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Communication

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A Cu/Pd Cooperative Catalysis for Enantioselective Allylboration of Alkenes

Tao Jia, Peng Cao, Bing Wang, Yazhou Lou, Xuemei Yin, Min Wang and Jian Liao*

Natural Products Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, 610041, China.

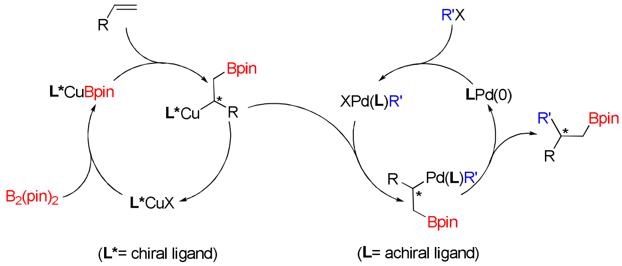
Supporting Information Placeholder

ABSTRACT: A cooperative Cu/Pd-catalyzed asymmetric three-component reaction of styrenes, $B_2(pin)_2$ and allyl carbonates was reported. This reaction, in the presence of chiral CuOAc/SOP and achiral $Pd(dppf)Cl_2$ catalysts, occurs smoothly with high enantioselectivities (up to 97% ee) . The allylboration products, which contain alkene (or diene) unite and alkylboron group, are easily functionalized. The utility of this protocol was demonstrated through the synthesis of an antipsychotic drug, (-)-preclamol.

Multifunctional and enantioenriched organoboranes are useful building blocks in the synthesis of natural products and bioactive compounds.[1] Transition metal-catalyzed asymmetric carboboration reaction is an efficient and straightforward approach to access chiral multi-substituted alkyl- or alkenylboranes.[2] For instance, Ito and coworkers developed a successful copper-catalyzed borylative cyclization to prepare optically pure *β*-aryl or silylated cyclopropylboronates.[3] The related asymmetric carboboration of allenes, alkynes and 1,3-enynes are also applied in the synthesis of chiral *di*-, *tri*- and *tetra*-substituted alkenylboron esters by Hoveyda[1c,4] and Lin.[5] However, up to date, enantioselective carboboration of alkenes for the construction of enantioenriched and muti-functional alkylborons are less developed. Sporadic examples were reported and limited to Cu-catalyzed borylative aldol carboboration[6] and Pd-catalyzed 1,1-arylboration.[7]

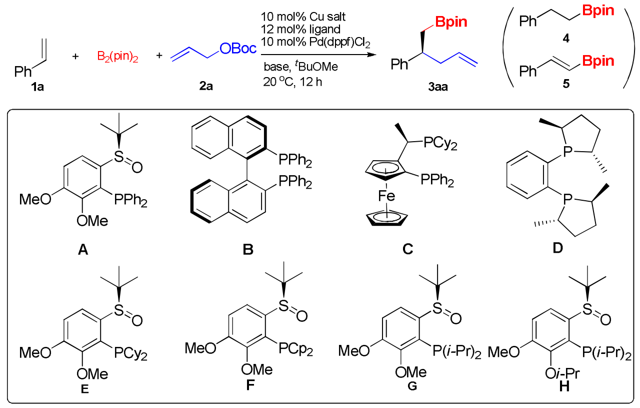
Very recently, Semba, Nakao[8] and Brown[9] independently reported a remarkable three-component carboboration of alkenes with bis(pinacolato)diboron ($B_2(pin)_2$) and aryl or vinyl halides by a Cu/Pd cooperative catalysis. We envisioned using this combination catalysis[10] as a platform to develop enantioselective carboboration of simple alkenes. The proposed procedure involves two cooperative catalytic cycles (Scheme 1), a Cu-catalyzed enantioselective generation of β-borylalkylcopper[11] and a Pd-catalyzed cross-coupling transformation of this enantioenriched reagent.[1a,12] We believe that the stereospecific transmetallation of alkylcopper with XPd(**L**)R' in the proposed mechanism, and the compatibility of the chiral L*Cu(I)-complex with the achiral Pd(0)- or Pd(II)-complex would be the key issues. In our previous work,[13] a sterespecific copper-tin transfer was observed in Cu(I)-catalyzed enantioselective alkene stannylboration when using chiral sulfoxide-(P-aryl)phosphine (SOP) ligand. In this work, we found that P-alkyl sulfoxide-phosphine ligands[14] can effectively promote the aforementioned Cu-Pd transmetallation and realize a highly enantioselective allylboration of alkenes.

Scheme 1. Strategy of Catalytic Asymmetric Intermolecular Carboboration of Alkenes



To test the feasibility, the three-component reaction of styrene (**1a**), B2(pin)2 and allylic electrophiles was performed in the presence of (SOP)CuCl catalyst precursor and Pd(dppf)Cl2 co-catalyst. After screening a series of allyl substrates with different leaving groups (e.g. halides, esters and carbonates), *t*-butyl allyl carbonate **2a** was confirmed as the best electrophile in terms of the reactivity and selectivity. (see supporting information for details) In the presence of chiral ligand **A**, three-component assembling **3aa** was afforded in 39% NMR yield with 90% ee, albeit low conversion and unavoidable generation of side products **4** and **5**. (Table 1, entry 1) Systematic survey to palladium complex, copper salt, base and solvent revealed that the use of CuOAc, KOH and *t*-BuOMe enabled improvements of the catalytic efficiency (Table 1, entry 4, for details see supporting information). However, the hydroboration and β-H elimination products still cannot be avoided and severely erode yields of desired reaction (**4**+**5**> 20% yield). Other P-diphenyl sulfoxide-phosphines or commercially available chiral phophine ligands, (i.e. **B**, **C** and **D**) were also evaluated but no better results were yielded. (entries 5-7 and see supporting informations) To our delight, P-dialkyl sulfoxide-phosphine ligands (**E**-**H**) effectively improve yields of **3aa**, concomitant formation of trace **4** and **5** (<5%). (entries 8-11) Accordingly, the P-diisopropyl ligand **H** provided **3aa** in 80% yield with 92% ee. (Table 1, entry 11) In the presence of optimal copper and palladium catalysts, the reaction was performed at 0°C and gave **3aa** in 80% isolated yield with 95% ee. (Table 1, entry 12)

Table 1. Asymmetric Allylboration of the Styrene[a]

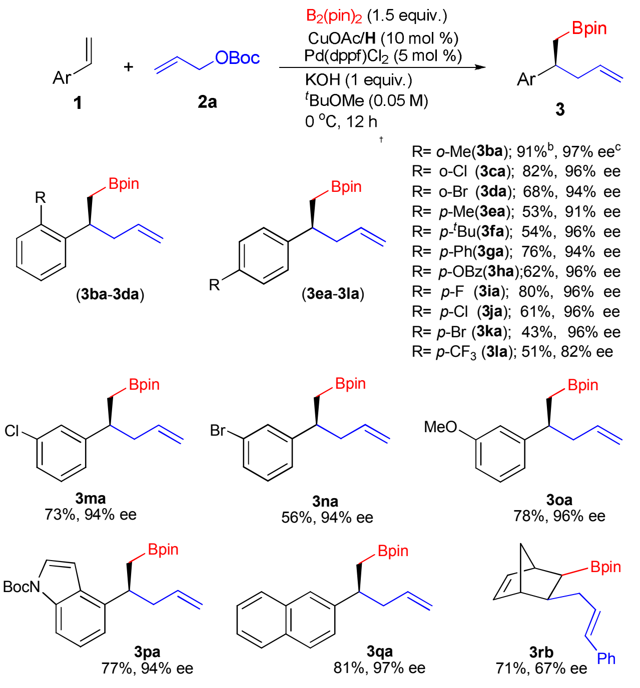


entry		copper salt	base	yield(%)[b] (**3aa**/**4**+**5**)	ee[c] (%)
1	**A**	CuCl	NaO^{t}Bu	39/19	90
2	**A**	CuBr	NaO^{t}Bu	25/14	88
3	**A**	CuOAc	NaO^{t}Bu	65/21	84
4	**A**	CuOAc	KOH	62/27	89
5	**B**	CuOAc	KOH	63/7	-20
6	**C**	CuOAc	KOH	53/28	-77
7	**D**	CuOAc	KOH	30/59	68
8	E	CuOAc	KOH	81/4	84
9	**F**	CuOAc	KOH	78/8	85
10	**G**	CuOAc	KOH	75/4	90
11	**H**	CuOAc	KOH	80/3	92
12[d]	**H**	CuOAc	KOH	81(80)[e]/5	95

[a]Reaction was performed with **1a** (0.2 mmol), **2a** (0.3 mmol), $B_2(pin)_2$ (0.3 mmol), Pd(dppf)Cl_2 (5 mol %), the copper salt (10 mol %), **L** (12 mol %), the base (0.2 mmol) in ^{t}BuOMe (4 mL) at 20 °C for 12h [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by HPLC analysis and the absolute configuration was assigned to (*S*) by comparing the optical rotation of (*S*)-**11** with literature (see scheme 2). [d]The reaction was performed at 0 °C. [e]The data in the parenthesis was isolated yield of **3aa**.

With these optimized conditions in hand, we next investigated the substrate scope of this Cu/Pd-catalyzed asymmetric allylboration. (Table 2) When **2a** was used as the electrophilic coupling partner, a wide range of vinyl arenes could be effectively converted into the corresponding three-component products with generally excellent enantioselectivities. The reaction is compatible with various functional groups such as alkyl, aryl, OBz, halogen bound to benzene ring. Particularly, most of halogens (i.e. F, Cl or Br), which (Cl and Br) are not tolerant of (NHC)CuBpin-catalyzed carboboration,[8,9,15] can be installed at *o*-, *m*- or *p*-site of styrene substrates and have little effects on this transformation. Styrenes with *p*-CF_3 (product **3la**, 51% yield, 82% ee) or *m*-OMe (product **3oa**, 78% yield, 96% ee) were also reactive. The product **3oa** was assigned to (*S*)-configuration, and this stereochemical outcome is consistent with that of Cu(I)/SOP-catalyzed boryl stannaylation when using the same ligand **A**.[13] Therefore, the transmetallation from Cu to Pd should proceed in stereochemically retentive manner, the same with Cu-Sn transferring process. Notably, 4-vinyl indole and 2-vinyl naphthalene are appropriate to provide **3pa** and **3qa** in good yields and ees. Although the attempted allylboration of 1,2-substituted styrene derivatives (i.e. *β*-methyl styrene), methyl crotonate (hydroboration product was observed) and alkyl-substituted alkenes were futile, that of bicyclo[2.2.1]hepta-2,5-diene proceeded smoothly and highly diastereoselective exo-**3rb** was afforded in good yield with moderate enantioselectivity.

Table 2. Substrate Scope of Three-Component Coupling Reaction[a]

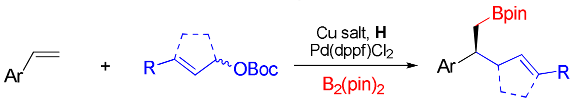


[a]Reactions conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $B_2(pin)_2$ (0.3 mmol), Pd(dppf)Cl2 (5 mol %), CuOAc (10 mol %), **H** (12 mol %), KOH (0.2 mmol) in *t*-BuOMe (4

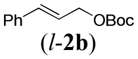
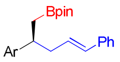
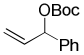
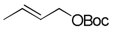
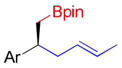
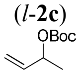
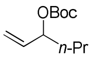
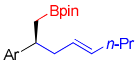
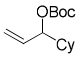
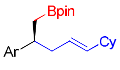
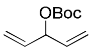
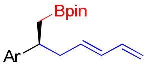
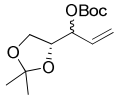
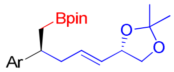
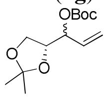
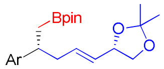
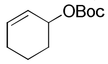
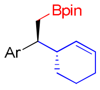
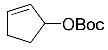
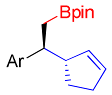
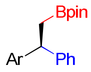
mL) at 0°C for 12h. [b]Isolated yields. [c]Determined by HPLC analysis.

This Cu/Pd catalysis is not only applicable to the unsubstituted symmetric allyl electrophile, but also compatible with mono- and disubstituted allyl systems. More complex and unsymmetrically substituted allylic electrophiles would make the reaction more complicated since regio- and/or diastereoisomeric products in the "allyl fragment" can be formed. When we examined the cross coupling of alkyl- and aryl-substituted allyl complexes with the in situ generated alkylcopper from **1b**, both branched (*b*) and linear (*l*) allyllic carbonates were used. (Table 3) Both phenyl-substituted *l*-**2b** and *b*-**2b** gave the only linear allylation product **3bb** in high yield with excellent ee.[16] (entry 1) Interestingly, for the coupling of alkyl-substituted substrates, *b*-**2c** was preferable to the corresponding *l*-**2c** allylic carbonate in terms of the reactivity and enantioselectivity, probably due to the "memory effect".[17] (entry 2) Other branched allyl electrophiles such as *n*-Pr (**2d**), Cy (**2e**) and vinyl-substituted (**2f**) carbonates are also established with high level of enantiopurities.(entries 3-5) When chiral **2g** was used in the asymmetric reaction, **3bg** or **3bg**' was provided by (*R*)-**H** or (*S*)-**H** ligand with the newly generated stereogenic center totally reversed. (95/5 vs 3/97 dr, entries 6-7) The current catalytic system also demonstrates excellent ability to control the diastereoselectivity when racemic cyclic allylic carbonates were applied. For instance, asymmetric alkylation of **2h** and **2i** afforded **3bh** and **3bi** bearing two adjacent and stereodefined C-centers. (entries 8-9) The product **3bh** is assigned to the *trans*-isomer by NOE analysis of the derivative **6**. (see supporting information) Notably, the enantioselective arylboration[8,9] can occur smoothly when using PhI (**2j**) as electrophile. (entry 10)

Table 3. The Scope of Allyl Boc Substrates[a]



1b (Ar= 2-MeC$_6$H$_4$) **2** **3**

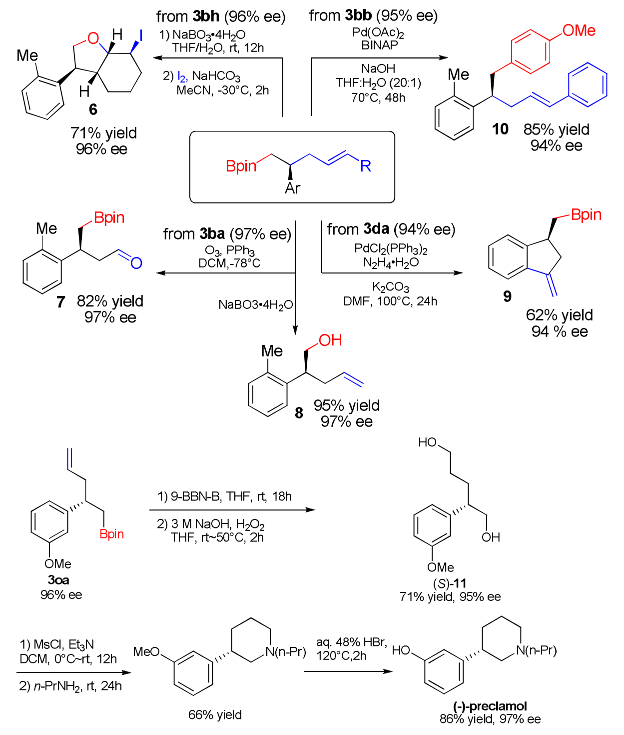
entry	2	3	yield[b] (%)	ee[c] (%)
1	 (*l*-**2b**)	 (**3bb**)	81	95
	 (*b*-**2b**)		82	95
2	 (*l*-**2c**)	 (**3bc**)	76	91
	 (*b*-**2c**)		86	97
3	 (**2d**)	 (**3bd**)	51	93
4	 (**2e**)	 (**3be**)	37	91
5	 (**2f**)	 (**3bf**)	50	96
6	 (**2g**)	 (**3bg**)	40	95:5[d]
7	 (**2g**)	 (**3bg'**)	38	3:97[d]
8	 (**2h**)	 (**3bh**)	47 (>20/1)	96
9	 (**2i**)	 (**3bi**)	70 (12/1)	94
10	PhI (**2j**)	 (**3bj**)	54	90

[a]The reaction was performed with **1** (0.2 mmol), **2** (0.3 mmol), $B_2(pin)_2$ (0.3 mmol), $Pd(dppf)Cl_2$ (5 mol %), the copper salt (10 mol %), **H** (12 mol %), the base (0.2 mmol) in ^{t}BuOMe (4 mL) at 0 °C for 12h [b]Isolated yields. [c]Determined by HPLC analysis. [d]The ratio of **3bg** and **3bg**' was checked by ^{1}H NMR.

To illustrate the versatility and potential of this methodology, site-selective transformations of enantioenriched *β*-allylboronic esters were implemented to construct chiral hydrocarbon building blocks. (Scheme 2) For instance, the ozonization[18] of **3ba** enables selective conversion of C=C bond to C=O bond without interference of C-B bond or loss of enantiopurity, whilst the oxidation by $NaBO_3$.4H2O[11c] selectively cleavages C-B bond. Thus either *γ*-carbonyl boronate (**7**) or pent-4-en-1-ol (**8**) can be obtained with high level of optical purities using different oxidative reagents. Accordingly, B-oxidation/iodine etherification[19] of **3bh**, provided bicyclic **6** with excellent diastereo- and enantioselectivity. Other transformations such as intramolecular Heck reaction[20] of **3da** to **9** and Suzuki coupling[13] of **3bb** to **10** also proceeded well with total retention of the stereocenter. The utility of this asymmetric allylboration was also demonstrated through the synthesis of (-)-preclamol,[21] an antipsychotic drug,[22] from the enantioenriched **30a** (96% ee). A sequential hydroboration/oxidation to (*S*)-**11**,[21a] followed by the ring close amination and hydrolysis, gave just the (-)-preclamol bearing (*S*)-stereocenter.

In summary, a cooperative Cu/Pd-catalyzed asymmetric three-component reaction of styrenes, B2(pin)2 and allyl carbonates was developed. This work presents the first example of catalytic asymmetric intermolecular 1,2-carboboration of alkenes, which contributes to the development of new catalytic asymmetric protocols of alkene difunctionalization.

Scheme 2. Products Transformations



ASSOCIATED CONTENT

Supporting Information

Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* jliao@cib.ac.cn

Notes

The authors declare no competing financial interest.

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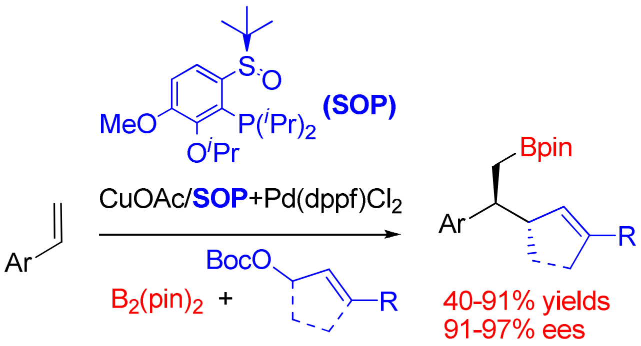
MeO
S
O
P(^{i}Pr)$_2$
O^{i}Pr
(SOP)
Ar
CuOAc/SOP+Pd(dppf)Cl$_2$
B$_2$(pin)$_2$ +
BocO
R
Bpin
Ar
R
40-91% yields
91-97% ees