Development of Oxidative Coupling Reactions of Arenols and Alkenes Using Hypohalite Salts

Takehiro Kato

Graduate School of Engineering, Nagoya University

Nagoya, 2023

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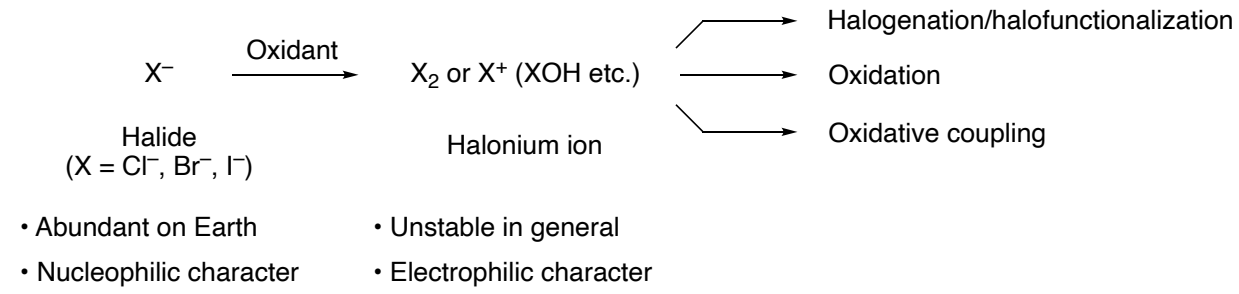
Chapter 1

Introduction and General Summary

1-1. Introduction

Halogens (X = F, Cl, Br, and I) are abundant on Earth, especially in seawater.[1] They mainly exist as halide salts (X^-) and behave as nucleophiles in chemical reactions; however, once they have been oxidized to the corresponding halonium ion (X^+; hypohalous acid: XOH) or molecular halogen (X_2), they instead exhibit electrophilic characteristics.[2] In biosynthesis, these electrophilic halogen species are generated *in situ* via halogenase-catalyzed oxidation of the corresponding halides and are used in the halogenation of organic compounds.[3] On the other hand, in organic chemistry, halogenation reactions are often carried out using toxic and corrosive molecular halogens.[4] To circumvent the use of molecular halogens, electrophilic halogenating reagents such as *N*-halosuccinimides have been developed.[4] However, byproducts derived from these reagents generate stoichiometric amounts of organic waste. To address these problems, strategies for the *in-situ* generation of X^+ species from the corresponding halides, except fluoride, in the presence of an oxidant such as hydrogen peroxide (H_2O_2), alkylhydroperoxide (ROOH), or oxone ($KHSO_5 \cdot 0.5KHSO_4 \cdot 0.5K_2SO_4$) have been developed (Scheme 1).[5] These oxidative halogenation reactions can be performed under mild conditions, and the side-products derived from the oxidants are only water, alcohol, and/or non-toxic inorganic salts. Moreover, compared to the conventional methods using stoichiometric halogenating reagents, these reactions tend to proceed chemoselectively, given that the concentration of active X^+ species remains low.

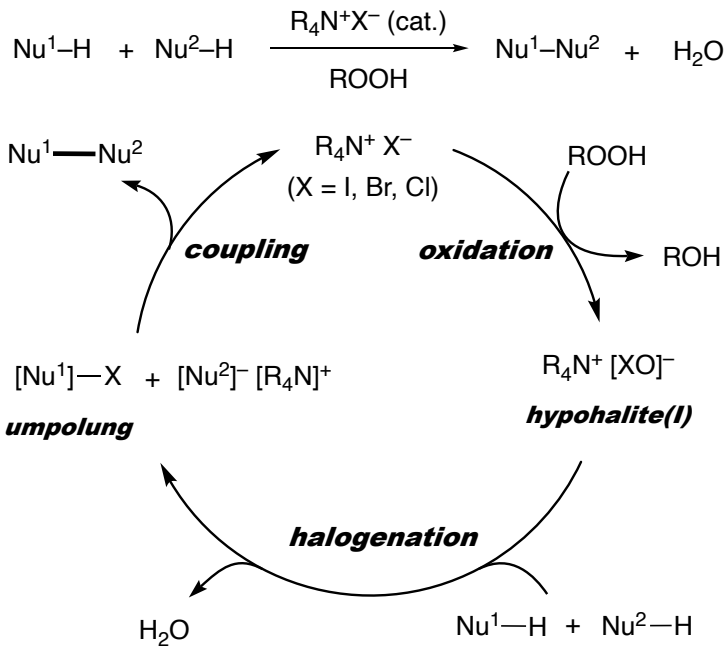
Scheme 1. An Overview of Oxidative Transformations Using Halogens



Given the high nucleofugality (leaving ability) and suitable oxidation potentials of X^+ species, they are often used as oxidants for oxidative functionalization reactions. In this context, Ishihara, Uyanik, and colleagues have developed catalytic hypoiodite reactions; a plausible mechanism for this type of oxidative coupling reaction is shown in Scheme 2 (X = I).[6] First, the hypoiodite species is generated *in situ* from the corresponding onium iodide in the presence of an oxidant. These catalytically active species then catalyze the dehydrogenative coupling of two nucleophilic partners (Nu^1–H and Nu^2–H). During this process, one of the nucleophiles (Nu^1–H) is iodinated to give an

electrophilic species (*umpolung*), while the other (Nu^2–H) is activated as an ion pair with a hypoiodite counter cation (R_4N^+) *via* deprotonation. A catalytic cycle can be completed by reductive elimination of the iodide to give the corresponding coupling product.

Scheme 2. Concept of Hypohalite Catalysis



This thesis focuses on the construction of halogen-based high-performance oxidation systems. In particular, the author has investigated which halogen-based active species are the most suitable for catalytic oxidative coupling reactions. According to the standard reduction potential of X^+/X^-,[7] their oxidizing ability increases in the order iodine < bromine < chlorine (Figure 1a); their atomization energy, electron affinity, hydration ability, and the acidity of the corresponding XOH species also follow this order (Figure 1b).[7,8] Moreover, the acidity increases with increasing oxidation ability (Figure 1a). In addition to the oxidation ability of X^+, the nucleofugality of X^- is also important for developing high-performance catalytic reactions, especially for the coupling step of the catalysis. If the nucleofugality of the halide is low (i.e., X = Cl), a stable Nu^1–X species may be generated, especially in the case of C–Cl moieties. As a result, the catalytic reaction may be hampered. In general, the reductive elimination of halides tends to proceed more readily with iodine than with bromine and chlorine (I > Br > Cl), in parallel with the increase in the bond dissociation energy (BDE) of carbon or oxygen halides[7,9] and the bond length of carbon halides[10] (Figures 1c and 1d).

a) Standard reduction potentials of the hypohalite/halide[7]

	$E°$/V X = I	Br	Cl
acidic conditions: XOH + H^+ + $2e^-$ = X^- + H_2O	0.99	1.33	1.48
basic conditions: XO^- + H_2O + $2e^-$ = X^- + $2HO^-$	0.49	0.76	0.81

b) pK_a values of the hypohalous acid and hydrogen halide[8]

	pK_a (H_2O) X = I	Br	Cl
H–X	–10	–9	–8
H–OX	11.0	8.7	7.3

c) BDE of X–CH_3, X–O[9]

	DH_{298} (kcal/mol) X = I	Br	Cl
X–CH_3	57.6	72.1	83.7
X–O	55.8	56.8	63.9

d) Carbon–halide bond length[10]

	Å X = I	Br	Cl
X–CH_3 (Obs.)	2.14	1.94	1.78

Figure 1. Selected analytical data for halogens.

An overview of the halogens (Cl, Br, and I) and their use, taking into account their mechanisms and properties, is shown in Figure 2. Although iodine has the lowest oxidation power, it can be used as a catalyst due to its high nucleofugality. Bromine can be used as both a catalyst and a stoichiometric electrophilic bromination reagent given that both its oxidation power and nucleofugality are moderate. Chlorine, in contrast to iodine, has the highest oxidation power but the lowest nucleofugality, which makes it generally difficult to use as a catalyst and more suitable as a stoichiometric electrophilic chlorination reagent. Based on the characteristics of each halogen, the author has developed oxidative transformations mediated or catalyzed by halogen-based active species.

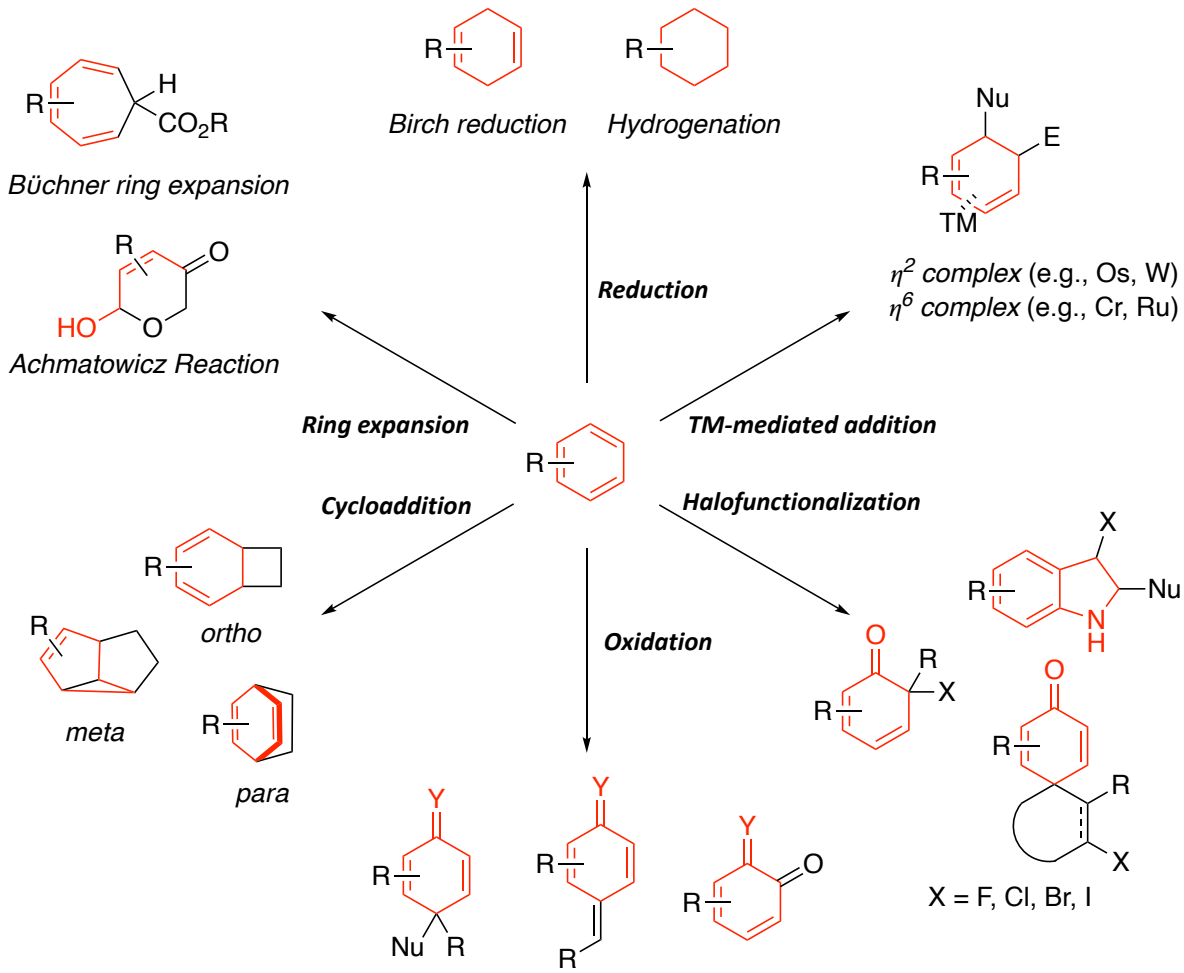
	Redox potential X^+/X^-	Nucleofugality of X^-	Usage
I	Low	High	Mainly Catalyst
Br	Medium	Medium	Catalyst & Reagent
Cl	High	Low	Mainly Reagent

Figure 2. General strategy for the use of *in-situ*-generated X^+ species.

1-2. High-performance Ammonium Hypoiodite/Oxone Catalysis for the Enantioselective Oxidative Dearomatization of Arenols *(Chapter 2)*

Arenes represent one of the most fundamental classes of building blocks and play an important role in organic chemistry and vast areas of the molecular sciences. One of the most characteristic features of arenes is their high stability due to the delocalization of the π-electrons.[11] Accordingly, these compounds are often used for electrophilic aromatic substitution reactions in which they retain their aromaticity.[12] On the other hand, the dearomatization of arenes, which represent readily available planar molecules, is a powerful method for the construction of complex three-dimensional molecular skeletons.[13] A number of strategies for dearomatization reactions have been developed, such as transition-metal-mediated addition,[14] halofunctionalization,[15] ring-expansion,[16] cycloaddition,[17] reductive,[18] and oxidative[19] dearomatization reactions (Scheme 3). Although several types of aromatic compounds can be dearomatized, harsh conditions are often required for these reactions. In contrast, the dearomatization of heteroaromatic compounds such as indoles, pyridines, and furans, or of electron-rich arenes such as arenols and anilines, can proceed under relatively mild conditions due to their reduced resonance-stabilization energy.[20]

Scheme 3. Representative Examples of Dearomatization Methods



Cyclohexadienone and its derivatives are important building blocks for the synthesis of natural products and bioactive compounds via e.g., Diels–Alder, 1,4-addition, and reduction reactions (Scheme 4).[21] In this context, the oxidative dearomatization of arenols has been developed as a conventional method for the synthesis of cyclohexadienone skeletons.[19] The process involves phenoxenium cation analogs, and any type of nucleophiles can be introduced to give the corresponding cyclohexadienones.

To date, many elegant strategies for catalytic asymmetric dearomatization (CADA[22d]) reactions of arenols have been developed using transition-metal or hypervalent organoiodine catalysis.[19,22] In this context, Ishihara, Uyanik, and colleagues have developed a catalytic reaction based on a conformationally flexible chiral hypervalent organoiodine(III) for highly enantioselective oxidative dearomative coupling reactions of a variety of arenols (Figure 3).[23,24] In this catalytic system, iodoarene is first oxidized by *meta*-chloroperbenzoic acid (*m*-CPBA) to form organoiodine(III) *in situ*. NMR spectroscopic and crystallographic analyses revealed that a suitable chiral cavity might be constructed by hydrogen-bonding interactions between the ligands (OR) of iodine(III) and the acidic

protons of the amide side chains.[23c] The reductive elimination of iodoarene then gives the corresponding coupling products. Notably, in this catalysis, the substrate and the catalyst are bound covalently, and the intramolecular hydrogen-bonding interactions allow the construction of a flexible yet suitable chiral cavity. However, expensive and potentially explosive *m*-CPBA is required as a stoichiometric oxidant and *meta*-chlorobenzoic acid (*m*-CBA) is generated as organic waste.

Scheme 4. Oxidative Dearomatization of Arenols and Synthetic Transformations

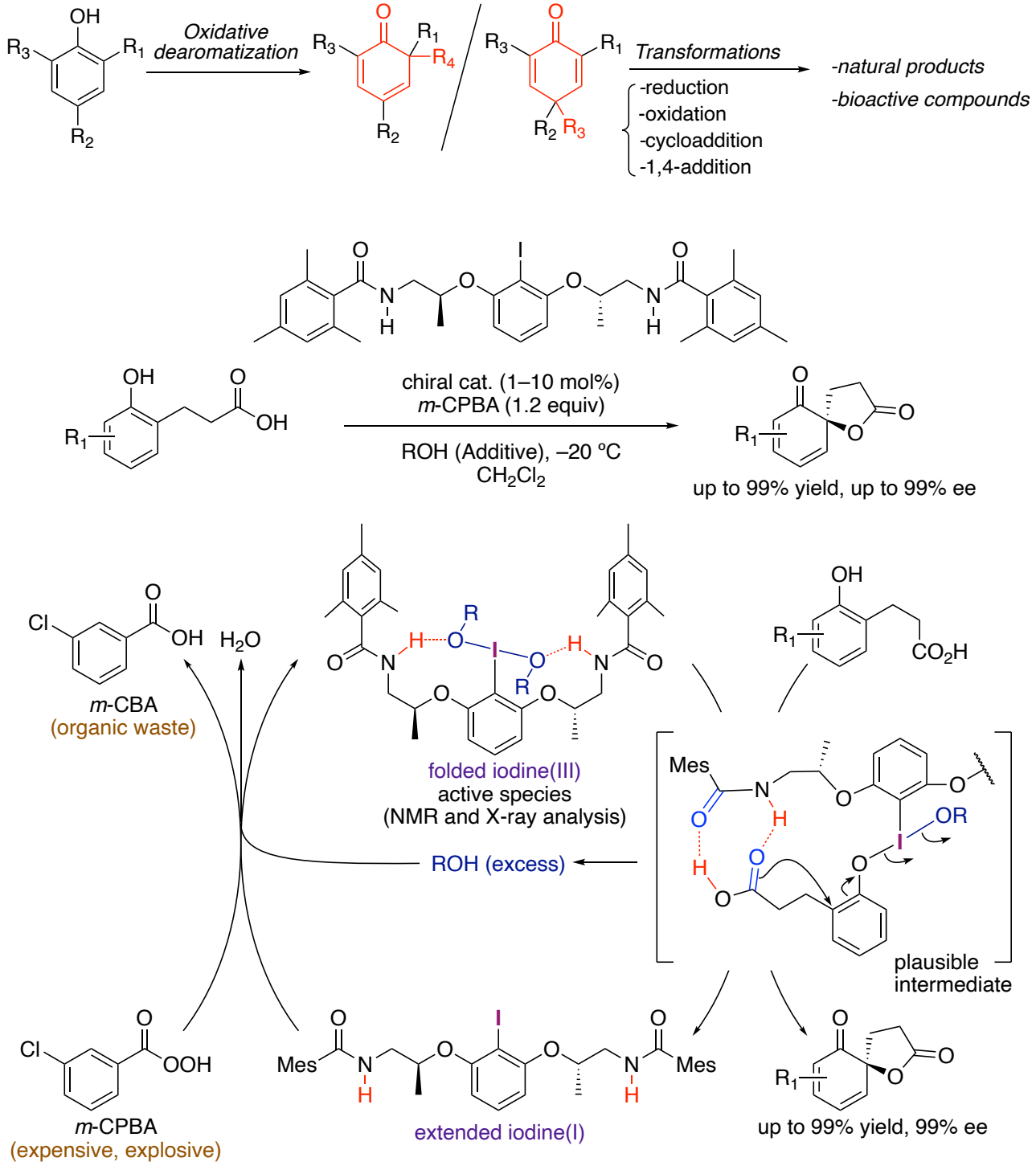
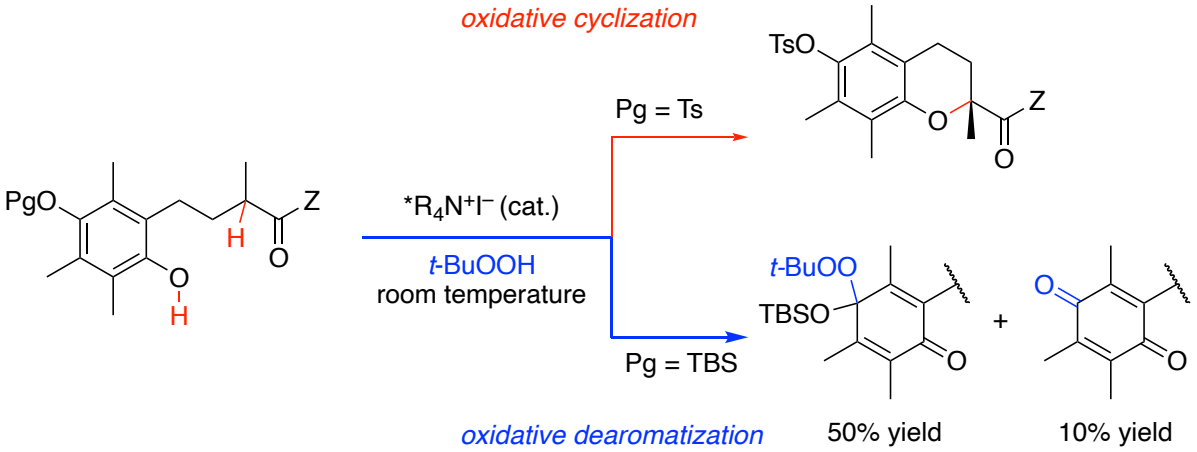


Figure 3. Catalytic oxidative dearomatization of arenols based on a conformationally flexible enantioselective hypervalent organoiodine(III) agent.[23]

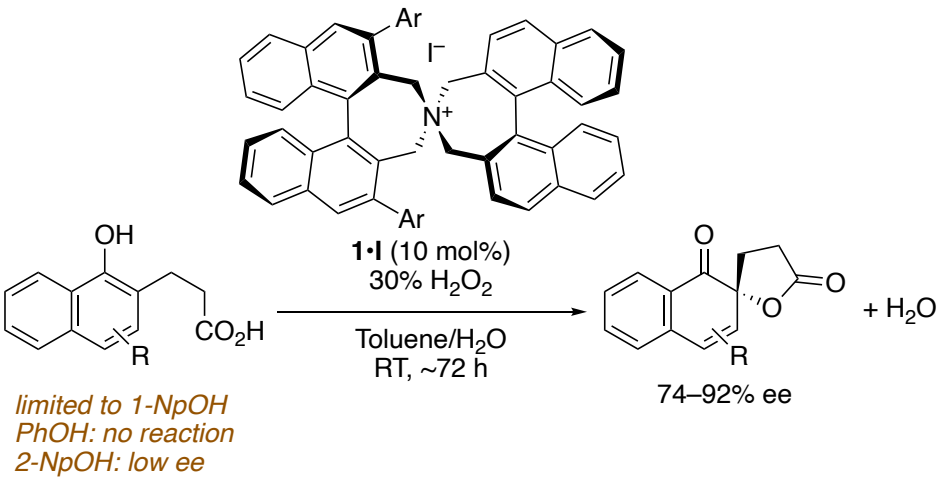
On the other hand, during a study of the enantioselective oxidative cycloetherification of ketophenols, Ishihara, Uyanik, and colleagues found that the electron density of the phenols significantly affects the chemoselectivity of the reaction (Scheme 5).[6d] While the desired oxidative cyclization proceeds efficiently using electron-deficient phenols as the substrate, the reaction of electron-rich phenols affords the quinone derivatives through an oxidative dearomatization.

Scheme 5. Preliminary Findings for the Oxidative Dearomatization of Phenols Using Hypoiodite Catalysis[6d]



In 2015, Ishihara, Uyanik, and colleagues reported the first chiral-ammonium-hypoiodite-catalyzed enantioselective oxidative dearomatization of arenols (Scheme 6).[6e] Notably, in contrast to covalently bound organoiodine(III) catalytic systems (Figure 3), the substrate and chiral ammonium cation are bound by ion-pair interactions during the enantiodiscrimination process in the ammonium-hypoiodite catalysis. C_2-symmetric chiral bis(binaphthyl)-based quaternary ammonium[25] iodides (**1•I**) are effective as chiral catalysts using 30% aqueous hydrogen peroxide as an oxidant. Compared to organoiodine(III) catalysis, the reaction proceeds under milder conditions in non-halogenated solvents such as toluene at ambient temperature. Only water is generated as waste from the oxidant used. However, the substrate scope is limited to 1-naphthols, and relatively long reaction times (~3 days) are required even for these highly reactive substrates. When the oxidation of phenols or 2-naphthols was attempted, no reaction occurred or only low levels of enantioselectivity (<30% ee) were observed, respectively.

Scheme 6. Hypoiodite/H_2O_2 Catalysis for the Oxidative Dearomatization of 1-Naphthols[6e]



A plausible mechanism for this hypoiodite catalysis[6] is shown in Figure 4. Ammonium hypoiodite $R_4N^+[IO]^-$ could be readily generated *in situ* as an unstable catalytically active species from tetraalkylammonium iodide and hydrogen peroxide or alkyl hydroperoxide (ROOH) as an oxidant. If the hypoiodite-mediated oxidative coupling process is slow, triiodide $[I_3]^-$, a stable inert species, can be generated using an alkyl hydroperoxide as an oxidant.[6d] On the other hand, when hydrogen peroxide is used for challenging reactions such as the oxidation of relatively unreactive arenols, the decomposition of hydrogen peroxide to water and oxygen gas catalyzed by the hypoiodite/iodide couple proceeds preferentially.[6l, 26]

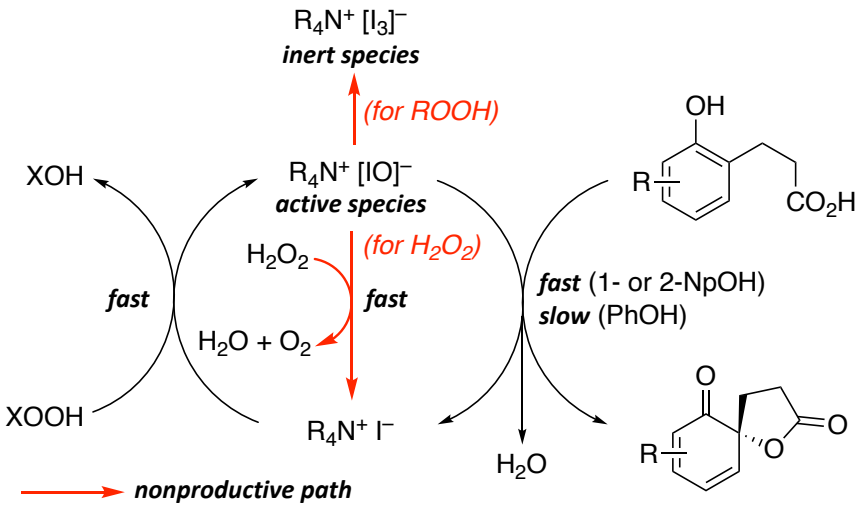


Figure 4. A plausible mechanism for the hypoiodite catalysis of arenols.

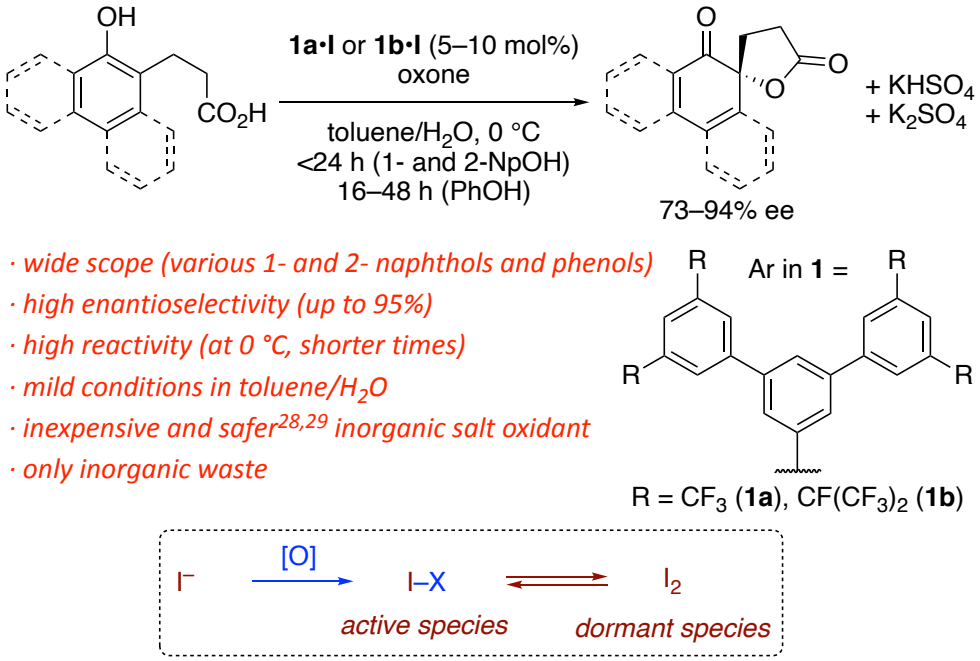
For the development of a high-performance hypoiodite catalysis, the nonproductive pathways mentioned above should be suppressed or eliminated. Additionally, the acidity of the reaction

conditions influences the redox potential of the I^+ species; generally, higher acidity results in increased oxidation ability (Figure 1a). However, the nonproductive paths for both the hydrogen peroxide and the alkyl hydroperoxide systems might also be accelerated under acidic conditions. Therefore, the development of a new oxidation system to achieve a high-performance hypoiodite catalysis for less-reactive substrates such as phenols would be desirable.

Taking into account the catalytic mechanism, the author developed a high-performance ammonium hypoiodite catalysis for such enantioselective dearomatization reactions using oxone as an environmentally benign oxidant, which is described in Chapter 2 (Scheme 7).[27] The oxidation of a wide variety of arenols, including 1- and 2-naphthols as well as phenols, proceeded readily under mild conditions in the presence of chiral quaternary ammonium iodide catalysts to afford the corresponding spirolactones with high enantioselectivity, and only inorganic waste was generated from the oxidant. Compared to previously discussed methods, the reaction proceeds much more efficiently under the optimized conditions to give the products with high enantioselectivity.

Control experiments and Raman analysis revealed the *in-situ* generation of unstable I^+ species such as hypoiodous acid as the active species and molecular iodine (I_2) as the stable dormant state of the catalyst. The generation of I_2 under acidic conditions might play a crucial role in suppressing the undesired decomposition or deactivation pathways that presented significant issues in previous hydrogen peroxide or alkyl hydroperoxide systems.

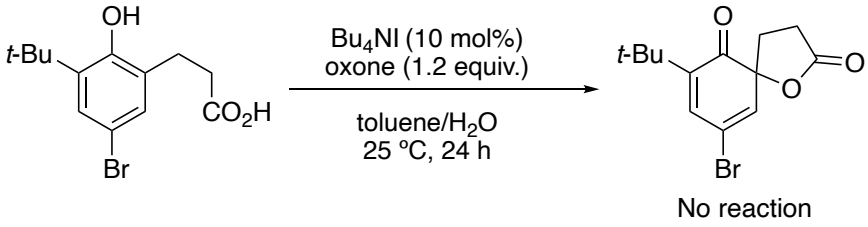
Scheme 7. General Summary of Chapter 2



1-3. Oxidative Dearomative Coupling Reaction of Relatively Unreactive Phenols Using Hypohalite Catalysis *(Chapter 3)*

The substrate scope of this I^+/oxone catalysis (Scheme 7) had so far been limited to electron-rich phenols, which are relatively reactive, and no reaction was observed for relatively unreactive phenols that bear electron-withdrawing groups (EWG) (Scheme 8). The author hypothesized that the use of a bromine-based catalysis might be more suitable for such relatively unreactive substrates given that Br^+ exhibits oxidation power than I^+ species and exhibits sufficient nucleofugality (Figures 1 and 2).[7]

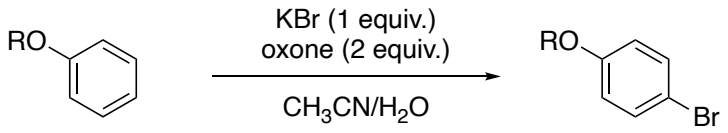
Scheme 8. I^+/Oxone Catalysis for the Oxidative Dearomatization of Electron-Deficient Phenols



Representative examples of the stoichiometric use of Br^+ species generated *in situ* from bromide and oxone are shown in Scheme 9.[30] Bedekar and colleagues have reported a simple and practical method for the *para*-selective bromination of arenols and aryl ethers (Scheme 9a).[30a] Moriyama, Togo, and colleagues have developed an oxidative intermolecular bromo-amination of various *N*-alkenyl sulfonamides and *N*-alkenoxyl sulfonamides (Scheme 9b).[30b] Nama and colleagues have reported a selective α-monobromination of carbonyl compounds using NH_4Br as the bromine source (Scheme 9c).[30c] Madabhushi and colleagues have reported the oxybromination of alkynes to α,α-dibromocarbonyl compounds (Scheme 9d).[30d] Tong and colleagues have reported bromocyclization reactions of tryptamine and tryptophol derivatives (Scheme 9e).[30e] All these reactions proceed under mild and non-toxic conditions without the generation of stoichiometric amounts of organic waste. In addition, these pioneering studies suggest that oxone is capable of oxidizing bromide to Br^+ species.

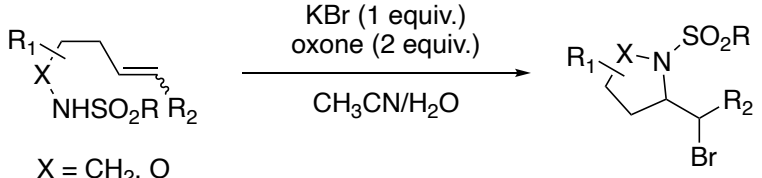
Scheme 9. Representative Examples of Br^+/ Oxone Systems

a) Bedekar *et al.*[30a]



up to 97% yield

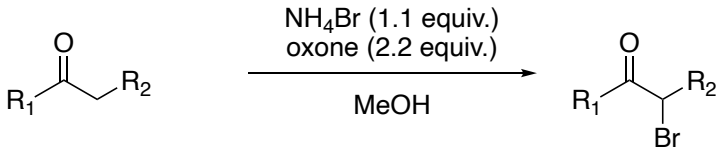
b) Moriyama and Togo *et al.*[30b]



X = CH_2, O

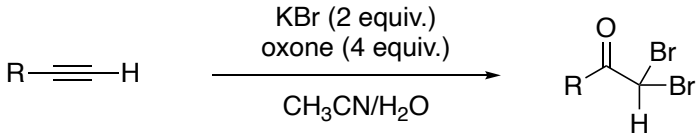
up to >99% yield

c) Nama *et al.*[30c]



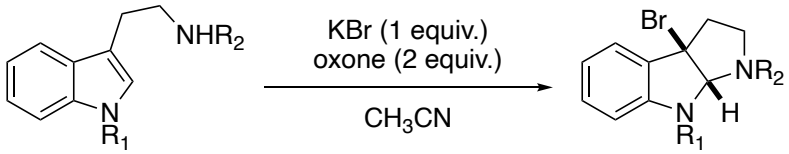
up to 98% yield

d) Madabhushi *et al.*[30d]



up to 99% yield

e) Tong *et al.*[30e]



up to 95% yield

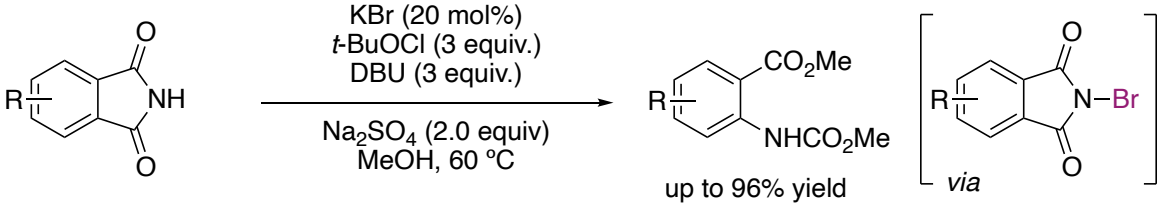
Moreover, Br^+-catalyzed oxidative reactions have been developed (Scheme 10).[31] Moriyama, Togo, and colleagues have reported a Hofmann-type rearrangement of imides (Scheme 10a).[31a] However, highly reactive *tert*-butyl hypochlorite was required as the oxidant under harsh conditions, and no reaction was observed using oxone as the oxidant. MacMillan and colleagues have reported a copper-bromide-catalyzed direct α-coupling of carbonyls with functionalized amines (Scheme 10b).[31b] Although aerobic oxidative coupling could be achieved, the use of copper as a cooperative catalyst was required. Tong and colleagues have reported Br^+-catalyzed oxidative dearomatization reactions of furans (Achmatowicz rearrangement) and indoles using oxone as the oxidant (Schemes 10c and 10d).[31c,d] These pioneering studies showcase the potential utility of such new and practical catalytic protocols for Br^+-catalyzed dearomatization reactions as an alternative to classical methods

using NBS or molecular bromine as the oxidant.

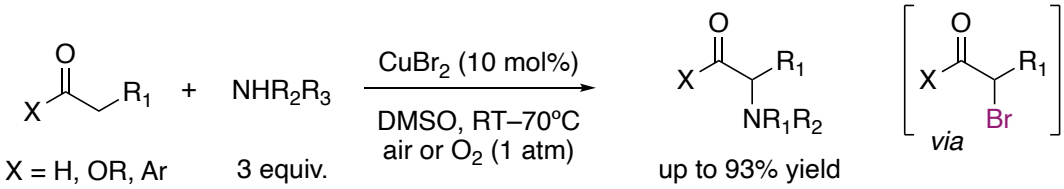
Despite the development of these elegant Br^+-based catalytic strategies, it has so far not been addressed why bromine is more active than other halogens, and the mechanisms of the reactions that involve other halides remain elusive. Moreover, a Br^+-based catalysis for enantioselective oxidative coupling reactions has not yet been achieved.

Scheme 10. Representative Examples of Br^+-based Catalysis for Oxidation Reactions

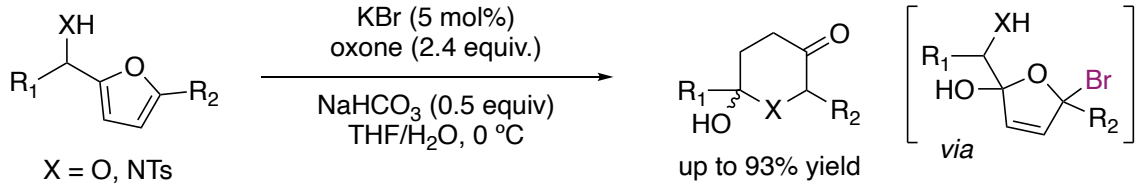
a) Moriyama and Togo *et al.*[31a]



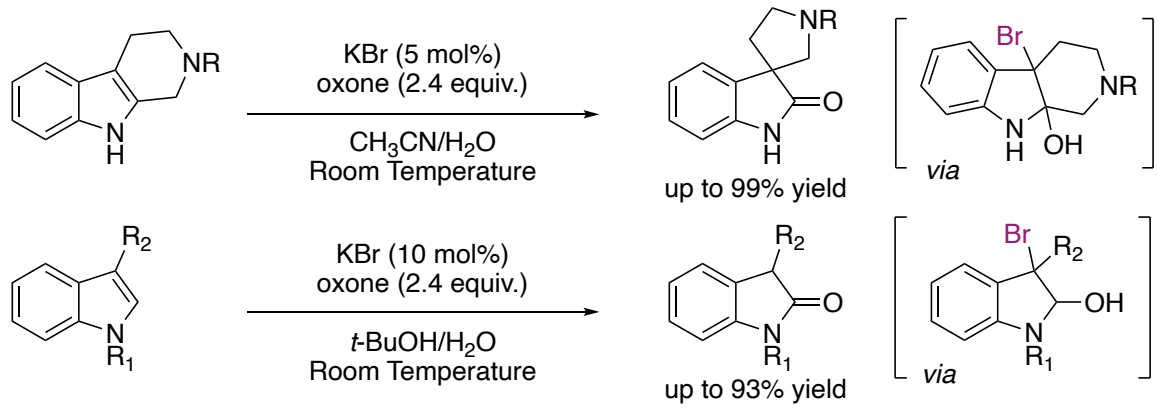
b) MacMillan *et al.*[31b]



c) Tong *et al.*[31c]

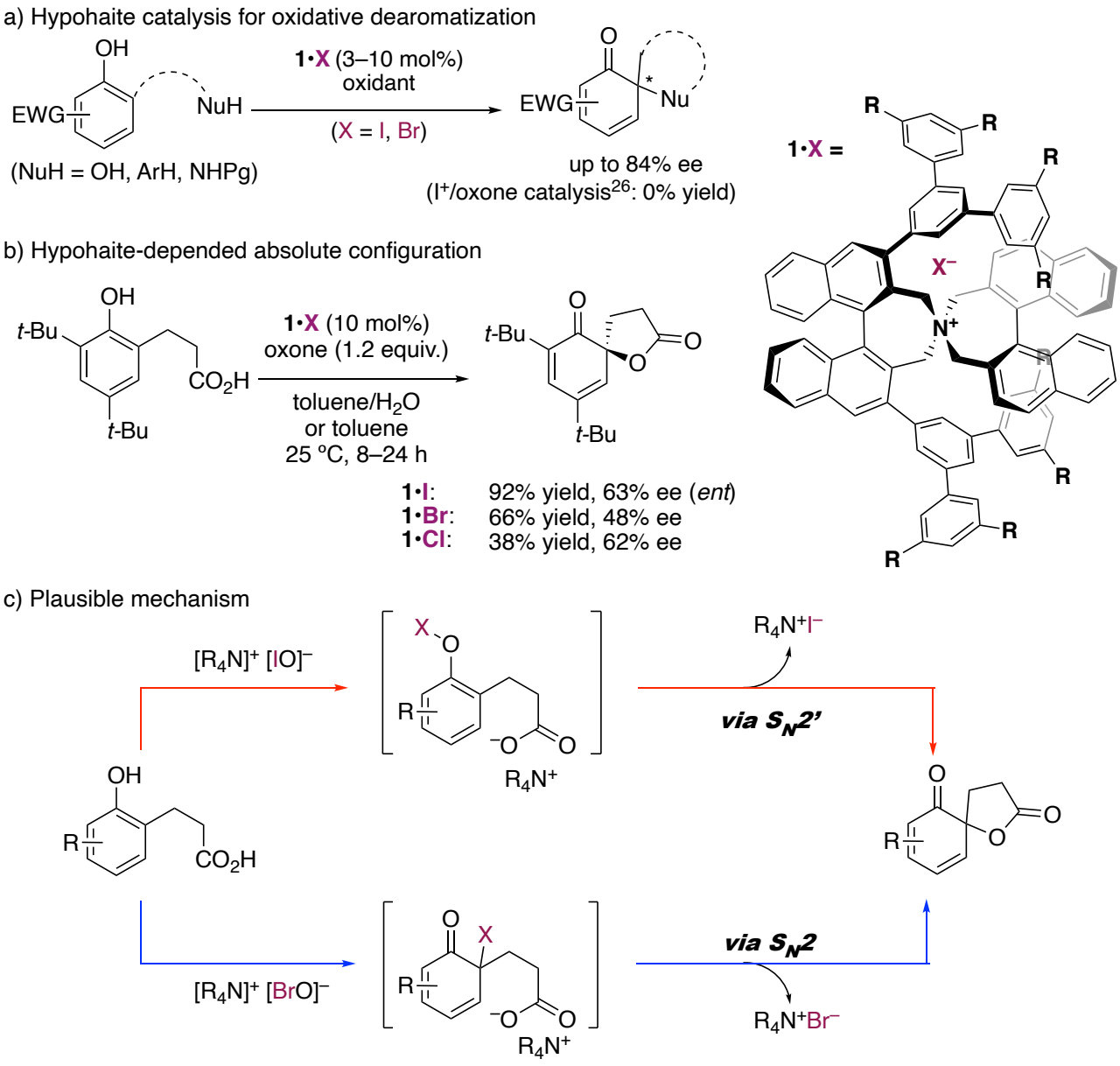


d) Tong et al.[31d,e]



In this context, Chapter 3 focuses on hypobromite catalysis for oxidative coupling reactions. After considering hypohalite catalysis, the author developed hypobromite catalysis for relatively unreactive electron-deficient phenols that did not afford the targeted products via hypoiodite catalysis (Scheme 11).[27] Notably, the reaction scope was successfully expanded to inter- and intramolecular oxidative dearomative C–O, C–N, and C–C coupling reactions. Moreover, the first enantioselective hypobromite catalysis for oxidative dearomative coupling reactions was achieved using a chiral ammonium cation[25] as the countercation for bromide. In addition, some interesting results were found during the oxidation of electron-rich substrates that could be oxidized using either the I^+- or Br^+-based catalytic strategies (Scheme 11b). Surprisingly, opposite enantiomers were obtained using the I^+- or Br^+-based catalytic strategies with the same chiral quaternary ammonium countercation. The use of ammonium chloride provided the product with the same absolute configuration as the Br^+-based catalytic system. These results and those of other control experiments suggested that the reaction mechanisms differ depending on the halide catalyst system used (Scheme 11c).

Scheme 11. General Summary of Chapter 3



1-4. Oxidative Ritter-type Chloroamidation of Alkenes Using NaCl and Oxone (*Chapter 4*)

Vicinal haloamides are used as versatile building blocks for the synthesis of various natural products and biologically active compounds (Figure 5).[32,33] Generally, these compounds are synthesized by the haloamidation of alkene feedstocks using electrophilic halogenation reagents. To date, many elegant strategies for the haloamidation of olefins have been developed using transition-metal catalysts or organocatalysts.[34]

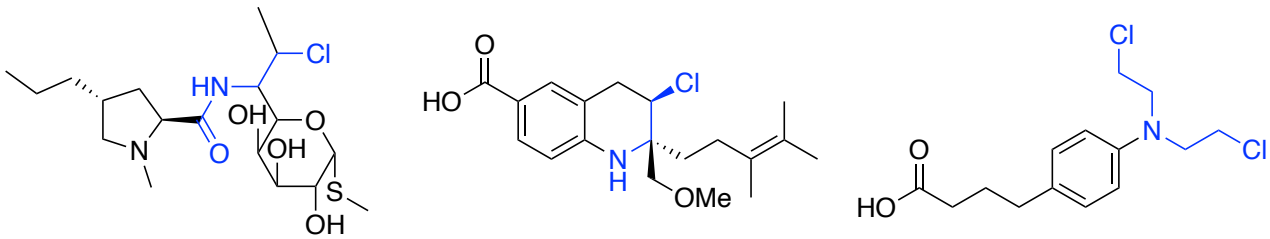
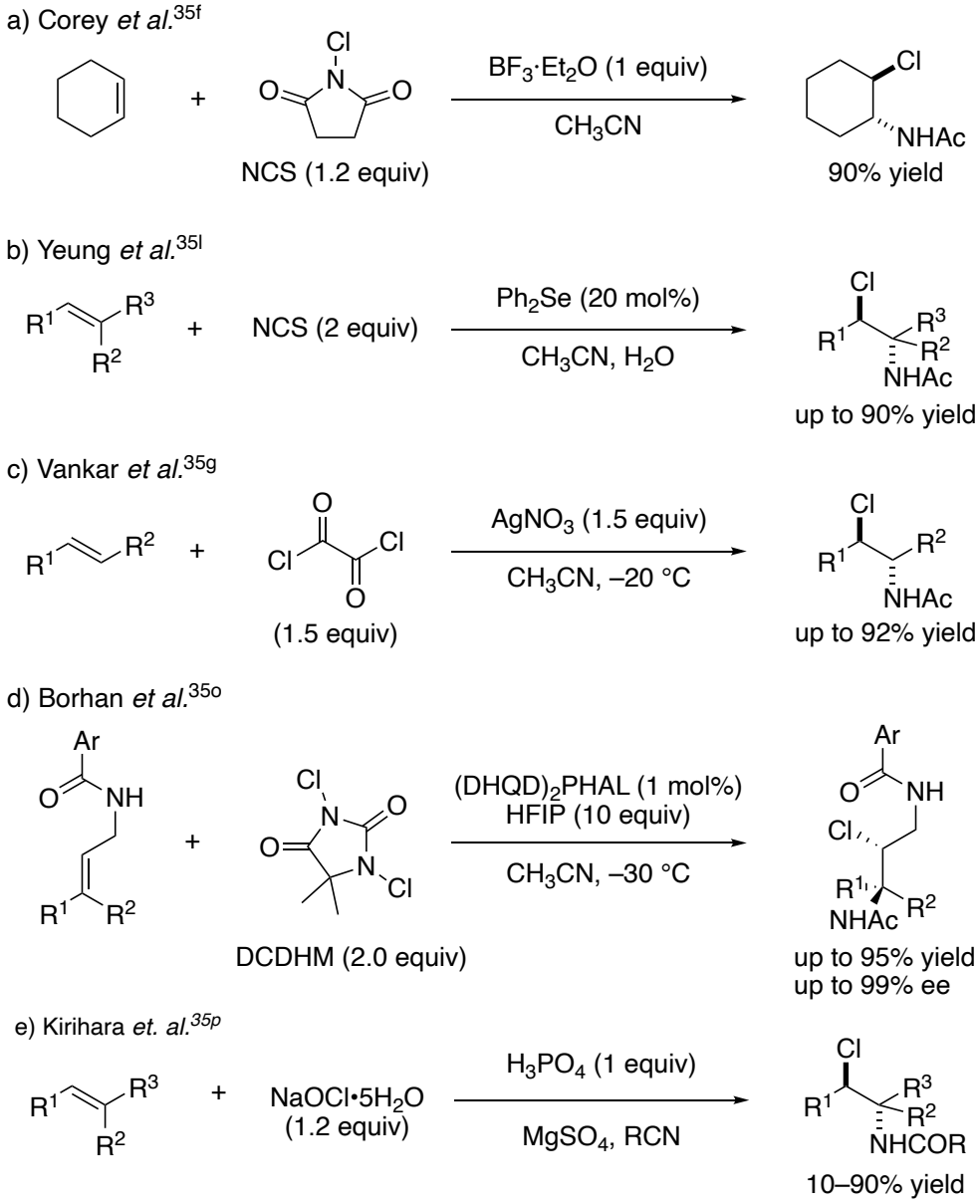


Figure 5. Representative examples of biologically active vicinal chloroamide compounds.

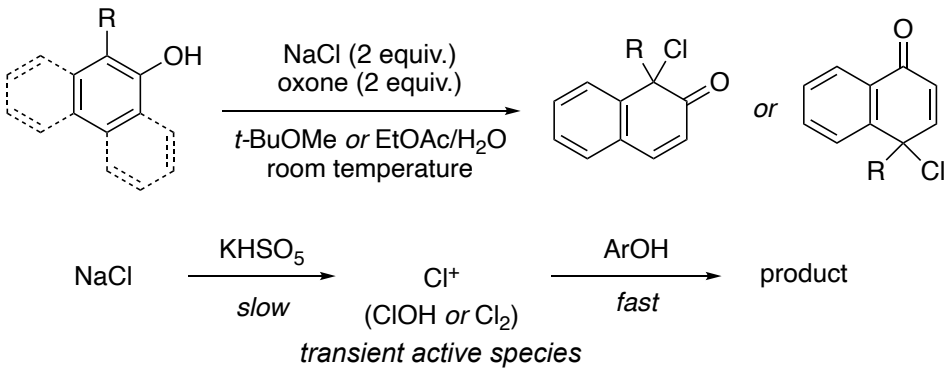
Among these strategies, the Ritter-type chloroamidation of alkenes using nitriles as the solvent and nucleophile is one of the most straightforward routes to such compounds (Scheme 12).[35] For example, the groups of Corey and Yeung have independently reported the Ritter-type chloroamidation of alkenes mediated by a Lewis acid or Lewis base, respectively (Schemes 12a and 12b).[35f,l] However, *N*-chlorosuccinimide (NCS) was used as an organic electrophilic chlorinating reagent, and succinimide is generated as organic waste. On the other hand, Vankar and colleagues have used oxalyl chloride as a chlorinating reagent, although a stoichiometric amount of silver salt is required for the reaction to proceed (Scheme 12c).[35g] Borhan and colleagues have reported the enantioselective Ritter-type chloroamidation of alkenes (Scheme 12d).[35o] Very recently, Kirihara and colleagues have reported the Ritter-type chloroamidation of alkenes using sodium hypochlorite pentahydrate ($NaOCl \cdot 5H_2O$)[36] as an inexpensive inorganic chlorinating reagent in the presence of phosphoric acid in nitrile solvents (Scheme 12e).[35p] However, the substrate scope is limited to aliphatic alkenes, and the reactions of vinyl arenes give a complex mixture.

Scheme 12. Representative Examples of the Ritter-type Chloroamidation of Alkenes



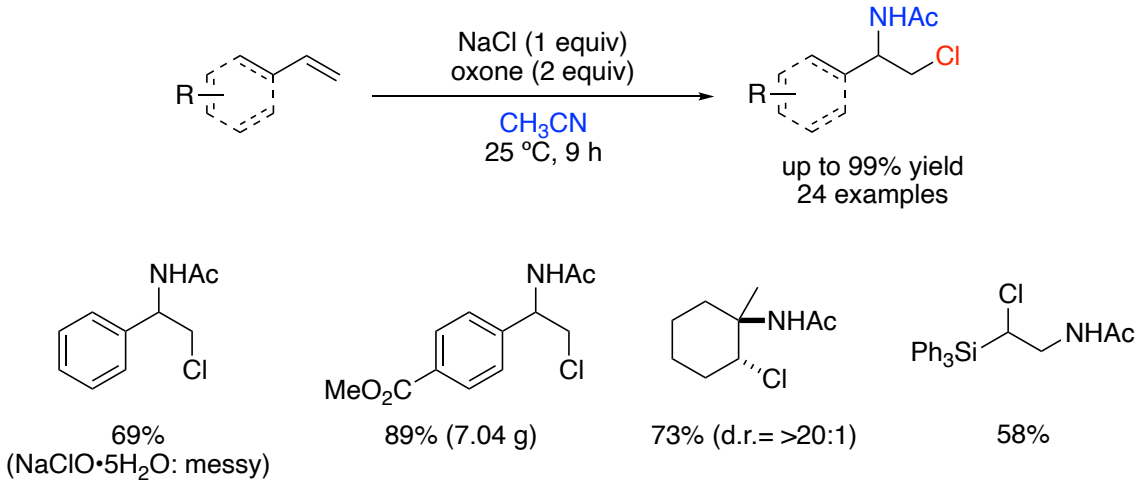
In 2019, Ishihara, Uyanik, and colleagues reported a practical oxidative dearomative chlorination of arenols using sodium chloride and oxone as the chlorinating reagent and oxidant, respectively (Scheme 13).[30e,31d,37,38] Under acidic conditions, it is possible to generate chlorine (Cl_2) or hypochlorous acid (HOCl) *in situ* as an active electrophilic chlorinating species. Most importantly, due to the slow generation and rapid consumption of these transient active species, the concentration of the highly reactive chlorinating species could be minimized to induce higher chemoselectivity compared to that achieved using stoichiometric chlorinating reagents such as sodium hypochlorite pentahydrate.

Scheme 13. Oxidative Dearomative Chlorination of Arenols[37]



Chapter 4 describes the development of a practical method for the oxidative Ritter-type chloroamidation of alkenes using NaCl and oxone as the chlorine source and oxidant, respectively, in acetonitrile under mild conditions (Scheme 14).[39] These reactions proceed smoothly under non-aqueous conditions without the use of any catalyst. Notably, excellent chemoselectivity (i.e., chloroamidation versus dichlorination) could be achieved for styrenes with electron-withdrawing group substituents. Moreover, this protocol can be easily upscaled to a seven-gram-scale synthesis.

Scheme 14. General Summary of Chapter 4



1.5. Conclusions

In summary, the author has developed three types of oxidative coupling reactions using hypohalite salts. The first involves high-performance ammonium hypoiodite catalysis for the enantioselective oxidative dearomatization of arenols using oxone as an acidic and environmentally benign oxidant. The generation of molecular iodine might be crucial to preventing the decomposition of the catalysts and achieving long-lived catalysis. The second is the oxidative dearomative coupling

reaction of relatively unreactive arenols using hypohalite catalysis. Mechanistic studies revealed that the reaction mechanism differs depending on the hypohalite catalyst used. The third reaction is the oxidative Ritter-type chloroamidation of alkenes using NaCl and oxone. These results showcase the high potential of hypohalite oxidation systems for the development of environmentally friendly oxidative transformations.

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Chapter 2

High-Performance Ammonium Hypoiodite/Oxone Catalysis for Enantioselective Oxidative Dearomatization of Arenols

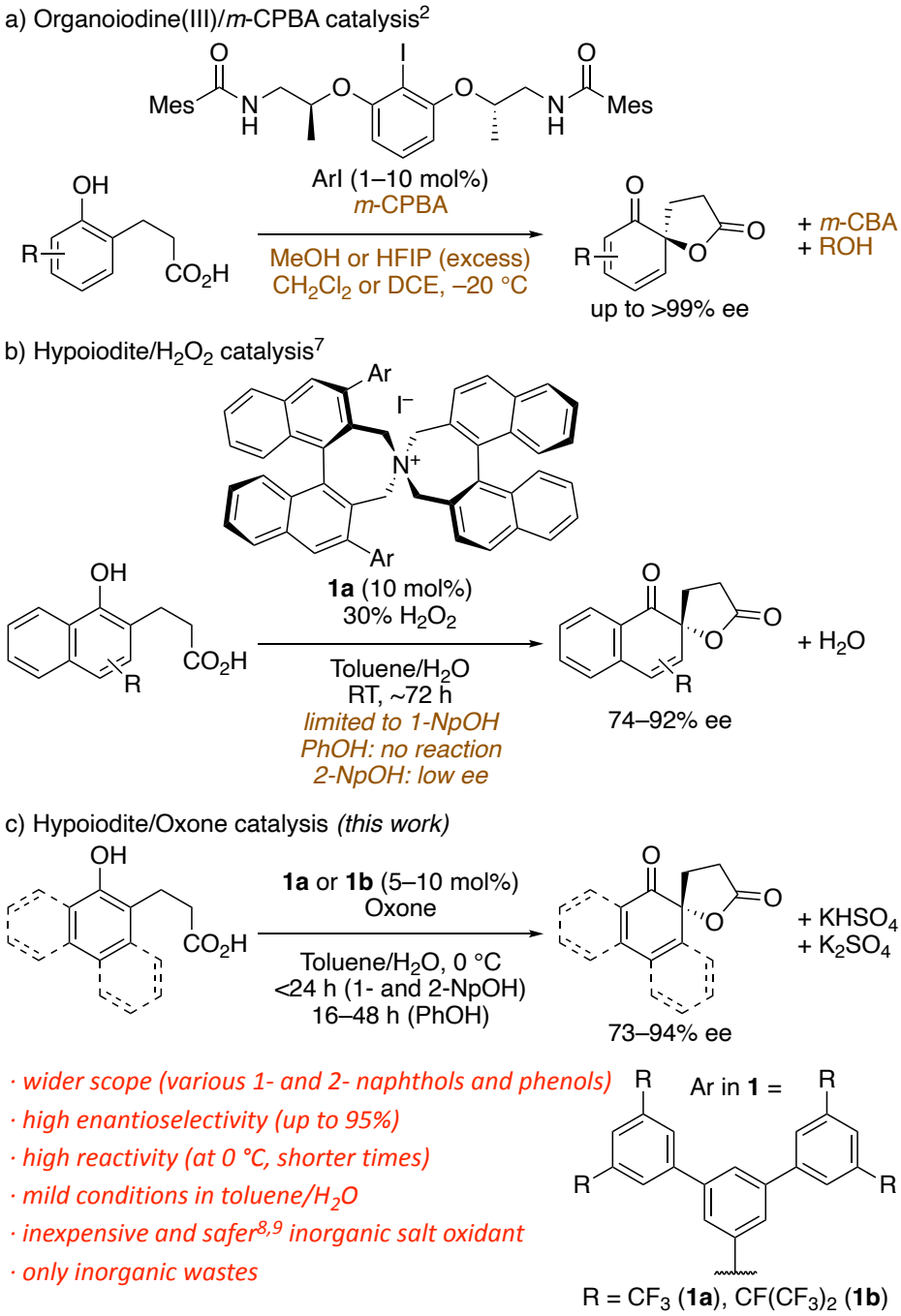
Abstract: A high-performance enantioselective quaternary ammonium hypoiodite catalysis was developed for the dearomatization of arenols using Oxone as an environmentally benign oxidant. The oxidation of not only 1- and 2-naphthols but also phenols, which were hardly reactive using the previous hypoiodite catalysis, readily proceeded under mild conditions, and only inorganic wastes were generated from the oxidant used. Control experiments and Raman analysis revealed the in situ generation of I^+ such as hypoiodous acid as an unstable active species and molecular iodine (I_2) as a stable dormant species. The most advantages of the present I^+/Oxone catalysis compared to previous I^+/(H_2O_2 or ROOH) systems may result from generation of the stable dormant state and the higher reactivity of catalysts under acidic conditions.

Introduction

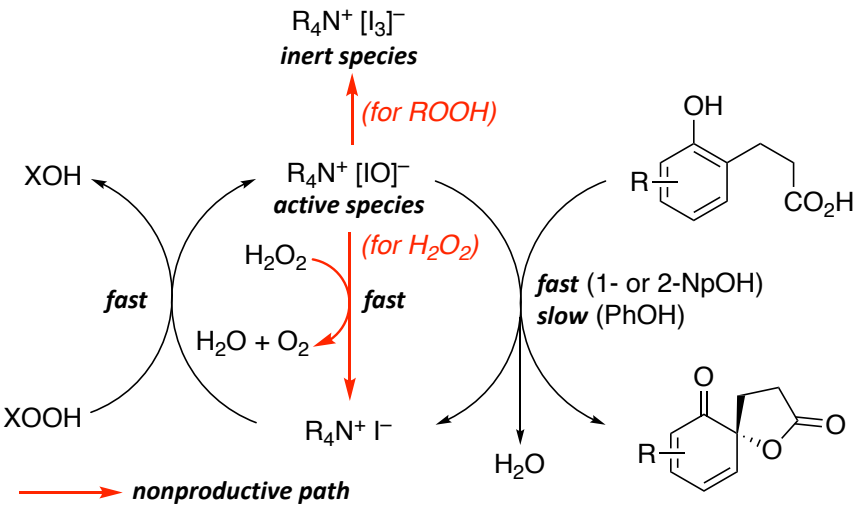
Oxidative dearomatization of arenols has recently been recognized as an important tool for the synthesis of various natural products and biologically relevant compounds.[1] To date, many elegant strategies have been developed using enantioselective reactions with transition metal or hypervalent iodine catalysts or reagents.[1] In this context, we have developed a conformationally flexible chiral hypervalent organoiodine(III) catalysis for the highly enantioselective oxidative dearomatizative spirolactonization of a variety of arenol derivatives (Scheme 1a).[2,3] However, *meta*-chloroperoxybenzoic acid (*m*-CPBA) as an expensive and potentially explosive oxidant was required, and *meta*-chlorobenzoic acid (*m*-CBA) was generated as an organic waste. Additionally, excess amounts of alcohol additives in halogenated solvents were also required to induce high enantioselectivity. To address these issues, we developed a chiral quaternary ammonium[4] hypoiodite catalysis[5,6] using aqueous hydrogen peroxide as an inexpensive and relatively safe oxidant (Scheme 1b).[7] The reaction could proceed under milder conditions and only water was generated as a waste from the oxidant used. However, the substrate scope of the H_2O_2 system was limited to 1-naphthols, and, in most cases, long times (~3 days) were required to complete the reactions even for these highly reactive substrates. Either no reaction took place or only low enantioselectivities (<30% ee) were observed for the oxidation of phenols or 2-naphthols, respectively. Based on a consideration of the catalytic mechanism, here we demonstrate a high-performance hypoiodite catalysis for the dearomatization of not only 1-naphthols but also phenols and 2-naphthols using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as an environmentally benign,[8] safe[9] and easy to handle inorganic oxidant (Scheme 1c).[10] The oxidation reactions could readily proceed under mild conditions in the presence of chiral quaternary ammonium iodide catalysts **1** to afford the corresponding spirolactones with high enantioselectivity, and only inorganic wastes were generated derived from the oxidant used. Control experiments and Raman analysis revealed the *in situ* generation of I^+ such as hypoiodous acid as an unstable active species and molecular iodine (I_2) as a stable dormant state of catalyst, which might play crucial roles to suppress non-productive deactivation pathways.[5] The mechanism of hypoiodite/(H_2O_2 or ROOH) catalysis is shown in Scheme 2.[5] Ammonium hypoiodite $R_4N^+[IO]^-$ would be readily generated in situ as an unstable catalytic active species from tetraalkylammonium iodide and hydrogen peroxide or alkyl hydroperoxide (TBHP or CHP) as an oxidant.[5b] If the desired oxidative coupling reaction is slow, triiodide $[I_3]^-$ as a stable inert species would be generated when an alkyl hydroperoxide was used as an oxidant.[5b,d] On the other hand, when hydrogen peroxide was used for challenging reactions, the decomposition of hydrogen peroxide to water and oxygen gas catalyzed by hypoiodite/iodide couple would proceed preferentially.[5c,d, 11] For the development of a

high-performance I^+ catalysis, these nonproductive pathways should be suppressed or completely eliminated. Additionally, the acidity of the reaction conditions would influence the redox potential of I^+ species; generally, the greater acidity, the greater oxidation ability.[12,13] However, both nonproductive paths for hydrogen peroxide or alkyl hydroperoxide systems might also be accelerated under acidic conditions. Therefore, a new oxidation system would be desired to achieve high-performance hypoiodite catalysis for less reactive substrates such as phenols.

Scheme 1. Enantioselective Oxidative Dearomatization of Arenols Using Iodine-based Catalysis



Scheme 2. Hypoiodite/(H_2O_2 or ROOH) Catalysis

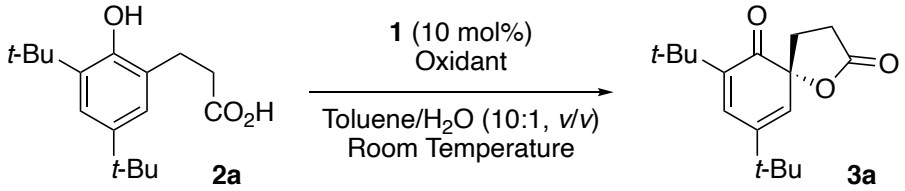


Results and Discussion

To seek a new oxidation system for low-reactive phenols, we investigated the oxidant and reaction parameters for hypoiodite catalysis using di-*tert*-butyl phenol **2a** as a model substrate (Table 1). Expectedly, the use of hydrogen peroxide or alkyl hydroperoxides afforded no dearomatization product (entries 1 and 2). We briefly investigated common oxidants,[14] and, to our delight, the oxidation of **2a** using Oxone ($KHSO_5$•$0.5KHSO_4$•$0.5K_2SO_4$) proceeded smoothly to afford the desired spirolactone (*R*)-**3a**[2c] in 89% yield with 59% ee (entry 3). Oxone, a triple salt, is an acidic oxidant due to a potassium hydrogen sulfate (pK_a 2.0)[13] component (pH of the aqueous phase ~1.6).[15] We considered that the reaction rate of the oxidative coupling might be accelerated under these acidic conditions, and hydrogen peroxide and TBHP were re-investigated in the presence of $KHSO_4$ as an acidic additive (entries 4 and 5). However, no reaction took place, which might suggest the competitive acceleration of nonproductive pathways. The acidity of Oxone might be crucial for both reactivity and enantioselectivity, since the oxidation of **2a** using buffered[16] Oxone prepared in the presence of potassium carbonate was too sluggish and gave **3a** in only 29% ee (entry 6). The beneficial effects of acidity on enantioselectivity are not yet clear. Additionally, no oxidation was observed under nonaqueous conditions where Oxone was not dissolved (entry 7). A brief screening of organic solvents under biphasic conditions revealed that toluene was optimal.[14] The use of almost an equimolar amount of Oxone (as 1.2 equiv of $KHSO_5$) was enough to complete the reaction after only 8 hours (entry 8). Additionally, the enantioselectivity was improved to 71% ee at 0 °C (entry 9). Moreover, the use of perfluoro-modified catalysts **1b** further improved the enantioselectivity (80% ee), albeit with very low reactivity (entry 10). The chemical yield of **4a** could be improved either after prolonged reaction times in the presence of a larger amount of Oxone (entry 11) or under higher

concentration (entry 12), but with a slight sacrifice in enantioselectivity.

Table 1. Enantioselective Dearomatization of Phenol 2a[a]



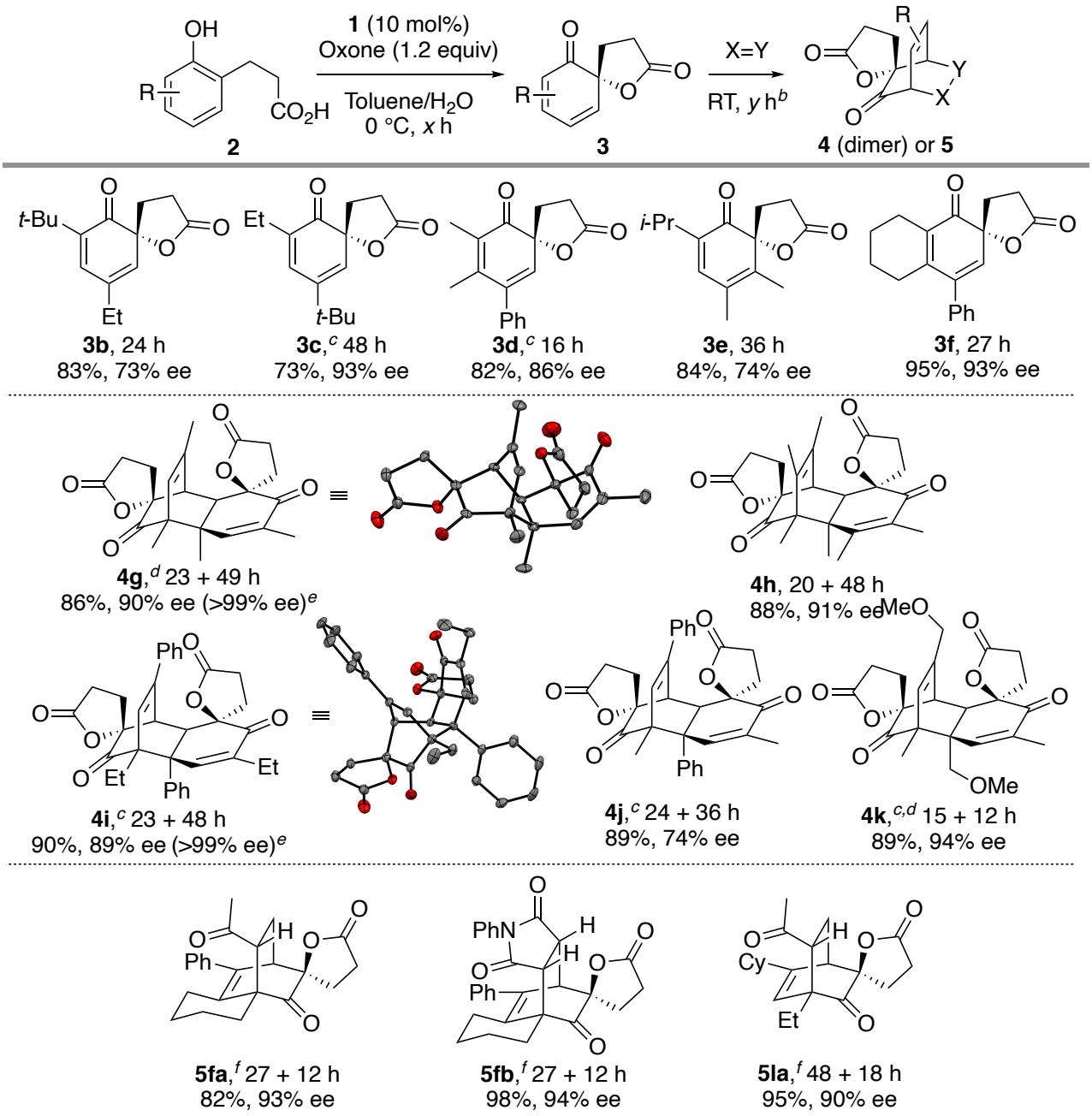
Entry	Oxidant (+ additive) (equiv)	1	Time (h)	Yield (%)[b]	Ee (%)
1	H_2O_2 (2)	**1a**	24	–[c]	–
2	TBHP or CHP (2)	**1a**	24	–[c]	–
3	Oxone (1.5)	**1a**	5	89	59
4	H_2O_2 (2) + $KHSO_4$ (2)	**1a**	24	–[c]	–
5	TBHP (2) + $KHSO_4$ (2)	**1a**	24	–[c]	–
6	Oxone (3) + K_2CO_3 (1)	**1a**	72	78	29
7[d]	Oxone (3)	**1a**	24	–[c]	
8	Oxone (1.2)	**1a**	8	92	63
9[e]	Oxone (1.2)	**1a**	25	98	71
10[e]	Oxone (1.2)	**1b**	24	20	80
11[e]	Oxone (1.2 + 1.2[f])	**1b**	72	94	75
12[e,g]	Oxone (1.2)	**1b**	24	80	73

[a] Unless otherwise noted, the reactions were performed in toluene (0.02 *M*)/H_2O (10:1). [b] Isolated yield. [c] No oxidation reaction. [d] In toluene (monophasic). [e] At 0 °C. [f] Oxone (0.6 equiv) was added after 24 h. [g] In toluene (0.1 *M*)/H_2O (2/1). For details, see Experimental Section.

Several phenols **2** were examined for enantioselective oxidative spirolactonization under the optimized conditions using chiral ammonium iodide **1a** (Scheme 3). Oxidation of phenols **2b**–**f** afforded the corresponding spirolactones **3** in high yield with good to high enantioselectivity (73–93% ee). A bulky substituent at the *ortho*-position diminished the enantioselectivity (**3a**, **3b** and **3e**). On the other hand, the cyclohexadienones **3** derived from the corresponding phenols **2g**–**l** were found to be unstable during the reaction or purification. These cyclohexadienones could be converted exclusively to the corresponding cyclodimers **4h**–**k** or [4+2]-cycloadduct **5la** of methyl vinyl ketone in excellent yield with perfect diastereoselectivities.[2c,17] Additionally, both cyclohexadienone **3f** and [4+2]-cycloadducts **5fa** and **5fb** could be obtained in excellent yields with 93–94% ee from the oxidation of **2f** and subsequent tandem cycloadditions, respectively. Notably, optically pure (>99% ee) **4g** and **4i** were obtained after a single recrystallization. Additionally, similar to the results with **2a**, the use of catalyst **1b** gave slightly higher enantioselectivity for the oxidation of **2i** and **2j** under higher concentration. The absolute stereo-chemistry of the cyclohexadienones **3** was assigned to be (*R*) by analogy to a known compound **3a**.[2c] On the other hand, the relative stereochemistries of

cyclodimers **4** and cycloadducts **5** were determined by single-crystal X-ray diffraction analysis of enantiomerically pure (>99% ee) **4g** and **4i**, and by analogy to the literature,[2c] respectively.[18] Notably, the present hypoiodite/Oxone catalysis is currently limited to electron-rich phenols, and no reaction occurred for phenols bearing electron-withdrawing groups.

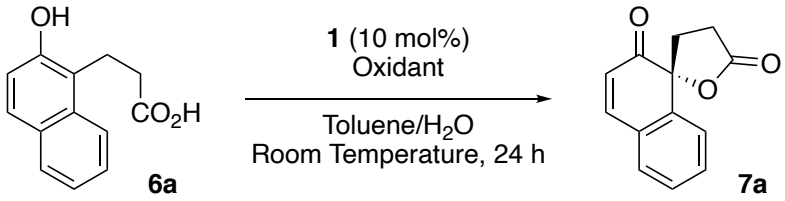
Scheme 3. Enantioselective Oxidation of Phenols 2[a]



[a] Unless otherwise noted, the reactions were performed with **2** (0.1 mmol) in toluene (0.02 *M*)/H_2O (10:1) at 0 °C using **1a** (for **2a**–**h**, **2k**, **2l**) or **1b** (for **2i** and **2j**). [b] After phenol **2** was fully consumed (TLC check), the reaction was allowed to warm to room temperature to afford the corresponding [4+2]-cyclodimer or cycloadduct **4** or **5**. Reaction time for oxidation and cycloaddition ($x + y$ h) are shown. [c] In toluene (0.1 *M*)/H_2O (2:1). [d] Cycloaddition reactions were also performed at 0 °C. [e] After a single re-crystallization. [f] Dienophile (10 equiv) was used. For details, see Experimental Section.

Next, we were interested in the oxidation of 2-naphthol **6a**, which could be oxidized using our previous hypoiodite/hydrogen peroxide[7] or alkyl hydroperoxide catalysis under toluene–water biphasic conditions, albeit with low enantioselectivity (Table 2, entries 1 and 2). Considering the beneficial effect of acidity on the enantioselectivity observed for the oxidation of phenols **2**, the oxidation of **6a** with these oxidants was examined under acidic conditions using $KHSO_4$ as an additive. As expected, enantioselectivity was remarkably improved for both oxidants, but with diminished reactivity which again suggested the competitive acceleration of nonproductive pathways under acidic conditions for these oxidants (entries 3 and 4). To our delight, oxidation of **6a** using Oxone proceeded smoothly to give (*R*)-**7a**[2e] in 88% yield with 62% ee (entry 5). The use of catalyst **1b** at 0 °C further improved enantioselectivity (entries 6 and 7). Given the fact that the oxidation of **6a** using a catalytic amount of potassium iodide with Oxone proceeded in water without any organic solvents,[14] we considered the possibility of nonselective oxidation in the aqueous phase. Additionally, as with phenols 2, no reaction occurred without water.[14] Based on these results, we investigated the amount of water used,[14] and **7a** was obtained quantitatively with highest enantioselectivity (94% ee) with the use of ten-fold less water (entry 8).

Table 2. Enantioselective Oxidation of 2-Naphthol 6a[a]

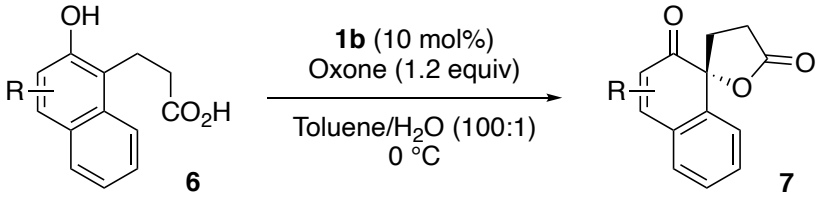


Entry	Oxidant (+ additive) (equiv)	Time (h)	**1**	Yield (%)[b]	Ee (%)
1	H_2O_2 (2)	24	**1a**	87	28
2[c]	TBHP (2)	24	**1a**	23	38
3	H_2O_2 (2) + $KHSO_4$ (2)	24	**1a**	4	62
4[c]	TBHP (2) + $KHSO_4$ (2)	24	**1a**	14	57
5	Oxone (1.2)	3	**1a**	88	62
6[d]	Oxone (1.2)	10	**1a**	85	78
7[d]	Oxone (1.2)	24	**1b**	91	87
8[d,e]	Oxone (1.2)	24	**1b**	98	94

[a] Unless otherwise noted, the reactions were performed in toluene (0.02 *M*)/H_2O (10:1). [b] Isolated yield. [c] In toluene (0.1 *M*)/H_2O (2/1). [d] At 0 °C. [e] In toluene (0.02 *M*)/H_2O (100/1). For details, see Experimental Section.

Under the optimized conditions, several 2-naphthol derivatives **6** could be oxidized to the corresponding spirolactones **7** in excellent yield with high enantioselectivity regardless of the electronic nature and position of the substituents (Table 3).

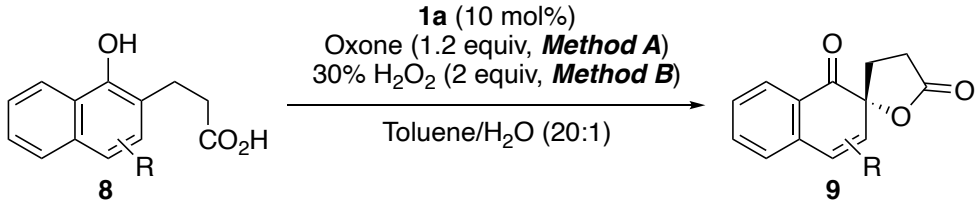
Table 3. Enantioselective Oxidation of 2-Naphthols 6[a]



Entry	**6** (R)	Time (h)	Yield (%)[b]	Ee (%)
1	**6b** (3-Br)	20	96	91
2	**6c** (6-Br)	12	88	90
3	**6d** (8-F)	24	95	87
4	**6e** (4-Me)	22	92	88
5	**6f** (7-OBn)	24	92	90
6	**6g** (7-OMe)	24	93	85

[a] The reactions were performed with **6** (0.1 mmol) in toluene (0.02 *M*)/H_2O (100:1). [b] Isolated yield. For details, see Experimental Section.

Table 4. Enantioselective Oxidation of 1-Naphthols 8[a]



R = 4-Cl (**8a**), 4-Br (**8b**), 4-Ph (**8c**), 4-[3,5-$(CF_3)_2C_6H_3$] (**8d**), 3-OMe (**8e**)

Entry	**8**	Method	*T* (°C)	*t* (h)	Yield (%)[b]	Ee (%)
1[c]	**8a**	A	0	27	97	91
2[d,e]	**8a**	B	20	72	84	88
3	**8b**	A	0	20	94	94
4[d,e]	**8b**	B	20	72	72	88
5[f]	**8c**	A	25	4	83	88
6[d,g]	**8c**	B	20	72	90	85
7	**8d**	A	0	23	96	94
8[d,e]	**8d**	B	20	72	75	92
9	**8e**	A	0	6.5	87	85
10[d,h]	**8e**	B	20	48	71	74

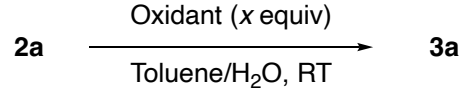
[a] Unless otherwise noted, the reactions were performed with **8** (0.1 mmol) in toluene (0.1 *M*)/H_2O (20:1). [b] Isolated yield. [c] With 5 mol% of **1a**. [d] Data were taken from Ref#7. Due to racemic background reactions with H_2O_2, the reaction conditions should be optimized for each substrate. [e] In toluene (0.1 *M*)/H_2O (2:1). [f] In toluene

(0.02 *M*)/H_2O (10:1) due to solubility issues. [g] In toluene (0.05 *M*)/H_2O (4:1). [h] In toluene (0.1 *M*). For details, see Experimental Section.

Finally, the oxidation of 1-naphthols **8** was examined using the present hypoiodite/Oxone catalysis (method A) and the results were compared to those with our previous hydrogen peroxide oxidation system (method B)[7] (Table 4).[14] In contrast to the H_2O_2 system, the reactions proceeded smoothly even at lower temperature (0 °C) and, especially, with a lower loading of catalyst **1a** (5 mol%, entry 1 versus entry 2), and the corresponding spirolactones **9** were obtained with higher chemical yield and enantioselectivity after much shorter reaction times. These results again demonstrated the substantial scope of the present hypoiodite/Oxone catalysis.

To probe the active species, several control experiments were performed (Scheme 4).[14] First, stoichiometric experiments using various iodine-based oxidants revealed that I_2, triiodide ($[I_3]^-$), and high-valence iodines ($[IO_3]^-$ and $[IO_4]^-$)[19] might not be active species for the oxidation of phenols (eq. 1). On the other hand, as in our previous reactions,[5,7] the oxidation of phenol **2a** using I_2 in the presence of Bu_4NOH proceeded to give spirolactone **3a**, suggesting that an I^+ species such as hypoiodite, $Bu_4N^+[IO]^-$, which would be under equilibrium with IOH and Bu_4NOH, could mediate the present oxidative dearomatization reactions (eq. 2). Interestingly, when I_2, which is an inert species itself, was used in the presence of Bu_4NHSO_4 as an additive, the reaction could proceed to give spirolactone **3a** (eq. 3). In contrast, no reaction was observed with $Bu_4N^+[I_3]^-$ in the presence of $KHSO_4$ (eq. 4). Additionally, the use of hexafluorophosphate (PF_6^-) as a weakly-coordinating counter anion instead of HSO_4^- gave no reaction (eq. 5). Moreover, several organic and inorganic acids such as H_2SO_4 (pKa –3.0),[13] phosphoric acid (pKa 2.2),[13] trifluoroacetic acid (pKa 0.5),[13] oxalic acid (pKa 1.3),[13] and acetic acid (pKa 4.8),[13] were examined as an additive instead of Bu_4NHSO_4 (pKa 2.0)[13] in the presence of I_2, however, no oxidation reaction proceeded at all, indicating that acidity alone might not be enough to generate reactive species (eq. 6).[14] On the other hand, oxidation of **2a** under catalytic conditions using 10 mol% of either $Bu_4N^+[I_3]^-$ or I_2 in the presence of Oxone afforded **3a** quantitatively (eqs. 7 and 8). These results suggested that highly reactive I^+ species such as hypoiodous acid[5] or sulfatyl hypoiodite, $[SO_4I]^-$,[20,21] might be generated from I_2 or $[I_3]^-$ in the presence of HSO_4^- (for I_2) or Oxone (for both I_2 and $[I_3]^-$). In contrast to the catalytic conditions, the low conversion of stoichiometric reactions with I_2 in the presence of Bu_4NHSO_4 or Bu_4NOH additives might be attributed to the generation of I_3^-, an inert species, from the fast reaction of I_2 or IOH species with I^-, which is generated as the reaction progresses (eqs. 2 and 3).[5b,22]

Scheme 4. Control Experiments to Probe Active Species



I_2 or Bu_4NI_3 or $NaIO_3$ or Bu_4NIO_4 (1), 24 h:	0%	(1)
I_2 (1) + Bu_4NOH (2), 24 h:	30%	(2)
I_2 (1) + Bu_4NHSO_4 (2), 24 h:	38%	(3)
Bu_4NI_3 (1) + $KHSO_4$ (2), 24 h:	0%	(4)
I_2 (1) + Bu_4NPF_6 (2), 24 h:	0%	(5)
I_2 (1) + acid additive* (2), 12 h:	0%	(6)
I_2 (0.1) + Oxone (0.6) + Bu_4NHSO_4 (0.1), 5 h:	>95%	(7)
Bu_4NI_3 (0.1) + Oxone (0.6), 5 h:	>95%	(8)

*acid: H_2SO_4, H_3PO_4, CF_3CO_2H, $(CO_2H)_2$, AcOH

Raman analysis of a mixture of $Bu_4N^+I^-$ and Oxone revealed the generation of only I_2, and neither $[I_3]^-$ nor high-valence species ($[IO_3]^-$ and $[IO_4]^-$) were detected even after prolonged reaction times (Figure 1). The generation of hypoiodite species (IOH or $[IO]^-$)[5b] could not be confirmed due to band-overlap with Oxone.[14] Additionally, no other I^+ species such as sulfatyl hypoiodite were detected, probably due to their instability under these conditions. In sharp contrast, in previous alkyl hydroperoxide systems, hypoiodite active species were easily converted to $[I_3]^-$, which would not be under equilibrium with active species under neutral or acidic conditions.[5b] Additionally, no iodine-based species were detected for the hydrogen peroxide system due to the rapid decomposition of oxidant catalyzed by a hypoiodite/iodide couple.[5c,d,11]

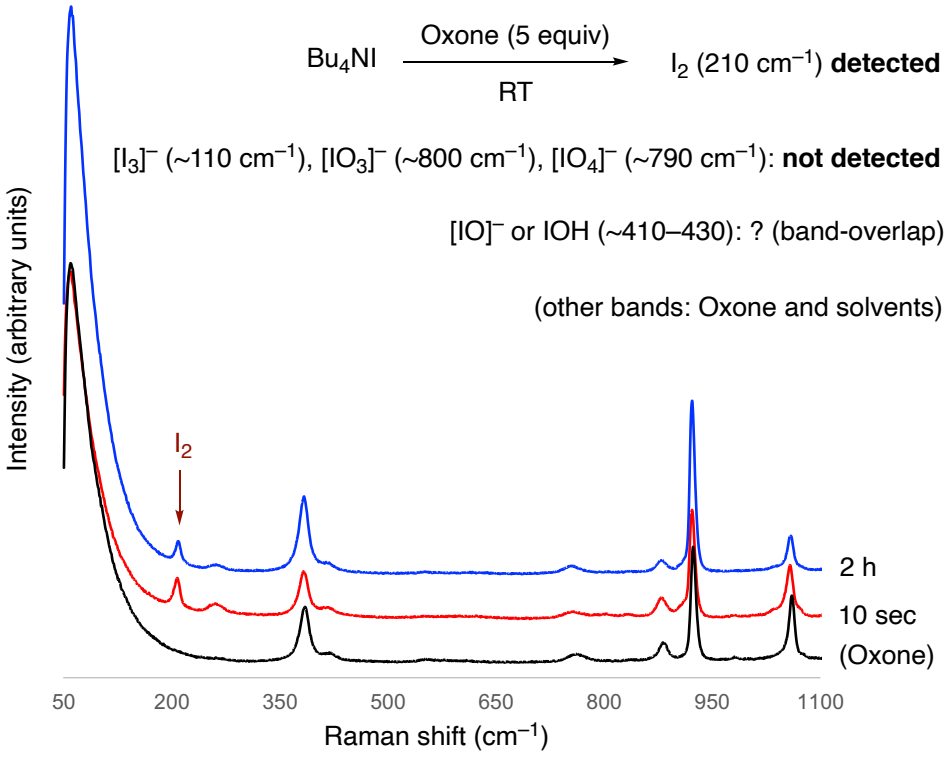
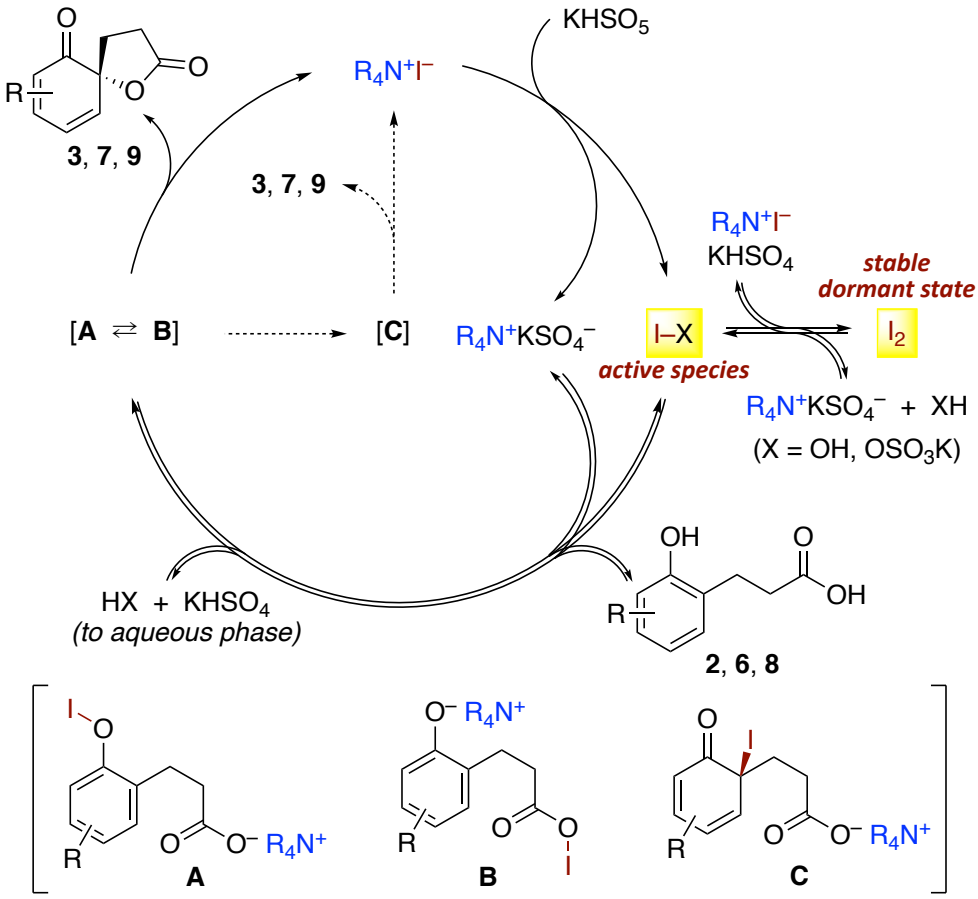


Figure 1. Raman analysis.

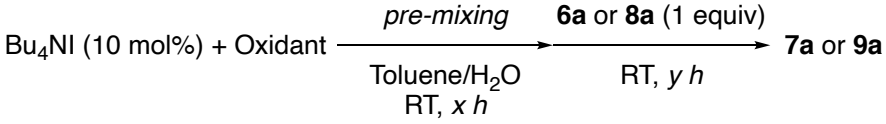
Based on these results and our previous findings,[5b,7] a plausible catalytic mechanism is depicted in Scheme 5. The oxidation of $R_4N^+I^-$ with Oxone ($KHSO_5$) would give an unstable I^+ catalytic active species such as IOH or $[SO_4I]^-$ that might be easily converted to I_2 in the absence of substrate under acidic conditions.[23] Most importantly, although I_2 itself was found to be an inert species, the active species might be under equilibrium with I_2 in the presence of ammonium bisulfate salt, suggesting that I_2 may be a stable dormant state of catalyst. Therefore, the superiority of the present hypoiodite/Oxone catalysis compared to previous H_2O_2 or ROOH systems may be explained by this stable state and the higher reactivity of catalysts under acidic conditions. Additionally, although $[I_3]^-$, another inert species, was not be detected under our catalytic conditions, if generated, $[I_3]^-$ might be also stable dormant species of I^+/Oxone catalysis (Scheme 4, eq. 8). A reversible reaction of I^+ species with arenols in the presence of ammonium bisulfate salt might give phenyl hypoiodite (**A**) or carboxyl hypoiodite (**B**) intermediates that would be under equilibrium. The enantioselective reductive elimination of quaternary ammonium iodide then might proceed from these intermediates through umpolung of phenol or carboxylate to give the corresponding spirolactones.[24] Alternatively, enantioselective dearomatizative *ortho*-iodination to intermediate **C** followed by intramolecular S_N2 cyclization might also be considered.

Scheme 5. Plausible Reaction Mechanism



To demonstrate the superiority of the present I^+/Oxone catalysis, the stability of the catalytic active species was investigated using 1- or 2-naphthols, which could be oxidized in both the Oxone and hydrogen peroxide systems, as a substrate (Table 5). As a result, the oxidation of 2-naphthol **6a** or 1 naphthol **8a** proceeded to give the corresponding **7a** or **9a** quantitatively even after 2~6 hours of premixing of $Bu_4N^+I^-$ and Oxone (entries 3–5 versus entries 1 and 2). In sharp contrast, no reaction or very low conversions were observed for hydrogen peroxide under identical conditions or acidic conditions even after a shorter premixing time (entries 8–11 versus entries 6 and 7). Additionally, while the oxidation of **8a** with Oxone even at lower catalyst loading (1 mol%) gave **9a** in high yield albeit after longer reaction time, a very low conversion was observed for hydrogen peroxide under similar conditions (entry 12 versus 13). These results strongly suggested that nonproductive decomposition of active species and/or oxidant might be suppressed in I^+/Oxone catalysis, which would be crucial to establish a high-performance catalysis.

Table 5. Comparison of the Stability of I^+ Catalysis

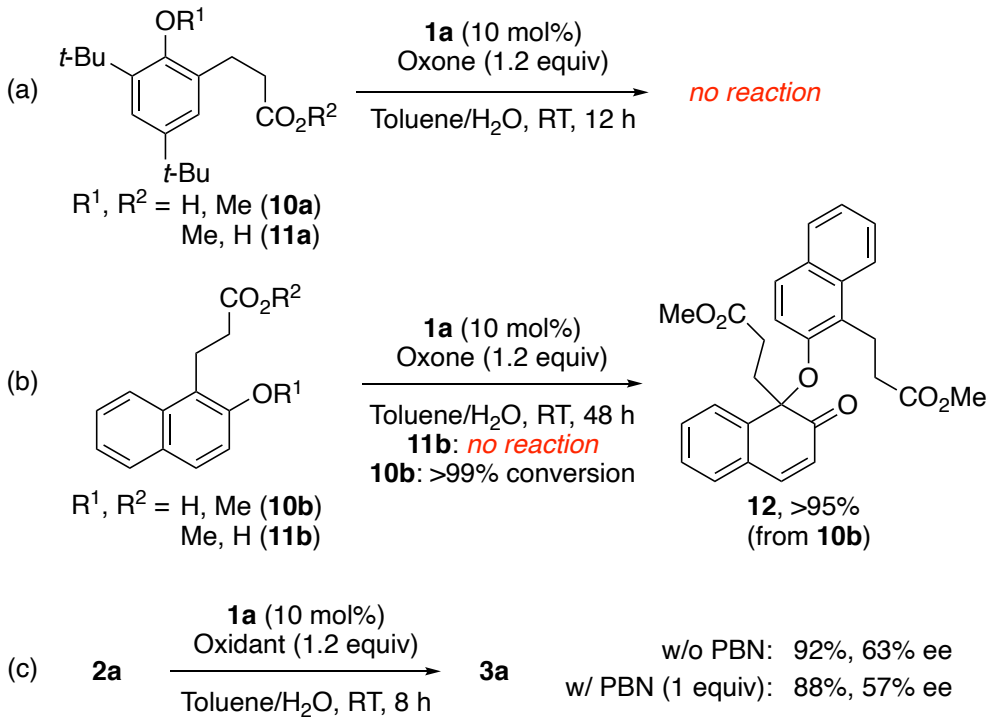


Entry	**6a** or **8a**	Oxidant (equiv)	*x*, *y* (h)	Yield (%)[a]
1	**6a**	Oxone (1.2)	0, 3	>95
2	**8a**	Oxone (1.2)	0, 2	>95
3	**6a**	Oxone (1.2)	2, 4	>95
4	**6a**	Oxone (1.2)	6, 18	>95
5	**8a**	Oxone (1.2)	2, 4.5	>95
6	**6a**	30% H_2O_2 (2)	0, 12	>95
7	**8a**	30% H_2O_2 (2)	0, 72	>95
8	**6a**	30% H_2O_2 (2)	2, 24	0
9[b]	**6a**	30% H_2O_2 (2)	2, 24	0
10	**6a**	30% H_2O_2 (2)	0.5, 24	19
11	**8a**	30% H_2O_2 (2)	2, 72	0
12[c]	**8a**	Oxone (0.6)	0, 22	81[d]
13[c]	**8a**	30% H_2O_2 (2)	0, 72	<10

[a] ^{1}H NMR analysis. [b] $KHSO_4$ (2 equiv) was added as an additive. [c] Bu_4NI (1 mol%) was used. [d] Intramolecular condensation byproduct lactone (10%) was also observed. For details, see Experimental Section.

Finally, to evaluate the roles of phenoxy and carboxyl groups of the substrates for the oxidative dearomatization reaction, methyl esters **10** and methyl ethers **11** were prepared and examined under the standard conditions (Schemes 6a and 6b). While no reactions were observed for either methyl ethers **11** or phenol-derived methyl ester **10a**, dearomatized dimer **12** was obtained quantitatively from the reaction of 2-naphthol-derived ester **10b**. No trace of spirolactones **3a** or **7a** was observed from these reactions, suggesting that both functional groups are needed for the oxidative spirolactonization reaction. The oxidative dimerization of 2-naphthol derivative **10b** suggested that spirolactonization might proceed via umpolung of phenol (intermediate **A**) rather than carboxylate (intermediate **B**). In contrast to **10b**, unreacted **10a** was fully recovered, perhaps due to the steric bulkiness of a *t*-Bu group. Since no *C*–iodinated intermediate or any of its decomposed products were observed, intermediate **C** might also be ruled out. Therefore, the generation of phenyl hypoiodite intermediate **A** might be most likely to produce cyclohexadienone spirolactones via enantioselective intramolecular S_N2' type cyclization of chiral ammonium carboxylate (Scheme 5). Additionally, the addition of *N-tert*-butyl-α-phenylnitrone (PBN) did not influence the yield or enantioselectivity in the oxidative spirolactonization of **2a**, suggesting that a free radical pathway might be unlikely (Scheme 6c).

Scheme 6. Control Experiments for Reaction Mechanism



Conclusion

In conclusion, we developed a high-performance ammonium hypoiodite catalysis for the enantioselective dearomatization reaction using Oxone as an environmentally benign oxidant. The oxidation of a wide variety of arenols including 1- and 2-naphthols and phenols could readily proceed under mild conditions in the presence of chiral quaternary ammonium iodide catalysts to afford the corresponding spirolactones with high enantioselectivity, and only inorganic wastes were generated derived from the oxidant used. Control experiments and Raman analysis revealed the *in situ* generation of unstable I^+ such as hypoiodous acid as an active species and molecular iodine (I_2) as a stable dormant state of catalyst. The generation of I_2 under acidic conditions might play a crucial role in suppressing the undesired decomposition or deactivation pathways that were important issues in the previous hydrogen peroxide or alkyl hydroperoxide systems.

Experimental Section

Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 (400 MHz) and Bruker AVANCE III HD (300 and 500 MHz) spectrometers at ambient temperature. Chemical shifts are reported in ppm from the solvent resonance (DMSO-*d*$_6$: 2.50 ppm, CD_3CN: 1.94 ppm) or Me_4Si resonance (0.00 ppm; $CDCl_3$) as internal standard. 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; quin = quintet; sept = septet; m = multiplet; brs = broad singlet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz) spectrometer and Bruker AVANCE III HD (75 and 125 MHz) spectrometer at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$: 77.00 ppm, CD_3CN: 1.32 ppm, DMSO-*d*$_6$: 39.52 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University [JEOL JMS-700 (FAB) or Bruker Daltonics micro TOF-QII (ESI)]. 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 OD–H (4.6 mm x 25 cm), OD–3 (4.6 mm x 25 cm), AD–3 (4.6 mm x 25 cm), IA–3 (4.6 mm x 25 cm), IC–3 (4.6 mm x 25 cm), and OH–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. X-ray analysis was performed by Rigaku PILATUS-200K. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm or silica gel 60 NH_2 F_{254}s 0.20 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385).

In experiments that required dry solvents, diethyl ether (Et_2O), tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF) and dichloromethane (CH_2Cl_2), were purchased from FUJIFILM Wako Pure Chemical Industries, Ltd. as the "anhydrous" and stored over 4Å molecular sieves. Other solvents were purchased from Aldrich Chemical Co., Inc., FUJIFILM Wako Pure Chemical Industries, Ltd. or Tokyo Chemical Industry Co., Ltd. and used without further purification. Tetrabutylammonium iodide (Bu_4NI), tetrabutylammonium triiodide (Bu_4NI_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 and 70% aqueous *tert*-butyl hydroperoxide (TBHP) were purchased from FUJIFILM Wako Pure Chemical

Industries, Ltd. Oxone and anhydrous TBHP (5.5 *M* nonane solution) 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.

Optimization of Reaction Conditions and Additional Control Experiments

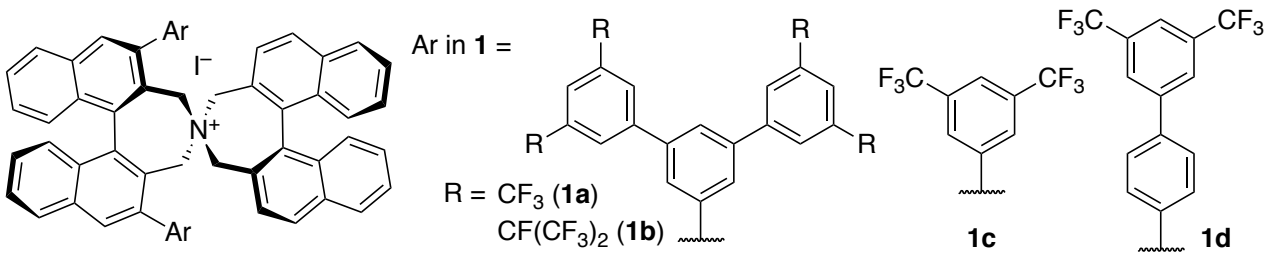
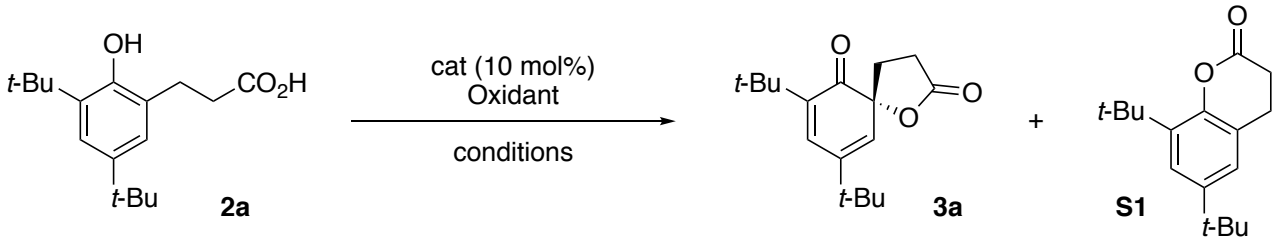


Table S1. Enantioselective Oxidative Dearomatization of Phenol 2a

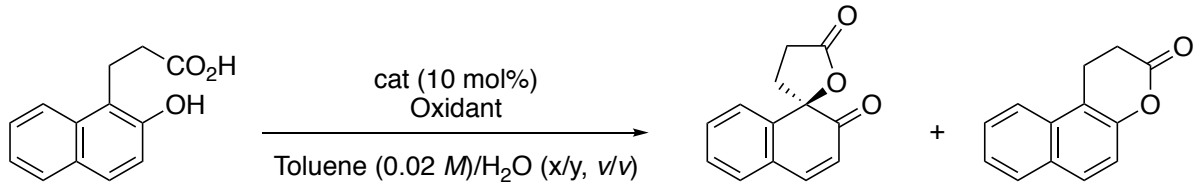


entry	cat	oxidant (equiv.)	solvent[a]	*T* (°C)	*t* (h)	**3a** (**S1**) yield (%)[b]	**3a** ee (%)
1	**1a**	30% H_2O_2 (2)	Toluene/H_2O (10/1)	25	24	<1 (<1)	–
2	**1a**	30% H_2O_2 (2) + H_2SO_4 (5)	Toluene/H_2O (10/1)	25	24	<1 (<1)	–
3	**1a**	30% H_2O_2 (2) + $KHSO_4$ (2)	Toluene/H_2O (10/1)	25	24	<1 (<1)	–
4	**1a**	TBHP (2)	Toluene	25	24	<1 (<1)	–
5	**1a**	TBHP (2) + $KHSO_4$ (2)	Toluene/H_2O (10/1)	25	24	<1 (<1)	–
6	**1a**	$Na_2CO_3 \cdot 1.5H_2O_2$ (2)	Toluene/H_2O (10/1)	25	24	<1 (<1)	–
7	**1a**	$NaBO_3 \cdot 4H_2O$ (2)	Toluene/H_2O (10/1)	25	5	7 (<5)	–
8	**1a**	*m*-CPBA (1.2)	Toluene	25	5	52[c] (13)[d]	43
9	**1a**	9% AcOOH (2)	Toluene	25	2	88[c] (<5)	50
10	**1a**	Oxone (3)	Toluene/H_2O (10/1)	25	5	89[c] (<5)	59
11	**1a**	Oxone (3)	Toluene/H_2O (2/1)	25	22	52[c] (30)	–
12	**1a**	Oxone (3)	Toluene	25	24	<5 (<5)	–
13	**1a**	Oxone (3)	*t*-BuOMe/H_2O (10/1)	25	24	<5 (<5)	–
14	**1a**	Oxone (3)	CH_3NO_2/H_2O (10/1)	25	5	20 (<5)	0
15	**1a**	Oxone (3)	$CO(OMe)_2$/H_2O (10/1)	25	6	10 (<1)	0
16	**1a**	Oxone (3)	CH_2Cl_2/H_2O (10/1)	25	6	40[c] (<5)	0
17	**1a**	Oxone (1.2)	Toluene/H_2O (10/1)	25	8	92[c] (<5)	63
18	**1a**	Oxone (1.2) + TsOH (0.1)	Toluene/H_2O (10/1)	25	24	37[c] (10)	59
19	**1a**	Oxone (1.2) + $KHSO_4$ (0.9)	Toluene/H_2O (10/1)	25	6	95 (<5)	63
20	**1a**	Oxone (1.2) + K_2CO_3 (1)	Toluene/H_2O (10/1)	25	72	90 (<1)	29
21	**1a**	Oxone (1.2)	Toluene/H_2O (10/1)	0	25	98[c] (<1)	71
22	**1a**	Oxone (1.2)	Toluene/H_2O (100/1)	0	24	29[c] (<1)	67
23	**1b**	Oxone (1.2)	Toluene/H_2O (10/1)	0	24	20[c] (<1)	80
24	**1b**	Oxone (1.2)	Toluene/H_2O (100/1)	0	24	24[c] (<1)	80

25	**1b**	Oxone (1.2+1.2[e])	Toluene/H_2O (10/1)	0	72	94[c] (<1)	75
26	**1b**	Oxone (1.2)	Toluene[f]/H_2O (2/1)	0	24	80[c] (<1)	73
27	–[g]	Oxone (1.2)	Toluene/H_2O (10/1)	25	48	<1 (26)	–

[a] Organic solvent (0.02 *M*)/H_2O (*v*/*v*). [b] Isolated yield. [c] ^{1}H NMR analysis of crude. <5%: Detectable amount of the compound observed by ^{1}H NMR analysis. <1%: Not detected by ^{1}H NMR analysis but detected by TLC analysis. [d] Several unknown byproducts were also detected. [e] Oxone (0.6 equiv.) was added after 24 h. [f] Toluene (0.1 *M*). [g] Bu_4NHSO_4 (10 mol%) was used as a phase transfer catalyst.

Table S2. Enantioselective Oxidative Dearomatization of 2-Naphthol 6a

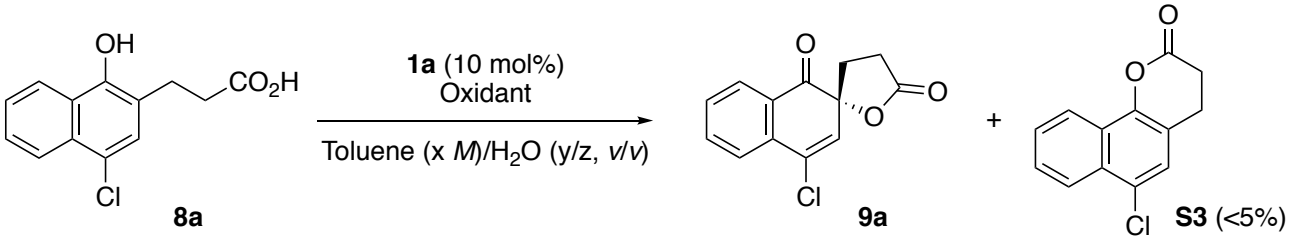


6a **7a** **S2** (<5%)

entry	cat	oxidant (equiv.)	x/y	*T* (°C)	*t* (h)	**7a**, yield (%)[a]	**7a**, ee (%)
1	**1a**	30% H_2O_2 (2)	10/1	25	24	87	28
2	**1a**	30% H_2O_2 (2) + $KHSO_4$ (2)	10/1	25	24	4	62
3	**1a**	TBHP (2)	2/1[b]	25	24	23	38
4	**1a**	TBHP (2) + $KHSO_4$ (2)	2/1[b]	25	24	14	57
5	**1a**	Oxone (1.2)	10/1	25	3	88	62
6	**1a**	Oxone (1.2)	10/1	0	10	85	78
7	**1b**	Oxone (1.2)	10/1	0	24	91	87
8	**1c**	Oxone (1.2)	10/1	0	24	89	53
9	**1d**	Oxone (1.2)	10/1	0	48	49	20
10	**1b**	Oxone (1.2)	2/1	0	24	90	75
11	**1b**	Oxone (1.2)	50/1	0	24	85	93
12	**1b**	Oxone (1.2)	100/1	0	24	98	94
13	**1b**	Oxone (1.2)	1/0	0	24	<5	–
14	KI	Oxone (1.2)	0/1[c]	25	11	68[d]	–

[a] Isolated yield. [b] In Toluene (0.1 *M*)/H_2O (2/1, *v*/*v*). [c] In H_2O (0.2 *M*). [d] **S2** was obtained in 9% yield.

Table S3. Enantioselective Oxidative Dearomatization of 1-Naphthol 8a



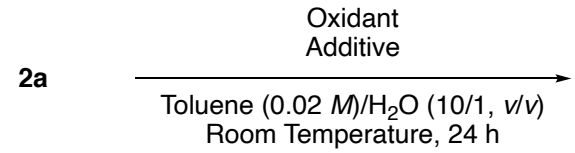
8a **9a** **S3** (<5%)

entry	oxidant (equiv)	x (*M*)	x/y	*T* (°C)	*t* (h)	**9a**, yield (%)[a]	**9a**, ee (%)
1[b]	30% H_2O_2 (2)	0.1	2/1	20	72	84	88
2	Oxone (1.2)	0.1	2/1	25	5	95	81

3	Oxone (1.2)	0.1	20/1	25	4.5	95[c]	88
4	Oxone (1.2)	0.1	20/1	0	20	95[c]	91
5[d]	Oxone (1.2)	0.1	20/1	0	27	97	91
6	Oxone (1.2)	0.02	100/1	25	6	88	81
7	Oxone (1.2)	0.02	100/1	0	48	73	90
8	Oxone (1.2)	0.02	10/1	25	6	88	77
9	Oxone (1.2)	0.02	1/0	25	24	<5	–
10	Oxone (1.2)	0.2	0/1	25	18	59	0

[a] Isolated yield. [b] Data from: Uyanik, M. *et al. Chem. Lett.* **2015**, *44*, 179–181. [c] ^{1}H NMR analysis of crude. [d] **1a** (5 mol%).

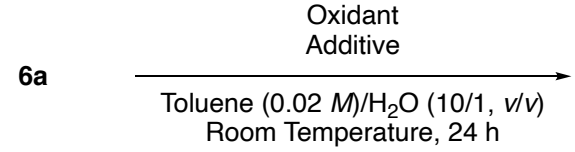
Table S4. Control Experiments to Probe Active Species Using Phenol 2a



entry	oxidant (equiv)	additive (equiv)	**3a**, yield (%)[a]	**S1**, yield (%)[a]
1	I_2 (1)	–	0	0
2	Bu_4NI_3 (1)	–	0	<5
3	$NaIO_3$ (1)	–	0	<5
4	Bu_4NIO_4 (1)	–	0	<5
5	I_2 (1)	40% Bu_4NOH aq. (2)	30	<5
6	I_2 (1)	$KHSO_4$ (2)	0	18
7	I_2 (1)	Bu_4NHSO_4 (2)	38	4
8	Bu_4NI_3 (1)	$KHSO_4$ (2)	0	<5
9	I_2 (1)	Bu_4NPF_6 (2)	0	<5
10[b]	I_2 (1)	H_2SO_4 (2)	0	84
11[b]	I_2 (1)	H_2PO_4 (2)	0	11
12[b]	I_2 (1)	CF_3CO_2H (2)	0	70
13[b]	I_2 (1)	$(CO_2H)_2$ (2)	0	<5
14[b]	I_2 (1)	AcOH (2)	0	<5
15[c,d]	I_2 (0.1) / Oxone (1.2)	Bu_4NHSO_4 (0.1)	>95	<5
16[c,d]	Bu_4NI_3 (0.1) / Oxone (1.2)	–	>95	<5

[a] ^{1}H NMR analysis of crude. [b] Reaction time was 12 h. [c] Reaction time was 5 h. [d] In toluene (0.2 *M*)/H_2O (1/1, *v*/*v*).

Table S5. Control Experiments to Probe Active Species Using 2-Naphthol 6a



entry	oxidant (equiv)	additive (equiv)	**7a**, yield (%)[a]	**S2**, yield (%)[a]

1	I_2 (1)	–	0	23
2	Bu_4NI_3 (1)	–	0	18
3[b,c]	$NaIO_3$ (1)	–	95	0
4[b,c]	Bu_4NIO_4 (1)	–	95	0
5	I_2 (1)	40% Bu_4NOH aq. (2)	46	<5
6	I_2 (1)	$KHSO_4$ (2)	0	37
7	I_2 (1)	Bu_4NHSO_4 (2)	35	20

[a] ^{1}H NMR analysis of crude. [b] Reaction time was less than 10 h. [c] Oxidative dearomatization of 1-naphthol **8a** was also proceeded with $NaIO_3$ or Bu_4NIO_4.

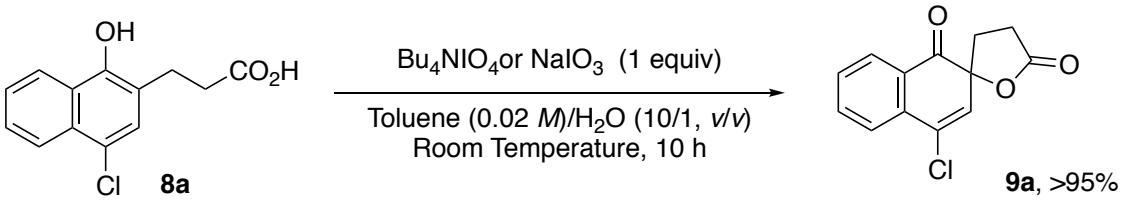
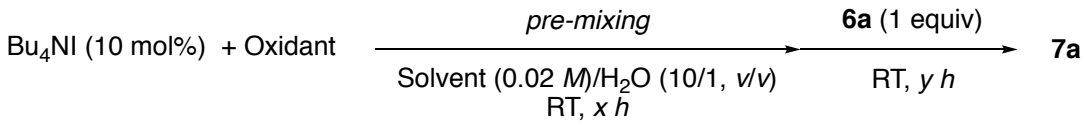


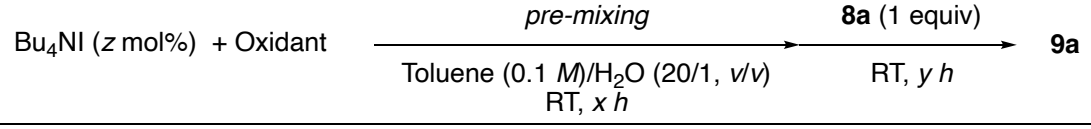
Table S6. Comparison of the Stability of I^+ Catalysis using 2-Naphthol 6a



entry	oxidant (equiv)	organic solvent	pre-mix. time *x* (h)	react. time *y* (h)	**7a**, yield (%)[a]
1	Oxone (1.2)	Toluene	0	3	>95
2	Oxone (1.2)	Toluene	2	4	>95
3	Oxone (1.2)	Toluene	6	18	>95
4	Oxone (1.2)	CH_3CN	0	12	>95
5	Oxone (1.2)	CH_3CN	3	16	77
6	30% H_2O_2 (2)	Toluene	0	12	>95
7	30% H_2O_2 (2)	Toluene	2	24	0
8[b]	30% H_2O_2 (2)	Toluene	2	24	0
9	30% H_2O_2 (2)	Toluene	0.5	24	18

[a] ^{1}H NMR analysis of crude. [b] $KHSO_4$ (2 equiv) was added as an additive.

Table S7. Comparison of the Stability of I^+ Catalysis using 2-Naphthol 8a



entry	Bu_4NI (mol%)	oxidant (equiv)	pre-mix. time *x* (h)	react. time *y* (h)	**9a**, yield (%)[a]
1	10	Oxone (1.2)	0	2	>95
2	10	Oxone (1.2)	2	4.5	>95
3	10	30% H_2O_2 (2)	0	72	>95
4	10	30% H_2O_2 (2)	2	72	0

5[b]	1	Oxone (1.2)	0	22	81[c]
6[b]	1	30% H_2O_2 (2)	0	72	<10

[a] ^{1}H NMR analysis of crude. [b] In toluene (0.5 *M*)/H_2O (10/1, *v*/*v*). [c] Intramolecular condensation byproduct lactone (10%) was also observed.

Raman Analysis

Raman spectra were recorded using JASCO Raman system NRS–1000 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 10 mW. The laser beam was focused on a point in the reaction mixture in the glass capillary.

The Raman measurements in toluene or toluene/water biphasic solvents were failed due to band-overlap with solvent and low solubility of reagents used. On the other hand, the experiments were successfully performed in aqueous acetonitrile. Notably, the oxidative dearomatization reaction could proceed in aqueous acetonitrile (Table S6, entries 4 and 5).

To a solution of tetrabutylammonium iodide (0.0369 mg, 0.100 mmol) in acetonitrile (0.100 mL) and water (0.100 mL) in 5-mL volume of test vial was added Oxone (0.307 g, 0.500 mmol) at 25 °C. After stirring for 10 seconds, the reaction mixture was then drawn into the glass capillary and the Raman spectra were measured (Fig. S1, spectrum **l**). A band at 210 cm^{-1} was assigned to I_2 based on our measurements (spectrum **d**) and literature.[26] The other bands were attributed to the solvents and reagents used (see spectrum **a**–**c**). The generation of hypoiodous acid (IOH) or hypoiodite ($[IO]^-$) species could not be confirmed due to band-overlap with Oxone (~410–430 cm^{-1}. For IOH and $[IO]^-$, see spectrum **j** and **k**[1,2]). After additional stirring for 2 h, the reaction mixture was drawn into the glass capillary and the Raman spectra were measured (Fig. S1, spectrum **m**). The band of I_2 was still remained and no other bands such as $[I_3]^-$, $[IO_3]^-$ and $[IO_4]^-$ were detected (see spectrum **e**–**i**).

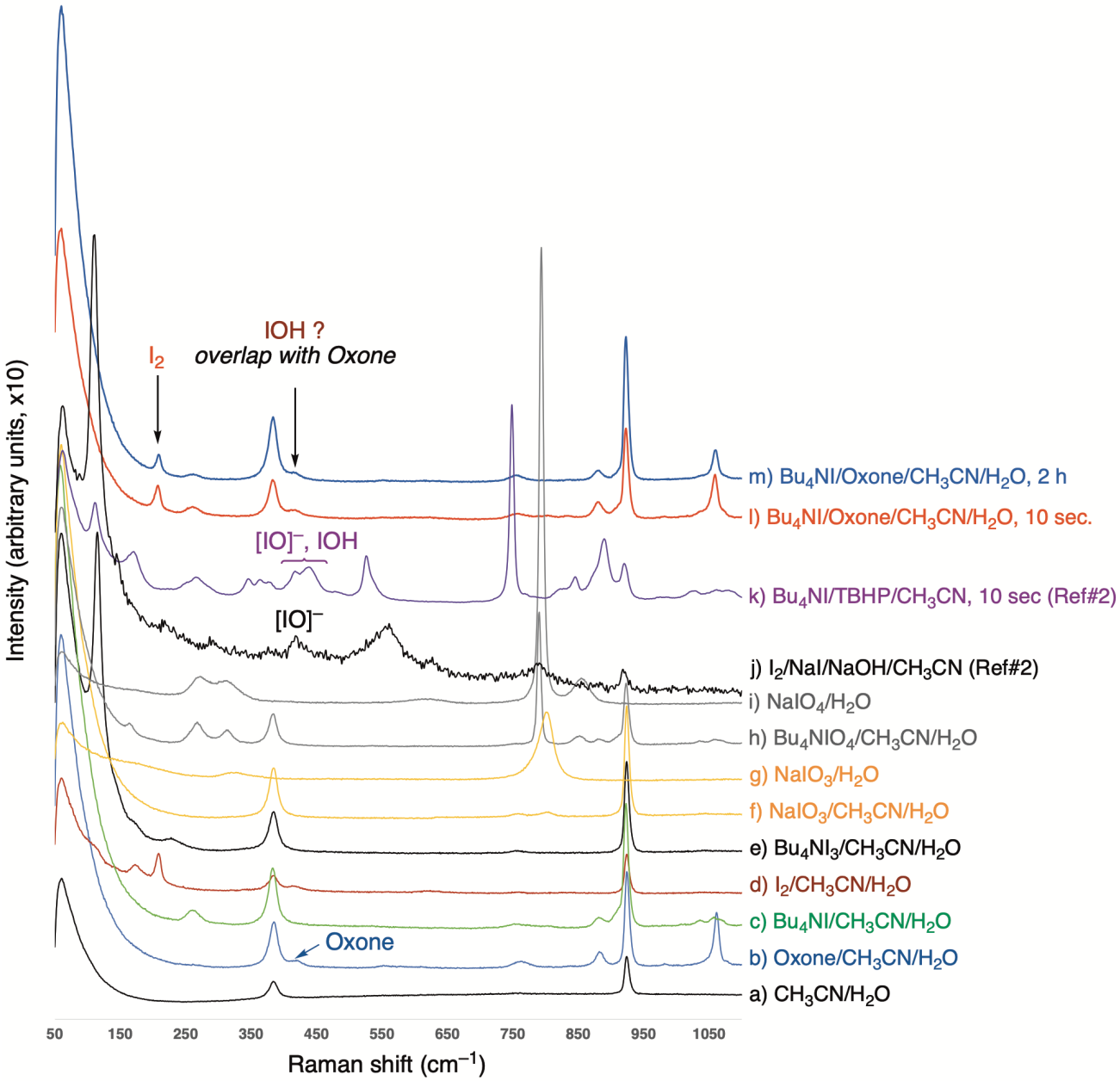


Figure S1. Raman spectra of the solution of Bu_4NI (0.5 M) and Oxone (2.5 M) in CH_3CN/H_2O (**l** and **m**). Raman spectra of authentic samples. **a**: CH_3CN/H_2O; **b**: Oxone in CH_3CN/H_2O); **c**: Bu_4NI in CH_3CN/H_2O; **d**: I_2 in CH_3CN/H_2O; **e**: Bu_4NI_3 in CH_3CN/H_2O; **f**: $NaIO_3$ in CH_3CN/H_2O; **g**: $NaIO_3$ in H_2O; **h**: Bu_4NIO_4 in CH_3CN/H_2O; **i**: $NaIO_4$ in H_2O; **j**: I_2, NaI, 10 *M* NaOH in CH_3CN (for $[IO]^-$)[27]; **k**: Bu_4NI, TBHP in CH_3CN, 10 sec. (for $[IO]^-$ and IOH)[27].

Color of Reaction Mixture

To ascertain whether the similar species are generated from the oxidation of iodide with Oxone in the presence of substrate, we also compared the color of the reaction mixtures (Fig. S2). As a result, I_2 might be main species generated in the presence of phenol **2a** (Fig. S2i). Additionally, we also confirmed the generation of I_2 from $[I_3]^-$ in the presence of Oxone (Fig. S2k), which is consisted well with the control experiment (Table S4, entry 16).

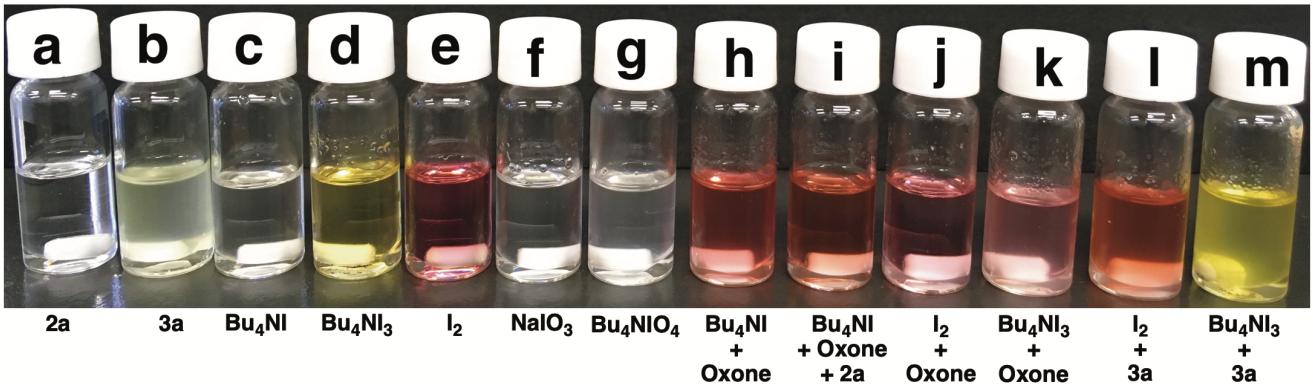
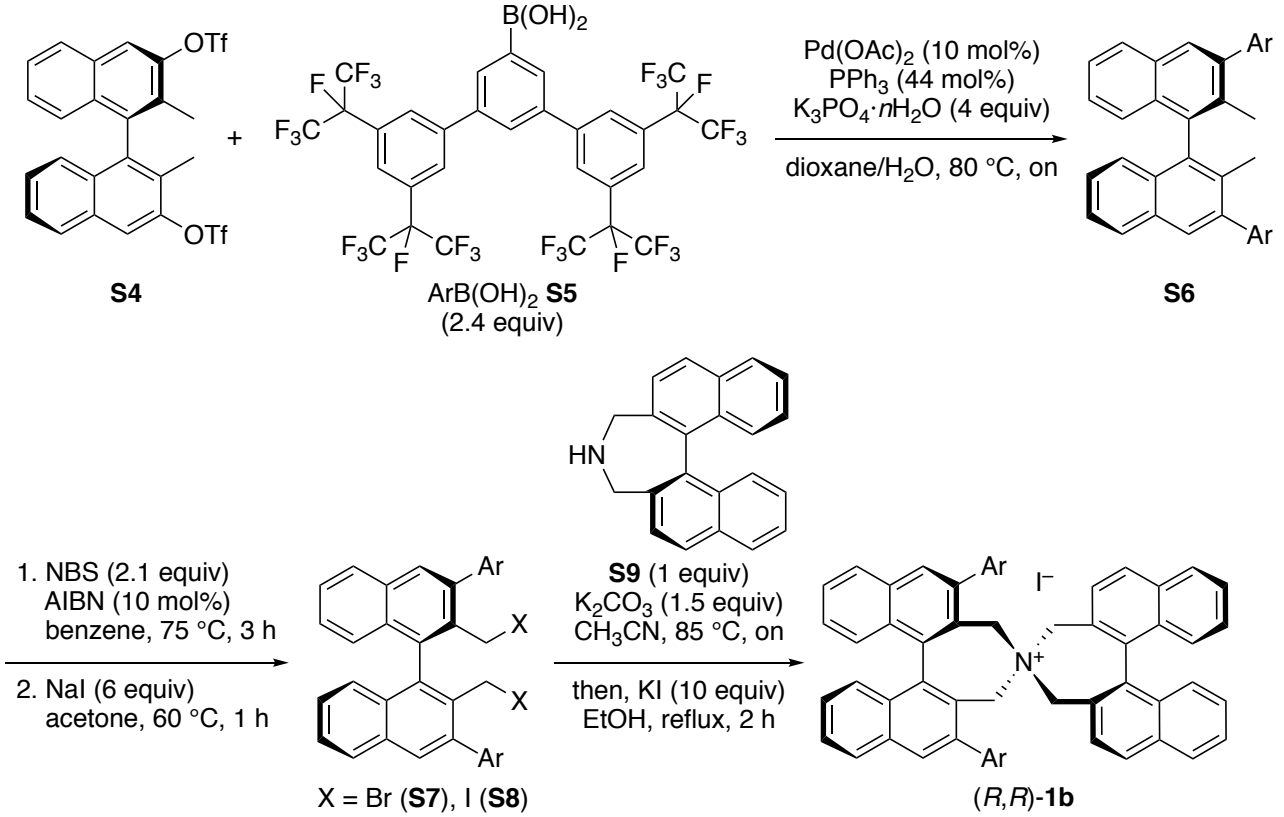


Figure S2. Color of the reaction mixture (**i**) and authentic samples (**a**–**h** and **j**–**m**). All samples were prepared in toluene (2.5 mL) and H_2O (0.25 mL) at room temperature. **a**: **2a** (0.05 mmol); **b**: **3a** (0.05 mmol); **c**: Bu_4NI (0.005 mmol); **d**: Bu_4NI_3 (0.0017 mmol); **e**: I_2 (0.0025 mmol); **f**: $NaIO_3$ (0.005 mmol); **g**: Bu_4NIO_4 (0.005 mmol); **h**: Bu_4NI (0.005 mmol), Oxone (0.03 mmol); **i**: Bu_4NI (0.005 mmol), Oxone (0.03 mmol), **2a** (0.05 mmol); **j**: I_2 (0.0025 mmol), Oxone (0.03 mmol); **k**: Bu_4NI_3 (0.0017 mmol), Oxone (0.03 mmol); **l**: I_2 (0.0025 mmol), **3a** (0.05 mmol); **m**: Bu_4NI_3 (0.0017 mmol), **3a** (0.05 mmol).

Synthesis and Characterization of Catalysts 1

1a[5] and **1c**,[5] and **1d**[5] were known compounds. **1b** was synthesized following the literature procedures.[5]



(*R*,*R*)-1b: To a solution of **S4**[27] (0.289 g, 0.500 mmol), **S5**[28] (1.14 g, 1.20 mmol) and K_3PO_4 (425 mg, 2.00 mmol) in degassed dioxane (5.00 mL) and H_2O (1.00 mL) were added $Pd(OAc)_2$ (11.0 mg, 0.0500 mmol) and PPh_3 (58.0 mg, 0.220 mmol) at 25 °C. After stirring overnight at 80 °C, the resulting mixture was filtered and washed with EtOAc (twice). The combined filtrates 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 **S6** (0.875 g, 0.420 mmol, 84% yield) as a white solid.

To a solution of **S6** (0.937 g, 0.450 mmol) and NBS (0.169 g, 0.950 mmol) in benzene (5.00 mL) was added AIBN (7.40 mg, 0.0450 mmol) at 25 °C. After stirring for 3 h at 75 °C, the resulting mixture was cooled to 25 °C, poured into water and extracted with Et_2O (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 **S7** (0.817 g, 0.364 mmol, 81% yield) as a yellow solid.

To a solution of **S7** (0.817 g, 0.364 mmol) in acetone (7.28 mL) was added NaI (0.327 g, 2.18 mmol) at 25 °C. After stirring for 2 h at 60 °C, the resulting mixture was cooled to 25 °C and the

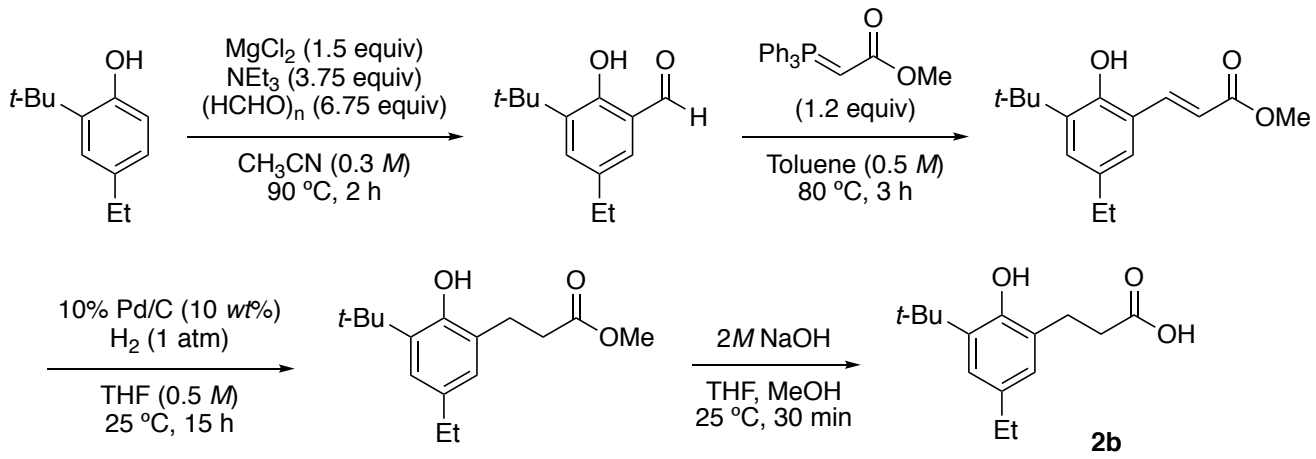
solvents were removed *in vacuo*. The resulting mixture was poured into water and extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, then the solvents were removed *in vacuo* to give **S8** (0.849 g, 0.364 mmol) as a yellow solid.

Without further purification, to a solution of **S8** (0.849 g, 0.364 mmol) and **S9**[4] (0.108 g, 0.364 mmol) in CH_3CN (7.28 mL) was added K_2CO_3 (0.0755 g, 0.546 mmol) at 25 °C. After stirring overnight at 85 °C, the resulting mixture was cooled to 25 °C, poured into water and extracted with CH_2Cl_2 (twice). The combined organic layers were washed with water and dried over anhydrous Na_2SO_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 **1b** (0.620 g, 0.248 mmol, 68% yield) as a brown solid.

To a solution of **1b** (0.751 g, 0.300 mmol) in EtOH (6.00 mL) was added KI (0.498 g, 3.00 mmol) at 25 °C. After stirring for 2 h at 90 °C, 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_2SO_4, then the solvents were removed *in vacuo*. The crude solid was re-precipitated in CH_2Cl_2/hexane to give **1b** (0.413 g, 0.165 mmol, 55% yield) as pale-yellow solid. **TLC**, R_f = 0.25 (hexane–EtOAc =1:1); **IR** (KBr) 3117, 1594, 1280, 1231, 985 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 3.64 (d, *J* = 10.4 Hz, 2H), 4.66 (d, *J* = 13.5 2H), 4.74 (d, *J* = 13.0 Hz, 2H), 4.91 (d, *J* = 13.5 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.18–7.21 (m, 2H), 7.24–7.30 (m, 4H), 7.40–7.43 (m, 2H), 7.47–7.53 (m, 4H), 7.69 (t, *J* = 7.5 Hz, 2H), 7.76–7.78 (m, 4H), 7.79–7.85 (m, 4H), 7.95 (s, 2H), 8.03 (brs, 2H), 8.20 (d, *J* = 8.0 Hz, 2H), 8.41 (brs, 4H), 8.49 (s, 2H), 8.85 (brs, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 57.7, 62.9, 89.9–90.6 (m), 91.5–92.3 (m), 116.8–117.0 (m), 118.8-119.3 (m), 121.1–121.9 (m), 122.7–123.9 (m), 124.7, 126.5, 127.2–128.1 (m), 128.8–129.9 (m), 130.6, 131.1 131.8, 133.8–134.2 (m), 136.9, 137.4, 139.7, 141.4, 142.2–142.4 (m); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ –75.5, –75.2, –75.1, –75.0; **HRMS** (ESI) m/z calcd for $[C_{104}H_{48}F_{56}N]^+$ 2375.2887, found 2375.2884; **$[\alpha]^{28.9}_D$** = 15.6 (*c* 1.0, $CHCl_3$).

Synthesis and Characterization of Substrates 2, 6, 8, 10 and 11

Phenols **2a**[5] and **2g**[5], 2-naphthols **6**[5], and 1-naphthols **8**[5] were known compounds and prepared by following the literature procedures.



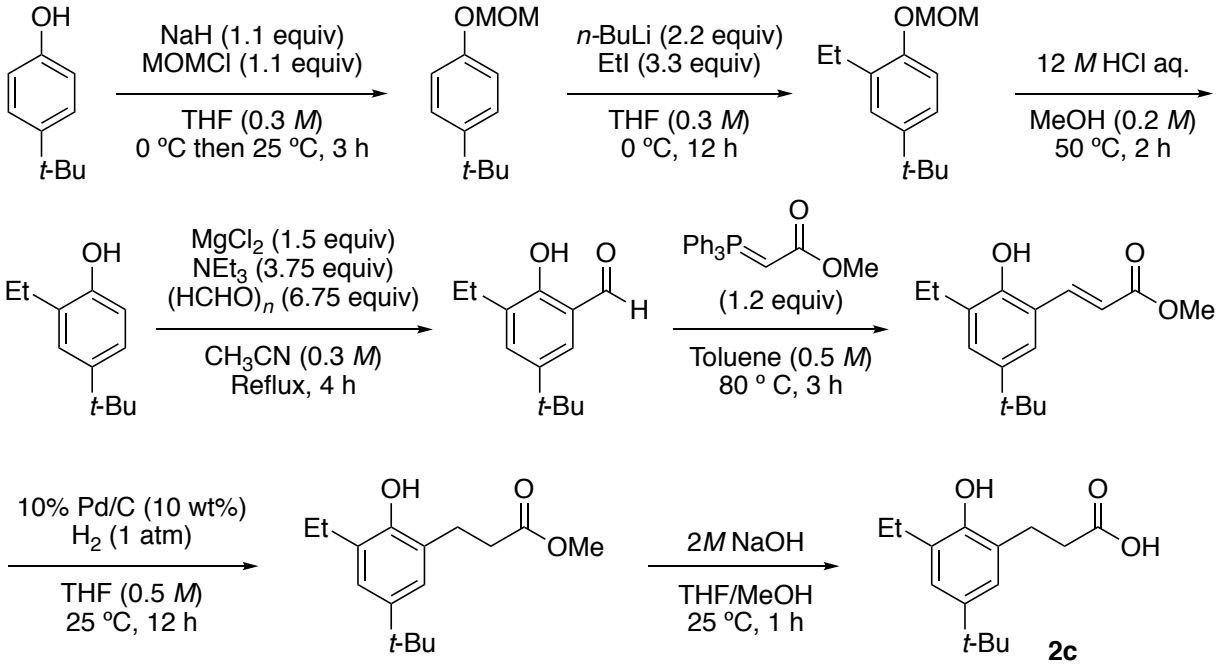
3-(3-(*tert*-Butyl)-5-ethyl-2-hydroxyphenyl)propanoic acid (2b): To a solution of $MgCl_2$ (1.43 g, 15.0 mmol) and NEt_3 (5.22 mL, 37.5 mmol) in CH_3CN (50.0 mL) were added 2-(*tert*-butyl)-4-ethylphenol (1.78 g, 10.0 mmol) and dry paraformaldehyde (2.03 g, 67.5 mmol) at 25 ºC under a nitrogen atmosphere. The mixture was refluxed at 90 °C for 2 h. The reaction mixture was cooled to 25 °C, and poured into 1*M* HCl, and the aqueous layers were extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1) to give 3-(*tert*-butyl)-5-ethyl-2-hydroxybenzaldehyde (1.55 g, 7.50 mmol, 75% yield) as a yellow liquid.

To a solution of this aldehyde in toluene (15.0 mL) was added methyl(triphenylphosphoranylidene)acetate (3.01 g, 9.01 mmol) at 25 ºC under a nitrogen atmosphere. After stirring for 3 h at 80 ºC, the resulting mixture was cooled to 25 ºC and diluted with water and EtOAc. The aqueous layers were separated and extracted with EtOAc (twice). The combined organic layers were washed with water 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 methyl (*E*)-3-(3-(*tert*-butyl)-5-ethyl-2-hydroxyphenyl)acrylate (1.48 g, 5.65 mmol, 75% yield) as a white solid.

To a solution of this olefin in THF (11.3 mL) was added 10% Pd/C (0.148 g) under a nitrogen atmosphere. The flask containing the mixture was then evacuated and purged with H_2 three times. In an H_2 gas environment, the resulting mixture was stirred at 25 ºC for 15 h. Upon the completion of the reaction, the mixture was filtered through celite with EtOAc and the crude product was obtained after removal of the solvent *in vacuo*.

Without further purification, to a solution of this methyl ester in THF (10.0 mL) and MeOH (10.0 mL) was added 2 *M* NaOH (10.0 mL) and the resulting mixture was stirred at 25 ºC for 30 min. Then, the resulting mixture was poured into 1 *M* HCl, extracted with EtOAc (twice) and washed with

brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*. The residue was purified by recrystallization from $CHCl_3$ to give **2b** (0.440 g, 1.70 mmol, 30% yield) as white solid. **TLC**, R_f = 0.45 (hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3430, 1686, 1427, 1227, 871 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.20 (t, *J* = 7.3 Hz, 2H), 1.40 (s, 9H), 2.55 (q, *J* = 7.3 Hz, 2H), 2.79–2.82 (m, 2H), 2.85–2.89 (m, 2H), 6.70 (brs, 1H), 6.80 (d, *J* = 2.3 Hz, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 9.75 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.8, 24.1, 28.3, 29.8, 34.6, 35.1, 125.0, 127.1, 127.4, 135.8, 137.5, 150.5, 181.2; **HRMS** (FAB+) *m*/*z* calcd for [$C_{15}H_{22}O_3$] 250.1569, found 250.1574.

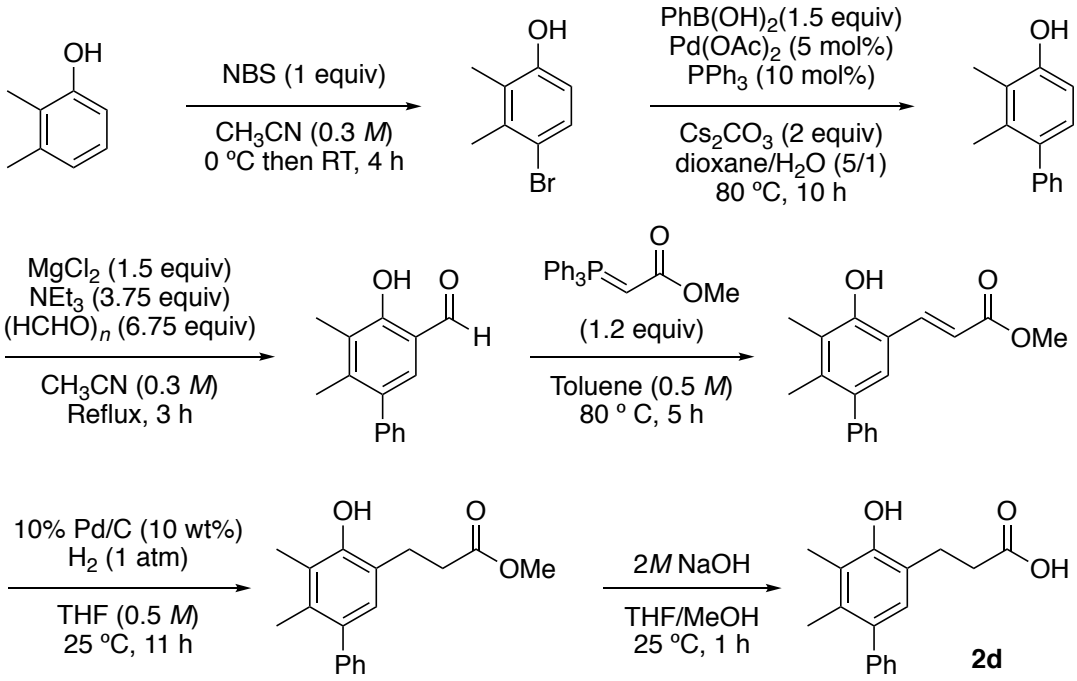


3-(5-(*tert*-Butyl)-3-ethyl-2-hydroxyphenyl)propanoic acid (2c): To a solution of sodium hydride (60-wt%, 0.880 g, 22.0 mmol) in THF (66.0 mL) was added 4-(*tert*-butyl)phenol (3.00 g, 20.0 mmol) at 0 ºC under a nitrogen atmosphere. The reaction mixture was allowed to warm to 25 ºC. After stirring for 30 min, the resulting mixture was re-cooled to 0 ºC and to the mixture was added chloromethyl methyl ether (1.67 mL, 22.0 mmol). The resulting mixture was allowed to warm to 25 ºC again. After stirring for 3 h, the resulting mixture was poured into H_2O, and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to give 1-(*tert*-butyl)-4-(methoxymethoxy)benzene.

Without further purification, to a solution of this MOM ether in THF (66.7 mL) was added *n*-BuLi (27.5 mL, 44.0 mmol, 1.60 *M* in hexane) at 0 ºC. After stirring for 1 h at 0 °C, to the resulting mixture was added iodoethane (5.30 mL, 66.0 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 ºC. After stirring for 12 h, the resulting mixture was quenched with saturated aqueous

NH_4Cl and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to give 4-(*tert*-butyl)-2-ethyl-1-(methoxymethoxy)benzene.

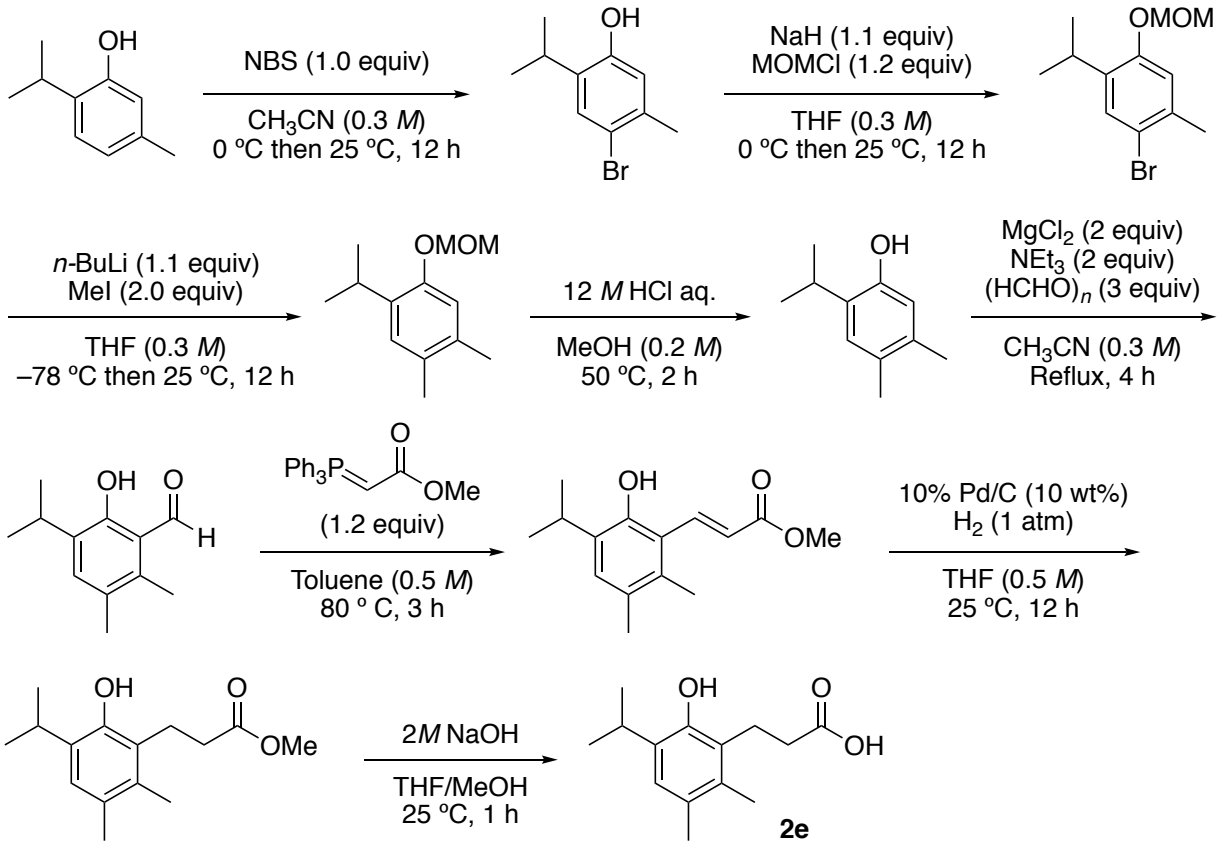
Without further purification, to a solution of this compound (0.509 g, 2.30 mmol) in MeOH (11.5 mL) was added *conc.* HCl aq. (ca. 0.100 mL). The reaction mixture was allowed to warm to 50 ºC. After stirring for 2 h, the reaction mixture was cooled to room temperature, and to the mixture was added water (20.0 mL) and the aqueous layers were 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 4-(*tert*-butyl)-2-ethylphenol. **2c** was synthesized from this compound as in **2b** in 39% yield (4 steps) as a yellow oil. **TLC**, R_f = 0.43 (Hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3429, 1686, 1427, 1227, 871 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.6 Hz, 3H), 1.28 (s, 9H), 2.63 (q, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 6.7 Hz, 2H), 2.90 (t, *J* = 6.7 Hz, 2H), 6.96 (d, *J* = 2.3 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 14.3, 23.7, 24.8, 31.5, 34.0, 34.9, 124.6, 124.8, 125.8, 130.3, 143.3, 149.4, 180.8; **HRMS** (FAB+) m/z calcd for $[C_{15}H_{22}O_3]^+$ 250.1569, found 250.1574.



3-(4-Hydroxy-5,6-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (2d): To a solution of 2,3-dimethylphenol (1.22 g, 10.0 mmol) in CH_3CN (30.0 mL) was added NBS (2.14 g, 12 mmol) at 0 ºC under a nitrogen atmosphere. After stirring for 3 h at 25 ºC, the resulting mixture was diluted with water and EtOAc. The aqueous layers were separated and extracted with EtOAc (twice). The combined organic layers were washed with water 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 = 15:1 to 8:1) to give 4-bromo-2,3-dimethylphenol (1.99 g, 9.90 mmol, 99% yield) as a white solid.

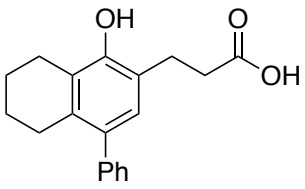
To a solution of this aryl bromide (1.99 g, 9.90 mmol), phenylboronic acid (1.83 g, 15.0 mmol) and Cs_2CO_3 (6.52 g, 20.0 mmol) in degassed dioxane (50.0 mL) and H_2O (10.0 mL) were added $Pd(OAc)_2$ (0.112 g, 0.500 mmol) and PPh_3 (0.262 g, 1.00 mmol) at 25 ºC. After stirring for 10 h at 80 ºC, the resulting mixture was poured into H_2O and extracted with EtOAc (twice). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. The organic layers were concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc =50:1 to 30:1) to give the 2,3-dimethyl-[1,1'-biphenyl]-4-ol (1.56 g, 7.87 mmol) in 79% yield as a white solid. **2d** was synthesized from this compound as in **2b** in 49% yield (4 steps) as white solid. **TLC**, R_f = 0.36 (Hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3442, 1694, 1220, 768 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 2.10 (s, 3H), 2.19 (s, 3H), 2.64 (t, *J* = 6.9 Hz, 2H), 2.83 (t, *J* = 6.9 Hz, 2H), 6.83 (s, 1H), 7.23–7.26 (m, 2H), 7.29–7.33 (m, 1H), 7.37–7.41 (m, 2H); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 13.0, 17.3, 25.6, 34.1, 123.8, 125.1, 126.2, 128.0, 128.1, 129.5, 132.1, 133.3, 142.4, 151.8, 174.4; **HRMS** (FAB+) m/z calcd for $[C_{17}H_{18}O_3]^+$ 270.1256, found 270.1253.



3-(2-Hydroxy-3-isopropyl-5,6-dimethylphenyl)propanoic acid (2e): To a solution of 2-isopropyl-5-methylphenol (1.50 g, 10.0 mmol) in CH_3CN (33.0 mL) was added NBS (1.78 g, 10 mmol) at 0 ºC under a nitrogen atmosphere. After stirring for 12 h at 25 ºC, the resulting mixture was diluted with water and EtOAc. The aqueous layers were separated and extracted with EtOAc (twice). The combined organic layers were washed with water 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 = 15:1 to 8:1) to give 4-bromo-2-isopropyl-5-methylphenol (1.61 g, 7.01 mmol, 70% yield).

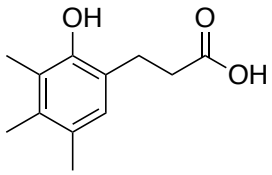
To a solution of sodium hydride (60-wt%, 0.308 g, 7.70 mmol) in THF (23.0 mL) was added this phenol at 0 ºC under nitrogen atmosphere. The reaction mixture was allowed to warm to 25 ºC. After stirring for 30 min, the reaction mixture was re-cooled to 0 ºC, and to the resulting mixture was added chloromethyl methyl ether (0.620 mL, 8.40 mmol). The reaction mixture was allowed to warm to 25 ºC again. After stirring for 12 h, the resulting mixture was poured into H_2O, and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed in *vacuo* to give 1-bromo-5-isopropyl-4-(methoxymethoxy)-2-methylbenzene.

Without further purification, to a solution of this MOM ether in THF (23.0 mL) was added *n*-BuLi (4.80 mL, 7.70 mmol, 1.60 *M* in hexane) at –78 ºC. After stirring for 1 h, to the resulting mixture was added iodomethane (1.30 mL, 21.0 mmol). The reaction mixture was allowed to warm to 25 ºC. After stirring for 12 h, the resulting mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed in *vacuo* to give 1-isopropyl-2-(methoxymethoxy)-4,5-dimethylbenzene. **2e** was synthesized from this compound as in **2c** in 14% yield (5 steps) as a white solid. **TLC**, R_f = 0.45 (Hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3505, 2955, 1697, 1455, 1301, 1216 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.22 (d, *J* = 6.9 Hz, 6H), 2.16 (s, 3H), 2.21 (s, 3H), 2.74 (t, *J* = 6.4 Hz, 1H), 2.98 (t, *J* = 6.4 Hz, 2H), 3.22 (sep, *J* = 6.9 Hz, 1H), 6.89 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.3, 20.3, 21.2, 22.8, 27.0, 33.5, 125.3, 125.8, 128.7, 132.7, 133.0, 149.3, 180.9; **HRMS** (FAB+) m/z calcd for $[C_{14}H_{20}O_3]^+$ 236.1412, found 236.1413.

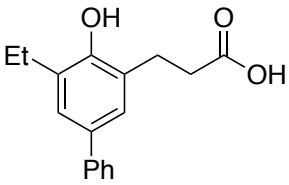


3-(1-Hydroxy-4-phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)propanoic acid (2f): This compound

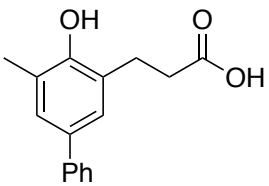
was prepared from 2,3-dimethylphenol as in **2d** in 68% yield (6 steps). White solid; **TLC**, R_f = 0.52 (Hexane–EtOAc–AcOH = 10:10:1); **IR** (KBr) 3552, 3250-2750, 1719, 1466, 1299, 1223 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.62–1.68 (m, 2H), 1.79–1.85 (m, 2H), 2.56 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 8.3 Hz, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.91 (t, *J* = 6.4 Hz, 2H), 6.55 (brs, 1H), 6.84 (s, 1H), 7.28–7.32 (m, 3H), 7.38 (t, *J* = 7.3 Hz, 2H), 8.61 (brs, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 22.3, 22.6, 24.0, 25.4, 28.3, 34.1, 124.2, 124.3, 126.3, 128.0, 128.1, 129.3, 132.8, 132.9, 141.9, 151.8, 174.5; **HRMS** (FAB+) m/z calcd for $[C_{19}H_{20}O_3+H]^+$ 297.1491, found 297.1491.



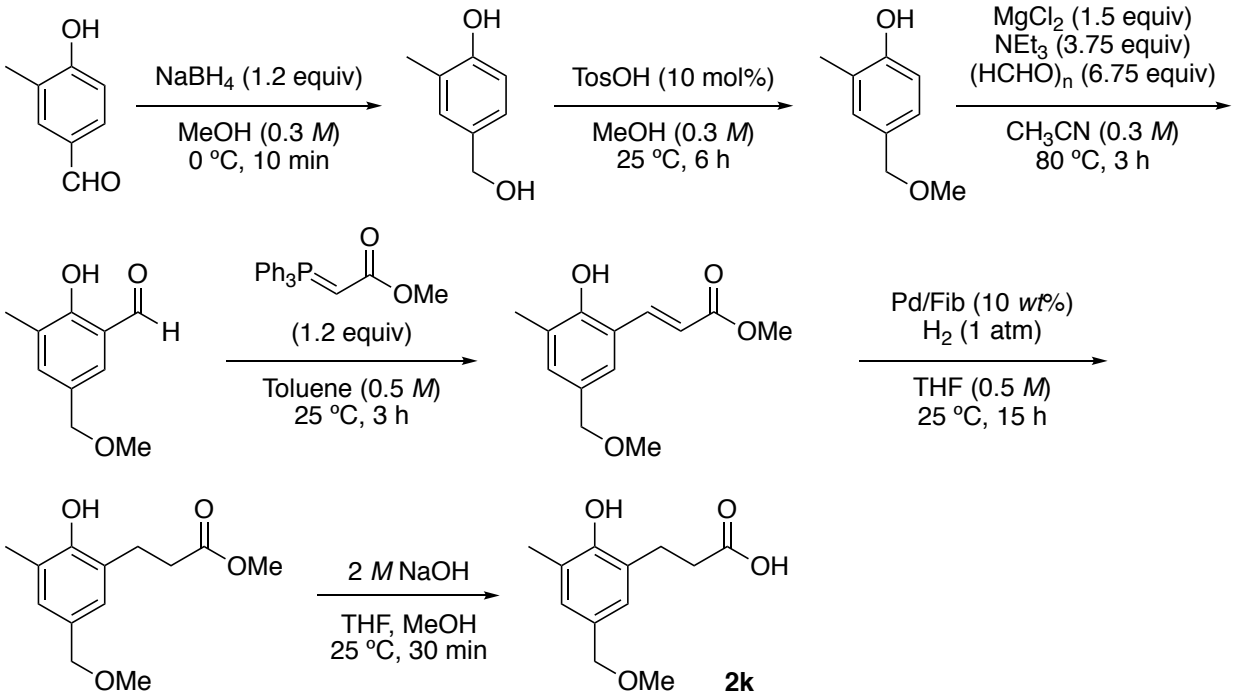
3-(2-Hydroxy-3,4,5-trimethylphenyl)propanoic acid (2h): This compound was synthesized from 2,3-dimethylphenol as in **2e** in 52% yield (8 steps). White solid; **TLC**, R_f = 0.36 (Hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3298, 1717, 1448, 1300, 1223 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.14 (s, 3H), 2.19 (s, 3H), 2.19 (s, 3H), 2.74–2.77 (m, 2H), 2.84 (t, *J* = 6.2 Hz, 2H), 6.39 (brs, 1H), 6.74 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 12.4, 15.8, 20.0, 24.3, 35.0, 123.3, 123.8, 128.4, 128.5, 134.6, 149.8, 180.8; **HRMS** (FAB+) m/z calcd for $[C_{12}H_{16}O_3]^+$ 208.1099, found 208.1099.



3-(5-Ethyl-4-hydroxy-[1,1'-biphenyl]-3-yl)propanoic acid (2i): This compound was synthesized from 2-ethylphenol as in **2d** in 19% yield (6 steps). White solid; **TLC**, R_f = 0.40 (Hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3459, 1717, 1460, 1304, 1213 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.21 (t, *J* = 7.6 Hz, 3H), 2.64–2.70 (m, 4H), 2.89 (t, *J* = 6.9 Hz, 2H), 7.26–7.31 (m, 3H), 7.39–7.43 (m, 2H), 7.57–7.59 (m, 2H); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 14.5, 23.1, 25.7, 34.0, 125.4, 125.7, 126.1, 126.4, 128.2, 128.8, 131.2, 131.5, 140.6, 152.2, 174.4; **HRMS** (FAB+) m/z calcd for $[C_{17}H_{18}O_3]^+$ 270.1256, found 270.1257.



3-(4-Hydroxy-5-methyl-[1,1'-biphenyl]-3-yl)propanoic acid (2j): This compound was synthesized from 2-methylphenol as in **2d** in 20% yield (6 steps). White solid; **TLC**, R_f = 0.39 (Hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3459, 1717, 1460, 1304, 1213 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 2.26 (s, 3H), 2.67 (t, J = 7.1 Hz, 2H), 2.89 (t, J = 7.1 Hz, 2H), 7.25–7.30 (m, 3H), 7.38–7.42 (m, 2H), 7.55–7.58 (m, 2H); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 16.9, 25.8, 34.0, 125.0, 125.8, 126.1, 126.4, 127.0, 128.1, 128.8, 131.3, 140.5, 152.7, 174.4; **HRMS** (FAB+) m/z calcd for $[C_{14}H_{20}O_3]^+$ 256.1099, found 256.1103.



3-(2-Hydroxy-5-(methoxymethyl)-3-methylphenyl)propanoic acid (2k): To a solution of 4-hydroxy-3-methylbenzaldehyde (1.36 g, 10.0 mmol) in MeOH (33.3 mL) at 0 °C was added $NaBH_4$ (0.459 g, 12.0 mmol) in several portions under a nitrogen atmosphere. After stirring for 10 min at 0 °C, the reaction was quenched with H_2O and the resulting mixture was extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*.

Without further purification, to a suspension of this alcohol in methanol (33.3 mL) was added *para*-toluenesulfonic acid monohydrate (0.190 g, 10.0 mol%), and the resulting mixture was stirred at 25 °C for 6 h. The resulting mixture was poured into saturated aqueous $NaHCO_3$ (30.0 mL), 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*.

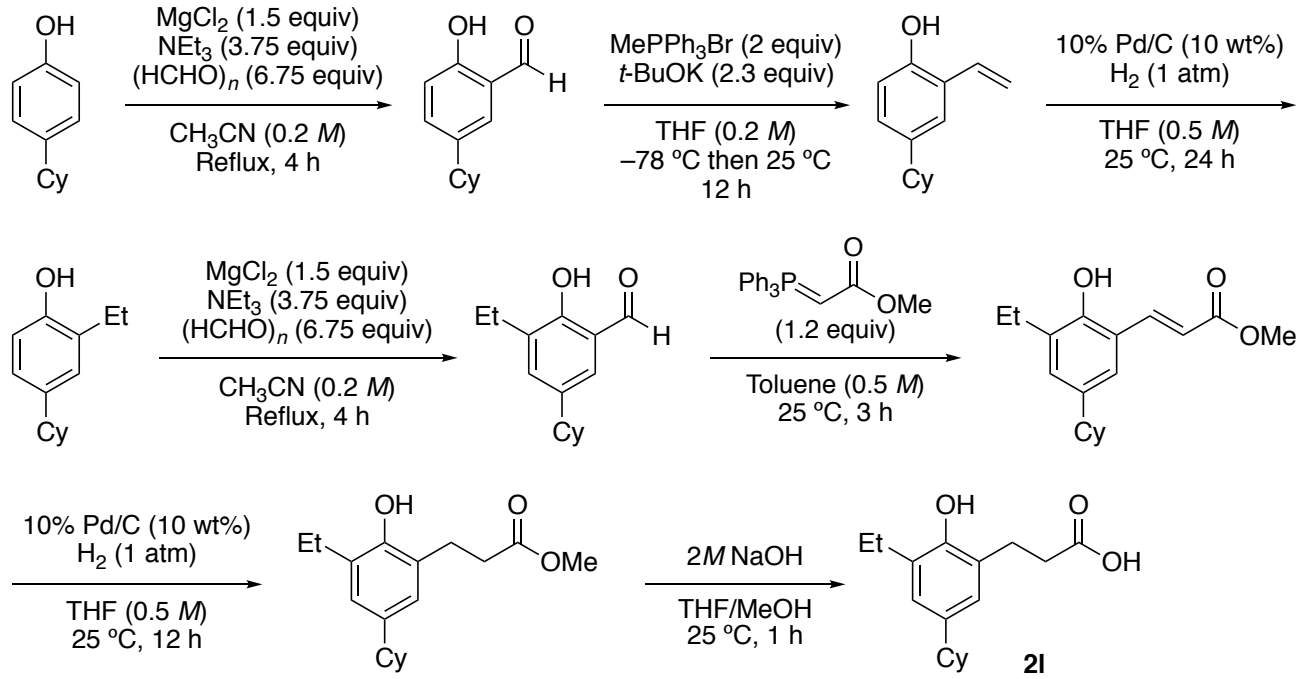
Without further purification, to a solution of $MgCl_2$ (1.43 g, 15.0 mmol) and NEt_3 (5.22 mL, 37.5 mmol) in CH_3CN (50.0 mL) were added this phenol and dry paraformaldehyde (2.03 g, 67.5

mmol) at 25 ºC under a nitrogen atmosphere. The mixture was refluxed at 90 °C for 3 h. The reaction mixture was cooled to 25 °C and poured into 1*M* HCl, and the aqueous layers were extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) to give 2-hydroxy-5-(methoxymethyl)-3-methylbenzaldehyde (1.44 g, 8.01 mmol, 80% yield for 3 steps) as a yellow liquid.

To a solution of this aldehyde in toluene (16.0 mL) was added methyl(triphenylphosphoranylidene)acetate (3.21 g, 9.60 mmol) at 25 ºC under a nitrogen atmosphere. After stirring for 3 h at 80 ºC, the resulting mixture was cooled to 25 ºC and diluted with water and EtOAc. The aqueous layers were separated and extracted with EtOAc (twice). The combined organic layers were washed with water 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 2:1) to give methyl (*E*)-3-(2-hydroxy-5-(methoxymethyl)-3-methylphenyl)acrylate (1.35 g, 5.71 mmol, 71% yield) as a white solid.

To a solution of this olefin (0.510 g, 2.00 mmol) in THF (4.00 mL) under a nitrogen atmosphere was added Pd/Fib (0.0510 g). The flask containing the mixture was then evacuated and purged with H_2 three times. In an H_2 gas environment, the resulting mixture was stirred 15 h at 25 ºC. Upon the completion of the reaction, the mixture was filtered through celite with EtOAc and the crude product was obtained after removal of the solvent *in vacuo*.

Without further purification, to a solution of this methyl ester in THF (10.0 mL) and MeOH (10.0 mL) was added 2 *M* NaOH (10.0 mL), and the resulting mixture was stirred at 25 ºC for 30 min. Then, the resulting mixture was poured into 1 *M* HCl, extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo* to give **2k** (0.449 g, 2.00 mmol, >99% yield for 2 steps) as a pale-yellow solid. **TLC**, R_f = 0.45 (Hexane–EtOAc–AcOH = 50:50:1); **IR** (neat) 3376, 2927, 2361, 1709, 1612 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.77 (t, *J* = 6.7 Hz, 2H), 2.89 (t, *J* = 6.7 Hz, 2H), 3.37 (s, 3H), 4.32 (s, 2H), 6.54 (brs, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 6.98 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 16.2, 24.6, 34.7, 57.6, 74.5, 125.3, 126.6, 128.0, 129.3, 129.4, 152.1, 179.6; **HRMS** (FAB+) m/z calcd for $[C_{12}H_{16}O_4]^+$ 224.1049, found 224.1058.

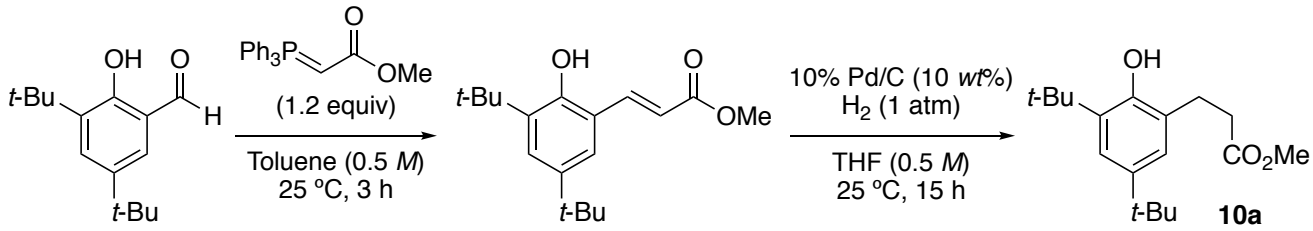


3-(5-Cyclohexyl-3-ethyl-2-hydroxyphenyl)propanoic acid (2l): To a solution of $MgCl_2$ (1.43 g, 15.0 mmol) and NEt_3 (5.22 mL, 37.5 mmol) in CH_3CN (50.0 mL) were added 4-cyclohexylphenol (1.76 g, 10.0 mmol) and dry paraformaldehyde (2.03 g, 67.5 mmol) at 25 ºC under a nitrogen atmosphere. The resulting mixture was refluxed at 90 °C for 4 h. The reaction mixture was cooled to 25 °C and poured into 1*M* HCl, and the aqueous layers were extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1) to give 5-cyclohexyl-2-hydroxybenzaldehyde (1.80 g, 8.80 mmol, 88% yield) as a yellow liquid.

To a solution of methyltriphenylphosphonium bromide (7.23 g, 20.2 mmol) in dry THF was added 1 *M t*-BuOK solution in THF (20.2 mL, 20.2 mmol). The resulting mixture was stirred at 25 ºC for 2 h and cooled to –78 ºC. To the resulting mixture was added this aldehyde (1.80 g, 8.80 mmol), and the reaction mixture was allowed to warm to 25 ºC slowly and stirred for 12 h. The reaction was quenched with 1 *M* HCl. The aqueous layers were extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1) to give 4-cyclohexyl-2-vinylphenol (1.64 g, 7.16 mmol, 81% yield).

To a solution of this olefin in THF (14.0 mL) was added 10% Pd/C (0.164 g) under a nitrogen atmosphere. The flask containing the mixture was then evacuated and purged with H_2 three times. In an H_2 gas environment, the resulting mixture was stirred for 12 h at 25 ºC. Upon the completion of

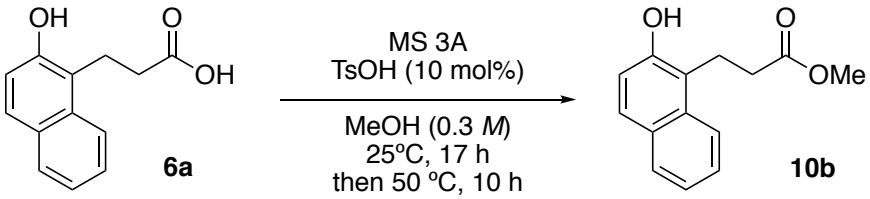
the reaction, the mixture was filtered through celite with EtOAc and the crude product of 4-cyclohexyl-2-ethylphenol, which was used without further purification for next step, was obtained after removal of the solvent *in vacuo*. **2l** was synthesized from this compound as in **2b** in 45% yield (4 steps) as a white solid. **TLC**, R_f = 0.45 (Hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3433, 1701, 1466, 1441, 1213 cm^{-1};**^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.20–1.27 (m, 1H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.30–1.42 (m, 4H), 1.71–1.74 (m, 1H), 1.82–1.84 (m, 4H), 2.35–2.42 (m, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 2.76–2.80 (m, 2H), 2.85–2.90 (m, 2H), 6.13 (brs, 1H), 6.79 (d, *J* = 2.3 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 10.7 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 14.1, 23.4, 24.6, 26.2, 27.0, 34.7, 34.8, 43.8, 126.0, 126.1, 126.1, 130.7, 140.4, 149.6, 180.7; **HRMS** (FAB+) m/z calcd for $[C_{14}H_{20}O_3]^+$ 276.1725, found 276.1728.



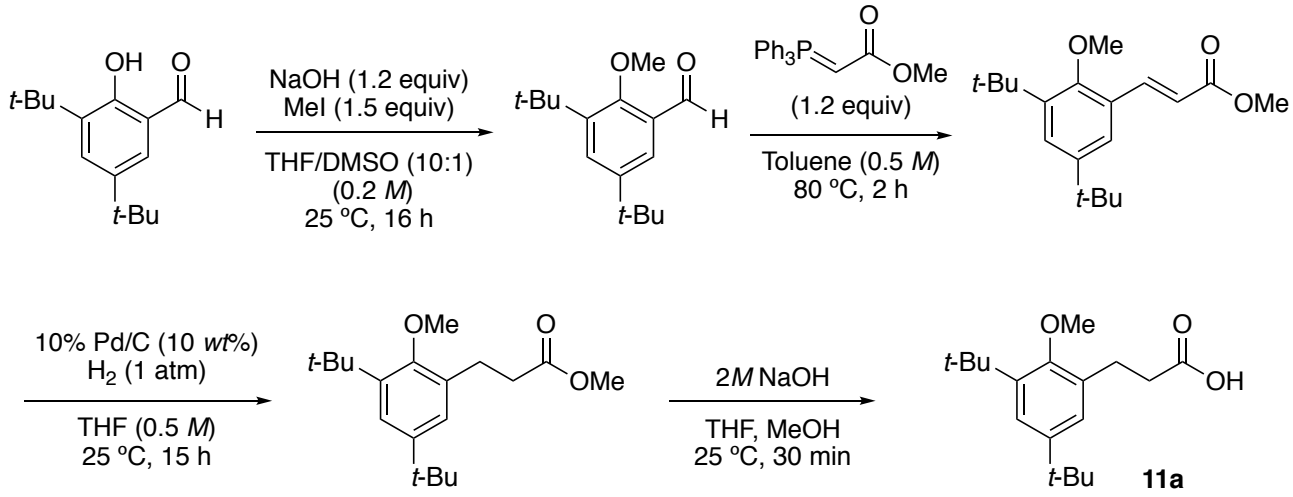
Methyl 3-(3,5-di-*tert*-butyl-2-hydroxyphenyl)propanoate (10a): To a solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (2.34 g, 10.0 mmol) in toluene (20.0 mL) was added methyl(triphenylphosphoranylidene)acetate (4.01 g, 12.0 mmol) at 25 ºC under a nitrogen atmosphere. After stirring for 3 h at 80 ºC, the resulting mixture was cooled to 25 ºC and diluted with water and EtOAc. The aqueous layers were separated and extracted with EtOAc (twice). The combined organic layers were washed with water 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 methyl (*E*)-3-(3,5-di-*tert*-butyl-2-hydroxyphenyl)acrylate (2.85 g, 9.81 mmol, 98% yield) as a white solid.

To a solution of this olefin in THF (19.6 mL) under a nitrogen atmosphere was added 10% Pd/C (0.285 g). The flask containing the mixture was then evacuated and purged with H_2 three times. In an H_2 gas environment the resulting mixture was stirred 15 h at 25 ºC. Upon the completion of the reaction, the mixture was filtered through celite with EtOAc and analytically almost pure **10a** (2.86 g, 9.78 mmol, 99% yield) was obtained as a white solid after removal of the solvent *in vacuo*. **TLC**, R_f = 0.63 (hexane–EtOAc = 2:1); **IR** (neat) 3361, 2955, 2873, 2361, 2343, 1712 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.29 (s, 9H), 1.43 (s, 9H), 2.74–2.77 (m, 2H), 2.87–2.90 (m, 2H), 3.69 (s, 3H), 6.95 (d, *J* = 2.7 Hz, 1H), 7.20 (d, *J* = 2.7 Hz, 1H), 7.45 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ24.6,

29.9, 31.6, 34.2, 35.1, 35.5, 52.3, 122.5, 124.9, 127.3, 137.3, 142.3, 150.8, 176.7; **HRMS** (FAB+) m/z calcd for $[C_{18}H_{28}O_3]^+$ 292.2038, found 292.2043.

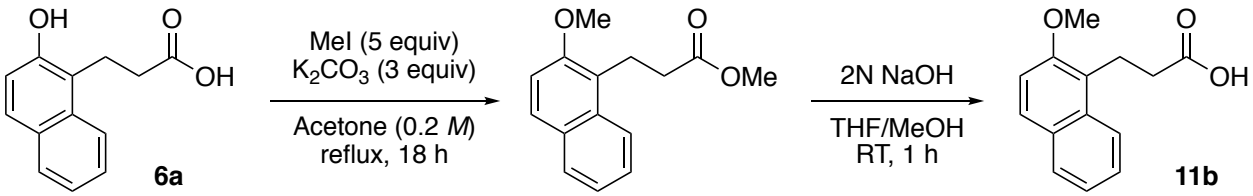


Methyl 3-(2-hydroxynaphthalen-1-yl)propanoate (10b): To a mixture of **6a** (0.216 g, 1.00 mmol) and dry MS 3Å (0.100 g) in MeOH (3.33 mL) was added *p*-toluenesulfonic acid monohydrate (0.0190 g, 0.100 mmol) at 25 ºC under a nitrogen atmosphere. After stirring for 17 h at 25 ºC, the resulting mixture was allowed to warm to 50 ºC. After stirring for 10 h, the resulting mixture was cooled to 25 ºC and filtered through celite with EtOAc. The resulting mixture was extracted with EtOAc (twice). The combined organic layers were washed with water 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 = 20:1 to 4:1) to **10b** (0.224 g, 0.0973 mmol, 10% yield) as white solid. **TLC**, R_f = 0.63 (hexane–EtOAc = 2:1); **IR** (neat) 3425, 2361, 1637, 1513, 1440 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.90 (t, *J* = 5.7 Hz, 2H), 3.32 (t, *J* = 5.7 Hz, 2H), 3.67 (s, 3H), 7.20 (d, *J* = 8.7 Hz, 1H), 7.33 (dd, *J* = 6.9, 7.8 Hz, 1H), 7.49 (dd, *J* = 6.9, 8.2 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.78 (dd, *J* = 7.8, 8.2 Hz, 2H), 8.11 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 19.6, 33.8, 52.5, 118.3, 119.9, 122.0, 123.0, 126.5, 128.6, 128.8, 129.5, 132.8, 152.2, 176.8; **HRMS** (FAB+) m/z calcd for $[C_{14}H_{14}O_3]^+$ 230.0943, found 230.0950.



3-(3,5-Di-*tert*-butyl-2-methoxyphenyl)propanoic acid (11a): To a solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.703 g, 3.00 mmol) and NaOH (0.144 g, 3.60 mmol) in THF (13.6 mL) and

DMSO (1.36 mL) was added iodomethane (0.280 mL, 4.50 mmol) at 25 ºC under a nitrogen atmosphere. The mixture was stirred at 25 ºC for 16 h. The reaction mixture was concentrated in *vacuo*, and then water (50.0 mL) was added. The aqueous layers were extracted with hexane (twice) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed *in vacuo* to obtain 3,5-di-*tert*-butyl-2-methoxybenzaldehyde (0.0745 g, 3.00 mmol) without further purification. **11a** was synthesized from 3,5-di-*tert*-butyl-2-methoxybenzaldehyde as in **2b** in 47% yield (3 steps) as a white solid. **TLC**, R_f = 0.37 (hexane–EtOAc = 2:1); **IR** (neat) 2953, 2874, 2561, 1712, 1231 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.29 (s, 9H), 1.39 (s, 9H), 2.71–2.75 (m, 2H), 3.00–3.04 (m, 2H), 3.79 (s, 3H), 7.05 (d, *J* = 2.8 Hz, 1H), 7.22 (d, *J* = 2.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.1, 31.2, 31.5, 34.5, 34.7, 35.3, 61.5, 122.7, 125.0, 132.6, 142.0, 145.7, 155.7, 179.8; **HRMS** (FAB+) m/z calcd for $[C_{18}H_{28}O_3]^+$ 292.2038, found 292.2043.

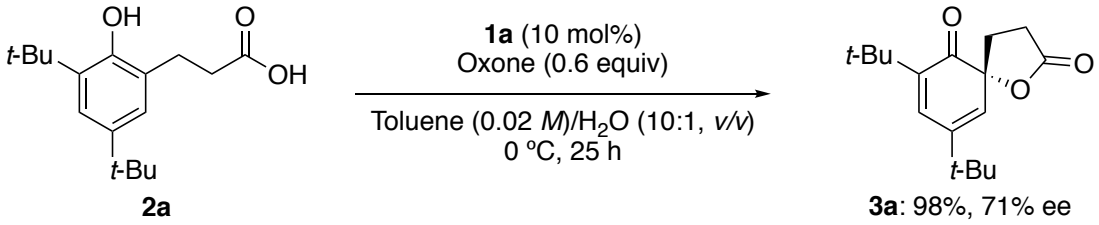


3-(2-Methoxynaphthalen-1-yl)propanoic acid (11b): To a solution of **6a** (0.216 g, 1.00 mmol) in acetone (5.00 mL) were added potassium carbonate (0.415 g, 3.00 mmol) and iodomethane (0.311 mL, 5.00 mmol) at 25 ºC under a nitrogen atmosphere. After stirring for 18 h at 60 ºC, the resulting mixture was cooled to 25 ºC and filtered through celite with EtOAc, and methyl 3-(2-methoxynaphthalen-1-yl)propanoate (0.244 g, 1.00 mmol, >99% yield) was obtained after removal of the solvent *in vacuo*.

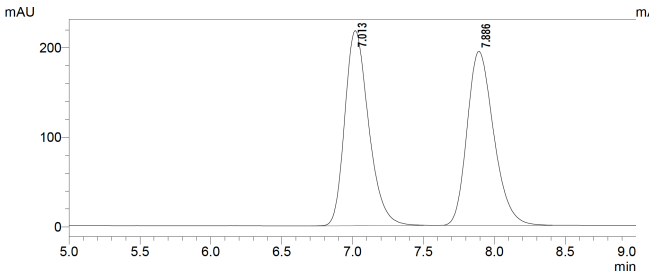
Without further purification, to a solution of this methyl ester in THF (1.00 mL) and MeOH (1.00 mL) was added 2 *M* NaOH (1.00 mL) and the resulting mixture was stirred at 25 ºC for 1 h. Then, the resulting mixture was poured into 1 *M* HCl, extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo* to give analytically almost pure **11b** (0.197 g, 0.856 mmol, 86% yield) as a white solid. **TLC**, R_f = 0.37 (hexane–EtOAc = 2:1); **IR** (neat) 3431, 2362, 2336 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.65–2.69 (m, 2H), 3.42–3.46 (m, 2H), 3.96 (s, 3H), 7.28 (d, *J* = 9.2 Hz, 1H), 7.33–7.37 (m, 1H), 7.48–7.52 (m, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.4, 33.9, 56.3, 113.0, 121.1, 122.6, 123.3, 126.6, 128.2, 128.6, 129.1, 132.6, 154.5, 179.5; **HRMS** (FAB+) m/z calcd for $[C_{14}H_{14}O_3]^+$ 230.0943, found 230.0934.

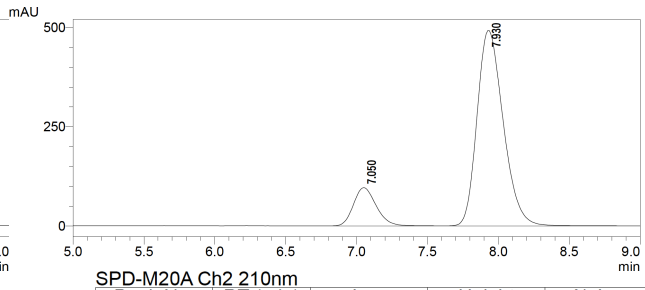
Procedures for Enantioselective Oxidation and Characterization of Products

Enantioselective Oxidative Dearomatization of Phenols 2



(*R*)-7,9-Di-*tert*-butyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (3a):[6] To a solution of **2a** (0.0278 g, 0.100 mmol) and **1a** (0.0170 g, 0.0100 mmol, 10 mol%) in toluene (5.00 mL) and H_2O (0.500 mL) was added Oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 25 h at 0 °C, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) at 0 °C. 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 = 6:1) to give (*R*)-**3a** (0.0271 g, 0.0980 mmol) in 98% yield as a yellow solid. Enantiomeric excess of **3a** was determined to be 71% ee by HPLC analysis (see below chart; left: *rac*-(**3a**), right: (*R*)-**3a**). **TLC**, R_f = 0.57 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.15 (s, 9H), 1.23 (s, 9H), 1.98–2.06 (m, 1 H), 2.30–2.36 (m, 1H), 2.51 (ddd, *J* = 1.4, 9.6, 17.8 Hz, 1H), 2.73–2.82 (m, 1H), 5.99 (d, *J* = 1.8 Hz, 1H), 6.89 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.0, 28.4, 29.0, 30.2, 34.4, 34.5, 85.5, 128.1, 135.8, 142.8, 143.7, 176.6, 199.0; **HPLC** (OD–H column), Hexane–EtOH = 30:1 as eluent, 1.0 mL/min, t_R = 7.0 min (*S*), t_R = 7.9 min (*R*); **$[\alpha]^{27.7}_D$** = 167.1 (*c* 0.5, $CHCl_3$) for 73% ee.





SPD-M20A Ch2 210nm

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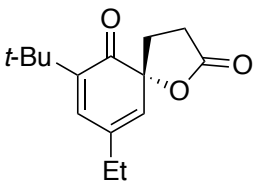
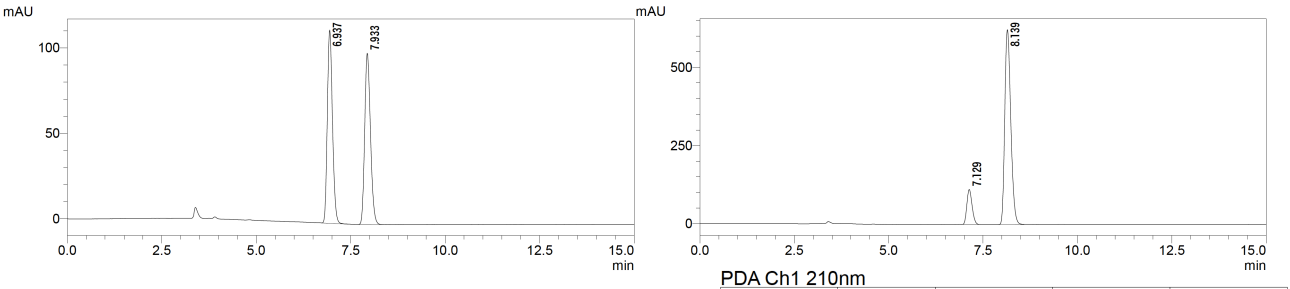


(*R*)-7-(*tert*-Butyl)-9-ethyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (3b): Following a similar procedure as for **3a**, **2b** (0.0250 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), Oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.500 mL), 0 ºC, 24 h: 83% yield (0.0206 g, 0.0830 mmol), 73% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1). Yellow oil; **TLC**, R_f = 0.57 (hexane–EtOAc = 1:1); **IR** (neat) 3447, 2956, 1791, 1659, 1155 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.12 (t, *J* = 7.3 Hz, 3H), 1.22 (s, 9H), 1.98–2.07 (m, 1 H), 2.21–2.27 (m, 2H), 2.30–2.36 (m, 1H), 2.52 (ddd, *J* = 2.3, 9.6, 13.7 Hz, 1H), 2.73–2.83 (m, 1H), 5.92–5.94 (m, 1H), 6.62 (d, *J* = 2.3 Hz, 1 H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 12.1, 26.1, 28.3, 29.0, 30.2, 34.2, 85.3, 129.7, 137.5, 138.5, 143.1, 176.7, 199.0; **HPLC** (OD–3 column), Hexane–EtOH = 95:5 as eluent, 1.0 mL/min, t_R = 6.9 min (*S*), t_R = 7.9 min (*R*); **HRMS** (FAB+) m/z calcd for $[C_{14}H_{18}O_3+H]^+$ 249.1491, found 249.1498; **$[\alpha]^{28.3}_D$** = 154.2 (*c* 1.2, $CHCl_3$) for 73% ee.



PDA Ch1 210nm

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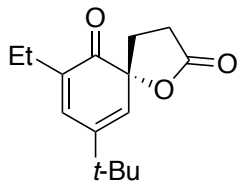
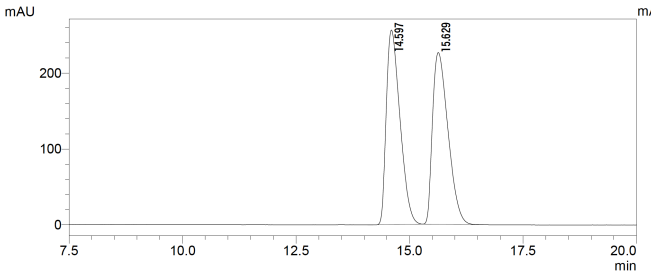
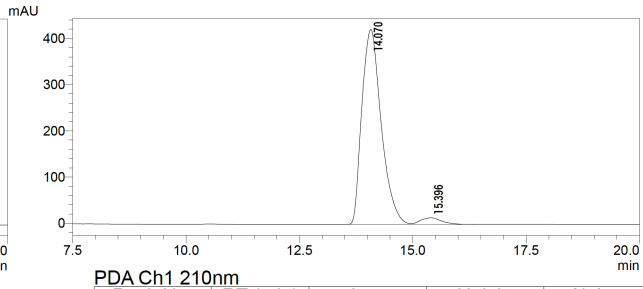


(*R*)-9-(*tert*-Butyl)-7-ethyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (3c): Following a similar procedure as for **3a**, **2c** (0.0250 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (1.00 mL), H_2O (0.500 mL), 0 ºC, 48 h: 73% yield (0.0182 g, 0.0732 mmol), 93% ee. *cf.*: Toluene (5.00 mL), H_2O (0.500 mL), 60 h: 42% yield (0.0103 g, 0.0415 mmol), 92% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1). Yellow solid; **TLC**, R_f = 0.60 (hexane–EtOAc = 1:1); **IR** (KBr) 3459, 2962, 1787, 1667, 1181 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.10 (t, *J* = 7.6 Hz, 3H), 1.15 (s, 9H), 2.04–2.12 (m, 1H), 2.28–2.40 (m, 3H), 2.55 (ddd, *J* = 2.3, 9.6, 9.7 Hz, 1H), 2.82–2.92 (m, 1H), 5.96 (d, *J* = 2.3 Hz, 1H), 6.87–6.89 (m, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 12.6, 22.0, 26.3, 28.4, 31.0, 34.3, 83.8, 127.9, 136.9, 137.2, 144.0, 176.6, 199.2; **HPLC** (AD–3 column), Hexane–EtOH = 30:1

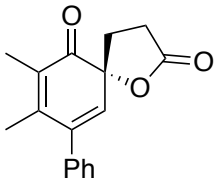
as eluent, 1.0 mL/min, t_R = 14.6 min (*R*), t_R = 15.6 min (*S*); **HRMS** (FAB+) m/z calcd for $[C_{15}H_{20}O_3+H]^+$ 249.1491, found 249.1483; **[α]$^{28.6}_D$** = 204.3 (*c* 1.0, $CHCl_3$) for 92% ee.



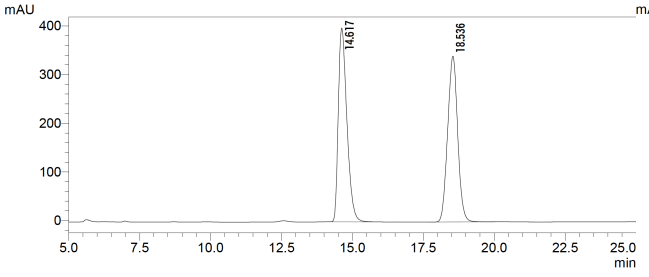


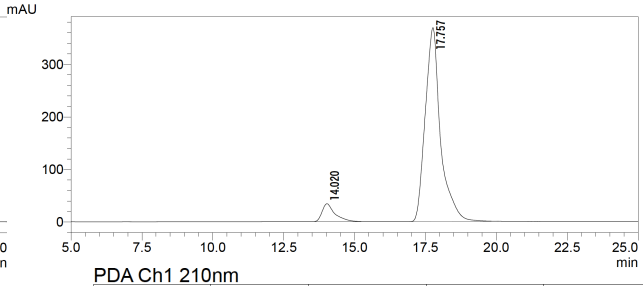
PDA Ch1 210nm

Peak No.	RT (min)	Area	Height	% Area
1	14.070	12527449	421846	96.434
2	15.396	463229	14467	3.566
Total		12990678	436313	100.000



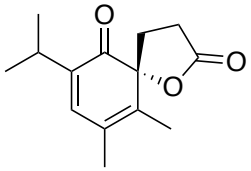
(*R*)-7,8-Dimethyl-9-phenyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (3d): Following a similar procedure as for **3a**, **2d** (0.0270 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (1.00 mL), H_2O (0.500 mL), 0 ºC, 16 h: 82% yield (0.0220 g, 0.0820 mmol), 86% ee. *cf*: Toluene (5.00 mL), H_2O (0.500 mL), 48 h: 30% yield (0.00810 g, 0.0302 mmol), 90% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1). Yellow solid; **TLC**, R_f = 0.60 (hexane–EtOAc = 1:1). Yellow solid; **TLC**, R_f = 0.53 (hexane–EtOAc = 1:1); **IR** (KBr) 3434, 2923, 2851, 1783, 1669, 1184 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.88 (s, 3H), 1.95 (s, 3H), 2.14–2.22 (m, 1H), 2.40–2.46 (m, 1H), 2.57 (ddd, *J* = 2.3, 9.6, 18.7 Hz, 1H), 2.89–2.97 (m, 1H), 6.10 (s, 1H), 7.18–7.21 (m, 2H), 7.35–7.42 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 11.4, 19.5, 26.4, 31.1, 82.7, 127.9, 128.3,128.4, 128.6, 133.6, 138.8, 140.8, 148.3, 176.6, 197.9; **HPLC** (OD–3 column), Hexane–EtOH = 9:1 as eluent, 1.0 mL/min, t_R = 14.7 min (*S*), t_R = 18.5 min (*R*); **HRMS** (FAB+) m/z calcd for $[C_{17}H_{16}O_3+H]^+$ 269.1178, found 269.1179; **[α]$^{28.6}_D$** = 186.6 (*c* 0.7, $CHCl_3$) for 90% ee.



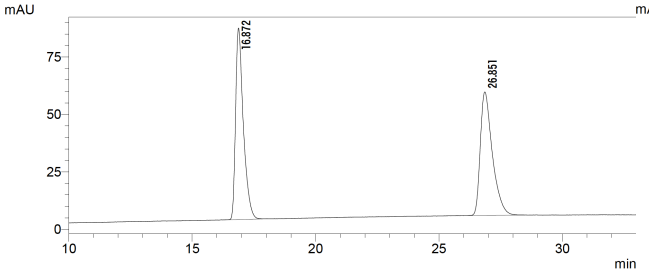


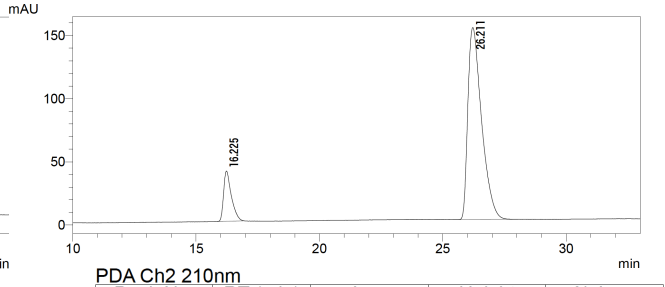
PDA Ch1 210nm

Peak No.	RT (min)	Area	Height	% Area
1	14.020	1060193	34105	7.125
2	17.757	13818993	369061	92.875
Total		14879186	403167	100.000



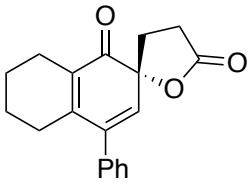
(*R*)-7-Isopropyl-9,10-dimethyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (3e): Following a similar procedure as for **3a**, **2e** (0.0236 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.500 mL), 0 ºC, 36 h: 84% yield (0.0197 g, 0.0841 mmol), 74% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1). Yellow solid; **TLC**, R_f = 0.67 (hexane–EtOAc = 1:1); **IR** (neat) 3444, 1781, 1651, 1162 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.08 (d, *J* = 6.9 Hz, 6H), 1.84 (s, 3H), 1.91 (s, 3H), 1.99–2.07 (m, 1H), 2.20–2.26 (m, 1H), 2.48–2.55 (m, 1H), 2.73–2.82 (m, 1H), 2.87 (sep, *J* = 6.9 Hz, 1H), 6.57 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 13.3, 18.6, 21.4, 21.5, 25.9, 26.2, 29.1, 87.4, 126.3, 138.3, 138.8, 141.0, 176.8, 199.3; **HPLC** (AD–3 column), Hexane–EtOH = 30:1 as eluent, 1.0 mL/min, t_R = 16.9 min (*S*), t_R = 26.9 min (*R*); **HRMS** (FAB+) m/z calcd for $[C_{14}H_{18}O_3+H]^+$ 235.1334, found 235.1341; **$[\alpha]^{25.4}_D$** = 35.9 (*c* 0.5, $CHCl_3$) for 74% ee.





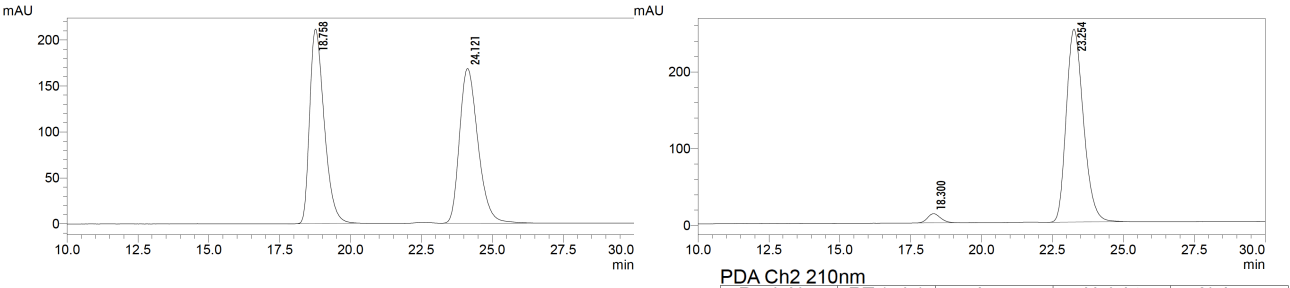
PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	16.225	868054	39806	12.873
2	26.211	5875052	152059	87.127
Total		6743106	191865	100.000



(*R*)-4'-Phenyl-3,4,5',6',7',8'-hexahydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-1',5-dione (3f): Following a similar procedure as for **3a**, **2f** (0.0296 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.500 mL), 0 ºC, 27 h: 95% yield (0.0281 g, 0.0954 mmol), 93% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1). White solid; **TLC**, R_f = 0.37 (hexane–EtOAc = 2:1); **IR** (KBr) 2932, 1790, 1658, 1167, 1028 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.56–1.74 (m, 4H), 2.04–2.22 (m, 3H), 2.28–2.35 (m, 1H), 2.40–2.48 (m, 2H), 2.54–2.61 (m, 1H), 2.89–

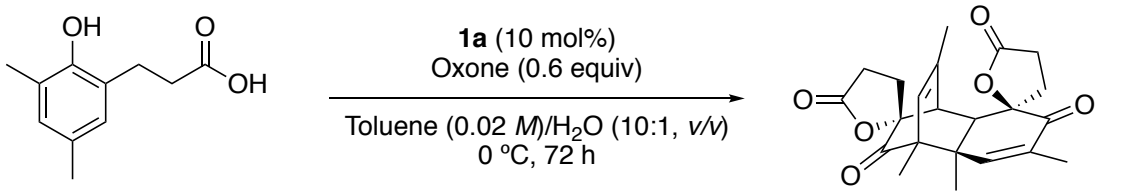
2.99 (m, 1H), 6.06 (s, 1H), 7.19–7.21 (m, 2H), 7.34–7.41 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 21.1, 21.9, 22.3, 26.6, 30.1, 31.3, 82.2, 127.9, 128.2, 128.5, 129.7, 133.4, 138.1, 140.5, 150.0, 176,7, 197.8; **HPLC** (OD–H column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 18.8 min (*S*), t_R = 24.1 min (*R*); **HRMS** (FAB+) m/z calcd for $[C_{19}H_{18}O_3+H]^+$ 295.1334, found 295.1327; **$[\alpha]^{27.1}_D$** = 158.4 (*c* 0.5, $CHCl_3$) for 93% ee.



PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	18.300	378303	11953	3.453
2	23.254	10578133	251043	96.547
Total		10956437	262996	100.000

Enantioselective Oxidative Spirocyclization and Tandem [4+2] Cycloaddition of Phenols 2

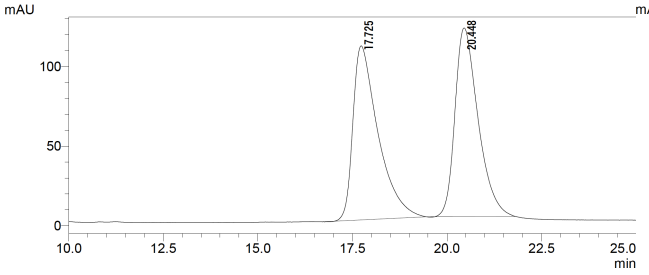


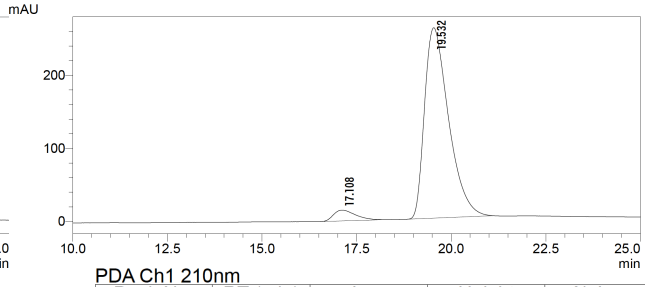
2g

4g: 86%, 90% ee (>99% ee)*
*after a single re-crystallization

(1'*R*,2*R*,4'*R*,4a'*R*,8a'*R*,10'*R*)-2',4',4a',6'-Tetramethyl-1',3,3'',4,4',4a',4'',8a'-octahydro-5*H*,5''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-5,5'',7',9'-tetraone (4g): To a solution of **2g** (0.0194 g, 0.100 mmol) and **1a** (0.0170 g, 0.0100 mmol, 10 mol%) in toluene (5.00 mL) and H_2O (0.500 mL) was added oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 72 h at 0 °C, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) at 0 °C. 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 1:1) to give **4g** (0.0165 g, 0.0859 mmol) in 86% yield as a white solid. Enantiomeric excess of **4g** was determined to be 90% ee by HPLC analysis. Enantiomerically pure (>99% ee) **4g** was obtained after a single re-crystallization. **TLC**, R_f = 0.55 (hexane–EtOAc = 1:1); **IR** (KBr) 2956, 1793, 1734, 1700, 1188 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.23 (s, 3H), 1.29 (s, 3H), 1.83 (d, *J* = 1.8 Hz, 3H), 1.85 (d, *J* = 1.8 Hz, 3H), 1.90–1.98 (m, 1H),

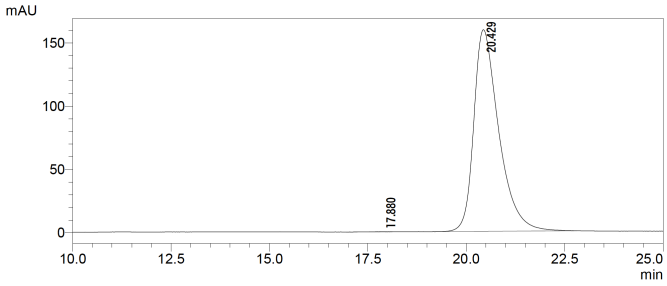
2.19–2.23 (m, 1H), 2.24–2.34 (m, 2H), 2.40–2.51 (m, 1H), 2.52–2.65 (m, 2H), 2.80–2.89 (m, 2H), 3.23 (t, J = 2.1 Hz, 1H), 5.25 (d, J = 1.8 Hz, 1H), 6.12 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 12.2, 16.5, 21.5, 23.7, 27.4, 28.4, 30.1, 36.6, 45.3, 48.5, 50.0, 57.7, 81.9, 85.3, 129.1, 134.4, 142.5, 144.1, 174.8, 175.8, 194.2, 207.3; **HPLC** (IC–3 column), Hexane–EtOH = 1:1 as eluent, 1.0 mL/min, t_R = 17.7 min (*minor*), t_R = 20.5 min (*major*); **HRMS** (FAB+) m/z calcd for $[C_{22}H_{24}O_6+H]^+$ 385.1651, found 385.1659; **$[\alpha]^{27.2}_D$** = 59.2 (*c* 1.0, $CHCl_3$) for 90% ee.





PDA Ch1 210nm

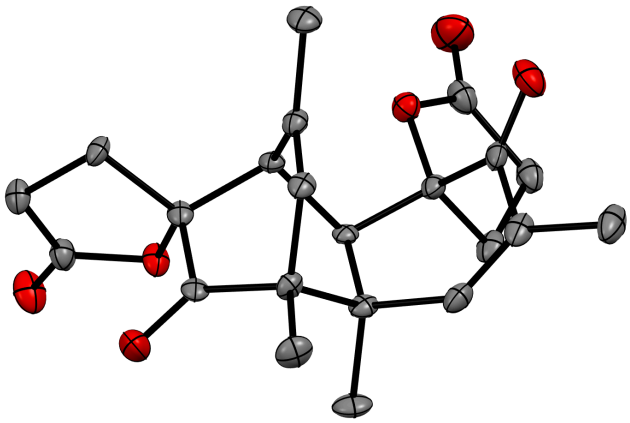
Peak No.	RT (min)	Area	Height	% Area
1	17.108	595345	14902	4.908
2	19.532	11533588	260612	95.092
Total		12128933	275514	100.000



PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	17.880	371	56	0.005
2	20.429	7034705	159288	99.995
Total		7035075	159344	100.000

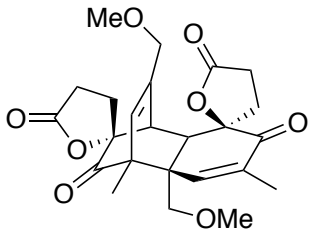
X-Ray Diffraction Analysis of 4g: Recrystallization of **4g** was carried out in the solution of EtOH at –20 °C. Mp: 218 °C (decomposed). X-Ray crystallographic analysis was performed with a Rigaku PILATUS-200K diffractometer (graphite monochromator, MoKa radiation, λ = 0.71075 Å) and the structure was solved by direct methods and expanded using Fourier techniques (SHELXT and SHELXL).[29] Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number **CCDC 1957772** for **4g**.



ORTEP drawing of 4g. Hydrogen atoms are omitted for clarity. Gray, carbon; red, oxygen.

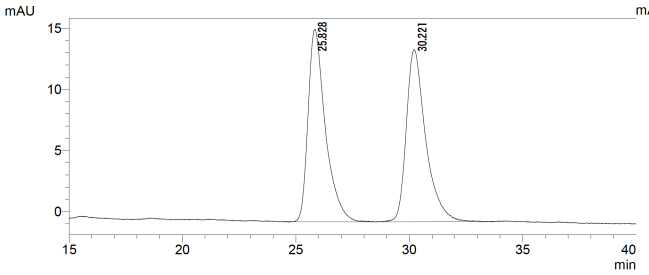
Crystallographic Data and Structure Refinement for 4g

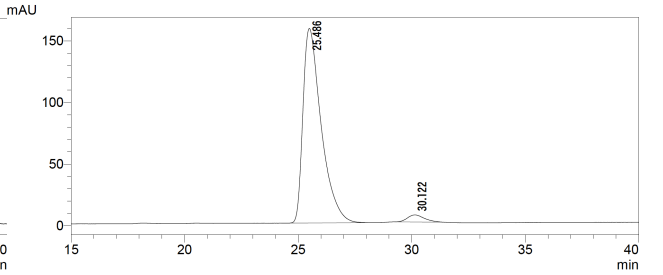
Formula	$C_{22}H_{24}O_6$	D_{calcd}	1.354g/cm^3
Formula weight	384.43	Absorption coefficient	0.098 mm^{-1}
T	123(2) K	*F*(000)	408.00
λ	0.71075 Å	Crystal size	0.2 x 0.2 x 0.2 mm^3
Crystal system	monoclinic	Theta range for data collection	3.40 to 27.50°
Space group	$P2_1$ (#4)	Reflections collected	3354
A	6.7404(17) Å	Refinement based on	F^2
B	10.0373(3) Å	No. of data	3354
C	13.488(4) Å	No. of parameters	253
α	90.0°	No. of restraints	1
β	90.437(7)°	GOF	1.071
γ	90.0°	R(*F*) for $I > 2s(I)$	0.0741
V	943.0(5) Å^3	wR2(F^2) for all data	0.2201
Z	2	Flack parameter	0.4(10)



(1'*R*,2*R*,4'*R*,4a'*S*,10'*R*)-2',4a'-bis(methoxymethyl)-4',6'-dimethyl-1',3,3'',4,4',4a',4'',8a'-octahydro-5*H*,5''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-5,5'',7',9'-tetraone (4k): Following a similar procedure as for **4g**, **2k** (0.0224 g, 0.100 mmol), **1a** (0.0170 g,

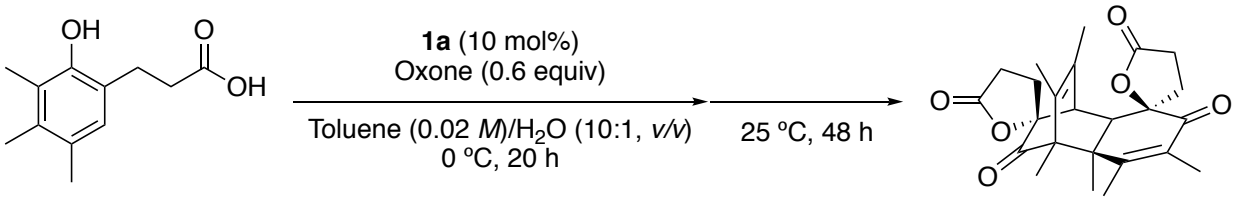
0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (1.00 mL), H_2O (0.500 mL), 31 h (0 ºC): 89% yield (0.0198 g, 0.0892 mmol), 94% ee. *cf.*: toluene (5.00 mL), H_2O (0.500 mL), 60 h (0 ºC): 60% yield (0.0133 g, 0.0598 mmol), 96% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1 to 2:1). White solid; **TLC**, R_f = 0.29 (hexane–EtOAc = 2:1); **IR** (neat) 3440, 2986, 2936, 2894, 2826, 1791 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H), 1.86 (d, *J* = 1.4 Hz, 3H), 2.03–2.21 (m, 3H), 2.32–2.65 (m, 4H), 2.77–2.86 (m, 1H), 3.08 (d, *J* = 2.3 Hz, 1H), 3.22 (d, *J* = 9.2 Hz, 1H), 3.34 (s, 3H), 3.36 (s, 3H), 3.34–3.37 (m, 1H), 3.52 (d, *J* = 9.2 Hz, 1H), 3.84–3.91 (m, 2H), 5.41 (d, *J* = 1.8 Hz, 1H), 6.23 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 13.1, 16.8, 27.5, 28.4, 30.6, 36.1, 45.5, 46.4, 50.3, 56.2, 59.1, 59.5, 72.4, 76.2, 81.6, 85.7, 129.2, 136.1, 142.5, 143.2, 175.4, 176.0, 194.8, 206.6; **HPLC** (AD–3 column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 25.8 min (*major*), t_R = 30.2 min (*minor*); **HRMS** (FAB+) m/z calcd for $[C_{24}H_{28}O_8+H]^+$ 445.1862, found 445.1871; **$[\alpha]^{24.9}_D$** = 120.8 (*c* 0.5, $CHCl_3$) for 96% ee.





PDA Ch1 210nm

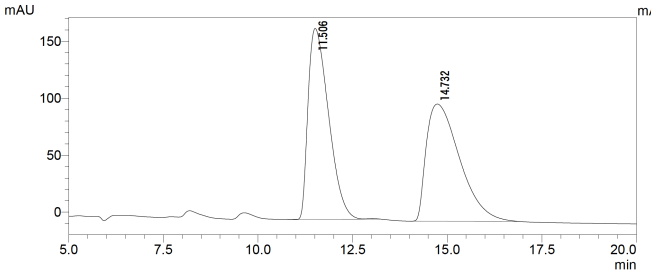
Peak No.	RT (min)	Area	Height	% Area
1	25.486	8829563	157849	96.754
2	30.122	296176	5724	3.246
Total		9125739	163574	100.000

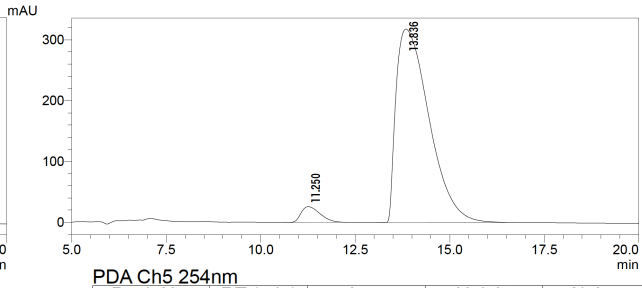


2h **4h**: 88%, 91% ee

(1'*R*,2*R*,4'*R*,4a'*S*,8a'*R*,10'*R*)-2',3',4',4a',5',6'-hexamethyl-1',3,3'',4,4',4a',4'',8a'-octahydro-5*H*,5''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-5,5'',7',9'-tetraone (4h): To a solution of **2h** (0.0194 g, 0.100 mmol) and **1a** (0.0170 g, 0.0100 mmol, 10 mol%) in toluene (5.00 mL) and H_2O (0.500 mL) was added oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 20 h at 0 ºC (**2h** was almost consumed), the cooling bath was removed and the resulting mixture was allowed to room temperature to enhance the cyclodimerization reaction. After stirring for 48 h at room temperature, the reaction was quenched by

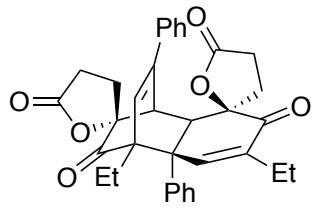
saturated aqueous $Na_2S_2O_3$ (1 mL). The aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1 to 1:1) to give **4h** (0.0364 g, 0.0879 mmol) in 88% yield as a white solid. Enantiomeric excess of **4h** was determined to be 91% ee by HPLC analysis. **TLC**, R_f = 0.53 (hexane–EtOAc = 1:1); **IR** (neat) 3437, 2927, 2852, 1792, 1727, 1680, 1181 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.20 (s, 3H), 1.36 (d, *J* = 0.1 Hz, 3H), 1.39 (s, 3H), 1.78 (d, *J* = 0.1 Hz, 3H), 1.85 (d, *J* = 0.1 Hz, 3H), 1.85–1.95 (m, 1H), 1.96 (d, *J* = 0.1 Hz, 3H), 2.07–2.19 (m, 3H), 2.40–2.46 (m, 1H), 2.51–2.63 (m, 3H), 2.80–2.86 (m, 1H), 3.15 (d, *J* = 2.5 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 12.8, 14.0, 14.2, 19.0, 19.5, 23.4, 27.4, 28.5, 30.5, 36.1, 48.6, 48.8, 49.9, 61.4, 81.3, 86.1, 132.6, 133.1, 135.9, 150.7, 174.8, 175.9, 193.1, 207.4; **HPLC** (OD–3 column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 11.5 min (*minor*), t_R = 14.7 min (*major*); **HRMS** (ESI) m/z calcd for $[C_{24}H_{28}O_6+Na]^+$ 435.1778, found 435.1778; **$[\alpha]^{27.5}_D$** = 87.8 (*c* 1.5, $CHCl_3$) for 91% ee.





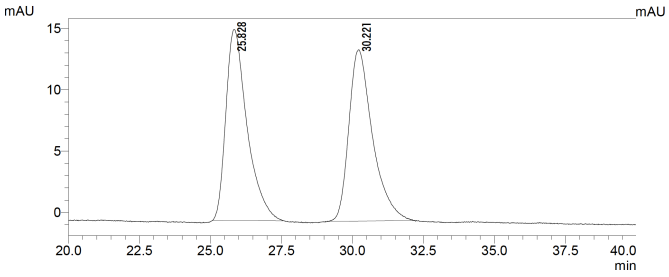
PDA Ch5 254nm

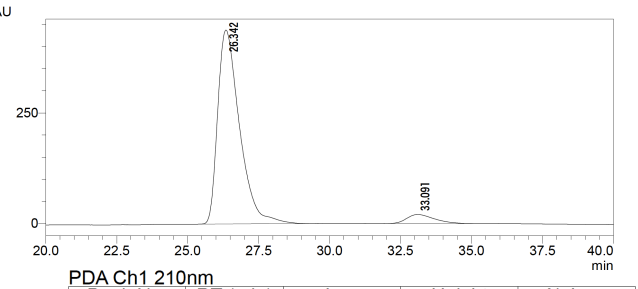
Peak No.	RT (min)	Area	Height	% Area
1	11.250	895894	25856	4.422
2	13.836	19361775	318316	95.578
Total		20257669	344172	100.000



(1'*R*,2*R*,4'*R*,4a'*R*,8a'*R*,10'*R*)-4',6'-diethyl-2',4a'-diphenyl-1',3,3'',4,4',4a',4'',8a'-octahydro-5*H*,5''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-5,5'',7',9'-tetraone (4i): Following a similar procedure as for **4h**, **2i** (0.0270 g, 0.100 mmol), **1b** (0.0250 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (1.00 mL), H_2O (0.500 mL), 23 h (0 ºC), 48 h (RT): 90% yield (0.0242 g, 0.0901 mmol), 89% ee. *cf.*: **1a** (0.0170 g, 0.0100 mmol, 10 mol%), toluene (0.500 mL), H_2O (0.500 mL), 40 h (0 ºC), 48 h (RT): 88% yield (0.0235 g, 0.0876 mmol), 78% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1 to 2:1). White solid; **TLC**, R_f = 0.55 (hexane–EtOAc = 1:1); **IR** (KBr) 3444, 2359, 2337, 1798, 1645 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.82 (t, *J* = 7.3 Hz, 3H), 0.91 (t,

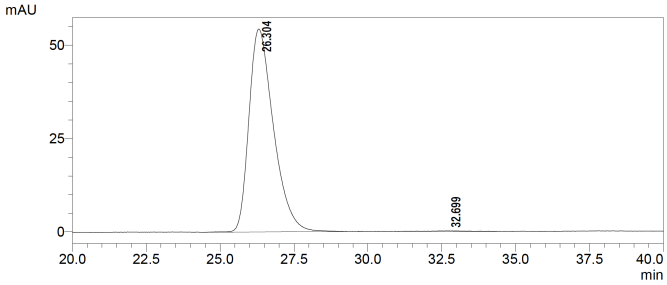
J = 7.3 Hz, 3H), 1.38–1.61 (m, 3H), 1.75–1.81 (m, 1H), 1.84–1.92 (m, 1H), 2.12–2.36 (m, 5H), 2.52–2.60 (m, 1H), 2.79–2.88 (m, 1H), 3.72 (s, 1H), 4.07 (d, J = 0.9 Hz, 1H), 6.21 (d, J = 2.3 Hz, 1H), 6.77 (s, 1H), 7.25–7.45 (m, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 9.5, 13.0, 18.9, 23.5, 27.3, 28.4, 30.6, 35.1, 46.6, 54.2, 57.4, 63.5, 84.0, 85.0, 125.1, 125.5, 127.3, 127.9, 129.0, 129.1, 129.2, 136.3, 140.7, 141.0, 142.8, 146.1, 175.0, 175.6, 192.5, 206.4; **HPLC** (IC–3 column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 25.8 min (*major*), t_R = 30.2 min (*minor*); **HRMS** (ESI) m/z calcd for $[C_{34}H_{32}O_6+Na]^+$ 559.2091, found 559.2091; **$[\alpha]^{27.2}_D$** = –55.1 (*c* 0.9, $CHCl_3$) for 78% ee.





PDA Ch1 210nm

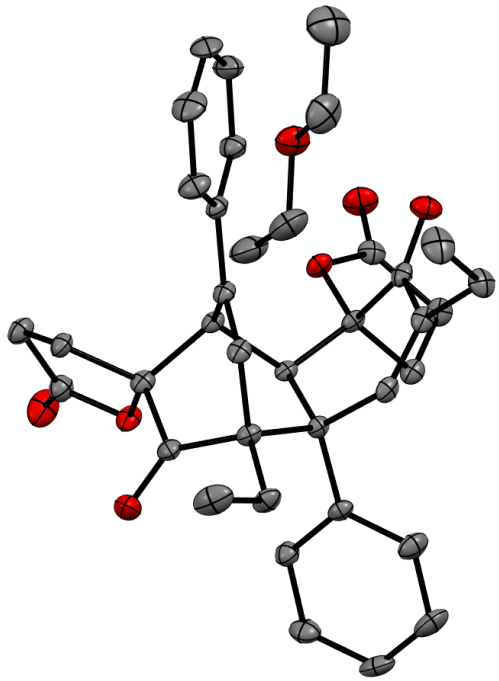
Peak No.	RT (min)	Area	Height	% Area
1	26.342	23526529	438732	94.541
2	33.091	1358444	20287	5.459
Total		24884974	459018	100.000



PDA Ch1 210nm

Peak No.	RT (min)	Area	Height	% Area
1	26.304	3136048	54333	99.685
2	32.699	9903	128	0.315
Total		3145951	54460	100.000

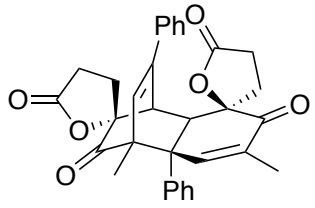
X-Ray Diffraction Analysis of 4i: Recrystallization of **4i** was carried out in the solution of Et_2O at 25 °C. Mp: 168 °C (decomposed). X-Ray crystallographic analysis was performed as in for **4g**. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number **CCDC 1957773** for **4i**.



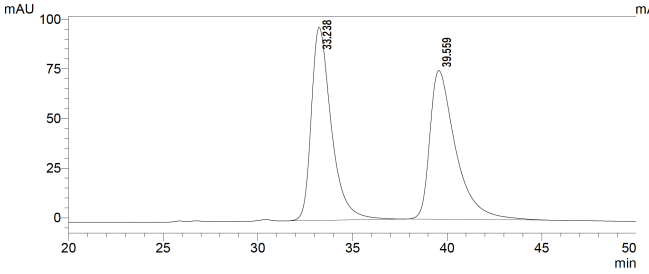
ORTEP drawing of 4i·Et_2O. Hydrogen atoms are omitted for clarity. Gray, carbon; red, oxygen.

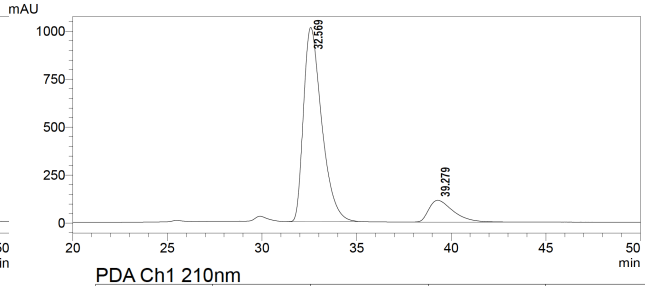
Crystallographic Data and Structure Refinement for 4i·Et_2O

Formula	$C_{38}H_{42}O_7$	D_{calcd}	1.290g/cm^3
Formula weight	610.75	Absorption coefficient	0.877 cm^{-1}
T	123(2) K	*F*(000)	1304
λ	0.71075 Å	Crystal size	0.150 x 0.150 x 0.100 mm^3
Crystal system	orthorhombic	Theta range for data collection	3.20 to 27.50°
Space group	*P2$_1$2$_1$2$_1$ (#19)*	Reflections collected	27156
A	9.8131(13) Å	Refinement based on	F^2
B	16.460(2) Å	No. of data	7200
C	19.469(3) Å	No. of parameters	325
α	90.0°	No. of restraints	0
β	90.0°	GOF	1.033
γ	90.0°	R(*F*) for $I > 2s(I)$	0.0414
V	3144.7(7) Å^3	wR2(F^2) for all data	0.1070
Z	4	Flack parameter	–0.1(4)



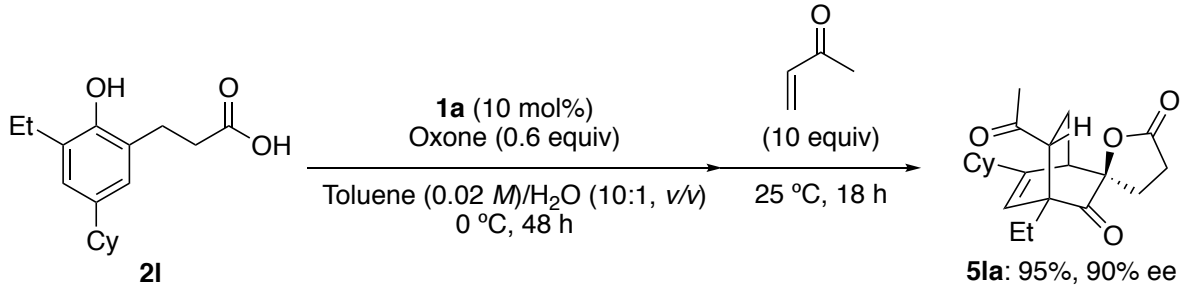
(1'*R*,2*R*,4'*R*,4a'*R*,8a'*R*,10'*R*)-4',6'-dimethyl-2',4a'-diphenyl-1',3,3'',4,4',4a',4'',8a'-octahydro-5*H*,5''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-5,5'',7',9'-tetraone (4j): Following a similar procedure as for **4h**, **2j** (0.0256 g, 0.100 mmol), **1b** (0.0250 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (1.00 mL), H_2O (0.500 mL), 24 h (0 ºC), 36 h (RT): 89% yield (0.0225 g, 0.0885 mmol), 74% ee. *cf.*: **1a** (0.0170 g, 0.0100 mmol, 10 mol%), toluene (0.500 mL), H_2O (0.500 mL), 24 h (0 ºC), 24 h (RT): 83% yield (0.0212 g, 0.0828 mmol), 63% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1 to 2:1). White solid; **TLC**, R_f = 0.53 (hexane–EtOAc = 1:1); **IR** (neat) 3437, 1790, 1737, 1691, 1655, 1176 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.08 (s, 3H), 1.60–1.68 (m, 1H), 1.83 (d, *J* = 0.9 Hz, 3H), 1.86–1.94 (m, 2H), 2.20–2.38 (m, 3H), 2.58–2.63 (m, 1H), 2.79–2.89 (m, 1H), 3.73 (s, 1H), 4.05 (d, *J* = 0.9 Hz, 1H), 6.01 (d, *J* = 2.1 Hz, 1H), 6.78 (s, 1H), 7.28–7.43 (m, 10H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 12.9, 16.4, 27.2, 28.5, 31.1, 35.2, 46.6, 53.9, 56.4, 59.6, 83.4, 84.9, 125.3, 127.3, 128.0, 128.6, 129.1, 129.2, 129.3, 135.7, 136.1, 141.1, 143.3, 146.1, 174.9, 175.5, 193.0, 206.9; **HPLC** (IC–3 column), Hexane–EtOH = 9:1 as eluent, 1.0 mL/min, t_R = 33.2 min (*major*), t_R = 39.6 min (*minor*); **HRMS** (ESI) m/z calcd for $[C_{32}H_{28}O_6+Na]^+$ 531.1787, found 531.1787; **$[\alpha]^{25.9}_D$** = –91.2 (*c* 2.0, $CHCl_3$) for 63% ee.





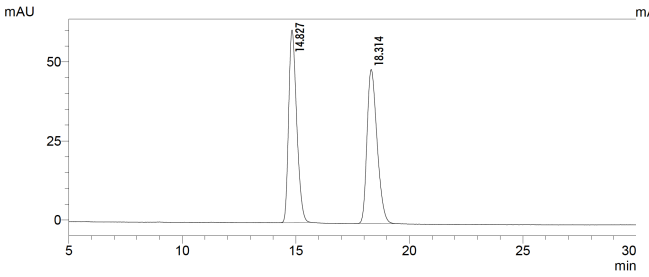
PDA Ch1 210nm

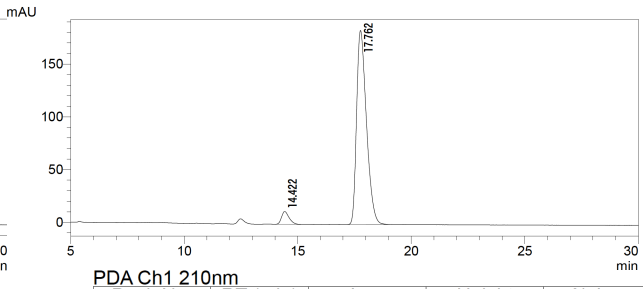
Peak No.	RT (min)	Area	Height	% Area
1	32.569	67776244	1012569	87.051
2	39.279	10081497	113324	12.949
Total		77857741	1125893	100.000



(1*R*,2*R*,4*R*)-8-Acetyl-6-cyclohexyl-4-ethyl-3',4'-dihydro-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-ene-3,5'-dione (5la): To a solution of **2l** (0.0276 g, 0.100 mmol) and **1a** (0.0170 g, 0.0100 mmol, 10 mol%) in toluene (5.00 mL) and H_2O (0.500 mL) was added oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 48 h at 0 °C (**2l** was

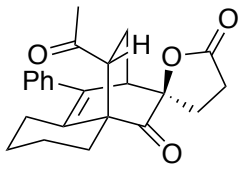
almost consumed), to the resulting mixture was added methyl vinyl ketone (0.082 mL, 1.00 mmol) at 0 ºC. The cooling bath was removed and the resulting mixture was allowed to warm to 25 ºC to enhance to cycloaddition reaction. After stirring for 18 h at room temperature, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 2:1) to give **5la** (0.0165 g, 0.0859 mmol) in 86% yield as a white solid. Enantiomeric excess of **5la** was determined to be 90% ee by HPLC analysis. **TLC**, R_f = 0.33 (hexane–EtOAc = 1:1); **IR** (KBr) 3437, 2926, 2851, 1794, 1734 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.06–1.31 (m, 5H), 1.34–1.41 (m, 1H), 1.69–1.93 (m, 8H), 2.04–2.21 (m, 2H), 2.11 (s, 3H), 2.52–2.62 (m, 2H), 2.83–2.93 (m, 2H), 2.99–3.03 (m, 1H), 5.59 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 9.3, 22.0, 25.9, 26.1, 26.2, 28.4, 29.0, 30.2, 30.6, 31.0, 31.5, 43.5, 45.0, 49.2, 53.9, 82.7, 121.9, 149.7, 176.4, 205.1, 206.9; **HPLC** (IC–3 column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 14.8 min (*minor*), t_R = 18.3 min (*major*); **HRMS** (FAB+) m/z calcd for $[C_{21}H_{28}O_4+H]^+$ 345.2066, found 345.2062; **$[\alpha]^{27.9}_D$** = –93.1 (*c* 1.4, $CHCl_3$) for 90% ee.





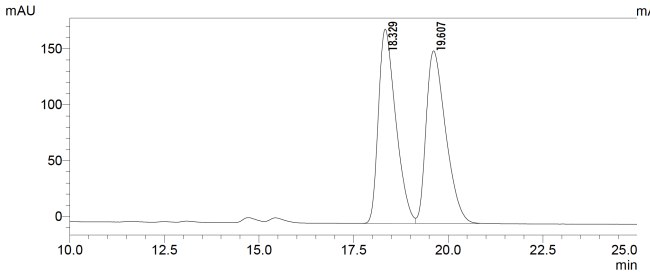
PDA Ch1 210nm

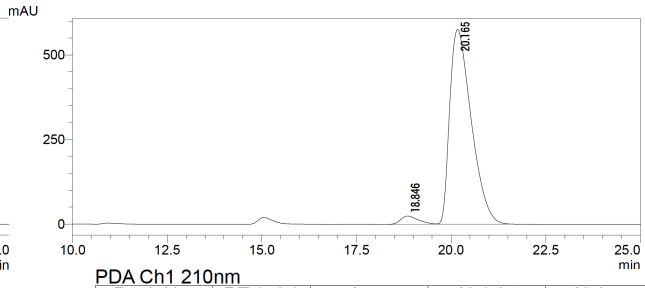
Peak No.	RT (min)	Area	Height	% Area
1	14.422	279726	12126	4.809
2	17.762	5537388	183947	95.191
Total		5817114	196073	100.000



(2*R*,2'*R*,4'*R*,4a'*S*)-4'-acetyl-1'-phenyl-3,3',4,4',5',6',7',8'-octahydro-2'*H*,5*H*-spiro[furan-2,10'-[2,4a]ethanonaphthalene]-5,9'-dione (5fa): Following a similar procedure as for **5la**, **2f** (0.0296 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.500 mL), 27 h (0 ºC), 12 h (25 ºC): 82% yield (0.0298 g, 0.0818 mmol), 93% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1). White solid; **TLC**, R_f = 0.43 (hexane–EtOAc = 2:1); **IR** (neat) 3545, 3438,

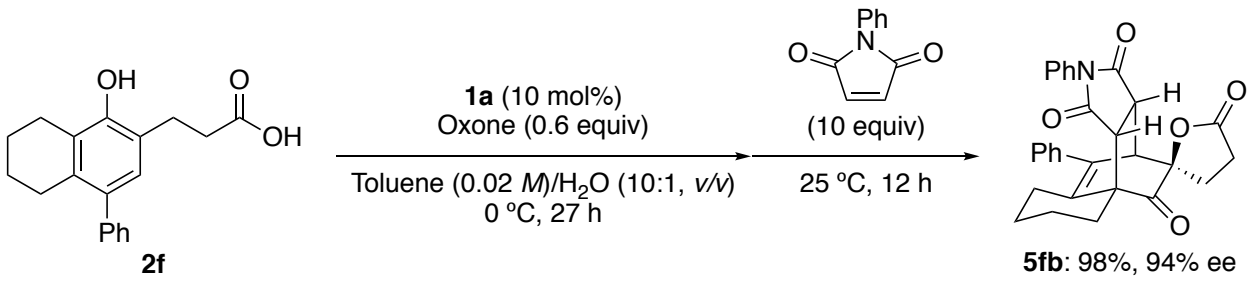
3025, 2950, 2867, 2358, 1784 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.30–1.33 (m, 1H), 1.53–1.73 (m, 5H), 2.03–2.10 (m, 1H), 2.19 (d, *J* = 0.6 Hz, 1H), 2.23–2.64 (m, 6H), 2.88–2.94 (m, 1H), 3.05 (dd, *J* = 6.6, 10.2 Hz, 1H), 3.21 (t, *J* = 3.0 Hz, 1H), 7.22–7.25 (m, 2H), 7.29–7.32 (m, 1H), 7.35–7.40 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ19.4, 20.8, 22.5, 25.5, 27.3, 29.0, 30.5, 31.9, 47.7, 50.6, 53.7, 82.3, 127.4, 127.9, 128.5, 135.6, 135.8, 138.6, 176.2, 204.9, 208.8; **HPLC** (IC–3 column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 18.3 min (*minor*), t_R = 19.6 min (*major*); **HRMS** (FAB+) m/z calcd for $[C_{23}H_{24}O_4+H]^+$ 365.1753, found 365.1744; **$[\alpha]^{23.7}_D$** = –110.0 (*c* 1.0, $CHCl_3$) for 93% ee.





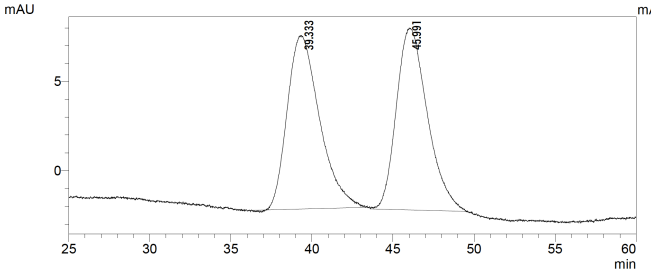
PDA Ch1 210nm

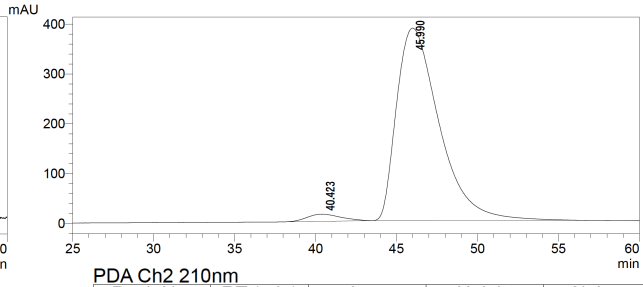
Peak No.	RT (min)	Area	Height	% Area
1	18.846	795984	24370	3.366
2	20.165	22849579	576459	96.634
Total		23645563	600829	100.000



(2*R*,3a'*R*,4'*R*,9a'*S*,9b'*R*)-2',5'-diphenyl-3,3a',4,6',7',8',9',9b'-octahydro-5*H*-spiro[furan-2,11'-[4,9a]ethanobenzo[*e*]isoindole]-1',3',5,10'(2'*H*,4'*H*)-tetraone (5fb): To a solution of **2f** (0.0276 g, 0.100 mmol) and **1a** (0.0170 g, 0.0100 mmol, 10 mol%) in toluene (5.00 mL) and H_2O (0.500 mL) was added oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 27 h at 0 °C (**2f** was almost consumed), 1-phenyl-1*H*-pyrrole-2,5-dione (0.173 g, 1.00 mmol) was added to the resulting mixture at 0 ºC. The cooling bath was removed and the resulting mixture was allowed to warm to 25 ºC to enhance the cycloaddition reaction. After stirring for 12 h at room temperature, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **5fb** (0.0458 g, 0.0979 mmol) in 98% yield as a white solid. Enantiomeric excess of **5fb** was determined to be 94% ee by HPLC analysis. **TLC**, R_f = 0.37 (hexane–EtOAc = 2:1); **IR** (neat)

3035, 2948, 2868, 1792, 1715 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.45–1.52 (m, 2H), 1.66–1.70 (m, 1H), 1.87–1.89 (m, 1H), 1.94–2.02 (m, 1H), 2.19–2.25 (m, 1H), 2.28–2.35 (m, 1H), 2.41–2.45 (m, 1H), 2.54–2.83 (m, 3H), 2.86–2.93 (m, 1H), 3.16 (d, *J* = 8.2 Hz, 1H), 3.81–3.85 (m, 2H), 7.09–7.12 (m, 2H), 7.22–7.24 (m, 2H), 7.29–7.46 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 19.2, 20.7, 20.9, 25.4, 28.5, 30.0, 41.2, 45.3, 49.6, 54.0, 80.8, 126.4, 127.9, 128.2, 129.0, 129.1, 129.3, 131.5, 135.4, 136.8, 137.4, 174.3, 175.2, 176.1, 203.9; **HPLC** (IH–3 column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 39.3 min (*minor*), t_R = 46.0 min (*major*); **HRMS** (ESI) m/z calcd for $[C_{29}H_{25}NO_5+Na]^+$ 490.1625, found 490.1625; **$[\alpha]^{24.8}_D$** = 49.0 (*c* 2.0, $CHCl_3$) for 94% ee.

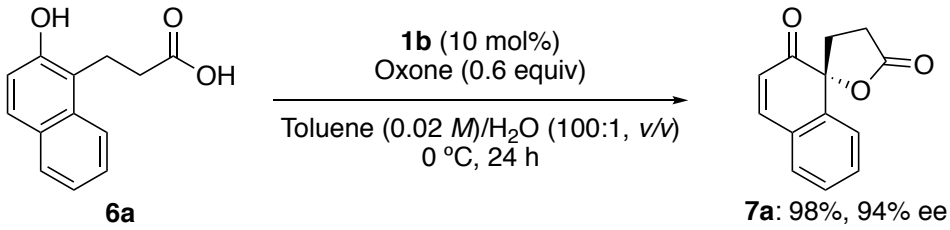




PDA Ch2 210nm

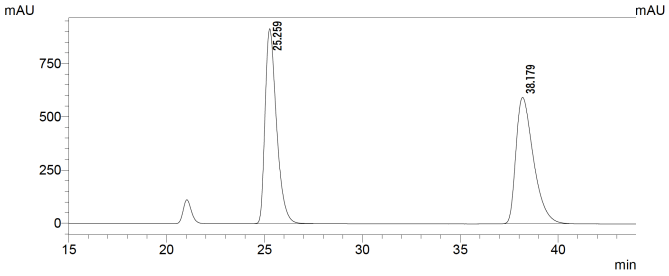
Peak No.	RT (min)	Area	Height	% Area
1	40.423	2075655	14385	2.852
2	45.990	70713864	386221	97.148
Total		72789518	400606	100.000

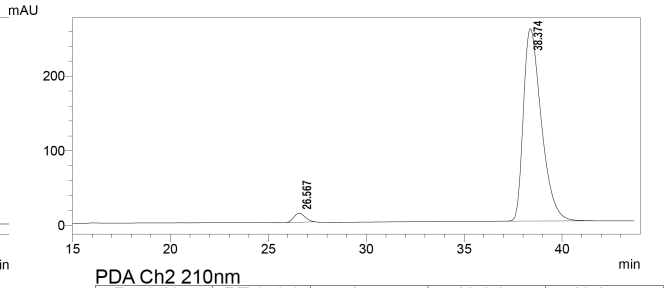
Enantioselective Oxidative Dearomatization of 2-Naphthols 6



6a **7a**: 98%, 94% ee

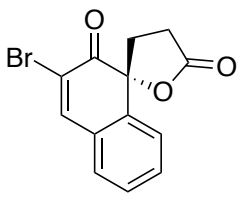
(*R*)-3,4-Dihydro-2'*H*,5*H*-spiro[furan-2,1'-naphthalene]-2',5-dione (7a):[7d] To a solution of **6a** (0.0216 g, 0.100 mmol) and **1b** (0.0250 g, 0.0100 mmol, 10 mol%) in toluene (5.00 mL) and H_2O (0.0500 mL) was added Oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 0 °C, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 2:1) to give (*R*)-**7a** (0.0210 g, 0.0978 mmol) in 98% yield as a white solid. Enantiomeric excess of **7a** was determined to be 94% ee by HPLC analysis. **TLC**, R_f = 0.70 (hexane–EtOAc = 1:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.11–2.20 (m, 1H), 2.62–2.70 (m, 2H), 2.81–2.90 (m, 1H), 6.18 (d, *J* = 9.6 Hz , 1H), 7.36 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.41 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.46–7.49 (m, 2H), 7.56 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.6, 35.8, 85.8, 122.6, 125.8, 129.1, 129.2, 129.7, 131.1, 140.6, 146.0, 176.4, 197.5; **HPLC** (OD–H column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 25.3 min (*S*), t_R = 38.2 min (*R*); **$[\alpha]^{27.2}_D$** = 180.7 (*c* 1.0, $CHCl_3$) for 94% ee.



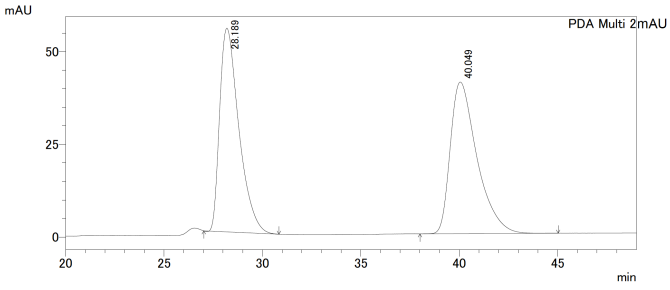


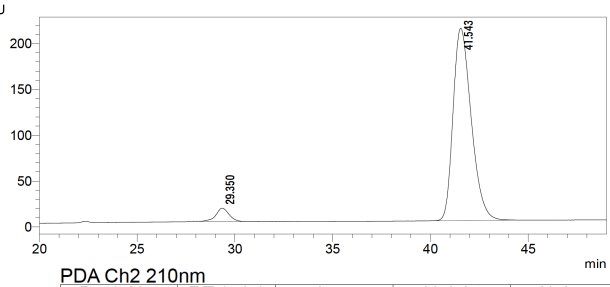
PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	26.567	485809	12181	2.872
2	38.374	16431623	257480	97.128
Total		16917432	269661	100.000



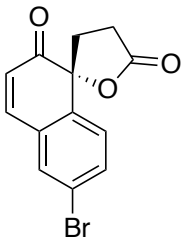
(*R*)-3'-Bromo-3,4-dihydro-2'*H*,5*H*-spiro[furan-2,1'-naphthalene]-2',5-dione (7b):[7d] Following a similar procedure as for **7a**, **6b** (0.0295 g, 0.100 mmol), **1b** (0.0250 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.0500 mL), 0 ºC, 20 h: 96% yield (0.0281 g, 0.0959 mmol), 91% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). White solid; **TLC**, R_f = 0.57 (hexane–EtOAc = 1:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.15–2.23 (m, 1H), 2.64–2.71 (m, 2H), 2.82–2.92 (m, 1H), 7.33 (d, J = 7.3Hz, 1H), 7.42 (dt, J = 1.4, 7.3Hz, 1H), 7.49–7.56 (m, 2H), 7.92 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.4, 36.1, 86.4, 118.2, 126.0, 128.8, 129.4, 129.6, 131.4, 139.9, 147.3, 175.8, 191.2; **HPLC** (OD–H column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 28.2 min (*S*), t_R = 40.1 min (*R*); **$[\alpha]^{28.4}_D$** = 266.1 (*c* 1.3, $CHCl_3$) for 91% ee.



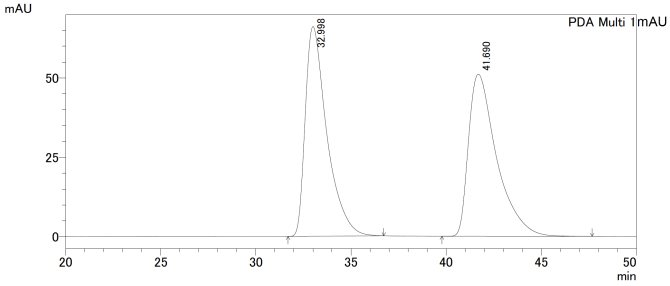


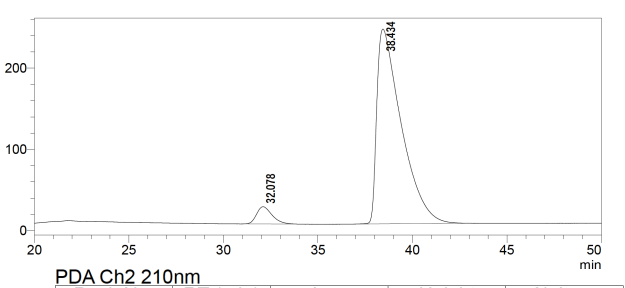
PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	29.350	675116	14478	4.742
2	41.543	13562156	210085	95.258
Total		14237272	224563	100.000



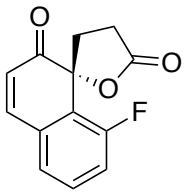
(*R*)-3'-Bromo-3,4-dihydro-2'*H*,5*H*-spiro[furan-2,1'-naphthalene]-2',5-dione (7c):[7d] Following a similar procedure as for **7a**, **6c** (0.0295 g, 0.100 mmol), **1b** (0.0250 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.0500 mL), 0 ºC, 12 h: 88% yield (0.0258 g, 0.0881 mmol), 90% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). White solid; **TLC**, R_f = 0.57 (hexane–EtOAc = 1:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.08–2.16 (m, 1H), 2.62–2.69 (m, 2H), 2.79–2.89 (m, 1H), 6.22 (d, J = 9.6 Hz , 1H), 7.41 (d, J = 9.6 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 1.8, 8.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.4, 35.6, 85.4, 123.1, 123.7, 127.4, 131.0, 132.3, 133.7, 139.2, 144.4, 176.0, 196.7; **HPLC** (OD–H column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 33.0 min (*S*), t_R = 41.7 min (*R*); **$[\alpha]^{28.9}_D$** = 116.2 (*c* 1.2, $CHCl_3$) for 90% ee.



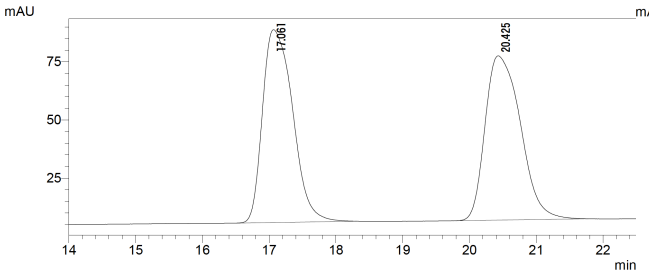


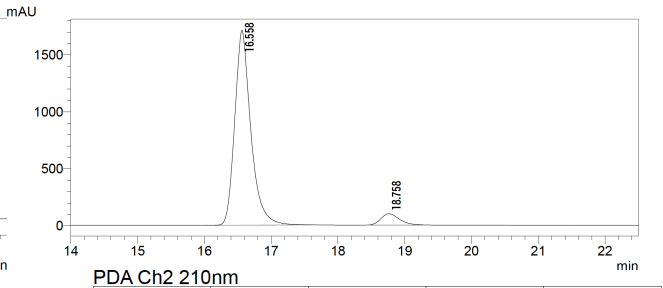
PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	32.078	1181430	21058	5.198
2	38.434	21548063	239490	94.802
Total		22729493	260547	100.000



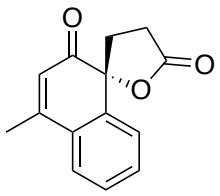
(*R*)-8'-Fluoro-3,4-dihydro-2'*H*,5*H*-spiro[furan-2,1'-naphthalene]-2',5-dione (7d):[7d] Following a similar procedure as for **7a**, **6d** (0.0234 g, 0.100 mmol), **1b** (0.0250 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.0500 mL), 0 ºC, 24 h: 95% yield (0.0221 g, 0.0953 mmol), 87% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). White solid; **TLC**, R_f = 0.57 (hexane–EtOAc = 1:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.41–2.56 (m, 2H), 2.73–2.82 (m, 1H), 2.93–3.03 (m, 1H), 6.23 (d, J = 10.1 Hz , 1H), 7.16–7.21 (m, 2H), 7.41–7.49 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 27.1, 32.6, 81.1, 118.8 (d, $J_{C–F}$ = 22.5 Hz), 123.7, 125.8 (d, $J_{C–F}$ = 3.8 Hz), 126.2 (d, $J_{C–F}$ = 10.0 Hz), 131.3, 131.4, 145.5 (d, $J_{C–F}$ = 3.8 Hz), 161.5 (d, $J_{C–F}$ = 252.5 Hz), 176.4, 196.3; **^{19}F NMR** (CDCl3, 376 MHz) δ –111.4; **HPLC** (IA–3 column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 17.1 min (*R*), t_R = 20.4 min (*S*); **[α]$^{27.3}_D$** = 73.6 (*c* 1.0, $CHCl_3$) for 87% ee.



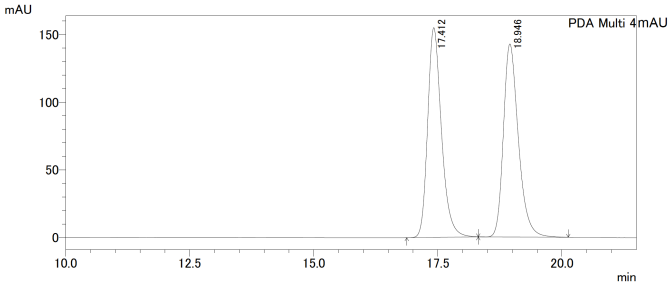


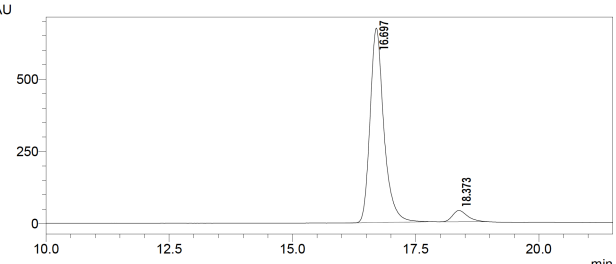
PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	16.558	28601911	1713152	93.510
2	18.758	1985126	100805	6.490
Total		30587038	1813957	100.000



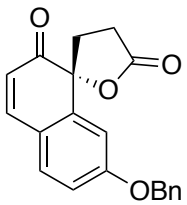
(*R*)-4'-Methyl-3,4-dihydro-2'*H*,5*H*-spiro[furan-2,1'-naphthalene]-2',5-dione (7e):[7d] Following a similar procedure as for **7a**, **6e** (0.0230 g, 0.100 mmol), **1b** (0.0250 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.0500 mL), 0 ºC, 22 h: 92% yield (0.0210 g, 0.0921 mmol), 88% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). White solid; **TLC**, R_f = 0.57 (hexane–EtOAc = 1:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.10–2.19 (m, 1H), 2.40 (d, J = 1.4 Hz, 3H), 2.61–2.68 (m, 2H), 2.81–2.91 (m, 1H), 6.11 (d, J = 1.4 Hz, 1H), 7.42–7.51 (m, 2H), 7.56–7.58 (d, J = 7.8 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.6, 26.8, 36.1, 85.7, 122.0, 125.6, 126.0, 128.9, 130.4, 130.8, 140.4, 154.0, 176.5, 196.7; **HPLC** (IA–3 column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 17.4 min (*R*), t_R = 18.9 min (*S*); **$[\alpha]^{27.4}_D$** = 225.0 (*c* 0.6, $CHCl_3$) for 88% ee.





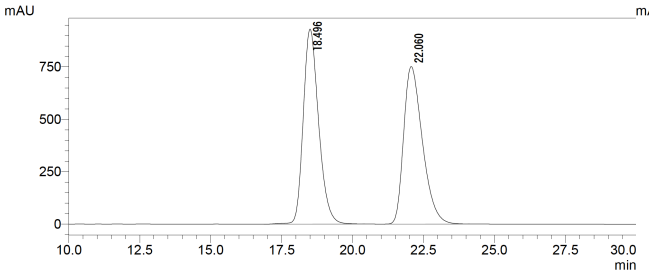
PDA Ch2 210nm

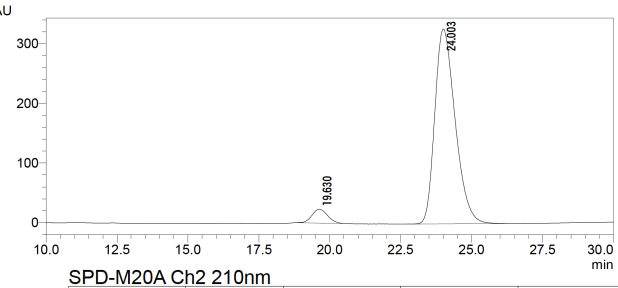
Peak No.	RT (min)	Area	Height	% Area
1	16.697	13104718	673035	94.052
2	18.373	828757	39076	5.948
Total		13933475	712112	100.000



(*R*)-7'-(Benzyloxy)-3,4-dihydro-2'*H*,5*H*-spiro[furan-2,1'-naphthalene]-2',5-dione (7f):[7d] Following a similar procedure as for **7a**, **6f** (0.0322 g, 0.100 mmol), **1b** (0.0250 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.0500 mL), 0 ºC, 24 h: 92% yield (0.0295 g, 0.0922 mmol), 90% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). Yellow solid; **TLC**, R_f = 0.50 (hexane–EtOAc = 1:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.07–2.15 (m, 1H), 2.58–2.68 (m, 2H), 2.79–2.88 (m, 1H), 5.12 (t, J = 12.1 Hz, 2H), 6.04 (d, J = 10.8 Hz, 1H), 6.95 (dd, J = 2.8, 8.5 Hz, 1H), 7.18

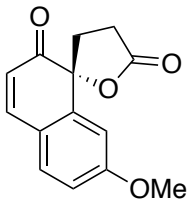
(d, J = 2.8 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.33–7.43 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.5, 36.1, 70.3, 85.8, 112.6, 115.1, 120.0, 122.3, 127.5, 128.3, 128.7, 131.5, 135.8, 143.0, 145.9, 161.2, 176.4, 197.6; **HPLC** (OD–H column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 18.5 min (*S*), t_R = 22.1 min (*R*); **[α]$^{25.2}_D$** = 119.6 (*c* 2.0, $CHCl_3$) for 90% ee.





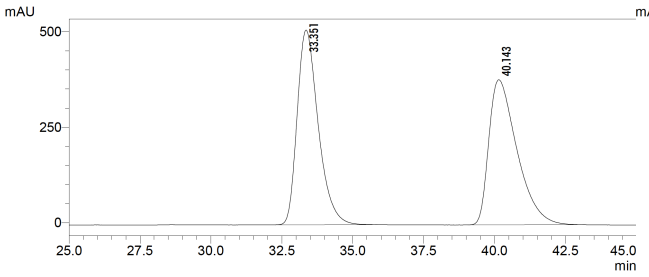
SPD-M20A Ch2 210nm

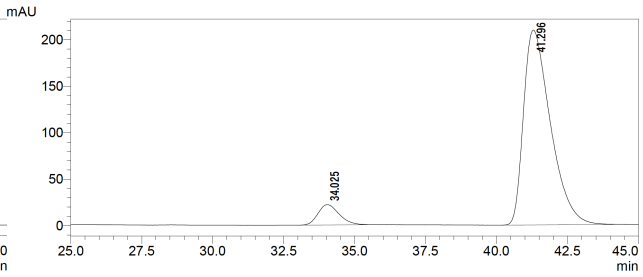
Peak No.	RT (min)	Area	Height	% Area
1	19.630	884848	23230	5.144
2	24.003	16318375	326576	94.856
Total		17203223	349806	100.000



(*R*)-7'-(Methoxy)-3,4-dihydro-2'*H*,5*H*-spiro[furan-2,1'-naphthalene]-2',5-dione (7g):[7d]

Following a similar procedure as for **7a**, **6g** (0.0246 g, 0.100 mmol), **1b** (0.0250 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.0500 mL), 0 ºC, 24 h: 92% yield (0.0227 g, 0.0915 mmol), 85% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). White solid; **TLC**, R_f = 0.60 (hexane–EtOAc = 1:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.08–2.18 (m, 1H), 2.61–2.70 (m, 2H), 2.80–2.89 (m, 1H), 3.87 (s, 3H), 6.04 (d, J = 10.1 Hz, 1H), 6.89 (dd, J = 2.8, 8.5 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 10.1 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.5, 36.1, 55.7, 86.0, 111.6, 114.4, 119.7, 122.1, 131.5, 143.0, 146.0, 162.1, 176.5, 197.5; **HPLC** (OD–H column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 33.4 min (*S*), t_R = 40.1 min (*R*); **[α]$^{26.6}_D$** = 94.4 (*c* 0.5, $CHCl_3$) for 85% ee.

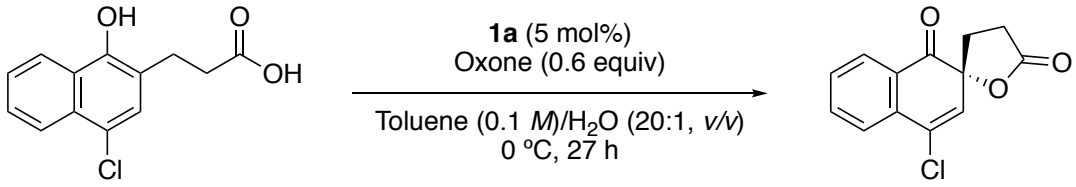




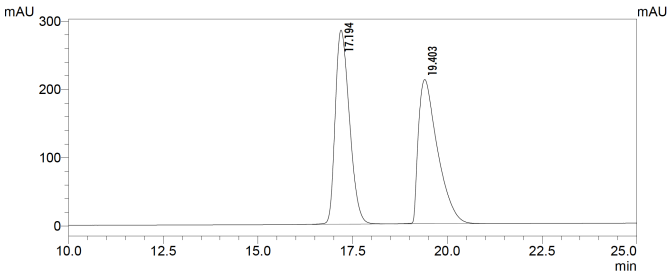
SPD-M20A Ch2 210nm

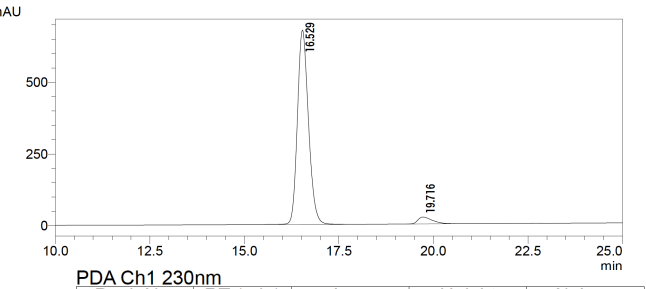
Peak No.	RT (min)	Area	Height	% Area
1	34.025	1141036	21976	7.618
2	41.296	13837929	209720	92.382
Total		14978965	231695	100.000

Enantioselective Oxidative Dearomatization of 1-Naphthols 8



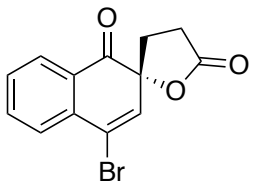
(*R*)-4'-Chloro-3,4-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-1',5-dione (9a):[7b–d] To a solution of **8a** (0.0216 g, 0.100 mmol) and **1a** (0.00851 g, 0.00500 mmol, 5 mol%) in toluene (1.00 mL) and H_2O (0.0500 mL) was added Oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 27 h, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) at 0 °C. 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 (*R*)-**9a** (0.0242 g, 0.0973 mmol) in 97% yield as a white solid. Enantiomeric excess of **9a** was determined to be 91% ee by HPLC analysis. **TLC**, R_f = 0.43 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.21–2.29 (m, 1H), 2.43–2.50 (m, 1H), 2.59–2.67 (m, 1H), 2.86-2.96 (m, 1H), 6.41 (s, 1H), 7.51–7.55 (m, 1H), 7.74–7.80 (m, 2H), 8.06–8.08 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.5, 31.4, 83.5, 126.1, 127.3, 128.0, 129.1, 130.1, 131.8, 134.5, 135.8, 175.8, 194.7; **HPLC** (OD–3 column), Hexane–EtOH = 9:1 as eluent, 1.0 mL/min, t_R = 17.2 min (*R*), t_R = 19.4 min (*S*); **$[\alpha]^{25.5}_D$** = 140.8 (*c* 0.5, $CHCl_3$) for 91% ee.





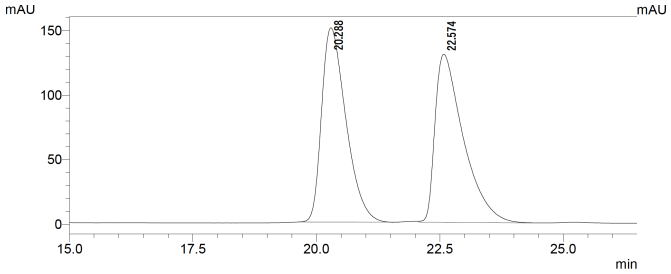
PDA Ch1 230nm

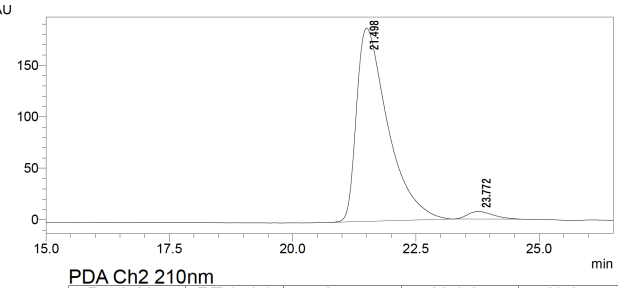
Peak No.	RT (min)	Area	Height	% Area
1	16.529	13755866	677578	95.660
2	19.716	624023	23821	4.340
Total		14379889	701399	100.000



(*R*)-4'-Bromo-3,4-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-1',5-dione (9b):[7b–d] Following a similar procedure as for **9a**, **8b** (0.0295 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%),

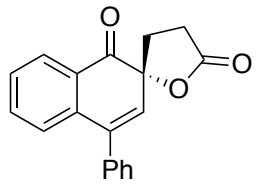
oxone (0.0369 g, 0.0600 mmol), toluene (1.00 mL), H_2O (0.0500 mL), 0 ºC, 20 h: 94% yield (0.0275 g, 0.0938 mmol), 94% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). White solid; **TLC**, R_f = 0.43 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.21–2.29 (m, 1H), 2.43–2.50 (m, 1H), 2.59–2.66 (m, 1H), 2.85–2.94 (m, 1H), 6.67 (s, 1H), 7.47–7.54 (m, 1H), 7.72–7.77 (m, 2H), 8.04 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.4, 31.2, 84.2, 122.5, 127.3, 128.0, 128.8, 130.1, 133.4, 135.1, 135.9, 175.7, 194.7; **HPLC** (OD–H column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 20.3 min (*R*), t_R = 22.6 min (*S*); **[α]$^{23.9}_D$** = 91.3 (*c* 2.1, $CHCl_3$) for 94% ee.



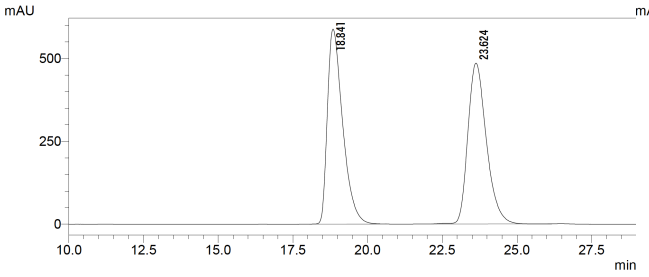


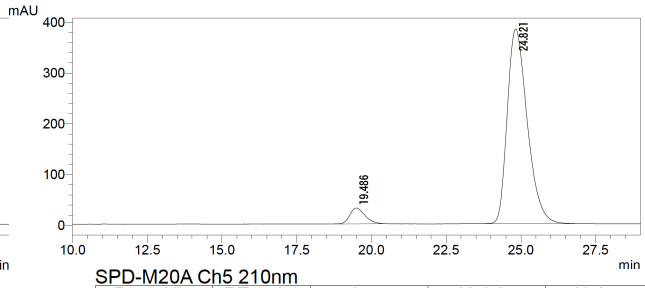
PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	21.498	8288520	187834	96.932
2	23.772	262299	7292	3.068
Total		8550819	195126	100.000



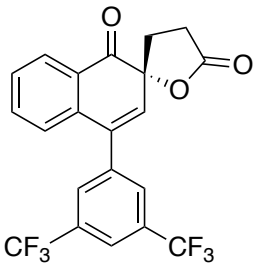
(*R*)-4'-Phenyl-3,4-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-1',5-dione (9c):[7b–d] Following a similar procedure as for **9a**, **8c** (0.0292 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (5.00 mL), H_2O (0.500 mL), 25 ºC, 4 h: 83% yield (0.0241 g, 0.0831 mmol), 88% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). White solid; **TLC**, R_f = 0.47 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.24–2.32 (m, 1H), 2.50–2.57 (m, 1H), 2.60–2.67 (m, 1H), 2.88–2.98 (m, 1H), 6.13 (s, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.34–7.37 (m, 2H), 7.41-7.49 (m, 4H), 7.56 (dt, *J* = 1.4, 7.7 Hz, 1H), 8.10 (dd, *J* = 1.4, 7.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 26.8, 31.5, 83.7, 127.4, 127.6, 128.2, 128.4, 128.7, 128.8, 128.9, 130.6, 135.3, 137.4, 137.6, 139.9, 176.4, 196.4; **HPLC** (OD–H column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 18.8 min (*S*), t_R = 23.6 min (*R*); **[α]$^{27.2}_D$** = 116.8 (*c* 1.0, $CHCl_3$) for 88% ee.



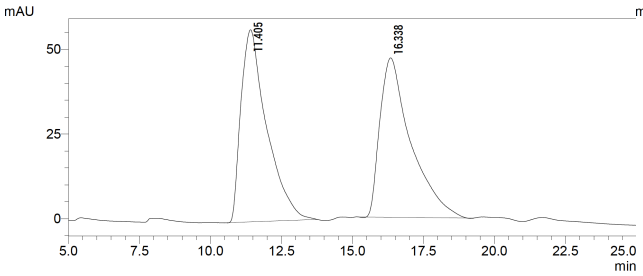


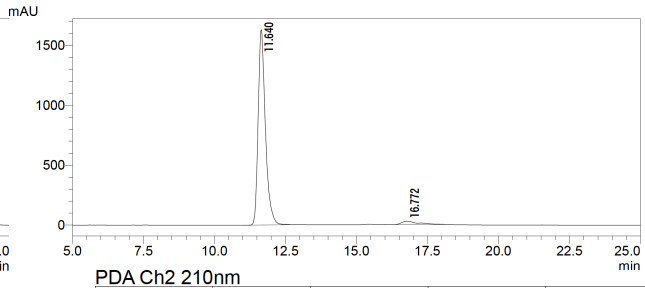
SPD-M20A Ch5 210nm

Peak No.	RT (min)	Area	Height	% Area
1	19.486	1091254	31010	5.755
2	24.821	17872000	383210	94.245
Total		18963254	414221	100.000



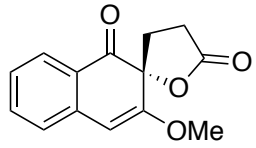
(*R*)-4'-(3,5-bis(trifluoromethyl)phenyl)-3,4-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-1',5-dione (9d):[7c] Following a similar procedure as for **9a**, **8d** (0.0428 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (1.00 mL), H_2O (0.0500 mL), 0 ºC, 23 h: 96% yield (0.0409 g, 0.0959 mmol), 94% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). White solid; **TLC**, R_f = 0.66 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.29–2.37 (m, 1H), 2.53–2.59 (m, 1H), 2.66 (ddd, J = 1.8, 9.6, 17.8 Hz, 1H), 2.89–2.99 (m, 1H), 6.23 (s, 1H), 6.97 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.84 (s, 2H), 7.98 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 26.4, 31.3, 83.3, 122.4 (q, $J_{C–F}$ = 3.8 Hz), 123.0 (q, $J_{C–F}$ = 271 Hz), 126.5, 127.4, 128.6, 129.1, 129.7, 132,2 (q, $J_{C–F}$ = 33.8 Hz), 132.7, 135.7, 135.9, 137.4, 139.8, 175.9, 195.8; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ –62.6; **HPLC** (IA–3 column), Hexane–EtOH = 10:1 as eluent, 1.0 mL/min, t_R = 11.4 min (*R*), t_R = 16.3 min (*S*); **[α]$^{24.5}_D$** = 84.3 (*c* 1.4, $CHCl_3$) for 92% ee.



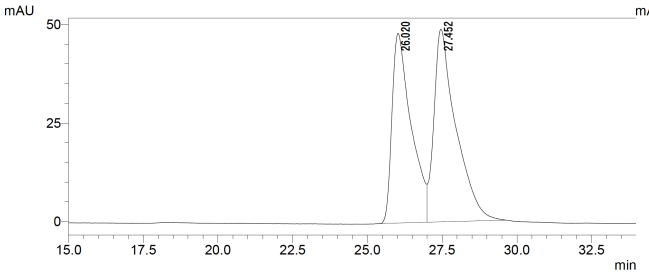


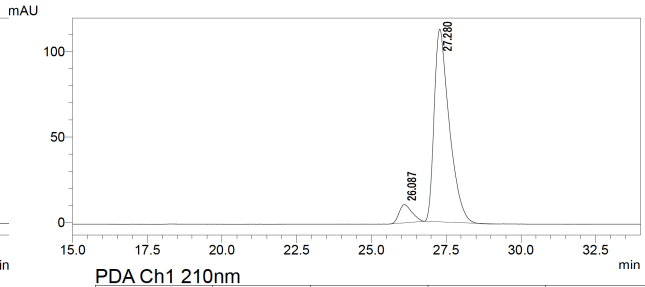
PDA Ch2 210nm

Peak No.	RT (min)	Area	Height	% Area
1	11.640	28864357	1629462	95.965
2	16.772	1213734	29285	4.035
Total		30078091	1658747	100.000



(*R*)-3'-Methoxy-3,4-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-1',5-dione (9e):[7b,d] Following a similar procedure as for **9a**, **8e** (0.0246 g, 0.100 mmol), **1a** (0.0170 g, 0.0100 mmol, 10 mol%), oxone (0.0369 g, 0.0600 mmol), toluene (1.00 mL), H_2O (0.0500 mL), 0 ºC, 6.5 h: 87% yield (0.0213 g, 0.0874 mmol), 85% ee. *cf.*: **1b** (0.0250 g, 0.0100 mmol, 10 mol%), toluene (1.00 mL), H_2O (0.0500 mL), 10.5 h (0 ºC): 90% yield (0.0220 g, 0.0902 mmol), 79% ee. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1). Pale yellow solid; **TLC**, R_f = 0.45 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 2.33–2.49 (m, 2H), 2.66–2.77 (m, 1H), 2.81–2.94 (m, 1H), 3.82 (s, 3H), 5.73 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.23 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.54 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.96 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 27.4, 30.5, 55.8, 82.8, 98.3, 124.7, 126.4, 126.8, 128.1, 136.0, 138.2, 157.6, 176.6, 195.2; **HPLC** (AD-3 column), Hexane–*i*PrOH = 85:15 as eluent, 0.7 mL/min, t_R = 26.0 min (*S*), t_R = 27.5 min (*R*); **$[\alpha]^{24.3}_D$** = 98.4 (*c* 1.0, $CHCl_3$) for 85% ee.





PDA Ch1 210nm

Peak No.	RT (min)	Area	Height	% Area
1	26.087	318297	10653	7.461
2	27.280	3947796	112621	92.539
Total		4266093	123274	100.000

Procedures for Control Experiments

Control Experiments to Probe Active Species

Using I_2, Bu_4NI_3, $NaIO_3$ or Bu_4NIO_4 (Scheme 4, Eq. 1; Table S4, Entries 1–4): To a solution of **2a** (0.0278 g, 0.100 mmol) in toluene (5.00 mL) and H_2O (0.500 mL) was added iodine (0.0254 g, 0.100 mmol) or tetrabutylammonium triiodide (0.0623 g, 0.100 mmol) or sodium iodate (0.0198 g, 0.100 mmol) or tetrabutylammonium (meta)periodate (0.0433 g, 0.100 mmol) at 25 ºC. The reaction was monitored by TLC analysis and ^{1}H NMR analysis (**2a** was recovered >95%). Similar control experiments were also performed using **6a** or **8a** instead of **2a** (Table S5, Entries 1–4). In contrast to **2a**, oxidation of **6a** or **8a** proceeded using $NaIO_3$ or Bu_4NIO_4 (Table S5, Entries 3 and 4).

Using I_2 and Bu_4NOH (Scheme 4, Eq. 2; Table S4, Entry 5): To a solution of iodine (0.0254 g,

0.100 mmol) in toluene (5.00 mL) and H_2O (0.500 mL) were added 40% aqueous tetrabutylammonium hydroxide (0.130 mL, 0.200 mmol) and **2a** (0.0278 g, 0.100 mmol) at 25 ºC. The reaction was monitored by TLC analysis and ^{1}H NMR analysis. After stirring for 24 h, small amount of reaction mixture was sampled *via* syringe and poured into saturated aqueous $Na_2S_2O_3$ to quench the reaction. The volatiles were removed under reduced pressure, and the residue was dissolved into $CDCl_3$ to measure the conversion yield, which was determined by ^{1}H NMR analysis. Similar control experiment was also performed using **6a** instead of **2a** and similar results were obtained (Table S5, entry 5).

Using I_2 and $KHSO_4$, Bu_4NHSO_4 or Bu_4NPF_6 (Scheme 4, Eqs. 3 and 5; Table S4, Entries 6, 7 and 9): To a solution of **2a** (0.0278 g, 0.100 mmol) in toluene (5.00 mL) and H_2O (0.500 mL) was added iodine (0.0254 g, 0.100 mmol) and $KHSO_4$ (0.0272 g, 0.200 mmol) or Bu_4NHSO_4 (0.0679 g, 0.200 mmol) or Bu_4NPF_6 (0.0775 g, 0.200 mmol) at 25 ºC. The reaction was monitored by TLC analysis and ^{1}H NMR analysis. After stirring for 24 h, small amount of reaction mixture was sampled *via* syringe and poured into saturated aqueous $Na_2S_2O_3$ to quench the reaction. The volatiles were removed under reduced pressure, and the residue was dissolved into $CDCl_3$ to measure the conversion yield, which was determined by ^{1}H NMR analysis. Similar control experiment was also performed using **6a** instead of **2a** with $KHSO_4$ or Bu_4NHSO_4 and similar results were obtained (Table S5, entries 6 and 7).

Using Bu_4NI_3 and $KHSO_4$ (Scheme 4, Eq. 4; Table S4, Entry 8): To a solution of **2a** (0.0278 g, 0.100 mmol) in toluene (5.00 mL) and H_2O (0.500 mL) was added Bu_4NI_3 (0.0623 g, 0.100 mmol) and $KHSO_4$ (0.0272 g, 0.200 mmol) at 25 ºC. The reaction was monitored by TLC analysis and ^{1}H NMR analysis. After stirring for 24 h, small amount of reaction mixture was sampled *via* syringe and poured into saturated aqueous $Na_2S_2O_3$ to quench the reaction. The volatiles were removed under reduced pressure, and the residue was dissolved into $CDCl_3$ to measure the conversion yield, which was determined by ^{1}H NMR analysis.

Using I_2 and Acid Additives (Scheme 4, Eq. 6; Table S4, Entries 10–14): To a solution of **2a** (0.0278 g, 0.100 mmol) and iodine (0.0254 g, 0.100 mmol) in toluene (5.00 mL) and H_2O (0.500 mL) was added sulfuric acid (0.0107 mL, 0.200 mmol) or 85-wt% aqueous phosphoric acid (0.0125 mL, 0.200 mmol) or trifluoroacetic acid (0.0153 mL, 0.200 mmol) or oxalic acid (0.0180 g, 0.200 mmol) or acetic acid (0.0114 mL, 0.200 mmol) at 25 ºC. The reaction was monitored by TLC analysis and ^{1}H NMR analysis. After stirring for 12 h, small amount of reaction mixture was sampled *via* syringe and poured into saturated aqueous $Na_2S_2O_3$ to quench the reaction. The volatiles were removed

under reduced pressure, and the residue was dissolved into $CDCl_3$ to measure the conversion yield, which was determined by ^1H NMR analysis.

Using I_2 or Bu_4NI_3 under Catalytic Conditions (Scheme 4, Eqs. 7 and 8; Table S4, Entries 15 and 16): To a solution of **2a** (0.0280 g, 0.100 mmol) and iodine (0.00250 g, 0.0100 mmol) or Bu_4NI_3 (0.00620 g, 0.0100 mmol) in toluene (0.500 mL) and H_2O (0.500 mL) was added Oxone (0.0369 g, 0.0600 mmol) at 25 ºC. When iodine was used, Bu_4NHSO_4 (0.00340 g, 0.0100 mmol) was used as a phase transfer catalyst. The reaction was monitored by TLC analysis and ^1H NMR analysis. After stirring for 5 h, small amount of reaction mixture was sampled *via* syringe and poured into saturated aqueous $Na_2S_2O_3$ to quench the reaction. The volatiles were removed under reduced pressure, and the residue was dissolved into $CDCl_3$ to measure the conversion yield, which was determined by ^1H NMR analysis.

Comparison of Stability of I^+ Catalysis with or without Pre-mixing (Tables 5, S6 and S7)

To a solution of Bu_4NI (0.00370 g, 0.0100 mmol) in toluene (5.00 mL) and H_2O (0.500 mL) was added Oxone (0.0369 g, 0.0600 mmol) or hydrogen peroxide (0.0206 mL, 0.200 mmol) at 25 ºC. After stirring for the indicated period (*premixing time*), to the resulting mixture was added **6a** (0.0216 g, 0.100 mmol) at 25 °C. After stirring for the indicated period (*reaction time*), small amount of reaction mixture was sampled *via* syringe and poured into saturated aqueous $Na_2S_2O_3$ to quench the reaction. The volatiles were removed under reduced pressure, and the residue was dissolved into $CDCl_3$ to measure the conversion yield, which was determined by ^1H NMR analysis.

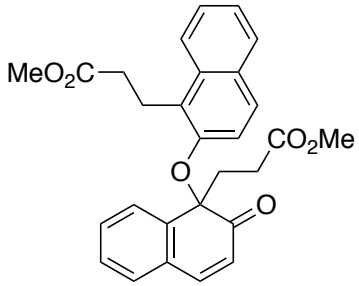
Comparison of Stability of I^+ Catalysis at Low Catalyst Loading (Tables 5 and S7)

To a solution of Bu_4NI (0.000900 g, 0.00250 mmol) in toluene (0.500 mL) and H_2O (0.500 mL) was added Oxone (0.0922 g, 0.0150 mmol) or hydrogen peroxide (0.0515 mL, 0.500 mmol) at 25 ºC. After stirring for the indicated period (*premixing time*), to the resulting mixture was added **8a** (0.0627 g, 0.250 mmol) at 25 °C. After stirring for the indicated period (*reaction time*), small amount of reaction mixture was sampled *via* syringe and poured into saturated aqueous $Na_2S_2O_3$ to quench the reaction. The volatiles were removed under reduced pressure, and the residue was dissolved into $CDCl_3$ to measure the conversion yield, which was determined by ^1H NMR analysis.

Control Experiments to Probe Reaction Intermediates (Scheme 6)

To a solution of **10a** (0.0146 g, 0.0500 mmol) or **10b** (0.0115 g, 0.0500 mmol) or **11a** (0.0146 g, 0.0500 mmol) or **11b** (0.0115 g, 0.0500 mmol) and **1a** (0.00851 g, 0.00500 mmol, 5 mol%) in toluene (2.50 mL) and H_2O (0.0250 mL) was added oxone (0.0184 g, 0.0300 mmol) at 25 ºC. The reaction

was monitored by TLC analysis and ^{1}H NMR analysis. No reaction was observed for **10a**, **10b** and **11a** even after 24 h. In sharp contrast a clean oxidation reaction was observed for **11b**. For **11b**, after stirring for 48 h at 25 °C, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) 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 = 6:1 to 2:1) to give **12** (0.0108 g, 0.0236 mmol**)** in 94% yield.



Methyl 3-(2-((1-(3-methoxy-3-oxopropyl)-2-oxo-1,2-dihydronaphthalen-1-yl)oxy)naphthalen-1-yl)propanoate (12): White solid; **TLC**, R_f = 0.49 (Hexane–EtOAc = 2:1); **IR** (neat) 3067, 2959, 2842, 2361, 1736, 1677, 1239 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.33–2.42 (m, 1H), 2.44–2.61 (m, 2H), 2.66–2.80 (m, 2H), 2.88–2.96 (m, 1H), 3.54–3.69 (m, 2H), 3.63 (s, 3H), 3.76 (s, 3H), 6.00 (d, *J* = 8.7 Hz, 1H), 6.32 (d, *J* = 9.6 Hz, 1H), 7.27–7.38 (m, 4H), 7.41–7.49 (m, 3H), 7.60 (t, *J* = 10.1 Hz, 2H), 7.99 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 21.2, 27.4, 33.9, 38.5, 51.6, 51.7, 83.7, 115.7, 122.0, 122.6, 123.4, 125.4, 126.0, 126.5, 127.1, 128.4, 128.5, 128.8, 129.5, 130.1, 130.7, 132.7, 143.0, 144.8, 150.0, 173.1, 173.9, 198.4; **HRMS** (ESI) m/z calcd for $[C_{28}H_{26}O_6+Na]^+$ 481.1622, found 481.1628.

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19. Interestingly, in contrast to phenols, oxidation of 2-naphthol **6a** and 1-naphthol **8a** proceeded with the use of high valent iodines ($NaIO_3$ and Bu_4NIO_4) to give the corresponding spirolactones **7a** and **9a** quantitatively. Nevertheless, according to the Raman analysis, these high valent species were not generated under the present Bu_4NI/Oxone catalytic conditions (Figure 1).
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Chapter 3

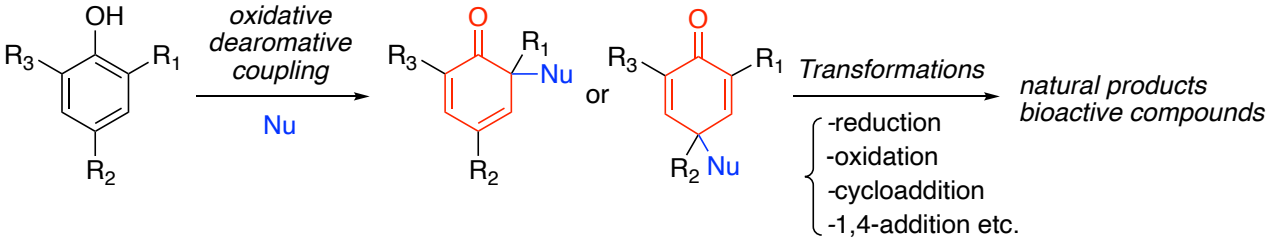
Oxidative Dearomative Coupling Reaction of Less-Reactive Arenols Using Hypohalite Catalysis

Abstract: We previously developed chiral hypoiodite catalysis for enantioselective oxidative dearomatization of highly reactive electron-rich arenols. On the other hand, no reaction was observed for relatively less-reactive phenols that bear electron-withdrawing groups (EWG). Considering the catalytic mechanism and the characteristics of halogens, here, we developed high-performance hypohalite catalysis for oxidative dearomatization of less-reactive electron-deficient phenols using a quaternary ammonium halide catalyst and a suitable oxidant. Notably, we succeeded in expanding the reaction scope to inter- and intramolecular oxidative dearomative C–O, C–N, and C–C coupling reactions. Moreover, we achieved the first enantioselective hypobromite catalysis for oxidative dearomative coupling reactions using chiral ammonium cation as a countercation of bromide. Mechanistic studies revealed that the reaction mechanisms might differ depending on the halide catalysts.

Introduction

Cyclohexadienone and its derivatives are important building blocks for the synthesis of natural products or bioactive compounds via, e.g., Diels–Alder, 1,4-addition, and reduction reactions (Scheme 1).[1] In this context, oxidative dearomatization of arenols has been developed as a conventional method for synthesizing cyclohexadienone skeletons.[2]

Scheme 1. Oxidative Dearomatization of Arenols and Synthetic Transformation



To date, many elegant strategies for catalytic asymmetric dearomatization (CADA[3]) reactions of arenols have been developed using transition-metal or organocatalysis.[2–4] In this context, we have developed hypoiodite catalysis for oxidative dearomatization of arenols.[5] A plausible mechanism is shown in Figure 1 (X = I). First, the hypoiodite species would be generated *in situ* from the corresponding onium iodide in the presence of an oxidant. These catalytic active species then catalyze the dehydrogenative coupling of two nucleophilic partners (Nu^1–H and Nu^2–H). During this process, while one of the nucleophiles (Nu^1–H) is iodinated to give an electrophilic species (*umpolung*), the other (Nu^2–H) is activated as an ion pair with a countercation (R_4N^+) of hypoiodite *via* deprotonation. A catalytic cycle can be accomplished by reductive elimination of iodide to give the corresponding coupling product. In this catalysis, the reaction of arenols **1** could proceed smoothly to give the corresponding spirolactones **2** in high yield with high enantioselectivity by using chiral quaternary ammonium iodide **3**·**I**[6] and oxone[7] ($KHSO_5 \cdot 0.5KHSO_4 \cdot 0.5K_2SO_4$) as a catalyst and an oxidant, respectively (Scheme 2a). However, the substrate scope of I^+/oxone catalysis had so far been limited to electron-rich arenols, which are relatively reactive, and no reaction was observed for relatively less-reactive phenols, such as **1a**, that bear electron-withdrawing groups (EWG) (Scheme 2b).

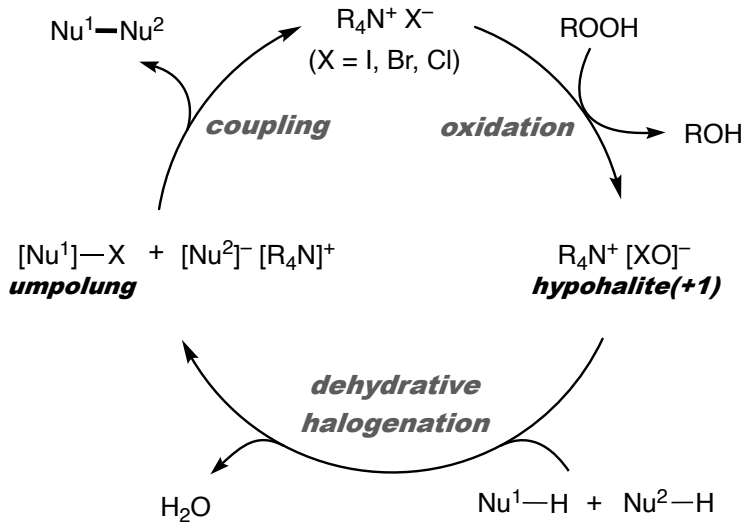
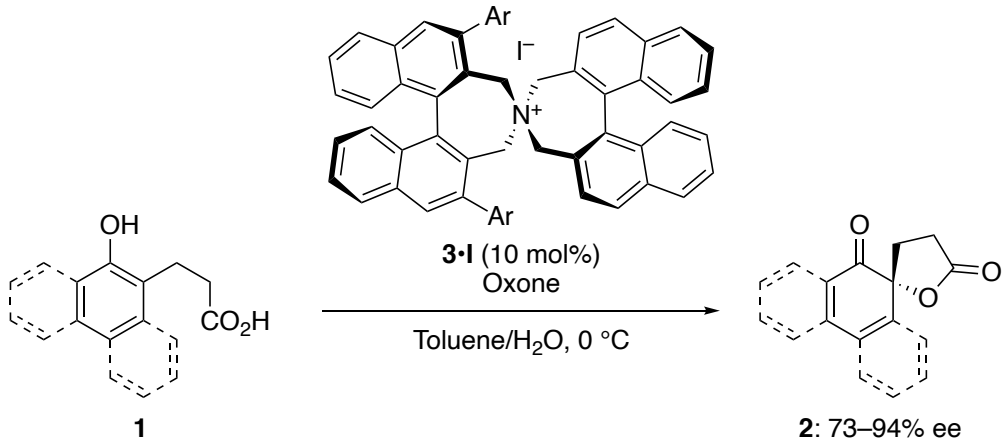


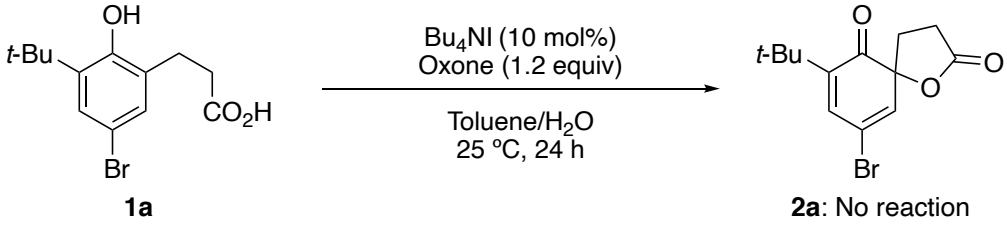
Figure 1. Concept of hypohalite catalysis.

Scheme 2. Hypoiodite Catalyzed Oxidative Dearomatization of Arenols

a) I^+/oxone catalysis for *e*-rich arenols[5]



b) Unsuccessful results for *e*-deficient arenols



According to the standard reduction potentials of X^+/X^-,[8] their oxidizing ability increases in the order iodine<bromine<chlorine (Figure 2a); their atomization energy, electron affinity, hydration ability, and the acidity of XOH species also follow this order (Figure 2b).[8,9] Moreover, the acidity increases with increasing oxidation ability (Figure 2a). In addition to the oxidation ability of X^+, the

nucleofugality of X^- is also important for developing high-performance catalytic reactions, especially for the coupling step of catalysis. If the nucleofugality of halide is low (i.e., X = Cl), a stable Nu^1–X species may be generated, especially in the case of C–Cl moieties. As a result, the catalytic reaction may be hampered. In general, reductive elimination of halides tends to proceed more readily with iodine than with bromine and chlorine (I > Br > Cl), in parallel with the increase in the bond dissociation energy (BDE) of carbon or oxygen halides[8,10] and the bond length of carbon halides[11] (Figures 2c and 2d).

a) Standard reduction potential[8] of the X^+/X^-

	$E°$/V		
	X = I	Br	Cl
acidic conditions: XOH + H^+ + $2e^-$ = X^- + H_2O	0.99	1.33	1.48
basic conditions: XO^- + H_2O + $2e^-$ = X^- + $2HO^-$	0.49	0.76	0.81

b) pK_a values of the hypohalous acid and hydrogen halide[8]

	pK_a (H_2O)		
	X = I	Br	Cl
H–X	–10	–9	–8
H–OX	11.0	8.7	7.3

c) BDE of $X–CH_3$, X–O[8,10]

	DH_{298} (kcal/mol)		
	X = I	Br	Cl
$X–CH_3$	57.6	72.1	83.7
X–O	55.8	56.8	63.9

d) Bond length of carbon–halide[11]

	Å		
	X = I	Br	Cl
$X–CH_3$ (Obs.)	2.14	1.94	1.78

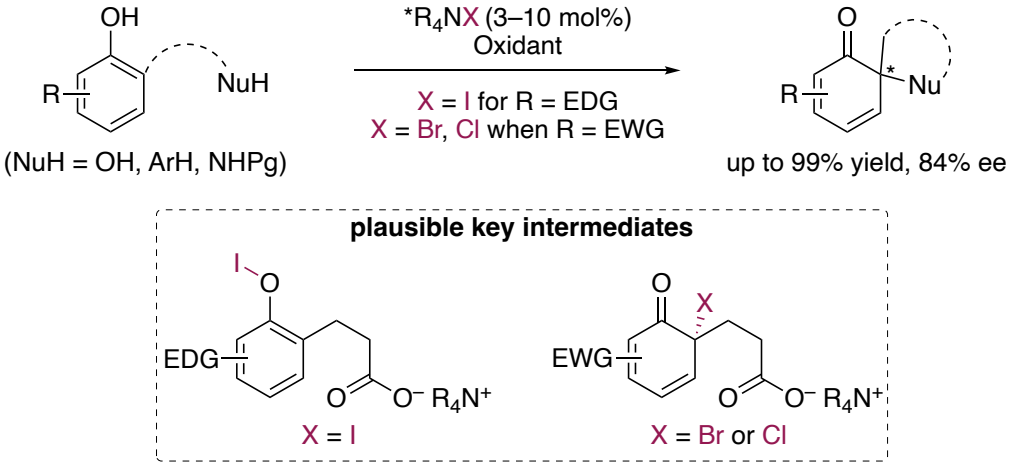
Figure 2. Selected analytical data for halogens.

To improve the catalytic activity of dearomative coupling reactions, especially for less-reactive substrates, we hypothesized that the use of bromine-based catalysis might be more suitable for such relatively less-reactive substrates given that Br^+ exhibits higher oxidation power than I^+ species and exhibits sufficient nucleofugality. Despite the development of several Br^+-based catalytic strategies,[12,13] it has so far not been addressed why bromine is more active than other halogens, and the mechanisms of the reactions that involve other halides remain elusive. In addition, Br^+-based catalysis for enantioselective oxidative coupling reaction has not yet been achieved.

Based on the characteristics of each halogen, here, we develop hypohalite, especially hypobromite, catalysis for oxidative dearomatization of less-reactive phenols by tuning the reaction conditions (e.g., oxidant, solvent). Notably, we succeeded in expanding the reaction scope to inter- and intramolecular dearomative C–O, C–N, and C–C coupling reactions (Scheme 3). In addition, we

achieved the first enantioselective hypobromite catalysis for oxidative dearomative coupling reactions. Interestingly, we found that the reaction mechanism might differ depending on the halide catalyst system used.

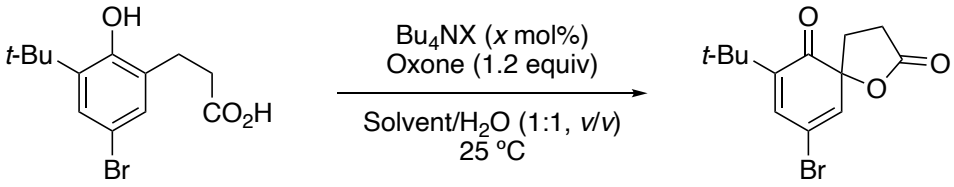
Scheme 3. Hypohalite Catalysis for Oxidative Dearomative Coupling of Less-Reactive Phenols (This Work)



Results and Discussion

We commenced our investigation using 4-bromophenol **1a**, in which no reaction was observed under the conditions using I^+/oxone catalysis[5] (Scheme 2b), as a model substrate (Table 1). To our delight, oxidative cyclization of **1a** proceeded by using 10 mol% of tetrabutylammonium bromide under otherwise identical conditions (entry 1 versus Scheme 2b). However, the desired product **2a** was obtained in only 23% yield due to the consumption of Br-based catalytic species by bromination of toluene solvent. We then changed the organic solvent from toluene to benzene to give **2a** quantitatively (entry 2). The amount of catalyst loading could be reduced to 5 mol% with an acceptable yield (entry 3). On the other hand, no sufficient results could be obtained by using tetrabutylammonium chloride as a catalyst due might to the generation of several chlorinated byproducts (entry 4). Finally, we confirmed that the reaction could not proceed with hypoiodite catalysis even under the modified conditions (entry 5).

Table 1. Investigation of Reaction Conditions[a]



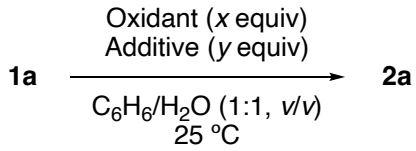
1a **2a**

Entry	X (*x* mol%)	Org. solvent	Yield (%)[b]
1	Br (10)	Toluene	23[c]
2	Br (10)	Benzene	99
3	Br (5)	Benzene	85
4	Cl (5)	Benzene	<5
5	I (10)	Benzene	0

[a] Reactions were conducted using 0.1-mmol of **1a**. [b] Isolated yield. [c] Benzyl bromide (<10%) was observed by *in situ* ^{1}H NMR analysis.

To probe the active species of Br-based catalysis for the oxidative dearomatization reaction, we conducted several control experiments using various bromine-based oxidants (Table 2). While the use of molecular bromine (Br_2) as an oxidant in benzene as a sole solvent gave only a trace amount of **2a**, the reaction proceeded efficiently in a mixed solvent of benzene/water (entries 1 and 2). These results suggested that bromine might not be an active species, but hypobromite, which might be generated from bromine in the presence of water,[14] might mediate the reaction. **2a** was obtained in high yield by using tribromide (Br_3^-) (entry 3). Tribromide might be under equilibrium with bromine and bromide, as well as with hypobromite under the aqueous conditions.[14] On the other hand, interestingly, while almost no reaction was observed using potassium bromate only (entry 4), **2a** was obtained quantitatively within 1.5 hours in the presence of tetrabutylammonium hydrogen sulfate as an acidic additive (entry 5). However, almost no reaction was observed for the initial 30 minutes. We speculated that disproportionation of bromate might first occur to generate bromide,[14] then high-valent bromine species, Br(+3 and +5), might be used as an oxidant for the oxidation of Br(-1) to Br(+1) species. Indeed, a faster reaction rate was observed by adding a catalytic amount of bromide source, probably by omitting the initial disproportionation step (entry 6). In addition, the use of 0.2 equivalent of potassium bromate gave **2a** in 58% yield, which was in good agreement with the theoretical value that the Br(+5) acts as an oxidant until all of it is converted to Br(-1) through Br(+3) and Br(+1) (entry 7). Notably, according to their standard reduction potentials,[8] Br(+5) may oxidize Br(-1) to Br(+1) under only acidic conditions (Figure 3), which are well consistent with the experimental results observed (entry 5 versus entry 4).

Table 2. Control Experiments to Probe the Active Species[a]



Entry	Oxidant (x equiv)	Additive (y equiv)	Time (h)	Yield (%)[b]
1[c]	Br_2 (1)	–	5	<5
2	Br_2 (1)	–	5	71
3	Bu_4NBr_3 (1)	–	5	87
4	$KBrO_3$ (1)	–	5	<5
5	$KBrO_3$ (1)	Bu_4NHSO_4 (1)	1.5	>90 [<5][d]
6	$KBrO_3$ (1)	Bu_4NBr (0.1) + Bu_4NHSO_4 (1)	0.15	>90
7	$KBrO_3$ (0.2)	Bu_4NHSO_4 (1)	5	58

[a] Reactions were conducted using 0.1 mmol of **1a**. [b] ^1H NMR analysis of crude. [c] Benzene was used as a sole solvent. [d] Conversion to **2a** after 30 minutes was shown in the brackets.

	Standard reduction potentials[8]			$E°/V$	
acidic conditions	$HBrO + H^+ + 2e$	$\rightleftharpoons$	$Br^- + H_2O$	1.33	(1)
	$BrO_3^- + 6H^+ + 6e$	$\rightleftharpoons$	$Br^- + 3H_2O$	1.42	(2)
basic conditions	$BrO^- + H_2O + 2e$	$\rightleftharpoons$	$Br^- + 2OH^-$	0.76	(3)
	$BrO_3^- + 3H_2O + 6e$	$\rightleftharpoons$	$Br^- + 6OH^-$	0.61	(4)

Figure 3. Standard reduction potentials of Br species.[9]

We next investigated the loading amount of bromide catalyst in the presence of potassium bromate and tetrabutylammonium hydrogen sulfate (Figure 4). As a result, the reaction rate was improved by increasing the amount of catalyst used. Finally, we found an optimal condition of high-performance hypobromite catalysis: 3 mol% of Bu_4NBr, 0.4 equivalent of $KBrO_3$ (as 1.2 equivalent of oxidant), 1 equivalent of Bu_4NHSO_4 or $KHSO_4$ as a mildly acidic additive in a mixed solvent of benzene/water. Although oxone, a triple salt, can also be used as an oxidant in this reaction, we used $KBrO_3$ mainly for further study, particularly with respect to atom economy, because no waste is generated from the oxidant used.

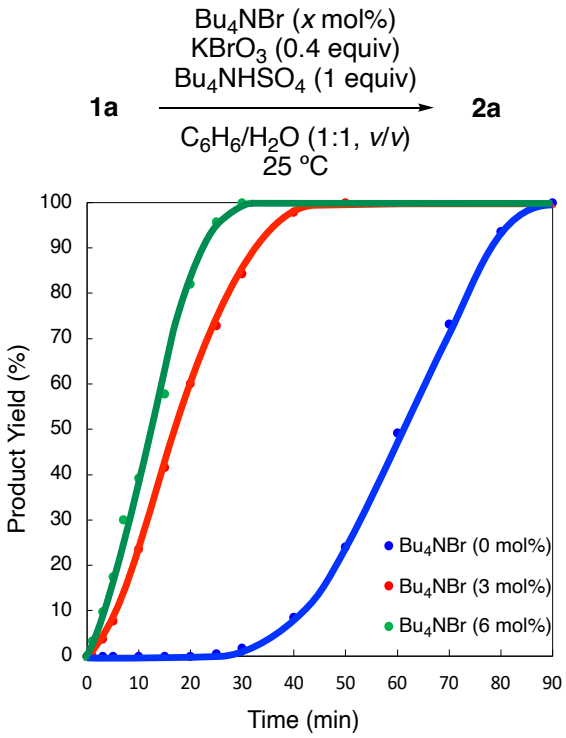
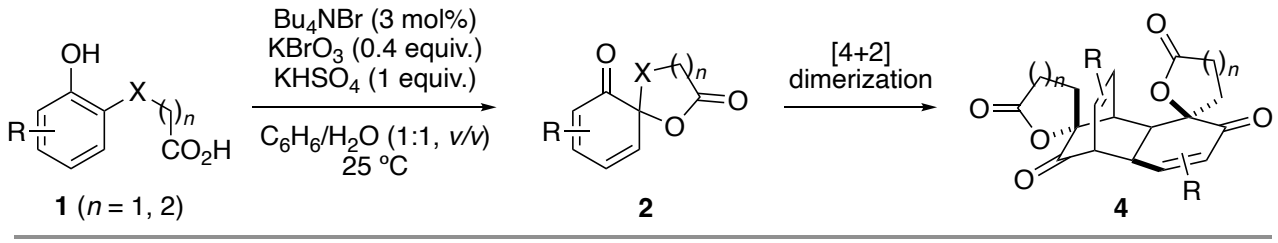


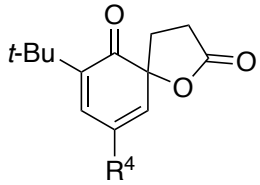
Figure 4. The effect of the loading amount of bromide catalyst.

We examined the oxidative dearomative spirolactonization of several electron-deficient phenols bearing electron-withdrawing groups under the optimized conditions (Scheme 4). The reaction of mono (**1a**, **1c**–**g**) or dihalo-substituted (**1h**–**k**) phenols proceeded smoothly to give the corresponding spirolactones **2** or [4+2] cyclodimers **4** in high to excellent yield. Cyclohexadienones **2** derived from less hindered phenols such as **2j** and **2k** were found to be unstable to isolate, which could be converted *in situ* to the corresponding [4+2] dimers **4j** and **4k** as single diastereomers. Notably, six-membered spirocyclization of **1k** also proceeded smoothly under the same reaction conditions. Besides halogens, carbonyl (**2b**) and cyano (**2l**) groups were also tolerated as electron-withdrawing groups for Br^+ catalysis, and oxone was used as an oxidant instead of potassium bromate for the latter. Dearomative *para*-spirolactonization of hydroquinone derivative **1m** under the slightly modified conditions to suppress the *ortho*-bromination gave masked *para*-benzoquinone **2m** in moderate yield.

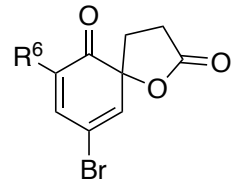
Scheme 4. Substrate Scope for Oxidative Spirolactonization of Less-reactive Phenols[a]



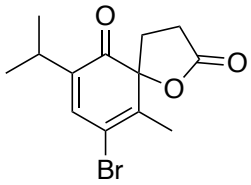
1 (*n* = 1, 2) **2** **4**



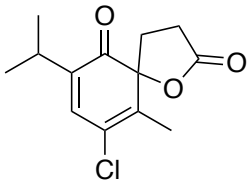
R^4 = Br (**2a**): 92%
Ac (**2b**): 98%



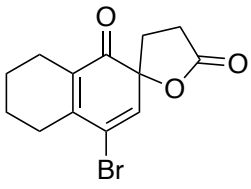
R^6 = *i*-Pr (**2c**): 85%
TIPS (**2d**): 62%[b]



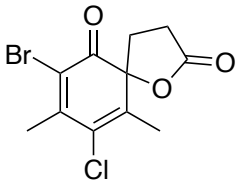
2e: 90%



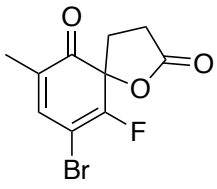
2f: 88%



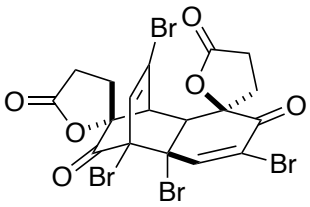
2g: 78%[x]



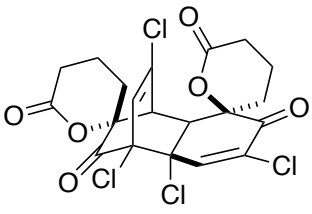
2h: 91%



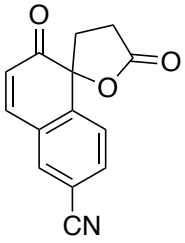
2i: 85%



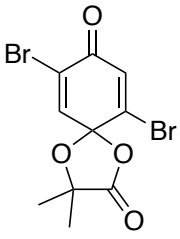
4j: 79%



4k: 82%



2l: 84%[c]



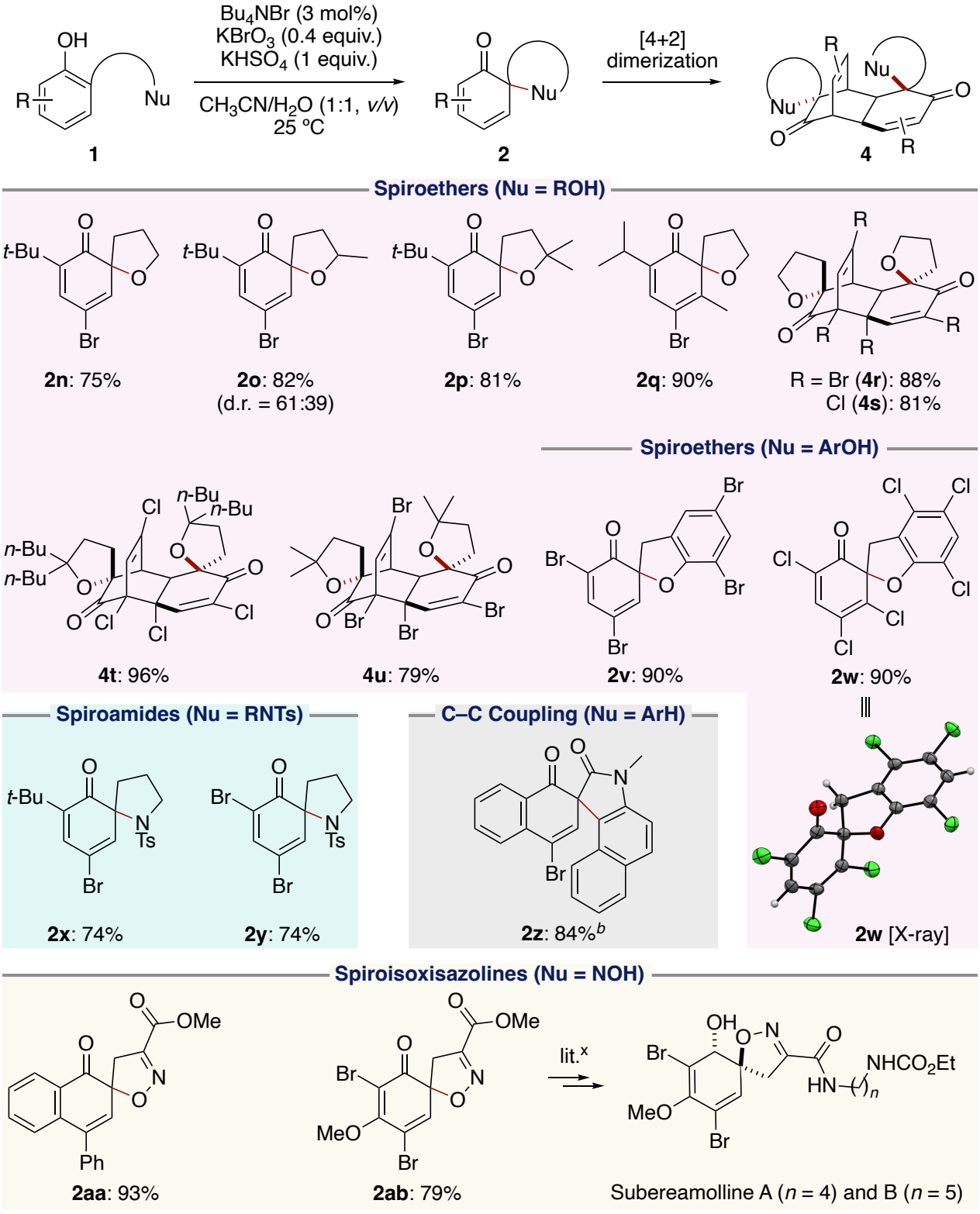
2m: 42%[d]

[a] Reactions were conducted using 0.1 mmol of **1**. [b] Bu_4NBr (10 mol%). [c] Oxone (1.2 equiv) was used instead of $KBrO_3$. [d] A mixture solvent of toluene/pH 8 buffer was used.

We next examined the other dearomative intramolecular coupling reactions of phenols tethered to *O*-, *N*-, or *C*-based internal nucleophiles with a small modification of the reaction conditions (Scheme 5). While the best results for the spirolactonization reactions were obtained using aromatic solvents such as benzene (Scheme 4), acetonitrile was the optimal organic solvent for other spirocyclization reactions shown in Scheme 5. First, we examined the spiroetherification of phenols **1n**–**u** tethered to 1º, 2º, or 3º alkanols. Although the corresponding spiroethers **2** or their cyclodimers **4** were obtained in high yield, low diastereoselectivity was observed for the cyclization of 2º alcohol **1o**. Dihydrobenzofurans **2v** and **2w** were also obtained in high yield from the spiroetherification of the corresponding bisphenols **1**, in which the structure of the latter was confirmed by single-crystal X-ray diffraction analysis. Similarly, spiroamides **2z** and **2aa** could be synthesized by oxidative C–N coupling of the corresponding bisphenols. An intramolecular oxidative C–C coupling of 1-naphthol

1z tethered to 2-naphthamide proceeded efficiently in a mixed solvent of DMF/water at 40 °C to give spirocyclic γ-lactam **2z** in good yield. Finally, oxidative spirocyclization of arenols **1aa** and **1ab** tethered to an oxime moiety gave spiro-isoxazolines **2aa** and **2ab**, for which the latter is a synthetic precursor of subereamollines,[15] bioactive natural products.

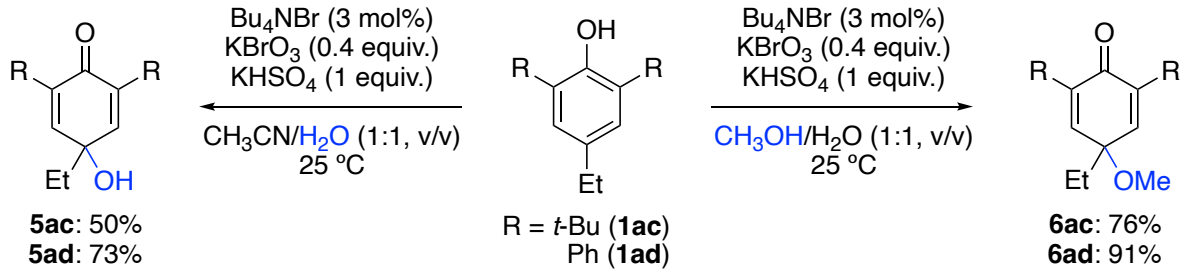
Scheme 5. Oxidative Intramolecular Spirocyclization of Less-reactive Phenols[a]



[a] Reactions were conducted using 0.1 mmol of **1**. [b] A mixed solvent of DMF/H_2O was used at 40 ºC.

Our Br^+ catalysis could be applied to the intermolecular oxidative coupling reactions (Scheme 12). The dearomative coupling of 2,4,6-trisubstituted phenols **1v** and **1w** with water or methanol solvent proceeded at the *para*-position to give the corresponding cyclohexa-2,5-dienones **5** or **6**, respectively, in moderate to high yield. Although the intermolecular reaction is currently limited to coupling with solvents, these preliminary results highlighted the potential of Br^+ catalysis.

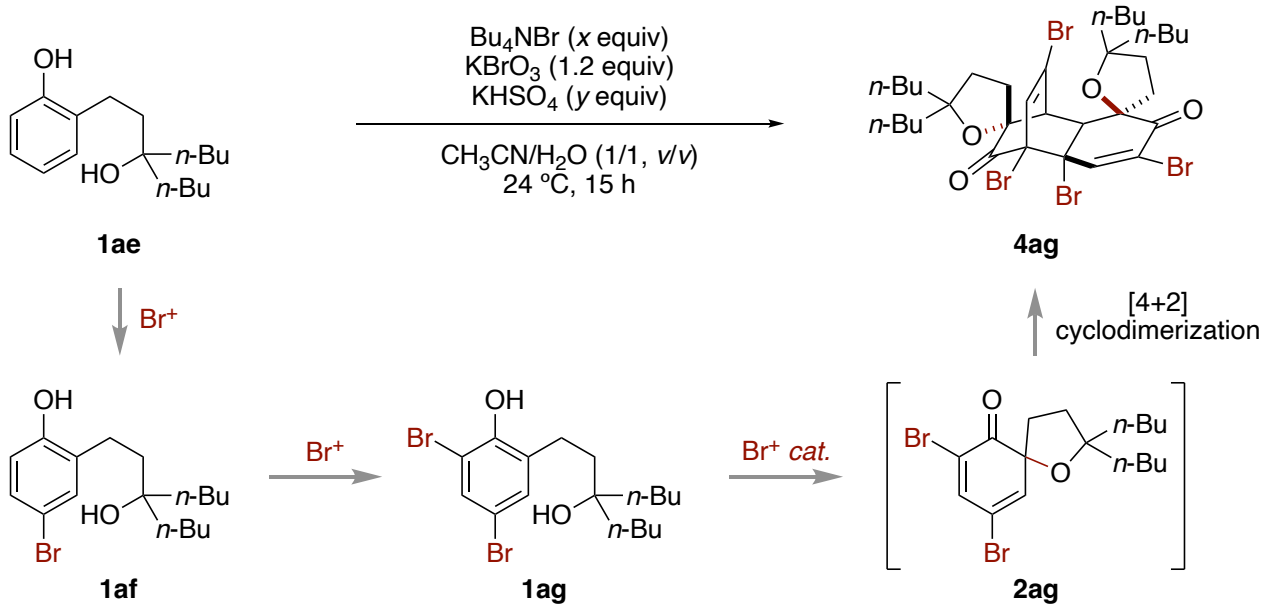
Scheme 6. Oxidative Intermolecular Coupling of Phenols with Solvent



In the abovementioned reactions, we focused on the catalytic dearomative coupling reactions of phenols substituted at all *ortho*- and *para*-positions. Br^+ species is an attractive bromination reagent in electrophilic aromatic substitution of arenols.[12] Next, we investigated a tandem oxidative di-bromination/dearomative spiroetherification of non-substituted phenol **1ae** tethered to an alcohol moiety at the *ortho*-position (Table 3). In this tandem process, 3 equivalents of oxidant are theoretically required, in which 2 equivalents for the di-bromination and 1 equivalent for the dearomative cyclization reactions. At first, we realized that electrophilic bromination is much faster than dearomatization. Indeed, when we used a catalytic amount (3 mol%) of bromide in the presence of 1.2 equivalents of potassium bromate (as 3.6 equivalents of oxidant) and 1 equivalent of potassium hydrogen sulfate, dearomative spirocyclization of phenol **1ae** did not proceed, and only a trace amount of mono-bromo phenol **1af** was obtained (entry 1). Interestingly, only the mono-bromination reaction proceeded to give **1af** quantitatively, even with the use of 2.1 equivalents of ammonium bromide (entry 2). As described above, the reactivity of Br^+ species enhances under acidic conditions (Figure 3). To our delight, the use of 3 equivalents (in correspondence to 3 reactions in the tandem process) of potassium hydrogen sulfate as a proton source gave the desired brominated/dearomatized product **4ag** quantitatively after *in situ* dimerization (entry 3). When 1 equivalent of bromide was used under identical conditions, mono-bromophenol **1af** and di-bromophenol **1ag** were obtained each in around 50% yield (entry 4), suggesting that second bromination (*ortho*-bromination) is also faster than the dearomative cyclization reaction. After a brief investigation, 1.35 equivalent of bromide was

found to be optimal to give **4ag** in 91% isolated yield (entry 5). Based on these observations, the reaction sequence of this tandem reaction is summarized in Table 4. At first, *para*-bromination of **1ae** with 1 equivalent of Br^+ would give **1af**. After full consumption of **1ae**, **1af** would then react at the non-substituted *ortho*-position by another equivalent of Br^+ to give **1ag**. Finally, Br^+-catalyzed oxidative cyclization followed by *in situ* [4+2] cyclodimerization would proceed to give **4ae**.

Table 3. Optimization of the Tandem Bromination/Dearomative Cyclization Reaction[a]



entry	Bu_4NBr (x equiv)	$KHSO_4$ (y equiv)	**1af**, yield (%)[b]	**1ag**, yield (%)[b]	**4ag**, yield (%)[b]
1	0.03	1	<5	0	0
2	2.1	1	>95	0	0
3	2.1	3	0	0	>90
4	1.0	3	44	56	0
5	1.35	3	0	0	>90 (91)[c]

[a] Reactions were conducted using 0.1 mmol of **1ae**. [b] ^1H NMR yield of crude. [c] Isolated yield.

A plausible mechanism for the generation of hypobromous acid (HBrO) as a Br^+ active species is briefly shown in Scheme 7. At first, since no reaction occurred with $KBrO_3$ only, $HBrO_3$ ($pK_a = -2.0$)[8,9] might be generated under the equilibrium conditions in the presence of $KHSO_4$ ($pK_a = 1.9$)[10] (eq. 1). $HBrO_3$ then might oxidize bromide (MBr, M = K^+ or R_4N^+) to give HBrO and $MBrO_2$ (eq. 2). Bromous acid ($HBrO_2$, pKa = 3~4)[8,9] might also under equilibrium with bromate in the presence of $KHSO_4$ (eq. 3). $HBrO_2$ is unstable species and might easily disproportionate to $HBrO_3$ and HBrO (eq. 4).[14] Beside disproportionation pathway, BrO_2 might also be used to oxidize bromide under acidic conditions to give 2 equivalents of HBrO (eq. 5). In either pathway (eqs. 1–3 with 4 or 5), 1.5 equivalents of HBrO species might be generated per 1 equivalent of MBr and 0.5 equivalent of $KBrO_3$

(eq. 6). Thus, ca. 2.025 equivalents of HBrO might be generated from 1.350 equivalents of bromide under the optimized conditions for the tandem reaction (Table 3, entry 5). As such, 2 equivalents of HBrO were used for the sequential electrophilic bromination, and the remainder might be used catalytically in the presence of $KBrO_3$ for the dearomative cyclization reaction.

Scheme 7. Plausible Mechanism for the Generation of Br^+ Active Species

$$KBrO_3 + KHSO_4 \rightleftharpoons HBrO_3 + K_2SO_4 \quad (1)$$

$$HBrO_3 + MBr \longrightarrow MBrO_2 + HBrO \quad (2)$$

$$MBrO_2 + KHSO_4 \rightleftharpoons HBrO_2 + KMSO_4 \quad (3)$$

$$HBrO_2 \longrightarrow 0.5HBrO_3 + 0.5HBrO \quad (4)$$

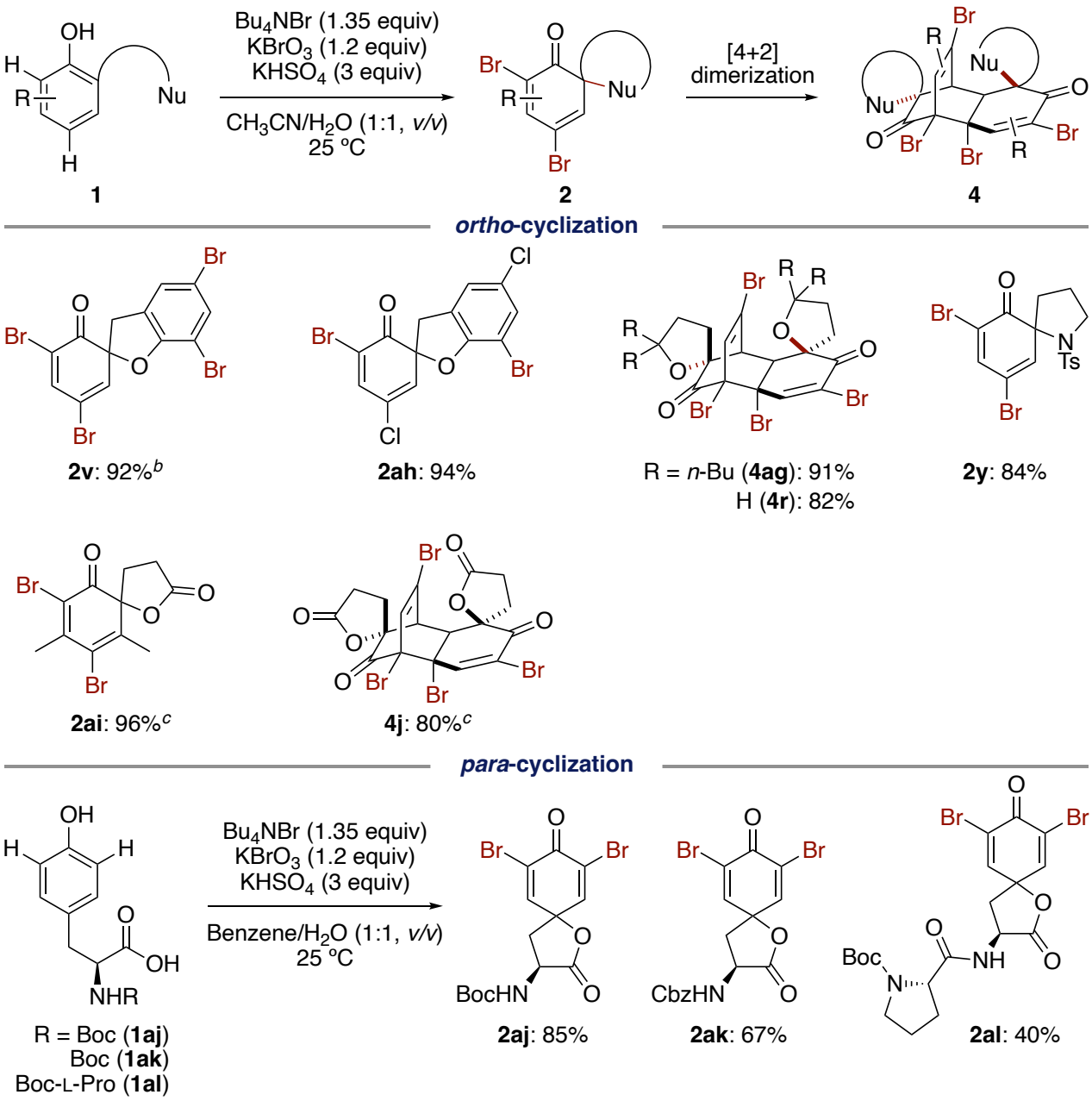
$$HBrO_2 + MBr + KHSO_4 \longrightarrow 2HBrO + KMSO_4 \quad (5)$$

$$MBr + 0.5KBrO_3 + 1.5KHSO_4 \longrightarrow 1.5HBrO + 0.5K_2SO_4 + KMSO_4 \quad (6)$$

(M = Bu_4N^+ or K^+)

Several phenols **1** were examined for the oxidative tandem bromination/cyclization reaction under the optimized conditions to give the corresponding cyclohexadienones **2** or their cyclodimers **4** (Scheme 8). Spiroethers (**2v**, **2ah**, **4ag**, and **4r**), spiroamides (**2y**), and spirolactones (**2ai** and **4j**) were obtained in high yield via *ortho*-spirocyclization. It is noteworthy that some of these products (**2v**, **2y**, **4j**, and **4r**), which were also obtained from the corresponding brominated phenols in Schemes 4 and 5, could be synthesized in similar or higher yields via a tandem process. Moreover, a tandem dibromination/*para*-cyclization of *N*-protected tyrosines (**1aj** and **1ak**) and dipeptide *N*-Boc-*L*-Pro-*L*-Tyr-OH (**1al**) provided the corresponding spirolactones **2** in moderate to high yield.

Scheme 8. Tandem Oxidative Bromination/Cyclization of Phenols[a]



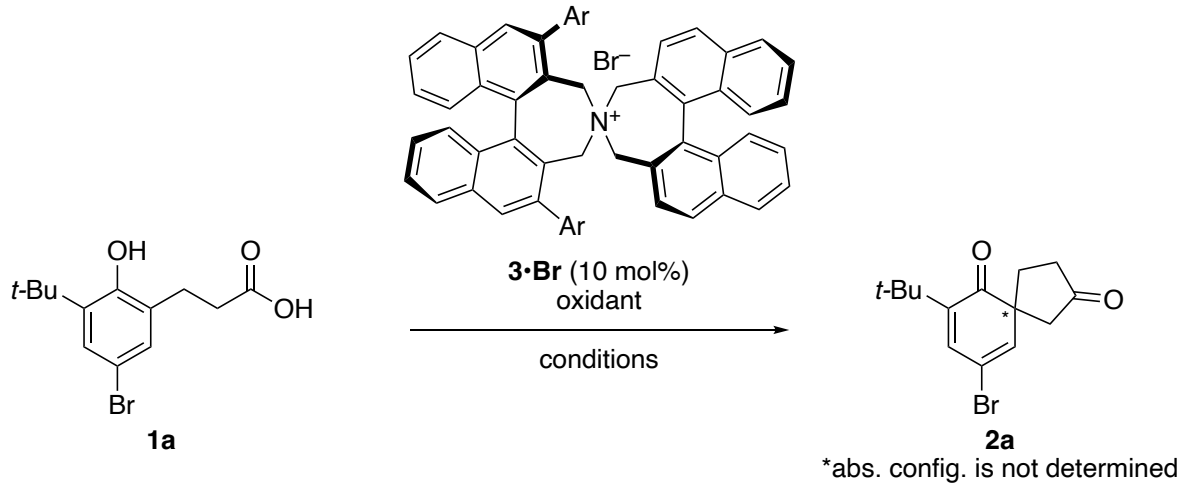
[a] Reactions were conducted using 0.1 mmol of **1**. [b] Bu_4NBr (2.7 equiv), $KBrO_3$ (2 equiv), $KHSO_4$ (5 equiv). [c] A mixed solvent of benzene/H_2O was used.

Next, we were interested in the development of an enantioselective variant of Br^+ catalysis for the dearomative spirolactonization of phenols (Table 6). At first, the use of $KBrO_3$ as an oxidant in the presence of binaphthyl-based chiral quaternary ammonium bromide **3a·Br** in a mixed solvent of benzene/H_2O gave **2a** in 96% yield with 34% ee (entry 1). We speculated that the background reaction might have proceeded due to a rapid generation of HBrO, and we changed the oxidant to oxone, which improved the enantioselectivity to 59% ee (entry 2). Because benzene could not be used under lower temperatures (e.g., 0 °C), we investigated the other organic solvent, and toluene was found to be optimal (entries 3–6). It is noteworthy that undesired bromination of toluene solvent was

suppressed in the absence of water co-solvent, and enantioselectivity was also improved (entry 6 versus entry 3). Although the reason for the improvement in the chemoselectivity is not clarified yet, we speculated that while oxone, an inorganic solid, is easily dissolved under aqueous conditions, and thus, rapid oxidation of bromide would proceed under the liquid–liquid phase transfer conditions, as the oxidation might be slower, the chemoselectivity might be improved under the solid–liquid phase transfer conditions in the absence of water co-solvent. In addition, enantioselectivity gradually increased with lowering the temperature, up to 67% ee at –20 °C (entries 7 and 8). A brief re-investigation of oxidants under room temperature (entries 9–12) revealed that peracetic acid gave the highest enantioselectivity (entries 12 and 13). Based on our previous[5] and current observations, we assumed that the enantioselectivity might be altered by even slight changes in the acidity of the conditions. We checked whether acetic acid that presents in peracetic acid solution might improve the enantioselectivity; however, the enantioselectivity of **2a** was decreased by using acetic acid as an additive (entries 14 and 15 versus entries 12 and 9). The effects of oxidants used for enantioselectivity are not clarified yet.

Next, we investigated the 3,3'-positions of binaphthyl moiety of catalyst **3** (entries 16–20). Interestingly, as the electronegativity of the substituents of the *m*-terphenyl group increased (Hammett constants σ[16] for H (**3d**) = 0.00, $CF(CF_3)_2$ (**3b**) = 0.52, CF_3 (**3a**) = 0.54, SF_5 (**3c**) = 0.68), the enantioselectivity of **2a** was also improved, and the best result up to 80% ee was obtained with the use of SF_5-substituted **3c·Br** (entry 17). The more electron-withdrawing group might enhance the acidity of the ammonium cation center or acidic α-hydrogen atoms of the catalyst, thereby likely elevating the effective interactions (e.g., electrostatic or hydrogen-bonding interactions) with the substrate. Catalysts bearing a bulkier quaterphenyl group (**3e·Br**) or less bulky 3,5-bis(trifluoromethyl)phenyl group (**3f·Br**) were also examined; however, enantioselectivity was too low (entries 19 and 20). To our delight, the reaction proceeded smoothly even at 0 ºC to give **2a** with improved enantioselectivity (84% ee) (entry 21). The loading amount of **3c·Br** could be reduced to 5 mol% without reducing the yield and selectivity, albeit with a prolonged reaction time (entry 22).

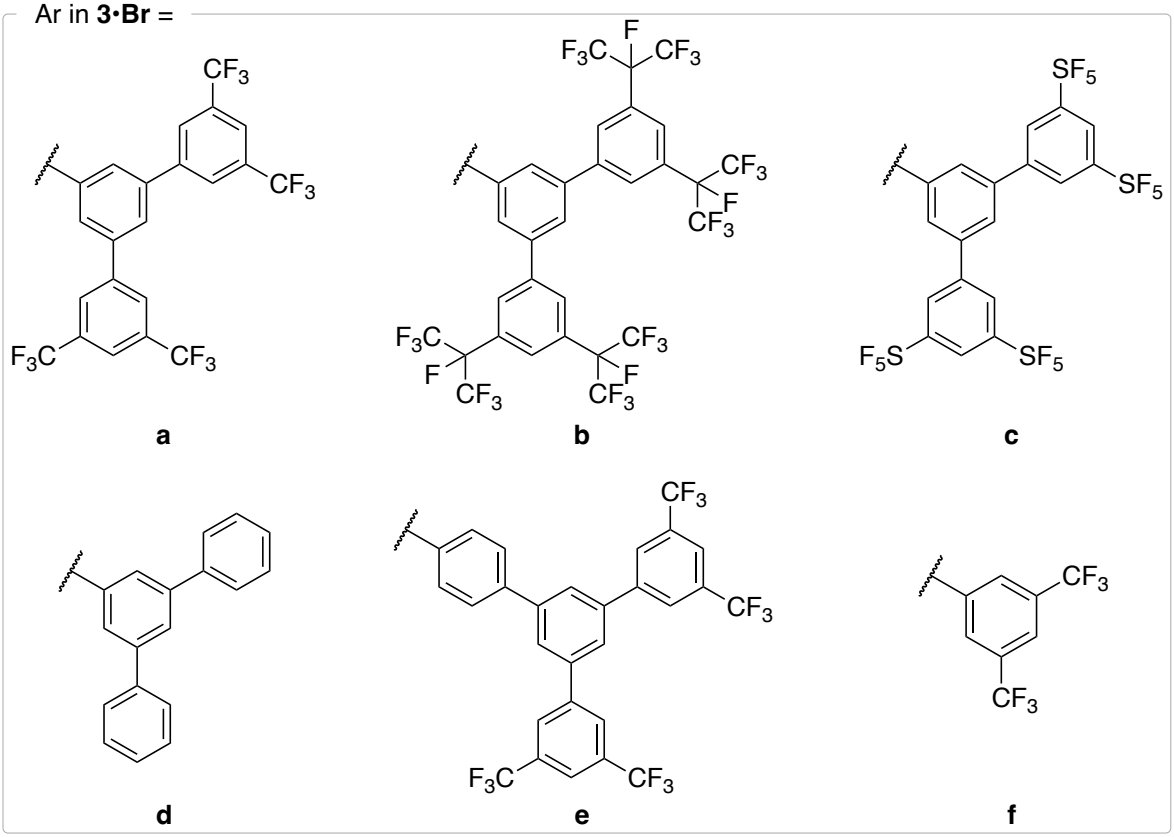
Table 4. Enantioselective Dearomative Spirolactonization of Phenol 1a



1a **2a**

*abs. config. is not determined

Ar in **3·Br** =



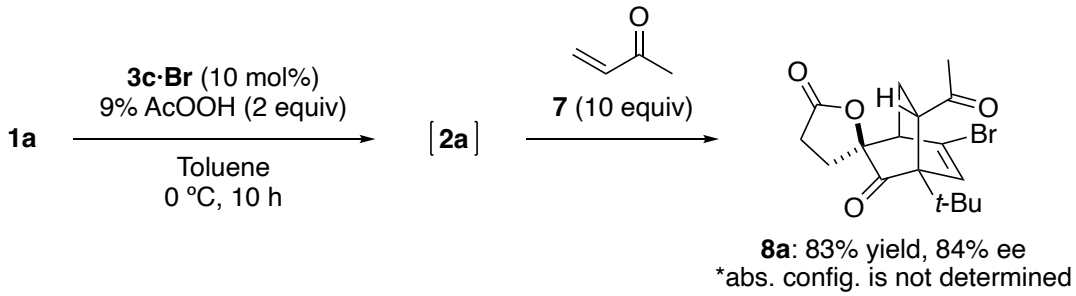
entry	**3·Br**	oxidant (equiv)	additive (equiv)	solvent	T (°C), *t* (h)	**2a**: yield,[a] ee[b] (%, %)
1	**3a**	$KBrO_3$ (1.2)	$KHSO_4$ (1)	Benzene/H_2O[c]	25, 1.5	96, 34
2	**3a**	Oxone (1.2)	–	Benzene/H_2O[c]	25, 8	98, 59
3	**3a**	Oxone (1.2)	–	Toluene/H_2O[c]	25, 8	23, 34
4	**3a**	Oxone (1.2)	–	*t*-BuOMe	25, 5	0, –
5	**3a**	Oxone (1.2)	–	$CO(MeO)_2$	25, 7	19, 24
6	**3a**	Oxone (1.5)	–	Toluene	25, 5	62, 48
7	**3a**	Oxone (1.5)	–	Toluene	0, 15	95, 60
8	**3a**	Oxone (1.5)	–	Toluene	–20, 49	77, 67
9	**3a**	30% H_2O_2 (2)	–	Toluene	25, 30	85, 27
10	**3a**	TBHP (2)	–	Toluene	25, 24	0, –

11	**3a**	*m*-CPBA (1.2)	–	Toluene	25, 1.5	85, 61
12	**3a**	9% AcOOH (2)	–	Toluene	25, 1.5	98, 72
13	**3a**	9% AcOOH (1)		Toluene	25, 1	98, 69
14	**3a**	9% AcOOH (2)	AcOH (10)	Toluene	25, 1.5	98, 68
15	**3a**	H_2O_2 (2)	AcOH (25)	Toluene	25, 12	84, 14
16	**3b**	9% AcOOH (2)	–	Toluene	25, 1.5	99, 61
17	**3c**	9% AcOOH (2)	–	Toluene	25, 1.5	99, 80
18	**3d**	9% AcOOH (2)	–	Toluene	25, 1.5	61, 22
19	**3e**	9% AcOOH (2)	–	Toluene	25, 1.5	85, 0
20	**3f**	9% AcOOH (2)	–	Toluene	25, 1.5	95, 15
21	**3c**	9% AcOOH (2)	–	Toluene	0, 10	99, 84
22[d]	**3c**	9% AcOOH (2)	–	Toluene	0, 28	98, 83

[a] Isolated yield. [b] Determined by HPLC analysis. [c] As a 1:1 (*v*/*v*) mixture. [d] **3c·Br** (5 mol%).

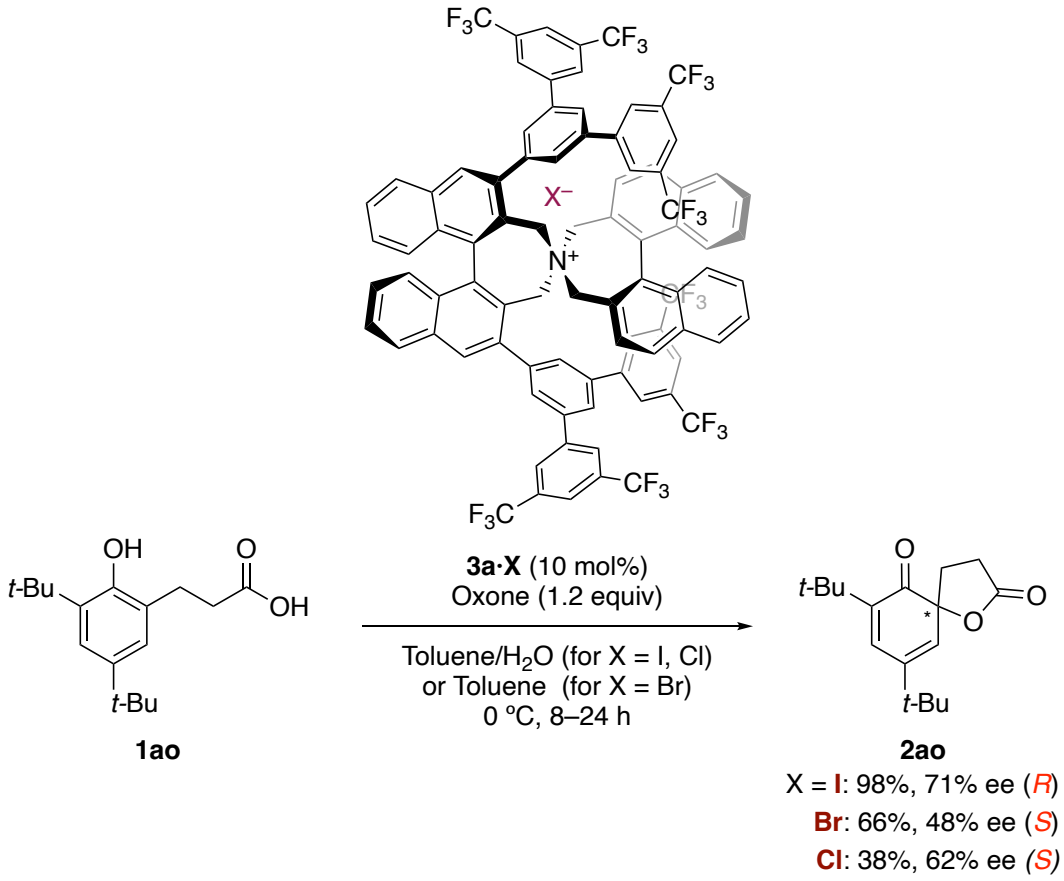
Although cyclohexadienone **2a** was found to be unstable and easily decomposed after storing at 0 ºC for a few days, **2a** could be transformed *in situ* to [4+2] cycloadduct **8a** in good yield without the loss of the enantioselectivity by a one-pot reaction with ethyl vinyl ketone (**7**) (Scheme 9). To determine the absolute configuration of **2a**, the re-crystallization of **2a** or its derivatives is under investigation.

Scheme 9. Enantioselective One-Pot Transformation



Although the scope of the enantioselective spirocyclization is currently limited to spirolactonization with moderate enantioselectivity and further investigations for the molecular design of much selective catalysts are required, we observed some interesting results during the oxidation of phenol **1ao**, an electron-rich substrate that could be oxidized by both I^+ and Br^+ catalysis. To our surprise, the use of (*R*,*R*)-**3a·Br** and (*R*,*R*)-**3a·I** with the same countercation afforded the opposite enantiomers of **2ao** under the optimized conditions (Scheme 10). In addition, the use of chloride (*R*,*R*)-**3a·Cl** also gave (*S*)-**2ao** as the same absolute configuration as with bromide catalyst (*R*,*R*)-**3a·Br**. These results suggested that the reaction mechanism might differ depending on the halide catalyst.

Scheme 10. Halide-Depended Absolute Configuration

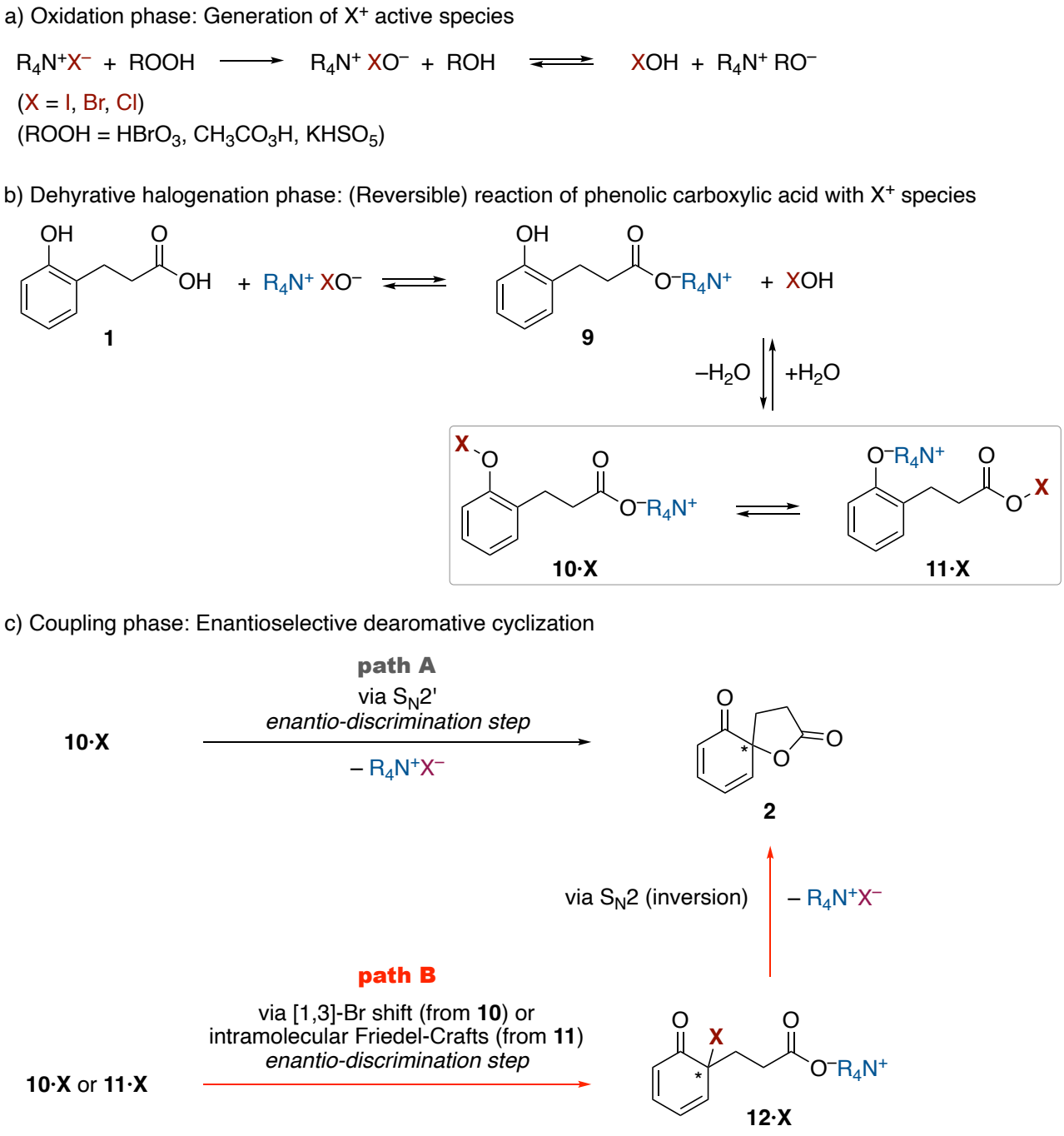


The plausible reaction mechanism of hypohalite-catalyzed oxidative dearomatization of phenol was shown in Scheme 11. The catalytic cycle consists of three steps (Figure 1): formation of the catalytically active species (oxidation phase), halogenation of phenolic carboxylic acid **1** (dehydrative halogenation phase), and intramolecular dearomative cyclization (coupling phase). First, ammonium halide would be oxidized by an oxidant to the corresponding hypohalite species (Scheme 11a). According to the standard potentials (Figure 2a), the generation rate of active species increases in the order $Cl^+<Br^+<I^+$.

Ammonium hypohalite, a mildly basic species (pK_a of XOH = ca. 7~11, Figure 2b), would then react with phenolic carboxylic acid **1** to form ammonium carboxylate **9** and hypohalous acid by deprotonation of the most acidic moiety of **1** (Scheme 11b). A reversible dehydrative halogenation of **9** with XOH might proceed to give any of or all intermediates **10** and **11** under equilibrium. Intermediates **10** and **11** are isomers in which halogen (X) and a quaternary ammonium cation (R_4N^+) are bonded to a phenoxy or a carboxyl moiety. Our previous work[5] suggested that in the case of I^+ catalysis, cyclization might proceed via **10·I** followed by S_N2'-type cyclization of ammonium carboxylate as an enantio-determining step (*path A*, Scheme 11c). Based on the results in Scheme 10,

we hypothesized that cyclization in the Br^+ and Cl^+ catalysis might proceed via **12·X**, a chiral dearomatized compound in which halogen is added to the *ortho*-position of phenol, followed by S_N2-type cyclization of ammonium carboxylate *(path B*, Scheme 11c). Because of very fast cyclization to **2**, especially for I^+ and Br^+ catalysis, we could not directly observe these putative intermediates **10**–**12**.

Scheme 11. Plausible Reaction Mechanism



To validate our proposal on the halide-dependent mechanism, we performed several control

experiments (Scheme 12). First, to confirm the necessity of the hydroxy group of phenol **1**, we investigated the reaction of 2-methoxy-1-methylnaphthalene (**13a**) using a stoichiometric amount of tetrabutylammonium halides in the presence of oxone (Scheme 12a). While no reaction was observed with the use of iodide, the corresponding α-halocarbonyl compounds **14a·Br** and **14a·Cl** were obtained in high yield when bromide or chloride was used. However, no spirolactonization reaction proceeded for the use of electron-deficient anisole **13b**, even under the conditions of Br^+ or C^+ catalysis. These results suggested that a direct Friedel–Crafts-type dearomative halogenation might be difficult for the less-reactive phenols.

Since the detection of putative intermediates, even relatively stable **12·X**, failed for the phenolic carboxylic acid substrates **1**, we attempted to isolate the dearomatized intermediate analogs **16·X** using the corresponding esters **15** instead of the carboxylic acids as substrates (Scheme 12b). The reaction of *t*-butyl ester-tethered 2-naphthol **15a** in the presence of a stoichiometric amount of tetrabutylammonium bromide and oxone provided α-bromocarbonyl compound **16a·Br** quantitively, which could be converted to spirolactone **2am** by one pot hydrolysis with $ZnBr_2$ as a Lewis acid. In addition, we succeeded in the isolation and full characterization by single-crystal X-ray diffraction analysis of α-chlorocarbonyl compound **16b·Cl** which was obtained from the reaction of electron-deficient phenol derivative **15b** using chloride and oxone. These results suggested that a Friedel-Crafts-type dearomative halogenation of arenols to intermediate **12·X** might be feasible for Br^+ and Cl^+ catalysis.

Another important clue to understanding the differences in the mechanism of I^+ and Br^+ catalysis was obtained from the reaction of salicyl alcohol **17** (Scheme 12c). While I^+ catalysis provided salicyl aldehyde **18** probably via an *ortho*-quinone methide intermediate,[6j] bromophenol **19** was obtained quantitatively (based on the amount of bromide used) probably via a dearomative bromination/retro aldol reaction sequence by using Br^+ catalysis.

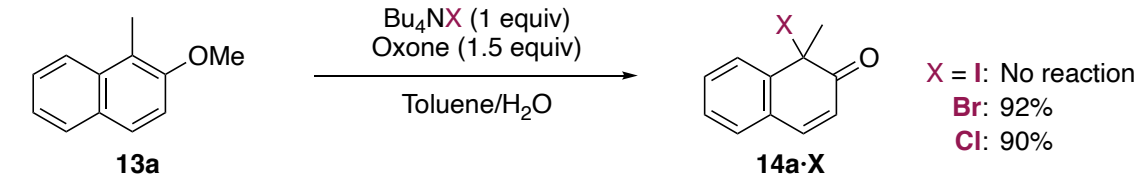
On the other hand, since a bromination of toluene was observed as a side reaction when toluene was used as an organic solvent (Table 1, entry 1), radical species might also be generated under these conditions. To check whether spirolactonization proceeded with a radical mechanism, the reaction of **1a** was performed in the presence of PBN as a radical scavenger. As a result, **2a** was obtained quantitatively, suggesting a radical pathway for the dearomatization reaction might be unlikely (Scheme 12d).

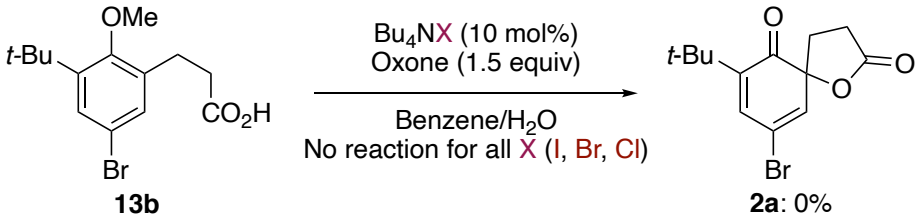
Collectively, the results of Schemes 10 and 12 suggested that the spirocyclization process of Br^+ and Cl^+ catalysis might proceed via intermediate **12·X**, which might be generated via a [1,3]-Br shift of **10·X** or an intramolecular Friedel-Crafts-type halogenation of **11·X** as an enantio-discrimination

step (*path B*, Scheme 11c). In either pathway to **12**·**X**, chiral ammonium cation might be ion-paired with the hydroxylate or carboxylate moiety of the substrate to induce enantioselectivity during the dearomative halogenation step.

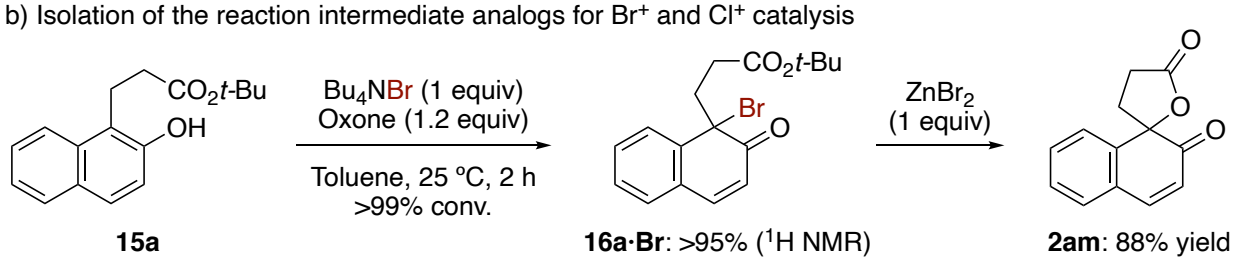
Scheme 12. Control Experiments to Probe the Reaction Mechanism

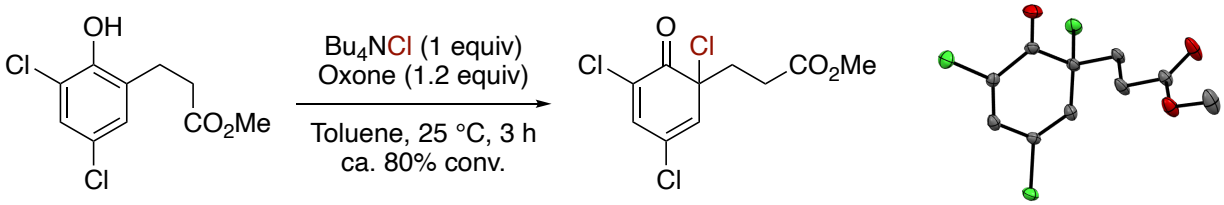
a) Necessity of hydroxyl group of phenol



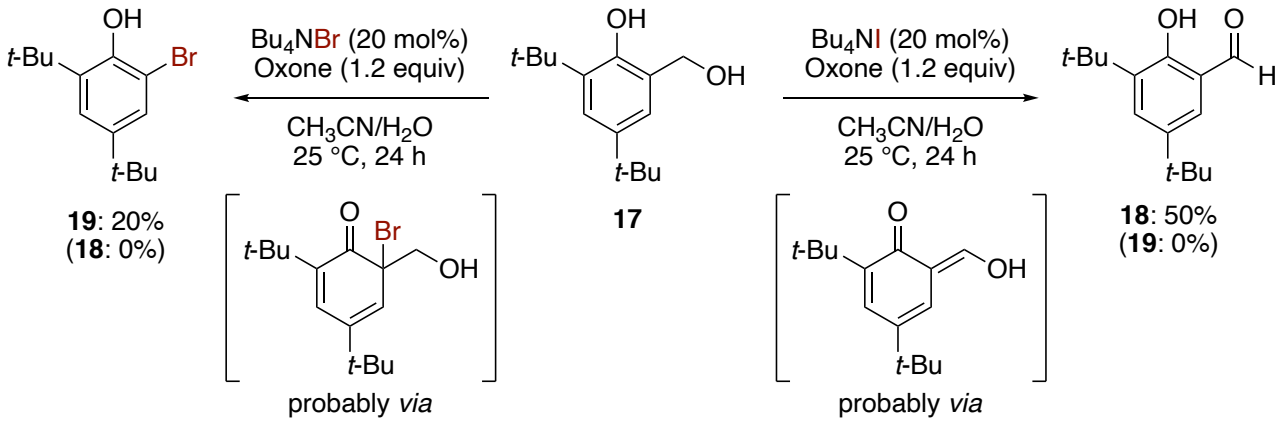


b) Isolation of the reaction intermediate analogs for Br^+ and Cl^+ catalysis

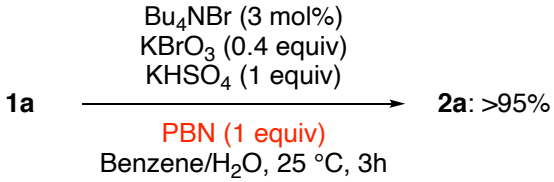




c) Clue to I^+ versus Br^+ catalysis

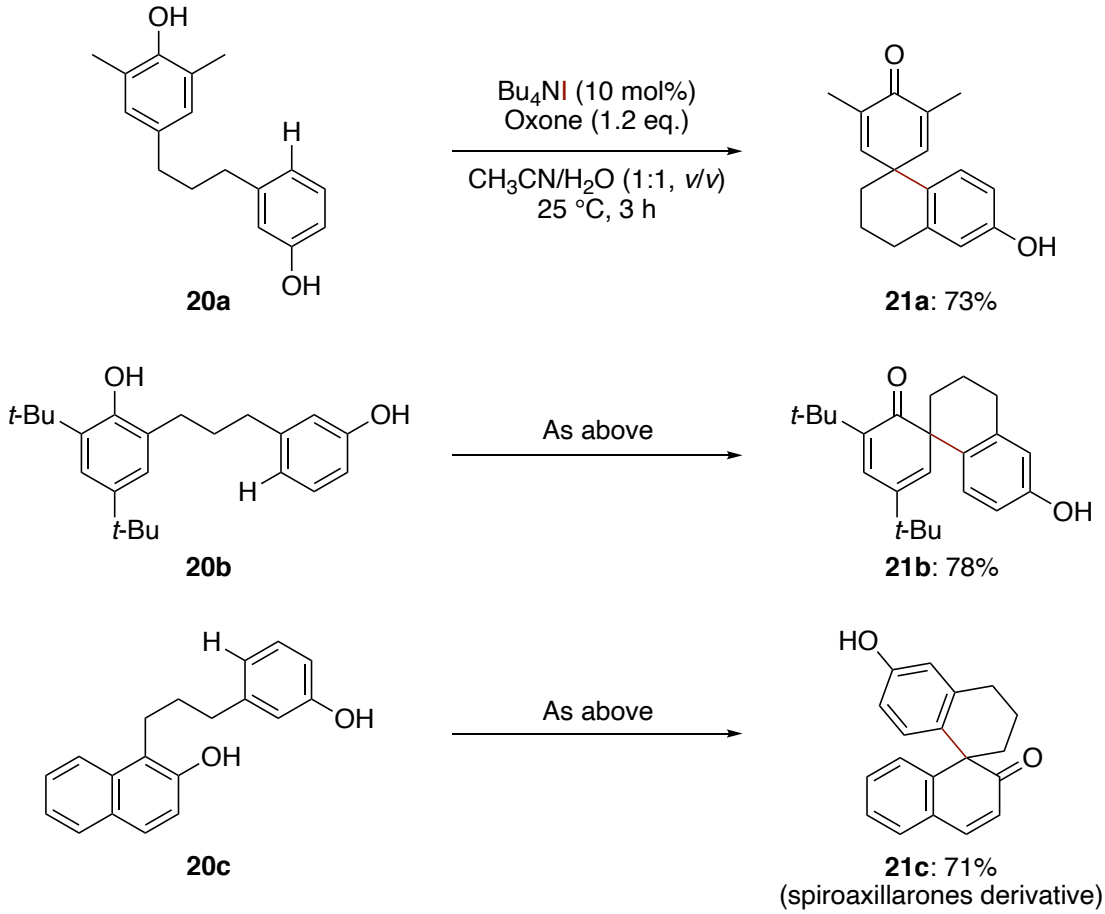


d) Investigation of radical pathway



Finally, we examined the oxidative dearomative C–C coupling of bisarenols **20** (Scheme 13). Since C–bromination of arenols proceeded easily, the catalytic dearomative cyclization of **20** was assumed to be not feasible for Br^+ catalysis. Indeed, the use of Br^+ catalysis afforded only brominated adducts, and no C–C coupling products **21** were detected. In sharp contrast, the desired dearomative coupling products **21,** including a core structure (**21c**) of natural products spiroaxillarones,[17] could be obtained in good yield by using I^+ catalysis.

Scheme 13. Oxidative Dearomative C–C Coupling of Bisarenols Using I^+ Catalysis



In summary, considering the catalytic mechanism and the characteristics of halogens, we developed high-performance hypobromite catalysis for oxidative dearomatization of arenols using a quaternary ammonium bromide catalyst and a suitable oxidant. Notably, we succeeded in expanding the reaction scope to inter- and intramolecular oxidative dearomative C–O, C–N, and C–C coupling reactions. Moreover, we achieved the first enantioselective hypobromite catalysis for oxidative dearomative coupling reactions using chiral ammonium cation as a countercation of bromide. Mechanistic studies revealed that the reaction mechanisms might differ depending on the halide catalysts.

Experimental Section

Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 (400 MHz) and Bruker AVANCE III HD (300 and 500 MHz) spectrometers at ambient temperature. Chemical shifts are reported in ppm from the solvent resonance (DMSO-d_6: 2.50 ppm, CD_3CN: 1.94 ppm, $(CD_3)_2CO$: 2.05 ppm) or Me_4Si resonance (0.00 ppm; $CDCl_3$) as internal standard. 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; quin = quintet; sept = septet; m = multiplet; brs = broad singlet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz) spectrometer and Bruker AVANCE III HD (75 and 125 MHz) spectrometer at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$: 77.00 ppm, CD_3CN: 1.32 ppm, DMSO-d_6: 39.52 ppm). Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University [JEOL JMS-700 (FAB). 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 OD–H (4.6 mm x 25 cm). X-ray analysis was performed by Rigaku PILATUS-200K. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm or silica gel 60 NH_2 F_{254}s 0.20 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385).

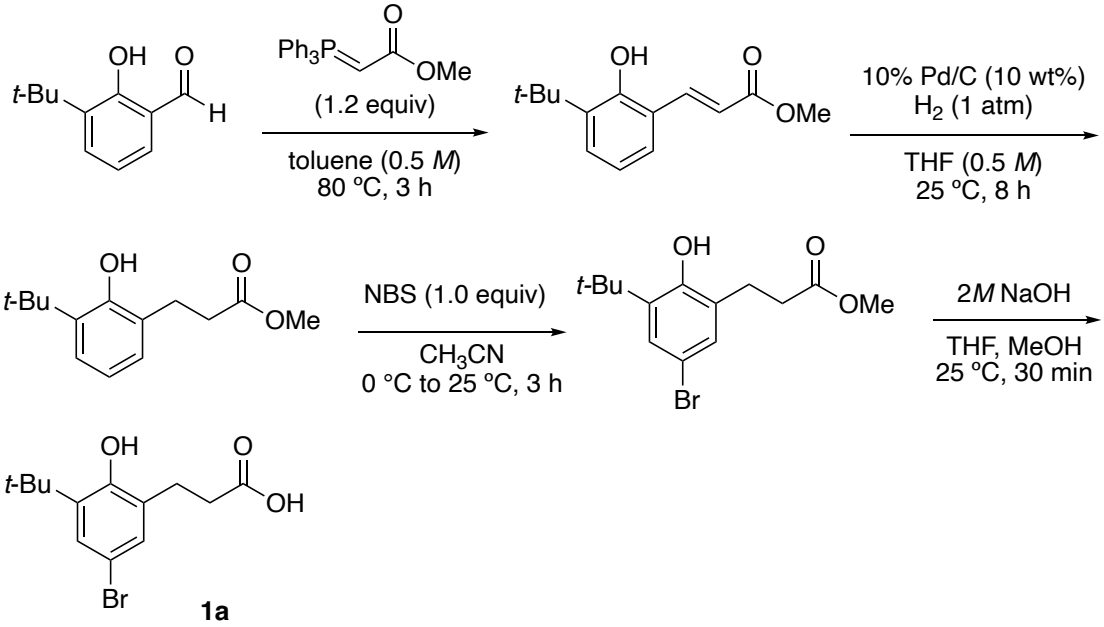
In experiments that required dry solvents, diethyl ether (Et_2O), tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF) and dichloromethane (CH_2Cl_2), were purchased from FUJIFILM Wako Pure Chemical Industries, Ltd. as the “anhydrous” and stored over 4Å molecular sieves. Other solvents were purchased from Aldrich Chemical Co., Inc., FUJIFILM Wako Pure Chemical Industries, Ltd. or Tokyo Chemical Industry Co., Ltd. and used without further purification. Tetrabutylammonium bromide (Bu_4NBr), 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 70% aqueous *tert*-butyl hydroperoxide (TBHP) were purchased from FUJIFILM Wako Pure Chemical Industries, Ltd. Oxone and anhydrous TBHP (5.5 *M* nonane solution) 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.

Synthesis and Characterization of Substrates 1

Arenols **1g–j**[18], **1l**[19], **1m**[20], **1z**[21], **1ab**[15], **1ad**[22], **9a**[23], **15**[24] and **18a**[25] were known compounds and prepared by following the literature procedures.

Arenols **1w, 1ac, 1aj, 1ak** and **1ai** were were purchased from Tokyo Chemical Industry Co., Ltd. All compounds were used without further purification.

Synthesis of 2a:



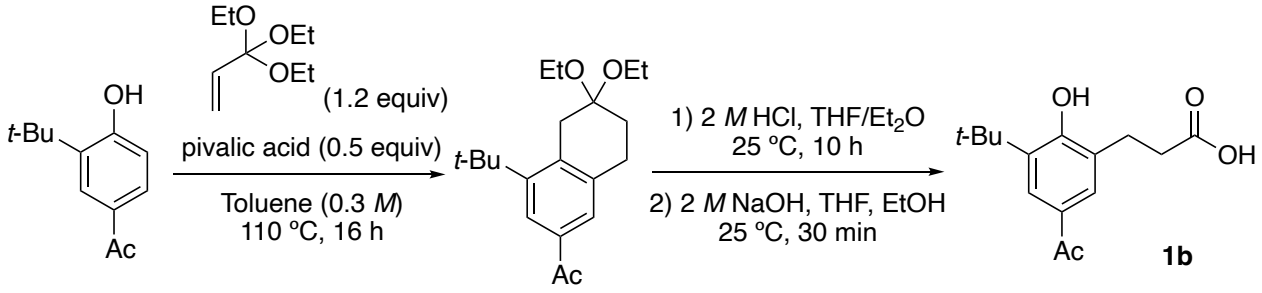
3-(5-Bromo-3-(*tert*-butyl)-2-hydroxyphenyl)propanoic acid (1a): To a solution of 3-*tert*-butyl-2-hydroxybenzaldehyde (2.85 g, 16.0 mmol) in toluene (32.0 mL) was added methyl(triphenylphosphoranylidene)acetate (6.42 g, 19.2 mmol) at 25 ºC under a nitrogen atmosphere. After stirring for 3 h at 80 ºC, the resulting mixture was cooled to 25 ºC and diluted with water and EtOAc. The aqueous layers were 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 (eluent: hexane–EtOAc = 2:1) to give methyl (*E*)-3-(3-(*tert*-butyl)-2-hydroxyphenyl)acrylate (2.85 g, 12.2 mmol, 76% yield) as a white solid.

To a solution of this olefin in THF (20.0 mL) was added 10% Pd/C (0.284 g). The flask containing the mixture was then evacuated and purged with H_2 three times. After stirring for 8 h at 25 ºC, the mixture was filtered through celite with EtOAc and the crude product was obtained after removal of the solvent *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc = 4:1) to give methyl 3-(3-(*tert*-butyl)-2-hydroxyphenyl)propanoate (2.84 g, 12.0 mmol, 99% yield) as a white solid.

To a solution of this methyl ester in CH_3CN (12.0 mL) under a nitrogen atmosphere was added

NBS (2.14 g, 12 mmol) at 0 ºC. After stirring for 3 h at 25 ºC, the resulting mixture was diluted with water and EtOAc. The aqueous layers were separated and extracted with EtOAc (twice). The combined organic layers were washed with water and dried over anhydrous $MgSO_4$, then the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc = 5:1) to give methyl 3-(5-bromo-3-(*tert*-butyl)-2-hydroxyphenyl)propanoate (3.78 g, 12.0 mmol, 99% yield) as a yellow solid.

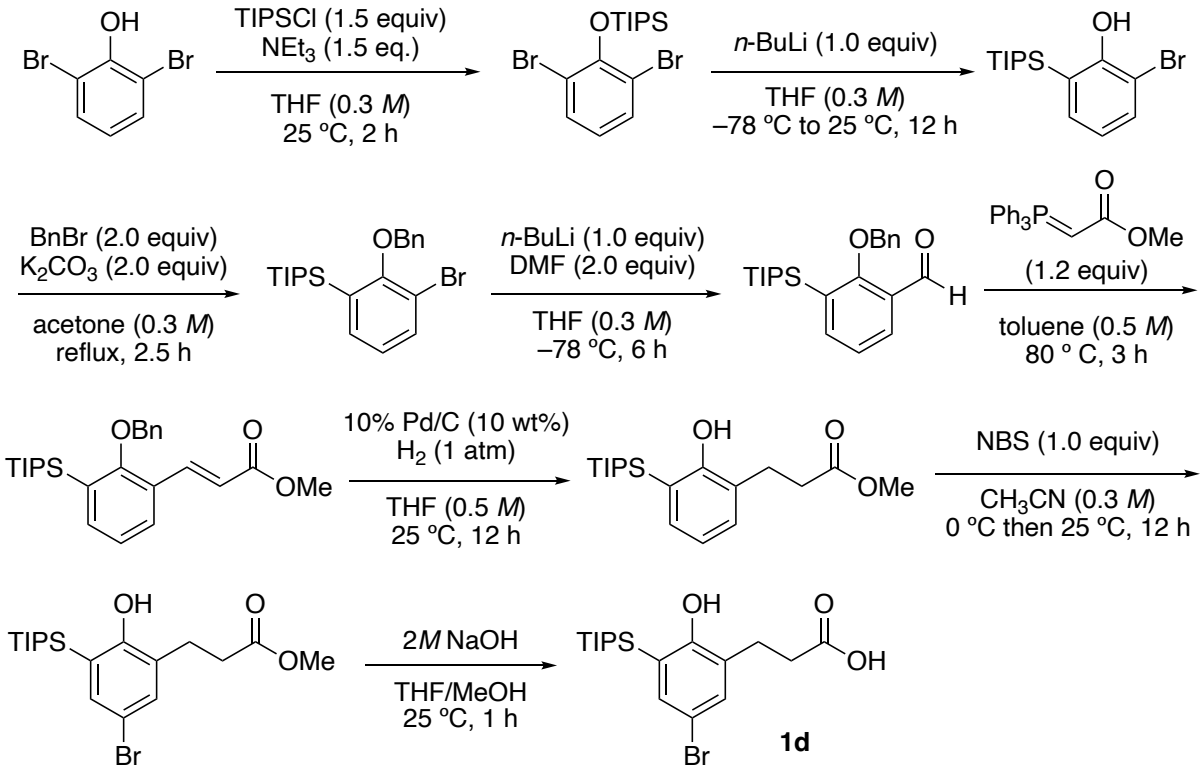
To a solution of this methyl ester in THF (10.0 mL) and MeOH (10.0 mL) was added 2 *M* NaOH (10.0 mL) and the resulting mixture was stirred at 25 ºC for 30 min. Then, the resulting mixture was poured into 1 *M* HCl, extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo* to give **1a** (3.60 g, 12.0 mmol, 99% yield) as white solid. **TLC**, R_f = 0.50 (Hexane–EtOAc–AcOH = 10:10:1); **IR** (KBr) 3477, 3250–2750, 1685, 1190 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 2.80–2.83 (m, 2H), 2.84–2.86 (m, 2H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.24 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 23.7, 29.5 (3C), 34.8, 35.0, 112.7, 128.6, 129.7, 130.5, 140.5, 152.1, 179.9; **HRMS** (FAB) m/z calcd for $[C_{13}H_{17}{}^{79}BrO_3+H]^+/[C_{13}H_{17}{}^{81}BrO_3+H]^+$ ([M]/[M+2]) 301.0439/303.0420, found 301.0441/303.0431.



3-(5-Acetyl-3-(*tert*-butyl)-2-hydroxyphenyl)propanoic acid (**1b**): To a solution of 1-(3-(*tert*-butyl)-4-hydroxyphenyl)ethan-1-one[13] (0.960 g, 5.00 mmol) and triethyl ortho acrylate[14] (1.30 g, 7.5 mmol) in toluene (15.0 mL) was added pivalic acid (0.250 g, 2.50 mmol) and the resulting mixture was refluxed for 16 h. The resulting mixture was poured into 1*M* NaOH (30.0 mL), extracted with Et_2O (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in *vacuo*. The residue was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc = 15:1) to give 1-(4-(*tert*-butyl)-6,6-diethoxy-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-one (1.36 g, 4.30 mmol, 85% yield) as colorless oil.

To a solution of 1-(4-(*tert*-butyl)-6,6-diethoxy-5,6,7,8-tetrahydronaphthalen-2-yl)ethan -1-one (1.36 g, 4.30 mmol) in Et_2O (10.0 ml) was added 2 *M* HCl (10.0 ml) and the resulting mixture was stirred for 10 h at 25 ºC. The resulting mixture was extracted with EtOAc (twice) and washed with

brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in *vacuo*. To a solution of the crude product in THF (10.0 mL) and MeOH (10.0 ml) was added 2*M* NaOH (10.0 mL) and the resulting mixture was stirred overnight at room temperature. The resulting mixture was poured into 1 *M* HCl, extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in *vacuo* to give **1b** (0.580 g, 2.20 mmol) in 51% yield (2 steps). **TLC**, R_f = 0.34 (hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3159, 2955, 2739, 2546, 1709, 1635, 1578, 1423, 1308, 1221 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.40 (s, 9H), 2.49 (s, 3H), 2.72–2.75 (m, 2H), 2.86–2.89 (m, 2H), 5.45 (s, 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.77 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 25.0, 26.3, 29.5, 33.9, 34.7, 125.0, 128.0, 128.5, 129.0, 136.8, 158.2, 174.5, 196.6; **HRMS** (FAB) m/z calcd for $[C_{15}H_{21}O_4]^+$ 265.1440, found 265.1438.



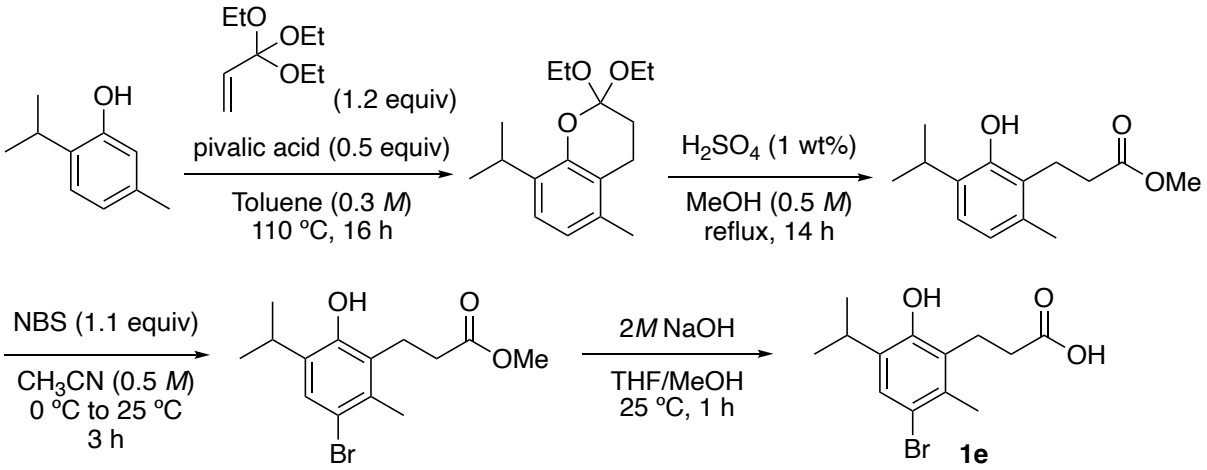
3-(5-Bromo-2-hydroxy-3-(triisopropylsilyl)phenyl)propanoic acid (**2d**): To a solution of 2,6-dibromophenol (5.04 g, 20.0 mmol) and NEt_3 (4.20 mL, 30.0 mmol) in THF (67.0 mL) was added chlorotriisopropylsilane (6.36 mL, 30.0 mmol) at 25 ºC under a nitrogen atmosphere. After stirring for 2 h at 25 ºC, the resulting mixture was filtered through celite with EtOAc and then the solvents were removed *in vacuo* to give (2,6-dibromophenoxy)triisopropylsilane as a pale yellow oil

Without futher purification, to a solution of this silyl ether in THF (67.0 mL) was added *n*-BuLi (12.5 mL, 20.0 mmol, 1.60 *M* in hexane) at –78 ºC under a nitrogen atmosphere. The reaction mixture was allowed to warm to 25 ºC. After stirring for 12 h, the resulting mixture was quenched with

saturated aqueous NH_4Cl (20.0 mL) and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to give 2-bromo-6-(triisopropylsilyl)phenol.

Without futher purification, to a solution of this phenol and K_2CO_3 (5.50 g, 40.0 mmol) in acetone (67.0 mL) was added benzyl bromide (4.80 mL, 40.0 mmol) at 25 ºC. The reaction mixture was refluxed at 60 °C for 2.5 h. The reaction mixture was cooled to 25 ºC and quenched with methanol (100 mL). The solvents were removed *in vacuo* and diluted with Et_2O (100 mL). the organic layers were washed with brine and dried over anhydrous MgSO4. The solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 20:1 to 10:1) to give (2-(benzyloxy)-3-bromophenyl)triisopropylsilane (7.04 g, 16.8 mmol, 84% yield for 3 steps).

To a solution of this benzyl ether (7.04 g, 16.8 mmol) in THF (56.0 mL) was added *n*-BuLi (10.5 mL, 16.8 mmol, 1.60 *M* in hexane) at –78 ºC under a nitrogen atmosphere. After stirring for 1.5 h, to the resulting mixture was added DMF (2.60 mL, 33.6 mmol). After stirring for 6 h, the resulting mixture was quenched with H_2O, and the aqueous layers were extracted with Et_2O (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 chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 20:1) to give 2-(benzyloxy)-3-(triisopropylsilyl)benzaldehyde (4.24 g, 11.5 mmol, 68% yield). **1d** was synthesized from this compound as in **1a** in 17% yield (4 steps) as a white solid. **TLC**, R_f = 0.51 (hexane–EtOAc–AcOH = 50:50:1); **IR** (KBr) 3415, 2938, 2861, 1695, 1249 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.06 (d, J = 7.3 Hz, 18H), 1.47 (sep, J = 7.3 Hz, 3 H), 2.66–2.70 (m, 2H), 2.76–2.80 (m, 2H), 7.30 (s, 2H), 7.66 (brs, 1H) ; **^{13}C NMR** (CD_3CN, 100 MHz) δ 12.4, 19.3, 25.1, 35.1, 113.4, 127.4, 130.9, 134.8, 137.8, 159.8, 177.3; **HRMS** (FAB+) *m*/*z* calcd for $[C_{18}H_{29}{}^{79}BrO_3Si+Na]^+$/$[C_{18}H_{29}{}^{81}BrO_3Si+Na]^+$ 423.0967/423.0949, found 423.0976/425.0944.



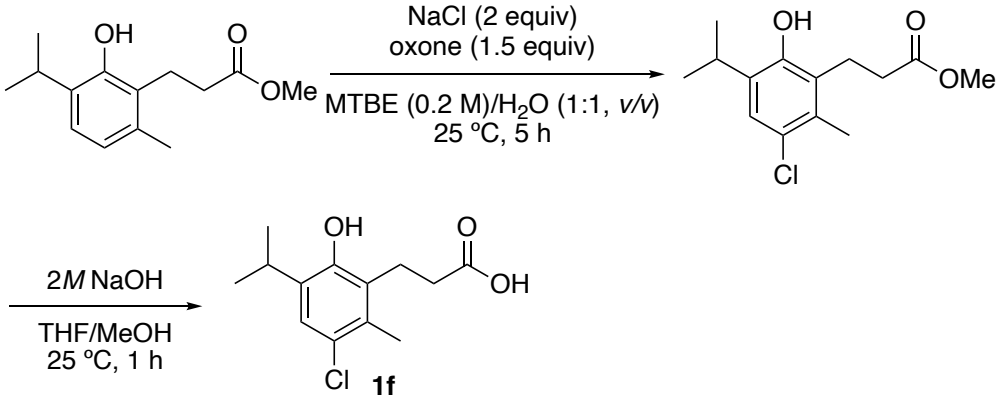
3-(3-Bromo-6-hydroxy-5-isopropyl-2-methylphenyl)propanoic acid (**1e**): To a solution of 2-isopropyl-5-methylphenol (3.00 g, 20.0 mmol) and triethyl ortho acrylate[26] (4.16 g, 24.0 mmol in toluene (66.7 mL) was added pivalic acid (1.02 g, 10.0 mmol) and the resulting mixture was refluxed for 16 h. The resulting mixture was poured into 1*M* NaOH (30.0 mL), extracted with Et_2O (twice) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in *vacuo*. The residue was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc = 15:1) to give 2,2-diethoxy-8-isopropyl-5-methylchromane (2.37 g, 8.49 mmol, 85% yield) as yellow oil.

To a solution of 2,2-diethoxy-8-isopropyl-5-methylchromane (2.37 g, 8.49 mmol) in MeOH (17.0 ml) was added H_2SO_4 (0.237 g) and the resulting mixture was was refluxed for 14 h. The resulting mixture was extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in *vacuo*.

Without futher purification, to a solution of of the crude product in CH_3CN (17.0 mL) under a nitrogen atmosphere was added NBS (1.66 g, 9.34 mmol) at 0 ºC. After stirring for 3 h at 25 ºC, the resulting mixture was diluted with water and Et_2O. The aqueous layers were separated and extracted with EtOAc (twice). The combined organic layers were washed with water (3 times) and dried over anhydrous $MgSO_4$, then the solvents were removed *in vacuo*.

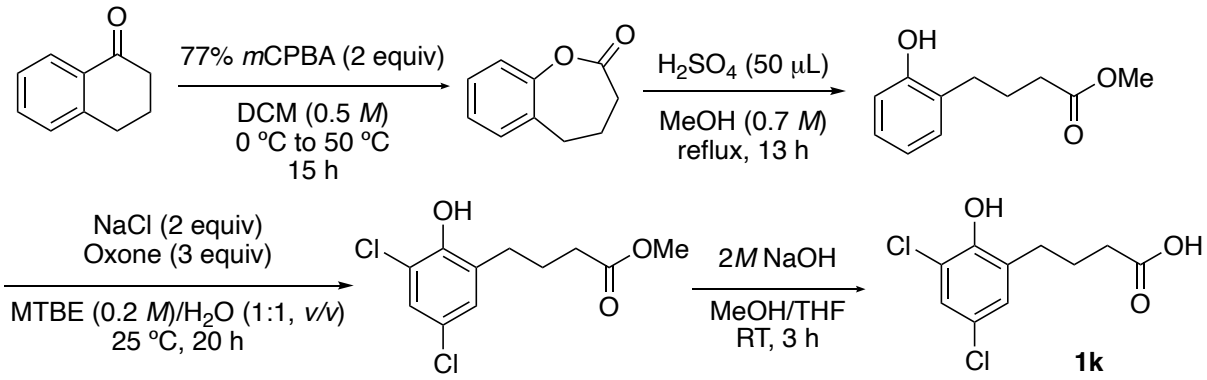
Without futher purification, to a solution of the crude product in THF (10 mL) and MeOH (10.0 ml) was added 2*M* NaOH (10.0 mL) and the resulting mixture was stirred overnight at room temperature. The resulting mixture was poured into 1*M* HCl, extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in *vacuo* to give **1e** (1.30 g, 4.33 mmol) in 51% yield (2 steps). **TLC**, R_f = 0.49 (hexane–EtOAc–AcOH = 50:50:1); **IR** (neat) 2961, 1700, 1461 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.19 (d, 6.9 Hz, 6H), 2.34 (s, 3H), 2.76 (t, *J* = 5.9 Hz, 2H), 2.99 (t, *J*= 5.9 Hz, 2H), 3.25 (sep, *J* =

6.9 Hz, 1H), 7.18 (brs, 1H), 7.25 (s, 1H).



3-(3-Chloro-6-hydroxy-5-isopropyl-2-methylphenyl)propanoic acid (**1f**): To a solution of methyl 3-(2-hydroxy-3-isopropyl-6-methylphenyl)propanoate (1.18 g, 5.00 mmol) and NaCl (0.584 g, 10.0 mmol) in MTBE (25.0 mL) and H_2O (25.0 mL) was added oxone (2.30 g, 7.50 mmol) at 25 ºC. After stirring for 5 h, the resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$ 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*.

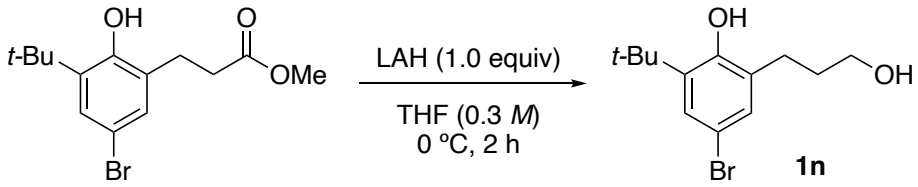
Without futher purification, to a solution of the crude product in THF (10 mL) and MeOH (10.0 ml) was added 2*M* NaOH (10.0 mL) and the resulting mixture was stirred overnight at room temperature. The resulting mixture was poured into 1*M* HCl, extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in *vacuo* to give **1f** (1.27 g, 4.93 mmol) in 99% yield as a pale yellow solid. **TLC**, R_f = 0.51 (hexane–EtOAc–AcOH = 50:50:1); **IR** (neat) 2961, 1705, 1461, 1413 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.20 (d, *J* = 6.9 Hz, 6H), 2.30 (s, 3H), 2.77 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 3.23 (sep, *J* = 6.9 Hz, 1H), 7.09 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 16.2, 21.5, 22.5, 27.1, 33.0, 125.1, 126.5, 127.0, 131.9, 135.6, 150.2, 179.5.



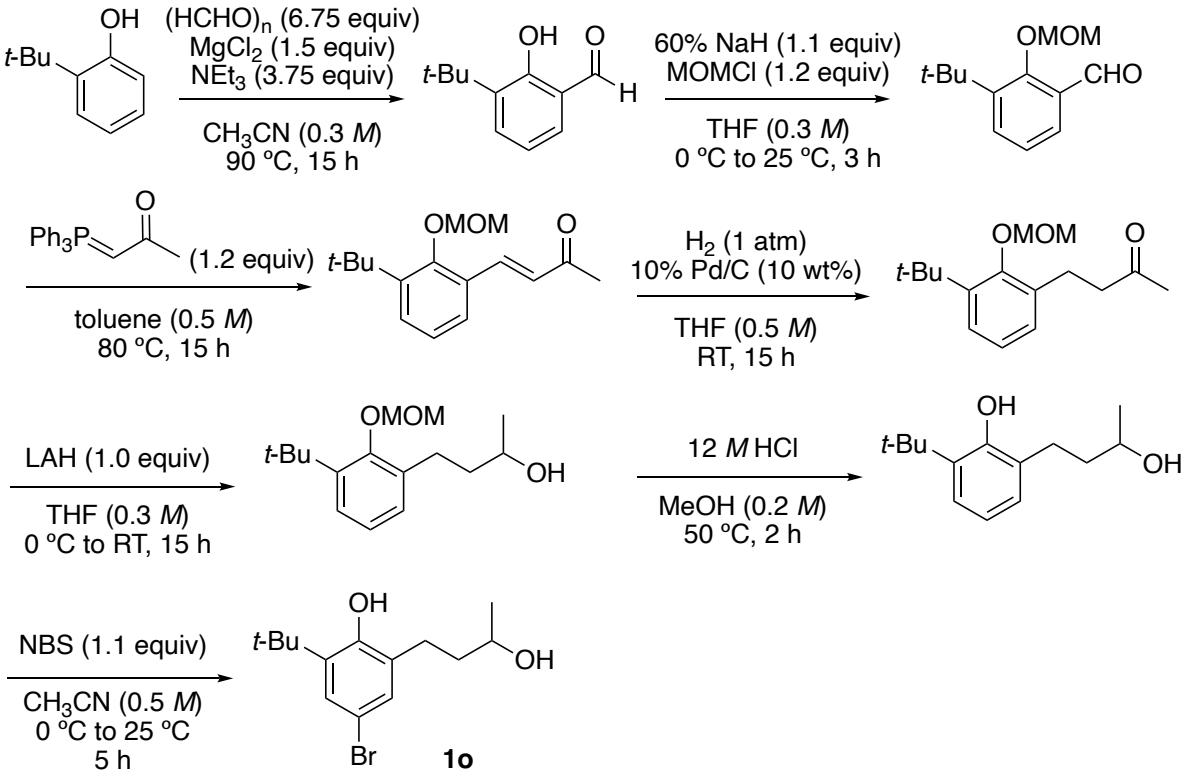
4-(3,5-Dichloro-2-hydroxyphenyl)butanoic acid (**1k**): To a solution of 3,4-dihydronaphthalen-1(2*H*)-one (1.46 g, 10.0 mmol) in DCM (20.0 mL) was added 77% *m*-CPBA (2.66 g, 20.0 mmol) at

0 ºC and the resulting mixture was stirred at 50 ºC for 15 h. The resulting mixture was quenched with saturated $Na_2S_2O_3$ at 0 ºC. The resulting mixture was extracted with EtOAc (twice) and washed with saturated $NaHCO_3$ and brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in *vacuo*.

Without futher purification, to a solution of the crude product in MeOH (14.3 ml) was added H_2SO_4 (0.0500 ml) and the resulting mixture was was refluixed for 13 h. The resulting mixture was extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in *vacuo*. The residue was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc = 15:1) to give methyl 4-(2-hydroxyphenyl)butanoate (1.47 g, 7.58 mmol, 76% yield). **1k** was synthesized from this compound as in **1h** in 82% yield (2 steps) as a white solid. **TLC**, R_f = 0.52 (hexane–EtOAc–AcOH = 50:50:1); **IR** (neat) 3400, 2961, 1700, 1466 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.95 (q, J = 7.3 Hz, 2H), 2.42 (t, J = 7.3 Hz, 2H), 2.70 (t, J = 7.3 Hz, 2H), 5.76 (brs, 1H), 7.03 (d, J = 2.8 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H); **^{13}C NMR** (DMSO-*d6*, 100 MHz) δ 24.4, 29.4, 33.2, 121.6, 123.1, 126.6, 128.4, 132.8, 149.8, 174.3.



4-Bromo-2-(*tert*-butyl)-6-(3-hydroxypropyl)phenol (**1n**): To a solution of methyl 3-(5-bromo-3-(*tert*-butyl)-2-hydroxyphenyl)propanoate (0.315 g, 1.00 mmol) in THF (3.33 mL) was added $LiAlH_4$ (0.0380 g, 1.00 mmol) at 0 ºC. After stirring for 2 h at room temperature, resulting mixture was cooled at 0 ºC and sequentially quenched by saturated aqueous Rochelle salt (15 mL). After stirring for 30 min at room temperature, the aqueous layers were 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 = 3:1) to give **1n** (0.282 g, 0.982 mmol, 98% yield). **TLC**, R_f = 0.27 (hexane–EtOAc = 4:1); **IR** (neat) 3322, 2961, 2874 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.40 (s, 9H), 1.84–1.91 (m, 3H), 2.75 (t, *J* = 6.4 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.23 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** (CD_3CN, 100 MHz) δ 25.1, 29.5, 31.6, 34.9, 60.4, 112.3, 128.0, 129.8, 130.5, 139.5, 152.7.



4-Bromo-2-(*tert*-butyl)-6-(3-hydroxybutyl)phenol (1o): To a solution of $MgCl_2$ (1.43 g, 15.0 mmol) and NEt_3 (5.22 mL, 37.5 mmol) in CH_3CN (33.3 mL) were added 2-(*tert*-butyl)phenol (1.50 g, 10.0 mmol) and dry paraformaldehyde (2.03 g, 67.5 mmol) at 25 ºC under a nitrogen atmosphere. The mixture was refluxed at 90 °C for 15 h. The reaction mixture was cooled to 25 °C, and poured into 1 *M* HCl, and the aqueous layers were extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*.

To a solution of the crude product in THF (33.3 mL) was added sodium hydride (60-wt%, 0.440 g, 22.0 mmol) in at 0 ºC under a nitrogen atmosphere. The reaction mixture was allowed to warm to 25 ºC. After stirring for 1 h, the resulting mixture was re-cooled to 0 ºC and to the mixture was added chloromethyl methyl ether (0.910 mL, 12.0 mmol). The resulting mixture was allowed to warm to 25 ºC again. After stirring for 3 h, the resulting mixture was poured into H_2O, and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*.

Without futher purification, to a solution of the crude product in toluene (20.0 mL) was added (acetylmethylene)triphenylphosphorane (3.82 g, 12.0 mmol) at 25 ºC under a nitrogen atmosphere. After stirring for 15 h at 80 ºC, the resulting mixture was cooled to 25 ºC and diluted with water and EtOAc. The aqueous layers were 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 (eluent: hexane–EtOAc = 8:1) to give

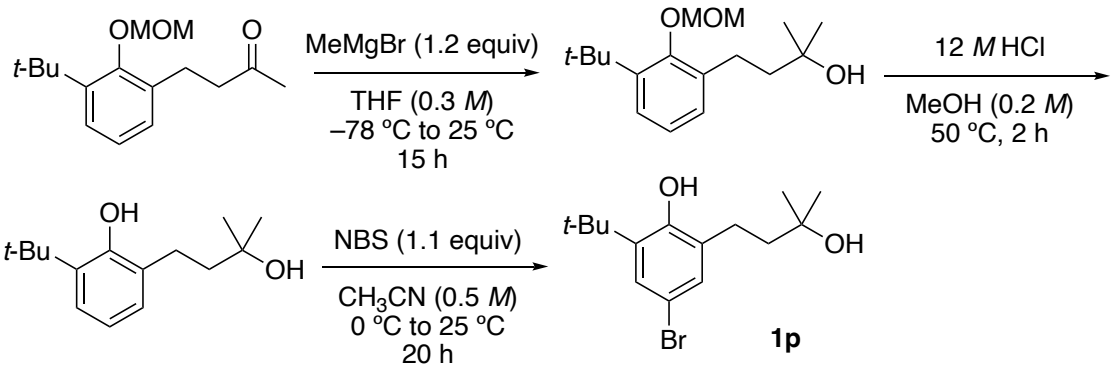
methyl (*E*)-4-(3-(*tert*-butyl)-2-(methoxymethoxy)phenyl)but-3-en-2-one (1.89 g, 7.21 mmol, 72% yield, 3 steps) as a white solid.

To a solution of this olefin in THF (14.4 mL) was added 10% Pd/C (0.189 g). The flask containing the mixture was then evacuated and purged with H_2 three times. After stirring for 15 h at 25 ºC, the mixture was filtered through celite with EtOAc and the crude product was obtained after removal of the solvent *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc = 8:1) to give 4-(3-(*tert*-butyl)-2-(methoxymethoxy)phenyl)butan-2-one (1.28 g, 4.83 mmol, 67% yield).

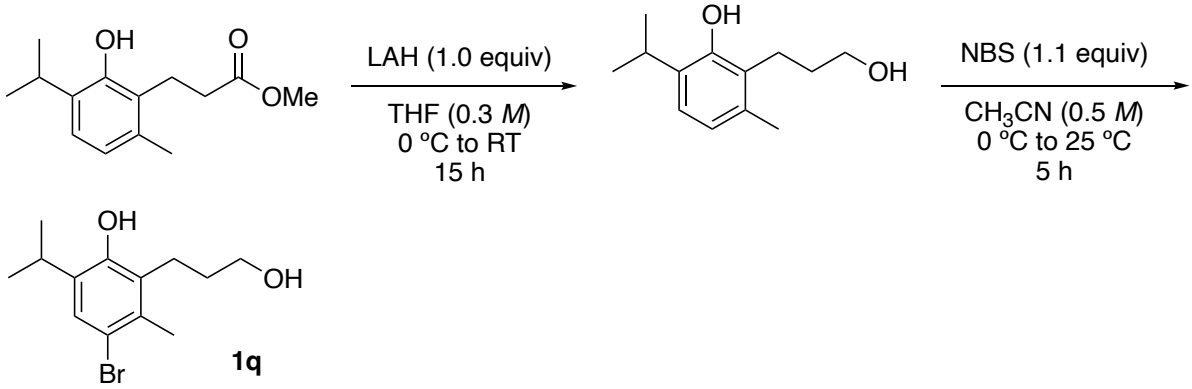
To a solution of this ether in THF (16.1 mL) was added $LiAlH_4$ (0.183 g, 4.83 mmol) at 0 ºC. After stirring for 15 h at room temperature, resulting mixture was cooled at 0 ºC and sequentially quenched by saturated aqueous Rochelle salt (15 mL). After stirring for 30 min at room temperature, the aqueous layers were 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*.

Without futher purification, to a solution of the crude product in MeOH (24.2 ml) was added 12 *M* HCl (0.100 ml) at 0 ºC and the resulting mixture was stirred at 50 ºC for 2 h. The resulting mixture was extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in *vacuo*.

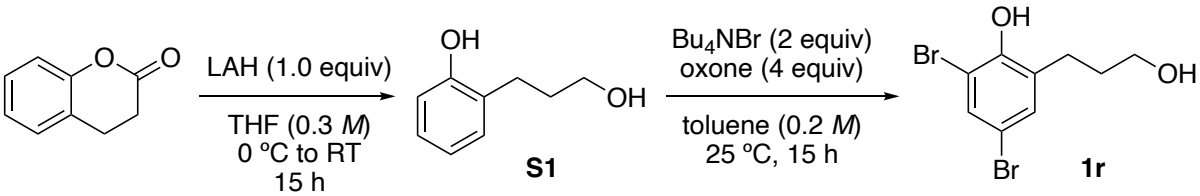
Without futher purification, to a solution of the crude product in CH_3CN (9.66 mL) under a nitrogen atmosphere was added NBS (946 g, 5.31 mmol) at 0 ºC. After stirring for 5 h at 25 ºC, the resulting mixture was diluted with water and EtOAc. The aqueous layers were separated and extracted with EtOAc (twice). The combined organic layers were washed with water and dried over anhydrous $MgSO_4$, then the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc = 5:1) to give 4-bromo-2-(*tert*-butyl)-6-(3-hydroxybutyl)phenol (1.45 g, 4.80 mmol, 99% yield, 3 steps) as a yellow oil. **TLC**, R_f = 0.28 (hexane–EtOAc= 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.23 (d, J = 6.0, 3H), 1.37 (s, 9H), 1.68–1.75 (m, 2H), 2.54–2.61 (m, 1H), 2.81–2.89 (m, 1H), 3.67–3.73 (m, 1H), 7.06 (d, J = 2.3 Hz, 1H), 7.21 (d, J = 2.3 Hz, 1H), 7.48 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 24.0, 25.6, 29.5, 35.0, 38.8, 66.6, 112.0, 128.0, 130.1, 130.6, 139.6, 153.0.



4-Bromo-2-(*tert*-butyl)-6-(3-hydroxy-3-methylbutyl)phenol (1p): To a solution of t 4-(3-(*tert*-butyl)-2-(methoxymethoxy)phenyl)butan-2-one (1.00 mmol, 0.264 g) in THF (3.33 mL) was slowly added MeMgBr (1.0 *M* in THF, 1.20 mL, 1.20 mmol) at –78 ºC. After stirring for 15 h at room temperature, resulting mixture was cooled at 0 ºC and sequentially quenched by saturated NH_4Cl (5 mL). The aqueous layers were 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*. **1p** was synthesized from this compound as in **1o** in 95% yield (3 steps) as a colorless oil. **TLC**, R_f = 0.48 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.29 (s, 6H), 1.38 (s, 9H), 1.68 (brs, 1H), 1.78 (t, J = 7.3 Hz, 2H), 2.68 (t, J = 7.3 Hz, 2H), 7.07 (d, J = 2.3 Hz, 1H), 7.21–7.22 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 24.6, 29.5, 29.6, 35.0, 42.6, 71.9, 111.7, 127.9, 130.1, 131.5, 139.3, 152.2.

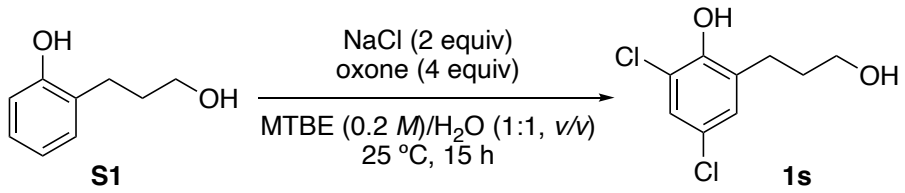


4-Bromo-2-(3-hydroxypropyl)-6-isopropyl-3-methylphenol (1q): **1p** was synthesized from methyl 3-(2-hydroxy-3-isopropyl-6-methylphenyl)propanoate as in **1q** in 80% yield (2 steps) as a pale yellow oil. **TLC**, R_f = 0.25 (hexane–EtOAc = 2:1); **H NMR** (CD_3CN, 400 MHz) δ 1.20 (d, *J* = 6.8 Hz, 6H), 2.34 (s, 3H), 2.36 (s, *3*H), 2.78 (t, *J* = 6.0 Hz, 2H), 3.00 (t, *J* = 6.0 Hz, 3H), 3.25 (q, *J* = 6.8 Hz, 1H), 7.19 (brs, 1H), 7.27 (s, 1H).

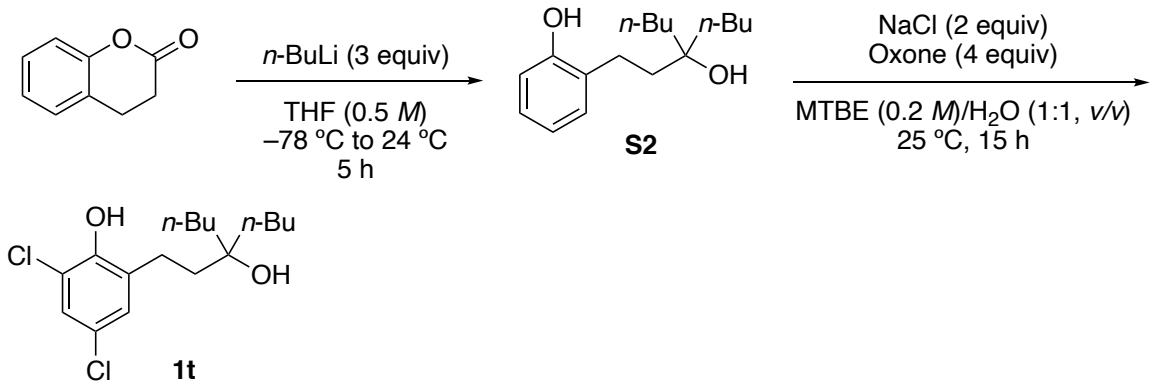


2,4-Bibromo-6-(3-hydroxypropyl)phenol (1r): To a solution of chroman-2-one (10.0 mmol) in THF (33.3 mL) was added $LiAlH_4$ (0.380 g, 10.0 mmol) at 0 ºC. After stirring for 15 h at room temperature, resulting mixture was cooled at 0 ºC and sequentially quenched by saturated aqueous Rochelle salt (15 mL). After stirring for 30 min at room temperature, the aqueous layers were 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*.

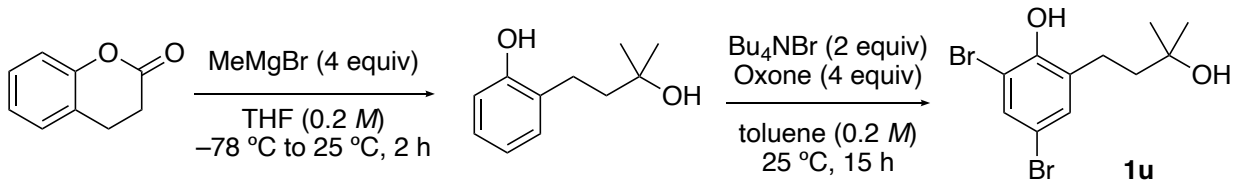
Without futher purification, to a solution of the crude product and Bu_4NBr (6.44 g, 20 mmol) in toluene (50.0 mL) was added oxone (12.3 g, 40.0 mmol) at 25 ºC. After stirring for 15 h, the resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$ and the aqueous layers were extracted with EtOAc (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 chromatography on silica gel (eluent: hexane–EtOAc = 2:1) to give **1r** (2.22 g, 7.16 mmol, 72% yield, 2 steps) as a pale yellow oil. **TLC**, R_f = 0.31 (hexane–EtOAc = 4:1); **IR** (neat) 2939, 1457, 1400 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.77 (brs, 1H), 1.84–1.91 (m, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 3.66 (t, *J* = 6.0 Hz, 2H), 6.46 (brs, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 7.48 (d, *J* =2.3 Hz, 1H); **^{13}C NMR** (CD_3CN, 100 MHz) δ 27.2, 32.6, 61.0, 112.2, 112.4, 133.2, 133.3, 133.4, 152.2.



2,4-dichloro-6-(3-hydroxypropyl)phenol (1s): To a solution of **S1** (0.152 g, 1.00 mmol) and NaCl (0.117 g, 2.00 mmol) in MTBE (5.00 mL) and H_2O (5.00 mL) was added oxone (1.23 g, 4.00 mmol) at 25 ºC. After stirring for 15 h, the resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$ 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 chromatography on silica gel (eluent: hexane–EtOAc = 2:1) to give **1s** (0.159 g, 0.720 mmol, 72% yield) as a pale yellow solid. **TLC**, R_f = 0.31 (hexane–EtOAc = 4:1); **IR** (neat) 3330, 2866, 1751, 1466 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.72 (brs, 1H), 1.85–1.91 (m, 2H), 2.76 (t, *J* = 6.9 Hz, 2H), 3.66 (dt, *J* = 5.0, 8.5 Hz, 2H), 6.34 (brs, 1H), 7.03 (d, *J* = 2.8 Hz, 1H), 7.20 (d, *J* = 2.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.1, 31.9, 61.2, 120.8, 125.0, 126.6, 129.0, 130.5, 148.7.

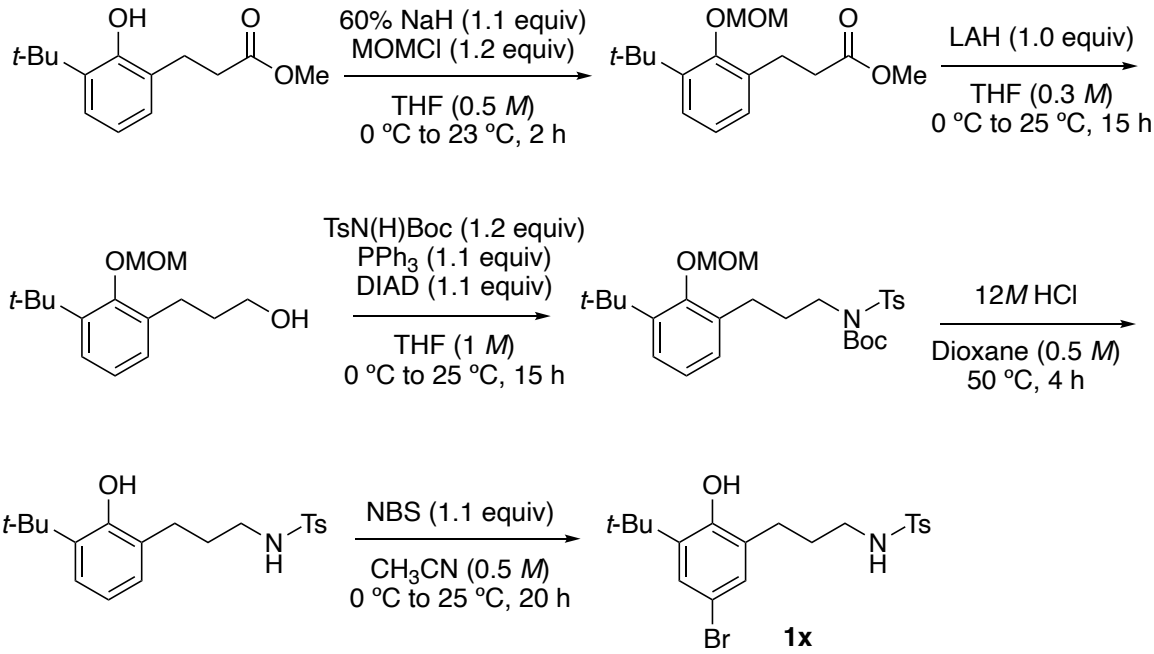


2,4-Dichloro-6-(3-hydroxypropyl)phenol (1t): To a solution of chroman-2-one (1.48 g, 10 mmol) in THF (20.0 mL) was added *n*-BuLi (1.6 *M* in hexane, 18.8 mL, 30.0 mmol) at –78 ºC. After stirring for 5 h at 24 ºC, the resulting mixture was quenched with saturated aqueous NH_4Cl and the aqueous layers 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 chromatography on silica gel (eluent: hexane–EtOAc = 2:1) to give **S2** (1.84 g, 6.96 mmol, 70% yield). **1t** was synthesized from this compound as in **1s** in 95% yield as a white solid. **TLC**, R_f = 0.48 (hexane–EtOAc = 4:1); **IR** (neat) 2935, 2874, 1466 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 0.92 (t, *J* = 7.3 Hz, 6H), 1.28–1.36 (m, 8H), 1.48–1.52 (m, 4H), 1.69–1.73 (m, 2H), 2.64–2.68 (m, 2H), 6.51 (m, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** (CD_3CN, 100 MHz) δ 25.2, 30.0, 35.4, 35.6, 124.9, 127.5, 127.9, 129.7, 129.9, s133.6, 139.0, 142.4, 153.9, 177.5, 191.3; **HRMS** (FAB+) *m*/*z* calcd for $[C_{17}H_{26}{}^{35}Cl_2O_2]$ 332.1310, found 332.1312.



2,4-Dibromo-6-(3-hydroxy-3-methylbutyl)phenol (1u): To a solution of t 4-(3-(*tert*-butyl)-2-(methoxymethoxy)phenyl)butan-2-one (1.48 g, 10.0 mmol) in THF (50.0 mL) was slowly added MeMgBr (1.0 *M* in THF, 40.0 mL, 40.0 mmol) at –78 ºC. After stirring for 15 h at room temperature, resulting mixture was cooled at 0 ºC and sequentially quenched by saturated NH_4Cl (30.0 mL). The aqueous layers were 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*. **1u** was synthesized from this compound as in **1r** in 95% yield (2 steps) as a white solid. **TLC**, R_f = 0.48 (hexane–EtOAc = 4:1); **IR** (neat) 3504, 3370, 2974, 1457 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.30 (s, 6H), 1.56 (brs, 1H), 1.76 (dt, *J* = 2.3, 8.2 Hz, 2H), 2.73 (dt, *J* = 2.3, 8.2 Hz, 2H), 6.48 (brs, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.5, 29.3, 42.9, 71.3, 111.1, 112.1,

131.9, 132.1, 132.2, 149.8.

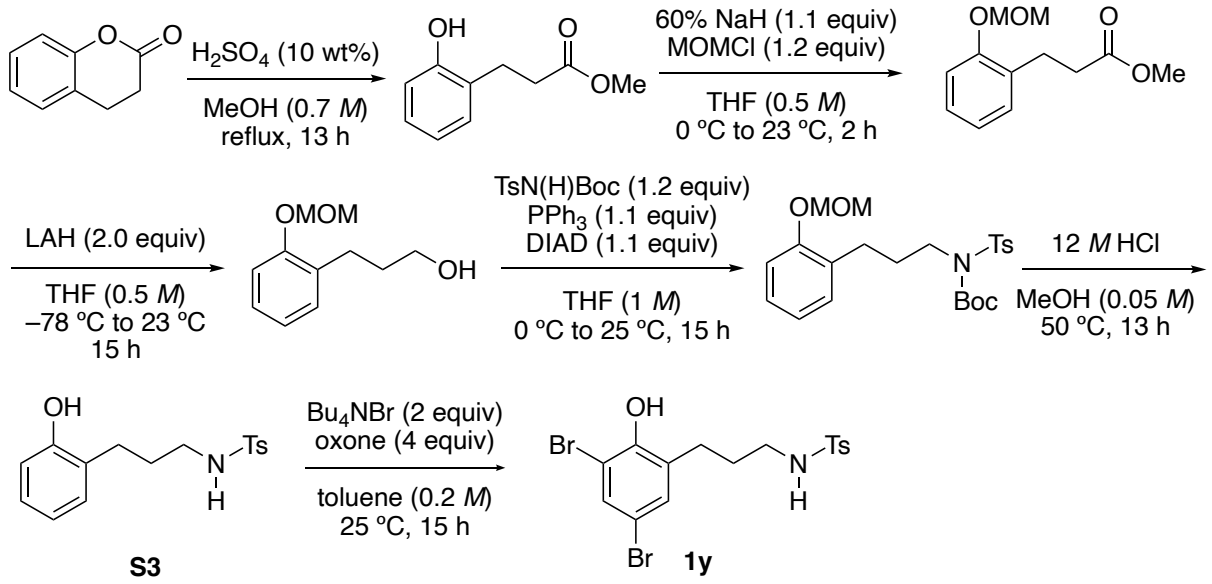


***N*-(3-(5-Bromo-3-(*tert*-butyl)-2-hydroxyphenyl)propyl)-4-methylbenzenesulfonamide (1x):** To a solution of methyl 3-(3-(*tert*-butyl)-2-hydroxyphenyl)propanoate (1.18 g, 5.00 mmol) in THF (10.0 mL) was added sodium hydride (60-wt%, 0.220 g, 5.50 mmol) in at 0 ºC under a nitrogen atmosphere. The reaction mixture was allowed to warm to 25 ºC. After stirring for 1 h, the resulting mixture was re-cooled to 0 ºC and to the mixture was added chloromethyl methyl ether (0.455 mL, 6.00 mmol). The resulting mixture was allowed to warm to 25 ºC again. After stirring for 2 h, the resulting mixture was poured into H_2O, and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*.

Without futher purificaton, to a solution of the crude product in THF (16.7 mL) was added $LiAlH_4$ (0.190 g, 5.00 mmol) at 0 ºC. After stirring for 15 h at room temperature, resulting mixture was cooled at 0 ºC and sequentially quenched by saturated aqueous Rochelle salt (15 mL). After stirring for 30 min at room temperature, the aqueous layers were 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*.

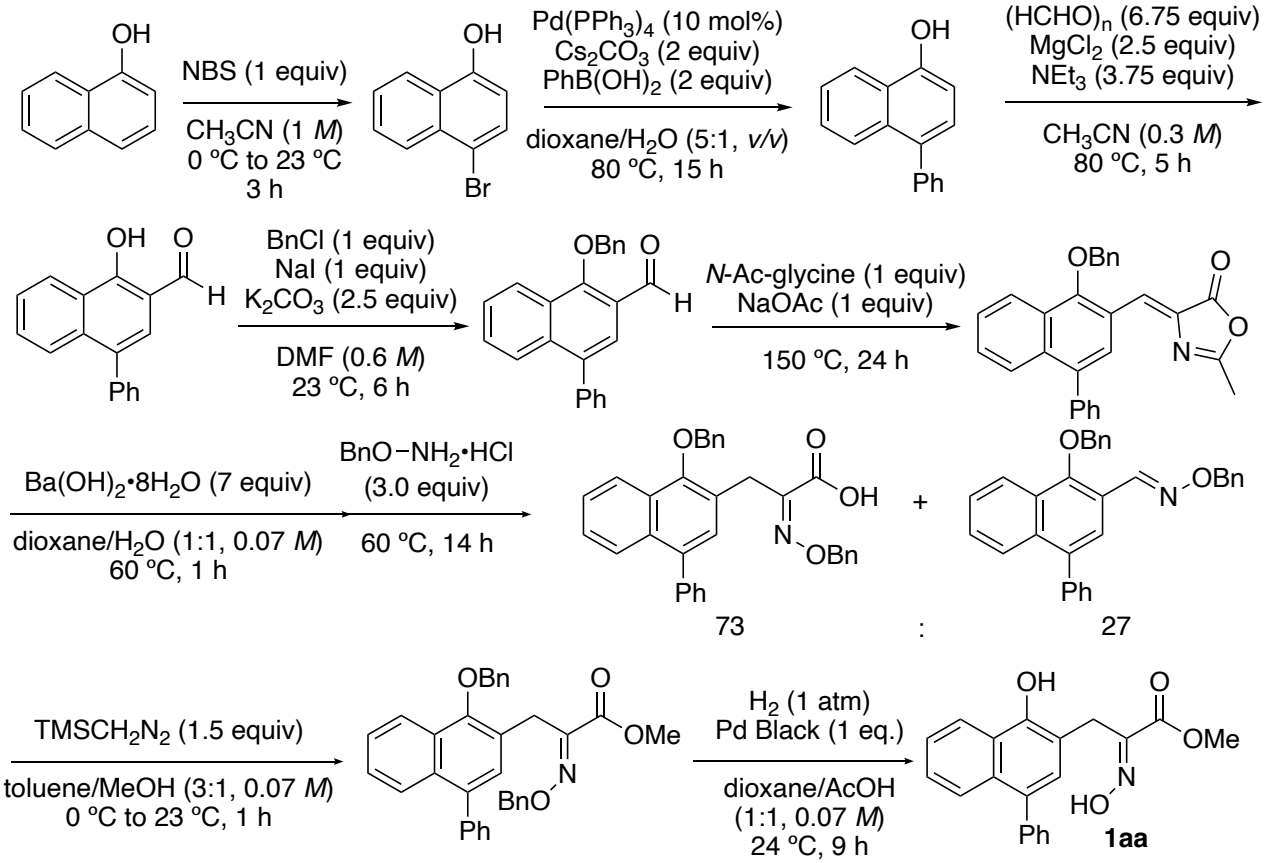
To a solution of this alcohol, *N*-(tert-butoxycarbonyl)-para-toluenesulfonamide (1.63 g, 6.00 mmol) and PPh_3 (1.45 g, 5.25 mmol) in THF (5.0 mL) was added diisopropyl azodicarboxylate (2.91 mL, 5.50 mmol, 1.9 *M* in toluene) dropwise at 0 ºC. After stirring for 15 h at room temperature, resulting mixture was poured into H_2O (20 mL) and the aqueous layers were 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 = 10:1) to give *tert*-butyl (3-(3-(*tert*-butyl)-2-(methoxymethoxy)phenyl)propyl)(tosyl)carbamate (1.49 g, 2.95 mmol, 59% yield, 4 steps). **1x** was synthesized from this compound as in **1x** in 95% yield as a yellow solid. **TLC**, R_f = 0.61 (hexane–EtOAc =1:1); **IR** (neat) 3500, 3274, 2952, 1722 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.36 (s, 9H), 1.73–1.80 (m, 2H), 2.42 (s, 3H), 2.59 (t, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 5.9 Hz, 2H), 5.33 (brs, 2H), 7.00 (d, *J* = 2.3 Hz, 1H), 7.20 (d, *J* =2.3 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (CD_3CN, 100 MHz) δ 21.5, 26.5, 29.4, 29.6, 34.7, 42.3, 112.6, 127.1, 128.0, 129.5, 129.8, 130.1, 136.2, 138.8, 143.7, 151.6.



***N*-(3-(3,5-Dibromo-2-hydroxyphenyl)propyl)-4-methylbenzenesulfonamide (1y):** To a solution of chroman-2-one (1.48 g, 10.0 mmol) in MeOH (14.3 ml) was added H_2SO_4 (0.148 g) and the resulting mixture was refluxed for 13 h. The resulting mixture was extracted with EtOAc (twice) and washed with $NaHCO_3$ and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in *vacuo*.

Without futher purification, to a solution of the crude product in THF (20.0 mL) was added sodium hydride (60-wt%, 0.440 g, 11.0 mmol) in at 0 ºC under a nitrogen atmosphere. The reaction mixture was allowed to warm to 25 ºC. After stirring for 1 h, the resulting mixture was re-cooled to 0 ºC and to the mixture was added chloromethyl methyl ether (0.911 mL, 12.0 mmol). The resulting mixture was allowed to warm to 25 ºC again. After stirring for 2 h, the resulting mixture was poured into H_2O, and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. **1aa** was synthesized from this compound as in **1x** in 95% yield (for 6 steps) as a white solid.



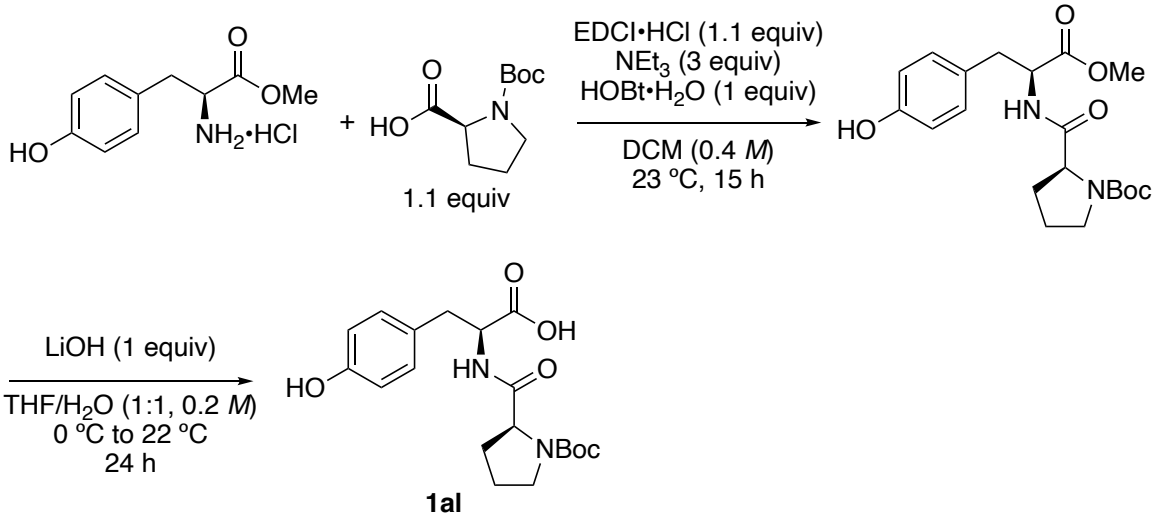
Methyl (E)-3-(1-hydroxy-4-phenylnaphthalen-2-yl)-2-(hydroxyimino)propanoate (1ab): To a solution of 1-naphthol (7.21 g, 50.0 mmol) in CH_3CN (50.0 ml) was added NBS (8.90 g, 50.0 ml) at 0 ºC and the resulting mixture was stirred for 3 h. The resulting mixture was extracted with EtOAc (twice) and washed with H_2O (3 times) and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in *vacuo*.

Without futher purification, to a solution of this aryl bromide (4.46 g, 20.0 mmol), phenylboronic acid (4.88 g, 40.0 mmol) and Cs_2CO_3 (13.0 g, 40.0 mmol) in degassed dioxane (100 mL) and H_2O (20.0 mL) were added $Pd(PPh_3)_4$ (2.31 g, 2.00 mmol) at 25 ºC. After stirring for 15 h at 80 ºC, the resulting mixture was filtered through celite pad and extracted with EtOAc (twice). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. The organic layers were concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc =50:1 to 30:1) to give 4-phenylnaphthalen-1-ol (3.52 g, 16.1 mmol) in 80% yield as a black solid.

To a solution of $MgCl_2$ (1.43 g, 15.0 mmol) and NEt_3 (5.22 mL, 37.5 mmol) in CH_3CN (50.0 mL) were added 4-phenylnaphthalen-1-ol (2.20 g, 10.0 mmol) and dry paraformaldehyde (2.03 g, 67.5 mmol) at 25 ºC under a nitrogen atmosphere. The mixture was refluxed at 80 °C for 5 h. The reaction mixture was cooled to 25 °C, and poured into 1*M* HCl, and the aqueous layers were extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over

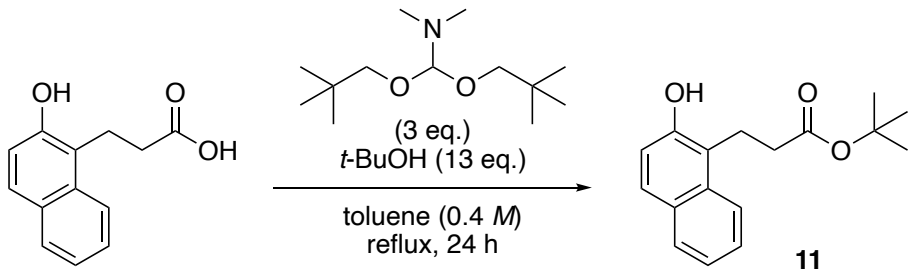
anhydrous $MgSO_4$ and solvents were removed *in vacuo*.

To a solution of this naphthol in DMF (16.7 mL) was added BnCl (1.15 mL, 10.0 mmol), NaI (1.50 g, 10.0 mmol) and K_2CO_3 (3.46 g, 25.0 mmol) at 23 ºC. The mixture was stirred for 6 h and the resulting mixture was diluted with Et_2O. The aqueous layers were extracted with Et_2O (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*. **1ab** was synthesized from this compound as following the literature procedure[15] in 27% yield (4 steps) as a white solid. **H NMR** ($CDCl_3$, 400 MHz) δ 3.90 (s, 3H), 4.10 (s, 2H), 7.25–7.49 (m, 6H), 7.80 (d, *J* = 7.8 Hz, 1H), 8.19 (s, 1H), 8.37–8.39 (m, 2H).

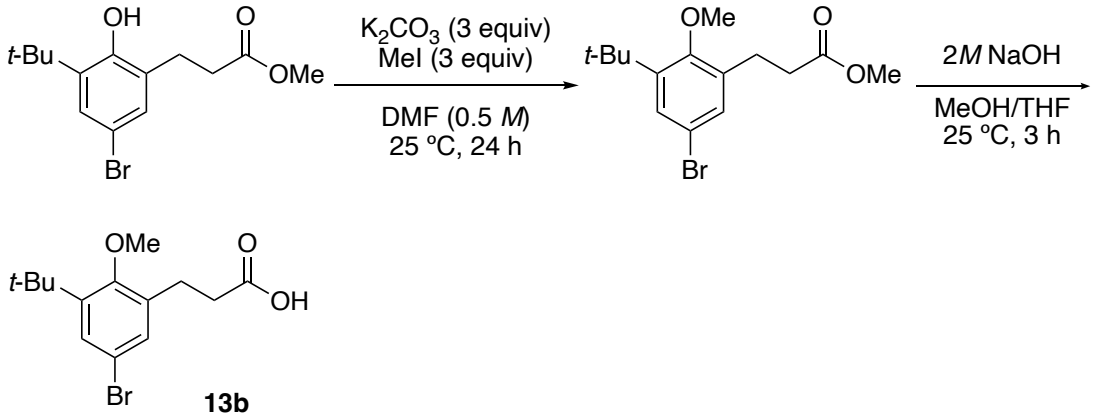


(*tert*-Butoxycarbonyl)-*L*-prolyl-*L*-tyrosine (1al): To a solution of *L*-tyrosine methyl ester hydrochloride (2.32 g, 10.0 mmol) and *N*-(*tert*-butoxycarbonyl)-*L*-proline (2.37 g, 11.0 mmol) in DCM (25.0 mL) were added 1-hydroxybenzotriazole (HOBt•H_2O, 1.53 g, 10.0 mmol), triethylamine (2.49 mL, 30.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI•HCl, 2.11 g, 11.0 mmol) at 23 ºC. The mixture was stirred for 12 h. The reaction was quenched by the addition of 1 *M* HCl (15 mL). The aqueous layers were extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*.

Without futher purification, to a solution of this methyl ester in THF (10.0 mL) and H_2O (10.0 mL) was added LiOH (0.240 g) at 0 ºC. The resulting mixture was stirred at 22 ºC for 24 h. The resulting mixture was poured into 1 *M* HCl, extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed *in vacuo*. The residue was purified by recrystallization from $CHCl_3$ to give **1al** (3.03 g, 80% yield, 2 steps). **IR** (KBr) 3322, 2974, 1660, 1518 cm^{-1}.

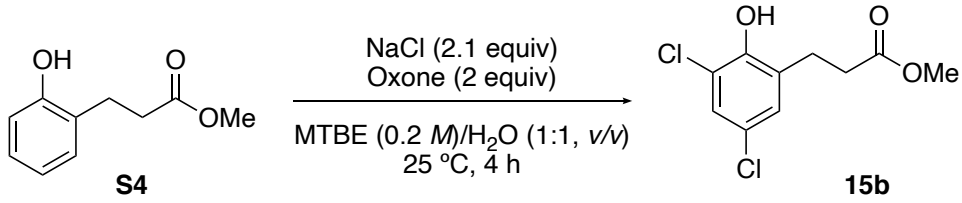


***tert*-Butyl 3-(2-hydroxynaphthalen-1-yl)propanoate (11):** To a solution of 3-(2-hydroxynaphthalen-1-yl)propanoic acid[19] (0.649 g, 3.00 mmol) and *tert*-butyl alchol (3.70 mL, 39.0 mmol) in toluene (7.50 mL) was added *N*,*N*-dimethyl-1,1-bis(neopentyloxy)methanamine (2.08 g, 9.00 mmol) at 0 ºC. The reaction mixture was refluxed for 24 h. The resulting mixture was extracted with EtOAc (twice) and washed with $NaHCO_3$ and brine. The combined organic layers were dried over anhydrous $MgSO_4$ and 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 **11** (0.643 g, 2.36 mmol) in 78% yield as a white solid. **TLC**, R_f = 0.48 (hexane–EtOAc = 6:1); **IR** (neat) 3339, 2974, 1700 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 2.81–2.84 (m, 2H), 3.25–3.27 (m, 2H), 7.21 (d, *J* = 9.2 Hz, 1H), 7.30–7.36 (m, 1H), 7.46–7.51 (m, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.76–7.80 (m, 2H), 8.58 (brs, 1H).

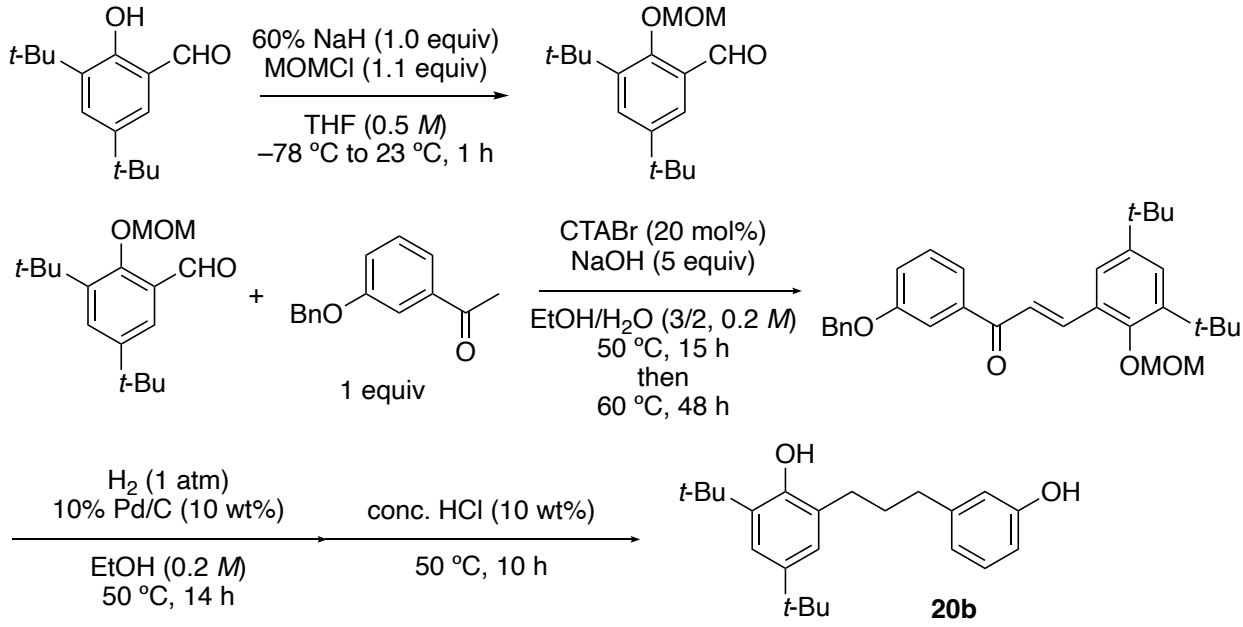


3-(5-bromo-3-(*tert*-butyl)-2-methoxyphenyl)propanoic acid (13b): To a solution of Methyl 3-(5-bromo-3-(tert-butyl)-2-hydroxyphenyl)propanoate (0.315 g, 1.00 mmol) in DMF (2.00 mL) were added K_2CO_3 (0.415 g, 3.00 mmol) and iodomethane (0.187 mL, 3.00 mmol) at 25 ºC. The mixture was stirred for 25 h. The reaction was quenched by the addition of saturated NH_4Cl (5.00 mL). The aqueous layers were extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and 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 methyl 3-(5-bromo-3-(*tert*-butyl)-2-methoxyphenyl)propanoate (0.265 g, 0.804 mmol) in 80% yield as a white solid.

To a solution of this methyl ester in MeOH (5.00 mL) and H_2O (5.00 mL) was added 2 *M* NaOH (5.00 mL) at 25 ºC. The resulting mixture was stirred at 25 ºC for 3 h. The resulting mixture was poured into 1 *M* HCl, extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and 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 **13b** (0.250 g, 7.93 mmol) in 99% yield as a white solid. **TLC**, R_f = 0.40 (hexane–EtOAc = 1:1); **IR** (neat) 2930, 1731, 1574 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.36 (s, 9H), 2.70 (t, *J* = 7.8 Hz, 2H), 2.99 (t, *J* = 7.8 Hz, 2H), 3.78 (s, 3H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.5, 30.8, 34.0, 35.3, 61.7, 116.6, 128.8, 130.8, 135.8, 145.5, 157.5, 178.7.

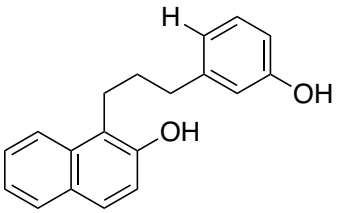


Methyl 3-(2-hydroxyphenyl)propanoate (15b): **15b** was synthesized from this compound as in **1s** in 47% yield as a white solid. **TLC**, R_f = 0.48 (hexane–EtOAc = 6:1); **IR** (neat) 3422, 2952, 1713 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 2.67 (t, *J* = 7.3 Hz, 2H), 2.93 (t, *J* = 7.3 Hz, 2H), 3.69 (s, 3H), 6.35 (brs, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.7, 33.6, 52.0, 121.1, 125.0, 127.0, 129.0, 129.6, 148.5, 174.0.



2,4-Di-*tert*-butyl-6-(3-(3-hydroxyphenyl)propyl)phenol (20b): To a solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (2.34 g, 10.0 mmol) in THF (20.0 mL) was added sodium hydride (60-wt%, 0.400 g, 10.0 mmol) in at 0 ºC under a nitrogen atmosphere. The reaction mixture was allowed to

warm to 25 ºC. After stirring for 1 h, the resulting mixture was re-cooled to 0 ºC and to the mixture was added chloromethyl methyl ether (0.835 mL, 11.0 mmol). The resulting mixture was allowed to warm to 25 ºC again. After stirring for 2 h, the resulting mixture was poured into H_2O, and the aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. **18b** was synthesized from this compound and 1-(3-(benzyloxy)phenyl)ethan-1-one as the following procedure[25] in 25% yield (2 steps) as a white solid. **IR** (neat) 3391, 2956, 2866 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 1.40 (s, 9H), 1.95 (quin, *J* = 7.8 Hz, 2H), 2.56 (t, *J* = 7.8 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H), 4.59 (brs, 1H), 4.60 (brs, 1H), 6.62–6.68 (m, 2H), 6.78 (d, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 2.3 Hz, 1H), 7.13–7.18 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 29.8, 29.9, 30.9, 31.6, 34.2, 34.7, 35.4, 112.9, 115.4, 120.8, 121.9, 124.3, 126.7, 129.6, 135.0, 142.2, 143.9, 149.8, 155.6.

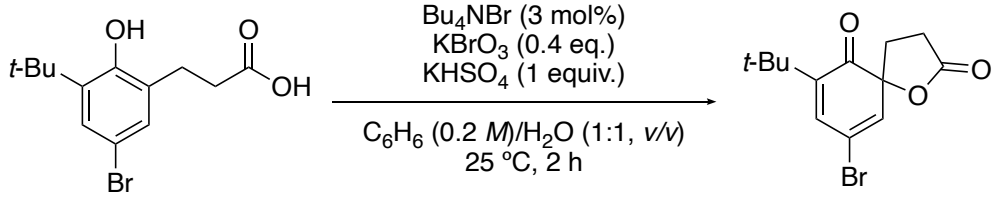


1-(3-(3-Hydroxyphenyl)propyl)naphthalen-2-ol (20c):

18c was synthesized from 1-(2-(benzyloxy)naphthalen-1-yl)ethan-1-one and 3-(benzyloxy)benzaldehyde as the following procedure[25] in 48% yield (2 steps) as a white solid. **IR** (neat) 3391, 2944, 2866 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.97–2.03 (m, 2H), 2.74 (t, *J* = 6.9 Hz, 2H), 3.06 (t, *J* = 7.8 Hz, 2H), 6.68 (dd, *J* = 2.8, 8.0 Hz, 1H), 6.73 (s, 1H), 6.79–6.81 (m, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.13–7.18 (m, 1H), 7.29–7.33 (m, 1H), 7.43–7.46 (m, 1H), 7.61 (dd, *J* = 2.8, 8.7 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H).

Procedures for Oxidation and Characterization of Products

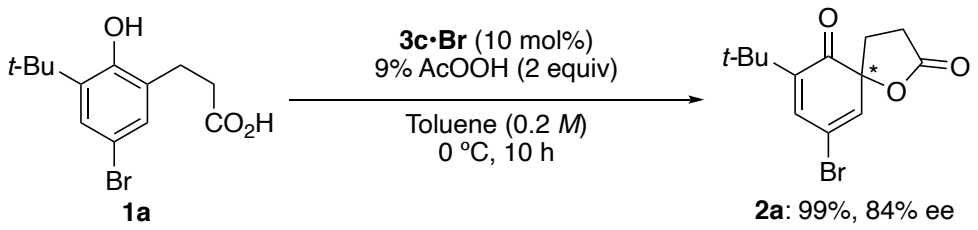
Oxidative Dearomatization of Phenols 1



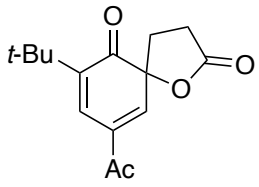
1a **2a:** 92% yield

9-Bromo-7-(*tert*-butyl)-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (2a): To a solution of **1a** (0.0602 g, 0.200 mmol), Bu_4NBr (0.00194 g, 0.00600 mmol, 3 mol%) and $KHSO_4$ (0.0272 g, 0.200 mmol) in benzene (1.00 mL) and H_2O (1.00 mL) were added $KBrO_3$ (0.0134 g, 0.0400 mmol) at 25

ºC. The reaction was monitored by TLC analysis. After stirring for 2 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **2a** (0.0552 g, 0.184 mmol) in 92% yield as a yellow solid. **TLC**, R_f = 0.49 (hexane–EtOAc = 2:1); **IR** (KBr) 2965, 1796, 1732, 1681, 1370 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.23 (s, 9H), 2.06–2.15 (m, 1H), 2.36–2.42 (m, 1H), 2.51–2.58 (m, 1H), 2.72–2.82 (m, 1H), 6.54 (d, J = 2.3 Hz, 1H), 6.76 (d, J = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 25.7, 28.9, 29.8, 34.7, 86.0, 117.9, 136.1, 139.2, 145.2, 175.6, 196.4; **HRMS** (FAB) m/z calcd for $[C_{13}H_{15}{}^{79}BrO_3+H]^+$/$[C_{13}H_{15}{}^{81}BrO_3+H]^+$ ([M]/[M+2]) 299.0283/301.0262, found 299.0278/301.0280.

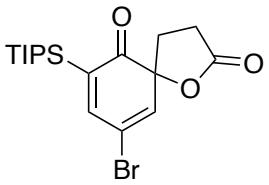


To a solution of **2a** (0.0301 g, 0.100 mmol) and **1d** (0.0250 g, 0.0100 mmol, 10 mol%) in toluene (0.500 mL) was added 9% AcOOH (0.0161 mL, 0.200 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 10 h at 0 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **3a** (0.0297 g, 0.0992 mmol) in 99% yield as a yellow solid. Enantiomeric excess of **3a** was determined to be 84% ee by HPLC analysis. **HPLC** (OD–H column), Hexane–EtOH = 30:1 as eluent, 1.0 mL/min, t_R = 12.7 min (major), t_R = 14.3 min (minor).

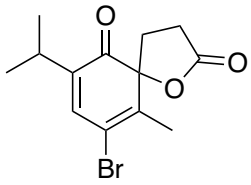


9-Acetyl-7-(*tert*-butyl)-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (2b): 0.0257 g, 0.0980 mmol, 98% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.58 (Hexane–EtOAc = 1:1); **IR** (neat) 2970, 1795,

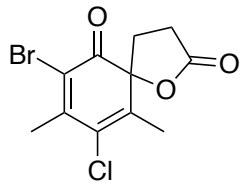
1683, 1365, 1273, 1235, 1178, 1161, 1026 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.25 (s, 9H), 2.13–2.22 (m, 1H), 2.40–2.46 (m, 1H), 2.45 (s, 3H), 2.54–2.62 (m, 2H), 2.74–2.83 (m, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.41 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.2, 28.9, 29.6, 30.9, 34.8, 84.8, 131.6, 134.0, 142.9, 144.3, 175.7, 195.1, 197.2; **HPLC** (OD–H column), Hexane–EtOH = 30:1 as eluent, 1.0 mL/min, t_R = 30.8 min (major), t_R = 50.0 min (minor); **HRMS** (FAB) m/z calcd for $[C_{15}H_{21}O_4+Na]^+$ 285.1103, found 285.1094.



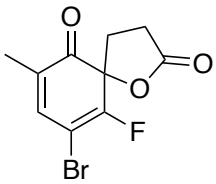
9-Bromo-7-(triisopropylsilyl)-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (2d): 0.0247 g, 0.0619 mmol, 62% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.62 (Hexane–EtOAc = 2:1); **IR** (neat) 2961, 2939, 2861, 1792, 1670, 1463, 1173, 1156, 1017, 923 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.03–1.06 (m, 18 H), 1.35 (sep, *J* = 7.3 Hz, 3H), 2.12–2.21 (m, 1H), 2.42–2.47 (m, 1H), 2.51–2.58 (m, 1H), 2.68–2.78 (m, 1H), 6.63 (t, *J* = 2.1 Hz, 1H), 7.06 (t, *J* = 2.1 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 11.0, 18.5, 18.6, 23.6, 30.3, 85.4, 118.3, 136.5, 138.1, 153.2, 175.4, 199.7; **HRMS** (FAB) m/z calcd for $[C_{18}H_{27}{}^{79}BrO_3Si+Na]^+$/ $[C_{18}H_{27}{}^{81}BrO_3Si+Na]^+$ ([M]/[M+2]) 421.0811/423.0792, found 421.0820/423.0773.



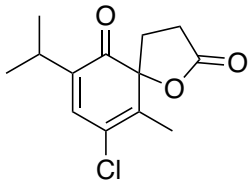
9-Bromo-7-isopropyl-10-methyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (2e): 0.0270 g, 0.0903 mmol, 90% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.58 (Hexane–EtOAc = 2:1); **IR** (neat) 3426, 2974, 1726, 1634 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.09 (d, J = 4.1 Hz, 3H), 1.11 (d, J = 4.1 Hz, 3H), 2.02 (s, 3H), 2.06–2.15 (m, 1H), 2.29–2.35 (m, 1H), 2.53–2.60 (m, 1H), 2.71–2.78 (m, 1H), 2.80–2.94 (m, 1H), 6.81 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 17.9, 21.1, 21.3, 25.5, 26.3, 29.1, 88.0, 115.4, 140.1, 140.5, 142.5, 175.8, 197.3.



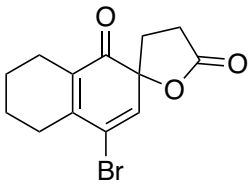
7-Bromo-9-chloro-8,10-dimethyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (2f):[18] 0.0278 g, 0.0910 mmol, 98% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.58 (Hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.05 (s, 3H), 2.15 (ddd, *J* = 9.2, 11.4, 13.7 Hz, 1H), 2.35 (ddd, *J* = 1.4, 9.2, 10.1 Hz, 1H), 2.48 (s, 3H), 2.59 (ddd, *J* = 1.4, 9.2, 10.1 Hz, 1H), 2.84 (ddd, *J* = 9.2, 11.4, 13.7 Hz. 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.8, 24.0, 25.5, 30.2, 86.8, 119.4, 127.3, 141.6, 152.5, 175.4, 190.8.



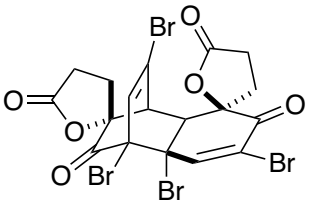
9-Bromo-10-fluoro-7-methyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (2g):[18] 0.0251 g, 0.0914 mmol, 91% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.58 (Hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.94 (m, 3H), 2.36–2.51 (m, 2H), 2.72 (ddd, *J* = 4.6, 9.6, 17.4 Hz, 1H), 2.89–2.98 (m, 1H), 6.93–6.96 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 14.5, 26.6, 29.0, 81.4 (d, $J_{C–F}$ = 19 Hz), 97.8 (d, $J_{C–F}$ = 22 Hz), 130.8 (d, $J_{C–F}$ = 7 Hz), 140.5, 156.1 (d, $J_{C–F}$ = 279 Hz), 174.9, 194.4.



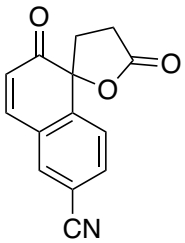
9-Chloro-7-isopropyl-10-methyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (2h): 0.0225 g, 0.0882 mmol, 88% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.51 (Hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.09 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 2.00 (s, 3H), 2.05–2.14 (m, 1H), 2.27–2.32 (m, 1H), 2.53–2.60 (m, 1H), 2.73–2.83 (m, 1H), 2.90 (sep, J = 6.9 Hz, 1H), 6.68 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 14.7, 21.2, 21.3, 25.6, 26.4, 29.2, 87.4, 125.2, 138.2, 139.2, 140.8, 175.9, 197.4.



4'-Bromo-3,4,5',6',7',8'-hexahydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-1',5-dione (2i): [18] 0.0231 g, 0.0777 mmol, 78% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.57 (Hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.52–1.82 (m, 4H), 2.16 (ddd, *J* = 9.6, 11.0, 13.3 Hz, 1H), 2.21–2.56 (m, 5H), 2.56 (ddd, *J* = 2.3, 9.6, 17.6 Hz, 1H), 2.90 (ddd, *J* = 9.6, 11.0, 17.6 Hz, 1H), 6.62 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.8, 22.0, 22.4, 26.2, 30.8, 31.1, 83.4, 124.0, 131.5, 135.7, 148.0, 175.9, 196.4

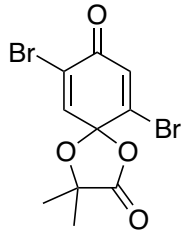


(1'*S*,2*R*,4'*R*,4a'*R*,10'*R*)-2',4',4a',6'-Tetrabromo-1',3,3'',4,4',4a',4'',8a'-octahydro-5*H*,5''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-5,5'',7',9'-tetraone (4j): 0.0222 g, 0.0345 mmol, 79% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 2:1) **TLC**, R_f = 0.28 (Hexane–EtOAc = 1:1); **TLC**, R_f = 0.48 (hexane–EtOAc = 1:1); **IR** (KBr) 3080, 1801, 1722, 1596, 1183 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.26–2.34 (m, 1H), 2.40–2.47 (m, 1H), 2.51–2.63 (m, 2H), 2.65–2.81 (m, 3H), 2.90–3.00 (m, 1H), 3.75–3.77 (m, 1H), 4.02 (s, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 7.33 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 26.8, 28.0, 30.2, 34.9, 53.0, 54.6, 60.1, 75.7, 80.4, 83.1, 121.8, 123.8, 133.2, 144.4, 173.2, 173.9, 185.3, 193.1.

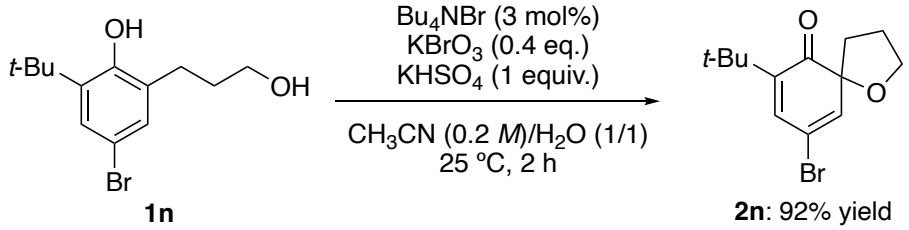


2',5-Dioxo-4,5-dihydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalene]-6'-carbonitrile (2l):[19] 0.0201 g, 0.0840 mmol, 84% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) **TLC**, R_f = 0.30 (Hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.04–2.20 (m, 1H), 2.65–2.73 (m, 2H), 2.78–2.89 (m, 1H), 6.32 (d, J =

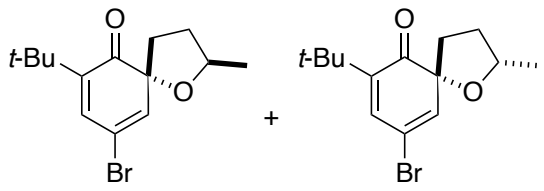
9.6 Hz, 1H), 7.49 (d, J = 9.6 Hz, 1H), 7.68 (s, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.2, 35.5, 85.2, 113.5, 117.4, 124.5, 126.6, 130.3, 132.6, 134.0, 143.4, 145.0, 175.5, 195.8.



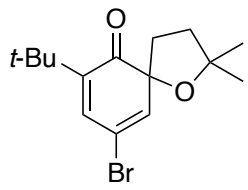
6,9-Dibromo-3,3-dimethyl-1,4-dioxaspiro[4.5]deca-6,9-diene-2,8-dione (2m):[20] 0.0148 g, 0.0420 mmol, 42% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1) **TLC**, R_f = 0.58 (Hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1H NMR (CDCl3, 400 MHz) δ 1.64 (s, 3H), 1.73 (s, 3H), 6.90 (s, 1H), 7.24 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 24.7, 82.7, 108.5, 118.1, 119.9, 125.2, 145.5, 149.4, 177.0.



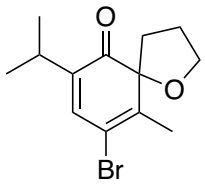
9-Bromo-7-(*tert*-butyl)-1-oxaspiro[4.5]deca-7,9-dien-6-one (2n): To a solution of **1n** (0.0574 g, 0.200 mmol), Bu_4NBr (0.00194 g, 0.00600 mmol, 3 mol%) and $KHSO_4$ (0.0272 g, 0.200 mmol) in CH_3CN (1.00 mL) and H_2O (1.00 mL) were added $KBrO_3$ (0.0134 g, 0.0400 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 2 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 = 3:1) to give **2n** (0.0526 g, 0.185 mmol) in 92% yield as a pale yellow solid.



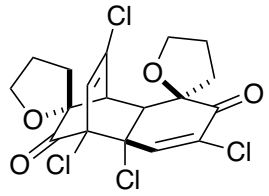
9-Bromo-7-(*tert*-butyl)-2-methyl-1-oxaspiro[4.5]deca-7,9-dien-6-one (2o): This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 10:1) **TLC**, R_f = 0.61 (Hexane–EtOAc = 4:1); **IR** (neat) 2965, 2869, 1683 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.20 (s, 9H, *major*), 1.21 (s, 9H, *minor*), 1.30 (d, *J* = 6.4 Hz, 3H, *major*), 1.42 (d, *J* = 6.4 Hz, 3H, *minor*), 1.52–1.61 (m, 1H, *major*), 1.69–1.78 (m, 1H, *minor*), 1.84–2.02 (m, 2H, *major*), 1.84–2.02 (m, 2H, *minor*), 2.13–2.23 (m, 2H, *major*), 2.13–2.23 (m, 2H, *minor*), 4.30–4.38 (m, 1H, *minor*), 4.49–4.57 (m, 1H, *major*), 6.50 (d, *J* = 2.3 Hz, 1H, *major*), 6.51 (d, *J* = 2.3 Hz, 1H, *minor*), 6.63 (d, *J* = 2.3 Hz, 1H, *minor*), 6.65 (d, *J* = 2.3 Hz, 1H, *major*); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.3 (*minor*), 21.4 (*major*), 29.0 (*major*), 29.0 (*minor*), 31.1 (*minor*), 32.7 (*major*), 34.4 (*major*), 35.4 (*minor*), 36.4 (*major*), 36.4 (*minor*), 78.2 (*minor*), 78.8 (*major*), 88.0 (*major*), 88.6 (*minor*), 114.6 (*minor*), 114.9 (*major*), 137.9 (*minor*), 138.2 (*major*), 141.1 (*minor*), 141.2 (*major*), 145.6 (*minor*), 145.7 (*major*), 201.0 (*minor*), 202.1 (*major*).



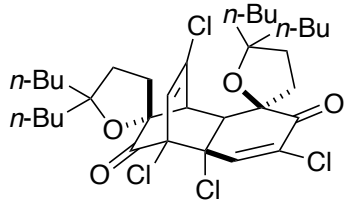
9-Bromo-7-(*tert*-butyl)-2,2-dimethyl-1-oxaspiro[4.5]deca-7,9-dien-6-one (2p): **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.21 (s, 9H), 1.32 (s, 3H), 1.48 (s, 3H), 1.75–1.80 (m, 1H), 1.92–2.07 (m, 2H), 2.18–2.27 (m, 1H), 6.49 (d, J = 2.8 Hz, 1H), 6.61 (d, J = 2.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 27.9, 29.0, 34.5, 35.3, 36.3, 84.9, 89.0, 114.6, 137.8, 142.0, 145.8, 201.0.



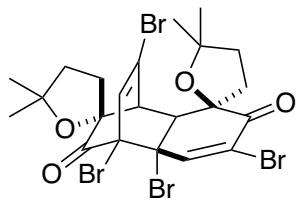
9-Bromo-7-isopropyl-10-methyl-1-oxaspiro[4.5]deca-7,9-dien-6-one (2q): 0.0257 g, 0.0900 mmol, 90% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.58 (Hexane–EtOAc = 1:1); **IR** (neat) 2956, 2930, 2852, 1722 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.06 (d, J = 7.3 Hz, 3H), 1.08 (d, J = 7.3 Hz, 3H), 1.81–1.88 (m, 1H), 1.93–2.03 (m, 1H), 1.97 (s, 3H), 2.08–2.18 (m, 2H), 2.87 (sep, J = 7.3 Hz, 1H), 4.04–4.15 (m, 1H), 4.34–4.39 (m, 1H), 6.69 (s, 1H).



(1'*S*,2*R*,4'*R*,4a'*R*,10'*R*)-2',4',4a',6'-tetrachloro-1',4,4',4a',4'',5,5'',8a'-octahydro-3*H*,3''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-7',9'-dione (4s): 0.0177 g, 0.0404 mmol, 81% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) **TLC**, R_f = 0.38 (Hexane–EtOAc = 1:1); **IR** (neat) 3426, 2979, 1639 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.96–2.05 (m, 4H), 2.11–2.17 (m, 2H), 2.21–2.42 (m, 1H), 3.35–3.36 (m, 1H), 3.58 (s, 1H), 4.03–4.16 (m, 4H), 5.92 (d, *J* = 2.5 Hz, 1H), 6.83 (d, *J* = 2.5 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 25.2, 26.1, 35.1, 38.3, 51.3, 53.5, 70.0, 70.7, 70.9, 81.3, 81.5, 84.5, 127.2, 132.9, 138.0, 138.7, 189.9, 197.6; **HRMS** (FAB+) m/z calcd for $[C_{18}H_{17}O_4{}^{35}Cl_3{}^{37}Cl+H]^+$ 438.9853 found 438.9844.

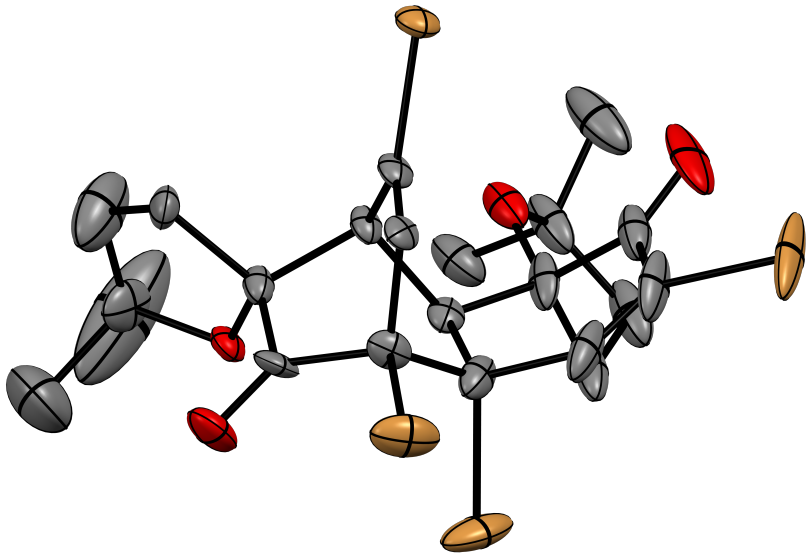


(1'*S*,2*R*,4'*R*,4a'*R*,10'*R*)-5,5,5'',5''-tetrabutyl-2',4',4a',6'-tetrachloro-1',4,4',4a',4'',5,5'',8a'-octahydro-3*H*,3''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-7',9'-dione (4t): 0.0318 g, 0.0481 mmol, 96% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.58 (Hexane–EtOAc = 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.85–0.96 (m, 12H), 1.21–1.87 (m, 27H), 1.95–2.10 (m, 2H), 2.14–2.25 (m, 2H), 2.43–2.50 (m, 1H), 3.36 (d, *J* = 1.8 Hz, 1H), 3.58 (s, 1H), 5.84 (d, *J* = 2.7 Hz, 1H), 6.77 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 14.1, 14.2, 14.3, 23.1, 23.2, 23.3, 23.4, 26.1, 26.6, 27.3, 27.5, 34.6, 35.3, 36.0, 36.8, 36.9, 38.6, 38.8, 38.9, 52.8, 54.3, 71.0, 81.7, 81.8, 84.9, 89.5, 90.6, 126.8, 132.9, 137.7, 139.0, 190.5, 197.6; **HRMS** (FAB+) m/z calcd for $[C_{34}H_{49}O_4{}^{35}Cl_4+H]^+$ 663.2361, found 663.2357.



(1'*S*,2*R*,4'*R*,4a'*R*,10'*R*)-2',4',4a',6'-tetrabromo-5,5,5'',5''-tetramethyl-1',4,4',4a',4'',5,5'',8a'-octahydro-3*H*,3''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-7',9'-dione (4u): 0.0265 g, 0.0395 mmol, 79% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1); **IR** (neat) 2974, 1757, 1717 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.23 (s, 3H), 1.28 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.77–1.94 (m, 3H), 2.05–2.19 (m, 2H), 2.21–2.31 (m, 2H), 2.68–2.75 (m, 1H), 3.52–3.53 (m, 1H), 3.85 (s, 1H), 6.29 (d, J = 2.8 Hz, 1H), 7.15 (d, J = 0.92 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 27.9, 28.0, 29.0, 29.1, 35.7, 36.9, 38.4, 38.5, 54.2, 54.9, 64.0, 78.5, 82.4, 84.5, 85.2, 85.6, 123.3, 126.4, 131.7, 143.2, 190.2, 197.4.

X-Ray Diffraction Analysis of 4u: Recrystallization of **4u** was carried out in the solution of Et_2O/hexane at –20 °C. X-Ray crystallographic analysis was performed with a Rigaku PILATUS-200K diffractometer (graphite monochromator, MoKa radiation, λ = 0.71075 Å) and the structure was solved by direct methods and expanded using Fourier techniques (SHELXT and SHELXL).

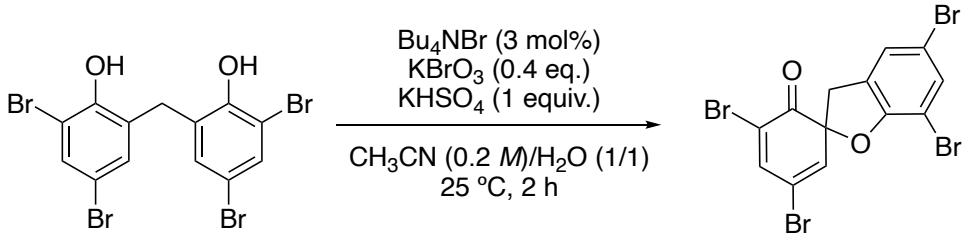


ORTEP drawing of 4u. Hydrogen atoms are omitted for clarity. Gray, carbon; red, oxygen; brown, bromine

Crystallographic Data and Structure Refinement for 4u

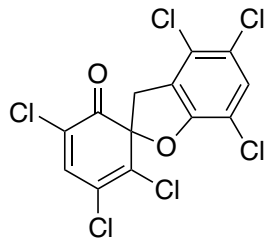
Formula	$C_{22}H_{24}Br_4O_4$	D_{calcd}	1.894g/cm^3
Formula weight	672.05	Absorption coefficient	6.876 mm^{-1}
T	123(2) K	*F*(000)	1312.00
λ	0.71075 Å	Crystal size	0.43 x 0.22 x 0.22 mm^3
Crystal system	orthorhombic	Theta range for data collection	3.40 to 27.50°
Space group	$P2_12_12_1$ (#19)	Reflections collected	20378
A	8.3774(11) Å	Refinement based on	F^2
B	13.9011(18) Å	No. of data	5399

C	20.241(3) Å	No. of parameters	271
α	90.0°	No. of restraints	0
β	90.0°	GOF	1.083
γ	90.0°	R(*F*) for $I > 2s(I)$	0.0624
V	2357.2(6) Å^3	wR2(F^2) for all data	0.1554
Z	4		



1v **2v:** 90% yield

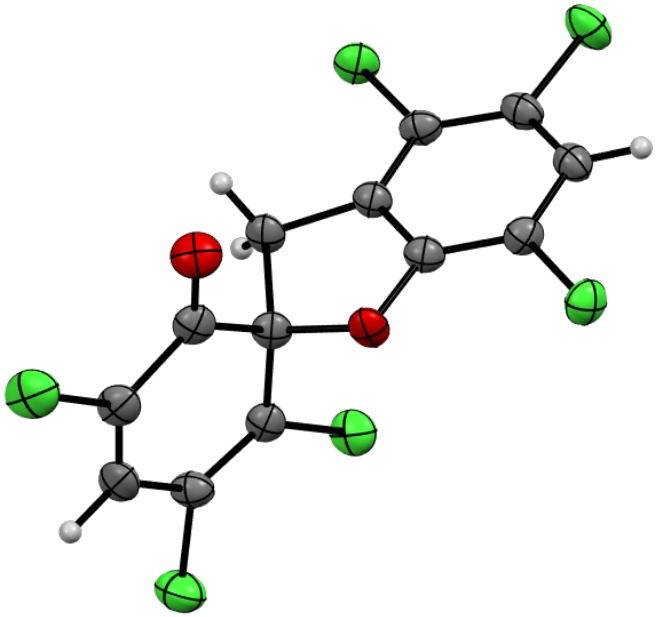
2,6-Di-*tert*-butyl-4-ethyl-4-hydroxycyclohexa-2,5-dien-1-one (2v): To a solution of **1v** (0.103 g, 0.200 mmol), Bu_4NBr (0.00194 g, 0.00600 mmol, 3 mol%) and $KHSO_4$ (0.0272 g, 0.200 mmol) in CH_3CN (1.00 mL) and H_2O (1.00 mL) were added $KBrO_3$ (0.0134 g, 0.0400 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 2 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 = 2:1) to give **2x** (0.0925 g, 0.179 mmol) in 90% yield as a yellow solid. **^{1}H NMR** (Acetone-*d6*, 400 MHz) δ 3.64 (d, *J* = 16.5 Hz, 1H), 3.75 (d, *J* = 16.5 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.54 (s, 1H), 7.77 (d, J = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 41.0, 87.6, 103.6, 113.9, 116.1, 122.4, 126.9, 127.0, 134.2, 137.6, 145.9, 155.3, 189.0; **HRMS** (FAB+) m/z calcd for [$C_{13}H_6{}^{79}Br_2{}^{81}Br_2O_2$] 513.7061 found 513.7063.



2',3',4,5,5',7-Hexachloro-3*H*-spiro[benzofuran-2,1'-cyclohexane]-2',4'-dien-6'-one (2w): 0.0365 g, 0.0901 mmol, 90% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1); **IR** (neat) 1757, 1440, 1296 cm^{-1}; **^{1}H**

NMR ($CDCl_3$, 400 MHz) δ 3.63 (d, J = 0.92 Hz, 2H), 7.32 (s, 1H), 7.36 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 42.3, 88.6, 113.9, 125.7, 125.9, 126.0, 127.1, 129.6, 130.4, 135.5, 140.0, 153.5, 188.0; **HRMS** (FAB+) m/z calcd for [$C_{13}H_4O_2{}^{35}Cl_5{}^{37}Cl$] 403.8314, found 403.8315.

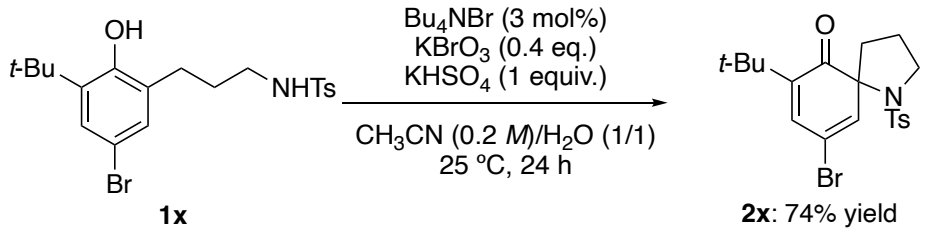
X-Ray Diffraction Analysis of 2w: Recrystallization of **2w** was carried out in the solution of $CHCl_3$/hexane at 23 °C. X-Ray crystallographic analysis was performed with a Rigaku PILATUS-200K diffractometer (graphite monochromator, MoKa radiation, λ = 0.71075 Å) and the structure was solved by direct methods and expanded using Fourier techniques (SHELXT and SHELXL).



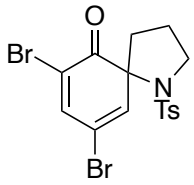
ORTEP drawing of 2w. Gray, carbon; red, oxygen; white, hydrogen; green, chlorine

Crystallographic Data and Structure Refinement for 2w

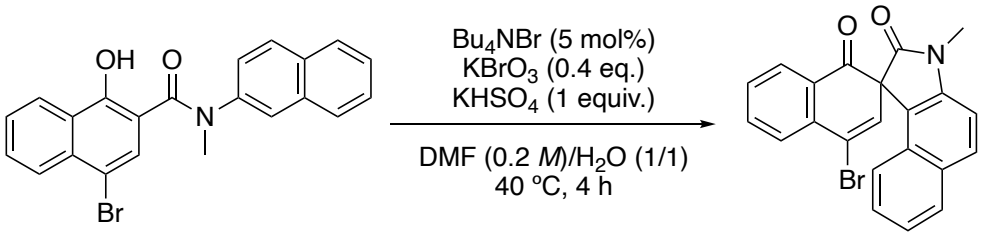
Formula	$C_{13}H_4Cl_6O_2$	D_{calcd}	1.817 g/cm^3
Formula weight	404.89	Absorption coefficient	1.156 mm^{-1}
T	123(2) K	*F*(000)	400.00
λ	0.71075 Å	Crystal size	0.2 x 0.2 x 0.2 mm^3
Crystal system	triclinic	Theta range for data collection	3.60 to 27.50°
Space group	P-1 (#2)	Reflections collected	6205
A	5.688(3) Å	Refinement based on	F^2
B	11.522(5) Å	No. of data	3170
C	11.811(5) Å	No. of parameters	190
α	101.229(7)º	No. of restraints	0
β	92.043(6)º	GOF	1.01
γ	102.039(9)º	R(*F*) for $I > 2s(I)$	0.0650
V	740.2(6) Å^3	wR2(F^2) for all data	0.1650
Z	2		



9-Bromo-7-(*tert*-butyl)-1-tosyl-1-azaspiro[4.5]deca-7,9-dien-6-one (2x): To a solution of **1x** (0.0881 g, 0.200 mmol), Bu_4NBr (0.00194 g, 0.00600 mmol, 3 mol%) and $KHSO_4$ (0.0272 g, 0.200 mmol) in CH_3CN (1.00 mL) and H_2O (1.00 mL) were added $KBrO_3$ (0.0134 g, 0.0400 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **2x** (0.0648 g, 0.147 mmol) in 74% yield as a yellow solid. **TLC**, R_f = 0.49 (hexane–EtOAc = 1:1); **IR** (neat) 3282, 2956, 1696 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.23 (s, 9H), 1.88–1.98 (m, 2H), 2.04–2.16 (m, 1H), 2.42 (s, 3H), 3.51–3.57 (m, 1H), 3.60–3.65 (m, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 21.5, 22.8, 28.9, 34.6, 38.8, 48.9, 74.0, 114.5, 127.6, 129.4, 137.0, 138.8, 140.4, 143.3, 145.4, 197.6; **HRMS** (FAB+) m/z calcd for $[C_{20}H_{25}{}^{79}BrNO_3S+H]^+$/$[C_{20}H_{25}{}^{81}BrNO_3S+H]^+$ ([M]/[M+2]) 438.0739/440.0720, found 438.0741/440.0681.

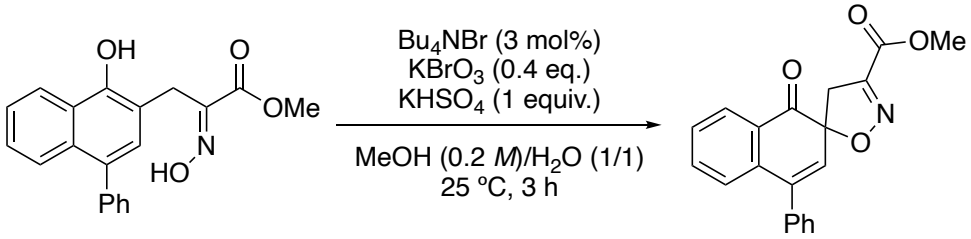


7,9-Dibromo-1-tosyl-1-azaspiro[4.5]deca-7,9-dien-6-one (2y): 0.0339 g, 0.0736 mmol, 74% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) **TLC**, R_f = 0.44 (hexane–EtOAc = 1:1); **IR** (neat) 3278, 3052, 2956, 2925 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.99–2.07 (m, 2H), 2.11–2.16 (m, 1H), 2.18–2.26 (m, 1H), 2.44 (s, 3H), 3.53–3.62 (m, 2H), 6.54 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 21.5, 23.1, 39.5, 48.7, 72.9, 112.4, 123.2, 127.5, 129.6, 136.2, 142.1, 143.8, 145.4, 191.8; **HRMS** (FAB+) m/z calcd for $[C_{16}H_{16}NO_3S^{79}Br^{81}Br+H]^+$ 461.9198 found 461.9203.



1z **2z**: 84%

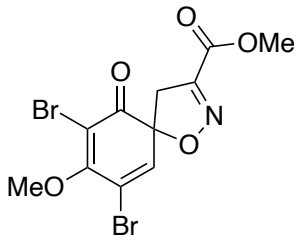
4'-Bromo-3-methyl-1'*H*-spiro[benzo[*e*]indole-1,2'-naphthalene]-1',2(3*H*)-dione (1z):[21] To a solution of **1ad** (0.0807 g, 0.200 mmol), Bu_4NBr (0.00322 g, 0.0100 mmol, 5 mol%) and $KHSO_4$ (0.0272 g, 0.200 mmol) in DMF (1.00 mL) and H_2O (1.00 mL) were added $KBrO_3$ (0.0134 g, 0.0400 mmol) at 40 ºC. The reaction was monitored by TLC analysis. After stirring for 4 h at 40 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **2ad** (0.0679 g, 0.167 mmol) in 84% yield as a yellow solid. **TLC**, R_f = 0.44 (hexane–EtOAc = 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.35 (s, 3H), 6.50 (s, 1H), 7.16 (dd, *J* = 3.2, 6.0 Hz, 1H), 7.23–7.27 (m, 1H), 7.33 (dd, *J* = 3.2, 6.2 Hz, 2H), 7.51–7.57 (m, 1H), 7.78–7.87 (m, 2H), 7.94–8.01 (m, 2H), 8.09 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 27.4, 66.7, 109.8, 121.4, 121.8, 122.4, 124.3, 128.2, 128.3, 129.0, 129.2, 129.4, 129.5, 129.9, 130.8, 131.0, 131.1, 135.7, 136.6, 142.8, 171.1, 192.1.



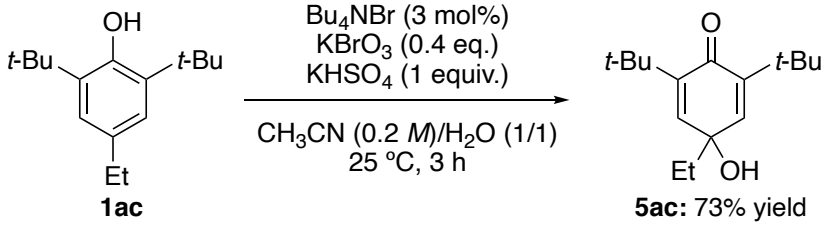
1aa **2aa**: 93%

Methyl 1'-oxo-4'-phenyl-1'*H*,4*H*-spiro[isoxazole-5,2'-naphthalene]-3-carboxylate (1aa): To a solution of **1ab** (0.0671 g, 0.200 mmol), Bu_4NBr (0.00194 g, 0.00600 mmol, 3 mol%) and $KHSO_4$ (0.0272 g, 0.200 mmol) in CH_3CN (1.00 mL) and H_2O (1.00 mL) were added $KBrO_3$ (0.0134 g, 0.0400 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **2aa** (0.0311 g, 0.0933 mmol) in 93% yield as a yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.28 (d, J = 17.4 Hz,

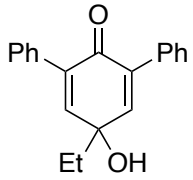
1H), 3.84 (d, J = 17.4 Hz, 1H), 3.92 (s, 3H), 6.10 (s, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.36–7.40 (m, 2H), 7.40–7.50 (m, 4H), 7.54 (td, J = 1.8, 7.6 Hz, 1H), 8.10 (dd, J = 1.8, 7.6 Hz, 1H); **HRMS** (FAB+) m/z calcd for $[C_{20}H_{16}NO_4+H]^+$ 334.1079 found 334.1085.



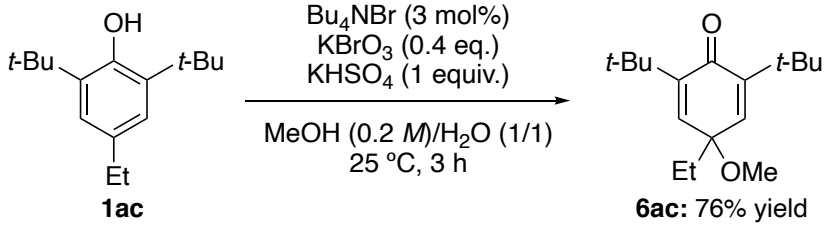
Methyl 7,9-dibromo-8-methoxy-10-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,8-triene-3-carboxylate (2ab):[15] 0.0626 g, 0.158 mmol, 79% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.67 (Hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.30 (d, *J* = 17.9 Hz, 1H), 3.62 (d, *J* = 17.9 Hz, 1H), 3.95 (s, 3H), 4.18 (s, 3H), 6.78 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) 44.4, 53.1, 62.1, 86.8, 106.7, 120.9, 135.9, 149.9, 159.6, 163.2, 188.6.



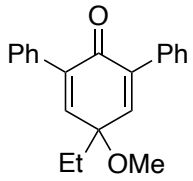
2,6-Di-*tert*-butyl-4-ethyl-4-hydroxycyclohexa-2,5-dien-1-one (5ac):[27] To a solution of **1ac** (0.0469 g, 0.200 mmol), Bu_4NBr (0.00194 g, 0.00600 mmol, 3 mol%) and $KHSO_4$ (0.0272 g, 0.200 mmol) in CH_3CN (1.00 mL) and H_2O (1.00 mL) were added $KBrO_3$ (0.0134 g, 0.0400 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 3 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 = 2:1) to give **5ac** (0.0371 g, 0.146 mmol) in 73% yield as a yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.74 (t, J = 7.8 Hz, 3H), 1.23 (s, 9H), 1.74 (q, J = 7.8 Hz, 2H), 1.84 (brs, 1H), 6.45 (s, 2H).



5'-Ethyl-5'-hydroxy-[1,1':3',1''-terphenyl]-2'(5'*H*)-one (5ad): 0.0212 g, 0.0728 mmol, 73% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1); **IR** (neat) 3256, 2945, 2925, 2860 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.00 (t, J = 7.8 Hz, 3H), 1.98 (q, J = 7.8 Hz, 2H), 2.07 (brs, 1H), 6.91 (s, 2H), 7.35–7.48 (m, 10H). **HRMS** (FAB+) m/z calcd for $[C_{20}H_{19}O_2+H]^+$ 291.1385, found 291.1395.

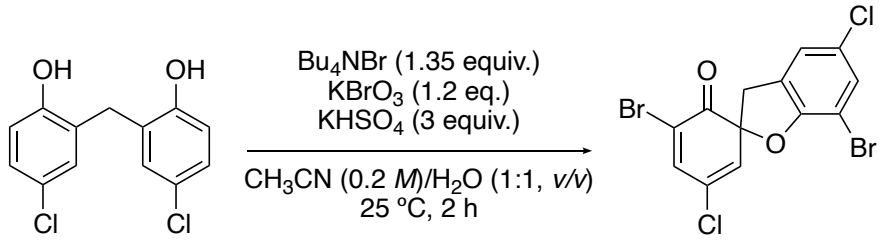


2,6-Di-*tert*-butyl-4-ethyl-4-methoxycyclohexa-2,5-dien-1-one (6ac):[27] To a solution of **1ac** (0.0469 g, 0.200 mmol), Bu_4NBr (0.00194 g, 0.00600 mmol, 3 mol%) and $KHSO_4$ (0.0272 g, 0.200 mmol) in MeOH (1.00 mL) and H_2O (1.00 mL) were added $KBrO_3$ (0.0134 g, 0.0400 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 3 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 = 2:1) to give **6ac** (0.0402 g, 0.152 mmol) in 76% yield as a yellow solid. **H NMR** ($CDCl_3$, 400 MHz) δ 0.72 (t, *J* = 7.8 Hz, 3H), 1.25 (s, 18H), 1.71 (q, *J* = 7.8 Hz, 2H), 3.17 (s, 3H), 6.36 (s, 2H).



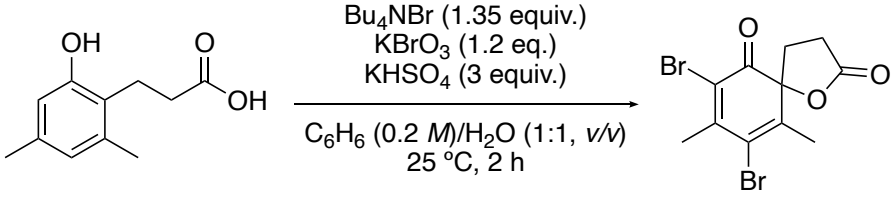
5'-Ethyl-5'-methoxy-[1,1':3',1''-terphenyl]-2'(5'*H*)-one (6ad): 0.0277 g, 0.0910 mmol, 91% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1)**; IR** (neat) 2965, 2360, 1083 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.4 Hz, 3H), 1.95 (q, J = 7.4 Hz, 2H), 3.37 (s, 3H), 6.85 (s, 2H), 7.35–7.59 (m, 10H); **^{13}C NMR**

($CDCl_3$, 100 MHz) δ 8.4, 33.3, 53.5, 128.2, 128.4, 128.9, 129.0, 135.5, 142.4, 147.6, 183.5; **HRMS** (FAB+) m/z calcd for $[C_{21}H_{21}O_2+H]^+$ 305.1542, found 305.1535.



1ah **2ah:** 94% yield

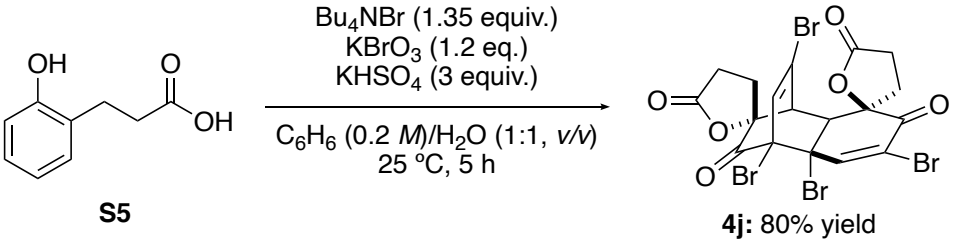
5',7-Dibromo-3',5-dichloro-3*H*-spiro[benzofuran-2,1'-cyclohexane]-2',4'-dien-6'-one (2ah): To a solution of **1ah** (0.0269 g, 0.100 mmol), Bu_4NBr (0.0434 g, 0.135 mmol) and $KHSO_4$ (0.0408 g, 0.300 mmol) in benzene (0.500 mL) and H_2O (0.500 mL) were added $KBrO_3$ (0.0402 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 2 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **2ah** (0.0398 g, 0.0940 mmol) in 94% yield as a orange solid. **TLC**, R_f = 0.49 (hexane–EtOAc = 2:1); **IR** (neat) 3409, 1752, 1452 cm^{-1}; **^{1}H NMR** (Acetone-*d6*, 400 MHz) δ 3.64 (d, *J* = 16.5 Hz, 1H), 3.75 (d, *J* = 16.5 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 7.30 (s, 1H), 7.42 (s, 1H), 7.70 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** (Acetone-*d6*, 125 MHz) δ 40.7, 87.0, 102.1, 121.9, 124.6, 126.4, 128.1, 128.7, 130.6, 134.0, 144.3, 155.2, 189.1.



1ai **2ai**: 96%

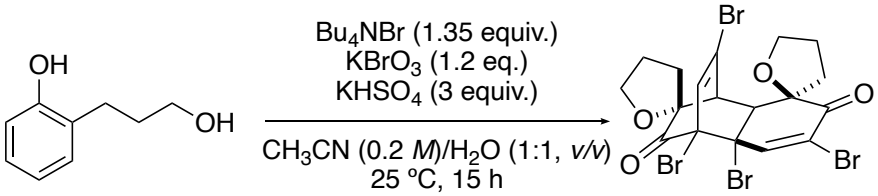
7,9-Dibromo-8,10-dimethyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (1ai): To a solution of **1ai** (0.0194 g, 0.100 mmol), Bu_4NBr (0.0434 g, 0.135 mmol) and $KHSO_4$ (0.0408 g, 0.300 mmol) in benzene (0.500 mL) and H_2O (0.500 mL) were added $KBrO_3$ (0.0402 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 2 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **2ai** (0.0335 g, 0.0957 mmol) in 96% yield as a yellow solid. **TLC**, R_f = 0.49 (hexane–EtOAc = 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.05 (s, 3H), 2.06–2.20 (m, 1H), 2.31–2.41 (m, 1H), 2.52 (s, 3H), 2.56–2.72 (m, 1H), 2.81–2.88 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 19.2, 25.4, 27.1, 30.2, 87.3, 118.9, 119.5, 144.9, 152.9, 175.2, 190.7; **HRMS** (FAB+) m/z calcd for $[C_{11}H_{10}{}^{79}Br^{81}BrO_3+Na]^+$ 372.8874 found 382.8884.



S5 **4j:** 80% yield

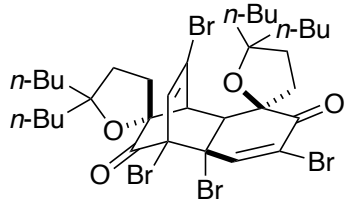
(1'*S*,2*R*,4'*R*,4a'*R*,10'*R*)-2',4',4a',6'-Tetrabromo-1',3,3'',4,4',4a',4'',8a'-octahydro-5*H*,5''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-5,5'',7',9'-tetraone (4j): To a solution of **S5** (0.0166 g, 0.100 mmol), Bu_4NBr (0.0434 g, 0.135 mmol) and $KHSO_4$ (0.0408 g, 0.300 mmol) in benzene (0.500 mL) and H_2O (0.500 mL) were added $KBrO_3$ (0.0402 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 5 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **4j** (0.0256 g, 0.0398 mmol) in 80% yield as a yellow solid.



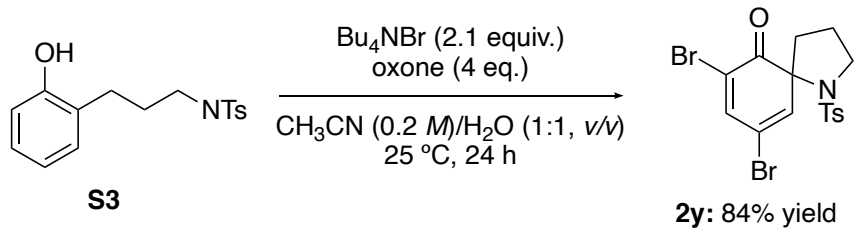
S1 **4r:** 82% yield

(1'*S*,2*R*,4'*R*,4a'*R*,10'*R*)-2',4',4a',6'-Tetrabromo-1',4,4',4a',4'',5,5'',8a'-octahydro-3*H*,3''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-7',9'-dione (4r): To a solution of **S1** (0.0152 g, 0.100 mmol), Bu_4NBr (0.0434 g, 0.135 mmol) and $KHSO_4$ (0.0408 g, 0.300 mmol) in CH_3CN (0.500 mL) and H_2O (0.500 mL) were added $KBrO_3$ (0.0402 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 15 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **4r** (0.0252 g, 0.0409 mmol) in 82% yield as

a white solid.

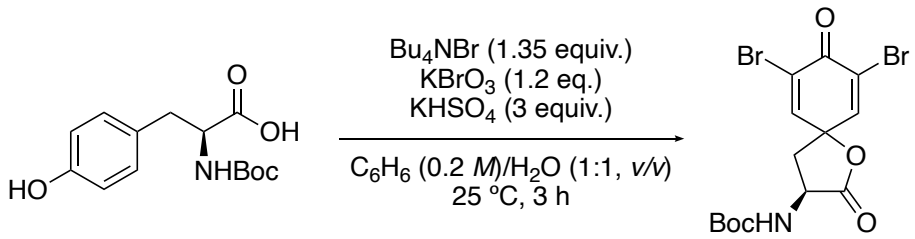


(1'*S*,2*R*,4'*R*,4a'*R*,10'*R*)-2',4',4a',6'-Tetrabromo-5,5,5'',5''-tetrabutyl-1',4,4',4a',4'',5,5'',8a'-octahydro-3*H*,3''*H*,7'*H*-dispiro[furan-2,8'-[1,4]ethanonaphthalene-10',2''-furan]-7',9'-dione (4ag): 0.0381 g, 0.0454 mmol, 91% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1) **TLC**, R_f = 0.58 (Hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.89–0.96 (m, 12H), 1.21–1.87 (m, 27H), 2.00–2.10 (m, 2H), 2.15–2.24 (m, 2H), 2.54–2.61 (m, 1H), 3.47 (s, 1H), 3.83 (s, 1H), 6.25 (d, J = 2.8 Hz, 1H), 7.17 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 14.1, 14.2, 23.1, 23.3, 23.4, 26.2, 26.7, 27.4, 27.5, 34.7, 35.3, 36.1, 36.9, 37.0, 38.3, 38.7, 38.9, 54.8, 55.6, 63.6, 78.9, 81.7, 85.1, 89.3, 90.6, 123.0, 126.9, 131.6, 143.5, 190.6, 197.2; **HRMS** (FAB+) m/z calcd for $[C_{34}H_{49}O_4Br^{79}{}_2Br^{81}{}_2+H]^+$ 841.0328, found 841.0337.

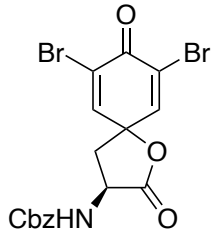


S3 **2y:** 84% yield

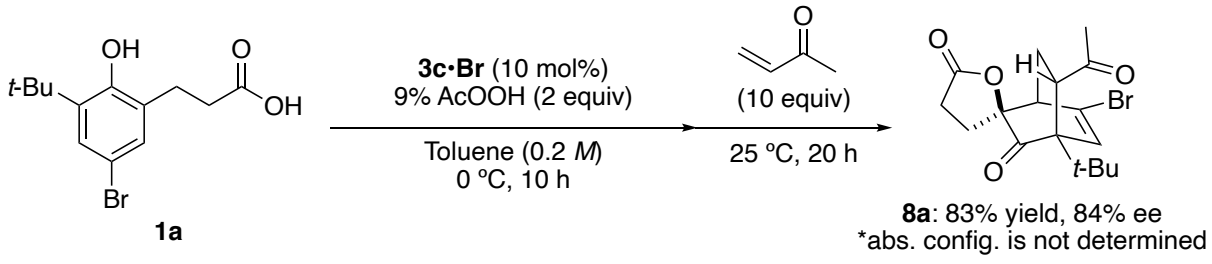
7,9-Dibromo-1-tosyl-1-azaspiro[4.5]deca-7,9-dien-6-one (2y): To a solution of **S3** (0.0305 g, 0.100 mmol), Bu_4NBr (0.0676 g, 0.210 mmol) in benzene (0.500 mL) and H_2O (0.500 mL) were added oxone (0.148 g, 0.400 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 **2y** (0.0648 g, 0.147 mmol) in 96% yield as a yellow solid.



***tert*-Butyl (*S*)-(7,9-dibromo-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)carbamate (2aj):** To a solution of **1aj** (0.0281 g, 0.100 mmol), Bu_4NBr (0.0434 g, 0.135 mmol) and $KHSO_4$ (0.0408 g, 0.300 mmol) in benzene (0.500 mL) and H_2O (0.500 mL) were added $KBrO_3$ (0.0402 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 3 h at 25 ºC, the resulting precipitated solids were collected by filtration and washed with Et_2O. 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 **2aj** (0.0371 g, 0.0849 mmol) in 85% yield as a white solid. **TLC**, R_f = 0.30 (hexane–EtOAc = 2:1); **IR** (neat) 3387, 3344, 2974, 2926, 1795 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.42 (s, 9H), 2.69–2.75 (m, 1H), 2.94–3.14 (m, 1H), 4.76–4.83 (m, 1H), 6.86 (d, J = 7.3Hz, 1H), 7.63 (d, J = 2.8 Hz, 1H), 7.93 (d, J = 2.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 28.5, 36.6, 50.3, 79.5, 80.4, 122.7, 123.3, 148.2, 149.0, 156.1, 172.1, 173.7.

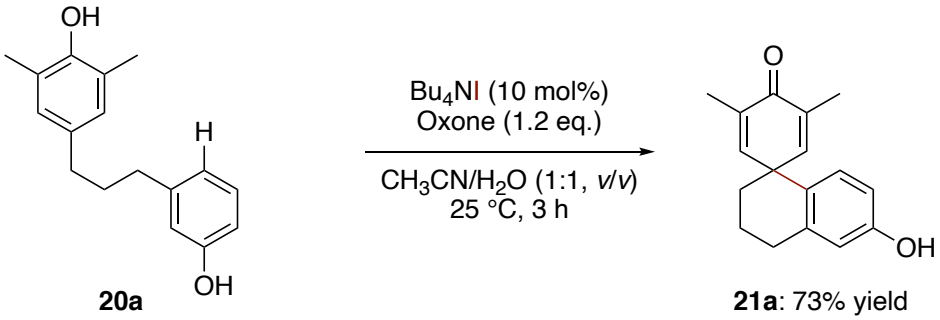


Benzyl (*S*)-(7,9-dibromo-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)carbamate (2ak): 0.0316 g, 0.0670 mmol, 67% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **TLC**, R_f = 0.38 (Hexane–EtOAc = 2:1); **IR** (neat) 3361, 1765, 1695 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.17–3.23 (m, 1H), 5.10–5.17 (m, 1H), 5.35 (s, 2H), 7.50–7.60 (m, 5H), 7.91 (d, J = 2.8 Hz, 1H), 7.82 (d, J = 2.8 Hz, 1H).



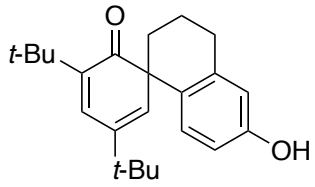
8-Acetyl-6-bromo-4-(tert-butyl)-3',4'-dihydro-5'H-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-

ene-3,5'-dione (8a): To a solution of **1a** (0.0301 g, 0.100 mmol) and **3c•Br** (0.0250 g, 0.0100 mmol, 10 mol%) in toluene (0.500 mL) was added 9% AcOOH (0.0161 mL, 0.200 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 10 h at 0 °C (**1a** was almost consumed), to the resulting mixture was added methyl vinyl ketone (0.0820 mL, 1.00 mmol) at 0 ºC. The cooling bath was removed and the resulting mixture was allowed to warm to 25 ºC to enhance to cycloaddition reaction. After stirring for 20 h at 25 ºC, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL). 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 2:1) to give **8a** (0.0305 g, 0.0826 mmol) in 84% yield as a white solid. Enantiomeric excess of **8a** was determined to be 83% ee by HPLC analysis. **TLC**, R_f = 0.41 (hexane–EtOAc = 2:1); **IR** (KBr) 2957, 1787, 1718, 1617, 1362, 1165 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H), 1.74–1.83 (m, 1H), 2.19–2.27 (m, 2H), 2.23 (s, 3H), 2.52–2.64 (m, 2H), 2.73–2.88 (m, 1H), 3.17–3.21 (m, 2H), 6.49 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 28.4, 28.6, 29.3, 29.7, 31.1, 34.1, 48.9, 51.7, 63.5, 83.2, 120.7, 129.3, 175.7, 203.6, 208.4; **HPLC** (OD–H column), Hexane–EtOH = 4:1 as eluent, 1.0 mL/min, t_R = 8.8 min (minor), t_R = 10.3 min (major); **HRMS** (FAB) m/z calcd for $[C_{17}H_{21}{}^{79}BrO_4+H]^+/[C_{17}H_{21}{}^{81}BrO_4+H]^+$ ([M]/[M+2]) 369.0701/371.0681, found 369.0696/371.0632.



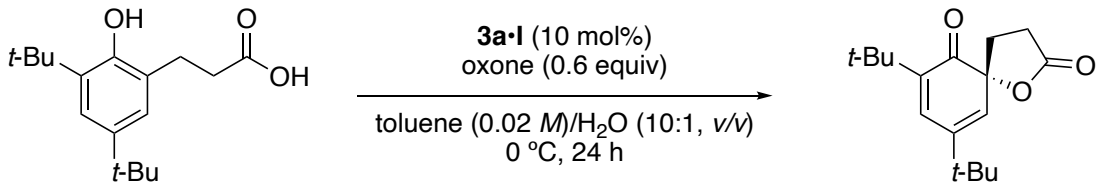
6'-Hydroxy-3,5-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-naphthalene]-2,5-dien-4-one (21a):[25] To a solution of **20a** (0.0256 g, 0.100 mmol), Bu_4NI (0.0369 g, 0.0100 mmol) in toluene (0.500 mL) and H_2O (0.500 mL) were added oxone (0.0368 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 3 h at 25 ºC, the resulting mixture was quenched by saturated $Na_2S_2O_3$ (2.00 mL). 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 **21a** (0.0186 g, 0.0730 mmol) in 73% yield as a white solid. **TLC**, R_f = 0.49 (hexane–EtOAc = 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.83–2.08 (m,

10 H), 2.83 (t, J = 5.8 Hz, 2H), 4.85 (brs, 1H), 6.55 (dd, J = 2.4, 8.2 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.71–6.81 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 16.2, 19.4, 29.9, 34.5, 43.5, 113.8, 116.0, 126.6, 130.0, 132.3, 138.2, 151.4, 154.6, 187.7.

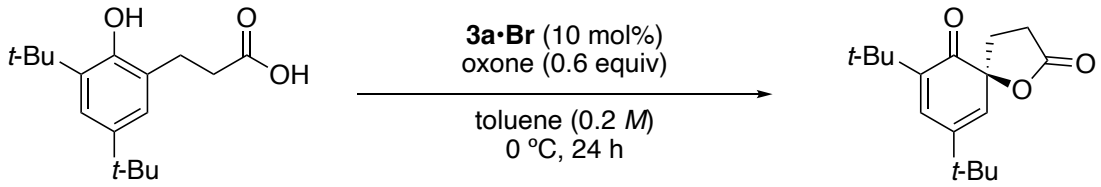


3,5-Di-*tert*-butyl-6'-hydroxy-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-naphthalene]-2,4-dien-6-one (21b): 0.0265 g, 0.0781 mmol, 78% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 4:1) **H NMR** ($CDCl_3$, 400 MHz) δ 1.15 (s, 9H), 1.25 (s, 9H), 1.68–1.77 (m, 2H), 1.93–2.01 (m, 2H), 2.64–2.69 (m, 1H), 2.79–2.83 (m, 1H), 5.71 (brs, 1H), 6.14 (s, 1H), 6.39 (s, 1H), 6.45–6.48 (m, 1H), 6.52–6.55 (m, 1H), 7.02 (s, 1H).

Experimental Procedure for Mechanistic Study

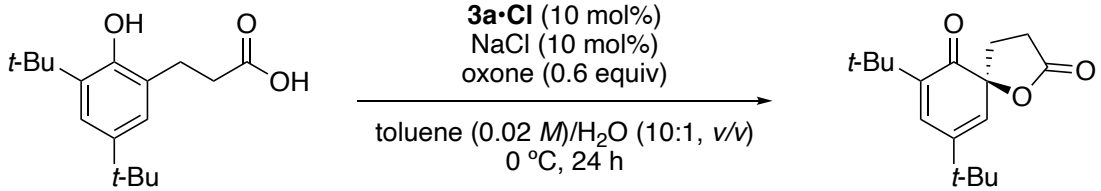


(*R*)-7,9-Di-*tert*-butyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (2ao):[5b] To a solution of **1ao** (0.0278 g, 0.100 mmol) and **3a•I** (0.0170 g, 0.0100 mmol, 10 mol%) in toluene (5.00 mL) and H_2O (0.500 mL) was added oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 0 °C, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) at 0 °C. 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 = 6:1) to give (*R*)-**3a** (0.0271 g, 0.0980 mmol) in 98% yield as a yellow solid. Enantiomeric excess of **2ao** was determined to be 71% ee by HPLC analysis. **TLC**, R_f = 0.57 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.15 (s, 9H), 1.23 (s, 9H), 1.98–2.06 (m, 1 H), 2.30–2.36 (m, 1H), 2.51 (ddd, *J* = 1.4, 9.6, 17.8 Hz, 1H), 2.73–2.82 (m, 1H), 5.99 (d, *J* = 1.8 Hz, 1H), 6.89 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.0, 28.4, 29.0, 30.2, 34.4, 34.5, 85.5, 128.1, 135.8, 142.8, 143.7, 176.6, 199.0; **HPLC** (OD–H column), Hexane–EtOH = 30:1 as eluent, 1.0 mL/min, t_R = 7.0 min (*S*), t_R = 7.9 min (*R*); **$[\alpha]^{27.7}_D$** = 167.1 (*c* 0.5, $CHCl_3$) for 71% ee.



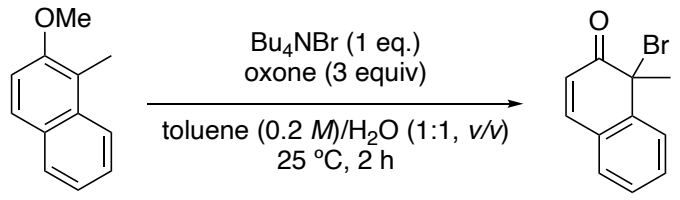
1ao **2ao**: 66%, 48% ee

(*S*)-7,9-Di-*tert*-butyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (3a): To a solution of **1ao** (0.0278 g, 0.100 mmol) and **3a•Br** (0.0166 g, 0.0100 mmol, 10 mol%) in toluene (0.500 mL) was added oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 0 °C, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) at 0 °C. 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 = 6:1) to give (*S*)-**3a** (0.0182 g, 0.0661 mmol) in 66% yield as a yellow solid. Enantiomeric excess of **3a** was determined to be 48% ee by HPLC analysis.



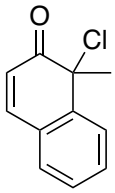
1ao **2ao**: 38%, 62% ee

(*S*)-7,9-Di-*tert*-butyl-1-oxaspiro[4.5]deca-7,9-diene-2,6-dione (3a): To a solution of **1ao** (0.0278 g, 0.100 mmol), NaCl (0.00584 g, 0.0100 mmol, 10 mol%) and **3a•Cl** (0.0162 g, 0.0100 mmol, 10 mol%) in toluene (5.00 mL) and H_2O (0.500 mL) was added oxone (0.0369 g, 0.0600 mmol) at 0 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 0 °C, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) at 0 °C. 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 = 6:1) to give (*S*)-**3a** (0.0105 g, 0.0380 mmol) in 38% yield as a yellow solid. Enantiomeric excess of **3a** was determined to be 62% ee by HPLC analysis.

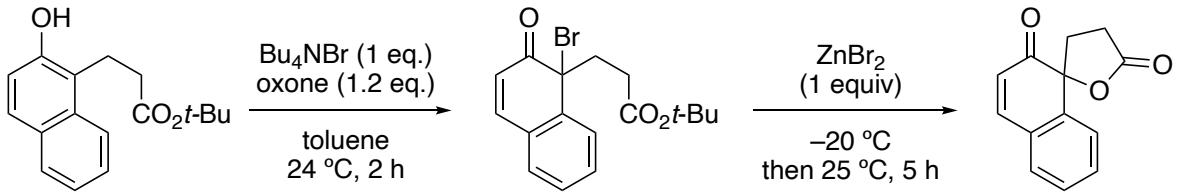


13a **14a•Br:** 92% yield

1-Bromo-1-methylnaphthalen-2(1H)-one (14a•Br):[28] To a solution of **13a** (0.0172 g, 0.100 mmol), Bu_4NBr (0.0322 g, 0.100 mmol) in toluene (0.500 mL) and H_2O (0.500 mL) were added oxone (0.921 g, 0.300 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 2 h at 25 ºC, 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 = 6:1) to give **14a•Br** (0.0218 g, 0.0920 mmol) in 92% yield as a yellow solid. **TLC**, R_f = 0.49 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H), 6.33 (d, *J* = 10.0 Hz, 1H), 7.33 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.39 (td, *J* = 1.6, 7.6 Hz, 2H), 7.45 (td, *J* = 1.5, 7.6 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.2, 57.4, 124.1, 128.0, 128.4, 129.4, 130.1, 130.7, 142.2, 143.6, 193.1.



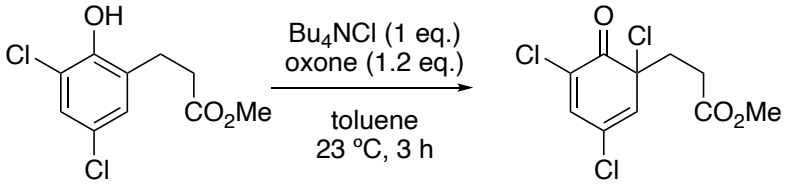
1-Chloro-1-methylnaphthalen-2(1H)-one (14a•Cl):[28] 0.0173 g, 0.0900 mmol, 90% yield. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 6:1) **TLC**, R_f = 0.49 (Hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.01 (s, 3H), 6.26 (d, J = 10.0, 1H), 7.32 (dd, J = 1.2, 7.6 Hz, 1H), 7.38 (td, J = 1.2, 7.6 Hz, 1H), 7.43 (d, J = 10.0 Hz, 1H), 7.47 (td, J = 1.2, 7.6 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 28.5, 65.6, 123.7, 128.1, 128.3, 129.1, 129.7, 130.8, 142.5, 144.8, 194.4.



15a | **16a•Br** >95% yield (^{1}H NMR) | **2am** 91% yield

3,4-Dihydro-2'*H*,5*H*-spiro[furan-2,1'-naphthalene]-2',5-dione (2am):[19] To a solution of **15a** (0.0272 g, 0.100 mmol), Bu_4NBr (0.0322 g, 0.100 mmol) in toluene (0.500 mL) were added oxone (0.0368 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 2 h at 24 ºC, the resulting mixture was cooled to –20 ºC and added $ZnBr_2$ (0.0225 g, 0.100 mmol). The reaction mixture was warm up to 25 ºC and stirred for 5 h. 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

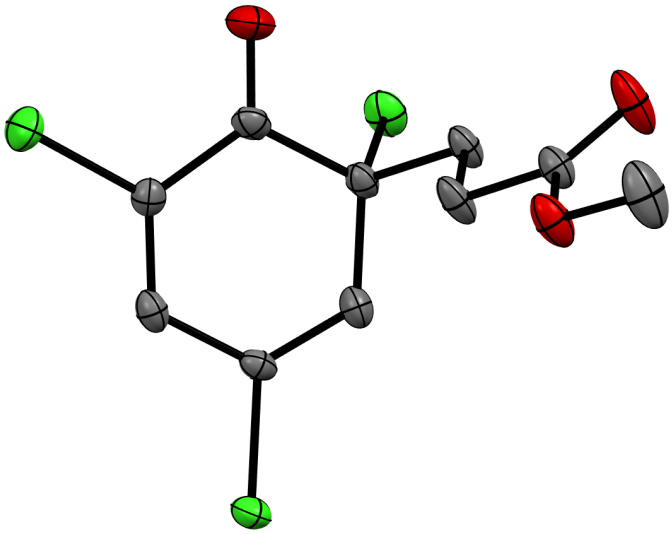
chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1) to give **2am** (0.0195 g, 0.0910 mmol) in 91% yield as a yellow solid. **TLC**, R_f = 0.70 (hexane–EtOAc = 1:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.11–2.20 (m, 1H), 2.62–2.70 (m, 2H), 2.81–2.90 (m, 1H), 6.18 (d, J = 9.6 Hz , 1H), 7.36 (dd, J = 1.6, 7.6 Hz, 1H), 7.41 (dt, J = 1.6, 7.6 Hz, 1H), 7.46–7.49 (m, 2H), 7.56 (d, J = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 26.6, 35.8, 85.8, 122.6, 125.8, 129.1, 129.2, 129.7, 131.1, 140.6, 146.0, 176.4, 197.5.



15b **16b•Cl**: 69% yield

Methyl 3-(1,3,5-trichloro-6-oxocyclohexa-2,4-dien-1-yl)propanoate (16b•Cl): To a solution of **15b** (0.0249 g, 0.100 mmol), Bu_4NCl (0.0278 g, 0.100 mmol) in toluene (0.500 mL) were added oxone (0.0368 g, 0.120 mmol) at 23 ºC. The reaction was monitored by TLC analysis. After stirring for 3 h at 23 ºC, 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 **16b•Cl** (0.0195 g, 0.0686 mmol) in 69% yield as a yellow solid. **TLC**, R_f = 0.49 (hexane–EtOAc = 2:1); **IR** (KBr) 3383, 2974, 1705, 1461 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.32–2.36 (m, 2H), 2.42–2.49 (m 1H), 2.55–2.66 (m, 1H), 3.68 (s, 3H), 6.38 (d, J = 2.8 Hz, 1H), 7.15 (d, J = 2.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 29.3, 34.9, 52.1, 65.3, 127.7, 132.1, 133.3, 139.4, 171.8, 186.2.

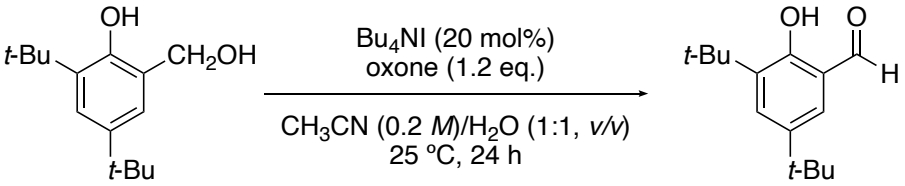
X-Ray Diffraction Analysis of 16b•Cl: Recrystallization of **16b•Cl** was carried out in the solution of Et_2O/hexane at 25 °C. X-Ray crystallographic analysis was performed with a Rigaku PILATUS-200K diffractometer (graphite monochromator, MoKa radiation, λ = 0.71075 Å) and the structure was solved by direct methods and expanded using Fourier techniques (SHELXT and SHELXL).



ORTEP drawing of 16b•Cl. Hydrogen atoms are omitted for clarity. Gray, carbon; red, oxygen; green, chlorine.

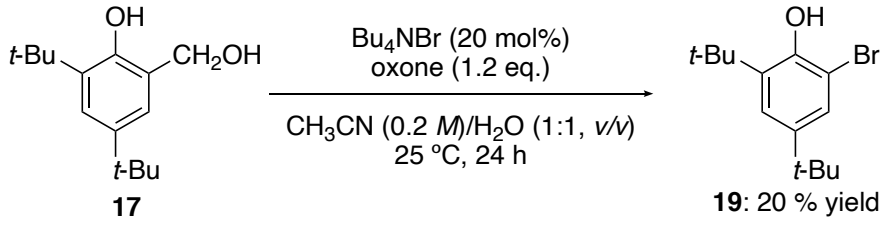
Crystallographic Data and Structure Refinement for 16b•Cl

Formula	$C_{10}H_9Cl_3O_3$	D_{calcd}	1.575g/cm^3
Formula weight	283.54	Absorption coefficient	0.752 mm^{-1}
T	123(2) K	*F*(000)	576.00
λ	0.71075 Å	Crystal size	0.2 x 0.2 x 0.2 mm^3
Crystal system	monoclinic	Theta range for data collection	3.40 to 27.50°
Space group	$P2_1$ (#4)	Reflections collected	9384
A	5.9737(16) Å	Refinement based on	F^2
B	9.617(2) Å	No. of data	2674
C	20.909(6) Å	No. of parameters	146
α	90.0°	No. of restraints	0
β	95.453(4)°	GOF	1.173
γ	90.0°	R(*F*) for $I > 2s(I)$	0.0734
V	1195.8(5) Å^3	wR2(F^2) for all data	0.2028
Z	4		



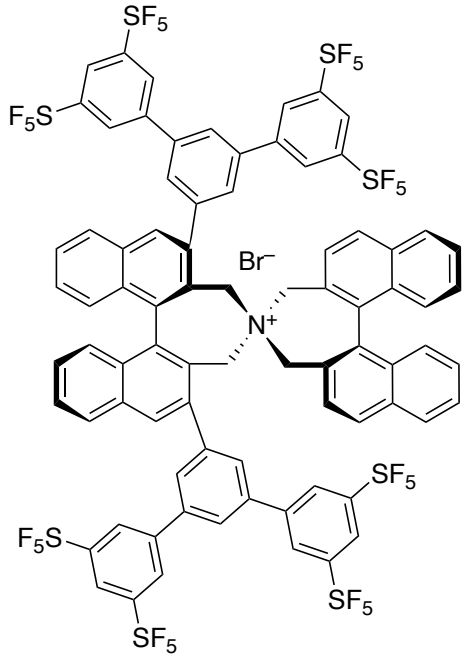
3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (18): To a solution of **17** (0.0236 g, 0.100 mmol), Bu_4NI (0.0738 g, 0.0200 mmol) in CH_3CN (0.500 mL) and H_2O (0.500 mL) were added oxone (0.0368 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 25 ºC, the resulting mixture was quenched by saturated $Na_2S_2O_3$ (2.00 mL). 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 = 5:1) to give **18** (0.0118 g, 0.0501 mmol) in 50% yield as a colorless oil.



2-Bromo-4,6-di-*tert*-butylphenol (19): To a solution of **17** (0.0236 g, 0.100 mmol), Bu_4NBr (0.0644 g, 0.0200 mmol) in CH_3CN (0.500 mL) and H_2O (0.500 mL) were added oxone (0.0368 g, 0.120 mmol) at 25 ºC. The reaction was monitored by TLC analysis. After stirring for 24 h at 25 ºC, the resulting mixture was quenched by saturated $Na_2S_2O_3$ (2.00 mL). 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 = 5:1) to give **19** (0.00560 g, 0.0198 mmol) in 20% yield as a white solid.

Characterization of Catalyst



(11b*R*,11b'*R*)-2,6-Bis(3,3'',5,5''-tetrakis(pentafluoro-λ^6-sulfaneyl)-[1,1':3',1''-terphenyl]-5'-yl)-3,3',5,5'-tetrahydro-4,4'-spirobi[dinaphtho[2,1-*c*:1',2'-*e*]azepin]-4-ium bromide (3c•Br): 3c•Br was prepared from (*R*)-2,2'-dimethyl-[1,1'-binaphthalene]-3,3'-diyl bis(trifluoromethanesulfonate) and (3,3'',5,5''-tetrakis(pentafluoro-λ6-sulfaneyl)-[1,1':3',1''-terphenyl]-5'-yl)boronic acid according to the literature.[5,6]

White solid; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.65 (d, *J* = 12.8 Hz, 2H), 4.54 (d, *J* = 12.8 Hz, 2H), 4.76 (d, *J* = 13.8 Hz, 2H), 4.89 (d, *J* = 13.8 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.20–7.30 (m, 8H), 7.39–7.43 (m, 2H), 7.50–7.57 (m, 4H), 7.66–7.70 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.94–7.97 (m, 6H), 8.07–8.15 (m, 6H), 8.34–8.57 (m, 6H), 8.95 (m, 2H).

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Chapter 4

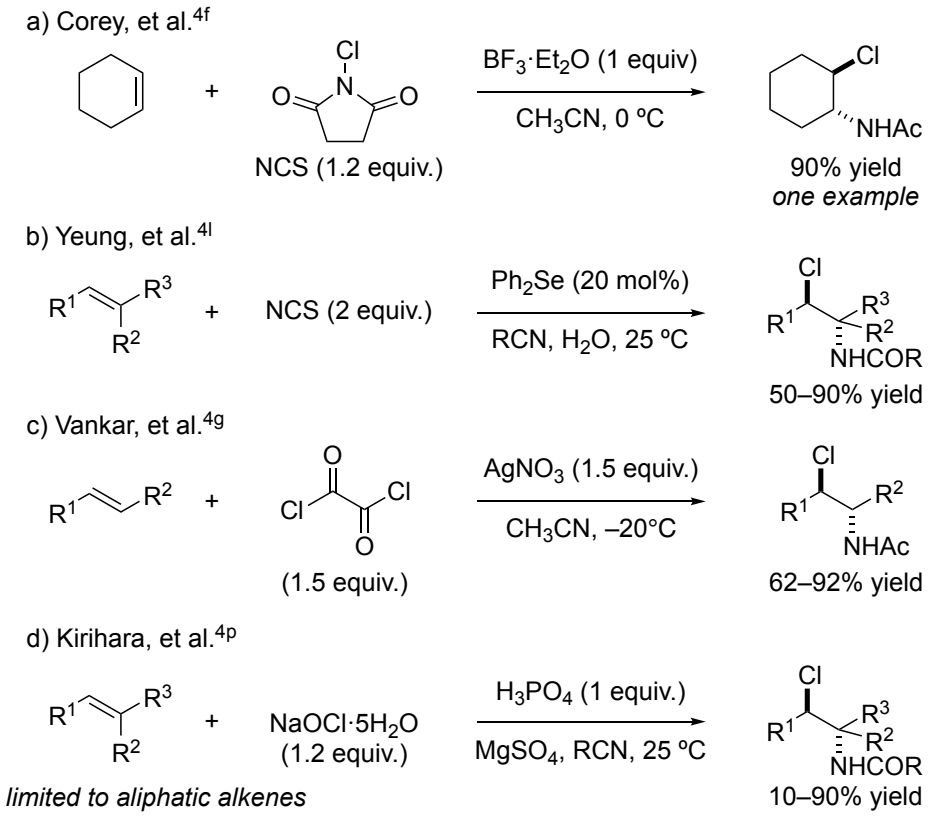
Oxidative Ritter-type Chloroamidation of Alkenes Using NaCl and Oxone

Abstract: We report a practical and environmentally benign method for the oxidative Ritter-type chloroamidation of alkenes using sodium chloride and oxone as a chlorinating source and an oxidant, respectively, in acetonitrile under mild conditions. The reaction proceeded smoothly under non-aqueous conditions without the use of any catalyst. Excellent chemoselectivity (i.e., chloroamidation versus dichlorination) could be achieved for electron-deficient styrenes. In addition, this protocol could be easily applied to 7-gram-scale synthesis.

Introduction

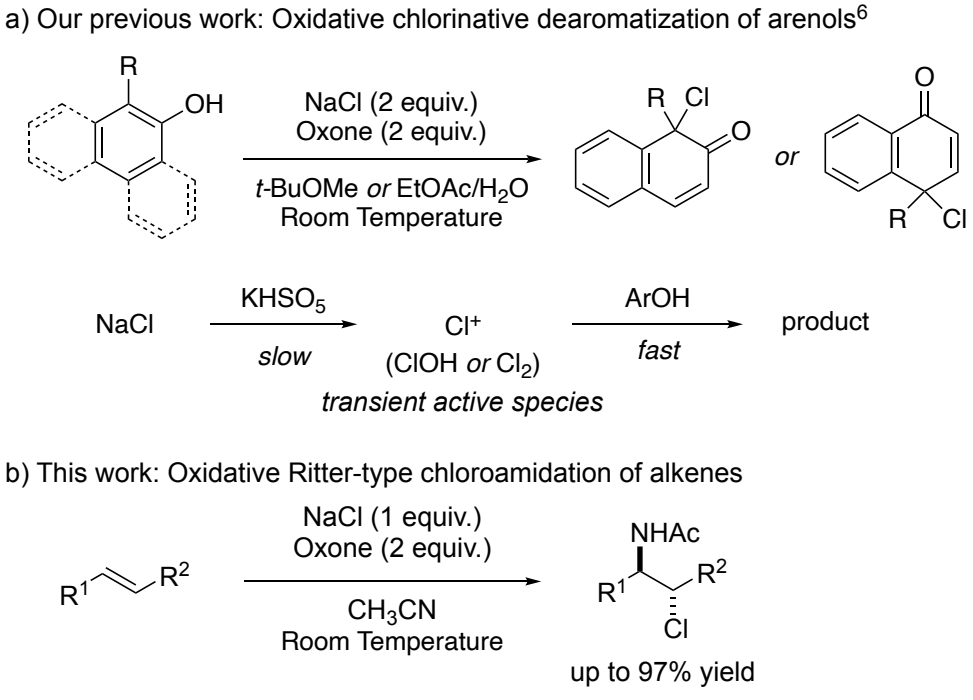
Vicinal haloamides are used as versatile building blocks for the synthesis of various natural products and biologically active compounds.[1,2] Generally, these compounds are synthesized by the haloamidation of alkene feedstocks using electrophilic halogenation reagents. To date, many elegant strategies for olefin haloamidation have been developed using transition-metal catalysts or organocatalysts.[3] Among these strategies, the Ritter-type chloroamidation of alkenes using nitriles as a solvent and nucleophile is one of the most straightforward routes to these compounds (Scheme 1).[4] For example, the groups of Corey and Yeung independently reported the Ritter-type chloroamidation of alkenes mediated by a Lewis acid or Lewis base, respectively (Schemes 1a and 1b).[4f,l] However, *N*-chlorosuccinimide (NCS) is used as an organic electrophilic chlorinating reagent, in which succinimide is generated as organic waste. On the other hand, Vankar and colleagues used oxalyl chloride as a chlorinating reagent, albeit the use of a stoichiometric amount of silver salt was required for the reaction to proceed (Scheme 1c).[4g] Very recently, Kirihara and colleagues reported the Ritter-type chloroamidation of alkenes using sodium hypochlorite pentahydrate ($NaOCl•5H_2O$)[5] as an inexpensive inorganic chlorinating reagent in the presence of phosphoric acid in nitrile solvents (Scheme 1d).[4p] However, the substrate scope is limited to aliphatic alkenes, and the reactions of vinylarenes give a complex mixture.

Scheme 1. Previous Representative Examples for Ritter-type Chloroamidation of Alkenes



Recently, we reported a practical oxidative dearomative chlorination of arenols using sodium chloride and oxone ($KHSO_5$•$0.5KHSO_4$•$0.5K_2SO_4$) as a chlorinating reagent and an oxidant, respectively (Scheme 2a).[6,7] Chlorine (Cl_2) or hypochlorous acid (HOCl) might be generated *in situ* as an active electrophilic chlorinating species under acidic conditions. Most importantly, thanks to the slow generation and rapid consumption of these transient active species, the concentration of the highly reactive chlorinating species could be minimized to induce high chemoselectivity compared to stoichiometric chlorinating reagents such as sodium hypochlorite pentahydrate. Here, we applied a NaCl/oxone system to the oxidative Ritter-type chloroamidation of alkenes (Scheme 2b). The oxidative chloroamidation of various substituted styrenes proceeded in nitrile solvents under mild conditions to give the corresponding vicinal chloroamides in good to high yield. Notably, excellent chemoselectivity (i.e., chloroamidation versus dichlorination) was achieved for the electron-withdrawing group-substituted styrenes under non-aqueous conditions. Aliphatic alkenes could also be used as substrates to give the corresponding chloroamides in moderate to good yield.

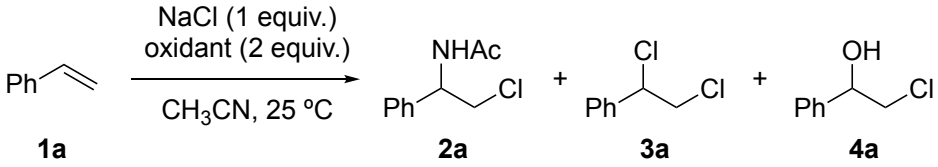
Scheme 2. Oxidative Dearomative Chlorination and Ritter-type Chloroamidation Using a NaCl/oxone System



We commenced our study by examining the oxidative chloroamidation of styrene (**1a**) (Table 1). First, following our previous report,[6] we used 1 equivalent of NaCl and 2 equivalents of oxone in a mixed solvent of acetonitrile and water at 25 ºC. However, desired chloroamide **2a** was not obtained, and chlorohydrin **4a** was isolated as a major side product along with a small amount of dichlorination

side product **3a** (entry 1). To our delight, the generation of chlorohydrin **4a** was suppressed entirely in nonaqueous acetonitrile, and desired **2a** was obtained in 68% isolated yield (entry 2). However, the dichlorination pathway remained as a side reaction. A brief screening of oxidants revealed that while almost no reaction proceeded with the use of hydrogen peroxide or alkyl hydroperoxides (TBHP and CHP) (entries 3–5), the use of *meta*-chloroperbenzoic acid (*m*-CPBA) gave a complex mixture of **2a**, **3a**, **4a** and several unidentified by-products (entry 6).

Table 1. Oxidative Ritter-type Chloroamidation of 1a [a]

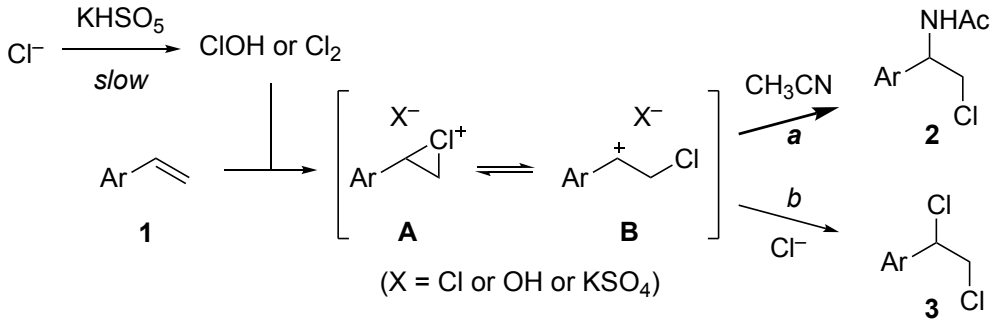


Entry	Oxidant	Time [h]	Yield [%][b]		
			2a	**3a**	**4a**
1[c]	Oxone	3	<1	10	78
2	Oxone	9	70 (68)[d]	13	<1
3[e]	H_2O_2	24	<1	<1	<1
4[e]	TBHP	24	<1	<1	<1
5[e]	CHP	24	<1	<1	<1
6[f]	*m*-CPBA	1	13	4	7

[a] A solution of **1a** (0.5 mmol), NaCl (1 equiv.) and oxidant (1 or 2 equiv.) in CH_3CN (0.2 *M*) was stirred at 25 °C. For details, see the Experimental Section. [b] Determined by ^1H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. [c] A CH_3CN/H_2O (1:1) mixed solvent was used. [d] Isolated yield. [e] Unreacted **1a** was recovered (>95%). [f] Several unidentified by-products were also observed.

Proposed reaction mechanism is briefly summarized in Scheme 3. First, chloride ion should be oxidized by oxone to ClOH or Cl_2.[6,7] These active species might react with vinylarene **1** to produce cyclic chloriranium ion intermediate **A**, which might exist in equilibrium with linear benzylic ion intermediate **B**. These intermediates **A** and/or **B** might react with the solvent acetonitrile (*path a*) to give desired chloramide **2** after hydrolysis of the nitrilium ion. On the other hand, because of the slow generation of Cl^+ active species under non-aqueous conditions that solid reagents could not be dissolved, chloride anion (X^-) in the reaction mixture might competitively react with intermediates **A** and/or **B** to afford undesired dichloride **3** (*path b*). Dichloride **3** might also be obtained by the ion-pair collapse of these intermediates (when X = Cl).[8]

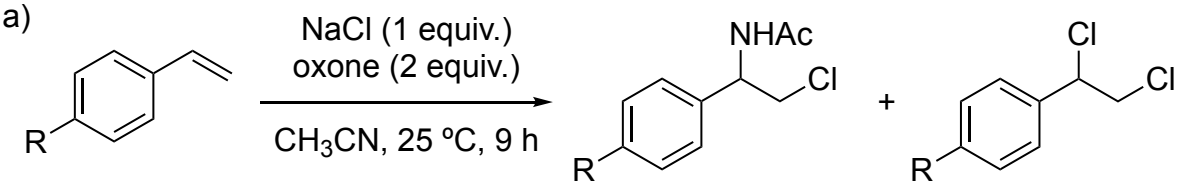
Scheme 3. Proposed Mechanism



To understand the origins of the chemoselectivity between the chloroamidation and dichlorination pathways, we first investigated the substituent effect of styrenes such as 4-methylstyrene (**1b**) and methyl 4-vinylbenzoate (**1c**) as electron-rich and electron-deficient substrates, respectively, and compared them to those of **1a** (Scheme 4a). The reaction of **1b** gave an equimolar mixture of chloroamide **2b** and dichloride **3b** along with several unidentified side products. In sharp contrast, electron-deficient styrene **1c** gave the corresponding chloroamide **2c** quantitatively after a clean reaction. Concisely, the lower the electron-donating ability of the substituent (i.e., the higher σ_p[9]), the higher the chemoselectivity of the chloroamidation pathway. The possible generation of **2c** from dichloride **3c** could be excluded by a control experiment using **3c** as a substrate under identical conditions (Scheme 4b). While benzylic cation intermediate **B** would be stabilized by electron-donating substituents, electron-withdrawing substituents would destabilize intermediate **B**, and chloriranium ion intermediate **A** would be favored.[10] Therefore, the results in Scheme 4a might suggest that acetonitrile tends to react with chloriranium ion intermediate **A**, and chloride ion tends to react with benzyl cation intermediate **B** under our conditions. We next investigated the stereoselectivity of the chloroamidation reaction using *trans*-β-methyl styrenes (*E*)-**1d**–**f** as substrates under optimized conditions (Scheme 4c). As a result, a mixture of *anti*- (**2**) and *syn*-adducts (**2'**) was observed in all cases, probably due to the equilibrium between the cyclic and linear intermediates **A** and **B**.[11,12] Nevertheless, the diastereoselectivity of **2d**–**f** as well as the chemoselectivity of the chloroamidation pathway increased as the electron-donating nature of the substituents decreased, which was consistent with the substituent effect of styrenes **1a**–**c** described above.

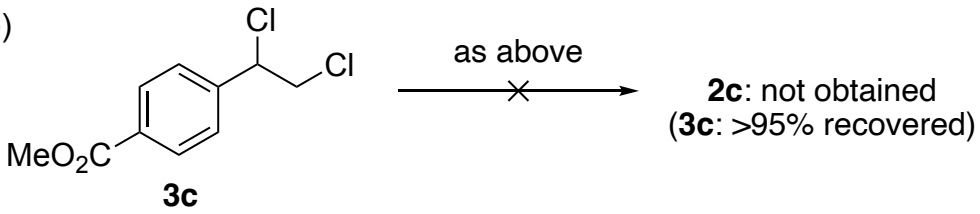
Scheme 4. Control experiments and stereoselective chloroamidation of *trans*-β-methylstyrenes 1d–f

a)



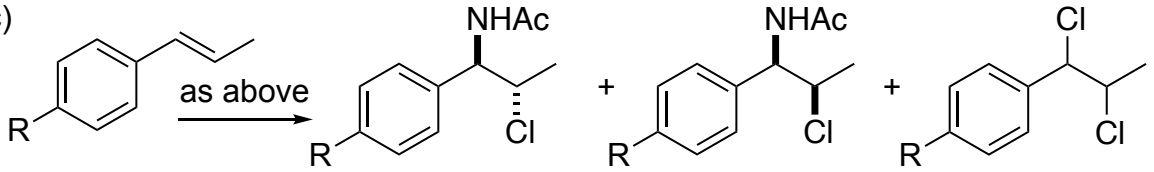
R (**1**)	σ_p of R[9]	**2** [%][a]	**3** [%][a]
Me (**1b**)	–0.17	25[b]	25
H (**1a**)	0	70 (68)[c]	13
CO_2Me (**1c**)	0.45	>99 (97)[c]	<1

b)



3c

c)



E-**1** **2** (*anti*-adduct) **2'** (*syn*-adduct) **3**

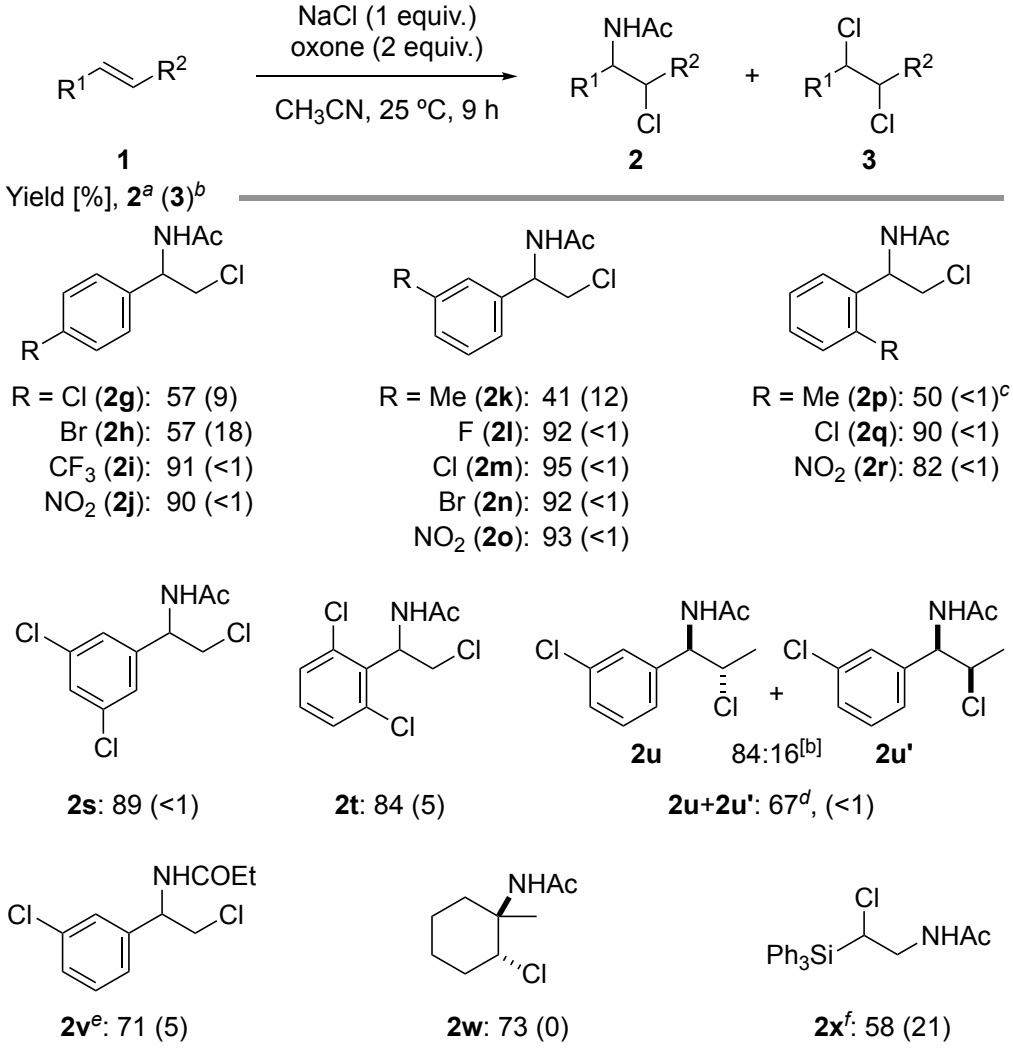
R (**1**)	**2+2'** [%][a]	**2:2'** [a]	**3** [%][a] (*anti*:*syn*)[a]
Me (**1d**)	14	65:35	36 (70:30)
H (**1e**)	58 (56)[c,d]	73:27	20 (66:34)
CO_2Me (**1f**)	89 (76)[c,d]	86:14	<5 (–)

[a] Determined by ^{1}H NMR analysis. [b] Several unidentified by-products were also observed. [c] Isolated yield. [d] Isolated as an inseparable mixture of **2** and **2'**. For details, see Experimental Section.

A series of vinylarenes **1** were examined for the oxidative chloroamidation reaction under optimized conditions (Scheme 5). As expected by the results discussed above, the chemoselective reaction of vinylarenes bearing electron-withdrawing groups such as CF_3 (**1i**) and NO_2 (**1j**, **1o**, and **1r**) at either the *ortho*-, *meta*- or *para*-positions and halogens (**1l**–**n**) at the *meta*-position proceeded to give the corresponding chloroamides **2** in high to excellent yields. On the other hand, while *ortho*-chloro-substituted **1q** gave chloroamide **2q** exclusively in 90% yield, *para*-halogen-substituted **1g** and **1h** gave the corresponding chloroamides **2** in moderate yield along with dichlorides **3** as side-

products. Although the differences of these *ortho*- and *para*-substitution effects of halogens are not yet fully understood, we speculated that the addition of chloride might be selectively suppressed due to steric reasons for *ortho*-chloro-substituted styrene **1q**, despite similar resonance effects of halogens at both the *ortho*- and *para*-positions. In addition, dichloro-substituted styrenes **1s** and **1t** afforded the corresponding chloroamides in good yield. However, the chemoselectivity and the chemical yield of chloroamides decreased for the reactions of *meta*- and *ortho*-methyl-substituted styrenes **1k** and **1p** as in that of **1b**. The reaction of 3-chloro-β-methylstyrene (*E*)-**1u** gave a mixture of *anti*/*syn*-adducts **2u** and **2u'** in 67% yield (d.r. 84:16). Propionitrile could also be used as a solvent to give propanamide **2v**, albeit in a lower yield than that of acetamide **2m**. Aliphatic alkenes were also applicable under the present oxidative conditions. For example, a chemoselective oxidative chloroamidation of 1-methylcyclohexene (**1w**) proceeded to give α-tertiary amide **2v** in good yield with *anti*-selectivity.[4l] In addition, vinyltriphenylsilane (**1x**) afforded chloroamide **2x** in moderate yield along with chloroamide **3x**. In this reaction, both the *anti*-Markovnikov addition to **2x** and the generation of dichlorides **3x** might be attributed to the β-silicon effect.[13]

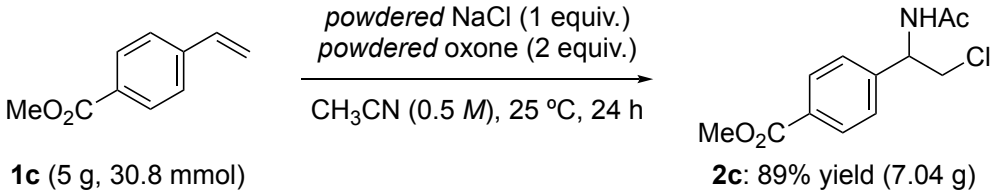
Scheme 5. Oxidative chloroamidation of alkenes 1



A solution of **1** (0.5 mmol), NaCl (1 equiv.), and oxone (2 equiv.) in CH_3CN (0.2 *M*) was stirred at 25 °C. [a] Isolated yield. [b] Determined by ^1H NMR analysis of the crude product. [c] Although we could not detect dichloride **3p**, several unidentified by-products were observed. [d] Isolated as an inseparable mixture of **2u** and **2u'**. [e] Propionitrile was used as a solvent instead of acetonitrile. [f] Oxone (1 equiv.) was used. For details, see the Supporting Information.

Finally, we achieved the 60-fold scale-up of oxidative chloroamidation of **1c** (30.8 mmol) under slightly modified conditions using *powdered* NaCl and *powdered* oxone[14] under non-aqueous conditions (Scheme 6). An analytically pure chloroamide **2c** could be easily isolated in 89% yield (7.04 g) by simply washing the crude product with diethyl ether.

Scheme 6. Gram-scale oxidative chloroamidation of 1c



Conclusion

In conclusion, we have developed a practical method for the oxidative Ritter-type chloroamidation of alkenes using NaCl and oxone as a chlorinating source and an oxidant, respectively, in acetonitrile under mild conditions. The reactions proceeded smoothly under non-aqueous conditions without the use of any catalyst. Notably, excellent chemoselectivity (i.e., chloroamidation versus dichlorination) could be achieved for the electron-withdrawing group-substituted styrenes. This protocol could be easily applied to 7-gram-scale synthesis.

Experimental Section

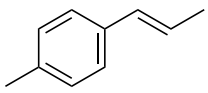
Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 (400 MHz) and Bruker AVANCE III HD (500 MHz) spectrometers at ambient temperature. Chemical shifts are reported in ppm from Me_4Si resonance (0.00 ppm in $CDCl_3$) as internal standard. 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; m = multiplet; brs = broad singlet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz) and Bruker AVANCE III HD (125 MHz) spectrometers at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.00 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University [JEOL JMS-700 (FAB). 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).

In experiments that required solvents were purchased from Aldrich Chemical Co., Inc., FUJIFILM Wako Pure Chemical Industries, Ltd. or Tokyo Chemical Industry Co., Ltd. and used without further purification. Oxone was purchased from Aldrich Chemical Co., Inc. and used without further purification. NaCl was purchased from FUJIFILM Wako Pure Chemical Industries, Ltd. and used without purification. Other simple chemicals were analytical-grade and obtained commercially and used without further purification.

Synthesis and Characterization of Substrates

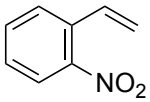
1a–**c**, (*E*)-**1e**, **1g**–**n**, **1p**–**r**, **1w** and **1x** were purchased from Tokyo Chemical Industry Co., Ltd. **1o** was purchased from Wako Pure Chemical Industries, Ltd. **1t** was purchased from Aldrich Chemical Co., Inc. All compounds were used without further purification.

1d,[15] **1r**,[16] **1s,**[17] and **1u**[15] are known compounds and prepared by following the literature procedures. **3c** was prepared in analogy to a reported procedure.[18]

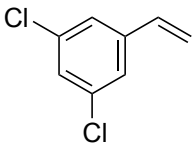


(*E*)-1-Methyl-4-(prop-1-en-1-yl)benzene (1d):[15] Colorless oil; **TLC**, R_f = 0.71 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.22 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.41–6.35 (m,

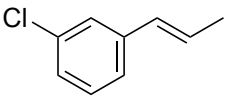
1H), 6.22–6.14 (m, 1H), 2.32 (s, 3H), 1.87 (dd, J = 6.4, 1.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 136.4, 135.1, 130.8, 129.1, 125.7, 124.6, 21.1, 18.5.



1-Nitro-2-vinylbenzene (1r):[16] Yellow oil; **TLC**, R_f = 0.65 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.94 (dd, J = 0.9, 8.2 Hz, 1H), 7.65–7.57 (m, 2H), 7.44–7.40 (m, 1H), 7.18 (dd, J = 11.0, 17.4 Hz, 1H), 5.75 (dd, J = 17.4, 0.9 Hz, 1H), 5.50 (dd, J = 11.0, 0.9 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 147.7, 133.2, 133.1, 132.3, 128.4, 128.3, 124.3, 118.9.

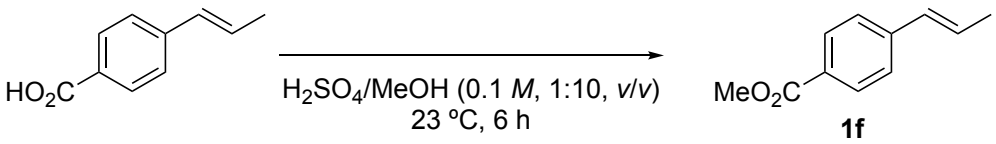


1,3-Dichloro-5-vinylbenzene (1s):[17] Yellow oil; **TLC**, R_f = 0.52 (hexane–EtOAc = 6:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.26–7.23 (m, 3H), 6.59 (dd, J = 17.4, 11.0 Hz, 1H), 5.77 (d, J = 17.4 Hz, 1H), 5.36 (d, J = 11.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 140.5, 135.1, 134.5, 127.6, 124.6, 116.8.



(*E*)-1-Chloro-3-(prop-1-en-1-yl)benzene (1u):[15] Colorless oil; **TLC**, R_f = 0.67 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31 (s, 1H), 7.25–7.14 (m, 3H), 6.36–6.20 (m, 2H), 1.89 (d, J = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 139.8, 134.4, 129.8, 129.6, 127.4, 126.6, 125.7, 124.0, 18.5.

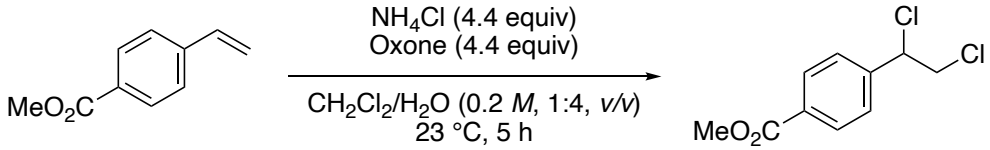
Synthesis of 1f:



To a stirring mixture of (*E*)-4-(prop-1-en-1-yl)benzoic acid[15] (0.324 g, 2.00 mmol) in methanol (20.0 mL) was slowly added H_2SO_4 (2.00 mL) at 0 ºC. After stirring for 6 h at 23 ºC, the resulting mixture was cooled to 0 ºC and treated with saturated aqueous $NaHCO_3$. The aqueous layers were separated and extracted with EtOAc (twice), and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, and the solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane only to hexane/EtOAc = 4:1) to give **1f** (0.129 g, 0.732 mmol, *E*:*Z* = 99:1) in 37% yield.

Methyl (*E*)-4-(prop-1-en-1-yl)benzoate (1f):[18] White solid; **TLC**, R_f = 0.38 (hexane–EtOAc = 6:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.96 (dd, J = 6.4, 1.8 Hz, 2H), 7.37 (dd, *J* = 6.4, 1.8 Hz, 2H), 6.46–6.33 (m, 2H), 3.90 (s, 3H), 1.92 (d, *J* = 5.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 166.8, 142.3, 130.2, 129.7, 128.6, 128.1, 125.5, 51.8, 18.5.

Synthesis of 3c:[18]

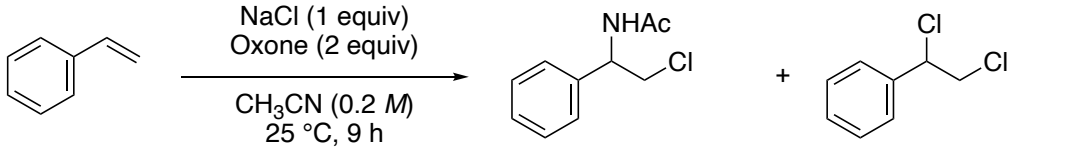


1c **3c**

To a stirring mixture of **1c** (0.324 g, 2.00 mmol) and NH_4Cl (0.471 g, 8.80 mmol) in CH_2Cl_2 (2.00 mL) and H_2O (8.00 mL) was added oxone (2.70 g, 8.80 mmol) at 23 °C. After stirring for 5 h, the reaction mixture was poured into saturated aqueous $Na_2S_2O_3$ (30 mL). The aqueous layers were separated and extracted with Et_2O (three times). 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 (eluent: hexane–EtOAc = 100:1) to give **3c** (0.364 g, 1.56 mmol) in 78% yield.

Methyl 4-(1,2-dichloroethyl)benzoate (3c): Colorless oil; **TLC**, R_f = 0.33 (hexane–EtOAc = 6:1); **IR** (neat) 2997, 2953, 1931, 1719, 1610, 1437, 1281 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (dd, J = 6.4, 1.8 Hz, 2H), 7.49 (dd, J = 6.4, 1.8 Hz, 2H), 5.03 (dd, J = 8.2, 6.0 Hz, 1H), 4.01 (dd, J = 11.5, 6.0 Hz, 1H), 3.94–3.89 (m, 1H), 3.93 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 166.4, 142.6, 130.8, 130.0, 127.5, 60.6, 52.3, 47.9; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{11}{}^{35}Cl_2O_2+H]^+$/$[C_{10}H_{11}{}^{35}Cl^{37}ClO_2+H]^+$/$[C_{10}H_{11}{}^{37}Cl_2O_2+H]^+$ 233.0136/235.0108/237.0082, found 233.0138/235.0125/237.0101.

Representative Procedure for Chloroamidation and Characterization of Products

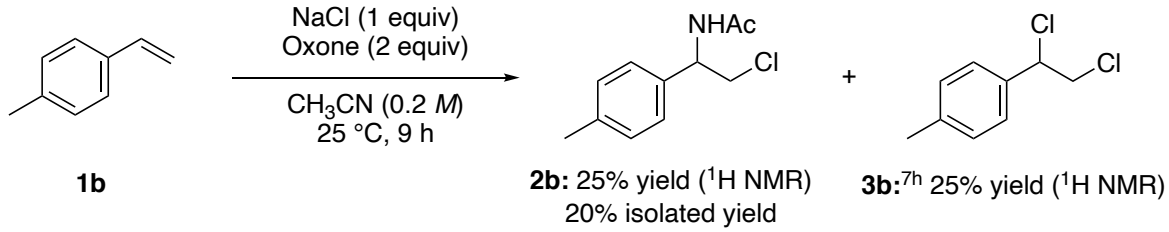


1a **2a:** 70% yield (^{1}H NMR) 68% yield **3a:**[7h] 9% yield (^{1}H NMR)

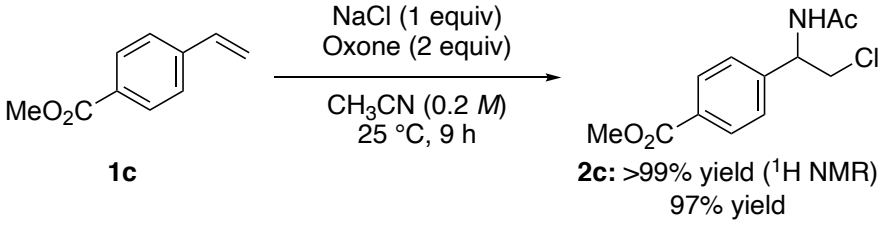
To a stirring mixture of **1a** (TCI, 0.0575 mL, 0.500 mmol), NaCl (FUJIFILM Wako, 0.0292 g, 0.500 mmol) and 1,1,2,2-tetrachloroethane (TCI, 0.0525 mL, 0.500 mmol, as an internal standard) in acetonitrile (FUJIFILM Wako, 2.50 mL) was added oxone (Aldrich, 0.307 g, 1.00 mmol) at 25 °C. The reaction was monitored by ^{1}H NMR analysis. After stirring for 9 h, the reaction mixture was

then analyzed by ^{1}H NMR to measure the yield of **2a** and **3a**[7h] (9%). The resulting mixture was poured into saturated aqueous $Na_2S_2O_3$ (10 mL). The aqueous layers were separated and extracted with Et_2O (three times). 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 (eluent: hexane–EtOAc = 1:1) to give **2a** (0.0673 g, 0.340 mmol) in 68% yield.

***N*-(2-Chloro-1-phenylethyl)acetamide (2a):**[41] White solid; **TLC**, R_f = 0.36 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.26 (m, 5H), 6.24 (d, *J* = 6.9 Hz, 1H), 5.35 (dt, *J* = 6.9, 5.0 Hz, 1H), 3.89–3.82 (m, 2H), 2.05 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.6, 138.3, 128.8, 128.1, 126.7, 53.5, 47.5, 23.3.

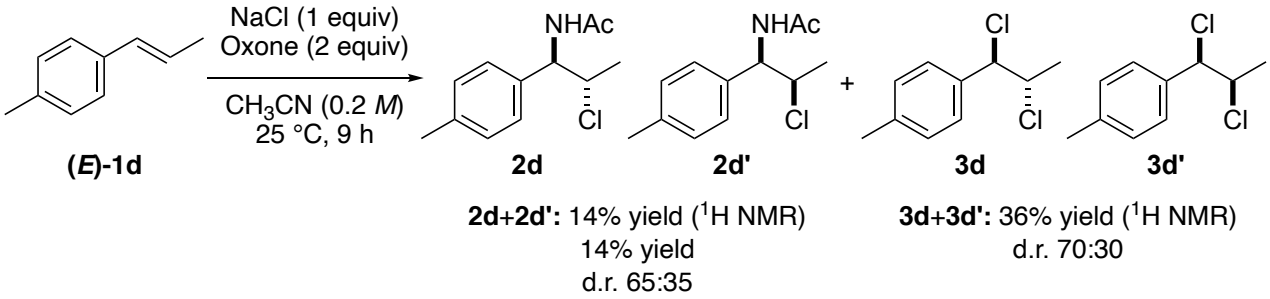


***N*-(2-Chloro-1-(*p*-tolyl)ethyl)acetamide (2b):** 20% yield (0.0209 g, 0.100 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.36 (hexane–EtOAc = 1:1); **IR** (neat) 3056, 2926, 1651, 1543 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.22–7.12 (m, 4H), 6.12 (brs, 1H), 5.33–5.29 (dt, *J* = 6.7, 5.5 Hz, 1H), 3.84 (d, *J* = 5.5 Hz, 2H), 2.34 (s, 3H), 2.05 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.6, 137.9, 135.3, 129.4, 126.6, 53.3, 47.5, 23.3, 21.1; **HRMS** (FAB+) m/z calcd for $[C_{11}H_{15}{}^{35}ClNO+H]^+$/$[C_{11}H_{15}{}^{37}ClNO+H]^+$ 212.0842/214.0815, found 212.0840/214.0818.



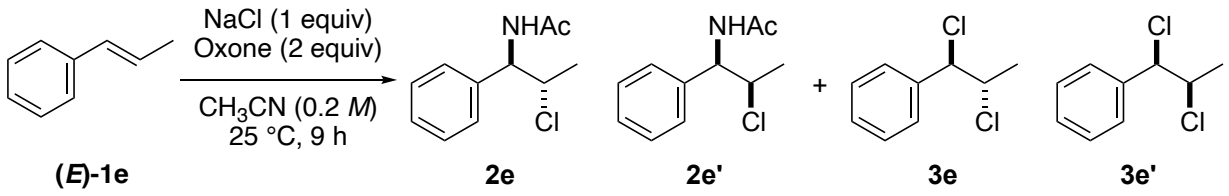
Methyl 4-(1-acetamido-2-chloroethyl)benzoate (2c): 97% yield (0.124 g, 0.484 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.26 (hexane–EtOAc = 1:1); **IR** (neat) 3367, 2953, 1716, 1653, 1281 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.03 (dd, *J* = 8.5, 3.0 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 6.36–6.28 (m, 1H), 5.42 (dt, *J* = 8.5, 4.0 Hz, 1H), 3.92 (s, 3H), 3.91–3.85 (m, 2H), 2.08 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 169.7, 166.6, 143.4, 130.0, 129.9, 126.7, 53.2, 52.2, 47.4, 23.2;

HRMS (FAB+) m/z calcd for $[C_{12}H_{14}{}^{35}ClNO_3+Na]^+/[C_{12}H_{14}{}^{37}ClNO_3+Na]^+$ 278.0560/280.0534, found 278.0558/280.0535.



***N*-(2-Chloro-1-(p-tolyl)propyl)acetamide (2d):** Inseparable mixture of **2d**/**2d'** (65:35). 14% yield (0.0156 g, 0.0691 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). Colorless oil; **TLC**, R_f = 0.34 (hexane–EtOAc = 1:1); **IR** (neat) 3431, 2088,1644, 1366, 1218, 1102 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz for **2d**) δ 7.30–7.14 (m, 4H), 6.28 (brs, 1H), 5.17 (dd, *J* = 8.5, 4.2 Hz, 1H), 4.46 (dq, *J* = 6.4, 4.2 Hz, 1H), 2.34 (s, 3H), 2.03 (s, 3H), 1.37 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **2d**) δ 169.2, 137.9, 133.6, 129.0, 128.0, 60.9, 57.4, 23.3, 21.8, 21.1; **^{1}H NMR** ($CDCl_3$, 400 MHz for **2d'**) δ 7.30–7.14 (m, 4H), 6.23 (brs, 1H), 5.26 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.38 (dq, *J* = 6.7, 3.2 Hz, 1H), 2.33 (s, 3H), 2.10 (s, 3H), 1.57 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **2d'**) δ 169.8, 137.5, 136.4, 129.2, 126.4, 62.2, 57.1, 23.3, 23.0, 21.0; **HRMS** (FAB+) m/z calcd for $[C_{12}H_{17}{}^{35}ClNO+H]^+/[C_{12}H_{17}{}^{37}ClNO+H]^+$ 226.0999/228.0969, found 226.1009/228.0958.

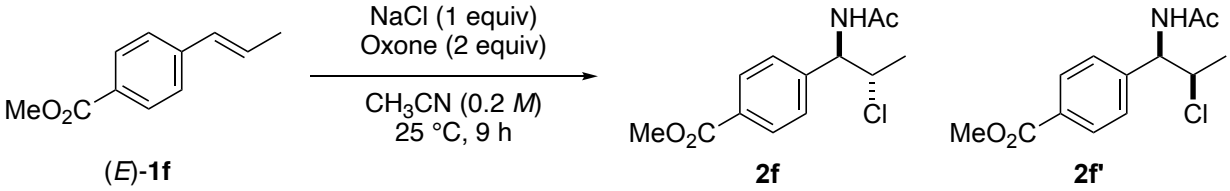
1-(1,2-Dichloropropyl)-4-methylbenzene (3d): Inseparable mixture of **3d**/**3d'** (70:30). Colorless oil; **TLC**, R_f = 0.78 (hexane–EtOAc = 9:1); **IR** (neat) 3395, 2985, 2078, 1645 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz for **3d**) δ 7.29 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.88 (d, *J* = 7.8 Hz, 1H), 4.42–4.34 (m, 1H), 2.36 (s, 3H), 1.71 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **3d**) δ 138.8, 135.7, 129.2, 127.6, 67.4, 60.2, 22.2, 21.2; **^{1}H NMR** ($CDCl_3$, 400 MHz for **3d'**) δ 7.29 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.96 (d, *J* = 6.0 Hz, 1H), 4.42–4.34 (m, 1H), 2.36 (s, 3H), 1.44 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **3d'**) δ 138.7, 134.4, 129.1, 127.9, 67.4, 61.3, 21.7, 21.2; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{12}{}^{35}Cl_2]^+/[C_{10}H_{12}{}^{35}Cl^{37}Cl]^+$ 202.0316/204.0287, found 202.0313/204.0279.



2e+2e': 58% yield (^{1}H NMR)
56% yield
d.r. 73:27

3e+3e':[19] 20% yield (^{1}H NMR)
d.r. 66:34

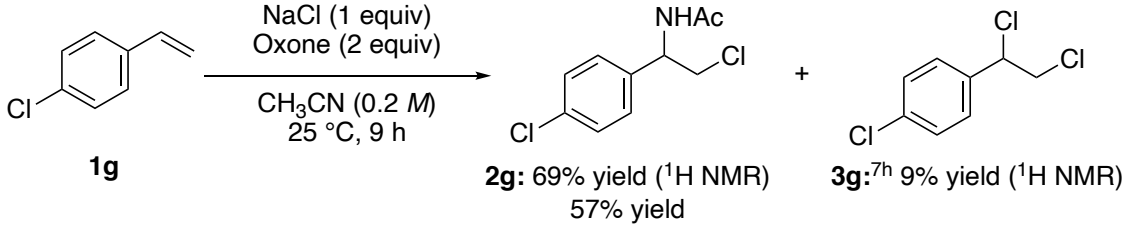
***N*-(2-Chloro-1-phenylpropyl)acetamide (2e):** Inseparable mixture of **2e**/**2e'** (73:27). 56% yield (0.0592 g, 0.280 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.58 (hexane–EtOAc = 1:1); **IR** (neat) 3063, 1651, 1540, 1455 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz for **2e**) δ 7.35–7.28 (m, 5H), 6.38 (d, *J* = 7.3 Hz, 1H), 5.21 (dd, *J* = 7.3, 4.4 Hz, 1H), 4.51–4.44 (m, 1H), 2.03 (s, 3H), 1.37 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **2e**) δ 169.2, 136.6, 128.3, 128.2, 126.5, 60.9, 57.6, 23.4, 21.8; **^{1}H NMR** ($CDCl_3$, 400 MHz for **2e'**) δ 7.35–7.28 (m, 5H), 6.33 (d, *J* = 9.2 Hz, 1H), 5.30 (dd, *J* = 3.7, 9.2 Hz, 1H), 4.42–4.37 (m, 1H), 2.11 (s, 3H), 1.58 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **2e'**) δ 169.8, 139.4, 128.5, 127.8, 126.5, 62.1, 57.3, 23.3, 23.1; **HRMS** (FAB+) m/z calcd for $[C_{11}H_{15}{}^{35}ClNO+H]^+$/$[C_{11}H_{15}{}^{37}ClNO+H]^+$ 212.0842/214.0815, found 212.0844/214.0821.



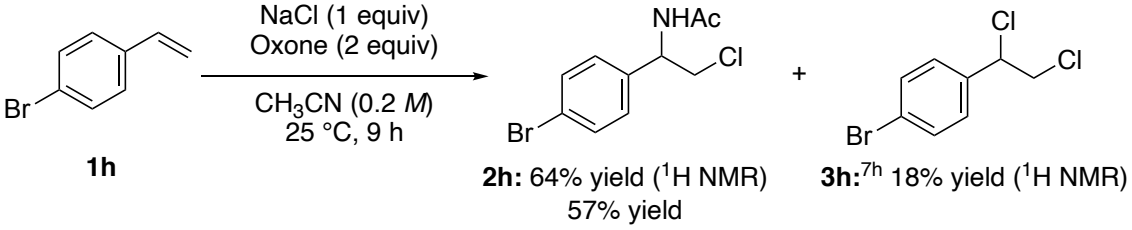
2f+2f': 89% yield (^{1}H NMR)
76% yield
d.r. 86:14

Methyl 4-(1-acetamido-2-chloropropyl)benzoate (2f): Inseparable mixture of **2f**/**2f'** (86:14). 76% yield (0.102 g, 0.378 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.24 (hexane–EtOAc = 1:1); **IR** (neat) 3435, 2947, 2847, 2084, 1649, 1540, 1281 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz for **2f**) δ 8.03–8.00 (m, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.54 (d, *J* = 8.2 Hz, 1H), 5.27 (dd, *J* = 8.2, 4.1 Hz, 1H), 4.48–4.43 (m, 1H), 3.91 (s, 3H), 2.05 (s, 3H), 1.38 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **2f**) δ 169.3, 166.6, 141.8, 129.8, 129.6, 128.2, 60.3, 57.4, 52.2, 23.3, 21.7; **^{1}H NMR** ($CDCl_3$, 400 MHz for **2f'**) δ 8.03–8.00 (m, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.48 (d, *J* = 9.2 Hz, 1H), 5.35 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.42–4.38 (m, 1H), 3.92 (s, 3H), 2.13 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **2f'**) δ 170.0, 166.6, 144.5, 129.9, 129.5, 126.6, 61.6, 57.2, 52.2, 23.2, 23.0; **HRMS** (FAB+) m/z calcd for $[C_{13}H_{17}{}^{35}ClNO_3+H]^+$/$[C_{13}H_{17}{}^{37}ClNO_3+H]^+$

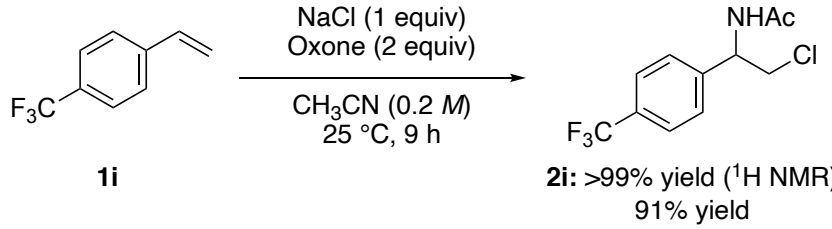
270.0897/272.0867, found 270.0903/272.0877.



***N*-(2-Chloro-1-(4-chlorophenyl)ethyl)acetamide (2g):** 57% yield (0.0663 g, 0.286 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.28 (hexane–EtOAc = 1:1); **IR** (neat) 3052, 1652, 1535, 1377 cm^{-1} **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33–7.30 (m, 2H), 7.27–7.23 (m, 2H), 6.49 (d, *J* = 7.8 Hz, 1H), 5.30 (dt, *J* = 7.8, 5.0 Hz, 1H), 3.80 (ddd, *J* = 15.8, 11.2, 5.0 Hz, 2H), 2.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.8, 137.0, 133.9, 128.8, 128.0, 53.0, 47.3, 23.1; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{11}{}^{35}Cl_2NO+Na]^+$/$[C_{10}H_{11}{}^{35}Cl^{37}ClNO+Na]^+$/$[C_{10}H_{11}{}^{37}Cl_2NO+Na]^+$ 254.0115/256.0087/258.0061, found 254.0123/256.0110/258.0023.

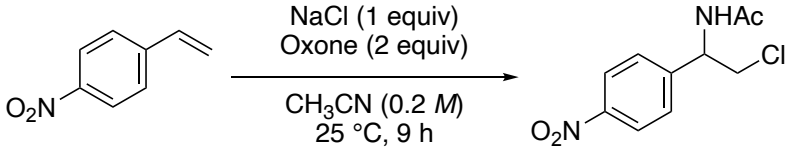


***N*-(1-(4-Bromophenyl)-2-chloroethyl)acetamide (2h):** 57% yield (0.0786 g, 0.284 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.36 (hexane–EtOAc = 1:1); **IR** (neat) 3052, 1651, 1535, 1491 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.52–7.48 (m, 2H), 7.21–7.18 (m, 2H), 6.06 (d, *J* = 6.4 Hz, 1H), 5.33 (dt, *J* = 6.4, 5.0 Hz, 1H), 3.85 (ddd, *J* = 17.4, 11.4, 5.0 Hz, 2H), 2.08 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.9, 137.5, 131.8, 128.4, 121.9, 53.2, 47.2, 23.1; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{12}{}^{79}Br^{35}ClNO+H]^+$/$[C_{10}H_{12}{}^{81}Br^{35}ClNO+H]^+$/$[C_{10}H_{12}{}^{81}Br^{37}ClNO+H]^+$ 275.9791/277.9769/279.9744, found 275.9790/277.9775/279.9742.



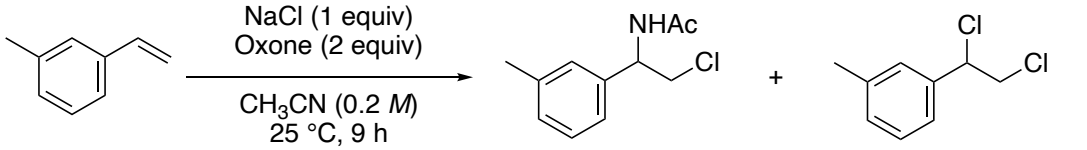
***N*-(2-Chloro-1-(4-(trifluoromethyl)phenyl)ethyl)acetamide (2i):** 91% yield (0.119 g, 0.451

mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 1:1); **IR** (neat) 3065, 1651, 1547, 1325 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.59 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 7.8 Hz, 1H), 5.36 (dt, J = 7.8, 6.6 Hz, 1H), 3.84–3.75 (m, 2H), 2.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.8, 142.6, 130.0 (q, $J_{C–F}$ = 32 Hz), 127.1, 125.6 (d, $J_{C–F}$ = 3.8 Hz), 123.8 (q, $J_{C–F}$ = 271 Hz), 53.5, 47.1, 23.0; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ –62.4.; **HRMS** (FAB+) m/z calcd for $[C_{11}H_{12}{}^{35}ClF_3NO+H]^+$/$[C_{11}H_{15}{}^{37}ClF_3NO+H]^+$ 266.0560/268.0533, found 266.0562/268.0526.



1j **2j:** >99% yield (^{1}H NMR), 90% yield

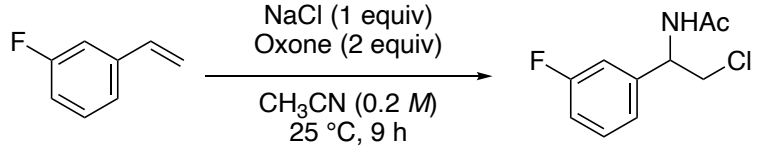
***N*-(2-Chloro-1-(4-nitrophenyl)ethyl)acetamide (2j):** 90% yield (0.110 g, 0.452 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). Yellow oil; **TLC**, R_f = 0.23 (hexane–EtOAc = 1:1); **IR** (neat) 3076, 1656, 1517, 1435 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.25–8.21 (m, 2H), 7.52–7.49 (m, 2H), 6.34 (d, J = 7.3 Hz, 1H), 5.50–5.46 (m, 1H), 3.90 (ddd, J = 21.5, 11.7, 4.6 Hz, 2H), 2.11 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.8, 147.6, 145.7, 127.7, 123.9, 52.9, 47.3, 23.2; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{11}{}^{35}ClN_2O_3+Na]^+$/$[C_{10}H_{11}{}^{37}ClN_2O_3+Na]^+$ 265.0356/267.0329, found 265.0360/267.0302.



1k **2k:** 59% yield (^{1}H NMR), 41% yield **3k:** 12% yield (^{1}H NMR)

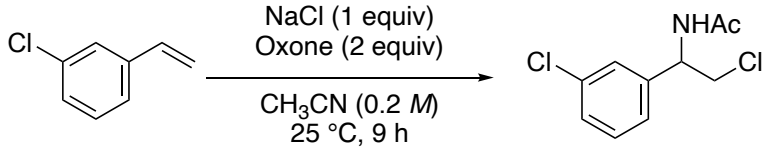
***N*-(2-Chloro-1-(*m*-tolyl)ethyl)acetamide (2k):** 41% yield (0.0438 g, 0.207 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 1:1); **IR** (neat) 3052, 1648, 1547, 1369 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.27–7.23 (m, 1H), 7.13–7.10 (m, 3H), 6.29 (brs, 1H), 5.29 (dt, J = 7.8, 5.5 Hz, 1H), 3.83 (dd, J = 5.5, 0.9 Hz, 2H), 2.35 (s, 3H), 2.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.6, 138.5, 138.3, 128.8, 128.6, 127.4, 123.6, 53.6, 47.5, 23.3, 21.4; **HRMS** (FAB+) m/z calcd for $[C_{11}H_{15}{}^{35}ClNO+H]^+$/$[C_{11}H_{15}{}^{37}ClNO+H]^+$ 212.0842/214.0815, found 212.0844/214.0821.

1-(1,2-Dichloroethyl)-3-methylbenzene (3k): Colorless oil; **TLC**, R_f = 0.56 (hexane–EtOAc = 20:1); **IR** (neat) 3406, 2950, 2925, 2862, 1638 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30–7.26 (m, 1H), 7.21–7.17 (m, 3H), 4.96 (dd, *J* = 8.1, 7.8 Hz, 1H), 4.01–3.90 (m, 2H), 2.38 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 138.6, 137.9, 129.9, 128.7, 128.0, 124.4, 61.9, 48.3, 21.4; **HRMS** (FAB+) m/z calcd for $[C_6H_9{}^{35}Cl_2]^+/[C_6H_9{}^{35}Cl^{37}Cl]^+/[C_6H_9{}^{37}Cl_2]^+$ 188.0160/190.0130/192.0101, found 188.0156/190.0135/192.0084.



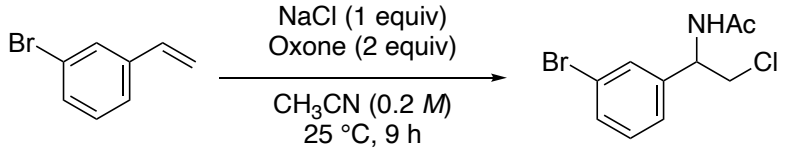
1l **2l:** 94% yield (^{1}H NMR)
92% yield

***N*-(2-Chloro-1-(3-fluorophenyl)ethyl)acetamide (2l):** 92% yield (0.0994 g, 0.461 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.21 (hexane–EtOAc = 1:1); **IR** (neat) 3059, 1648, 1547, 1443 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37–7.32 (m, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.04–6.99 (m, 2H), 6.09 (d, *J* = 6.0 Hz, 1H), 5.38 (dt, *J* = 6.0, 5.0 Hz, 1H), 3.87 (ddd, *J* = 17.0, 11.5, 5.0 Hz, 2H), 2.09 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.0, 162.8 (d, $J_{C–F}$ = 245 Hz), 141.1 (d, $J_{C–F}$ = 7.63 Hz), 130.2 (d, $J_{C–F}$ = 7.63 Hz), 122.4 (d, $J_{C–F}$ = 2.86 Hz), 114.9 (d, $J_{C–F}$ = 20.1 Hz), 113.6 (d, $J_{C–F}$ = 21.9 Hz), 53.3, 47.2, 23.0; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ –112.0; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{11}{}^{35}ClFNO+Na]^+/[C_{10}H_{11}{}^{37}ClFNO+Na]^+$ 238.0411/240.0384, found 238.0413/240.0351.



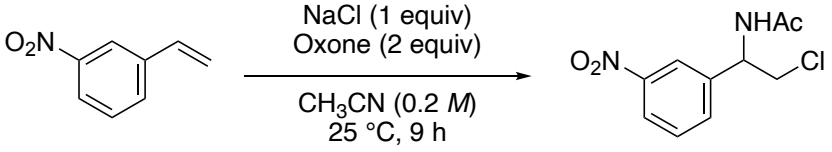
1m **2m:** 95% yield (^{1}H NMR)
95% yield

***N*-(2-Chloro-1-(3-chlorophenyl)ethyl)acetamide (2m):** 95% yield (0.110 g, 0.473 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.31 (hexane–EtOAc = 1:1); **IR** (neat) 3063, 1652, 1540, 1435 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.32–7.28 (m, 3H), 7.23–7.19 (m, 1H), 6.26 (d, *J* = 6.9 Hz, 1H), 5.34 (dt, *J* = 6.9, 5.0 Hz, 1H), 3.84 (ddd, *J* = 17.2, 11.5, 5.0 Hz, 2H), 2.08 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.0, 140.6, 134.5, 129.9, 128.1, 126.8, 125.0, 53.4, 47.1, 23.0; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{11}{}^{35}Cl_2NO+Na]^+/[C_{10}H_{11}{}^{35}Cl^{37}ClNO+Na]^+/[C_{10}H_{11}{}^{37}Cl_2NO+Na]^+$ 254.0115/256.0087/258.0061, found 254.0123/256.0130/258.0124.



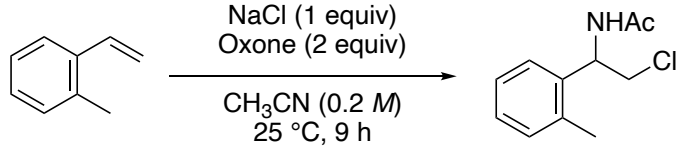
1n **2n:** >99% yield (^{1}H NMR)
92% yield

***N*-(1-(3-Bromophenyl)-2-chloroethyl)acetamide (2n):** 92% yield (0.1271 g, 0.460 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.38 (hexane–EtOAc = 1:1); **IR** (neat) 3052, 1647, 1538, 1426 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46–7.40 (m, 2H), 7.27–7.19 (m, 2H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.28 (dt, *J* = 7.8, 5.5 Hz, 1H), 3.77 (ddd, *J* = 16.3, 11.2, 5.5 Hz, 2H), 2.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.9, 140.8, 131.1, 130.2, 129.7, 125.5, 122.7, 53.2, 47.2, 23.1; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{12}{}^{79}Br^{35}ClNO+H]^+$/$[C_{10}H_{12}{}^{81}Br^{35}ClNO+H]^+$/$[C_{10}H_{12}{}^{81}Br^{37}ClNO+H]^+$ 275.9791/277.9769/279.9744, found 275.9799/277.9781/279.9770.



1o **2o:** >99% yield (^{1}H NMR)
93% yield

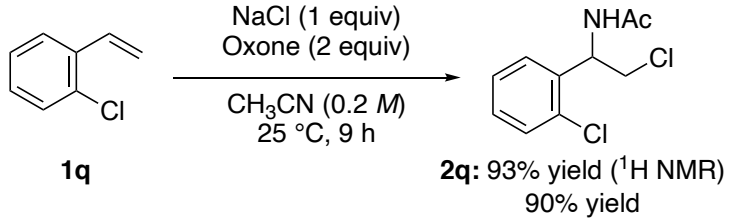
***N*-(2-Chloro-1-(3-nitrophenyl)ethyl)acetamide (2o):**[41] 93% yield (0.113 g, 0.466 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:2). White solid; **TLC**, R_f = 0.13 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.22 (d, *J* = 1.8 Hz, 1H), 8.16 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 8.2, 7.8 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 5.48 (dt, *J* = 7.8, 5.0 Hz, 1H), 3.86 (ddd, *J* = 17.4, 12.1, 5.0 Hz, 2H), 2.10 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.1, 148.3, 140.9, 133.3, 129.7, 123.0, 121.5, 53.1, 47.3, 23.1.



1p **2p:** 55% yield (^{1}H NMR)
50% yield

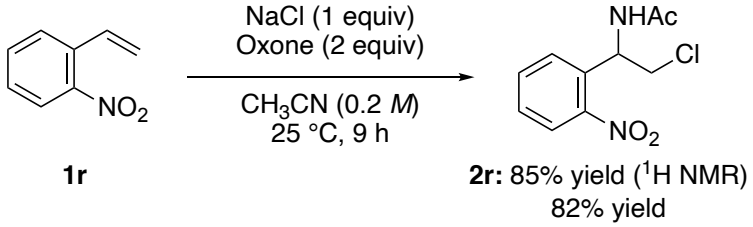
***N*-(2-Chloro-1-(*o*-tolyl)ethyl)acetamide (2p):**[41] 50% yield (0.531 g, 0.251 mmol). Several unidentified byproducts were also observed. This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30–7.19 (m, 4H), 5.97 (d, *J* = 6.0

Hz, 1H), 5.52 (dt, *J* = 6.0, 6.0 Hz, 1H), 3.80 (d, *J* = 6.0 Hz, 2H), 2.41 (s, 3H), 2.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.6, 136.7, 136.1, 130.8, 128.0, 126.2, 125.4, 50.4, 46.1, 23.1, 19.3.



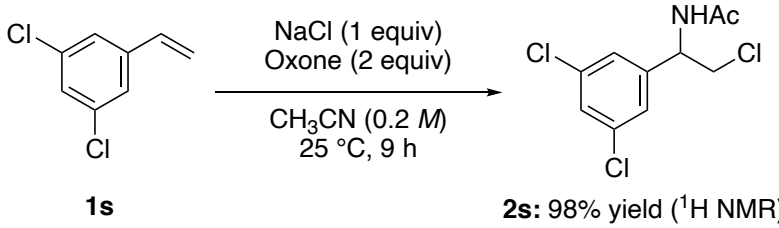
1q **2q:** 93% yield (^{1}H NMR)
90% yield

***N*-(2-Chloro-1-(2-chlorophenyl)ethyl)acetamide (2q):** 90% yield (0.105 g, 0.451 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 1:1); **IR** (neat) 3060, 1656, 1547, 1377 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.33 (m, 2H), 7.28–7.22 (m, 2H), 6.71 (brs, 1H), 5.69 (dt, *J* = 7.4, 5.5 Hz, 1H), 3.91–3.78 (m, 2H), 2.05 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.6, 135.8, 132.8, 130.0, 129.2, 128.2, 126.9, 51.5, 46.2, 23.1; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{12}{}^{35}Cl_2NO+H]^+$/$[C_{10}H_{12}{}^{35}Cl^{37}ClNO+H]^+$/$[C_{10}H_{12}{}^{37}Cl_2NO+H]^+$ 232.0296/234.0268/236.0241, found 232.0302/234.0287/236.0282.



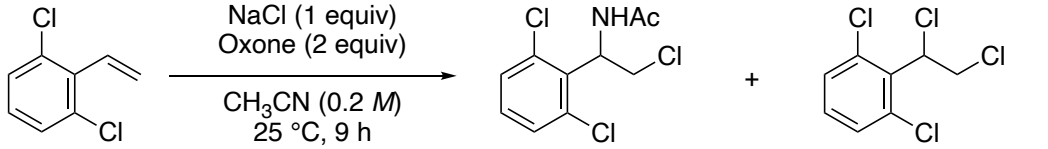
1r **2r:** 85% yield (^{1}H NMR)
82% yield

***N*-(2-Chloro-1-(2-nitrophenyl)ethyl)acetamide (2r):** 82% yield (0.908 g, 0.374 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:2). Yellow solid; **TLC**, R_f = 0.30 (hexane–EtOAc = 1:1); **IR** (neat) 3064, 1652, 1526, 1348, 727 cm^{-1} **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.02 (dd, *J* = 0.9, 7.4 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.48 (dt, *J* = 7.4, 1.4 Hz, 1H), 6.53 (brs, 1H), 5.34 (dt, *J* = 7.4, 5.0 Hz, 1H), 4.04–3.96 (m, 2H), 2.05 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.5, 148.3, 134.1, 133.5, 129.9, 129.0, 125.4, 50.8, 46.9, 23.1; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{11}{}^{35}ClN_2O_3+Na]^+$/$[C_{10}H_{11}{}^{37}ClN_2O_3+Na]^+$ 265.0356/267.0329, found 265.0349/267.0290.



1s **2s:** 98% yield (^{1}H NMR)
89% yield

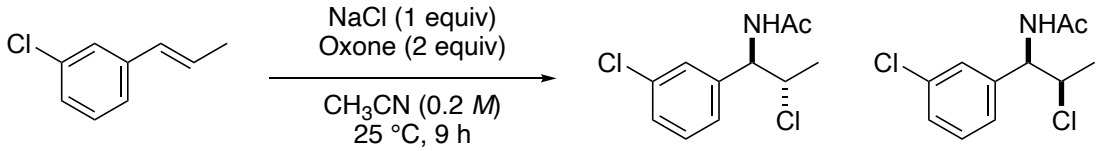
***N*-(2-Chloro-1-(3,5-dichlorophenyl)ethyl)acetamide (2s):** 89% yield (0.119 g, 0.446 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.52 (hexane–EtOAc = 1:1); **IR** (neat) 3431, 2077, 1751, 1649, 1568, 1430, 1218 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31 (t, *J* = 1.8 Hz, 1H), 7.20 (d, *J* = 1.8 Hz, 2H), 6.31 (d, *J* = 7.8 Hz, 1H), 5.32 (dt, *J* = 7.8, 4.6 Hz, 1H), 3.82 (ddd, *J* = 22.2, 11.5, 4.6 Hz, 2H), 2.09 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.0, 142.0, 135.3, 128.2, 125.3, 52.9, 47.2, 23.1; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{11}{}^{35}Cl_3NO+H]^+/[C_{10}H_{11}{}^{35}Cl_2{}^{37}ClNO+H]^+/[C_{10}H_{11}{}^{35}Cl^{37}Cl_2NO+H]^+$ 265.9906/267.9877/239.9847, found 265.9910/267.9890/269.9863.



1t **2t:** 90% yield (^{1}H NMR) 84% yield **3t:** 5% yield (^{1}H NMR)

***N*-(2-Chloro-1-(2,6-dichlorophenyl)ethyl)acetamide (2t):** 84% yield (0.112 g, 0.420 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.41 (hexane–EtOAc = 1:1); **IR** (neat) 3060, 1651, 1544, 1434, 769 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.33 (d, J = 8.0 Hz, 2H), 7.21–7.17 (m, 1H), 6.65 (brs, 1H), 6.24 (dt, *J* = 15.0, 7.0 Hz, 1H), 3.97–3.87 (m, 2H), 2.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.4, 133.2, 129.8, 129.5, 129.4, 51.3, 43.3, 23.2; **HRMS** (FAB+) m/z calcd for $[C_{10}H_{11}{}^{35}Cl_3NO+H]^+/[C_{10}H_{11}{}^{35}Cl_2{}^{37}ClNO+H]^+/[C_{10}H_{11}{}^{35}Cl^{37}Cl_2NO+H]^+$ 265.9906/267.9877/269.9847, found 265.9906/267.9903/269.9848.

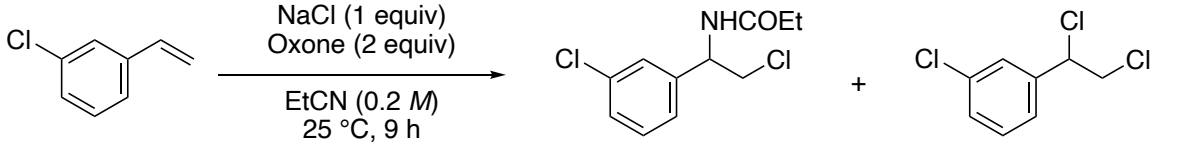
1,3-Dichloro-2-(1,2-dichloroethyl)benzene (3t): Colorless oil; **TLC**, R_f = 0.61 (hexane–EtOAc = 20:1); **IR** (neat) 3403, 2922, 2854, 1649, 1437 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38–7.35 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 5.97 (dd, J = 9.2, 6.9 Hz, 1H), 4.54 (dd, J = 11.5, 9.2 Hz, 1H), 4.16 (dd, J = 11.5, 6.9 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 132.0, 130.7, 130.4, 128.7, 55.8, 44.6; **HRMS** (FAB+) m/z calcd for $[C_8H_6{}^{35}Cl_4]^+/[C_8H_6{}^{35}Cl_3{}^{37}Cl]^+/[C_8H_6{}^{35}Cl_2{}^{37}Cl_2]$ 241.9224/243.9194/245.9165, found 241.9215/243.9188/245.9165.



(*E*)-**1u** **2u** **2u'**

2u+2u': 79% yield (^{1}H NMR)
67% yield
d.r. 84:16

***N*-(2-Chloro-1-(3-chlorophenyl)propyl)acetamide (2u):** Inseparable mixture of **2u**/**2u'** (84:16). 67% yield (0.313 g, 0.127 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). Colorless oil; **TLC**, R_f = 0.40 (hexane–EtOAc = 1:1); **IR** (neat) 3062, 1651, 1543, 1433 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz for **2u**) δ 7.35–7.16 (m, 4H), 6.35 (d, *J* = 8.0 Hz, 1H), 5.18 (dd, *J* = 8.0, 4.4 Hz, 1H), 4.46–4.37 (m, 1H), 2.05 (s, 3H), 1.38 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **2u**) δ 169.3, 138.9, 134.1, 129.5, 128.3, 126.7, 126.6, 60.3, 57.2, 23.2, 21.7; **^{1}H NMR** ($CDCl_3$, 400 MHz for **2u'**) δ 7.35–7.16 (m, 4H), 6.30 (d, *J* = 8.7 Hz, 1H), 5.27 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.40–4.34 (m, 1H), 2.13 (s, 3H), 1.59 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz for **2u'**) δ170.0, 141.6, 134.4, 129.8, 128.1, 127.9, 124.8, 61.6, 57.0, 23.2, 23.0; **HRMS** (FAB+) m/z calcd for $[C_{11}H_{13}{}^{35}Cl_2NO+Na]^+$/$[C_{11}H_{13}{}^{35}Cl^{37}ClNO+Na]^+$ 268.0272/270.0244/272.0213, found 268.0268/270.0267/272.0252.



1m

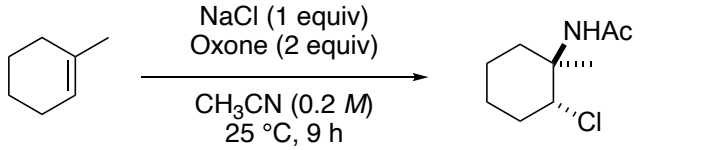
2v: 74% yield (^{1}H NMR)
71% yield

3m: 5% yield (^{1}H NMR)

***N*-(2-Chloro-1-(3-chlorophenyl)ethyl)propionamide (2v):** Propionitrile was used instead of acetonitrile. 71% yield (0.0879 g, 0.357 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:1). White solid; **TLC**, R_f = 0.40 (hexane–EtOAc = 1:1); **IR** (neat) 3300, 2975, 2875, 2069, 1645, 1543 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33–7.28 (m, 3H), 7.23–7.19 (m, 1H), 6.08 (brs, 1H), 5.36 (dt, *J* = 5.0, 7.8 Hz, 1H), 3.90–3.81 (m, 2H), 2.32 (q, *J* = 7.5 Hz, 2H), 1.20 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 173.4, 140.6, 134.6, 130.0, 128.2, 126.8, 124.9, 52.8, 47.5, 29.5, 9.7; **HRMS** (FAB+) m/z calcd for $[C_{11}H_{14}{}^{35}Cl_2NO+H]^+$/$[C_{11}H_{14}{}^{35}Cl^{37}ClNO+H]^+$/$[C_{11}H_{14}{}^{37}Cl_2NO+H]^+$ 246.0452/248.0423/250.0398, found 246.0458/248.0437/250.0383.

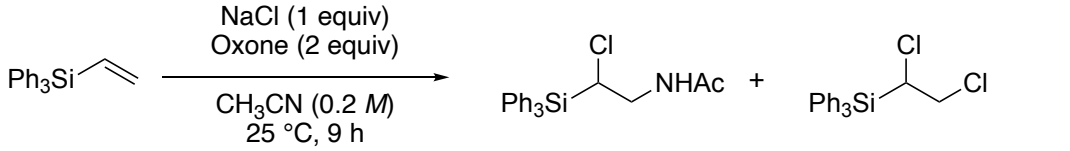
1,3-Dichloro-2-(1,2-dichloroethyl)benzene (3m): This compound was contained small amount of inpurity (~3%). Colorless oil; **TLC**, R_f = 0.65 (hexane–EtOAc = 20:1); **IR** (neat) 3437, 2953, 2069,

1642, 1477 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41 (s, 1H), 7.36–7.28 (m, 3H), 4.95 (dd, J = 8.3, 6.4 Hz, 1H), 3.98 (dd, J = 11.0, 6.4 Hz, 1H), 3.89 (11.0, 8.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 139.9, 134.7, 130.0, 129.3, 127.6, 125.8, 60.6, 48.0; **HRMS** (FAB+) m/z calcd for $[C_8H_6{}^{35}Cl_3]^+/[C_8H_6{}^{35}Cl_2{}^{37}Cl]^+$ 207.9613/209.9584/211.9554, found 207.9606/209.0783.



1w **2w:** 78% yield (^{1}H NMR)
73% yield
d.r. >20:1

***N*-(2-Chloro-1-methylcyclohexyl)acetamide (2w):**[41] 73% yield (0.0692 g, 0.365 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 1:2). White solid; **TLC**, R_f = 0.16 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.47 (brs, 1H), 4.80 (dd, *J* = 10.8, 4.1 Hz, 1H), 2.18–2.00 (m, 3H), 1.96 (s, 3H), 1.81–1.71 (m, 2H), 1.69–1.53 (m, 1H), 1.51–1.39 (m, 2H), 1.36 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.7, 64.4, 58.0, 35.2, 32.7, 24.8, 24.6, 21.8, 19.2.

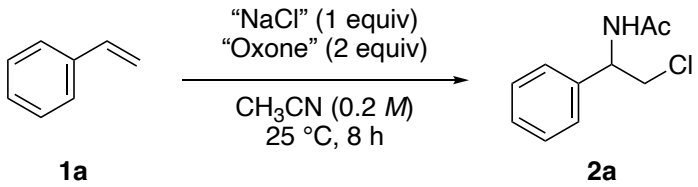


1x **2x:** 58% yield (^{1}H NMR) **3x:** 21% yield (^{1}H NMR)
58% yield

N-(2-Chloro-2-(triphenylsilyl)ethyl)acetamide (2x):[41] 58% yield (0.110 g, 0.289 mmol). This compound was purified by flash column chromatography on silica gel (E. Merck Art. 9385, eluent: hexane–EtOAc = 3:1). White solid; **TLC**, R_f = 0.53 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.65 (d, *J* = 6.4 Hz, 6H), 7.44–7.37 (m, 9H), 6.01 (brs, 1H), 4.33 (d, *J* = 10.6 Hz, 1H), 4.15 (dd, *J* = 14.7, 3.7 Hz, 1H), 3.31–3.25 (m, 1H), 1.86 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.2, 136.1, 131.4, 130.2, 128.1, 47.8, 43.3, 23.0.

(1,2-Dichloroethyl)triphenylsilane (3x): White solid; **TLC**, R_f = 0.72 (hexane–EtOAc = 9:1); **IR** (neat) 3437, 3070, 3048, 3006, 1656 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.64–7.61 (m, 6H), 7.50–7.43 (m, 3H), 7.41–7.39 (m, 6H), 4.25 (dd, *J* = 2.3, 11.9 Hz, 1H), 4.15 (dd, *J* = 2.3, 11.9 Hz, 1H), 3.83 (t, *J* = 11.9 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 136.0, 130.9, 130.5, 128.2, 49.5, 48.9; **HRMS** (FAB+) m/z calcd for $[C_{20}H_{18}{}^{35}Cl_2Si+Na]^+/[\ C_{20}H_{18}{}^{35}Cl_2Si+Na]^+$ 379.0453/381.0423, found 379.0458/381.0492.

Comparison of Commercial and Powdered Solid Reagents



1a **2a**

Powdered NaCl and powdered oxone[14] were prepared by grinding these commercial chemicals with mortar and pestle. To a stirring mixture of **1a** (TCI, 0.0575 mL, 0.500 mmol), NaCl (FUJIFILM Wako) or *powdered* NaCl (0.0292 g, 0.500 mmol) and 1,1,2,2-tetrachloroethane (TCI, 0.0525 mL, 0.500 mmol, as an internal standard) in acetonitrile (FUJIFILM Wako, 2.50 mL) was added oxone (Aldrich) or *powdered* oxone (0.307 g, 1.00 mmol) at 25 ℃. At the specified time, a part of the solution (ca. 0.05−0.075 mL) was transferred to an NMR tube, and then $CDCl_3$ (0.8 mL) was added. The yield of **2a** was determined by ^1H NMR analysis (400 MHz, $CDCl_3$).

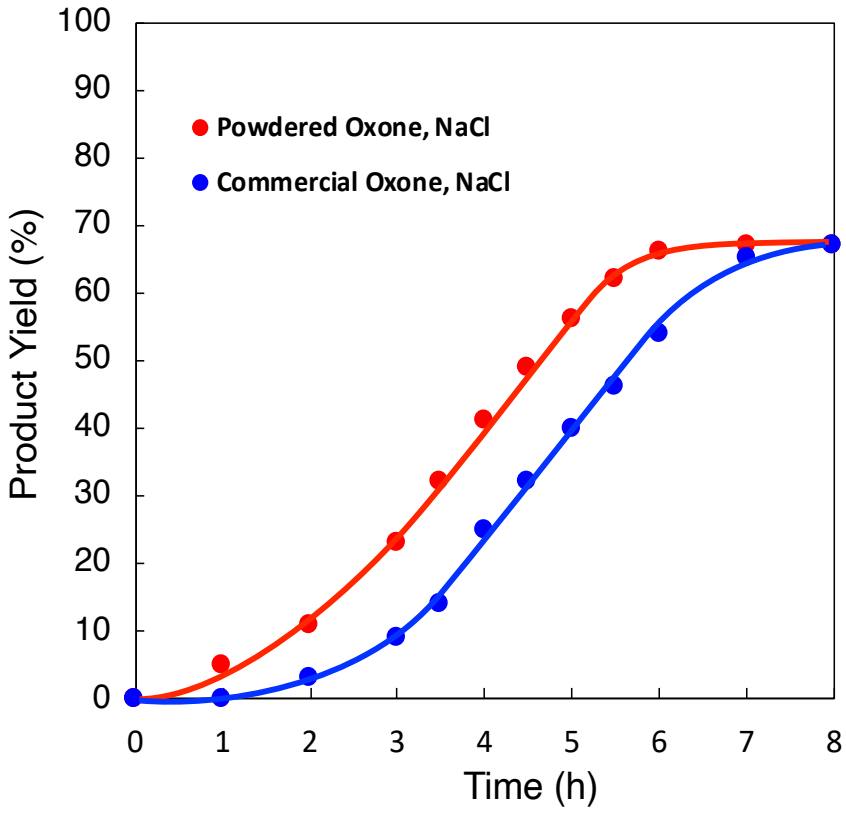
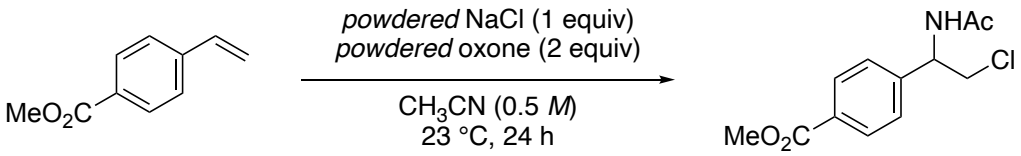


Figure S1. Comparison of commercial and powdered solid reagents.

Gram Scale Synthesis of 2c



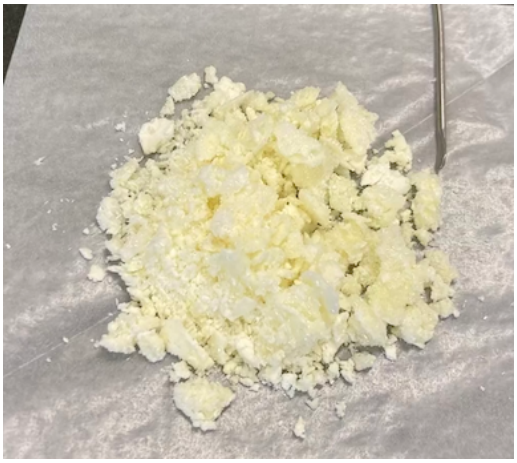
1c
(5.00 g, 30.8 mmol)

2c: 89% yield
(7.04 g, 27.5 mmol)

To a stirring mixture of **1c** (TCI, 5.00 g, 30.8 mmol), *powdered* NaCl (Wako, 1.80 g, 30.8 mmol) in acetonitrile (61.6 mL) was added *powdered* oxone (Aldrich, 18.9 g, 61.6 mmol) at 25 ℃. The reaction was monitored by ^{1}H NMR analysis. After stirring for 24 h, the resulting mixture was poured into saturated aqueous $Na_2S_2O_3$ (200 mL) at 0 ºC. The aqueous layers were separated and extracted with EtOAc (five times). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo.* The crude was purified by washing with Et_2O (50.0 mL) to give **2c** (7.04 g, 27.5 mmol) in 89% yield.

Reaction mixture (0 h)

Reaction mixture (24 h)



Isolated **2c**

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Research Achievement

Publication List

Chapter 2

1. High-Performance Ammonium Hypoiodite/Oxone Catalysis for Enantioselective Oxidative Dearomatization of Arenols
   Muhammet Uyanik, Takehiro Kato, Naoto Sahara, Outa Katade, Kazuaki Ishihara
   ACS Catal. **2019**, *9*, 11619–11626. DOI: 10.1021/acscatal.9b04322

Chapter 3

2. Oxidative Dearomative Coupling Reaction of Less-Reactive Arenols Using Hypohalite Catalysis
   Takehiro Kato, Naoto Sahara, Muhammet Uyanik, Kazuaki Ishihara
   Manuscript in preparation.

Chapter 4

3. Oxidative Ritter-type Chloroamidation of Alkenes Using NaCl and Oxone
   Takehiro Kato, Yuya Okada, Yuto Fujii, Muhammet Uyanik, Kazuaki Ishihara
   Asian J. Org. Chem. **2021**, *10*, 2907–2910. DOI: 10.1002/ajoc.202100575

Oral Presentations

4. “キラル次亜ヨウ素酸塩触媒を用いるエナンチオ選択的脱芳香族型スピロラクトン化反応”
   加藤丈裕; 佐原直登; UYANIK Muhammet; 石原一彰
   日本化学会第 98 春季年会、3H5-20、千葉、2018 年 3 月

5. “高活性次亜ハロゲン酸塩触媒を用いるフェノールのエナンチオ選択的酸化的脱芳香族化反応”
   加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
   日本化学会第 99 春季年会、3F1-42、兵庫、2019 年 3 月

6. “高活性キラル次亜ヨウ素酸塩触媒を用いるアレノールのエナンチオ選択的酸化的脱芳香族化反応”
   加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
   日本化学会第 100 春季年会、3B4-09、千葉、 2020 年 3 月

7. “Oxidative Dearomatization of Arenols Using High-performance Hypohalite Catalysis”
   Takehiro Kato; Muhammet Uyanik; Kazuaki Ishihara
   日本化学会第 101 春季年会、A20-1m-01、オンライン、2020 年 3 月

8. “Enantioselective Oxidative Dearomatization of Arenols Using High-performance Hypohalite Catalysis”
   Takehiro Kato; Muhammet Uyanik; Kazuaki Ishihara

日本化学会第 102 春季年会、K307-1pm-04、オンライン、2022 年 3 月

9. “高活性次亜ハロゲン酸塩触媒を用いるアレノールのエナンチオ選択的酸化的脱芳香族化反応”
加藤　丈裕; ウヤヌクムハメット; 石原　一彰
第 53 回中部化学関係学協会支部連合秋季大会、2D02、愛知、2022 年 11 月

10. “Oxidative Dearomative Coupling Reaction of Arenols Using Hypohalite Catalysis”
Takehiro Kato; Muhammet Uyanik; Kazuaki Ishihara
日本化学会第 103 春季年会、K705-1pm-05、千葉、2023 年 3 月

Poster Presentations

11. “キラル次亜ヨウ素酸塩触媒を用いるフェノール類のエナンチオ選択的脱芳香族型スピロラクトン化反応”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
第５１回有機金属若手の会　夏の学校、1P-23、京都、2018 年 7 月

12. “キラル次亜ヨウ素酸塩触媒を用いるフェノール類のエナンチオ選択的脱芳香族型スピロラクトン化反応”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
日本化学会秋季事業第８回 CSJ 化学フェスタ、P3-033、東京、2018 年 10 月

13. “高活性次亜ハロゲン酸塩触媒を用いるフェノールのエナンチオ選択的酸化的脱芳香族型反応”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
ITbM/IGER Chemistry Workshop 2018、P9、愛知、2018 年 12 月

14. “高活性次亜ハロゲン酸塩触媒を用いるフェノールのエナンチオ選択的酸化的脱芳香族化反応”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
GTR キックオフミーティング、P101、愛知、2019 年 1 月

15. “高活性次亜ハロゲン酸塩触媒を用いるフェノール類のエナンチオ選択的酸化的脱芳香族化反応”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
GTR リトリート合宿「異分野融合に向けた研究会」、P-63、三重、2019 年 6 月

16. “高活性次亜ハロゲン酸塩触媒を用いるフェノール類のエナンチオ選択的酸化的脱芳香族化反応”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
第 52 回有機金属若手の会　夏の学校、1P-34、岡山、2019 年 6 月

17. “高活性次亜ハロゲン酸塩触媒を用いたフェノール類のエナンチオ選択的酸化的脱芳

香族化反応”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
第 36 回有機合成化学セミナー、P-05、岐阜、2019 年 9 月

18. “高活性次亜ハロゲン酸塩触媒を用いるフェノールのエナンチオ選択的酸化的脱芳香族化反応”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 石原一彰
第 50 回中部化学関係学協会支部連合秋季大会、2P05、長野、2019 年 11 月

19. “High-Performance Hypohalite Catalysis for Enantioselective Oxidative Dearomatization of Arenols”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 長谷川淳也; 石原一彰
GTR Annual Meeting 2019、P-201、愛知、 2020 年 1 月

20. “High-Performance Hypohalite Catalysis for Enantioselective Oxidative Dearomatization of Arenols”
加藤丈裕; 佐原直登; ウヤヌクムハメット; 長谷川淳也; 石原一彰
GTR Annual Meeting 2020、P-201、オンライン、2021 年 1 月

21. “高活性次亜ハロゲン酸塩触媒を用いるアレノールの酸化的脱芳香族化反応”
加藤丈裕; ウヤヌクムハメット; 石原一彰
第 24 回ヨウ素学会シンポジウム、P12、オンライン、2021 年 9 月

22. “高活性次亜ハロゲン酸塩触媒を用いるアレノールの酸化的脱芳香族化反応”
加藤丈裕; ウヤヌクムハメット; 石原一彰
第 37 回有機合成化学セミナー、P12、オンライン、2021 年 9 月

23. “High-Performance Hypohalite Catalysis for Enantioselective Oxidative Dearomatization of Arenols”
加藤丈裕; ウヤヌクムハメット; 長谷川淳也; 石原一彰
GTR Annual Meeting 2021、P-101、オンライン、2022 年 1 月

Awards

1. 日本化学会秋季事業第 8 回 CSJ 化学フェスタ 2018 優秀ポスター賞 (2018 年 11 月 14 日)
2. 第 50 回中部化学関係学協会支部連合秋季大会 優秀賞 (2019 年 11 月 22 日)
3. 2019 年度 GTR 成果報告会 優秀ポスター賞（2020 年 1 月 9 日）
4. GTR プログラム・リトリート 2020「異分野融合研究提案コンテスト」第一位表彰（2020 年 9 月 25 日）
5. 第 24 回ヨウ素学会シンポジウム 優秀ポスター賞（2021 年 9 月 10 日）
6. 第 37 回有機合成化学セミナー 最優秀ポスター賞［Bulletin of Chemical Society of Japan 賞］（2021 年 9 月 25-27 日）
7. GTR Poster Award (2022 年 1 月 7 日）
8. 第 53 回中部化学関係学協会支部連合秋季大会 VIP 賞 (2022 年 11 月 24 日）

Acknowledgement

I would like to express my grateful acknowledgment to my supervisors, Professor Dr. Kazuaki Ishihara and Associate Professor Dr. 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 Dr. Manabu Hatano (Kobe Pharmaceutical University), Dr. Takahiro Horibe and Assistant Professor Dr. Shuhei Ohmurafor their practical and fruitful discussions. I especially thank Dr. Naoto Sahara and Mr. Outa Katade for their assistance during the initial investigation of the research. I also thank Yuya Okada, Soki Ihara, Yuto Fujii, Shunki Matsuyama, Yaohan Liang and Takaharu Morino for collaborative research. It is pleasant to express my appreciation to the former and present colleagues, especially Lu Yao, Katsuya Yamakawa, Lu Yanhui, Tastuhiro Sakamoto, Kohei Nishioka, Takuya Mochizuki, Yasutaka Tsuji, Kazuki Nishimura, and Hiroki Tanaka, Mrs. Keita Nakagawa, Masato Sakakibara, Kosuke Nishio, Rin Hiramatsu, Ryutaro Kondo, Kohei Toh, Shotaro Yasukochi, Takashi Hazeyama, Ng Ji Qi, Weiwei Guo, Kei Katagiri, Hiroyuki Hayashi, Shinichi Ishizaki, Toshihiro Yasui, Tatsuya Ishikawa, Hiro Arima, Jianhao Huang, Xue Zhao, Kai Matsui, Kazuki Takeda, Sachiko Kumagai, Haruna Kato, Yasuo Tsukimori, Shogo, Yamamoto, Kosuke Nomura, Qianchun Huang, Keigo Nagami, Shunsuke Minabe, Yanghao Zhang, Hayato Akao, Kotaro Asada, Mayu Urata, Chie Joko, Chengyi Shan and all of my colleagues in Ishihara group. I also would like to express my gratitude to Michiko Yoshimura for her dedicated support in administrative work.

I would like to express special thanks to Professors Drs. Takashi Ooi, Toshio Nishikawa, Yoshihiko Yamamoto and Jun-ya Hasegawa for serving on my discussion committee.

I am very grateful to the Fellowships from the Program for “GraduateProgram of Transformative Chem-Bio Research” in Nagoya University, supported by MEXT (WISEprogram), JST SPRING and HOSHIZAKI Scholarship.

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 2023

Takehiro Kato