Asymmetric Catalysis

DOI: 10.1002/anie.201007145

Catalytic Asymmetric Addition of Alkyl Enol Ethers to 1,2-Dicarbonyl Compounds: Highly Enantioselective Synthesis of Substituted 3-Alkyl-3-Hydroxyoxindoles**

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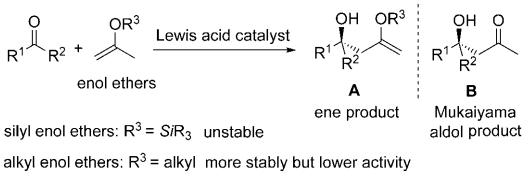
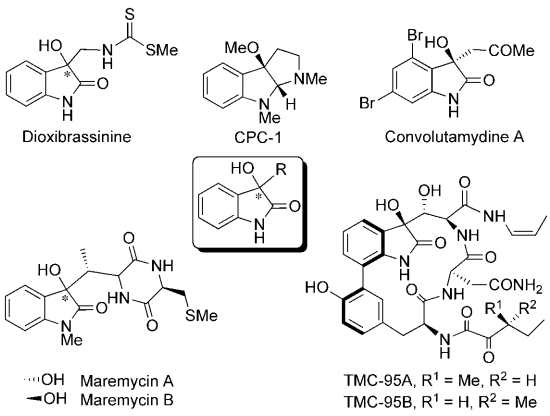
The catalytic asymmetric ene reaction of carbonyl compounds has attracted much attention because it provides an efficient way to construct versatile and useful building blocks.[1] In contrast to the extensive and fruitful studies on asymmetric ene reactions using α-methyl styrene[2] as a nucleophile, fewer cases have been reported in which enol ethers serve as the nucleophile.[3,4] The problems associated with the reaction are the instability of enol ethers in the presence of a Lewis acid and the competitive Mukaiyama aldol reaction (Scheme 1, product B). In addition, the nucleophilicity of an alkyl enol ether is lower than that of a silyl enol ether, which has been used in asymmetric carbonyl-ene reactions.[3] To date, only one successful transformation of aryl aldehydes reacting with an alkyl enol ether as the ene component was disclosed by Jacobsen and co-workers, and the ene products are isolated in high yields enantioselectivity by using a chiral Cr^{III} catalyst.[4b] The nucleophilic addition of alkyl enol ethers to construct chiral quaternary carbon centers seems more interesting and challenging (Scheme 1, product A). Herein, we report the first catalytic enantioselective hetero-ene reaction of alkyl enol ethers with three kinds of 1,2-dicarbonyl compounds (including isatins, α-ketoesters, and glyoxal derivatives) using the chiral *N,N′*-dioxide complex of either $Mg(OTf)_2$ or $Cu(OTf)_2$ to afford β-hydroxyenol ether products with excellent outcomes (up to 98% yield, >99% *ee*) under mild reaction conditions.



Scheme 1. Competing formation of ene product A and the Mukaiyama aldol product B in the Lewis acid catalyzed addition of enol ethers to electrophiles.

3-Substituted 3-hydroxyoxindoles constitute a common structural motif in various natural products and biologically active compounds, and they have a stereogenic quaternary carbon atom (Scheme 2).[5,6] Molecules that include this structural unit constitute major targets in the development of drug candidates. Therefore, we initially aimed to develop a catalytic asymmetric hetero-ene reaction of isatins.



Scheme 2. Examples of biologically active 3-substituted 3-hydroxyoxindoles.

The isatin **1l** was chosen to react with 2-methoxypropene (**2a**) in the presence of our established *N,N′*-dioxide/metal complex as a catalyst.[7] Accordingly, several chiral Lewis acid catalysts that were generated in situ from metal salts and the *N,N′*-dioxide **L4** were screened to evaluate their performance in the hetero-ene reaction. As shown in Table 1, the reaction proceeded sluggishly in the presence of metal salts such as $Ca(ClO_4)_2$, $Zn(OTf)_2$, and $Sc(OTf)_3$; however, both the **L4**/$Cu(OTf)_2$ and **L4**/$Mg(OTf)_2$ complexes promoted the reaction to afford the 3-substituted 3-hydroxyoxindole **3l** (Table 1, entries 1–5 versus entries 6 and 7). The **L4**/$Mg(OTf)_2$ complex furnished the products with moderate yield and excellent enantioselectivity (Table 1, entry 7). Gratifyingly, none of the corresponding Mukaiyama aldol products **4** were detected under these reaction conditions. To improve the reactivity and enantioselectivity of the reaction, various *N,N′*-dioxides were investigated. Notably, only the ligands having *i*Pr substituents at the *ortho* position of aniline were found to be appropriate for this transformation (Table 1,

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[**] We appreciate the financial support from the National Natural Science Foundation of China (Nos. 20732003 and 21021001 and 20872096) and the National Basic Research Program of China (973 Program: No. 2010CB833300). We thank the Sichuan University Analytical & Testing Centre for NMR and X-ray diffraction analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007145.

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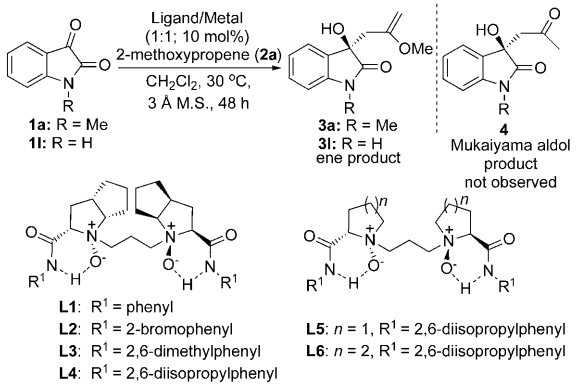
Table 1: Optimization of the reaction conditions.[a]



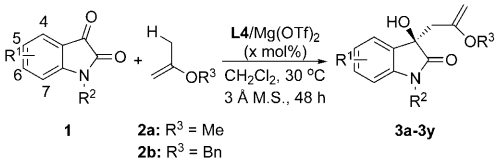
Entry	Metal	Ligand	1	Yield of 3 [%][b]	*ee* [%][c]
1	$Ca(ClO_4)_2$	**L4**	**1l**	45 (**3l**)	3
2	$Ba(ClO_4)_2$	**L4**	**1l**	43 (**3l**)	−17
3	$[Cu(acac)_2]$	**L4**	**1l**	trace (**3l**)	–
4	$Zn(OTf)_2$	**L4**	**1l**	40 (**3l**)	20
5	$Sc(OTf)_3$	**L4**	**1l**	trace (**3l**)	–
6	$Cu(OTf)_2$	**L4**	**1l**	53 (**3l**)	94
7	$Mg(OTf)_2$	**L4**	**1l**	55 (**3l**)	98
8	$Mg(OTf)_2$	**L1**	**1l**	trace (**3l**)	–
9	$Mg(OTf)_2$	**L2**	**1l**	trace (**3l**)	–
10	$Mg(OTf)_2$	**L3**	**1l**	trace (**3l**)	–
11	$Mg(OTf)_2$	**L5**	**1l**	50 (**3l**)	47
12	$Mg(OTf)_2$	**L6**	**1l**	48 (**3l**)	95
13[d]	$Mg(OTf)_2$	**L4**	**1l**	75 (**3l**)	98
14[d]	$Mg(OTf)_2$	**L4**	**1a**	92 (**3a**)	>99
15[d]	$Cu(OTf)_2$	**L4**	**1a**	85 (**3a**)	>99

[a] Unless otherwise noted, the reaction conditions were: isatins **1** (0.1 mmol), **2a** (2.0 equiv), 3 Å molecular sieves (25 mg), CH_2Cl_2 (0.5 mL), 30 °C, 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 5.0 equiv **2a** was used. acac = acetylacetonate, M.S. = molecular sieves, Tf = trifluoromethanesulfonyl.

entry 7), and ligands having other substituents on aniline showed poor activity under the standard reaction conditions (Table 1, entries 8–10). These facts indicated that the nature of the substituents on aniline had an impact on reactivity and suggested that a bulkier electron-donating group at the *ortho* position of aniline would greatly adjust the electronic and stereoinductive environment of the catalyst. A change in the chiral backbone of the ligand affected neither the yield nor the enantioselectivity. For example, neither the L-pipecolic acid derived **L6** nor L-proline derived **L5** exhibited superior results (Table 1, entries 11 and 12). In the above cases, the lack of reactivity might be attributed to the weak nucleophilicity and lower boiling point of **2a** (b.p. 34–36 °C). Therefore, the amount of **2a** was increased to 5.0 equivalents, and as expected the yield was improved to 75% with a 98% *ee* (Table 1, entry 13).[8] To our delight, when the N-methyl-protected isatin **1a**, which has better solubility in CH_2Cl_2, was used instead of isatin **1l**, both the yield and enantioselectivity were improved (Table 1, entry 14). Similar results were obtained when the reaction was carried out using the **L4**/$Cu(OTf)_2$ complex as catalyst (Table 1, entry 15). The process is insensitive to both atmospheric oxygen and humidity, thus making the catalytic system practical. Other conditions such as the temperature, solvent, and additives were also examined, but no superior results were obtained (see the Supporting Information).

With the optimal reaction conditions established, the substrate scope was extended. As summarized in Table 2, both N-protected isatins and N-unprotected isatins gave the desired 3-substituted 3-hydroxyoxindoles with good enantioselectivity. Up to greater than 99% *ee* values were obtained for all N-protected isatins (Table 2, entries 1–11 and entries 22–24), and the reactions of the N-unprotected isatins proceeded with slightly decreased yields and enantioselectivity as a result of the poor solubility in CH_2Cl_2 (Table 2, entries 12–21). The electronic nature and the position of the substituents on the isatins had no influence on the selectivity, but they did have a significant effect on the activity, especially for N-unprotected istatins. For example, the isatins having electron-withdrawing substitutents showed higher reactivity and enantioselectivity even with a catalyst loading of 1–5 mol% (Table 2, entries 2–7 and entries 13–18). In contrast,

Table 2: Substrate scope for the catalytic asymmetric hetero-ene reaction of isatins.[a]



Entry	1: R^1, R^2	2	x	Product	Yield [%][b]	*ee* [%][c]
1[d]	**1a**: H, Me	**2a**	10	**3a**	93	>99
2	**1b**: 5-F, Me	**2a**	2	**3b**	94	>99
3	**1c**: 7-F, Me	**2a**	5	**3c**	96	>99
4	**1d**: 5-Cl, Me	**2a**	2	**3d**	85	>99
5[e]	**1e**: 4-Br, Me	**2a**	1	**3e**	98	>99
6	**1f**: 5-Br, Me	**2a**	2	**3f**	92	>99
7	**1g**: 6-Br, Me	**2a**	5	**3g**	97	>99
8	**1h**: 5-Me, Me	**2a**	10	**3h**	93	>99
9	**1i**: 5,7-Me_2, Me	**2a**	10	**3i**	88	>99
10	**1j**: 5-OMe, Me	**2a**	10	**3j**	91	>99
11	**1k**: 5-NO_2, Me	**2a**	10	**3k**	94	>99
12	**1l**: H, H	**2a**	10	**3l**	75	98
13	**1m**: 5-F, H	**2a**	10	**3m**	78	94
14	**1n**, 7-F, H	**2a**	10	**3n**	78	97
15	**1o**: 5-Cl, H	**2a**	10	**3o**	90	96
16	**1p**: 4-Br, H	**2a**	5	**3p**	92	>99
17	**1q**: 5-Br, H	**2a**	10	**3q**	72	95
18	**1r**: 6-Br, H	**2a**	10	**3r**	68	98
19	**1s**: 5-Me, H	**2a**	10	**3s**	58	98
20	**1t**: 5,7-Me_2, H	**2a**	10	**3t**	64	96
21	**1u**: 5-OMe, H	**2a**	10	**3u**	62	98
22	**1v**: H, Bn	**2a**	10	**3v**	82	>99
23	**1w**: H, 2-methylallyl	**2a**	10	**3w**	95	>99
24	**1a**: H, Me	**2b**	10	**3x**	80	>99
25	**1l**: H, H	**2b**	10	**3y**	52	97

[a] Unless otherwise noted, the reaction conditions were: isatins **1** (0.1 mmol), **2a** (5.0 equiv), 3 Å molecular sieves (25 mg), CH_2Cl_2 (0.5 mL), 30 °C, 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The reaction was carried out with 5.0 mmol isatin **1a**, 5.0 equiv enol ether **2a**, and 3 Å molecular sieves (500 mg) in CH_2Cl_2 (25 mL) at 30 °C for 48 h. [e] The absolute configuration of the adduct (*R*)-**3e** was determined by X-ray diffraction analysis.[9]

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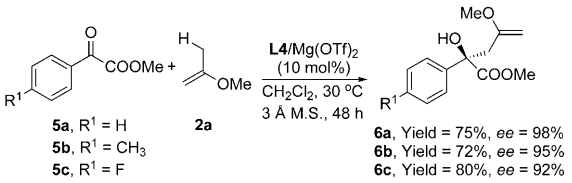
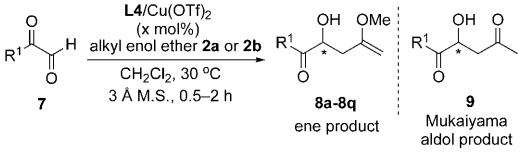
istatins having electron-donating substituents reacted to give moderate product yields (Table 2, entries 19–21). Notably, the isatin **1e** having the an electron-withdrawing group at C4 showed extremely high reactivity, thus giving the desired product in 98% yield and greater than 99% *ee* by using only 1.0 mol% of the catalyst (Table 2, entry 5). The protecting group on the isatin had little effect on the product yields; both the *N*-benzyl-protected isatin **1v** and *N*-(2-*m*ethylallyl)-protected isatin **1w** gave satisfying results (Table 2, entries 22 and 23). Moreover, another nucleophile, **2b**, was also tested with both the *N*-methyl-protected isatin **1a** and the N-unprotected isatin **1l**, giving the products in 80% yield with a greater than 99% *ee* and 52% yield with 97% *ee*, respectively (Table 2, entries 24 and 25). The absolute configuration of **3e** was determined by X-ray crystallography to be *R*.[9]

Encouraged by the above results, α-ketoesters were also examined under the optimal reaction conditions. As shown in Scheme 3, the results revealed that the α-ketoesters were suitable substrates for this hetero-ene reaction. The electronic nature of the aryl ring of the α-ketoesters had little effect on the reaction efficiency and stereoselectivity.



Scheme 3. Catalytic asymmetric hetero-ene reaction of α-ketoesters.

Table 3: Substrate scope for the catalytic asymmetric hetero-ene reaction of glyoxal derivatives.[a]



Entry	**7**: R^1	**2**	x	Product	Yield [%][b]	*ee* [%][c]
1[d]	**7a**: C_6H_5	**2a**	1	**8a/9a**	78/18	95/92
2	**7a**: C_6H_5	**2a**	1	**8a/9a**	87/10	98/95
3	**7a**: C_6H_5	**2a**	0.2	**8a**	97	98
4	**7b**: 2-MeC_6H_4	**2a**	0.2	**8b**	89	98
5	**7c**: 3-MeC_6H_4	**2a**	0.2	**8c**	92	98
6	**7d**: 4-MeC_6H_4	**2a**	0.5	**8d**	96	98
7	**7e**: 4-FC_6H_4	**2a**	0.2	**8e**	80	97
8	**7f**: 3-ClC_6H_4	**2a**	0.5	**8f**	94	97
9	**7g**: 4-ClC_6H_4	**2a**	0.2	**8g**	90	97
10	**7h**: 3,4-$Cl_2C_6H_3$	**2a**	0.5	**8h**	94	95
11	**7i**: 4-BrC_6H_4	**2a**	0.2	**8i**	96	96
12	**7j**: 3-$MeOC_6H_4$	**2a**	0.2	**8j**	90	97
13	**7k**: 4-$MeOC_6H_4$	**2a**	0.2	**8k**	80	97
14	**7l**: 3,4-$(MeO)_2C_6H_3$	**2a**	0.5	**8l**	95	97
15	**7m**: 2-naphthyl	**2a**	0.5	**8m**	92	97
16	**7n**: 2-furyl	**2a**	0.5	**8n**	98	96
17	**7o**: Cy	**2a**	0.2	**8o**	90	98
18	**7p**: OEt	**2a**	0.2	**8p**	89	87
19	**7a**: C_6H_5	**2b**	0.2	**8q**	97	98

[a] Unless otherwise noted, the reaction conditions were: glyoxal derivatives **7** (0.1 mmol), enol ether **2** (1.2 equiv), 3 Å molecular sieves (50 mg), CH_2Cl_2. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The reaction was carried out with **L4**/$Mg(OTf)_2$. Cy = cyclohexyl.

Next glyoxal derivatives were tested in the reaction with alkyl enol ethers. To our delight, the addition of the **2a** to phenylglyoxal (**7a**) in the presence of 1 mol% of the **L4**/$Mg(OTf)_2$ complex resulted in an efficient reaction, thus achieving up to greater than 98% conversion after 30 minutes. The reaction can be monitored easily by the color change of the catalyst system, which changes from yellow to colorless, and the ene product **8a** was afforded in 78% yield with 95% *ee*. However, the Mukaiyama aldol product **9a** was also obtained in 18% yield with 92% *ee* (Table 3, entry 1). The Mukaiyama aldol product might be generated from the high reactivity of the glyoxal derivatives and the easily hydrolysis of **8a** under the acidic conditions.[10] We envisioned that decreasing the activity of the catalyst might achieve two objectives: 1) slow the competitive reaction and 2) avoid the subsequent hydrolysis of the hetero-ene products. Pleasingly, when we used the less active **L4**/Cu$(OTf)_2$ complex instead of **L4**/$Mg(OTf)_2$ as the catalyst, the yield of the ene products improved and excellent enantioselectivity was obtained (Table 3, entry 2). An additional decrease in the catalyst loading to 0.2 mol% did hinder the Mukaiyama aldol reaction, and only the ene product **8a** was obtained with up to 97% yield and 98% *ee* (Table 3, entry 3). Next, the scope of the glyoxal derivatives was explored as shown in Table 3. Neither electron-donating nor electron-withdrawing substituents on the aromatic ring at the *ortho*, *meta*, or *para* positions had an impact on the enantioselectivity, and all of them underwent the hetero-ene reaction in less than 2 hours (Table 3, entries 3–14). Notably, the condensed-ring glyoxal **7m** and the heteroaromatic glyoxal **7n** performed well, giving the corresponding products in high yields with excellent *ee* values (Table 3, entries 15 and 16). The aliphatic glyoxal **7o** also reacted with **2a** in excellent enantioselectivity (Table 3, entry 17). In addition, the hetero-ene product **8p** resulting from glyoxylate **7p** was obtained with 89% yield and 87% *ee* (Table 3, entry 18). The nucleophile **2b** was also tolerated, giving the desired product **8q** in 97% yield with 98% *ee* (Table 3, entry 19).

To show the utility of the current method, a demonstration of the synthetic value of the reaction was described (Scheme 4). Asymmetric synthesis of (*R*)-convolutamydine A, which exhibits a potent inhibitory activity towards the differentiation of HL-60 human promyelocytic leukaemia cell discovered by Kamano et al. in 1995,[5a] could be efficiently achieved. As shown in Scheme 4, 4,6-dibromoisatin (**1z**) was used as the substrate under optimized reaction conditions to synthesize the hetero-ene product **3z** in 87% yield and 97% *ee*. Product **3z** then underwent hydrolysis upon treatment with 2 N HCl to generate (*R*)-convolutamydine A in 98% yield with 97% *ee* (Scheme 4A). The *β*-hydroxyenol ether products formed in these reactions are also valuable chiral building blocks. For example, the cyclopenta[*b*]indole derivative **11**, which contains the key structural unit of many natural products and biologically active com-

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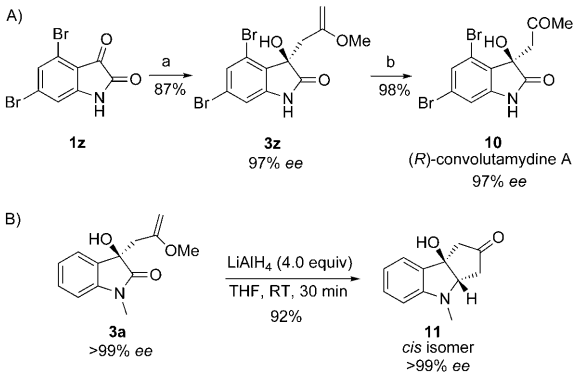

Scheme 4. Asymmetric synthesis of A) (*R*)-convolutamydine A and B) the cyclopenta[*b*]indole derivative **11**. a) 10 mol% **L4**-$Mg(OTf)_2$, 3 Å M.S., CH_2Cl_2, 24 h, 87% yield, 97% *ee*; b) 2 N HCl, Et_2O, 1 h, 98% yield, 97% *ee*.

pounds,[11] was readily obtained in excellent yield and enantioselectivity by treatment of product **3a** with $LiAlH_4$ in THF (Scheme 4B).

Preliminary studies of the mechanism were carried out, and HRMS analysis on the dynamic intermediates showed that the complex $[Mg^{2+} + \mathbf{L4} + (\mathbf{1a})]$ was the main intermediate in the reaction.[12] The X-ray analysis of the **L4**/$Mg(OTf)_2$ complex indicated that both oxygen atoms of the amide and *N*-oxide were coordinated with the central metal in the complex.[9] On the basis of the absolute configuration of the product and X-ray structure analysis of the catalyst, a concerted transition-state model was proposed (Figure 1).

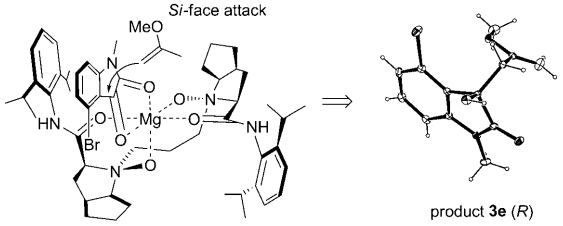

Figure 1. Proposed transition state and the X-ray crystallographic structure of the *R*-configured product **3e**. Thermal ellipsoids shown at 30% probability.

The isatin could coordinate to the Mg^{II} in a bidentate fashion with its dicarbonyl groups. The *Re* face of the isatin is therfore shielded by the neighboring 2,6-diisopropylphenyl group of the ligand, and the nucleophile **2a** attacks from the *Si* face predominantly to give the *R*-configured product.

In conclusion, we have described the first highly enantioselective hetero-ene reaction of 1,2-dicarbonyl compounds (including isatins, α-ketoesters, and glyoxal derivatives) catalyzed by chiral *N*,*N*′-dioxide complexes of either Mg(OTf)$_2$ or Cu(OTf)$_2$ using alkyl enol ethers as nucleophiles. The method enables efficient access to enantioenriched 3-substituted 3-hydroxyoxindole derivatives, which are important building blocks for the synthesis of natural products and pharmaceuticals. (*R*)-Convolutamydine A was synthesized with an excellent *ee* value and in high yield (97% *ee* and 85% yield). Moreover, the extremely high enantioselectivity, broad substrate scope, facile procedure, and mild reaction conditions demonstrate the potential of the catalytic system for practical syntheses. Additional studies of the application of this catalyst to other reactions are underway.

Received: November 14, 2010
Published online: February 14, 2011

Keywords: asymmetric catalysis · copper · ene reaction · heterocycles · magnesium

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[8] The excess 2-methoxypropene (**2a**) could be readily removed in vacuo after the completion of the reaction.

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