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Application of bis(oxazoline) in asymmetric β-amination of chalcones†

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An effective enantioselective β-amination of chalcones with *N*-bromosuccinimide into β-imidoketones using a bis(oxazoline) ligand is described. A wide variety of β-imidoketone derivatives containing various functional groups can be obtained with high enantioselectivities. The products are highly valuable molecules regarding their vast applications as building blocks of drugs and biologically active compounds.

Over the past decade, tremendous progress has been achieved by employing different nitrogen nucleophiles and new acceptors as well as more efficient catalyst systems for carbon–nitrogen bond formation.[1] Especially in the past several years, the development of efficient and conventional approaches[2] (for example, the iminium-activated nucleophilic additions to α,β-unsaturated aldehydes[3] and the Mannich-type reaction of bis(dialkylamino)-boron enolates with aldehydes[4]), leading to chiral β-imidoketones and their derivatives has attracted much attention in organic synthesis, as the β-imidoketones obtained are highly valuable molecules regarding their vast applications as building blocks of drugs and biologically active compounds.[5] Very recently, Han and co-workers developed an acid-functionalized ionic liquid as catalyst for hetero-Michael addition of nitrogen nucleophiles to α,β-unsaturated ketones.[6] Brenna *et al.* reported that Ni(II) and Pd(II) pyridinyloxazolidine-compound catalyzed aza-Michael addition of aliphatic amines to α,β-unsaturated ketones[7] is an efficient approach toward the synthesis of β-imidoketones.

Although a variety of methods have been reported, further development of asymmetric β-amination reactions still remains a hot topic. Therefore, the necessity to explore appropriate conditions to improve the ee is sometimes required. Among various subareas of the rapidly growing field of organocatalysis, the use of bis(oxazoline)-containing ligands including C_2-symmetric bis(oxazoline) or aza-bis(oxazoline) turned out to be a powerful approach for the asymmetric synthesis of a great variety of highly enantioenriched organic compounds.[8]

With all of these precedents in mind, we were interested in exploring the enantioselectivity for the asymmetric β-amination reaction[9] when NBS reacted as a nucleophilic nitrogen source with chalcones. Herein, we report the details of our studies and disclose improved enantiomeric ratios using an optimized bis(oxazoline) ligand.

Our initial studies were carried out with chalcone (**1a**) as the substrate and *N*-bromosuccinimide (NBS) as the nucleophilic nitrogen source under basic conditions. A variety of commonly used chiral ligands were examined (Fig. 1). Only modest ee values were generally obtained except for bis(oxazoline) (L3); good yield and ee value could be obtained with bis(oxazoline) (L3) (Table 1, entry 4). Decreasing L3 to 5 mol% led to a lower yield with obvious loss of ee (Table 1, entry 5).

As shown in Table 2, no reaction occurred in MeCN at room temperature upon utilizing NaOH, K_2CO_3, Et_3N, DABCO, and DMAP as bases (Table 2, entries 1–5). The reaction with pyridine (1.2 equiv.) as the base in MeCN gave 1-(3-oxo-1, 3-diphenyl-propyl)-pyrrolidine-2, 5-dione (**2a**) in 39% yield (Table 2, entry 7).

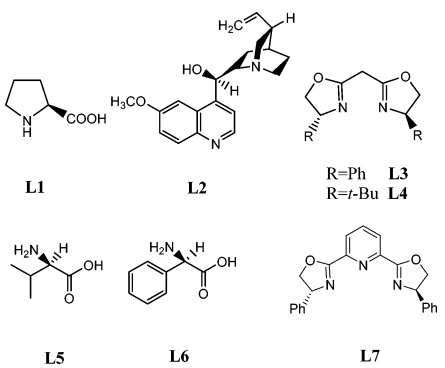

Fig. 1 Selected examples of chiral ligands examined.

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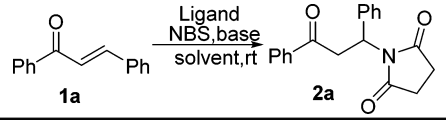
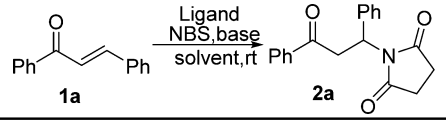
Table 1 Screening of ligands[a]



Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	—	69	Racemic
2	L1	64	19
3	L2	61	18
4	L3	76	90
5[d]	L3	73	64
6	L4	74	65
7	L5	58	9
8	L6	60	13
9	L7	68	10

[a] Reactions were carried out with **1a** (1.0 mmol), NBS (1.2 mmol), ligand (0.1 mmol) and DBU (1.2 mmol) in MeCN (2.0 mL) for 15 h. [b] Determined by HPLC analysis. [c] The ee was checked by chiral HPLC using an Ultron ES-OVM column. [d] With L3 (0.05 mmol).

Table 2 Effect of different bases on β-amination of chalcones[a]



Entry	Base	Yield[b] (%)	ee[c] (%)
1	NaOH	n.r.	—
2	K_2CO_3	n.r.	—
3	Et_3N	n.r.	—
4	DABCO	n.r.	—
5	DMAP	n.r.	—
6	DBU	76	90
7	Pyridine	39	71

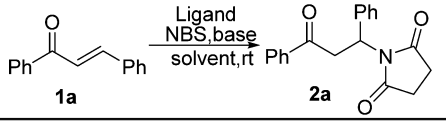
[a] Reactions were carried out with **1a** (1.0 mmol), NBS (1.2 mmol), L3 (0.1 mmol) and base (1.2 mmol) in 2.0 mL MeCN for 15 h. [b] Determined by HPLC analysis. [c] The ee was checked by chiral HPLC using an Ultron ES-OVM column.

To our delight, DBU was found to be the most suitable base in terms of yield and enantioselectivity (Table 2, entry 6).

The reaction was further optimized with respect to solvents (Table 3). When CH_2Cl_2, THF, EtOH, MeOH and DMF were selected as the solvents, the yields decreased (Table 3, entries 1–5). Additionally, no desired product was obtained with H_2O as the solvent in the presence of TBAB (Table 3, entry 6). Among all the solvents tested, MeCN was the most efficient. 1-(3-Oxo-1, 3-diphenylpropyl)-pyrrolidine-2,5-dione (**2a**) was obtained in 76% yield with 90% ee using 10 mol% L3 in MeCN at room temperature (Table 3, entry 7). Other nucleophilic nitrogen sources were also examined (Table 3, entries 8 and 9). Moderate yield and ee were obtained with *N*-iodosuccinimide (NIS). However, no reaction was observed with *N*-chlorosuccinimide (NCS).

The scope of this reaction was then evaluated with respect to substituted chalcones under the optimized conditions to form the corresponding β-imidoketones in 52–85% yield with 40–94% ee using 10 mol% L3 (Table 4, entries 1–15). The introduction of strong electron-donating groups (such as methoxy and methyl) at the *para*-position on the phenyl ring R_1, led to a drop in yields

Table 3 Optimization of reaction conditions[a]

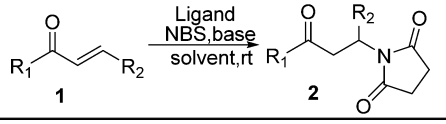


Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	57	51
2	THF	62	63
3	EtOH	33	73
4	MeOH	29	57
5	DMF	61	29
6[d]	H_2O	n.r.	—
7	MeCN	76	90
8[e]	MeCN	54	84
9[f]	MeCN	n.r.	—

[a] Reactions were carried out with **1a** (1.0 mmol), NBS (1.2 mmol), L3 (0.1 mmol) and DBU (1.2 mmol) in solvent (2.0 mL) for 15 h. [b] Determined by HPLC analysis. [c] The ee was checked by chiral HPLC using an Ultron ES-OVM column. [d] TBAB (0.05 mmol) was added. [e] With NIS (1.2 equiv.). [f] With NCS (1.2 equiv.).

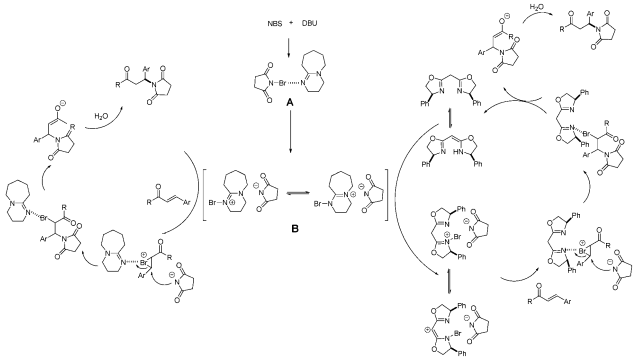
and enantioselectivities (Table 4, entries 1, 12 and 13). When electron-withdrawing groups (such as *para*-bromo or trifluoromethyl groups) were introduced on the phenyl ring R_1, lower enantioselectivities but higher yields were obtained (Table 4, entries 1, 14 and 15). However, the electron-donating groups (such as *para*-methyl or *para*-dimethylamino) on the phenyl ring R_2 seemed to be less favorable in this protocol providing the corresponding products with moderate enantioselectivities (Table 4, entries 1, 5 and 6). Furthermore, with strong electron-withdrawing substituents (such as *para*-fluoro or *para*-nitro groups) on the phenyl ring R_2, the reactions did not occur (Table 4, entries 2 and 4). It was notable that *para*-chloro substituents gave better ee in this reaction (Table 4, entry 3). Upon replacing the phenyl ring R_2, with 1-naphthyl or other

Table 4 Scope of substrates[a]



Entry	R_1	R_2	Product	Yield[b] (%)	ee[c] (%)
1	Ph	Ph	**2a**	76	90
2	Ph	4-FC_6H_4	—	n.r.	—
3	Ph	4-ClC_6H_4	**2b**	83	94
4	Ph	4-$NO_2C_6H_4$	—	n.r.	—
5	Ph	4-MeC_6H_4	**2c**	73	80
6	Ph	4-$NMe_2C_6H_4$	**2d**	62	40
7	Ph	1-Naphthyl	—	n.r.	—
8	Ph	2-ClC_6H_4	—	n.r.	—
9	Ph	2-BrC_6H_4	—	n.r.	—
10	Ph	Me	—	n.r.	—
11	Ph	4-Pyridinyl	**2e**	67	64
12	4-$MeOC_6H_4$	Ph	**2f**	52	80
13	4-MeC_6H_4	Ph	**2g**	71	76
14	4-$CF_3C_6H_4$	Ph	**2h**	79	66
15	4-BrC_6H_4	Ph	**2i**	85	92

[a] Reactions were carried out with **1** (1.0 mmol), NBS (1.2 mmol), L3 (0.1 mmol) and DBU (1.2 mmol) in MeCN (2.0 mL) for 15 h. [b] Determined by HPLC analysis. [c] The ee was checked by chiral HPLC using an Ultron ES-OVM column.



Scheme 1 Plausible mechanism for the formation of β-aminoketones.

ortho-substituted phenyl on the phenyl ring R_2, no desired products were obtained (Table 4, entries 7–9). This may be attributed to the effect of steric hindrance. Besides, this protocol could also be applied to heterocyclic chalcones as exemplified by (*E*)-1-phenyl-3-(pyridin-4-yl)prop-2-en-1-one in 67% yield and 64% ee (Table 4, entry 11). We further expanded the scope of this reaction to aliphatic chalcones. Unfortunately, we found that no desired product was obtained when a methyl substituent was introduced (R_2 = Me) due to side reactions (Table 4, entry 10).

The reaction begins with the formation of intermediate A from NBS and DBU *via* halogen bond interaction. Then A transforms into a more electrophilic species B. Although the precise reaction mechanism is not clear, we proposed a possible plausible mechanism based on our work and on pertinent literature[9] (Scheme 1).

In summary, we have developed an efficient enantioselective β-amination reaction of chalcones into β-imidoketones using NBS as nucleophilic nitrogen source and bis(oxazoline) as ligand. A wide variety of β-imidoketone derivatives with various functional groups were obtained in generally good yields with high enantioselectivities. Further transformations of these compounds provide access to useful intermediates with diverse functionality, such as building blocks of drugs and biologically active compounds.

Experimental section

General remarks

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. NMR spectra were recorded at 500 MHz using $CDCl_3$ as the solvent. Elemental analysis was performed on a Vario EL III recorder. Mass spectra were obtained using an automated Fininigan TSQ Advantage mass spectrometer. Most of the products were known compounds and were identified by comparison of their physical and spectral data with those of authentic samples. The enantiomeric excess of the β-imidoketones was determined by HPLC on an Ultron ES-OVM column.

Synthesis of chalcones (1a as an example)

A mixture of acetophenone (10 mmol) and benzaldehyde (1.1 equiv.) in anhydrous EtOH (15 mL) was stirred at room temperature for 5 min. Then, NaOH (3 equiv.) was added. The reaction mixture was stirred at room temperature overnight until aldehyde consumption. After that, HCl (10%) was added until neutrality. Then dichloromethane was added to dilute the reaction mixture. The organic layer was dried over anhydrous Na_2SO_4 and concentrated on Rotavapor under reduced pressure. Finally, the residue was purified by silica gel column chromatography to give **1a**.

A typical procedure for the β-amination of chalcones

A general procedure for the preparation of **2** (**2a** as an example): a mixture of chalcone **1a** (208 mg, 1.0 mmol), L3 (30.6 mg, 0.1 mmol), and DBU (0.18 mL, 1.2 mmol) in MeCN (2.0 mL) was stirred at room temperature. NBS (213 mg, 1.2 mmol) was then added to the mixture. After starting material **1a** was consumed as indicated by TLC, the reaction mixture was poured into water and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography.

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