Asymmetric Catalysis

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Copper-Catalyzed Enantioselective 1,6-Boration of *para*-Quinone Methides and Efficient Transformation of *gem*-Diarylmethine Boronates to Triarylmethanes

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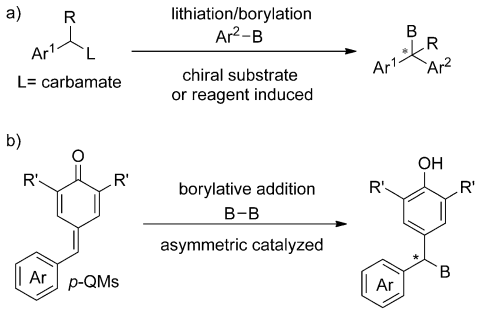
Abstract: *Presented is the first enantioselective copper-catalyzed 1,6-conjugate addition of bis(pinacolato)diboron to para-quinone methides. The reaction proceeds with excellent yields and good to excellent enantioselectivities, and provides an attractive approach to the construction of optically active gem-diarylmehtine boronic esters. Additionally, the subsequent conversion of the derived potassium trifluoroborates into triarylmethanes with highly enantiospecificity was realized.*

Enantiomerically pure organoboranes are interesting pharmaceutical molecules[1] in medical chemistry and powerful building blocks[2] in asymmetric synthesis. Chiral dibenzylic (*gem*-diarylmethine) boronates, as a class of potential precursors for important triarylmethanes[3] and *gem*-diaryl hydrocarbons,[4] has been employed by Aggarwal and co-workers[5] in the synthesis of *gem*-diaryl-containing pharmaceuticals.[5d–e] However, despite the importance of these compounds, the approaches to access nonracemic *gem*-diarylmethine boronates are still very scarce. Lithiation/borylation of benzylic carbamates[6] is an exclusive route which relies on either a substrate- or reagent-controlled strategy. (Scheme 1 a). For instance, Crudden and co-workers recently reported an elegant chiral bis(*i*Pr-oxazoline)-controlled protocol to obtain chiral nonracemic *gem*-diarylmethine boronic esters, albeit with substantial substrate restrictions.[7] To our knowledge, to date, catalytic asymmetric approaches to access *gem*-diarylmethine boronic esters, bearing a chiral benzylic C–B bond, remain unexplored.

Transition-metal catalyzed[8] or organocatalyzed[9] asymmetric conjugate borations of electron-deficient olefins with diboron reagents, such as bis(pinacolato)diboron [$B_2(pin)_2$], represent a powerful and site-selective route to access chiral alkylboranes.[10] In particular, the use of chiral copper catalysts has been highly successful in transforming a variety of β-aryl-substituted α,β-unsaturated compounds into benzylic boronic esters with excellent levels of enantiopurity.[11]



Scheme 1. Approaches to chiral *gem*-diarylmethine boronates.

para-Quinone methides (*p*-QMs),[12] which are classified as electron-deficient alkenes with a unique assembly of carbonyl and olefinic moieties, are versatile intermediates in many chemical, medicinal, and biological processes.[13] We envisioned that copper-catalyzed enantioselective 1,6-conjugate boration of *p*-QMs could deliver nonracemic *gem*-diarylmethine boronates. (Scheme 1 b). However, *p*-QMs have been less-well studied in enantioselective catalysis, and to date, only three organocatalysis cases, including anionic polymerizations,[14] phase-transfer catalysis,[15] and 1,6-conjugate addition of enamines,[16] have been reported. Herein, we report the first copper-catalyzed asymmetric 1,6-conjugate addition of $B_2(pin)_2$ to *p*-QMs, and stereoselective conversion of the chiral *gem*-diarylmethine boronates into enantionenriched triarylmethanes.

To test the feasibility of the 1,6-addition, we examined the reaction of the *p*-QM **1a** with $B_2(pin)_2$ using a P-diisopropyl sulfoxide phosphine[17] (SOP; **L1**), and systematically screened reaction conditions, such as copper salts, solvents, additives, and bases (Table 1; see the Supporting Information for details). With 10 mol% of CuCl, **L1**, and NaO*t*Bu, the reaction proceeded smoothly at −20 °C in the presence of 2 equivalents of MeOH and toluene as the solvent. **1a** was consumed within 15 hours and the 1,6-conjugate adduct, the dibenzylic boronic ester **2a**, was afforded in excellent yield with a 93.5:6.5 e.r. (entry 1). By employing MeOK as the base, the reaction proceeded within 30 min and gave **2a** with 95:5 e.r. (entry 2). Ligand screening revealed that P-substituents of SOPs have dramatic effects on the enantioselectivity. For instance, P-diethyl and P-dicyclohexyl SOPs (**L2** and **L3**) show much worse enantiocontrol than **L1**, and **L4** gave nearly racemic dibenzylic boronic ester (entries 3–5). The commercially available ligand (*R*)-BINAP was chosen to evaluate this transformation, and modest enantioselectivity was afforded (entry 6). Furthermore, the modified P-diisopropyl **L6** was

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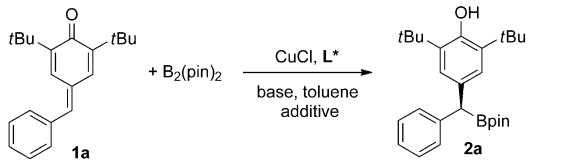
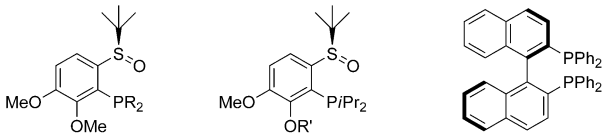
Table 1: Screening of reaction conditions.[a]

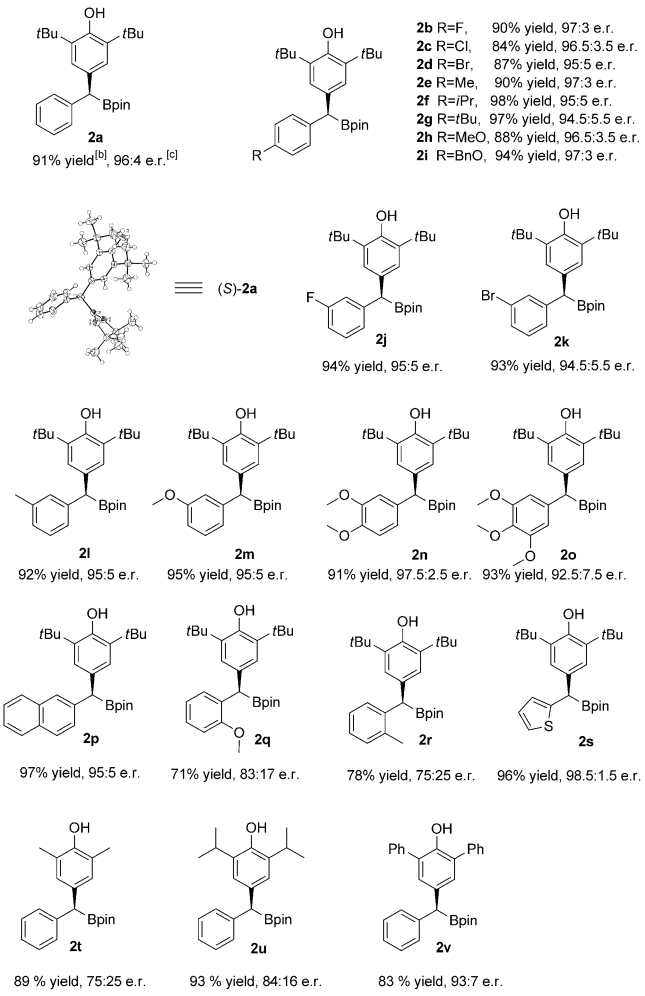




Entry	Ligand	Base	*t* [h]	Yield [%][b]	e.r.[c]
1	**L1**	NaO*t*Bu	15	98	93.5:6.5
2	**L1**	MeOK	0.5	96	95:5
3	**L2**	MeOK	0.5	86	70:30
4	**L3**	MeOK	0.5	74	89:11
5	**L4**	MeOK	0.5	85	55:45
6	(*R*)-BINAP	MeOK	0.5	89	75.5:24.5
7	**L5**	MeOK	0.5	85	95:5
8	**L6**	MeOK	0.5	94	95.5:4.5
9[d]	**L6**	MeOK	4.5	91	96:4
10[e]	**L6**	MeOK	15	86	95:5
11[f]	**L6**	MeOK	48	97 (65)	94:6 (>99.5:0.5)

[a] Conducted with **1a** (0.2 mmol), $B_2(pin)_2$ (0.3 mmol), CuCl (10 mol%), ligand (11 mol%), MeOK (12 mol%), MeOH (0.4 mmol) in toluene (1.0 mL) at −20°C. [b] Yield of isolated product. [c] Determined by HPLC. [d] Conducted with 5.0 mol% of CuCl at −40°C. [e] Conducted with 2.5 mol% of CuCl at −40°C. [f] The reaction was performed in the presence of 1.60 g (8.1 mmol) of **1a** and 0.1 mol% of CuCl at 0°C. Data within parentheses is that obtained after one crystallization.

Table 2: Scope with respect to the *p*-QMs.[a]



[a] Conducted with **1** (0.2 mmol), $B_2(pin)_2$ (0.3 mmol), CuCl (5 mol%), ligand (5.5 mol%), MeOK (6 mol%), MeOH (0.4 mmol) in toluene (1.0 mL) at −40°C. [b] Yield of isolated product. [c] Determined by chiral HPLC. Thermal ellipsoids shown at 50% probability.

used and it led to a slight enantiomeric excess increase (entry 8). Reaction temperature and catalyst loading were also optimized (entries 9 and 10). At −40°C and with 5 mol% of catalyst, **1a** reacted completely with $B_2(pin)_2$ within 4.5 hours to furnish **2a** in 91% yield and 96:4 e.r. The reaction can also be run on a gram scale (1.60 g) with 0.1 mol% catalyst at 0°C, thus delivering **2a** in excellent yield (2.23 g, 97%) and good enantioselectivity (94:6 e.r.). After one recrystallization from *n*-hexane, enantiopure **2a** (>99.5:0.5 e.r.) can be obtained in 65% yield (1.50 g; entry 11).

Under the optimized reaction conditions, we examined the scope of the reaction. As shown in Table 2, a series of stable *p*-QMs with electron-neutral, electron-deficient, and electron-rich aryls reacted with $B_2(pin)_2$ to provide chiral *gem*-diarylmethine boronates (**2a**–**m**) in good yields with generally high levels of enantiopurities. Multisubstituted (**2n** and **2o**), polycyclic (**2p**), and heterocyclic (**2s**) aryls were tolerated in this reaction and resulted in excellent yields with high enantioselectivities. *o*-Methoxy- and *o*-methyl-substituted*p*-QMs provided **2q** and **2r**, respectively, with decreased e.r. values (83:17 and 75:25), probably because of the steric effects. In addition, replacement of the bulky *tert*-butyl group by methyl (**2t**), isopropyl (**2u**), and phenyl (**2v**) groups did not lead to better enantioselectivities. The stereocenter of the generated dibenzylic boronic esters was assigned to be *S* by X-ray crystallographic analysis of **2a**.[18] Accordingly, a model was proposed to rationalize this stereochemical outcome. As shown in Figure 1, the planar **1a** approaches the (SOP)Cu/Bpin species from *Si*-face (**A**) to avoid steric interactions between the phenyl ring of **1a** and *tert*-butyl sulfinyl group of **L6** (the steric hindrance is shown in **B**), thus (*S*)-**2a** was obtained in a large excess. For *o*-methoxy- or *o*-methyl-

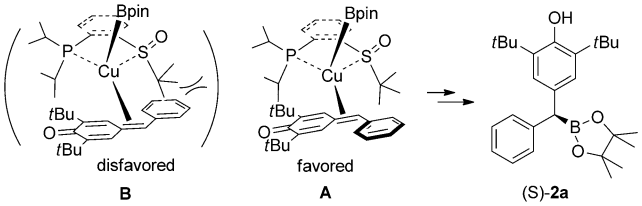
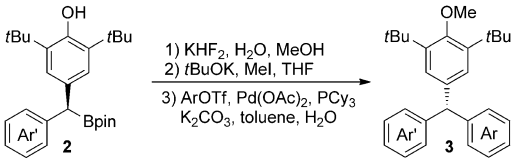
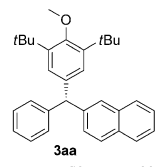


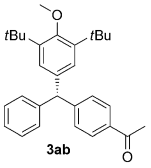
Figure 1. Stereochemical models of 1,6-boration.

Table 3: Palladium-catalyzed cross-coupling of *gem*-diarylmethine trifluoroborates with ArOTf.[a]

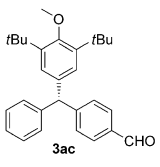




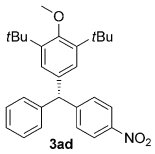
74% yield[b], 98:2 e.r.[c]
97% es[d]



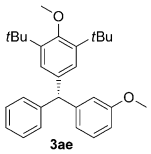
78% yield, 98:2 e.r.
97% es



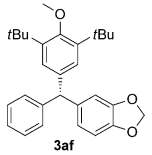
53% yield, 96:4 e.r.
93% es



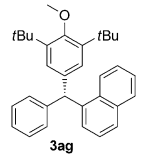
66% yield, 93:7 e.r.
87% es



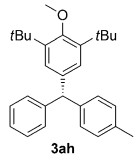
70% yield, 97.5:2.5 e.r.
96% es



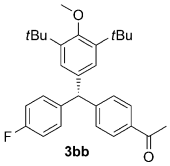
80% yield, 98:2 e.r.
97% es



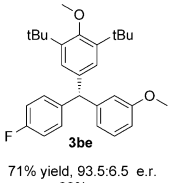
57% yield, 96.5:3.5 e.r.
94% es



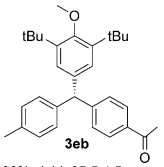
50% yield, 98:2 e.r.
97% es



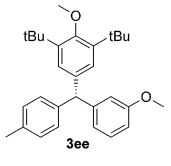
62% yield, 92:8 e.r.
89% es



71% yield, 93.5:6.5 e.r.
93% es



68% yield, 95.5:4.5 e.r.
97% es



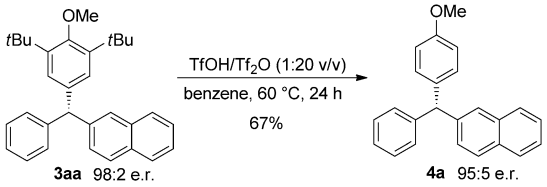
65% yield, 95.5:4.5 e.r.
97% es

[a] Reaction condition of the cross-coupling reaction: **2** (0.07 mmol, e.r. > 99.5:0.5 for **2a**), ArOTf (0.07 mmol), $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), K_2CO_3 (0.2 mol) in toluene/H_2O(1.1 mL, v/v = 10:1) at 60 °C for 15 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] $es = ee_{Product}/ee_{S.M.} \times 100\%$. Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

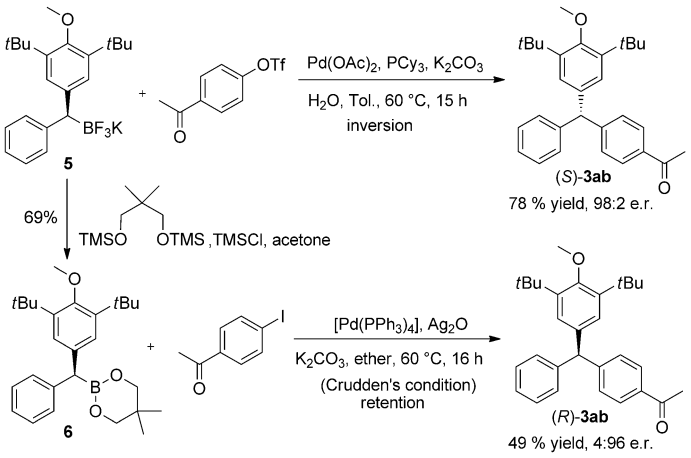
substituted *p*-QMs, an assumed orthogonal orientation of cyclohexadiene ring with the sterically bulky aryl ring might render the enantioface discrimination elusive, thus resulting in moderate e.r. values of 1,6-borylative adducts.

To demonstrate the utility of this enantioselective 1,6-boration in asymmetric synthesis, we sought to transform the 1,6-adducts into enantionenriched triaryls by stereospecific Suzuki–Miyaura cross-coupling reactions.[19] Firstly, all attempts at the palladium-catalyzed cross-coupling of **2a** with aryl halides or pseudohalides failed, and is probably a result of the facile decomposition of the dibenzylic palladium intermediate when bearing a phenolic hydroxy group. Fortunately, we can readily transfer boronic esters to potassium trifluoroborates and then protect the phenols with a methyl group in a one-pot procedure in satisfactory yields (Table 3). The new dibenzylic trifuoroborates can be readily coupled with aryltrifluoromethanesulfonates (ArOTf) in the presence of catalytic amounts of $Pd(OAc)_2$ and PCy_3 under milder reaction conditions. By using this method, a series of enantioenriched triarylmethanes were successfully constructed with high enantiospecificity.[20] Electronic properties of ArOTf have a slight influence on yield as well as specificity, and the cross-coupling procedure was tolerated for a wide range of functional groups, such as carbonyl(**3ab**), formyl (**3ac**), nitro (**3ad**), and alkoxy (**3ae** and **3af**). This method also enables efficient synthesis of four different functionalized triarylmethanes (**3bb**, **3be**, **3eb**, **3ee**). The current method, using ArOTf as electrophiles, represents a practical cross-coupling technique owing to the availability of phenols and their lack of toxicity compared to aryl halides.[7,19b,21,22]

By exposing **3aa** to a mixture of Tf_2O and TfOH, the enantioenriched triarylmethane was readily converted into the de-*tert*-butylated triarylmethane **4a** in 67% yield with a slight loss of stereopurity (Scheme 2). The absolute configuration of **4a** was determined to be *R* by comparison of the optical rotation with the literature value.[20c] It is noteworthy that both enantiomers (*R* and *S*) of the triarylmethanes can be obtained from the 1,6- adducts **2**. Thus whilst coupling of the trifluoroborate **5** with ArOTf occurred with inversion,[23] the opposite stereochemistry (retention) was observed when coupling the dibenzylic neopentyl glycol boronic ester **6** with aryliodide.[7] (Scheme 3).



Scheme 2. De-*tert*-butylation of triarylmethane.



Scheme 3. Stereospecific cross-coupling experiments. TMS = trimethylsilyl.

In summary, we have demonstrated that copper-catalyzed asymmetric 1,6-addition of $B_2(pin)_2$ to the *p*-QMs proceeds with excellent yield and good to excellent enantioselectivities. For the first time, enantioenriched *gem*-diarylmethine boronates were prepared by a catalytic asymmetric method. Subsequently, the derived chiral potassium trifluoroborates were converted into enantioenriched triarylmethanes in good yield and with high enantiospecificity. Additional asymmetric transformations of *gem*-diarylmethine boronates are underway in our laboratory.

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Keywords: asymmetric catalysis · boron · copper · cross-coupling · synthetic methods

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