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Catalytic Asymmetric Direct-Type 1,4-Addition Reactions of Simple Amides

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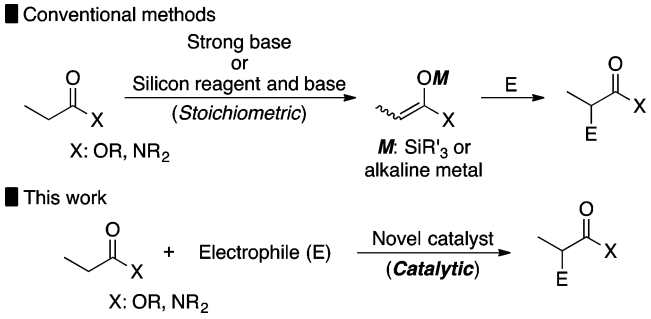
Supporting Information

ABSTRACT: The development of catalytic asymmetric direct-type reactions of less acidic carbonyl compounds such as amides and esters has been a challenging theme in organic chemistry for decades. Here we describe the asymmetric direct 1,4-addition reactions of simple amides with α,β-unsaturated carbonyl compounds using a catalytic amount of a novel chiral catalyst consisting of a potassium base and a macrocyclic chiral crown ether. The desired 1,5-dicarbonyl compounds were obtained in high yields with excellent diastereo- and enantioselectivities. This is the first example of a highly enantioselective catalytic direct-type reaction of simple amides. In addition, the structure of the chiral potassium catalyst has been investigated by X-ray crystallographic, dynamic ^{1}H NMR, and MALDI-TOF MS analyses.

Carbon−carbon bond formation at the α-position of carbonyl compounds is one of the most fundamental and frequently employed methodologies for the construction of complex molecules in organic synthesis.[1,2] A catalytic variant of this reaction in which a catalytic amount of a mediator (such as an acid or base) works efficiently was recently investigated in detail from the viewpoint of atom economy.[3−5] However, applicable carbonyl compounds are limited to aldehydes and ketones in most cases,[6] and the development of catalytic reactions that involve amides or esters is still very challenging (Scheme 1).[7] The main issue is considered to be the Brønsted acidity of the α-hydrogen of a carbonyl compound for deprotonation; the hydrogens of amides (pK_a in DMSO ≈ 35) or esters (pK_a in DMSO ≈ 31) are normally much less acidic than those of aldehydes or ketones (pK_a in DMSO ≈ 27).[8] Hence, currently the most reliable method for C−C bond formation with amides or esters is still the use of *stoichiometric* amounts of metal enolates with strong bases[9] such as lithium diisopropylamide (LDA) or potassium hexamethyldisilazide (KHMDS) or the use of isolable silicon enolates with stoichiometric amounts of silicon reagents and bases (Mukaiyama-type reactions).[10] As an approach to the catalytic variants, some modified amides or esters have been developed;[11] however, the use of additional functional groups for activation of the α-hydrogen often requires tedious procedures for their attachment and release, and this can limit the substrate scope and applications of the reaction. In 2011, our group reported a catalytic direct Mannich-type reaction of an amide using a catalytic amount of a silicon Lewis acid and a base; however, its stereoselectivity, especially enantioselectivity, remained unsatisfactory.[7a] To our knowledge, there have been no other examples of catalytic reactions with simple amides or esters (Scheme 1).

Scheme 1. Nucleophilic Reactions of Simple Amides and Esters



We recently reported on the catalytic direct Mannich-type reactions of simple esters with no activating group at the α-position using a catalytic amount of potassium hydride (KH) through the product base mechanism.[7b] In this reaction, an intermediate (a potassium amide species) possesses strong Brønsted basicity for deprotonation of simple esters directly without regeneration of KH. Thus, the catalytic turnover in this reaction depends on the reaction intermediates. We envisioned that it might be possible to expand this concept to other types of reactions. Here we report the first example of catalytic enantioselective 1,4-addition reactions of simple amides without any activating group at the α-position.

1,4-Addition reactions of carbonyl compounds with α,β-unsaturated carbonyl compounds provide an important method for constructing 1,5-dicarbonyl compounds directly. Although several successful examples have been reported,[5] there has been no example of the reaction using amides without any activating group on their structure as nucleophilic partners.[12] On the basis of a consideration of the product base mechanism, the basicity of the reaction intermediate is important for catalytic turnover. In 1,4-addition reactions of α,β-unsaturated carbonyl compounds, the Brønsted basicity of the reaction intermediate, a metal enolates, can be determined by the structure of the carbonyl moiety. Model 1,4-addition reactions were conducted using *N*,*N*-dimethylpropionamide (**2a**) and cinnamate derivatives in the presence of a catalytic amount of KH. Whereas chalcone (**1a**), methyl cinnamate (**1b**), and *S*-*tert*-butyl

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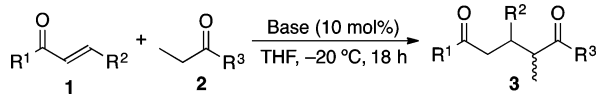
thiocinnamate (**1c**) either did not react or reacted sluggishly under the conditions (Table 1, entries 1−3), it was found that

Table 1. Catalytic 1,4-Addition Reactions of Simple Amides[a]



1 2 3

entry	1[b]	2[c]	base	yield (%)	anti/syn
1[d]	**1a**	**2a**	KH	0	–
2[d]	**1b**	**2a**	KH	<5	–
3[d]	**1c**	**2a**	KH	0	–
4[d]	**1d**	**2a**	KH	quant.	90:10
5	**1d**	**2a**	LiHMDS	9	65:35
6	**1d**	**2a**	NaHMDS	quant.	77:23
7	**1d**	**2a**	KHMDS	97	90:10
8	**1d**	**2b**	KHMDS	97	98:2
9[e,f]	**1d**	**2b**	KHMDS	86	98:2
10[e,f]	**1e**	**2b**	KHMDS	87	98:2

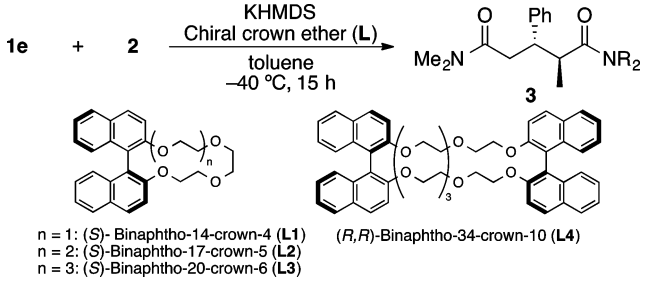
[a]Reaction conditions (unless otherwise noted): **1** (0.400 mmol), **2** (0.800 mmol), base catalyst (0.0400 mmol), THF, −20 °C, 18 h. [b]**1a**: R^1 = Ph, R^2 = Ph; **1b**: R^1 = OMe, R^2 = Ph; **1c**: R^1 = S^{t}Bu, R^2 = Ph; **1d**: R^1 = N−$(CH_2)_4$−, R^2 = Ph; **1e**: R^1 = NMe_2, R^2 = Ph. [c]**2a**: R^3 = NMe_2; **2b**: R^3 = NPh_2. [d]The reaction was conducted at 20 °C. [e]**2b** (1.2 equiv) was used. [f]The reaction time was 3 h.

cinnamamide **1d** reacted with **2a** to afford the desired 1,5-dicarbonyl compound **3da** in high yield with high diastereoselectivity (entry 4). This result indicated that the reaction intermediate, a metal amide enolate, had a Brønsted basicity that was strong enough to deprotonate substrate **2a** and that the reaction proceeded through the product base mechanism. Among the metal amides screened (entries 5−7), KHMDS was found to be the optimum Brønsted base, giving the desired product in high yield with high diastereoselectivity compared with those obtained with other alkaline-metal amides (entry 7). Substituents on the nitrogen atom of propionamide influenced the diastereoselectivity of the reaction, and the use of the sterically bulky *N*,*N*-diphenylpropionamide (**2b**) improved the diastereoselectivity (entry 8). Finally, the 1,4-addition reaction proceeded even with 1.2 equiv of nucleophile (entry 9), and the reaction with *N*,*N*-dimethylcinnamamide (**1e**) also gave a similar result (entry 10).

An asymmetric variant of this 1,4-addition reaction was then investigated. Chiral crown ethers were used to modify the potassium cation.[13] Whereas the typical binaphtho crown ethers binaphtho-14-crown-4 (**L1**), binaphtho-17-crown-5 (**L2**), and binaphtho-20-crown-6 (**L3**) were not effective (Table 2, entries 1−3), the chiral macro crown ether binaphtho-34-crown-10 (**L4**) afforded the desired product with high enantioselectivity (entry 4). The use of this type of very large chiral macro crown ether to modify potassium metal in asymmetric catalysis has not been reported previously. It was also found that **2b** gave the desired product in higher yield and diastereoselectivity than **2a** (entry 5). Increasing the amount of KHMDS relative to the amount of crown ether improved the reactivity without loss of enantioselectivity at −78 °C (entries 6 and 7), and the desired 1,4-addition reaction proceeded even in the presence of 5 mol % KHMDS and 2.8 mol % **L4** (entry 8; for the structure, vide infra). KHMDS itself did not show any catalytic activity under the reaction conditions (entry 9).

The substrate scope was surveyed under the optimized conditions (Table 3).[14] Excellent enantioselectivities of the 1,4-

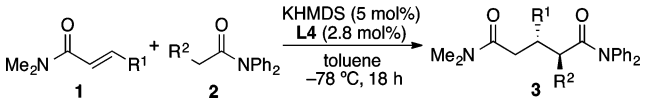
Table 2. Catalytic Asymmetric 1,4-Addition Reactions of Simple Amides in the Presence of Crown Ethers[a]



entry	KHMDS (mol %)	L (mol %)	2	yield (%)	anti/syn	ee (%)
1	10	**L1** (11)	**2a**	86	98:2	60[b]
2	10	**L2** (11)	**2a**	77	92:8	8[b]
3	10	**L3** (11)	**2a**	86	91:9	41[b]
4	10	**L4** (11)	**2a**	81	99:1	93
5	10	**L4** (11)	**2b**	95	>99:1	93
6[c]	3	**L4** (3.3)	**2b**	88	>99:1	98
7[c]	6	**L4** (3.3)	**2b**	quant.	>99:1	98
8[c]	5	**L4** (2.8)	**2b**	96	>99:1	98
9[c]	3	none	**2b**	NR	–	–

[a]Reaction conditions: **1e** (0.400 mmol), **2** (0.800 mmol), toluene, −40 °C, 15 h, catalyst prepared from KHMDS and **L**. [b]The absolute configuration of the product is opposite. [c]The reaction was conducted using **2b** (1.2 equiv) with 4 Å MS at −78 °C for 18 h.

Table 3. Substrate Scope of Catalytic Asymmetric 1,4-Addition Reactions of Simple Amides[a]



1 2 3

entry	R^1	2	yield (%)	anti/syn	ee (%)
1[b]	*o*-MeC_6H_4 (**1f**)	**2b**	91	>99:1	98
2	*m*-MeC_6H_4 (**1g**)	**2b**	92	>99:1	97
3[c]	*p*-MeC_6H_4 (**1h**)	**2b**	99	>99:1	96
4[c,d]	*p*-$MeOC_6H_4$ (**1i**)	**2b**	95	>99:1	98
5	*p*-ClC_6H_4 (**1j**)	**2b**	90	>99:1	96
6	*p*-BrC_6H_4 (**1k**)	**2b**	95	>99:1	96
7	2-furyl (**1l**)	**2b**	93	>99:1	95
8	1-naphthyl (**1m**)	**2b**	97	>99:1	98
9[c,e,f,g]	2-naphthyl (**1n**)	**2b**	93	>99:1	93
10[e,h]	Me (**1o**)	**2b**	quant.	>99:1	96
12[c,e]	^{i}Pr (**1p**)	**2b**	90	>99:1	98
13[c]	^{i}Bu (**1q**)	**2b**	89	>99:1	97
14[c]	Cy (**1r**)	**2b**	89	>99:1	98
15[c]	Ph (**1e**)	**2c**[i]	94	>99:1	94

[a]Reaction conditions (unless otherwise noted): **1** (0.400 mmol), **2** (0.480 mmol), toluene, 4 Å MS, −78 °C, 18 h, catalyst prepared from KHMDS (0.0200 mmol) and **L4** (0.0112 mmol). [b]The reaction time was 30 h. [c]The reaction was conducted at −60 °C. [d]KHMDS (8 mol %) and **L4** (4.4 mol %) were used. [e]KHMDS (10 mol %) and **L4** (5.5 mol %) were used. [f]The concentration was 0.1 M. [g]The reaction was conducted without 4 Å MS. [h]**1** (2.0 equiv) and **2** (1.0 equiv) were used. [i]**2c**: R^2 = C_2H_5.

addition reactions were maintained by changing the position of the methyl substituent on the aromatic ring of the cinnamamide (entries 1−3). *α*,*β*-Unsaturated amides bearing either electron-rich or electron-deficient substituents on the aromatic moiety gave the desired products in high yields with high stereo-

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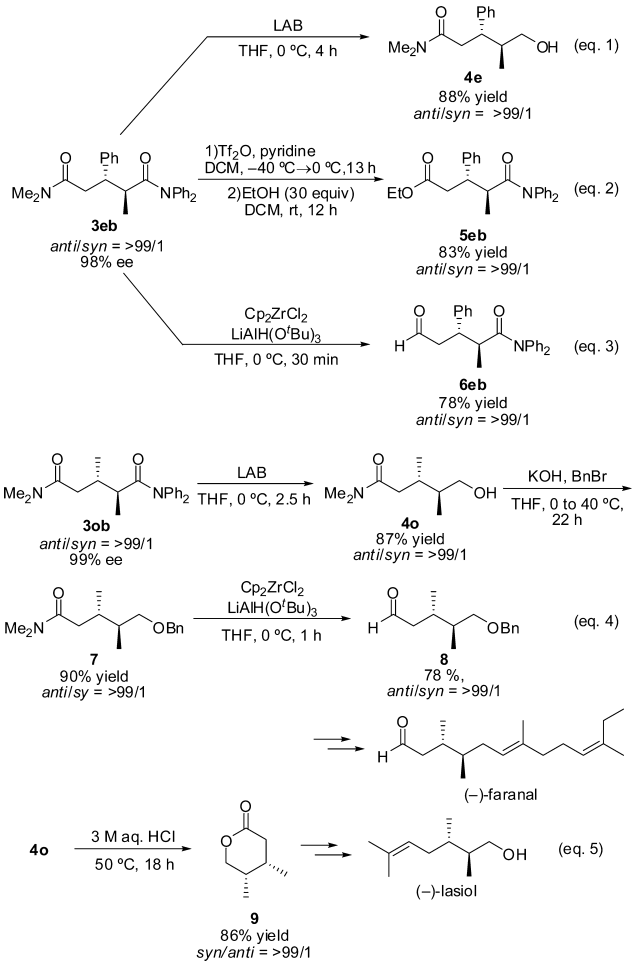
selectivities (entries 4−6). Outstanding diastereo- and enantioselectivity were also obtained with the 2-furyl-substituted α,β-unsaturated amide (entry 7). The steric bulk of hindered aromatic rings (1-naphthyl and 2-naphthyl) affected neither the yield nor the stereoselectivity of the reaction (entries 8 and 9). Furthermore, the asymmetric 1,4-addition reactions with aliphatic α,β-unsaturated amides also proceeded cleanly without any loss of enantioselectivity (entries 10−14). As a nucleophile, butyramide (**2c**) was also found to work well under the reaction conditions (entry 15). Notably, excellent yields, perfect anti selectivities, and outstanding diastereo- and enantioselectivities were obtained with all of the substrates tested.

To demonstrate the synthetic utility of this reaction, several transformations of the products were conducted (Scheme 2).

Scheme 2. Transformations of the Products



The diphenylamide moiety of **3eb** was selectively converted into an alcohol to give **4e** (eq 1).[15] The dimethylamide moiety of **3eb** was converted into either an ethyl ester to give **5eb** (eq 2)[16] or an aldehyde to form **6eb** (eq 3).[17] Furthermore, the obtained 1,4-addition product was successfully transformed into useful intermediates of natural products (eqs 4 and 5). The 1,4-adduct **3ob** was treated with lithium dimethylaminoborohydride (LAB) to afford alcohol **4o**, and after benzylation of the alcohol moiety, the second amide part was reduced with Schwartz reagent to afford the desired aldehyde **8**, which is an intermediate in the total synthesis of (−)-faranal (eq 4).[18]

Alcohol **4o** was also converted into **9**, a useful intermediate for (−)-lasiol, by acidic lactone formation (eq 5).[19]

Since the use of chiral macro crown ethers such as **L4** for asymmetric catalysis is rare (to the best of our knowledge, this is the first case), we were interested in the structure of the catalyst. When a mixture of potassium triflate (2 equiv) and **L4** (1 equiv) was put in a mixed solvent of hexane/ethyl acetate, small colorless crystals appeared.[20] X-ray crystallographic analysis of a crystal indicated that the potassium−**L4** complex consisted of a 1:1 ratio of each component (Figure 1).

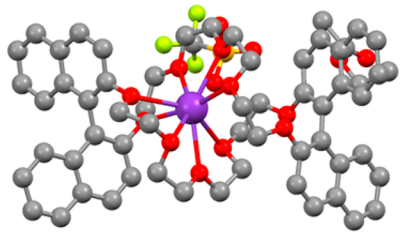
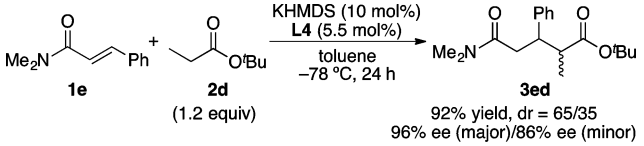


Figure 1. X-ray structure of the binaphtho-34-crown-10 (**L4**)−KOTf complex.

Although this result implied that the stable complex ratio was 1:1, it was not consistent with the fact that the desired reaction proceeded without any loss of enantioselectivity using KHMDS and **L4** in a 2:1 ratio (Table 2). We further conducted NMR and MS analyses of the catalyst.[21] In ^{1}H NMR analysis at −60 °C, a ca. 2.5:1 ratio of a potassium−**L4** complex and free **L4** were observed when KHMDS and **L4** were combined in a 1:1 ratio.[21] The signals of the free **L4** disappeared and only the potassium−**L4** complex was observed KHMDS and **L4** were combined in a 2:1 ratio.[21] These results strongly suggest that the catalyst formation from KHMDS and **L4** (1:1) occurs under equilibrium conditions and that the equilibrium moves to the 1:1 complex formation in the presence of an excess amount of KHMDS. Moreover, the formation of the 1:1 complex was also supported by MALDI-TOF MS analysis.[21]

We also conducted a preliminary study of the reaction of a simple ester. It was found that *tert*-butyl propionate (**2d**) reacted with α,β-unsaturated amide **1e** in the presence of KHMDS−**L4** to afford the desired product in high yield with high enantioselectivity (Scheme 3). It is noteworthy that asymmetric catalysis with a simple ester has been demonstrated, although there is still room for improvement of the diastereoselectivity.

Scheme 3. Catalytic Asymmetric 1,4-Addition Reaction of a Simple Ester



In summary, we have developed catalytic asymmetric 1,4-addition reactions of simple amides that do not bear any activating groups. To our knowledge, this is the first example of a catalytic, highly enantioselective direct reaction using simple amides as nucleophiles. Binaphtho-34-crown-10 was found to be effective for chiral modification of the potassium cation, and the desired reaction proceeded in excellent yields with

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outstanding diastereo- and enantioselectivities. The use of the chiral macro crown ether in asymmetric catalysis is also unique. The synthetic utility of this novel reaction was demonstrated by conversion of several of the products into useful derivatives, including the formal syntheses of natural products. Moreover, the structure of the chiral potassium catalyst was studied by X-ray crystallographic, dynamic ^{1}H NMR, and MALDI-TOF MS analyses. Further investigations aimed at clarifying the catalyst structure more in detail and extending the application of the reaction system to other catalytic reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, spectra, and CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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