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Communication

Chiral Metal Salts as Ligands for Catalytic Asymmetric Mannich Reactions with Simple Amides

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ABSTRACT: Catalytic asymmetric Mannich reactions of imines with weakly acidic simple amides were developed using a chiral potassium hexamethyldisilazide (KHMDS)−bis(oxazoline) potassium salt (K-Box) catalyst system. The desired reactions proceeded to afford the target compounds in high yields with high diastereo- and enantioselectivities. It was suggested that a K enolate interacted with K-Box to form a chiral K enolate that reacted with imines efficiently. In this system, K-Box (potassium salt of Box) worked as a chiral ligand of the active potassium species.

Asymmetric catalysis is a robust methodology for providing optically active molecules with high efficiency. To date, many kinds of chiral metal- and organo-catalysts have been developed and employed in asymmetric transformations.[1] Alkaline metal compounds have often been employed as stoichiometric Brønsted bases or strong nucleophiles in organic synthesis. Among them, lithium compounds modified by chiral ligands have been investigated extensively and applied for asymmetric reactions.[2−6] However, successful examples of chiral modification using other alkaline metal species such as sodium and potassium compounds are limited. This is presumably because their Lewis acidity is lower and their ionic radius is larger than those of a lithium ion; however, their reactivity is high, especially in Brønsted base catalysis.[7] Chiral multidentate Lewis base ligands such as chiral crown ethers have traditionally been employed for chiral modification;[8−17] however, other effective methodologies are yet to be developed.[18,19] Here, we report that a chiral potassium salt−potassium base mixed aggregate system is an effective chiral potassium Brønsted base catalyst in asymmetric reactions. In this system, the chiral potassium salt functions as a chiral ligand (Figure 1).[20,21]

Catalytic asymmetric Mannich reactions of imines with amides and esters are one of the most powerful and atom-economical methods to provide optically active β-amino acid derivatives without any redox process.[22−30] To date, although several catalytic asymmetric Mannich reactions with easily enolizable carbonyl compounds such as aldehydes and ketones ($pK_a \leq 30$ in DMSO)[31] have been developed,[32−41] the reactions with amides and esters without any electron-withdrawing groups at their α-positions ($pK_a \geq 30$ in DMSO) have been unsuccessful.[42−45] The most commonly employed methods still utilize preformed metal/metalloid enolates such as lithium enolates and ketene silyl acetals, which generate significant amounts of waste. Recently, Shibasaki and Kumagai et al. reported catalytic asymmetric Mannich reactions with 1-acyl-7-azaindoles as well-designed amides.[46−55] In these reactions, many kinds of 1-acyl-7-azaindoles were available as acyl donors, while a 7-azaindole part was always required to obtain high reactivity and stereoselectivity.

Recently, we have focused on developing strong Brønsted base catalyzed addition reactions with weakly acidic carbon pronucleophiles by designing strongly basic reaction intermediates.[56,57] Addition reactions of weakly acidic carbonyl and related compounds, such as esters, amides, and alkylnitriles (pK_a = 30−35 in DMSO), and their asymmetric variants have been developed.[58−67] However, catalytic asymmetric Mannich reactions with weakly acidic simple amides such as propionamides have not yet been achieved. We report here our efforts to realize these reactions using a newly discovered chiral strong Brønsted base catalyst system.

We investigated the Mannich reaction of the benzaldehyde imine bearing 2,4-dimethoxyphenyl (DMP) group on the nitrogen atom as a protecting group (**1a**) with *N*,*N*-dimethylpropionamide (**2a**) as substrates in the presence of potassium hexamethyldisilazide (KHMDS) and a chiral ligand.[68] Initially, chiral crown ethers were employed as chiral

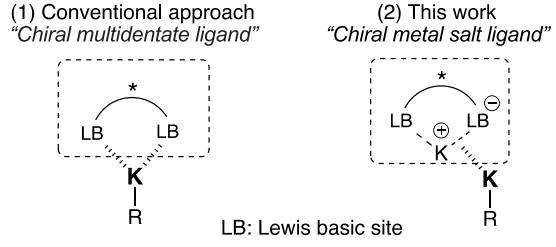

Figure 1. Chiral modification methods for metal species

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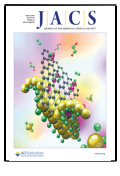

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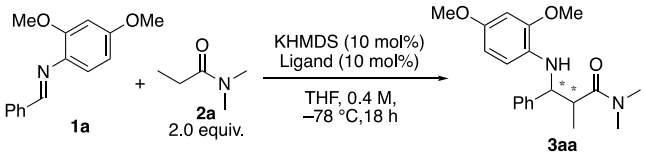
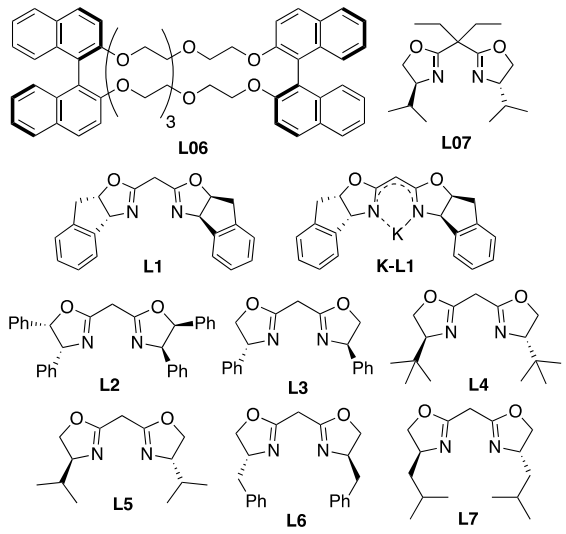
ligands; however, no significant enantioselectivity was observed (Table 1, entry 1; also see Table S1 in the Supporting Information (SI)). We then examined the use of typical chiral bis(oxazoline) (Box) ligands **L07**, with a disubstituted methylene tether, and **L1**, with an unsubstituted methylene tether, and it was found that the reactions did not proceed at all in either case (entries 2 and 3; see also Scheme S1 in SI). Indeed, KHMDS reacted with **L1** to form a potassium salt **K-L1** (See Chart S1 in SI). Unexpectedly, it was found that **K-L1** itself was effective for chiral modification of KHMDS, and the desired reaction proceeded smoothly in THF at −78 °C to obtain the product **3aa** in high yield with high diastereo- and enantioselectivity (entry 4). It seemed that the chiral potassium salt **K-L1** worked as a chiral ligand; however, such a chiral metal salt ligand was unprecedented, and it is generally thought to be difficult to create a strict asymmetric environment around a potassium enolate without a significant Lewis basic coordination site.

Table 1. Initial Investigation of Asymmetric Mannich Reaction



entry	ligand	yield (%)[a]	*anti*/*syn*[b]	ee (%, *anti*)
1[c]	**L06**	70	67:33	18
2	**L07**	NR	–	–
3	**L1**	NR	–	–
4[d]	**K-L1**	98	99:1	91

[a]Isolated yield. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]KHMDS (15 mol %) and **L06** (16.5 mol %) in toluene. [d]The catalyst prepared from KHMDS (20 mol %) and **L1** (10 mol %).



Using an interesting catalyst system, optimization of the reaction conditions was conducted (Table S3 in SI). The effect of solvents on the reaction was first examined. While cyclopentyl methyl ether (CPME) and *tert*-butyl methyl ether (TBME) gave good enantioselectivities among the ether solvents, THF was found to be the best solvent. We then investigated potassium-Box salts **K-L**. While **K-L2** and **K-L4** were ineffective for this reaction, the other Box derivatives **K-L3**, **K-L5-7** worked well, and good to high levels of enantioselectivities were obtained. Among them, the best K-Box was **K-L1**, which was selected for further investigations (for the effect of other alkaline metal bases, see Tables S4 and S5 in SI). Catalyst loading and the amount of **2a** were optimized, and the use of 1.1 equiv of **2a** with 5 mol % KHMDS and 5 mol % **K-L1** system was found to be the best conditions. The use of excess KHMDS to **K-L1** still gave good enantioselectivity. KHMDS itself also promoted the reaction, but the yield was very low. The effect of the *N*-aryl group was also investigated (Table S6 in SI). It was found that the 2-methoxy group on the *N*-aryl group was important to achieve high enantioselectivity in this reaction.

The substrate scope of the reaction was then examined (Table 2). Tolyl imines were used in the reaction, and high yields and high diastereo- and enantioselectivities were obtained (entries 2−4). Ethyl and phenyl substituents on the phenyl group were also effective (entries 5 and 6). In reactions using imines bearing a methoxy group, high selectivities were observed, but the reactivity of the *p*-methoxyphenyl imine was lower (entries 7−9). Halogen-substituted imines were also successfully employed, and the desired products were obtained in good yields (entries 10−14). An imine bearing a CF_3 group and a 2-naphthyl imine gave the products in high yields with high selectivities (entries 15 and 16). The pyridyl imines were also effective; however, the 2-pyridyl imine showed lower enantioselectivity (entries 17−19). Alkyl imines were also available; cyclopropyl, *tert*-butyl, and 2-phenyl-1,1-dimethylethyl imines reacted with **2a**, and high enantioselectivities were obtained (entries 20−22).[69] The scope of the amide structure was also investigated. It was found that less hindered Box salt **K-L5** was effective when longer alkylamides (**2b**−**e**) were used, and high diastereo- and enantioselectivities were obtained (entries 23−26). *N*,*N*-Dimethylacetamide (**2f**) also showed good enantioselectivity using **K-L1** as the ligand (entry 27). Other propionamides **2h**−**2j** were further tested, and good to high enantioselectivities were obtained (entries 28−30). It was also found that *tert*-butyl propionate (**2k**) gave the desired product in high yield with high enantioselectivity; however, the diastereoselectivity was moderate (entry 31).

The DMP group on the nitrogen atom of the product was successfully removed using cerium ammonium nitrate (CAN), and **5aa** was obtained in high yield after benzoylation without any loss of enantioselectivity (Scheme 1, eq 1).[70,71] On the other hand, the amide part was converted into the ester under acidic conditions to obtain *β*-amino ester **6aa** in high yield (eq 2). In addition, the asymmetric Mannich reaction in a gram-scale also proceeded smoothly without a decrease in reactivity or selectivity (eq 3).

Synthesis of SCH-48462, a cholesterol absorption inhibitor possessing a *β*-lactam core, was then performed (Scheme 2).[72−75] The reaction of imine **1g** with amide **2g** was conducted using KHMDS and **K-L5**. The desired adduct **3gg** was obtained in high yield with high diastereo- and enantioselectivities. The adduct **3gg** was treated with Tf_2O followed by NaOH to obtain *β*-lactam **7gg** in good yield.[76,77] After the DMP group was removed, NH-free *β*-lactam **8gg** was obtained, the optical purity of which was enhanced by recrystallization. After the introduction of a *p*-methoxyphenyl group, SCH-48462 was obtained in optically pure form.[75]

The structure of the K enolate−**K-L1** complex was investigated by DFT calculations (Figure 2).[78,79] The results

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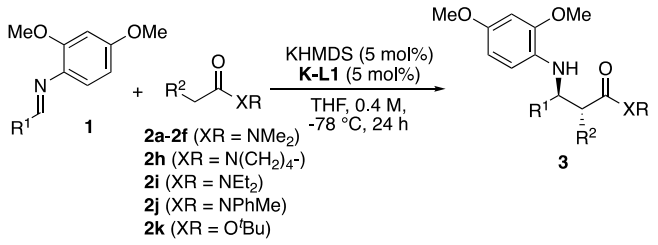
J. Am. Chem. Soc. 2021, 143, 5598−5604

Table 2. Substrate Scope



entry	R^1	R^2	yield (%)[a]	*anti*/*syn*[b]	ee (%, *anti*)
1	Ph (**1a**)	Me (**2a**)	96	99:1	92
2	*p*-MeC_6H_4 (**1b**)	Me (**2a**)	91	99:1	94
3	*m*-MeC_6H_4 (**1c**)	Me (**2a**)	85	98:2	89
4	*o*-MeC_6H_4 (**1d**)	Me (**2a**)	87	98:2	89
5	*p*-EtC_6H_4 (**1e**)	Me (**2a**)	86	99:1	94
6	*p*-PhC_6H_4 (**1f**)	Me(**2a**)	68	99:1	95
7[c]	*p*-$MeOC_6H_4$ (**1g**)	Me (**2a**)	89	98:2	94
8	*m*-$MeOC_6H_4$ (**1h**)	Me (**2a**)	82	98:2	89
9	*o*-$MeOC_6H_4$ (**1i**)	Me (**2a**)	97	99:1	91
10[c]	*p*-FC_6H_4 (**1j**)	Me (**2a**)	91	99:1	93
11[c]	*p*-ClC_6H_4 (**1k**)	Me (**2a**)	84	99:1	94
12[c]	*p*-BrC_6H_4 (**1l**)	Me (**2a**)	83	99:1	95
13[d]	*m*-BrC_6H_4 (**1m**)	Me (**2a**)	78	98:2	84
14[c]	*o*-BrC_6H_4 (**1n**)	Me (**2a**)	82	96:4	85
15[d]	*m*-$CF_3C_6H_4$ (**1o**)	Me (**2a**)	77	98:2	85
16	2-naphthyl (**1p**)	Me (**2a**)	85	99:1	90
17[d]	4-pyridyl (**1q**)	Me (**2a**)	65	97:3	85
18[d]	3-pyridyl (**1r**)	Me (**2a**)	82	99:1	92
19[d]	2-pyridyl (**1s**)	Me (**2a**)	96	94:6	72
20[d,e]	Cyclopropyl (**1t**)	Me (**2a**)	86	>99:1	92
21[c,d,f]	^{t}Bu (**1u**)	Me (**2a**)	64	99:1	88
22[c,d,f]	$PhCH_2CMe_2$ (**1v**)	Me (**2a**)	71	>99:1	88
23[e,g]	Ph (**1a**)	Et (**2b**)	78	99:1	94
24[d,e]	Ph (**1a**)	C_5H_{11}(**2c**)	92	>99:1	93
25[c,d,e]	Ph (**1a**)	^{i}Pr (**2d**)	61	>99:1	91
26[c,e]	Ph (**1a**)	$PhCH_2$ (**2e**)	quant.	99:1	97
27	Ph (**1a**)	H (**2f**)	67	–	82
28[d]	Ph (**1a**)	Me (**2h**)	quant.	99:1	89
29[d]	Ph (**1a**)	Me (**2i**)	81	98:2	94
30	Ph (**1a**)	Me (**2j**)	99	>99:1	78
31[d,h]	Ph (**1a**)	Me (**2k**)	96	68:32[i]	85[j]

[a]Isolated yield. [b]Determined by ^{1}H NMR analysis of a crude mixture. [c]For 48 h. [d]KHMDS (20 mol %) and **L** (10 mol %) were used. [e]**K-L5** was used instead of **K-L1**. The opposite enantiomer was obtained. [f]At −40 °C with 2.0 equiv of **2a**. *N*-(2-Methoxyphenyl) imine was used instead of *N*-DMP imine. [g]In 0.8 M. [h]In 0.2 M for 18 h with 2.0 equiv of **2k**. [i]Ratio of the major and minor diastereomers. [j]Ee of the major diastereomer.

suggested that the two potassium ions were situated between the two nitrogen atoms of **L1** symmetrically and that the enolate was sited between the two potassium ions. The stability of the complex was due to a significant electrostatic interaction between the K enolate and **K-L1**. This finding indicated that the K and O atoms of the K enolate were tightly fixed in an asymmetric environment. This symmetrical structure was also supported by NMR studies (see SI).

The reaction mechanism was considered to follow the pathway proposed in Chart 1. KHMDS interacts with the K-Box formed in situ[80,81] to form KHMDS−K-Box complex **I**, which might work as a base to form chiral K enolate−K-Box complex **II** by deprotonation of **2**.[82] Reactivity of the complex **II** would be higher than free K enolate species due to the greater Lewis acidic nature of complex **II** or difference of their aggregation states.[83] Formation of complex **II** could be supported by NMR studies (see SI).[84] Complex **II** reacts with imine **1** to form K-Box and intermediate complex **III**.[85−88] There are two possible pathways to regenerate complex **II** from this species (paths A and B).[89] At the current stage, both pathways are possible and it is difficult to distinguish between them.

In summary, we developed catalytic asymmetric Mannich reactions of imines with weakly acidic simple amides using a chiral KHMDS−Box potassium salt (K-Box) catalyst system. The desired reactions proceeded to obtain the target compounds in high yields with high diastereo- and enantioselectivities. A wide substrate scope and applications of the reaction were demonstrated. Preliminary mechanistic studies and calculations suggested that the K enolate interacted with K-Box to form a symmetric chiral K enolate. In this catalyst system, the K-Box worked as a chiral ligand to form active potassium species in a mixed aggregation state. To our knowledge, this kind of chiral modification of potassium

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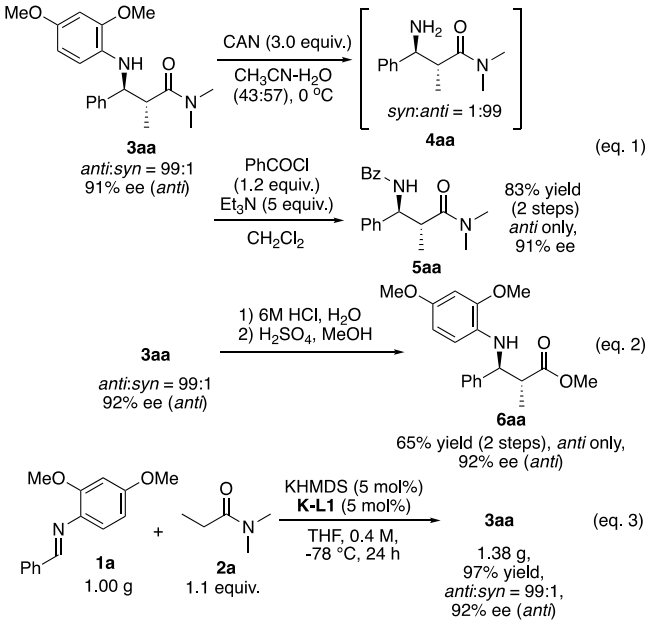
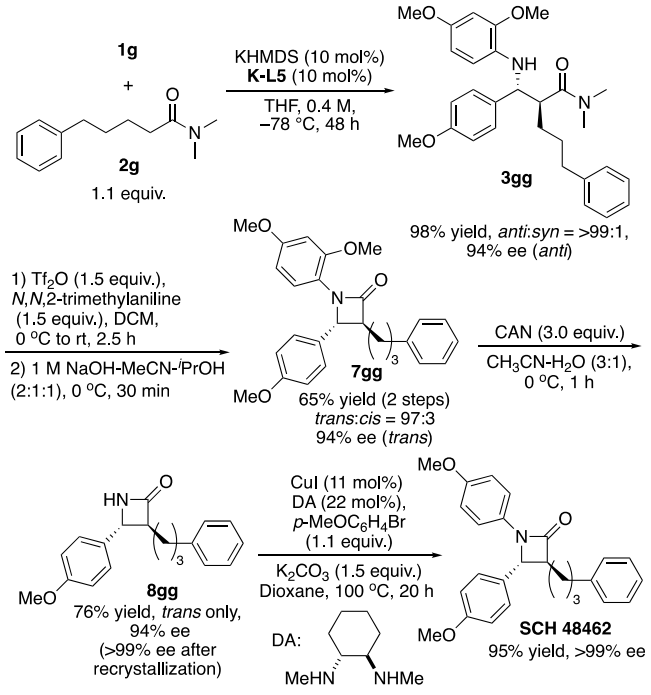
J. Am. Chem. Soc. 2021, 143, 5598−5604

Scheme 1. Deprotection and Transformation of the Mannich Adduct and Gram-Scale Reaction



Scheme 2. Synthesis of SCH-48462



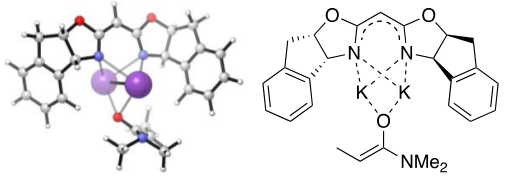
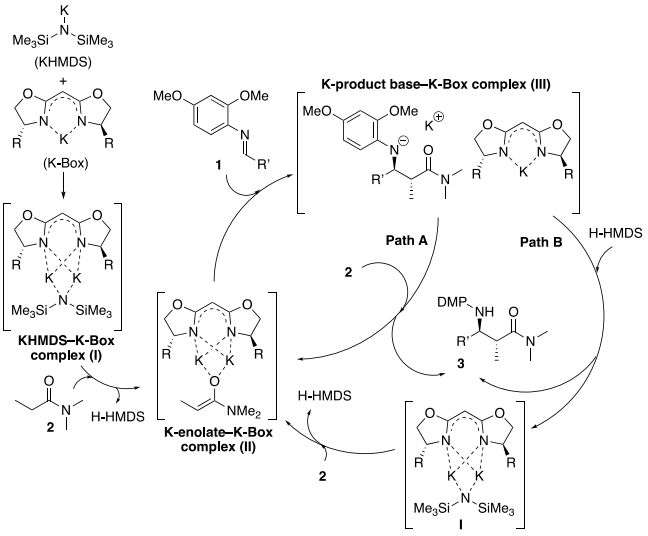


Figure 2. Most stable structure of K enolate−**K-L1** obtained by an exhaustive geometry search using the multicomponent artificial force-induced reaction (MC-AFIR) method[78,79] (see SI for computational details).

Chart 1. Proposed Catalytic Cycle



species for asymmetric catalysis is unprecedented. Conceptually, not only the chiral Box derivatives but also other types of chiral acids might be applicable for the preparation of chiral potassium salts. Further investigations to expand this new concept are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c13317.

Supporting experiments including optimization of reaction conditions, mechanistic studies, calculation studies, and experimental details including reaction procedures, characterization data, spectra and charts (PDF)

Accession Codes

CCDC 1956655 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(88) The 2-MeO group on the *N*-aryl moiety of the imine was important for obtaining high enantioselectivity. It is assumed that some chelation between one of the potassium ions and the 2-MeO group might control the transition state; however, its detailed structure is unclear at this stage and is under investigation.
(89) We confirmed that alkylpotassium (KCH_2SiMe_3) promoted this reaction catalytically. See the SI.

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J. Am. Chem. Soc. 2021, 143, 5598−5604