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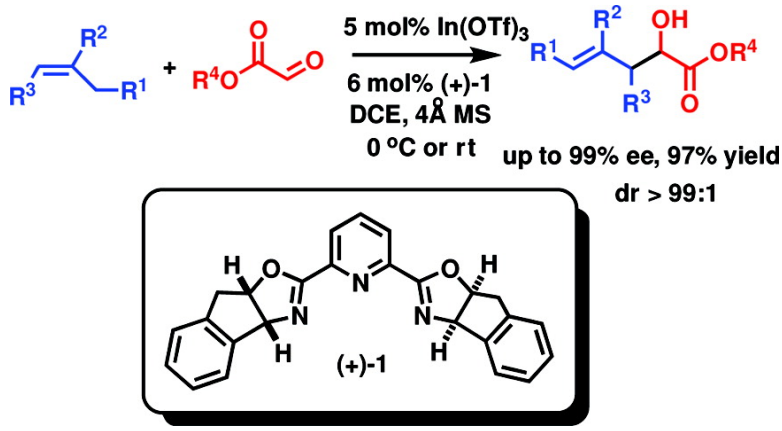

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Highly Enantioselective Carbonyl-ene Reactions Catalyzed by In(III)−PyBox Complex

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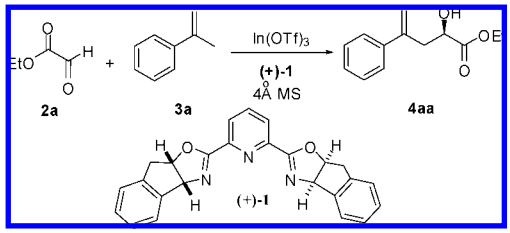
The carbonyl-ene reaction has gained tremendous attention[1] because it allows the atom-economic construction of homoallylic alcohols, which are important building blocks for the synthesis of many natural products and pharmaceutical compounds.[2] Accordingly, several research groups have reported the chiral metal complexes mediated asymmetric carbonyl-ene reaction. Initially, Yamamoto's[3] aluminum-based and Mikami's titanium-based[4] BINOL complexes were developed. Subsequently, Evans and coworkers reported that both Cu−Box[5] and Sc−PyBox[6] are efficient catalysts for this reaction. Other metal complexes derived from Co,[7] Pd,[8] Pt,[9] Cr,[10] and several lanthanides[11] had also been used to mediate the asymmetric carbonyl-ene reaction. Most recently, Terada[12] and Rueping[13] have independently reported the organocatalyzed enantioselective carbonyl-ene reaction. While extraordinary advances have been achieved, most of them still have limitations such as high catalyst loading, harsh reaction conditions, limited substrate scope, or difficult preparation of catalyst. Therefore, the asymmetric carbonyl-ene reaction remains a challenging topic. We herein present the In(III)−pybox complex[14] catalyzed highly enantioselective carbonyl-ene reactions.

Preliminary studies[15] demonstrated that the chiral indium complex, formed in situ from commercially availiable $In(OTf)_3$ and pybox **1** in the presence of 4 Å molecular sieves, did indeed promote the enantioselective carbonyl-ene reaction in excellent yield and with satisfactory enantioselectivity (Table 1, entry 1). Next, we evaluated the effect of solvent, temperature, and amount of catalyst on the reaction. As shown in Table 1, this reaction was sensitive to solvent, and 1,2-dichloroethane (DCE) was the optimum choice of solvent (Table 1, entries 1−6). Importantly, the catalyst loading could be reduced to 5 mol % with improved enantioselectivity (Table 1, entry 8). We also found that the enantioselectivity could be further improved by decreasing the concentration of the reaction system (Table 1, entry 10). While room temperature offered good results, the best results were attained at 0 °C (Table 1, entries 10 and 11).

Table 1. Optimization Studies[a]

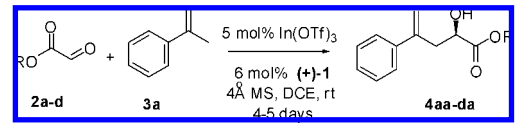


entry	catalyst (mol %)	solvent	time (day)	yield (%)[b]	ee (%)[c]
1	20	CH_2Cl_2	1	97	83
2	20	CH_3CN	1	trace	nd
3	20	toluene	1	45	47
4	20	$CHCl_3$	1	trace	nd
5	20	THF	1	trace	nd
6	20	DCE	1	98	86
7	10	DCE	2	89	89
8	5	DCE	4	95	91
9	2	DCE	4	63	77
10[d]	5	DCE	4	93	94
11[e]	**5**	**DCE**	**6**	**96**	**95**

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of α-methylstyrene in 2.0 mL of solvent at room temperature, unless noted otherwise. [b] Isolated yield. [c] The ee values were determined by chiral-phase HPLC analysis, and the absolute configuration of the major products was *R*, assigned by comparing HPLC with the literature; nd = not detected. [d] This reaction was carried out in 4.0 mL of solvent at room temperature. [e] This reaction was carried out in 4.0 mL of solvent at 0 °C.

We then investigated the effect of ester group of glyoxylate. The carbonyl-ene reactions between α-methyl styrene and representative glyoxylate esters were carried out under the optimized conditions (Table 2). All the glyoxylate esters proceeded smoothly to give

Table 2. In(III)−PyBox Complex-Catalyzed Asymmetric Carbonyl-ene Reactions of α-Methylstyrene with Various Glyoxylates[a]



entry	R	product	yield (%)[b]	ee (%)[c]
1	Et **2a**	**4aa**	93	94
2	Me **2b**	**4ba**	95	93
3	*i*-Pr **2c**	**4ca**	80	92
4	*n*-Bu **2d**	**4da**	96	92

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of α-methylstyrene in 4.0 mL of DCE, unless noted otherwise. [b] Isolated yield. [c] The ee values were determined by chiral-phase HPLC analysis, and the absolute configuration of the major products was *R*, assigned by comparing HPLC with the literature.

the ene products in good to excellent yields and with high enantioselectivities.

To further examine the scope and limitation of the methodology, carbonyl-ene reactions between the commercially available ethyl glyoxylate and various 1,1-disubstituted and trisubstituted alkenes were explored, and the results were summarized in Table 3. Both the aromatic and aliphatic alkenes afforded the expected homoallylic

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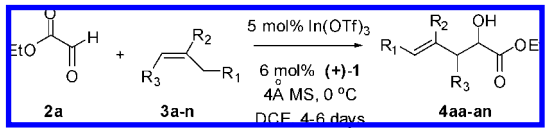
Table 3. In(III)−PyBox Complex-Catalyzed Aymmetric Carbonyl-ene Reactions of Ethyl Glyoxylate with Various Olefins[a]



entry	ene	product	yield (%)[b]	ee (%)[c]
1	3a	4aa	96	95
2	3b	4ab	96	94
3	3c	4ac	90	95
4	3d	4ad	83	89
5	3e	4ae	95	90
6	3f	4af	60	97
7	3g	4ag	80	90
8	3h	4ah	20	91
9	3i	4ai	96	96
10	3j	4aj	18	76
11	3k	4ak	75	95
12	3l	4al	96	95
13	3m	4am	97	90
14[d]	3n	4an	60	99

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of olefins in 4.0 mL of DCE at 0 °C, unless indicated otherwise. [b] Isolated yield. [c] The ee values were determined by chiral-phase HPLC analysis or GC, and the absolute (*R*)-configuration of the major products was assigned by comparing HPLC with the literature. [d] Regioselectivity and diastereoselectivity were >99:1, and the absolute configuration was not determined.

alcohol products in good to excellent yields and excellent enantioselectivities. Interestingly, it was found that the position and the electronic property of the substituents on the phenyl ring of ene have some subtle effects on the reaction efficiency. While weak electron-donating and withdrawing substituents (Table 3, entries 2−7) were tolerated, strong electron-donating (Table 3, entries 8−10) and withdrawing substituents influenced the reaction significantly. The yield or the enantioselectivity or both were sacrificed when the methoxy group was at ortho or para position (Table 3, entries 8, 10). There was no reaction when 4-nitro-α-methyl styrene or 4-methylsulfonly-α-methyl styrene was used as substrate. The reaction of trisubstituted alkene (Table 3, entry 14) is notable: the regioselectivity, diastereoselectivity, and enantioselectivity were very high and gave the product almost in optically pure form albeit in moderate yield. Finally, cyclic and acyclic aliphatic alkenes also underwent the carbonyl-ene reaction effectively to furnish the desired products in high yields and with excellent enantioselectivities (Table 3, entries 11−13).

In conclusion, we have developed a highly enantioselective and efficient indium(III)−pybox complex-promoted carbonyl-ene reaction. The catalyst is easily prepared from commercially availiable $In(OTf)_3$ and pybox **1**. This protocol offers several advantages including operational simplicity, mild reaction conditions, low catalyst loading, and high enantioselectivities and yields, which makes it a useful and attractive strategy for the synthesis of chiral homoallylic alcohols.

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Supporting Information Available: Additional experimental procedures, all chromatograms, and spectral data for reactions products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For screening of chiral ligands and indium salts, see Supporting Information.

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