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Enantioselective Synthesis of 1,2-Dihydronaphthalene-1-carbaldehydes by Addition of Boronates to Isochromene Acetals Catalyzed by Tartaric Acid

Yi Luan, Keith S. Barbato, Philip N. Moquist, Tomohiro Kodama, and Scott E. Schaus*

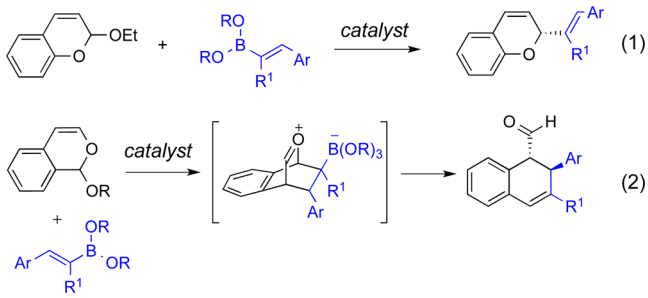
Department of Chemistry, Boston University, 24 Cummington Street, Boston, Massachusetts 02215, United States

Supporting Information

ABSTRACT: Tartaric acid is an ideal asymmetric catalyst as it is abundant, cheap, and environmentally friendly. (+)-Tartaric acid was found to catalyze a novel enantioselective [4 + 2] cycloaddition of isochromene acetals and vinylboronates. A variety of substituted isochromene acetals were tolerated, furnishing the desired dihydronaphthalenes and dihydrobenzofluorene products in good yields. High enantiomeric ratios (up to 98.5:1.5) and excellent diastereoselectivities (all >99:1) were observed employing 10 mol % of (+)-tartaric acid as the catalyst, in combination with 5 mol % of $Ho(OTf)_3$.

Since its discovery, the Diels—Alder cycloaddition reaction has become one of the most actively studied and synthetically implemented reactions.[1] This observation is due to the bond forming efficiency as well as the predictable chemo- and stereoselectivity of the reaction.[2] This area of study has borne witness to many seminal advances; for example, the use of Lewis acid and transition metal mediated catalysis,[3] asymmetric methods to control stereochemistry,[4] and the use of heteroatoms in the 4π and 2π components.[5] One long held challenge has been to promote the reaction under ambient conditions using boronates as 4π or 2π components.[6] One successful approach utilized boronate ester Lewis acids, enabling faster rates by altering the LUMO component of the frontier orbital interactions.[7] With this in mind, we postulated that the converse would hold true. A few examples of boronates in Diels–Alder reactions have been described[8] and more recently were demonstrated as HOMO raising substituents in an inverse-electron demand fashion by Sun and coworkers.[9] By first activating the boronate, the boronate dienophile can engage in a [4 + 2] cycloaddition reaction, whereas the unactivated precursor would not, due to the vacant *p*-orbital of the boron.[10] To this end, we report a new example of a boronate inverse-electron demand Diels—Alder reaction catalyzed by chiral tartaric acid to access chiral dihydronaphthalene structures.[11]

Although oxocarbenium ions have been extensively utilized in Diels–Alder reactions for the synthesis of natural products and bioactive molecules,[12] there has been a long-standing challenge of using highly reactive oxocarbenium intermediates in a stereoselective and catalytic manner.[13] Recently, a number of innovations have been published to address these issues.[14] Jacobsen demonstrated a thiourea-catalyzed asymmetric addition of silyl ketene acetal to 1-chloroisochromans, which were generated in situ from an isochroman acetal.[15] Later, he reported the use of a dual catalyst system to promote a [5 + 2] cycloaddition reaction, which utilized an oxidopyrylium intermediate.[16] Watson developed an enantioselective Cu(I)-catalyzed addition of terminal alkynes to isochroman acetal.[17] We have studied the enantioselective addition of boronates to oxocarbenium and iminium precursors, such as chromene acetals and *N*-acyl quinoliniums, catalyzed by tartaric acid and its derivatives (eq 1).[18,19] Further studies revealed that the



reaction of isochromene acetals with boronates form the dihydronaphthalene structural motif rather than the direct addition product (eq 2). We postulated that a similar oxocarbenium could be generated under the same acidic reaction conditions and that the dihydronaphthalene was generated through a Diels—Alder pathway. A similar observation was only recently described by Sun and coworkers.[9]

Dihydronaphthalene derivatives are useful starting materials for the synthesis of biologically active cyclic molecules.[20] Cannabisin C and negundin B are dihydronaphthalene natural products found in the roots of *cannabis sativa* and *vitex negundo*, respectively.[21] (+)-Phyltetralin was one of five constituents isolated from *pkyllantkus niruri*, which has been used in the treatment of jaundice, asthma, and bronchial infections.[22] Previously, several approaches have been reported to access substituted 1,2-dihydronaphthalene structures. A. I. Meyers pioneered access to these chiral building blocks by the addition of lithium anions to chiral naphthyloxazolines.[23] He applied this strategy toward the synthesis of (+)-phyltetralin.[24] Tomioka then extended this development with an asymmetric variant to an α,β-unsaturated aldimine.[25] Y. Yamamoto reported a copper-catalyzed [4 + 2] cycloaddition of *o*-alkynyl(oxo)-

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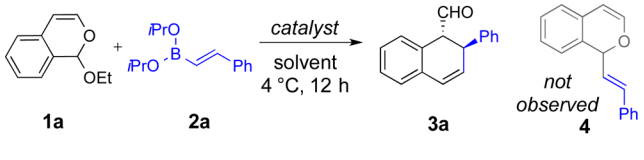
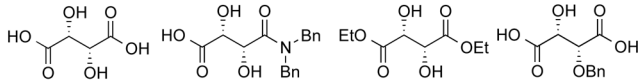
benzenes with alkenes to form functionalized 1,2-dihydronaphthalenes in a racemic fashion.[26] In comparison to previously reported synthetic approaches, our boronate strategy provides a complementary approach to access a variety of chiral dihydronaphthalene structures in high yields, enantioselectivities, and diastereoselectivities.

We started our investigation with acetic acid and $Yb(OTf)_3$, a Lewis acid–Brønsted acid catalytic system we have used in similar reactions.[18] The reaction afforded the 1,2-dihydronaphthalene product **3a** as a single diastereomer (Table 1, entry 1). The 1,2-addition product **4** was not observed under any circumstance. While it is known that tartaric acid derivatives, together with borane, have been utilized in enantioselective Diels—Alder reactions,[27] tartaric acid **5** has found little use as a catalyst in asymmetric synthesis. (+)-Tartaric acid **5** gave a 71% yield and 93:7 er with a 10 mol % catalyst loading (Table 1, entry 2). Tartaric acid derived catalyst **6** (10 mol %) gave a comparable yield in the reaction, but at lower er (Table 1, entry 3). Other tartaric acid derived catalysts were evaluated as well. (+)-Diethyl tartrate **7** did not perform well, providing the desired product **3a** in only 22% yield with no enantioselectivity (Table 1, entry 4). Monoprotection of the diol of tartaric acid with a benzyl group resulted in a low yield and er (catalyst **8**, Table 1, entry 5), which indicates the crucial role of the diol group to promote both ligand exchange and selectivity. Furthermore, to test for the optimal solvent for this Diels—Alder reaction, a solvent screen was performed in an attempt to further improve the enantioselectivity. Ethyl acetate and diethyl ether gave a poor yield and er (Table 1, entries 6 and 7). Due to the low solubility of (+)-tartaric acid in toluene, a low yield and er were correspondingly observed (Table 1, entry 8). The catalysts were more soluble in trifluorotoluene, a polar aprotic solvent. However, both the yield and er were still similar to the case with THF (Table 1, entry 9). We then decided to introduce an aromatic solvent mixture by combining THF and toluene.

Table 1. Asymmetric Diels—Alder Reaction of Boronates and Isochromene Acetals[a]





5 6 7 8

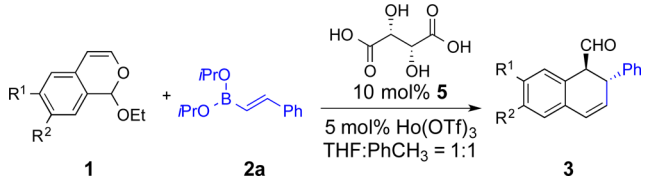
entry	cat.	metal salt	solvent	yield[b]	er[c]
1	AcOH	$Yb(OTf)_3$	THF	64%	–
2	**5**	$Yb(OTf)_3$	THF	71%	93:7
3	**6**	$Yb(OTf)_3$	THF	65%	75:25
4	7	$Yb(OTf)_3$	THF	22%	50:50
5	**8**	$Yb(OTf)_3$	THF	38%	58:42
6	**5**	$Yb(OTf)_3$	Et_2O	24%	91:9
7	**5**	$Yb(OTf)_3$	EtOAc	40%	75:25
8	**5**	$Yb(OTf)_3$	$PhCH_3$	45%	67:33
9	**5**	$Yb(OTf)_3$	$PhCF_3$	75%	92:8
10	**5**	$Yb(OTf)_3$	THF–$PhCH_3$	71%	95:5
11	**5**	–	THF–$PhCH_3$	0%	–
12	**5**	$Sc(OTf)_3$	THF–$PhCH_3$	80%	72:28
13	**5**	$Ce(OTf)_4$	THF–$PhCH_3$	71%	93:7
14	**5**	$Ce(OTf)_3$	THF–$PhCH_3$	70%	94:6
15	**5**	$Ho(OTf)_3$	THF–$PhCH_3$	76%	95.5:4.5

[a]Reactions were run with 0.2 mmol of isochromene acetal **1a**, 0.3 mmol of boronate **2a**, 10 mol % of catalyst, and 5 mol % metal salt in solvent (1 mL) for 12 h at 4 °C under Ar, followed by flash chromatography on silica gel, for THF–$PhCH_3$ mix solvent (1:1). [b]Yield of isolated product. [c]Enantiomeric ratios determined by HPLC analysis.

The best ratio was determined to be 1:1, which provided the optimal reaction conditions and produced dihydronaphthalene **3a** in 74% yield and 95:5 er (Table 1, entry 10). The use of isopropyl boronates proved to be the best balance of reactivity and enantioselectivity, with other acyclic boronates resulting in lower selectivity. Rare-earth lanthanide triflates were evaluated as cocatalysts to improve the rate of reaction.[18,28] In the absence of a lanthanide triflate, the reaction does not proceed (Table 1, entry 11). $Sc(OTf)_3$ performed this transformation poorly (Table 1, entry 12). $Ce(OTf)_4$ and $Ce(OTf)_3$ also gave similar results as $Yb(OTf)_3$, which was observed in the previous boronate addition to 2*H*-chromene acetal (Table 1, entries 13 and 14). $Ho(OTf)_3$ gave the best yield and er among other metal salts we screened (Table 1, entry 15). Of note, the results with cerium, ytterbium, and holmium catalysts are similar, and although no significant trends could be discerned, the use of holmium gave the most reproducible results.[29] The relative and absolute stereochemistry was determined by X-ray analysis of compound **3a**, and the newly formed *trans* stereochemistry was assigned to be 1*R*, 2*S*.

The scope of the reaction was evaluated under the optimized reaction conditions (Table 1, entry 15) using 10 mol % (+)-tartaric acid, 5 mol % $Ho(OTf)_3$, and a 1:1 THF/toluene mixture as solvent. First, we examined the effect of substituents on the isochromene acetal **1**. Electron-withdrawing groups on acetal **1** gave good selectivity, although prolonged reaction times at ambient temperature (20 °C) were required for good yields (Table 2, entries 2–4). Electron-donating groups on acetals gave good yields and selectivity as well (Table 2, entries 5–6). The higher reactivity of the electron-rich isochromene acetal precursors indicates the importance of stabilizing the

Table 2. (+)-Tartaric Acid Catalyzed Diels—Alder Reaction of Boronates and Isochromene Acetals[a]



1 2a 3

entry	isochromene acetal (**1**)	**3**	*T* [°C]	yield[b]	er
1	R^1 = H, R^2 = H (**1a**)	**3a**	4	76%	95.5:4.5
2[c]	R^1 = H, R^2 = Cl (**1b**)	**3b**	20	71%	98:2
3[c]	R^1 = F, R^2 = H (**1c**)	**3c**	20	81%	96.5:3.5
4[c]	R^1 = H, R^2 = F (**1d**)	**3d**	20	83%	95:5
5	R^1 = H, R^2 = OCH_3 (**1e**)	**3e**	4	80%	95:5
6	R^1, R^2 = 6,7-(OCH_2O) (**1f**)	**3f**	4	70%	96:4

[a]Reactions were run with 0.2 mmol of isochromene acetal, 0.3 mmol of boronate, 10 mol % tartaric acid, and 5 mol % $Ho(OTf)_3$ in 1 mL of THF/$PhCH_3$ 1:1 for 12 h under Ar, followed by flash chromatography on silica gel. [b]Yield of isolated product. [c]24 h at room temperature.

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positive charge on the benzopyrylium during the oxocarbenium formation step. This trend of reactivity was also observed in the tartaramide-catalyzed additions of boronates to 2*H*-chromene acetal.[18a]

The [4 + 2] cycloaddition of alkenyl boronates gave good results regardless of electron-withdrawing or -donating groups (Figure 1, products **10a**−**10d**). The cycloaddition of a

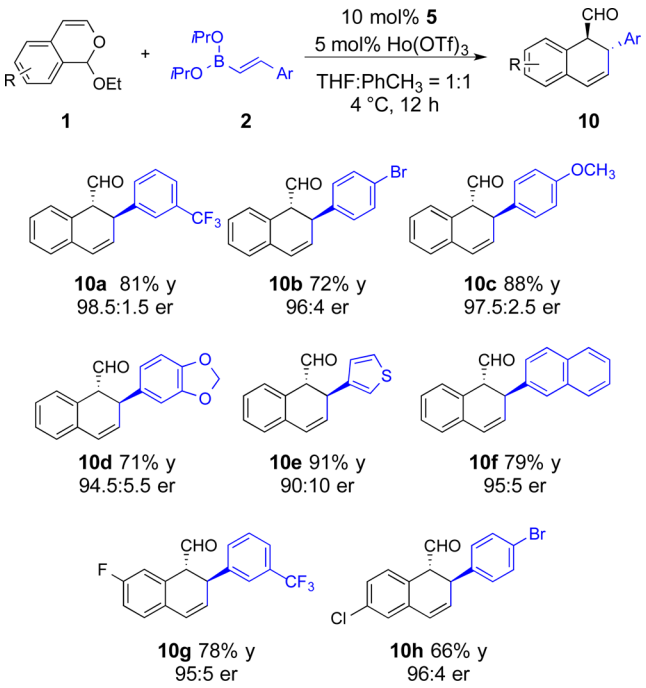

Figure 1. Enantioselective [4 + 2] cycloaddition of alkenyl boronates.

heteroaromatic vinylboronate afforded an excellent yield with a slightly compromised er (Figure 2, product **10e**). 2-Naphthyl

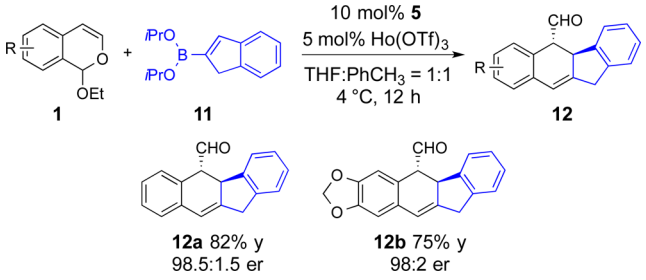

Figure 2. Enantioselective [4 + 2] cycloaddition of diisopropyl indene boronate **11**.

vinylboronate **2e** also reacted well, and naphthyl-substituted dihydronaphthalene was generated in good yield and enantioselectivity (Figure 2, product **10f**). The reaction of functionalized acetals **1b** and **1c** paired with substituted vinylboronates **2b** and **2c** proceeded well (Figure 2, products **10g**−**10h**). However, aliphatic substituted vinyl boronates did not react under these conditions. To prevent products **3** and **10** from being oxidized over time, all dihydronaphthalene products were reduced in methanol with $NaBH_4$ for further storage.

Diisopropyl indene boronate **11** was evaluated as an α-substituted vinylboronate to form a dihydrobenzofluorene **12**. These carbocyclic structures are interesting because they are frequently found in biologically active natural products.[30] Boronate **11** reacted successfully with acetal **1a** and dioxo acetal **1f**. Products **12a** and **12b** were obtained in 82% yield, 98.5:1.5 er and 75% yield, 98:2 er, respectively (Figure 2).

In summary, we have developed a catalytic method to make dihydronaphthalenes bearing two chiral centers with high enantio- and diastereoselectivity using boronates and tartaric acid as the catalyst. The reaction provides access to chiral dihydronaphthalene building blocks that can be used to make interesting natural products and biological active compounds. The discovery of the reaction increases the understanding of enantioselective Diels—Alder reactions of boronates and opens up the possibility of developing similar catalyst-controlled reactions for synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, structural characterizations, spectral data for all new compounds and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*seschaus@bu.edu

Notes

The authors declare no competing financial interest.

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