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Asymmetric Catalytic Enantio- and Diastereoselective Boron Conjugate Addition Reactions of α-Functionalized α,β-Unsaturated Carbonyl Substrates

Jian-Bo Xie,*[,†,‡] Siqi Lin,[†] Shuo Qiao,[†] and Guigen Li[†,§]

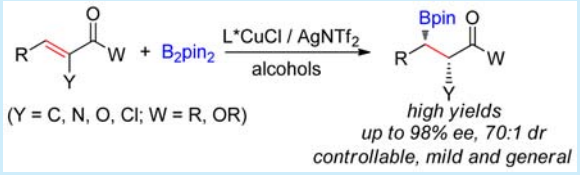
[†]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States

[‡]New York University Abu Dhabi, P.O. Box 129188, Abu Dhabi, United Arab Emirates

[§]Institute of Chemistry & BioMedical Sciences (ICBMS), Nanjing University, Nanjing 210093, People's Republic of China

Supporting Information

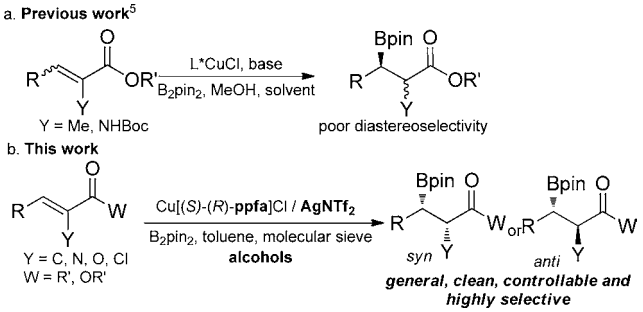
ABSTRACT: An efficient catalytic system has been established for the asymmetric boron conjugate addition of B_2pin_2 onto α-functionalized (involving C, N, O, and Cl) α,β-unsaturated carbonyls under mild, neutral conditions involving Cu[(*S*)-(*R*)-ppfa]Cl, $AgNTf_2$, and alcohols. The dual additives of $AgNTf_2$ and alcohols were found to play crucial roles for achieving high catalytic activity and enantio- and diastereoselectivity (up to 98% ee and 70:1 dr).



In the past several decades, enantio- and diastereoselective catalysis has been one of the most challenging topics in chemical synthesis,[1] particularly for those examples involving the control of multiple stereogenic centers in a concise manner.[2] Recently, asymmetric catalytic boron conjugate additions to α,β-unsaturated carbonyl compounds has attracted much attention[3] due to the importance of its resulting chiral β-substituted boron products that are versatile building blocks for chemical synthesis and drug development.[4] For example, the resulting carbon−boron bonds can be readily transformed into C−O, C−N, and C−C bonds through many reactions, such as 1,2-migration[4i,j] and Suzuki−Miyaura cross-coupling.[4c,h] Even though progress has been made on asymmetric catalytic boron conjugate additions, its use on α-substituted α,β-unsaturated substrates still faces a serious challenge as shown by the following: (1) the reactivity of trisubstituted alkene substrates has been substantially diminished with known catalytic systems (see Scheme S1); (2) nonstereospecific protonation complicates its diastereoselective control; and (3) it lacks mild, neutral conditions to avoid or minimize epimerization and the formation of side products. Therefore, successful examples on such reactions were quite rare (Scheme 1).[5]

So far, the work on asymmetric catalytic β-boration of α,β-unsaturated substrates has been mainly focused on the use of copper catalysts under alkaline conditions.[3] However, these conditions would not favor the diastereoselective boron conjugate additions onto α-substituted α,β-unsaturated compounds. For example, the previous work by Lillo[5a] or by He[5b] could only achieve low dr values or no diastereoselectivity, which were very likely affected by the racemization on the α-positions of the carbonyl products under alkaline conditions. Thus, to achieve both high enantio- and diastereoselectivity, mild and neutral conditions should be used. In this paper, we report an efficient, general, and mild catalytic system for

Scheme 1. Copper-Catalyzed Boron Conjugate Additions to α-Substituted α,β-Unsaturated Substrates



asymmetric boron conjugate additions to α-substituted α,β-unsaturated substrates that contain various functional moieties (C, N, O, and halogen) on their α-positions. It is worth noting that these α-functionalized α,β-unsaturated starting materials can be readily obtained via well-known and classical methods, such as condensation reactions, Wittig−Horner reaction, and halogenation.

Recently, we have found that the complex of CuOTf and Josiphos catalyzed the boron conjugate addition to chalcone with high yield and enantioselectivity by using MeOH as an additive in the absence of any base.[6] Unfortunately, no reaction was observed when the α-substituted enone **1a** was used under the same catalytic conditions, which was probably due to the increased steric hindrance. Careful screening of the chiral ligands (Scheme S1) showed that only the aminophosphine ligands (*S*)-(*R*)-ppfa (**L1**) afforded the desired product with high yields and diastereoselectivity but low enantioselectivity

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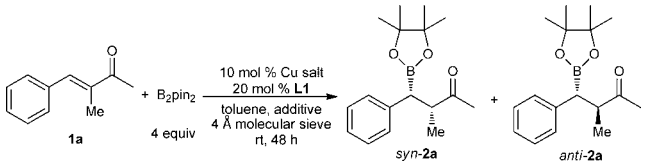
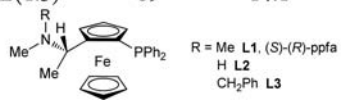
(98% conv, 24:1 dr, 47% ee, with 5 equiv MeOH, 10 mol % of CuOTf, and 12 mol % of **L1**), and the *syn* isomer was the main product (Table 1, entry 2). This might be because, compared to

Table 1. Optimization of Reaction Conditions[a]



entry	additive (equiv)	conv (%)[b]	dr (syn/anti)[b]	ee (%, syn/anti)[c]
1[d,e]	MeOH(1)	42	25:1	0 / -
2[d,e]	MeOH(5)	98	24:1	47 / -
3[d]	MeOH(5)	97	30:1	54 / -
4[d]	MeOH(12)	35	13:1	40 / -
5	MeOH(1)	42	11:1	62 / -
6	MeOH(5)	58	32:1	80 / -
7	MeOH(10)	64	20:1	82 / -
8	MeOH(15)	45	20:1	75 / -
9	EtOH(10)	95	20:1	87 / -
10	^{n}PrOH(10)	80	14:1	84 / -
11	^{i}PrOH(10)	86	17:1	88 / -
12	BnOH(10)	56	30:1	80 / -
13	^{t}BuOH(10)	29	12:1	88 / -
14	TFE(10)	99	11:1	93 / -
15	HFIP(10)	99	1:1.2	92 / 85
16	PhOH(10)	33	8:1	ND
17	C_6F_5OH(10)	14	1.3:1	ND
18[f]	EtOH(10)	15	50:1	85 / -
19[g]	TFE(10)	100	6:1	80 / -
20[h]	TFE(5)	99	24:1	92 / -
21[i]	TFE(1.5)	89	14:1	90 / -



[a]General reaction conditions: **1a** (0.192 mmol), B_2pin_2 (4 equiv), CuCl (10 mol %), chiral ligand (20 mol %), $AgNTf_2$ (10 mol %), 4 Å molecular sieves (~70 mg), toluene (2.5 mL), additives were added with indicated amount. [b]Determined by ^{1}H NMR analysis of crude product. [c]Determined by HPLC. [d]CuOTf (10 mol %) was used; no $AgNTf_2$. [e]12 mol % of **L1** was used. [f]**L2** was used. [g]**L3** was used. [h]5 mol % of catalyst was used. [i]1 mol % of catalyst was used with 2 equiv of B_2pin_2.

phosphine that could form π-backbonding or oxazoline ligand, the use of the amino ligand could increase the electron density of Cu and thus the nucleophilicity of boron that is bonded to Cu. We then investigated other means to increase the enantioselectivity. While increased loading of **L1** could slightly enhance the enantioselectivity (54% ee, with 20 mol % **L1**, entry 3), the use of more MeOH (12 equiv) significantly harmed the reactivity (35% conv, entry 4). Surprisingly, only the racemic product was obtained when 1 equiv of MeOH was added (entry 1). We assume that the use of more MeOH might help the coordination of the chiral ligand to the active copper species.

In our previous work,[6] we proposed that the catalyst dimerization[7] might contribute to the low reactivity. Thus, the use of a weaker Lewis base ($-NTf_2$ compared to $-OTf$) as counterion (which should decrease dimerization) instead of $-OTf$ might enhance the reactivity and thus enantioselectivity. Moreover, according to the HSAB theory, the "harder acid" $CuNTf_2$ might favor the coordination of the "hard base" amino ligand. On the basis of the above consideration, the anion-exchange reagent, $AgNTf_2$, was added in situ to the CuCl complex with **L1** without further separation (AgCl precipitated as dark solid). Fortunately, we found that the resulting catalyst showed much higher enantioselectivity (80% ee) over the CuOTf/ligand. Further study on the amount of MeOH indicated that 10 equiv of MeOH was the optimal amount for good enantioselectivity (82% ee, entries 5–8). Encouraged by the influence of MeOH on the reactivity and selectivity, we screened other alcohol additives, including phenols with CuCl/ligand and $AgNTf_2$ (entries 9–17). While both the pK_a and steric bulk of the additives might contribute to the reactivity and selectivity, the results seemed to lack distinct patterns or trends. To simplify the analysis, we compared the results of TFE (CF_3CH_2OH, 99% conv, 11:1 dr, 93% ee) to the results of EtOH (95% conv, 20:1 dr, 87% ee), as their sizes are similar. We then concluded that the lower pK_a of the additive had a positive effect on the enantioselectivity and reactivity but a negative effect on the diastereoselectivity (entries 9 and 14). When the pK_a of the additive was further decreased [HFIP, $(CF_3)_2CHOH$], a dramatic change in the diastereoselectivity occurred as the *anti* isomer became the dominant product (1:1.2 dr, entry 15). Finally, we compared the substitution groups on the N atom of the ligand and found that **L1** was superior to **L2** and **L3** for improving the enantioselectivity (entries 18 and 19). With the optimized conditions in hand (TFE as additive, **L1** as ligand), we found that the catalyst was quite effective (entries 20 and 21) and the results could be suitably maintained (89%, 90% ee, 14:1 dr) with 1 mol % of catalyst. Notably, the reaction was very clean, and no side products were observed for any of the studied cases.

The scope of α-alkyl-substituted starting materials was then screened with 5 mol % (conditions A) or 10 mol % (conditions B) catalyst under the optimized conditions (Scheme 2). Good to excellent enantioselectivities (79–98% ee) were achieved for all cases, while the *syn* diastereomer was obtained as the major product for each case. The highest diastereoselectivity was obtained with *o*-Cl substrate **1c** (70:1 dr, likely due to the *ortho* effect or contribution of Cl–B to the conformation). For some substrates with increased steric hindrance (**1n–p**), increased loading of catalyst, ligand, and additive (condition B) was used to achieve high yields with excellent enantioselectivities. For the substrate with a larger alkyl group on the α-position (**1n**), the *syn* product (**2n**) was generated with a relatively lower dr ratio of 3.2:1 and 94% ee (*syn*) and 93% ee (*anti*), respectively. When the β-position was substituted with a methyl group rather than an aryl group, a moderate dr value was also obtained (**2q**, 3.1:1 dr). The cyclic product **2r** can also be formed in quantitative yield and good diastereoselectivity (12:1) with 79% ee for the major *syn* product. The absolute configuration of the product was determined by single-crystal X-ray diffraction analysis of *anti*-**2k**, which was obtained in the presence of HFIP with 1:1.5 dr (*syn*/*anti*, Scheme 3).

Given the mild, neutral conditions, a wide scope of α-functionalized α,β-unsaturated carbonyls were examined (Scheme 4). For the α-amino-substituted unsaturated ester **3**, the high pK_a and bulky additive, ^{t}BuOH, gave the highest dr values for *syn* products. When the *tert*-butyl ester (**3d**) was applied, the dr could be increased to 16:1, with 97% ee. α-

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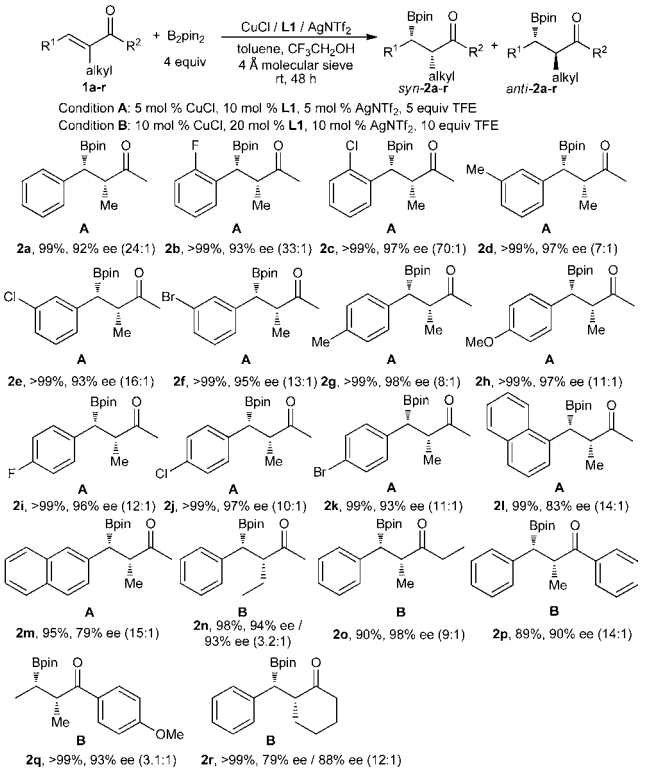
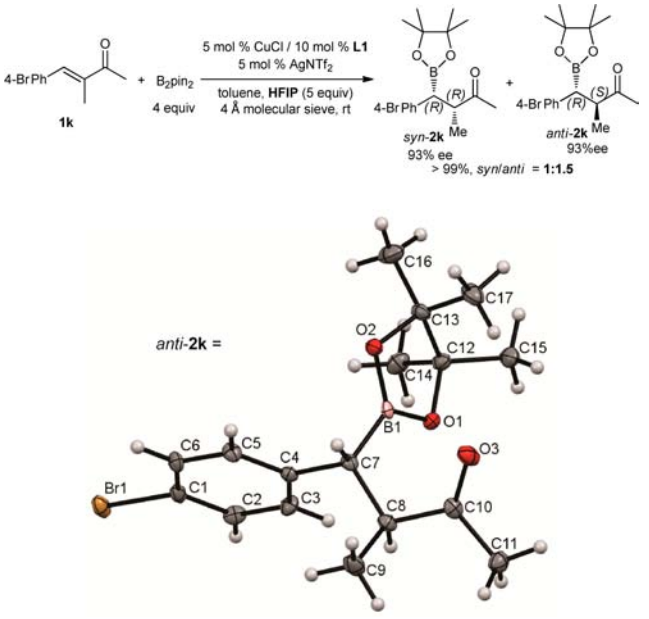
Scheme 2. α-Alkyl Substrates

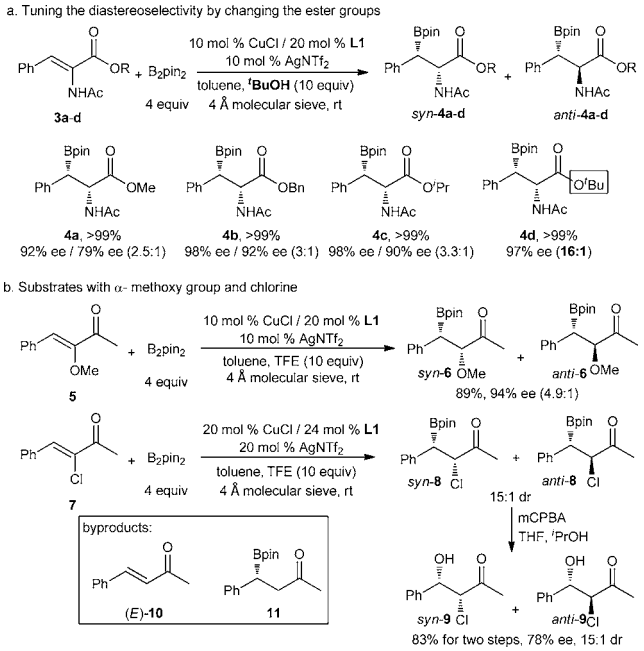


Scheme 3. Absolute Configuration of *anti*-2k by X-ray Study



Methoxy and α-chloro substrates (**5** and **7**) were also investigated. A good chemical yield (89%) was obtained for *syn*-**6** product with 94% ee and 4.9:1 dr. For the halogenated substrate **7**, a higher loading of CuCl (20 mol %) with 24 mol % of chiral ligand was required because the elimination byproduct ClBpin released the harmful chloride anion into the reaction and poisoned the Cu catalyst (the resulting CuCl was catalytically inert). A small amount of byproducts (*E*)-**10** and **11** (~12%) was observed, while the desired product **8** was obtained with high diastereoselectivity (15:1 dr). Further

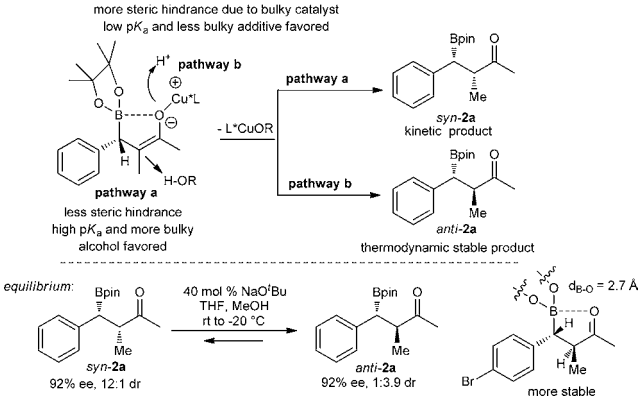
Scheme 4. α-Functionalized Substrates



oxidation with *m*-CPBA gave the hydroxylated product **9** in 83% yield with 15:1 dr and 78% ee.

A plausible mechanism for the diastereoselectivity is proposed in Scheme 5. First, we assume that there is an *O*-

Scheme 5. Plausible Mechanism for the Diastereoselective Control



donation to the B atom in the enolate transition state, which is then protonated with the alcohol additives. There are two main possible pathways, and one is via protonation from the *C*-terminal of the enolate (pathway a). In this case, the *syn* product was favored because of the relatively lower steric hindrance on the H side. Thus, the more bulky alcohol additives could give higher dr for the *syn* products. The other is via protonation from the *O*-terminal of the enolate with H^+ (pathway b). In this case, the thermodynamic product would be favored as the proton has little steric effect on the kinetic selectivity. Thus, the low pK_a additives tend to induce the more thermodynamically stable product (in our case, the *anti* product; see the equilibrium experiment in Scheme 5). Moreover, the steric effect of the bulky ligand might influence the diastereoselectivity as well. The protonation usually tends to occur through pathway a because of the steric hindrance at

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the *O*-terminal, making it easier to control the *syn* selectivity (up to 70:1, **2c**) over the *anti* selectivity (only up to 1:1.7, **4b**) with the alcohol additives. This is further supported by the equilibrium experiment that showed that a higher dr for *anti* product (1:3.9 dr for **2a**) could be achieved. The thermodynamic stability could be explained by the crystal structure of *anti*-**2k**, in which the B atom and the O atom of the carbonyl group have a relatively short distance (2.7 Å). The aryl group and the methyl group are aligned on the *trans* positions, which is thermodynamically favorable. This equilibrium reaction provides a facile method for the preparation of *anti* products. When the steric hindrance on the α-position was increased (for example, comparing **1n** to **1a**) or the steric hindrance on the *O*-terminal side of the enolate was decreased (for example, comparing **3a** to **3d**), pathway b would be more favored; this significantly decreased the diastereoselectivity for *syn* products. The influence of the additives on the diastereoselectivities for **1n** and **3b** was investigated, and the results were in agreement with the mechanism (Table S1).

By simple oxidation with $NaBO_3$, the borated product *syn*-**2a** (92% ee, 50:1 dr) could be transformed to the chiral alcohol *syn*-**12** with slightly higher ee (94% ee) and lower dr (14:1 dr). This was followed by stereospecific reduction, and the enantioenriched diol epimers (**13** and **14**) with three stereogenic centers could be efficiently and stereodivergently obtained (see Scheme S2). For example, Bu_4NBH_4 in acetic acid[8a] gave *anti* diol **13** in about 80% yield (16:1 dr), while DIBAL[8b] gave *syn* diol **14** in 95% yield (19:1 dr).

In summary, we have developed a strategy of obtaining enantioenriched products bearing two adjacent stereogenic centers with various functional groups by an enantio- and diastereoselective boron conjugate addition to α-substituted α,β-unsaturated compounds using a copper catalyst. In fact, the diastereoisomers of the products could be stereodivergently synthesized by changing the additives or simple transformation with base. The influence of steric bulk and pK_a of the additives on the diastereoselectivity was investigated. The boron conjugate addition product was used for the synthesis of epimers of 1,3-diol, which contain three stereogenic centers. We expect the enantio- and diastereoselective control of the conjugate addition product of α-substituted α,β-unsaturated compounds could be applied to broader substrate scope and more reactions, as the enantioenriched products with various functional groups could be synthesized concisely.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01998.

Experimental details and data (PDF)

X-ray crystallographic data for *anti*-**2k** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nkjbxie@gmail.com.

Notes

The authors declare no competing financial interest.

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