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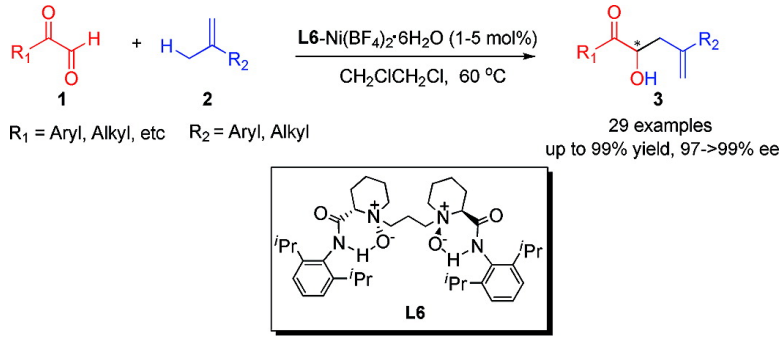

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Asymmetric Carbonyl-Ene Reaction Catalyzed by Chiral *N,N′*-Dioxide-Nickel(II) Complex: Remarkably Broad Substrate Scope

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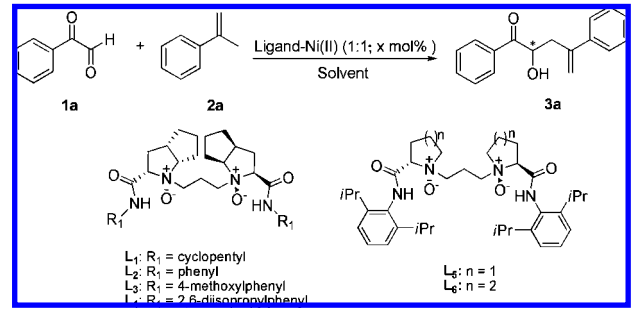
The optically active α-hydroxy carbonyl compounds are widespread in natural products and have been frequently used as convenient building blocks in organic synthesis.[1] The asymmetric carbonyl-ene reaction of glyoxal derivatives and glyoxylate could provide access to nonracemic γ,δ-unsaturated α-hydroxy carbonyl compounds which are more synthetically versatile intermediates by the further transformation of the carbonyl group and carbon−carbon double bond. Since the pioneering work of Yamamoto and co-workers,[2] a massive effort has been devoted to the development of enantioselective carbonyl-ene reactions, and numerous impressive successes have been recorded.[3−5] However, the previous studies mainly focused on glyoxylate,[3] and only a few examples of highly enantioselective carbonyl-ene reactions with glyoxal derivatives have been reported.[5] Therefore, searching for a highly effective catalyst system with high enantioselectivity and a broad substrate scope is still challenging and interesting. As excellent chiral scaffolds,[6,7] *N,N′*-dioxides could coordinate with many metals[7] and exhibited great potential in many asymmetric reactions. Herein, we present a novel and efficient chiral catalyst system based on *N,N′*-dioxide-nickel(II) complexes for the asymmetric carbonyl-ene reaction. Excellent enantioselectivities (up to >99% ee) were obtained for a broad range of substrates including aromatic, aliphatic glyoxal derivatives, as well as glyoxylate with various alkenes.

Initially, we examined the carbonyl-ene reaction of phenylglyoxal (**1a**) and phenylpropene (**2a**), promoted by the nickel(II)-*N,N′*-dioxide complex (Table 1). *N,N′*-Dioxide **L2** derived from aromatic amine exhibited superior results to **L1** based on aliphatic amine with moderate enantioselectivity (Table 1, entry 1 vs 2). To further improve the enantioselectivity of the reaction, the steric and electronic effects of the ligand were examined (Table 1, entries 2−6). As shown in Table 1, ligand with bulkier group at the *ortho* position of aniline, such as *iso*-propyl, could achieve higher enantioselectivities (up to 99% ee; entry 4 vs entries 2, 3). As for the chiral backbone moiety, when (*S*)-pipecolic acid derived *N,N′*-dioxide **L6** was used instead of the *L*-proline and (*S*)-ramipril derived ones, the yield was dramatically improved (Table 1, entry 6 vs entries 4, 5).

To further improve the efficiency of the reaction, several other reaction conditions such as solvent and reaction temperature were investigated (Table 1, entries 7−10).[8] As shown in Table 1, $Ni(ClO_4)_2$ and $Ni(BF_4)_2$ could give almost the same results in DCE (Table 1, entries 7, 8). However, the behavior of the catalyst **L6**-$Ni(BF_4)_2$ and **L6**-$Ni(ClO_4)_2$ at lower catalyst loading was unusual,[8] and the best results were obtained with 5 mol% **L6**-$Ni(BF_4)_2$ at 60 °C (Table 1, entries 9, 10). And the catalyst loading could even be decreased to 1 mol%, while the enantioselectivity was basically maintained (Table 1, entry 12). Extensive screening showed that the optimized conditions were 5 mol% **L6**-$Ni(BF_4)_2 \cdot 6H_2O$ complex (molar ratio: 1/1), 0.1 mmol of phenylglyoxal, and 0.3 mmol of phenylpropene in 0.5 mL of DCE (CH_2ClCH_2Cl) at 60 °C. Furthermore, this process could tolerate air and moisture.

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	Ni(II)	*x* (mol%)	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	$Ni(ClO_4)_2$	20	CH_2Cl_2	32	51
2	**L2**	$Ni(ClO_4)_2$	20	CH_2Cl_2	42	57
3	**L3**	$Ni(ClO_4)_2$	20	CH_2Cl_2	57	63
4	**L4**	$Ni(ClO_4)_2$	20	CH_2Cl_2	75	99
5	**L5**	$Ni(ClO_4)_2$	20	CH_2Cl_2	70	80
6	**L6**	$Ni(ClO_4)_2$	20	CH_2Cl_2	99	99
7	**L6**	$Ni(ClO_4)_2$	20	DCE	99	>99
8	**L6**	$Ni(BF_4)_2$	20	DCE	99	>99
9[d]	**L6**	$Ni(ClO_4)_2$	5	DCE	95	96
10[d]	**L6**	$Ni(BF_4)_2$	5	DCE	98	>99
11[d]	**L6**	$Ni(BF_4)_2$	2.5	DCE	89	99
12[d]	**L6**	$Ni(BF_4)_2$	1	DCE	83	99

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol of phenylglyoxal and 3.0 equiv of 2-phenylpropene in solvent (0.5 mL) at 25 °C for 64 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction was performed at 60 °C for 16−32 h.

Under the optimized conditions, a series of glyoxal derivatives were examined in asymmetric carbonyl-ene reactions with various alkenes, and the corresponding products were gained in high yields with excellent ee values in the range of 97−>99% (Table 2). It was noteworthy that this catalyst system exhibited a remarkably broad substrate scope. Whether the electronic properties or the steric hindrance of the substituent at the aromatic ring had no obvious effect on the enantioselectivity (ee values generally >99%; Table 2, entries 1−16). The condensed-ring glyoxal (1-naphthylglyoxal) reacted smoothly with 2-phenylpropene, giving the desired product with >99% ee (Table 2, entry 17). Inspiringly, the excellent enantioselectivities have been achieved for the first time in the asymmetric carbonyl-ene reaction of heteroaromatic glyoxals and aliphatic glyoxals (97−>99% ee; Table 2, entries 18−21). Moreover, either the 2-methyl and 4-fluoro substituted phenylpropenes

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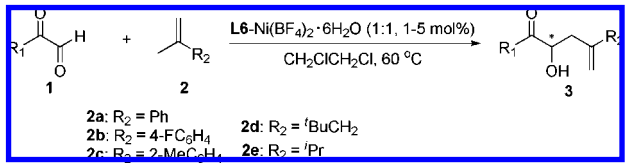
Table 2. Substrate Scope for the Catalytic Asymmetric Carbonyl-Ene Reaction[a]



entry	R_1	2	yield (%)[b]	ee (%)[c]
1	Ph	**2a**	98 (83)	>99 (99)[g]
2	2-MeC_6H_4	**2a**	95 (78)	>99 (98)[h]
3	3-MeC_6H_4	**2a**	92 (82)	99 (98)[h]
4	4-MeC_6H_4	**2a**	97 (80)	>99 (97)[h]
5	3-$MeOC_6H_4$	**2a**	91 (78)	>99 (98)[h]
6	4-$MeOC_6H_4$	**2a**	99 (85)	>99 (96)[g]
7	3,4-$(MeO)_2C_6H_3$	**2a**	90 (87)	>99 (97)[h]
8	2-ClC_6H_4	**2a**	74	>99
9	3-ClC_6H_4	**2a**	92 (70)	99 (97)[h]
10	4-ClC_6H_4	**2a**	86 (75)	>99 (98)[h]
11	3,4-$Cl_2C_6H_3$	**2a**	92 (75)	99 (99)[h]
12	2-FC_6H_4	**2a**	85	99
13	4-FC_6H_4	**2a**	92 (73)	>99 (99)[h]
14	4-BrC_6H_4	**2a**	95 (70)	99 (97)[h]
15	3-$NO_2C_6H_4$	**2a**	72	>99
16	4-$NO_2C_6H_4$	**2a**	78	>99
17	2-naphthyl	**2a**	93 (77)	>99 (99)[h]
18	2-furyl	**2a**	95 (80)	>99 (98)[g]
19	2-thienyl	**2a**	90 (83)	98 (98)[h]
20	*c*-hexyl	**2a**	80	97
21	Me	**2a**	75	99
22	Ph	**2b**	93 (82)	>99 (99)[h]
23[e]	Ph	**2c**	73	>99
24	Ph	**2d**	84	98
25[e]	Ph	**2e**	86	>99
26[f]	OEt	**2a**	99	99 (*S*)[d]
27[f]	OEt	**2b**	94	97
28[e,f]	OEt	**2c**	77	99
29[f]	OEt	**2d**	87	98 (*S*)[d]

[a] Unless otherwise noted, the reaction was carried out with 5 mol% **L6**-Ni$(BF_4)_2$·$6H_2O$, 0.1 mmol of glyoxal derivative (glyoxylate), and 3.0 equiv of alkene in DCE (0.5 mL) at 60 °C for 14−48 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The absolute configuration was determined by comparison with literature data.[3r] [e] With 10 mol% catalyst. [f] The reaction was performed at 40 °C. [g] The results in parentheses were obtained with 1 mol% catalyst. [h] The results in parentheses were obtained with 2.5 mol% catalyst.

or 1,1-dialkyl substituted ethenes (such as 2,4,4-trimethyl-1-pentene (**2d**) and 2,3-dimethyl-1-butene (**2e**)) all proceeded smoothly with phenylglyoxal in high yields and 98−>99% ee (Table 2, entries 22−25). For most glyoxyl derivatives, excellent ee (96−99% ee; Table 2, data in parentheses) with good yield was obtained using 2.5 mol% even as low as 1 mol% catalyst (for more data, see Supporting Information).

The scope of the ene methodology was extended successfully to glyoxylate (Table 2, entries 26−29). While the reaction of various alkenes (**2a**, **2b**, and **2d**) with glyoxylate could achieve excellent enantioselectivities (up to 99% ee) and high yields, the 2-methyl substituted phenylpropene (**2c**) also reacted well but required more catalyst loading (10 mol%) and a longer time to complete the reaction (Table 2, entry 28).

In conclusion, we have developed a novel chiral *N*,*N*′-dioxide-nickel(II) complex for the asymmetric carbonyl-ene reaction of both glyoxal derivatives and glyoxylate. Significant progress has been obtained with an extremely broad substrate scope, giving chiral γ,δ-unsaturated α-hydroxy carbonyl compounds in high yields with excellent enantioselectivities (up to >99% ee). The operational simplicity, practicability, and mild conditions rendered it an attractive approach for the asymmetric synthesis of optical γ,δ-unsaturated α-hydroxy carbonyl compounds. Further studies of the reaction mechanism and the application of this catalyst to other reactions are underway.

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

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