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Catalytic hetero-ene reactions of 5-methyleneoxazolines: highly enantioselective synthesis of 2,5-disubstituted oxazole derivatives†

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An efficient catalytic asymmetric hetero-ene reaction of 5-methyleneoxazolines with 1,2-dicarbonyl compounds (including α-ketoesters and glyoxal derivatives) was realized using Ni(II)–*N*,*N*′-dioxide complexes as the catalysts. It provides a rapid, high yielding (up to 99%) route for the preparation of 2,5-disubstituted oxazole derivatives in a highly enantioenriched form (up to >99% ee) under mild conditions.

Oxazoles are very important structural motifs towards a wide variety of natural products, pharmaceuticals, and synthetic intermediates.[1] Specifically, 2- and 5-substituted oxazoles exist in a wide range of compounds that show potent antibacterial, antiviral, and antitumor activity.[2] Traditional methodologies for the formation of substituted oxazole derivatives mainly include cyclization of acyclic precursors,[3] oxidation of oxazolines,[4] and functionalization of the parent oxazole ring.[5] In recent years, the cyclization of acetylenic amides to the corresponding oxazole derivatives has been a focus of interest.[6a,b] In some cases, the synthesis of oxazoles from *N*-propargylcarboxamides stopped at the alkylideneoxazoline stage, which provides an alternative route to synthesis of 5-functionalized oxazoles.[6c–e] A one-pot combination of alkylideneoxazoline synthesis with an Alder-ene reaction of azodicarboxylates was designed to form oxazolemethylhydrazinedicarboxylates by Hashmi and coworkers.[6f] We envision that using methyleneoxazolines as the ene analogues and with the assistance of chiral catalysts, a variety of carbonyl compounds as the enophiles could be coupled. Thus, optically active alcohol derivatives with pendant oxazole units could be afforded readily from such an enantioselective hetero-ene reaction, which has not yet been reported.

An asymmetric hetero-ene reaction is useful in carbon–carbon bond forming processes which has received remarkable progress in the past decade.[7,8] While the addition of acyclic enol ethers has been widely applied,[8a–g] the use of exocyclic enol ethers as the ene components has been less studied. The hetero-ene reaction using 2-methylene-2,3-dihydrofuran[8h] and 2-methylene-tetrahydropyrans[8i] as the nucleophiles was reported by Miles and Totah, respectively. However, a comprehensive study on the asymmetric hetero-ene reaction of exocyclic enol ethers has not been carried out. Along these lines, we report the realization of such a method that a number of α-ketoesters and glyoxal derivatives were employed in the catalytic enantioselective hetero-ene reaction with 5-methyleneoxazoline. The chiral *N*,*N*′-dioxide complex[9] of $Ni(BF_4)_2{\cdot}6H_2O$ afforded the desired products with excellent outcomes (up to 99% yield, >99% ee) under mild reaction conditions.

Our preliminary experiment surveyed the asymmetric reaction between 5-methyleneoxazoline **2a** and methyl 2-oxo-2-phenylacetate **1a** considering that the resulting product contains two privileged moieties: α-hydroxyl esters with a quaternary carbon center[10] and 2,5-disubstituted oxazole. Initial observations revealed that both the metal precursor and the chiral ligands were crucial to the yields and enantioselectivities (Table 1, entries 1–5). Using *N*,*N*′-dioxide **L1** as the chiral ligand, the reaction proceeded sluggishly in the presence of metal salts such as $Sc(OTf)_3$ and $Zn(OTf)_2$ (Table 1, entries 1 and 2); however, the **L1**–$Yb(OTf)_3$ complex gave the desired product in 29% yield and 83% ee (Table 1, entry 3); and better outcomes were obtained when $Y(OTf)_3$ was used as the metal precursor (69% yield and 87% ee; entry 4). It was gratifying to find that the **L1**–$Ni(BF_4)_2{\cdot}6H_2O$ complex furnished the products with excellent enantioselectivity although the yield was low (16% yield and >99% ee; entry 5). Inspired by these results, the efficiency of other *N*,*N*′-dioxide ligands with $Ni(BF_4)_2{\cdot}6H_2O$ was explored. The observations suggested that L-pipecolic-acid derived **L2** exhibited superior reactivity compared with L-proline derived ligand **L1** and L-ramipril derived **L3** (Table 1, entry 6 *versus* entries 5 and 7). Steric hindrance on the phenyl ring of the ligand plays a key role in promoting both the enantioselectivity and reactivity. Poor results were observed by using the aniline-derived ligand **L4** (Table 1, entry 8 *versus* entry 6). Further attempts to improve the yield were focused on the reaction temperature and the additives. Fortunately, elevating the reaction temperature from 30 °C to 40 °C benefited the yield (Table 1, entry 9 *versus* entry 6). Moreover, addition of 4 Å molecular sieves (MS) to the system could improve the yield to

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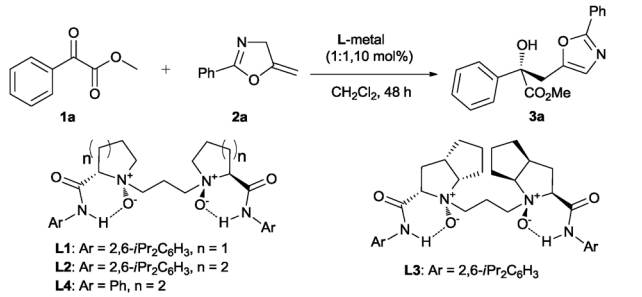
Table 1 Optimization of the reaction conditions



Entry[a]	L	Metal	T (°C)	Yield[b] (%)	ee[c] (%)
1	**L1**	$Sc(OTf)_3$	30	0	—
2	**L1**	$Zn(OTf)_2$	30	Trace	—
3	**L1**	$Yb(OTf)_3$	30	29	83
4	**L1**	$Y(OTf)_3$	30	69	87
5	**L1**	$Ni(BF_4)_2{\cdot}6H_2O$	30	16	>99
6	**L1**	$Ni(BF_4)_2{\cdot}6H_2O$	30	59	>99
7	**L2**	$Ni(BF_4)_2{\cdot}6H_2O$	30	31	97
8	**L3**	$Ni(BF_4)_2{\cdot}6H_2O$	30	7	92
9	**L3**	$Ni(BF_4)_2{\cdot}6H_2O$	40	64	>99
10[d]	**L3**	$Ni(BF_4)_2{\cdot}6H_2O$	40	86	>99
11[d,e]	**L3**	$Ni(BF_4)_2{\cdot}6H_2O$	40	95	>99
12[d–f]	**L3**	$Ni(BF_4)_2{\cdot}6H_2O$	40	97	>99

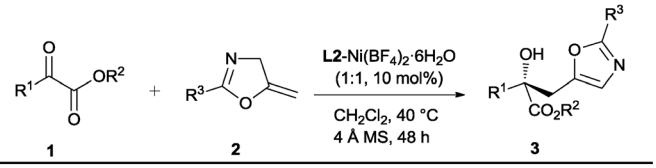
[a] Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol) and 1.1 equiv. of **2a** in CH_2Cl_2 (1.0 mL) at 30 °C for 48 h. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel IB column. [d] 4 Å MS (20 mg) was added. [e] 2.0 equiv. of **2a** was used. [f] Reactions were carried out with **1a** (0.2 mmol) in CH_2Cl_2 (1.0 mL).

86% with the ee being maintained (Table 1, entry 10). Pleasingly, when the ratio of α-ketoester **1a** and methyleneoxazoline **2a** was fixed to 1 : 2, the desired product **3a** was generated in 95% yield and >99% ee (Table 1, entry 11). Furthermore, increasing the reaction concentration also favoured the improvement of the yield (Table 1, entry 12). Remarkably, we found that the catalytic system was insensitive to both atmospheric oxygen and moisture, thus making the catalytic system practical.

With the optimized reaction conditions identified, the substrate scope was investigated by using a series of α-ketoesters. It seemed that methyl, ethyl, isopropyl and *tert*-butyl esters gave identical excellent results (Table 2, entries 1–4). Generally, the reactions were remarkably tolerant of functional groups in terms of enantioselectivity regardless of the electronic properties and steric hindrance of the substituents on the α-aryl group of the α-ketoesters (Table 2, entries 5–23). The catalyst system was also applicable to heteroaryl α-ketoesters, which delivered the related adducts in excellent outcomes (Table 2, entries 24 and 25). The aliphatic α-ketoesters also reacted with **2a** in excellent enantioselectivity even though the yield decreased a little (Table 2, entries 26–28). Moreover, when nucleophiles, like **2b** and **2c**, were subjected to the reaction, the desired products with up to 98% yield and >99% ee were achieved (Table 2, entries 29 and 30).

Encouraged by the above results, glyoxal derivatives were tested in the reaction with 5-methyleneoxazoline. Pleasingly, the **L2**–$Ni(BF_4)_2{\cdot}6H_2O$ complex was more suitable for such kinds of substrates even at 0.5 mol% catalyst loading, and the desired products were obtained in excellent yields (60–99% yields) with excellent ee values in the range of 95–>99% (Scheme 1a).[11] To show the utility of the current method, the hetero-ene reaction of

Table 2 Substrate scope for the catalytic asymmetric hetero-ene reaction of α-ketoesters



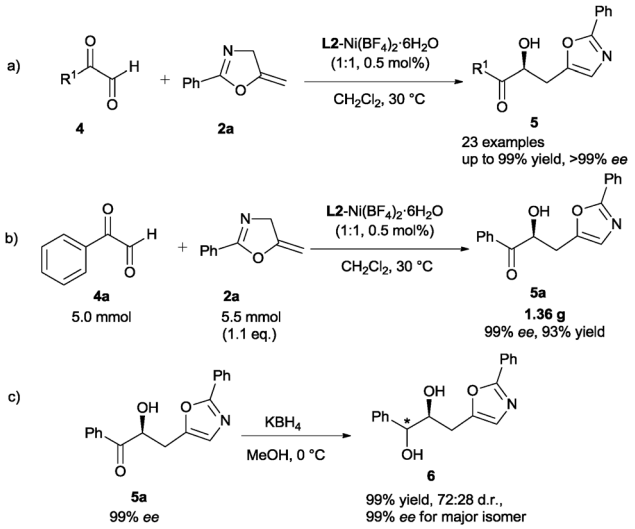
Entry[a]	1, R^1, R^2	2, R^3	Yield[b] (%)	ee[c] (%)
1	**1a**, C_6H_5, Me	**2a**, C_6H_5	97 (**3a**)	>99
2	**1a²**, C_6H_5, Et	**2a**, C_6H_5	99 (**3a²**)	>99
3	**1a³**, C_6H_5, iPr	**2a**, C_6H_5	98 (**3a³**)	>99
4	**1a⁴**, C_6H_5, *t*Bu	**2a**, C_6H_5	98 (**3a⁴**)	>99
5	**1b**, 3-MeC_6H_4, Me	**2a**, C_6H_5	95 (**3b**)	>99
6	**1c**, 4-MeC_6H_4, Me	**2a**, C_6H_5	77 (**3c**)	>99
7[d]	**1d**, 2-$MeOC_6H_4$, Me	**2a**, C_6H_5	42 (**3d**)	99
8	**1e**, 3-$MeOC_6H_4$, Me	**2a**, C_6H_5	97 (**3e**)	>99 (*S*)[e]
9	**1f**, 4-$MeOC_6H_4$, Me	**2a**, C_6H_5	63 (**3f**)	>99
10	**1g**,  , Me	**2a**, C_6H_5	66 (**3g**)	>99
11	**1h**, 3-FC_6H_4, Me	**2a**, C_6H_5	99 (**3h**)	>99
12	**1i**, 4-FC_6H_4, Me	**2a**, C_6H_5	95 (**3i**)	>99
13	**1j**, 3-ClC_6H_4, Me	**2a**, C_6H_5	98 (**3j**)	>99
14	**1k**, 4-ClC_6H_4, Me	**2a**, C_6H_5	99 (**3k**)	>99
15	**1l**, 3-$F_3CC_6H_4$, Me	**2a**, C_6H_5	99 (**3l**)	>99
16	**1m**, 4-$F_3CC_6H_4$, Me	**2a**, C_6H_5	97 (**3m**)	99
17	**1n**, 3-$CH_2{=}CHC_6H_4$, Me	**2a**, C_6H_5	97 (**3n**)	>99
18	**1o**, 4-$CH_2{=}CHC_6H_4$, Me	**2a**, C_6H_5	95 (**3o**)	>99
19	**1p**, 3,5-$Me_2C_6H_3$, Me	**2a**, C_6H_5	93 (**3p**)	>99
20	**1q**, 3-iPrC_6H_4, Me	**2a**, C_6H_5	95 (**3q**)	>99
21	**1r**, 4-*t*BuC_6H_4, Me	**2a**, C_6H_5	96 (**3r**)	>99
22	**1s**, 4-phC_6H_4, Me	**2a**, C_6H_5	95 (**3s**)	>99
23	**1t**, 2-naphthyl, Me	**2a**, C_6H_5	98 (**3t**)	>99
24	**1u**, 2-thienyl, Et	**2a**, C_6H_5	98 (**3u**)	99
25	**1v**, 2-furyl, Me	**2a**, C_6H_5	96 (**3v**)	>99
26	**1w**, *c*-hexyl, Me	**2a**, C_6H_5	40 (**3w**)	>99
27	**1x**, Me, Me	**2a**, C_6H_5	84 (**3x**)	>99
28	**1y**,  , Et	**2a**, C_6H_5	75 (**3y**)	>99
29	**1a**, C_6H_5, Me	**2b**, 3-$MeOC_6H_4$	91 (**3ba**)	>99
30	**1a**, C_6H_5, Me	**2c**, 4-MeC_6H_4	98 (**3ca**)	>99

[a] Unless otherwise noted, all reactions were carried out with 10 mol% of **L2**–$Ni(BF_4)_2{\cdot}6H_2O$, 0.2 mmol of α-ketoester **1**, 2.0 equiv. of **2**, and 20 mg of 4 Å MS in CH_2Cl_2 (1.0 mL) at 40 °C for 48 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The reaction was carried out for 96 h. [e] The absolute configuration was determined by X-ray analysis.

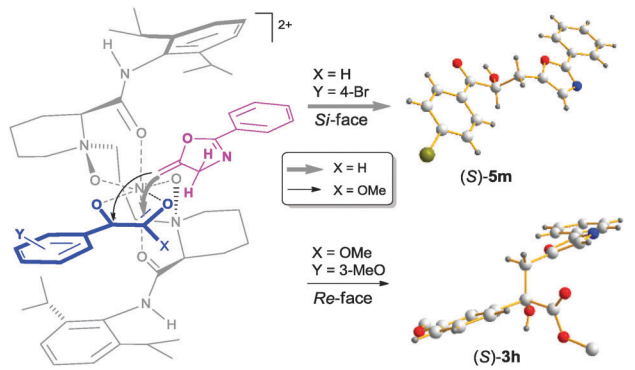
phenylglyoxal **4a** was expanded to a gram scale, and the desired product **5a** was accomplished in 93% yield with 99% ee (Scheme 1b). Notably, the reduction of the carbonyl group in **5a** by using KBH_4 afforded the 1,2-diol **6** in quantitative yield with the maintained enantioselectivity, which is a valuable intermediate in the synthesis of drugs and natural products (Scheme 1c).[12]

Based on the X-ray crystal structure of the catalyst,[9a] as well as the absolute configuration of the products,[13] a possible transition state was proposed (Scheme 2). The α-ketoester or glyoxal derivative tended to coordinate to nickel(II) in a bidentate fashion by the dicarbonyl group. The *Si* face of the α-ketoester was shielded by the neighboring 2,6-diisopropylphenyl group of the ligand, and the nucleophile attacked from the *Re* face predominantly to give the *S*-configured product **3h**. In a similar manner, the 5-methyleneoxazoline would attack from the *Si* face of the glyoxal derivative to give the *S*-configured product **5m**.

In conclusion, we have developed a highly efficient catalytic asymmetric hetero-ene reaction that involves methyleneoxazoline



Scheme 1 (a) Substrate scope for the catalytic asymmetric hetero-ene reaction of glyoxal derivatives (see ESI† for full lists); (b) scaled-up version of the asymmetric hetero-ene reaction; (c) transformation of product **5a**.



Scheme 2 Proposed transition-state and the X-ray crystallographic structure of (*S*)-product **3h** and (*S*)-product **5m**.

as the reaction partner for the enantioselective synthesis of 2,5-disubstituted oxazole derivatives. In the presence of the *N*,*N*′-dioxide–Ni(BF_4)$_2$·6H_2O catalysts, both α-ketoesters and glyoxal derivatives underwent the reaction smoothly, thus providing the corresponding products in excellent yields (up to 99%) and extremely high enantioselectivities (up to >99% ee). In particular, this new process proceeds under mild conditions, exhibits a broad substrate scope and functional-group tolerance, and features good air and moisture tolerance. Application of this chemistry to natural product synthesis and additional studies of alkylideneoxazolines is currently ongoing.

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