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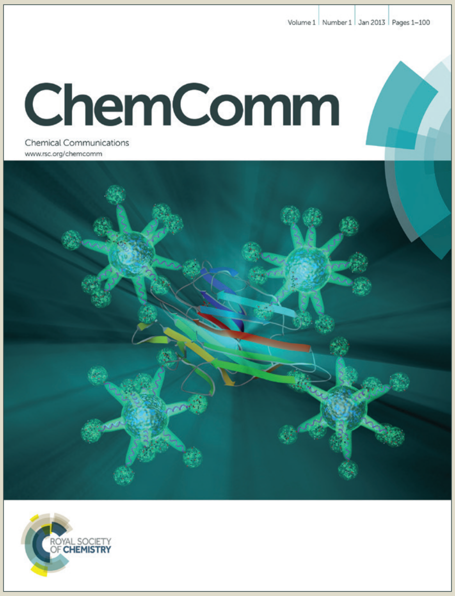

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Cu(II)-Based strategy for catalytic enantioselective β-borylation of α,β-unsaturated acceptors

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Cu(I)-based chemistry has flourished over the last decade because of the reliable use of such species as soft acids. However, the unique nature of Cu(II) catalysts is allowing the well-documented Cu(I)-based chemistry to be extended. Prominent advantages of this approach include ease of handling, the avoidance of strong base, and wider substrate scope in enantioselective β-borylation.

Enantioenriched α-chiral boron derivatives are an important class of compounds because of their versatile range of applications. Their C–B linkage can be transferred into C–O, C–N, as well as C–C bonds through 1,2-migration of intermediary ate complexes with appropriate nucleophiles, while retaining the integrity of stereogenic centers.[1] In recent years, the Suzuki–Miyaura cross-coupling reaction has been expanded to include the conversion of optically active organoboranes with retention of stereoconfiguration.[2] In addition to their chemical importance as versatile intermediates, boron compounds have been targeted directly for pharmaceutical applications because they can be used to generate reversible covalent complexes with carbohydrates, amino acids, and hydroxamic acids.[3]

Borylation of alkenes represents one of the most efficient routes to organoboron compounds. A plethora of approaches have been developed based on the formation of an isolatable borylcopper(I) species *in situ* through σ-bond metathesis between diboron reagents and Cu(I) salts; this approach was described in concomitant reports by Hosomi[4] and Miyaura[5] in 2000. The Cu(I)-based enantioselective protocols were further embellished through the use of air-sensitive chiral phosphine-based ligands or *N*-heterocyclic carbenes by Yun,[6] Hoveyda,[7] Shibasaki,[8] McQuade,[9] Ma,[10] and other groups.[11] The tendency of Cu(I) to undergo disproportionation means that this chemistry has required the use of anhydrous organic solvents and an inert atmosphere. Given the soft nature of Cu(I), such catalytic systems are highly active for couplings with sp^2 carbon centers, as represented by conjugate additions through d–π interactions. High catalytic activity is usually ensured by the addition of a strong base such as NaO^{t}Bu and more than 1 equivalent of alcohol as a proton source, substrate tolerance depends on ligand structures. In contrast to chiral Cu(I) protocols for enantioselective β-borylation of α,β-unsaturated acceptors, which have been investigated extensively, chiral Cu(II) catalysis has not been investigated until recently. We have developed chiral Cu(II)-catalyzed enantioselective borylation of α,β-unsaturated acceptors, which proceed well in water.[1a,12,13] Unique reactivity and selectivity are often observed in organic reactions in water. Indeed, the corresponding Cu(II) chemistry in organic solvents was unprecedented.

Intrigued by the unique nature of Cu(II) catalysts, which are distinct from Cu(I) systems, we wanted to extend the range of Cu(II)-based chemistry to include enantioselective β-borylation of α,β-unsaturated acceptors (Table 1). We expected that, given the relatively hard nature of Cu(II) compared with Cu(I), this Lewis acid could be used to activate carbonyl groups rather than the double bonds of α,β-unsaturated acceptors. At the outset, we studied Cu(II) catalysis under the same general conditions developed for Cu(I)-based strategies. Thus, Cu(OAc)$_2$ was mixed with a phosphine-based ligand such as BINAP (**L1**) or Josiphos (**L2**), which are often used in Cu(I)-based approaches, with an equimolar amount of methanol as a proton source. In the presence of the catalysts, chalcone (**1a**) was treated with bis(pinacolato)diboron (B$_2$(pin)$_2$, **2**) at room temperature for 12 h, and the crude adduct was treated with NaBO$_3$ to form a stable alcohol (**3a**). Whereas the reaction did not proceed at all by using **L1** (entry 1), a moderate yield, albeit with poor enantioselectivity, was obtained by using **L2** (entry 2). Although a number of reports on Cu(II) complexes have described the effective combination of Cu(II) salts with bis(oxazolidine) (box), bis(oxazolinyl)pyridine (pybox), and dibenzylamine ligands, the reactions generally suffer from moderate yields and enantioselectivities (entries 3–6). On the other hand, the use of chiral 2,2′-bipyridine **L7**[14] rendered the product in a highly selective manner (entry 7). In contrast, substituting Cu(I) salt for Cu(II) led to a significant reduction in the enantioselectivity (entry 8). The reaction took place with decreased selectivity in methanol and with low selectivity in acetonitrile (entries 9 and 10). Extensive clustering of copper(II) acetate species in methanol[15] may lead to a reduction in the number of solvated monomer species, which would cause chiral induction to be restricted, leading to moderate selectivity. The best performance of the Cu(II)-**L7** complex was achieved when the reaction was conducted in Et$_2$O (entry 11). It seems that solvents that do not coordinate Cu(II), such as THF and Et$_2$O,

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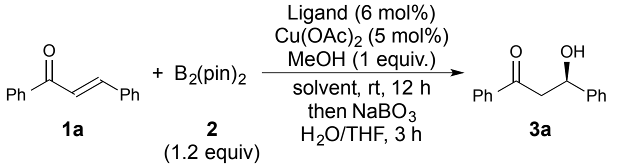
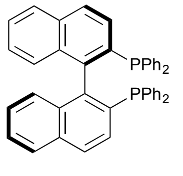
facilitate liberation of monomeric Cu(II) species under dilute conditions.

Table 1. Cu(II) catalysis for enantioselective β-borylation of chalcone.

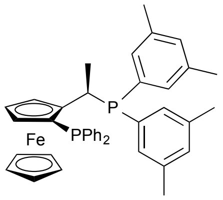


Entry	Ligand	Solvent	Yield (%)[a]	Ee (%)[b]
1	**L1**	THF	NR	–
2	**L2**	THF	57	4
3	**L3**	THF	50	56
4	**L4**	THF	56	10
5	**L5**	THF	55	37
6	**L6**	THF	36	–6
7	**L7**	THF	61	81
8[c]	**L7**	THF	56	10
9	**L7**	MeOH	82	46
10	**L7**	MeCN	71	13
11	**L7**	Et_2O	95	94

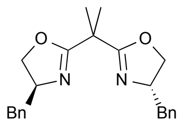
[a] Isolated yield of oxidized product. [b] Determined by HPLC analysis.
[c] CuCl was used instead of $Cu(OAc)_2$. NR = no reaction.



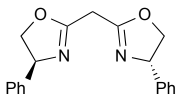
L1



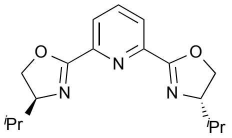
L2



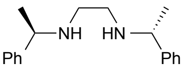
L3



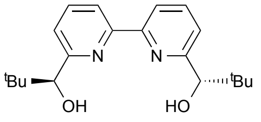
L4



L5



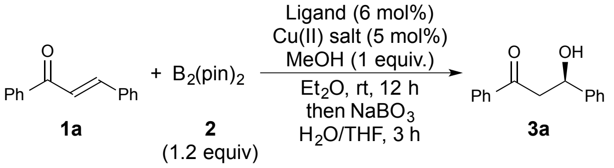
L6



L7

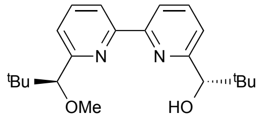
The role of the Cu(II)-**L7** complex was investigated in detail (Table 2). Mono-protection of the hydroxyl group in **L7** with a methyl group (**L8**) did not impair the catalytic performance of Cu(II), whereas bis-protection (**L9**) resulted in significant inhibition of the catalytic cycle and serious enantiomeric erosion (entries 2 and 3). This result suggests that complexation in a tridentate fashion through *N*,*N*,*O*-type coordination is essential for the catalytic activity of the Cu(II)-**L7** species, which is consistent with crystallographic representation of a reported $CuBr_2$-**L7** complex adopting a square pyramidal structure.[16] A reasonable outcome that was comparable to that obtained with $Cu(OAc)_2$ (entry 1) was also achieved when $Cu(OMe)_2$ was used as Cu(II) source (entry 4). When the interaction between the Cu(II) core and the counterpart was significantly covalent in nature, the progress of the reaction appeared to be impeded completely (entries 5 and 6). Based on ESI-MS analysis, the small decrease in catalytic performance observed for the $Cu(acac)_2$-**L7** complex may originate from incomplete formation of the active 1:1 complex, which may result in diboron hydrolysis taking place instead of the desired nucleophilic addition pathway (entry 7). In addition to a high level of enantioselectivity obtained by using insoluble $Cu(OH)_2$ (entry 8), the remarkable catalytic activity of insoluble CuO combined with **L7** was impressive and suggestive of heterogeneity of catalyst behavior (entry 9).

Table 2. Optimizing the reaction with the Cu(II)-**L7** complex.

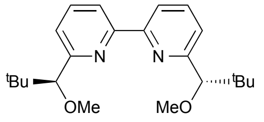


Entry	Ligand	Cu(II) salt	Yield (%)[a]	Ee (%)[b]
1	**L7**	$Cu(OAc)_2$	95	94
2	**L8**	$Cu(OAc)_2$	92	92
3	**L9**	$Cu(OAc)_2$	31	4
4	**L7**	$Cu(OMe)_2$	92	91
5	**L7**	$CuCl_2$	NR	–
6	**L7**	$CuBr_2$	trace	–
7	**L7**	$Cu(acac)_2$	68	84
8	**L7**	$Cu(OH)_2$	44	81
9	**L7**	CuO	96	93

[a] Isolated yield of oxidized product. [b] Determined by HPLC analysis. NR = no reaction. acac = acetylacetonate.



L8



L9

Notably, the Cu(II)-based catalyst system was applicable to various types of α,β-unsaturated acceptors (Scheme 1). Both acyclic and cyclic enones bearing a range of functional groups reacted smoothly to afford the corresponding β-borylated products, which were treated with $NaBO_3$ to provide β-hydroxy ketones **3b–l** and **3q** in good to excellent yields with high to excellent enantioselectivities. α,β-Unsaturated esters also worked well (**3m**, **3n**), with the sterically unfavored tertiary alcohol **3n**, formed from the β,β-disubstituted ester, being obtained in high yield and with high enantioselectivity. Furthermore, an α,β-unsaturated amide and an α,β-unsaturated nitrile were also good substrates, giving **3o** and **3p**, respectively. In the case of α,β,γ,δ-unsaturated dienones, it is noted that only 1,4-addition occurred, affording the corresponding adducts **3r** and **3s**; no 1,6-addition products were obtained.

Given that the reaction system in Et_2O appeared to be heterogeneous, we conducted filtration experiments to establish whether the active catalyst was present in solution or in the solid state (Scheme 2). $Cu(OAc)_2$, **L7**, and $B_2(pin)_2$ (**2**) were stirred in Et_2O for 1 h at room temperature, then chalcone (**1a**) and methanol were added. The mixture was stirred for a further 2 h at the same temperature, then filtrated through a 0.2 μm membrane filter. To this filtrate, benzalacetone (**1h**), **2**, and methanol were added and the mixture was stirred for 12 h at room temperature. The crude adducts were then treated with $NaBO_3$ to afford **3a** in 92% yield with 92% ee and **3h** in 70% yield with 86% ee. This experiment strongly suggests that the active species in this asymmetric borylation exists in solution.

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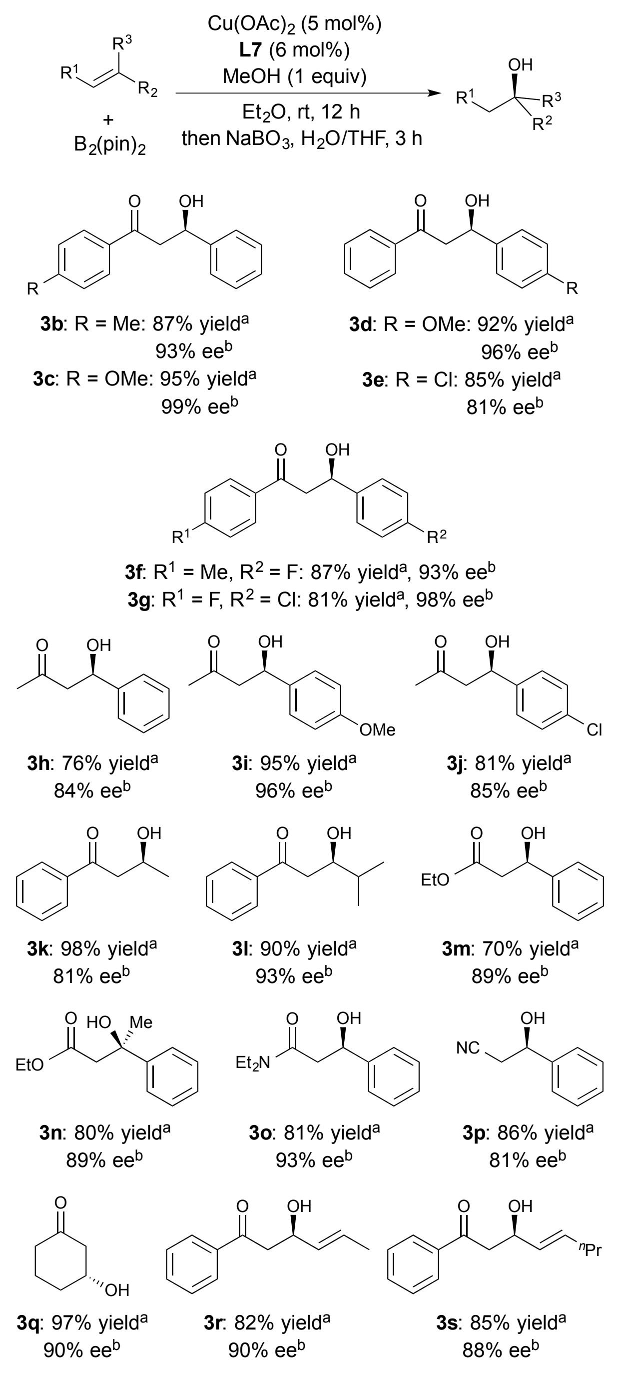
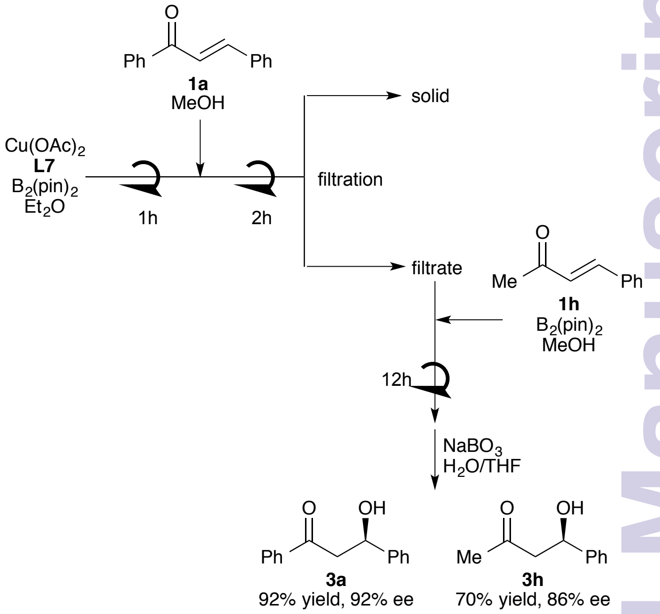
The solubility of $Cu(OAc)_2$ even with **L7** in Et_2O is not high, which indicates that a small amount of the active species works efficiently in this reaction. Indeed, when we conducted the reaction of **1a** with **2** in the presence of 0.005 mol% catalyst, it was found that the turnover frequency (TOF) reached 31,200 h^{-1},[17] which demonstrates the remarkably high catalytic performance of this simple catalyst.

Scheme 1. Scope of the reaction with α,β-unsaturated acceptors.



[a] Isolated yield of oxidized product. [b] Determined by HPLC analysis.

Scheme 2. Filtration experiment.



In conclusion, the exploration of a Cu(II)-based strategy instead of using conventional Cu(I)-based chemistry led to an increase in the range of α,β-unsaturated acceptors that are amenable to catalytic asymmetric β-borylation. The ready availability of Cu(II) species, coupled with the ease of operating the reaction in the absence of a strong base, underscore the value of the Cu(II)-based catalyst over an array of well-documented Cu(I)-based catalysts. Mechanistic differences between reactions catalyzed by Cu(II) and Cu(I) species will be discussed in due course.

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17 TOFs in the reaction of **1a** with **2**: Cu(OAc)$_2$ in water,[1a] 12,800 h^{-1}; Cu(OH)$_2$ in water,[1a] 43,200 h^{-1}; Cu(OH)$_2$ in Et$_2$O, 0.73 h^{-1}.