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Enantioselective Addition of Boronates to *o*-Quinone Methides Catalyzed by Chiral Biphenols

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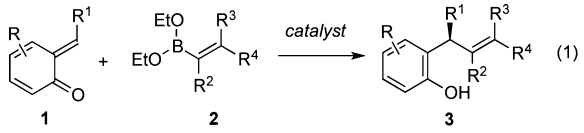
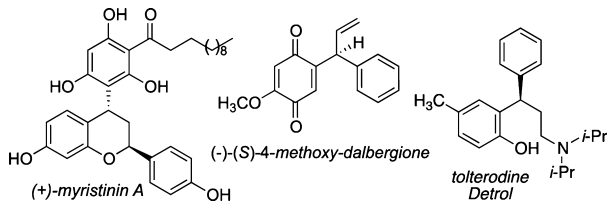
Supporting Information

ABSTRACT: Chiral biphenols were found to catalyze the enantioselective asymmetric addition of aryl- or alkenylboronates to *o*-quinone methides. Substituted 2-styryl phenols were obtained in good yields (up to 95%) with high enantiomeric ratios (up to 98:2) in the presence of 10 mol % 3,3′-Br_2-BINOL. A two-step synthesis of (*S*)-4-methoxydalbergione in good yield and selectivity was achieved.

o-Quinone methides (*o*QMs) are employed as synthetic intermediates, most notably in hetero-Diels–Alder reactions.[1] Within this context, they are proposed as reactive intermediates in a number of biomimetic natural product syntheses.[2] *o*QMs exhibit other modes of reactivity, including but not limited to 1,4-conjugate addition reactions at the exocyclic carbon with nucleophiles.[3] Exploiting this reactivity, Sigman developed a Pd-catalyzed vinylphenol difunctionalization process that includes a nucleophilic addition to the quinone methide intermediate.[4] Pettus described a mild and efficient anionic approach to generate *o*QMs and used this approach in the synthesis of a collection of natural products.[5] Enantioselective nucleophilic boronate chemistry has proven to be widely useful in asymmetric synthesis.[6] We sought to develop a collection of enantioselective catalytic boronate addition reactions to *o*QMs and related intermediates.[7] Inspiration for this target class of reactions is derived from the numerous bioactive natural products and drugs (a few of which are depicted in Scheme 1) that can be made via this type of enantioselective addition (eq 1).[8]



Scheme 1



The recent work of Letka[9] and Sigman[10] illustrates the potential utility of these intermediates and the challenges in developing enantioselective addition reactions. We[11] and others[12] have developed a series of asymmetric boronate addition reactions catalyzed by chiral diols. We envisaged that enantioselective addition of vinyl- and arylboronates to *o*QMs would result in compounds with a benzylic chiral carbon center.[13] Leveraging the driving force for quinone methide rearomatization would allow the boronate addition to be conducted under extremely mild conditions, generating chiral phenols having the general structure **3** (eq 1). Herein we describe the development of an enantioselective boronate addition to *o*QMs catalyzed by chiral diols.[14]

We initiated our investigation by evaluating the reaction of arylboronate **2a** with *o*QM **1a** in toluene at room temperature. Although **2a** is known to be a weak nucleophile, it reacted smoothly with **1a** in the presence or absence of catalyst, giving a 54 or 36% yield, respectively, after 12 h. Chiral BINOLs and tartaric acid derivatives were evaluated as catalysts in the presence of **1a** and **2a** (Table 1).[15] 3,3′-Br_2-BINOL (**4b**) afforded the product with the highest er (3:97; entry 2). Toluene proved to be the best solvent in our solvent screen (entries 3–5). Compared with **4b**, aryl-substituted BINOLs **4c** and **4d** gave slightly lower yields and enantioselectivities (entries 6 and 7). 9-Anthracyl-substituted BINOL **4e** performed similarly to **4b** (entry 8). The use of H_8-BINOL (**4f**) catalyzed the reaction with much lower enantioselectivity (entry 9). Monoprotected BINOL **4g** afforded racemic product in lower yield (entry 10). Lastly, tartaric acid (**4h**) and its derivitive **4i** were evaluated and gave only low to moderate enantioselectivies (entries 11 and 12). Commercially available **4b** was chosen for use in the assessment of the substrate scope for the reaction.

The aforementioned conditions were successfully applied to a range of boronate additions to *o*QMs (Table 2). Similar yields and enantioselectivities were observed with *o*QMs bearing either electron-deficient or electron-rich vinyl groups (entries 1–4). Quinone methide **1e** with a terminal prenyl group was successfully prepared,[16] and it provided the desired aryl addition product under the same conditions in good yield with excellent enantioselectivity (entry 5) Good yields and high enantioselectivities were achieved with different arylboronate nucleophiles (entries 6 and 7). Reactions with heteroarylboronates were also successful in terms of yield and selectivity

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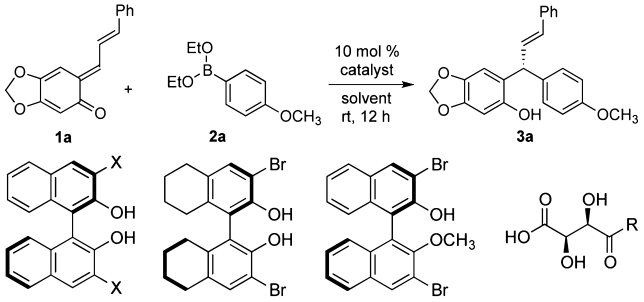
Table 1. Asymmetric Arylboration Catalyzed by Chiral Brønsted Acids[a]



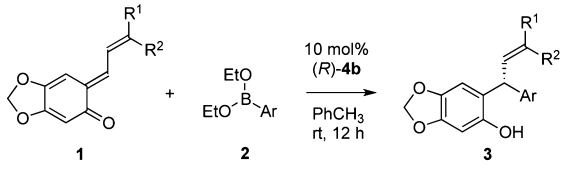
entry	catalyst	solvent	yield[b]	er[c]
1	**4a**	$PhCH_3$	54%	86:14
2	**4b**	$PhCH_3$	76%	97:3
3	**4b**	$PhCF_3$	70%	96:4
4	**4b**	CH_2Cl_2	75%	95:5
5	**4b**	THF	72%	90:10
6	**4c**	$PhCH_3$	65%	92.5:7.5
7	**4d**	$PhCH_3$	65%	90:10
8	**4e**	$PhCH_3$	73%	97:3
9	**4f**	$PhCH_3$	66%	74:26
10	**4g**	$PhCH_3$	57%	50:50
11	**4h**	$PhCH_3$	47%	52:48
12	**4i**	$PhCH_3$	72%	77:23

[a]Reactions were run with 0.25 mmol of *o*QM and 0.5 mmol of boronate in solvent (2.5 mL, 0.1 M). [b]Isolated yields. [c]Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase.

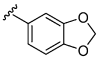
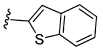
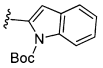
(entries 8 and 9). Benzo-2-thiopheneboronate **2j** and *N*-Boc-indole-2-boronate **2k** gave lower yields but similar enantioselectivities (entries 10 and 11). The vinyl group on the *o*QM could also be replaced by an electron-rich aromatic group without destabilizing the quinone methide moiety.[17] We evaluated *o*QM **5** in combination with alkenylboronate **6a** under the same conditions. This alkenylation of **5** furnished the *S* enantiomer of **3a** in good yield with good selectivity in a shorter reaction time (Scheme 2).

At this stage in our investigations, the substrate scope was limited by the number of isolable *o*QMs. Our attention then turned to the development of a method for the generation of *o*QMs in situ under mild acidic conditions. Reactive *o*QMs would ideally be trapped by nucleophilic boronates before dimerization or polymerization can occur. Of the methods for *o*QM generation,[18] the use of hydroxybenzyl alcohol as the *o*QM precursor involves substrate alcoholysis, which may be possible using boronates. Hydroxy-substituted benzyl alcohols have been employed in the photolytic generation of *o*QMs.[19] Snyder completed the total synthesis of resveratrol-based natural products employing in situ-generated quinone methides.[20] Thermal generation of *o*QMs from hydroxybenzyl alcohol precursors has also been studied[21] and used in the synthesis of natural products.[22−25] Substitution reactions using vinylboron dihalides have been achieved with *n*-BuLi activation.[26] Alkenyl-[27] and allylsilanes[28] and enol acetates[29] perform substitution of secondary benzylic alcohols.

Table 2. Enantioselective Addition of Boronates 2 to Vinyl *o*-QMs 1[a]

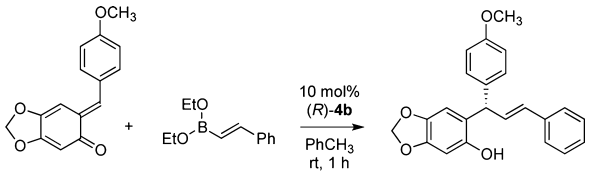


1a-1d, R^2 = H
1e, R^2 = CH_3

entry	R^1[b]	Ar	yield	er[c]
1	Ph (1a)	4-$CH_3OC_6H_4$	76% (3a)	97:3
2	4-$CH_3OC_6H_4$ (1b)	4-$CH_3OC_6H_4$	74% (3b)	96.5:3.5
3	4-FC_6H_4 (1c)	4-$CH_3OC_6H_4$	85% (3c)	96.5:3.5
4	4-BrC_6H_4 (1d)	4-$CH_3OC_6H_4$	84% (3d)	97:3
5	CH_3 (1e)	4-$CH_3OC_6H_4$	71% (3e)	96:4
6	Ph (1a)		82% (3f)	95:5
7	Ph (1a)	2,4-$CH_3OC_6H_3$	76% (3g)	90:10
8	Ph (1a)		62% (3h)	96:4
9	Ph (1a)		70% (3i)	98:2
10	Ph (1a)		71% (3j)	97.5:2.5
11	Ph (1a)		46% (3k)	96:4

[a]Isolated yields. [b]R^2 = H, except for **1e** (R^2 = CH_3). [c]Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase.

Scheme 2. Alkenylation of *o*QM 5 Catalyzed by (*R*)-4b



At the outset of our investigation using hydroxybenzyl alcohol **7a**, boronate **6a** was found to be acidic enough to promote *o*QM formation in the presence of BINOL catalysts. (*R*)-**4b** was once again the best catalyst in terms of yield and enantiopurity in our initial screen (Table 3, entries 1−5). The addition of 4 Å molecular sieves improved the yield (entry 6). Switching from hydroxybenzyl alcohol **7a** to its ethyl ether **7b** gave an er of 95:5, together with an isolated yield of 95% (entry 7). The use of BINOL **4g** once again resulted in no enantioselectivity and lower yield. The optimal conditions were determined to be 4 °C with 1.5 equiv of boronate and 10 mol % (*R*)-**4b** as the catalyst (entry 9). The 2-hydroxy group was determined to be crucial for reactivity, as its absence resulted in no product (entry 10). Also, no product was observed when 2-OCH_3-substituted substrate **7d** was used (entry 11), consistent with a quinone methide intermediate. Constituent electron-rich arenes of the hydroxybenzyl ethers proved to be important for rate and selectivity.

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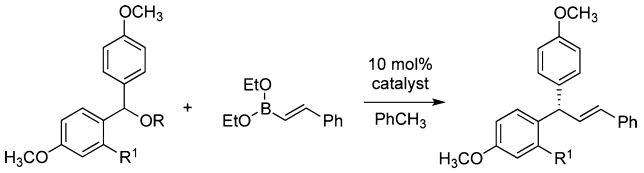
Table 3. Enantioselective Alkenylation of Hydroxybenzyl Alcohols and Ethers[a]



7a, R = H, R^1 = OH
7b, R = Et, R^1 = OH
7c, R = Et, R^1 = H
7d, R = Et, R^1 = OCH_3

6a

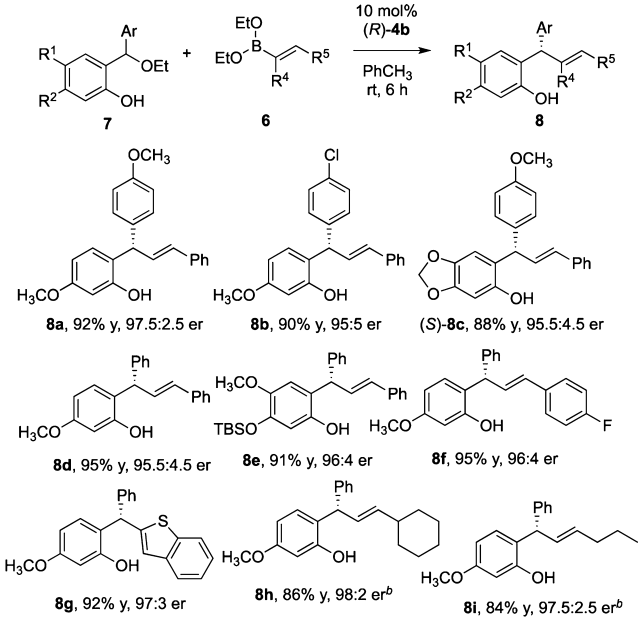
8

entry	catalyst	7	R	R^1	yield[b]	er[c]
1	**4a**	**7a**	H	OH	46%	59:41
2	**4b**	**7a**	H	OH	53%	75:25
3	**4c**	**7a**	H	OH	26%	70:30
4	**4d**	**7a**	H	OH	40%	58:42
5	**4e**	**7a**	H	OH	11%	66:34
6[d]	**4b**	**7a**	H	OH	71%	80:20
7	**4b**	**7b**	Et	OH	95%	95:5
8	**4g**	**7b**	Et	OH	85%	50:50
9[e]	**4b**	**7b**	Et	OH	92%	97.5:2.5
10	**4b**	**7c**	Et	H	0%	–
11	**4b**	**7d**	Et	OCH_3	0%	–

[a]Reactions were run with 0.25 mmol of **7** and 0.5 mmol of boronate in solvent (2.5 mL, 0.1 M). [b]Isolated yields. [c]Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase. [d]With 4 Å molecular sieves. [e]4 °C.

With these optimal conditions in hand, we evaluated 2-hydroxybenzyl ethers and alkenylboronate nucleophiles in the reaction (Table 4). Electron-rich and -poor substrates (products **8a**–**e**) were effective in the reaction. The absolute stereochemistry was determined by X-ray analysis of compound **8b**.[30] Simple alkenylboronate nucleophiles also reacted well (products **8f** and **8g**), and elevated temperatures were necessary for reaction (products **8h** and **8i**).

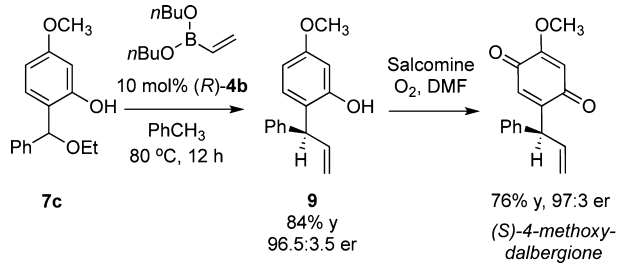
Table 4. Enantioselective Addition of Vinylboronates to Hydroxybenzyl Ethyl Ethers[a]



[a]Reactions were run with 0.25 mmol of **7** and 0.5 mmol of boronate in solvent (2.5 mL, 0.1 M) at 4 °C for 12 h. [b]60 °C for 12 h.

A short synthesis of the natural product (*S*)-4-methoxydalbergione was accomplished using a vinylboronate as the nucleophile (Scheme 3). Good yield and enantioselectivity of vinyl adduct **9** were achieved at 80 °C and prolonged reaction times using 10 mol % catalyst. (*S*)-4-Methoxydalbergione was obtained with 97:3 er by oxidation of phenol **9** with salcomine in *N*,*N*-dimethylformamide (DMF) under oxygen.[31] The stereochemical outcome of the reaction is consistent with the selectivity observed in 1,4-conjugate addition reactions[12] and additions to acyl imines.[11e] The biphenol character of the catalyst is paramount for selectivity. The mechanistic details of the reaction are currently under investigation and will be disclosed in due course.

Scheme 3. Synthesis of (*S*)-4-Methoxydalbergione



7c

9
84% y
96.5:3.5 er

76% y, 97:3 er
(S)-4-methoxy-dalbergione

In summary, we have developed a novel enantioselective addition of boronates to *o*-quinone methides catalyzed by chiral biphenols. Good yields and selectivities were achieved using stable *o*QMs and aryl- or alkenylboronates. A procedure for in situ generation of *o*QMs under extremely mild conditions has also been developed. The method was applied to an improved synthesis of the natural product (*S*)-4-methoxydalbergione. Continuing investigations include detailed mechanistic studies and further reaction development.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, structural proofs, 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.

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Notes

The authors declare no competing financial interest.

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