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Bimolecular Coupling Reactions through Oxidatively Generated Aromatic Cations: Scope and Stereocontrol

Yubo Cui, Louis A. Villafane, Dane J. Clausen, and Paul E. Floreancig

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, Telephone: (+1)412-62408727

Paul E. Floreancig: florean@pitt.edu

Abstract

Chromenes, isochromenes, and benzoxathioles react with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to form stable aromatic cations that react with a range of nucleophiles. These oxidative fragment coupling reactions provide rapid access to structurally diverse heterocycles. Conducting the reactions in the presence of a chiral Brønsted acid results in the formation of an asymmetric ion pair that can provide enantiomerically enriched products in a rare example of a stereoselective process resulting from the generation of a chiral electrophile through oxidative carbon–hydrogen bond cleavage.

Keywords

oxidation; fragment coupling; heterocycles; chiral counterions; enantioselectivity

1. Introduction

Efficient fragment-coupling reactions expedite the preparation of structurally diverse compound collections. Cross-coupling reactions have proven to be exceedingly valuable in this regard and are now an invaluable component in the synthesis of medicinal agents and subunits that can be employed in fragment-based screening assays.¹ The latter protocol generally requires the preparation of libraries of low molecular weight compounds that are rich in heteroatoms. Further diversification would be accessible through the incorporation of stereocenters into these collections.² Access to these libraries would be facilitated by the development of new coupling reactions that are broad in scope and allow for structural variability while generating one or more stereocenters.

Fragment-coupling through oxidative carbon–hydrogen bond cleavage is emerging as a useful approach for rapidly accessing diverse structures.³ These transformations proceed through the formation of stabilized carbocations via pathways that are initiated by single electron oxidation or hydrogen atom abstraction. Tetrahydroisoquinoline derivatives have served as the substrates for a significant number of these methods due to the facility by

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Correspondence to: Paul E. Floreancig, florean@pitt.edu.

Supporting Information

Spectra for all new compounds and HPLC traces to determine enantiomeric excess can be found in the Supporting Information.

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which the intermediate iminium ion can be accessed.⁴ Oxygen-containing heterocycles can also engage in oxidative fragment-coupling reactions,⁵ though the processes often require forcing conditions or the incorporation of electron-donating groups into the structure.

We have developed a number of cyclization reactions that proceed through oxidative carbon–hydrogen bond cleavage by employing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant.⁶ DDQ is an easily handled reagent that tolerates a wide range of solvents and can be used as a catalyst in the presence of a range of terminal oxidants.⁷ Our mechanistic studies for DDQ-mediated oxocarbenium ion formation from allylic and benzylic ethers⁸ implicate a reaction pathway that proceeds through an electron transfer to form a radical cation intermediate followed by a hydrogen atom abstraction. The rate of oxocarbenium ion formation is thus dictated by the oxidation potential, which controls the radical cation concentration, and the stability of the resulting carbocation, which controls the rate of hydrogen atom abstraction. Substrates with low oxidation potentials that can generate stable carbocations react quite quickly under these conditions, but the presence of a rapid nucleophilic addition is required to drive the reaction forward since cation formation is reversible and usually thermodynamically disfavored.

Utilizing DDQ-mediated oxidative carbon–hydrogen bond cleavage as a prelude to bimolecular coupling reactions requires the intermediacy of a highly stabilized carbocation to balance the diminished rates of addition by an untethered nucleophile. This led us to explore aromaticity as a stabilizing factor for cations. Herein we describe the use of chromenes, isochromenes, and benzoxathioles as precursors to aromatic cations that can react with a range of nucleophiles.⁹ The high stability of the intermediates leads to the need for a catalyst to promote the coupling. We report that the use of chiral phosphoric acids as catalysts can promote asymmetric induction in the coupling step to provide enantiomerically enriched products. This constitutes a rare example of asymmetric, oxidative fragment coupling through a chiral electrophilic intermediate.

2. Results and Discussion

2*H*-Chromene (**1**, Scheme 1) served as our initial substrate for the development of oxidative bimolecular coupling reactions. This structure has a low oxidation potential due to the electron-rich aromatic ring, thereby assuring access to radical cation intermediate **2** in the presence of a mild oxidant like DDQ. Subsequent hydrogen atom abstraction provides aromatic cation **3** that should be suitable for nucleophilic additions. Similarly, 1*H*-isochromene (**4**) should also be a suitable substrate for the oxidative formation of cation **5**.

The project commenced with the coupling of **1** with allyl trimethylsilane. The oxidation of **1** with DDQ proceeded rapidly (< 30 min) in a number of solvents of varying polarity, ranging from dichloromethane to nitromethane. Molecular sieves were added because the intermediate cation reacts quite rapidly with adventitious water to yield alcohol and ether products. Allyl trimethylsilane reacts with the intermediate cation, but the reaction proceeds more efficiently in the presence of LiClO₄. This suggests that the intermediate that forms upon oxidation is not the oxocarbenium ion and is most likely mixed acetal **6**. The addition of LiClO₄ promotes the breakdown of this intermediate to form ion pair **7**,¹⁰ which reacts with the nucleophile to yield **8**. The addition proceeded when the nucleophile was added after the initial alkylation was complete rather than before the addition of DDQ. This “cation pool” approach¹¹ to the coupling is useful because it allows for the addition of nucleophiles that might be oxidized in preference to the substrate. Optimal yields of 74% were observed when the reaction was conducted in CH₃CN. Isochromene **4** underwent oxidation significantly more rapidly. Complete starting material disappearance was observed instantaneously at –30 °C. The intermediate electrophile, however, reacted inefficiently with

allyl trimethylsilane in CH₃CN. These results indicated that cation **5** is much more stable than cation **3**. Therefore we conducted the reaction in CH₂Cl₂ to destabilize the cation and utilized the more nucleophilic¹² allyl tributyltin in to form **9** in 79% yield. The rapid oxidation of **4** highlights the utility of proceeding through aromatic cation intermediates, since related dihydroisocoumarin structures require elevated temperatures and/or prolonged reaction times for complete reaction.^{5d}

Considerable substitution was tolerated on the substrates, as shown in Table 1. The chromene derivatives were prepared through gold-mediated Friedel-Crafts cyclizations¹³ of aryl propargyl ethers or by ring closing metathesis reactions of allylic ethers of substituted *o*-hydroxystyrenes. Electron-rich chromenes **10** and **12** (entries 1 and 2) proceeded through the oxidation step smoothly but the intermediate cations were somewhat less reactive than the cation that was derived from **1**. Electron poor chromene **14** (entry 3) required heating to 75 °C to effect oxidation but the intermediate cation reacted smoothly to provide **15** in 92% yield. Substitution on the pyran subunit is also tolerated. Methyl substituted chromene **16** (entry 4) reacted in a similar manner to **1** to yield **17**. Silyl-substituted chromene **17** (entry 5) required 2 h to complete the oxidation step but reacted with the nucleophile smoothly to yield **19**. Substituted isochromenes are not as readily accessible as substituted chromenes, but chloroisochromene **20** (entry 6) could be prepared through a known protocol.¹⁴ This compound required slightly higher temperatures than **4** for the oxidation step but the intermediate cation reacted smoothly with allyl tributyltin to yield **21**.

These reactions proved to be important in defining the roles of various structural features on the rates of oxidation and nucleophilic addition. Electron-donating groups facilitate carbocation formation but inhibit nucleophilic addition by stabilizing the intermediate cation. Electron-withdrawing groups slow cation formation but facilitate subsequent nucleophilic additions by destabilizing the intermediate carbocation. Forming cationic intermediates that contain electron-withdrawing groups again highlights the capacity of aromatic intermediates to facilitate oxidative carbon–hydrogen bond cleavage. The significant steric bulk of the phenyl dimethylsilyl group slows the oxidation by inhibiting the approach of DDQ,¹⁵ but the cation reacts in an expected manner. The silyl and chloro groups provide an additional handle for functionalizing these structures following the oxidative coupling reactions.

Various nucleophiles can also be used in these processes. A summary of representative transformations is shown in Table 2. (*E*)-Substituted allylsilane **22** (entry 1) adds with excellent diastereocontrol to form branched product **23**. Enolsilane **24** (entry 2) adds efficiently, though with negligible stereocontrol, to form ketone **25**. Potassium vinyltrifluoroborate **26** (entry 3) and alkynyl trifluoroborate **28** (entry 4) add to form alkenyl- and alkynyl-substituted chromenes **27** and **29**, respectively. Potassium phenyltrifluoroborate (**30**) does not add to the parent cation (entry 5), but adds at 70 °C to the electron deficient cation derived from **14** in moderate yield (entry 6).^{16,17}

The successful completion of this phase of the project led us to consider other aromatic cation intermediates that could be accessed through carbon–hydrogen bond cleavage. Cationic aromatic five-membered rings can, in principle, be prepared from precursors that contain two heteroatoms (Scheme 3). Nucleophilic addition into these intermediates would provide heteroatom-rich products that are difficult to access through conventional protocols. For example direct condensation reactions between *o*-disubstituted benzene derivatives and aldehydes often fails because of the kinetically disfavored cyclization step,¹⁸ and Kwon's elegant phosphine-mediated protocol¹⁹ requires the use of electron-deficient allenes.

This investigation was initiated (Scheme 4) through the oxidation of benzo[*d*][1,3]oxathiole (**32**) followed by quenching with allyl tributyltin to yield **33**. Extensive parameter screening revealed that non-polar solvents provided the best yields for these reactions, with 1,2-dichloroethane being optimal. The addition of LiClO₄ significantly facilitated the addition and was most effective when added in excess (1.5 equiv). A 90% yield of **33** was obtained under these conditions. Benzo[*d*][1,3]dioxole (**34**) was inert toward these reaction conditions despite having the capacity to form an aromatic cation. This suggests that the intermediate radical cation intermediate is localized on the aromatic ring in the benzodioxole structure and delocalizes onto the sulfur in the benzoxathiole structure. Localizing spin density onto sulfur weakens the adjacent carbon–hydrogen bond and allows for hydrogen abstraction.

Many of the nucleophiles that successfully add to the chromene-derived cations add to the benzoxathiole-derived cations, as shown in Table 3. Allyl trimethylsilane adds with only slightly lower efficiency than allyl tributyltin (entry 1). Modest diastereocontrol is observed through the addition of substituted allylic silanes (entries 2 and 3), indicating that these reagents can marginally distinguish between oxygen and sulfur as they approach the electrophile. Alkynyl and vinyl trifluoroborates add smoothly (entries 4 and 5), but aromatic trifluoroborates are unreactive toward the parent compound (entry 6). Bromination of **32** provided **38**. The incorporation of bromine in the substrate inhibited the oxidation step at room temperature. The cation could be accessed through heating to 50 °C, and the resulting species was considerably more reactive than the parent system. An improved yield was observed with allyl trimethylsilane and potassium phenyl trifluoroborate added to form **39** in 30% yield (entry 7).

The products of these coupling reactions contain a hydrogen that could also undergo oxidative cleavage, thus allowing for additional bond formation (Scheme 5). This was confirmed in the chromene series by the oxidation of **40** to form spirocycle **41**. Spirocyclization was also observed through the oxidation of **42** to yield **43**, which is remarkably stable despite being at the ortho ester oxidation state. The synthesis of **43** from benzoxathiole **32** and allylsilane **44** could also be achieved directly by a double oxidation sequence. This transformation represents a unique approach to spiroannulation via consecutive carbon–hydrogen bond cleavage reactions.

Asymmetric additions into oxidatively generated carbocations are quite rare, and the few examples that exist in the literature employ chiral nucleophiles to achieve enantioselectivity.^{5f,20} We postulated that stereoselective additions into oxocarbenium ions could be accomplished through the oxidative formation of chiral ion pairs. This could be achieved (Scheme 6) by generating acetal intermediate **6** and promoting an ion exchange with a chiral acid rather than LiClO₄. The resulting chiral ion pair has the potential to engage in stereoselective nucleophilic addition reactions. Asymmetric additions through oxocarbenium ion intermediates have been promoted by chiral phosphoric acids²¹ and by chiral thioureas²² despite the absence of conventional hydrogen bonding sites. The association between the oxocarbenium ion and phosphoric acids has been attributed to C–H–X hydrogen bonds.²³ Thus we envisioned a transformation in which a chiral phosphoric acid is added to **6** to generate ion pair **45** followed by a nucleophilic addition reaction to yield enantiomerically enriched products.

The first step in this process was the identification of reaction conditions in which the non-stereoselective uncatalyzed nucleophilic addition reaction is suppressed. This was achieved by forming **6** from the reaction of **1** with DDQ, then monitoring its disappearance in the presence of allyl trimethylsilane but in the absence of LiClO₄. Complete consumption of the intermediate was observed with 1.5 h in CH₃CN and 2 h in CH₂Cl₂ at 0 °C. The reaction in toluene was considerably slower, however, requiring 12 h for consumption of the

intermediate. This indicated that an uncatalyzed background reaction leading to a racemic product would be suppressed in aromatic solvents.

These reactions were subsequently run in the presence binaphthol-based phosphoric and thiophosphoric acids **46–51**. The reactions were conducted by exposing chromene **1** to DDQ and the acid in toluene at 0 °C. The nucleophile was added upon consumption of the starting material (approximately 30 min). The enantiomeric ratios were determined by HPLC using a Lux Cellulose 3 column. These studies showed that triisopropylphenyl-substituted phosphoramidate **49**²⁴ was the optimal catalyst for this transformation (Table 4), providing (*R*)-**8** in 62% ee. The absolute stereochemistry was determined through independent synthesis (see below) and comparing optical rotations and HPLC retention times with the chiral stationary phase. The phosphoryl triflimide group proved to be superior to a phosphoric acid group, and thiophosphoric acids were inferior to phosphoric acids. Conducting the reaction with **49** in trifluorotoluene provided a further improvement in stereocontrol to yield (*R*)-**8** in 77% ee.

Additional allylation agents were screened for selectivity (Table 5). These reactions were conducted in PhCF₃ with 1 equivalent of catalyst **49** at 0 °C. Allyl phenyl dimethylsilane, a less reactive nucleophile²⁵ than allyl trimethylsilane, showed improved selectivity, providing (*R*)-**8** in 92% ee. Allyl tributyltin proved to be less selective (48% ee), but allyl triphenyltin provided (*R*)-**8** in 89% ee. These selectivities cannot be attributed solely to differences in nucleophilicity, since allyl triphenyltin is more nucleophilic than allyl trimethylsilane,²⁵ indicating that electrofuge sterics or aromatic interactions could also play a role in asymmetric induction.

Allyl triphenyltin and allyl phenyl dimethylsilane were selected for subsequent studies directed toward determining the impact of lowering the catalyst loading (Table 6). Reducing the catalyst loading to 20 mol% caused a drop in selectivity, with both nucleophiles showing an ee of 62%. Lowering the temperature to –25 °C, approaching the freezing point of PhCF₃, resulted in an increase in selectivity with allyl triphenyltin adding in 81% ee and 66% yield, and allyl phenyl dimethylsilane adding in 86% ee and 56% yield. Reducing the catalyst loading to 10 mol% led to the isolation of (*R*)-**8** in 68% ee and 66% yield from allyl triphenyltin, and 79% ee and 52% yield from allyl phenyl dimethylsilane. At 5% loading the selectivity drops further for allyl triphenyltin, resulting in a 31% ee. These reactions show that the background reaction can become competitive at lower catalyst loading but useful enantioselectivities with substoichiometric quantities of the acid. To the best of our knowledge this is the first report of useful enantioselectivities through the intermediacy of chiral in pairs that originate from an oxidative carbon–hydrogen bond cleavage reaction.

Compound **8** has not previously been prepared in enantiomerically pure form. Therefore assigning the absolute stereochemistry required an independent synthesis through a vetted sequence. This was achieved as shown in Scheme 7. *o*-Bromohydrocinnamic acid (**52**) was converted to homoallylic alcohol **53** through a three step sequence that utilized a Brown allylation reaction²⁶ to dictate a predictable stereochemical outcome. A palladium-mediated cyclization²⁷ followed by alkene hydrogenation provided **54** (observed [α]_D = +99.1).

Attempts to expand the scope of the process met with little success (Scheme 8). Replacing allyl phenyl dimethylsilane with methallyl phenyl dimethylsilane, for example, under our optimal conditions resulted in the isolation of **55** in 33% ee. The absolute stereochemistry that is designated in Scheme 7 was based on analogy and not through independent synthesis. Conducting the reaction with methoxy chromene **10** provided **11** in 6% ee. Reactions conducted in the absence of **48**, however, showed that the background reactions for both processes are quite fast. We postulate that the enhanced nucleophilicity of the methallyl

nucleophile in comparison to the allyl nucleophile creates the potential for reaction with intermediates related to **6** (Scheme 2). The electron donation from the methoxy group stabilizes the intermediate cation and weakens its interaction with the counterion.

3. Conclusions

We have demonstrated that DDQ-mediated carbon–hydrogen bond cleavage reactions are useful for preparing aromatic carbocations that react with a number of nucleophile classes to generate a range of heterocyclic products. The parent chromene and isochromene structures oxidize rapidly to form the intermediate cations, and electron-deficient analogs react under slightly more forcing conditions, thereby demonstrating that the generation of aromatic intermediates significantly facilitates oxidative carbon–hydrogen bond cleavage. Several nucleophilic classes react with the cations, including allyl silanes, allylstannanes, potassium vinyl and alkynyl trifluoroborates, and enolsilanes. Cations that are derived from electron-deficient substrates are highly reactive toward nucleophiles and can react with potassium aryl trifluoroborates.

This protocol also works for the preparation of 5-membered aromatic cations that contain two heteroatoms. This process requires one of the heteroatoms to harbor sufficient spin density to weaken the adjacent carbon–hydrogen bond sufficiently for cleavage. Sulfur is particularly effective at promoting oxidation, and a number of benzoxathiole derivatives can be accessed.

Mechanistic studies implicate the formation of a mixed acetal intermediate upon cation formation that ionizes in the presence of acid to generate the reactive intermediate. Chiral Brønsted acids can be used to generate ion pairs that react with nucleophiles to yield enantiomerically enriched products. While the scope of this process is still quite limited several important observations have been noted. The background reaction to form racemic products is a significant competitive process. This reaction can be slowed by conducting the reactions in a non-polar aromatic solvent (PhCF₃ is optimal) at low temperature. Selectivity is higher for weaker nucleophiles, indicating that stronger nucleophiles can react with the initially formed mixed acetal intermediate. Incorporating electron-donating groups into the substrate reduces selectivity through weakening the attraction in the ion pair. Despite these limitations we were able to conduct reactions with good enantiocontrol at reasonable catalyst loadings. These processes are, to the best of our knowledge, the first examples of enantioselective reactions with chiral electrophiles that arise from oxidative carbon–hydrogen bond cleavage.

4. Experimental section

4.1. General information

Proton (¹H NMR) and carbon (¹³C NMR) nuclear magnetic resonance spectra were recorded at 300, 400, or 500 MHz and 75, 100, or 125 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Tetramethylsilane (TMS) or the solvent peak was used as a reference value, for ¹H NMR: TMS (in CDCl₃) = 0.00 ppm, for ¹³C NMR: TMS (in CDCl₃) = 0.00. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH₂Cl₂ and then evaporating the CH₂Cl₂. Analytical TLC was performed on pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using 32–63 60 Å silica gel. Methylene chloride was distilled under N₂ from CaH₂. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were used as purchased for chromatography. Benzene was

dried with 4 Å molecular sieves. THF was distilled from sodium. Other reagents were obtained from commercial sources without further purification. All reactions were performed in oven or flame-dried glassware with magnetic stirring unless otherwise noted. Spectroscopic data and procedures for the preparation of compounds **8**, **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23**, **25**, **27**, **29**, **31**, and **41** have been reported elsewhere.⁹

4.2. Benzo[d][1,3]oxathiole (**32**)

Dibromomethane (5.01 mL, 59.4 mmol) and Adogen 464 (1.21 g, 2.77 mmol) were added to a flask of refluxing H₂O (15 mL). A solution of 2-mercaptophenol (5.0 g, 40 mmol) and NaOH (3.96 g, 99.1 mmol) in H₂O (18 mL) was added over 4.5 h. After the addition was complete the reaction mixture was stirred while refluxing for an additional 5 h. The solution cooled to room temperature, was poured into H₂O, and was extracted with EtOAc (5 × 25 mL). The organic layer was dried over MgSO₄, concentrated under reduced pressure, and purified via flash chromatography (SiO₂, 4:1 pentane:Et₂O) to yield **32** as a clear oil (2.91 g, 53% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.18 (dd, 1H, *J* = 10.0, 1.6 Hz), 7.00 (td, 1H, *J* = 10.0, 1.6 Hz), 6.88 (td, 1H, *J* = 10.0, 1.6 Hz), 6.83 (dd, 1H, *J* = 10.0, 1.2 Hz), 5.68 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 156.4, 126.2, 126.0, 122.7, 122.6, 110.6, 75.3; IR (neat) 3066, 2925, 2871, 1468, 1450, 1326, 1208, 744 cm⁻¹; HRMS (ESI): *m/z* calcd for C₇H₆O₇S [M]⁺ 138.0139, found 138.0136.

4.3. General procedure for oxidative coupling

To a solution of benzoxathiole (1.0 equiv) in DCE (0.1 M) were added LiClO₄ (1.5 equiv) and DDQ (1.2 equiv). The reaction mixture was stirred until complete starting material consumption was indicated by TLC analysis. The nucleophile (1.2 equiv) was added and the reaction is stirred until the consumption of the intermediate is complete (monitored via TLC). The mixture was concentrated and purified directly via flash chromatography.

4.4. 2-Allylbenzo[d][1,3]oxathiole (**33**)

The general procedure for oxidative coupling was followed using **32** (200 mg, 1.45 mmol), LiClO₄ (231 mg, 2.17 mmol), 4 Å MS (200 mg), DDQ (395 mg, 1.74 mmol), and DCE (14 mL). After 30 min the oxidation was complete and allyl tributyltin (0.67 mL, 2.17 mmol) was added. The reaction was stirred for 1 h, then was purified directly via flash chromatography (SiO₂, pentane) to give **33** as a clear oil (232 mg, 90% yield): δ ¹H NMR (400 MHz, CDCl₃) 7.12 (dd, 1H, *J* = 7.6, 1.2 Hz), 6.99 (td, 1H, *J* = 7.6, 1.2 Hz), 6.87 (td, 1H, *J* = 7.6, 0.8 Hz), 6.80 (dd, 1H, *J* = 8.0, 0.8 Hz), 6.09 (t, 1H, *J* = 6.4 Hz), 5.86 (ddt, 1H, *J* = 24.0, 10.0, 6.8 Hz), 5.23 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.19 (dd, 1H, *J* = 10.0, 1.2 Hz), 2.85–2.92 (m, 1H), 2.70–2.77 (m, 1H); ¹³C NMR δ (100 MHz, CDCl₃) 155.9, 132.1, 126.0, 125.8, 122.5, 122.3, 119.4, 110.5, 89.7, 41.7; IR (neat) 3074, 2978, 2973, 2903, 1463, 1213, 745 cm⁻¹; HRMS (ESI): *m/z* calcd for C₁₀H₁₀OS [M+H]⁺ 179.0486, found 179.0549.

4.5. 2-(Hept-1-en-3-yl)benzo[d][1,3]oxathiole (**35**)

The general procedure for oxidative coupling was followed using benzoxathiole **32** (100 mg, 0.723 mmol), LiClO₄ (116 mg, 1.09 mmol), 4 Å MS (103 mg), DDQ (196 mg, 0.868 mmol), and DCE (7 mL). The reaction mixture was stirred for 30 min, then (*E*)-hept-2-en-1-yltrimethylsilane (148 mg, 0.868 mmol) was added. The solution was stirred for 1 h, then was purified directly via flash chromatography (SiO₂, hexanes) to give **35** (3.1:1 dr) as a clear oil (122 mg, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.10 (dd, 1H, *J* = 7.6, 1.2 Hz), 6.97 (td, 1H, *J* = 7.6, 1.2 Hz), 6.84 (td, 1H, *J* = 7.6, 1.2 Hz), 6.77 (dd, 1H, *J* = 8.0, 0.8 Hz), 6.02 (d, 0.76H, *J* = 5.6 Hz), 5.99 (d, 0.26H, *J* = 6.8 Hz), 5.61–5.71 (m, 1H), 5.14–5.23 (m, 2H), 2.54–2.64 (m, 1H), 1.58–1.68 (m, 1H), 1.30–1.45 (m, 5H), 0.89 (t, 3H, *J* = 6.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 156.1, 136.9, 125.6, 122.1, 121.9, 121.8, 118.4, 110.0, 93.4,

50.3, 29.6, 29.1, 22.6, 14.0; IR (neat) 3073, 2956, 2929, 2859, 1577, 1464, 1209, 1119, 920, 743 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{19}\text{OS}$ $[\text{M}+\text{H}]^+$ 235.1078, found 235.1150.

4.6. 2-(Hept-1-en-3-yl)benzo[d][1,3]oxathiole (**35'**)

The general procedure for oxidative coupling was followed using benzoxathiole **32** (100 mg, 0.723 mmol), LiClO_4 (116 mg, 1.09 mmol), 4 Å MS (103 mg), DDQ (196 mg, 0.868 mmol), and DCE (7 mL). The reaction mixture was stirred for 30 min, then (*Z*)-hept-2-en-1-yltrimethylsilane (149 mg, 0.868 mmol) was added. The solution was stirred for 1 h and then purified directly via flash chromatography (SiO_2 , hexanes) to give **35'** (1:4.6 dr) as a clear oil (112 mg, 66% yield): ^1H NMR (400 MHz, CDCl_3) δ 7.10 (d, 1H, $J = 7.6$ Hz), 6.96 (t, 1H, $J = 7.6$ Hz), 6.84 (t, 1H, $J = 7.6$ Hz), 6.76 (d, 1H, $J = 8.0$ Hz), 6.01 (d, 0.18H, $J = 6.8$ Hz), 5.99 (d, 0.82H, $J = 6.8$ Hz), 5.62–5.72 (m, 1H), 5.14–5.24 (m, 2H), 2.60–2.72 (m, 1H), 1.24–1.43 (m, 6H), 0.90 (t, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 156.3, 136.6, 125.8, 125.6, 122.0, 121.8, 118.8, 110.0, 93.5, 50.5, 30.2, 29.1, 22.6, 14.0; IR (neat) 3073, 2956, 2929, 2859, 1762, 1577, 1464, 1209, 1119, 920, 743 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{19}\text{OS}$ $[\text{M}+\text{H}]^+$ 235.1078, found 235.1154.

4.7. (E)-2-(Dec-1-en-1-yl)benzo[d][1,3]oxathiole (**36**)

The general procedure for oxidative coupling was followed using benzoxathiole **32** (100 mg, 0.723 mmol), LiClO_4 (115 mg, 1.09 mmol), 4 Å MS (100 mg), DDQ (197 mg, 0.868 mmol), and DCE (7 mL). The reaction mixture was stirred for 30 min, then potassium (*E*)-dec-1-enyltrifluoroborate (214 mg, 0.868 mmol) was added. The solution was stirred for 1 h and then purified directly via flash chromatography (SiO_2 , hexanes) to give **36** as a clear oil (110 mg, 55% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.11 (dd, 1H, $J = 7.6, 1.2$ Hz), 6.98 (td, 1H, $J = 7.6, 1.2$ Hz), 6.86 (td, 1H, $J = 7.6, 1.2$ Hz), 6.80 (dd, 1H, $J = 8.0, 0.8$ Hz), 6.41 (d, 1H, $J = 7.2$ Hz), 5.81–5.96 (m, 2H), 2.09 (q, 2H, 6.0 Hz), 1.37–1.44 (m, 2H), 1.23–1.32 (m, 10H), 0.88 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 155.6, 136.6, 126.6, 126.2, 125.8, 122.3, 122.0, 110.2, 90.0, 31.9, 31.8, 29.4, 29.3, 29.2, 28.6, 22.7, 14.1; IR (neat) 3068, 2925, 2854, 1462, 1233, 1119, 1150, 1020, 960, 743 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{25}\text{OS}$ $[\text{M}+\text{H}]^+$ 277.1548, found 277.1602.

4.8. 2-(dec-1-yn-1-yl)benzo[d][1,3]oxathiole (**37**)

The general procedure for oxidative coupling was followed using **32** (200 mg, 1.45 mmol), LiClO_4 (231 mg, 2.17 mmol), 4 Å MS (200 mg), DDQ (395 mg, 1.74 mmol), and DCE (14 mL). The reaction mixture was stirred for 30 min, then the potassium alkynyl trifluoroborate (424 mg, 1.74 mmol) was added. The solution was stirred for 1 h and then was purified directly via flash chromatography (SiO_2 , pentane) to give **37** as a clear oil (258 mg, 65% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.13 (d, 1H, $J = 7.6$ Hz), 7.02 (t, 1H, $J = 7.6$ Hz), 6.90 (t, 1H, $J = 7.6$ Hz), 6.84 (d, 1H, $J = 8.0$ Hz), 6.54 (s, 1H), 2.27 (t, 2H, $J = 7.2$ Hz), 1.53 (t, 2H, $J = 7.6$), 1.36 (m, 2H), 1.26 (s, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.8, 126.3, 125.7, 122.9, 122.2, 111.0, 90.9, 76.6, 76.0, 32.0, 29.3, 29.2, 29.0, 28.3, 22.8, 19.1, 14.3; IR (neat) 3069, 2926, 2855, 2239, 1462, 1247, 962, 743 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{22}\text{OS}$ $[\text{M}]^+$ 274.1391, found 274.1374.

4.9. 5-Bromo-2-phenylbenzo[d][1,3]oxathiole (**39**)

The general procedure for oxidative coupling was followed using benzoxathiole **38** (100 mg, 0.461 mmol), LiClO_4 (74 mg, 0.69 mmol), 4 Å MS (103 mg), DDQ (126 mg, 0.553 mmol), and DCE (5 mL). The reaction mixture was stirred for 1 h at 50 °C, then was cooled to rt and potassium trifluorophenyl borate (102 mg, 0.553 mmol) was added. The reaction was stirred for 20 min and then was purified directly via flash chromatography (SiO_2 , hexanes) to give **39** as a clear oil (41 mg, 30% yield): ^1H NMR (400 MHz, CDCl_3) δ 7.79 (s, 2H),

7.63 (s, 2H), 7.48 (d, 2H, $J = 7.2$ Hz), 7.33 (dd, 1H, $J = 7.2, 1.2$ Hz), 6.94 (m, 1H), 5.93 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 154.9, 137.8, 129.7, 128.9, 128.8, 126.6, 124.8, 235.5, 225.4, 222.6, 91.2, 75.8; IR (neat) 3084, 2923, 2872, 1744, 1454, 1327, 1248, 1206, 1071, 999, 861, 740 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_9\text{BrOS}$ $[\text{M}]^+$ 291.9557, found 291.9540.

4.10. 4'-Methylene-4',5'-dihydro-3'H-spiro[benzo[d][1,3]oxathiole-2,2'-furan] (43)

To a solution of **42** (150 mg, 0.535 mmol) in DCE (5 mL) was added DDQ (292 mg, 1.28 mmol). The reaction mixture was stirred for 10 min and then was purified directly by flash chromatography (10% EtOAc in hexanes) to yield **43** as a colorless oil (91 mg, 82% yield): ^1H NMR (400 MHz, CDCl_3) δ 7.20 (d, 1H, $J = 7.6$ Hz), 7.05 (t, 1H, $J = 7.6$ Hz), 6.94 (t, 1H, $J = 7.6$ Hz), 6.90 (d, 1H, $J = 8.0$ Hz), 5.17 (t, 1H, $J = 2.4$ Hz), 5.07 (t, 1H, $J = 2.4$ Hz), 4.59–4.71 (m, 2H), 3.21–3.36 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.1, 142.7, 125.7, 124.7, 124.4, 122.5, 121.7, 110.6, 106.7, 72.1, 44.5; IR (neat) 3070, 2930, 2873, 1577, 1463, 1424, 1277, 1240, 1170, 1019, 960, 874, 745 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{11}\text{H}_{11}\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 207.0402, found 207.0472.

4.11. 4'-methylene-4',5'-dihydro-3'H-spiro[benzo[d][1,3]oxathiole-2,2'-furan] (43)

The general procedure for oxidative coupling was followed using benzoxathiole **32** (100 mg, 0.723 mmol), LiClO_4 (115 mg, 1.09 mmol), 4 Å MS (100 mg), DDQ (197 mg, 0.868 mmol), and DCE (7mL). The reaction mixture was stirred for 30 min, then nucleophile **44**²⁸ (188 mg, 0.868 mmol) was added. The solution was stirred for 1 h and then DDQ (199 mg, 0.876 mmol) was added. The reaction mixture was stirred for 20 min followed by a third addition of DDQ (101 mg, 0.438 mmol). The resulting solution was purified directly via flash chromatography (SiO_2 , 10% EtOAc in hexanes) to give **43** as a clear oil (55 mg, 36% yield). All data matched the product from the previously described stepwise protocol.

4.12. General protocol for asymmetric catalyst screening

To a solution of **1** (1.0 equiv) in a corresponding solvent (0.1 M concentration) at 0 °C were added powdered 4Å molecular sieves (60 mg/mL) and the corresponding catalyst (0.05 to 1 equiv). DDQ (1.4 equiv) was added to the reaction mixture, and it was stirred until TLC analysis showed complete consumption of the substrate. After cooling to the corresponding specified temperature, the nucleophile (2~3 equiv) was added, and the reaction was stirred until TLC analysis showed complete consumption of the oxidized intermediate. The reaction was quenched with 10% aqueous NaHCO_3 solution, extracted with diethyl ether, and carefully concentrated under reduced pressure. Flash column chromatography (3% Et_2O in pentane) afforded the desired product. An aliquot was taken and analyzed by chiral HPLC for enantiomeric excess.

4.13. Optimized catalytic protocol

The reaction was performed at -25 °C for 3 h, using **1** (41.5 mg, 0.32 mmol, 1.0 equiv), **29** (55.7 mg, 0.063 mmol, 20% equiv), 4Å molecular sieves powder (200 mg), DDQ (100 mg, 0.44 mmol, 1.4 equiv), allylphenyldimethylsilane (169 mg, 0.96 mmol, 3 equiv) and anhydrous $\text{1,1,1-trifluorotoluene}$ (3 mL). Normal workup and flash column chromatography (3% Et_2O in pentane) afforded the desired product (30 mg, 56%). The enantiomeric excess was determined to be 86% by chiral HPLC (1% *i*-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

4.14. Synthesis of 53

To a solution of **52** (2.29 g, 10.0 mmol) in methanol (20 mL) stirred at 0 °C, was added thionyl chloride (1.47 mL, 20.0 mmol) dropwise. The mixture was stirred overnight at rt.

The reaction was carefully quenched with saturated aqueous NaHCO₃ solution (10 mL), neutralized with powder NaHCO₃, and extracted with diethyl ether (3 × 20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (10% EtOAc in hexane afforded the desired ester (2.19 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.20–7.26 (m, 2H), 7.06 (dd, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 3.07 (t, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 172.7, 139.5, 132.7, 130.2, 127.9, 124.1, 51.4, 33.7, 31.2.

To the solution of the ester (1.22 g, 5.0 mmol) in dichloromethane (20 mL) at –78 °C, 1M DIBAL-H solution in hexanes (6 mL, 6.0 mmol) was added dropwise. The reaction was stirred at –78 °C for 1 hour, quenched with methanol (2 mL), and concentrated under reduced pressure. Flash column chromatography with 10% ethyl acetate in hexanes afforded the desired aldehyde (0.81 g, 76%). ¹H NMR (300 MHz, CDCl₃) δ 9.85 (d, *J* = 0.9 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.24–7.28 (m, 2H), 7.07–7.13 (m, 1H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 200.9, 139.6, 132.9, 130.4, 128.0, 127.6, 124.2, 43.6, 28.6.

To a solution of (+)-IPC-Cl (1.80 g, 5.6 mmol, 1.87 equiv) in diethyl ether (3 mL) stirred at 0 °C, freshly prepared 0.5 M allylmagnesium bromide solution in diethyl ether (10.5 mmol, 5.25 mmol, 1.75 equiv) was added dropwise over 20 min. The reaction was stirred at 0 °C for an additional 30 min, decanted, extracted two times with diethyl ether (5 mL), and concentrated under reduced pressure. The residual oil was dissolved in dry pentane (10 mL), filtered through Millex syringe filter, and added dropwise into a solution of the above aldehyde (640 mg, 3.0 mmol, 1.0 equiv) in diethyl ether (5 mL) at –100 °C over 45 min. The addition was in such a pattern that the allylmagnesium bromide solution touched the inner wall of the reaction flask before entering the solution. After one additional hour at –100 °C, the reaction was quenched with methanol (2 mL) and concentrated under reduced pressure. The residual oil was dissolved in THF (3 mL), cooled to 0 °C, and treated with saturated aqueous NaHCO₃ solution (7.0 mL) and 30% H₂O₂ (5.6 mL). After 3 hours at room temperature, the reaction mixture was extracted three times with diethyl ether (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash column chromatography with 15% ethyl acetate in hexanes afforded the chiral alcohol (510 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.1 Hz, 1H), 7.11–7.17 (m, 2H), 6.93–6.99 (m, 1H), 5.58–5.82 (m, 1H), 5.07 (d, *J* = 15.6 Hz, 1H), 5.06 (d, *J* = 11.7 Hz, 1H), 3.58–3.66 (m, 1H), 2.80–2.90 (m, 1H), 2.67–2.77 (m, 1H), 2.22–2.30 (m, 1H), 2.07–2.17 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 141.3, 134.5, 132.8, 130.4, 127.6, 127.4, 124.4, 118.3, 70.0, 41.9, 36.8, 32.4; IR (film) 3371, 3072, 2927, 1640, 1567, 1471, 1439, 1045, 1022, 994, 916, 749 cm⁻¹; HRMS (ESI) calc. for C₁₂H₁₅BrONa [M+Na]⁺: 277.0204, found 277.0197; [α]_D²⁵ = –9.7 (c = 2.56, CH₂Cl₂).

4.15. Synthesis of 54

A round bottom flask was charged with Pd(OAc)₂ (11.2 mg, 0.05 mmol, 5 mol%), (2-biphenyl)di-*tert*-butylphosphine (18.6 mg, 0.063 mmol, 6.3 mol%), and Cs₂CO₃ (652 mg, 2.0 mmol, 2.0 equiv). The flask was evacuated and backfilled with argon, and the above alcohol (255 mg, 1.0 mmol, 1.0 equiv) in toluene (2 mL) was added via syringe. The flask was then placed into an oil bath pre-heated at 65 °C and stirred overnight. The reaction mixture was then cooled to room temperature, quenched with water (10 mL), and extracted two times with diethyl ether (10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Flash column chromatography with 3% Et₂O/pentane afforded the chiral allyl ether (100 mg, 75%). ¹H NMR (300 MHz, CDCl₃) δ 7.07 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.80–6.86 (m, 2H), 5.86–6.00 (m, 1H), 5.10–5.20 (m, 2H), 4.02–4.09 (m, 1H), 2.71–2.85 (m, 2H), 2.54–2.61 (m, 1H), 2.37–2.45 (m, 1H), 1.98–2.06 (m, 1H), 1.70–1.79 (m, 1H).

A mixture of the above allyl chroman (83 mg, 0.62 mmol) and 10% Pd/C (20 mg) in dichloromethane (3 mL) was stirred under a hydrogen atmosphere for 4 h. Flash column chromatography (3% Et₂O/pentane) afforded the desired ether (67 mg, 81%). ¹H NMR (300 MHz, CDCl₃) δ 7.03–7.10 (m, 2H), 6.78–6.84 (m, 2H), 3.94–4.04 (m, 1H), 2.72–2.90 (m, 2H), 1.95–2.03 (m, 1H), 1.72–2.02 (m, 2H), 1.45–1.62 (m, 3H), 0.98 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.1, 129.5, 127.1, 122.1, 119.8, 116.7, 75.6, 37.6, 34.1, 27.4, 24.8, 22.3, 18.6, 14.1, 14.0; IR (film) 2957, 2872, 1582, 1488, 1457, 1302, 1232, 1119, 984, 885, 752 cm⁻¹; HRMS (EI) *m/z* calcd for C₁₂H₁₆O [M]⁺ 176.1201, found 176.1219; [α]_D²⁵ = +99.1 (*c* = 1.96, CH₂Cl₂).

4.16. Hydrogenation of **8**

A mixture of **8** (30 mg, 0.22 mmol, 74% ee by HPLC) and 10% Pd/C (10 mg) in dichloromethane (3 mL) was stirred under a hydrogen atmosphere for 4 h. Flash column chromatography (3% Et₂O in pentane) afforded hydrogenated chiral ether **53** (19.6 mg, 64%). [α]_D²⁵ = +73.0 (*c* = 1.96, CH₂Cl₂).

4.17. (R)-2-(2-methylallyl)-2H-benzopyran (**55**)

The reaction was performed at -25 °C for 3 h, using **1** (38 mg, 0.29 mmol, 1.0 equiv), **49** (50.9 mg, 0.058 mmol, 0.2 equiv), 4 Å molecular sieves (200 mg), DDQ (92 mg, 0.41 mmol, 1.4 equiv), methylallyl phenyldimethylsilane (162 mg, 0.87 mmol, 3 equiv), and anhydrous PhCF₃ (3 mL). Normal workup and flash column chromatography with 3% Et₂O/pentane afforded the desired product (36.4 mg, 68%). The enantiomeric excess was determined to be 33% by chiral HPLC (1% *i*-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.⁹ ¹H NMR (300 MHz, CD₂Cl₂) δ 7.12 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 6.98 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.85 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 9.9 Hz, 1H), 5.74 (dd, *J* = 9.9, 3.6 Hz, 1H), 4.96–5.03 (m, 1H), 4.89 (aps, 1H), 4.79 (d, *J* = 0.9 Hz, 1H), 2.56 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.35 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.82 (s, 3H); ¹³C NMR (75 MHz, CD₂Cl₂) δ 153.8, 142.2, 129.7, 127.0, 126.3, 124.4, 122.7, 121.6, 116.7, 113.6, 74.2, 43.8, 23.1; IR (film) 3075, 2936, 1640, 1606, 1486, 1457, 1229, 1208, 1113, 1055, 1034, 891, 767, 753 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₃H₁₃O [M - H]⁺ 185.0966, found 185.0971; [α]_D²⁵ = +55.7 (*c* = 2.51, CH₂Cl₂).

4.18. 2-Allyl-6-methoxy-2H-benzopyran (**11**)

The reaction was performed at -25 °C for 3 h, using **10** (48 mg, 0.30 mmol, 1.0 equiv), **49** (53 mg, 0.06 mmol, 0.2 equiv), 4 Å molecular sieves (200 mg), DDQ (95 mg, 0.42 mmol, 1.4 equiv), allylphenyldimethylsilane (158 mg, 0.9 mmol, 3 equiv) and PhCF₃ (3 mL). Normal workup and flash column chromatography (5% Et₂O in pentane) afforded the desired product (32.4 mg, 53%). The enantiomeric excess was determined to be 9% by chiral HPLC (1% *i*-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.⁹ ¹H NMR (400 MHz, CDCl₃) δ 6.72 (d, *J* = 8.4 Hz, 1H), 6.66 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.54 (d, *J* = 2.8 Hz, 1H), 6.38 (d, *J* = 9.6 Hz, 1H), 5.88 (ddt, *J* = 18.0, 10.4, 7.2 Hz, 1H), 5.74 (dd, *J* = 9.6, 3.2 Hz, 1H), 5.15 (d, *J* = 8.8 Hz, 1H), 5.12 (s, 1H), 4.84 (brs, 1H), 3.75 (s, 3H), 2.53–2.60 (m, 1H), 2.40–2.47 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 153.9, 147.1, 133.4, 126.1, 124.3, 122.5, 117.8, 116.5, 114.2, 111.6, 74.3, 55.6, 39.4. [α]_D²⁵ = -8.7 (*c* = 0.33, CH₂Cl₂).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

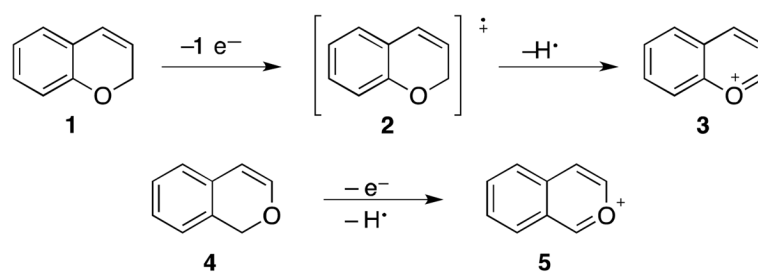
Acknowledgments

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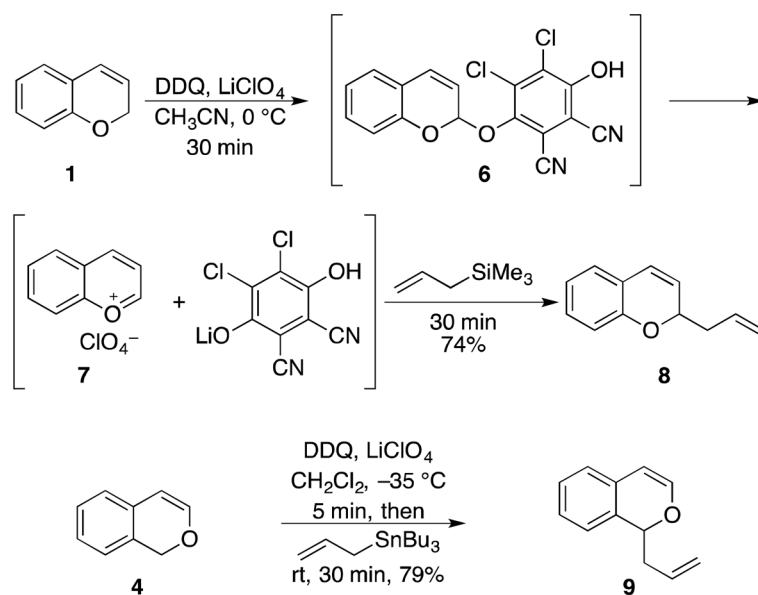
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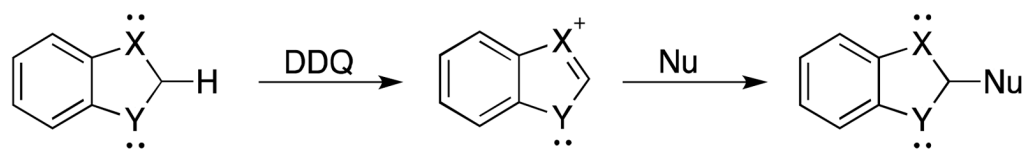
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**Scheme 1.**

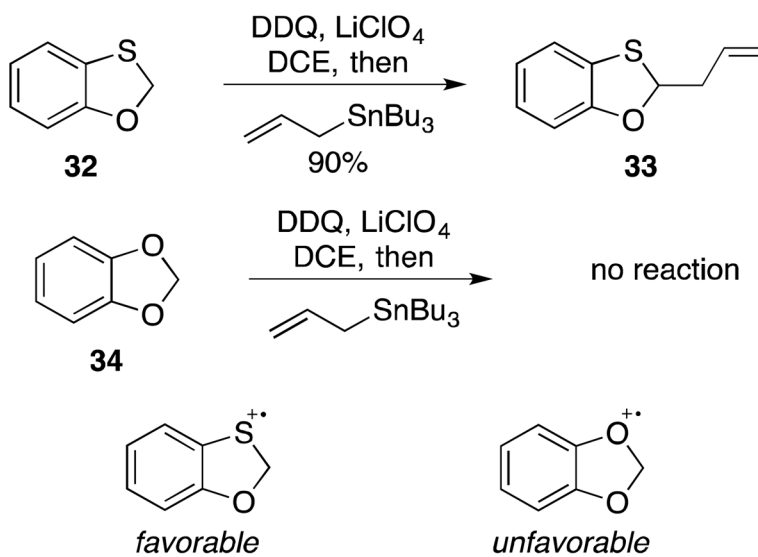
Aromatic cation formation through oxidative carbon–hydrogen bond cleavage.



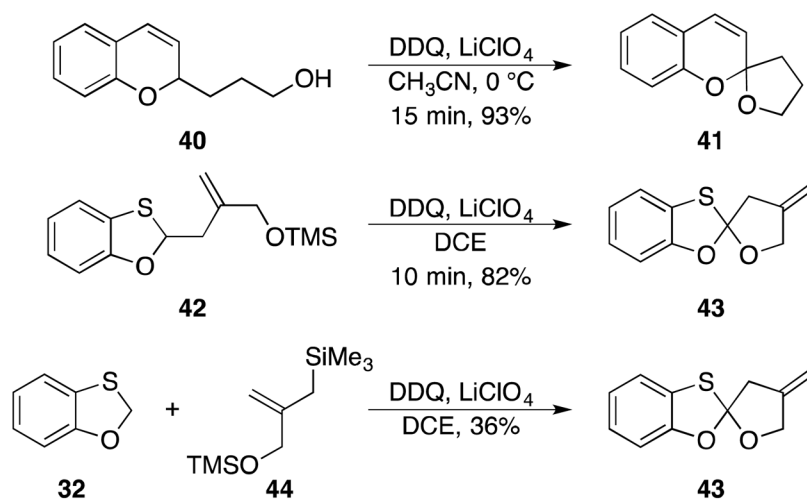
Scheme 2.
Oxidative allylation reactions.



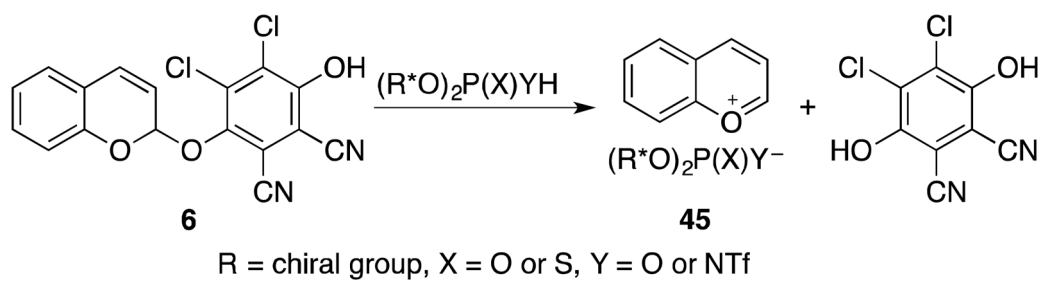
Scheme 3.
Substitution via aromatic 5-membered ring cations.



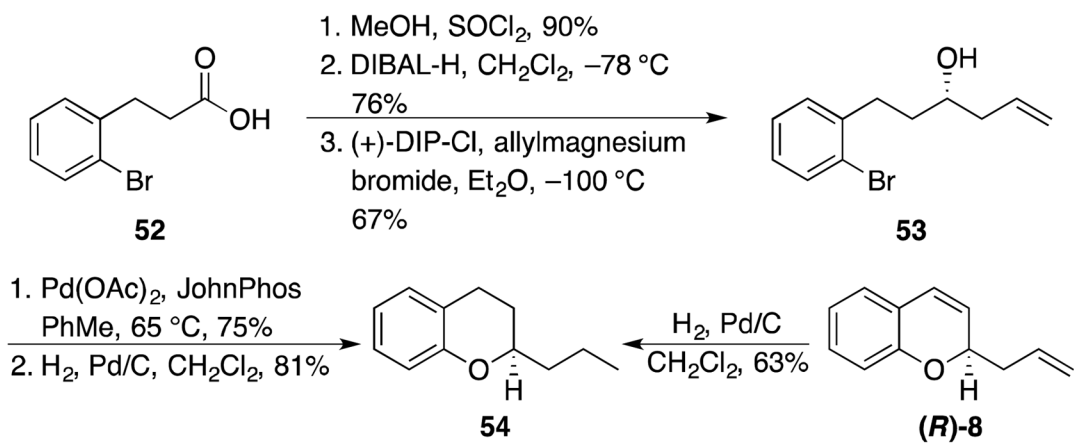
Scheme 4.
Alkylation of benzoxathiole.



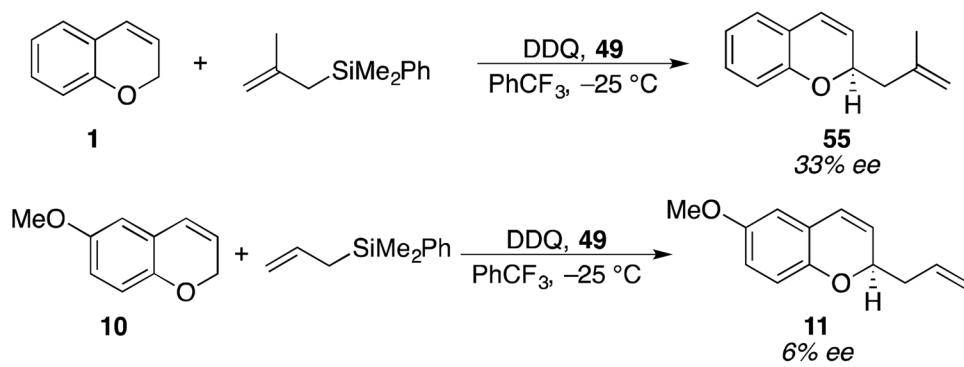
Scheme 5.
Oxidative spirocycle formation.

**Scheme 6.**

Chiral ion pair from an oxidatively generated intermediate.



Scheme 7.
Absolute stereochemistry determination.



Scheme 8.
Attempts to expand the reaction scope.

Table 1

Scope studies of chromenes and isochromenes.

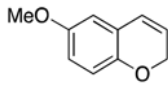
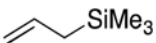
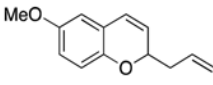
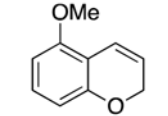
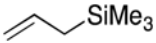
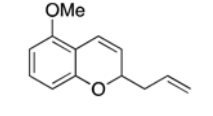
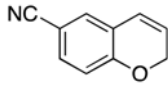
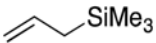
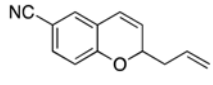
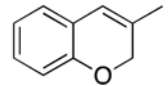
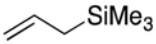
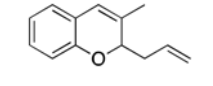
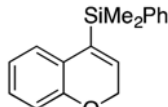
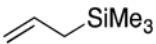
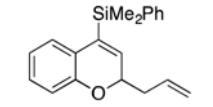
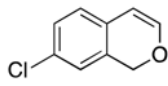
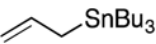
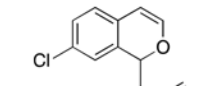
| entry | substrate | nucleophile | product | yield (%) |
|-------|---|--|---|-----------|
| 1 |  10 |  SiMe ₃ |  11 | 64 |
| 2 |  12 |  SiMe ₃ |  13 | 46 |
| 3 |  14 |  SiMe ₃ |  15 | 92 |
| 4 |  16 |  SiMe ₃ |  17 | 60 |
| 5 |  18 |  SiMe ₃ |  19 | 72 |
| 6 |  20 |  SnBu ₃ |  21 | 91 |

Table 2

Nucleophile scope.

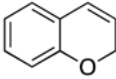
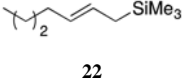
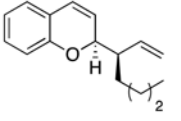
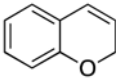
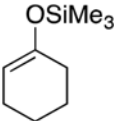
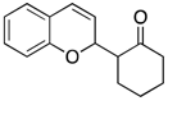
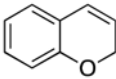
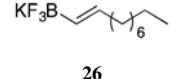
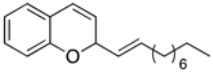
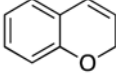
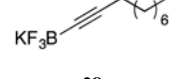
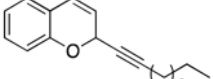
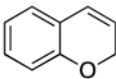
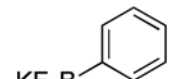
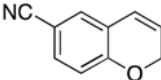
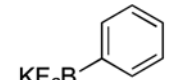
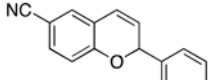
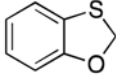
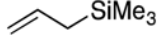
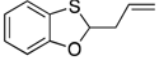
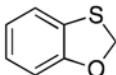
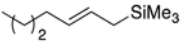
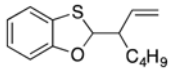
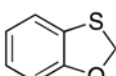
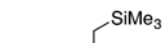
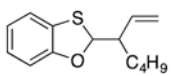
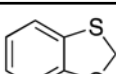
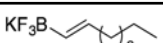
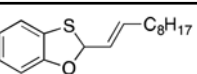
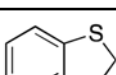
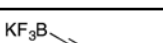
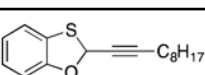
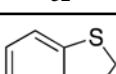
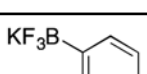
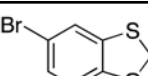
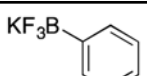
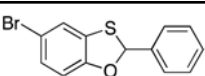
| entry | substrate | nucleophile | product | yield (%) |
|-------|---|---|---|------------------|
| 1 |  1 |  22 |  23 | 63 dr = 1:0 |
| 2 |  1 |  24 |  25 | 71 dr = 1.6:1 |
| 3 |  1 |  26 |  27 | 65 |
| 4 |  1 |  28 |  29 | 66 |
| 5 |  1 |  30 | – | – |
| 6 |  14 |  30 |  31 | 46 |

Table 3

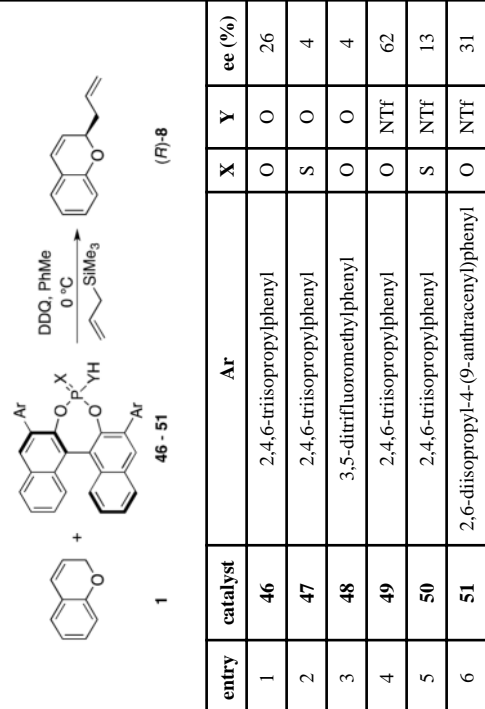
Nucleophile scope in benzoxathiole coupling.

| entry | substrate | nucleophile | product | yield (%) |
|----------------|---|--|---|------------------|
| 1 |  32 |  23 |  33 | 79 |
| 2 ^a |  32 |  23 |  35 | 72 dr = 3.2:1 |
| 3 ^a |  32 |  23-(<i>cis</i>) |  35' | 66 dr = 1:4.6 |
| 4 |  32 |  26 |  36 | 55 |
| 5 |  32 |  28 |  37 | 65 |
| 6 |  32 |  30 | – | – |
| 7 |  38 |  30 |  39 | 30 |

^a 35 and 35' are diastereomers. The relative stereochemical orientations have not been assigned.

Table 4

Screening with one equivalent of catalyst.



| entry | catalyst | Ar | X | Y | ee (%) |
|-------|----------|---|---|-----|--------|
| 1 | 46 | 2,4,6-trisopropylphenyl | O | O | 26 |
| 2 | 47 | 2,4,6-trisopropylphenyl | S | O | 4 |
| 3 | 48 | 3,5-ditrifluoromethylphenyl | O | O | 4 |
| 4 | 49 | 2,4,6-trisopropylphenyl | O | NTf | 62 |
| 5 | 50 | 2,4,6-trisopropylphenyl | S | NTf | 13 |
| 6 | 51 | 2,6-diisopropyl-4-(9-anthracenyl)phenyl | O | NTf | 31 |

Table 5

Influence of the nucleophile.

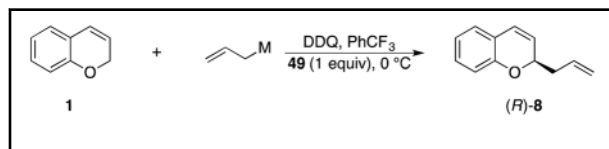
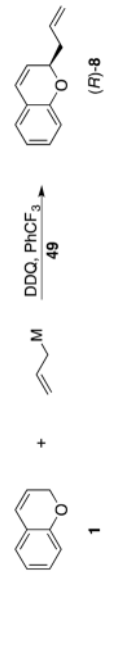
|  | | |
|---|----------------------|--------|
| entry | M | ee (%) |
| 1 | SiMe ₂ Ph | 92 |
| 2 | SnBu ₃ | 48 |
| 3 | SnPh ₃ | 89 |

Table 6

Effects of lowering the catalyst loading and temperature.



| entry | M | temperature | catalyst loading (mol%) | ee (%) | yield (%) |
|-------|----------------------|-------------|-------------------------|--------|-----------|
| 1 | Ph ₃ Sn | 0 °C | 20 | 62 | — |
| 2 | Ph ₃ Sn | -25 °C | 20 | 81 | 66 |
| 3 | Ph ₃ Sn | -25 °C | 10 | 68 | 66 |
| 4 | Ph ₃ Sn | -25 °C | 5 | 31 | 57 |
| 5 | PhMe ₂ Si | 0 °C | 20 | 62 | — |
| 6 | PhMe ₂ Si | -25 °C | 20 | 86 | 56 |
| 7 | PhMe ₂ Si | -25 °C | 10 | 79 | 52 |
| 8 | PhMe ₂ Si | -25 °C | 5 | 17 | 53 |