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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.7b00300 • Publication Date (Web): 17 Feb 2017

Modular Synthesis of Enantioenriched 1,1,2-Triarylethanes by an Enantioselective Arylboration and Cross-Coupling Sequence

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ABSTRACT: An enantioselective Cu/Pd-catalyzed borylative coupling of styrenes with aryl/alkenyl iodides was realized using a chiral sulfoxide-phosphine (SOP) ligand. Enantioenriched 1,1-diarylethyl and β-aryl-homoallylic boronates are readily prepared. A streamlined procedure merging arylboration and subsequent Pd-catalyzed Suzuki-Miyaura cross-coupling enables the modular assembly of enantioenriched 1,1,2-triarylethanes, including two medicinally important chiral small-molecule targets.

KEYWORDS: *asymmetric catalysis, 1,1,2-triarylethanes, arylboration, cross-coupling, modular synthesis*

INTRODUCTION

Chiral 1,1,2-triarylethanes, in which three aryl groups are installed on one ethane skeleton, are fundamental structural motifs present in numerous bioactive compounds and drugs, including an orally active anti-inflammatory phosphodiesterase IV inhibitor CDP840 (**A**),[1] a glucagon receptor antagonist for treating type-II diabetes (**B**),[2] lasofoxifene[3] (**C**) for treating osteoporosis, and bedaquiline[4] (**D**) for treating tuberculosis (Figure 1). All these optically-pure chiral compounds contain a *gem*-diarylmethine stereocenter, a common skeleton in many pharmaceuticals and natural products.[5] Although asymmetric methods[6] for the construction of *gem*-diarylmethine stereocenters are well established, few are applicable to the synthesis of chiral 1,1,2-triaryethanes.[7] To date, catalytic asymmetric hydrogenation[8] of 1,1,2-triaryethenes and stereospecific cross-coupling[9] of enantioenriched 1-boryl-1,2-diarylethanes are among the most well-established approaches. In order to obtain more structurally diverse enantioenriched 1,1,2-triaryethanes, new and straightforward methods for rapidly assembling these motifs are highly desired.

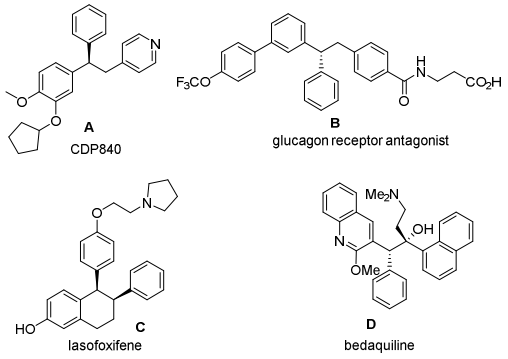
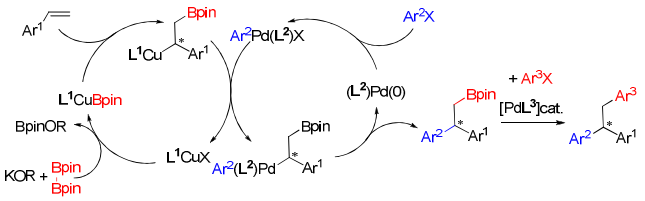


Figure 1. Selected chiral 1,1,2-triarylethanes

Recent advances in transition metal-catalyzed carboboration chemistry have provided a new platform for the discovery and synthesis of organoboron compounds.[10] The carboboration of olefins readily furnishes multifunctional and chiral C(sp^3)-boronates.[11] In 2014, Semba and Nakao,[12] as well as Brown,[13] disclosed elegant tactics for the Cu/Pd-catalyzed arylboration of styrenes toward the preparation of racemic 2-boryl-1,1-diarylethanes, which demonstrate substantial utility for the syntheses of *gem*-diaryl and polyaryl compounds. We envisioned that an enantioselective arylboration[14] could provide a concise method for the synthesis of otherwise difficult to access homochiral *gem*-diarylethyl boronic esters.[15] More importantly, this method, if coupled with the robust *B*-alkyl Suzuki-Miyaura cross-coupling, would reveal opportunities for the modular construction of chiral 1,1,2-triarylethanes. (Scheme 1)

Scheme 1. This Strategy for Construction of Enantioenriched 1,1,2-Triarylethanes

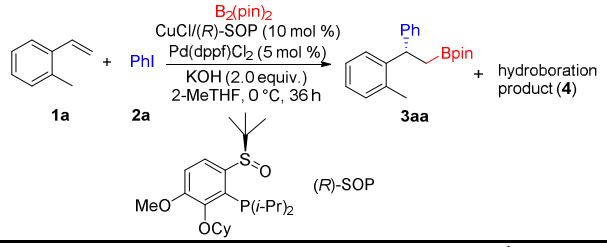


RESULTS AND DISCUSSION

We recently demonstrated that chiral sulfoxide-phosphine ligands (SOP) are highly effective for the Cu and Pd co-catalyzed enantioselective allylboration of styrenes under mild conditions.[11e] We have also showed that under these conditions, the borylative coupling of *o*-methyl styrene (**1a**) and phenyl iodide (**2a**) was feasible, generating the chiral *gem*-diarylethyl boronic ester (**3aa**) in 54% yield with 90% ee. Further systematic optimization led to conditions that furnish (*S*)-**3aa** in excellent NMR yield (97%) with high ee (96%) (see Table S1-S7 in SI for details, see below for absolute stereochemical assignment). Control experiments demonstrated that, in the absence of Pd(dppf)Cl_2, only the hydroboration product (**4**) was generated (Table 1, entries 2 and 3). Moreover, the loading of Pd catalyst exhibited a high correlation with the yield of **3aa** (Table 1, entries 4 and 5). These results indicated that **3aa** was generated via a Cu^{I}-Pd^{II} transmetallation process, instead of the direct cross-coupling of a benzylcopper intermediate with the aryl iodide.[16] Palladium complexes ligated by

X-Phos, PPh_3 or *rac*-BINAP generated **3aa** in much lower yield and enantioselectivity (Table 1, entries 6-8). The assessment of copper catalysts revealed that commercially available (*S*,*S*)-Me-Duphos and (*R*)-BINAP are much less effective than (*R*)-SOP (Table 1, entries 9-10 vs. entry 1). Following our best observed reaction conditions, neither PhBr nor PhCl afforded the targeted product (Table 1, entries 10-12). When PhOTf was employed as the electrophile, **3aa** was observed in low yield even at higher reaction temperature. (Table 1, entries 13-14) Lastly, PhBr became an viable substrate at elevated temperature (100 °C, Table 1, entry 15), giving **3aa** in reasonable yield and enantiomeric excess.

Table 1. Enantioselective Arylboration: Effect of Changing Reaction Parameters[a]

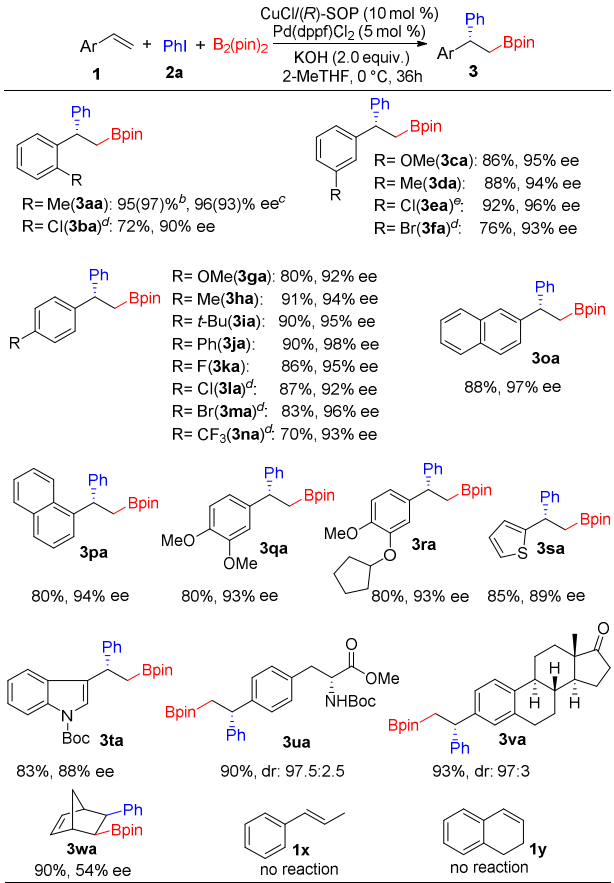


Entry	Change from optimized conditions	**3aa**/**4**[b] (%)	ee[c] (%)
1	None	97/trace	96
2	no $Pd(dppf)Cl_2$	0/50	-
3	no $Pd(dppf)Cl_2$, 100 °C	0/45	-
4	2.5 mol% of $Pd(dppf)Cl_2$	92/5	96
5	1 mol% of $Pd(dppf)Cl_2$	60/30	91
6	Pd/XPhos precatalyst instead of $Pd(dppf)Cl_2$	24/62	85
7	$(PPh_3)_2PdCl_2$ instead of $Pd(dppf)Cl_2$	17/60	80
8	*rac*-BINAP/$PdCl_2$ instead of $Pd(dppf)Cl_2$	65/26	87
9	(*S*,*S*)-Me-Duphos instead of (*R*)-SOP	17/65	-78
10	(*R*)-BINAP instead of (*R*)-SOP	68/26	-50
11	PhCl instead of PhI	0/50	-
12	PhBr instead of PhI	0/50	-
13	PhOTf instead of PhI	25/20	95
14	PhOTf instead of PhI, 60 °C	40/15	91
15	PhBr instead of PhI, 100 °C	66/30	82

[a]Reaction was performed with **1a** (0.2 mmol), **2a** (0.3 mmol), $B_2(pin)_2$ (0.3 mmol), CuCl (10 mol %), (*R*)-SOP (12 mol %), $Pd(dppf)Cl_2$ (5 mol %), KOH (0.4 mmol), 2-MeTHF (2 mL) at 0 °C for 36 h. [b]Determined by ^1H NMR spectroscopy. [c]Determined by chiral HPLC.

With improved reaction conditions in hand, the substrate scope of this Cu/Pd co-catalyzed enantioselective arylboration was surveyed. As shown in Table 2, a broad range of styrenes with diverse functional groups (alkyl, aryl, ethers, and halogens) could be effectively converted into the corresponding chiral *gem*-diarylethylboronic esters **3** in good to excellent isolated yields (70-95%) and high enantioselectivities (90-98% ee). Notably, for electron-deficient styrenes, higher loading of the Pd-catalyst (10 mol %) and higher reaction temperatures (25 °C instead of 0 °C) were needed to afford **3ba**, **3ea**, **3fa**, **3la**, **3ma** and **3na** in good yields. Presumably, these modified conditions enhanced the rate of the Pd-mediated cycle to match that of the Cu-mediated cycle, which is faster with more electron-deficient substrates.[6t,17] Furthermore, vinyl heteroaryls, such as 3-vinyl indole and 2-vinyl thiophene, also worked well to afford *gem*-(hetero)diarylethylboronates (**3sa** and **3ta**) in good yields and ee's. In addition, this reaction provided an attractive platform for the late-stage modification of some important bioactive compounds such as α-amino esters (**3ua**, 90% yield, dr = 97.5/2.5) and steroids (**3va**, 93% yield, dr = 97/3). To note, the model reaction can be scaled up to 5 mmol, with 1.53 g of **3aa** (93% ee) being obtained with the use of 2 mol % of catalyst loading (both Cu catalyst and Pd catalyst). Recently, Brown demonstrated that chiral NHC-carbene ligands are effective for the asymmetric arylboration of β-substituted styrenes.[14] Under our conditions, however, the β-substituted styrenes (e.g. **1x** and **1y**) were inert even at higher reaction temperatures, probably due to the failure of the addition of (SOP)CuBpin to these olefins. The arylboration of norbornadiene was surveyed and *exo*-**3wa** was afforded in good yield, high diastereoselectivity, and moderate enantioselectivity. The stereochemical outcomes of these reactions are consistent with that of our previously reported enantioselective allylboration[11e] and borylstannation[18] processes, suggesting that the Cu/Pd transmetallation process occurrs in a stereorentive manner, probably through the intermediates **I** and **II**. (Scheme 2)

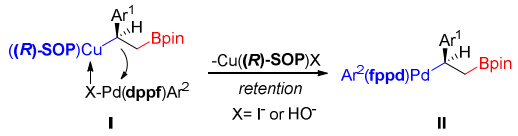
Table 2. Scope of styrenes[a]



[a]Conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $B_2(pin)_2$ (0.3 mmol), CuCl (10 mol %), (*R*)-SOP (12 mol %), $Pd(dppf)Cl_2$ (5 mol %), KOH (0.4 mmol), 2-MeTHF (2 mL) at 0 °C for 36 h. [b]Isolated yield and the data in parentheses was the isolated yield of **3aa** in 5

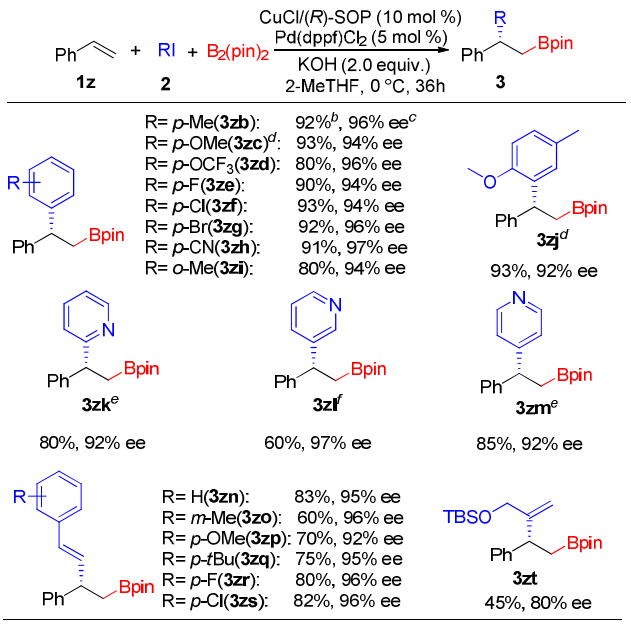
mmol scale reaction. [c]Determined by chiral HPLC and the data in parentheses was ee value of **3aa** in 5 mmol scale reaction. [d]$Pd(dppf)Cl_2$ (10 mol %), 2-MeTHF (3 mL) at 25 °C. [e]$Pd(dppf)Cl_2$ (10 mol %), 2-MeTHF (3 mL) at 0 °C.

Scheme 2. Proposed model of this stereospecific Cu to Pd transmetallation



We next examined the arylboration of parent styrene (**1z**) with substituted phenyl iodides. As shown in Table 3, both electron-rich and poor aryl iodides could afford the desired products in excellent yields (80-93%) with high ee's (94-97%) (**3zb-3zh**). It should be noted that the reaction is highly selective for the iodide leaving group, F, Cl and Br substituents survive this transformation without any competitive coupling products. Sterically hindered aryl iodides also reacted smoothly with styrene to provide **3zi** and **3zj** in good yields and enantioselectivities. The absolute configuration of (*R*)-**3zj** was confirmed by conversion to a known compound and comparison of the resulting optical rotation with literature values.[19] Notably, 1-, 2- and 3-iodopyridines all worked well when the ratio of styrene to pyridine electrophiles was tuned slightly (**3zk-3zm**). Alkenyl halides are also competent electrophiles allowing for the productions of enantioenriched β-aryl-homoallylic boronates (**3zn-3zt**) in good yields (45-83%) with good to excellent enantioselectivities (80-96% ee).

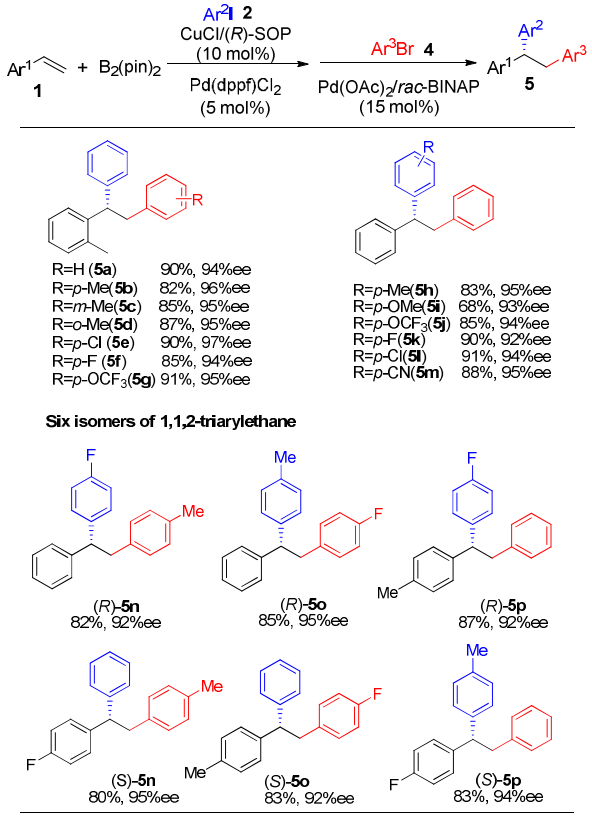
Table 3. Scope of aryl iodides[a]



[a]Conditions: **1z** (0.2 mmol), **2** (0.3 mmol), $B_2(pin)_2$ (0.3 mmol), CuCl (10 mol %), (*R*)-SOP (12 mol %), $Pd(dppf)Cl_2$ (5 mol %), KOH (0.4 mmol), 2-MeTHF (2 mL) at 0 °C for 36h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]$Pd(dppf)Cl_2$ (10 mol %), 2-MeTHF (3 mL) at 25 °C. [e]**1z** (0.3 mmol), **2** (0.2 mmol), at 25 °C. [f]**1z** (0.3 mmol), **2** (0.2 mmol), at 0 °C

After establishing satisfactory conditions for the asymmetric arylboration protocol with Cu/Pd catalysis, following work focused on the $C(sp^3)$-$C(sp^2)$ Suzuki-Miyaura cross-coupling of the resulting products. Initial evaluations of the Pd-catalysts found that neither $Pd(dppf)Cl_2$ nor RuPhos/$Pd(OAc)_2$ gave good results, although these catalysts were appropriate for previously reported cross-couplings of primary alkylborons.[20] Interestingly, *rac*-BINAP/$Pd(OAc)_2$ is quite effective for the coupling of **3aa** (93% ee) and bromobenzene, giving the expected 1,1,2-triarylethane **5a** in excellent yield (95%) without any detectable erosion of ee (93% ee, see Table S9 in SI for details). Encouraged by this result, we envisioned merging the cross-coupling and Cu/Pd-catalyzed arylboration procedures without the isolation of **3**. This can be realized by directly adding the second aryl electrophile (3.0 equiv), *rac*-BINAP/$Pd(OAc)_2$ and aqueous KOH to the arylboration reaction mixture.[21] Following this sequence, **5a** was afforded in good overall yield (80%) with high enantioselectivity (94% ee). An additional filtration of the arylboration reaction mixture through Celite can insure reproducibility and effectively increase the reaction yield (95% NMR and 90% isolated). With this streamlined procedure, diverse enantioenriched 1,1,2-triarylethane molecules can be modularly assembled (Table 4). For instance, a wide range of substituted phenyl bromides were quite reactive in the second cross-coupling and were thus incorporated into the corresponding triarylethanes (**5b-5g**) in good to excellent yields (82-91%) with excellent enantioselectivties (94-97% ee). An array of triarylethanes (**5h-5m**) derived from substituted phenyl iodides are also readily accessed under our standard conditions in good yields with similar ee values to our arylborylated intermediates (**3zb-3zh**). The power of this modular strategy is further demonstrated by the asymmetric synthesis of (*R*)-**5n-5p** and their enantiomers under standard conditions, with both high yields (80-87%) and ee's (92-95%).

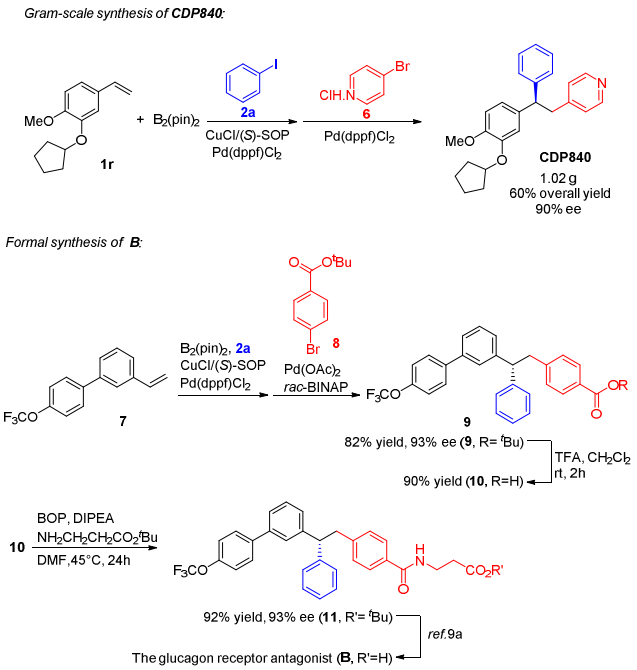
Table 4. Scope of chiral 1, 1, 2-triarylethyane[a]



[a]Conditions: **1** (0.3 mmol), **2** (0.2 mmol), CuCl (10 mol %), (*R*)-SOP (12 mol %), Pd(dppf)Cl_2 (5 mol %), KOH (0.4 mmol), 2-MeTHF (2 mL) at 0 °C for 36h. The resulted mixture was filtrated through a pad of Celite and concentrated *in vacuo*, then the crude enantioenriched 1,1-diaryethylboronate was reacted with aryl-boromide **4** (0.6 mmol) in the presence of *rac*-BINAP-Pd$(OAc)_2$ (15 mol %), KOH (3 mmol), THF (3 mL) and H_2O (0.3 mL) at 100 °C for 12h. [b]Isolated yield. [c]Determined by chiral HPLC.

To illustrate the efficiency and convenience of the established streamlined methodology, two medically-relevant chiral molecules, CDP840 (**A**)[7,9b,12,22] and the glucagon receptor antagonist **B**,[2,9a] were synthesized (Scheme 3). Firstly, the enantioselective borylative coupling of **1r** and **2a**, followed by cross-coupling with **6** catalyzed by Pd(dppf)Cl_2,[23] afforded CDP840 (1.02 g with 90% optical purity). The formal synthesis of **B** stems from the asymmetric transformation of **7** with **2a** and **8**. Using our streamlined procedure, the key intermediate **9** was obtained in good yield (82%) with high enantioselectivity (93% ee). Hydrolysis of **9** to **10** (90% yield) and the following condensation with the appropriate amine to afford **11** (92% yield, 93% ee) accomplished the formal synthesis of **B**.

Scheme 3. Synthesis of CDP840 and glucagon receptor antagonist B.



CONCLUSION

We herein report a streamlined procedure for the modular synthesis of enantioenriched 1,1,2-triarylethanes by an enantioselective arylboration and *B*-alkyl Suzuki-Miyaura coupling sequence. The synthetic strategy employs readily available chemical feedstocks (styrenes and aryl halides) and relatively inexpensive metal catalysts (copper and palladium), avoids the isolation of intermediates, and allows for easy scale-up. The generality and modularity of this reaction promises its use in the syntheses of the medically relevant, structurally diverse 1,1,2-triarylethanes.

ASSOCIATED CONTENT

Supporting Information.
Experimental details, analytic data (NMR, HPLC, ESI-HRMS) (PDF). 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.

ACKNOWLEDGMENT

We thank the NSFC (Nos. 21472184, 21272226, 21572218, and 21402186) and Western-Light Foundation of CAS for financial support. J. J. Chruma (Sichuan University) provided valuable manuscript revisions.

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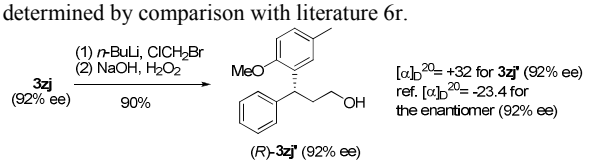

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Modular synthesis via a streamlined procedure