Development of High Turnover Hypoiodite Salt Catalysis for Enantioselective Oxidative Cyclization Reactions

Hiroki Hayashi

Graduate School of Engineering, Nagoya University

Nagoya, 2016
Contents

Chapter 1  Introduction and General Summary ................................................................. 1

Chapter 2  High-Turnover Hypoiodite Catalysis for Asymmetric Synthesis of Tocopherols .......... 23

Chapter 3  Chiral Ammonium Hypoiodite Salt-Catalyzed Enantioselective Oxidative Cycloetherification to 2-Acyl Tetrahydrofurans ........................................................................ 83

Research Achievement ........................................................................................................ 101

Acknowledgement .................................................................................................................. 106
Chapter 1

Introduction and General Summary
1-1 Introduction

Over the past several decades, transition-metal-catalyzed coupling reactions between a nucleophile and an electrophile have been developed to create carbon–carbon or carbon–heteroatom bonds (Scheme 1).\(^1\) Although these reactions have played a central role in synthetic organic chemistry, most of them require the pre-functionalization of substrates through multi-step syntheses to prepare compounds such as organometallic complexes or organic halides. In particular, several electrophiles have been prepared from the corresponding nucleophiles. Moreover, the side-products derived from such pre-functionalized substrates are also generated (X–Y). To avoid the multi-step preparation of substrates and the generation of waste, the development of a direct coupling process is important for green and sustainable chemistry.

An oxidative coupling reaction can proceed directly between two nucleophiles without such pre-functionalization, and the side-products derived from the substrates, such as hydrogen gas, water or hydrogen peroxide as are environmentally clean (Scheme 1).\(^2\) In contrast to the traditional coupling process, oxidative coupling reactions proceed via the in situ activation of a substrate to form reactive intermediates. To date, numerous methods for oxidative coupling have been developed. However, in most cases, precious transition metal or heavy metal complexes have been used to promote the reactions. To achieve green and sustainable chemistry, the use of these metals should be avoided.

**Scheme 1. Transition-Metal-Catalyzed Traditional and Oxidative Coupling Reactions**

\[
\begin{align*}
R^1-X & \quad + \quad R^2-Y \quad \xrightarrow{\text{transition-metal catalysts}} \quad R^1-R^2 \quad + \quad X-Y \\
\text{(X,Y = BR}_2, \text{SiR}_3, \text{SnR}_3, \text{Cl, Br, I, OTf, etc.)}
\end{align*}
\]

Iodine has attracted considerable attention as an alternative to transition or heavy metals due to its environmentally benign characteristics. Iodine can be easily oxidized to an oxidation state of +1, +3, +5, or +7, since it is the most polarizable and least electronegative halogen. Thus, over the past three decades, hypervalent organoiodine reagents (III or V), which are less toxic, milder and cleaner oxidants, have been used in various oxidative transformations.\(^3\) However, the stoichiometric use of these reagents should be avoided because of their potential shock-sensitive
explosiveness. In 2005, in situ-generated hypervalent organoiodine-catalyzed oxidative coupling reactions were developed by using a catalytic amount of iodoarenes in the presence of an oxidant such as meta-chloroperbenzoic acid (m-CPBA) (Figure 1, left). Ochiai and colleagues developed an α-oxyacetylation of ketones by using iodobenzene in the presence of Lewis acid additives in acetic acid. Kita and colleagues reported a similar catalytic system for the oxidative spirolactonization of phenols by using 4-methyl iodobenzene in the presence of trifluoroacetic acid. After these pioneer works, various oxidative coupling reactions, including enantioselective reactions with chiral hypervalent organoiodine catalysts, have been developed. However, these reactions have used relatively expensive and explosive peracids and Lewis or Brønsted acid additives. Moreover, side-products derived from the oxidants and additives are generated.

![Figure 1. Hypervalent Organoidine(III) and Hypoiodite Catalytic Oxidation Systems](image)

On the other hand, inorganic hypervalent iodines have been recognized as powerful oxidants. Although iodate (IO₃⁻) and periodate (IO₄⁻) species are stable and well-known reagents for oxidative reactions, hypoiodite (IO⁻) and iodite (IO₂⁻) species have been less developed because of their instability. Hypoiodite salts can be prepared in situ by the hydrolysis of stoichiometric molecular iodine in alkaline solutions for oxidation and iodofunctionalization. Recently, hypoiodite-catalyzed oxidative coupling reactions have been developed (Figure 1, right). The hypoiodite salts are generated in situ from the corresponding iodides in the presence of inexpensive and mild oxidants such as hydrogen peroxide or alkyl hydroperoxides. In contrast to hypervalent organoiodine catalysis, this catalytic oxidation system proceeds under milder conditions and the only side-products derived from the oxidants are water or alcohol. In 2007, Kirihara and colleagues reported the first hypoiodite-catalyzed oxidative homocoupling of sulfides with a catalytic amount of sodium iodide or molecular iodine in the presence of hydrogen peroxide as an oxidant. In 2010, our group developed the first chiral hypoiodite salt-catalyzed enantioselective oxidative cycloetherification of ketophenols by using a catalytic amount of chiral quaternary
ammonium iodide in the presence of hydrogen peroxide or tert-butyl hydroperoxide (TBHP) as an oxidant. After these pioneering findings, rapid progress has been made in the development of inorganic iodine-catalyzed oxidative transformations.

This thesis focuses on the development of a high-turnover chiral hypoiodite salt catalysis for enantioselective oxidative coupling, especially, oxidative cyclization reactions.

1-2 Chiral Hypoiodite-Catalyzed Enantioselective Oxidative Cycloetherification to Chromans (Chapter 2)

Chiral chroman is a key structure in many medicinally and biologically active compounds (Figure 2). In particular, the most prominent chiral chroman is α-tocopherol which belongs to the vitamin E family analog with β-, γ- and δ-tocopherols and tocochromanols. α-Tocopherol is a fat-soluble chain-breaking antioxidant that acts as a scavenger of radical or singlet oxygen in tissues. In addition, α-tocopherol possesses physiologically diverse properties, including antitumor, anti-inflammatory, anti-atherosclerosis, and cell-signaling activities. Various non-natural tocopherol analogues have also been developed because of their potency and distinct structural features. Trolox, a water-soluble analogue of α-tocopherol, has been used as a chiral derivatizing reagent and its derivatives are able to release nitric oxide to prevent the oxidative modification of low-density lipoprotein (LDL). MDL-73404 has cardio-protective properties for reperfusion of the myocardium. SNK-860 is a potent aldose reductase inhibitor that is used in the treatment of diabetic neuropathy. Dihydrodaedalin A is a synthetic intermediate of daedalin A, which is a potent tyrosinase inhibitor that has been shown to suppress melanogenesis in human skin without affecting cell viability. Clusifoliol, a natural product isolated from a plant of *Peperomia clusifolia*, has antitumor activity. C48, developed by Merck laboratories, is a potent, selective PPARGα/γ dual agonist and exhibits substantial antihyperglycemic and hypolipidemic activities. Nebivolol is a β1-selective adrenergic receptor blocker that is used for the treatment of hypertension.

Natural \( D-\alpha \)-tocopherol is formally \( (2R,4'R,8'R)-2,5,7,8\)-tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chromanol. On the other hand, commercial, totally synthetic α-tocopherol is produced as a mixture of all eight stereoisomers (~35,000 ton per year worldwide). A semisynthetic, isomerically pure \( D-\alpha \)-tocopherol is obtained by the enrichment and purification of mixtures of tocopherol homologues from soya distillates in a limited volume (~2,000 tons per year) due to the limited availability of the starting materials from natural sources and the need for complex technology. Among the three stereocenters present in α-tocopherol, that at the chroman ring with a \( (2R) \)-configuration is critical
for its biological activity, since the (2S)-enantiomer is not recognized by the tocopherol transfer protein. Thus, the development of a method for enantioselective construction of the chroman ring has been an important subject in synthetic organic chemistry. To address this issue, enantioselective processes have been developed by using chiral transition-metal complexes or organocatalysts.

Figure 2. Medicinally and Biologically Active Chromans

Achiwa and Trost independently reported asymmetric allylic substitution catalyzed by chiral palladium complexes (Scheme 2a, b). In particular, Trost and colleagues achieved the construction of a chiral chroman core of D-α-tocopherol with high enantioselectivity by using C₂-symmetric dianinocyclohexyl ligands (Scheme 2b). Tietze and colleagues reported the palladium-catalyzed enantioselective Wacker-type cyclization and subsequent Heck reaction with methyl acrylate to give chroman derivatives with excellent enantioselectivity (Scheme 2c).

Recently, Kitamura and Rueping independently reported the enantioselective dehydrative cyclization to give the chromans with high enantioselectivities catalyzed by chiral ruthenium or gold complexes, respectively (Scheme 2d, e).
Scheme 2. Representative Examples of Transition-Metal-Catalyzed Enantioselective Synthesis of Chromans

a) Achiwa et al.\textsuperscript{24a}

\[
\begin{align*}
\text{BnO} & \quad \text{OCO}_2\text{Me} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
Pd_2\text{dba}_3 (3 \text{ mol\%}) \\
(R,S)-\text{BPPFA} (6 \text{ mol\%})
\end{align*}
\]

\[
\begin{align*}
\text{THF, } 40 \, ^\circ \text{C, } 20 \, \text{h}
\end{align*}
\]

55\% yield, 54\% ee

b) Trost et al.\textsuperscript{24b,c}

\[
\begin{align*}
\text{BnO} & \quad \text{OCO}_2\text{Me} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
Pd_2\text{dba}_3 (1 \text{ mol\%}) \\
(R,R)-\text{Trost Ligand} (3 \text{ mol\%})
\end{align*}
\]

\[
\begin{align*}
\text{Et}_3\text{N} (1.5 \text{ equiv}) \\
\text{CH}_2\text{Cl}_2, \text{ RT, } 3 \, \text{h}
\end{align*}
\]

89\% yield, 86\% ee

c) Tietze et al.\textsuperscript{24d,e}

\[
\begin{align*}
\text{BnO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
Pd(\text{OTFA})_2 (10 \text{ mol\%}) \\
(S,S)-\text{Bn-BOXAX} (40 \text{ mol\%})
\end{align*}
\]

\[
\begin{align*}
\text{Methy acrylate} (5 \text{ equiv}) \\
\text{p-Benzоquinone} (4 \text{ equiv}) \\
\text{CH}_2\text{Cl}_2, \text{ RT, } 3 \, \text{days}
\end{align*}
\]

84\% yield, 97\% ee

d) Kitamura et al.\textsuperscript{24f}

\[
\begin{align*}
\text{BnO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
[Cp\text{Ru(\text{CH}_3\text{CN})}_3]PF_6 (1 \text{ mol\%}) \\
(R)-\text{Cl-Naph-Py-CO}_2\text{Allyl} (1 \text{ mol\%})
\end{align*}
\]

\[
\begin{align*}
t-\text{BuOH/DMA, } 100 \, ^\circ \text{C, } 24 \, \text{h}
\end{align*}
\]

97\% yield, 94\% ee

e) Rueping et al.\textsuperscript{24g}

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{AuCl·DMS} (2.5 \text{ mol\%}) \\
(R)-\text{DM-SEGPHOS} (1.25 \text{ mol\%})
\end{align*}
\]

\[
\begin{align*}
\text{AgOTf} (2.5 \text{ mol\%}) \\
\text{Toluene, RT, } 24 \, \text{h}
\end{align*}
\]

98\% yield, 85\% ee
On the other hand, enantioselective organocatalysis has also been developed for the asymmetric synthesis of chromans. Woggon and colleagues reported the intermolecular asymmetric aldol/Michael cascade reactions to construct the chiral chroman with high enantio- and diastereoselectivity towards the total synthesis of D-α-tocopherol (Scheme 3a). Ishikawa and colleagues reported an intramolecular Michael addition to give the chroman derivatives in moderate yield with high enantioselectivity (Scheme 3b). However, low catalytic activities and/or moderate enantioselectivities have limited their utility.

**Scheme 3. Representative Examples of the Organocatalyzed Enantioselective Synthesis of Chromans**

**a) Woggon et al.**

\[ \text{MeO} \quad \text{CHO} + \quad \text{OHC} \quad \text{(1.5 equiv)} \quad \rightarrow \quad \text{BnO} \quad \text{Ar} \quad \text{Ar} \quad \text{OTES} \quad \text{PhCO}_2\text{H (30 mol%) Toluene, RT, 3 days} \]

58% yield, 99% ee 98.5:1.5 dr

**b) Ishikawa et al.**

\[ \text{MeO} \quad \text{OH} \quad \text{CO}_2\text{Me} \quad \rightarrow \quad \text{BnO} \quad \text{R} \quad \text{CO}_2\text{Me} \quad \text{CH}_2\text{Cl}_2, \text{RT, 4 days} \]

39%, 87% ee

Thus, the significant and diverse biological activities of tocopherols and their analogues have inspired considerable interest in their efficient asymmetric synthesis in both academia and the pharmaceutical industry. However, the asymmetric synthesis of naturally identical D-α-tocopherol has not yet been industrialized, presumably due to the insufficient turnover frequency of the catalysts, insufficient selectivity, and/or the formation of excessive amounts of waste materials.

In 2010, our group developed a chiral hypoiodite salt catalysis for the enantioselective cycloetherification reactions (Scheme 4). The chiral hypoiodite salts are generated in situ from the corresponding ammonium iodides in the presence of hydrogen peroxide or TBHP. Enantioselective oxidative five-membered-ring cyclization of β-(2-hydroxyphenyl)ketones 2 to 2-acyl-2,3-dihydrobenzofurans 3 has been developed for the synthesis of chiral 2,3-dihydrobenzofurans. The use of chiral spirobis(binaphthyl)-based quaternary ammonium
cation 1a\textsuperscript{26} and an \textit{N}-phenylimidazol-2-yl group as an auxiliary of the substrate\textsuperscript{27} were important for obtaining high enantioselectivities.

**Scheme 4.** Chiral Hypoiodite-Catalyzed Enantioselective Oxidative Five-Membered Cycloetherification to Give 2-Acyl-2,3-Dihydrobenzofurans

We envisioned that this hypoiodite salt catalysis could be used for the enantioselective oxidative six-membered cyclization of hydroquinone-derived \(\gamma\)-(2-hydroxyphenyl)ketones 4 directed towards \textit{D-\(\alpha\)-tocopherol} (\textit{Chapter 2}).\textsuperscript{28} However, to our surprise, the oxidative cycloetherification of 4a did not proceed to give the desired chroman product 5a, and dearomatization by-product 6 was obtained under conditions identical to those in five-membered-ring cyclization (Scheme 5).\textsuperscript{11}

**Scheme 5.** Initial Investigation of Six-Membered Oxidative Cycloetherification towards \textit{D-\(\alpha\)-Tocopherol}

- **5-Membered cyclization\textsuperscript{10c}**

- **6-Membered cyclization\textsuperscript{28}**

To consider these distinct features of the cyclization of similar substrates, the catalytic
mechanism and side-reaction pathway are summarized in Figure 3. Kinetic studies revealed that bond-forming cyclization was a rate-determining step in the catalytic cycle. Since six-membered cyclization was found to be much slower than five-membered cyclization, undesired side reactions such as the dearomatization of phenol via phenyl hypoiodite intermediate 7 preferentially proceeded to give byproduct 6. In addition, inactivation of the catalyst was a significant problem since an unstable hypoiodite species was easily converted to an inert species via disproportionation or reductive decomposition. For the construction of an efficient catalytic cycle, the oxidative cyclization step should not be rate-limiting. To address this issue, the oxidation of iodide should be decelerated, oxidative cyclization should be accelerated, or inactivation should be suppressed or reversed.

![Proposed Catalytic Mechanism for Oxidative Cycloetherification and Side Reactions](image)

**Figure 3. Proposed Catalytic Mechanism for Oxidative Cycloetherification and Side Reactions**

After intensive investigations, we achieved a highly chemo- and enantioselective oxidative cycloetherification of 4 to tocopherol derivatives 5 (*Scheme 6*). The use of alkyl hydroperoxide such as TBHP or cumene hydroperoxide (CHP) as a weaker oxidant instead of hydrogen peroxide
decelerated the oxidation of iodide\textsuperscript{31} and suppressed the reductive decomposition of hypoiodite.\textsuperscript{30d} The tuning of the acidity of the 2-hydroxyphenyl moieties of substrates 4 with electron-withdrawing protective groups was crucial for the chemoselective oxidative carbon–oxygen coupling because electron-rich 2-hydroxyphenyl moieties are easily dearomatized in the oxidative reactions. The chiral catalyst 1b bearing perfluoroalkyl group-substituted biphenyl at the 3,3’-position led to the highest chemical yields and enantioselectivities. We achieved the formal syntheses of D-\(\alpha\)-tocopherol, D-\(\alpha\)-tocotrienol and (S)-trolox. Moreover, potential synthetic intermediates for other tocopherols, tocotrienols, and other biologically active compounds such as dihydrodaedalin A and Merck’s compound C48 can be prepared with excellent enantioselectivities.

**Scheme 6. High-Turnover Hypoiodite Catalysis for the Enantioselective Synthesis of Tocopherols**

\[\text{Raman Analysis} \quad [R_4N]^+I^- \quad \xrightarrow{\text{ROOH}} \quad [R_4N]^+\{IO\}^- \quad \text{active species} \quad \text{(unstable)} \quad \xrightarrow{\text{I}^-} \quad [R_4N]^+\{I_3\}^- \quad \text{inert species} \quad \text{(stable)} \]

Raman spectroscopic analysis and control experiments revealed that hypoiodite salt was an unstable catalytic active species and triiodide salt was a stable inert species for the hypoiodite/TBHP oxidation system (Scheme 6). In contrast, the main inactivation path for the
hypoiodite/hydrogen peroxide oxidation system might be the catalytic decomposition of hydrogen peroxide by the hypoiodite (or hypiodous acid)/iodide couple. 11 By considering these important findings, a high-performance catalytic oxidation system (turnover number of the catalyst ~2000) has been achieved by reversible equilibrium between hypoiodite and triiodide in the presence of an inorganic base like potassium carbonate. These findings may lead to new concepts for the development of high-turnover redox organocatalysis.

To gain mechanistic insight into our oxidative cyclization, we examined the oxidative cyclization of β-(2-hydroxyphenyl)ketones and β-(2-aminophenyl)ketone. There are several possible reaction mechanisms for the cyclization step (Scheme 7). We speculated that cyclization might proceed via ammonium enolate intermediate 8 (path a) or ammonium phenoxide (X = O) or anilide (X = NPG) intermediates 9 or 10 (path b). However, the positions of the iodine(+1) and the ammonium cation, and the E/Z-selectivities of 8 and 9 were not clear. Hammett studies using para-substituted phenols and anilines indicated that a partial positive charge is developed in the transition state. Thus, intramolecular cyclization might proceed via intermediate 8 (path a) rather than 9 or 10. 34 We are currently investigating the detailed reaction mechanism by further experimental and computational studies.

Scheme 7. Proposed Mechanism for Hypoiodite-Catalyzed Oxidative Cyclization

During the course of our investigation to develop methods for the synthesis of chroman, electron-rich phenols were found to be dearomatized under the hypoiodite catalytic conditions (Scheme 5, Figure 3). 28 Based on this finding, our group achieved a chiral ammonium hypoiodite-catalyzed enantioselective oxidative dearomatization of 1-naphthols tethered to a carboxylic acid moiety at the 2-positions in the presence of hydrogen peroxide (Scheme 8).
Importantly, high enantioselectivity could be achieved in this oxidative dearomatization even in the absence of an imidazolyl auxiliary, which was required for our previous oxidative cyclization reactions.\textsuperscript{11,28}

**Scheme 8. Chiral Hypoiodite-Catalyzed Enantioselective Oxidative Dearomatization**

On the other hand, in 2015, Nachtsheim and colleagues reported the oxidative intra- and intermolecular coupling of phenols and 2-aminoacetophenones by using tetrabutylammonium iodide in the presence of TBHP (Scheme 9).\textsuperscript{35b}

**Scheme 9. Hypoiodite-Catalyzed Intra- and Intermolecular Coupling of Phenols and 2-Aminoacetophenones**

1-3 **Chiral Hypoiodite-Catalyzed Enantioselective Oxidative Cycloetherification to 2-Acyl Tetrahydrofurans (Chapter 3)**

A chiral tetrahydrofuran (THF) core is a fundamental structure in natural products and pharmaceuticals (Figure 4).\textsuperscript{36} In particular, many biologically active compounds contain a tetrahydro-2-furoyl skeleton. For example, terazosin is a drug that is used as a \( \alpha_1 \)-adrenergic blocker for the treatment of hypertension and benign prostatic hypertrophy, and can alleviate organ damage \textit{in vivo} by binding to phosphoglycerate kinase 1.\textsuperscript{37a,b} Alfuzosin is another drug that is prescribed as a clinically uroselective \( \alpha_1 \)-adrenergic blocker for the treatment of benign prostatic hypertrophy.\textsuperscript{37c} Furnidipine, which can be prepared from tetrahydrofuran-2-carboxylic acid, is a
Ca\(^{2+}\) antagonist that is used for the treatment of cardiomyopathy associated with hypertension.\(^{37d}\) A cathepsin K inhibitor exhibits a biological activity in diseases caused by an increase in bone resorption.\(^{37e}\) Faropenem is an oral penem antibiotic that is used for the treatment of community-acquired respiratory tract infections.\(^{37f}\) While some of these compounds are used as racemic mixtures, the configuration of the C2 position of tetrahydrofurans is important for their biological activities.\(^{37}\) In the synthesis of these compounds, tetrahydrofuran-2-carboxylic acid is used to introduce the tetrahydro-2-furoyl moiety. Thus, the development of a straightforward method for the preparation of chiral 2-acyl tetrahydrofurans is an important subject in synthetic organic chemistry and medicinal chemistry.

\[ \text{Figure 4. Medicinally and Biologically Active Tetrahydrofuran Derivatives} \]

Several methods have been developed using transition-metal catalysts for intra- and intermolecular enantioselective synthesis of 2-substituted tetrahydrofurans (Scheme 10). Toste and colleagues reported a chiral gold-catalyzed intramolecular hydroalkoxylation of allenes to give 2-vinyl tetrahydrofurans (Scheme 10a).\(^{38a}\) Kitamura and colleagues reported an enantioselective dehydrative cyclization to give 2-vinyl tetrahydrofurans catalyzed by chiral ruthenium complexes (Scheme 10b).\(^{24f}\) Sigman and colleagues reported a palladium-catalyzed enantioselective intramolecular oxyfunctionalization of alkenes via an ortho-quinone methide intermediate (Scheme 10c).\(^{38b}\) Johnson and colleagues reported a chiral Lewis acid-catalyzed enantioselective cycloaddition of cyclopropanes and aldehydes to give tetrahydrofurans (Scheme 10d).\(^{38c}\) Trost and colleagues reported a palladium-catalyzed enantioselective cycloaddition of trimethylenemethane with aldehydes or ketones to give methylenetetrahydrofurans (Scheme 10e).\(^{38d,e}\)
Scheme 10. Representative Examples of the Metal-Catalyzed Enantioselective Synthesis of 2-Substituted Tetrahydrofurans

a) Toste et al.\textsuperscript{38a}

\[
\begin{align*}
R^1 & R^1 \quad R^1 \quad R^1 \\
R^2 & R^2 \quad R^2 \quad R^2
\end{align*}
\]

![Diagram](image1)

\[
dppm(AuCl)\textsubscript{2} (2.5 mol\%) \\
(R)-Ag-phosphate (5 mol\%)
\]

Benzene, RT, 1–30 h

\[
\begin{align*}
R^1 & R^1 \quad R^3 \\
R^2 & R^2 \quad R^3
\end{align*}
\]

81–96% yield, 90–99% ee

b) Kitamura et al.\textsuperscript{24f}

\[
\begin{align*}
\text{HO} & \text{OH} \\
R & R
\end{align*}
\]

![Diagram](image2)

\[
\begin{align*}
[\text{CpRu(CH\textsubscript{3})\textsubscript{3}]PF}_6 & (1 \text{ mol}\%) \\
(R)-\text{Cl-Naph-Py-COOAllyl} & (1 \text{ mol}\%)
\end{align*}
\]

DMA, 100 °C, 1 h

>99% yield, 88–94% ee

c) Sigman et al.\textsuperscript{38b}

\[
\begin{align*}
\text{HO} & \text{OH} \\
R & R
\end{align*}
\]

![Diagram](image3)

\[
Pd(\text{MeCN})\textsubscript{2}Cl\textsubscript{2} (4 \text{ mol}\%)
\]

(S)-i-PrQuinox (14 mol%)

CuCl (8 mol%)

ROH or NaN\textsubscript{3} (50 equiv)

KHCO\textsubscript{3} (40 mol%)

O\textsubscript{2}, RT, 3–24 h

51–72% yield, 88–98% ee

4:1–10:1 dr

d) Johnson et al.\textsuperscript{38c}

\[
\begin{align*}
\text{CO\textsubscript{2}Me} & \text{CO\textsubscript{2}Me} \\
R^1 & R^2
\end{align*}
\]

![Diagram](image4)

\[
\begin{align*}
\text{O} & \text{H} \\
R^1 & R^2
\end{align*}
\]

51–72% yield, 88–98% ee

4:1–10:1 dr

e) Trost, et al.\textsuperscript{38d,e}

\[
\begin{align*}
\text{O} & \text{R^1} \\
R^2 & \text{TMS}
\end{align*}
\]

![Diagram](image5)

\[
\begin{align*}
\text{In(acac)}\textsubscript{3} & (0 \text{ or } 10 \text{ mol}\%) \\
\text{Toluene} & \text{RT–50 °C}
\end{align*}
\]

60–99% yield, 70–95% ee

On the other hand, Matsubara and colleagues reported an enantioselective Michael addition catalyzed by chiral bifunctional organocatalysts to give 2-substituted tetrahydrofurans (Scheme IIa).\textsuperscript{39a,b} With the use of a haloetherification strategy, Yeung and colleagues recently reported an
enantioselective bromoetherification and desymmetrization to give chiral tetrahydrofurans by using chiral sulfide-based Lewis base organocatalysts (Scheme 11b). 39c

Scheme 11. Representative Examples of the Organocatalyzed Enantioselective Synthesis of 2-Substituted Tetrahydrofurans

Although numerous methods have been developed for the synthesis of chiral tetrahydrofurans (Schemes 10 and 11), there have been few reports of a direct enantioselective synthesis of chiral 2-acyl tetrahydrofurans. Conventionally, biologically active compounds that contain a chiral tetrahydro-2-furoyl moiety have been prepared by the enzyme-catalyzed kinetic resolution of racemic mixtures or the diastereoselective hydrogenation of furan-2-carboxylic acid derivatives with chiral auxiliaries. 40 In contrast, to the best of our knowledge, only two enantioselective methods have been developed for the preparation of tetrahydrofuran-2-carboxylic acid. Baiker and colleagues developed the enantioselective hydrogenation of furan-2-carboxylic acid by using Pd/Al₂O₃ and cinchonidine catalysts (Scheme 12a). 41a-c However, the product was obtained with only 42% ee. Zhou and colleagues reported a copper-catalyzed enantioselective intramolecular O–H insertion of ω-hydroxy-α-diazoesters to give the corresponding 2-acyl tetrahydrofurans (Scheme 12b). 41d Although high enantioselectivities were achieved, the substrates were limited to highly reactive α-diazoesters. Smith and colleagues reported a chiral Lewis base-promoted enantioselective Michael addition/lactonization reaction of enone acids followed by nucleophilic
ring-opening (Scheme 12c). Although the corresponding cis-3-substituted 2-acyl THFs were obtained with excellent enantio- and diastereoselectivities, in situ activation of the carboxylic acid with pivaloyl chloride is required to generate a Michael donor. Moreover, chiral tetrahydrofuran-2-carboxylic acid, which is an essential core for many pharmaceuticals, as shown in Figure 4, is not easily synthesized. Thus, the development of an efficient and highly enantioselective method for the synthesis of highly valuable 2-acyl tetrahydrofuran derivatives is still needed.

Scheme 12. Enantioselective Construction of Chiral Tetrahydrofuran-2-Carboxylic Acid and Its Esters

a) Baiker et al.\textsuperscript{41a–c}

\[
\begin{align*}
&\text{Baiker et al.}^\text{41a–c} \\
&\text{Cinchonidine (15 mol\%)} \\
&\text{H}_2 (30 \text{ bar}), \text{THF, RT, 3 h} \\
&\text{12\% yield, 42\% ee}
\end{align*}
\]

b) Zhou et al.\textsuperscript{41d}

\[
\begin{align*}
&\text{Zhou et al.}^\text{41d} \\
&\text{CuOTf (5 mol\%)} \\
&\text{Spiro bisoxazoline (6 mol\%)} \\
&\text{CH}_2\text{Cl}_2, \text{RT, 15 min} \\
&\text{X = CH}_2, \text{H}_2 \\
&\text{up to 81\% yield, 95\% ee}
\end{align*}
\]

c) Smith et al.\textsuperscript{41e}

\[
\begin{align*}
&\text{Smith et al.}^\text{41e} \\
&\text{1. t-BuCOCl, i-Pr}_2\text{NEt} \\
&\text{CH}_2\text{Cl}_2, \text{RT} \\
&\text{2. (S)-Tetramisole·HCl (5 mol\%)} \\
&\text{i-Pr}_2\text{NEt, RT} \\
&\text{3. NuH, RT} \\
&\text{up to 76\% yield, 99\% ee} \\
&\text{ (>99:1 dr)}
\end{align*}
\]

We envisioned that our chiral hypooxidite catalysis could be applied to the enantioselective synthesis of 2-acyl tetrahydrofurans by using δ-hydroxyketones as substrates (Chapter 3).\textsuperscript{42} However, the oxidative cyclization of δ-hydroxyketone 11a did not proceed and only a trace amount of desired product 12a was obtained under conditions identical to those used for β-(2-hydroxyphenyl) ketones 2a (Scheme 13).\textsuperscript{11}
Scheme 13. Initial Investigation for the Enantioselective Oxidative Cycloetherification of δ-Hydroxyketones

After investigation of the reaction conditions, we succeeded in the enantioselective oxidative cycloetherification of δ-hydroxyketones 11 to 2-acyl tetrahydrofurans 12 (Scheme 14). The highest yields and enantioselectivities were obtained with the use of chiral ammonium iodide 1a in the presence of CHP in methyl tert-butyl ether (MTBE). In particular, as in our previous studies towards chromans (vide supra), the use of alkyl hydroperoxides such as TBHP or CHP instead of hydrogen peroxide was crucial to increase the chemical yields. Moreover, to our delight, the products could be obtained in higher chemical yield under concentrated conditions (0.2–0.5 M) without any loss of enantioselectivity. In sharp contrast, highly diluted conditions (0.02 M) are required to induce high enantioselectivity in the oxidative cyclization of ketophenols. An (N-phenylimidazol-2-yl)carbonyl group of the products could be transformed to give chiral tetrahydrofuran-2-carboxylic acid, which is a synthetic intermediate for medicinal compounds shown in Figure 4. This environmentally benign method could provide various chiral 2-acyltetrahydrofurans for use in medicinal chemistry to discover new drug-candidates, which are difficult to access by previous methods.

Scheme 14. Chiral Hypoiodite-Catalyzed Enantioselective Synthesis of 2-Acyl Tetrahydrofurans (Chapter 3)
Conclusion

In summary, a high-turnover chiral hypoiodite-catalysis has been developed for the chemo- and enantioselective oxidative cyclization reactions. This catalytic system provides new and greener methods for the enantioselective synthesis of 2-acylchromans and 2-acyltetrahydrofurans that are synthetic intermediates for tocopherols and various other biologically active compounds. Investigation of the catalytic mechanism for the hypoiodite/alkyl hydroperoxide oxidation system revealed that a hypoiodite salt was a catalytically active but unstable species and a triiodide salt was an inert but stable species. An equilibrium between an active species and an inert species in the presence of potassium carbonate is a breakthrough for the development of high-turnover hypoiodite catalysis. We believe that these findings will encourage the further development of high-turnover, environmentally benign redox organocatalysis for challenging oxidative coupling reactions.
Reference and Notes


Abstract: The diverse biological activities of tocopherols and their analogues have inspired considerable interest in developing routes for their efficient asymmetric synthesis. Here, we report that chiral ammonium hypoiodite salts catalyze highly chemo- and enantioselective oxidative cyclization of \( \gamma \)-(2-hydroxyphenyl)ketones to 2-acyl chromans bearing a quaternary stereocenter, which serve as productive synthetic intermediates for tocopherols. Raman spectroscopic analysis of a solution of tetrabutylammonium iodide and tert-butyl hydroperoxide revealed the in situ generation of the hypoiodite salt as an unstable catalytic active species and triiodide salt as a stable inert species. A high-performance catalytic oxidation system (turnover number of ~200) has been achieved by reversible equilibration between hypoiodite and triiodide in the presence of potassium carbonate base. We anticipate that these findings will open further prospects for development of high-turnover redox organocatalysis.
Chapter 2. High-Turnover Hypoiodite Catalysis for Asymmetric Synthesis of Tocopherols

Introduction

Biologically active compounds containing a chiral chroman skeleton are abundant in nature. The most prominent chiral chromans are \( \alpha \)-tocopherol, which is in the same family as vitamin E, together with \( \beta \)-, \( \gamma \)-, and \( \delta \)-tocopherols and the corresponding \( \alpha \)-, \( \beta \)-, \( \gamma \)-, and \( \delta \)-tocotrienols (Figure 1). \( \alpha \)-Tocopherol acts as a lipid-soluble, chain-breaking antioxidant by capturing free radicals or singlet oxygen formed by oxidative metabolism in tissues. Furthermore, tocopherols show physiologically diverse properties, including antitumor, anti-inflammatory, anti-atherosclerosis, and cell-signaling activities. Various non-natural tocopherol analogues have also been developed because of their potency and distinct structural features. For example, trolox and its derivatives have been used as a chiral derivatizing reagent and NO-releasing drug candidates. Dihydrodaedalin A, a synthetic intermediate for the natural product daedalin A, is a potent tyrosinase inhibitor and has been shown to suppress melanogenesis in human skin without affecting cell viability. C48 developed by Merck laboratories is a potent, selective PPAR\( \alpha/\gamma \) dual agonist and exhibits substantial antihyperglycemic and hypolipidemic activities.

![Figure 1. Biologically active tocopherols and other chromans](image)

Natural \( D\)-\( \alpha \)-tocopherol is formally (2\( R \),4\( R \),8\( R \))-2,5,7,8-tetramethyl-2-(4\( ' \),8\( ' \),12\( ' \)-trimethyltridecyl)-6-chromanol. The (2\( R \))-configuration at the chroman ring among the three stereocenters of \( \alpha \)-tocopherol is critical for its bioactivity, (2\( S \))-stereoisomers are not accepted by the tocopherol transfer protein. Thus, asymmetric construction of the chroman ring has been an important challenge. Enantioselective processes have been developed to address this need using chiral transition metal complexes (Pd or Ru) or organocatalysts. However, the low catalytic activities and/or moderate enantioselectivities have limited their utility. Here, we report a transition metal-free approach
for the enantioselective synthesis of tocopherols and their analogues using chiral hypoiodite catalysts\textsuperscript{17-19} generated \textit{in situ} from the corresponding quaternary ammonium iodide with alkyl hydroperoxides as environmentally benign co-oxidants (\textit{Scheme I}). Chemoselective oxidative cyclization of hydroquinone-derived γ-(2-hydroxyphenyl)ketones gives \textgreater95\% yield of the corresponding 2-acyl chromans, with the quaternary stereocenter set in high enantioselectivity, these products are poised for elaboration to a range of tocopherols.

\textbf{Results and Discussion}

Previously, we developed \textit{in situ}-generated chiral quaternary ammonium hypoiodite catalysis for the enantioselective oxidative cyclization of β-(2-hydroxyphenyl)ketones (2) to the five-membered ring products 2-acyl-2,3-dihydrobenzofurans (3) with hydrogen peroxide or \textit{tert}-butyl hydroperoxide (TBHP) as co-oxidants (\textit{Scheme 1a})\textsuperscript{17}. The use of chiral binaphthyl-based quaternary ammonium\textsuperscript{20} iodide (1) as a precatalyst and an \textit{N}-phenylimidazol-2-yl (\textit{Z})\textsuperscript{21} group as an auxiliary of β-(2-hydroxyphenyl)ketones was effective for inducing high enantioselectivities. We envisioned that the enantioselective oxidative cyclization of γ-(2-hydroxyphenyl)ketones (4) would give the desired 6-membered ring 2-acyl chromans (5, \textit{Scheme 1b}).

\textbf{Scheme 1. Chiral Hypoiodite-Catalyzed Enantioselective Oxidative Cycloetherification}

\textit{a) Previous Work (five-membered ring cyclization)\textsuperscript{17}}

\textit{b) This Work (six-membered ring cyclization)\textsuperscript{18}}

To begin our investigation, we compared the enantioselective oxidative cyclization of (5-\textit{tert}-butyldimethylsilyloxy-2-hydroxyphenyl)ketones (2a and 4a) derived from trimethyl hydroquinone (\textit{Scheme 2}). Oxidative cyclization of 2a under previous conditions using 10 mol\% of ammonium iodide (\textit{R,R})-1a and hydrogen peroxide (2 equivalents) as an oxidant in methyl
3H-1a (10 mol%) 30% H₂O₂ (2 equiv) MTBE, RT, 3 h

Ph
N
O
O
Z
H
TBSO
TBSO

1a (10 mol%) Oxidant (2 equiv) MTBE, RT

3a: 95% yield, 93% ee

1a (10 mol%) Oxidant (2 equiv) MTBE, RT

30% H₂O₂, 24 h <1% (60% of 4a was rec) 15% yield, 18% ee 10% yield 50% yield 50% yield

Oxidant (2 equiv) MTBE, RT

5a 6a 6b

The posited catalytic mechanism and side-reaction pathway are summarized in Figure 2. The above results and competition experiments with unsubstituted phenols (2b and 4b, Table 1) suggested that oxidative cyclization to a 6-membered ring was much slower than cyclization to a 5-membered ring. Thus, undesired side reactions such as the dearomatization of 4a preferentially proceeded to give side-products 6a and/or 6b presumably via phenoxenium ion 7. The cyclization step might be rate-limiting for 6-membered ring oxidative cyclization. Consequently the in situ-generated catalytic active species (hypiodite) was easily converted to an inert species such as triiodide salts, as confirmed by Raman analysis (vide infra) or reductive decomposition of hypiodite. For the construction of an efficient catalytic cycle, the oxidative cyclization step should not be rate-limiting. To address this issue, the oxidation of iodide (path a) should be decelerated, oxidative cyclization (path b) should be accelerated, or the inactivation (path c) should be suppressed or reversed. The use of TBHP as a weaker oxidant instead of hydrogen peroxide solved this problem partially by deceleration of the generation of active species. Substrate 4a was consumed within one hour, however the desired product 5a was obtained in only 15% yield with 18% ee (Scheme 2). Undesired dearomatization dominated again, and quinone 6a and peroxy quinol 6b were obtained in a combined yield of 65%.

tert-butyl ether (MTBE) gave 5-membered ring dihydrobenzofuran (R)-3a in 95% yield with 93% enantiomeric excess (ee) (Scheme 2a). In sharp contrast, oxidative cyclization of 4a to the 6-membered ring under the same conditions was sluggish, and only a trace amount of the desired 2-acyl chroman 5a was obtained together with a small amount (10% yield) of phenol-oxidation product 6 (Scheme 2b).

Scheme 2. Comparison of 5- and 6-Membered Enantioselective Oxidative Cyclizations

a) 5-Membered cyclization

b) 6-Membered cyclization

15% yield, 18% ee 10% yield 50% yield –

50% yield

5a

6b

6a
Chapter 2. High-Turnover Hypoiodite Catalysis for Asymmetric Synthesis of Tocopherols

Figure 2. Proposed catalytic mechanism and side-reaction pathway

Table 1. Competition Experiments Between 2b and 4b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>TBHP (x equiv)</th>
<th>Time (h)</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b (1 equiv)</td>
<td>2</td>
<td>4</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>4b (1 equiv)</td>
<td>2</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>2b + 4b (1 + 1 equiv)</td>
<td>1</td>
<td>24</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis.

To prevent undesired dearomatization and accelerate the desired cyclization path, we investigated the protecting group of 4a (Table 2). As expected, the side-reaction could be suppressed by using electron-withdrawing protecting groups (entries 1–4). The oxidative cyclization of 4e bearing para-toluenesulfonyl (Ts) group with 10 mol% of (R,R)-1a gave desired (R)-5e quantitatively with 60% ee (entry 3). The 3,3'-substituents of the binaphthyl moiety of (R,R)-1 had a dramatic effect on enantioselectivity and reactivity (entries 5–7). To our surprise,
the use of \((R,R)-1b\) in place of \((R,R)-1a\) gave \((S)-5e\) as an opposite enantiomer with higher enantioselectivity (86% ee) (entry 5). The opposite absolute stereoselectivity was observed with the use of not only \((R,R)-1b\) but also \((R,R)-1c\) and \((R,R)-1d\), which have biphenyl groups at the 3,3'-positions (entries 6 and 7). The best result (96% yield, 89% ee) was obtained after a shorter reaction time with perfluoroalkyl-substituted ammonium iodide \((R,R)-1d\) (entry 7).

### Table 2. Investigation of Reaction Parameters Toward \(\alpha\)-Tocopherol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>PG</th>
<th>Conditions</th>
<th>5 Yield (%)(^a)</th>
<th>Ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4c 1a</td>
<td>TBHP</td>
<td>(4-Cl-C(_6)H(_4))CO</td>
<td>MTBE, 3 h</td>
<td>((R)-5c) 92</td>
</tr>
<tr>
<td>2</td>
<td>4d 1a</td>
<td>TBHP</td>
<td>MeSO(_2)</td>
<td>MTBE, 3 h</td>
<td>((R)-5d) 95</td>
</tr>
<tr>
<td>3</td>
<td>4e 1a</td>
<td>TBHP</td>
<td>(4-Me-C(_6)H(_4))SO(_2)</td>
<td>MTBE, 3 h</td>
<td>((R)-5e) 98</td>
</tr>
<tr>
<td>4(^c)</td>
<td>4f 1a</td>
<td>TBHP</td>
<td>(4-CF(_3)-C(_6)H(_4))SO(_2)</td>
<td>MTBE, 29 h</td>
<td>((R)-5f) 34</td>
</tr>
<tr>
<td>5</td>
<td>4f 1b</td>
<td>TBHP</td>
<td>(4-Me-C(_6)H(_4))SO(_2)</td>
<td>MTBE, 24 h</td>
<td>((S)-5e) 99</td>
</tr>
<tr>
<td>6</td>
<td>4f 1c</td>
<td>TBHP</td>
<td>(4-Me-C(_6)H(_4))SO(_2)</td>
<td>MTBE, 24 h</td>
<td>((S)-5e) 94</td>
</tr>
<tr>
<td>7</td>
<td>4f 1d</td>
<td>TBHP</td>
<td>(4-Me-C(_6)H(_4))SO(_2)</td>
<td>MTBE, 5 h</td>
<td>((S)-5e) 96</td>
</tr>
<tr>
<td>8</td>
<td>4d 1d</td>
<td>TBHP</td>
<td>(4-Me-C(_6)H(_4))SO(_2)</td>
<td>MTBE, 1 h</td>
<td>((S)-5e) 95</td>
</tr>
<tr>
<td>9</td>
<td>4d 1d</td>
<td>CHP</td>
<td>(4-Me-C(_6)H(_4))SO(_2)</td>
<td>MTBE, 50 min</td>
<td>((S)-5e) 96</td>
</tr>
<tr>
<td>10</td>
<td>4d 1d</td>
<td>CHP</td>
<td>(4-Me-C(_6)H(_4))SO(_2)</td>
<td>Et(_2)O, 45 min</td>
<td>((S)-5e) 99</td>
</tr>
</tbody>
</table>

\(^a\) Isolated Yield. \(^b\) Determined by HPLC analysis. \(^c\) Quinone 6a, 12% yield. The absolute configuration of 5e was determined by comparing the optical rotation of 9 (Scheme 4) with the literature value,\(^{36}\) and all other chromans 5 were assigned by analogy. PG: protecting group. TBHP: tert-butyl hydroperoxide. CHP: Cumene hydroperoxide. MTBE: Methyl tert-butyl ether. CPME: Cyclopentyl methyl ether.
Because the oxidative cyclization step might not be rate-limiting for 4e, which was more reactive than 4a, hydrogen peroxide could be used as an oxidant, albeit with a slightly reduced enantioselectivity (entry 8). When cumene hydroperoxide (CHP) was used as an oxidant, the reaction was complete in 50 minutes (entry 9). Furthermore, the reaction in diethyl ether in place of MTBE gave (S)-5e quantitatively with 93% ee (entry 10).

A reduction in the catalyst loading might cause competition between inactivation (path c) and oxidative cyclization (path b) in this catalytic system (Figure 2). When 1 mol% of 1d was used, no reaction occurred and the starting material was recovered fully (Table 3, entry 1). To overcome this problem, suppression or reversible control of the inactivation path was considered. It is known that hypoiodite salts can be prepared by the hydrolysis of triiodide salts in alkaline solutions, and these species are in equilibrium under basic conditions. We envisioned that the hypoiodite species might be regenerated from triiodide species in the presence of appropriate base additives under our catalytic conditions. While the product could be obtained with 2 mol% of 1d, the yield was dramatically increased in the presence of inorganic base additives (entries 3–5 versus entry 2).

### Table 3. Investigation of Base Additives

<table>
<thead>
<tr>
<th>Entry</th>
<th>1d (mol%)</th>
<th>Additive (equiv)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>–</td>
<td>24</td>
<td>no reaction</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>–</td>
<td>26</td>
<td>14</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (0.5)</td>
<td>22</td>
<td>47</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (0.5)</td>
<td>5</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (0.5)</td>
<td>24</td>
<td>no reaction</td>
<td>–</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (1)</td>
<td>10</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (1)</td>
<td>48</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>10</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (0.5)</td>
<td>24</td>
<td>15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>Powdered K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (0.5)</td>
<td>24</td>
<td>13&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>2 M aq. K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>20&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt; (1 g/mmol)</td>
<td>24</td>
<td>no reaction</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>i-Pr&lt;sub&gt;2&lt;/sub&gt;NEt (2)</td>
<td>24</td>
<td>15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>2,6-Di-t-butyl pyridine (2)</td>
<td>24</td>
<td>12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated Yield.  <sup>b</sup> Determined by HPLC analysis.  <sup>c</sup> Determined by <sup>1</sup>H NMR analysis.  <sup>d</sup> The reaction was performed in 1.5 g-scale.

Especially, potassium carbonate was found to be most effective inorganic base additive for the
Chapter 2. High-Turnover Hypoiodite Catalysis for Asymmetric Synthesis of Tocopherols

present reaction (entry 4). Moreover, the catalyst loading could be reduced to 1 or even 0.5 mol% [turnover number (TON) of the catalyst = 200] for the oxidation of 5e in the presence of 1 equivalent of potassium carbonate without reducing the chemical yield or enantioselectivity (entries 6 and 7). While no further improvement was observed by using 2 equivalent of potassium carbonate, the chemical yield was significantly decreased by using 0.5 equivalent of potassium carbonate (entries 8–10). Moreover, the use of an aqueous solution of potassium carbonate was less effective for the reaction (entry 11). Sodium sulfate in place of potassium carbonate was also not effective for the reaction, which might excluded a dehydrating role of potassium carbonate (entry 12). Organic bases, such as Hunig’s base or 2,6-di-tert-butylpyridine, were found to be less effective for the present reaction (entries 13 and 14).

Furthermore, the TON of the catalyst was 2000 for the 5-membered oxidative cyclization of 2c (Scheme 3). These reaction conditions were compatible with gram-scale synthesis (Table 3, entry 6 and Scheme 3).

**Scheme 3. Enantioselective Oxidative Cycloetherification of 2c with 0.05 mol% of 1d**

![Scheme 3](image)

We examined several γ-(2-hydroxyphenyl)ketones 4 under optimized conditions (Table 4). (S)-2-Acylchromans 5g–5i, which would be a synthetic intermediate for β-, γ-, and δ-tocopherols, were obtained quantitatively with high enantioselectivities using 1 mol% of (R,R)-1d. The reactions of γ-[(4-chlorobenzoyloxy)-2-hydroxyphenyl]ketone 4j and γ-(4-tosyloxy-2-hydroxyphenyl)ketone 4k using (R,R)-1a gave (R)-5j and (R)-5k, respectively. Compounds (R)-5i and (R)-5j would potentially offer a different route to dihydrodaedalin A11,12 and Merck’s compound C48,13 respectively. The oxidative cyclizations of 4l using 1 mol% of (R,R)-1a and (R,R)-1d under the same conditions provided both enantiomers of the chroman 5l with high enantioselectivities. The optically pure enantiomers 5l could be obtained after a single re-crystallization.

The formal syntheses of D-α-tocopherol, D-α-tocotrienol and (S)-trolox were achieved (Scheme 4). The (N-phenylimidazol-2-yl)carbonyl group of product 5e was easily transformed to the methyl ester (8), which could be obtained in optically pure form after a single re-crystallization.
Subsequent deprotection of the tosyl group of 8 under mild conditions gave 9 in high chemical yield. The ester 9 is a common synthetic intermediate for D-α-tocopherol,26 D-α-tocotrienol27 and (S)-trolox.28 Other tocopherols and their biologically active analogues could be easily prepared in a similar manner.

Table 4. Enantioselective Oxidative Cycloetherification of Various γ-(2-Hydroxyphenyl)ketones 1 to Chromans 2

<table>
<thead>
<tr>
<th>Products 5, reaction times, isolated yields and enantiomeric excess are shown.</th>
<th>Unless otherwise noted, 1 mol% of (R,R)-1a or (R,R)-1d was used in the presence of potassium carbonate. b The reaction was performed using 10 mol% (R,R)-1a in the absence of K2CO3 with TBHP instead of CHP at 0 °C. c (R)-5l and (S)-5l were obtained in optically pure forms after a single recrystallization. 4-ClBz, 4-chlorobenzoyl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,R)-1a or 1d (1 mol%)</td>
<td>CHP (2 equiv)</td>
</tr>
<tr>
<td>K2CO3 (1 equiv)</td>
<td></td>
</tr>
<tr>
<td>Et2O, Room Temperature</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Scheme 4. Asymmetric Formal Syntheses of (S)-Trolox, D-α-Tocopherol and D-α-Tocotrienol

To gain insight into the catalytic mechanism, we performed various control experiments. The reactions proceeded smoothly in the presence of radical-trapping reagents such as TEMPO, BHT or
$N$-tert-butyl-$\alpha$-phenylnitronitrene (Scheme 5). These results suggested that a free radical pathway might be unlikely.

**Scheme 5. Control Experiments Using Radical-Trapping Reagents**

![Control Experiments Using Radical-Trapping Reagents](image)

The control experiments were conducted using 4b to identify the catalytic active iodine species for the present oxidative coupling reactions (Tables 5).\textsuperscript{17,29} In contrast to the catalytic oxidative conditions (entry 1), the reaction did not occur in the presence of $N$-iodosuccinimide (NIS) or molecular iodine under neutral conditions (entries 2 and 3). The desired product was obtained in 67\% yield in the presence of molecular iodine under basic conditions (entry 4). Hypoiodite anion ([IO\textsuperscript{-}]) might be generated from molecular iodine under basic conditions.\textsuperscript{30} Iodate ([IO\textsubscript{3}\textsuperscript{-}]) and periodate ([IO\textsubscript{4}\textsuperscript{-}]) species were also inert in the presence or absence of base additives (entries 5–8).

**Table 5. Control Experiment for the Investigation of Catalytic Active Species**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>Conditions</th>
<th>Yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu\textsubscript{4}NI (0.1) + TBHP (2)</td>
<td>RT, 24 h</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>NIS (1)</td>
<td>RT, 24 h</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>I\textsubscript{2} (1)</td>
<td>RT, 24 h</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>I\textsubscript{2} + Bu\textsubscript{4}NOH (2)</td>
<td>RT, 4 h</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>Bu\textsubscript{4}NIO\textsubscript{3} (1)</td>
<td>RT to 70 °C, 72 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>Bu\textsubscript{4}NIO\textsubscript{3} (1) + Bu\textsubscript{4}NOH (2)</td>
<td>RT to 70 °C, 72 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>Bu\textsubscript{4}NIO\textsubscript{3} (1)</td>
<td>RT to 70 °C, 72 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>Bu\textsubscript{4}NIO\textsubscript{3} (1) + Bu\textsubscript{4}NOH (2)</td>
<td>RT to 70 °C, 72 h</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Determined by $^1$H NMR analysis.

To understand the catalytic mechanism, spectroscopic analysis was conducted. Ford and colleagues succeeded in the detection of several iodine species such as hypoiodite [IO\textsuperscript{-}], iodite [IO\textsubscript{2}\textsuperscript{-}] and iodate [IO\textsubscript{3}\textsuperscript{-}] by Raman spectroscopic analysis during the investigation of disproportionation of hypoiodite species under basic conditions (Figure 3).\textsuperscript{31}
Chapter 2. High-Turnover Hypoiodite Catalysis for Asymmetric Synthesis of Tocopherols

Figure 3. Plausible mechanisms for the conversion of hypoiodite to triiodide, iodite, iodate and periodate species.

Encouraged by these precedent, we considered Raman spectroscopic analysis for the investigation of detailed catalytic mechanism for the present reaction. First, the measurement was conducted under similar conditions with literature. The spectrum obtained in water was matched well to literature spectrum. The bands at 105, 429, 572 and 799 cm\(^{-1}\) were assigned to \([\text{I}_3^-]\), \([\text{IO}^-]\), \([\text{I}_2\text{OH}]^-\) (or \([\text{I}_2\text{O}]^2^-\)) and \([\text{IO}_3^-]\), respectively (Figure 4, Spectrum a). Next, the Raman measurements were conducted in organic solvents. Unfortunately, the measurements in ethereal solvents were failed. The same experiment was conducted in CH\(_3\)CN. The solvent-dependent shift of bands was observed. To compare with spectrum obtained in water (Figure 4, Spectrum a), the bands of \([\text{IO}^-]\), \([\text{I}_2\text{OH}]^-\) (or \([\text{I}_2\text{O}]^2^-\)) and \([\text{IO}_3^-]\) were shifted to left, while the band of \([\text{I}_3^-]\) was shifted to right (Figure 4, Spectrum b).

Next, the measurements were conducted in our catalytic oxidation conditions (Figure 5). To our delight, we detected unstable \([\text{IO}^-]\) and \([\text{IOH}]^-\) species. Spectrum c, which includes three main bands at 110, 417 and 438 cm\(^{-1}\), was recorded immediately after the mixing of Bu\(_4\)NI with TBHP. The other bands were attributed to the solvents and reagents used. The band at 110 cm\(^{-1}\) is characteristic of \([\text{I}_3^-]\). The bands at 417 and 438 cm\(^{-1}\) were assigned to \([\text{IO}^-]\) and \([\text{IOH}]^-\) species, respectively, based on the literature and our control experiments (vide infra, Figure 7). These two species (\([\text{IO}^-]\) and \([\text{IOH}]^-\)) might be in equilibrium under these conditions and disappeared steadily with time, and only a band of triiodide was observed after 2 h (spectrum d). No other inert species such as iodate and periodate were observed at this time. The band of triiodide decreased immediately under basic conditions (spectrum e). A new band at 768 cm\(^{-1}\), which is characteristic of the iodate \([\text{IO}_3^-]\) spectrum, was observed. The same experiments were also

\[
\begin{align*}
\text{IO}^- + \text{I}^- + 2\text{H}^+ & \rightleftharpoons \text{I}_2 + \text{H}_2\text{O} \quad (1) \\
\text{I}_2 + \text{I}^- & \rightleftharpoons \text{I}_3^- \quad (2) \\
\text{IO}^- + 2\text{I}^- + \text{H}_2\text{O} & \rightleftharpoons \text{I}_3^- + 2\text{HO}^- \quad (3) \\
\text{IO}^- + \text{I}^- + \text{H}_2\text{O} & \rightleftharpoons \text{I}_2\text{OH}^- + \text{HO}^- \quad (3-1) \\
\text{I}_2\text{OH}^- + \text{I}^- & \rightleftharpoons \text{I}_3^- + \text{HO}^- \quad (3-2) \\
2\text{IO}^- & \rightarrow \text{IO}_2^- + \text{I}^- \quad (4) \\
\text{IO}^- + \text{I}_2\text{OH}^- & \rightarrow \text{IO}_2^- + 2\text{I}^- + \text{H}^+ \quad (5) \\
\text{IO}_2^- + \text{IO}^- & \rightarrow \text{IO}_3^- + \text{I}^- \quad (6) \\
\text{IO}_2^- + \text{I}_2\text{OH}^- & \rightarrow \text{IO}_3^- + 2\text{I}^- + \text{H}^+ \quad (7) \\
\text{IO}_3^- + \text{IO}^- & \rightarrow \text{IO}_4^- + \text{I}^- \quad (8) \\
\text{IO}_3^- + \text{IO}_2^- & \rightarrow \text{IO}_4^- + \text{IO}^- \quad (9)
\end{align*}
\]
conducted under diluted (0.1 M) conditions (Figure 6). Notably, the concentration-dependent shift of bands was also observed here. Compared to spectra in Figure 5, the bands of [IO]−, [IOH] and [IO3]− were shifted from 417, 438 and 768 cm−1 to 414, 434 and 790 cm−1, respectively. This indicated the rapid generation and subsequent disproportionation of hypoiodite species. These results revealed that hypoiodite is an unstable catalytic active species, and triiodide is a stable inert species under our conditions (Figure 2). Although iodite species [IO2]− could not be detected, we could not completely rule out a catalytic role of [IO3]−.

Figure 4. Spectrum a: Raman spectrum of the solution of I2 (0.1 M)/NaI (0.6 M) in water in the presence of an equal volume of 2 M NaOH (aq.). Spectrum b: Raman spectrum of the solution of I2 (0.36 M) and NaI (1.1 M) in CH3CN in the presence of an equal volume of 10 M NaOH aq.
Figure 5. Raman spectra of the solution of Bu$_4$NI (1 M) and TBHP (20 M) in CH$_3$CN in the absence [purple (c) and red lines (d)] and presence [blue Line (e)] of an equal volume of 1 M NaOH aq. Raman spectra of solvent and reagents [CH$_3$CN, TBHP, $t$-BuOH, Bu$_4$NI (1 M in CH$_3$CN)] used, and triiodide (1 M in CH$_3$CN) and iodine (1 M in CH$_3$CN) are shown below.
Figure 6. Raman spectra of the solution of Bu₄NI (0.1 M) and TBHP (20 M) in CH₃CN in the absence [purple (c')] and red lines (d')] and presence [blue Line (e')] of an equal volume of 1 M NaOH aq.

The Raman measurement for the investigation of equilibrium, \([\text{IOH}]= [\text{IO}]^- + \text{H}^+\), was conducted (Figure 7). The bands at 417 and 438 cm\(^{-1}\) of spectrum c in Figure 5 were disappeared after addition of a solution of NaOH and the bands at 430 and 566 cm\(^{-1}\) were observed. The equilibrium, \([\text{IOH}]= [\text{IO}]^- + \text{H}^+\), was completely to the right under basic conditions. Considering the solvent-dependent shift of bands observed above, the band at 430 cm\(^{-1}\) should be [IO]\(^-\). Based on this control experiments and literature,\(^{31}\) the bands at 417 and 438 cm\(^{-1}\) observed under neutral conditions were assigned to [IO]\(^-\) and [IOH], respectively. The similar change in the I–O vibration frequency was seemed typical of that observed for similar halogen system: \(\nu_{XO}\) in [ClOH] and [ClO]\(^-\) was 729 and 713 cm\(^{-1}\), and in [BrOH] and [BrO]\(^-\) was 626 and 620 cm\(^{-1}\), respectively.\(^{31}\)
Additionally, the band at 566 cm\(^{-1}\) was assigned to [I\(_2\)OH\(^-\)] (or [I\(_2\)O\(^2-\)]).\(^{31}\)

![Raman Spectra](image)

**Figure 7. Raman Spectra of the Solution of Bu\(_4\)NI (1 \(M\)) and TBHP (20 \(M\)) in CH\(_3\)CN in the Presence of 2 \(M\) NaOH**

The re-generation of hypoiodite from triiodide was also confirmed by control experiments (*Table 6*). Oxidative cyclization of two different substrates 4\(b\) and 4\(l\) did not occur with the use of a stoichiometric amount of \(n\)-tetrabutylammonium triiodide (entries 1–3), but proceeded in the presence of potassium carbonate under identical conditions (entries 4–6).

**Table 6. Oxidation of 4 with Bu\(_4\)NI\(_3\) in the Absence or Presence of K\(_2\)CO\(_3\)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>4</th>
<th>Additive</th>
<th>Solvent</th>
<th>5</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4(b)</td>
<td>–</td>
<td>CH(_3)CN</td>
<td>5(b)</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>4(b)</td>
<td>–</td>
<td>MTBE</td>
<td>5(b)</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>4(l)</td>
<td>–</td>
<td>MTBE</td>
<td>5(l)</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>4(b)</td>
<td>K(_2)CO(_3) (10 equiv)</td>
<td>CH(_3)CN</td>
<td>5(b)</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>4(b)</td>
<td>K(_2)CO(_3) (10 equiv)</td>
<td>MTBE</td>
<td>5(b)</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>4(k)</td>
<td>K(_2)CO(_3) (10 equiv)</td>
<td>MTBE</td>
<td>5(k)</td>
<td>73</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR analysis.

We also investigate the effect of the inorganic base additive on the enantioselective oxidative
Cycloetherification (Scheme 6). The reaction of 4e using 10 mol% of 1d in the presence or absence of K$_2$CO$_3$ gave the almost same results, which suggested that inorganic base might not to be effective for the oxidative cyclization step (Scheme 6a). Moreover, no epimerization was observed for 4b in the presence of inorganic base (Scheme 6b).

**Scheme 6. Enantioselective Oxidative Cycloetherification of 4 in the Absence or Presence of K$_2$CO$_3$**

*a) No rate acceleration for cyclization step:*

![Reaction Scheme 6a](image)

K$_2$CO$_3$ (0 equiv), 45 min: 98% yield, 93% ee
K$_2$CO$_3$ (1 equiv), 50 min: 98% yield, 93% ee

*b) No epimerization:

![Reaction Scheme 6b](image)

K$_2$CO$_3$ (0 equiv), 4 h: 99% yield, 76% ee
K$_2$CO$_3$ (1 equiv), 4 h: 99% yield, 76% ee

**Conclusion**

In summary, we developed chemo- and enantioselective oxidative cyclization of γ-(2-hydroxyphenyl)ketones gives the corresponding 2-acyl chromans bearing a quaternary stereocenter as potent synthetic intermediates for all kinds of tocopherols (α, β, γ, δ) as well as all kinds of tocotrienols (α, β, γ, δ) quantitatively and with excellent enantioselectivities. Raman spectroscopic analysis of a solution of tetrabutylammonium iodide and tert-butyl hydroperoxide reveals the in situ generation of the hypoiodite salt as an unstable catalytic active species and triiodide salt as a stable inert species. A high-performance catalytic oxidation system (turnover number of the catalyst = ≤2000) has been achieved by reversible equilibrium between hypoiodite and triiodide in the presence of an inorganic base like potassium carbonate. Furthermore, potential synthetic intermediates for other biologically active compounds such as dihydrodaxedalin A and Merck’s compound C48 can be prepared in excellent enantioselectivities. We anticipate that these findings will lead to new concepts for the development of high-turnover redox organocatalysis.
Experimental Section

Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. $^1$H NMR spectra were measured on a Varian INOVA-500 (500 MHz) or a JEOL ECS-400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the \( \delta \) scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), integration, and assignment. $^{13}$C NMR spectra were measured on a Varian INOVA-500 (125 MHz) or a JEOL ECS-400 (100 MHz) spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF\(_{254}\) 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High-resolution mass spectral analysis (HRMS) and elemental analysis was performed at Chemical Instrument Center, Nagoya University. Raman spectroscopic analysis was performed at Venture Business Laboratory (VBL), Nagoya University. High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL AD-H (4.6 mm x 25 cm), AD-3, (4.6 mm x 25 cm), AS-H (4.6 mm x 25 cm) and IC-3, (4.6 mm x 25 cm). Optical rotations were measured on Rudolph Autopol IV digital polarimeter. Melting points were measured on MPA100, Standard Research Systems. In experiments that required dry solvents, toluene, diethyl ether (Et\(_2\)O), methyl tert-butyl ether (MTBE), tetrahydrofuran (THF) and dichloromethane were purchased from Wako Pure Chemical Industries, Ltd. as the “anhydrous” and stored over 4A molecular sieves. Other solvents were purchased from Aldrich Chemical Co., Inc. or Wako Pure Chemical Industries, Ltd. and used without further purification. Tetrabutylammonium iodide (Bu\(_4\)NI), tetrabutylammonium triiodide (Bu\(_4\)NI\(_3\)) and cumene hydroperoxide (CHP, contains ca. 20% aromatic hydrocarbon) were purchased from Tokyo Chemical Industry Co. Ltd. and used without further purification. 30-wt% aqueous hydrogen peroxide, anhydrous tert-butyl hydroperoxide (TBHP, 5.5 \( M \) nonane solution) and 70% aqueous TBHP solutions were purchased from Aldrich Chemical Co., Inc. and used without further purification. Other simple chemicals were analytical-grade and obtained commercially and used without further purification.

Raman spectroscopy

Raman spectra were recorded using Renishaw inVia Raman microscope equipped with thermoelectrically cooled CCD camera and fiber-optic cable for excitation and collection of Raman spectra. The 532-nm beam of the diode YAG laser was used as the excitation source. The laser
power at the sample was about 150 mW. The laser beam was focused on a point in the reaction mixture in the glass capillary.

Detection of hypoiodite and other species in water or CH$_3$CN (Figure 4)

First, the measurement was conducted under similar conditions with literature.$^{31}$ To a solution of I$_2$ (25.4 mg, 0.1 mmol) in water (1 mL, in 5 mL volume of test vial) was added NaI (90 mg, 0.6 mmol) at 25 °C. After stirring for 1 h, the resulting mixture was drawn into the glass capillary, then an equal volume of 2 M NaOH aq. was charged in it. The Raman spectrum was measured after 10 seconds (Figure 4, Spectrum a).

Next, the Raman measurements were conducted in organic solvents. Unfortunately, the measurements in ethereal solvents were failed. The same experiment was conducted in CH$_3$CN. To a solution of I$_2$ (25.4 mg, 0.1 mmol) in CH$_3$CN (0.28 mL, in 5 mL volume of test vial) was added NaI (45 mg, 0.3 mmol) at 25 °C. After stirring for 1 h, the resulting reaction mixture was drawn into the glass capillary, then an equal volume of 10 M NaOH aq. was charged in it. The Raman spectrum was measured after 10 seconds (Figure 4, Spectrum b).

Detection of catalytic species (Figures 5 and 6)

To a solution of Bu$_4$NI (36.9 mg, 0.1 mmol) in CH$_3$CN (0.1 mL, in 5 mL volume of test vial) was added tert-butyl hydroperoxide (5.5 M in nonane, 0.364 mL, 2 mmol) at 25 °C. After stirring for 10 seconds, the reaction mixture was drawn into the glass capillary and the Raman spectra were measured (Figure 5, Spectrum c). After stirring for 2 h, the reaction mixture was drawn into the glass capillary and the Raman spectra were measured (Figure 5, Spectrum d). Then, an equal volume of 1 M NaOH was drawn into this solution. The Raman spectrum was measured after 1 minute (Figure 5, Spectrum e).

The same experiments were also conducted under diluted (0.1 M) conditions (Figure 6). To a solution of Bu$_4$NI (36.9 mg, 0.1 mmol) in CH$_3$CN (1 mL, in 5 mL volume of test vial) was added tert-butyl hydroperoxide (5.5 M in nonane, 0.364 mL, 2 mmol) at 25 °C. After stirring for 10 seconds, the reaction mixture was drawn into the glass capillary and the Raman spectra were measured (Figure 6, Spectrum c'). After stirring for 24 h, the reaction mixture was drawn into the glass capillary and the Raman spectra were measured (Figure 6, Spectrum d'). Then, an equal volume of 1 M NaOH was drawn into this solution. The Raman spectrum was measured after 1 minute (Figure 5, Spectrum e').

Equilibrium Between [IO]$^-$ and IOH Species (Figure 7)

To a solution of Bu$_4$NI (36.9 mg, 0.1 mmol) in CH$_3$CN (0.1 mL, in 5 mL volume of test vial)
was added tert-butyl hydroperoxide (5.5 M in nonane, 0.364 mL, 2 mmol) at 25 °C and shook it for 1 minute. 2 M NaOH aq. (0.2 mL, 0.4 mmol) was added to the reaction mixture. After shaking the vial for 1 minute, the reaction mixture was drawn into the glass capillary and the Raman spectrum was measured (Figure 7).

Synthesis and Characterization of Catalysts 1:

\[ \text{(R,R)-1a is known compound.}^{17} \]  \[ \text{(R,R)-1b–d were synthesized from b–d by following the literature procedures (Step B).}^{17} \]  \[ \text{S3b–d were prepared from S1}^{37} \text{ and aryl boronic acids S2b–d (Step A).}^{37} \]  \[ \text{S2b is known compound,}^{38} \text{ and S2c is commercially available.} \]  \[ \text{S2d was prepared from diiodobenzene and perfluorohexyl iodide by following the literature procedure.}^{39} \]
General Procedure for Step A:

To a solution of S1 (1 mmol), S2 (2.4 mmol) and K$_3$PO$_4$ (849 mg, 4 mmol) in degassed dioxane (10 mL) and H$_2$O (1 mL) were added Pd(OAc)$_2$ (22 mg, 0.1 mmol) and PPh$_3$ (115 mg, 0.44 mmol) [For synthesis of S3b, Pd(PPh$_3$)$_4$ (115 mg, 0.1 equiv) was used instead of Pd(OAc)$_2$ and PPh$_3$] at 25 °C and stirred at 80 °C. After stirring overnight, the resulting mixture was filtered through a plug of tightly packed celite and washed with EtOAc. The combined filtrates were washed with water, brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S3.

General Procedure for Step B:

To a solution of S3 (0.5 mmol) and NBS (1.05 mmol) in benzene (10 mL) was added AIBN (8.2 mg, 0.05 mmol) at 25 °C and stirred at 75 °C. After stirring for 3 h, the resulting mixture was cooled to 25 °C, poured into water and extracted with Et$_2$O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S4 in quantitative yield.

To a solution of S4 in acetone (10 mL) was added NaI (3 mmol) at 25 °C and stirred at 60 °C. After stirring for 2 h, the resulting mixture was cooled to 25 °C, poured into water and extracted with Et$_2$O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S5 quantitatively.

To a solution of S5 and S6 (0.5 mmol) in CH$_3$CN (10 mL) was added K$_2$CO$_3$ (104 mg, 0.75 mmol) at 25 °C and stirred at 85 °C. After stirring overnight, the resulting mixture was cooled to 25 °C, poured into water and extracted with CH$_2$Cl$_2$ (twice). The combined organic layers were washed with water and dried over anhydrous Na$_2$SO$_4$, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give 1.

To a solution of 1 (0.5 mmol) in EtOH (5 mL) was added KI (830 mg, 5 mmol) at 25 °C and stirred at 90 °C. After stirring for 2 h, the resulting mixture was cooled to 25 °C, poured into water and extracted with EtOAc (twice). The combined organic layers were washed with water and dried over anhydrous Na$_2$SO$_4$, then the solvents were removed in vacuo to give 1.

(R,R)-1b [Step A: 50%, Step B: 86% overall]: Brown solid; IR (KBr) 2927, 1366, 1280, 1178,
1136 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 9.00–7.00 (m, 6H), 8.44 (s, 2H), 8.17 (d, \(J = 8.2\) Hz, 2H), 8.07–8.06 (m, 4H), 8.01 (s, 4H), 7.92 (s, 2H), 7.67 (t, \(J = 7.3\) Hz, 2H), 7.42–7.35 (m, 4H), 7.24–7.13 (m, 10H), 7.07 (d, \(J = 8.2\) Hz, 2H), 6.48 (d, \(J = 8.2\) Hz, 2H), 5.08 (d, \(J = 13.8\) Hz, 2H), 4.61 (d, \(J = 13.8\) Hz, 2H), 4.37 (d, \(J = 13.3\) Hz, 2H), 3.80 (d, \(J = 13.3\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 142.7, 142.5, 140.8, 140.1, 139.4, 139.3, 138.3, 136.3, 134.1, 133.7, 133.1, 132.73, 132.66, 132.4, 132.1, 131.4, 131.1, 129.0, 128.7, 128.5, 127.7–127.3 (m), 126.9, 126.8, 126.7, 125.9, 124.9, 124.6, 122.4, 121.9, 119.1, 62.8 (2C), 57.6 (2C); \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –62.5; HRMS (ESI) m/z calcd for [C\(_{100}\)H\(_{56}\)F\(_{24}\)N]\(^+\) 1726.4024, found 1726.4022; \([\alpha]^{26.7\text{D}} = -110.8\) (c 1.0, CHCl\(_3\)).

(R,R)-1c: [Step A: 99%, Step B: 56% overall]: Brown solid; IR (KBr) 2962, 1382, 1280, 1182, 1134 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 9.00–7.00 (m, 8H), 8.43 (s, 2H), 8.23 (s, 4H), 8.16 (d, \(J = 8.2\) Hz, 2H), 8.06 (s, 2H), 7.64 (t, \(J = 7.4\) Hz, 2H), 7.58 (d, \(J = 8.2\) Hz, 2H), 7.46 (t, \(J = 7.6\) Hz, 2H), 7.34 (t, \(J = 7.8\) Hz, 2H), 7.21–7.16 (m, 4H), 7.09–7.06 (m, 4H), 6.41 (d, \(J = 8.7\) Hz, 2H), 5.02 (d, \(J = 13.8\) Hz, 2H), 4.55 (d, \(J = 13.8\) Hz, 2H), 4.30 (d, \(J = 13.3\) Hz, 2H), 3.76 (d, \(J = 13.3\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 142.5, 139.8, 139.4, 138.6, 137.9, 136.4, 134.0, 133.8, 133.2, 132.9, 132.7, 132.5, 132.4–131.5 (m), 131.4, 131.1, 128.9, 128.7, 128.5, 128.4, 127.8, 127.7, 127.5, 127.4, 127.0, 126.6, 124.7, 124.6, 122.2, 121.9, 121.6, 119.2, 62.7 (2C), 57.6 (2C); \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –62.5; HRMS (ESI) m/z calcd for [C\(_{72}\)H\(_{44}\)F\(_{12}\)N]\(^+\) 1150.3277, found 1150.3277; \([\alpha]^{27.6\text{D}} = -119.56\) (c 1.0, CHCl\(_3\)).

(R,R)-1d [Step A: 53%, Step B: 44% overall]: Brown solid; IR (KBr) 3060, 1362, 1242, 1203, 1146 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 9.00–7.00 (m, 8H), 8.41 (s, 2H), 8.23 (s, 4H), 8.16 (d, \(J = 8.2\) Hz, 2H), 7.97 (s, 2H), 7.67 (t, \(J = 7.6\) Hz, 2H), 7.54 (d, \(J = 8.3\) Hz, 2H), 7.42–7.36 (m, 4H), 7.21–7.18 (m, 4H), 7.09 (d, \(J = 8.3\) Hz, 4H), 6.45 (d, \(J = 8.2\) Hz, 2H), 5.01 (d, \(J = 14.0\) Hz, 2H), 4.61 (d, \(J = 14.0\) Hz, 2H), 4.37 (d, \(J = 13.3\) Hz, 2H), 3.75 (d, \(J = 13.3\) Hz, 2H); \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –80.7, –111.1, –121.4, –121.9, –122.7, –126.1; HRMS (ESI) m/z calcd for [C\(_{92}\)H\(_{54}\)F\(_{52}\)N]\(^+\) 2150.2638, found 2150.2629; \([\alpha]^{26.9\text{D}} = -63.6\) (c 1.0, CHCl\(_3\)).
Synthesis and Characterization of Starting Materials:

**Synthesis of 2a:**

To a solution of 2,3,5-trimethyl-1,4-hydroquinone (S7, 2.28 g, 15 mmol) in methanesulfonic acid (21 mL) was added methacrylic acid (1.4 mL, 16.5 mmol) at 25 °C and stirred at 90 °C. After stirring for 1 h, the reaction mixture was cooled to 0 ºC and ice was added. The resulting mixture was extracted with EtOAc (twice). The combined organic layers were washed with saturated aq. NaHCO$_3$ and brine, and then dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S8 (1.01 g, 4.6 mmol) in 30% yield.

To a solution of S8 (264 mg, 1.2 mmol) and DBU (209 µL, 1.4 mmol) in CH$_2$Cl$_2$ (12 mL) was added TBSCl (211 mg, 1.4 mmol) at 25 °C. After stirring for 5 h, the resulting mixture was poured into 1 M HCl and extracted with CHCl$_3$ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S9 (360 mg, 0.9 mmol) in 75% yield over 2 steps.
To a solution of S9 (360 mg, 0.9 mmol) and K$_2$CO$_3$ (249 mg, 1.8 mmol) in acetone (3 mL) was added BnBr (212 µL, 1.8 mmol) at 25 °C and refluxed. After stirring for 4 h, the resulting mixture was concentrated in vacuo. The residue was washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S10 (355 mg, 0.73 mmol) in 81% yield.

To a solution of N-phenylimidazole (190 µL, 1.5 mmol) in THF (2.1 mL) was added n-BuLi (1.6 M in hexane, 940 µL, 1.5 mmol) at −78 °C. After stirring at −78 °C for 30 min, the reaction mixture was added to S10 (355 mg, 0.73 mmol) in THF (3.7 mL) via cannula at −78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into saturated aq. NH$_4$Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S11 (358 mg, 0.63 mmol) in 86% yield.

To a solution of S11 (148 mg, 0.26 mmol) in EtOH (2.6 mL) was added 10% palladium on carbon (30 mg) at 25 °C. The flask was shortly evacuated and a balloon filled with hydrogen put on it. The reaction mixture was stirred at 25 °C. After stirring for 3 h, the resulting mixture was filtered through a plug of tightly packed celite and washed with EtOAc. The combined filtrates were concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 2a (72 mg, 0.15 mmol) in 58% yield.

4-(3-((tert-Butyldimethylsilyl)oxy)-6-hydroxy-2,4,5-trimethylphenyl)-2-methyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (2a): White solid; TLC, $R_f$ = 0.47 (hexane–EtOAc = 1:1); IR (neat) 3430, 1685, 1461, 1406, 1251, 1084, cm$^{-1}$; $^1$H NMR δ 9.21 (brs, 1H), 7.50−7.48 (m, 3H), 7.40 (d, $J = 0.92$ Hz, 1H), 7.31−7.29 (m, 2H), 7.20 (d, $J = 0.92$ Hz, 1H), 3.84−3.80 (m, 1H), 3.36 (dd, $J = 14.2$, 10.1 Hz, 1H), 2.65 (dd, $J = 14.2$, 10.1 Hz, 1H), 2.25 (s, 3H), 2.14 (s, 6H), 1.09 (d, $J = 6.4$ Hz, 3H), 1.04 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); $^{13}$C NMR (CD$_3$OD, 100 MHz) δ 193.3, 148.0, 144.2, 141.4, 137.9, 129.1, 129.0 (3C), 126.8, 126.6, 125.9 (2C), 124.5, 122.1, 121.6, 43.8, 33.2, 26.1 (3C), 18.6, 14.9, 14.6, 13.8, 12.7, −3.2, −3.5; HRMS (FAB) m/z calcd for [C$_{29}$H$_{40}$N$_2$O$_3$Si+H]$^+$ 493.2881, found 493.2879.

Synthesis of 2c:
To a solution of S8 (1.01 g, 4.6 mmol), Et$_3$N (1.3 mL, 9 mmol) and DMAP (55 mg, 0.45 mmol) in CH$_2$Cl$_2$ (9 mL) was added TsCl (1.28 g, 6.8 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into 1 M HCl and extracted with CHCl$_3$ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S12 (1.54 g, 4.5 mmol) in 90% yield.

To a solution of N-phenylimidazole (0.78 mL, 6.2 mmol) in THF (9 mL) was added n-BuLi (1.6 M in hexane, 3.8 mL, 6.2 mmol) at -78 °C. After stirring at -78 °C for 30 min, the reaction mixture was added to S12 (1.54 g, 4.5 mmol) in THF (8 mL) via cannula at -78 °C. After stirring at -78 °C for 1 h, the resulting mixture was poured into saturated aq. NH$_4$Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 2c (1.39 g, 2.7 mmol) in 65% yield.

4-Hydroxy-2,3,6-trimethyl-5-(2-methyl-3-oxo-3-(1-phenyl-1H-imidazol-2-yl)propyl)phenyl 4-methylbenzenesulfonate (2c): White solid; TLC, $R_f$ = 0.24 (hexane–EtOAc = 1:1); IR (neat) 3248, 2928, 1691, 1450, 1405, 1176, cm$^{-1}$; $^1$H NMR δ 9.98 (brs, 1H), 7.81 (d, $J$ = 8.7 Hz, 2H), 7.51–7.49 (m, 3H), 7.42 (d, $J$ = 0.92 Hz, 1H), 7.34–7.29 (m, 4H), 7.22 (d, $J$ = 0.92 Hz, 1H), 3.77–3.69 (m, 1H), 3.38–3.34 (m, 1H), 2.60 (dd, $J$ = 14.2, 10.8 Hz, 1H), 2.46 (s, 3H), 2.23 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H), 1.04 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 192.4, 152.3, 144.9, 141.1, 140.1, 137.7, 134.1, 130.0, 129.7 (2C), 129.1, 129.0 (2C), 128.9, 128.2 (2C), 127.9, 126.8, 125.8 (2C), 123.0, 122.0, 43.6, 33.0, 21.6, 14.7, 14.6, 13.5, 12.6; HRMS (FAB) m/z calcd for [C$_{29}$H$_{30}$N$_2$O$_5$S+]$^+$ 519.1948, found 517.1948.

Synthesis of 4a:

46
To a solution of S13 (1.54 g, 8 mmol), imidazole (1.63 g, 24 mmol) in CH$_2$Cl$_2$ (16 mL) was added TBSCl (1.20 g, 8 mmol) at 25 °C. After stirring for 1 h, the resulting mixture was poured into water and extracted with CHCl$_3$ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S14 (797 mg, 2.6 mmol) in 32% yield.

To a stirred solution of S14 (613 mg, 2 mmol) in CH$_2$Cl$_2$ (10 mL) was added DIBAL (1 M in hexane, 2.4 mL, 2.4 mmol) over 1 h at –78 °C. After stirring at –78 °C for 1 h, the resulting mixture was poured into 1 M HCl at –78 °C, allowed to warm to 25 °C and extracted with CHCl$_3$ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. To a solution of the crude product in CH$_2$Cl$_2$ (10 mL) was added S15 (1.39 g, 4 mmol) at 25 °C. After stirring overnight, the resulting mixture was directly purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S16 (757 mg, 2 mmol) in quantitative yield over 2 steps.

To a solution of S16 (757 mg, 2 mmol) and K$_2$CO$_3$ (553 mg, 4 mmol) in acetone (10 mL) was added BnBr (475 µL, 4 mmol) at 25 °C and refluxed. After stirring for 4 h, the resulting mixture was concentrated in vacuo. To the residue was added water and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the
solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S17 (693 g, 1.9 mmol) in 94% yield.

To a solution of S17 (281 g, 0.6 mmol) and N,O-dimethylhydroxylamine hydrochloride (117 mg, 1.2 mmol) in THF (3 mL) was added i-PrMgCl (2 M in THF, 1.2 mL, 2.4 mmol) at −78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring for 1 h, the resulting mixture was poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S18 (150 mg, 0.3 mmol) in 50% yield.

To a solution of N-phenylimidazole (76 µL, 0.6 mmol) in THF (1 mL) was added n-BuLi (1.6 M in hexane, 380 µL, 0.6 mmol) at −78 °C. After stirring at −78 °C for 30 minutes, the reaction mixture was added to S18 (150 mg, 0.3 mmol) in THF (1 mL) via cannula at −78 °C. After stirring at −78 °C for 3 h, the resulting mixture was poured into saturated aq. NH₄Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:2) to give S19 (140 mg, 0.24 mmol) in 80% yield.

To a solution of S19 (140 mg, 0.24 mmol) in EtOH (3 mL) was added 10% palladium on carbon (50 mg) at 25 °C. The flask was shortly evacuated and a balloon filled with hydrogen put on it. The resulting mixture was stirred at 25 °C. After stirring overnight, the resulting mixture was filtered through a plug of tightly packed celite and washed with EtOAc. The combined filtrates were concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 4a (108 mg, 0.22 mmol) in 92% yield.

4-(3-((tert-Butyldimethylsilyl)oxy)-6-hydroxy-2,4,5-trimethylphenyl)-2-methyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (4a): White solid; TLC, Rf = 0.47 (hexane–EtOAc = 1:1); IR (neat) 3430, 1685, 1461, 1406, 1251, 1084, cm⁻¹; ¹H NMR δ 7.47–7.45 (m, 3H), 7.32 (d, J = 0.92 Hz, 1H), 7.27–7.25 (m, 2H), 7.20 (d, J = 0.92 Hz, 1H), 6.31 (br s, 1H), 3.84–3.76 (m, 1H), 2.79–2.71 (m, 1H), 2.57–2.50 (m, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.01–1.89 (m, 1H), 1.66–1.57 (m, 1H), 1.22 (d, J = 6.4 Hz, 3H), 1.03 (s, 9H), 0.10 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 195.4, 146.7, 144.9, 142.6, 138.2, 129.4, 129.0 (2C), 128.8, 127.0, 125.74, 125.70 (2C), 124.5, 124.0, 121.8, 42.2, 32.6, 26.1 (3C), 25.5, 18.6, 17.8, 14.5, 13.8, 12.6, −3.4 (2C); HRMS (FAB) m/z calcd for [C₉₂H₄₀N₂O₅Si+H]⁺ 493.2881, found 493.2879.
Synthesis of 4b:

To a solution of α-tetralone (S20, 17.5 g, 120 mmol) in ClCH₂CH₂Cl (240 mL) was added mCPBA (51.8 g, 300 mmol) at 0 °C and stirred at 50 °C. After stirring overnight, the resulting mixture was dilu4ted with Et₂O, quenched with saturated aq. Na₂S₂O₃ at 0 °C and extracted with Et₂O (twice). The combined organic layers were washed with saturated aq. NaHCO₃, brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S21 (18.3 g, 113 mmol) in 94% yield.

To a solution of S21 (4.22 g, 26 mmol) and pyridine (8.4 mL, 104 mmol) in THF (52 mL) was added N,O-dimethylhydroxylamine hydrochloride (5.07 g, 52 mmol) at 25 °C. After stirring for 24 h, the resulting mixture was poured into 1 M HCl and extracted with CHCl₃ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo to give S22 without further purification.

To a solution of S22 and imidazole (5.31 g, 78 mmol) in CH₂Cl₂ (52 mL) was added TBSCl (3.92 g, 26 mmol) at 25 °C. After stirring for 6 h, the resulting mixture was poured into water and extracted with CHCl₃ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S23 without further purification.

To a solution of N-phenylimidazole (3.75 g, 26 mmol) in THF (40 mL) was added n-BuLi (1.6 M in hexane, 16 mL, 26 mmol) at −78 °C. After stirring at −78 °C for 30 min, the reaction mixture was added to S23 in THF (100 mL) via cannula at −78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring for 1 h, the resulting mixture was poured into 1 M NH₄Cl and extracted with EtOAc (twice). The combined organic layers were
washed with brine and dried over anhydrous MgSO\(_4\), then the solvents were removed \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give \textbf{S24} (9.27 g, 22 mmol) in 85% yield over 3 steps.

To a solution of \textbf{S24} (9.27 g, 22 mmol) in THF (52 mL) was added tetrabutylammonium fluoride (26 mL, 26 mmol, 1 M in THF) at 25 °C. After stirring 30 min, the resulting mixture was poured into saturated aq. NH\(_4\)Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO\(_4\), then the solvents were removed \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give \textbf{4b} (22 mmol, 6.78 g) in quantitative yield.

\textbf{4b} (2-(Hydroxyphenyl)-1-(phenyl-1H-imidazol-2-yl)butan-1-one (4b):} White solid; TLC, \(R_f = 0.31\) (hexane–EtOAc = 1:1); IR (KBr) 3131, 2952, 1691, 1494, 1412, 1361, 1226, 1150 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 7.48–7.47\) (m, 3H), 7.31 (s, 1H), 7.29–7.23 (m, 2H), 7.21 (s, 1H), 7.12–7.07 (m, 2H), 7.00 (brs, 1H) 6.84–6.81 (m, 2H), 3.22 (t, \(J = 6.4\) Hz, 2H), 2.63 (t, \(J = 7.6\) Hz, 2H), 1.99–1.93 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta 192.3, 154.6, 142.7, 138.1, 130.1, 129.5, 129.0\) (2C), 128.9, 127.49, 127.46, 127.3, 125.8 (2C), 120.1, 116.0, 38.0, 29.4, 24.4; HRMS (FAB) m/z calcd for [C\(_{19}\)H\(_{18}\)N\(_2\)O\(_2\)+H]\(^+\) 307.1441, found 307.1433.

Synthesis of 4c–f\(^{14,45}\): To a solution of \(N\)-phenylimidazole (3.2 mL, 25 mmol) in THF (36 mL) was added \(n\)-BuLi (1.6 \(M\) in hexane, 15.6 mL, 25 mmol) at –78 °C. After stirring at –78 °C for 30 minutes, the reaction mixture was added to a solution of glutaric anhydride (\textbf{S25}, 2.85 g, 25 mmol) in THF (100 mL) \textit{via} cannula at –78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into water. The aqueous layer was acidified with 1 \(M\) HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried
over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:2) to give S26 (2.97 g, 12 mmol) in 46% yield.

To a solution of S26 (4.13 g, 16 mmol) in DMF was added sodium hydride (60% dispersion in mineral oil, 1.40 g, 35 mmol) at 0 °C. After stirring at 0 °C for 1 h, MeI (2.2 mL, 35 mmol) was added at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was cooled to 0 °C, poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give the methyl ester of S27.

To a solution of the methyl ester of S27 in MeOH (32 mL) and water (8 mL) was added lithium hydroxide (2.30 g, 96 mmol) at 25 °C. After stirring for 1 h, the reaction mixture was cooled to 0 °C, then quenched with 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo to give S27 (3.62 g, 13 mmol) in 83% yield.

To a solution of S27 (1.36 g, 5 mmol) and 2,3,5-trimethyl-1,4-benzoquinone (S28, 751 mg, 5 mmol) in CH₃CN (80 mL) and water (40 mL) was added silver nitrate (934 mg, 5.5 mmol) at 25 °C. The reaction mixture was warmed to 75 °C and potassium persulfate (1.62 g, 6 mmol) in water (40 mL) was added slowly over 1 h. After stirring for 3 h, the reaction mixture was cooled to 25 °C, poured into water and extracted with EtOAc (twice). The combined organic layers were washed with saturated aq. NaHCO₃, brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give S29 (350 mg, 0.9 mmol) in 19% yield.

To a solution of S29 (1.05 g, 2.8 mmol) in acetone (20 mL) was added saturated aq. sodium hydrosulfite (20 mL) at 25 °C. After stirring for 1 h, the reaction mixture was poured into water and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. To a solution of the crude product in CH₂Cl₂ (8 mL) was added Et₃N (0.78 mL, 5.6 mmol) and DMAP (94 mg, 0.28 mmol) at 0 °C, then TsCl (534 mg, 2.8 mmol) in CH₂Cl₂ (8 mL) was added slowly over 1 h at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was cooled to 0 °C, poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give 4e (626 mg, 1.2 mmol) in 42% yield.
4-Hydroxy-2,3,6-trimethyl-5-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)phenyl methanesulfonate (4d): This compound was prepared as 1b from S28 with MsCl (1 equiv) instead of TsCl in 35% yield. White solid; TLC, Rf = 0.26 (hexane–EtOAc = 1:1); IR (neat) 3412, 2935, 1684, 1457, 1405, 1350, 1175 cm\(^{-1}\); \(^1^H\) NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.49–7.47 (m, 3H), 7.34 (d, \(J = 0.92\) Hz, 1H), 7.28–7.26 (m, 2H), 7.22 (d, \(J = 0.92\) Hz, 1H), 7.13 (brs, 1H), 3.81–3.72 (m, 1H), 3.22 (s, 3H), 2.83–2.75 (m, 1H), 2.56–2.49 (m, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H), 1.99–1.90 (m, 1H), 1.71–1.60 (m, 1H), 1.24 (d, \(J = 7.3\) Hz, 3H); \(^1^C\) NMR (CDCl\(_3\), 100 MHz) \(\delta\) 195.4, 151.3, 142.5, 140.3, 138.1, 129.5, 129.1 (2C), 128.93, 128.89, 127.21, 127.18, 125.7 (2C), 124.8, 122.9, 42.3, 38.6, 32.2, 25.4, 18.1, 14.7, 14.0, 12.5; HRMS (FAB) m/z calcd for \([C_{34}H_{28}N_2O_5S]+\) 574.1689, found 574.1687.

4-Hydroxy-2,3,6-trimethyl-5-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)phenyl 4-chlorobenzoate (4c): This compound was prepared as 1b from S28 with 4-chlorobenzoyl chloride (1 equiv) and pyridine (2 equiv) instead of TsCl and Et\(_3\)N in 22% yield. White solid; TLC, Rf = 0.47 (hexane–EtOAc = 1:1); IR (neat) 3421, 2966, 1732, 1684, 1594, 1402, 1234, 1090 cm\(^{-1}\); \(^1^H\) NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.18 (d, \(J = 8.7\) Hz, 2H), 7.80 (d, \(J = 8.7\) Hz, 2H), 7.49–7.47 (m, 3H), 7.34 (d, \(J = 0.92\) Hz, 1H), 7.29–7.26 (m, 2H), 7.22 (d, \(J = 0.92\) Hz, 1H), 6.89 (brs, 1H), 3.83–3.75 (m, 1H), 2.85–2.77 (m, 1H), 2.58–2.52 (m, 1H), 2.20 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.04–1.93 (m, 1H), 1.70–1.61 (m, 1H), 1.24 (d, \(J = 6.9\) Hz, 3H); \(^1^C\) NMR (CDCl\(_3\), 100 MHz, two rotamers) \(\delta\) 195.4, 164.2, 150.5, 142.6, 141.2, 139.9, 139.2, 131.5, 129.5, 129.1, 128.93, 128.85, 128.0, 127.1, 127.0, 125.7, 125.3, 124.4, 122.3, 42.3, 32.6, 32.5, 25.30, 25.26, 18.0, 17.9, 13.1, 12.6, 12.4; HRMS (FAB) m/z calcd for \([C_{36}H_{29}ClN_2O_4]+\) 517.1889, found 515.1887.

4-Hydroxy-2,3,6-trimethyl-5-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)phenyl 4-(trifluoromethyl)benzenesulfonate (4f): This compound was prepared as 1b from S28 with
4-(trifluoromethyl)benzenesulfonyl chloride (1 equiv) instead of TsCl in 43% yield. White solid; TLC, Rf = 0.32 (hexane–EtOAc = 1:1); IR (neat) 3408, 2931, 1683, 1406, 1323, 1181, 1137, 1064 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.08 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.50–7.48 (m, 3H), 7.35 (d, J = 0.9 Hz, 1H), 7.30–7.27 (m, 2H), 7.23 (d, J = 0.9 Hz, 1H), 3.80–3.71 (m, 1H), 2.79–2.71 (m, 1H), 2.54–2.47 (m, 1H), 2.14 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.99–1.89 (m, 1H), 1.64–1.56 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 195.0, 151.3, 142.2, 140.7, 140.6, 138.0, 135.5 (d, J_C-F = 33.4 Hz), 129.2, 129.1 (2C), 129.0 (2C), 128.8 (2C), 127.2 (2C), 126.2 (d, J_C-F = 3.8 Hz, 2C), 125.7 (2C), 124.9, 123.03 (d, J_C-F = 270 Hz), 122.96, 42.3, 32.1, 25.2, 17.9, 14.5, 13.8, 12.5; ¹⁹F NMR (CDCl₃, 376 MHz) δ −63.1; HRMS (FAB) m/z calcd for [C₃₀H₂₉F₃N₂O₅S+H]⁺ 587.1822, found 587.1828.

An Alternative Route to 4e:

To a solution of S₁₇ (1.44 g, 7.5 mmol), Et₃N (2.50 mL, 18 mmol) and DMAP (98 mg, 0.8 mmol) in CH₂Cl₂ (38 mL) was added TsCl (1.72 g, 9 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into 1 M HCl and extracted with CHCl₃ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S₂₉ (1.56 g, 4.5 mmol) in 60% yield.

To a solution of S₂₉ (1.56 g, 4.5 mmol) in CH₂Cl₂ (20 mL) was added DIBAL (1 M in hexane, 5 mL, 5 mmol) over 1 h at −78 °C. After stirring at −78 °C for 1 h, the resulting mixture was poured into 1 M HCl at −78 °C, warmed to 25 °C and extracted with CHCl₃ (twice). The
combined organic layers were washed with brine and dried over anhydrous MgSO\(_4\), then the solvents were removed in vacuo. To a solution of the crude product in CH\(_2\)Cl\(_2\) (20 mL) was added S19\(^{13}\) (1.74 g, 5 mmol) was added at 25 °C and the resulting mixture was stirred for 1 h. The resulting mixture was directly purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S30 (1.88 g, 4.5 mmol) in quantitative yield over 2 steps.

To a solution of S30 (1.88 g, 4.5 mmol) and K\(_2\)CO\(_3\) (1.24 g, 9 mmol) in acetone (9 mL) was added BnBr (1.1 mL, 9 mmol) at 25 °C and refluxed. After stirring for 6 h, the resulting mixture was concentrated in vacuo. To the residue was added water and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO\(_4\), then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S31 (2.19 g, 4.3 mmol) in 96% yield.

To a solution of S31 (2.19 g, 4.3 mmol) and \(N,O\)-dimethylhydroxylamine hydrochloride (839 mg, 8.6 mmol) in THF (11 mL) was added \(i\)-PrMgCl (2 M in THF, 8.6 mL, 17.2 mmol) at –78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring for 1 h, the resulting mixture was poured into 1 \(M\) HCl at 0 °C and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO\(_4\), then the solvents were removed in vacuo to give S32 (2.24 g, 4.2 mmol) in 97% yield without further purification.

To a solution of \(N\)-phenylimidazole \(767 \mu\)L, 6.3 mmol) in THF (9 mL) was added \(n\)-BuLi (1.6 \(M\) in hexane, 3.9 mL, 6.3 mmol) at –78 °C. After stirring for 30 minutes, the reaction mixture was added to S32 (2.24 g, 4.2 mmol) in THF (21 mL) via cannula at –78 °C. After stirring at –78 °C for 2 h, the resulting mixture was poured into saturated aq. NH\(_4\)Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO\(_4\), then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S33 (2.21 g, 3.6 mmol) in 86% yield.

To a solution of S33 (2.21 g, 3.6 mmol) in EtOH (36 mL) was added 10% palladium on carbon (200 mg) at 25 °C. The flask was shortly evacuated and a balloon filled with hydrogen put on it. The reaction mixture was stirred at 25 °C. After stirring for 2 h, the resulting mixture was filtered through a plug of tightly packed celite and washed with EtOAc (twice). The combined filtrates were concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 1b (1.84 g, 3.45 mmol) in 97% yield.

**Synthesis of 4g:**\(^{44,45}\)
To a solution of S27 (631 mg, 2.3 mmol) and 2,5-dimethyl-1,4-benzoquinone (S35, 313 mg, 2.3 mmol) in CH3CN (23 mL) and water (10 mL) was added silver nitrate (425 mg, 2.5 mmol) at 25 °C. The reaction mixture was warmed to 75 °C and potassium persulfate (757 mg, 2.8 mmol) in water (10 mL) was added slowly over 1 h. After stirring for 3 h, the reaction mixture was cooled to 25 °C, poured into water and extracted with EtOAc (twice). The combined organic layers were washed with saturated aq. NaHCO3, brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give S36 (163 mg, 0.45 mmol) in 20% yield.

To a solution of S36 (163 mg, 0.45 mmol) in acetone (4.5 mL) was added saturated aq. sodium hydrosulfite (4.5 mL) at 25 °C. After stirring for 1 h, the reaction mixture was poured into water and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. To a solution of the crude product in CH2Cl2 (2.5 mL) was added Et3N (126 µL, 0.9 mmol) and DMAP (6 mg, 0.05 mmol) at 0 °C, then TsCl (86 mg, 0.45 mmol) in CH2Cl2 (2.5 mL) was added slowly over 1 h at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was cooled to 0 °C, poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give 4g as white solid (161 mg, 0.31 mmol) in 69% yield.

4-Hydroxy-2,5-dimethyl-3-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)phenyl 4-methylbenzenesulfonate (4g): White solid; TLC, Rf = 0.57 (hexane–EtOAc = 1:1); IR (neat) 3382, 2929, 1682, 1405, 1368, 1189 cm⁻¹; ¹H NMR (CDCl3, 400 MHz) δ 7.70 (d, J = 8.7 Hz, 2H), 7.49–7.45 (m, 3H), 7.33 (d, J = 0.9 Hz, 1H), 7.30–7.25 (m, 4H), 7.21 (d, J = 0.9 Hz, 1H), 7.12 (brs, 1H), 6.68 (s, 1H), 3.77–3.68 (m, 1H), 2.75–2.67 (m, 1H), 2.50–2.45 (m, 1H), 2.44 (s, 3H), 2.14 (s, 3H), 1.88 (s, 3H), 1.95–1.83 (m, 1H), 1.58–1.49 (m, 1H), 1.20 (d, J = 7.3 Hz, 3H); ¹³C NMR (CDCl3, 100 MHz) δ 195.1, 151.4, 144.9, 142.3, 140.9, 138.0, 133.0, 129.5 (2C), 129.3, 129.0 (2C),
128.7, 128.3 (2C), 127.4, 127.1, 125.5 (2C), 123.1, 121.9, 42.0, 32.0, 25.0, 21.5, 17.7, 16.2, 12.3; HRMS (FAB) m/z calcd for \([C_{29}H_{30}N_{2}O_{5}S+H]^+\) 519.1948, found 519.1942.

**Synthesis of 4h:**

To a solution of S27 (817 mg, 3 mmol) and 2,3-dimethyl-1,4-benzoquinone (S37, 409 mg, 3 mmol) in CH3CN (50 mL) and water (25 mL) was added silver nitrate (561 mg, 3.3 mmol) at 25 °C. The reaction mixture was warmed to 75 °C and potassium persulfate (973 mg, 3.6 mmol) in water (25 mL) was added slowly over 1 h. After stirring for 3 h, the reaction mixture was cooled to 25 °C, poured into water and extracted with EtOAc (twice). The combined organic layers were washed with saturated aq. NaHCO3, brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give S38 (217 mg, 0.6 mmol) in 21% yield.

To a solution of S38 (217 mg, 0.6 mmol) in acetone (6 mL) was added saturated aq. sodium hydrosulfite (6 mL) at 25 °C. After stirring for 1 h, the reaction mixture was poured into water and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. To a solution of the crude product in CH2Cl2 (3 mL) was added Et3N (168 μL, 1.2 mmol) and DMAP (7.3 mg, 0.06 mmol) at 0 °C, then TsCl (114 mg, 0.6 mmol) in CH2Cl2 (3 mL) was added slowly over 1 h at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was cooled to 0 °C, poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give 4h as white solid (200 mg, 0.39 mmol) in 64% yield.

**4-hydroxy-2,3-dimethyl-5-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)phenyl 4-methylbenzenesulfonate (4h):** White solid; TLC, Rf = 0.52 (hexane–EtOAc = 1:1); IR (neat) 3423, 2929, 1685, 1405, 1367, 1176 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.71 (d, J = 8.5 Hz, 2H), 7.54 (brs, 1H), 7.48–7.44 (m, 3H), 7.32 (d, J = 0.9 Hz, 1H), 7.30–7.23 (m, 4H), 7.21 (d, J = 0.9 Hz,
Chapter 2. High-Turnover Hypoiodite Catalysis for Asymmetric Synthesis of Tocopherols

57

1H), 6.52 (s, 1H), 3.71–3.62 (m, 1H), 2.66–2.58 (m, 1H), 2.47–2.40 (m, 1H), 2.43 (s, 3H), 2.12 (s, 3H), 2.05–1.96 (m, 1H), 1.95 (s, 3H), 1.60–1.51 (m, 1H), 1.17 (d, J = 7.1 Hz, 3H); 13C NMR (CDCl3, 100 MHz) δ 195.1, 151.2, 144.9, 142.4, 141.2, 138.1, 133.1, 129.6, (2C), 129.3, 129.1, 129.0 (2C), 128.9, 128.5 (2C), 127.2, 125.7 (2C), 125.6, 125.3, 120.5, 41.7, 33.9, 28.7, 21.6, 17.8, 13.2, 12.5; HRMS (FAB) m/z calcd for [C29H30N2O5S+H]+ 519.1948, found 519.1942.

Synthesis of 4i:44,45

To a solution of S27 (1.23 g, 4.5 mmol) and S39 (840 mg, 3 mmol) in CH3CN (30 mL) and water (15 mL) was added silver nitrate (254 mg, 1.5 mmol) at 25 °C. The reaction mixture was warmed to 75 °C and potassium persulfate (1.62 g, 6 mmol) in water (15 mL) was added slowly over 1 h. After stirring for 1 h, the reaction mixture was cooled to 25 °C, poured into water and extracted with EtOAc (twice). The combined organic layers were washed with saturated aq. NaHCO3, brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give S40 (1.04 g, 2 mmol) in 67% yield.

To a solution of S40 (1.04 g, 2 mmol) in MeOH (20 mL) was added 10% palladium on carbon (100 mg) at 25 °C. The flask was shortly evacuated and a balloon filled with hydrogen put on it. The reaction mixture was stirred at 25 °C. After stirring for 4 h, the resulting mixture was filtered through a plug of tightly packed celite and washed with EtOAc. The combined filtrates were washed with 10% aq. NaHCO3, brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. To a solution of the crude product in CH2Cl2 (10 mL) was added 2,4,6-collidine (263 µL, 2 mmol) and DMAP (24 mg, 0.2 mmol) at 0 °C, then TsCl (381 mg) in CH2Cl2 (8 mL) was added slowly over 1 h at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was cooled to 0 °C, poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO4, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give 4i as white solid (757 mg, 1.5 mmol) in 75% yield.

4-Hydroxy-3-methyl-5-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)phenyl
4-methylbenzenesulfonate (4i): White solid; TLC, Rf = 0.47 (hexane–EtOAc = 1:1); IR (neat) 3485, 2930, 1683, 1598, 1404, 1369 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.70 (brs, 1H), 7.69 (d, J = 7.8 Hz, 2H), 7.48–7.47 (m, 3H), 7.34 (s, 1H) 7.30–7.25 (m, 4H), 7.22 (s, 1H), 6.66 (d, J = 3.0 Hz, 1H), 6.46 (d, J = 3.0 Hz, 1H), 3.67–3.59 (m, 1H), 2.68–2.59 (m, 1H), 2.43 (s, 3H), 2.46–2.38 (m, 1H), 2.17 (s, 3H), 2.04–1.95 (m, 1H), 1.58–1.49 (m, 1H), 1.15 (d, J = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 195.0, 151.7, 144.9, 142.3, 141.9, 138.0, 132.4, 129.5 (2C), 129.3, 129.0 (2C), 128.8, 128.5 (2C), 128.1, 127.2, 126.5, 125.6 (2C), 122.3, 120.9, 41.5, 33.8, 28.6, 21.6, 17.7, 16.4; HRMS (FAB) m/z calcd for [C₂₈H₂₈N₂O₅S+H]⁺ 505.1792, found 505.1789.

Synthesis of 4j:

To a solution of 6-hydroxytetralone (S₄₁, 5.03 g, 31 mmol) and imidazole (6.13 g, 90 mmol) in CH₂Cl₂ (100 mL) were added t-butyldimethylchlorosilane (6.03 g, 40 mmol) at 25 °C. After stirring overnight, the resulting mixture was poured into water and extracted with CHCl₃ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo to give S₄₂.
To a solution of S42 in CH₂Cl₂ (60 mL) was added mCPBA (10.5 g, 62 mmol) at 0 °C and stirred at 25 °C. The combined organic layers were washed with saturated aq. NaHCO₃, brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo to give S43 (8.8 g, 30 mmol) in 98% yield over 2 steps.

To a solution of S43 (8.8 g, 30 mmol) and pyridine (5.3 mL, 66 mmol, 2.2 equiv) in THF (75 mL) were added N,O-dimethylhydroxylamine hydrochloride (3.22 g, 33 mmol) at 25 °C. After stirring overnight, the resulting mixture was poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S44 (7.8 g, 22 mmol) in 73% yield.

To a solution of S44 (7.8 g, 31 mmol) and imidazole (4.49 g, 66 mmol) in CH₂Cl₂ (55 mL) were added t-butyldiphenylchlorosilane (7.97 g, 29 mmol) at 25 °C. After stirring overnight, the resulting mixture was poured into water and extracted with CHCl₃ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S45 (11.3 g, 19 mmol) in 87% yield.

To a solution of N-phenylimidazole (2.66 mL, 21 mmol) in THF (30 mL) was added n-BuLi (1.6 M in hexane, 12.5 mL, 20 mmol) at −78 °C. After stirring at −78°C for 30 min, the reaction mixture was added to a solution of S45 (11.3 g, 19 mmol) in THF (8 mL) via cannula at −78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into saturated aq. NH₄Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S46 (8.32 g, 12.3 mmol) in 65% yield.

To a solution of diisopropylamine (970 µL, 6.9 mmol) in THF (40 mL) was added n-BuLi (1.6 M in hexane, 4.3 mL, 6.8 mmol) at −78 °C and the resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was cooled back to −78 °C and S46 (8.32 g, 12.3 mmol) and HPMA (922 µL) were added. After stirring at −78 °C for 30 min, MeI (330 µL, 5.3 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into aqueous NH₄Cl and extracted with Et₂O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S47 (2.1 g, 3.1 mmol) in 58% yield.
yield.

To a solution of S47 (2.1 g, 3.1 mmol) in DMF (16 mL) and H₂O (0.3 mL) was added lithium acetate (198 mg, 0.3 mmol) at 25 °C and stirred at 35 °C. After stirring 5 d, the resulting mixture was poured into water and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 5:1) to give S48 (912 mg, 1.6 mmol) in 51% yield.

To a solution of S48 (912 mg, 1.6 mmol) and pyridine (291 µL, 3.6 mmol) in CH₂Cl₂ (15 mL) was added p-chlorobenzoyl chloride (315 mg, 1.8 mmol) at –78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into 1 M HCl and extracted with Et₂O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 5:1) to give S49 (1.0 g, 1.4 mmol) in 90% yield.

To a solution of S49 (164 g, 0.23 mmol) in THF (4.6 mL) was added tetrabutyl ammonium fluoride (1 M in THF, 0.46 mL, 0.46 mmol) at 25 °C. After stirring overnight, the resulting mixture was poured into aqueous NH₄Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 4j (71 mg, 0.15 mmol) in 65% yield.

4-Hydroxy-3-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)phenyl 4-chlorobenzoate (4j): White solid; TLC, R₅f = 0.46 (hexane–EtOAc = 1:1); IR (neat) 3407, 2932, 1734, 1683, 1403, 1265, 1091 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.11 (d, J = 8.7 Hz, 2H), 7.82 (brrs, 1H), 7.48–7.46 (m, 5H), 7.33 (d, J = 0.92 Hz, 1H), 7.29–7.26 (m, 2H), 7.20 (d, J = 0.92 Hz, 1H), 6.93–6.88 (m, 3H), 3.81–3.72 (m, 1H), 2.80–2.72 (m, 1H), 2.62–2.55 (m, 1H), 2.18–2.05 (m, 1H), 1.78–1.70 (m, 1H), 1.21 (d, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 195.3, 164.8, 152.7, 143.7, 142.5, 139.9, 138.1, 131.5 (2C), 129.3, 129.1 (3C), 128.93, 128.87 (2C), 128.2, 127.2, 125.7 (2C), 122.7, 120.2, 117.2, 41.8, 33.9, 28.7, 17.8; HRMS (FAB) m/z calcd for [C₂₇H₂₅ClN₂O₄+H]⁺ 475.1419, found 475.1418.

Synthesis of 4k:
To a solution of 7-hydroxy-1-tetralone (S50, 1.46 g, 9 mmol) and imidazole (1.84 g, 27 mmol) in CH$_2$Cl$_2$ (23 mL) was added TBSCl (1.36 g, 9 mmol) at 25 °C. After stirring overnight, the resulting mixture was poured into water and extracted with CHCl$_3$ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo to give S51 (2.21 g, 8 mmol) in 89% yield.

To a solution of S51 (2.21 g, 8 mmol) in CH$_2$Cl$_2$ (16 mL) was added mCPBA (2.76 g, 16 mmol) at 0 °C and stirred at 25 °C. After stirring overnight, additional mCPBA (6.63 g, 24 mmol) was added at 0 °C and was stirred at 25 °C. After stirring overnight, the resulting mixture was diluted with Et$_2$O, quenched with saturated aq. Na$_2$S$_2$O$_3$ at 0 °C and extracted with Et$_2$O (twice). The combined organic layers were washed with saturated aq. NaHCO$_3$, brine and dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo to give S52 (1.55 g, 5.3 mmol) in 66% yield.

To a solution of S52 (1.55 g, 5.3 mmol) and pyridine (970 µL, 12 mmol) in THF (5.3 mL) was added N,O-dimethylhydroxylamine hydrochloride (570 mg, 5.8 mmol) at 25 °C. After stirring
overnight, the reaction mixture was poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give the S53 (1.87 g, 5.3 mmol) in quantitative yield.

To a solution of S53 (1.87 g, 5.3 mmol) and K₂CO₃ (3.04 g, 22 mmol) in acetone (14 mL) was added BnBr (1.9 mL, 16 mmol) at 25 °C and refluxed. After stirring for 5 h, additional BnBr (850 µL, 8 mmol) and K₂CO₃ (2.21 g, 16 mmol) were added at 25 °C and refluxed. After stirring for 3 h, the resulting mixture was concentrated in vacuo. To the residue was added water and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S54 (1.55 g, 3.5 mmol) in 64% yield.

To a solution of N-phenylimidazole (670 µL, 5.3 mmol) in THF (8 mL) was added n-BuLi (1.6 M in hexane, 3.3 mL, 5.3 mmol) at −78 °C. After stirring at −78°C for 30 min, the reaction mixture was added to a solution of S54 (1.55 g, 3.5 mmol) in THF (7 mL) via cannula at −78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring for 8 h, the resulting mixture was poured into saturated aq. NH₄Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S55 (990 mg, 1.9 mmol) in 54% yield.

To a solution of diisopropylamine (180 µL, 1.3 mmol) in THF (2.6 mL) was added n-BuLi (1.6 M in hexane, 750 µL, 1.2 mmol) at −78 °C and the resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was cooled back to −78 °C and HPMA (840 µL) was added. After stirring at −78 °C for 2 h, S55 (632 mg, 1.2 mmol) was added. After stirring at −78 °C for 2 h, EtI (145 µL, 1.8 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into aqueous NH₄Cl and extracted with Et₂O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S55 (187 mg, 0.34 mmol) in 28% yield. To a solution of S56 (200 mg, 0.36 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (1 M in THF, 440 µL, 0.44 mmol) at 25 °C. After stirring overnight, the resulting mixture was poured into aqueous NH₄Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄,
then the solvents were removed \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give \textbf{S57} (159 mg, 0.36 mmol) in quantitative yield.

To a solution of \textbf{S57} (159 mg, 0.36 mmol), Et$_3$N (140 µL, 0.54 mmol) and DMAP (4.9 mg, 0.04 mmol) in CH$_2$Cl$_2$ (2 mL) was added TsCl (103 mg, 0.54 mmol) at 0 °C and stirred at 25 °C. After stirring overnight, the resulting mixture was poured into 1 M HCl and extracted with CHCl$_3$ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$, then the solvents were removed \textit{in vacuo}. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give \textbf{S58} (214 g, 0.36 mmol) in quantitative yield.

To a solution of \textbf{S58} (214 mg, 0.36 mmol) in EtOH (4 mL) was added 10% palladium on carbon (100 mg) at 25 °C. The flask was shortly evacuated and a balloon filled with hydrogen put on it. The resulting mixture was stirred at 25 °C. After stirring for 3 h, the resulting mixture was filtered through a plug of tightly packed celite and washed with EtOAc. The combined filtrates were concentrated \textit{in vacuo} and the residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give \textbf{4k} (145 mg, 0.29 mmol) in 80% yield.

\textbf{3-Hydroxy-4-(3-(1-phenyl-1H-imidazole-2-carbonyl)pentyl)phenyl 4-methylbenzenesulfonate (4k):} White solid; \textbf{TLC}, $R_f = 0.58$ (hexane–EtOAc = 1:1); \textbf{IR} (KBr) 3438, 2963, 1686, 1600, 1494, 1371, 1192 cm$^{-1}$; \textbf{1H NMR} (CDCl$_3$, 400 MHz) δ 8.70 (brs, 1H), 7.71 (d, $J = 8.2$ Hz, 2H), 7.52–7.47 (m, 3H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.30–7.23 (m, 3H), 7.21 (s, 1H), 6.93 (d, $J = 8.2$ Hz, 1H), 6.54 (d, $J = 2.3$ Hz, 1H), 6.43 (dd, $J = 8.2, 2.3$ Hz, 1H), 3.60–3.53 (m, 1H), 2.75–2.67 (m, 1H), 2.51–2.43 (m, 1H), 2.43 (s, 3H), 2.03–1.94 (m, 1H), 1.81–1.66 (m, 2H), 1.55–1.43 (m, 1H), 0.80 (t, $J = 7.6$ Hz, 3H); \textbf{13C NMR} (CDCl$_3$, 100 MHz) δ 195.2, 155.7, 148.6, 145.1, 143.0, 138.1, 132.5, 130.4, 129.6 (2C), 129.12 (2C), 129.98, 128.08, 128.5 (2C), 127.3, 127.2, 125.7 (2C), 113.6, 110.5, 48.6, 32.0, 28.1, 25.7, 21.7, 11.6; \textbf{HRMS} (FAB) m/z calcd for [C$_{28}$H$_{28}$N$_2$O$_5$S+H]$^+$ 505.1792, found 505.1780.

\textbf{Synthesis of 4l:}
To a solution of diisopropylamine (6.0 mL, 43 mmol) in THF (84 mL) was added n-BuLi (1.6 M in hexane, 27 mL, 43 mmol) at −78 °C. The reaction mixture was allowed to warm to 0 °C. After stirring for 1 h, the resulting mixture was cooled back to −78 °C and 5,7-dimethyl-1-tetralone (S59, 5.23 g, 30 mmol) and HPMA (21 mL) was added. After stirring at −78 °C for 2 h, MeI (2.6 mL, 42 mmol) was added at −78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into saturated aq. NH₄Cl and extracted with Et₂O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S60 (3.58 g, 19 mmol) in 64% yield.

To a solution of S60 (3.58 g, 19 mmol) in CH₂Cl₂ (40 mL) was added mCPBA (6.9 g, 40 mmol) at 0 °C and stirred at 25 °C. After stirring overnight, the resulting mixture was diluted with Et₂O, quenched with saturated aq. Na₂S₂O₃ at 0 °C and extracted with Et₂O (twice). The combined organic layers were washed with saturated aq. NaHCO₃, brine and dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 50:1) to give S61 (1.94 g, 9.5 mmol) in 50% yield.

To a solution of S61 (1.94 g, 9.5 mmol) and pyridine (1.8 mL, 11 mmol) in THF (52 mL) was added N,O-dimethylhydroxylamine hydrochloride (1.07 g, 11 mmol) at 25 °C. After stirring for 24 h, the resulting mixture was poured into 1 M HCl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the
solvents were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S62 (2.23 g, 8.4 mmol) in 88% yield.

To a solution of S62 (2.23 g, 8.4 mmol) and imidazole (1.70 g, 25 mmol) in CH₂Cl₂ (20 mL) was added TBSCl (1.66 g, 11 mmol) at 25 °C. After stirring overnight, the resulting mixture was poured into water and extracted with CHCl₃ (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed *in vacuo*. To a solution of N-phenyl imidazole (1.4 mL, 11 mmol) in THF (16 mL) was added n-BuLi (1.6 M in hexane, 6.7 mL, 11 mmol,) at –78 °C. After stirring at –78 °C for 30 min, the reaction mixture was added to the crude product in THF (3 mL) via cannula at –78 °C. The reaction mixture was allowed to warm to 25 °C. After stirring for 3 h, the resulting mixture was poured into saturated aq. NH₄Cl and extracted with Et₂O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S63 (2.13 g, 4.6 mmol) in 85% yield over 2 steps.

To a solution of S63 (3.33 g, 7.2 mmol) in THF (21 mL) was added tetrabutylammonium fluoride (1 M in THF, 11 mL, 11 mmol) at 25 °C. After stirring overnight, the resulting mixture was poured into saturated aq. NH₄Cl and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S64 (2.51 g, 7.2 mmol) in quantitative yield.

To a solution of S64 (193 mg, 0.55 mmol) in CH₃CN (2 mL) was added NBS (196 mg, 1.1 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring overnight, the resulting mixture was poured into water and extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄, then the solvents were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 4l (253 mg, 0.5 mmol) in 91% yield.

4-(3,5-Dibromo-2-hydroxy-4,6-dimethylphenyl)-2-methyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (4l): Pale yellow solid; TLC, R₁ = 0.41 (hexane–EtOAc = 1:1); IR (neat) 3501, 2968, 1683, 1445, 1404, 1380, 1302, 1150 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.49–7.44 (m, 3H), 7.30 (s, 1H), 7.27–7.25 (m, 2H), 7.19 (s, 1H), 6.13 (brs, 1H), 3.96–3.88 (m, 1H), 2.89–2.80 (m, 1H), 2.75–2.67 (m, 1H), 2.57 (s, 3H), 2.35 (s, 3H), 2.01–1.91 (m, 1H), 1.65–1.56 (m, 1H), 1.23 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 194.9, 149.4, 142.6, 138.4, 136.4, 134.8, 129.5, 129.0 (2C), 128.7,
Procedures for the enantioselective oxidative cycloetherification of 2 and 4

General Procedures for the Synthesis of Authentic Samples:

To a stirring mixture of 2 or 4 (0.1 mmol) and Bu₄NI (3.7 mg, 0.01 mmol, 10 mol%) in CH₃NO₂ (0.5 mL) was added tert-butyl hydroperoxide (5.5 M nonane solution, Aldrich, 36.4 µL, 0.2 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 24 h, the resulting mixture was poured into saturated aq. Na₂S₂O₃ (4 mL), and the aqueous phase was extracted with EtOAc (twice). The combined organic layers were washed with brine. The combined organic layers were dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 3 or 5 in 10–79% yield.

Procedure for the Enantioselective Oxidative Cycloetherification of 2a with Hydrogen Peroxide (Scheme 2):

To a stirring mixture of 2a (23.9 mg, 0.05 mmol) and (R,R)-1a (8.5 mg, 0.005 mmol, 10 mol%) in MTBE (2.5 mL) was added 30-wt% aqueous hydrogen peroxide (10 µL, 0.1 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 30 min, the resulting mixture was poured into saturated aq. Na₂S₂O₃ (4 mL), and the aqueous phase was extracted with EtOAc (twice). The combined organic layers were washed with brine. The combined organic layers were dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 3a (22.7 mg, 0.048 mmol) in 95% yield. Enantiomeric excess of 3a was determined to be 93% ee by HPLC analysis.

(R)-(5-((tert-Butyldimethylsilyloxy)-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran-2-yl)(1-phenyl-1H-imidazol-2-yl)methanone (3a): White solid; TLC, Rₜ = 0.38 (hexane–EtOAc = 4:1); IR
(neat) 2927, 1696, 1460, 1252, 1083 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.43–7.42 (m, 3H), 7.34 (s, 1H), 7.24–7.22 (m, 2H), 7.18 (s, 1H), 3.82 (d, \(J = 16.3\) Hz, 1H), 3.34 (d, \(J = 16.3\) Hz, 1H), 2.10 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.03 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); \(^{13}\)C NMR (CD\(_2\)OD, 100 MHz) \(\delta\) 192.8, 152.1, 146.8, 142.0, 139.8, 130.4, 130.2 (2C), 129.7, 128.2, 127.8, 126.8 (2C), 123.3, 123.0, 117.3, 92.3, 41.9, 26.6 (3C), 26.0, 19.5, 14.9, 14.6, 12.5, –3.0 (2C); HRMS (FAB) m/z calcd for [C\(_{28}\)H\(_{36}\)N\(_2\)O\(_3\)Si+H]\(^+\) 477.2568, found 477.2558; HPLC (AD–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \(t_R = 4.6\) min, \(t_S = 7.0\) min; \([\alpha]^{244}_D = -26.1\) (c 1.2, CHCl\(_3\)) for 93% ee.

**Procedure for the Enantioselective Oxidative Cycloetherification of 2c Using (R,R)-1a with Cumene Hydroperoxide (Scheme 3):**

![Scheme 3](image)

To a stirring mixture of 2c (1.04 g, 2 mmol), (R,R)-1a (1.7 mg, 0.001 mmol, 0.05 mol%) and K\(_2\)CO\(_3\) (276 mg, 2 mmol, 1 equiv) in Et\(_2\)O (20 mL) was added cumene hydroperoxide (contains ca. 20% aromatic hydrocarbon, TCI, 732 µL, 4 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 24 h, the resulting mixture was poured into saturated aq. Na\(_2\)S\(_2\)O\(_3\) (10 mL), and the aqueous phase was extracted with EtOAc (twice). The combined organic layers were washed with brine. The combined organic layers were dried over anhydrous MgSO\(_4\), then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 3c (1.03 mg, 1.99 mmol) in 99% yield. Enantiomeric excess of 3c was determined to be 88% ee by HPLC analysis. Importantly, no reaction occurred and starting material was recovered fully without K\(_2\)CO\(_3\).

(R)-2,4,6,7-Tetramethyl-2-(1-phenyl-1H-imidazole-2-carbonyl)-2,3-dihydrobenzofuran-5-yl 4-methylbenzenesulfonate (3c): White solid; TLC, \(R_f = 0.30\) (hexane–EtOAc = 1:1); IR (neat) 2926, 1693, 1457, 1396, 1368, 1176 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.81 (d, \(J = 7.6\) Hz, 2H), 7.44–7.43 (m, 3H), 7.34 (d, \(J = 7.6\) Hz, 2H), 7.33 (s, 1H), 7.26–7.23 (m, 2H), 7.19 (s, 1H), 3.83 (d, \(J = 16.5\) Hz, 1H), 2.46 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.86 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 189.0, 154.8, 144.9, 141.0, 140.0, 138.3, 134.1, 130.6, 129.7 (2C), 129.6, 129.0 (2C), 128.7, 128.2 (2C), 126.9, 125.8 (2C), 125.6, 122.7, 116.8, 91.4, 40.7, 26.3, 21.7, 14.5, 13.9, 12.3; HRMS (FAB) m/z calcd for [C\(_{29}\)H\(_{38}\)N\(_2\)O\(_3\)S+H]\(^+\) 517.1792, found 517.1796; HPLC (AD-H column) Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, \(t_R = 15.0\) min, \(t_S = 15.0\) min.
17.1 min; [α]^{21.3}_D = −18.8 (c 1.0, CHCl₃) for 88% ee.

Procedure for the Enantioselective Oxidative Cycloetherification of 4a with Hydrogen Peroxide (Scheme 2):

To a stirring mixture of 4a (24.6 mg, 0.05 mmol) and (R,R)-1a (8.5 mg, 0.005 mmol, 10 mol%) in MTBE (2.5 mL) was added 30-wt% aqueous hydrogen peroxide (10 µL, 0.1 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 24 h, the resulting mixture was poured into saturated aq. Na₂S₂O₃ (4 mL), and the aqueous phase was extracted with EtOAc (twice). The combined organic layers were washed with brine. The combined organic layers were dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 5a (2 mg, 0.005 mmol) in 10% yield, and 1a (14 mg, 0.028 mmol) was recovered. Only trace amount of 2a was obtained (TLC analysis).

2,3,5-Trimethyl-6-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)cyclohexa-2,5-diene-1,4-dione (5a): Yellow oil; TLC, Rₛ = 0.41 (hexane–EtOAc = 1:1); IR (neat) 2932, 1683, 1641, 1445, 1404, 1304 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.47–7.44 (m, 3H), 7.32–7.29 (m, 2H), 7.26 (s, 1H), 7.19 (s, 1H), 3.95–3.86 (m, 1H), 2.61–2.54 (m, 1H), 2.44–2.36 (m, 1H), 1.99 (s, 3H), 1.965 (s, 3H), 1.957 (s, 3H), 1.91–1.81 (m, 1H), 1.58–1.49 (m, 1H), 1.23 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 194.5, 187.7, 186.8, 143.8, 142.5, 140.4 (2C), 140.3, 138.5, 129.5, 128.9 (2C), 128.6, 127.1, 125.8 (2C), 41.3, 31.6, 24.2, 17.2, 12.32, 12.28, 12.0; HRMS (FAB) m/z calcld for [C₂₃H₂₄N₂O₃+H]⁺ 377.1860, found 377.1868.
Procedure for the Enantioselective Oxidative Cycloetherification of 4a with tert-Butyl Hydroperoxide (Scheme 2):

To a stirring mixture of 4a (42.9 mg, 0.0871 mmol) and (R,R)-1a (14.8 mg, 0.00871 mmol, 10 mol%) in MTBE (4.4 mL) was added tert-butyl hydroperoxide (5.5 M nonane solution, Aldrich, 32 mL, 0.174 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 1 h, the resulting mixture was poured into saturated aq. (6 mL), and the aqueous phase was extracted with EtOAc (twice). The combined organic layers were washed with brine. The combined organic layers were dried over anhydrous MgSO₄, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 5a (6.2 mg, 0.0126 mmol) in 15% yield, 6a (4.2 mg, 0.0112 mmol) in 15% yield and 6b (26.8 mg, 0.046 mmol) in 50% yield. Enantiomeric excess of 5a was determined to be 18% ee by HPLC analysis.

(−)-(6-((tert-Butyldimethylsilyl)oxy)-2,5,7,8-tetramethylchroman-2-yl)(1-phenyl-1H-imidazol-2-yl)methanone (5a): White solid; TLC, Rₛ = 0.72 (hexane–EtOAc = 1:1); IR (neat) 2926, 1689, 1459, 1405, 1255, 1092 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.35–7.26 (m, 3H), 7.23 (s, 1H), 7.05 (s, 1H), 6.77 (d, J = 7.8 Hz, 2H), 2.89 (ddd, J = 13.3, 6.9, 2.3 Hz, 1H), 2.57–2.51 (m, 1H), 2.41–2.32 (m, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.99 (s, 1H), 1.93 (s, 3H), 2.06–1.93 (m, 1H), 1.03 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 193.5, 146.3, 144.9, 141.5, 138.1, 128.9 (2C), 128.8, 128.2, 126.0, 125.7, 125.3 (2C), 123.3, 123.2, 117.7, 81.7, 30.6, 26.0 (3C), 25.5, 21.2, 18.5, 14.3, 13.3, 12.0, −3.4 (2C); HRMS (FAB) m/z calcd for [C₂₉H₃₈N₂O₅Si+H]⁺ 491.2724, found 491.2720; HPLC (AD–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, t_minor = 5.6 min, t_major
= 6.9 min; [α]D25.5 = −2.6 (c 0.4, CHCl3) for 18% ee.

4-((tert-Butyldimethylsilyl)oxy)-4-(tert-butylperoxy)-2,3,5-trimethyl-6-(3-methyl-4-oxo-4-(1-phenyl-1H-imidazol-2-yl)butyl)cyclohexa-2,5-dien-1-one (6b): Obtained as a diastereomeric mixture. Colorless oil; TLC, Rf = 0.69 (hexane–EtOAc = 1:1); IR (neat) 2930, 1685, 1637, 1445, 1405, 1093 cm−1; 1H NMR (CDCl3, 400 MHz, diastereomers) δ 7.49–7.45 (m, 3H), 7.33–7.30 (m, 2H), 7.26 (s, 1H), 7.18 (s, 1H), 3.97–3.90 (m, 1H), 2.52–2.20 (m, 2H), 1.89–1.88 (m, 6H), 1.82 (s, 3H), 1.79–1.73 (m, 1H), 1.53–1.43 (m, 1H), 1.23–1.22 (m, 3H), 1.17 (s, 4.5H), 1.15 (s, 4.5H), 0.872 (s, 4.5H), 0.868 (s, 4.5H), −0.01 (s, 3H), −0.02 (s, 3H); 13C NMR (CDCl3, 100 MHz, diastereomers) δ 195.2, 184.70, 184.68, 150.8, 150.7, 150.33, 150.28, 142.86, 142.85, 138.6, 135.69, 135.62, 131.9, 129.4, 129.1, 128.9, 128.6, 126.9, 125.9, 125.8, 95.89, 95.86, 79.54, 79.52, 41.66, 41.63, 31.54, 31.47, 26.6, 25.6, 23.6, 23.5, 18.3, 16.88, 16.82, 14.60, 14.57, 13.9, 11.3, −3.22, −3.25, −3.48, −3.50; HRMS (FAB) m/z calcd for [C33H48N2O5Si+H]+ 581.3405, found 581.3405.

Typical Procedure for the Enantioselective Oxidative Cycloetherification of 4 Using (R,R)-1d with Cumene Hydroperoxide (Method A; Table 2, entry 10):

To a stirring mixture of 4e (1.53 g, 2.9 mmol), (R,R)-1d (65 mg, 0.029 mmol, 1 mol%) and K2CO3 (397 mg, 2.9 mmol, 1 equiv) in Et2O (290 mL) was added cumene hydroperoxide (contains ca. 20% aromatic hydrocarbon, TCI, 1.05 mL, 5.7 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 10 h, the resulting mixture was poured into saturated aq. Na2S2O3 (50 mL), and the aqueous phase was extracted with Et2O (twice). The combined organic layers were washed with brine. The combined organic layers were dried over anhydrous MgSO4, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give analytically pure (S)-5e (1.5 g, 2.8 mmol) in 98% yield. Enantiomeric excess of (S)-5e was determined to be 93% ee by HPLC analysis.
Typical Procedure for the Enantioselective Oxidative Cycloetherification of 4 Using (R,R)-1a with tert-Butyl Hydroperoxide (Method B; Table 4, 5j):

To a stirring mixture of 4j (47.5 mg, 0.1 mmol), (R,R)-1a (1.7 mg, 0.001 mmol, 1 mol%) and K$_2$CO$_3$ (13.8 mg, 0.1 mmol, 1 equiv) in Et$_2$O (5.0 mL) was added tert-butyl hydroperoxide (5.5 M nonane solution, Aldrich, 36.4 µL, 0.2 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 18 h, the resulting mixture was poured into saturated aq. Na$_2$S$_2$O$_3$ (6 mL), and the aqueous phase was extracted with EtOAc (twice). The combined organic layers were washed with brine. The combined organic layers were dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give analytically pure (R)-5j (45.0 mg, 0.95 mmol) in 95% yield. Enantiomeric excess of (R)-5j was determined to be 92% ee by HPLC analysis.

Typical Procedure for the Enantioselective Oxidative Cycloetherification of 4 Using (R,R)-1a with tert-Butyl Hydroperoxide in the absence of K$_2$CO$_3$ (Method C; Table 1, 5b):

To a stirring mixture of 4b (30.6 mg, 0.1 mmol) and (R,R)-1a (17.0 mg, 0.01 mmol, 10 mol%) in MTBE (5.0 mL) was added tert-butyl hydroperoxide (5.5 M nonane solution, Aldrich, 36.4 µL, 0.2 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 4 h, the resulting mixture was poured into saturated aq. Na$_2$S$_2$O$_3$ (6 mL), and the aqueous phase was extracted with EtOAc (twice). The combined organic layers were washed with brine. The combined organic layers were dried over anhydrous MgSO$_4$, then the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give analytically pure (R)-5b (30.4 mg, 0.99 mmol) in 99% yield. Enantiomeric excess of (R)-5b was determined to be 76% ee by HPLC analysis.

Characterization of Products 5

(R)-Chroman-2-yl(1-phenyl-1H-imidazol-2-yl)methanone (5b): Method C: 30.4 mg, 99% yield,
76% ee. White solid; TLC, \( R_f = 0.44 \) (hexane–EtOAc = 1:1); IR (neat) 2927, 1697, 1489, 1456, 1406, 1234, 1117 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.45–7.43 (m, 3H), 7.32 (d, \( J = 0.92 \) Hz, 1H), 7.31–7.29 (m, 2H), 7.24 (d, \( J = 0.92 \) Hz, 1H), 7.08 (d, \( J = 7.8 \) Hz, 1H), 7.01 (d, \( J = 7.8 \) Hz, 1H), 6.90 (d, \( J = 7.8 \) Hz, 1H), 6.82 (d, \( J = 7.8 \) Hz, 1H), 5.91 (dd, \( J = 7.3, 3.7 \) Hz, 1H), 2.93 (ddd, \( J = 14.2, 7.8, 5.5 \) Hz, 1H), 2.74–2.67 (m, 1H), 2.57–2.49 (m, 1H), 2.33–2.24 (m, 1H); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 187.2, 154.1, 140.6, 137.8, 130.0, 129.3, 129.0 (2C), 128.9, 127.5, 127.4, 125.9 (2C), 121.3, 120.3, 116.7, 76.5, 25.1, 23.4; HRMS (FAB) m/z calcd for \([C_{19}H_{16}N_2O_2+H]^+\) 305.1285, found 305.1290; HPLC (AS–H column) Hexane–EtOH = 4:1 as eluent, 1 mL/min, \( t_f = 7.1 \) min, \( t_R = 8.2 \) min; [\( \alpha \)]\(^{22}\) = –29.7 (c 1.4, CHCl\(_3\)) for 76% ee.

**(R)-2,5,7,8-Tetramethyl-2-(1-phenyl-1H-imidazole-2-carbonyl)chroman-6-yl 4-chlorobenzoate (5c):** Method C: 3h; 47.2 mg, 92% yield, 26% ee. White solid; TLC, \( R_f = 0.59 \) (hexane–EtOAc = 1:1); IR (neat) 2929, 1734, 1688, 1593, 1400, 1240, 1092 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz, two rotamers) \( \delta \) 8.18–8.16 (m, 2H), 7.50–7.48 (m, 2H), 7.35–7.32 (m, 3H), 7.26 (s, 0.5H), 7.23 (s, 0.5H), 7.09 (s, 0.5H), 7.06 (s, 0.5H), 6.93–6.91 (m, 1H), 6.74–6.73 (m, 1H), 3.10–3.06 (m, 0.5H), 2.82–2.77 (m, 0.5H), 2.64–2.56 (m, 1H), 2.46–2.39 (m, 1H), 2.13–2.10 (m, 3H), 1.99–1.92 (m, 10H); \(^13\)C NMR (CDCl\(_3\), 100 MHz, two rotamers) \( \delta \) 193.6, 192.1, 164.2, 164.1, 149.9, 149.7, 141.7, 141.6, 141.1, 139.9, 138.3, 138.0, 131.5, 129.1, 128.9, 128.7, 128.5, 128.4, 127.9, 127.2, 127.0, 126.2, 125.9, 125.6, 125.5, 125.2, 124.9, 124.0, 123.5, 118.4, 117.7, 82.2, 81.9, 30.5, 30.1, 25.5, 21.0, 20.9, 13.0, 12.0, 11.93, 11.86; HRMS (FAB) m/z calcd for \([C_{30}H_{25}ClN_2O_4+H]^+\) 515.1732, found 515.1733; HPLC (IC–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \( t_f = 11.9 \) min, \( t_R = 14.4 \) min; [\( \alpha \)]\(^{22}\) = –6.1 (c 1.0, CHCl\(_3\)) for 26% ee.

**(R)-2,5,7,8-Tetramethyl-2-(1-phenyl-1H-imidazole-2-carbonyl)chroman-6-yl methanesulfonate (5d):** Method C: 3 h; 43.0 mg, 95% yield, 54% ee. White solid; TLC, \( R_f = 0.58 \) (hexane–EtOAc = 1:1); IR (neat) 2932, 1685, 1457, 1397, 1174 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.36–7.31 (m, 3H), 7.24 (d, \( J = 0.9 \) Hz, 1H), 7.08 (d, \( J = 0.9 \) Hz, 1H), 6.86–6.83 (m, 2H), 3.22 (s, 3H), 3.02 (ddd, \( J = 13.8, 6.9, 2.8 \) Hz, 1H), 2.61–2.56 (m, 1H), 2.41–2.32 (m, 1H), 2.19 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.96 (s, 1H), 2.01–1.93 (m, 1H); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 195.4, 151.2, 142.5, 140.3, 138.1, 129.5, 129.1 (2C), 128.9, 127.20, 127.18, 125.7 (2C), 124.8, 122.9, 42.3, 38.6, 32.2, 25.4, 18.1, 14.7, 14.0, 12.5; HRMS (FAB) m/z calcd for \([C_{26}H_{26}N_2O_4S+H]^+\) 455.1635, found 455.1641; HPLC (AD–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \( t_f = 28.0 \) min, \( t_R = 33.7 \) min; [\( \alpha \)]\(^{24}\) = –6.6 (c 1.5, CHCl\(_3\)) for 54% ee.

**(S)-2,5,7,8-Tetramethyl-2-(1-phenyl-1H-imidazole-2-carbonyl)chroman-6-yl**
4-methylbenzenesulfonate (5e): Method A: \((R,R)-1\text{d}\) (1 mol%), 10 h; 1.50 g, 98% yield, 93% ee or \((R,R)-1\text{d}\) (0.5 mol%), 48 h; 52.2 mg, 98% yield, 93% ee. White solid; TLC, \(R_i = 0.52\) (hexane–EtOAc = 1:1); \(\text{IR}\) (neat) 2928, 1686, 1457, 1403, 1368, 1176 cm\(^{-1}\); \(^1\text{H NMR}\) (CDCl\(_3\), 400 MHz) \(\delta \) 7.78 (d, \(J = 8.0\) Hz, 2H), 7.36–7.34 (m, 3H), 7.32 (d, \(J = 8.0\) Hz, 2H), 7.24 (d, \(J = 0.9\) Hz, 1H), 7.09 (d, \(J = 0.9\) Hz, 1H), 6.87–6.83 (m, 2H), 3.00 (ddd, \(J = 13.3, 6.9, 2.3\) Hz, 1H), 2.55 (ddd, \(J = 17.4, 6.4, 2.3\) Hz, 1H), 2.46 (s, 3H), 2.38–2.30 (m, 1H), 2.04 (s, 3H), 2.03–1.96 (m, 1H), 1.97 (s, 3H), 1.95 (s, 3H), 1.83 (s, 3H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz) \(\delta \) 192.1, 150.2, 144.9, 141.1, 140.7, 138.1, 134.2, 129.7 (2C), 129.1 (2C), 129.05, 128.9, 128.5, 128.2 (2C), 127.6, 126.2, 125.4 (2C), 124.0, 118.3, 82.2, 30.4, 25.7, 21.7, 21.1, 14.1, 13.6, 12.0; \(\text{HRMS}\) (FAB) m/z calcd for \([\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_5\text{S}+\text{H}]^+\) 531.1948, found 531.1944; \(\text{HPLC}\) (IC–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \(t_s = 42.3\) min, \(t_R = 49.5\) min; \([\alpha]^{23.8}_D = -2.7\) (c 1.6, CHCl\(_3\)) for 93% ee.

\((R)-2,5,7,8\)-Tetramethyl-2-(1-phenyl-1H-imidazole-2-carbonyl)chroman-6-yl

4-(trifluoromethyl)benzenesulfonate (5f): Method C: 29 h; 14.8 mg, 34% yield, 48% ee. White solid; TLC, \(R_i = 0.69\) (hexane–EtOAc = 1:1); \(\text{IR}\) (neat) 2927, 1684, 1405, 1322, 1368, 1180 cm\(^{-1}\); \(^1\text{H NMR}\) (CDCl\(_3\), 400 MHz) \(\delta \) 8.05 (d, \(J = 8.2\) Hz, 2H), 7.81 (d, \(J = 8.2\) Hz, 2H), 7.36–7.34 (m, 3H), 7.25 (s, 1H), 7.10 (s, 1H), 6.91–6.89 (m, 2H), 3.08 (ddd, \(J = 13.8, 6.9, 2.5\) Hz, 1H), 2.60–2.53 (m, 1H), 2.38–2.29 (m, 1H), 2.06 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 2.04–1.95 (m, 1H), 1.84 (s, 3H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz) \(\delta \) 191.5, 150.5, 140.9, 140.51, 140.48, 138.1, 135.4 (q, \(J_{C-F} = 33.8\) Hz), 129.1 (2C), 129.0, 128.73 (2C), 128.68, 128.5, 127.3, 126.3, 126.2 (d, \(J_{C-F} = 3.8\) Hz, 2C), 125.4 (2C), 124.1, 123.0 (q, \(J_{C-F} = 272\) Hz), 118.4, 82.2, 30.3, 25.5, 21.0, 14.1, 13.5, 12.0; \(^{19}\text{F NMR}\) (CDCl\(_3\), 376 MHz) \(\delta \) –63.0; \(\text{HRMS}\) (FAB) m/z calcd for \([\text{C}_{28}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_5\text{S}+\text{H}]^+\) 585.1666, found 585.1671; \(\text{HPLC}\) (IC–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \(t_s = 15.3\) min, \(t_R = 16.8\) min; \([\alpha]^{23.9}_D = 2.1\) (c 1.2, CHCl\(_3\)) for 48% ee.

(S)-2,5,8-Trimethyl-2-(1-phenyl-1H-imidazole-2-carbonyl)chroman-6-yl

4-methylbenzenesulfonate (5g): Method A: 10 h; 50.7 mg, 98% yield, 92% ee. White solid; TLC, \(R_i = 0.68\) (hexane–EtOAc = 1:1); \(\text{IR}\) (neat) 2926, 1687, 1474, 1369, 1189, 1176 cm\(^{-1}\); \(^1\text{H NMR}\) (CDCl\(_3\), 400 MHz) \(\delta \) 7.71 (d, \(J = 8.2\) Hz, 2H), 7.38–7.28 (m, 5H), 7.24 (d, \(J = 0.9\) Hz, 1H), 7.08 (d, \(J = 0.9\) Hz, 1H), 6.85–6.77 (m, 2H), 6.48 (s, 1H), 2.98 (ddd, \(J = 9.2, 6.9, 2.3\) Hz, 1H), 2.56–2.49 (m, 1H), 2.44 (s, 3H), 2.37–2.28 (m, 1H), 2.04 (s, 3H), 2.00–1.92 (m, 1H), 1.94 (s, 3H), 1.89 (s, 3H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz) \(\delta \) 195.1, 151.4, 144.9, 142.3, 140.9, 138.0, 133.0, 129.5 (2C), 129.3, 129.0 (2C), 128.7, 128.3 (2C), 127.4, 127.3, 127.1, 125.5 (2C), 123.1, 121.9, 42.0, 32.0, 25.0, 21.5, 17.7, 16.2, 12.3; \(\text{HRMS}\) (FAB) m/z calcd for \([\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_5\text{S}+\text{H}]^+\) 517.1792, found 505.1796;
HPLC (AD–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \( t_s = 26.8 \) min, \( t_R = 30.4 \) min; \([\alpha]^{25.6D}_D = 4.1 \) (c 2.4, CHCl\(_3\)) for 92% ee.

**4-methylbenzenesulfonate (5h):** Method A: 10 h; 50.3 mg, 97% yield, 92% ee. White solid; TLC, \( R_f = 0.64 \) (hexane–EtOAc = 1:1); IR (neat) 2923, 1687, 1443, 1494, 1369, 1176, 1053 cm\(^{-1}\); \( ^1\text{H} \) NMR (CDCl\(_3\), 400 MHz) \( \delta = 7.68 \) (d, \( J = 8.2 \) Hz, 2H), 7.39–7.35 (m, 3H), 7.27–7.24 (m, 3H), 7.10 (d, \( J = 0.9 \) Hz, 1H), 7.00–6.96 (m, 2H), 6.62 (s, 1H), 3.05 (ddd, \( J = 9.2, 6.0, 3.2 \) Hz, 1H), 2.64–2.58 (m, 1H), 2.52–2.45 (m, 1H), 2.42 (s, 3H), 2.03 (s, 3H), 2.02–1.95 (m, 1H), 1.93 (s, 3H), 1.78 (s, 3H); \( ^{13}\text{C} \) NMR (CDCl\(_3\), 100 MHz) \( \delta = 192.1, 150.8, 145.0, 141.1, 140.9, 138.0, 133.2, 129.6 \) (2C), 129.1 (2C), 129.0, 128.6, 128.4 (2C), 127.5, 126.2, 125.4 (2C), 124.9, 121.8, 120.9, 82.2, 30.2, 25.4, 21.7, 21.1, 15.9, 12.2; HRMS (FAB) m/z calcd for \([\text{C}_{29}\text{H}_{48}\text{N}_{2}\text{O}_{5}\text{S}+\text{H}]^+\) 517.1792, found 505.1796.

HPLC (AD–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \( t_R = 7.2 \) min, \( t_s = 12.8 \) min; \([\alpha]^{26.4D}_D = −35.3 \) (c 0.9, CHCl\(_3\)) for 92% ee.

**4-methylbenzenesulfonate (5i):** Method A: 10 h; 48.8 mg, 97% yield, 93% ee. White solid; TLC, \( R_f = 0.67 \) (hexane–EtOAc = 1:1); IR (neat) 2922, 1687, 1473, 1371, 1227, 1177 cm\(^{-1}\); \( ^1\text{H} \) NMR (CDCl\(_3\), 400 MHz) \( \delta = 7.69 \) (d, \( J = 8.3 \) Hz, 2H), 7.40–7.37 (m, 3H), 7.29–7.23 (m, 3H), 7.11 (s, 1H), 6.99–6.96 (m, 2H), 6.55 (d, \( J = 2.7 \) Hz, 1H), 6.44 (d, \( J = 2.7 \) Hz, 1H), 3.06 (ddd, \( J = 8.7, 6.0, 2.8 \) Hz, 1H), 2.64–2.58 (m, 1H), 2.53–2.47 (m, 1H), 2.44 (s, 3H), 2.07 (s, 3H), 2.03–1.95 (m, 1H), 1.93 (s, 3H); \( ^{13}\text{C} \) NMR (CDCl\(_3\), 100 MHz) \( \delta = 190.8, 150.9, 145.0, 142.0, 140.7, 138.3, 132.7, 129.6 \) (2C), 129.1 (3C), 128.6, 128.5 (2C), 127.6, 126.6, 125.5 (2C), 122.0, 121.3, 120.0, 83.1, 30.3, 25.6, 22.7, 21.7, 16.1; HRMS (FAB) m/z calcd for \([\text{C}_{29}\text{H}_{48}\text{N}_{2}\text{O}_{5}\text{S}+\text{H}]^+\) 503.1635, found 503.1626; HPLC (AD–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \( t_R = 50.0 \) min; \([\alpha]^{25.0D}_D = 74.2 \) (c 1.0, CHCl\(_3\)) for 93% ee.

**4-methylbenzenesulfonate (5j):** Method B: 45.0 mg, 95% yield, 92% ee. White solid; TLC, \( R_f = 0.57 \) (hexane–EtOAc = 1:1); IR (neat) 2930, 1736, 1687, 1492, 1397, 1263, 1092 cm\(^{-1}\); \( ^1\text{H} \) NMR (CDCl\(_3\), 400 MHz) \( \delta = 8.10 \) (d, \( J = 8.2 \) Hz, 2H), 7.47 (d, \( J = 8.2 \) Hz, 2H), 7.41–7.39 (m, 3H), 7.29 (d, \( J = 0.9 \) Hz, 1H), 7.13 (d, \( J = 0.9 \) Hz, 1H), 7.09–7.05 (m, 2H), 6.92–6.85 (m, 3H), 3.15 (ddd, \( J = 13.8, 6.0, 3.2 \) Hz, 1H), 2.74 (ddd, \( J = 16.9, 5.5, 3.2 \) Hz, 1H), 2.63–2.55 (m, 1H), 2.15–2.07 (m, 1H), 1.95 (s, 3H); \( ^{13}\text{C} \) NMR (CDCl\(_3\), 100 MHz) \( \delta = 190.6, 164.7, 151.9, 143.8, 140.6, 139.9, 138.3, 131.4 \) (2C), 129.3, 129.1 (2C), 128.9 (2C), 128.6, 128.1, 126.8, 125.7 (2C), 122.0, 121.7, 120.5, 117.7, 83.1, 30.4, 25.5, 22.7; HRMS...
Chapter 2. High-Turnover Hypoiodite Catalysis for Asymmetric Synthesis of Tocopherols

(FAB) m/z calcd for [C_{27}H_{21}ClN_{2}O_{4}+H]^+ 473.1263, found 473.1264; HPLC (AD–3 column) Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_r = 29.6 min, t_s = 32.5 min; [α]^{224}_D = −49.9 (c 1.1, CHCl_3) for 92% ee.

**(R)**-2-Ethyl-2-(1-phenyl-1H-imidazole-2-carbonyl)chroman-7-yl 4-methylbenzenesulfonate (5k): Method C: 0 °C, 58 h; 25.2 mg, 99% yield, 93% ee. White solid; TLC, R_f = 0.4 (hexane–EtOAc = 1:1); IR (neat) 2927, 1687, 1444, 1368, 1176, 1054 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 400 MHz) δ 7.67 (d, J = 8.5 Hz, 2H), 7.39–7.35 (m, 3H), 7.26 (s, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.13 (s, 1H), 7.07–7.04 (m, 2H), 6.85 (d, J = 7.8 Hz, 1H), 6.50–6.47 (m, 2H), 3.10 (ddd, J = 13.8, 6.0, 3.2 Hz, 1H), 2.70–2.43 (m, 3H), 2.41 (s, 3H), 2.27–2.18 (m, 1H), 2.14–2.05 (m, 1H), 0.95 (t, J = 7.6, 3H); \(^13\)C NMR (CDCl_3, 100 MHz) δ 189.8, 154.8, 148.5, 145.0, 140.6, 138.4, 132.5, 129.7 (2C), 129.5, 129.2, 129.1 (2C), 128.6, 128.4 (2C), 126.8, 125.7 (2C), 120.3, 114.1, 111.0, 86.1, 31.1, 28.4, 22.1, 21.7, 7.7; HRMS (FAB) m/z calcd for [C_{28}H_{26}N_{2}O_{5}S+H]^+ 503.1635, found 503.1627; HPLC (AD–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, t_s = 8.9 min, t_r = 9.8 min; [α]^{23.9}_D = 61.1 (c 0.8, CHCl_3) for 93% ee.

**(S)**-(6,8-Dibromo-2,5,7-trimethylchroman-2-yl)(1-phenyl-1H-imidazol-2-yl)methanone (5l): Method A: 10 h; 48.7 mg, 96% yield, 90% ee ((S)-5l). Method B: MTBE was used as solvent instead of Et_2O, 24 h; 41.9 mg, 83%, 85% ee ((R)-5l). Optically pure ((S)-5l (>99%) and (R)-5l (>99%) were obtained after a single recrystallization from hexane/EtOH at 25 °C. Colorless crystal; TLC, R_f = 0.45 (hexane–EtOAc = 1:1); IR (KBr) 2936, 1491, 1442, 1399, 1158 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 400 MHz) δ 7.38–7.33 (m, 3H), 7.27 (d, J = 0.9 Hz, 1H), 7.12 (d, J = 0.9 Hz, 1H), 7.06–7.00 (m, 2H), 3.31 (ddd, J = 13.8, 6.4, 2.8 Hz, 1H), 2.70 (ddd, J = 16.5, 5.5, 2.8 Hz, 1H), 2.57 (s, 3H), 2.45–2.36 (m, 1H), 2.23 (s, 3H), 2.09–2.03 (m, 1H), 2.01 (s, 3H); \(^13\)C NMR (CDCl_3, 100 MHz) δ 189.4, 149.9, 140.3, 138.2, 136.1, 135.1, 129.2, 129.0 (2C), 128.6, 126.8, 125.6 (2C), 119.5, 118.8, 111.8, 83.6, 30.9, 25.2, 24.9, 22.4, 19.7; HRMS (FAB) m/z calcd for [C_{22}H_{20}Br_{2}N_{2}O_{2}+H]^+ 502.9965, 504.9944, 506.9924, found 502.9970, 504.9944, 506.9913; HPLC (IA column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, t_s = 9.1 min, t_r = 11.1 min; [α]^{223}_D = −34.4 (c 0.5, CHCl_3) for >99% ee of (S)-5l.
Conversion of (S)-5e to 8 and 9:\textsuperscript{21,36,49}

To a stirring mixture of (S)-5e (637 mg, 1.2 mmol, 93% ee) and activated 4Å molecular sieves (500 mg) in CH$_2$Cl$_2$ (12 mL) was added MeOTf (656 µL, 6 mmol, 5 equiv) at 25 °C. The reaction was stirred at ambient temperature until (S)-5e was all consumed (ca. 1 h). The solvents were removed \textit{in vacuo}. To the resulting residue were added MeOH (12 mL) and DBU (209 µL, 1.4 mmol, 1.2 equiv) and the resulting mixture was stirred at ambient temperature. The reaction was monitored by TLC analysis. After stirring for 1 h, the resulting mixture was diluted with CH$_2$Cl$_2$ (5.0 mL) and solids were removed by filtration. The filtrate was poured into brine (10 mL), and the aqueous phase was extracted with CHCl$_3$ (twice). The combined organic layers were washed with 1 M HCl and brine. The combined organic layers were dried over anhydrous MgSO$_4$, then the solvents were removed \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give 8 (452 mg, 1.1 mmol) in 90% yield.

Methyl (S)-2,5,7,8-tetramethyl-6-(tosyloxy)chromane-2-carboxylate (8): White solid; TLC, $R_f$ = 0.47 (hexane–EtOAc = 1:1); IR (KBr) 2927, 1751, 1598, 1455, 1369, 1176 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.81 (d, $J$ = 8.3 Hz, 2H), 7.34 (d, $J$ = 8.3 Hz, 2H), 3.69 (s, 3H), 2.61–2.55 (m, 1H), 2.47 (s, 3H), 1.61 (s, 3H), 2.45–2.38 (m, 1H), 2.12 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H), 1.90–1.81 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 174.0, 149.7, 144.9, 140.8, 134.2, 129.7 (2C), 129.2, 128.2 (2C), 127.5, 123.5, 117.6, 77.4, 52.4, 30.1, 25.3, 21.7, 20.8, 14.2, 13.5, 11.9; HRMS (FAB) m/z calcd for [C$_{22}$H$_{25}$O$_6$S$^+$]$^+$ 419.1523, found 419.1519; HPLC (IC–3 column) Hexane–EtOH =
40:1 as eluent, 1.0 mL/min, \( t_s = 19.4 \text{ min} \), \( t_R = 25.2 \text{ min} \); \([\alpha]_{D}^{216} = -24.5 \text{ (c 1.3, CHCl}_3\) for >99% ee.

**(S)-Methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate (9):** White solid; TLC, \( R_f = 0.38 \) (hexane–EtOAc = 1:1); IR (KBr) 3528, 2926, 1739, 1458, 1262, 1194 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta 7.81 \text{ (d, } J = 8.3 \text{ Hz, 2H), } 7.34 \text{ (d, } J = 8.3 \text{ Hz, 2H), } 3.69 \text{ (s, 3H), } 2.61\text{–}2.55 \text{ (m, 1H), } 2.47 \text{ (s, 3H), } 2.45\text{–}2.38 \text{ (m, 2H), } 2.12 \text{ (s, 3H), } 1.94 \text{ (s, 3H), } 1.93 \text{ (s, 3H), } 1.90\text{–}1.81 \text{ (m, 1H), } 1.61 \text{ (s, 3H); } ^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta 174.5, 145.4, 145.2, 122.5, 121.2, 118.4, 116.8, 76.98, 52.3, 30.6, 25.4, 20.9, 12.2, 11.8, 11.2; HRMS (FAB) m/z calcld for [C\(_{15}\)H\(_{20}\)O\(_4\)+H]\(^+\) 265.1434, found 265.1438; HPLC (AD–3 column) Hexane–EtOH = 40:1 as eluent, 1.0 mL/min, \( t_s = 21.6 \text{ min}, t_R = 23.6 \text{ min}; [\alpha]_{D}^{26.8} = -61.2 \text{ (c 1.0, MeOH) for >99% ee.} \)
X-Ray Diffraction Analysis of (S)-5l

X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, MoKa radiation, \( \lambda = 0.71073 \) Å) and the structure was solved by direct methods and expanded using Fourier techniques (DIRDIF-99 and SHELXL).\(^{50}\)

Recrystallization of \( 5l \) was carried out in the solution of CH\(_2\)Cl\(_2\)/EtOH at 25 °C. Mp: 212–214 °C. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 996935 for 5l. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Table S1. Crystallographic data and structure refinement for (S)-5l.

<table>
<thead>
<tr>
<th>Empirical formula</th>
<th>( C_{22}H_{20}Br_2N_2O_2 )</th>
<th>( D_{\text{calc}} )</th>
<th>1.683 g/cm(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula weight</td>
<td>504.22</td>
<td>Absorption coefficient</td>
<td>4.095 mm(^{-1})</td>
</tr>
<tr>
<td>( T )</td>
<td>173(2) K</td>
<td>( F(000) )</td>
<td>504</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>0.71073 Å</td>
<td>Crystal size</td>
<td>0.50 x0.50 x 0.50 mm(^3)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
<td>Theta range for data collection</td>
<td>0.94 to 28.28°</td>
</tr>
<tr>
<td>Space group</td>
<td>( P1 )</td>
<td>Reflections collected</td>
<td>7082</td>
</tr>
<tr>
<td>( A )</td>
<td>6.7612(14) Å</td>
<td>Refinement based on</td>
<td>( F^2 )</td>
</tr>
<tr>
<td>( B )</td>
<td>6.8039(15) Å</td>
<td>No. of data</td>
<td>5008</td>
</tr>
<tr>
<td>( C )</td>
<td>21.887(5) Å</td>
<td>No. of parameters</td>
<td>511</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>97.995(4)°</td>
<td>No. of restraints</td>
<td>3</td>
</tr>
<tr>
<td>( \beta )</td>
<td>93.663(4)°</td>
<td>GOF</td>
<td>1.050</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>90.330(4)°</td>
<td>( R(F) ) for ( I &gt; 2s(I) )</td>
<td>0.0389</td>
</tr>
<tr>
<td>( V )</td>
<td>994.9(4) Å(^3)</td>
<td>( wR2(F^2) ) for all data</td>
<td>0.0956</td>
</tr>
<tr>
<td>( Z )</td>
<td>2</td>
<td>Flack parameter</td>
<td>0.020(10)</td>
</tr>
</tbody>
</table>
Reference and Notes

47. Perumal, P. T.; Bhatt, M. V. A. Synthesis 1979, 3, 205.
Chapter 3

Chiral Ammonium Hypoiodite Salt-Catalyzed
Enantioselective Oxidative Cycloetherification to 2-Acyl THFs

Abstract: 2-Acyl tetrahydrofuran is one of the fundamental structures in natural products and pharmaceuticals. We achieved a chiral quaternary ammonium hypoiodite salt-catalyzed enantioselective oxidative cycloetherification of the δ-hydroxyketone derivatives. The corresponding 2-acyl tetrahydrofurans were obtained in high chemical yield and enantioselectivity.
Introduction

Tetrahydrofuran (THF) is a ubiquitous and privileged core structure in biologically active compounds. In particular, a tetrahydro-2-furoyl skeleton is found in many pharmaceuticals, such as terazosin, alfuzosin, faropenem, cathepsin K inhibitor, etc. (Figure 1). While some of these are used as racemic mixtures, the configuration at the C2-position of 2-acyl THFs is often important for their biological activities. For the synthesis of these pharmaceuticals, tetrahydrofuran-2-carboxylic acid (1) has been used to introduce the tetrahydro-2-furoyl moiety. Thus, the development of a straightforward method for the preparation of enantioenriched 1 is an important subject in synthetic organic chemistry and medicinal chemistry.

Figure 1. 2-Acyl THF-Derived Pharmaceuticals.

Although numerous methods have been developed for the asymmetric synthesis of tetrahydrofurans, a little is known about the direct enantioselective synthesis of 2-acyl THF. Conventionally, biologically active compounds that contain a chiral tetrahydro-2-furoyl moiety have been prepared by the enzyme-catalyzed kinetic resolution of racemic mixtures or the diastereoselective hydrogenation of furan-2-carboxylic acid derivatives with chiral auxiliaries. In contrast, to the best of our knowledge, only three enantioselective methods have been developed for the preparation of 2-acyl THFs. Baiker and colleagues developed an enantioselective hydrogenation of furan-2-carboxylic acid by using Pd/Al₂O₃ and cinchonidine catalysts (Scheme 1a). However, the product was obtained with low enantioselectivity. Zhou and colleagues reported a copper-catalyzed enantioselective intramolecular O–H insertion of ω-hydroxy-α-diazoesters to give the corresponding 2-acyl THFs (Scheme 1b). Although high enantioselectivities were achieved, the substrates were limited to highly reactive α-diazoesters. On the other hand, Smith and colleagues reported a chiral Lewis base-promoted enantioselective
Michael addition/lactonization reaction of enone acids followed by nucleophilic ring-opening (Scheme 1c).9 Although the corresponding cis-3-substituted 2-acyl THFs were obtained with excellent enantio- and diastereoselectivities, in situ activation of the carboxylic acid with pivaloyl chloride is required to generate a Michael donor. Moreover, compound 1, which is an essential core for many pharmaceuticals, as shown in Figure 1, is not easily synthesized. Thus, the development of an efficient and highly enantioselective method for the synthesis of highly valuable 2-acyl THF derivatives is still needed. Here, we report a chiral hypoiodite salt-catalyzed enantioselective oxidative cycloetherification of δ-hydroxyketones 2 to 2-acyl THF 3 in high yield and with high enantioselectivity (Scheme 1d).

Scheme 1. Previous Examples and This Work on the Enantioselective Synthesis of 2-Acyl THFs.

\begin{align*}
\text{a) } \text{Baiker et al.}^7 & \quad \text{5 wt\% Pd/Al}_2\text{O}_3 \quad \text{Cinchonidine (15 mol\%)} \\
\text{OH} & \quad \text{H}_2 (30 \text{ bar}), \text{THF, RT} \\
\text{12\% yield, 42\% ee} \\
\text{b) Zhou et al.}^8 & \quad \text{CuOTf (5 mol\%)} \\
\text{OH} & \quad (\text{Sa,S,S})-\text{SpiroBOX (6 mol\%)} \\
\text{up to 81\% yield, 95\% ee} \\
\text{c) Smith et al.}^9 & \quad \text{1. } \text{t-BuCOCl, i-Pr}_2\text{NEt} \\
\text{OH} & \quad \text{CH}_2\text{Cl}_2, \text{RT} \\
\text{up to 76\% yield, 99\% ee} \\
\text{d) This work:}^{10} & \quad \text{*R}_4\text{NI 4 (1–10 mol\%)} \\
\text{HO} & \quad \text{ROOH} \\
\text{high yield, high ee} \
\end{align*}

Results and Discussion

Recently, we have developed enantioselective oxidative cyclization reactions of β-(2-hydroxyphenyl) ketones 5 into 2-acyl-2,3-dihydrobenzofuran derivatives 6 catalyzed by chiral
quaternary ammonium hypoiodite salt catalysts (Scheme 2). The hypoiodite salts were generated in situ from the corresponding ammonium iodides (4) in the presence of hydrogen peroxide, tert-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CHP) as an oxidant.

**Scheme 2. Enantioselective Cycloetherification of β-(2-Hydroxyphenyl) Ketones 5.**

We envisioned that our chiral hypoiodite catalysis could be used for the enantioselective synthesis of 2-acyl THFs 3 by using δ-hydroxyketones 2 as substrates. However, the oxidative cyclization of δ-hydroxyketone 2a did not proceed and only a trace amount of the desired product 3a was obtained under conditions identical to those for β-(2-hydroxyphenyl) ketone 5 with hydrogen peroxide as an oxidant (Table 1, entry 1 versus Scheme 2). Since the cyclization of 2 proceeded much more slowly than that of 5, a catalyst-inactivation path (i.e., disproportionation or reductive decomposition of hypoiodite species) might proceed preferentially. As in our previous studies, to decelerate the oxidation of iodide and suppress the catalyst-inactivation path, alkyl hydroperoxides were evaluated as weaker oxidants instead of hydrogen peroxide. As a result, the desired product 3a was obtained in 55% yield with 82% ee by the use of TBHP in methyl tert-butyl ether (MTBE) (entry 2). The reactivity and enantioselectivity were further increased by the use of CHP in place of TBHP (entry 3). The catalyst 4a, which was effective for the enantioselective oxidative 5-membered-ring cycloetherification of 5, gave the highest yield and enantioselectivity among catalysts examined (entries 4–6). The solvent was also important for both reactivity and enantioselectivity (entries 7–12). The reaction proceeded smoothly in ethereal solvents and the highest yield and enantioselectivity were obtained in MTBE (entries 3, 7–12). Moreover, to our delight, 3a could be obtained in higher chemical yield under more concentrated conditions (0.2 M) without any loss of enantioselectivity (entry 4). In sharp contrast, highly diluted conditions (0.02 M) were required to induce high enantioselectivity for the oxidative cyclization of ketophenols 5 (Scheme 2). Almost optically pure 3a could be obtained after a single recrystallization (entry 4).
### Table 1. Enantioselective Cycloetherification of δ-Hydroxyketones 2a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent (X M)</th>
<th>Time (h)</th>
<th>3a, Yield (%)</th>
<th>3a, Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>30% H₂O₂</td>
<td>MTBE (0.02)</td>
<td>24</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>TBHP</td>
<td>MTBE (0.02)</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>CHP</td>
<td>MTBE (0.02)</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>4b</td>
<td>CHP</td>
<td>MTBE (0.02)</td>
<td>6</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>4c</td>
<td>CHP</td>
<td>MTBE (0.02)</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>4d</td>
<td>CHP</td>
<td>MTBE (0.02)</td>
<td>6</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>4a</td>
<td>CHP</td>
<td>THF (0.02)</td>
<td>6</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>4a</td>
<td>CHP</td>
<td>EtOAc (0.02)</td>
<td>6</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>4a</td>
<td>CHP</td>
<td>CCl₄ (0.02)</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>4a</td>
<td>CHP</td>
<td>Et₂O (0.02)</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>4a</td>
<td>CHP</td>
<td>i-Pr₂O (0.02)</td>
<td>6</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>4a</td>
<td>CHP</td>
<td>CPME (0.02)</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>13</td>
<td>4a</td>
<td>CHP</td>
<td>MTBE (0.2)</td>
<td>2</td>
<td>81</td>
</tr>
</tbody>
</table>

*Isolated yield. †Determined by HPLC analysis. ‡Unreacted 2a was recovered (>95%). ††After a single recrystallization. The absolute configuration of 3a was determined by comparing the optical rotation of 1 to the value in the literature.*

TBHP: tert-Butyl hydroperoxide. CHP: Cumene hydroperoxide. MTBE: Methyl tert-butyl ether. THF: Tetrahydrofuran. CPME: Cyclopentyl methyl ether.

The (N-phenylimidazol-2-yl)carbonyl group of 3a was easily transformed to give (R)-1, which is the key synthetic intermediate for pharmaceuticals shown in Figure 1 (Scheme 3).

**Scheme 3. Derivatization of 3a to (R)-1.**

\[
\begin{align*}
3a \text{ (91% ee)} & \xrightarrow{1. \text{ MeOTf then DBU/n-BuOH}} (R)-1 \text{ (91% ee): 87% yield (for 2 steps)}
\end{align*}
\]
We examined various substituted δ-hydroxyketones 2 under optimized conditions (Table 2). The oxidative cyclization of γ,γ-dialkyl substituted 2b and 2c gave the corresponding 2-acyl THFs 3b and 3c in higher chemical yield with higher enantioselectivities than that of 3a (entries 1 and 5). The catalyst loading could be reduced to 1 mol% for the oxidation of highly reactive 2b without reducing the enantioselectivity (entry 2). Although the reaction did not proceed to completion, the chemical yield of 3b was increased about 2-fold (TON was up to 58) in the presence of 1 equivalent of potassium carbonate, which is required to regenerate the catalytic active species from inert species (entry 2 versus entry 3). This method could be applied to a gram-scale reaction. The oxidation of 2b on a 1.1-gram scale with 2 mol% of 4a in the presence of potassium carbonate gave 3b in 93 yield (1.02 g) with 92% ee (entry 4). The oxidation of γ,γ-diphenyl- and γ,γ-diester-substituted 2d and 2e gave the corresponding 3 quantitatively (entries 6 and 7). However, the enantioselectivity was reduced to 78% ee for 3e (entry 7). On the other hand, the oxidation of β,β-dimethyl-substituted 2f was sluggish, presumably due to steric reasons, and 3f was obtained in low chemical yield with moderate enantioselectivity (entry 8).

Table 2. Enantioselective Cycloetherification of Substituted δ-Hydroxyketones 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>3</th>
<th>Time (h)</th>
<th>3, Yield (%)</th>
<th>3, ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3b</td>
<td>2</td>
<td>95</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>24</td>
<td>58</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>24</td>
<td>31</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3b</td>
<td>6</td>
<td>93</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3c</td>
<td>2</td>
<td>98</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3d</td>
<td>2</td>
<td>95</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3e</td>
<td>2</td>
<td>95</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3f</td>
<td>24</td>
<td>30</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

Unless otherwise noted, a solution of 2 (0.1 mmol), 4a (10 mol%) and CHP (2 equiv) in MTBE (0.2 M) was stirred at room temperature. Isolated yields. Determined by HPLC analysis. 4a (1 mol%), K2CO3 (1 equiv), MTBE (0.02 M). 4a (1 mol%), MTBE (0.02 M). 2b (4.1 mmol), 4a (2 mol%), K2CO3 (1 equiv), (0.02 M). The absolute configuration of 3b–f was assigned by analogy.
Conclusion

In summary, we developed a quaternary ammonium hypoiodite salt-catalyzed oxidative cyclization of δ-hydroxyketones to give chiral THF derivatives with high enantioselectivity. This environmentally benign method could provide various chiral 2-acyl THFs for the discovery of new drug candidates, which might be difficult to access by previous methods.
Experimental Section

$^1$H NMR spectra were measured on a JEOL ECS-400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, Q = quintuplet, m = multiplet, brs = broad singlet), coupling constant (Hz), integration, and assignment. $^{13}$C NMR spectra were measured on a JEOL ECS-400 (100 MHz) spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). Gas-liquid-phase chromatography (GC) was performed with Shimadzu Model 17A instrument with a flame-ionization detector and a capillary column of CP-Cyclodextrin-β-2,3,6-M-19 (i.d. 0.25 mm × 25 m; CHROMPACK; GL Science Inc.) or CHIRALDEX B-DM (i.d., 0.25 mm × 20 m; Tokyo Kasei Kogyo Co., LTD). High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL AD-H (4.6 mm x 25 cm). Optical rotations were measured on Rudolph Autopol IV digital polarimeter. Melting points were measured on MPA100, Standard Research Systems. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF$_{254}$ 0.25 mm) were used. Visualization was accomplished by UV light (254 nm), anisaldehyde, KMnO$_4$, or phosphomolybdic acid. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High-resolution mass spectral analysis (HRMS) and elemental analysis was performed at Chemical Instrument Center, Nagoya University.

In experiments that required dry solvents, tetrahydrofuran (THF), dichloromethane, and toluene were purchased from Wako as the “anhydrous” and stored over 4Å molecular sieves. Other solvents were purchased from Kanto Chemical Co., Inc., Aldrich Chemical Co., Inc., Tokyo Chemical Industry (TCI) Co. Ltd., Nacalai Tesque, Inc. or Wako Pure Chemical Industries, Ltd., and used without further purification. Tetrabutylammonium iodide (Bu$_4$NI) and cumene hydroperoxide (CHP, contains ca. 20% aromatic hydrocarbon) were purchased from Tokyo Chemical Industry Co. Ltd. and used without further purification. 30-wt% aqueous hydrogen peroxide and anhydrous tert-butyl hydroperoxide (TBHP, 5.5 M nonane solution) were purchased from Aldrich Chemical Co., Inc. and used without further purification. Catalysts 4 and S1–3 are known compounds.$^{12a,b}$ Other simple chemicals were commercially obtained as an analytical-grade and used without further purification.
Chapter 3. Chiral Ammonium Hypoiodite Salt-Catalyzed Enantioselective Oxidative Cycloetherification to 2-Acyl THFs

Synthesis and Characterization of Starting Materials 2

Isolated \( \gamma \)-hydroxyketones 2 were found to be in equilibrium with the corresponding hemiacetal forms and used as a mixture for the oxidative cycloetherification reactions (2:hemiacetal = ~95:5 to ~80:20). In oxidative cyclization reactions, both 2 and their hemiacetal forms were consumed to give the corresponding 2-acyl THFs 3.

Synthesis of 2a–d and 2f:

\[
\begin{align*}
\text{S4a–d, S4f} & \xrightarrow{n-\text{BuLi (1.5 equiv)}} (1.5 \text{ equiv}) \xrightarrow{\text{THF, } -78 \text{ to } 25 \degree C, 1 \text{ h}} \text{2a–d, 2f} \\
\text{R'} & = H, H (2a) \\
\text{H, Me (2b)} & \\
\text{–CH}_2\text{(CH}_2)_3\text{CH}_2– (2c) & \\
\text{Ph, Ph (2d)} & \\
\text{Me, H (2f)} & \\
\end{align*}
\]

2a–d and 2f were synthesized through the nucleophilic ring opening of the corresponding lactones S4a–d with lithiated N-phenylimidazole.\(^ {12a,b} \) S4a is commercially available. S4b,\(^ {15} \) S4c,\(^ {16} \) S4d\(^ {17} \) and S4f\(^ {18} \) were prepared by following the literature procedure.

Synthesis of 2e:

\[
\begin{align*}
\text{S7} & \xrightarrow{\text{formaldehyde (1 equiv)}} \text{S6} \\
\text{S5} & \xrightarrow{\text{MnO}_2 (5 \text{ equiv})} \text{S6} \\
\text{S7} & \xrightarrow{\text{EtOH, } \text{H}_2\text{O, } 25 \degree C, 24 \text{ h}} \text{2e} \\
\end{align*}
\]

The conditions were not optimized. To a solution of \( N \)-phenylimidazole (1.26 ml, 10.0 mmol) in THF (33.0 mL) was added \( n \)-BuLi (1.6 \( M \) in hexane, 6.25 mL, 10.0 mmol) at \(-78 \degree C\). After stirring at \(-78 \degree C\) for 30 min, acrolein (0.667 mL, 10.0 mmol) was added to the reaction mixture at \(-78 \degree C\). The reaction mixture was allowed to warm to 25 \degree C. After stirring for 30 min, the resulting mixture was poured into saturated aqueous \( \text{NH}_4\text{Cl} \) and the aqueous layers were extracted with \( \text{Et}_2\text{O} \) (twice). The combined organic layers were washed with brine and dried over anhydrous \( \text{MgSO}_4 \). The solvents were removed \textit{in vacuo} to give \( \text{S5} \), which was used for next step without further purification.

To a crude solution of \( \text{S5} \) in \( \text{CH}_2\text{Cl}_2 \) (20.0 mL) was added \( \text{MnO}_2 \) (4.35 g, 50.0 mmol) at 25 \degree C. After stirring for 12 h, the reaction mixture was filtered through a plug of tightly packed celite and washed with \( \text{Et}_2\text{O} \). The solvents were removed \textit{in vacuo}. The residue was
purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to S6 (792 mg, 4.00 mmol) in 40% yield over 2 steps.

To a suspension of NaH (192 mg, 4.80 mmol) in THF (9.60 mL) was added diethyl malonate (0.732 mL, 4.80 mmol) at 25 °C. After stirring for 1 h, the resulting mixture was added to a solution of S6 (792 mg, 4.00 mmol) in THF (8.00 mL) at 25 °C. The reaction mixture was warmed to 40 °C. After stirring for 24 h, the reaction mixture was poured into saturated aqueous NH$_4$Cl and the aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$. The solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give S7 (429 mg, 1.20 mmol) in 30% yield.

To a solution of S7 (429 mg, 1.20 mmol) and NaHCO$_3$ (11.0 mg) in ethanol (12.0 mL) and water (6.00 mL) was a 37% aqueous solution of formaldehyde (0.0890 mL, 1.20 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring for 24 h, the resulting mixture was transferred to a separation funnel and the aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$. The solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give 2e (324 mg, 0.840 mmol) in 70% yield.

Characterization of Starting Materials 2:

5-Hydroxy-1-(1-phenyl-1H-imidazol-2-yl)pentan-1-one (2a): White solid; TLC, $R_f = 0.32$ (hexane–EtOAc = 1:3); IR (neat) 3500–3000, 1684, 1494, 1407 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.60–1.67 (m, 2H), 1.74–1.83 (m, 2H), 3.16–3.20 (m, 3H), 3.65–3.69 (m, 2H), 7.18 (m, 1H), 7.26–7.29 (m, 3H), 7.45–7.47 (m, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 20.0, 31.9, 38.5, 61.9, 125.8, 126.9, 128.7, 128.9, 129.3, 138.2, 142.7, 191.3; HRMS (FAB) m/z calcd for [C$_{14}$H$_{17}$N$_2$O$_2$+H]$^+$ 245.1285, found 245.1290.

5-Hydroxy-4,4-dimethyl-1-(1-phenyl-1H-imidazol-2-yl)pentan-1-one (2b): Colorless oil; TLC, $R_f = 0.30$ (hexane–EtOAc = 1:3); IR (neat) 3500–3000, 2954, 1686, 1598, 1404 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.91 (s, 6H), 1.66–1.72 (m, 2H), 3.01–3.05 (m, 2H), 3.39 (m, 3H), 7.17 (m, 1H), 7.26–7.28 (m, 3H), 7.45–7.47 (m, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 24.3, 32.6, 34.8, 35.3, 70.2, 125.8, 126.9, 128.8, 129.0, 129.4, 138.2, 142.3, 191.8; HRMS (FAB) m/z calcd for [C$_{16}$H$_{21}$N$_2$O$_2$+H]$^+$ 273.1598, found 273.1601.
3-(1-(Hydroxymethyl)cyclohexyl)-1-(1-phenyl-1H-imidazol-2-yl)propan-1-one (2c): Pale yellow oil; TLC, Rf = 0.32 (hexane–EtOAc = 1:3); IR (neat) 3500–3000, 2926, 1686, 1495, 1405 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.17–1.55 (m, 10H), 1.77–1.84 (m, 2H), 2.93–2.97 (m, 2H), 3.41–3.72 (m, 2H), 3.87–3.91 (m, 1H), 7.16 (m, 1H), 7.26–7.29 (m, 3H), 7.39–7.47 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 21.5, 26.4, 29.5, 32.8, 34.2, 37.5, 67.9, 125.8, 126.9, 128.8, 128.9, 129.3, 138.2, 142.1, 192.0; HRMS (FAB) m/z calcd for [C₁₉H₂₅N₂O₂+H]⁺ 313.1911, found 313.1908.

5-Hydroxy-4,4-diphenyl-1-(1-phenyl-1H-imidazol-2-yl)pentan-1-one (2d): White solid; TLC, Rf = 0.50 (hexane–EtOAc = 1:3); IR (neat) 3500–3000, 3021, 1685, 1495, 1406 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.60–2.64 (m, 2H), 2.92–2.96 (m, 3H), 4.26–4.28 (m, 2H), 7.14 (d, J = 0.92 Hz, 1H), 7.17–7.30 (m, 13H), 7.45–7.47 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 30.3, 35.0, 51.1, 68.0, 125.8, 126.2, 126.9, 128.0, 128.1, 128.7, 128.8, 129.3, 138.2, 142.3, 145.6, 191.1; HRMS (FAB) m/z calcd for [C₂₇H₂₇N₂O₂+H]⁺ 397.1911, found 397.1905.

Diethyl 2-(hydroxymethyl)-2-(3-oxo-3-(1-phenyl-1H-imidazol-2-yl)propyl)malonate (2e): Pale yellow oil; TLC, Rf = 0.32 (hexane–EtOAc = 1:3); IR (neat) 3500–3000, 2981, 1730, 1688, 1495, 1408 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.25 (t, J = 7.2 Hz, 6H), 2.36 (t, J = 7.7 Hz, 2H), 3.15 (t, J = 7.7 Hz, 2H), 4.05 (brs, 1H), 4.18 (m, 2H), 4.21 (q, J = 7.2 Hz, 4H), 7.18 (m, 1H), 7.25–7.29 (m, 3H), 7.46–7.47 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 13.9, 25.0, 34.3, 58.9, 61.5, 63.5, 125.8, 127.1, 128.8, 128.9, 129.5, 138.1, 142.1, 170.3, 190.0; HRMS (FAB) m/z calcd for [C₃₀H₃₈N₂O₄+H]⁺ 389.1707, found 389.1703.

5-Hydroxy-3,3-dimethyl-1-(1-phenyl-1H-imidazol-2-yl)pentan-1-one (2f): White solid; TLC, Rf = 0.31 (hexane–EtOAc = 1:3); IR (neat) 3500–3000, 2957, 1679, 1495, 1403 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.06 (s, 6H), 1.65 (t, J = 6.6 Hz, 2H), 2.81–2.82 (m, 1H), 3.15 (s, 2H), 3.76–3.81 (m, 2H), 7.16 (d, J = 0.92 Hz, 1H), 7.25–7.27 (m, 3H), 7.46–7.47 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 28.6, 33.8, 43.2, 48.7, 59.8, 125.8, 127.2, 128.7, 129.0, 129.3, 138.5, 144.0, 191.5; HRMS (FAB) m/z calcd for [C₁₆H₂₅N₂O₂+H]⁺ 273.1598, found 273.1602.

General Procedures for the Oxidative Cycloetherification

Synthesis of Authentic Samples:

![Diagram of synthesis](image-url)
To a stirring mixture of 2 (0.100 mmol) and Bu$_4$NI (7.40 mg, 0.0200 mmol, 20 mol%) in EtOAc (1.00 mL) was added cumene hydroperoxide (contains ca. 20% aromatic hydrocarbon, TCI, 0.0370 mL, 0.200 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 24 h, the resulting mixture was poured into saturated aqueous NaHSO$_3$ (1.00 mL), and the aqueous layers were extracted with Et$_2$O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$. The solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 3 in 30–60% yield.

**Representative Procedure for Enantioselective Oxidative Cycloetherification of 2a:**

\[
\begin{array}{c}
\text{2a} \\
\text{HO} \\
\end{array} \quad \xrightarrow{\text{4 (10 mol\%), CHP (2 equiv)}} \\
\text{MTBE (0.2 M), 25 °C, 2 h} \quad \xrightarrow{\text{3a}} \\
\text{3a}
\end{array}
\]

To a stirring mixture of 2 (24.4 mg, 0.100 mmol), (R,R)-4 (17.0 mg, 0.0100 mmol, 10 mol%) in methyl tert-butyl ether (0.500 mL) was added cumene hydroperoxide (contains ca. 20% aromatic hydrocarbon, TCI, 0.0370 mL, 0.200 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 2 h, the resulting mixture was poured into saturated aqueous NaHSO$_3$ (1.00 mL), and the aqueous layers were extracted with Et$_2$O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$. The solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give (R)-3a (19.8 mg, 0.0810 mmol) in 81% yield. Enantiomeric excess of 3a was determined to be 91% ee by HPLC analysis.

**Procedure for Gram-Scale Oxidation:**

To a stirring mixture of 2 (1.12 g, 4.11 mmol), (R,R)-4 (140 mg, 0.0820 mmol, 2 mol%) in methyl tert-butyl ether (206 mL) was added cumene hydroperoxide (contains ca. 20% aromatic hydrocarbon, TCI, 1.50 mL, 8.22 mmol, 2 equiv) at 25 °C. The reaction was monitored by TLC analysis. After stirring for 6 h, the resulting mixture was poured into saturated aqueous NaHSO$_3$ (50 mL), and the aqueous layers were extracted with Et$_2$O (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$. The solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give (R)-3a (1.02 g, 3.77 mmol) in 93% yield. Enantiomeric excess of 3a was determined to be 92% ee by HPLC analysis.
Characterization of Products 3:

(R)-(1H-Imidazol-2-yl)(tetrahydrofuran-2-yl)methanone (3a): The optical purity of (R)-3a could be increased from 91% to 98% after a single recrystallization from hexane/Et₂O at 25 °C. Colorless crystal; Mp 85.0 °C; TLC, R₁ = 0.56 (hexane–EtOAc = 1:1); IR (neat) 2975, 1697, 1597, 1492, 1405 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.89–2.00 (m, 2H), 2.01–2.11 (m, 1H), 2.40–2.49 (m, 1H), 3.93–4.03 (m, 2H), 5.59 (dd, J = 5.9 Hz, 1H), 7.21 (s, 1H), 7.27–7.30 (m, 3H), 7.44–7.46 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 25.5, 30.2, 69.6, 79.6, 125.8, 127.1, 128.8, 128.9, 130.0, 137.9, 141.9, 190.0; HRMS (FAB) m/z calcd for [C₁₅H₁₅N₂O₂H]+ 243.1128, found 243.1128; HPLC (AD–H column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, tᵣ = 13.6 min (R), tᵣ = 22.8 min (S); [α]248²⁸ _D = −107.8 (c 2.14, CHCl₃) for 98% ee.

(R)-(4,4-Dimethyltetrahydrofuran-2-yl)(1H-Imidazol-2-yl)methanone (3b): Colorless oil; TLC, R₁ = 0.55 (hexane–EtOAc = 1:1); IR (neat) 2959, 2869, 1698, 1493, 1406 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.08 (s, 3H), 1.19 (s, 3H), 1.80–1.86 (m, 1H), 2.28–2.32 (m, 1H), 3.64 (s, 2H), 5.67 (t, J = 8.2 Hz, 1H), 7.21 (s, 1H), 7.27–7.31 (m, 3H), 7.44–7.47 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 24.8, 26.3, 40.1, 44.6, 79.9, 81.1, 125.9, 127.1, 128.8, 128.9, 130.0 137.9, 141.3, 189.9; HRMS (FAB) m/z calcd for [C₁₄H₁₉N₂O₂H]+ 271.1441, found 271.1439; HPLC (AD–H column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, tᵣ = 11.0 min (R), tᵣ = 15.2 min (S); [α]²⁷.⁵ _D = −131.9 (c 1.11, CHCl₃) for 92% ee.

(R)-(1H-Imidazol-2-yl)(2-oxaspiro[4.5]decan-3-yl)methanone (3c): Colorless oil; TLC, R₁ = 0.55 (hexane–EtOAc = 1:1); IR (neat) 2924, 2851, 1697, 1446, 1405 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.36–1.56 (m, 10H), 1.73–1.78 (m, 1H), 2.37–2.42 (m, 1H), 3.66 (d, J = 8.2 Hz, 1H), 3.79 (d, J = 8.2 Hz, 1H), 5.61 (t, J = 8.2 Hz, 1H), 7.21 (s, 1H), 7.27–7.32 (m, 3H), 7.44–7.46 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 23.4, 24.2, 26.0, 34.9, 35.3, 44.2, 44.3, 79.2, 79.4, 125.8, 127.1, 128.8, 128.9, 130.0, 137.9, 141.3, 190.0; HRMS (FAB) m/z calcd for [C₁₉H₂₃N₂O₂H]+ 311.1754, found 311.1754.; HPLC (AD–H column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, tᵣ = 14.7 min (R), tᵣ = 16.9 min (S); [α]³⁶.⁹ _D = −115.1 (c 1.71, CHCl₃) for 95% ee.

(R)-(4,4-Diphenyltetrahydrofuran-2-yl)(1H-Imidazol-2-yl)methanone (3d): Pale yellow solid; TLC, R₁ = 0.56 (hexane–EtOAc = 1:1); IR (neat) 3022, 1698, 1597, 1493, 1405 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.74–2.80 (m, 1H), 3.16–3.21 (m, 1H), 4.26 (d, J = 8.7 Hz, 1H), 4.73 (d, J = 8.7 Hz, 1H), 5.65 (dd, J = 7.3 Hz, 1H), 7.16–7.45 (m, 17H); ¹³C NMR (CDCl₃, 100 MHz) δ 42.8, 56.0, 78.1, 79.7, 125.8, 126.4, 126.5, 127.1, 127.2, 127.3, 128.3, 128.4, 128.8, 128.9, 130.1, 137.8, 141.3, 144.7, 145.6, 189.2; HRMS (FAB) m/z calcd for [C₂₉H₂₃N₂O₂H]+ 395.1754, found
The reaction was monitored by TLC analysis. After stirring for 30 min, the resulting mixture was removed in vacuo. To the resulting residue were added n-butyl alcohol (12.0 mL) and DBU (0.0280 mL, 0.190 mmol, 1.2 equiv) and the resulting mixture was stirred at ambient temperature. The reaction was monitored by TLC analysis. After stirring for 30 min, the resulting mixture was diluted with CH₂Cl₂ (5.00 mL) and solids were removed by filtration. The filtrate was poured into brine (10.0 mL), and the aqueous layers were extracted with Et₂O (twice). The combined organic
layers were washed with 1 M HCl and brine, and dried over anhydrous MgSO₄. The solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) to give S₈⁶b (26.4 mg, 0.150 mmol) in 94% yield. Enantiomeric excess of S₈ was determined to be 91% ee by GC analysis.

To a solution of S₈ (26.4 mg, 0.150 mmol) in MeOH (0.800 mL) and THF (0.800 mL) was added 1 M NaOH (0.800 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C. After stirring for 30 min, the resulting mixture was acidified with 1 M HCl and the aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous MgSO₄. The solvents were removed in vacuo to give (R)-1⁶ (16.7 mg, 0.140 mmol) in 93% yield without further purification. Optical purity of (R)-1 was determined to be 91% ee by GC analysis of methyl ester derivative.

**Butyl (R)-tetrahydrofuran-2-carboxylate (S₈):**⁶ Colorless oil; TLC, Rᵢ = 0.62 (hexane–EtOAc = 4:1); ¹H NMR (CDCl₃, 400 MHz) δ 0.94 (t, J = 7.5 Hz, 3H), 1.34–1.43 (m, 2H), 1.60–1.67 (m, 2H), 1.89–2.06 (m, 3H), 2.22–2.29 (m, 1H), 3.90–3.95 (m, 1H), 4.00–4.05 (m, 1H), 4.12–4.17 (m, 2H), 4.44–4.47 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 13.7, 19.1, 25.2, 30.2, 30.6, 64.7, 69.3, 76.7, 173.5; GC (CHIRALDEX B-DM, 100 °C), tᵣ = 7.5 min (S), tᵣ = 7.7 min (R); [α]²⁷²D = +2.5 (c 1.45, CHCl₃) for 91% ee.

**(R)-Tetrahydrofuran-2-carboxylic acid (1):**⁵ Pale yellow oil; ¹H NMR (CDCl₃, 400 MHz) δ 1.93–2.00 (m, 2H), 2.06–2.16 (m, 1H), 2.27–2.38 (m, 1H), 3.91–3.98 (m, 1H), 4.01–4.07 (m, 1H), 4.50–4.53 (m, 1H), 10.5 (brs, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 25.3, 30.1, 69.6, 76.3, 177.9; [α]²⁶⁶D = +28.1 (c 1.01, CHCl₃) for 91% ee. [lit.⁶⁺ +30.4 (c 1.01, CHCl₃) for (R)-1, 99% ee]. These data were consistent with those previously reported.⁶
Reference and Notes


Research Achievements

A. Publication List

Chapter 2
1. “High-Turnover Hypoiodite Catalysis for Asymmetric Synthesis of Tocopherols”
   Muhammet Uyanik, Hioki Hayashi, Kazuaki Ishihara
   DOI: 10.1126/science.1254976

Chapter 3
2. “Chiral Ammonium Hypoiodite Salt-Catalyzed Enantioselective Oxidative Cycloetherification to 2-Acyl Tetrahydrofurans”
   Muhammet Uyanik, Hioki Hayashi, Hirokazu Iwata, Kazuaki Ishihara
   DOI: 10.1246/cl.160004

*Following study is not included in this thesis*

3. “Chiral Hypoiodite Catalysis for Enantioselective Oxidative Cycloamination to N-Heterocycles”
   Muhammet Uyanik, Daisuke Suzuki, Hiroki Hayashi, Kazuaki Ishihara
   *Manuscript under preparation.*
B.  Oral and Poster Presentations

1. “Enantioselective Synthesis of 2-Acylchroman Derivatives Using Chiral (Hypo)iodite Catalysis”
   Hiroki Hayashi, Muhammet Uyanik, Kazuaki Ishihara
   Thieme Nagoya Symposium, Nagoya University, Japan, May 23, 2013 (Poster).

2. “Base-Induced High-Turnover Hypoiiodite Catalysis for Enantioselective Synthesis of Tocopherols”
   Hiroki Hayashi, Muhammet Uyanik, Kazuaki Ishihara
   IGER International Symposium on Chemical Science in Asia Facilitating Singapore-Japan Scientific Interchange, Nagoya University, Japan, May 26, 2014 (Poster).

3. “Chiral Hypoiiodite-Catalyzed Enantioselective Synthesis of 2-Acylchroman Derivatives”
   Hiroki Hayashi, Muhammet Uyanik, Kazuaki Ishihara

4. “High-Turnover Hypoiiodite Catalysis for Enantioselective Oxidative Cycloetherification to Synthesize Optically Active Tocopherols”
   Muhammet Uyanik, Hiroki Hayashi, Kazuaki Ishihara
   19th International Symposium on Homogeneous Catalysis (ISHC-XIX), Ottawa Convention Centre, Canada, July 6–11, 2014 (Poster).

5. “High-Turnover Hypoiiodite Catalysis for Asymmetric Synthesis of Tocopherols”
   Hiroki Hayashi
   2015 Reaxys PhD Prize Symposium, Hyatt Regency, Hong Kong, September 7–8, 2015 (Poster).
   Selected as a finalist.

6. “キラル(次)亜ヨウ素酸塩触媒によるエナンチオ選択的分子内酸化的エーテル化反応を鍵とする光学活性クロマン誘導体合成”
   林 裕樹, UYANIK Muhammet, 石原 一彰
   日本化学会第91回春季年会, 神奈川大学, 2011年3月28日（口頭A講演）。

7. “キラル(次)亜ヨウ素酸塩触媒によるエナンチオ選択的分子内酸化的エーテル化反応を鍵とする光学活性2-アシルクロマン誘導体合成”
   林 裕樹, UYANIK Muhammet, 石原 一彰
理化学研究所研修, 理化学研究所, 2012 年 3 月 19 日 (口頭発表)。

8. “キラル(次)亜ヨウ素酸塩触媒によるエナンチオ選択的分子内酸化的エーテル化反応を鍵とする光学活性 2-アシルクロマン誘導体合成”
林 裕樹, UYANIK Muhammet, 石原 一彰
日本プロセス化学会 2012 サマーサンポジウム, 京都テルサ, 2012 年 7 月 19–20 日 (ポスター発表)。

9. “キラルヨウ素酸塩類を触媒に用いる酸化的カップリング反応による 2-アシルクロマン誘導体の不斉合成”
林 裕樹, UYANIK Muhammet, 石原 一彰
第 43 回中部化学関係協会支部連合秋季大会 特別討論会, 名古屋工業大学, 2012 年 11 月 10–11 日 (口頭発表)。
VIP 賞受賞

林 裕樹, UYANIK Muhammet, 石原 一彰
IGER Annual Meeting 2012, 名古屋大学, 2013 年 1 月 10 日 (ポスター発表)。
ポスター賞受賞

11. “キラル(次)亜ヨウ素酸塩触媒を用いるエナンチオ選択的 2-アシルクロマン誘導体の不斉合成”
林 裕樹, UYANIK Muhammet, 石原 一彰
日本化学会第 93 回春季年会, 立命館大学, 2013 年 3 月 24 日 (口頭 A 講演)。

12. “キラル(次)亜ヨウ素酸塩触媒を用いる 2-アシルクロマン誘導体のエナンチオ選択的合成”
林 裕樹, UYANIK Muhammet, 石原 一彰
第 48 回天然物談話会, アヤハレークサイドホテル, 滋賀, 2013 年 7 月 3–5 日 (ポスター発表)。

13. “Chiral Hypoiodite-Catalyzed Enantioselective Oxidative Cycloetherification to 2-Acylchromans and Investigation of Catalytic Mechanism”
林 裕樹, UYANIK Muhammet, 石原 一彰
IGER Annual meeting 2013, 名古屋大学, 2014 年 1 月 8 日（ポスター発表）。

ポスター賞受賞

14. “キラル次亜ヨウ素酸塩を触媒とするエナンチオ選択的酸化的エーテル環化反応による 2-アシルクロマン誘導体の不斉合成及び触媒機構の解明”
林 裕樹, UYANIK Muhammet, 石原 一彰
日本化学会第 94 回春季年会, 名古屋大学, 2014 年 3 月 27 日（口頭 B 講演）。

15. “キラル次亜ヨウ素酸塩触媒を用いるトコフェロールの不斉合成”
林 裕樹, UYANIK Muhammet, 石原 一彰
創薬懇話会 2014, ホテルパーク岐阜, 2014 年 7 月 10–11 日（ポスター発表）。

16. “高活性次亜ヨウ素酸塩触媒を用いるトコフェロールの不斉合成”
林 裕樹, UYANIK Muhammet, 石原 一彰
第 31 回有機合成化学セミナー, 休暇村 志賀島, 2014 年 9 月 17–19 日（ポスター発表）。

ポスター賞受賞

17. “ペルフルオロアルキル鎖を利用するキラルヨウ化第四級アンモニウム触媒の設計：エナンチオ選択的脱水素カップリング反応の開発”
石原 一彰, UYANIK Muhammet, 鈴木 大介, 林 裕樹
フルオラス化学研究会第 7 回シンポジウム, 北海道大学, 2014 年 9 月 9 日（口頭発表）。

18. “Chiral Hypoiodite-Catalyzed Enantioselective Cyclization to Alicyclic Ethers”
林 裕樹, UYANIK Muhammet, 石原 一彰
日本化学会第 95 回春季年会, 日本大学, 2015 年 3 月 26 日（口頭 A 英語講演）。

19. “次亜ヨウ素酸塩触媒を用いる環境低付加型酸化的カップリング反応の開発”
林 裕樹
第 6 回大津会議, 大津プリンスホテル, 2015 年 10 月 19–20 日（口頭発表）。

大津会議アワードフェロー

20. “Chiral Hypoiodite-Catalyzed Enantioselective Oxidative Cyclization and Mechanistic Study”
林 裕樹, 鈴木大介, UYANIK Muhammet, 石原 一彰
IGER Annual meeting 2016, 名古屋大学, 2016 年 1 月 8 日（ポスター発表）。

21. “Chiral Hypoiodite-Catalyzed Enantioselective Oxidative Cyclization and Mechanistic Study”
Research Achievements

林 裕樹, 鈴木大介, UYANIK Muhammet, 石原 一彰
日本化学会第 96 回春季年会, 同志社大学, 2016 年 3 月 24–27 日 (口頭 B 英語講演)。
22. “キラル次亜ヨウ素酸塩触媒を用いるエナンチオ選択的酸化的エーテル環化反応”
岩田寛和, 林 裕樹, UYANIK Muhammet, 石原 一彰
日本化学会第 96 回春季年会, 同志社大学, 2016 年 3 月 24–27 日 (口頭 A 講演)。

Awards
1. 第 43 回中部化学関係協会支部連合秋季大会 特別討論会 VIP 賞 (2012 年)
2. 第 1 回 IGER Annual Meeting Poster Award (2012 年)
3. 名古屋大学グリーン自然科学教育研究プログラム 独創的研究採択 (2013 年)
4. 第 2 回 IGER Annual Meeting Poster Award (2013 年)
5. 名古屋大学グリーン自然科学教育研究プログラム 独創的研究採択 (2014 年)
6. 第 31 回有機合成化学セミナーポスター賞 (2014 年)
7. 日本学術振興会特別研究員-DC2 (2015 年)
8. 平成 26 年度日本学生支援機構大学院第一種奨学金返還全額免除 (2015 年)
9. Reaxys PhD Prize Finalist (2015 年)
10. 大津会議アワードフェロー (2015 年)

Visiting Scholar
“Development of transition-metal catalyzed reactions”
Professor John. F. Hartwig, Department of Chemistry, University of California, Berkeley.
Acknowledgement

I would like to express my grateful acknowledgment to my supervisors, Professor Kazuaki Ishihara and Assistant Professor Muhammet Uyanik. Their encouragement and helpful suggestions have been indispensable in the completion of the present thesis. The excitement with which they approach synthesis and their dedication to the goal of producing good science is inspiring. Their teaching style in the laboratory and positive attitude for the research work motivated me to be engaged in chemistry. It has been a privilege to work under tutelage of them.

I am indebted to Professor Akira Sakakura (Okayama University), Associate Professor Manabu Hatano and Assistant Professor Takahiro Horibe for their practical and fruitful discussions. It is pleasant to express my appreciation to the former and present colleagues in Ishihara’s group, especially Drs. Atsuto Izumiseki, Hidefumi Nakatsuji, Keisuke Nishikawa, Kazushi Hayashi, Shuhei Umemura, Shinji Suzuki, Yoshiki Koshikari, Takeshi Yasui, Masayuki Sakuma, Tomokazu Mizuno, Hiroki Yamada, Masahiro Hori, Daisuke Suzuki, Niiha Sasakura, Yasuhiro Sawamura and Mrs. Hiroaki Okamoto, Ryota Fukatsu, Daisuke Nakashima, Yoshihiro Ogura, Erina Kaneko, Tatsuya Mutsuga, Dai Nagata, Haruka Okamoto, Yuta Goto, Kenji Yamashita, Mayuko Tsukahara, Katsuya Yamakawa, Kento Ohori, Kouhei Nishioka, Masahiro Mizuno, Tatsuhiro Sakamoto, Naoto Sahara, Naoya Ukegawa, Kirara Saeda, Hirokazu Iwata, Yuhei Hattori, Fumio Nakashima and all of my colleagues in Ishihara group.

I am grateful to Professor John F. Hartwig, who kindly gave me an opportunity for working at University of California Berkeley, USA, 2014.

I would like to thank Professors, Takashi Ooi, Toshio Nishikawa and Yoshihiko Yamamoto for serving on my discussion committee.

I am very grateful to the Fellowships from the Japan Society for the promotion of Science for Japanese Junior Scientist (JSPS) the Program for Leading Graduate Schools "Integrative Graduate Education and Research in Green Natural Sciences", MEXT, Japan.

Finally, I would like to thank my friends and especially my parents for their true regard and unwavering support during my PhD study. Thank you.

January 2016
Hiroki Hayashi