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Asymmetric Catalytic 1,3-Dipolar Cycloaddition Reaction of Nitrile Imines for the Synthesis of Chiral Spiro-Pyrazoline-Oxindoles

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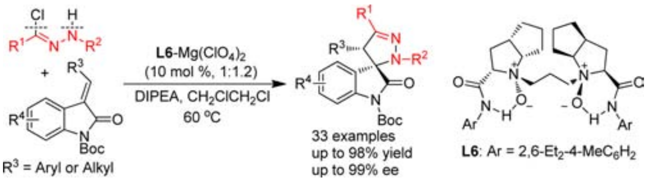
ABSTRACT



A new 1,3-dipolar cycloaddition of nitrile imines with 3-alkenyl-oxindoles was catalyzed by a new chiral Mg(ClO_4)$_2$ complex of an *N,N′*-dioxide ligand. The reaction is so far the sole catalytic synthesis of spiro-pyrazoline-oxindole derivatives. A wide variety of substrates were explored to obtain good yields (up to 98%) and excellent enantioselectivities (up to 99%). This cycloaddition expands the scope of propargyl anion type 1,3-dipole in the construction of 2-pyrazoline subunit.

The enantioselective 1,3-dipolar cycloaddition reaction (1,3-DCR) provides a useful route to synthesize a variety of chiral heterocycles, which can serve as useful synthetic building blocks.[1] The majority of advances in this area focused on the reaction of allyl anion type dipoles, such as nitrones,[2] azomethine imines,[3] and azomethine ylides.[4] However, of the propargyl anion type 1,3-dipoles, such as nitrile imines,[5] catalytic asymmetric 1,3-DCR is underdeveloped. To our knowledge, the only innovative result for the reactions of nitrile imine with oxazolidinone crotonates was achieved by Sibi's group in 2005.[6] Extremely low reaction temperature was needed for the generation of chiral dihydropyrazole scaffold in highly enantioselective

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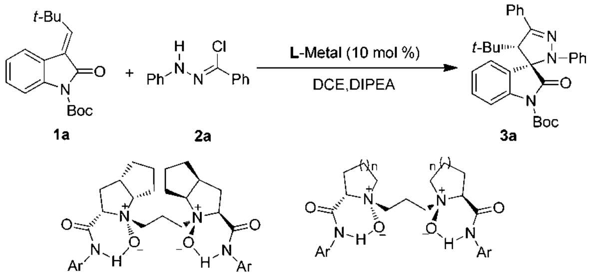
form. As a matter of fact, the catalytic asymmetric 1,3-DCR of nitrile imine encounters some difficulties. The selectivity challenge is to control the regio-, diastereo-, and enantioselectivity. Usually, the active nitrile imine is generated in situ by dehydrohalogenation of the corresponding hydrazonyl halide in the presence of an equivalent base, which causes strong background reaction, as well as the coordination with Lewis acid catalysts. Moreover, such a dipole bearing a linear bond and two terminal substituents makes the asymmetric induction using chiral catalyst difficult.

With regard to the dipolarophile variety, 3-alkenyl-oxindoles reagents have been employed in the construction of different types of spirooxindoles.[7] These densely functionalized core structures represent an attractive synthetic target due to the biological activity and physical property. For example, the asymmetric synthesis of spiro-pyrrolidine-oxindole derivatives was realized via 1,3-dipolar additions of azomethine ylides by Gong's, Waldmann's and Wang's groups, respectively.[8] We envisioned that the oxindole skeleton, decorated with a 2-pyrazoline in a spiro ring form, would be useful for studying structure–activity relationships of these two privileged units.[9] The asymmetric 1,3-DCR of nitrile imine with 3-alkenyl-oxindole provides a straightforward route to obtain optically active spiro-pyrazoline-oxindole. Considering that chiral *N*,*N*′-dioxide-metal complex catalysts developed in our group could perform excellent and flexible stereoenvironment,[10] we then focused on their application toward this object.

Table 1. Optimization of the Reaction Conditions[a]



L1: Ar = 2,6-*i*-Pr$_2$C$_6$H$_3$
L4: Ar = 2,6-Et$_2$C$_6$H$_3$
L5: Ar = 2,6-Me$_2$C$_6$H$_3$
L6: Ar = 2,6-Et$_2$-4-MeC$_6$H$_2$

L2: Ar = 2,6-*i*-Pr$_2$C$_6$H$_3$, n = 2
L3: Ar = 2,6-*i*-Pr$_2$C$_6$H$_3$, n = 1

entry	ligand	metal	*t* (°C)	yield (%)[b]	ee (%)[c]
1	–	–	35	96	0
2	**L1**	Ca(OTf)$_2$	35	94	0
3	**L1**	Sc(OTf)$_3$	35	94	0
4	**L1**	Mg(OTf)$_2$	35	92	55
5	**L1**	Mg(ClO$_4$)$_2$	35	86	65
6	**L2**	Mg(ClO$_4$)$_2$	35	75	54
7	**L3**	Mg(ClO$_4$)$_2$	35	88	53
8	**L4**	Mg(ClO$_4$)$_2$	35	86	89
9	**L5**	Mg(ClO$_4$)$_2$	35	88	88
10	**L6**	Mg(ClO$_4$)$_2$	35	86	92
11	**L6**	Mg(ClO$_4$)$_2$	−20	67	89
12	**L6**	Mg(ClO$_4$)$_2$	−78	trace	–
13	**L6**	Mg(ClO$_4$)$_2$	60	93	96
14	**L6**	Mg(ClO$_4$)$_2$	80	72	92

[a] Unless specified, all reactions were performed with **L**–metal (10 mol %, 1:1.2), **1a** (0.10 mmol), **2a** (0.12 mmol), *i*-Pr$_2$NEt (0.12 mmol) at 35 °C for 4 h. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel IC).

Initially, we selected (*E*)-1-Boc-3-*tert*-butylideneindolinone **1a** as a dipolarophile on account of that the Boc-group on the nitrogen atom of **1a** would reduce its energy of the lowest unoccupied molecular orbital (LUMO) and enhance the polarizability.[1c–e] The noncoordinating diisopropylethylamine was used to generate the nitrile imine by dehydrohalogenation of hydrazonyl chloride **2a**. Without a Lewis acid catalyst, the desired racemic spiro-pyrazoline-oxindole **3a** was obtained within 4 h in 96% yield at 35 °C (Table 1, entry 1). The reaction was regioselective, with the carbon end of the dipole adding to the *β*-position of 3-alkenyl-oxindole **1a**. Next, we set out to find a compatible chiral Lewis acid catalyst by screening across an array of chiral ligands and metal ions. Mg(ClO$_4$)$_2$ was proven to be the best metal salt for the reaction, affording 65% ee, albeit the yield was slightly reduced (Table 1, entry 5). Gratifyingly, the introduction of 2,6-diethyl and 4-methyl groups into the ligand **L6** provided the single diastereomer with 86% yield and 92% ee (Table 1, entry 10).

Further attempts to improve the yield and enantioselectivity focused on the reaction temperature. Interestingly, in this case the enantioselectivity declined as the temperature decreased, and the reactivity was almost diminished at −78 °C (Table 1, entries 11–12). However, when the reaction temperature was elevated to 60 °C, both the yield

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(7) For reviews, see: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003. (c) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (d) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (e) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. For recent examples see: (f) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (g) Tan, B.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2011**, *133*, 4672. (h) Bergonzini, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *57*, 971.

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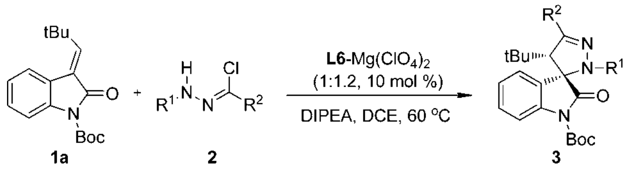
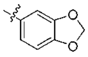
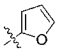
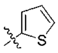
and the enantioselectivity improved a little (Table 1, entry 13 vs entry 10). It implied that the enhancement of the reactivity of the chiral catalyst was crucial to the enantioselectivity, which could greatly overwhelm the highly competing background reaction. HRMS analysis was performed to clarify the interaction between the catalyst and the other components in the catalytic system. The results showed that both **1a** and the product could coordinate the metal ion (see Supporting Information for details). As a result, the increased temperature would also benefit to release the catalyst to participate in the catalytic cycle. The optimized reaction temperature was 60 °C, at which 93% yield and 96% ee were obtained within 4 h. Further increasing the temperature to 80 °C led to a sharp drop in the yield (Table 1, entry 14). It was worthy of noting that N−H-free alkylidene oxindole, which is sluggish in the 1,3-dipolar cycloaddition reaction, was detected in the presence of the catalyst system.

Table 2. Substrate Scope of the Nitrile Imines[a]

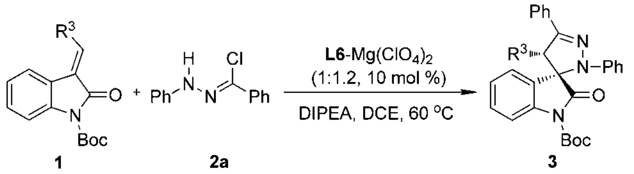


entry	R¹, R² (**2**)	time (h)	yield (%)[b]	ee (%)[c]
1	Ph, 2-ClC$_6$H$_4$ (**2b**)	4	91 (**3b**)	98
2	Ph, 3-ClC$_6$H$_4$ (**2c**)	4	94 (**3c**)	92
3	Ph, 4-ClC$_6$H$_4$ (**2d**)	4	92 (**3d**)	96
4	Ph, 2,4-Cl$_2$C$_6$H$_3$ (**2e**)	4	92 (**3e**)	99
5	Ph, 2,6-Cl$_2$C$_6$H$_3$ (**2f**)	4	98 (**3f**)	97
6	Ph, 4-FC$_6$H$_4$ (**2g**)	4	96 (**3g**)	96
7	Ph, 4-BrC$_6$H$_4$ (**2h**)	4	87 (**3h**)	96
8	Ph, 4-MeOC$_6$H$_4$ (**2i**)	4	92 (**3i**)	98
9	Ph, 3-FC$_6$H$_4$ (**2j**)	4	96 (**3j**)	95
10	Ph, 3-BrC$_6$H$_4$ (**2k**)	4	88 (**3k**)	97
11	Ph, 3-MeC$_6$H$_4$ (**2l**)	8	78 (**3l**)	97
12	Ph, 3-CF$_3$C$_6$H$_4$ (**2m**)	4	98 (**3m**)	93
13	Ph, 3-OPhC$_6$H$_4$ (**2n**)	12	85 (**3n**)	94
14	Ph, 1-naphthyl (**2o**)	12	89 (**3o**)	99
15	Ph, 2-naphthyl (**2p**)	12	89 (**3p**)	98
16	Ph,  (**2q**)	12	96 (**3q**)	93
17	Ph,  (**2r**)	8	78 (**3r**)	80
18	Ph,  (**2s**)	12	56 (**3s**)	91
19	4-BrC$_6$H$_4$, Ph (**2t**)	8	95 (**3t**)	89
20	3-ClC$_6$H$_4$, Ph (**2u**)	8	90 (**3u**)	97
21	4-MeC$_6$H$_4$, Ph (**2v**)	8	98 (**3v**)	96

[a] Unless otherwise noted, all reactions were performed with the ligand **L6** (10 mol %), Mg(ClO$_4$)$_2$ (12 mol %), **1a** (0.1 mmol), **2** (0.12 mmol), *i*-Pr$_2$NEt (0.12 mmol) in CH$_2$ClCH$_2$Cl (0.5 mL) at 60 °C. [b] Isolated yield. [c] Determined by HPLC analysis. The absolute configuration of the products **3a**−**3v** were determined to be (3*R*,4′*S*) by comparing the circular dichroism spectra with **3s**.

A combination of (*i*-Pr$_2$NEt)−**L6**−Mg(ClO$_4$)$_2$ and at 60 °C were defined to be the most general set of reaction conditions with which to examine a variety of nitrile imines (Table 2). Excellent regioselectivity and diastereoselectivity were observed for the reaction of different hydrazonyl chlorides precursor with 3-alkenyl-oxindoles **1a**. The chlorides **2** derived from electron-donating and electron-withdrawing substituted aromatic aldehydes performed well, with the enantioselectivity ranging from 92−99% ee (Table 2, entries 1−13). The electron-donating substituent on the *meta*-position of R^2 proceeded with slightly lower yields (Table 2, entries 11−13). Naphthaldehyde-derived hydrazonyl chlorides were tolerable, affording the corresponding spiro ring products in excellent enantioselectivities (98−99% ee; Table 2, entries 14, and 15). Heteroaromatic aldehyde-derived hydrazonyl chlorides were employed, and the pyrazolines were given in moderate yields and good ee values (entries 17−18). Entries 19−21 show that a *p*-methylbenzene or a *m*-chlorobenzene located in nitrogen of nitrile imine resulted in higher enantioselectivity than a *p*-bromobenzene substituent (entries 20−21 vs entry 19).

Table 3. Substrate Scope of the Dipolarophiles[a]



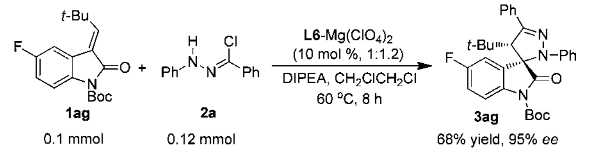
entry	R³ (**1**)	time (h)	yield (%)[b]	ee (%)[c]
1	*i*-Pr (**1w**)	4	65 (**3w**)	83
2[d]	Ph (**1x**)	12	97 (**3x**)	77
3	2-ClC$_6$H$_4$ (**1y**)	8	96 (**3y**)	88
4	4-ClC$_6$H$_4$ (**1z**)	8	96 (**3z**)	63
5	2,6-Cl$_2$C$_6$H$_3$ (**1aa**)	12	92 (**3aa**)	93
6	2,3-(OMe)$_2$C$_6$H$_3$ (**1ab**)	8	88 (**3ab**)	87
7	2-BrC$_6$H$_4$ (**1ac**)	8	98 (**3ac**)	84
8	9-anthracenyl (**1ad**)	12	88 (**3ad**)	92
9	1-naphthyl (**1ae**)	12	98 (**3ae**)	75
10[d]	2-NO$_2$C$_6$H$_4$(**1af**)	12	82 (**3af**)	94

[a] The procedure was similar to that in Table 2. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The yield was combined with other isomers (approx. 90:10 for **3w**, and 80:20 for **3af**, determined by NMR).

Further extension was focused on the performance of other dipolarophiles. The steric nature of substituents on 3-alkenyl-oxindoles had great influence on the enantioselectivity. The example of alkyl substrate **1w** showed that decrease the steric hindrance of R^3 resulted in reduced enantioselectivity (Table 3, entry 1). Cycloaddition of aryl substituted dipolarophiles gave the products in moderate to good enantioselectivities, depending on the position of the substituent (Table 3, entries 2−7). Acceptors in which R^3 is functionalized as an *ortho*-substituted phenyl group performed in higher ee values (up to 94% ee; Table 3, entries 5 and 10). The enantioselectivity was lower with 4-chlorobenzene substituted 3-alkenyl-oxindoles (63% ee; Table 3, entry 4). The electronic property of the substrates had no obvious effect on the yield and enantioselectivity (Table 3, entry 4 vs entry 6). The enantioselectivity of

9-anthryl-substituted dipolarphile was better than 1-naphthyl-substituted one (Table 3, entries 8–9). In most cases, nearly one isomer was generated with the exception of phenyl substituted **1x** and 2-nitrophenyl substituted **1af** (90:10 and 80:20 ratio, respectively).[11] The 5-fluor-substituted oxindole derivatives **1ag** could tolerate the reaction, giving moderate yield and high enantioselectivity (Scheme 1).

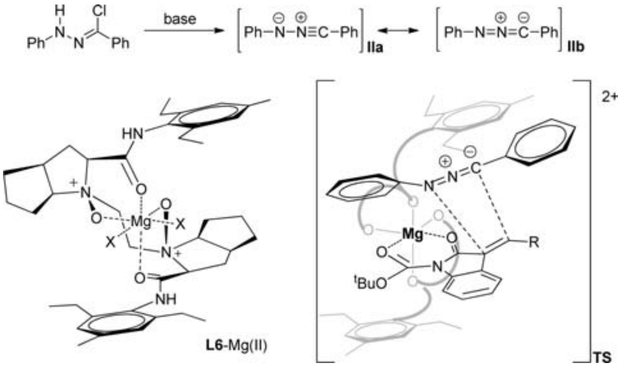
Scheme 1. Reaction of 5-Fluor-Substituted Oxindole



To evaluate the synthetic utility of the catalyst system, the reaction was enlarged to a gram scale under the optimized reaction conditions. Satisfiying results of 88% yield and 96% ee were obtained. The crystal structures were obtained for the cycloadducts **3s** and **3x**. The absolute configurations were assigned as (3*R*,4′*S*).[12]

A mechanism to explain the reaction process is shown in Scheme 2. Dipolar was generated from the dehydrochlorination of hydrazonyl chloride assisted by the organic base. The nitrile imine can present as two zwitterionic resonance forms, of which **IIb** reacted with the alkylidene oxindole to afford spiro[pyrazolin-3,3′-oxindole] derivatives. The 1,3-DC reaction is controlled by the $\mathrm{HOMO_{dipolar}{-}LUMO_{dipolarophile}}$ interaction. HRMS analysis of a mixture of 3-alkenyl-oxindole **1a** and the catalyst suggested that the dipolarophile could interact with the Mg(II) center in a bidentate fashion. This coordination will lower the energy of the $\mathrm{LUMO_{dipolarophile}}$ and lead to a decrease in the energy difference between E_{HOMO} of the dipole and E_{LUMO} of the alkene. In light of the steric arrangement of the product and the catalyst,[10g] we rationalized a possible intermediate. The nitrile imine should preferentially approach the 3-alkenyl-oxindole from the *Si*–*Si* face in a concert manner. Therefore, a unique spiro quaternary stereogenic center at C3 site with a tertiary carbon on the pyrazoline ring is created.

Scheme 2. Proposed Mechanism for the 1,3-DCR and the X-ray Structures of the Products



In summary, we have developed a new asymmetric catalytic 1,3-dipolar cycloaddition of nitrile imines with 3-alkenyl-oxindoles by using a new chiral $\mathrm{Mg(ClO_4)_2}$ complex of an *N*,*N*′-dioxide ligand. It expanded the scope of propargyl anion type 1,3-dipole in the construction of 2-pyrazoline subunit. This reaction is so far the sole catalytic synthesis of spiro-pyrazoline-oxindole derivatives in high stereoselectivity. The protocol for efficient synthesis of the privileged spirooxindole architecture is important for further development of related compounds as potential medicinal agents. The mild reaction conditions and facile procedure show the potential of the catalytic system. Further application of the catalyst to the diversity-oriented synthesis is underway.

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Supporting Information Available. Experimental procedures, spectral and analytical data for the products, and crystal CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] In some cases, trace amount of isomers were detected. The structure could not be determined to be the *N*-adduct or the diastereomer of *C*-adduct.

[12] CCDC 905687 (**1a**), CCDC 892985 (**3s**), and CCDC 892840 (**3x**) contain the supplementary crystallographic data for this paper. They can be obtained free of charge from The Cambrige Crystallographic Data Centere via www.ccdc.cam.ac.uk/data_request/cif.