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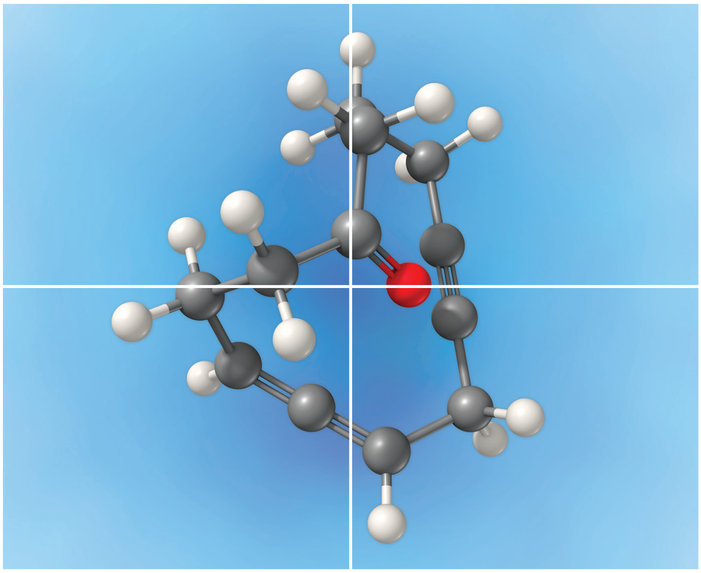

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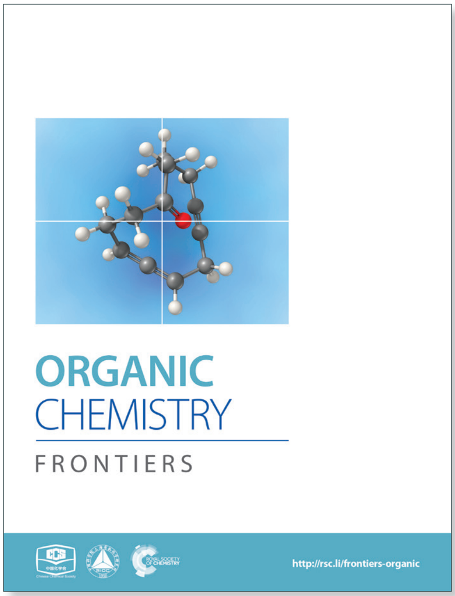

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ARTICLE TYPE

Asymmetric Boron Conjugate Addition to α,β-Unsaturated Carbonyl Compounds Catalyzed by CuOTf/Josiphos under Non-Alkaline Condition

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The asymmetric boron conjugate addition onto α,β-unsaturated ketones and esters has been developed by using the CuOTf/Josiphos complex as the catalyst under non-alkaline condition. It was found that the addition of MeOH into the reaction system is crucial to catalytic reactivity. Good to excellent enantioselectivity (up to 96% *ee*) and yields (up to 98%) have been achieved for 15 examples.

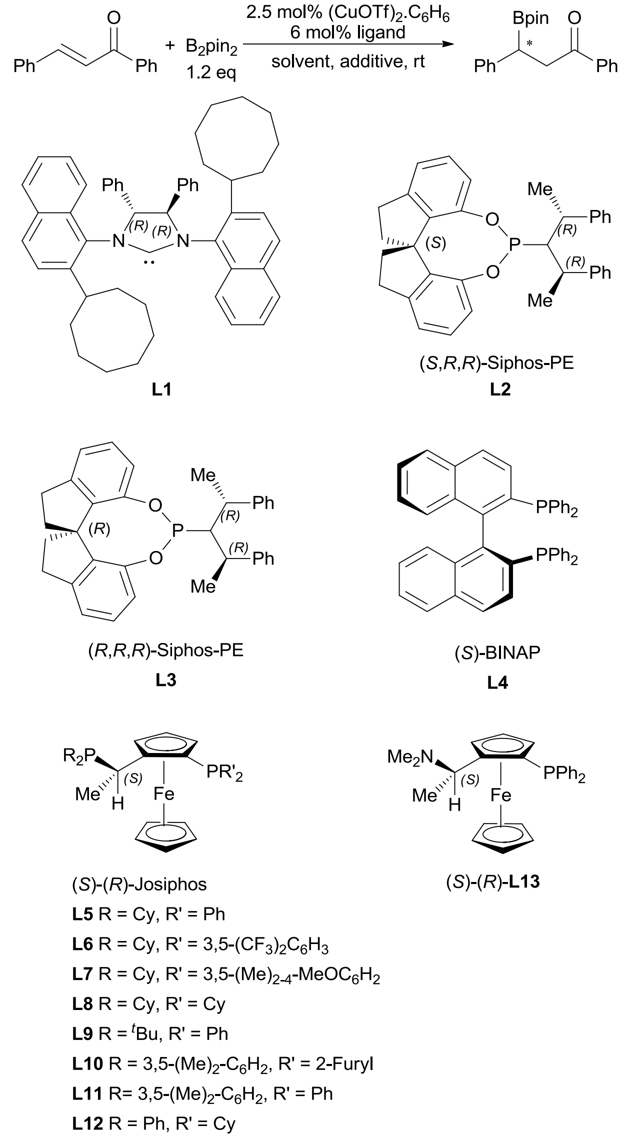
In the past decades, the synthesis of α-chiral boron compounds has attracted many attentions in chemical synthesis since they serves as precursors to many chiral products containing C–O, C–N and C–C bonds;[1] they are also important bioactive building blocks for drug design and synthesis.[2] Among the efforts to get α-chiral boron compounds, the copper catalyzed asymmetric boron conjugate addition to α,β-unsaturated carbonyl compounds has undoubtedly achieved great success.[3] However, to the best of our knowledge, all the existing asymmetric catalytic systems with copper salts require the use of strong inorganic bases, such as NaO^{t}Bu, Cs_2CO_3, etc, as additives, or, copper precursors (*e.g.* $Cu(OH)_2$,[4a] $CuCO_3$,[4b] etc.[4c,d]) should be used with water as the solvent. The strong base additives were believed to play important roles for achieving high catalytic reactivity,[5] and they can also act as catalysts in the boron additions under high temperatures.[6] It would be necessary to develop the catalytic system in the absence of base additives to avoid potential problems like elimination or racemization in complex compounds.[3q,7]

Several examples under non-alkaline catalytic systems for the boron conjugate addition reaction have been reported, which includes the use of platinum catalysts,[8] CuOTf/monophosphine catalysts[9] and organo catalysts (phosphines,[10a] NHC,[10b] etc). Meanwhile, a mixed sp^2-sp^3 hybridized diboron reagent[11] would enable this reaction to be performed under non-alkaline conditions. However, there is no successful enantioselective boron addition example based on these catalytic systems reported so far. Herein, we would like to report a new Cu(I)-catalyzed asymmetric boron conjugate addition reaction under non-alkaline conditions.

We initialed this work with 5 mol% CuOTf and 6 mol% monodentate ligands as it was described that no desired product was formed with the bidentate phosphine ligand under room temperature in Hosomi's work.[9] The commercial available bis(pinacolato)diboron (B_2Pin_2) and chalcone were chosen as the boron reagent and the standard substrate, respectively. We first employed the C2 symmetric chiral NHC ligand (**L1**).[12] However, only poor or moderate enantioselectivity was obtained (Table 1, entry 1-3). When methanol was added as an additive, the enantioselectivity and reactivity were significantly enhanced (Table 1, entry 2).[13] The reactivity can be further increased albeit it caused slightly harm to enantioselectivity while methanol was used as solvent (entry 3). The spiro mono phosphoramidite ligand [(*S*,*R*,*R*)-**L2**] was then applied for this boron addition reaction. The enantioselectivity was close to the result obtained by the NHC ligand **L1** while the reactivity was much higher (entry 4). When its diastereoisomer, (*R*,*R*,*R*)-**L3**, was applied, we observed the inversed configuration in the product which means the chirality on the spiro backbone is more important than the chirality on the amine part of the ligand (entry 5). We also increased the loading of ligand to 12 mol% for comparison and almost the same result was obtained (entry 6) which could indicate that only one molecule of phosphoramidite was cooperated to the Cu(I) catalyst species.

As the enantioselectivity has been proven to be low to moderate by using mono dentate ligand, we next attempted to utilize bidentate diphosphine ligands (**L4** and **L5**) and aminophos ligand (**L12**). Although the bidentate ligands were proven to show no catalytic activity at all in the boron addition reaction (Table 1, entry 10) in Hosomi's work, the reactivity was dramatically changed by adding MeOH as an additive into the reaction system, and the enantioselectivity reached 92% ee by use of Josiphos (**L5**) (entry 8). Nevertheless, another diphosphine ligand, Binap, showed very poor catalytic activity even by addition of MeOH (entry 7). The aminophos ligand (**L12**) achieved a higher reactivity though only 43% ee was obtained (entry 9). Then we continued the condition experiments with Jisophos **L5**. Increasing the loading of methanol could enhance the reactivity further while a slightly decrease of entioselectivity was also observed with 25 equiv of MeOH (entry 12). If methanol was used as the solvent, the enantioselectivity dropped to 33% (entry 13). We screened several other common solvents, but only DMF could give moderate enantioselectivity and good reactivity (entry 14-17). We then compared other protonic additives in toluene. When various alcohols were used (Table 1), the reactivity decreased while the bulk of alcohol increased. But the enantioselectivity can be maintained well with the two alcohol additives (entry 18-20). The acidic additives, such as acetic acid and phenol, would lead to dramatically decreases of reactivity and enantioselectivity (entry 21, 22). Other Josiphos type ligands were also checked for this reaction with results shown in Table 1. However, changing the substituent groups on the P atoms can not lead to higher enantioselectivity (entry 23-29).

Table 1 Asymmetric Catalytic Boron Conjugate Addition to Chalcone under Various Conditions[a]

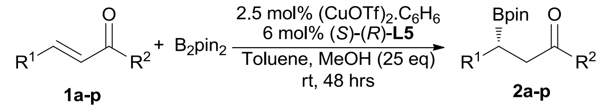


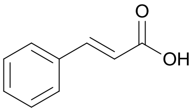
entry	ligand	solvent	additive (equiv)	time (h)	conv. (%)[b]	ee (%)[c]
1[d]	**L1**	Toluene	-	16	7	8(*S*)
2[d]	**L1**	Toluene	MeOH (1)	16	17	47
3[d]	**L1**	MeOH	-	16	46	41
4	**L2**	Toluene	MeOH (1.5)	30	97	42
5	**L3**	Toluene	MeOH (1.5)	46	35	-50(*R*)
6[e]	**L2**	Toluene	MeOH (1.5)	30	95	43
7	**L4**	Toluene	MeOH (1.5)	30	2	ND
8	**L5**	Toluene	MeOH (1.5)	30	74	-92
9	**L13**	Toluene	MeOH (1.5)	30	100	-45
10	**L5**	Toluene	-	30	0	-
11	**L5**	Toluene	MeOH (12)	30	80	-93
12	**L5**	Toluene	MeOH (25)	18	93	-91
13	**L5**	MeOH	-	30	100	-33
14	**L5**	DCM	MeOH (25)	30	0	-
15	**L5**	THF	MeOH (25)	30	62	-6
16	**L5**	CH_3CN	MeOH (25)	30	5	ND
17	**L5**	DMF	MeOH (25)	30	94	-51
18	**L5**	Toluene	EtOH (25)	46	64	-92
19	**L5**	Toluene	^{i}PrOH (25)	46	24	-93
20	**L5**	Toluene	^{t}BuOH (25)	46	< 2	ND
21	**L5**	Toluene	AcOH (25)	46	14	0
22	**L5**	Toluene	PhOH (2.5)	46	23	-4
23	**L6**	Toluene	MeOH (25)	46	44	-70
24	**L7**	Toluene	MeOH (25)	20	95	-13
25	**L8**	Toluene	MeOH (25)	20	90	7
26	**L9**	Toluene	MeOH (25)	46	< 2	ND
27	**L10**	Toluene	MeOH (25)	20	100	-4
28	**L11**	Toluene	MeOH (25)	20	94	-13
29	**L12**	Toluene	MeOH (25)	20	51	-39

[a] Reactions were run under argon protection and mostly repeated twice. Reaction conditions: 0.1 mmol scale, [substrate] = 0.04 M, 2.5 mol% $(CuOTf)_2$. Benzene, 6 mol% ligand, solvent volume = 2.5 mL, room temperature (23–26 °C). [b] Determined by crude ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis. [d] The (NHC)CuOTf catalyst was prepared by anion exchange with (NHC)CuCl and AgOTf. [e] 12 mol% ligand.

The substrate scope was examined by using CuOTf (5 mol%) and Josiphos ligand **L5** (6 mol%) in toluene and MeOH (25.0 eq) as additive for 48 h (Table 2). The reactions were very clean with no side product observed by crude ^{1}H-NMR analysis. For the chalcone substrates, the substituents on the phenyl rings had small influence on the enantioselectivity (entry 2-11). But the substituents on the *ortho* position of the phenyl ring which is adjacent to the newly formed chiral center, led to a significant decrease on the reactivity (entry 2, 11). It should be noted that the NO_2 substituent can tolerate the catalytic condition and give the desired product with 95% yield and 95% *ee* (entry 3). As far as we know, it is the first example to use a substrate with NO_2 group in such a catalytic boron addition reaction. When the phenyl group on the C=C bond in chalcone was replaced by methyl group, the highest *ee* value (96%) was obtained (entry 13). But its isomer, (*E*)-4-phenylbut-3-en-2-one only gave 72% *ee* and lower conversion (entry 12). The α,β-unsaturated esters were also surveyed in this reaction. Good enantioselectivity was obtained for both of the tested ester substrates (entry 14, 15). As we have developed a non alkaline catalytic system, cinnamic acid was also studied as the substrate. Unfortunately, no reaction was observed in this case.

Table 2 Asymmetric Boron Conjugate Addition to α,β-Unsaturated Compounds[a]

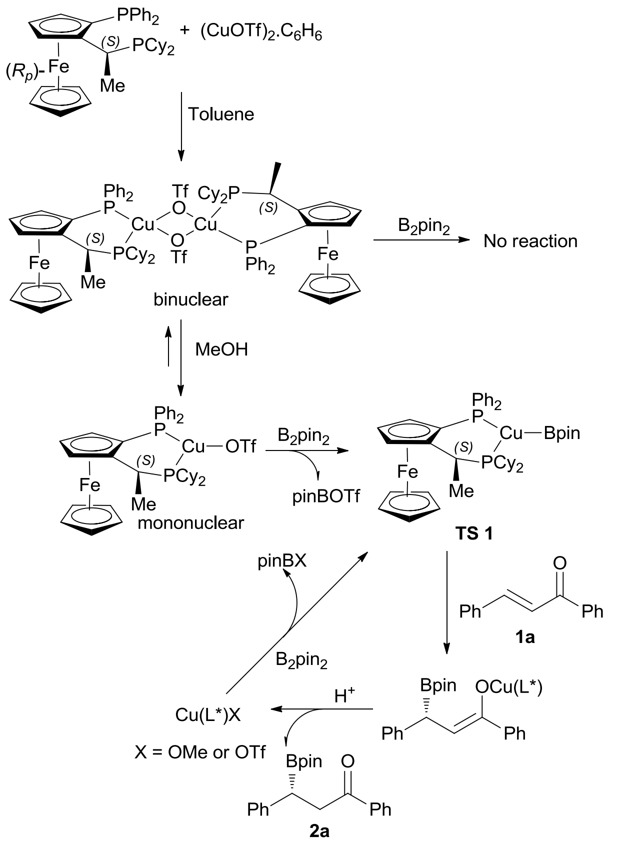


entry	R^1	R^2	prod	yield (%)[b]	ee (%)[c]
1	C_6H_5	C_6H_5	**2a**	90	91(*R*)
2	2-ClC_6H_4	C_6H_5	**2b**	24	93(*R*)
3	3-$NO_2C_6H_4$	C_6H_5	**2c**	95	95(+)
4	4-$MeOC_6H_4$	C_6H_5	**2d**	89	93(*R*)
5	4-FC_6H_4	C_6H_5	**2e**	96	95(-)
6	4-ClC_6H_4	C_6H_5	**2f**	98	95(*R*)
7	C_6H_5	4-$MeOC_6H_4$	**2g**	98	90(*R*)
8	C_6H_5	4-FC_6H_4	**2h**	96	95(*R*)
9	C_6H_5	4-ClC_6H_4	**2i**	86	92(-)
10	4-FC_6H_4	4-FC_6H_4	**2j**	95	94(-)
11	2,4-$(MeO)_2C_6H_3$	4-FC_6H_4	**2k**	50	82(-)
12	C_6H_5	Me	**2l**	76	72(*R*)
13	Me	C_6H_5	**2m**	95	96(*S*)
14	C_6H_5	OBn	**2n**	62	84(*R*)
15	Me	OBn	**2o**	96	88(*S*)
16	 O OH		**2p**	NR	-

[a] Reaction conditions are the same as those listed in Table 1, entry 12. [b]Yields of isolated producst. [c] % *ee* was determined by chiral HPLC analysis, absolute configuration determined by comparison of optical rotation with literature data.

The catalytic mechanism and the role of MeOH in this reaction is proposed as Scheme 1, based on the previous catalytic boron conjugate addition work involving copper[14] and the coordination chemistry between Cu(I)X and Josiphos in various solvents reported by Feringa and his co-workers.[15] The Cu(I)X and Josiphos forms different complexes in different solvents, which could be the mononuclear or the binuclear complex. Furthermore, the rapid equilibration to form either a mononuclear or a binuclear complex depending on the solvent employed was also observed by Feringa's group and indeed the mononuclear complex would form in methanol. We assume that CuOTf and Josiphos firstly formed the binuclear complex in toluene, in which the copper has already four coordination numbers and cannot react with B_2Pin_2 as the copper was saturated with 18e. By adding MeOH, the mononuclear copper complex is formed and reacted with B_2Pin_2 to produce (L*)Cu–BPin species (**TS 1**). The (L*)Cu–BPin species has been known as efficient catalyst in the boron addition reaction, which reacts with chalcone followed by protonation to release the chiral product and (L*)CuX species. The species of (L*)CuX then reacts with B_2Pin_2 to produce (L*)Cu–BPin species (**TS 1**) again and finally to complete the catalytic cycle.

In conclusion, we have developed a novel non-alkaline catalytic system for asymmetric boron conjugate addition reaction with α,β-unsaturated ketones and esters, which involved the Cu(I) triflate and Josiphos ligand as catalyst and chiral ligand, respectively. Methanol was proven to be as a crucial additive for high reactivity while there would be no reaction in absence of additive in toluene. Further study on the mechanism and applications of the non-alkaline catalytic system to other base sensitive chiral products is ongoing in our laboratory.



Scheme 1 Proposed Mechanism for the Non-Alkaline Catalytic System

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Notes and references

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† Electronic Supplementary Information (ESI) available: [^{1}H-, ^{13}C-NMR data and spectra, HRMS for new compounds; 1H NMR data, HPLC spectra and optical rotation for all products; experimental procedures and details]. See DOI: 10.1039/b000000x/

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