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Multinuclear Zinc Bisamidinate Catalyzed Asymmetric Alkylation of α-Ketoesters and Its Unique Chemoselectivity

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The multinuclear Zn-bisamidinate catalyzed enantioselective addition of Et_2Zn to α-ketoesters has been developed. The steric tuning of two amidinate units as well as multiple coordination on the Zn atoms play a key role in achieving high enantioselectivity (up to 98% ee) and unique chemoselectivity. The present catalyst exhibited the preferential alkylation of α-ketoesters even in the presence of aldehydes.

The rational design and development of a highly efficient catalyst for asymmetric catalytic reaction is of ongoing considerable interest in organic chemistry. Multimetallic catalysts, in particular, have attracted much attention due to their potential to have a synergistic effect that is not possible using monometallic catalysts.[1,2] Multinuclear metals positioned suitably on the chiral scaffold could achieve higher level of catalytic activity and stereocontrol ability. In our effort to develop new chiral multi-nucleating ligand, the bisamidinate ligand found to be a promising scaffold due to the conformational versatility of metal amidinate complexes based on σ and π coordination modes (Fig. 1).[3] Our designed bisamidine ligand could incorporate three metals positioned in *cis* arrangement to cooperatively activate the highly coordinative substrates (e.g., dicarbonyl compound) in a site-dependent/selective manner (Fig. 1). Furthermore, electronic and steric properties of the amidinate moiety and the chiral scaffold connecting them can be easily modified. To assess catalytic activity and stereocontrol ability of our designed multimetallic bisamidinate catalyst, we herein studied enantioselective addition of Et_2Zn to α-ketoesters.

Although numerous catalysts are available for the related asymmetric alkylation of aldehydes,[4] the number of catalysts in the α-ketoester version is scarce due to serious side reactions; reduction and uncatalyzed reaction. Several reports have appeared regarding the catalytic enantioselective addition of Me_2Zn[5] having low nucleophilic and non-reducing activities. Only two catalysts for the enantioselective addition of more reactive Et_2Zn to α-ketoesters[6,7] have been reported by Kozlowski[6a-c] and Hoveyda.[6d]

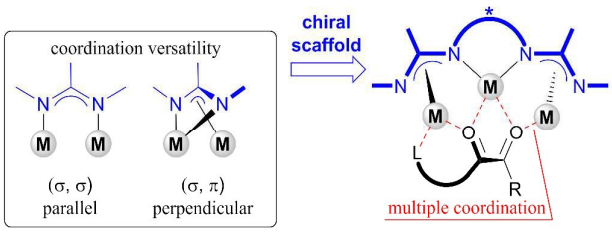

Fig. 1 Design of multi-nucleating bisamidine ligand

Chiral bisamidine ligands **L1** - **L6** derived from (1*R*,2*R*)-cyclohexanediamine were designed to allow multimetallic reactive sites in *cis* orientation on the C_2-symmetric reaction space (Fig. 2). We firstly investigated catalytic activity and stereocontrol ability of chiral bisamidine ligands **L1** - **L6** (Table 1). The reduction product was predominantly obtained in the reaction of Et_2Zn with **1a** in toluene at 0 °C (89%, entry 1). **L1** accelerated the addition pathway (entry 2) and lowering the reaction temperature significantly increased the yield of addition product **2a** (74%, entry 4). A survey of various solvents revealed the superiority of toluene in terms of yield and ee value (Table S1 in SI). Two amidinate units in *cis* orientation play a key role in the preferential addition reaction (entry 10). This indicates the importance of the multiple and simultaneous coordination of the Zn atoms in activating α-ketoesters.

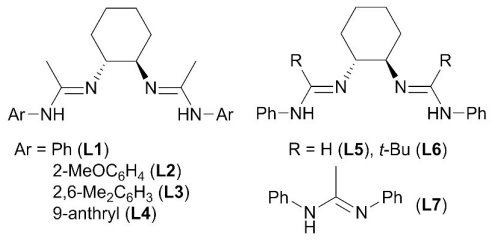

Fig. 2 Designed bisamidine ligands

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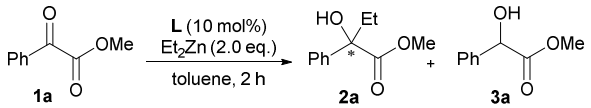
Table 1. Optimization of reaction conditions



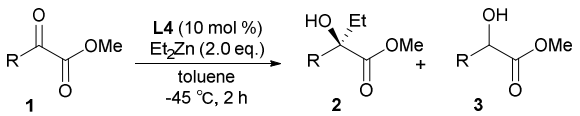
Entry	L	Temp (°C)	2a Yield (%)[a]	2a ee (%)[b]	3a Yield (%)[a]
1	-	0	9	-	89
2	**L1**	0	44	18 (*S*)	56
3	**L1**	-20	50	15 (*S*)	49
4	**L1**	-45	74	20 (*S*)	24
5	**L2**	-45	78	35 (*S*)	20
6	**L3**	-45	89	35 (*R*)	11
7	**L4**	-45	52	49 (*R*)	43
8	**L5**	-45	73	10 (*R*)	25
9	**L6**	-45	13	4 (*S*)	84
10	**L7**[c]	-45	14	-	72

[a]Determined by ^{1}H NMR analysis of the crude mixture. [b]Determined by chiral HPLC. [c]20 mol % of **L7** was used.

The steric environment on the amidine carbon atom exhibited a significant effect on the α-ketoester activation ability (entries 8, 9). The most potent substituent R was Me group due to the adequate balance between the conformational rigidity and the flexibility, constructing an appropriate C_2-symmetric reaction space. The Ar groups attached to the terminal N atoms of the bisamidine ligands have a great effect on the reactivity as well as the enantioselectivity (entries 5-7). Increasing the steric hindrance on the terminal Ar group (**L3** and **L4**) reversed the absolute stereochemistry at the quaternary carbon center with increased enantioselectivity. In particular, **L4** having a sterically demanding 9-anthryl group resulted in the promising ee value.

Next, the scope and limitations of this reaction with various α-ketoesters were explored under the optimal reaction condition (Table 2). No steric effect of the aryl group was observed in a variety of aryl α-ketoesters (entries 1-3). On the other hand, both reactivity and enantioselectivity strongly depend on the steric environment of alkyl α-ketoesters (entries 4-8). Whereas **1d** resulted in moderate yield with nonselective transformation, **1e-h** afforded the addition product in quantitative yields with noticeably improved enantioselectivities of 70-88% ee (entries 5-8). A significant increase in the enantioselectivity was achieved with introduction of the coordinating groups (e.g., OMe and SMe) at the ortho positon of the Ph group of **1a** (entries 9 and 12). In particular, *o*-SMe substituted **1l** exhibited higher reactivity than *o*-OMe substituted **1i**. A comparable product yield (85%) was achieved remaining the enantioselectivity (98% ee) albeit with a decrease in the catalyst loading to 5 mol%. Fortunately, the SMe group could be removed by reductive dethiomethylation with Raney-Ni to afford **2a** in quantitative yield without lowering the enantiomeric excess. In contrast, both *m*- and *p*-OMe substituted **1j** and **1k** resulted in comparable enantioselectivities to **1a**. In accordance with our prediction (Fig. 1), the multiple coordination of the *o*-OMe and *o*-SMe group with Zn atoms enhances the asymmetric induction in a site-dependent manner.

Table 2. Substrate scope



Entry	R	2 Yield (%)[a]	2 Ee (%)[b]	3 Yield (%)[a]
1	Ph (**a**)	52	49	43
2	2-Naph (**b**)	61	31	25
3	3,5-$Me_2C_6H_3$ (**c**)	63	45	20
4	$PhCH_2CH_2$ (**d**)	39	1	0
5	*i*-Pr (**e**)	88	88[c]	0
6	*c*-C_5H_9 (**f**)	88	70[c]	12
7	*c*-C_6H_{11} (**g**)	>99	86[c]	0
8	*c*-C_7H_{13} (**h**)	>99	86[c]	0
9	*o*-$MeOC_6H_4$ (**i**)	65 (85)[d]	94 (95)[d]	13 (10)[d]
10	*m*-$MeOC_6H_4$ (**j**)	56	39	35
11	*p*-$MeOC_6H_4$ (**k**)	60	48	2
12	*o*-$MeSC_6H_4$ (**l**)	99 (85)[e]	97 (98)[e]	1 (15)[e]

[a]Determined by ^{1}H NMR analysis of the crude mixture. [b]Determined by chiral HPLC. The absolute configuration was determined to be *R* for **2a**, **2i**, and **2l**. All other configurations were assigned by analogy. [c]Determined by chiral GC. [d]Reaction conditions: Et_2Zn (6.0 eq.), MS 4A (activated with a heat gun under reduced pressure, 100 mg/mmol of **1g**), 10 h. [e]5 mol% of **L4** was used

To gain insight into the catalytically active species of the present reaction, the relationship between the ee values of **L4** and **1g**, stoichiometric experiments in several ratios of Et_2Zn/**L1** or **L4**, and DFT calculations of transition state (TS) were conducted. The almost linear relationship was observed between ee values of **L4** and **1g**, indicating a monomeric catalytic species (Fig. 3). The catalytic activity was significantly affected by the ratio of Et_2Zn/bisamidine (Table 3). Whereas the Zn-bisamidinate catalysts prepared with lower molar ratios than Et_2Zn/**L1** = 2/1 found to be inactive (entries 1 and 2), those prepared with 3/1 ratio resulted in comparable ee value to the catalytic reaction with good yield (entry 3). Almost the same results were obtained with the higher than 3/1 ratio (entry 4). A similar tendency was observed in the Et_2Zn/**L4** ratio effect (entries 5 and 6). The Based on these experimental analyses, the trimetallic TS model consisting of Zn species, **L4**, and **1a** in a ratio of 3 : 1 : 1 was proposed.

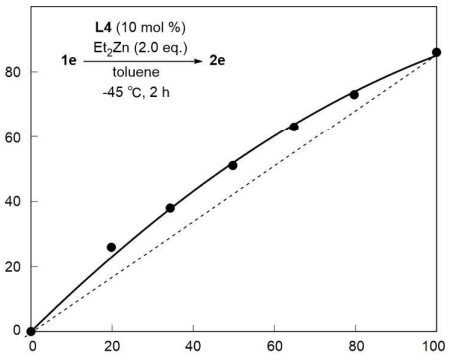


Fig. 3 Relationship between the ee values of **L4** and **1g**

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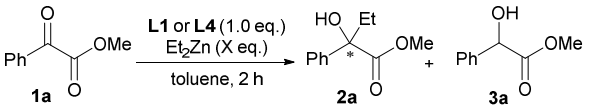
Table 3. Et_2Zn/**L** ratio effect under stoichiometric condition



Entry	L	Et_2Zn/L	2a Yield (%)[a]	2a ee (%)[b]	3a Yield (%)[a]
1	L1-	1/1	n.r.	-	-
2	L1	2/1	n.r.	-	-
3	L1	3/1	82	27 (*S*)	2
4	L1	4/1	89	25 (*S*)	1
5	L4	2/1	n.r.	-	-
6	L4	3/1	71	61 (*R*)	2

[a]Determined by ^{1}H NMR analysis of the crude mixture. [b]Determined by chiral HPLC. [c]20 mol % of **L7** was used.

DFT calculation[8] of the proposed TS model revealed that the trinuclear Zn-bisamidinate catalyst activates **1a** through the multiple coordination with the Zn atoms. The C_2-symmetric reaction space constructed by the sterically demanding 9-anthryl groups on the terminal N atoms is suitable for the **1a** arrangement in the *Si*-facial attacking TS (**TS$_{major}$**, Fig. 4i) which leads to the major enantiomer (*R*-**2**). In contrast, the steric repulsion between the 9-anthryl group of **L4** and the Ph group of **1a** destabilizes the *Re*-facial attacking TS (**TS$_{minor}$**, Fig. S1 in SI). Increasing the bulkiness of alkyl α-ketoesters (e.g., **1e**-**h**) would enhance the steric repulsion to destabilize the **TS$_{minor}$** and thus increase the enantioselectivity (Fig. 4ii). In addition to the steric effect, coordinative aryl α-ketoesters (e.g., **1i** and **1l**) would allow the additional coordination with the Zn atom and stabilize **TS$_{major}$** to achieve much higher enantioselectivity in a site-dependent manner. These plausible TS models in good agreement with the experimental results motivated us to further investigate molecular recognition ability of the present multinuclear Zn-bisamidinate catalyst.

The computational TS model predicted a unique chemoselectivity in the competing asymmetric alkylation of α-ketoesters with aldehydes. In spite of the competing or lower reactivity of α-ketoesters than aldehydes,[9] the multinuclear Zn-bisamidinate catalyst was expected to promote the preferential alkylation of α-ketoesters through the multiple coordination with the Zn atoms even in the presence of aldehydes. In fact, the chiral ligands/catalysts previously employed in the asymmetric Et_2Zn addition of aldehydes performed poorly with α-ketoesters. The enantioselective addition of Et_2Zn to an equimolar mixture of **1a** and benzaldehyde **4a** using (-)-MIB [(2*S*)-3-exo-aminoisoborneol] and (*R*)-BINOLate-Ti(O*i*Pr)$_2$ at 0 °C in toluene preferentially afforded the corresponding addition product **5a** from **4a** in 88% yield, 88% ee (*S*) and 74% yield, 58% ee (*R*), respectively.[10] The addition product **2a** from **1a** was obtained only with 5 % and 9%, respectively. On the other hand, in an equimolar mixture of **1a** and **4a**, **L4** achieved exclusive formation of **2a** with retaining the moderate enantioselectivity observed in the single-substrate system (entry 1, Table 4). The sterically less demanding **L1** also exhibited high molecular recognition ability for **1a** albeit with significantly reduced enantioselectivity (entry 2). The trimetallic reactive site would be disturbed by coordination of **4a** to the Zn atoms. This indicates that the 9-anthryl group has an essential role in sterically protecting the trimetallic reactive site in the C_2-symmetric reaction space (Fig. 4). Regardless of keto groups (R) in α-ketoesters **1**, the addition products **2** were obtained with complete chemoselectivity and high enantioselectivity even in the presence of various aldehydes **4** (entries 3-8). The more challenging substrates **6** and **9** having both α-ketoester and formyl substituents was further employed using **L4** (Scheme 1).[11] The α-ketoester group of **6** was preferentially reacted but unfortunately the addition reaction was significantly retarded with reduced enantioselectivity. The electron-withdrawing formyl group electrophilically activates the α-ketoester group through the conjugated monoaryl unit in **6** to promote reduction and uncatalyzed reaction.

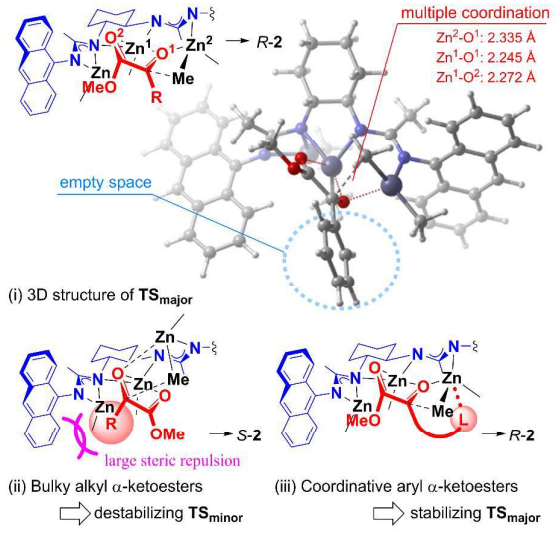
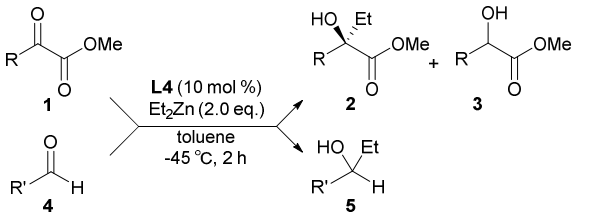


Fig. 4 (i) 3D structure of **TS$_{major}$** and schematic descriptions of (ii) steric effect of **TS$_{minor}$** and (iii) coordination effect of **TS$_{major}$**

Table 4. Chemoselective and enantioselective addition of Et_2Zn to $RCOCO_2Me$ in the presence of R'CHO



Entry	R	R'	2/3 Yield (%)[a]	2 ee (%)[b]	5 Yield (%)[a]
1	Ph (**1a**)	Ph (**4a**)	42 / 41	45	<1
2[c]	Ph (**1a**)	Ph (**4a**)	77 / 23	2	<1
3	*c*-C_6H_{11} (**1g**)	Ph (**4a**)	96 / 0	89	0
4	*c*-C_6H_{11} (**1g**)	*c*-C_6H_{11} (**4g**)	99 / 0	84	0
5	*c*-C_6H_{11} (**1g**)	*o*-$MeSC_6H_4$ (**4l**)	95 / 0	84	0
6	*o*-$MeSC_6H_4$ (**1l**)	Ph (**4a**)	97 / 3	96	0
7	*o*-$MeSC_6H_4$ (**1l**)	*c*-C_6H_{11} (**4g**)	97 / 0	96	0
8	*o*-$MeSC_6H_4$ (**1l**)	*o*-$MeSC_6H_4$ (**4l**)	97 / 3	96	0

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Determined by chiral HPLC. [c] **L1** was used.

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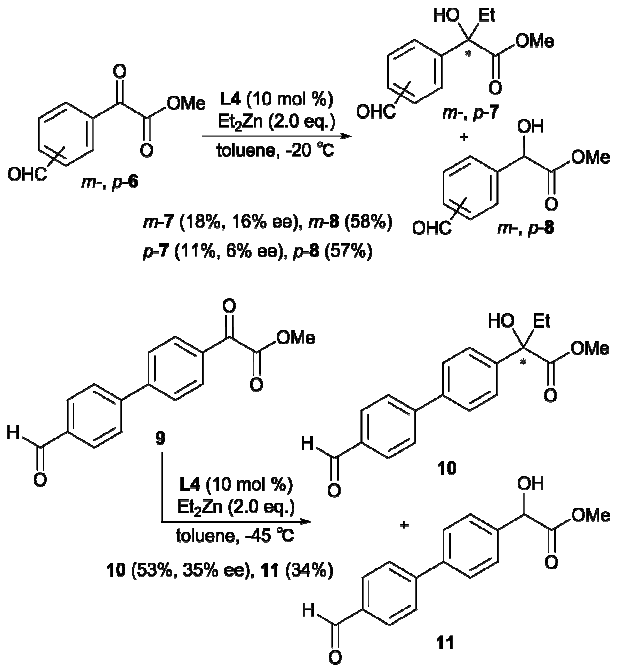

Scheme 1 Designed bisamidine ligands

In **9** built on the biaryl unit, the formyl group was expected to less affect the reactivity of the α-ketoester group. The preferential alkylation of **9** proceeded to afford **10** with the same level of yield and the slightly reduced enantioselectivity as using **2a**. Even though the moderate enantioselectivity, to the best of our knowledge, there is no precedent for the enantioselective addition of Et_2Zn to the α-ketoester group rather than the formyl group in a site-selective manner.

In conclusion, we have developed a newly designed multinuclear Zn-bisamidinate catalyst for the enantioselective addition of Et_2Zn to α-ketoesters. Both the arrangement and the steric tuning of the two amidine moieties are essential for the high catalyst activity and enantioselectivity. The highly coodinative α-ketoesters, in which introduction of OMe or easily removable SMe at the *ortho* position of the Ph group of **1a**, yielded the highest enantioselectivities. The significant site-dependent asymmetric induction is caused by the multiple coordination with the Zn atoms of the catalyst. Furthermore, the multimetallic reactive site exhibited high molecular recognition ability. The preferential alkylation of α-ketoesters even in the presence of aldehydes was achieved. Further studies on the mechanistic detail of the unique chemoselectivity and the application of the chiral multinuclear Zn-bisamidinate catalyst to other catalytic asymmetric reactions are underway.

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