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Asymmetric Ring Opening/Cyclization/Retro-Mannich Reaction of Cyclopropyl Ketones with Aryl 1,2-Diamines for the Synthesis of Benzimidazole Derivatives

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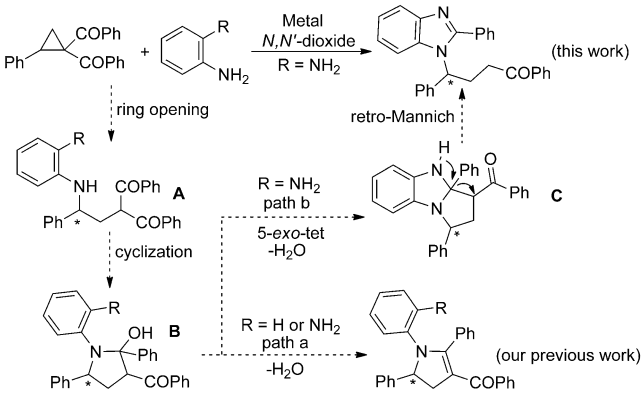
Abstract: *A highly efficient asymmetric ring-opening/cyclization/retro-Mannich reaction of cyclopropyl ketones with aryl 1,2-diamines has been realized using a chiral N,N′-dioxide/Sc^{III} catalyst. Benzimidazoles containing chiral side chains were generated under mild reaction conditions in excellent outcomes (up to 99% yield and 97% ee). This method also provides efficient access to chiral benzimidazole-substituted amide and cycloheptene derivatives.*

Benzimidazoles, particularly bearing chiral side chains, are ubiquitously found in natural products and biologically active compounds.[1] Consequently, substantial efforts have been dedicated to developing efficient methods toward their preparation.[2] The most common synthetic strategies are focused on the construction of benzimidazole backbones by using chiral precursors.[3] With regard to the catalytic asymmetric transformation, several successful examples involving the direct enantioselective functionalization of prochiral benzimidazole compounds have been developed by the groups of Hartwig,[4] Guo,[5] and Terada.[6] However, these strategies often require additional steps to prepare either the chiral precursors or prochiral benzimidazoles. Thus, discovery of a new strategy for constructing benzimidazole backbones and simultaneously establishing stereochemistry in their side chains is highly desirable.

Donor–acceptor (D–A) cyclopropanes[7] have been recognized as one of most useful reagents able to generate polyfunctional reactive intermediates through a ring-opening process. In the last decade, the use of D–A cyclopropanes for the preparation of open-chain 1,3-bifunctionalized, carbocyclic and heterocyclic scaffolds has experienced a renaissance.[8–13] And many reports on the enantioselective nucleophilic ring-opening reactions of D–A cyclopropanes have appeared. Recently, our group has demonstrated that a chiral *N,N′*-dioxide/Sc^{III} complex[14] was able to catalyze the ring-opening reaction of cyclopropyl ketones with amines efficiently, thus generating chiral 2,3-dihydropyrroles in excellent results. The process is thought to proceed through nucleophilic ring opening of the cyclopropyl ketone to generate **A**, then intramolecular nucleophilic addition to afford the intermediate **B**, with subsequent dehydration to give the 2,3-dihydropyrrole product (path a, Scheme 1).[8a,h,k]



Scheme 1. Proposed pathway for the synthesis of benzimidazoles.

Inspired by these results, we recently questioned whether it is possible to capture **B** by using another nucleophilie. We envisaged that if 1,2-diaminobenzene was used as a nucleophilie, the capture process might be brought to fruition through a 5-*exo*-tet cyclization[15] to give **C**, and would be facilitated by the good leaving ability of water (path b, Scheme 1). And then, **C** could undergo retro-Mannich[16] reaction to deliver the benzimidazole. Thus, a straightforward synthetic method for enantioenriched benzimidazole derivatives through a catalytic asymmetric ring opening/cyclization/retro-Mannich sequence of cyclopropyl ketones with benzene-1,2-diamines might be realized. It was noteworthy that the dehydration of **B** to give chiral 2,3-dihydropyrrole might be a competitive process (path a). Herein, we describe our efforts on developing a new ring-opening/cyclization/retro-Mannich reaction of cyclopropyl ketones with benzene-1,2-diamines in the presence of a chiral *N,N′*-dioxide/metal complex as the catalyst for the enantioselective synthesis of benzimidazole derivatives.

To evaluate our hypothesis, the cyclopropyl ketone **1a** and *o*-diaminobenzene (**2a**) were reacted in the presence of a chiral *N,N′*-dioxide metal complex (Table 1). To our delight, when Sc(OTf)$_3$ complexed with L-PiPr$_3$, derived from (*S*)-pipecolic acid, was used, the ring-opening/cyclization/retro-Mannich reaction occurred. And the benzimidazole **3aa** was generated in 95% yield with 91% *ee* as expected, without the

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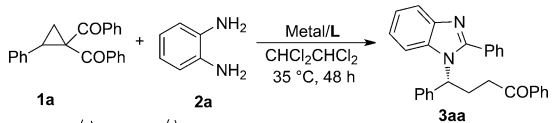
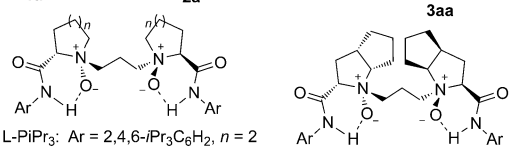
Table 1: Optimization of the reaction conditions.[a]





L-PiPr$_3$: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$, *n* = 2
L-PrPr$_3$: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$, *n* = 1
L-PiPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, *n* = 2

L-RaPr$_3$: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$

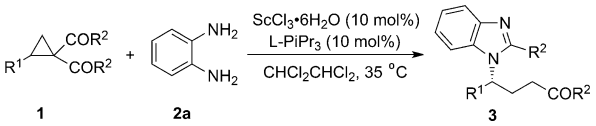
Entry	Metal	L	Yield [%][b]	*ee* [%][c]
1	$Sc(OTf)_3$	L-PiPr$_3$	95	91
2	$Yb(OTf)_3$	L-PiPr$_3$	83	48
3	$Ni(ClO_4)_2{\cdot}6H_2O$	L-PiPr$_3$	trace	n.d.
4	$ScCl_3{\cdot}6H_2O$	L-PiPr$_3$	97	95
5	$ScCl_3{\cdot}6H_2O$	L-RaPr$_3$	<5	40
6	$ScCl_3{\cdot}6H_2O$	L-PrPr$_3$	33	82
7	$ScCl_3{\cdot}6H_2O$	L-PiPr$_2$	95	89

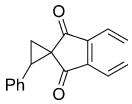
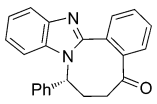
[a] Unless otherwise noted, all reactions were carried out with **1a** (0.22 mmol), **2a** (0.1 mmol), **L**/metal (1:1, 10 mol%) in $CHCl_2CHCl_2$ (0.5 mL) under nitrogen at 35 °C for 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. OTf = trifluoromethanesulfonate.

observation of the 2,3-dihydropyrrole side product (entry 1). Further investigation with other metal salts led to poorer results (entries 2 and 3). Then the counterion of the metal salts was evaluated. Pleasingly, when $ScCl_3{\cdot}6H_2O$ was used, a slight improvement on the reactivity and enantioselectivity was observed (entry 4). Next, the structure of ligand was investigated. It was found that the steric hindrance of the amide moieties as well as the amino-acid backbone of the ligand influenced the reaction greatly. Decreasing the steric bulk of the amide substituent, or either using the L-ramipril-derived L-RaPr$_3$ or (*S*)-proline-derived L-PrPr$_3$ as ligands resulted in poorer outcomes (entries 5–7). Thus, the optimized reaction conditions entailed the use of L-PiPr$_3$/$ScCl_3{\cdot}6H_2O$ as the catalyst in $CHCl_2CHCl_2$ at 35 °C for 48 hours (entry 4).

The substrate with respect to the cyclopropyl ketones was investigated under the optimized reaction conditions. As summarized in Table 2, the reaction was suitable for a variety of cyclopropyl ketones, and excellent levels of reactivity and enantioselectivity were achieved. Cyclopropyl ketones with either electron-rich or electron-poor substituted aryl groups (R^1) at the 2-position were efficiently converted into the corresponding products with excellent results (entries 1–9). For the dichloro-substituted substrate **1j**, a prolonged reaction time was needed and the corresponding product was obtained in 84% yield with 94% *ee* (entry 10). In addition, naphthyl-substituted substrates were suitable for this reaction, thus producing the desired products with excellent results (entries 11 and 12). Notably, a vinyl-substituted cyclopropane was also compatible in this catalytic system, and the product was isolated in good yield with excellent enantioselectivity (entry 13). However, when the aliphatic-substituted cyclopropyl ketone **1n** was submitted to this catalytic system, only trace amounts of the product were observed. By using

Table 2: Substrate scope with respect to the cyclopropyl ketones.[a]



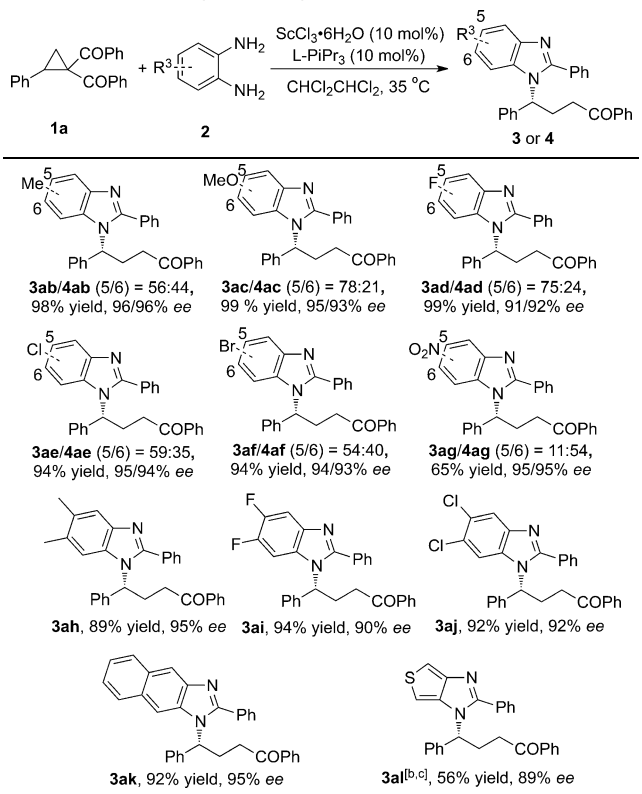
Entry	R^1, R^2	3	Yield [%][b]	*ee* [%][c]
1	Ph, Ph (**1a**)	**3aa**	97	95
2	4-MeC$_6$H$_4$, Ph (**1b**)	**3ba**	98	95
3	4-MeOC$_6$H$_4$, Ph (**1c**)	**3ca**	99	89
4	4-FC$_6$H$_4$, Ph (**1d**)	**3da**	96	94
5[d]	4-ClC$_6$H$_4$, Ph (**1e**)	**3ea**	94	95 (*R*)
6	4-BrC$_6$H$_4$, Ph (**1f**)	**3fa**	96	94
7	3-MeC$_6$H$_4$, Ph (**1g**)	**3ga**	94	94
8	3-ClC$_6$H$_4$, Ph (**1h**)	**3ha**	87	95
9	2-MeC$_6$H$_4$, Ph (**1i**)	**3ia**	96	80
10[e]	3,4-Cl$_2$C$_6$H$_3$, Ph (**1j**)	**3ja**	85	94
11	1-naphthyl, Ph (**1k**)	**3ka**	96	92
12	2-naphthyl, Ph (**1l**)	**3la**	97	93
13[e]	vinyl, Ph (**1m**)	**3ma**	86	90
14[f,g]	Me, Ph (**1n**)	**3na**	73	86
15	Ph, 4-MeC$_6$H$_4$ (**1o**)	**3oa**	92	97
16	Ph, 4-FC$_6$H$_4$ (**1p**)	**3pa**	98	97
17[f]	 (**1q**)	 **3qa**	98	62
18[h]	Ph, Ph (**1a**)	**3aa**	98	94

[a] Unless otherwise noted, all reactions were performed with **1** (0.22 mmol), **2a** (0.1 mmol), L-PiPr$_3$ (10 mol%), and $ScCl_3{\cdot}6H_2O$ (10 mol%) in $CHCl_2CHCl_2$ (0.5 mL) under nitrogen at 35 °C for 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration was determined to be *R* by X-ray analysis.[17] [e] Reaction time was 96 h. [f] $Sc(OTf)_3$ (10 mol%) was used instead of $ScCl_3{\cdot}6H_2O$ and LiCl (0.1 mmol) was used as additive. [g] At 60 °C for 96 h. [h] The reaction was carried out on a gram scale.

$Sc(OTf)_3$ instead of $ScCl_3{\cdot}6H_2O$ and using LiCl as the additive, the reactivity increased and **3na** was generated in 73% yield with 86% *ee* (entry 14). The electronic nature of the *para*-substituted benzoyl group at the 1-position of cyclopropanes had no obvious influence on the outcomes (entries 15 and 16). Remarkably, the spirocyclopropane **1q** also proved to be a viable substrate, thus delivering the eight-membered ring product **3qa** in 98% yield with 62% *ee* (entry 17). This method provides promising access to chiral eight-membered N-heterocyclic motifs. However, no benzimidazole product was observed when 2-phenyl-cyclopropane-1,1-dimethylketones were used. In addition, the absolute configuration of **3ea** was determined to be *R* by X-ray crystallography.[17] Furthermore, when the reaction of **1a** with **2a** was carried out on a gram scale, **3aa** was isolated with results similar to those obtained on milligram scale (entry 18 vs. entry 1).

Next, the spectrum of *o*-diaminobenzenes was probed and the results are listed in Table 3. Generally, good to excellent yields and excellent enantioselectivities were obtained for both electron-donating and electron-withdrawing substituents on the aryl groups (**3ab–aj**, **4ab–ag**). Remarkably,

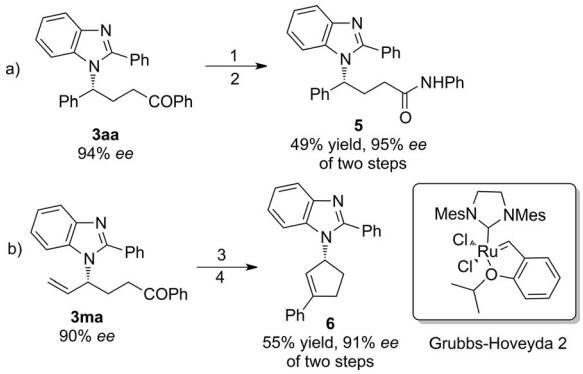
Table 3: Substrate scope with respect to *o*-diaminobenzenes.[a]



[a] Unless otherwise noted, all reaction conditions were the same as detailed in Table 2. The ratio of **3**/**4** (products derived from substitutions at either the 5- or 6-positions, respectively) was determined for the isolated products except for that of **3ab**/**4ab**, which was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] $Sc(OTf)_3$ (10 mol%) was used instead of $ScCl_3{\cdot}6H_2O$ and LiCl (0.1 mmol) was used as additive. [c] At 60°C for 96 h.

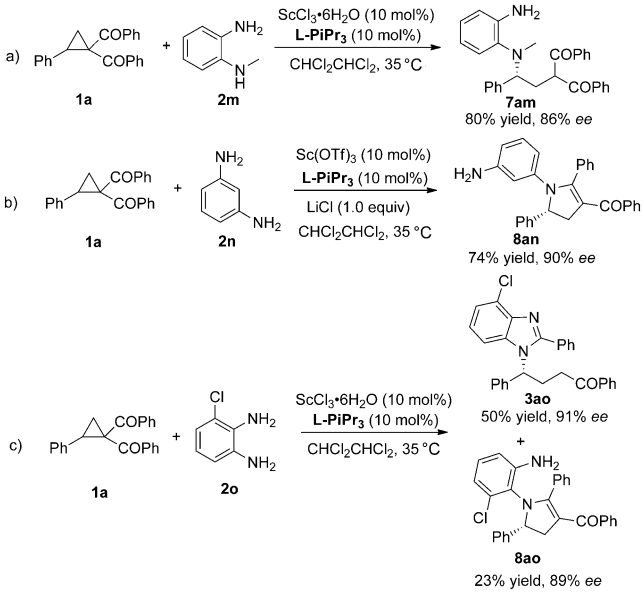
regioselectivities were discovered when unsymmetric substituted *o*-diaminobenzenes were examined. The regioisomers of MeO-, F-, Cl-, Br-, and NO_2-substituted benzimidazoles were distinguished well and they could be separated by flash chromatography on silica gel (**3ac**–**ag**, **4ac**–**ag**), but the Me-substituted substrate offered an inseparable mixture (**3ab**, **4ab**). For the symmetric substituted *o*-diaminobenzenes, both electron-rich and electron-deficient substituents gave excellent results (**3ah**–**aj**). When a naphthyl-substituted substrate was employed, an excellent result (92% yield, 95% *ee*) was obtained. Heteroaryl thiophene-3,4-diamine also reacted with the cyclopropyl ketone to generate the chiral thienoimidazole derivative **3al** in 89% *ee*, albeit with a moderate yield (56%), by employing the $Sc(OTf)_3$/LiCl catalytic system. Ethane-1,2-diamine and cyclohexane-1,2-diamine were also investigated, however, no ring opening/cyclization/retro-Mannich products were observed.

To evaluate the synthetic potential of the methodology, additional transformations were carried out. The benzimidazole derivative **3aa** was easily transformed into the amide **5** in moderate yield and high enantioselectivity through an oximation/Beckmann rearrangement sequence (Scheme 2a). Meanwhile, the cycloheptene compound **6** was obtained by a Wittig olefination of **3ma**, followed by ring-closing metathesis in the presence of the Grubbs–Hoveyda second-generation catalyst (Scheme 2b).



Scheme 2. a) Transformation of **3aa** into **5**: 1) $NH_2OH{\cdot}HCl$, pyridine, EtOH; 2) PCl_5, toluene, 0°C. b) Transformation of **3ma** into **6**: 3) $[Ph_3PCH_3]^+I^-$, *n*BuLi, THF, reflux; 4) Grubbs-Hoveyda 2 (20 mol%), toluene, 105°C.

To gain some insight on the mechanism of this reaction, several control experiments were carried out. Firstly, the direct ring-opening product **7am** was generated in 80% yield when *N*-methyl-1,2-benzenediamine (**2m**) was employed (Scheme 3a), thus indicating that ring-opening might be the first step (Scheme 1). When *m*-diaminobenzene was used, only the 2,3-dihydropyrrole **8an** was isolated (Scheme 3b). It revealed that the two amino groups should be installed at a suitable position to undergo 5-*exo*-tet cyclization. Notably, when 3-chlorobenzene-1,2-diamine was subjected to this catalytic system, the 4-chloro-substituted benzimidazole **3ao** was obtained along with the formation of the 2,3-dihydropyrrole **8ao** (Scheme 3c), which suggested that the reaction might proceed via the formation of intermediate **B** (Scheme 1).[18]



Scheme 3. Control experiments.

In summary, we have accomplished the first asymmetric ring opening/cyclization/retro-Mannich reaction of cyclopropyl ketones with *o*-diaminobenzenes to construct benzimidazoles and simultaneously establish stereochemistry in their side chains. A chiral *N*,*N*′-dioxide/Sc^{III} complex could efficiently accelerate the asymmetric process, and the corresponding benzimidazoles were obtained in moderate to excellent yields (up to 99%) with excellent enantioselectivities (up to 97% *ee*). The process proceeds under mild reaction conditions and exhibits broad substrate scope. Additional studies on related reactions are underway.

Experimental Section

Reaction conditions: $ScCl_3{\cdot}6H_2O$ (0.01 mmol), L-$PiPr_3$ (0.01 mmol) and the cyclopropyl ketone **1a** (0.22 mmol) were stirred in $CHCl_2CHCl_2$ (0.5 mL) at 35 °C for 0.5 h under nitrogen atmosphere. Then **2a** (0.1 mmol) was added. The reaction was stirred at 35 °C for 48 h, and then directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford the desired product **3aa** (97% yield, 95% *ee*.).

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Keywords: asymmetric catalysis · enantioselectivity · heterocycles · scandium · small ring systems

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[17] CCDC 1414840 (**3ea**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[18] For more details, see the Supporting Information.

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