1234, 1197, 1093, 1066 cm^{-1}. HRMS Calcd for $C_{23}H_{22}F_3NO_4Na$: $[M+Na]^+$, 456.1393. Found: *m*/*z* 456.1406. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 8.5 min, t_{major} = 10.8 min.

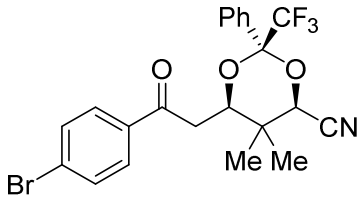
5,5-Dimethyl-6-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4c).



Yield: 84%, >19:1 dr, 67% *ee*, white solid. $[\alpha]_D^{20}$ –2.6 (*c* 1.27, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.13 (m, 2H), 7.79 (m, 2H), 7.58–7.53 (m, 5H), 4.43 (s, 1H), 4.32 (dd, *J* = 9.0, 1.5 Hz, 1H), 3.53 (dd, *J* = 17.0, 9.0 Hz, 1H), 2.88 (dd, *J* = 17.0, 1.5 Hz, 1H), 1.46 (s, 3H), 0.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 195.8, 139.5, 134.9 (q, *J* = 32.6 Hz), 130.9, 129.2, 129.0, 128.6 (2C), 125.8 (q, *J* = 3.8

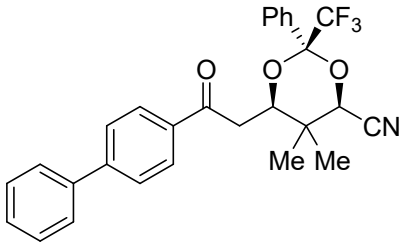
Hz), 123.4 (q, J = 273.3 Hz), 120.7 (q, J = 284.8 Hz), 114.6, 99.3 (q, J = 32.6 Hz), 74.8, 70.7, 38.7, 36.2, 20.5, 15.3. ^{19}F NMR ($CDCl_3$) δ 98.6, 77.2. Mp. 141.0–142.0 °C. TLC: R_f 0.31 (hexane/EtOAc = 3:1). IR (KBr): 3080, 2985, 2909, 1702, 1514, 1474, 1416, 1335, 1074, 1020 cm^{-1}. HRMS Calcd for $C_{23}H_{19}F_6NO_3Na$: $[M+Na]^+$, 494.1161. Found: *m*/*z* 494.1176. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 95.0/5.0, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{major} = 10.6 min, t_{minor} = 11.2 min.

6-(2-(4-Bromophenyl)-2-oxoethyl)-5,5-dimethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4d).



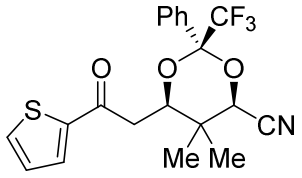
Yield: 85%, >19:1 dr, 87% *ee*, white solid. $[\alpha]_D^{20}$ –18.3 (*c* 1.29, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.67 (m, 2H), 7.57–7.52 (m, 5H), 4.42 (s, 1H), 4.29 (dd, J = 9.0, 2.0 Hz, 1H), 3.47 (dd, J = 16.5, 9.0 Hz, 1H), 2.82 (dd, J = 16.5, 2.0 Hz, 1H), 1.44 (s, 3H), 0.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 195.6, 135.6, 132.1, 130.9, 129.8, 129.2, 129.1, 129.0, 128.7, 120.8 (q, J = 286.7 Hz), 114.7, 99.2 (q, J = 33.6 Hz), 74.8, 70.7, 38.4, 36.2, 20.5, 15.3. ^{19}F NMR ($CDCl_3$) δ 77.2. Mp. 65.5–66.5 °C. TLC: R_f 0.15 (hexane/EtOAc = 5:1). IR (KBr): 3069, 2975, 1693, 1586, 1399, 1324, 1297, 1180, 1120, 1065, 1009 cm^{-1}. HRMS Calcd for $C_{22}H_{19}BrF_3NO_3Na$: $[M+Na]^+$, 504.0393. Found: *m*/*z* 504.0406. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 8.1 min, t_{minor} = 9.1 min.

6-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)-5,5-dimethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4e).



Yield: 79%, >19:1 dr, 90% *ee*, white solid. $[\alpha]_D^{20}$ –31.6 (*c* 0.31, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 2H), 7.51 (m, 2H), 7.66 (m, 2H), 7.62–7.61 (m, 2H), 7.56–7.49 (m, 5H), 7.43 (m, 1H), 4.44 (s, 1H), 4.35 (d, *J* = 9.0 Hz, 1H), 3.55 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.91 (dd, *J* = 16.5, 1.5 Hz, 1H), 1.47 (s, 3H), 0.93 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 196.1, 146.3, 139.6, 135.5, 130.9, 129.2 (2C), 129.0, 128.9 (2C), 128.4, 127.4, 127.3, 120.8 (q, *J* = 284.8 Hz), 114.8, 99.3 (q, *J* = 32.6 Hz), 74.8, 70.8, 38.5, 36.2, 20.6, 15.3. ^{19}F NMR ($CDCl_3$) δ 77.2. Mp. 71.2–72.2 °C. TLC: R_f 0.17 (hexane/EtOAc = 5:1). IR (KBr): 3065, 2977, 1684, 1604, 1326, 1298, 1232, 1199, 1124, 1066 cm^{-1}. HRMS Calcd for $C_{28}H_{24}F_3NO_3Na$: $[M+Na]^+$, 502.1600. Found: *m*/*z* 502.1616. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99.0/1.0, flow rate = 0.7 mL/min, λ = 254 nm, 40 °C): t_{major} = 13.0 min, t_{minor} = 17.4 min.

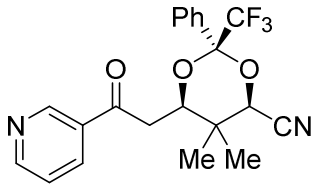
(2*R*,4*R*,6*R*)-5,5-Dimethyl-6-(2-oxo-2-(thiophen-2-yl)ethyl)-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4f).



Yield: 72%, >19:1 dr, 92% *ee*, white solid. $[\alpha]_D^{20}$ –6.6 (*c* 1.13, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.81 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.73 (d, *J* = 5.0, 1,0 Hz, 1H), 7.56–7.51 (m, 5H), 7.19 (dd, *J* = 5.0, 4.0 Hz, 1H), 4.41 (s, 1H), 4.26 (dd, *J* = 9.0, 1.5 Hz, 1H), 3.40 (dd, *J* = 16.0, 9.0 Hz, 1H), 2.85 (dd, *J* = 16.0, 1.5 Hz, 1H), 1.43 (s, 3H), 0.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 189.1, 143.9, 134.7, 132.9, 130.9, 129.2, 129.1, 128.7, 128.4, 120.8 (q, *J* = 284.8 Hz), 114.7, 99.2 (q, *J* = 33.6 Hz), 74.8, 70.7,

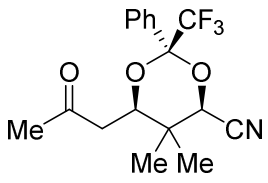
39.2, 36.2, 20.5, 15.2. ^{19}F NMR ($CDCl_3$) δ 77.2. Mp. 59.0–60.0 °C. TLC: R_f 0.11 (hexane/EtOAc = 5:1). IR (KBr): 3073, 2973, 1667, 1520, 1472, 1415, 1358, 1319, 1231, 1110, 1116, 1063, 1004 cm^{-1}. HRMS Calcd for $C_{20}H_{18}F_3NO_3SNa$: $[M+Na]^+$, 432.0852. Found: *m*/*z* 432.0864. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 7.7 min, t_{minor} = 8.5 min.

(2*S*,4*S*,6*S*)-5,5-Dimethyl-6-(2-oxo-2-(pyridin-3-yl)ethyl)-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4g).



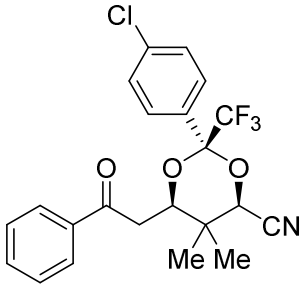
Yield: 43%, >19:1 dr, 70% *ee*, white solid. $[\alpha]_D^{20}$ +4.8 (*c* 0.82, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 9.24 (s, 1H), 8.85 (d, *J* = 3.0 Hz, 1H), 8.31 (ddd, *J* = 8.0, 2.0, 2.0 Hz 1H), 7.57–7.52 (m, 5H), 7.49 (m, 1H), 4.43 (s, 1H), 4.31 (dd, *J* = 9.5, 2.0 Hz, 1H), 3.52 (dd, *J* = 17.0, 9.5 Hz, 1H), 2.88 (dd, *J* = 17.0, 2.0 Hz, 1H), 1.45 (s, 3H), 0.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 195.6, 154.0, 149.7, 135.6, 132.2, 130.9, 129.2, 129.0, 128.7, 123.7, 120.7 (q, *J* = 284.8 Hz), 114.6, 99.3 (q, *J* = 33.6 Hz), 74.7, 70.7, 38.7, 36.2, 20.6, 15.3. ^{19}F NMR ($CDCl_3$) δ 77.2. Mp. 100.5–101.5 °C. TLC: R_f 0.11 (hexane/EtOAc = 1:1). IR (KBr): 3078, 2976, 1701, 1688, 1587, 1420, 1325, 1232, 1180, 1124, 1068 cm^{-1}. HRMS Calcd for $C_{21}H_{19}F_3N_2O_3Na$: $[M+Na]^+$, 427.1240. Found: *m*/*z* 427.1251. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 15.2 min, t_{major} = 22.3 min.

5,5-Dimethyl-6-(2-oxopropyl)-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4h).



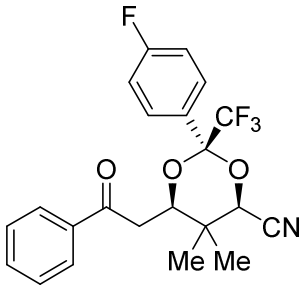
Yield: 73%, 6.7:1 dr, 75% *ee*, colorless oil. $[\alpha]_D^{20}$ +31.1 (*c* 1.02, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.58–7,52 (m, 5H), 4.36 (s, 1H), 4.10 (dd, *J* = 9.5, 1.5 Hz, 1H), 2.88 (dd, *J* = 16.5, 9.5 Hz, 1H), 2.45 (dd, *J* = 16.5, 1.5 Hz, 1H), 1.33 (s, 3H), 0.83 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 205.1, 130.9, 129.2, 129.1, 128.8, 120.8 (q, *J* = 284.8 Hz), 114.7, 99.2 (q, *J* = 33.6 Hz), 74.5, 70.7, 42.8, 35.9, 31.6, 20.4, 15.1. ^{19}F NMR ($CDCl_3$) δ 77.2. TLC: R_f 0.14 (hexane/EtOAc = 3:1). IR (neat): 3434, 3066, 2976, 1725, 1471, 1451, 1401, 1378, 1360, 1323, 1294, 1194, 1100, 1070 cm^{-1}. HRMS Calcd for $C_{17}H_{18}F_3NO_3Na$: $[M+Na]^+$, 364.1131. Found: *m*/*z* 364.1143. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.0 min, t_{major} = 6.7 min.

2-(4-Chlorophenyl)-5,5-dimethyl-6-(2-oxo-2-phenylethyl)-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4i).



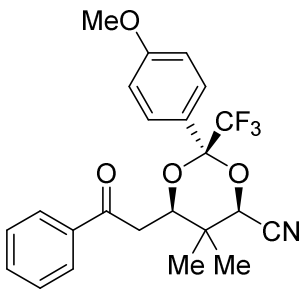
Yield: 89%, >19:1 dr, 84% *ee*, colorless oil. $[\alpha]_D^{20}$ –22.4 (*c* 1.65, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 8.01 (m, 2H), 7.64 (m, 1H), 7.58 (m, 2H), 7.55–7.51 (m, 4H), 4.38 (s, 1H), 4.30 (dd, *J* = 9.0, 1.5 Hz, 1H), 3.50 (dd, *J* = 17.0, 9.0 Hz, 1H), 2.90 (dd, *J* = 17.0, 1.5 Hz, 1H), 1.44 (s, 3H), 0.93 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 196.2, 137.3, 136.7, 133.8, 131.4, 129.6, 128.8, 128.2, 127.8, 120.6 (q, *J* = 284.8 Hz), 114.5, 98.9 (q, *J* = 33.5 Hz), 74.7, 70.8, 38.3, 36.2, 20.5, 15.2. ^{19}F NMR ($CDCl_3$) δ 77.2. TLC: R_f 0.23 (hexane/EtOAc = 5:1). IR (neat): 2976, 1695, 1598, 1491, 1450, 1402, 1323, 1296, 1180, 1119, 1009 cm^{-1}. HRMS Calcd for $C_{22}H_{19}ClF_3NO_3Na$: $[M+Na]^+$, 460.0898. Found: *m*/*z* 460.0915. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 8.2 min, t_{minor} = 12.1 min.

2-(4-Fluorophenyl)-5,5-dimethyl-6-(2-oxo-2-phenylethyl)-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4j).



Yield: 81%, >19:1 dr, 90% *ee*, white solid. $[\alpha]_D^{20}$ –2.9 (*c* 1.55, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.01 (m, 2H), 7.66–7.60 (m, 3H), 7.53 (m, 2H), 7.23 (m, 2H), 4.40 (s, 1H), 4.31 (dd, *J* = 9.0, 1.5 Hz, 1H), 3.51 (dd, *J* = 17.0, 9.0 Hz, 1H), 2.90 (dd, *J* = 17.0, 1.5 Hz, 1H), 1.44 (s, 3H), 0.93 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 196.3, 164.3 (d, J = 250.3 Hz), 136.7, 133.8, 131.1, 128.8, 128.2, 125.0 (d, *J* = 2.8 Hz), 120.7 (q, *J* = 285.7 Hz), 116.4 (d, *J* = 22.0 Hz), 114.6, 98.8 (q, *J* = 32.7 Hz), 74.6, 70.8, 38.3, 36.2, 20.6, 15.2. ^{19}F NMR ($CDCl_3$) δ 77.1, 52.0. Mp. 112.0–113.0 °C. TLC: R_f 0.20 (hexane/EtOAc = 5:1). IR (KBr): 3081, 2974, 1683, 1600, 1513, 1450, 1402, 1379, 1320, 1160, 1133, 1070 cm^{-1}. HRMS Calcd for $C_{22}H_{19}F_4NO_3Na$: $[M+Na]^+$, 444.1193. Found: *m*/*z* 444.1208. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 8.0 min, t_{minor} = 11.6 min.

2-(4-Methoxyphenyl)-5,5-dimethyl-6-(2-oxo-2-phenylethyl)-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (4k).



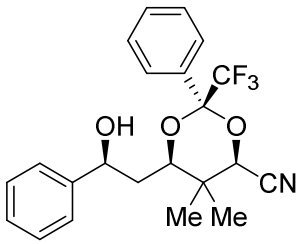
Yield: 32%, >19:1 dr, 92% *ee*, white solid. $[\alpha]_D^{20}$ –18.1 (*c* 0.69, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.01 (m, 2H), 7.63 (m, 1H), 7.54–7.49 (m, 3H), 7.03 (m, 1H), 4.44 (s, 1H), 4.33 (dd, *J* = 9.0, 2.0

Hz, 1H), 3.86 (s, 3H), 3.50 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.86 (dd, *J* = 16.5, 2.0 Hz, 1H), 1.43 (s, 3H), 0.92 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 196.6, 161.5, 136.9, 133.7, 130.3, 128.8, 128.3, 120.9 (q, *J* = 284.8 Hz), 120.7, 114.9, 114.5, 99.3 (q, *J* = 33.6 Hz), 74.6, 70.6, 55.4, 38.4, 36.2, 20.6, 15.3. ^{19}F NMR ($CDCl_3$) δ 76.9. Mp. 54.5–55.3 °C. TLC: R_f 0.26 (hexane/EtOAc = 3:1). IR (KBr): 2977, 1701, 1610, 1514, 1470, 1450, 1296, 1231, 1169, 1107 cm^{-1}. HRMS Calcd for $C_{23}H_{22}F_3NO_4Na$: $[M+Na]^+$, 456.1393. Found: *m*/*z* 456.1407. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 9.5 min, t_{minor} = 13.1 min.

Procedure for synthesis of 9[11]

To a 30-mL round-bottom flask, **4a** (90% *ee*, 40 mg, 0.10 mmol), Et_2O (10 mL), and $EuCl_3$ (0.13 g, 0.50 mmol) were sequentially added. After the mixture was stirred at –78 °C for 0.5 h under argon atmosphere, lithium borohydride (0.12 mg, 0.50 mmol) was added and the solution was stirred at the same temperature for 6 h. The reaction was quenched with 10 mL of H_2O, and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1 to 3:1) as an eluent gave 6-(2-Hydroxy-2-phenylethyl)-5,5-dimethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (**9**).

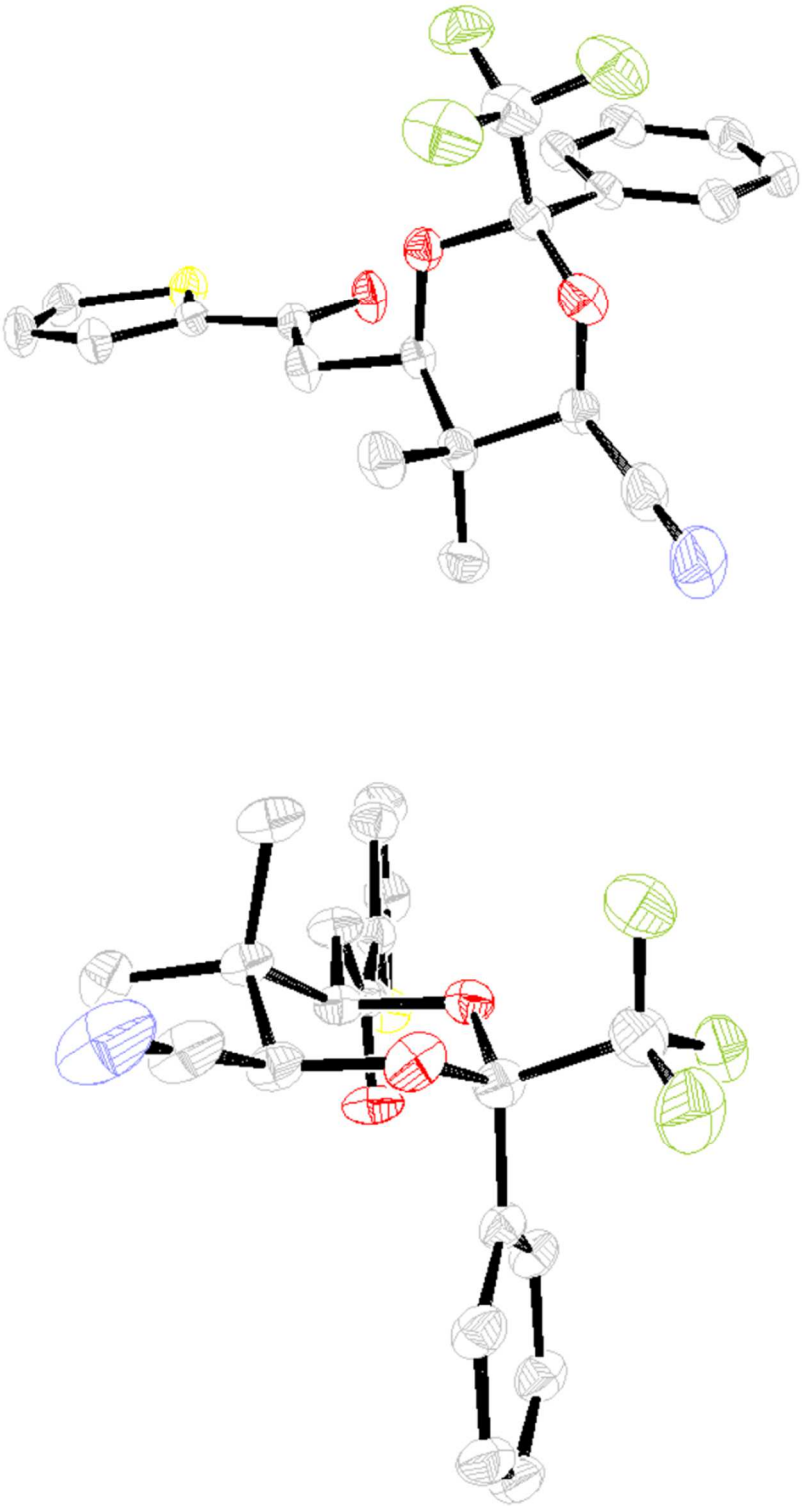
6-(2-Hydroxy-2-phenylethyl)-5,5-dimethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxane-4-carbonitrile (9).



Yield: 96% (39 mg), 90% *ee*, 11:1 dr, colorless oil. $[\alpha]_D^{20}$ +23.8 (*c* 0.86, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ 7.53–7.46 (m, 5H), 7.41–7.36 (m, 4H), 7.32 (m, 1H), 4.99 (dd, *J* = 7.0, 5.5 Hz, 1H), 4.28 (s, 1H), 3.59 (dd, *J* = 9.5, 1.5 Hz, 1H), 2.81 (br s, 1H), 2.17 (ddd, *J* = 15.0, 9.5, 7.0 Hz, 1H), 2.00 (ddd, *J* = 15.0, 5.5, 1.5 Hz, 1H), 1.35 (s, 3H), 0.79 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 142.8, 130.9, 129.4, 129.2, 128.8, 128.5, 128.2, 126.2, 120.8 (q, *J* = 284.8 Hz), 114.6, 99.1 (q, *J* = 32.7 Hz), 78.5, 73.1, 70.8, 38.1, 36.5, 20.4, 14.8. ^{19}F NMR ($CDCl_3$) δ 77.2. TLC: R_f 0.18 (hexane/EtOAc = 3:1). IR (neat): 3408, 3034, 2977, 2885, 1470, 1452, 1323, 1197, 1113, 1067, 1004, 909 cm^{-1}. HRMS Calcd for $C_{22}H_{22}F_3NO_3Na$: $[M+Na]^+$, 428.1444. Found: *m*/*z* 428.1448. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95.0/5.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 14.3 min, t_{minor} = 15.2 min.

ORTEP Drawing of 4f



A. Crystal Data

Empirical Formula	$C_{20}H_{18}F_3NO_3S$
Formula Weight	409.42
Crystal Color, Habit	Colorless, Prism
Crystal Dimensions	0.420 × 0.300 × 0.200 mm
Crystal System	Monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 8.8716(8) Å
	b = 9.2031(8) Å
	c = 12.079(1) Å
	β = 100.236(7) °
	V = 970.5(2) $Å^3$
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.401 g/cm^3
F_{000}	424.00
μ(MoKα)	2.151 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å)
	Graphite monochromated
Voltage, Current	50 kV, 12mA
Temperature	20.0 °C
Detector Aperture	75 mm (diameter)
Data Images	540 exposures
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°

Detector Position	50.00 mm
Pixel Size	0.146 mm
$2\theta_{max}$	55.0°
No. of Reflections Measured	Total: 10326
	Unique: 4450 (R_{int} = 0.0225)
	Friedel pairs: 2082
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.840–0.958)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (F_0^2 - F_c^2)^2$
Least Squares Weights	$w = 1/[\sigma^2(F_0^2) + (0.0446 \cdot P)^2$ $+ 0.1068 \cdot P]$ where $P = (Max(F_0^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	55.0°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	4450
No. Variables	254
Reflection/Parameter Ratio	17.52
Residuals: R1 (I>2.00σ(I))	0.0414
Residuals: R (All reflections)	0.0511
Residuals: wR2 (All reflections)	0.0936
Goodness of Fit Indicator	1.034
Flack Parameter (Friedel pairs = 2082)	0.03(7)
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.19 $e^-/Å^3$
Minimum peak in Final Diff. Map	–0.18 $e^-/Å^3$

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Chapter 5

Kinetic Resolution of Acylsilane Cyanohydrins via Organocatalytic Cycloetherification

An asymmetric cyanation of acylsilanes involving the in situ formation of chiral acylsilane cyanohydrins followed by their kinetic resolution via organocatalytic cycloetherification is described. The highly enantio- and diastereoselective cycloetherification was crucial for achieving a high efficiency in the kinetic resolution. Consequently, acylsilane cyanohydrins containing a tetrasubstituted chiral carbon atom bearing silyl, cyano, and hydroxy groups were obtained in an enantioenriched form. This protocol therefore offers an efficient catalytic approach to optically active acylsilane cyanohydrins, which exhibit potential as chiral building blocks for the synthesis of pharmaceutically relevant chiral organosilanes.

Introduction

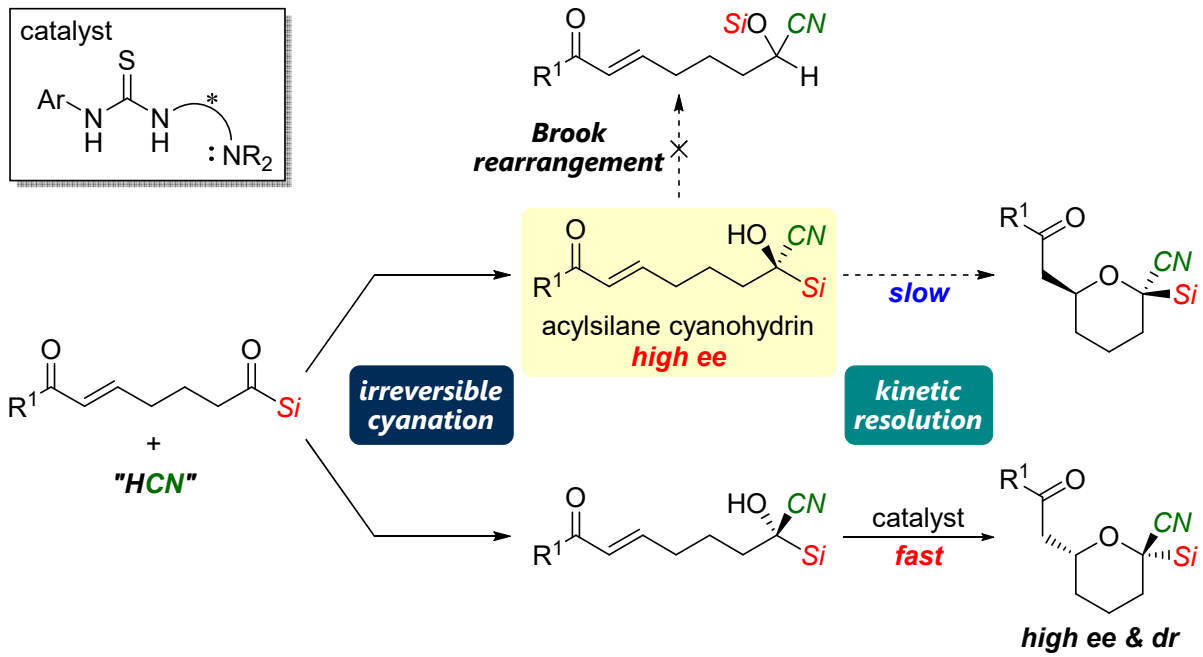
The catalytic asymmetric cyanation of ketones constitutes a straightforward method for the construction of tetrasubstituted chiral carbon centers, which is of particular interest in synthetic organic chemistry.[1,2] Indeed, due to the synthetic utility of optically active tertiary alcohols bearing a cyano group,[3,4] various methods for their asymmetric synthesis have been reported to date.[1,2a–c] However, the asymmetric cyanation of acylsilanes has been limited to a few enzymatic approaches employing only one example substrate,[5] although several reports into the catalytic asymmetric addition of other carbon nucleophiles to acylsilanes have recently appeared due to the increasing interest in silicon-containing small molecules in drug design and development.[6–8] One possible reason for the lack of such methods is the competing Brook rearrangement,[9] which is known to easily take place under basic conditions.[10] Thus, as an alternative synthetic approach to optically active acylsilane cyanohydrins, the author focused on their kinetic resolution.[11] In this context, it would be efficient to develop a kinetic resolution protocol involving the in situ formation of chiral cyanohydrins from more easily available acylsilanes under nearly neutral conditions, which prevent the Brook rearrangement from taking place.

Recently, Asano and Matsubara developed a kinetic resolution of chiral tertiary alcohols bearing an α,β-unsaturated ketone moiety via an organocatalytic intramolecular oxy-Michael addition procedure.[12] They also reported a highly enantio- and diastereoselective cycloetherification reaction using cyanohydrins generated in situ from ketones as chiral tertiary alcohols;[13] this process quantitatively afforded optically active cyclic products by dynamic kinetic resolution, due to the reversible nature of cyanohydrin formation. The author therefore envisaged that these methods could be applied in the asymmetric cyanation of acylsilanes via classical kinetic resolution to irreversibly afford optically active acylsilane cyanohydrins as the cyanation of acylsilanes is more favorable than that of normal ketones (Scheme 1).[14,15]

According to this reaction design, the obtained chiral acylsilane cyanohydrins could then undergo organocatalytic mutation from a single enantiomer by virtue of the highly enantio- and

diastereoselective nature of the cycloetherification reaction. Consequently, the mismatched enantiomer of the acylsilane cyanohydrin, which contains a tetrasubstituted chiral carbon center bearing silyl, cyano, and hydroxy groups, would be obtained in an enantioenriched form. Thus, the author herein presents an efficient protocol for the enantioselective cyanation of acylsilanes involving kinetic resolution via an asymmetric cycloetherification process based on the use of bifunctional aminothiourea catalysts.[16,17]

Scheme 1. Asymmetric Cyanation of Acylsilanes via Organocatalytic Cycloetherification

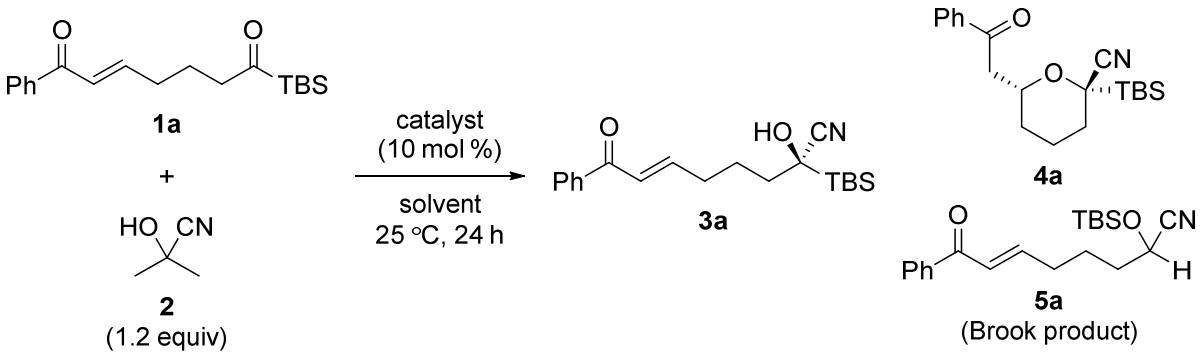


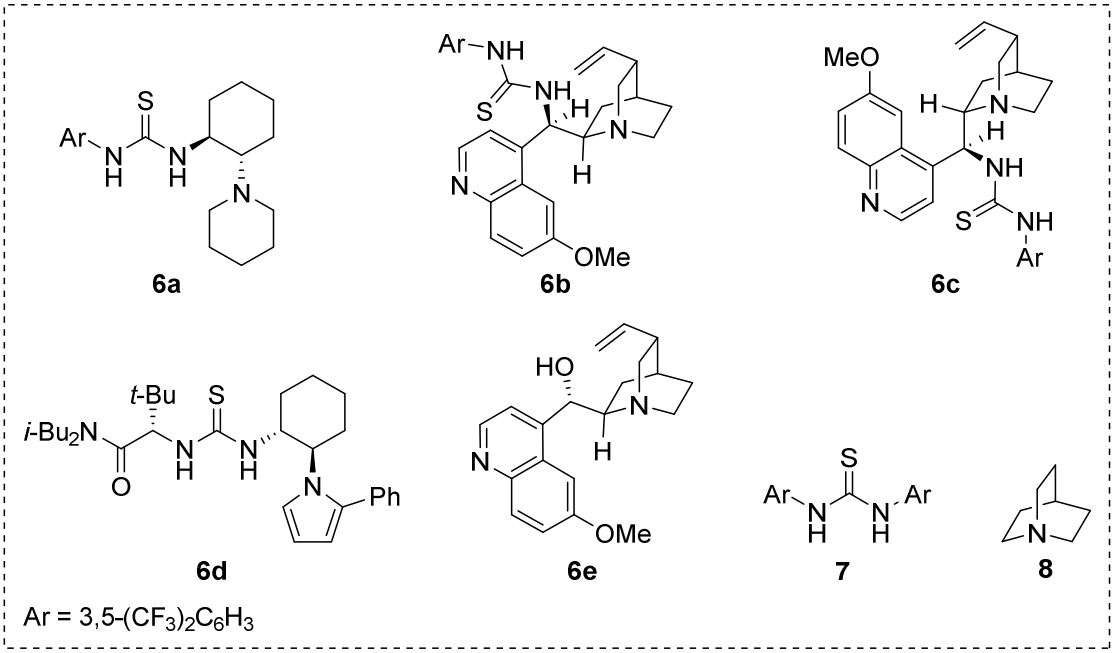
Results and Discussion

The author initially investigated the reaction using acylsilane **1a**, which contains an α,β-unsaturated ketone moiety, and acetone cyanohydrin (**2**) as the cyanation reagent. In the presence of bifunctional aminothiourea catalyst **6a**, which bears a cyclohexanediamine moiety, the desired acylsilane cyanohydrin **3a** was obtained in only 5% yield, although tetrahydropyran derivative **4a**

was obtained in 61% yield (Table 1, entry 1), in addition to a significant amount of *O*-silylated cyanohydrin **5a**. The formation of **5a** indicates that the in situ generated acylsilane cyanohydrin **3a** rapidly underwent a Brook rearrangement as a competing side reaction. The author then investigated the use of other catalysts and found that the quinidine-derived aminothiourea catalyst **6b** afforded **3a** in a high yield and with excellent enantioselectivity (Table 1, entry 2); it is notable that the formation of Brook product **5a** was largely suppressed under these reaction conditions. In addition, when the reaction was carried out using quinine-derived aminothiourea catalyst **6c**, which is a pseudo-enantiomer of **6b**, the opposite enantiomer of **3a** was obtained in high enantioselectivity (Table 1, entry 3). In contrast, catalyst **6d**, which contains a significantly less basic nitrogen atom, displayed no catalytic activity for this transformation (Table 1, entry 4). Furthermore, the reaction using quinidine (**6e**) as the catalyst exclusively afforded Brook product **5a** (Table 1, entry 5). The same trend was also observed when achiral thiourea **7** was employed in combination with quinuclidine (**8**) (Table 1, entry 6). These results imply that the bifunctionality of the catalysts containing thiourea and tertiary amino groups on the optimized molecular skeleton is crucial for obtaining the desired acylsilane cyanohydrin **3a** in high yields.[18,19] In addition, the author also found that the solvent significantly influences the reaction outcomes (Table 1, entries 7–12). Specifically, halogenated solvents and toluene gave satisfactory results with respect to both reactivity and enantioselectivity (Table 1, entries 2, 7, and 8). In contrast, the reaction in *n*-hexane afforded only trace quantities of the cyclized product **4a**, and thus **3a** was obtained quantitatively but with a low enantioselectivity (Table 1, entry 9).[20] Reactions in EtOAc, MeCN, and THF resulted in a reduced reactivity for the cycloetherification reaction (Table 1, entries 10 and 11) or no conversion of starting material **1a** (Table 1, entry 12).

Table 1. Optimization of Reaction Conditions[a]





Entry	Catalyst	Solvent	Yield of **3a** (%)[b]	*ee* of **3a** (%)	Yield of **4a** (%)[b]	Yield of **5a** (%)[b]
1	**6a**	CH_2Cl_2	5	–66	61	34
2	**6b**	CH_2Cl_2	49	96	48	2
3	**6c**	CH_2Cl_2	44	–97	52	4
4	**6d**	CH_2Cl_2	<1	–	<1	<1
5	**6e**	CH_2Cl_2	<1	–	<1	99
6	**7** + **8**	CH_2Cl_2	<1	–	5	77
7	**6b**	$CHCl_3$	52	92	47	1

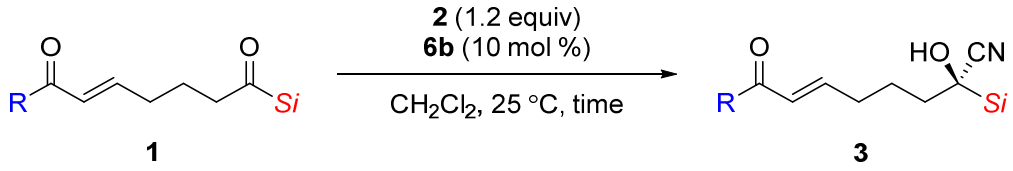
Table 1. (Continued)

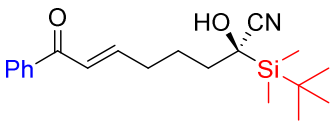
8	**6b**	Toluene	49	95	49	2
9	**6b**	*n*-hexane	>95	14	3	2
10	**6b**	EtOAc	41	58	13	2
11	**6b**	MeCN	33	63	14	24
12	**6b**	THF	<1	–	<1	<1

[a]Reactions were run using **1a** (0.15 mmol), **2** (0.18 mmol), and the catalyst (0.015 mmol) in the solvent (0.30 mL). [b]Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard.

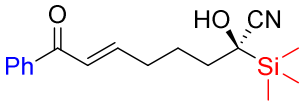
With the optimal conditions in hand, the author moved on to explore the substrate scope of the reaction (Table 2). In the presence of aminothiourea catalyst **6b**, acylsilanes **1a**–**1c** bearing trialkylsilyl groups were found to be suitable substrates for this reaction, and the corresponding acylsilane cyanohydrins **3a**–**3c** were obtained in good yields with high enantioselectivities. In the cases of substrates bearing benzyl- and phenyl-substituted silyl groups, the cycloetherification reaction was faster, and the prompt formation of acylsilane cyanohydrins by the use of larger quantities of **2** was necessary; the corresponding acylsilane cyanohydrins **3d** and **3e** were obtained in high enantioselectivities. The influence of the enone moiety was also examined. Indeed, products **3f** and **3g**, containing electron-rich and electron-deficient enone moieties, respectively, were obtained in high yields, and the reaction of electron-rich substrate **1f** resulted in a further enhanced enantioselectivity. It is also noteworthy that carboxylic acid derivatives could be employed as substrates, affording the corresponding ester **3h** and thioester **3i**. Although phenyl ester **1h** reacted more slowly and with moderate enantioselectivity, phenyl thioester **1i** smoothly afforded the corresponding product **3i** in a high yield with good enantioselectivity. Due to the utility of carboxylic acid derivatives as synthetic intermediates, the potential of these compounds as building blocks is enhanced, providing approaches to various chiral organosilanes. The absolute configuration of **3i** was determined by X-ray crystallography, and the configurations of all other materials were assigned analogously.

Table 2. Substrate Scope[a]

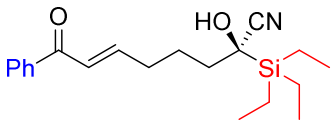




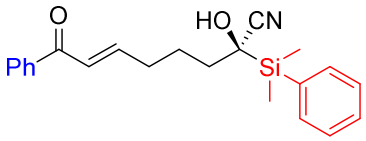
3a
18 h, 49%, 96% *ee*



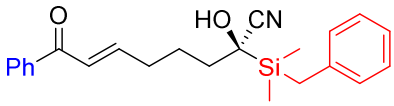
3b
6 h, 41%, 93% *ee*



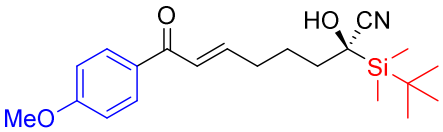
3c
24 h, 35%, 95% *ee*



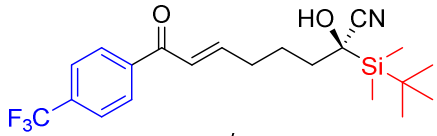
3d[b]
6 h, 29%, 83% *ee*



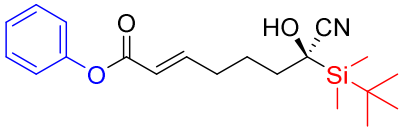
3e[b]
3 h, 37%, 91 % *ee*



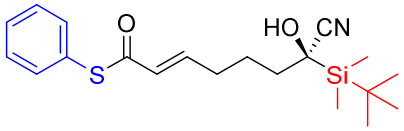
3f
24 h, 47%, 93% *ee*



3g[b]
12 h, 47%, 83% *ee*



3h
72 h, 48%, 63% *ee*



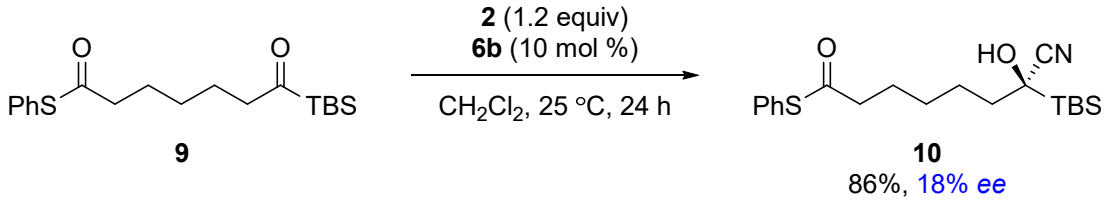
3i
24 h, 45%, 94% *ee*

[a]Reactions were run using **1** (0.15 mmol), **2** (0.18 mmol), and **6b** (0.015 mmol) in CH_2Cl_2 (0.30 mL). Yields represent the material isolated after silica gel column chromatography. [b]3.0 equivalents of **2** (0.45 mmol) were used.

To examine whether cyanohydrin formation via a 1,2-addition mechanism proceeds enantioselectively in the presence of **6b**, the reaction was carried out using acylsilane **9**, which does not contain a Michael acceptor, under the optimized conditions (Scheme 2). Indeed, cyanohydrin **10** was obtained in a high yield, but the enantioselectivity was significantly lower than that of the

reaction of **1i** (Table 2). Hence, the 1,2-addition process appeared not to be the enantiodetermining step.

Scheme 2. Cyanohydrin Formation from Acylsilane 9



The yield of **4a** and the enantiomeric excess of **3a** were then monitored (Figure 1). The reaction profiles shown in Figure 1a indicate that the enantiomeric excess of **3a** increased as **4a** formed, with 96% *ee* being reached when the yield of **4a** was approximately 50%. This trend is consistent with typical kinetic resolution reaction profiles.[11] The same experiments were also carried out using isolated racemic cyanohydrin **3a** as a substrate (Figure 1b). The reaction profiles are similar to those shown in Figure 1a, although the initial quantity of **3a** was larger in the reaction depicted in Figure 1b. These results support the reaction design shown in Scheme 1, in that cyanohydrin formation via a 1,2-addition mechanism proceeds irreversibly, and the subsequent highly stereoselective cycloetherification is crucial for obtaining **3** in high enantioselectivity.

Furthermore, a gram-scale synthesis of **3i** was also attempted (Scheme 3). In this case, the reaction proceeded smoothly using 2.4 g (6.9 mmol) of **1i** under the optimized conditions, and 1.1 g (2.8 mmol, 41%) of **3i** was obtained in 98% *ee*. To demonstrate the utility of the products, further transformations of **3i** were carried out (Scheme 4). More specifically, the Fukuyama reduction[21] of **3i** afforded **11**, which bears a synthetically useful formyl group. In addition, the selective 1,4-reduction of **3i** was accomplished, with its thioester moiety remaining intact, using Pd/C and hydrogen gas to give **10** in high enantiomeric purity; this product failed to be synthesized by the direct cyanation method outlined in Scheme 2. Moreover, modification of the tertiary alcohol moiety of **10** with *p*-toluenesulfonyl isocyanate proceeded smoothly, and the resulting

chiral carbamate **12** was further transformed using lithium aluminum hydride into heterocyclic compound **13** containing a tetrasubstituted chiral carbon bearing a silyl group without any loss of enantiomeric purity.

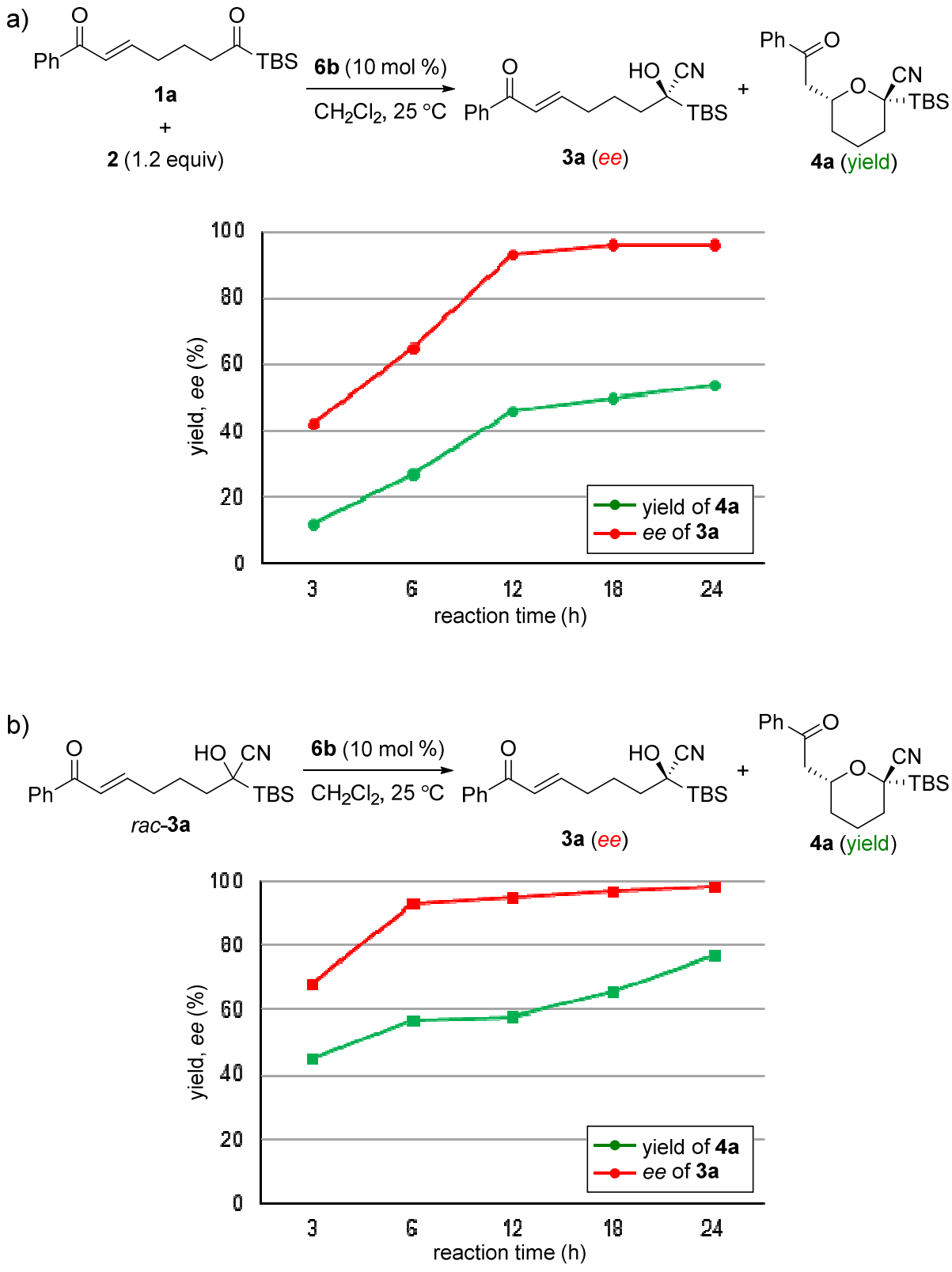
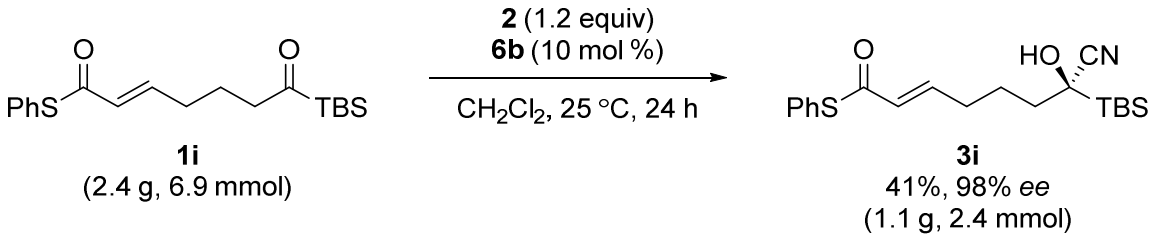
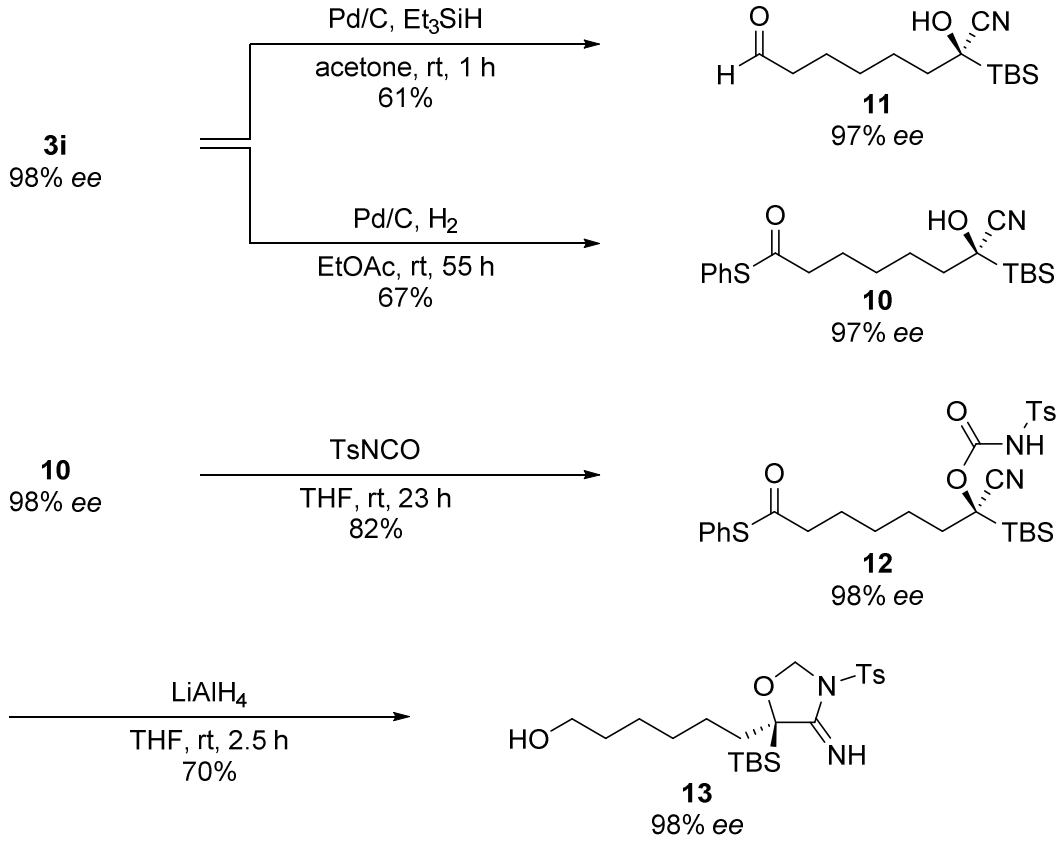


Figure 1. Reaction profiles for the asymmetric synthesis of **3a**.

Scheme 3. Gram-scale Synthesis of 3i



Scheme 4. Transformations of 3i



Conclusion

In conclusion, the author successfully developed a novel, highly enantioselective method for the cyanation of acylsilanes. This route involved the kinetic resolution of in situ generated

acylsilane cyanohydrins, in addition to a highly enantio- and diastereoselective organocatalytic cycloetherification reaction, which was crucial to obtaining highly efficient transformations. To the best of the author's knowledge, this is the first example of a non-enzymatic catalytic asymmetric approach to optically active acylsilane cyanohydrins, which are otherwise difficult to prepare. Interestingly, the obtained products contain a densely functionalized tetrasubstituted stereogenic carbon center bearing silyl, cyano, and hydroxy groups, and can be employed in the synthesis of pharmaceutically relevant chiral organosilanes. This work therefore offers a new avenue for the catalytic asymmetric construction of synthetically challenging tetrasubstituted chiral carbons, which can serve as structural platforms for accumulating multiple functionalities on this chiral carbon center.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without further purifications.

Experimental Procedure

General procedure for asymmetric synthesis of acylsilane cyanohydrins 3

To a solution of acylsilane **1** (0.15 mmol) in CH_2Cl_2 (0.30 mL) were added acetone cyanohydrin (**2**, 17 μL, 0.18 mmol) and bifunctional organocatalyst **6b** (8.9 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded the corresponding acylsilane cyanohydrin **3** and tetrahydropyran **4**.

General procedure for synthesis of racemic acylsilane cyanohydrins rac-3

To a solution of **1** (0.10 mmol) in 2-propanol (0.20 mL) were added trimethylsilyl cyanide (15 μL, 0.12 mmol) and 1,4-diazabicyclo[2.2.2]octane (1.1 mg, 0.010 mmol), and the resulting mixture was stirred at ambient temperature for 3 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded the corresponding racemic acylsilane cyanohydrin *rac*-**3**.

General procedure for synthesis of racemic tetrahydropyran (rac-4)

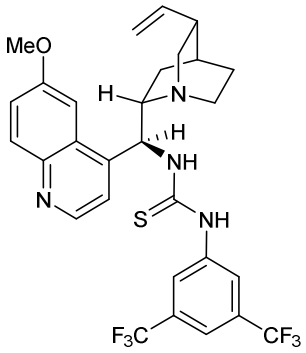
To a solution of **1** (0.10 mmol) in dichloromethane (0.20 mL) were added acetone cyanohydrin (**2**, 18.3 μL, 0.20 mmol) and 1,3-bis[3,5-bis(trifluoromethyl)-phenyl]thiourea as catalysts (1.1 mg, 0.010 mmol), and the resulting mixture was stirred at ambient temperature for 24 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded the corresponding racemic tetrahydropyran **4**.

Procedure for reaction of 9

To a solution of acylsilane **9** (53 mg, 0.15 mmol) in CH_2Cl_2 (0.30 mL) were added acetone cyanohydrin (**2**, 17 μL, 0.18 mmol) and bifunctional organocatalyst **6b** (8.9 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1) as an eluent afforded **10**.

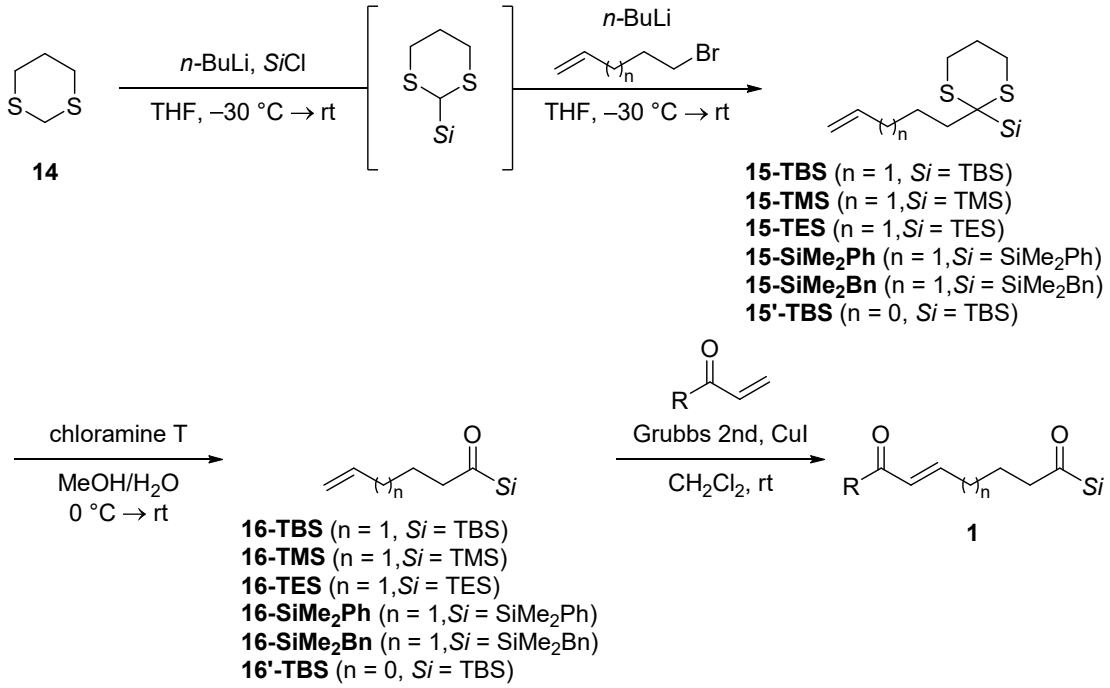
Procedure for preparation of bifunctional catalyst 6c

Bifunctional organocatalysts **6b** and **6c** was prepared by the procedure described in Experimental Section of Chapter 4. The characterization results of **6c** is below.



6c. White solid; 27% yield (for 2steps from quinine, 0.80 g). $[\alpha]_D^{23}$ –99.0 (*c* 1.24, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.82 (br s, 2H), 7.68 (s, 1H), 7.62 (br s, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.18 (br s, 1H), 5.84 (br s, 1H), 5.70 (m, 1H), 5.01 (m, 2H), 3.96 (s, 3H), 3.37 (br s, 1H), 3.30 (br s, 1H), 3.18 (m, 1H), 2.79 (br s, 2H), 2.35 (br s, 1H), 1.72 (s, 1H), 1.68 (m, 2H), 1.41 (m, 1H), 0.92 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 181.0, 158.2, 147.4, 144.8, 144.0, 140.6, 140.0, 132.6 (q, *J* = 33.6 Hz), 131.8, 127.9, 123.6, 122.9 (q, *J* = 273.0 Hz), 122.0, 118.8, 115.1, 102.1, 61.2, 55.7, 54.9, 41.3, 39.0, 27.5, 27.1, 25.7. Mp. 121.0–121.5 °C. IR (KBr): 3220, 2946, 2360, 1623, 1510, 1475, 1384, 1279, 1180, 1134, 1032, 959, 917, 885, 850, 683 cm^{-1}. HRMS Calcd for $C_{29}H_{29}F_6N_4OS$: $[M+H]^+$, 595.1966. Found: *m*/*z* 595.1961.

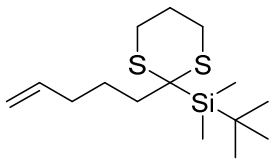
General procedure for preparation of 1



General procedure for preparation of **15**[22]

To a solution of **14** (6.0 g, 50 mmol) in dry THF (100 mL) was added *n*-butyllithium (31 mL, 1.60 M in hexane, 50 mmol) dropwise at –30 °C. After the mixture was stirred for 0.5 h, a chlorosilane (30 mmol) in dry THF (20 mL) was added, and the reaction was allowed to warm to ambient temperature. After being stirred for additional 24 h, the reaction mixture was cooled to –30 °C, and then *n*-butyllithium (34 mL, 1.63 M in hexane, 55 mmol) was added to the reaction mixture. After the mixture was stirred for 1 h, alkenyl bromide (60 mmol) in dry THF (20 mL) was added dropwise at –30 °C. The reaction mixture was allowed to warm to ambient temperature over 5 h, and then the reaction was quenched with H_2O (100 mL). The aqueous layers were extracted with Et_2O (50 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 30:1) as an eluent gave **15**.

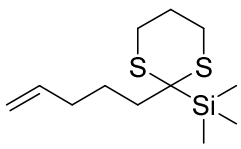
***tert*-Butyldimethyl(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)silane (15-TBS)**.



Colorless oil; 99% yield (from **14**).

^{1}H NMR ($CDCl_3$) δ 5.83 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.04 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.98 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.04 (m, 2H), 2.39 (m, 2H), 2.32 (m, 2H), 2.11 (dt, *J* = 7.0, 7.0 Hz, 2H), 2.02 (m, 1H), 1.88 (m, 1H), 1,41 (m, 2H), 1.03 (s, 9H), 0.20 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 138.5, 114.9, 40.9, 37.3, 34.1, 28.2, 27.2, 25.0, 23.4, 19.7, –5.3. TLC: R_f 0.23 (hexane/EtOAc = 30:1). IR (neat): 2932, 2905, 2857, 1472, 1465, 1364, 1250, 911, 822, 759 cm^{-1}. HRMS Calcd for $C_{15}H_{30}S_2SiNa$: $[M+Na]^+$, 325.1450. Found: *m*/*z* 325.1446.

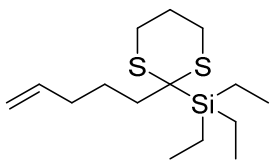
Trimethyl(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)silane (15-TMS): CAS RN [174710-29-3].



Colorless oil; 89% yield (from **14**).

^{1}H NMR ($CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.02 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.97 (dd, *J* = 10.0, 1.0 Hz, 1H), 3.00 (m, 2H), 2.41 (m, 2H), 2.18 (m, 2H), 2.09 (dt, *J* = 7.0, 7.0 Hz, 2H), 2.02 (m, 1H), 1.86 (m, 1H), 1.56 (m, 2H), 0.16 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 138.4, 114.9, 38.6, 36.5, 34.0, 26.8, 25.0, 23.2, –2.6.

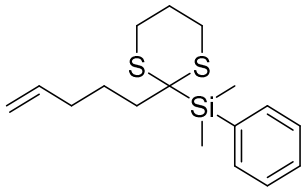
Triethyl(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)silane (15-TES).



Colorless oil; 99% yield (from **14**).

^{1}H NMR ($CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.01 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.95 (dd, *J* = 10.0, 1.0 Hz, 1H), 3.00 (m, 2H), 2.34 (m, 2H), 2.20 (m, 2H), 2.08 (dt, *J* = 7.0, 7.0 Hz, 2H), 2.00 (m, 1H), 1.86 (m, 1H), 1.57 (m, 2H), 1.02 (t, *J* = 8.0 Hz, 9H), 0.76 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 138.3, 114.8, 39.5, 36.7, 34.0, 27.0, 25.1, 23.2, 8.0, 2.8. TLC: R_f 0.10 (hexane/EtOAc = 50:1). IR (neat): 3077, 2950, 2909, 2876, 1457, 1415, 1269, 1237, 1010, 910, 719 cm^{-1}. HRMS Calcd for $C_{15}H_{30}S_2SiNa$: $[M+Na]^+$, 325.1450. Found: *m*/*z* 325.1445.

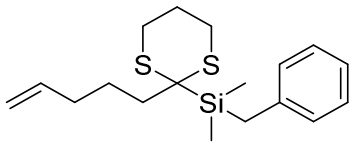
Dimethyl(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)(phenyl)silane (15-SiMe$_2$Ph).



Colorless oil; 64% yield (from **14**).

^{1}H NMR ($CDCl_3$) δ 7.67 (m, 2H), 7.43–7.37 (m, 3H), 5.73 (ddt, *J* = 17.5, 10.5, 6.5 Hz, 1H), 4.99–4.92 (m, 2H), 2.97 (m, 2H), 2.43 (m, 2H), 2.09 (m, 2H), 2.04–1.97 (m, 3H), 1.88 (m, 1H), 1.50 (m, 2H), 0.53 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 138.4, 135.5, 134.7, 129.5, 127.5, 114.7, 38.9, 36.5, 33.9, 26.5, 24.8, 23.6, –4.0. TLC: R_f 0.18 (hexane/EtOAc = 30:1). IR (neat): 3070, 2942, 2903, 1427, 1248, 1115, 993, 911, 816, 733, 702 cm^{-1}. HRMS Calcd for $C_{17}H_{26}S_2SiNa$: $[M+Na]^+$, 345.1137. Found: *m*/*z* 345.1147.

Benzyldimethyl(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)silane (15-SiMe$_2$Bn): CAS RN [868522-93-4].



Colorless oil; 98% yield (from **14**).

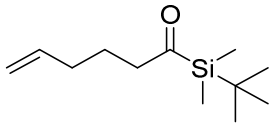
^{1}H NMR ($CDCl_3$) δ 7.22 (m, 2H), 7.09 (m, 1H), 7.05 (m, 2H), 5,84 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.08 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.02 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.07 (m, 2H), 2.48 (m, 2H),

2.38 (s, 2H), 2.26 (m ,2H), 2.13 (dt, *J* = 7.0, 7.0 Hz, 2H), 2.08 (m, 1H), 1.93 (m, 2H), 1.63 (m, 1H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 139.2, 138.4, 128.5, 128.1, 124.2, 115.0, 38.7, 36.8, 34.1, 26.9, 25.0, 23.4, 22.9, –4.8.

General procedure for preparation of **16**[23]

To a solution of **15** (25 mmol) in MeOH/H_2O solution (v/v = 4:1, 100 mL) was added chloramine T trihydrate (28 g, 100 mmol) in one portion at 0 °C, and then the reaction mixture was allowed to warm to ambient temperature. After the resulting mixture was stirred for additional 1 h, H_2O (100 mL) was added. The aqueous layers were extracted with Et_2O/hexane (v/v = 1:1, 50 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 30:1) as an eluent gave **16**.

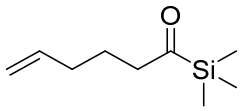
1-(*tert*-Butyldimethylsilyl)hex-5-en-1-one (16-TBS): CAS RN [144668-16-6].



Colorless oil; 51% yield.

^{1}H NMR ($CDCl_3$) δ 5.74 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 4.98 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H), 4.94 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H), 2.59 (t, *J* = 7.0 Hz, 2H), 2.00 (dddt, *J* = 7.0, 1.5, 1.0, 7.0 Hz, 2H), 1.60 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.91 (s, 9H), 0.16 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 247.6, 138.2, 114.9, 49.3, 33.1, 26.4, 20.9, 16.5, –7.0.

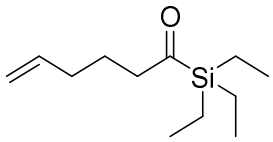
1-(Trimethylsilyl)hex-5-en-1-one (16-TMS): CAS RN [174710-35-1].



Colorless oil; 56% yield.

^{1}H NMR ($CDCl_3$) δ 5.74 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 4.98 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.94 (m, 1H), 2.59 (t, *J* = 7.0 Hz, 2H), 2.01 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.61 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.18 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 248.3, 138.2, 115.0, 47.5, 33.2, 21.1, –3.2.

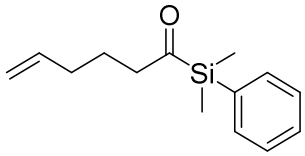
1-(Triethylsilyl)hex-5-en-1-one (16-TES): CAS RN [1237741-39-7].



Colorless oil; 40% yield.

^{1}H NMR ($CDCl_3$) δ 5.74 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 4.98 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.94 (m, 1H), 2,56 (t, *J* = 7.0 Hz, 2H), 2.00 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.60 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.71 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 248.0, 138.2, 114.9, 49.2, 33.2, 20.8, 7.2, 2.1.

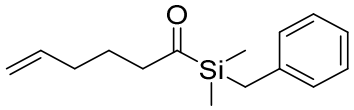
1-(Dimethyl(phenyl)silyl)hex-5-en-1-one (16-SiMe$_2$Ph): CAS RN [547744-75-2].



Colorless oil; 57% yield.

^{1}H NMR ($CDCl_3$) δ 7.55 (m, 2H), 7.44–7.37 (m, 3H), 5.68 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 4.94–4.89 (m, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.94 (dddt, *J* = 7.0, 1.5, 1.0, 7.0 Hz, 2H), 1.56 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.49 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 246.2, 138.1, 134.4, 133.9, 129.8, 128.1, 114.9, 47.8, 33.0, 21.1, –4.8.

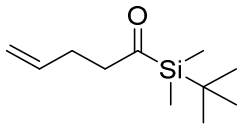
1-(Benzyldimethylsilyl)hex-5-en-1-one (16-SiMe$_2$Bn): CAS RN [855531-76-9].



Colorless oil; 72% yield.

^{1}H NMR ($CDCl_3$) δ 7.21 (m, 2H), 7.09 (m, 1H), 6.99 (m, 2H), 5.73 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.00–4.94 (m, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.26 (s, 2H), 1.98 (dddt, *J* = 7.0, 1.5, 1.0, 7.0 Hz, 2H), 1.57 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.18 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 247.0, 138.2, 138.1, 128.4, 128.1, 124.5, 115.0, 48.4, 33.1, 23.3, 20.9, –5.0.

1-(*tert*-Butyldimethylsilyl)pent-4-en-1-one: CAS RN [151569-16-3].



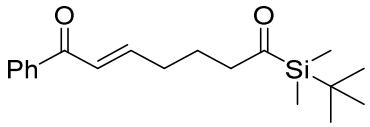
Colorless oil; 42% yield.

^{1}H NMR ($CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.00 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H), 4.94 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.26 (dt, *J* = 7.0, 7.0, 1.5 Hz, 2H), 0.93 (s, 9H), 0.18 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 246.6, 137.7, 114.9, 49.4, 26.4, 26.0, 16.6, –7.0.

General procedure for preparation of **1**

To a solution of **16** (3.0 mmol) and α,β-unsaturated carbonyl compound (12 mmol) in anhydrous CH_2Cl_2 (50 mL) was added Grubbs 2nd generation catalyst (0.13 g, 0.15 mmol) and CuI (34 mg, 0.18 mmol). After being stirred for 24 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 20:1) as an eluent gave **1**.

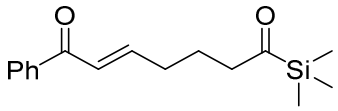
(*E*)-7-(*tert*-Butyldimethylsilyl)-1-phenylhept-2-ene-1,7-dione (1a).



Colorless oil; 66% yield.

^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7,56 (m, 1H), 7.47 (m, 2H), 7.02 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.88 (dt, *J* = 15.5, 1.5 Hz, 1H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.30 (ddt, *J* = 7.0, 1.5, 7.0 Hz, 2H), 1.77 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.92 (s, 9H), 0.18 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 246.9, 190.7, 149.0, 137.8, 132.7, 128.5 (2C), 126.2, 49.2, 32.1, 26.4, 20.2, 16.5, –7.0. TLC: R_f 0.13 (hexane/EtOAc = 10:1). IR (neat): 2951, 2930, 2884, 2858, 1668, 1624, 1622, 1285, 1250, 1224, 838, 777, 692 cm^{-1}. HRMS Calcd for $C_{19}H_{28}O_2SiNa$: $[M+Na]^+$, 339.1751. Found: *m*/*z* 339.1755.

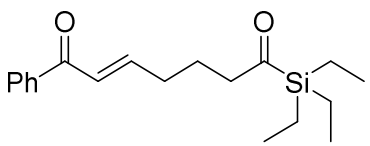
(*E*)-1-Phenyl-7-(trimethylsilyl)hept-2-ene-1,7-dione (1b).



Colorless oil; 72% yield.

^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 7.02 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.85 (d, *J* = 15.0 Hz, 1H), 2.68 (t, *J* = 7.0 Hz, 2H), 2.29 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.77 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 247.6, 190.7, 149.0, 137.8, 132.7, 128.5 (2C), 126.3, 47.3, 32.1, 20.4, –3.2. TLC: R_f 0.13 (hexane/EtOAc = 10:1). IR (neat): 2957, 1672, 1624, 1597, 1579, 1447, 1336, 1284, 1249, 1222, 846 cm^{-1}. HRMS Calcd for $C_{16}H_{22}O_2SiNa$: $[M+Na]^+$, 297.1281. Found: *m*/*z* 297.1289.

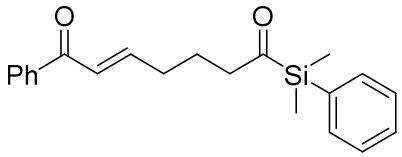
(*E*)-1-Phenyl-7-(triethylsilyl)hept-2-ene-1,7-dione (1c).



Colorless oil; 76% yield.

^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.56 (m, 1H), 7.47 (m, 2H), 7.02 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.88 (dt, *J* = 15.0, 1.5 Hz, 1H), 2.64 (t, *J* = 7.0 Hz, 2H), 2.29 (ddt, *J* = 7.0, 1.5, 7.0 Hz, 2H), 1.77 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 9H), 0.73 (q, *J* = 7.5 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 247.4, 190.7, 149.0, 137.8, 132.6, 128.5 (2C), 126.1, 49.0, 32.1, 20.2, 7.2, 2.0. TLC: R_f 0.18 (hexane/EtOAc = 10:1). IR (neat): 2954, 2912, 2876, 1668, 1622, 1448, 1416, 1336, 1226, 1021, 736, 693 cm^{-1}. HRMS Calcd for $C_{19}H_{28}O_2SiNa$: $[M+Na]^+$, 339.1751. Found: *m*/*z* 339.1756.

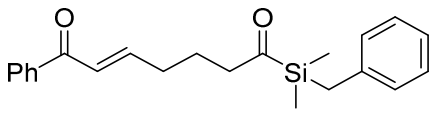
(*E*)-7-(Dimethyl(phenyl)silyl)-1-phenylhept-2-ene-1,7-dione (1d).



Colorless oil; 79% yield.

^{1}H NMR ($CDCl_3$) δ 7.89 (m ,2H), 7.58–7.52 (m, 3H), 7.47 (m, 2H), 7.42–7.35 (m, 3H), 6.94 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.78 (dt, *J* = 15.5, 1.5 Hz, 1H), 2.63 (t, *J* = 7.0 Hz, 2H), 2.20 (ddt, *J* = 7.0, 1.5, 7.0 Hz, 2H), 1.70 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.49 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 245.6, 190.7, 148.8, 137.8, 134.2, 133.9, 132.6, 130.0, 128.5, 128.2, 127.8, 126.2, 47.6, 32.0, 20.4, –4.9. TLC: R_f 0.15 (hexane/EtOAc = 5:1). IR (neat): 3049, 2959, 1669, 1643, 1624, 1285, 1250, 1110, 837, 783, 738, 698. HRMS Calcd for $C_{21}H_{24}O_2SiNa$: $[M+Na]^+$, 359.1438. Found: *m*/*z* 359.1445.

(*E*)-7-(Benzyldimethylsilyl)-1-phenylhept-2-ene-1,7-dione (1e).

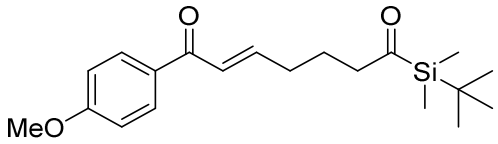


Colorless oil; 84% yield.

^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.56 (m, 1H), 7.47 (m, 2H), 7.20 (m, 2H), 7.08 (m, 1H), 7.01–6.96 (m, 3H), 6.85 (d, *J* = 15.0 Hz, 1H), 2.51 (t, *J* = 7.0 Hz, 2H), 2.25 (s, 2H), 2.23 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.70 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.19 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 246.3, 190.7, 148.9, 138.1, 137.8, 132.7, 128.51 (2C), 128.45, 128.1, 126.2, 124.6, 48.3, 32.0, 23.3, 20.2, –4.9. TLC:

R_f 0.20 (hexane/EtOAc = 5:1). IR (neat): 3058, 3024, 2931, 1669, 1642, 1622, 1599, 1494, 1448, 1345, 1285, 1249, 824, 700, 668 cm^{-1}. HRMS Calcd for $C_{22}H_{26}O_2SiNa$: $[M+Na]^+$, 373.1594. Found: *m*/*z* 373.1601.

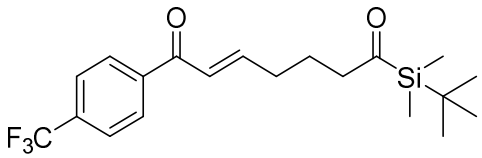
(*E*)-7-(*tert*-Butyldimethylsilyl)-1-(4-methoxyphenyl)hept-2-ene-1,7-dione (1f).



Colorless oil; 29% yield.

^1H NMR ($CDCl_3$) δ 7.94 (m, 2H), 6.99 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.93 (m, 2H), 6.89 (d, *J* = 15.0 Hz, 1H), 3,86 (s, 3H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.27 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.73 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.91 (s, 9H), 0.17 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 247.0, 188.9, 163.3, 147.9, 130.8, 130.6, 125.8, 113.7, 55.4, 49.2, 32.0, 26.4, 20.3, 16.5, –7.0. TLC: R_f 0.25 (hexane/EtOAc = 5:1). IR (neat): 2954, 2930, 2858, 1667, 1621, 1601, 1259, 1171, 1026, 838, 777 cm^{-1}. HRMS Calcd for $C_{20}H_{30}O_3SiNa$: $[M+Na]^+$, 369.1856. Found: *m*/*z* 369.1861.

(*E*)-7-(*tert*-Butyldimethylsilyl)-1-(4-(trifluoromethyl)phenyl)hept-2-ene-1,7-dione (1g).

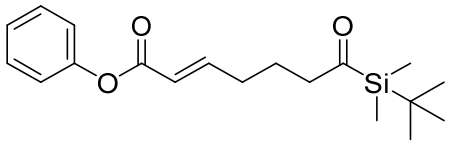


Yellow oil; 64% yield.

^1H NMR ($CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.05 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.85 (d, *J* = 15.0 Hz, 1H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.30 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.77 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.92 (s, 9H), 0.18 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 246.8, 189.8, 150.6, 140.7, 133.9 (q, *J* = 32.8 Hz), 128.8, 125.9, 125.7 (q, *J* = 3.4 Hz), 123.6 (q, *J* = 272.7 Hz), 49.2, 32.2, 26.4, 20.2, 16.5, 7.0. ^{19}F NMR ($CDCl_3$) δ 98.7. TLC: R_f 0.075 (hexane/EtOAc = 5:1). IR (neat): 2952,

2931, 2885, 2859, 1675, 1634, 1623, 1472, 1410, 1323, 1251, 1168, 1130, 1068, 1016, 836, 776 cm^{-1}. HRMS Calcd for $C_{20}H_{27}F_3O_2SiNa$: $[M+Na]^+$, 407.1625. Found: *m*/*z* 407.1619.

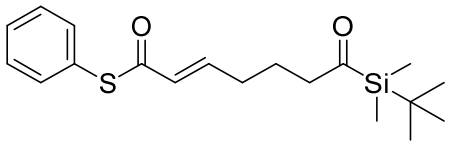
Phenyl (*E*)-7-(*tert*-butyldimethylsilyl)-7-oxohept-2-enoate (1h).



Colorless oil; 83% yield.

^1H NMR ($CDCl_3$) δ 7.39 (m, 2H), 7.24 (m, 1H), 7.16–7.10 (m, 3H), 6.02 (m, 1H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.26 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.75 (m, 2H), 0.94 (s, 9H), 0.20 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 246.7, 164.9, 150.9, 150.6, 129.4, 125.7, 121.6, 121.0, 49.1, 31.7, 26.4, 20.0, 16.5, –7.0. TLC: R_f 0.35 (hexane/EtOAc = 5:1). IR (neat): 2951, 2929, 2884, 2858, 1740, 1640, 1595, 1494, 1249, 1198, 1163, 1135, 823, 777, 668 cm^{-1}. HRMS Calcd for $C_{19}H_{28}O_3SiNa$: $[M+Na]^+$, 355.1700. Found: *m*/*z* 355.1705.

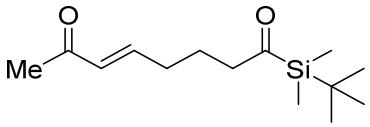
***S*-Phenyl (*E*)-7-(*tert*-butyldimethylsilyl)-7-oxohept-2-enethioate (1i)**.



Yellow oil; 59% yield.

^1H NMR ($CDCl_3$) δ 7.46–7.40 (m, 5H), 6.93 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.18 (d, *J* = 15.5 Hz, 1H), 2.64 (t, *J* = 7.0 Hz, 2H), 2.21 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.72 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.93 (s, 9H), 0.19 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 246.7, 188.0, 145.9, 134.6, 129.3, 129.1, 128.1, 127.5, 49.0, 31.6, 26.4, 20.0, 16.5, –7.0. TLC: R_f 0.20 (hexane/EtOAc = 10:1). IR (neat): 2948, 2928, 2882, 2857, 1690, 1636, 1250, 1024, 838, 777 cm^{-1}. HRMS Calcd for $C_{19}H_{28}O_2SSiNa$: $[M+Na]^+$, 371.1471. Found: *m*/*z* 371.1476.

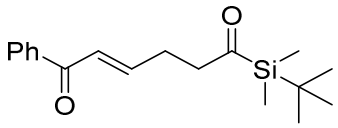
(*E*)-1-(*tert*-Butyldimethylsilyl)oct-5-ene-1,7-dione (1j).



Colorless oil; 69% yield.

^{1}H NMR ($CDCl_3$) δ 6.75 (dt, *J* = 16.0, 7.0 Hz, 1H), 6.05 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.63 (t, *J* = 7.0 Hz, 2H), 2.24 (s, 3H), 2.19 (ddt, *J* = 7.0, 1.5, 7.0 Hz, 2H), 1.70 (tt, *J* = 7.0, 7.0 Hz, 2H), 0.92 (s, 9H), 0.17 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 246.8, 198.7, 147.7, 131.6, 49.2, 31.9, 26.9, 26.4, 20.1, 16.5, –7.0. TLC: R_f 0.23 (hexane/EtOAc = 5:1). IR (neat): 2951, 2930, 2885, 2858, 1701, 1676, 1636, 1363, 1252, 978, 839, 775 cm^{-1}. HRMS Calcd for $C_{14}H_{26}O_2SiNa$: $[M+Na]^+$, 277.1594. Found: *m*/*z* 277.1597.

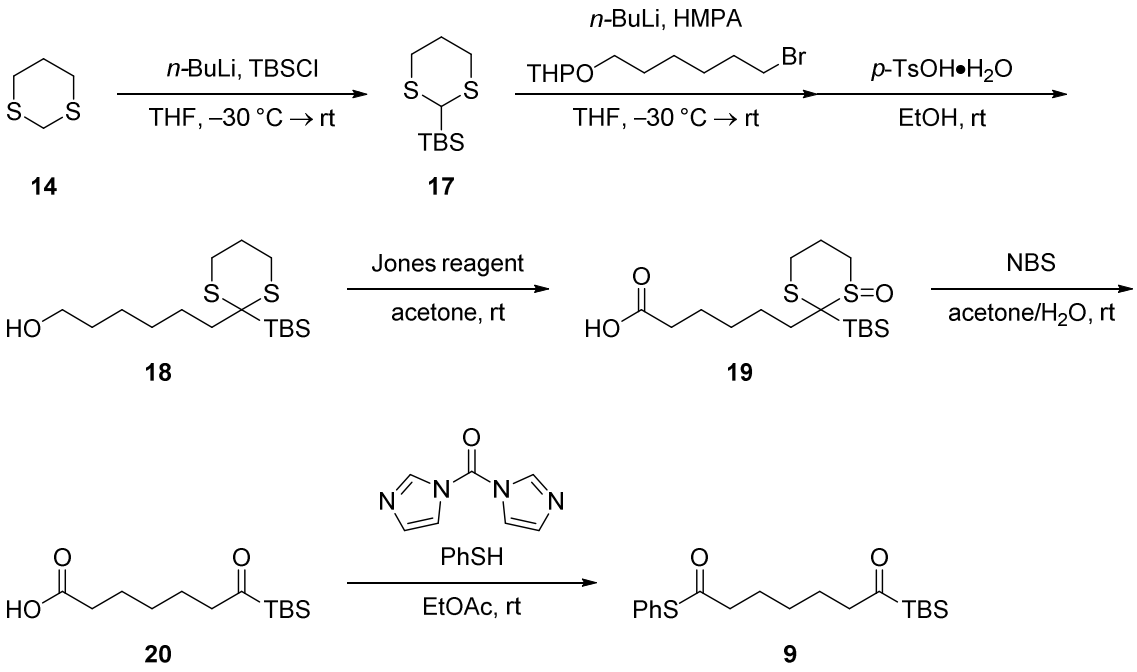
(*E*)-6-(*tert*-Butyldimethylsilyl)-1-phenylhex-2-ene-1,6-dione (1a').



Yellow oil; 41% yield.

^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 6.99 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.88 (dt, *J* = 15.5, 1.5 Hz, 1H), 2.82 (t, *J* = 7.0 Hz, 2H), 2.53 (ddt, *J* = 7.0, 1.5, 7.0 Hz, 2H), 0.93 (s, 9H), 0.20 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 245.0, 190.8, 148.5, 137.8, 132.7, 128.5 (2C), 126.5, 48.3, 26.4, 25.1, 16.5, –7.0. TLC: R_f 0.30 (hexane/EtOAc = 5:1). IR (neat): 2954, 2929, 2885, 2858, 1668, 1642, 1623, 1349, 1249, 838, 824, 775 cm^{-1}. HRMS Calcd for $C_{18}H_{26}O_2SiNa$: $[M+Na]^+$, 325.1594. Found: *m*/*z* 325.1599.

Procedure for preparation of 9



Procedure for preparation of **17**

To a solution of **14** (3.0 g, 25 mmol) in dry THF (40 mL) was added *n*-butyllithium (16 mL, 1.60 M in hexane, 25 mmol) dropwise at –30 °C. After the mixture was stirred for 1 h, *tert*-butyldimethylsilyl chloride (4.1 g, 28 mmol) in dry THF (10 mL) was added, and the reaction was allowed to warm to ambient temperature. After being stirred for additional 24 h, the reaction was quenched with H_2O (50 mL). The aqueous layers were extracted with EtOAc (50 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford **17**, and the crude product was used for the next step without further purification.

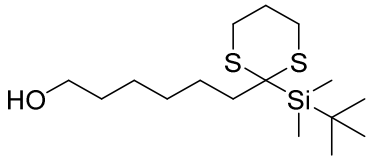
Procedure for preparation of **18**

To a solution of **17** (4.4 g, 19 mmol) and hexamethylphosphoric triamide (1.4 mL, 19 mmol) in dry THF (40 mL) was added *n*-butyllithium (13 mL, 1.60 M in hexane, 21 mmol) dropwise at –30 °C. After the mixture was stirred for 2 h, 2-((6-bromohexyl)oxy)tetrahydro-2*H*-pyran (5.0 g,

19 mmol) in dry THF (10 mL) was added dropwise at –30 °C, and the reaction was allowed to warm to ambient temperature. After being stirred for additional 19 h, the reaction was quenched with H_2O (50 mL). The aqueous layers were extracted with EtOAc (50 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 20:1) as an eluent gave the mixture of the corresponding alkylated product and the unreacted starting materials.

Next, to a solution of the mixture in EtOH (150 mL) was added *p*-toluenesulfonic acid monohydrate (0.57 g, 3.0 mmol). After the resulting mixture was stirred for 19 h at ambient temperature, saturated aqueous $NaHCO_3$ (40 mL) was added. The mixture was evaporated to remove EtOH, and the aqueous layers were extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent gave **18**.

6-(2-(*tert*-Butyldimethylsilyl)-1,3-dithian-2-yl)hexan-1-ol (18).



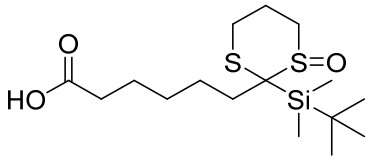
Colorless oil; 47% yield (from **17**).

^{1}H NMR ($CDCl_3$) δ 3.66 (t, *J* = 7.0 Hz, 2H), 3.05 (m, 2H), 2.40 (m, 2H), 2.32 (m, 2H), 2.03 (m, 1H), 1.89 (m, 1H), 1.62–1.52 (m, 4H), 1.46 (br s, 1H), 1.43–1.35 (m, 4H), 1.03 (s, 9H), 0.20 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 63.0, 41.0, 37.8, 32.8, 30.0, 28.3, 28.0, 25.7, 25.0, 23.4, 19.8, –5.2. TLC: R_f 0.15 (hexane/EtOAc = 5:1). IR (neat): 3360, 2851, 1465, 1442, 1249, 1057, 1007, 910, 806, 759, 670 cm^{-1}. HRMS Calcd for $C_{16}H_{34}OS_2SiNa$: $[M+Na]^+$, 357,1713. Found: *m*/*z* 357.1716.

Procedure for preparation of **19**

To a solution of **18** (2.5 g, 7.6 mmol) in dry acetone (76 mL) was added Jones reagent (9.0 mL, ca. 2.5 M in aqueous H_2SO_4, ca. 23 mmol) dropwise at ambient temperature. After the resulting mixture was stirred for 10 min, H_2O (50 mL) was added. The mixture was evaporated to remove acetone, and the aqueous layers were extracted with EtOAc (50 mL × 4). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using $CHCl_3$/MeOH (v/v = 20:1–10:1) as an eluent gave **19**.

6-(2-(*tert*-Butyldimethylsilyl)-1-oxido-1,3-dithian-2-yl)hexanoic acid (19).



Colorless oil; 49% yield.

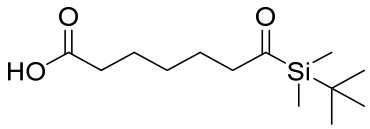
^{1}H NMR ($CDCl_3$) δ 3.10 (dt, *J* = 13.0, 3.0 Hz, 1H), 2.95 (dt, *J* = 13.0, 3.0 Hz, 1H), 2.53 (m, 1H), 2.35–2.32 Hz (m, 3H), 2.29–2.21 (m, 2H), 2.14–2.05 (m, 2H), 1.82 (m, 1H), 1.69 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.50–1.46 (m, 3H), 1.05 (s, 9H), 0.24 (s, 3H), 0.17 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 177.6, 54.5, 43.1, 34.0, 29.7, 29.6, 28.1, 24.7, 24.6, 23.5, 21.1, 19.5, –4.9, –5.1. TLC: R_f 0.25 ($CHCl_3$/MeOH = 10:1). IR (neat): 2954, 2593, 1703, 1470, 1367, 1249, 1147, 1009, 823, 779, 755 cm^{-1}. HRMS Calcd for $C_{16}H_{32}O_3S_2SiNa$: $[M+Na]^+$, 387.1454. Found: *m*/*z* 387.1458.

Procedure for preparation of **20**[24]

To a solution of *N*-bromosuccinimide (2.8 g, 16 mmol) in acetone/H_2O (v/v = 9:1, 200 mL) was added a solution of **19** (0.97 g, 2.7 mmol) in acetone (5.0 mL) dropwise at 0 °C. After being stirred for 10 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was evaporated to remove acetone, and the aqueous layers were extracted with EtOAc (30 mL × 4).

The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using $CHCl_3$/MeOH (v/v = 20:1) as an eluent gave **20**.

7-(*tert*-Butyldimethylsilyl)-7-oxoheptanoic acid (20).



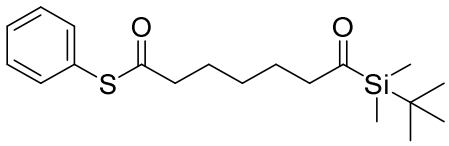
Yellow oil; 88% yield.

^{1}H NMR ($CDCl_3$) δ 2.60 (t, J = 7.0 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 1.62 (tt, J = 7.5, 7.5 Hz, 2H), 1.52 (tt, J = 7.0, 7.0 Hz, 2H), 1.29 (m, 2H), 0.92 (s, 9H), 0.17 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 247.7, 179.5, 50.0, 33.8, 28.6, 26.4, 24.5, 21.4, 16.5, –7.0. TLC: R_f 0.23 ($CHCl_3$/MeOH = 20:1). IR (neat): 2931, 2859, 1710, 1636, 1463, 1420, 1363, 1250, 823, 777, 673 cm^{-1}. HRMS Calcd for $C_{13}H_{26}O_3SiNa$: $[M+Na]^+$, 281.1543. Found: *m*/*z* 281.1547.

Procedure for preparation of **9**

To a solution of **20** (0.13 g, 0.50 mmol) in dry EtOAc (1.0 mL) was added 1,1'-biscarbonyldiimidazole (89 mg, 0.55 mmol). After the resulting mixture was stirred for 30 min at ambient temperature, thiophenol (51 μL, 0.50 mmol) was added, and the mixture was stirred for additional 1.5 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 20:1–10:1) as an eluent gave **9**.

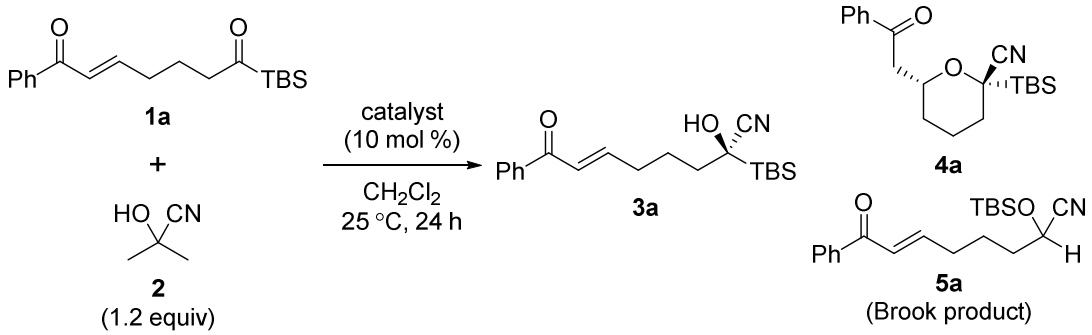
_S_-Phenyl 7-(*tert*-butyldimethylsilyl)-7-oxoheptanethioate (9).



Colorless oil; 77% yield.

^{1}H NMR ($CDCl_3$) δ 7.40 (m, 5H), 2.65 (t, J = 7.5 Hz, 2H), 2.60 (t, J = 7.0 Hz, 2H), 1.70 (tt, J = 7.5, 7.5 Hz, 2H), 1.53 (tt, J = 7.0, 7.0 Hz, 2H), 1.32 (m, 2H), 0.92 (s, 9H), 0.17 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 247.5, 197.5, 134.5, 129.3, 129.1, 127.8, 49.9, 43.4, 28.5, 26.4, 25.4, 21.4, 16.5, –7.0. TLC: R_f 0.45 (hexane/EtOAc = 5:1). IR (neat): 2929, 2858, 1719, 1710, 1636, 1479, 1441, 1249, 837, 745, 689 cm^{-1}. HRMS Calcd for $C_{19}H_{30}O_2SSiNa$: $[M+Na]^+$, 373.1628. Found: m/z 373.1634.

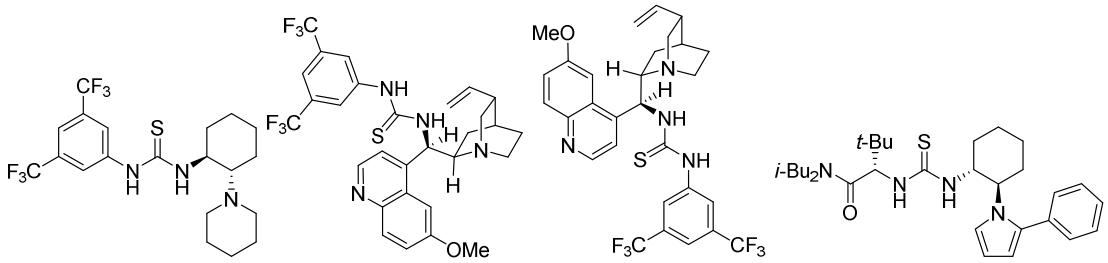
Table 3. Screening of Catalysts[a]



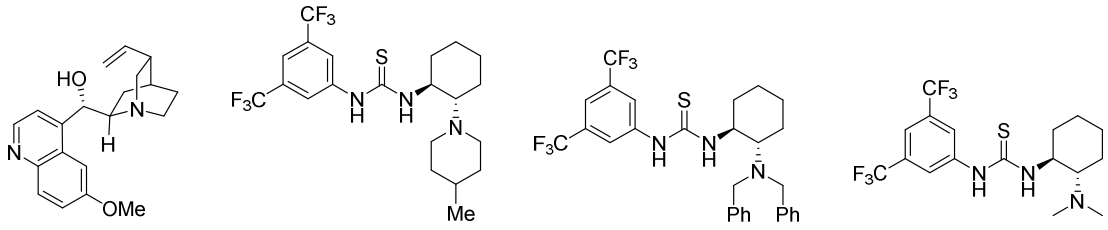
entry	catalyst	yield of **3a** (%)[b]	*ee* of **3a** (%)	yield of **4a** (%)[b]	dr of **4a**[b]	*ee* of **4a** (%)	yield of **5a** (%)[b]
1	none	<1	–	<1	–	–	<1
2	**6a**	5	–66	61	12:1	–50	34
3	**6b**	49	96	48	8.0:1	86	2
4	**6c**	44	–97	52	6.6:1	–82	4
5	**6d**	<1	–	<1	–	–	<1
6	**6e**	<1	–	<1	–	–	99
7	**6f**	62	–87	25	>19:1	–73	6
8	**6g**	<1	–	<1	–	–	<1
9	**6h**	20	–98	68	11:1	–34	12
10	**6i**	51	–93	47	>19:1	–90	1
11	**6j**	15	–98	60	5.5:1	–77	21
12	**6k**	42	–94	42	>19:1	–84	4
13	**6l**	71	–41	28	>19:1	–90	4
14	**6m**	59	–27	<1	–	–	4
15	**6n**	<1	–	<1	–	–	99
16	**6o**	40	3	<1	–	–	<1
17	**7** + **8**	<1	–	5	–	–	77

[a]Reactions were run using **1a** (0.15 mmol), **2** (0.18 mmol), and the catalyst (0.015 mmol) in CH_2Cl_2 (0.30 mL). [b]Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

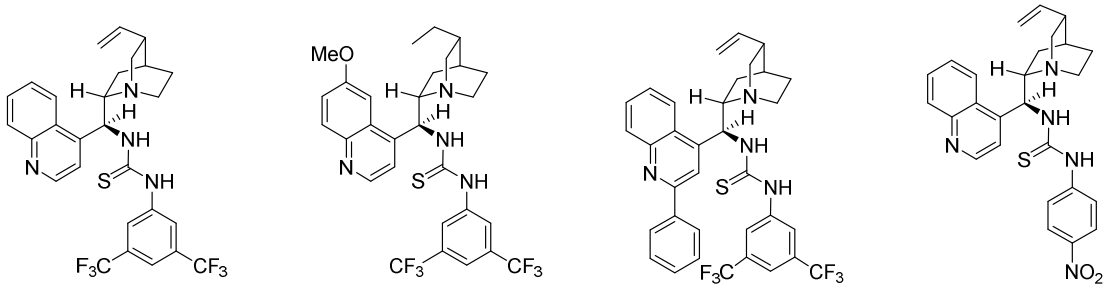
Table 3. (Continued)



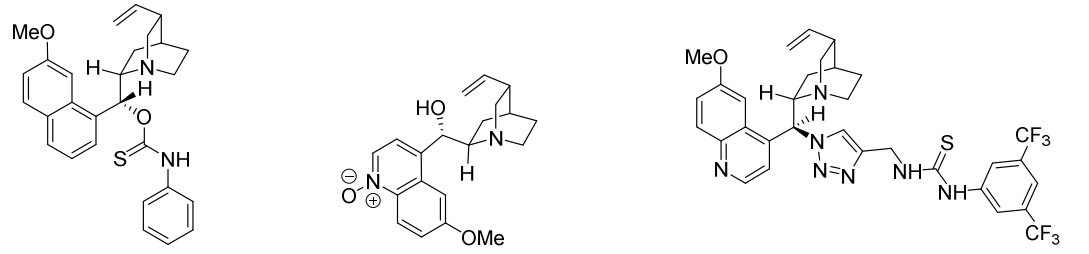
6a **6b** **6c** **6d**



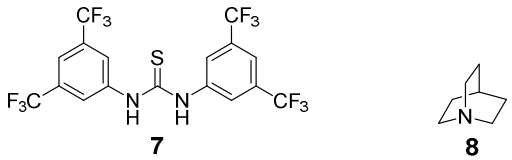
6e **6f** **6g** **6h**



6i **6j** **6k** **6l**

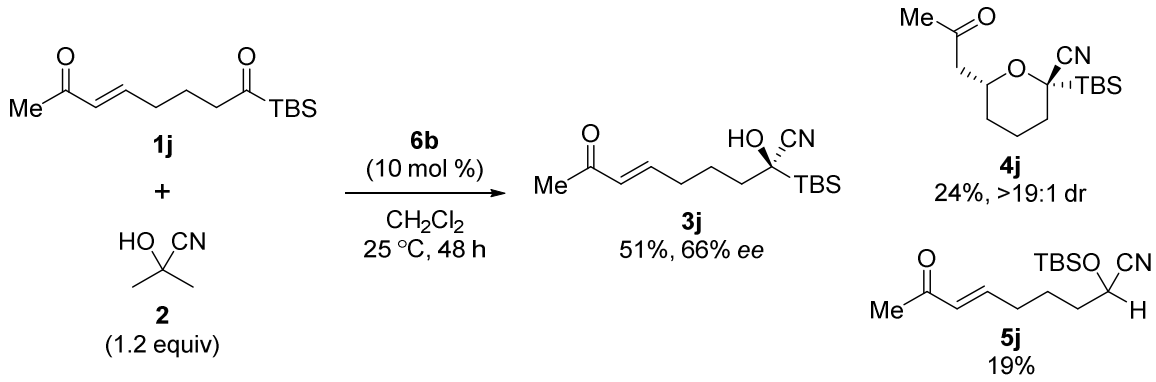


6m **6n** **6o**



7 **8**

Scheme 5. Reaction of Aliphatic Substrate 1j

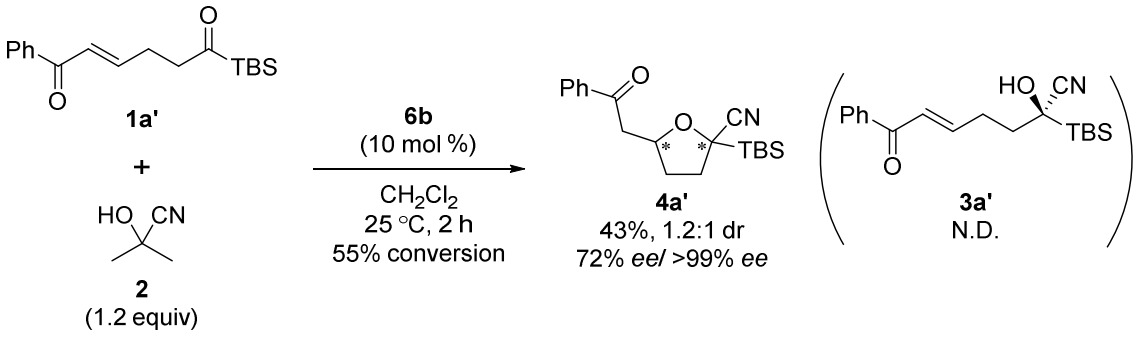


The reaction was applied to substrate **1j**, which has an aliphatic enone as Michael acceptor. While acylsilane cyanohydrin **3j** was afforded after 2 days in nearly 50% yield with moderate enantioselectivity, a significant amount of Brook product **5j** was also obtained.

Procedure

To a solution of acylsilane **1j** (38 mg, 0.15 mmol) in CH_2Cl_2 (0.30 mL) were added acetone cyanohydrin (**2**, 17 μL, 0.18 mmol) and bifunctional organocatalyst **6b** (8.9 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 48 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1) as an eluent afforded the corresponding acylsilane cyanohydrin **3j** along with the corresponding tetrahydropyran **4j** and the Brook product **5j**.

Scheme 6. Reaction of Substrate 1a' Bearing a Shorter Tether

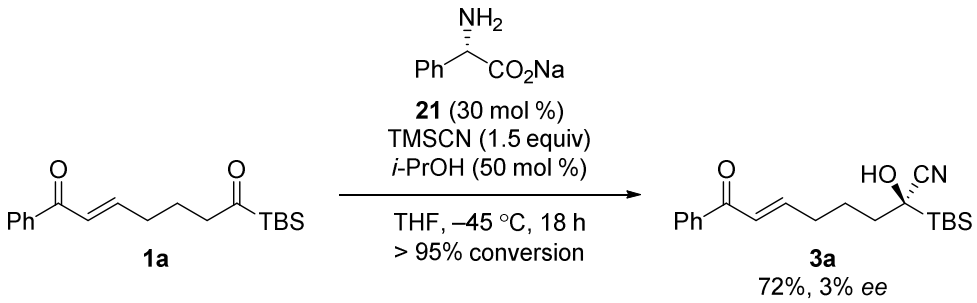


The reaction was applied to substrate **1a'**, which has a Michael acceptor closer to an acylsilane moiety. After ~50% conversion, an optically active tetrahydrofuran **4a'** was obtained as a mixture of diastereomers, and the corresponding acylsilane cyanohydrin **3a'** was not detected probably due to its rapid consumption by the following cycloetherification.

Procedure

To a solution of acylsilane **1a'** (45 mg, 0.15 mmol) in CH_2Cl_2 (0.30 mL) were added acetone cyanohydrin (**2**, 17 μL, 0.18 mmol) and bifunctional organocatalyst **6b** (8.9 mg, 0.015 mmol), and the resulting mixture was stirred in an oil bath maintained at 25 °C for 2 h. The reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1) as an eluent afforded **4a'**.

Scheme 7. Asymmetric Cyanation of 1a by Feng's Protocol

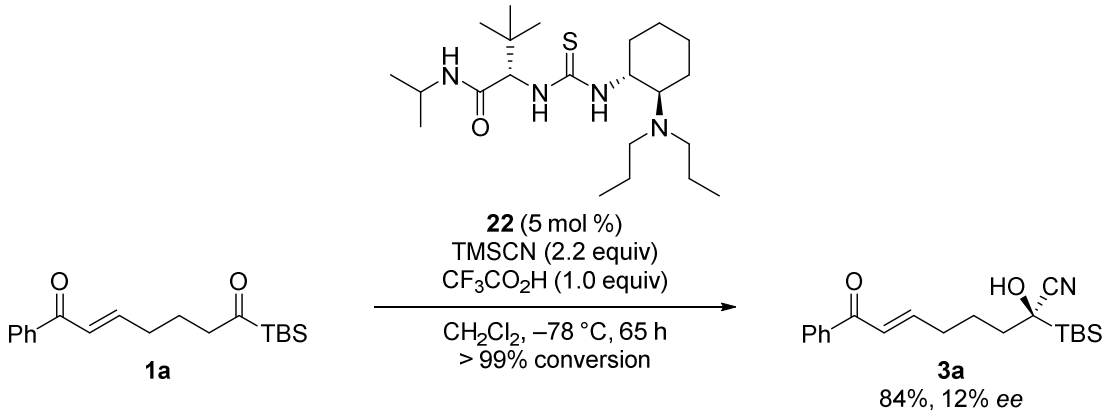


Substrate **1a** was subjected to Feng's cyanation protocol.[1k] Under the conditions employing L-phenylglycine sodium salt (**21**) as a catalyst, the desired acylsilane cyanohydrin **3a** was obtained in only 3% *ee*.

Procedure

To a solution of **21** (8.2 mg, 0.045 mmol) in THF (0.15 mL) was added trimethylsilyl cyanide (28 μL, 0.23 mmol) at –20 °C, and the mixture was stirred at 30 °C for 1 h. Then the solution of **1a** (47 mg, 0.15 mmol) in THF (0.15 mL) was added at –45 °C, and the mixture was stirred for 15 min. *i*-PrOH (5.7 μL, 0.075 mmol) and THF (0.15 mL), respectively, were then added, and the resulting mixture was stirred for 18h. After being warmed to ambient temperature, the reaction mixture was filtered, and the residue was concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1 – 5/1) as an eluent afforded **3a**.

Scheme 8. Asymmetric Cyanation of 1a by Jacobsen's Protocol

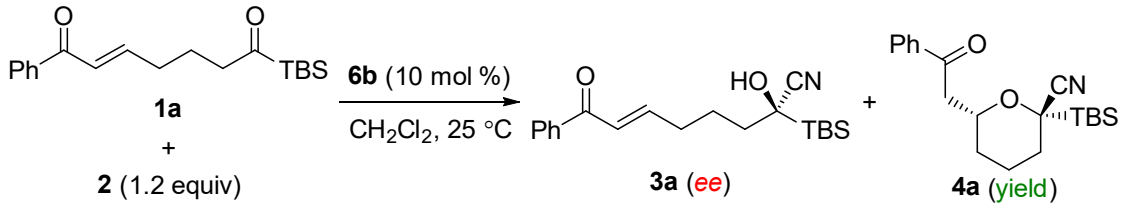


Substrate **1a** was subjected to Jacobsen's cyanation protocol.[1j] Under the conditions employing Jacobsen's catalyst **22**, **3a** was obtained in only 12% *ee*. Thus, on the basis of these results, the author considers the presented protocol is quite useful for obtaining the desired acylsilane cyanohydrins **3** in highly enantioenriched form.

Procedure

To a 5-mL round bottom flask were sequentially added **22** (3.1 mg, 0.0075 mmol), **1a** (47mg, 0.15 mmol), trimethylsilylcyanide (41 μL, 0.33 mmol) and CH_2Cl_2 (0.30 mL). The reaction mixture was stirred at –78 °C for 15 min. 2,2,2-Trifluoroethan-1-ol (11 μL, 0.15 mmol) was then added, and the mixture was stirred at the same temperature for 65 h. After being warmed to ambient temperature, the reaction mixture was subsequently diluted with EtOAc, passed through a short silica gel pad to remove **22**, and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 5/1–3/1) as an eluent afforded **3a**.

Table 4. Reaction Profiles for Asymmetric Synthesis of 3a from 1a



time (h)	yield of **4a** (%)	*ee* of **3a** (%)
3	12	42
6	27	65
12	46	93
18	50	96
24	54	96

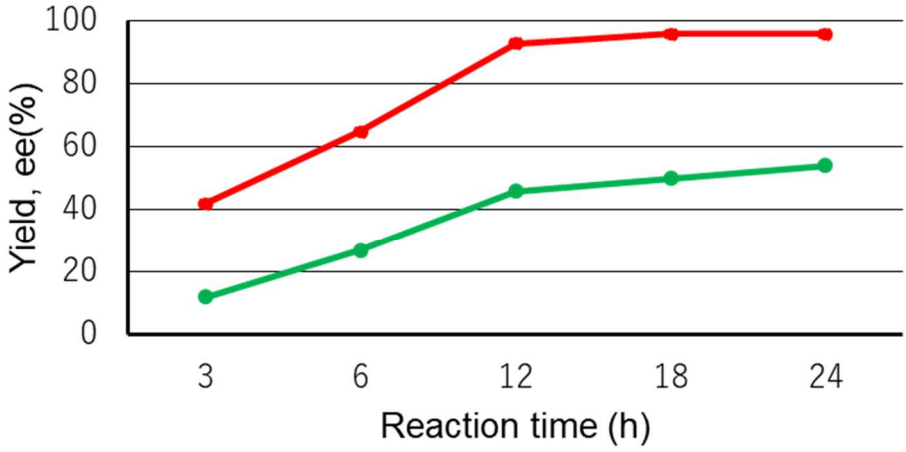
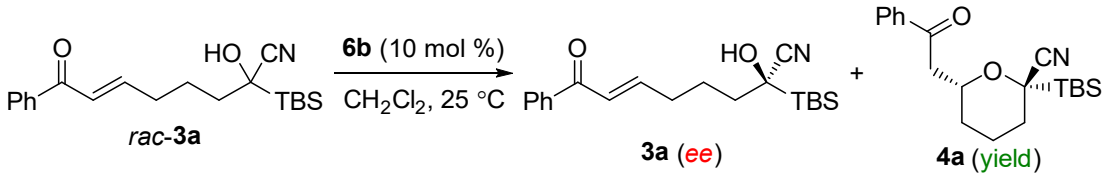
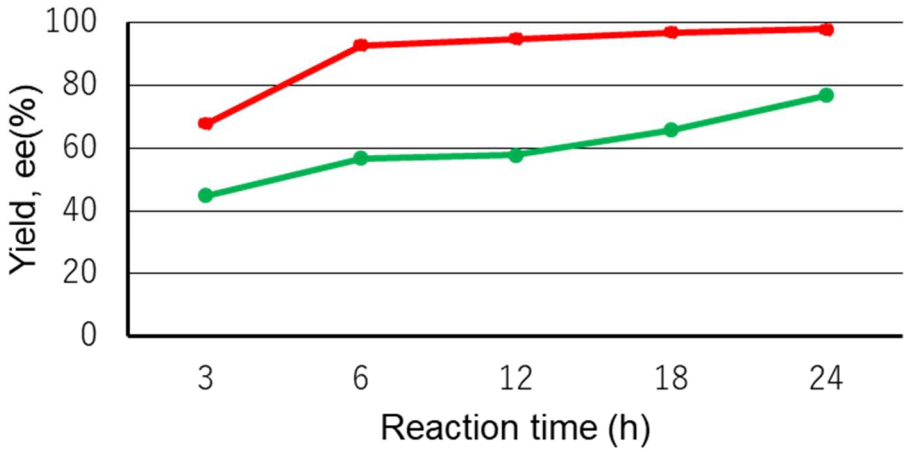


Table 5. Reaction Profiles for Asymmetric Synthesis of 3a from *rac*-3a

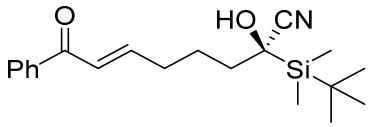


time (h)	yield of **4a** (%)	*ee* of **3a** (%)
3	45	68
6	57	93
12	58	95
18	66	97
24	77	98



Characterization Data of Products

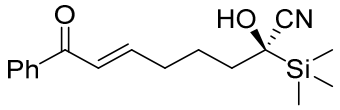
(*R*,*E*)-2-(*tert*-Butyldimethylsilyl)-2-hydroxy-8-oxo-8-phenyloct-6-enenitrile (3a).



Yield: 49%, 96% *ee*, white solid (**4a**: yield: 48%, 8.0:1 dr, 86% *ee*).

$[\alpha]_D^{20}$ +8.1 (*c* 0.57, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.96 (m, 2H), 7.14–7.09 (m, 3H), 7.05 (m, 1H), 6.73 (d, *J* = 15.0 Hz, 1H), 2.45 (br s, 1H), 1.82 (m, 2H), 1.65–1.38 (m, 4H), 1.03 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (C_6D_6) δ 189.9, 148.3, 138.3, 132.6, 128.9, 128.7, 126.2, 122.4, 64.0, 36.7, 32.3, 27.5, 22.6, 18.3, –7.6, –8.1. Mp. 115.0–116.0 °C. TLC: R_f 0.10 (hexane/EtOAc = 5:1). IR (KBr): 3310, 2952, 2927, 2857, 1659, 1620, 1595, 1576, 1472, 1447, 1351, 1294, 1246, 1213, 1015, 984 cm^{-1}. HRMS Calcd for $C_{20}H_{29}NO_2SiNa$: $[M+Na]^+$, 366.1860. Found: *m*/*z* 366.1855. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.6 min, t_{major} = 8.5 min.

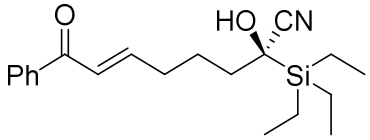
(*R*,*E*)-2-Hydroxy-8-oxo-8-phenyl-2-(trimethylsilyl)oct-6-enenitrile (3b).



Yield: 41%, 93% *ee*, colorless oil (**4b**: yield: 59%, 8.0:1 dr, 71% *ee*).

$[\alpha]_D^{20}$ +7.5 (*c* 0.40, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.94 (m, 2H), 7.14–7.08 (m, 3H), 7.05 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.73 (d, *J* = 15.0 Hz, 1H), 2.54 (br s, 1H), 1.84 (m, 2H), 1.55 (m, 2H), 1.44 (m, 2H), 0.07 (s, 9H). ^{13}C NMR (C_6D_6) δ 189.8, 148.3, 138.3, 132.6, 128.8, 128.7, 126.2, 122.0, 63.8, 35.4, 32.3, 22.9, –4.8. TLC: R_f 0.10 (hexane/EtOAc = 5:1). IR (neat): 3422, 2954, 2213, 1662, 1615, 1448, 1286, 1253, 1180, 1004, 983, 845, 752 cm^{-1}. HRMS Calcd for $C_{17}H_{23}NO_2SiNa$: $[M+Na]^+$, 324.1390. Found: *m*/*z* 324.1387. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 8.5 min, t_{major} = 9.8 min.

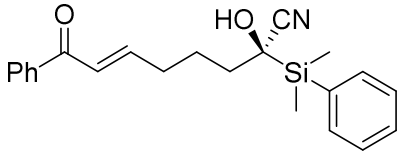
(*R*,*E*)-2-Hydroxy-8-oxo-8-phenyl-2-(triethylsilyl)oct-6-enenitrile (3c).



Yield: 35%, 95% *ee*, colorless oil (**4c**: yield: 59%, 8.3:1 dr, 71% *ee*).

$[\alpha]_D^{20}$ +9.3 (*c* 0.40, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.95 (m, 2H), 7.14–7.08 (m, 3H), 7.05 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.24 (d, *J* = 15.5 Hz, 1H), 2.40 (br s, 1H), 1.84 (m, 2H), 1.59–1.52 (m, 4H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.68 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (C_6D_6) δ 189.7, 148.2, 138.3, 132.6, 128.8, 128.7, 126.2, 122.3, 63.6, 36.2, 32.3, 22.6, 7.5, 1.7. TLC: R_f 0.15 (hexane/EtOAc = 5:1). IR (neat): 3424, 2954, 2878, 2213, 1662, 1621, 1579, 1447, 1347, 1288, 1179, 1004, 982, 738 cm^{-1}. HRMS Calcd for $C_{20}H_{29}NO_2SiNa$: $[M+Na]^+$, 366.1860. Found: *m*/*z* 366.1855. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 8.2 min, t_{major} = 9.9 min.

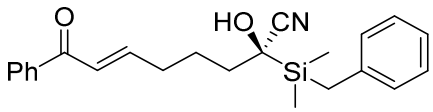
(*R*,*E*)-2-(Dimethyl(phenyl)silyl)-2-hydroxy-8-oxo-8-phenyloct-6-enenitrile (3d).



Yield: 29%, 83% *ee*, colorless oil (**4d**: yield: 69%, 14:1 dr, 80% *ee*).

$[\alpha]_D^{20}$ +5.0 (*c* 0.44, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.91 (m, 2H), 7.57 (m, 2H), 7.16–7.08 (m, 6H), 6,93 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.61 (d, *J* = 15.0 Hz, 1H), 2.22 (br s, 1H), 1.67 (m, 2H), 1.47–1.32 (m, 4H), 0.38 (s, 3H), 0.37 (s, 3H). ^{13}C NMR (C_6D_6) δ 189.7, 148.1, 138.4, 135.0, 133.1, 132.6, 130.6, 128.8, 128.7, 128.5, 126.2, 121.9, 64.0, 35.6, 32.1, 22.8, –6.3, –6.5. TLC: R_f 0.10 (hexane/EtOAc = 5:1). IR (neat): 3417, 3052, 2917, 2213, 1676, 1616, 1578, 1448, 1428, 1282, 1252, 1180, 1114, 983, 835 cm^{-1}. HRMS Calcd for $C_{22}H_{25}NO_2SiNa$: $[M+Na]^+$, 386.1547. Found: *m*/*z* 386.1545. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 12.1 min, t_{major} = 21.1 min.

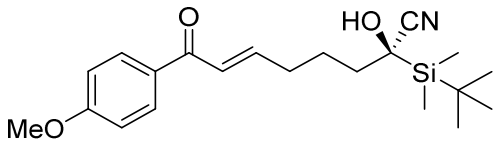
(*R*,*E*)-2-(Benzyldimethylsilyl)-2-hydroxy-8-oxo-8-phenyloct-6-enenitrile (3e).



Yield: 37%, 91% *ee*, colorless oil (**4e**: yield: 61%, 14:1 dr, 87% *ee*).

$[\alpha]_D^{20}$ +11.4 (*c* 0.47, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.95 (m, 2H), 7.14–7.07 (m, 5H), 7.04 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.98 (m, 1H), 6.92 (m, 2H), 6.74 (d, *J* = 15.5 Hz, 1H), 2.41 (br s, 1H), 2.24 (br s, 1H), 2.23 (br s, 1H), 1.84 (m, 2H), 1.55 (m, 2H), 1.42 (m, 2H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (C_6D_6) δ 189.8, 148.1, 138.3, 138.1, 132.7, 128.8, 128.71, 128.67, 128.5, 126.3, 125.1, 121.9, 63.8, 35.6, 32.2, 22.9, 22.0, –6.4, –6.6. TLC: R_f 0.10 (hexane/EtOAc = 5:1). IR (neat): 3421, 3059, 3024, 2953, 2213, 1662, 1620, 1494, 1448, 1347, 1291, 1252, 1160, 1058, 823 cm^{-1}. HRMS Calcd for $C_{23}H_{27}NO_2SiNa$: $[M+Na]^+$, 400.1703. Found: *m*/*z* 400.1698. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.2 min, t_{major} = 11.5 min.

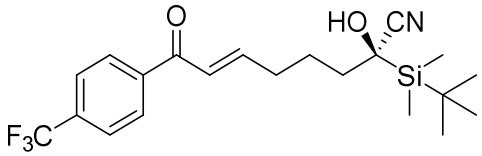
(*R*,*E*)-2-(*tert*-Butyldimethylsilyl)-2-hydroxy-8-(4-methoxyphenyl)-8-oxooct-6- enenitrile (3f).



Yield: 47%, 93% *ee*, colorless oil (**4f**: yield: 41%, >19:1 dr, 89% *ee*).

$[\alpha]_D^{20}$ +6.0 (*c* 0.57, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 8.03 (m, 2H), 7.15 (dt, *J* = 15.0, 7.0 Hz, 1H), 6,84 (d, *J* = 15.0 Hz, 1H), 6.70 (m, 2H), 3.18 (s, 3H), 2.79 (br s, 1H), 1.90 (m, 2H), 1.67–1.59 (m, 4H), 1.05 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (C_6D_6) δ 188.2, 163.7, 147.5, 131.2 (2C), 125.9, 122.5, 114.1, 64.0, 54.8, 36.8, 32.3, 27.5, 22.7, 18.3, –7.5, –8.1. TLC: R_f 0.075 (hexane/EtOAc = 5:1). IR (neat): 3419, 2955, 2931, 2859, 2213, 1661, 1616, 1599, 1512, 1465, 1418, 1306, 1260, 1171, 1028, 839 cm^{-1}. HRMS Calcd for $C_{21}H_{31}NO_3SiNa$: $[M+Na]^+$, 396.1965. Found: *m*/*z* 396.1958. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 13.2 min, t_{major} = 16.7 min.

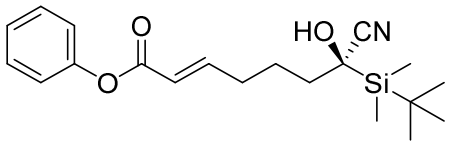
(*R*,*E*)-2-(*tert*-Butyldimethylsilyl)-2-hydroxy-8-oxo-8-(4-(trifluoromethyl)phenyl)oct-6-enenitrile (3g).



Yield: 47%, 83% *ee*, colorless oil (**4g**: yield: 33%, 14:1 dr, 88% *ee*).

$[\alpha]_D^{20}$ +5.6 (*c* 0.52, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.69 (m, 2H), 7.23 (m, 2H), 6.98 (m, 1H), 6.57 (d, *J* = 15.5 Hz, 1H), 1.83 (m, 2H), 1.56–1.51 (m, 4H), 1.36 (br s, 1H), 1.01 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (C_6D_6) δ 188.6, 149.2, 140.9, 133.7 (q, *J* = 32.7 Hz), 129.0, 125.8, 125.7 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 273.3 Hz), 122.2, 64.0, 36.5, 32.2, 27.4, 22.5, 18.2, –7.7, –8.2. ^{19}F NMR (C_6D_6) δ 100.1. TLC: R_f 0.16 (hexane/EtOAc = 5:1). IR (neat): 3423, 2954, 2932, 2862, 2215, 1674, 1624, 1474, 1410, 1323, 1168, 1129, 1068, 1015, 839 cm^{-1}. HRMS Calcd for $C_{21}H_{28}F_3NO_2SiNa$: $[M+Na]^+$, 434.1734. Found: *m*/*z* 434.1729. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.4 min, t_{major} = 8.1 min.

Phenyl (*R*,*E*)-7-(*tert*-butyldimethylsilyl)-7-cyano-7-hydroxyhept-2-enoate (3h).

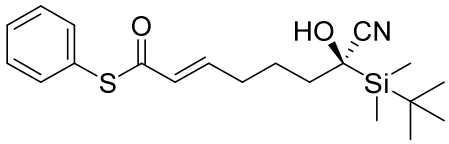


Yield: 48%, 63% *ee*, white solid (**4h**: yield: 25%, >19:1 dr, 18% *ee*).

$[\alpha]_D^{20}$ +6.7 (*c* 0.74, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.15 (m, 2H), 7.09 (m, 2H), 7.05 (m, 1H), 6.93 (m, 1H), 5,96 (d, *J* = 15.5 Hz, 1H), 2.13 (br s, 1H), 1,69 (m, 2H), 1.46–1.35 (m, 4H), 1.02 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (C_6D_6) δ 164.6, 151.4, 150.3, 129.6, 125.8, 122.2, 122.0, 121.4, 63.9, 36.6, 31.9, 27.4, 22.3, 18.3, –7.6, –8.2. Mp. 79.0–79.9 °C. TLC: R_f 0.15 (hexane/EtOAc = 5:1). IR (KBr): 3382, 2930, 2860, 2227, 1735, 1655, 1592, 1494, 1252, 1190, 1148, 983, 838 cm^{-1}. HRMS Calcd for $C_{20}H_{29}NO_3SiNa$: $[M+Na]^+$, 382.1809. Found: *m*/*z*

382.1821. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.5 min, t_{major} = 7.4 min.

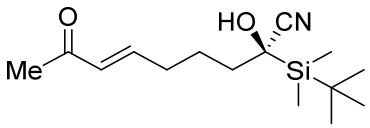
_S_-Phenyl (_R_,_E_)-7-(_tert_-butyldimethylsilyl)-7-cyano-7-hydroxyhept-2-enethioate (3i).



Yield: 41%, 98% *ee*, white solid (**4i**: yield: 46%, >19:1 dr, 92% *ee*).

$[\alpha]_D^{20}$ +6.6 (98% *ee*, *c* 0.68, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.48 (m, 2H), 7.07 (m, 2H), 7.02 (m, 1H), 6,84 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.06 (d, *J* = 15.0 Hz, 1H), 2.06 (br s, 1H), 1,59 (m, 2H), 1.46–1.34 (m, 3H), 1.28 (m, 1H), 1.02 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (C_6D_6) δ 186.9, 145.3, 135.0, 129.4, 129.3, 128.53, 128.48, 122.2, 63.9, 36.6, 31.7, 27.5, 22.3, 18.3, –7.6, –8.2. Mp. 88.9–89.5 °C. TLC: R_f 0.23 (hexane/EtOAc = 5:1). IR (KBr): 3398, 2954, 2223, 1670, 1634, 1472, 1246, 1150, 1022, 973, 897, 842 cm^{-1}. HRMS Calcd for $C_{20}H_{29}NO_2SSiNa$: $[M+Na]^+$, 398.1580. Found: *m*/*z* 398.1592. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.0 min, t_{major} = 7.9 min.

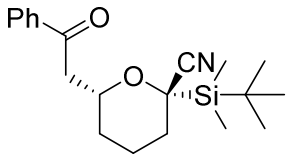
(_R_,_E_)-2-(_tert_-Butyldimethylsilyl)-2-hydroxy-8-oxonon-6-enenitrile (3j).



Yield: 51%, 66% *ee*, white solid. $[\alpha]_D^{20}$ +6.1 (*c* 0.82, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 6.37 (dt, *J* = 16.5, 7.0 Hz, 1H), 5.95 (d, *J* = 16.5 Hz, 1H), 2.75 (br s, 1H), 1.89 (s, 3H), 1.69 (m, 2H), 1.52–1.51 (m, 4H), 1.04 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (C_6D_6) δ 197.9, 146.9, 131.6, 122.5, 63.9, 36.8, 31.9, 27.5, 26.7, 22.6, 18.3, –7.6, –8.1. Mp. 64.0–64.8 °C. TLC: R_f 0.10 (hexane/EtOAc = 5:1). IR (KBr): 3365, 2924, 2855, 2226, 2676, 1638, 1465, 1367, 1257, 1063, 979, 891, 778, 676 cm^{-1}. HRMS Calcd for $C_{15}H_{27}NO_2SiNa$: $[M+Na]^+$, 304.1703. Found: *m*/*z*

304.1704. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.3 min, t_{major} = 6.8 min.

(2*S*,6*R*)-2-(*tert*-Butyldimethylsilyl)-6-(2-oxo-2-phenylethyl)tetrahydro-2*H*-pyran-2-carbonitrile (4a).

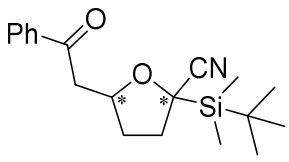


Yield: 48%, 84% *ee*, 8.0:1 dr, white solid. $[\alpha]_D^{20}$ –14.4 (*c* 0.54, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 4.39 (dddd, *J* = 13.0, 6.5, 6.5, 2.0 Hz, 1H), 3.20 (dd, *J* = 15.5, 6.5 Hz, 1H), 2.96 (dd, *J* = 15.5, 6.5 Hz, 1H), 1.95 (m, 1H), 1.89–1.71 (m, 4H), 1.34 (m ,1H), 0.94 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.6, 137.1, 133.1, 128.5, 128.2, 120.5, 72.2, 68.5, 44.9, 31.0, 30.2, 27.2, 20.3, 18.0, –8.1, –8.4. Mp. 54.8–55.5 °C. TLC: R_f 0.30 (hexane/EtOAc = 5:1). IR (KBr): 2961, 2923, 2859, 1683, 1465, 1451, 1412, 1248, 1216, 1199, 836, 761 cm^{-1}. HRMS Calcd for $C_{20}H_{29}NO_2SiNa$: $[M+Na]^+$, 366.1860. Found: *m*/*z* 366.1857. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99.0/1.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 11.7 min, t_{major} = 14.3 min.

2-(*tert*-Butyldimethylsilyl)-5-(2-oxo-2-phenylethyl)tetrahydrofuran-2-carbonitrile (4a').

The diastereomers were separated by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1) as an eluent.

Yield: 43%, 1.2:1 dr.



Major diastereomer: 72% *ee*, colorless oil. $[\alpha]_D^{20}$ +13.4 (*c* 0.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.94 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 4.66 (m, 1H), 3.46 (dd, *J* = 16.0, 5.0 Hz, 1H), 3.02 (dd,

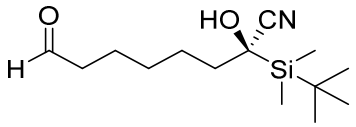
J = 16.0, 7.0 Hz, 1H), 2.48 (m, 1H), 2.30 (m, 1H), 2.12 (m, 1H), 1.68 (m, 1H), 1.01 (s, 9H), 0.123 (s, 3H), 0.119 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.6, 136.7, 133.3, 128.6, 128.2, 122.3, 77.3, 70.0, 43.8, 34.1, 30.9, 27.1, 17.8, –8.0, –8.4. TLC: R_f 0.29 (hexane/EtOAc = 5:1). IR (neat): 2951, 2931, 2885, 2860, 2213, 1677, 1597, 1581, 1473, 1409, 1299, 1251, 1213, 1044, 1002 cm^{-1}. HRMS Calcd for $C_{19}H_{27}NO_2SiNa$: $[M+Na]^+$, 352.1703. Found: *m*/*z* 352.1708. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 99.0/1.0, flow rate = 0.7 mL/min, λ = 254 nm, 40 °C): t_{minor} = 23.9 min, t_{major} = 33.9 min.

Minor diastereomer: >99% *ee*, colorless oil. $[\alpha]_D^{20}$ –7.0 (*c* 0.23, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.99 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 4.51 (m, 1H), 3.65 (dd, *J* = 17.0, 6.0 Hz, 1H), 3.18 (dd, *J* = 17.0, 7.0 Hz, 1H), 2.49 (m, 1H), 2,36 (m, 1H), 2.11 (m, 1H), 1.94 (m, 1H), 1.00 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 198.3, 136.8, 133.3, 128.6, 128.3, 123.3, 78.6, 69.5, 45.2, 35.6, 32.8, 27.1, 17.8, –8.0, –8.2. TLC: R_f 0.27 (hexane/EtOAc = 5:1). IR (neat): 2958, 2931, 2884, 2860, 2213, 1681, 1598, 1472, 1448, 1253, 1212, 1045, 1002 cm^{-1}. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 99.0/1.0, flow rate = 0.7 mL/min, λ = 254 nm, 40 °C): t_{minor} = 45.2 min, t_{major} = 47.3 min.

Procedure for synthesis of 11

To a suspension of **3i** (0.11 g, 0.30 mmol) and palladium (32 mg, 10% on carbon, 0.030 mmol) in dry acetone (2.0 mL) was added triethylsilane (0.48 mL, 3.0 mmol) dropwise at ambient temperature. After being stirred for 1 h, the reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1) as an eluent afforded **11**.

(*R*)-2-(*tert*-Butyldimethylsilyl)-2-hydroxy-8-oxooctanenitrile (11).

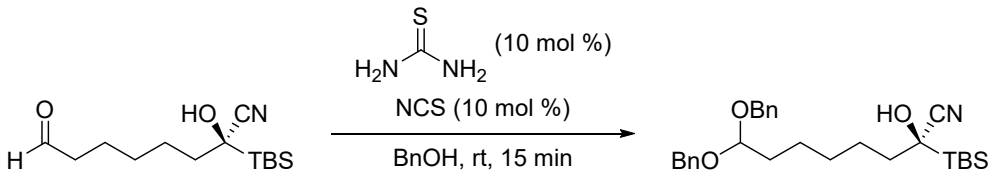


Yield: 61%, 97% *ee*, colorless oil. $[\alpha]_D^{20}$ +15.8 (*c* 0.41, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ 9.78 (t, *J* = 1.5 Hz, 1H), 2,48 (dt, *J* = 7.0, 1.5 Hz, 2H), 2.13 (br s, 1H), 1.77 (m, 2H), 1.72–1.57 (m, 4H), 1.41 (m, 2H), 1.05 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 202.5, 122.3, 64.4, 43.7, 36.4, 28.9, 27.3, 23.5, 21.8, 18.1, –7.7, –8.2. TLC: R_f 0.18 (hexane/EtOAc = 5:1). IR (neat): 3426, 2956, 2854, 2781, 2216, 1714, 1466, 1362, 1252, 1141, 841, 775 cm^{-1}. HRMS Calcd for $C_{14}H_{27}NO_2SiNa$: $[M+Na]^+$, 292.1703. Found: *m*/*z* 292.1704.

The enantiomeric excess of **11** was determined by HPLC after acetalization with benzyl alcohol.

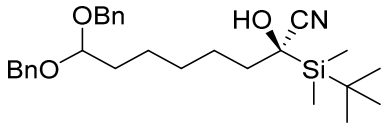
Procedure for acetalization of 11[25]



11 **21**

To a solution of thiourea (0.39 mg, 0.0052 mmol) and *N*-chlorosuccinimide (0.68 mg, 0.0052 mmol) in benzyl alcohol (0.20 mL) was added a solution of **11** (14 mg, 0.052 mmol) in benzyl alcohol (0.30 mL) at ambient temperature. After being stirred for 15 min, the reaction mixture was directly purified by flash silica gel column chromatography using hexane/EtOAc (v/v = 20:1–10:1) as an eluent to afford the corresponding acetal product **21**.

(*R*)-8,8-Bis(benzyloxy)-2-(*tert*-butyldimethylsilyl)-2-hydroxyoctanenitrile (21).



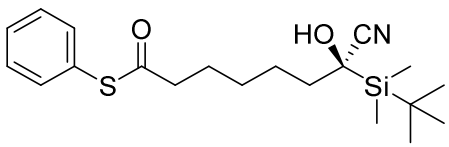
Yield: 66%, 97% *ee*, colorless oil. $[\alpha]_D^{20}$ +12.0 (*c* 0.51, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ 7.38–7.34 (m, 8H), 7.30 (m, 2H), 4.74 (t, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 2H), 4.57 (d, *J* = 11.5 Hz, 2H), 2.01 (br s, 1H), 1.80–1.71 (m, 4H), 1.62–1.55 (m, 2H), 1.45 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.38 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.05 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 138.2, 128.4, 127.8, 127.6, 122.4, 101.9, 67.2, 64.5, 36.6, 33.1, 29.2, 27.3, 24.6, 23.6, 18.2, –7.7, –8.2. TLC: R_f 0.20 (hexane/EtOAc = 5:1). IR (neat): 3427, 2932, 2861, 2214, 1465, 1455, 1365, 1253, 1121, 1045, 1023, 839, 778, 732 cm^{-1}. HRMS Calcd for $C_{28}H_{41}NO_3SiNa$: $[M+Na]^+$, 490.2748. Found: *m*/*z* 490.2747. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 2.0 mL/min, λ = 220 nm, 40 °C): t_{minor} = 3.0 min, t_{major} = 3.4 min.

Procedure for synthesis of 10

In a round-bottom flask were placed palladium (0.28 g, 10% on carbon, 0.27 mmol), **3i** (0.20 g, 0.53 mmol), and dry EtOAc (5.0 mL). The resulting mixture was stirred at ambient temperature under hydrogen atmosphere (760 torr, balloon). After being stirred for 55 h, the mixture was filtered to remove palladium, and the filtrate was concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent afforded **10**.

***S*-Phenyl (*R*)-7-(*tert*-butyldimethylsilyl)-7-cyano-7-hydroxyheptanethioate (10)**.



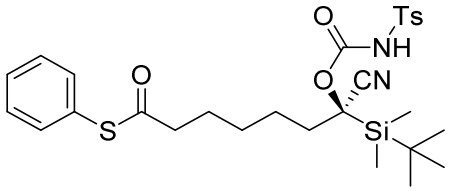
Yield: 67%, 97% *ee*, colorless oil. $[\alpha]_D^{20}$ +10.8 (*c* 1.26, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ 7.41 (m, 5H), 2.69 (t, J = 7.0 Hz, 2H), 2.04 (br s, 1H), 1.82–1.71 (m, 4H), 1.64 (m, 2H), 1.46 (m, 2H), 1.05 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.5, 134.5, 129.4, 129.2, 127.7, 122.3, 64.4, 43.3, 36.4, 28.7, 27.3, 25.3, 23.4, 18.2, –7.7, –8.2. TLC: R_f 0.10 (hexane/EtOAc = 10:1). IR (neat): 3426, 2932, 2860, 2215, 1710, 1479, 1465, 1366, 1252, 1024, 839, 778 cm^{-1}. HRMS Calcd for $C_{20}H_{31}NO_2SSiNa$: $[M+Na]^+$, 400.1737. Found: *m*/*z* 400.1733. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.2 min, t_{major} = 6.7 min.

Procedure for synthesis of 12[26]

To a solution of **10** (38 mg, 0.10 mmol) in dry THF (0.50 mL) was added *p*-toluenesulfonyl isocyanate (30 μL, 0.20 mmol) at ambient temperature. After being stirred for 23 h, the reaction mixture was passed through a short silica gel pad and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–5:1) as an eluent gave **12**.

_S_-Phenyl (_R_)-7-(*tert*-butyldimethylsilyl)-7-cyano-7-((tosylcarbamoyl)oxy)- heptanethiolate (12).



Yield: 82%, 98% *ee*, colorless oil. $[\alpha]_D^{20}$ +40.4 (*c* 0.21, CH_2Cl_2).

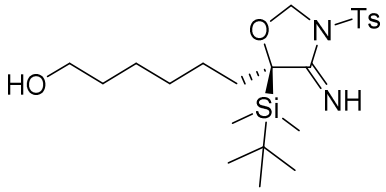
^{1}H NMR ($CDCl_3$) δ 9.16 (br s, 1H), 7.95 (m, 2H), 7.42–7.40 (m, 5H), 7.38 (m, 2H), 2.56 (t, J = 7.5 Hz, 2H), 2.45 (s, 3H), 1.96 (m, 2H), 1.53 (m, 2H), 1.26 (m, 2H), 1.07 (m, 1H), 0.94 (m, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.2, 157.4, 150.6, 147.0, 134.5, 133.9, 130.0, 129.4, 129.2, 128.4, 127.7, 86.8, 43.3, 35.1, 28.5, 27.3, 25.2, 21.8, 21.1, 18.2, –7.9, –8.0. TLC: R_f 0.21 (hexane/EtOAc = 5:1). IR (neat): 3325, 2930, 2861, 1798, 1703, 1683, 1384, 1308,

1178, 1153, 1089, 830 cm^{-1}. HRMS Calcd for $C_{28}H_{38}N_2O_5S_2SiNa$: $[M+Na]^+$, 597.1884. Found: *m*/*z* 597.1885. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 225 nm, 40 °C): t_{minor} = 10.3 min, t_{major} = 11.1 min.

Procedure for synthesis of 13

To a suspension of lithium aluminum hydride (12 mg, 0.33 mmol) in dry THF (1.0 mL) was added a solution of **12** (38 mg, 0.065 mmol) in dry THF (1.0 mL) dropwise at 0 °C. The reaction was allowed to warm to ambient temperature. After the resulting mixture was stirred for 2.5 h, saturated aqueous solution of Rochelle salt (2.0 mL) was added slowly. The mixture was stirred for 1 h, and the aqueous layers were extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1–1:1) as an eluent gave **13**.

(*R*)-6-(5-(*tert*-Butyldimethylsilyl)-4-imino-3-tosyloxazolidin-5-yl)hexan-1-ol (13).

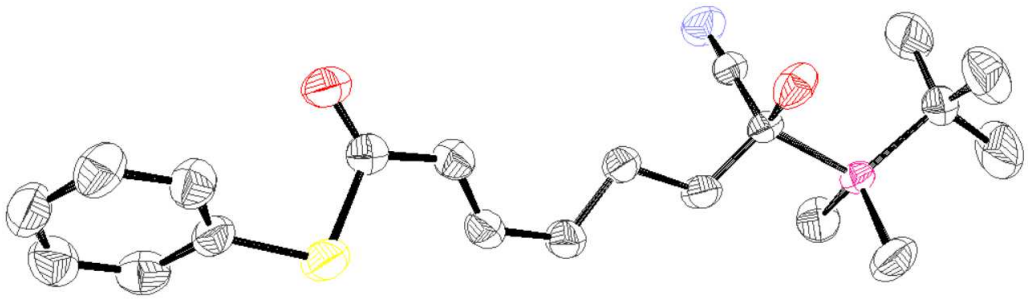


Yield: 70%, 98% *ee*, colorless oil. $[\alpha]_D^{20}$ +25.0 (*c* 0.56, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ 8.44 (br s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.24 (d, *J* = 2.0 Hz, 1H), 5.17 (d, *J* = 2.0 Hz, 1H), 3.59 (m, 2H), 2.40 (s, 3H), 1.82 (m, 2H), 1.66 (br s, 1H), 1.48 (m, 2H), 1.35 (m, 1H), 1.23–1.18 (m, 4H), 1.01 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), –0.11 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.2, 142.9, 139.1, 129.2, 126.3, 86.7, 81.5, 62.9, 35.3, 32.4, 29.0, 27.3, 25.3, 22.6, 21.5, 18.2, –7.1, –7.3. TLC: R_f 0.20 (hexane/EtOAc = 1:1). IR (neat): 3485, 3353, 2908, 1755, 1616, 1471, 1410, 1332, 1274, 1149, 1056, 1011, 929, 832 cm^{-1}. HRMS Calcd for $C_{22}H_{38}N_2O_4SSiNa$: $[M+Na]^+$, 477.2214. Found: *m*/*z* 477.2213. HPLC (Daicel Chiralpak IA,

hexane/*i*-PrOH = 90.0/10.0, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 23.3 min, t_{major} = 25.2 min.

ORTEP Drawing of 3i



A. Crystal Data

Empirical Formula	$C_{20}H_{29}NO_2SSi$
Formula Weight	375.60
Crystal Color, Habit	Colorless, Prism
Crystal Dimensions	0.560 × 0.220 × 0.130 mm
Crystal System	Monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 11.355(2) Å
	b = 7.1427(9) Å
	c = 13.848(2) Å
	β = 105.804(7)°
	V = 1080.7(3) $Å^3$
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.154 g/cm^3
F_{000}	404.00
μ(MoKα)	2.172 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å)
	Graphite monochromated
Voltage, Current	50 kV, 12mA
Temperature	20.0 °C
Detector Aperture	75 mm (diameter)
Data Images	1080 exposures
ω Oscillation Range	–60.0–120.0°
Exposure Rate	4.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	64.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	64.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	64.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	64.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	64.0 sec./°
Detector Swing Angle	30.00°

Detector Position	50.00 mm
Pixel Size	0.146 mm
$2\theta_{max}$	55.0°
No. of Reflections Measured	Total: 10611
	Unique: 4922 (R_{int} = 0.0191)
	Friedel pairs: 2248
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.854–0.972)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w $(F_0^2 - F_c^2)^2$
Least Squares Weights	$w = 1/[\sigma^2(F_0^2) + (0.0504.P)^2$
	+ 0.2026.P]
	where $P = (Max(F_0^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	55.0°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	4922
No. Variables	227
Reflection/Parameter Ratio	21.68
Residuals: R1 (I>2.00σ(I))	0.0389
Residuals: R (All reflections)	0.0448
Residuals: wR2 (All reflections)	0.1008

Goodness of Fit Indicator	1.041
Flack Parameter (Friedel pairs = 2248)	0.07(9)
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.34 $e^{-}/Å^3$
Minimum peak in Final Diff. Map	–0.33 $e^{-}/Å^3$

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18. Results of further catalyst screening are described in Table 3. These results imply that the appropriate bulkiness around a basic amino group of bifunctional catalysts is crucial for suppressing the Brook rearrangement.
19. Reported cyanation methods were applied to the substrate **1a** (refs 1j and 1k); these methods afforded **3a** in much lower enantioselectivities than the presented method. See Scheme 7 and 8 for details.
20. The in situ generated acylsilane cyanohydrin **3a** was insoluble to *n*-hexane, which seems to prevent the following cycloetherification.
21. (a) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050. (b) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121. (c) Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87.
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Publication List

1. Parts of present Thesis have been or are to be published in the following journals.

Chapter 1 Matsumoto, A.; Asano, K.; Matsubara, S. A chiral phosphoric acid catalyst for asymmetric construction of 1,3-dioxanes. *Chem. Commun.* **2015**, *51*, 11693–11696. – Reproduced by permission of The Royal Society of Chemistry.

Chapter 2 Matsumoto, A.; Asano, K.; Matsubara, S. Diastereoselective Reduction of β-(1,3-Dioxan-4-yl)ketones. *Synlett* **2015**, *26*, 1872–1874.
(Chapter 2 is the unedited Author's version of a Submitted Work that was subsequently accepted for publication in *Synlett*. To access the final edited and published work, see the following website: https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0034-1378725.)

Chapter 3 Matsumoto, A.; Asano, K.; Matsubara, S. Asymmetric *syn*-1,3-Dioxane Construction via Kinetic Resolution of Secondary Alcohols Using Chiral Phosphoric Acid Catalysts. *To be submitted.*
(Chapter 3 is the Author's version of an Unsubmitted Work that will be submitted for publication.)

Chapter 4 Matsumoto, A.; Asano, K.; Matsubara, S. Organocatalytic Enantio- and Diastereoselective Acetalization of δ-Oxoenones via Cyanohydrin Formation. *To be submitted.*
(Chapter 4 is the Author's version of an Unsubmitted Work that will be submitted for publication.)

Chapter 5 Matsumoto, A.; Asano, K.; Matsubara, S. Kinetic Resolution of Acylsilane Cyanohydrins via Organocatalytic Cycloetherification. *Chem.—Asian J.* **2019**, *14*, 116–120.
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2. Following publication is not included in this Thesis.

1. Yoneda, N.; Matsumoto, A.; Asano, K.; Matsubara, S. Asymmetric Cycloetherification via the Kinetic Resolution of Alcohols Using Chiral Phosphoric Acid Catalysts. *Chem. Lett.* **2016**, *45*, 1300–1303.

2. Miyaji, R.; Wada, Y.; Matsumoto, A.; Asano, K.; Matsubara, S. Bifunctional Organocatalysts for the Asymmetric Synthesis of Axially Chiral Benzamides. *Beilstein J. Org. Chem.* **2017**, *13*, 1518–1523.

3. Yoneda, N.; Fujii, Y.; Matsumoto, A.; Asano, K.; Matsubara, S. Organocatalytic Enantio- and Diastereoselective Cycloetherification via Dynamic Kinetic Resolution of Chiral Cyanohydrins. *Nat. Commun.* **2017**, *8*, 1397.

4. Einaru, S.; Shitamichi, K.; Nagano, T.; Matsumoto, A.; Asano, K.; Matsubara, S. *trans*-Cyclooctenes as Halolactonization Catalysts. *Angew. Chem., Int. Ed.* **2018**, *57*, 13863–13867.

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