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Asymmetric Synthesis

Catalytic Asymmetric Addition of Diorganozinc Reagents to Pyrazole-4,5-Diones and Indoline-2,3-Diones

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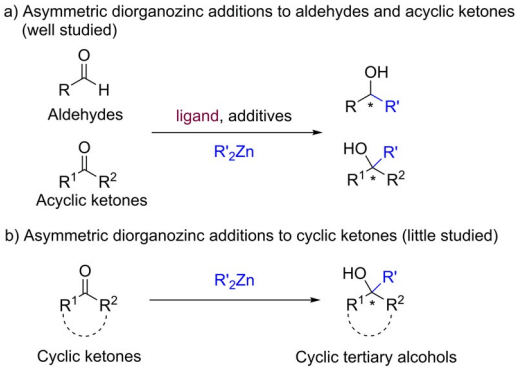
Abstract: The catalytic enantioselective diorganozinc additions to cyclic diketones including pyrazolin-4,5-diones and isatins have been developed. In the presence of morpholine-containing chiral amino alcohol ligand, the corresponding chiral cyclic tertiary alcohols were produced in good to excellent yields (up to 97%) and enantioselectivities (up to 95% *ee*). The notable feature of this protocol includes its mild reaction conditions, Lewis acid additives free and broad functional group tolerance.

Chiral tertiary alcohols represent an important class of frameworks which has been widely exists in a variety of natural products and clinical pharmaceuticals.[1] Besides that, They are also a versatile family of chiral building blocks that are found wide application in synthetic organic chemistry.[2] Therefore, it is of great significance to develop asymmetric new methods for the synthesis of these compounds. In contrast to chiral secondary alcohols, the asymmetric construction of chiral tertiary alcohols remains a great challenge in asymmetric synthesis, due to the less reactive nature of precursors and the decreased enantioface differentiation between the two substituents at prochiral carbon center.[3] Nevertheless, various strategies towards the synthesis of these scaffolds have been disclosed in the last decades. Among them, the asymmetric nucleophilic additions to ketones using organometallic reagents represent one of the most straightforward methods for the production of chiral tertiary alcohols.[4] Diorganozinc reagents were considered as the reagents of choice due to the mild reaction conditions and good tolerance to many functionalities.[5] However, Lewis acid additives are often required for these transformations because of the lowered reactivity of ketones (Scheme 1 a).[6] In addition, the substrate scope is mainly limited to acyclic ketones(Scheme 1 b). Walsh's group reported the first catalytic asymmetric addition of organozinc reagents to cyclic ketones using bis(sulfonamide) diols as chiral ligand with $Ti(O\text{-}iPr)_4$.[7] Since then, little progress has been made in this area. Therefore, the development of effective protocols for the enantioselective diorganozinc addition to cyclic ketones is highly desirable.



Scheme 1. Studies of asymmetric diorganozinc additions to aldehydes and ketones.

Chiral pyrazolones and their derivatives are a unique class of five membered heterocyclic compounds, which have been found diverse applications in medicinal, analytical and dye chemistry, as well as potential utility as chelating agents, photographic couplers and synthetic building blocks.[8] Great efforts have been devoted to the synthesis of these structural motifs.[9] However, the asymmetric version of these transformations, especially the use of pyrazolin-4,5-diones as a C-4 nucleophile, has been rarely studied (Scheme 2 a). In 2018, Enders's group reported the first organocatalytic Friedel–Crafts reaction of pyrazole-4,5-diones with indoles, delivering the indolypyrazolone derivatives in medium to good enantioselectivies.[10] Later on, Mukherjee's group reported a direct organocatalytic asymmetric vinylogous aldol reaction of allyl ketones to pyrazole-4,5-diones.[11] In 2019, Wu reported a copper-catalyzed enantioselective alkynylation of pyrazole-4,5-diones with alkynes.[12] Very recently, Bhat's group developed an asymmetric [3+2] annulation between MBH carbonates derived from isatin and pyrazole-4,5-diones.[13] Inspired by previous reports on

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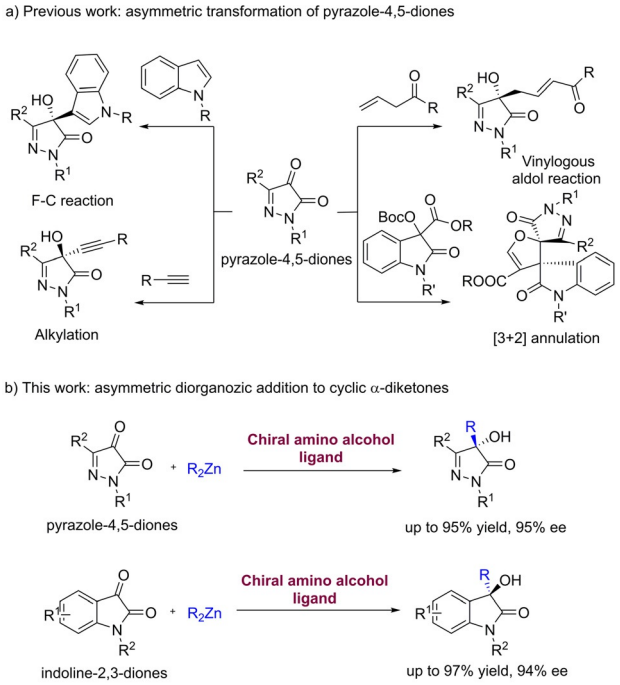
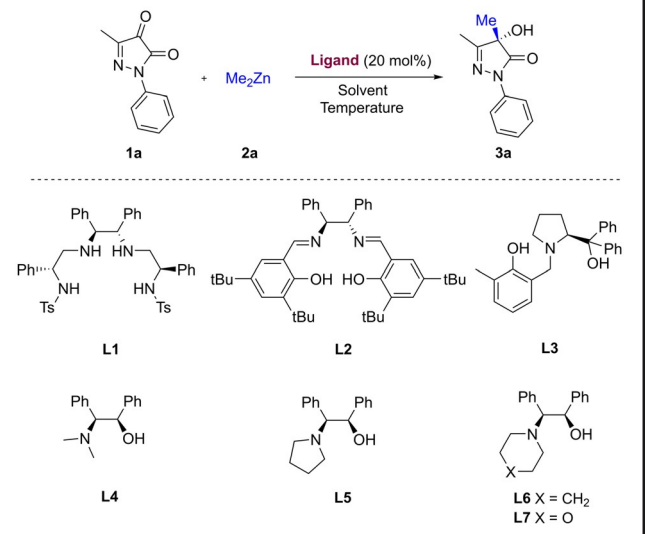


Scheme 2. Asymmetric transformation of pyrazolin-4,5-diones and isatins.

asymmetric nucleophilic addition to pyrazole-4,5-diones, we herein described an asymmetric addition of diorganozinc reagents to pyrazole-4,5-diones by the use of chiral amino alcohol ligand for the construction of optically pure tertiary alcohols (Scheme 2b). In addition, we extended this methodology to the asymmetric diorganozinc addition to isatin derivatives (Scheme 2b).

Initially, the asymmetric addition between pyrazole-4,5-dione **1a** and dimethylzinc **2a** was selected as the model reaction. First, the reaction was performed with 20 mol% of diamine ligand **L1** in CH_2Cl_2 with 2 equivalent of Me_2Zn at 0 °C, the desired chiral tertiary alcohol product **3a** could be obtained in moderate yield and low enantioselectivity (Table 1, entry 1). Changing the chiral ligand **L1** to salen ligand **L2** resulted in a better catalytic activity and stereoselectivity (entry 2). Inspired by the preliminary results, we turned our attention to the use of different chiral amino alcohol ligands for chiral induction. We observed that the reactions performed proceed smoothly to deliver the corresponding product in good to high yields, albeit with moderate enantioselectivities (entries 3–7). Among the amino alcohol ligand tested, morpholine-containing ligand **L7**[14] showed the best results in terms of yield and enantioselectivity (entry 7). Meanwhile, ligand loading had obvious effects on the reaction stereoselectivity. A dramatically decreased *ee* was observed with 10 mol% of ligand **L7** (entry 8). Next, we investigated the reaction temperature and it was found that decreasing the temperature proved to be not beneficial for the stereoselective control (entries 9–10). Finally, we examined the effects of various solvents such as toluene, THF, Et_2O and ethyl acetate (EA), and the results indicated EA was the best solvent, affording the desired product in 95% yield and 95% *ee* (entries 11–14). It is important to note that reducing the amount

Table 1. Optimization of asymmetric dimethylzinc addition to pyrazole-4,5-dione **1a**.[a]

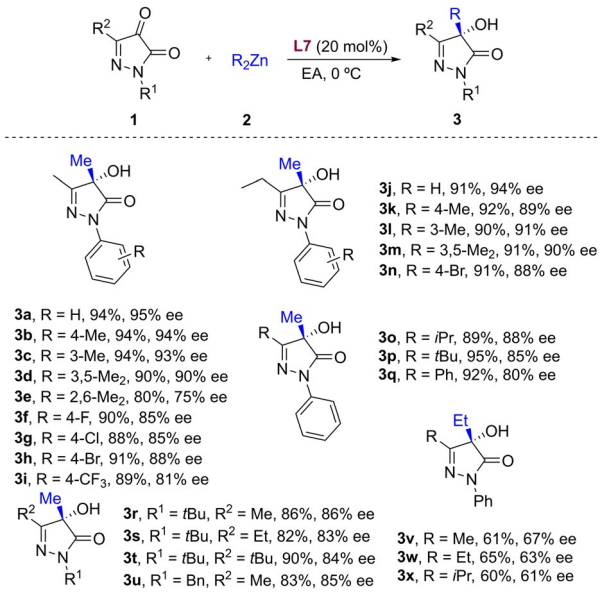


Entry	Ligand	Temp. [°C]	Solvent	Yield [%][b]	*ee* [%][c]
1	**L1**	0	DCM	51	0
2	**L2**	0	DCM	54	9
3	**L3**	0	DCM	69	17
4	**L4**	0	DCM	94	37
5	**L5**	0	DCM	87	53
6	**L6**	0	DCM	89	55
7	**L7**	0	DCM	92	82
8[d]	**L7**	0	DCM	90	45
9[e]	**L7**	−20	DCM	79	57
10[e]	**L7**	−40	DCM	74	27
11	**L7**	0	toluene	89	85
12	**L7**	0	THF	71	82
13	**L7**	0	Et_2O	90	80
14	**L7**	0	EA	95	95
15[f]	**L7**	0	EA	94	95

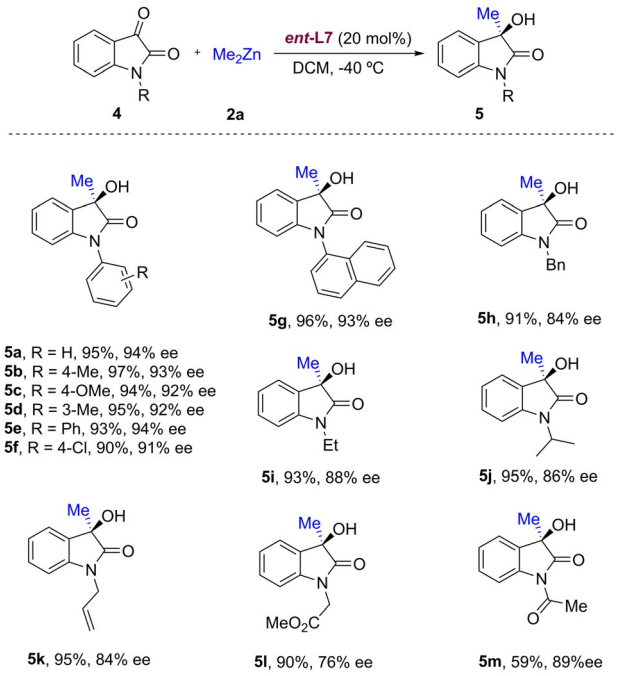
[a] Reaction conditions unless specified otherwise: **1a** (0.1 mmol), **2a** (0.2 mmol), ligand (0.02 mmol), solvent (1.0 mL), 18 h. [b] Isolated yield. [c] The *ee* values were determined by HPLC. [d] 10 mol% of ligand. [e] reaction time is 24 h. [f] 1.5 equiv of **2a** was used, 24 h.

of Me_2Zn to 1.5 equivalent do not influence the yield and enantioselectivity of this reaction (entry 15).

With the optimal reaction conditions in hand, the scope of the enantioselective addition of diorganozinc reagents to various pyrazole-4,5-diones **1** was explored (Scheme 3). First, the reactions of 3-methyl pyrazole-4,5-diones with electron-donating group at 1-aryl proceeded smoothly to afford the chiral tertiary alcohols **3a**–**3d** in excellent yields (90–94%) and enantioselectivities (90–95%), while product **3e** was obtained in lower yield and stereoselectivity due to steric effect. In addition, slightly lower yield and *ee* (**3f**–**3i**, 88–91%, 81–88% *ee*) were generated when substrates bearing electron-withdrawing group at 1-aryl were applied. 3-ethyl pyrazole-4,5-dione with different substituents at 1-aryl also worked well in identical reaction conditions, affording the corresponding products **3j**–**3n** in up to 92% yield and 94% *ee*. Next, other substituents at C3-position of pyrazole-4,5-dione **1** such as isopropyl, *tert*-butyl and phenyl were examined, giving the corresponding prod-



Scheme 3. Substrate scope of the asymmetric diorganozinc additions to pyrazole-4,5-dione **1**. Reaction conditions: 0.2 mmol of **1**, 1.5 equiv of **2**, 20 mol% of **L7**, EA, 0 °C, 12–24 h.



Scheme 4. Substrate scope of the asymmetric dimethylzinc additions to *N*-substituted isatin **4**. Reaction conditions: 0.2 mmol of **4**, 2.0 equiv of **2**, 20 mol% of ***ent*-L7**, DCM, −40 °C, 20–36 h.

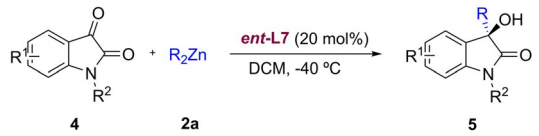
ucts **3o–3q** in high yields (89–95%) and enantioselectivities (80–88%). Furthermore, alkyl analogues at C1-position were also tolerated in this reaction, although a relatively low *ee* were obtained (**3r-3u**, 82–90%, 83–86% *ee*). Finally, we tested the Et_2Zn addition to prochiral ketone **1**. To our delight, the desired tertiary alcohols **3v–3x** bearing ethyl group could be obtained in moderated yield and enantioselectivity. Our repeated attempts to use other diorganozinc reagents were unsuccessful, only very low enantioselectivity could be generated (see details in Supporting Information). The chiral tertiary alcohols were assigned to the *S*-configuration, based on the X-ray analysis of the single crystal of product **3a**.

To further demonstrate the synthetic utility of this methodology, we extended the substrate scope to the synthesis of 3-substituted-3-hydroxy-2-oxindoles, which is present in various natural products and biological compounds.[15] Arundaphine, convolutamydine C, maremycin B and paratunamide D are representative examples of a growing list of bioactive natural products.[15d] Especially, there are few methods for the catalytic asymmetric synthesis of chiral 3-hydroxy-3-methyl-2-oxindoles in previous report.[16] Shibashaki[16d] and Pedro's group[16e] reported the enantioselective addition of Me_2Zn to isatins catalyzed by proline-derived aminodiol and α-hydroxyamides ligand, respectively, and only moderate *ee* values were obtained. We performed the reaction between *N*-substituted isatins **4** and Me_2Zn in the presence of DCM at −40 °C. Most of the isatin derivatives reacted smoothly with Me_2Zn to afford the corresponding 3-hydroxy-3-methyl-2-oxindoles **5** in excellent yields with excellent enantioselectivities (Scheme 4). For example, either electron-donating or withdrawing group of the phenyl ring at *N*-aryl position were compatible under the optimized conditions to give the desired product **5a–5f** in 90–97% yields and 91–94% *ee*. Other *N*-substituted electron-donating groups, such as 1-naphthyl, benzyl, ethyl, et al were also tolerated in this reaction, providing diverse 3-hydroxy-3-methyl-2-oxindoles **5g–5l** in excellent yield and high enantioselectivities. However, when the protecting group was electron-withdrawing group such as acetyl, the product **5m** was obtained in moderate yield, albeit with high *ee*. The absolute configuration of **5** was determined by comparison to reported literature.[16e]

Next, the effect of substitution on the benzene ring of *N*-phenyl protected isatins **4** was evaluated (Table 2). In general, electron-donating group at different position on the benzene ring afforded the desired products in higher enantioselectivities in comparison with the electron-withdrawing group (entries 1–6). Very importantly, we observed that other diorganozinc reagents such as Et_2Zn and nBu_2Zn were also tolerated in this reaction, although a slightly lower yields and enantioselectivities were obtained (entries 7–10).

In order to understand the mechanism of this reaction, a non-linear effect (NLE) study was conducted. The enantiopurities of the products were evaluated using various chiral amino ligands **L7** with 20%, 40%, 60% and 80% *ee*, respectively, and a (+)-NLE was observed in this study (see detailed results in Supporting Information). Based on the previous report[6f,17] and the NLE studies, we proposed a plausible catalytic mechanism of this reaction. As shown in Scheme 5, amino alcohol **L7** is deprotonated to form a zinc aminoalkoxide species which could further coordinates to pyrazole-4,5-diones **1**. In addition, another molecular of Me_2Zn might coordinate with oxygen atom, resulting in a *si*-face attack of Me_2Zn through a six-membered transition-state. The outcome of the diorganozinc addition of

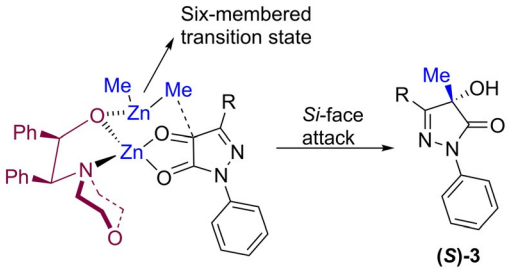
Table 2. Substrate scope of the asymmetric diorganozinc additions to substituted isatin **4**.[a]



4 **2a** **5**

Entry	R^1	R^2	R	Yield [%][b]	*ee* [%][c]
1	5-Me	Ph	Me	**5n**, 95	90
2	5-OMe	Ph	Me	**5o**, 92	88
3	5,7-Me_2	Ph	Me	**5p**, 96	92
4	5-F	Ph	Me	**5q**, 92	89
5	5-Cl	Ph	Me	**5r**, 95	76
6	6-Cl	Ph	Me	**5s**, 90	87
7	H	Bn	Et	**5t**, 75	80
8	6-Cl	Bn	Et	**5u**, 77	79
9	5-OMe	Bn	Et	**5v**, 72	69
10	H	Ph	*n*Bu	**5w**, 62	70

[a] Reaction conditions: 0.2 mmol of **4**, 2.0 equiv of **2**, 20 mol% of *ent*-**L7**, DCM, −40 °C, 20–36 h. [b] Isolated yields. [c] The *ee* values were determined by HPLC.



Scheme 5. Plausible transition state for the diorganozinc addition to pyrazole-4,5-diones.

isatins **4** could also be explained by the similar transition model.

In conclusion, the asymmetric additions of diorganozinc reagents to cyclic ketones including pyrazole-4,5-diones and substituted isatins were achieved without any additives. In the presence of a chiral amino alcohol ligand **L7** under mild conditions, a wide range of highly functionalized tertiary alcohol products with pyrazolone and 2-oxindole motifs could be obtained in excellent yields (up to 97% yield) and high to excellent enantioselectivities (up to 95% *ee*). This methodology provides an efficient approach for the asymmetric addition of diorganozinc reagents to the challenging cyclic ketones. Studies toward clarifying the detained reaction mechanism are under way in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chiral amino alcohol · diorganozinc addition · indoline-2,3-diones · pyrazole-4,5-diones

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