

Arylboronic Acid-Catalyzed Racemization of Secondary and Tertiary Alcohols

Gregory R. Boyce,* Stefania F. Musolino, Jianing Yang, Andrew D. Smith,* and James E. Taylor*

Cite This: <https://doi.org/10.1021/acs.joc.2c01602>

Read Online

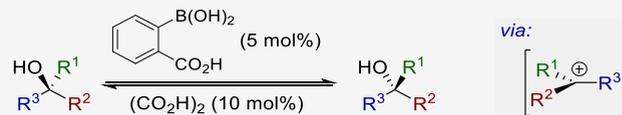
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

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.

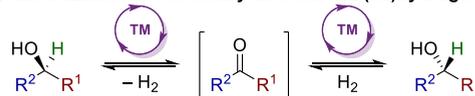


Despite tremendous advances in enantioselective synthesis, the kinetic resolution (KR) of racemic mixtures remains a cornerstone of asymmetric synthesis in academia and industry.¹ The major limitation of this widely used approach to generate enantiomerically pure compounds is the theoretical maximum 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.²

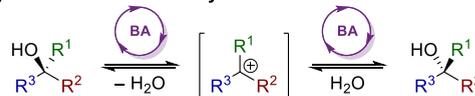
Owing to the synthetic importance of enantioenriched secondary alcohols, several methods have been developed for their racemization to enable recirculation of the undesired enantiomer in DKR processes.² The most widely used methods in this area rely on reversible removal of the stereogenic carbinol hydrogen 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).³ 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,⁴ acidic resins,⁵ and vanadyl sulfate,⁶ 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

Scheme 1. Catalytic Racemization of Alcohols^a

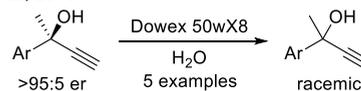
a) Racemization of secondary alcohols via (de)hydrogenation



b) Racemization of tertiary alcohols via C–OH bond cleavage



c) Bäckvall, 2018⁷



^aTM = transition metal catalyst; BA = Brønsted acid catalyst.

small range of acyclic tertiary alcohols where water was used as a solvent (Scheme 1c) to avoid undesired elimination and/or rearrangement processes.⁷ In 2020, Gröger and co-workers reported the only example of the DKR of a tertiary alcohol,⁸ 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.

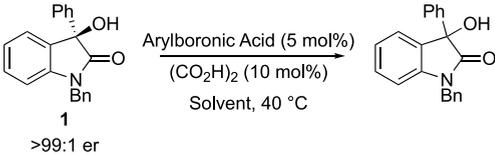
Building upon this work, the development of a more general homogeneous Brønsted acid-catalyzed dehydrative racemization that could potentially be applied to both secondary and tertiary alcohols would represent an advance on existing

Received: July 8, 2022

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_N1 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

Table 1. Reaction Optimization



>99:1 er

	Ar		Ar	
Ar–B(OH) ₂	2	Ph	5	3,4,5-F ₃ C ₆ H ₂
	3	2-(NO ₂)C ₆ H ₄	6	C ₆ F ₅
	4	3,5-(CF ₃) ₂ C ₆ H ₃	7	2-(CO ₂ H)C ₆ H ₄

entry	Boronic acid	solvent	yield (%) ^a	er ^b
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 ^c	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 ^d	7	2-Butanone	70 ^e	50:50

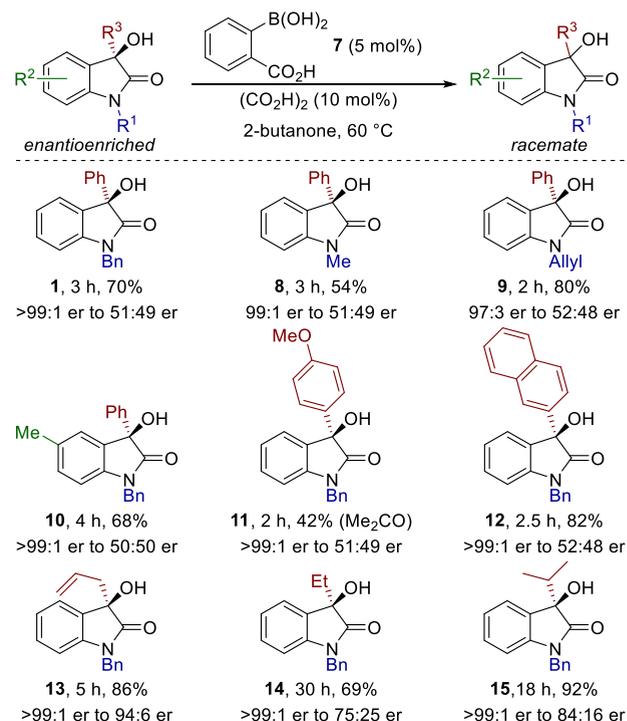
^aDetermined by ¹H NMR using relative integrals of product peak and impurities. ^bDetermined by HPLC analysis on a chiral stationary phase. ^cNo oxalic acid. ^dReaction at 60 °C, 3 h. ^eIsolated yield.

as a single enantiomer through isothiurea-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 **6** and 2-carboxyphenylboronic acid **7**, with the latter generating the racemate of **1** (entries 5 and 6). Control studies indicated that oxalic acid (10 mol %) alone was not capable of promoting racemization (entry 7) and neither was 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 ¹H NMR. Possible side reactions arising from formation of a possible carbocation intermediate include etherification,^{12b}

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** returned (entry 9). Inspired by the work of Niggemann,¹⁴ ketone-based solvents capable of stabilizing a cationic intermediate were trialed. 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-butanone 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

Scheme 2. Scope and Limitations of Tertiary Alcohol Racemization^a



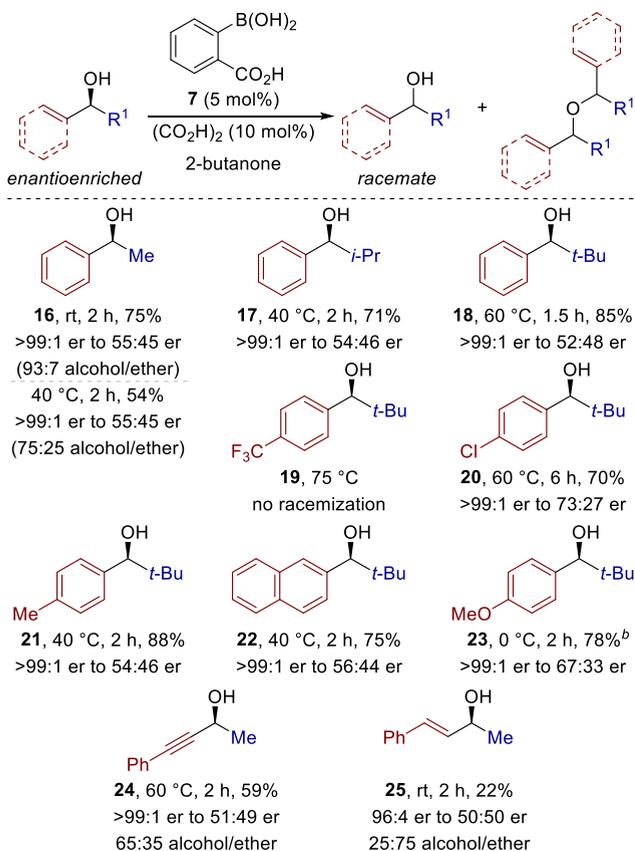
^aIsolated yields after purification by column chromatography. er determined by HPLC analysis on a chiral stationary phase.

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 enantioenriched 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-MeOC₆H₄ 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.^{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

Scheme 3. Scope and Limitations of Secondary Alcohol Racemization^a



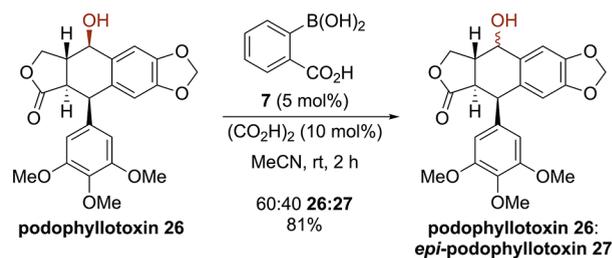
^aIsolated yields after purification by column chromatography. er determined by HPLC analysis on a chiral stationary phase. ^bReaction performed in MeCN.

16 with 2-carboxyphenylboronic acid **7** (5 mol %) and oxalic acid (10 mol %) showed that racemization proceeded at a lower temperature than observed for the tertiary alcohols, with reaction at 40 °C in 2-butanone giving a 75:25 mixture of *rac*-**16** to the corresponding symmetric ether (50:50 dr). Performing the reaction at room temperature improved the selectivity for the racemization, providing a 93:7 mixture of

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 *t*-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 carbinol was next investigated. The introduction of electron-withdrawing aryl groups disfavored racemization, with a 4-CF₃C₆H₄ 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.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.¹⁵ This suggests that the mechanism is likely via Brønsted acid catalysis instead of Lewis acid catalysis.

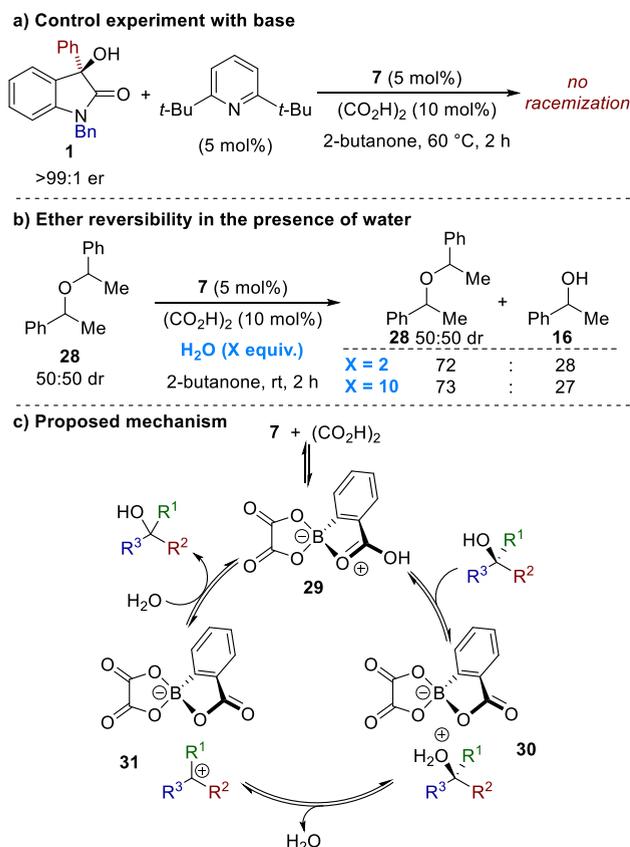
To further exemplify this protocol, the application to the epimerization of a bioactive secondary alcohol, podophyllotoxin **26**, containing multiple stereocenters and functional group moieties was investigated. Derivatives of podophyllotoxin **26** and its diastereoisomer, *epi*-podophyllotoxin **27**, 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.¹⁶ Treatment of commercially available podophyllotoxin **26** to the catalytic protocol in acetonitrile at room temperature resulted in selective epimerization at the benzylic carbinol 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.

Scheme 4. Application to the Epimerization of Podophyllotoxin



Although much controversy over the mode of action of alcohol activation with boronic acids exists, recent work by both Hall¹³ and Taylor^{12b} 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 Brønsted 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 Sa). No racemization was observed after 2 h at 60 °C,

Scheme 5. Mechanistic Considerations



with inhibition being consistent with a Brønsted 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 Sb). This further supports the hypothesis that this process proceeds through a Brønsted acid catalyzed S_N1 process.

A possible mechanism for racemization is outlined in Scheme Sc. In situ condensation between 2-carboxyphenylboronic acid **7** and oxalic acid is assumed to form boronate complex **29** with increased Brønsted acidity compared with either starting material. In this context, both Mattson^{17a} and Maruoka^{17b} have reported that cyclic boronate esters derived from 2-carboxyphenylboronic acid can act as Lewis acid-assisted Brønsted 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-*d*₆ reacting **7** with oxalic acid (2 equiv) showed one predominant species in solution, consistent with the formation of a tetrahedral sp³-hybridized boron compound ($\delta_B = 9.6$ ppm).¹⁸ Direct HRMS analysis of this solution also confirmed the molecular ion of **29** as the major compound present.¹⁰

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 Brønsted 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 nonselective 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 Brønsted acid-catalyzed C–O bond cleavage to form an achiral carbocation intermediate.

EXPERIMENTAL SECTION

1. General Information. Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under a nitrogen (N₂) atmosphere using standard vacuum line techniques and using anhydrous solvents. Anhydrous solvents (CH₂Cl₂ and toluene) were obtained from an anhydrous solvent system (purified using an alumina column, Mbraun SPS-800). All other reagents were performed in standard glassware with no precautions to exclude air or moisture. Solvents and commercial reagents were used as supplied without further purification unless otherwise stated. Room temperature (r.t.) refers to 20–25 °C. Temperatures of 0 °C and –78 °C were obtained using ice/water and CO₂(s)/acetone baths, respectively. Reflux conditions were obtained using a DrySyn, oil bath, or sand bath equipped with a contact thermometer. Analytical thin layer chromatography was performed on precoated aluminum plates (Kieselgel 60 F₂₅₄ silica). TLC visualization was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO₄ solution. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated. Automated chromatography was performed on a Biotage Isolera Four running Biotage OSS78 with a UV–vis detector using the method stated and cartridges filled with Kieselgel 60 silica. Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected. Optical rotations [α]_D²⁰ were measured on a PerkinElmer Model 341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C. HPLC analyses were obtained using either a Shimadzu HPLC consisting of a DGU-20AS degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven; or a Shimadzu HPLC consisting of a DGU-20ASR degassing unit, LC-20AD liquid chromatography pump, SIL-20AHT autosampler, SPD-20A UV/vis detector and a CTO-20A column oven. Separation was achieved using DAICEL CHIRALCEL OD-H or DAICEL CHIRALPAK AD-H or AS-H columns. All HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra. ¹H, ¹³C, ¹⁹F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (¹H 300 MHz), Bruker Avance II 400 (¹H 400 MHz; ¹³C 101 MHz; ¹⁹F 376 MHz), or a Bruker Avance II 500 (¹H 500 MHz; ¹³C 126 MHz; ¹⁹F 476 MHz) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) and referenced to the residual solvent peak. All coupling

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 (ν_{\max}) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wave numbers (max) reported in cm^{-1} . High resolution mass spectrometry (HRMS) data were acquired by electrospray ionization time-of-flight (ESI-TOF) at the University of St Andrews.

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 ^1H 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 Et_2O and washed sequentially with 1 M 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 ^1H 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 total volume of the mixture had reached 2 mL.

Preparation of Oxalic Acid Stock Solution (0.11 M). Oxalic acid (20 mg, 0.22 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 total 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** (>99:1 er, 200 mg, 0.64 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 2.1 mL, 32 μmol , 5 mol %), and oxalic acid (0.11 M, 570 μL , 64 μmol , 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 **1** (140 mg, 0.45 mmol, 70%). Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.25 mL min^{-1} , 211 nm, 40 °C) t_{R} (R): 17.8 min, t_{R} (S): 21.6 min, 51:49 (R:S) er.

Racemization of (R)-3-Hydroxy-1-methyl-3-phenylindolin-2-one (8). Following General Procedure A, (R)-3-hydroxy-1-methyl-3-phenylindolin-2-one **8** (>99:1 er, 68 mg, 0.3 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 1.0 mL, 15 μmol , 5 mol %), and oxalic acid (0.11 M, 270 μL , 30 μmol , 10 mol %) were reacted in 2-butanone (1.2 mL) for 3 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:1) to give *rac*-3-hydroxy-1-methyl-3-phenylindolin-2-one **8** (37 mg, 0.16 mmol, 54%). Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1.0 mL min^{-1} , 211 nm, 30 °C) t_{R} (R): 27.4 min, t_{R} (S): 30.7 min, 51:49 (R:S) er.

Racemization of (R)-3-Hydroxy-1-allyl-3-phenylindolin-2-one (9). Following General Procedure A, (R)-3-hydroxy-1-allyl-3-phenylindolin-2-one **9** (97:3, 80 mg, 0.3 mmol), 2-carboxyphenylboronic

acid **7** (0.015 M, 1.0 mL, 15 μmol , 5 mol %), and oxalic acid (0.11 M, 270 μL , 30 μmol , 10 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 **9** (64 mg, 0.24 mmol, 80%). Chiral HPLC analysis, Chiralpak OD-H (95:5 hexane:IPA, flow rate 1.0 mL min^{-1} , 211 nm, 30 °C) t_{R} (S): 14.0 min, t_{R} (R): 16.0 min, 52:48 (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** (>99:1 er, 99 mg, 0.3 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 1.0 mL, 15 μmol , 5 mol %), and oxalic acid (0.11 M, 270 μL , 30 μmol , 10 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^{-1} , 211 nm, 40 °C) t_{R} (R): 12.2 min, t_{R} (S): 15.6 min, 50:50 (R:S) er.

Attempted Racemization of (R)-1-Benzyl-3-hydroxy-3-(4-methoxyphenyl)indolin-2-one (11) in 2-Butanone. Following General Procedure A, (R)-1-benzyl-3-hydroxy-3-(4-methoxyphenyl)indolin-2-one **11** (>99:1 er, 98 mg, 0.28 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 0.94 mL, 14 μmol , 5 mol %), and oxalic acid (0.11 M, 255 μL , 28 μmol , 10 mol %) were reacted in 2-butanone (1.1 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-methoxyphenyl)-3-(3-oxobutan-2-yl)indolin-2-one **S23** (25 mg, 0.073 mmol, 26%) as a colorless oil and **S24** (25 mg, 0.073 mmol, 26%) as a white solid. 1-Benzyl-3-(4-methoxyphenyl)-3-(3-oxobutan-2-yl)indolin-2-one **S23**: ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.74 (1H, dd, J 7.6, 0.9), 7.38–7.44 (2H, m), 7.18–7.32 (6H, m), 7.10 (1H, td, J 7.6, 1.1), 6.79–6.85 (2H, m), 6.75 (1H, d, J 7.8), 4.90 (2H, d, J 1.7), 4.00 (1H, q, J 7.2), 3.77 (3H, s), 2.02 (3H, s), 0.97 (3H, d, J 7.2); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} 209.6, 178.1, 158.9, 143.4, 136.0, 130.6, 129.1, 128.9, 128.4, 128.3, 128.0, 127.7, 127.3, 122.6, 114.0, 109.4, 57.6, 55.3, 53.5, 44.2, 31.1, 13.3; IR ν_{\max} (film) 2931 (C–H), 2359, 1701 (C=O), 1607 (C=C), 1508, 1352, 1250, 1182 cm^{-1} ; HRMS (NSI $^+$) calculated for $\text{C}_{26}\text{H}_{25}\text{NO}_3\text{Na}^+$ [$M + \text{Na}$] $^+$ requires 422.1727, found 422.1713 (–3.3 ppm). 1-Benzyl-3-(4-methoxyphenyl)-3-(3-oxobutan-2-yl)indolin-2-one **S24**: mp 105–108 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.33–7.40 (3H, m), 7.18–7.29 (6H, m), 7.07 (1H, td, J 7.6, 1.0), 6.81–6.87 (2H, m), 6.74 (1H, d, J 7.8), 4.94 (1H, d, J 16.1), 4.84 (1H, d, J 16.1), 3.86 (1H, q, J 7.7), 3.78 (3H, s), 2.06 (3H, s), 1.37 (3H, d, J 7.7); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} 208.5, 178.8, 159.1, 143.8, 136.0, 130.3, 130.1, 128.7, 128.7, 128.2, 127.5, 127.2, 125.8, 122.0, 114.1, 109.8, 56.6, 55.4, 54.8, 44.2, 29.0, 12.8; IR ν_{\max} (solid) 2926 (C–H), 1697 (C=O), 1607 (C=C), 1508, 1354, 1253, 1180 cm^{-1} ; HRMS (NSI $^+$) calculated for $\text{C}_{26}\text{H}_{25}\text{NO}_3\text{Na}^+$ [$M + \text{Na}$] $^+$ requires 422.1727, found 422.1710 (–4.0 ppm).

Racemization of (R)-1-Benzyl-3-hydroxy-3-(4-methoxyphenyl)indolin-2-one (11) in acetone. Following General Procedure D, (R)-1-benzyl-3-hydroxy-3-(4-methoxyphenyl)indolin-2-one **11** (>99:1 er, 49 mg, 0.14 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 0.47 mL, 7 μmol , 5 mol %), and oxalic acid (0.11 M, 178 μL , 14 μmol , 10 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_2Cl_2 :EtOAc 95:5) to give *rac*-**11** as a yellow solid (21 mg, 42%), and 1-benzyl-3-(4-methoxyphenyl)-3-(2-oxopropyl)indolin-2-one **S25** as white solid (21 mg, 39%). 1-Benzyl-3-hydroxy-3-(4-methoxyphenyl)indolin-2-one **11**: Chiral HPLC analysis: Chiralpak IC (80:20 hexane:IPA, flow rate 1.0 mL min^{-1} , 211 nm, 30 °C) t_{R} (R): 15.6 min, t_{R} (S): 21.0 min, 51:49 (R:S) er. 1-Benzyl-3-(4-methoxyphenyl)-3-(2-oxopropyl)indolin-2-one **S25**: mp 104–106 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.20–7.35 (8H, m), 7.18 (1H, td, J 7.8, 1.3), 7.03 (1H, td, J 7.7, 0.9), 6.80–6.85 (2H, m), 6.73 (1H, d, J 7.9), 5.00 (1H, d, J 15.9), 4.90 (1H, d, J 15.9), 3.77

(3H, s), 3.65(1H, d, *J* 18.0), 3.52 (1H, d, *J* 18.0), 2.06 (3H, s); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} 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 ν_{max} (solid) 2912 (C–H), 1705 (C=O), 1606 (C=C), 1508, 1355, 1256, 1180, 1168 cm^{-1} ; HRMS (NSI $^+$) calculated for $\text{C}_{25}\text{H}_{23}\text{NO}_3\text{Na}^+$ [*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 A, (R)-1-benzyl-3-hydroxy-3-(naphthalen-2-yl)indolin-2-one **12** (>99:1 er, 95 mg, 0.26 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 0.86 mL, 13 μmol , 5 mol %), and oxalic acid (0.11 M, 234 μL , 26 μmol , 10 mol %) were reacted in 2-butanone (1.0 mL) for 2.5 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:3) to give *rac*-1-benzyl-3-hydroxy-3-(naphthalen-2-yl)indolin-2-one **12** (78 mg, 0.20 mmol, 82%). Chiral HPLC analysis: Chiralpak IA (70:30 hexane:IPA, flow rate 0.5 mL min^{-1} , 211 nm, 30 °C) t_{R} (R): 24.8 min, t_{R} (S): 31.0 min, 52:48 (R:S) er.

Racemization of (R)-3-Allyl-1-benzyl-3-hydroxyindolin-2-one (13). Following General Procedure A, (R)-3-allyl-1-benzyl-3-hydroxyindolin-2-one **13** (>99:1 er, 84 mg, 0.30 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 1.0 mL, 15 μmol , 5 mol %), and oxalic acid (0.11 M, 270 μL , 30 μmol , 10 mol %) were reacted in 2-butanone (1.2 mL) for 5 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography to provide 1-benzyl-3-ethyl-3-hydroxyindolin-2-one **13** (72 mg, 0.26 mmol, 86%). Chiral HPLC analysis: Chiralpak OD-H (98:2 hexane:IPA, flow rate 1.0 mL min^{-1} , 254 nm, 30 °C) t_{R} (R): 32.1 min, t_{R} (S): 38.4 min, 94:6 (R:S) er.

Racemization of (R)-1-Benzyl-3-ethyl-3-hydroxyindolin-2-one (14). Following General Procedure A, (R)-1-benzyl-3-ethyl-3-hydroxyindolin-2-one **14** (>99:1 er, 75 mg, 0.28 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 0.93 mL, 14 μmol , 5 mol %), and oxalic acid (0.11 M, 255 μL , 28 μmol , 10 mol %) were reacted in 2-butanone (1.1 mL) for 30 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (Petrol:EtOAc 1:3) to give *rac*-1-benzyl-3-ethyl-3-hydroxyindolin-2-one **14** (51.4 mg, 0.19 mmol, 69%). Chiral HPLC analysis: Chiralpak IC (80:20 hexane:IPA, flow rate 1.0 mL min^{-1} , 211 nm, 30 °C) t_{R} (R): 7.6 min, t_{R} (S): 12.5 min, 75:25 (R:S) er.

Racemization of (R)-1-Benzyl-3-hydroxy-3-isopropylindolin-2-one (15). Following General Procedure A, (R)-1-benzyl-3-hydroxy-3-isopropyl indolin-2-one **15** (>99:1 er, 60 mg, 0.21 mmol), 2-carboxyphenylboronic acid **7** (0.015 M, 1.66 μL , 10.7 μmol , 5 mol %), and oxalic acid (0.11 M, 19 μL , 21 μmol , 10 mol %) were reacted in 2-butanone (0.85 mL) for 18 h at 60 °C. The reaction was concentrated under reduced pressure and purified by column chromatography 1-benzyl-3-hydroxy-3-isopropyl indolin-2-one **15** (55 mg, 0.19 mmol, 92%). Chiral HPLC analysis: Chiralpak AD-H (98:2 hexane:IPA, flow rate 1.0 mL min^{-1} , 211 nm, 30 °C) t_{R} (R): 23.6 min, t_{R} (S): 28.5 min, 84:16 (R:S) er.

Racemization of (S)-1-Phenylethanol (16). Following General Procedure B, (S)-1-phenylethanol **16** (99.5:0.5 er, 366.5 mg, 3.0 mmol), 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-butanone (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) t_{R} (R): 8.1 min, t_{R} (S): 9.9 min, 55:45 (S:R) er.

Etherification of *rac*-1-Phenylethanol (16). Following a modified General Procedure D, *rac*-1-phenylethanol **16** (366.5 mg, 3.0 mmol), 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-butanone (12 mL) for 4 h at 50 °C. The reaction was concentrated under reduced pressure and purified by column chromatography (2% EtOAc:Hexane) to give (oxybis(ethane-1,1-diyl)dibenzene as a colorless oil **28** (114 mg, 2.25 mmol, 31%) as a 1:1 mixture of

diastereomers. Spectroscopic data in accordance with the literature.¹⁹ (Oxybis(ethane-1,1-diyl)dibenzene (**28**) (1:1 mixture of diastereomers): ^1H NMR (500 MHz, CDCl_3) δ_{H} 7.24–7.47 (10H, m), 4.61 (1H, q, *J* 6.4), 4.33 (1H, q, *J* 6.5), 1.55 (3H, d, *J* 6.4), 1.47 (3H, d, *J* 6.5).

Racemization of (S)-2-Methyl-1-phenylpropanol (17). Following General Procedure B, (S)-2-methyl-1-phenylpropanol **17** (>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-butanone (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) t_{R} (R): 21.6 min, t_{R} (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-butanone (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) t_{R} (S): 6.3 min, t_{R} (R): 8.9 min, 52:48 (S:R) er.

Attempted 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-butanone (0.35 mL) for 2 h at 75 °C. The reaction was then diluted with ether, washed with 1 M NaOH, brine, dried with MgSO_4 , 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 enantioenrichment. Chiral HPLC analysis: Chiralpak OJ-H (99:1 hexane:IPA, flow rate 1.0 mL min^{-1} , 220 nm, 30 °C) t_{R} (S): 9.1 min, t_{R} (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-butanone (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 (99.8:0.2 hexane:IPA, flow rate 1.0 mL min^{-1} , 211 nm, 30 °C) t_{R} (S): 7.7 min, t_{R} (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-butanone (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 (98:2 hexane:IPA, flow rate 1.0 mL min^{-1} , 220 nm, 30 °C) t_{R} (S): 6.8 min, t_{R} (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-butanone (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-

(naphthalen-2-yl)propan-1-ol **22** (15.0 mg, 0.070 mmol, 75%). Chiral HPLC analysis: Chiralpak OJ-H (99:1 hexane:IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) *t_R* (S): 19.4 min, *t_R* (R): 24.8 min, 56:44 (S:R) er.

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 **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 MeCN (0.76 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*-1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol **23** (29.0 mg, 0.15 mmol, 78%). 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_R* (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** (6.4 mg, 0.039 mmol, 5 mol %), and oxalic acid (7 mg, 0.077 mmol, 10 mol %) were reacted in 2-butanone (3 mL) for 2 h at 60 °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-yn-3,1-diyl))dibenzene **S26** (36 mg, 0.25 mmol, 32%). Spectroscopic data in accordance with the literature.²⁰ 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_R* (S): 28.5 min, *t_R* (R): 11.3 min, 50:50 (S:R) er. (Oxybis(but-1-yn-3,1-diyl))dibenzene **S26** (1:1 mix of diastereomers): ¹H NMR (400 MHz, CDCl₃) δ_H 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, (S,E)-4-phenylbut-3-en-2-ol **25** (95:5 er, 60 mg, 0.40 mmol), 2-carboxyphenylboronic acid **7** (3.4 mg, 20 μmol, 5 mol %), and oxalic acid (3.6 mg, 40 μmol, 10 mol %) were reacted in 2-butanone (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** (13.2 mg, 0.09 mmol, 22%) and ((1E,1'E)-oxybis(but-1-ene-3,1-diyl))dibenzene **S27** (37 mg, 0.25 mmol, 62%, ~ 2.6:1 dr). Spectroscopic data in accordance with the literature.²¹ (E)-4-Phenylbut-3-en-2-ol **25**: Chiral HPLC analysis: Chiralpak OD-H (95:5 hexane:IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) *t_R* (S): 25.0 min, *t_R* (R): 15.1 min, 50:50 (S:R) er. ((1E,1'E)-Oxybis(but-1-ene-3,1-diyl))dibenzene **S27** (2.6:1 mixture of diastereomers): ¹H NMR (400 MHz, CDCl₃) δ_H 7.20–7.45 (5H, m), 6.55 (1H, d, *J* 16.0, minor diastereomer), 6.52 (1H, d, *J* 15.9, major diastereomer), 6.21 (1H, dd, *J* 16.0, 7.0, minor diastereomer), 6.14 (1H, dd, *J* 16.0, 7.8, major diastereomer), 4.13–4.31 (1H, m), 1.37 (3H, m).

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-butanone (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 (76 mg, 0.19 mmol, 37%, 2:1 dr 26:27) for an overall yield of 81% 60:40 dr. Spectroscopic data in accordance with the literature.²² Podophyllotoxin **26**: ¹H NMR (400 MHz, CDCl₃) δ_H 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**: ¹H NMR (500 MHz, CDCl₃) δ_H 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, tdt, *J* 11.0, 7.7, 3.3), 1.82 (1H, d, *J* 4.3).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.2c01602>.

Full experimental procedures, characterization data, NMR spectra, and HPLC chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Gregory R. Boyce – *EaStCHEM, School of Chemistry, University of St Andrews, St Andrews, Fife KY16 9ST, U.K.; Department of Chemistry and Physics, Florida Gulf Coast University, Fort Myers, Florida 33965, United States;* orcid.org/0000-0002-5295-3378; Email: gboyce@fgcu.edu

Andrew D. Smith – *EaStCHEM, School of Chemistry, University of St Andrews, St Andrews, Fife KY16 9ST, U.K.;* orcid.org/0000-0002-2104-7313; Email: ads10@st-andrews.ac.uk

James E. Taylor – *Department of Chemistry, University of Bath, Bath, Somerset BA2 7AY, U.K.;* Email: jet21@bath.ac.uk

Authors

Stefania F. Musolino – *EaStCHEM, School of Chemistry, University of St Andrews, St Andrews, Fife KY16 9ST, U.K.;* orcid.org/0000-0002-0990-1855

Jianing Yang – *EaStCHEM, School of Chemistry, University of St Andrews, St Andrews, Fife KY16 9ST, U.K.*

Complete contact information is available at: <https://pubs.acs.org/10.1021/acs.joc.2c01602>

Notes

The authors declare no competing financial interest. Research data supporting this publication can be accessed at DOI: [10.17630/32d1c9e3-d14e-4653-98a1-3a5f13cb408c](https://doi.org/10.17630/32d1c9e3-d14e-4653-98a1-3a5f13cb408c).

■ ACKNOWLEDGMENTS

G.R.B. is grateful to Florida Gulf Coast University for a sabbatical award. The Engineering and Physical Sciences Research Council, University of St Andrews, and the EPSRC Centre for Doctoral Training in Critical Resource Catalysis (CRICAT) are thanked for financial support [Ph.D. studentship to S.F.M.; Grant Code: EP/L016419/1 and EP/J018139/1]. J.E.T. thanks the Leverhulme Trust (Grant Code: ECF-2014-005) and the EPSRC (Grant Code: EP/V051423/1).

■ REFERENCES

- (1) (a) Breuer, M.; Dittrich, K.; Habicher, T.; Hauer, B.; Keßler, M.; Stürmer, R.; Zelinski, T. Industrial Methods for the Production of Optically Active Intermediates. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824. (b) Wang, Y.; Chen, A. Crystallization-Based Separation of Enantiomers. In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds.; John Wiley and Sons, Inc.: Hoboken, NJ, 2013; pp 1–20. (c) Pellissier, H. Catalytic Kinetic Resolution. In *Separation of Enantiomers*; Todd, M., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2014; pp 75–122. (d) Nakano, K.; Kitamura, M. Dynamic Kinetic Resolution (DKR). In *Separation of Enantiomers*; Todd, M., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2014; pp 161–216.
- (2) (a) Ebbens, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. Controlled racemization of optically active

organic compounds: Prospects for asymmetric transformation. *Tetrahedron* **1997**, *53*, 9417–9476. (b) Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. Racemization catalysts for the dynamic kinetic resolution of alcohols and amines. *Coord. Chem. Rev.* **2008**, *252*, 647–658. (c) Parvulescu, A.; Janssens, J.; Vanderleyden, J.; De Vos, D. Heterogeneous Catalysts for Racemization and Dynamic Kinetic Resolution of Amines and Secondary Alcohols. *Top. Catal.* **2010**, *53*, 931–941.

(3) For selected examples, see: (a) Klomp, D.; Maschmeyer, T.; Hanefeld, U.; Peters, J. A. Mechanism of Homogeneously and Heterogeneously Catalysed Meerwein–Ponndorf–Verley–Oppenauer Reactions for the Racemisation of Secondary Alcohols. *Chem. Eur. J.* **2004**, *10*, 2088–2093. (b) Bosson, J.; Poater, A.; Cavallo, L.; Nolan, S. P. Mechanism of Racemization of Chiral Alcohols Mediated by 16-Electron Ruthenium Complexes. *J. Am. Chem. Soc.* **2010**, *132*, 13146–1319. (c) Warner, M. C.; Bäckvall, J.-E. Mechanistic Aspects on Cyclopentadienylruthenium Complexes in Catalytic Racemization of Alcohols. *Acc. Chem. Res.* **2013**, *46*, 2545–2555.

(4) (a) Wuyts, S.; De Temmerman, K.; De Vos, D.; Jacobs, P. A zeolite-enzyme combination for biphasic dynamic kinetic resolution of benzylic alcohols. *Chem. Commun.* **2003**, 1928–1929. (b) Wuyts, S.; De Temmerman, K.; De Vos, D. E.; Jacobs, P. A. Acid Zeolites as Alcohol Racemization Catalysts: Screening and Application in Biphasic Dynamic Kinetic Resolution. *Chem. Eur. J.* **2005**, *11*, 386–397. (c) Zhu, Y.; Fow, K. L.; Chuah, G. K.; Jaenicke, S. Dynamic Kinetic Resolution of Secondary Alcohols Combining Enzyme-Catalyzed Transesterification and Zeolite-Catalyzed Racemization. *Chem. Eur. J.* **2007**, *13*, 541–547. (d) Costa, L. F. A.; Lemos, F.; Ribeiro, F. R.; Cabral, J. M. S. Zeolite screening for the racemization of 1-phenylethanol. *Catal. Today* **2008**, *133–135*, 625–631.

(5) (a) Cheng, Y.; Xu, G.; Wu, J.; Zhang, C.; Yang, L. Highly efficient dynamic kinetic resolution of secondary aromatic alcohols with low-cost and easily available acid resins as racemization catalysts. *Tetrahedron Lett.* **2010**, *51*, 2366–2369. (b) Xu, G.; Wang, L.; Chen, Y.; Cheng, Y.; Wu, J.; Yang, L. Highly efficient dynamic kinetic resolution of secondary aromatic alcohols using a low-cost solid super acid as a racemization catalyst. *Tetrahedron Lett.* **2013**, *54*, 5026–5030. (c) Wu, J.-P.; Meng, X.; Wang, L.; Xu, G.; Yang, L.-R. Highly efficient dynamic kinetic resolution of secondary aromatic alcohols at low temperature using a low-cost sulfonated sepiolite as racemization catalyst. *Tetrahedron Lett.* **2014**, *55*, 5129–5132.

(6) (a) Wuyts, S.; Wahlen, J.; Jacobs, P. A.; De Vos, D. E. Heterogeneous vanadium catalysts for racemization and chemoenzymatic dynamic kinetic resolution of benzylic alcohols. *Green Chem.* **2007**, *9*, 1104–1108. (b) de Miranda, A. S.; de M. Silva, M. V.; Dias, F. C.; de Souza, S. P.; Leao, R. A. C.; de Souza, R. O. M. A. Continuous flow dynamic kinetic resolution of rac-1-phenylethanol using a single packed-bed containing immobilized CAL-B lipase and VO_2^+ as racemization catalysts. *React. Chem. Eng.* **2017**, *2*, 375–381.

(7) Görbe, T.; Lihammar, R.; Bäckvall, J.-E. Heterogeneous Acid-Catalyzed Racemization of Tertiary Alcohols. *Chem. Eur. J.* **2018**, *24*, 77–80.

(8) Kühn, F.; Katsuragi, S.; Oki, Y.; Scholz, C.; Akai, S.; Gröger, H. Dynamic kinetic resolution of a tertiary alcohol. *Chem. Commun.* **2020**, *56*, 2885–2888.

(9) (a) Zheng, H.; Hall, D. G. Boronic Acid Catalysis: an Atom-Economical Platform for Direct Activation and Functionalization of Carboxylic Acids and Alcohols. *Aldrichimica Acta* **2014**, *47*, 41–51. (b) Hall, D. G. Boronic acid catalysis. *Chem. Soc. Rev.* **2019**, *48*, 3475–3496. (c) Estopiñá-Durán, S.; Taylor, J. E. Brønsted Acid-Catalysed Dehydrative Substitution Reactions of Alcohols. *Chem. Eur. J.* **2021**, *27*, 106–120.

(10) See the [Supporting Information](#) for further details.

(11) (a) Greenhalgh, M. D.; Smith, S. M.; Walden, D. M.; Taylor, J. E.; Brice, Z.; Robinson, E. R. T.; Fallan, C.; Cordes, D. B.; Slawin, A. M. Z.; Richardson, H. C.; Grove, M. A.; Cheong, P. H. Y.; Smith, A. D. A C=O...Isothiouonium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolutions of Tertiary Heterocyclic

Alcohols. *Angew. Chem., Int. Ed.* **2018**, *57*, 3200–3206. (b) Smith, S. M.; Greenhalgh, M. D.; Feoktistova, T.; Walden, D. M.; Taylor, J. E.; Cordes, D. B.; Slawin, A. M. Z.; Cheong, P. H.-Y.; Smith, A. D. Scope, Limitations and Mechanistic Analysis of the HyperBTM-Catalyzed Acylative Kinetic Resolution of Tertiary Heterocyclic Alcohols. *Eur. J. Org. Chem.* **2022**, *2022*, e202101111.

(12) (a) Wolf, E.; Richmond, E.; Moran, J. Identifying lead hits in catalyst discovery by screening and deconvoluting complex mixtures of catalyst components. *Chem. Sci.* **2015**, *6*, 2501–2505. (b) Estopiñá-Durán, S.; Donnelly, L. J.; Mclean, E. B.; Hockin, B. M.; Slawin, A. M. Z.; Taylor, J. E. Aryl Boronic Acid Catalysed Dehydrative Substitution of Benzylic Alcohols for C–O Bond Formation. *Chem. Eur. J.* **2019**, *25*, 3950–3956. (c) Estopiñá-Durán, S.; McLean, E. B.; Donnelly, L. J.; Hockin, B. M.; Taylor, J. E. Arylboronic Acid Catalyzed C-Alkylation and Allylation Reactions Using Benzylic Alcohols. *Org. Lett.* **2020**, *22*, 7547–7551.

(13) Ang, H. T.; Rygus, J. P. G.; Hall, D. G. Two-component boronic acid catalysis for increased reactivity in challenging Friedel–Crafts alkylations with deactivated benzylic alcohols. *Org. Biomol. Chem.* **2019**, *17*, 6007–6014.

(14) Stopka, T.; Niggemann, M. Cyclopentanone as a Cation-Stabilizing Electron-Pair Donor in the Calcium-Catalyzed Intermolecular Carbohydroxylation of Alkynes. *Org. Lett.* **2015**, *17*, 1437–1440.

(15) Zheng, H.; Lejkowski, M.; Hall, D. G. Mild and selective boronic acid catalyzed 1,3-transposition of allylic alcohols and Meyer-Schuster rearrangement of propargylic alcohols. *Chem. Sci.* **2011**, *2*, 1305–1310.

(16) For selected examples, see: (a) Kamal, A.; Kumar, B. A.; Arifuddin, M. A one-pot, efficient and facile synthesis of 4 β -arylamino-podophyllotoxins: synthesis of NPF and GL-331 as DNA topoisomerase II inhibitors. *Tetrahedron Lett.* **2003**, *44*, 8457–8459. (b) Wan, J.-H.; Hu, Y.; Liu, H.; Tu, Y.-H.; He, Z.-Y.; Sun, J.-S. The Catalytically Lignan-Activation-Based Approach for the Synthesis of (*epi*)-Podophyllotoxin Derivatives. *J. Org. Chem.* **2017**, *82*, 5652–5662. (c) Lazzarotto, M.; Hammerer, L.; Hetmann, M.; Borg, A.; Schmermund, L.; Steiner, L.; Hartmann, P.; Belaj, F.; Kroutil, W.; Gruber, K.; Fuchs, M. Chemoenzymatic Total Synthesis of Deoxy-, *epi*-, and Podophyllotoxin and a Biocatalytic Kinetic Resolution of Dibenzylbutyrolactones. *Angew. Chem., Int. Ed.* **2019**, *58*, 8226–8230.

(17) (a) Auvil, T. J.; Mattson, A. E. Internal Lewis Acid Assisted Benzoic Acid Catalysis. *Synthesis* **2012**, *44*, 2173–2180. (b) Hashimoto, T.; Gálvez, A. O.; Maruoka, K. In Situ Assembled Boronate Ester Assisted Chiral Carboxylic Acid Catalyzed Asymmetric Trans-Aziridinations. *J. Am. Chem. Soc.* **2013**, *135*, 17667–17670.

(18) Rzepa, H. S.; Arkhipenko, S.; Wan, E.; Sabatini, M. T.; Karaluka, V.; Whiting, A.; Sheppard, T. D. An Accessible Method for DFT Calculation of ^{11}B NMR Shifts of Organoboron Compounds. *J. Org. Chem.* **2018**, *83*, 8020–8025.

(19) Bivona, L. A.; Quertinmont, F.; Beejapur, H. A.; Giacalone, F.; Buaki-Sogo, M.; Gruttadauria, M.; Aprile, C. Thiazolium-Based Catalysts for the Etherification of Benzylic Alcohols under Solvent-Free Conditions. *Adv. Synth. Catal.* **2015**, *357*, 800–810.

(20) Aridoss, G.; Sarca, V.-D.; Ponder, J.-F., Jr; Crowe, J.; Laali, K.-K. Electrophilic chemistry of propargylic alcohols in imidazolium ionic liquids: Propargylation of arenes and synthesis of propargylic ethers catalyzed by metallic triflates $[\text{Bi}(\text{OTf})_3, \text{Sc}(\text{OTf})_3, \text{Yb}(\text{OTf})_3]$, TfOH , or $\text{B}(\text{C}_6\text{F}_5)_3$. *Org. Biomol. Chem.* **2011**, *9*, 2518–2529.

(21) Zheng, H.; McDonald, R.; Hall, D. G. Boronic Acid Catalysis for Mild and Selective [3 + 2] Dipolar Cycloadditions to Unsaturated Carboxylic Acids. *Chem. Eur. J.* **2010**, *16*, 5454–5460. Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D. G. Boronic Acid Catalysis as a Mild and Versatile Strategy for Direct Carbo- and Heterocyclizations of Free Allylic Alcohols. *Angew. Chem., Int. Ed.* **2012**, *51*, 6187–6190.

(22) Lazzarotto, M.; Hammerer, L.; Hetmann, M.; Borg, A.; Schmermund, L.; Steiner, L.; Hartmann, P.; Belaj, F.; Kroutil, W.; Gruber, K.; Fuchs, M. Chemoenzymatic Total Synthesis of Deoxy-, *epi*-, and Podophyllotoxin and a Biocatalytic Kinetic Resolution of Dibenzylbutyrolactones. *Angew. Chem., Int. Ed.* **2019**, *58*, 8226–8230.