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Chiral Co(II) complex catalyzed asymmetric Michael reactions of β-ketoamides to nitroolefins and alkynones

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ABSTRACT

The catalytic enantioselective Michael additions of cyclic β-ketoamides to nitroolefins and alkynones were accomplished in the presence of chiral *N,N′*-dioxide–Co(II) complexes. The desired adducts were obtained in high yields (up to 98%) with excellent enantioselectivities (up to 97% ee).

Introduction

In the past decade, the Michael reaction of carbon nucleophiles to α,β-unsaturated compounds has been found to be attractive for the construction of new carbon—carbon bonds.[1,2] A wide variety of β-diketones, β-ketoesters, as well as α-substituted-1,3-dicarbonyls[3] have been extensively and successfully used as the nucleophiles in such reactions. In contrast to the Michael reaction of β-diketones and β-ketoesters, the conjugate addition using β-ketoamides as the nucleophile is interesting.[4] Using α,β-unsaturated aldehydes or ketones as the electrophiles, a Michael-initiated cyclization can occur. For example, Rodriguez and co-workers utilized the electrophilic and nucleophilic property of simple β-ketoamides to realize a multicomponent domino reaction, furnishing highly functionalized 2,6-diazabicylco[2,2,2]octane skeleton.[4a,l] Cooperative participation of the amido group of β-ketoamides can be employed to construct azaspirocyclic derivatives,[4c,m] and spiroaminals.[4g] The modified β-ketoamides containing an acidic methane group and pendant nucleophilic substituent with α,β-unsaturated carbonyl compounds can perform diverse stereodivergent catalytic one-pot addition/cyclization/annulation sequence to synthesize quinolizidine derivatives,[4d,e] oxzaine and oxazolidine derivatives,[4f] as well as other tetracyclic alkaloid derivatives.[4b] In addition, the direct asymmetric addition of α-substituted β-ketoamides with other Michael acceptors provides an easy synthetic route to quaternary stereocenters. Chiral organocatalysts are generally utilized to promote these enantioselective processes. For instance, chiral proline derivatives were used for the β-ketoamide addition to α,β-unsaturated aldehydes,[4d,e] and chiral multifunctional thiourea catalysts were efficient for the cascade reaction between β-ketoamide and α,β-unsaturated ketones[4f,g,l], or formal [3+3] cyclization between amide and α,β-unsaturated acyl cyanides.[4m] Chiral squaramide bearing cinchonine unit promoted the addition between cyclobutanone derivatives with an amide moiety and nitroalkenes in high diastereo- and enantioselectivities.[4i] However, extending the Michael donors and developing the efficient catalyst system for the Michael reactions of β-ketoamides are still desirable.

In recent years, the application of the less expensive and more abundant early transition metals gains momentum for the introduction of asymmetric centers in molecules. Nevertheless, the total number of chiral cobalt complex mediated asymmetric processes still remains small compared to other metals.[5,6j] As excellent chiral ligands, *N,N′*-dioxide-metal complexes have shown powerful catalytic capability in many different types of reactions owing to their easily tunable electronic and steric chiral scaffolds.[6] On our going work, we develop chiral *N,N′*-dioxide–Co(II) complex catalysts for the asymmetric Michael additions of α-substituted β-ketoamides. Both nitroolefins and alkynones are tolerable in the process, furnishing the desired nitro-derivatives with vicinal quartery–tertiary carbon centers and α,β-unsaturated enone derivatives, respectively. High enantioselectivities are obtained for the two kinds of Michael donors, although the diastereoselectivities or *Z*/*E* selectivities are moderate. The *Z*/*E* adducts of alkynones underwent

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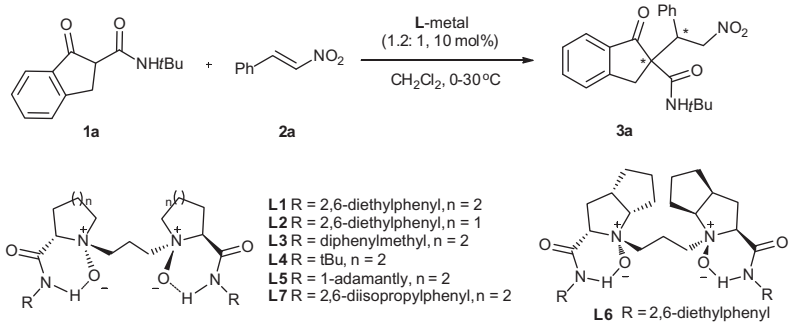
isomerization to afford the *E*-isomers and chloride derivatives by the treatment with HCl. Thermodynamically stable *E*-adduct could be obtained in high enantioselectivity after isomerization with TsOH.

Results and discussion

Initially, we examined various metal salts coordinated with chiral *N*,*N*′-dioxide **L1** in situ to catalyze the Michael reaction of *N*-*tert*-butyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxamide (**1a**) to nitroolefin (**2a**) in CH_2Cl_2 at 0 °C. As shown in Table 1, $Sc(OTf)_3$ did not promote the reaction at all (Table 1, entry 1). Other lanthanides such as $Y(OTf)_3$, $Gd(OTf)_3$, and $Lu(OTf)_3$ could mediate the reaction but in low reactivities and inefficient selectivities (Table 1, entries 2–4). When using $Hf(OTf)_4$ as the metal precursor, the reaction could get 2.0/1 diastereoselectivity, 50%/19% ees, but the yield was very low (Table 1, entry 5). The combination of nickel salts with **L1** could afford the Michael adduct **3a** with delightful yield and enantioselectivity but with poor diastereoselectivity (Table 1, entries 6, 7). And $Ni(BF_4)_2{\cdot}6H_2O$ was superior to $Ni(OTf)_2$ in terms of stereoselectivity. To our delight, the enantioselectivity could be further improved when $Co(BF_4)_2{\cdot}6H_2O$ was used as the center metal, and 89% and 66% ees were obtained for the major and minor diastereomers, respectively (Table 1, entry 8). Encouraged by the initial results, various *N*,*N*′-dioxide ligands were then tested (Table 1, entries 8–15). The screening of chiral amino acids backbone of ligands indicated that **L1** (derived from L-pipecolic acid) gave higher enantioselectivities than the ligand **L2** (derived from L-proline) and the ligand **L6** (derived from L-ramipril) (Table 1, entry 8 vs entry 9, 10). The amide subunits of the ligands also play a crucial role in the enantiocontrol. Comparing to the aryl substituted amide moieties, the introduction of diphenylmethyl group obviously increased the ee value to 97% and 84% ees for the two diastereomeric products (Table 1, entry 11 vs entry 8). Meanwhile, the diastereoselection of the reaction reversed although the dr value was not satisfied in the presence of chiral **L3**–$Co(BF_4)_2{\cdot}6H_2O$ complex. However, both the yield and the enantioselectivity of the reaction significantly decreased when *N*,*N*′-dioxides **L4** and **L5** bearing other sterically hindered alkyl amide moieties were used as the ligands (Table 1, entries 12, 13). Ligand **L7** derived from 2,6-diisopropylaniline accelerated the reaction with satisfied enantioselectivity inferior to that of the ligand **L3** (Table 1, entry 14). Further optimization of the reaction conditions is in vain for the improvement of the diastereoselectivity of the reaction. Other ordinary solvents gave both low yield and enantioselectivity, and CH_2Cl_2 was the most suitable (Table 1, entries 15–19). Thus, the optimized experimental conditions are as follows: 10 mol % of **L3**–$Co(BF_4)_2{\cdot}6H_2O$ (1.2:1) as the catalyst and CH_2Cl_2 as the solvent.

Under the optimized reaction conditions (Table 1, entry 7), the scope of nitroolefins and β-ketoamides was examined and the

Table 1
Optimization of the Michael addition of β-ketoamide (**1a**) to nitroolefin (**2a**) [a]



Entry	Ligand	Metal	Solvent	Yield[b] (%)	*D.r.*[c]	*ee*[d] (%)
1	**L1**	$Sc(OTf)_3$	CH_2Cl_2	n.r.	n.d.	n.d.
2[e]	**L1**	$Y(OTf)_3$	CH_2Cl_2	50	1/1	27/7
3[e]	**L1**	$Gd(OTf)_3$	CH_2Cl_2	51	1/1.4	0/0
4[e]	**L1**	$Lu(OTf)_3$	CH_2Cl_2	19	1.6/1	44/22
5[e]	**L1**	$Hf(OTf)_4$	CH_2Cl_2	8	2.0/1	50/19
6	**L1**	$Ni(OTf)_2$	CH_2Cl_2	84	1/1	60/77
7	**L1**	$Ni(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	87	1/1.7	64/85
8	**L1**	$Co(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	88	1/1.6	66/89
9	**L2**	$Co(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	84	1/2	37/75
10	**L6**	$Co(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	57	1/1.9	36/64
11	**L3**	$Co(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	84	1.7/1	97/84
12	**L4**	$Co(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	87	4/1	40/50
13	**L5**	$Co(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	75	1/1	6/60
14	**L7**	$Co(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	80	1/1.3	94/58
15	**L3**	$Co(BF_4)_2{\cdot}6H_2O$	$CHCl_3$	46	2.1/1	78/51
16	**L3**	$Co(BF_4)_2{\cdot}6H_2O$	THF	81	1/1.2	68/38
17	**L3**	$Co(BF_4)_2{\cdot}6H_2O$	Toluene	33	1/1.2	18/<5
18	**L3**	$Co(BF_4)_2{\cdot}6H_2O$	CH_3OH	64	1/1	58/69
19	**L3**	$Co(BF_4)_2{\cdot}6H_2O$	Et_2O	25	1.8/1	88/52

[a] Unless otherwise noted, the reactions were carried out with the ligand **L** (12 mol %), metal (10 mol %), **1a** (0.1 mmol), and **2a** (0.12 mmol) in solvent (0.6 mL) at 0 °C for 2 days and then at 30 °C for 1 day.
[b] Isolated yield; n.r. = no reaction.
[c] Determined by ^1H NMR analysis, n.d. = not determined.
[d] Determined by chiral HPLC analysis.
[e] The reaction was carried out at 0 °C for 2 days, and the yield was determined by ^1H NMR analysis (using CH_2Br_2 as internal standard).