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Magnesium(II)-catalyzed asymmetric hetero-Diels–Alder reaction of Brassard's dienes with isatins†

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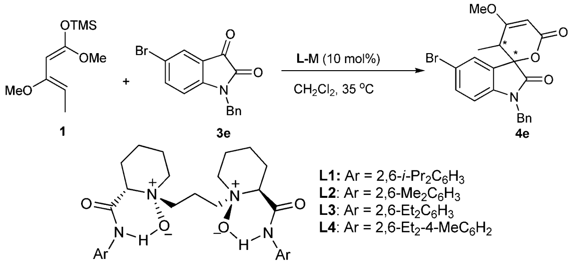
The first catalytic asymmetric hetero-Diels–Alder reaction of Brassard's dienes with isatins was realized using Mg(II)/*N*,*N*′-dioxide complexes as catalysts, affording the corresponding chiral spirolactones bearing tetrasubstituted centers in up to 99% yield with up to 99% ee and >99 : 1 dr within 3 hours. In the mechanism, based on the operando IR experiments, a predominant Diels–Alder pathway was found in the reaction. A possible transition state model was also proposed.

The enantioselective hetero-Diels–Alder (HDA) reaction[1] of Brassard's dienes[2] with carbonyl compounds is a classic approach to access optically active six-membered δ-lactones,[3] which are widely found in bioactive natural products and have been frequently used as versatile intermediates for further manipulations.[4] Compared with Danishefsky's dienes, the terminal twofold substitutions of Brassard's dienes enhanced the difficulty of controlling the enantioselectivity of the HDA reaction.[5] Still, several catalytic systems, including chiral TADDOL,[6a] Ti or Cu/Schiff base,[6b,c] Ti/BINOL[6d] and In/*N*,*N*′-dioxide,[6e] have been developed for highly enantioselective HDA reaction of Brassard's dienes with aldehydes. Meanwhile, chiral phosphoric acid[7a] and Yb/*N*,*N*′-dioxide[7b] have also been applied to catalyze the asymmetric HDA reaction of Brassard's dienes with imines. However, there is still no report on catalytic asymmetric HDA reaction between Brassard's dienes and any kind of ketones up to now. Recently, isatins have emerged as one of the most promising new classes of carbonyl compounds.[8,9] The HDA reaction of Brassard's dienes with isatins can construct bio-potential chiral spirolactone frameworks straightforwardly. As part of our efforts in developing highly enantioselective HDA reaction with ketones, we herein report our achievements in the catalytic asymmetric HDA reaction of Brassard's dienes with isatins under mild reaction conditions using metal/*N*,*N*′-dioxide complexes as catalysts developed by our group.[10]

The HDA reaction of Brassard type diene **1** with isatin **3e** was selected as the model reaction because of the easy separation of four isomers of the corresponding spirolactone **4e** in chiral HPLC. Firstly, various metal salts coordinated *in situ* with *N*,*N*′-dioxide **L1** derived from L-pipecolic acid were examined in CH_2Cl_2 at 35 °C. As shown in Table 1, $Sc(OTf)_3$, $In(OTf)_3$, and $Cu(OTf)_2$, that once showed good efficiency in HDA reaction, gave very poor results (Table 1 entries 1–3). To our delight, the **L1**–$Mg(OTf)_2$ complex promoted the reaction much better, giving the desired spirolactone **4e** in 50% yield, 95% ee and 93 : 7 dr (Table 1, entry 4). The yield could be slightly improved to 56% by using $Mg(ClO_4)_2$ instead of $Mg(OTf)_2$ as the metal salt (Table 1, entry 5). The abundance and low toxicity of magnesium make the chiral magnesium(II) complexes more attractive.[11] Encouraged by these results, various chiral *N*,*N*′-dioxide ligands

Table 1 Optimization of the reaction conditions



Entry[a]	Ligand	Metal	Yield[b] (%)	dr[c]	ee[c] (%)
1	**L1**	$Sc(OTf)_3$	0	—	—
2	**L1**	$In(OTf)_3$	26	36 : 64	7
3	**L1**	$Cu(OTf)_2$	23	55 : 45	11
4	**L1**	$Mg(OTf)_2$	50	93 : 7	95
5	**L1**	$Mg(ClO_4)_2$	56	95 : 5	96
6	**L2**	$Mg(ClO_4)_2$	53	76 : 24	50
7	**L3**	$Mg(ClO_4)_2$	68	96 : 4	95
8	**L4**	$Mg(ClO_4)_2$	70	95 : 5	96
9[d]	**L4**	$Mg(ClO_4)_2$	93	95 : 5	96

[a] Unless specified, all reactions were performed using **L**–metal (10 mol%, 1 : 1), **1** (0.15 mmol), **3e** (0.10 mmol) at 35 °C for 1 hour. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel IB). [d] TFA (30 μL) was added after the reaction. TFA = Trifluoro acetic acid.

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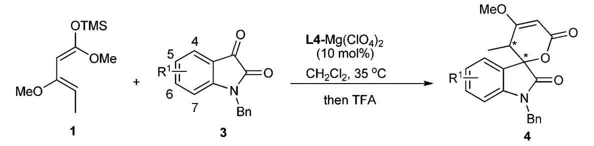
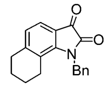
were synthesized and coordinated with $Mg(ClO_4)_2$ to promote the reaction. The results showed that the steric hindrance of *ortho*-substituents on the aniline ring of the *N*,*N*′-dioxide played a crucial role in the selectivity of the reaction (Table 1, entries 6 and 7). When **L2** with a small methyl group was used, the ee and dr values were decreased dramatically to 50% and 76 : 24, respectively. Meanwhile, upon changing the steric isopropyl to the ethyl substituent (**L3**), no obvious effect was found. When ligand **L4** containing the 2,6-diethyl-4-methylaniline moiety was used, **4e** was obtained in 70% yield with 96% ee and 95 : 5 dr (Table 1, entry 8). In the above cases, besides the cycloaddition adduct, a small amount of Mukaiyama aldol product with the same ee value as **4e** can also be isolated. But not all of the aldol product could be transformed to the cycloadduct **4e** in the optimized **L4**–$Mg(ClO_4)_2$ catalytic system. The yield of the desired spirolactone **4e** could be improved to 93% by treatment of the reaction mixture with TFA, which could accelerate the transformation of the aldol product to **4e** (Table 1, entry 9).

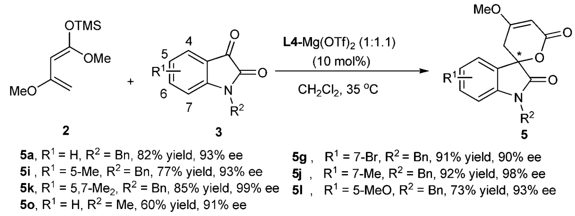
With the optimized reaction conditions in hand, the scope of the HDA reaction of **1** with various isatins **3** was explored. As summarized in Table 2, neither electron-donating nor electron-withdrawing substituted groups on the aromatic ring of isatins had obvious impact on the outcomes of the reaction. The desired chiral spirolactones were isolated in excellent yields (90–99%) with excellent diastereo- and enantioselectivities (92 : 8–99 : 1 dr) (Table 2, entries 1–11). In addition, isatin **3n** containing a fused saturated ring was also tolerated in the reaction, giving the corresponding spirolactone **4n** in 99% yield with 96% ee and 96 : 4 dr (Table 2, entry 12). The absolute configuration of **4e** was determined by X-ray crystallography to be (2′*R*,3′*R*), while the absolute configuration of **4b–4d** and **4f–4m** was also determined to be (2′*R*,3′*R*) by comparing their circular-dichroism spectra with that of **4e**.

Table 2 Substrate scope of the HDA reaction of Brassard type diene **1** with isatins **3**



Entry^a	R^1	Yield^b (%)	dr^c	ee^c (%)
1	5-F	99 (**4b**)	95 : 5	96 (*R*,*R*)
2	5-Cl	96 (**4c**)	96 : 4	98 (*R*,*R*)
3	4-Br	98 (**4d**)	99 : 1	99 (*R*,*R*)
4	5-Br	93 (**4e**)	95 : 5	96 (*R*,*R*)
5	6-Br	90 (**4f**)	94 : 6	98 (*R*,*R*)
6	5-I	90 (**4h**)	92 : 8	96 (*R*,*R*)
7	5-Me	99 (**4i**)	96 : 4	98 (*R*,*R*)
8	7-Me	99 (**4j**)	98 : 2	99 (*R*,*R*)
9	5,7-Me_2	90 (**4k**)	98 : 2	98 (*R*,*R*)
10	5-MeO	99 (**4l**)	97 : 3	99 (*R*,*R*)
11	7-CF_3	99 (**4m**)	92 : 8	98 (*R*,*R*)
12		99 (**4n**)	96 : 4	96

^{a} All reactions were carried out using 10 mol% **L4**–$Mg(ClO_4)_2$ (1 : 1) as catalyst at 35 °C for 1 h. After reaction, TFA was added and the mixture was continuously stirred at rt for 2 h. ^{b} Isolated yield. ^{c} Determined by HPLC analysis.



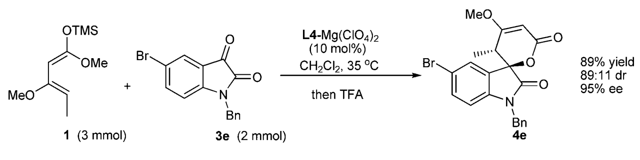
Scheme 1 Substrate scope of the HDA reaction of Brassard's diene **2** with isatins **3**.

We also examined the HDA reaction of Brassard's diene **2** with isatins in the presence of Mg(II)/*N*,*N*′-dioxide complexes (Scheme 1). After surveying the effect of the magnesium counteranion using the reaction of Brassard's diene **2** with isatin **3a** as model reaction, the desired chiral spirolactone **5a** was isolated in 82% yield and 93% ee in the presence of a 1 : 1.1 molar ratio of **L4** to $Mg(OTf)_2$. Under the optimized reaction conditions, various isatins **3** were tested. As shown in Scheme 1, for both electron-donating and electron-withdrawing substituted isatins, the desired spirolactones were obtained in moderate to good yields (73–92%) and excellent enantioselectivites (90–99% ee). *N*-Methyl protected isatin **3o** also gave the corresponding δ-lactone **5o** in 60% yield and 91% ee.

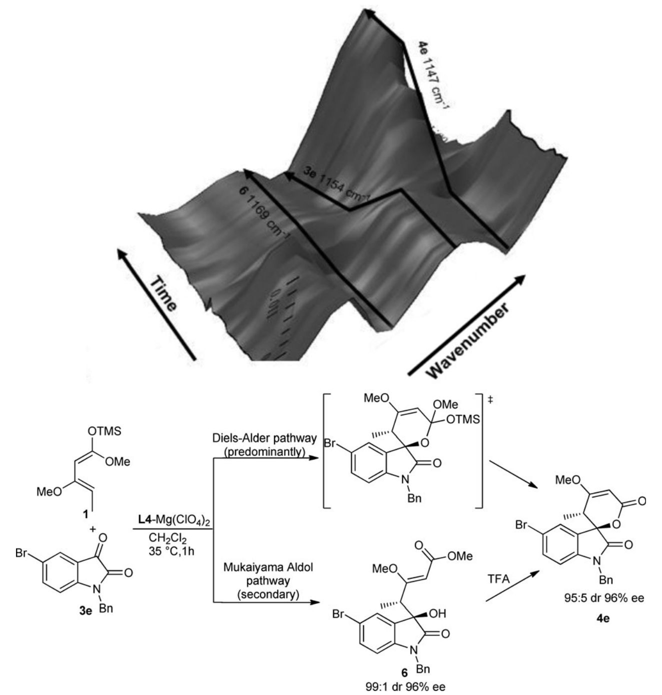
To show the prospect of the methodology in synthesis, a gram-scale synthesis of **4e** was carried out. By treatment of 2 mmol of **3e** in the **L4**–$Mg(ClO_4)_2$ catalytic system, **4e** was obtained in 89% yield (0.76 g) with 89 : 11 dr and 95% ee (Scheme 2).

When Lewis acid catalyzed HDA reactions are considered, two pathways known as the Mukaiyama Aldol pathway[12] and the Diels–Alder pathway[13] have generally been taken into account. In order to probe the pathway proceeding in the Mg(II)/*N*,*N*′-dioxide-catalyzed HDA reaction, operando IR experiments of **1** with isatin **3e** were carried out. It can be seen from Scheme 3 that both a great amount of cycloaddition product **4e** and a small amount of Mukaiyama aldol product **6** are formed at the beginning of the reaction. And, the amount of **4e** increased sharply while that of **6** decreased slightly with the reaction proceeding. These were matched with the reaction phenomena that cycloaddition product **4e** and the Mukaiyama aldol product **6** can both be isolated before treatment with TFA; and the isolated **6** can be partly cyclized to the corresponding cycloadduct **4e** under the optimized catalytic conditions. These observations indicate that Diels–Alder and stepwise Mukaiyama aldol pathways both existed in the magnesium(II)-catalyzed HDA reaction of Brassard type diene **1** with isatins but the Diels–Alder pathway is found to be the predominant one.

On the basis of the absolute configuration of product **4e** and our previous reports,[10] a possible transition state was proposed



Scheme 2 Gram-scaled version of the reaction.



Scheme 3 The 3D ATR-FTIR profile and the reaction pathway of the HDA reaction of Brassard type diene **1** with isatin **3e**.

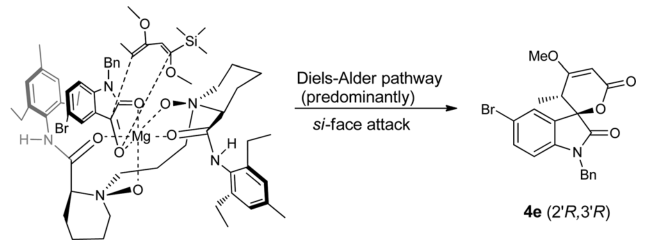


Fig. 1 Proposed transition state model and the absolute configuration of **4e**.

to illustrate the origin of the asymmetric induction. Both oxygen atoms of the amide and *N*-oxide were coordinated with the central metal in the complex. The isatin coordinates to the Mg(II) in a bidentate fashion with its dicarbonyl groups. The *Re* face of the isatin is shielded by the neighboring 2,6-diethyl-4-methylphenyl group of the ligand, therefore, the diene **1** attacks from the *Si* face to afford (2′*R*,3′*R*)-**4e** (Fig. 1).

In summary, we have developed a highly enantioselective HDA reaction of Brassard's dienes **1** and **2** with isatins catalyzed by chiral Mg(II)/*N*,*N*′-dioxide complexes. The reaction could proceed smoothly in less than 3 hours, affording the corresponding chiral spirolactones in up to 99% yield, 99% ee and >99 : 1 dr. In terms of the mechanism of the reaction, both the Diels–Alder pathway and the stepwise Mukaiyama aldol pathway were found but the Diels–Alder pathway was the predominant one. And a possible transition state model was also proposed. Further investigation of the HDA reaction of Brassard's dienes with simple ketones is underway in our group.

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