Arylboronic Acid-Catalyzed Racemization of Secondary and Tertiary Alcohols

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ABSTRACT: The use of 2-carboxyphenylboronic acid (5 mol %) and oxalic acid (10 mol %) with 2-butanone as a solvent for the racemization of a range of enantiomerically pure secondary and tertiary alcohols is demonstrated. The process is postulated to proceed via reversible Brønsted acid-catalyzed C−O bond cleavage through an achiral carbocation intermediate. Despite tremendous advances in enantioselective synthesis, the kinetic resolution (KR) of racemic mixtures remains a cornerstone of asymmetric synthesis in academia and industry. The major limitation of this widely used approach to generate enantiomerically pure compounds is the theoretical maximum 50% yield of a single enantiomer. One strategy to improve efficiency is to racemize the undesired enantiomer to allow recycling of the material. In the most effective case, a dynamic kinetic resolution (DKR) involves the process of combining rapid in situ substrate racemization with a KR, potentially leading to quantitative product yields in enantiomerically pure form.

Owing to the synthetic importance of enantioenriched secondary alcohols, several methods have been developed for their racemization to enable recirculation of the undesired enantiomer in DKR processes. The most widely used methods in this area rely on reversible removal of the stereogenic carbinol hydrogen atom, either through deprotonation of enolizable protons or, more commonly, through transition-metal promoted hydrogen-transfer through a dehydrogenation−hydrogenation mechanism via an achiral ketone intermediate (Scheme 1a). A limitation of such processes is that they cannot be applied to tertiary alcohols where no carbinol hydrogen exists. This type of racemization requires a conceptually distinct approach where the reversible dehydration of the C−OH bond to form an achiral carbocation intermediate is the most feasible method (Scheme 1b). This approach can be challenging to implement since generating the highly reactive carbocation intermediate can lead to several undesired pathways including alkene formation, rearrangement, and etherification. To date, only a limited number of heterogeneous catalysts, including acidic zeolites, acidic resins, and vanadyl sulfate, have been investigated for the racemization of secondary benzylic alcohols via a cationic intermediate and employed in a DKR. Furthermore, only two examples of acid-promoted racemization of tertiary alcohols have been reported. Bäckvall and co-workers used Dowex 50wX8 resin for the efficient heterogeneous racemization of a small range of acyclic tertiary alcohols where water was used as a solvent (Scheme 1c) to avoid undesired elimination and/or rearrangement processes. In 2020, Gröger and co-workers reported the only example of the DKR of a tertiary alcohol, using an oxovanadium-catalyst immobilized on mesoporous silica for the racemization in combination with enzymatic kinetic resolution. Only one substrate was investigated in this protocol, and multiple sequential additions of each catalyst were required over 13 days to achieve high conversion to product with excellent enantioselectivity.

Building upon this work, the development of a more general homogeneous Brønsted acid-catalyzed dehydrative racemization that could potentially be applied to both secondary and tertiary alcohols would represent an advance on existing...
methods. In this context, an investigation of arylboronic acids as potential catalysts for the racemization of alcohols is described. While the ability of arylboronic acids to promote catalytic dehydration in a variety of $S_N$ type substitution processes has previously been demonstrated, their use as racemization catalysts has not been detailed to date.\(^9\)

Initial studies focused on the racemization of (R)-3-phenyl-3-hydroxyoxindole 1 (Table 1),\(^10\) which was readily obtained as a single enantiomer through iso_thiourea-catalyzed acylative kinetic resolution.\(^11\) A range of arylboronic acids 2–7 (5 mol %) was screened in combination with oxalic acid (10 mol %) as a cocatalyst, which is known to reversibly condense with arylboronic acids to form the corresponding boronate ester in situ.\(^12\) Preliminary screening was performed on a small-scale and the enantiomeric excess of the crude material was assessed by analytical HPLC on a chiral stationary phase. Phenylboronic acid 2 gave minimal racemization after 16 h at 40 °C in chloroform (entry 1); however, the more electron-deficient arylboronic acids 3–7 provided greater reduction in enantiomeric excess under the same conditions (entries 2–4). The most promising catalysts identified were pentafluorophenylboronic acid 3 and 2-carboxyphenylboronic acid 7 (5 mol %) in isolation (entry 8), demonstrating that the combination of the arylboronic acid and oxalic acid is essential for reactivity. The use of Dowex 50wX8 also did not lead to racemization.\(^10\)

Repeating the successful racemization on a preparative scale revealed competing decomposition of 1 through analysis of the crude $^1$H NMR. Possible side reactions arising from formation of a possible carbocation intermediate include etherification,\(^12\)

and Friedel–Crafts alkylation processes,\(^9,13\) which are both preceded under arylboronic acid catalysis. Unfortunately, the side products could not be isolated in sufficient quantities to allow for unambiguous identification. A solvent screen was therefore conducted to find conditions that promoted clean racemization with minimal loss of material. The use of arylboronic acid 7 and oxalic acid in acetonitrile gave complete racemization of 1, but was accompanied by significant decomposition, with only 25% of rac-1 recovered (entry 9). Inspired by the work of Niggemann,\(^14\) ketone-based solvents capable of stabilizing a cationic intermediate were trialled. The use of cyclopentanone diminished the racemization (entry 10), while acetone gave scalemic 1 in 84:16 er and with a more promising 81% recovery by NMR (entry 11). The use of 2-butanol gave a good balance of reactivity and selectivity, providing 1 in 61:39 er and 82% recovery (entry 12). Increasing the reaction temperature to 60 °C gave complete racemization after only 3 h, with rac-1 recovered in 70% isolated yield (entry 13).

With the optimized conditions for racemization developed, the scope and limitations of this process were assessed by changing the steric and electronic parameters of the heterocyclic tertiary alcohol substrate (Scheme 2). Variation

| Table 1. Reaction Optimization |
|-----------------------------|
| **Entry** | **Boronic Acid** | **Solvent** | **Yield (%)** | **er** |
| 1 | 2 | CHCl$_3$ | N/D | 93:7 |
| 2 | 3 | CHCl$_3$ | N/D | 82:18 |
| 3 | 4 | CHCl$_3$ | N/D | 65:35 |
| 4 | 5 | CHCl$_3$ | N/D | 79:21 |
| 5 | 6 | CHCl$_3$ | N/D | 54:46 |
| 6 | 7 | CHCl$_3$ | N/D | 50:50 |
| 7 | None | CHCl$_3$ | N/D | >99:1 |
| 8 | 7 | CHCl$_3$ | N/D | >99:1 |
| 9 | 7 | MeCN | 25 | 50:50 |
| 10 | 7 | Cyclopentanone | 99 | 91:9 |
| 11 | 7 | Acetone | 81 | 84:16 |
| 12 | 7 | 2-Butanone | 82 | 61:39 |
| 13 | 7 | 2-Butanone | 70$^a$ | 50:50 |

$^a$Determined by $^1$H NMR using relative integrals of product peak and impurities. $^b$Determined by HPLC analysis on a chiral stationary phase. No oxalic acid. $^c$Reaction at 60 °C, 3 h. $^d$Isolated yield.

of the N-substituent showed that N-benzyl, N-methyl, and N-allyl substituents are all tolerated in this protocol, giving racemic material 1, 8, and 9, respectively, from enantiomeric substrates in good to excellent yield. Similarly, incorporation of a C(5)-methyl substituent within oxindole 10 was tolerated. Incorporation of an electron-donating 4-MeOC$_2$H$_4$ substituent at the C(3) position within 11 leads to significant byproduct formation under the standard conditions,
likely due to the increased stability of the intermediate carbocation. Two racemic diastereoisomeric products were obtained, consistent with undesired C–C bond formation with the enol tautomer of the 2-butanone solvent.\textsuperscript{10,12c} Switching the solvent to acetone allowed racemic 11 to be isolated in 42% yield, alongside 39% of the ketone obtained from C–C bond formation with the enol of acetone. In contrast, incorporation of a 2-naphthyl group gave effective racemization, forming racemic 12 in 82% yield. Extension to alternative C(3)-alkyl substituted alcohols 13–15 showed a reduction in enantiomeric ratio from that of the starting materials but slower racemization than that observed with the C(3)-aryl-substituted oxindoles. This trend is consistent with the expectedly enhanced cation stabilizing properties of the doubly benzylic carbocation compared to the C(3)-alkyl-substituted carbocation.

Extension of this methodology to the racemization of secondary alcohol substrates was then investigated (Scheme 3). The reaction of enantiomerically pure (S)-1-phenylethanol alcohol 16 (55:45 er) to its symmetric ether (50:50 dr), which allowed the alcohol to be recovered in 75% yield. Increasing the steric bulk of the alcohol through introduction of branched alkyl substituents disfavored ether formation but required increasing temperature to achieve racemization likely due to diminished solvation of the carbocation intermediate. For example, i-Pr-substituted alcohol 17 was isolated in 71% yield and 54:46 er at 40 °C, while i-Bu-substituted alcohol 18 was isolated in 85% yield and 52:48 er after 1.5 h at 60 °C. Varying the electronic characteristics of the aryl substituent at the carbonil was next investigated. The introduction of electron-withdrawing aryl groups disfavored racemization, with a 4-ClC₆H₄ substituent on alcohol 19 leading to no racemization even after prolonged heating at 75 °C, while the 4-ClC₆H₄ variant 20 provided partial racemization at 60 °C. These results mirror the findings of Bäckvall and co-workers, where electron-deficient benzylic alcohols underwent racemization at a significantly slower rate.\textsuperscript{7} Alcohol 21 bearing a weakly electron-donating 4-MeC₆H₄ substituent was readily racemized at 40 °C, as was a 2-naphthyl variant 22. The racemization of alcohol 23 bearing a strongly electron-donating 4-MeOC₆H₄ substituent proceeded even at 0 °C, with higher temperatures leading to multiple side products. Alkynyl alcohol 24 racemized readily at 60 °C, giving a 65:35 mixture of rac-24 (59% yield) to the corresponding symmetric ether (32% yield, 50:50 dr). Decreasing the temperature to 40 °C inhibits the etherification pathway; however, the rate of racemization was slowed. In contrast, allylic alcohol 25 led to extensive formation of the ether side-product even at room temperature, forming rac-25 in only 22% yield. It is noteworthy that the allylic 24 and propargylic 25 alcohols provided no rearranged products via the known boronic acid-catalyzed transposition.\textsuperscript{15} This suggests that the mechanism is likely via Brønsted acid catalysis instead of Lewis acid catalysis.

To further exemplify this protocol, the application to the epimerization of a bioactive secondary alcohol, podophyllotoxin 26, containing multiple stereocenters and functional group moieties was investigated. Derivatives of podophyllotoxin 26 and its diastereoisomer, epi-podophyllotoxin 27, have been widely investigated due to their potent activity against cancer cells via inhibition of tubulin polymerization, and a number of methods for their synthesis have been developed.\textsuperscript{16} Treatment of commercially available podophyllotoxin 26 to the catalytic protocol in acetonitrile at room temperature resulted in selective epimerization at the benzylic carbonil center to give a 60:40 mixture of podophyllotoxin 26 to epi-podophyllotoxin 27 in 81% yield with purification allowing for partial separation (Scheme 4). Given that commercial epi-podophyllotoxin 27 is significantly more expensive than podophyllotoxin 26, this protocol provides a method for its preparation.
Although much controversy over the mode of action of alcohol activation with boronic acids exists, recent work by both Hall and Taylor indicates that a Brønsted acid or H-bonding pathway dominates over the alternative Lewis acid route. To probe whether the combined 2-carboxyphenylboronic acid 7/oxalic acid system acts as either a Lewis acid or Bronsted acid in the developed racemization process, a control experiment was performed with enantiomerically pure (R)-3-hydroxyoxindole 1 under the standard reaction conditions with the addition of catalytic 2,6-di-tert-butylpyridine (5 mol %, Scheme 5a). No racemization was observed after 2 h at 60 °C, with inhibition being consistent with a Bronsted acid-catalyzed pathway likely being operational. The symmetric ether of 1-phenylethanol 28 (50:50 dr) was also subjected to the reaction conditions in the presence of water (2 or 10 equiv) to determine the reversibility of the etherification. Conversion by 1H NMR demonstrated that the ratio of ether 28 (50:50 dr) to alcohol 16 was equivalent regardless of the amount of water added (Scheme 5b). This further supports the hypothesis that this process proceeds through a Bronsted acid catalyzed S_{N}1 process.

A possible mechanism for racemization is outlined in Scheme 5c. In situ condensation between 2-carboxyphenylboronic acid 7 and oxalic acid is assumed to form boronate complex 29 with increased Bronsted acidity compared with either starting material. In this context, both Matsson and Maruoka have reported that cyclic boronate esters derived from 2-carboxyphenylboronic acid can act as Lewis acid-assisted Bronsted acid catalysts, with the latter providing X-ray crystallographic evidence for formation of spirocyclic boronate species similar to 29. A 11B NMR experiment in acetone-d6 reacting 7 with oxalic acid (2 equiv) showed one predominant species in solution, consistent with the formation of a tetrahedral sp3-hybridized boron compound (δ = 9.6 ppm). Direct HRMS analysis of this solution also confirmed the molecular ion of 29 as the major compound present. However, under the reaction conditions, 29 may exist as part of a dynamic equilibrium with other hydrated forms, and it is therefore difficult to unambiguously define the active catalyst present in solution. Boronate 29, or a related hydrate, is proposed to behave as an enhanced Bronsted acid that can protonate the enantiopure alcohol, leading to an initial ion pair such as 30. Reversible C–O bond cleavage is achieved through ionization to generate the corresponding carbocation intermediate 31, followed by a nonsel ective hydration event resulting in racemization.

In conclusion, 2-carboxyphenylboronic acid 7 (5 mol %) in combination with oxalic acid (10 mol %) is an efficient catalytic system for the racemization of enantiomerically enriched tertiary 3-hydroxy-3-substituted oxindoles and a range of secondary benzylic alcohols. The process is thought to occur by reversible Bronsted acid-catalyzed C–O bond cleavage to form an achiral carbocation intermediate.
constants, \( J \), are quoted in Hz. Multiplicities are indicated by \( s \) (singlet), \( d \) (doublet), \( t \) (triplet), \( q \) (quartet), and combinations thereof, and \( m \) (multiplet). The abbreviation \( Ar \) is used to denote aromatic, Ph to denote phenyl, Bn to denote benzyl, br to denote broad, and app to denote apparent. Infrared spectra (\( \nu_{\text{max}} \)) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory.

2. General Procedures. General Procedure A: Racemization of Tertiary Oxindoles. The appropriate alcohol (1 equiv), boronic acid (5 mol \%), and oxalic acid (10 mol \%) were added to a vial. If the reaction was performed on a small-scale, stock solutions (vide infra) of the two catalysts were used and the THF from the stock solution was removed in vacuo prior to the start of the reaction. The reactants were then dissolved in the required solvent (0.25 M) and the mixture was heated at 60 °C. The reaction was stirred for the required time and then filtered through a silica pad and concentrated under reduced pressure. The alcohol was analyzed by chiral HPLC and \(^{1}H\) NMR.

General Procedure B: Racemization of Secondary Alcohols. The appropriate alcohol (1 equiv), boronic acid (5 mol \%), and oxalic acid (10 mol \%) were added to a vial. If the reaction was performed on a small-scale, stock solutions (vide infra) of the two catalysts were used and the THF from the stock solution was removed in vacuo prior to the start of the reaction. The reactants were dissolved in the required solvent (0.25 M) and the mixture was heated to the required temperature for the described time. The reaction was diluted with \( \text{Et}_2\text{O} \) and washed sequentially with 1 M \( \text{NaOH} \), brine, then dried with MgSO\(_4\), filtered, and concentrated in vacuo. The reaction mixture was then filtered through a silica pad and concentrated under reduced pressure. The alcohol was analyzed by chiral HPLC and \(^{1}H\) NMR.

Preparation of 2-Carboxyphenylboronic Acid Stock Solution (0.015 M). Boronic acid (5 mg, 0.03 mmol) and THF (1 mL) were added to a 2 mL volumetric flask. Once the mixture was homogeneous (after sonication) THF was added until the final volume of the mixture had reached 2 mL.

Preparation of Oxalic Acid Stock Solution (0.11 M). Oxalic acid (20 mg, 0.02 mmol) and THF (1 mL) were placed in a 2 mL volumetric flask. Once the mixture was homogeneous (after sonication) THF was added until the final volume of the mixture had reached 2 mL.

3. Racemization of Enantioenriched Alcohols. Racemization of (R)-1-Benzyl-3-hydroxy-3-phenylindolin-2-one (1). Following General Procedure A, (R)-1-benzyl-3-hydroxy-3-phenylindolin-2-one (1) (0.015 M, 2.1 mL, 32 \( \mu \)mol, 5 \%), and oxalic acid (0.11 M, 570 \( \mu \)mol, 10 mol \%) were reacted in 2-butanone (2.6 mL) for 3 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 3:1) to give rac-1-benzyl-3-hydroxy-3-phenylindolin-2-one (2) (70%). Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.5 mL/min, 211 nm, 40 °C) \( t_{R} \) (R): 12.2 min, \( t_{S} \) (S): 15.6 min, 50:50 (R:S) er.

Racemization of (R)-1-Benzyl-3-hydroxy-5-methyl-3-phenylindolin-2-one (10). Following General Procedure D, (R)-1-benzyl-3-hydroxy-5-methyl-3-phenylindolin-2-one (10) (0.011 M, 98 mg, 0.3 mmol, 2-carboxyphenylboronic acid 7 (0.015 M, 1.0 mL, 15 mol \%), and oxalic acid (0.11 M, 270 \( \mu \)mol, 30 mol \%) were reacted in 2-butanone (1.2 mL) for 2 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:3) to give rac-3-hydroxy-1-allyl-3-phenylindolin-2-one (2) (64 mg, 0.24 mmol, 80%). Chiral HPLC analysis, Chiralpak OD-H (95:5 hexane:IPA, flow rate 1.0 mL/min, 211 nm, 30 °C) \( t_{R} \) (S): 14.0 min, \( t_{S} \) (R): 16.01 min, 52:48 (R:S) er.

Racemization of (R)-1-Benzyl-3-hydroxy-5-methyl-3-phenylindolin-2-one (10) in 2-Butanone. Following General Procedure A, (R)-1-benzyl-3-hydroxy-5-methyl-3-phenylindolin-2-one (10) (0.011 M, 98 mg, 0.3 mmol, 2-carboxyphenylboronic acid 7 (0.015 M, 1.0 mL, 15 mol \%), and oxalic acid (0.11 M, 270 \( \mu \)mol, 30 mol \%) were reacted in 2-butanone (1.2 mL) for 4 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:5) to give rac-1-benzyl-3-hydroxy-5-methyl-3-phenylindolin-2-one (10) (67 mg, 0.20 mmol, 68%). Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.5 mL/min, 211 nm, 40 °C) \( t_{R} \) (R): 12.2 min, \( t_{S} \) (S): 15.6 min, 50:50 (R:S) er.

Attempted Racemization of (R)-1-Benzyl-3-hydroxy-3-(4-methoxystyryl)indolin-2-one (11) in 2-Butanone. Following General Procedure A, (R)-1-benzyl-3-hydroxy-3-(2-oxopropyl)indolin-2-one (11) (0.017 M, 47 mg, 0.2 mmol, 10 mol \%) was reacted in 2-butanone (1.2 mL) for 2 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:3) to give two isomers of 1-benzyl-3-(4-methoxystyryl)-3-(3-oxobut-2-enyl)indolin-2-one (S24, 25 mg, 0.073 mmol, 26%) as a colorless oil and S25 (24 mg, 0.073 mmol, 26%) as a white solid. 1-Benzyl-3-(4-methoxystyryl)-3-(3-oxobut-2-enyl)indolin-2-one (S22) (20 mg, 0.057 mmol, 26%) was reacted in 2-butanone (1.2 mL) for 4 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:3) to give two isomers of 1-benzyl-3-(4-methoxystyryl)-3-(3-oxobut-2-enyl)indolin-2-one (S23, 25 mg, 0.073 mmol, 26%) as a white solid. 1-Benzyl-3-(4-methoxystyryl)-3-(3-oxobut-2-enyl)indolin-2-one (S23): \( t_{R} \) (S): 15.6 min, 50:50 (R:S) er.

Racemization of (R)-1-Benzyl-3-hydroxy-3-(4-methoxystyryl)indolin-2-one (11) in Acetone. Following General Procedure D, (R)-1-benzyl-3-hydroxy-3-(4-methoxystyryl)indolin-2-one (11) (0.019 M, 84 mg, 0.14 mmol, 2-carboxyphenylboronic acid 7 (0.015 M, 1.0 mL, 15 mol \%), and oxalic acid (0.11 M, 270 \( \mu \)mol, 30 mol \%) were reacted in acetone (0.6 mL) for 2 h at 40 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:2) followed by flash column chromatography (CH\(_2\)Cl\(_2\):EtOAc 95:5) to give rac-11 as a yellow solid (21 mg, 42%), and 1-benzyl-3-(4-methoxystyryl)-3-(2-oxopropyl)indolin-2-one (S25) as white solid (21 mg, 39%). 1-Benzyl-3-hydroxy-3-(4-methoxystyryl)indolin-2-one (11): Chiral HPLC analysis: Chiralpak IC (80:20 hexane:IPA, flow rate 1.0 mL/min, 211 nm, 30 °C) \( t_{R} \) (S): 15.6 min, \( t_{S} \) (R): 21.0 min, 51:49 (R:S) er.

Racemization of (R)-1-Benzyl-3-hydroxy-1-allyl-3-phenylindolin-2-one (9). Following General Procedure A, (R)-1-benzyl-3-hydroxy-1-allyl-3-phenylindolin-2-one (9) (973, 80 mg, 0.3 mmol), 2-carboxyphenylboronic acid 7 (0.015 M, 1.0 mL, 15 \mu mol, 5 \%), and oxalic acid (0.11 M, 270 \( \mu \)mol, 30 mol \%) were reacted in 2-butanone (1.2 mL) for 2 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:3): 13371
(3H, s), 3.65(1H, d, J = 18.0), 3.52 (1H, d, J = 18.0), 2.06 (3H, s); 1H NMR (101 MHz, CDCl₃) δ 204.4, 178.8, 159.1, 143.9, 136.2, 131.8, 131.6, 128.8, 128.4, 127.9, 127.5, 127.3, 124.0, 122.4, 114.2, 109.7, 55.4, 52.6, 51.2, 44.3, 30.3; IR cm⁻¹ (KBr) 2912 (C-H), 1705 (C=O), 1606 (C=C), 1508, 1355, 1256, 1180, 1168 cm⁻¹; HRMS (NSI) calculated for C₂₈H₂₂NO₃Na [M + Na⁺] requires 408.1576, found 408.1557 (4.7 ppm).

**Racemization of (R)-1-Benzyl-3-hydroxy-3-(naphthalen-2-yl)-indolin-2-one (12).** Following General Procedure C, (R)-1-benzyl-3-hydroxy-3-(naphthalen-2-yl)-indolin-2-one (51.0 mg, 0.31 mmol, 85%). Chiral HPLC analysis: Chiralpak IC (98:2 hexane:IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tₚ (R): 23.6 min, tₚ (S): 28.5 min, 84:16 (R:S) er.

**Racemization of (S)-1-Benzyl-3-ethyl-3-hydroxyindolin-2-one (14).** Following General Procedure C, (S)-1-benzyl-3-ethyl-3-hydroxyindolin-2-one (274 mg, 2.25 mmol, 75%). Chiral HPLC analysis: Chiralpak OD-H (95:5 hexane:IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tₚ (R): 8.1 min, tₚ (S): 9.9 min, 55:45 (S:R) er.

**Eterification of rac-1-Phenylethanol (16).** Following a modified General Procedure D, rac-1-Phenylethanol (16) (366.5 g, 3.0 mol), 2-carboxyphenylboronic acid (7 (25 mg, 0.15 mmol, 5 mol %), and oxalic acid (27 mg, 0.3 mmol, 10 mol %) were reacted in 2-butanol (12 mL) for 2 h at room temperature. The reaction was concentrated under reduced pressure, and purified by column chromatography (10% EtOAc:Hexane) to give rac-1-Phenylethanol (16) (274 mg, 2.25 mmol, 75%). Chiral HPLC analysis: Chiralpak OD-H (95:5 hexane:IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tₚ (R): 8.1 min, tₚ (S): 9.9 min, 55:45 (S:R) er.

**Racemization of (S)-2-Methyl-1-phenylpropanol (17).** Following General Procedure B, (S)-2-methyl-1-phenylpropanol (7 (>99.1 er, 45 mg, 0.30 mmol), 2-carboxyphenylboronic acid (7 (2.5 mg, 0.015 mmol, 5 mol %), and oxalic acid (2.7 mg, 0.03 mmol, 10 mol %) were reacted in 2-butane (1.2 mL) for 2 h at room temperature. The reaction was concentrated under reduced pressure and purified by column chromatography (10% EtOAc:Hexane) to give rac-2-methyl-1-phenylpropanol (17) (32 mg, 0.21 mmol, 71%). Chiral HPLC analysis: Chiralpak AD-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tₚ (R): 21.6 min, tₚ (S): 24.1 min, 55:46 (S:R) er.

**Racemization of (S)-2,2-Dimethyl-1-phenylpropanol (18).** Following General Procedure B, (S)-2,2-dimethyl-1-phenylpropanol (18) (>99:1 er, 60 mg, 0.37 mmol), 2-carboxyphenylboronic acid (7 (0.015 M, 1.21 mL, 18 μmol, 5 mol %), and oxalic acid (0.11 M, 329 μL, 37 μmol, 10 mol %) were reacted in 2-butane (1.5 mL) for 1.5 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (10% EtOAc:Hexane) to give rac-2,2-dimethyl-1-phenylpropanol (18) (51.0 mg, 0.31 mmol, 85%). Chiral HPLC analysis: Chiralpak OD-H 95:5 hexane:IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tₚ (S): 6.3 min, tₚ (R): 8.9 min, 52:48 (S:R) er.

**Racemization of 2,2-Dimethyl-1-(4-( trifluoromethyl)phenyl)propan-1-ol (19).** Following General Procedure B, (S)-2,2-dimethyl-1-(4-( trifluoromethyl)phenyl)propan-1-ol (19) (97.3 er, 20 mg, 0.06 mmol), 2-carboxyphenylboronic acid (7 (0.015 M, 0.27 mL, 4.3 μmol, 5 mol %), and oxalic acid (0.11 M, 0.08 mL, 8.6 μmol, 10 mol %) were reacted in 2-butane (0.35 mL) for 2 h at 75 °C. The reaction was then diluted with ether, washed with 1 M NaOH, brine, dried with MgSO₄, and filtered. The resulting (S)-2,2-dimethyl-1-(4-( trifluoromethyl)phenyl)propan-1-ol (19) was analyzed by HPLC and showed no erosion of enantiomeric chirality. Chiral HPLC analysis: Chiralpak OJ-H (99:1 hexane:IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tₚ (S): 9.1 min, tₚ (R): 10.0 min, 97:3 (S:R) er.

**Racemization of 1-(4-Chlorophenyl)-2,2-dimethylpropan-1-ol (20).** Following General Procedure B, (S)-1-(4-chlorophenyl)-2,2-dimethylpropan-1-ol (20) (98.2 er, 37 mg, 0.19 mmol), 2-carboxyphenylboronic acid (7 (0.015 M, 0.63 mL, 9.5 μmol, 5 mol %), and oxalic acid (0.11 M, 0.17 mL, 19 μmol, 10 mol %) were reacted in 2-butane (0.75 mL) for 6 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (10% EtOAc:Hexane) to give 1-(4-chlorophenyl)-2,2-dimethylpropan-1-ol (20) (26.0 mg, 0.13 mmol, 70%). Chiral HPLC analysis: Chiralpak IC (98:2 hexane:IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tₚ (S): 7.7 min, tₚ (R): 7.2 min, 73:27 (S:R) er.

**Racemization of 2,2-Dimethyl-1-(p-tolyl)propan-1-ol (21).** Following General Procedure B, (S)-2,2-dimethyl-1-(p-tolyl)propan-1-ol (21) (>99:1 er, 77 mg, 0.43 mmol), 2-carboxyphenylboronic acid (7 (3.88 mg, 22 μmol, 5 mol %), and oxalic acid (3.58 mg, 43 μmol, 10 mol %) were reacted in 2-butane (1.7 mL) for 2 h at 40 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (10% EtOAc:Hexane) to give rac-2,2-dimethyl-1-(p-tolyl)propan-1-ol (21) (68.0 mg, 0.38 mmol, 88%). Chiral HPLC analysis: Chiralpak OJ-H (98.8:2 hexane:IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tₚ (S): 6.8 min, tₚ (R): 7.1 min, 54:46 (S:R) er.

**Racemization of 2,2-Dimethyl-1-(naphthalen-2-yl)propan-1-ol (22).** Following General Procedure B, (S)-2,2-dimethyl-1-(naphthalen-2-yl)propan-1-ol (22) (97:3 er, 20 mg, 0.093 mmol), 2-carboxyphenylboronic acid (7 (0.015 M, 0.31 mL, 4.7 μmol, 5 mol %), and oxalic acid (0.11 M, 0.09 mL, 9.3 μmol, 10 mol %) were reacted in 2-butane (0.4 mL) for 2 h at 40 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (10% EtOAc:Hexane) to give rac-2,2-dimethyl-1-
Racemization of 1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-ol (23). Following General Procedure B, (S)-1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol 23 (>99.1 er, 37 mg, 0.19 mmol), 2-carboxyphenylboronic acid (0.76 mL) for 2 h at 0 °C. Chiral HPLC analysis: Chiralpak AD-H (99:1 hexane:IPA, flow rate 1.0 mL min\(^{-1}\), 220 nm, 30 °C) \(t\)_R (R): 23.6 min, \(t\)_S (S): 25.7 min, 67:33 (S:R) er.

Racemization of 4-Phenylbut-3-yn-2-ol (24). Following General Procedure B, (S)-4-phenylbut-3-yn-2-ol 24 (>99.1 er, 113.0 mg, 0.77 mmol), 2-carboxyphenylboronic acid 7 (3.4 mg, 0.039 mmol, 5 mol %), and oxalic acid (7 mg, 0.077 mmol, 10 mol %) were reacted in 2-butane (3 mL) for 2 h at 0 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (10% EtOAc:Hexane) to give rac-4-phenylbut-3-yn-2-ol 24 (67 mg, 0.48 mmol, 62%) and (oxybis(but-1-yne-3,1-diyl)) dibenzene S26 (36 mg, 0.25 mmol, 32%). Spectroscopic data in accordance with the literature. 24 4-Phenylbut-3-yn-2-ol 24: Chiral HPLC analysis: Chiralpak OD-H (95:5 hexane:IPA, flow rate 1.0 mL min\(^{-1}\), 254 nm, 30 °C) \(t\)_S (S): 28.5 min, \(t\)_R (R): 11.3 min, 50:50 (S:R) er. Chiral HPLC analysis: Chiralpak AD-H (99:1 hexane:IPA, flow rate 1.0 mL min\(^{-1}\), 220 nm, 30 °C) \(t\)_S (S): 25.0 min, \(t\)_R (R): 15.1 min, 50:50 (S:R) er. (1E,1’E)-Oxysib(but-1-yne-3,1-diyl) dibenzene S26 (1:1 mix of diastereomers): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.41–7.51 (4H, m), 7.25–7.35 (6H, m), 4.86 (1H, q, \(J\) 6.6), 4.73 (1H, q, \(J\) 6.6), 1.60 (3H, d, \(J\) 2.4), 1.59 (3H, d, \(J\) 2.4).

Racemization of (E)-4-Phenylbut-3-en-2-ol (25). Following General Procedure B, (E)-4-phenylbut-3-en-2-ol 25 (95:5 er, 60 mg, 0.40 mmol), 2-carboxyphenylboronic acid 7 (3.4 mg, 0.039 mmol, 5 mol %), and oxalic acid (3.6 mg, 0.040 mmol, 10 mol %) were reacted in 2-butane (1.6 mL) for 2 h at room temperature. The reaction was concentrated under reduced pressure and purified by column chromatography (20% EtOAc:Hexane) to give rac-(E)-4-phenylbut-3-en-2-ol 25 (12.4, 1.4), 4.66 (2H, m), 3.80 (3H, \(J\) 9.7), 2.83 (1H, t, \(J\) 4.4). Chiral HPLC analysis: Chiralpak OD-H (95:5 hexane:IPA, flow rate 1.0 mL min\(^{-1}\), 220 nm, 30 °C) \(t\)_S (S): 23.6 min, \(t\)_R (R): 25.7 min, 67:33 (S:R) er.

Epimerization of Podophyllotoxin (26) to epi-Podophyllotoxin (27). Following General Procedure B, podophyllotoxin 26 (>20:1 dr, 207 mg, 0.5 mmol), 2-carboxyphenylboronic acid 7 (4.1 mg, 0.025 mmol, 5 mol %), and oxalic acid (4.5 mg, 0.05 mmol, 10 mol %) were reacted in 2-butane (2 mL) for 2 h at room temperature. The reaction was concentrated under reduced pressure and purified by column chromatography (50% EtOAc:Hexane) to give podophyllotoxin 26 (60 mg, 0.15 mmol, 30%) and epi-podophyllotoxin 27 (33 mg, 0.08 mmol, 16%) and (75 mg, 0.19 mmol, 37%, 2:1 dr 26:7) for an overall yield of 81% 60:40 dr. Spectroscopic data in accordance with the literature. 22 Podophyllotoxin 26: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.11 (1H, d, \(J\) 0.8), 6.51 (1H, s), 6.37 (2H, s), 5.98 (2H, dd, \(J\) 8.2, 1.3), 4.78 (1H, t, \(J\) 8.7), 4.57–4.66 (2H, m), 4.10 (1H, dd, \(J\) 9.9, 8.7), 3.81 (3H, s), 3.76 (6H, s), 2.69–2.89 (2H, m), 1.98 (1H, dd, \(J\) 8.3, 0.8). epi-Podophyllotoxin 27: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.87 (1H, s), 6.55 (1H, s), 6.28 (2H, s), 5.98 (2H, dd, \(J\) 12.4, 1.4), 4.86 (1H, t, \(J\) 3.9), 4.61 (1H, d, \(J\) 5.2), 4.31–4.42 (2H, m), 3.80 (3H, s), 3.74 (6H, s), 3.27 (1H, dd, \(J\) 14.1, 5.2), 2.83 (1H, t, \(J\) 11.0, 7.7, 3.3), 1.82 (1H, d, 4.3).
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