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

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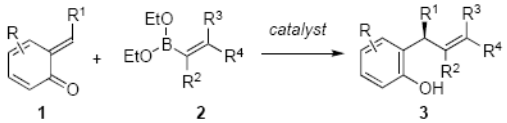
Abstract

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

Ortho-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] *Ortho*-quinone methides 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 including a nucleophilic addition to the quinone methide intermediate.[4] Pettus described a mild and efficient anionic approach to generate *ortho*-quinone methides 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 *ortho*-quinone methides and related intermediates.[7] Inspiration for this target class of reactions is derived from the numerous bioactive natural products and drugs, only a few depicted in Scheme 1, all of which can be made *via* this type of enantioselective addition (Eq. 1).[8]



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SUPPORTING INFORMATION

Experimental procedures, structural proofs, and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(1)

The recent work of Letka[9] and Sigman[10] illustrate the potential utility of these intermediates and the challenges in developing enantioselective addition reactions. Our lab[11] along with others[12] have developed a series of asymmetric boronate addition reactions catalyzed by chiral diols. We envisaged an enantioselective addition of vinyl- and aryl boronates to *ortho*-quinone methides would result in compounds with a benzylic chiral carbon center.[13] By leveraging the driving force of quinone methide rearomatisation, the boronate addition could be conducted under extremely mild conditions to generate chiral phenols of general structure **3** [Eq. 1]. Herein, we describe the development of an enantioselective boronate addition to *ortho*-quinone methides catalyzed by chiral diols.[14]

We initiated our investigation by evaluating the reaction of aryl boronate **2a** with *ortho*-quinone methide **1a** in toluene at room temperature. Aryl boronate **2a** is known to be a weak nucleophile, but it reacted smoothly with **1a** in the presence and absence of catalyst, 54% and 36% yield respectively after 12 h. Chiral BINOLs and tartaric acid derived catalysts were evaluated as catalyst in the presence of **1a** and boronate **2a** (Table 1).[15] 3,3′-Br_2-BINOL **4b** afforded the product in the highest er (3:97, Table 1, entry 2) Toluene proved to be the best solvents among our solvent screens (Table 1, entries 3-5). Compared to **4b**, aryl substituted BINOLs **4c** and **4d** gave slightly low yields and enantioselectivities (Table 1, 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 in much lower enantioselectivity (entry 9). Mono-protected BINOL **4g** resulted in racemic product and lower yield (entry 10). Lastly, tartaric acid and its derivitives **4g** and **4h**, were evaluated as well, but only gave low to moderate enantioselectivies (entries 11 and 12). The 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 *ortho*-quinone methides. Similar yields and enantioselectivities were observed with *o*QMs bearing both electron-deficient and electron-rich vinyl groups (Table 2, entries 1-4).

Preparation of quinone methide **1e** with a terminal prenyl group was also successful.[16] Quinone methide **1e** provided the desired aryl addition product under the same conditions in good yield and excellent enantioselectivity (Table 2, entry 5) Good yields and high enantioselectivities were achieved with different aryl boronate nucleophiles (Table 2, entries 6-7). Reactions with hetero-aryl boronates also successful in terms of yield and selectivity (Table 2, entries 8-9). Benzo-2-thiophene boronate **2j** and *N*-boc-indole-2-boronate **2k** gave lower yield but similar enantioselectivities (Table 2, entries 10-11). The vinyl group on the *ortho*-quinone methide could also be replaced by an electron rich aromatic group without destabilizing the quinone methide moiety.[17] We evaluated the *o*QM **5**, in combination with alkenyl boronate **6a**, under the same conditions. This alkenylation of **5** furnished the *S*-enantiomer of **3a** in good yield and selectivity in a shorter reation time (Scheme 2).

At this stage in our investigations, the substrate scope was limited by the number of isolable *ortho*-quinone methides. Our attention then turned to the development of a method for the generation of *in-situ ortho*-quinone methide 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] use of hydroxybenzyl alcohol as the *o*QM precursor, substrate alcoholysis may be possible by the boronate. Hydroxy-substituted benzyl alcohols have been employed in the photolytic generation of *o*QMs.[19] Scott Snyder completed the total synthesis of resveratrol-based natural products employing *in-situ* generated quinone methides.[20] Thermal generation of *ortho*-quinone methides from hydroxybenzyl alcohol precursors has also been studied[21] used in the synthesis of natural products.[22-25] Substitution reactions using vinylboron dihalides have been achieved with *n*-BuLi activation.[26] Alkenyl-,[27] allylsilanes[28] and enol acetates[29] perform substitution of secondary benzylic alcohols.

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

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

A short synthesis of the natural product (*S*)-4-methoxy-dalbergione was accomplished using vinyl boronate as the nucleophile (Scheme 3). Good yield and enantioselectivity of vinyl adduct **9** was achieved at 80 °C and prolonged reaction times using 10 mol% of the catalyst. (*S*)-4-Methoxy-dalbergione was obtained in 97:3 er by oxidation of phenol **9** with salcomine in DMF under oxygen.[32] 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 summary, we have developed a novel enantioselective addition of boronates to *ortho*-quinone methides catalyzed by chiral biphenols. Good yields and selectivities were achieved using stable *o*QM with aryl or alkenyl boronates. An *in-situ* generation of *o*QMs has also been developed under extremely mild conditions. The method was applied to an improved synthesis of natural product (*S*)-4-methoxy-dalbergione. Continued investigations include detailed mechanistic studies and further reaction development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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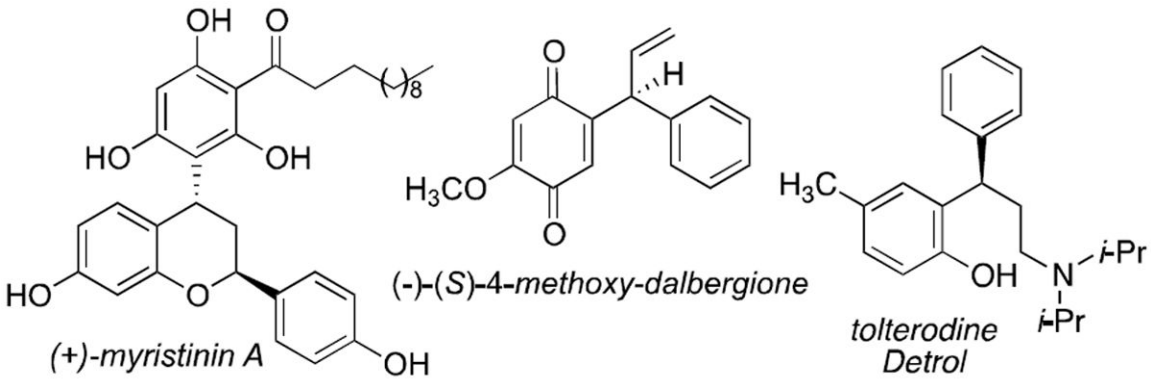
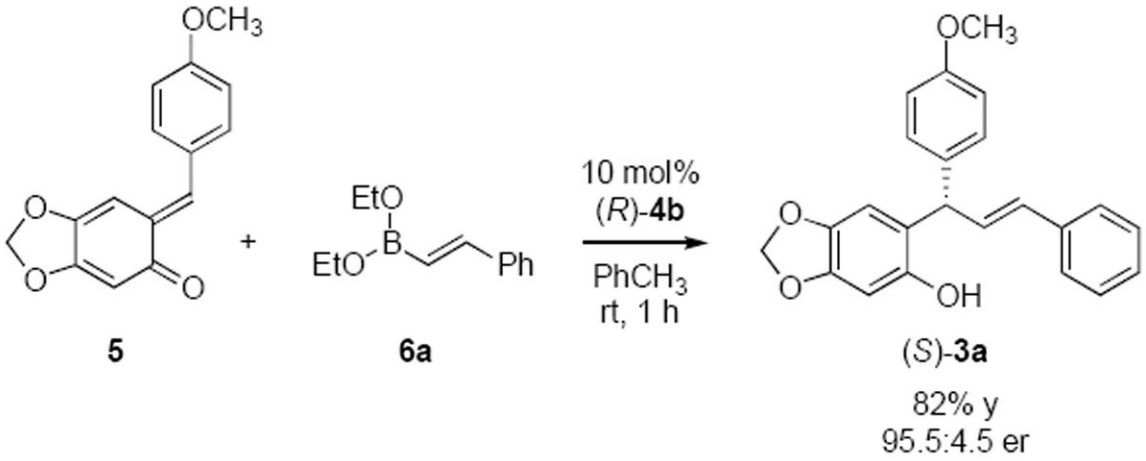
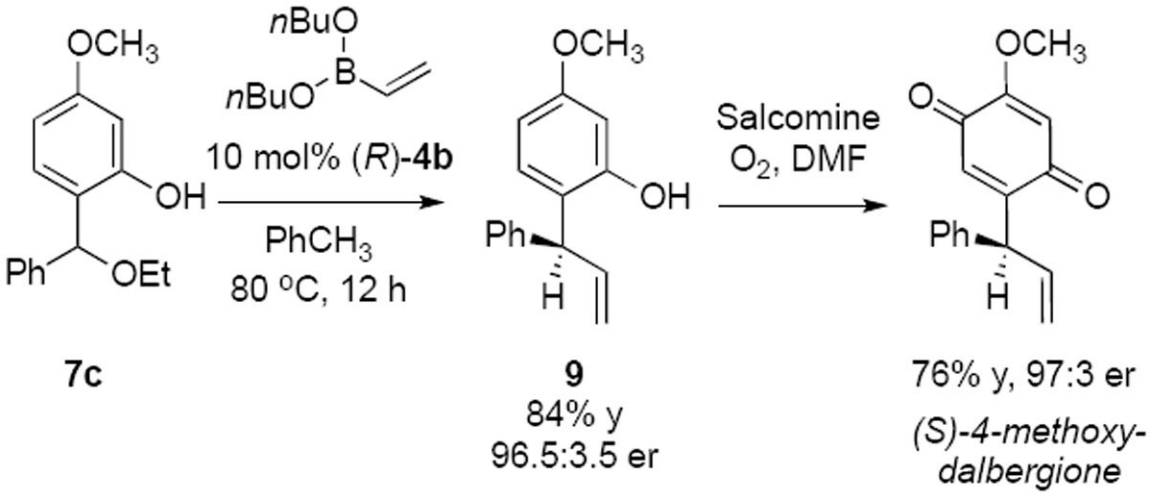


Scheme 1.



Scheme 2.
Alkenylation of *Ortho*-quinone Methides (5) Catalyzed by (*R*)-4b



7c

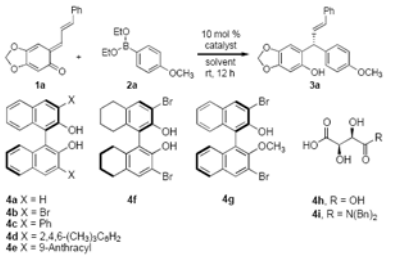
9
84% y
96.5:3.5 er

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

Scheme 3.
Synthesis of (*S*)-4-Methoxy-dalbergione

Table 1

Asymmetric Arylboration Catalyzed by Chiral Brønsted Acids[a]



entry	catalyst	solvent	yield[b]	e. r.[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

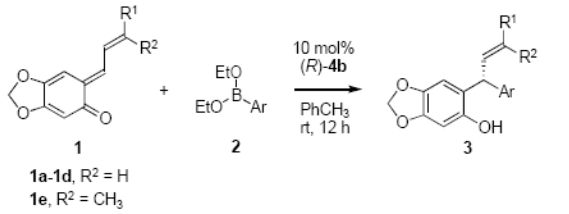
[a] Reactions were run with 0.25 mmol of *o*QM, 0.5 mmol of boronate in solvent (2.5mL, 0.1M)

[b] Isolated yields.

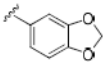
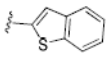
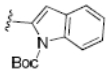
[c] Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase.

Table 2

Enantioselective Addition of Boronates (2) to Vinyl *Ortho*-Quinone Methides (1)[a]



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

entry	R1[b]	Ar	yield	e. r.[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

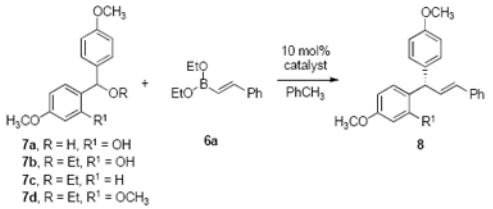
[a] Isolated yields.

[b] R^2 = H, except for **1e**.

[c] Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase.

Table 3

Enantioselective Alkenylation of Hydroxybenzyl Alcohols and Ethers[a]



entry	catalyst	7	R	R^1	yield[b]	e. r[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, 0.5 mmol of boronate in solvent (2.5mL, 0.1M)

[b] Isolated yields.

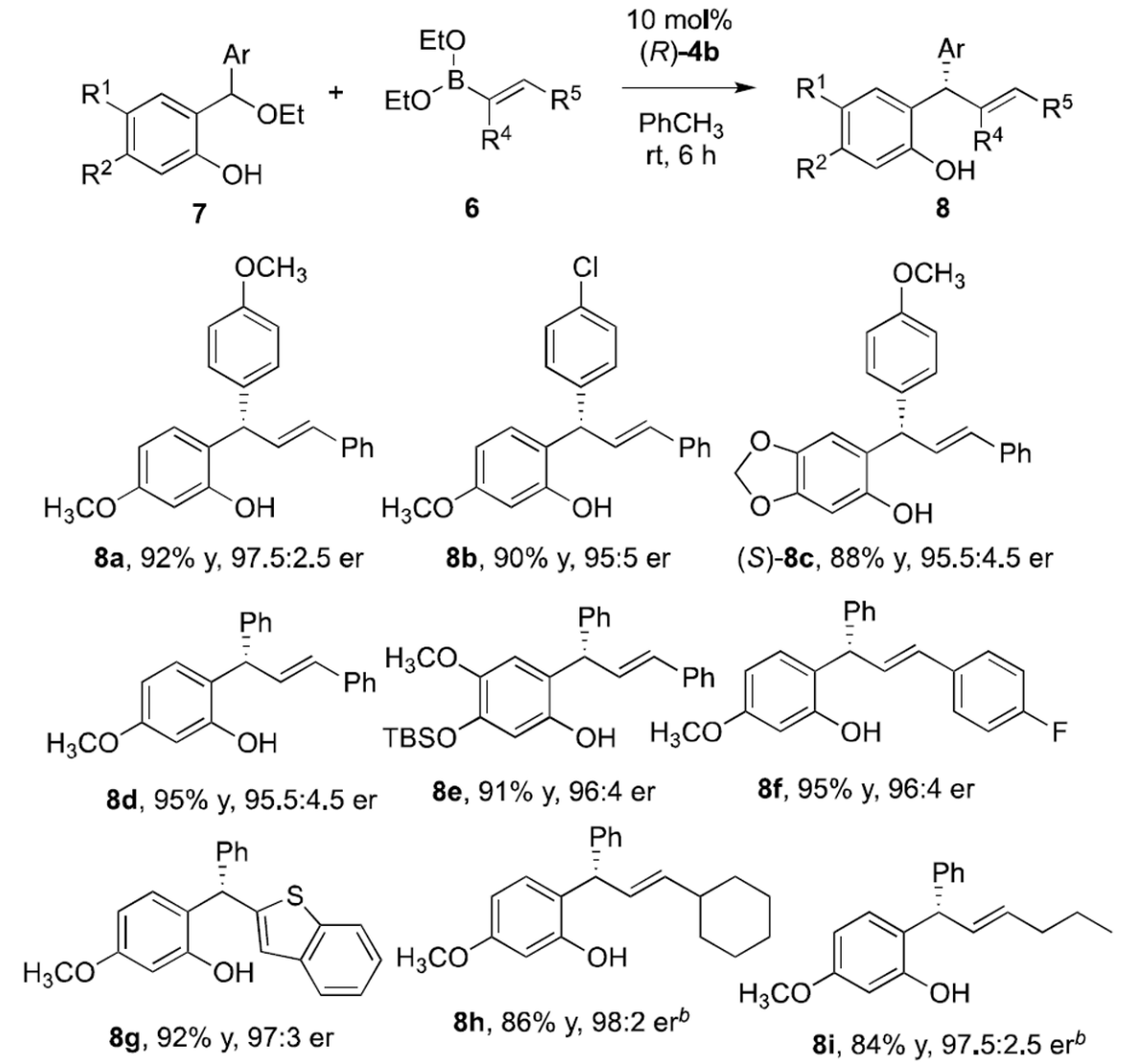
[c] Enantiomeric ratios determined by HPLC analysis using a chiral stationary phase.

[d] With 4Å molecular sieves

[e] 4 °C.

Table 4

Enantioselective Addition of Vinyl Boronates to Hydroxybenzyl Ethyl Ethers[a]



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

[b] 60 °C for 12 h.