

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

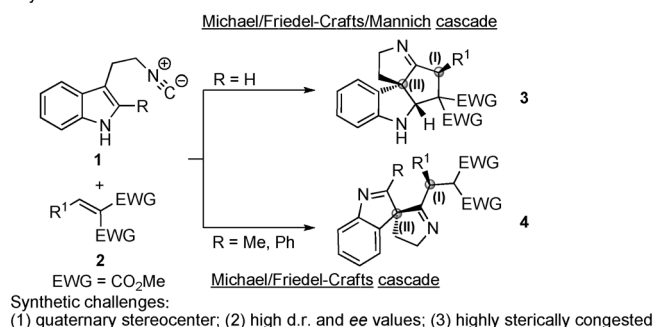
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Abstract: A highly efficient asymmetric dearomatization of indoles was realized through a cascade reaction between 2-isocyanoethylindole and alkylidene malonates catalyzed by a chiral N,N' -dioxide/ Mg^{II} catalyst. Fused polycyclic indolines containing 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).

Asymmetric dearomative cascade:



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 **1-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]

1a: R' = H
1p: R' = Me
2a: R = Et
2b: R = Me
3aa: R' = H, R = Et
3ab: R' = H, R = Me
3pb: R' = Me, R = Me

L-PrPr₂: Ar = 2,6-*i*Pr₂C₆H₃, *n* = 1
 L-PrEt₂: Ar = 2,6-Et₂C₆H₃, *n* = 1
 L-PrMe₂: Ar = 2,6-Me₂C₆H₃, *n* = 1
 L-PiPr₂: Ar = 2,6-*i*Pr₂C₆H₃, *n* = 2
 L-RaPr₂: Ar = 2,6-*i*Pr₂C₆H₃

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 ₄ ^F	60	91
10 ^[e,f]	Mg(OTf) ₂	L-PrPr ₂	NaBAR ₄ ^F	63	92
11 ^[e,f,g]	Mg(OTf) ₂	L-PrPr ₂	NaBAR ₄ ^F	65	93
12 ^[e,f,h]	Mg(OTf) ₂	L-PrPr ₂	NaBAR ₄ ^F	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 CH₂Cl₂ (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 % NaBAR₄^F was added. [f] At –8 °C for 40 h. [g] **1a** and **2b** were used. [h] **1p** and **2b** were used.

which are abundant and display low toxicity, accelerated the Michael/Friedel–Crafts/Mannich cascade enantioselectively. Specifically, the L-PrPr₂/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-PiPr₂ and L-RaPr₂, 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 NaBAR₄^F as an additive, which could be used for the exchange of the counterion.^[14] The addition of NaBAR₄^F 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

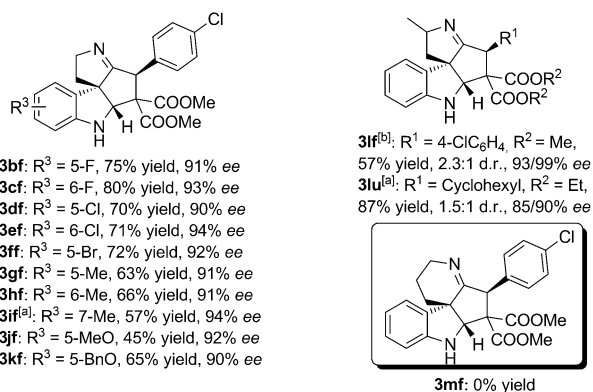
Table 2: Substrate scope of the alkylidene malonates **2**.^[a]

Entry	R ¹	R ²	3	<i>t</i> [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 ₆ H ₄	Me	3ad	40	74	91
5	3-ClC ₆ H ₄	Me	3ae	40	75	87
6	4-ClC ₆ H ₄	Me	3af	40 (72) ^[d]	76 (84) ^[d]	94 (90) ^[d]
7	3,4-Cl ₂ C ₆ H ₃	Me	3ag	40	78	90
8	3-BrC ₆ H ₄	Me	3ah	40	71	84
9	4-BrC ₆ H ₄	Me	3ai	40 (72) ^[d]	77 (82) ^[d]	93 (90) ^[d]
10	4-O ₂ NC ₆ H ₄	Me	3aj	40	90	90
11	4-F ₃ CC ₆ H ₄	Me	3ak	40	87	90
12	3-MeC ₆ H ₄	Me	3al	50	61	92
13	4-MeC ₆ H ₄	Me	3am	40	64	94
14	3-MeOC ₆ H ₄	Me	3an	50	53	91
15	3-PhOC ₆ H ₄	Me	3ao	40	71	85
16	4-PhOC ₆ H ₄	Me	3ap	40	70	90
17	4-PhC ₆ H ₄	Me	3aq	40	63	95
18	4-BnOC ₆ H 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>i</i> Pr	Et	3av	40	98	81

[a] **1a**, **2** (1.5 equiv) and NaBAR₄^F (20 mol %), L-PrPr₂/Mg(OTf)₂ (1:1, 10 mol %) in CH₂Cl₂ under N₂ 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 NaNTf₂ instead of NaBAR₄^F at 0 °C for 72 h (see the Supporting Information for details).

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



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 $\text{L-RaPr}_2/\text{Mg}(\text{OTf})_2$ (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 ali-

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	90	3.5:1
				(99) ^[f]	(90) ^[f]	(3.5:1) ^[f]
9	4-BnOC ₆ H ₄	Me	Ph	4or : 96	96	2.9:1

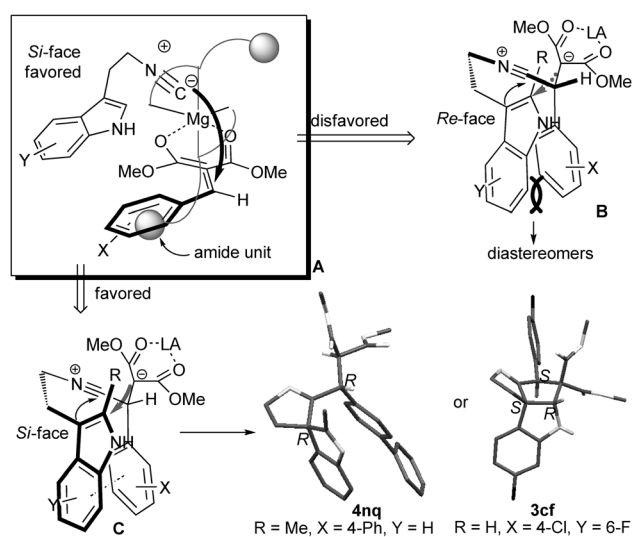
[a–c] The same as in Table 2. [d] The d.r. value was determined by ¹H NMR spectroscopy. [e] The absolute configuration of **4nq** was determined to be *R,R*. [f] Data within parentheses are the results of the reaction conducted on a gram-scale (4.0 mmol of **1o**).

phatic 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 (*4S*, *5aR*, *10bS*) 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 R¹-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



Scheme 3. Proposed stereoselective models of the asymmetric cascade.

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-PrPr₂ (0.01 mmol), NaBAR^F₄ (0.02 mmol), and dimethyl 2-benzylidenemalonate (**2b**; 0.15 mmol) were stirred in 1.0 mL of CH₂Cl₂ 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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