Heterocycle Synthesis

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Asymmetric Dearomatization of Indoles through a Michael/Friedel–Crafts-Type Cascade To Construct Polycyclic Spiroindolines**

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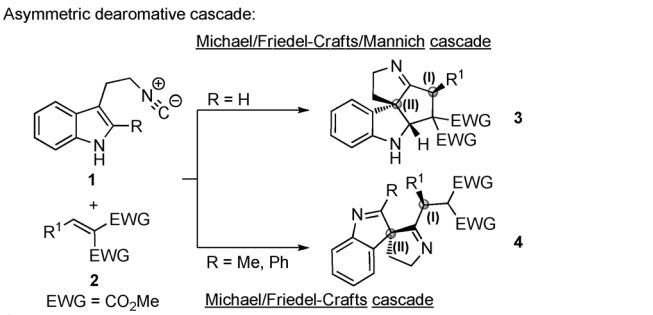
Abstract: *A highly efficient asymmetric dearomatization of indoles was realized through a cascade reaction between 2-isocyanoethylindole and alkylidene malonates catalyzed by a chiral N,N′-dioxide/Mg^{II} catalyst. Fused polycyclic indolines containing three stereocenters were afforded in good yields with excellent diastereo- and enantioselectivities through a Michael/Friedel–Crafts/Mannich cascade. When 2-substituted 2-isocyanoethylindoles were used, spiroindoline derivatives were obtained through a Michael/Friedel–Crafts reaction.*

The spiroindoline unit is a privileged heterocyclic substructure in a series of natural products and biologically active compounds.[1] The desire to build such appealing polycyclic skeletons with complete control over their stereochemistry has inspired the development of numerous efficient synthetic strategies.[2] Cascade reactions are an attractive topic in organic synthesis because of the rapid construction of molecular complexity from simple starting materials.[3] Particularly with the indole substrates, a dearomative cascade annulation is efficient for novel polycyclic spiroindoline compounds. A number of chemo-, regio-, and enantioselective methods have been used to modify and dearomatize the indole unit.[4–8] You and co-workers have made significant contributions to the catalytic enantioselective dearomatization of indoles, thus affording a series of enantioenriched indoline derivatives.[9] The group of MacMillan has discovered the iminium catalysis for asymmetric construction of various complex alkaloids through a dearomative process.[6]

Isocyanides are versatile precursors which are used widely in cascade reactions to synthesize heterocyclic compounds.[10] 2-Isocyanoethylindole[11] bearing a pendant nucleophilic isocyanide at the C3-position of the indole serves as a readily available starting material and has potential as a precursor for spiroindolines having multiple stereocenters (Scheme 1).



Scheme 1. Asymmetric dearomative cascade of 2-isocyanoethylindole.

Chemoselective synthesis of spiroindolines and pyrroles have been achieved by using a 2-isocyanoethylindole-based cascade reaction.[12] Developing an enantioselective catalytic version of this synthetic strategy towards these scaffolds is lacking and interesting. In view of only a single diastereoisomer of polycyclic spiroindoline formed in the cascade reaction,[12] we surmise that the initial stereocenter generated by an asymmetric Michael reaction would direct the enantioselective dearomative annulation, thus yielding the desired spiroindoline with high stereoselectivity, even if the first stereocenter disappeared in the end.[12] Additionally, the rational choice of a Michael acceptor is critical because of both background reactions and stereoselection. The reaction performed well under catalyst-free conditions when the malononitrile-derived acceptors were employed (EWG = CN; Scheme 1).[12a] The reactivity decreased quite a bit after one ester group was introduced.[12b] As a key design element, the alkylidene malonates incorporated a bidentate carbonyl group (EWG = ester) to provide an opportunity to coordinate chiral Lewis acid catalysts for both activation and stereocontrol.[13c,f] Our group has successfully realized a number of highly efficient asymmetric reactions by the privileged *N,N′*-dioxide/metal complex catalysts.[13] To construct enantiopure polycyclic frameworks, we developed the catalytic asymmetric dearomative cascade reactions of 2-isocyanoethylindole and alkylidene malonates. A readily available chiral *N,N′*-dioxide/$Mg(OTf)_2$[13g,h] complex afforded the fused polycyclic indolines and spiroindolines through Michael/Friedel–Crafts-type cascades, and moderate to high yield, as well as excellent diastereo- and enantioselectivity were achieved under mild reaction conditions.

In the initial study, we chose diethyl 2-benzylidenemalonate (**2a**) and 2-isocyanoethylindole (**1a**) as the model substrates. The performance of metal salts combined with the chiral *N,N′*-dioxide ligand L-$PrPr_2$ was evaluated (Table 1, entries 1–3). To our delight, the alkaline-earth metal sources,

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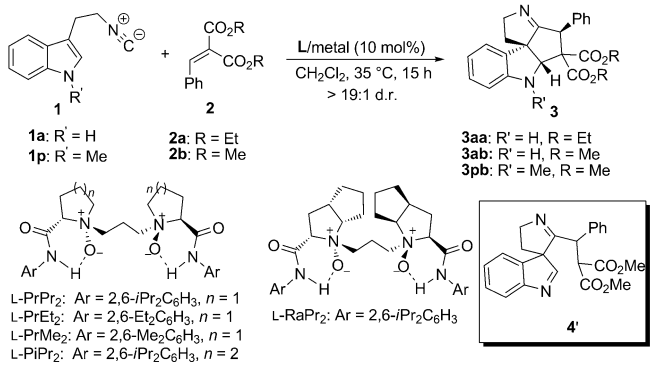
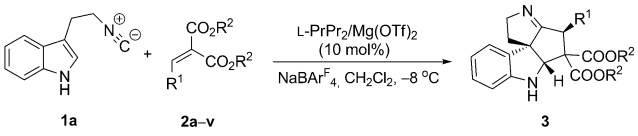
Table 1: Optimization of the reaction conditions.[a]



Entry	Metal salts	L	Additive	Yield [%][b]	*ee* [%][c]
1	$Ba(OTf)_2$	L-$PrPr_2$	–	24	69
2	$Ca(OTf)_2$	L-$PrPr_2$	–	50	38
3	$Mg(OTf)_2$	L-$PrPr_2$	–	97	76
4	$Mg(OTf)_2$	L-$PrEt_2$	–	60	63
5	$Mg(OTf)_2$	L-$PrMe_2$	–	67	42
6	$Mg(OTf)_2$	L-$PiPr_2$	–	61	67
7	$Mg(OTf)_2$	L-$RaPr_2$	–	48	76
8[d]	$Mg(OTf)_2$	L-$PrPr_2$	–	30	85
9[d,e]	$Mg(OTf)_2$	L-$PrPr_2$	$NaBAr^F_4$	60	91
10[e,f]	$Mg(OTf)_2$	L-$PrPr_2$	$NaBAr^F_4$	63	92
11[e,f,g]	$Mg(OTf)_2$	L-$PrPr_2$	$NaBAr^F_4$	65	93
12[e,f,h]	$Mg(OTf)_2$	L-$PrPr_2$	$NaBAr^F_4$	54	57

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), and **L**/metal (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) under nitrogen at 35°C for 15 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] At 0°C for 24 h. [e] 20 mol% $NaBAr^F_4$ was added. [f] At −8°C for 40 h. [g] **1a** and **2b** were used. [h] **1p** and **2b** were used.

Table 2: Substrate scope of the alkylidene malonates **2**.[a]



Entry	R^1	R^2	**3**	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	Me	**3ab**	40 (72)[d]	65 (74)[d]	93 (90)[d]
2	Ph	Et	**3aa**	40	63	92
3	Ph	Bn	**3ac**	40	61	90
4	4-FC_6H_4	Me	**3ad**	40	74	91
5	3-ClC_6H_4	Me	**3ae**	40	75	87
6	4-ClC_6H_4	Me	**3af**	40 (72)[d]	76 (84)[d]	94 (90)[d]
7	3,4-$Cl_2C_6H_3$	Me	**3ag**	40	78	90
8	3-BrC_6H_4	Me	**3ah**	40	71	84
9	4-BrC_6H_4	Me	**3ai**	40 (72)[d]	77 (82)[d]	93 (90)[d]
10	4-$O_2NC_6H_4$	Me	**3aj**	40	90	90
11	4-$F_3CC_6H_4$	Me	**3ak**	40	87	90
12	3-MeC_6H_4	Me	**3al**	50	61	92
13	4-MeC_6H_4	Me	**3am**	40	64	94
14	3-$MeOC_6H_4$	Me	**3an**	50	53	91
15	3-$PhOC_6H_4$	Me	**3ao**	40	71	85
16	4-$PhOC_6H_4$	Me	**3ap**	40	70	90
17	4-PhC_6H_4	Me	**3aq**	40	63	95
18	4-$BnOC_6H_4$	Me	**3ar**	40 (72)[d]	51 (60)[d]	94 (90)[d]
19	2-naphthyl	Me	**3as**	40	45	91
20	3-thienyl	Et	**3at**	40	64	94
21	cyclohexyl	Et	**3au**	40	97	81
22	*i*Pr	Et	**3av**	40	98	81

[a] **1a**, **2** (1.5 equiv) and $NaBAr^F_4$ (20 mol%), L-$PrPr_2$/$Mg(OTf)_2$ (1:1, 10 mol%) in CH_2Cl_2 under N_2 at −8°C. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Data within parentheses are the result of using $NaNTf_2$ instead of $NaBAr^F_4$ at 0°C for 72 h (see the Supporting Information for details).

which are abundant and display low toxicity, accelerated the Michael/Friedel–Crafts/Mannich cascade enantioselectively. Specifically, the L-$PrPr_2$/$Mg(OTf)_2$ complex catalyzed the asymmetric dearomatization of **1a**, and the desired product **3aa** was obtained in 97% yield and 76% *ee*, and only a single diastereomer was detected. By decreasing the steric hindrance of amide substituents of the ligand, as well as using L-$PiPr_2$ and L-$RaPr_2$, led to poor outcomes (entries 4–7). Running the reaction at 0°C resulted in dramatic loss of reactivity (entry 8). To promote the enantioselectivity of the reaction, we investigated $NaBAr^F_4$ as an additive, which could be used for the exchange of the counterion.[14] The addition of $NaBAr^F_4$ resulted in a dramatic improvement of the *ee* value to 91% (entry 9). Furthermore, further reduction of the temperature to −8°C and changing the ethyl ester of substrate **2** into a methyl ester resulted in further improvement (entry 11). The reduced yield of the desired product is due to the generation of the spiroindoline intermediate **4′** and a small amount of unknown byproducts. Notably, the N-methyl protected 2-isocyanoethylindole **1p** was employed to afford the desired adduct with only 57% *ee* (entry 12).

With the reaction standard conditions established (Table 1, entry 11), the substrate scope was explored (Table 2). A wide range of alkylidene malonates participated in the reaction with **1a**, thus affording the corresponding fused polycyclic products in moderate to good yields with satisfactory enantioselectivities. Nearly one diastereomer was detected in these cases. Varying the ester group of alkylidene malonates (**2a–c**) had no adverse effect on the yield and selectivity (entries 1–3). It was found that the electronic nature and position of the substituents on the aryl group of the alkylidene malonates **2** had a slight influence on the enantioselectivity and yield. Meanwhile, *meta*-substituted substrates gave the desired products with slightly lower enantioselectivity (entries 5, 8, and 15). Higher yield was observed with substrates containing electron-withdrawing groups than those containing electron-donating ones (entries 4–11 versus entries 12–18). Notably, fused-ring (**2s**) and heteroaromatic (**2t**) substrates also reacted well, thus affording the corresponding products in excellent enantioselectivity (entries 19 and 20). To our delight, the substrates **2u** and **2v**, derived from aliphatic aldehydes, were also tolerated and gave the desired products with excellent yields and high *ee* values (entries 21 and 22).

With the results in hand, we then investigated the scope with respect to a series of 2-isocyanoethylindole derivatives (Scheme 2). Both the indole derivatives with electron-withdrawing and electron-donating substituents were tolerated and gave the corresponding products (**3bf–kf**) with excellent enantioselectivities. Remarkably, the racemic substrate having a methyl group at the α-position of the isocyanides underwent the reaction smoothly, thus affording the desired spiroindolines **3lf** and **3lu** with moderate diastereoselectivity

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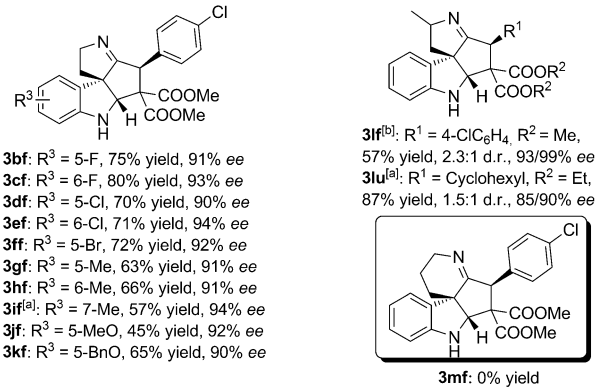


Scheme 2. Substrate scope of the 2-isocyanoethylindole derivatives. [a] The reaction was performed at −20 °C for 72 h. [b] The reaction was performed with L-RaPr$_2$/Mg(OTf)$_2$ (1:1, 10 mol %) at −20 °C for 72 h.

and excellent enantioselectivity. The results indicated that partial racemization at the α-position of the isocyanides occurred in the process. However, the desired product **3mf** was not formed with 3-isocyanopropylindole. It is noteworthy that the fused polycyclic products **3** bearing three stereocenters, differed from the products obtained from using malonodinitriles as the Michael acceptors as described in the work of Ji and co-workers.[12]

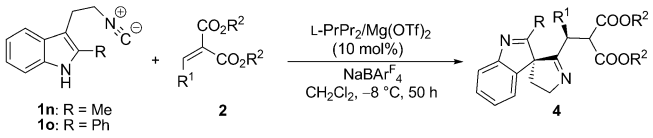
We next evaluated the suitability of 2-isocyanoethylindole derivatives bearing a substituent at the C2-position of the indole. Interestingly, a Michael/Friedel–Crafts cascade proceeded well and only the spiroindoline **4** was generated with excellent results (Table 3). The sequential addition of malonate to the imine intermediate could not occur because of steric hindrance and low electrophilicity of the C2-position of **4**. Under the identical optimal reaction conditions, regardless of the aryl substituent and heteroaromatic substituent at the β-position, or the ester group of alkylidene malonates **2**, the reaction with the 2-methyl-substituted 2-isocyanoethylindole **1n** proceeded with excellent results (entries 1–6). The aliphatic substrate **2u** proved compatible and afforded the desired product **4nu** (entry 7). Pleasingly, the 2-phenyl-substituted 2-isocyanoethylindole **1o** gave excellent yields and enantioselectivities, although in moderate diastereoselectivity (entries 8 and 9).

To evaluate the synthetic potential of the catalytic system, the polycyclic product **3ai** was efficiently transformed into highly functionalized compound though an oxidation process (see the Supporting Information for details).

The absolute configuration of the spiroindolines **3cf** and **4nq** was unambiguously determined to be (4*S*, 5*aR*, 10*bS*) and (*R*,*R*), respectively by single-crystal X-ray diffraction analysis (Scheme 3).[15] The two adducts displayed the same absolute spatial arrangement at both the R^1-bonded carbon center (I; see Scheme 1) and the quaternary spiroindoline center (II).[15]

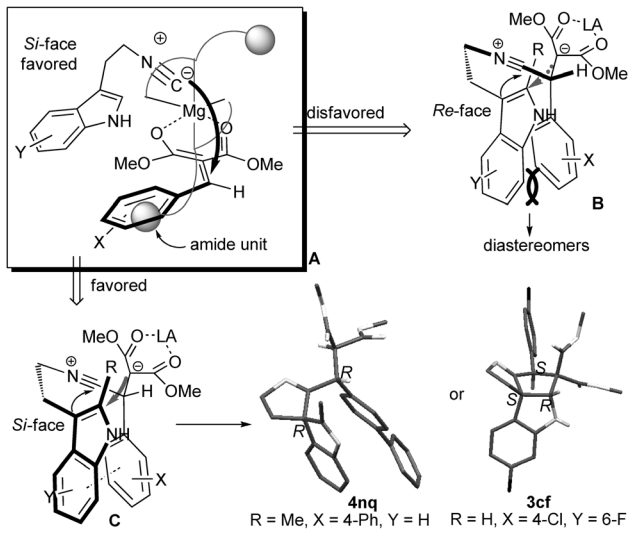
Based on the X-ray crystal structure of the *N,N′*-dioxide/metal complexes,[13b] the absolute configuration of the product,[15] and previous reports,[12,13c,f] the origin of the enantioselectivity for the cascade reaction is rationalized (Scheme 3). The catalytic model of asymmetric nucleophilic addition of 2-benzylidenemalonate in the presence of the *N,N′*-dioxide/metal complex catalyst has been well established.[13c,f,h] In the initial Michael addition step, chiral *N,N′*-dioxide/Mg^{II} complex could efficiently activate the alkylidene malonates **2** through bidentate bonding. As shown in **A** in Scheme 3, the *Re* face of the alkylidene malonate is shielded by the amide unit underneath. It is suitable for a selective attack of the isocyanide group of 2-isocyanoethylindole from the *Si* face. The first stereocenter (I) forms in the Michael intermediate, which leads to the Friedel–Crafts and Mannich sequences in a highly diastereoselective manner. Two possible dearomative annulation pathways are shown as **B** and **C** in Scheme 3. If the C3-position of the indole unit nucleophilically attacks the isocyanide intramolecularly with its *Si* face (**B**), there should be steric repulsion between the two aromatic groups, which are situated side-by-side. On the contrary, if the Friedel–Crafts step occurs from the *Re* face of C3-position of the indole (**C**), a stacking interaction might exist between the two

Table 3: Substrate scope for the reaction of 2-isocyanoethylindole derivatives.[a]



Entry	R^1	R^2	R	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	Ph	Me	Me	**4nb**: 86	92	>19:1
2	Ph	Et	Me	**4na**: 82	90	>19:1
3	4-BrC$_6$H$_4$	Me	Me	**4ni**: 72	92	>19:1
4	4-F$_3$CC$_6$H$_4$	Me	Me	**4nk**: 80	92	>19:1
5	4-PhC$_6$H$_4$	Me	Me	**4nq**: 75	94[e]	>19:1
6	3-thienyl	Et	Me	**4nt**: 70	93	>19:1
7	cyclohexyl	Et	Me	**4nu**: 99	85	>19:1
8	4-BrC$_6$H$_4$	Me	Ph	**4oi**: 98 (99)[f]	90 (90)[f]	3.5:1 (3.5:1)[f]
9	4-BnOC$_6$H$_4$	Me	Ph	**4or**: 96	96	2.9:1

[a–c] The same as in Table 2. [d] The d.r. value was determined by ^{1}H NMR spectroscopy. [e] The absolute configuration of **4nq** was determined to be *R*,*R*. [f] Data within parentheses are the results of the reaction conducted on a gram-scale (4.0 mmol of **1o**).



Scheme 3. Proposed stereoselective models of the asymmetric cascade.

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aryl groups. Therefore, **C** is favorable, thus leading to the desired (*R*,*R*)-**4nq** and (4*S*, 5*aR*, 10*bS*)-**3cf** preferably.

In summary, we have developed a novel asymmetric dearomatization of 2-isocyanoethylindoles based on Michael/Friedel–Crafts-type cascade with alkylidene malonates. A chiral *N*,*N*′-dioxide/Mg^{II} complex could efficiently accelerate the asymmetric process, thus giving access to a variety of fused polycyclic indolines and spiroindolines in moderate to excellent yield (up to 99%) and excellent stereoselectivity (up to >19:1 d.r. and up to 96% *ee*). Additionally, the process exhibits broad substrate scope under mild reaction conditions. Further application of *N*,*N*′-dioxide/metal complexes in asymmetric cascade reactions is underway.

Experimental Section

3ab: $Mg(OTf)_2$ (0.01 mmol), the *N*,*N*′-dioxide ligand L-$PrPr_2$ (0.01 mmol), $NaBAr^F_4$ (0.02 mmol), and dimethyl 2-benzylidenemalonate (**2b**; 0.15 mmol) were stirred in 1.0 mL of CH_2Cl_2 at 35 °C for 0.5 h under nitrogen atmosphere. Subsequently, 2-isocyanoethylindole (**1a**; 0.1 mmol) was added at −8 °C. The reaction was stirred at −8 °C for 40 h, followed by direct purification by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate 3:1) to afford **3ab** (65% yield, 93% *ee*, and >19:1 d.r.).

Keywords: aromaticity · asymmetric catalysis · cascade reactions · heterocycles · magnesium

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[15] CCDC 1032237 (**3cf**) and 1032467 (**4nq**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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