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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Communication

Enantioselective Desymmetrization of 2-Aryl-1,3-propanediols by Direct *O*-Alkylation with a Rationally Designed Chiral Hemiboronic Acid Catalyst That Mitigates Substrate Conformational Poisoning

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Cite This: *J. Am. Chem. Soc.* 2021, 143, 4162–4167
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ABSTRACT: Enantioselective desymmetrization by direct monofunctionalization of prochiral diols is a powerful strategy to prepare valuable synthetic intermediates in high optical purity. Boron acids can activate diols toward nucleophilic additions; however, the design of stable chiral catalysts remains a challenge and highlights the need to identify new chemotypes for this purpose. Herein, the discovery and optimization of a bench-stable chiral 9-hydroxy-9,10-boroxarophenanthrene catalyst is described and applied in the highly enantioselective desymmetrization of 2-aryl-1,3-diols using benzylic electrophiles under operationally simple, ambient conditions. Nucleophilic activation and discrimination of the enantiotopic hydroxy groups on the diol substrate occurs via a defined chairlike six-membered anionic complex with the hemiboronic heterocycle. The optimal binaphthyl-based catalyst **1g** features a large aryloxytrityl group to effectively shield one of the two prochiral hydroxy groups on the diol complex, whereas a strategically placed "methyl blocker" on the boroxarophenanthrene unit mitigates the deleterious effect of a competing conformation of the complexed diol that compromised the overall efficiency of the desymmetrization process. This methodology affords monoalkylated products in enantiomeric ratios equal or over 95:5 for a wide range of 1,3-propanediols with various 2-aryl/heteroaryl groups.

The catalytic enantioselective desymmetrization of simple bifunctional substrates such as diols is an attractive strategy to prepare useful optically enriched materials where, unlike kinetic resolution strategies, quantitative yields can theoretically be achieved.[1,2] To this end, direct and selective monofunctionalization of prochiral 1,3-diols can afford chiral building blocks of great synthetic value, and nonenzymatic methods often demonstrate a wider substrate scope (Figure 1A). Compared to meso-1,2-diols, available methodology for enantioselective desymmetrization of 1,3-diols is limited. Indirect,[3] intramolecular (cyclative),[4−8] and other catalytic methods exist to desymmetrize narrow classes of substrates such as 2-heteroatom substituted (halo, N, O) 1,3-diols.[9−16] Direct intermolecular catalytic desymmetrization methods for 2-alkyl/aryl 1,3-diols include enantioselective monoacylations of 2-aryl-1,3-propanediols catalyzed by a chiral dinuclear zinc catalyst, from Trost and co-workers,[17] the chiral 4-amino-pyridine catalyzed method of Suga and co-workers,[18] and the aminophosphonite catalyzed benzoylation of Fujimoto and co-workers[19] (Figure 1B). While these methods produce monofunctionalized 1,3-diols with good to high enantioselectivities, they are restricted by the use of cryogenic conditions, variable selectivity, and/or competing difunctionalization. Furthermore, these methods provide base-sensitive acylated products. Consequently, there remains a need for mild catalytic methods to access optically enriched derivatives of 2-substituted-1,3-propanediols *O*-functionalized with complementary groups. Because of their stability and their ease of removal using hydrogenolysis or Lewis acids, benzylic ethers represent an ideal option.

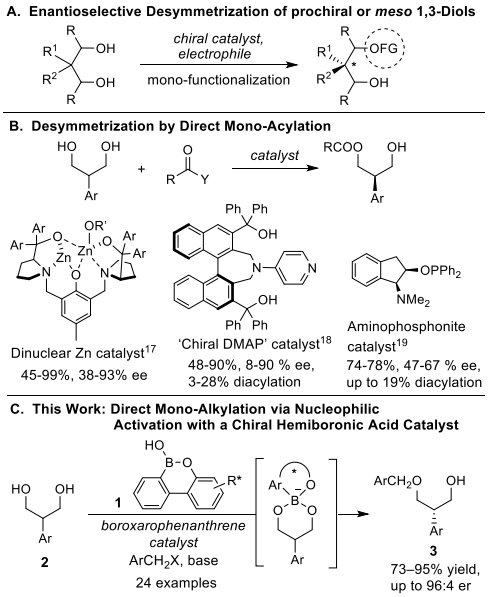
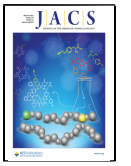


Figure 1. Direct and catalytic enantioselective intermolecular desymmetrization of prochiral 1,3-diols.

Received: January 20, 2021
Published: March 15, 2021

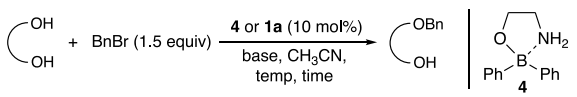


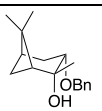
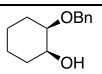
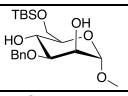
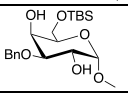
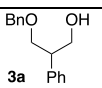
https://dx.doi.org/10.1021/jacs.1c00759
J. Am. Chem. Soc. 2021, 143, 4162–4167

Activation of diols can be achieved using boron acids, under basic conditions, by way of a transient tetravalent anionic complex inducing an increase of the charge and nucleophilicity of the diol's oxygen atoms.[20] Although great progress has been made in regioselective monofunctionalization of carbohydrates using diarylborinic acid catalysts,[21] limitations include the relative instability of borinic acids toward oxidation (typically they must be handled as ethanolamine adducts) and the considerable challenge to render this scaffold chiral.[22] Compared to borinic acids, boronic acids are generally more stable to ambient conditions and can be handled without special precautions.[23,24] However, to date very few examples of chiral boronic acid catalyzed reactions exist, and selectivities are moderate.[25−30] In search of an improved catalyst scaffold, we were drawn to evaluate cyclic hemiboronic acids. The 9-hydroxy-9,10-boroxarophenanthrene **1a**, a compound first reported by Dewar in 1959,[31] is known to exchange reversibly with alcohols.[32,33] Herein, we report the rational optimization of a bench-stable chiral boroxarophenanthrene catalyst for the highly enantioselective desymmetrization of 2-aryl-1,3-diols by direct mono-*O*-alkylation using benzylic electrophiles under operationally simple, ambient conditions (Figure 1C).

At the onset, the capability of 9-hydroxy-9,10-boroxarophenanthrene (**1a**) to catalyze the functionalization of polyols was determined through a screen of different hemiboronic heterocycles.[34] The efficiency of **1a** was subsequently assessed in comparison with that of diphenylborinic acid, as the borinate **4**, using a diverse panel of model 1,2- and 1,3-diols (Table 1). Using conditions reported by Taylor and co-workers,[35] catalytic monobenzylation of simple diols was achieved in good yields and high selectivities. Remarkably, using two distinct sets of reaction conditions, catalyst **1a** was found to be superior to borinate **4** in effecting the alkylation of model 1,3-diol **2a** to afford the monobenzylated product **3a** in good yield (entries 5−6). In all cases, poor conversions were observed in the absence of a catalyst.

Table 1. Comparison of Boroxarophenanthrene 1a and Borinate 4 in the Benzylation of 1,2- and 1,3-Diols[a]



entry	base	T (°C)	*t* (h)	product	yield (%) with **4**[b]	yield (%) with **1a**[b]
1	K_2CO_3 (1.1 equiv), KI (1.0 equiv)	60	24		78	82 (11.8:1 rr)
2	*i*-Pr_2NEt (1.7 equiv)	60	24		99	87
3	Ag_2O (1.1 equiv)	40	48		91	85 (4:1 O3:O4)
4	Ag_2O (1.1 equiv)	40	48		77	82[c]
5[d]	*i*-Pr_2NEt (1.5 equiv)	25	24	 **3a**	58	69
6[d,e]	K_2CO_3, KI	25	24	**3a**	47	65

[a]Conditions: 0.20 mmol of polyol, 0.30 mmol BnBr, 10 mol % **4** or **1a**, in 1 mL of CH_3CN (except entry 6: 0.10 mmol scale). [b]Isolated yields. [c]A single regioisomer was observed. [d]Reaction without catalyst (NMR yield): entry 5: 7.5% monobenzylated, 3.5% dibenzylated; 15% monobenzylated, 5.5% dibenzylated. [e]Conditions: BnCl (1.5 equiv), K_2CO_3 (1.7 equiv), KI (1.0 equiv) (rr, regioisomer ratio).

By analogy with borinic acid catalysts,[21] diol activation by catalyst **1a** is expected to arise through a tetrahedral anionic boron intermediate that imparts an increase in the oxygen's atomic charge. When mixing **1a** with equimolar 1,3-diol **2a** in the presence of potassium carbonate, an upfield resonance of 2.8 ppm corresponding to a tetravalent intermediate (**5a**) can be observed by ^{11}B NMR spectroscopy, which was corroborated by ESI HRMS, negative mode (Figure 2A).

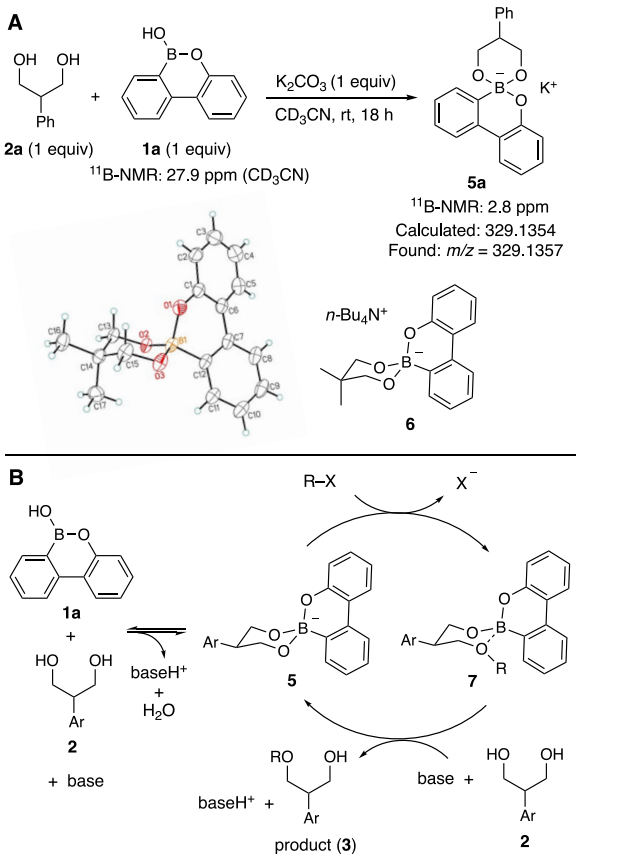


Figure 2. (A) Structure of the complex between boroxarophenanthrene **1a** and 1,3-diol **2a**. (B) Catalytic cycle for monoalkylation of 2-aryl-1,3-diols **2**.

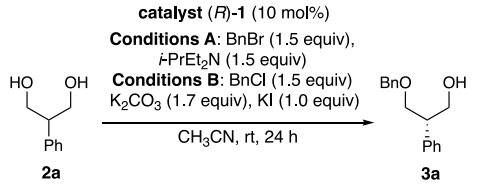
The X-ray crystallographic structure of a tetrahedral boron complex between **1a** and neopentyl alcohol was successfully resolved as the tetrabutyl ammonium salt **6**. Close inspection of its structure reveals a defined six-membered chairlike conformation in which the aryloxy B−O bond of the stereogenic boron atom occupies the axial position and the larger aryl B−C fragment is placed equatorially. Presumably, once the activated anionic species **5** forms in solution, one of the bound oxygen atoms is functionalized by the electrophile, with catalytic turnover arising from exchange of intermediate **7** with another molecule of diol **2** that concomitantly releases the monofunctionalized product (**3**) (Figure 2B). Functionalization occurs at one of the two alkoxy ligands as opposed to the less nucleophilic phenoxy ligand, and double alkylation is

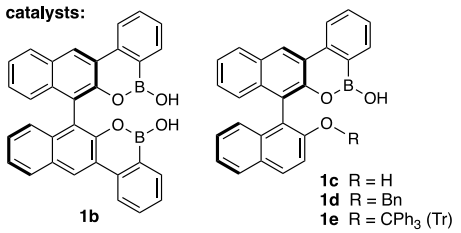
https://dx.doi.org/10.1021/jacs.1c00759
J. Am. Chem. Soc. 2021, 143, 4162−4167

prevented as two hydroxy groups are required for effective substrate activation with the catalyst.

Realizing the potential for enantioselective desymmetrization, we sought to design a chiral variant of catalyst **1a**. To this end, we first evaluated the 1,1′-bi-2-naphthol (BINOL)-derived axially chiral bis(boroxarophenanthrene) **1b** reported by Hosoya and co-workers (Table 2).[36] Utilizing (*R*)-**1b** as a chiral catalyst and model substrate **2a** under the monobenzylation conditions of Table 1 (entries 5−6), the desymmetrized product **3a** was isolated in good yield with moderate enantioselectivity (Table 2, entry 1, "conditions A"). Because it delivered monobenzylated diol **3a** with higher enantioselectivity (entry 2), conditions B (BnCl, K_2CO_3, KI) were selected for further optimization of the catalyst.

Table 2. Initial Optimization of Alkylation Conditions and Chiral Catalyst





entry	conditions[a]	catalyst	yield (%)[b]	er
1	**A**	**1b**	97	80:20
2	**B**	**1b**	99	83:17
3	**B**	**1c**	62	69:31
4	**B**	**1d**	83	79:21
5	**B**	**1e**	94	93:7

[a]Conditions: 0.10 mmol of diol **2a** in 0.5 mL of CH_3CN. [b]Isolated yields.

In consideration of the dimeric structure of catalyst **1b**, we posited that a single boronyl unit may be sufficient to complex the diol. To test this hypothesis, monohemiboronic acid **1c** was synthesized using a similar sequence starting from (*R*)-3-bromo-2,2′-dimethoxy-1,1′-binaphthalene.[34] Moreover, etherification of the hydroxy group of **1c** with a large group may provide a catalyst that can differentiate more efficiently the two diol oxygen atoms bound in the tetravalent boronate complex. Thus, whereas catalyst **1c** and **1d** provided the desymmetrized product with poorer enantioselectivity compared to **1b** (Table 2, entries 3−4), the trityl ether of catalyst **1e** provides much greater steric hindrance, and it led to a significantly higher er of 93:7 (entry 5). According to a stereochemical induction model informed by the above X-ray crystallographic structure of adduct **6**, which assumes a pseudoequatorial 2-aryl group in the chairlike complex, alkylation of the most accessible oxygen atom would result in formation of (*S*)-**3a** (Figure 3). Indeed, the (*S*) absolute stereochemistry of the major enantiomer was confirmed by the X-ray crystallographic analysis of the 3,5-dinitrobenzoyl derivative of **3a**.[34]

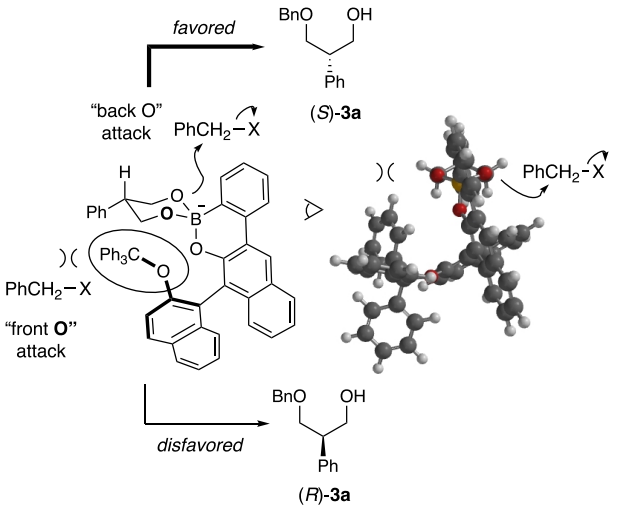


Figure 3. Stereochemical model for the monobenzylation of 1,3-diol **2a** using catalyst (*R*)-**1e**.

A final round of optimization was attempted to further increase the catalyst's enantioselectivity. Using catalyst **1e**, lowering the temperature, or a switch to other polar solvents and carbonate bases, provided no improvement.[34] Control experiments suggested that the background reaction is not competing under these conditions and that the enantioselectivity is truly limited by the structure of the catalyst.[34] A crucial clue for further improving the catalyst's enantioselectivity emerged from the ^{1}H NMR analysis of complex **5a**, which showed a second, minor set of resonances likely attributable to another slow-exchanging conformer.[34] As inferred from the above X-ray crystallographic structure (**6**, Figure 2A), the conformer of **5a** with a pseudoaxial aryloxy group is expected to be favored; however, the diol's phenyl group may be positioned either pseudoequatorial or pseudoaxial (Figure 4A). In the absence of H⇔Ph 1,3-diaxial interactions (such as in phenylcyclohexane), the pseudoaxial conformer **II** may be very close in energy relative to the pseudoequatorial conformer **I**.

As shown with catalyst (*R*)-**1e** in Figure 4B, this minor conformer can cause a significant erosion of the enantioselectivity of the desymmetrization because it is expected to lead, by alkylation of the least hindered O atom, to the antipode of product (*S*)-**3a**. The four possible conformers of **4** were minimized computationally using density functional theory (DFT) calculations (B3LYP/6-31G*). Although the relative energies of the conformers are to be considered approximate, the calculations confirmed the large preference for the two conformers with the pseudoaxial aryloxy group, **I** and **II** (Figure 4A). However, the desired conformer **I** with the pseudoequatorial phenyl substituent is only slightly lower in energy (~0.5 kJ/mol). It was hypothesized that the addition of a "methyl blocker" in position 1 of the boroxarophenanthrene scaffold would cause unfavorable nonbonded interactions in the minor, undesired conformer **II** that would help minimize this conformer and its deleterious effect on the reaction's enantioselectivity. Computations evaluating the effect of 1-methyl substitution are in full agreement with this proposal, revealing a larger energy difference in favor of conformer **I** (Figure 4A, R = Me). These calculations are corroborated by NMR spectroscopic studies comparing the conformer ratio between **1a** and the methylated derivative **1f** (Figure 4C). Although the minor conformer is still observed with **1f**, its

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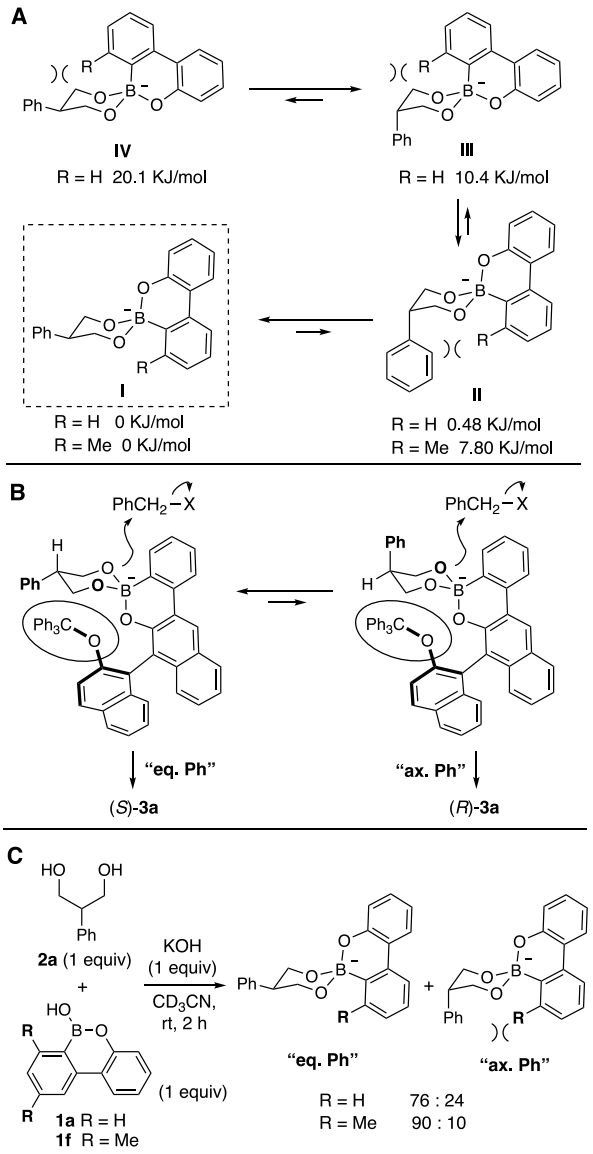
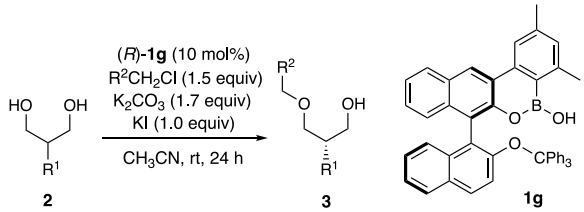


Figure 4. Analysis (A) and stereochemical implications (B) of possible conformations of catalysts **1** complexed with diol **1a**. (C) NMR study of the effect of a "methyl blocker" on the conformational equilibrium (ax., axial; eq., equatorial).

proportion is significantly reduced from 1:4 to 1:9. Additionally, due to the additional steric hindrance of a pseudoaxial aryl group in the approach of the electrophile, it is plausible that the minor conformer **II** is intrinsically less reactive. To test the idea of substrate conformational control, chiral catalyst **1g** with the "methyl blocker" was prepared.[34] When compared with catalyst **1e** in the benzylation of diol **2a**, the methylated derivative **1g** afforded a reproducible increase of enantioselectivity from 93:7 (cf. Table 2, entry 5) to 95:5 er with both the (*R*) (Table 3, entry 1) and (*S*) catalyst (entry 2). Further supporting its ability to control the substrate's conformation, the methylated catalyst **1g** was found to consistently outperform catalyst **1e** when compared with several other substrates (e.g., **2f**: 95:5 vs 92:8; **2g**: 95:5 vs 93:7; **2m**: 94.5:4.5 vs 91:9).[34]

The scope of the 2-substituent was examined with the optimal catalyst (*R*)-**1g**. High yields and consistently high enantioselectivity ratios were obtained for aryl groups

Table 3. Scope of 2-Substituted 1,3-Diol Substrates with Catalyst (*R*)-1g[a]



entry	diol	R^1	R^2	yield[b] (%)	er
1	**2a**	Ph	Ph	90	95:5
2[c]	**2a**	Ph	Ph	95	5:95
3	**2b**	2-MeC_6H_4	Ph	86	96:4
4	**2c**	3-MeC_6H_4	Ph	90	94.5:5.5
5	**2d**	4-MeC_6H_4	Ph	88	95.5:4.5
6	**2e**	2-MeOC_6H_4	Ph	84	95.5:4.5
7	**2f**	3-MeOC_6H_4	Ph	91	95:5
8[d]	**2g**	4-MeOC_6H_4	Ph	93	95:5
9	**2h**	2-FC_6H_4	Ph	95	95:5
10	**2i**	4-FC_6H_4	Ph	84	95:5
11	**2j**	2-ClC_6H_4	Ph	85	95:5
12[d]	**2k**	2-BrC_6H_4	Ph	76	95:5
13	**2l**	3-BrC_6H_4	Ph	81	95:5
14	**2m**	4-BrC_6H_4	Ph	88	94.5:5.5
15[d]	**2n**	4-$CF_3C_6H_4$	Ph	73	93.5:6.6
16	**2o**	4-$NO_2C_6H_4$	Ph	81	93.5:6.5
17	**2p**	3-indolyl	Ph	81	92.5:7.5
18	**2q**	3-thienyl	Ph	91	94:6
19	**2r**	1-naphthyl	Ph	90	92.5:7.5
20	**2s**	*t*-Bu	Ph	70	92:8
21	**2t**	CH_2Ph	Ph	89	75:25
22	**2a**	Ph	4-$CF_3C_6H_4$	87	95.6:4.4
23	**2a**	Ph	4-MeOC_6H_4	88	94.2:5.8
24	**2a**	Ph	2-naphthyl	74	95.7:4.3
25	**2u**	N-Phthalamido	Ph	50	91.8:8.2

[a]Conditions: 0.10 mmol of diol **2** in 0.5 mL of CH_3CN. [b]Isolated yields. [c]With catalyst (*S*)-**1g**, affording product (*R*)-**3a**. [d]With recycled catalyst.

substituted at all positions. For example, all three positional isomers of tolyl and methoxyphenyl groups provided er's of 95:5 and over (entries 3−8). Halogenated 2-aryl 1,3-diols are suitable substrates regardless of the position of the halide substituent (entries 9−14). Strong electron-withdrawing substituents like trifluoromethyl and nitro lead to slightly decreased enantioselectivities (entries 15−16), as are the 2-heteroaryl substrates (entries 17−18). In contrast, aliphatic groups such as *tert*-butyl (entry 20) and benzyl (entry 21) led to significantly lower er's. Overall the obtained er's roughly parallel substituent A values (e.g., Bn 1.9, Ph 3.0 kcal/mol). Satisfactorily, high selectivities are maintained when using other electrophiles like functionalized benzylic chlorides and even a naphthyl derivative (entries 22−24). Finally, a 2-amino derivative (entry 25) and a 1,3-disubstituted 1,3-diol[34] demonstrate potential toward other substrate classes. Notably, catalyst **1g** is recyclable (cf. entries 8, 12, 15).

In summary, highly enantioselective desymmetrization of 2-aryl-1,3-propanediols by direct *O*-alkylation was achieved under mild ambient conditions using a novel class of chiral hemiboronic acid organocatalyst derived from BINOL. Nucleophilic activation and discrimination of the enantiotopic hydroxy groups on the substrate occurs via a defined, chairlike

https://dx.doi.org/10.1021/jacs.1c00759
J. Am. Chem. Soc. 2021, 143, 4162−4167

six-membered anionic boronate complex. Catalyst optimization featured the judicious addition of a steric blocking group to help disfavor a poisoning conformer, leading to higher enantiomeric ratios equal or over 95:5 for a wide range of 2-aryl/heteroaryl groups embodying various, synthetically useful substituents. It can be anticipated that the chiral boroxarophenanthrene scaffold will be amenable to further improvements, along with applications with other electrophiles and transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00759.

Full experimental details, analytical data, and spectral reproductions for all new compounds; initial screening of catalyst **1a**; further reaction optimization studies; details of molecular modeling (PDF)

Accession Codes

CCDC 2051073 and 2063743 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada (Discovery Grant RGPIN-2017-05086 to D.G.H.). We thank Mr. Ed Fu for help with chiral HPLC analysis of the enantiomeric ratio and Dr. Michael Ferguson (X-ray Crystallography Laboratory, University of Alberta) for X-ray crystallographic analyses.

■ REFERENCES

(1) Díaz-de-Villegas, M.; Gálvez, J. A.; Badorrey, R.; López-Ram-de-Víu, M. P. Organocatalyzed Enantioselective Desymmetrization of Diols in the Preparation of Chiral Building Blocks. *Chem. - Eur. J.* **2012**, *18*, 13920−13935.

(2) Suzuki, T. Recent Topics in the Desymmetrization of meso-Diols. *Tetrahedron Lett.* **2017**, *58*, 4731−4739.

(3) Meng, S.-S.; Liang, Y.; Cao, K.-S.; Zou, L.; Lin, X.-B.; Yang, H.; Houk, K. N.; Zheng, W.-H. Chiral Phosphoric Acid Catalyzed Highly Enantioselective Desymmetrization of 2-Substituted and 2,2-Disubstituted 1,3-Diols via Oxidative Cleavage of Benzylidene Acetals. *J. Am. Chem. Soc.* **2014**, *136*, 12249−12252.

(4) Chen, Z.; Sun, J. Enantio- and Diastereoselective Assembly of Tetrahydrofuran and Tetrahydropyran Skeletons with All-Carbon-Substituted Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2013**, *52*, 13593−13596.

(5) Tay, D. W.; Leung, G. Y. C.; Yeung, Y.−Y. Desymmetrization of Diolefinic Diols by Enantioselective Aminothiocarbamate-Catalyzed Bromoetherification: Synthesis of Chiral Spirocycles. *Angew. Chem., Int. Ed.* **2014**, *53*, 5161−5164.

(6) Ke, Z.; Tan, C. K.; Chen, F.; Yeung, Y.−Y. Catalytic Asymmetric Bromoetherification and Desymmetrization of Olefinic 1,3-Diols with C2-Symmetric Sulfides. *J. Am. Chem. Soc.* **2014**, *136*, 5627−5630.

(7) Zi, W.; Toste, F. D. Gold(I)-Catalyzed Enantioselective Desymmetrization of 1,3-Diols Through Intramolecular Hydroalkoxylation of Allenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 14447−14451.

(8) Wu, Z.; Wang, J. Enantioselective Medium-Ring Lactone Synthesis Through an NHC−Catalyzed Intramolecular Desymmetrization of Prochiral 1,3-Diols. *ACS Catal.* **2017**, *7*, 7647−7652.

(9) Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. Desymmetrization of Glycerol Derivatives with Peptide-Based Acylation Catalysts. *Org. Lett.* **2005**, *7*, 3021−3023.

(10) Honjo, T.; Nakao, M.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y.; Nagao, Y. Nonenzymatic Enantioselective Monoacetylation of Prochiral 2-Protected Amino-2-Alkyl-1,3-Propanediols Utilizing a Chiral Sulfonamide-Zn Complex Catalyst. *Org. Lett.* **2007**, *9*, 509−512.

(11) Hong, M. S.; Kim, T. W.; Jung, B.; Kang, S. H. Enantioselective Formation of tert-Alkylamines by Desymmetrization of 2-Substituted Serinols. *Chem. - Eur. J.* **2008**, *14*, 3290−3296.

(12) You, Z.; Hoveyda, A. H.; Snapper, M. L. Catalytic Enantioselective Silylation of Acyclic and Cyclic Triols: Application to Total Syntheses of Cleroindicins D, F, and C. *Angew. Chem., Int. Ed.* **2009**, *48*, 547−550.

(13) Lee, J. Y.; You, Y. S.; Kang, S. H. Asymmetric Synthesis of All-Carbon Quaternary Stereocenters via Desymmetrization of 2,2-Disubstituted 1,3-Propanediols. *J. Am. Chem. Soc.* **2011**, *133*, 1772−1774.

(14) Li, B.-S.; Wang, Y.; Proctor, R. S. J.; Jin, Z.; Chi, Y. R. Carbene-Catalyzed Desymmetrization of 1,3-Diols: Access to Optically Enriched Tertiary Alkyl Chlorides. *Chem. Commun.* **2016**, *52*, 8313−8316.

(15) Meng, S.-S.; Tang, W.-B.; Zheng, W.-H. Catalytically Enantioselective Synthesis of Acyclic α-Tertiary Amines through Desymmetrization of 2-Substituted 2-Nitro-1,3-diols. *Org. Lett.* **2018**, *20*, 518−521.

(16) Yamamoto, K.; Ishimaru, S.; Oyama, T.; Tanigawa, S.; Kuriyama, M.; Onomura, O. Enantioselective Synthesis of α-Substituted Serine Derivatives via Cu-Catalyzed Oxidative Desymmetrization of 2-Amino-1,3-Diols. *Org. Process Res. Dev.* **2019**, *23*, 660−666.

(17) Trost, B. M.; Mino, T. Desymmetrization of meso 1,3- and 1,4-Diols with a Dinuclear Zinc Asymmetric Catalyst. *J. Am. Chem. Soc.* **2003**, *125*, 2410−2411.

(18) Mandai, H.; Ashihara, K.; Mitsudo, K.; Suga, S. Enantioselective Desymmetrization of 1,3-Diols by a Chiral DMAP Derivative. *Chem. Lett.* **2018**, *47*, 1360−1363.

(19) Aida, H.; Mori, K.; Yamaguchi, Y.; Mizuta, S.; Moriyama, T.; Yamamoto, I.; Fujimoto, T. Enantioselective Acylation of 1,2- and 1,3-Diols Catalyzed by Aminophosphinite Derivatives of (*1S,2R*)-1-Amino-2-Indanol. *Org. Lett.* **2012**, *14*, 812−815.
(20) Oshima, K.; Aoyama, Y. Regiospecific Glycosidation of Unprotected Sugars via Arylboronic Activation. *J. Am. Chem. Soc.* **1999**, *121*, 2315−2316.
(21) Taylor, M. S. Catalysis Based on Reversible Covalent Interactions of Organoboron Compounds. *Acc. Chem. Res.* **2015**, *48*, 295−305.
(22) Although examples of enantioselective functionalization of vicinal diols were reported, these systems require a chiral cocatalyst in addition to a nonchiral borinic acid: (a) Pawliczek, M.; Hashimoto, T.; Maruoka, K. Alkylative Kinetic Resolution of Vicinal Diols Under Phase-Transfer Conditions: a Chiral Ammonium Borinate Catalysis. *Chem. Sci.* **2018**, *9*, 1231−1235. (b) Li, R. Z.; Tang, H.; Yang, K. R.; Wan, L. Q.; Zhang, X.; Liu, J.; Fu, Z.; Niu, D. Enantioselective Propargylation of Polyols and Desymmetrization of meso 1,2-Diols by Copper/Borinic Acid Dual Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 7213−7217.
(23) Hall, D. G. In *Boronic Acids − Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2011; Chapter 1, pp 1−133.
(24) Hall, D. G. Boronic Acid Catalysis. *Chem. Soc. Rev.* **2019**, *48*, 3475−3496.
(25) Arnold, K.; Davies, B.; Hérault, D.; Whiting, A. Asymmetric Direct Amide Synthesis by Kinetic Amine Resolution: A Chiral Bifunctional Aminoboronic Acid Catalyzed Reaction Between a Racemic Amine and an Achiral Carboxylic Acid. *Angew. Chem., Int. Ed.* **2008**, *47*, 2673−2676.
(26) Lee, D.; Newman, S. G.; Taylor, M. S. Boron-Catalyzed Direct Aldol Reactions of Pyruvic Acids. *Org. Lett.* **2009**, *11*, 5486−5489.
(27) Hashimoto, T.; Gálvez, A. O.; Maruoka, K. Boronic Acid-Catalyzed, Highly Enantioselective Aza-Michael Additions of Hydroxamic Acid to Quinone Imine Ketals. *J. Am. Chem. Soc.* **2015**, *137*, 16016−16019.
(28) Hayama, N.; Azuma, T.; Kobayashi, Y.; Takemoto, Y. Chiral Integrated Catalysts Composed of Bifunctional Thiourea and ArylBoronic Acid: Asymmetric Aza-Michael Addition of alpha,beta-Unsaturated Carboxylic Acids. *Chem. Pharm. Bull.* **2016**, *64*, 704−717.
(29) Hayama, N.; Kuramoto, R.; Földes, T.; Nishibayashi, K.; Kobayashi, Y.; Pápai, I.; Takemoto, Y. Mechanistic Insight Into Asymmetric Hetero-Michael Addition of alpha,beta-Unsaturated Carboxylic Acids Catalyzed by Multifunctional Thioureas. *J. Am. Chem. Soc.* **2018**, *140*, 12216−12225.
(30) Kuwano, S.; Hosaka, Y.; Arai, T. Chiral Benzazaboroles as Catalysts for Enantioselective Sulfonylation of cis-1,2-Diols. *Org. Biomol. Chem.* **2019**, *17*, 4475−4482.
(31) Dewar, M. J. S.; Dietz, R. Aromatic Boron-Oxygen Heterocycles. *Tetrahedron Lett.* **1959**, *1*, 21−23.
(32) Greig, L. M.; Kariuki, B. M.; Habershon, S.; Spencer, N.; Johnston, R. L.; Harris, K. D. M.; Philp, D. Solid-State and Solution Phase Reactivity of 10-Hydroxy-10,9-Boroxophenanthrene: a Model Building Block for Self-Assembly Processes. *New J. Chem.* **2002**, *26*, 701−710.
(33) Greig, L. M.; Slawin, A. M. Z.; Smith, M. H.; Philp, D. The Dynamic Covalent Chemistry of Mono- and Bifunctional Boroxoaromatics. *Tetrahedron* **2007**, *63*, 2391−2403.
(34) See Supporting Information materials for details.
(35) Lee, D.; Williamson, C. L.; Chan, L.; Taylor, M. S. Regioselective, Borinic Acid-Catalyzed Monoacylation, Sulfonylation and Alkylation of Diols and Carbohydrates: Expansion of Substrate Scope and Mechanistic Studies. *J. Am. Chem. Soc.* **2012**, *134*, 8260−8267.
(36) Sumida, Y.; Harada, R.; Kato-Sumida, T.; Johmoto, K.; Uekusa, H.; Hosoya, T. Boron-Selective Biaryl Coupling Approach to Versatile Dibenzoxaborins and Application to Concise Synthesis of Defucogilvocarcin M. *Org. Lett.* **2014**, *16*, 6240−6243.

https://dx.doi.org/10.1021/jacs.1c00759
J. Am. Chem. Soc. 2021, 143, 4162−4167