

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

Jun-Feng Zhao, Hoi-Yan Tsui, Pei-Jia Wu, Jun Lu, and Teck-Peng Loh*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

Received September 22, 2008; E-mail: teckpeng@ntu.edu.sg

The carbonyl-ene reaction has gained tremendous attention¹ 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's³ aluminum-based and Mikami's titanium-based⁴ BINOL complexes were developed. Subsequently, Evans and co-workers reported that both Cu–Box⁵ and Sc–PyBox⁶ are efficient catalysts for this reaction. Other metal complexes derived from Co,⁷ Pd,⁸ Pt,⁹ Cr,¹⁰ and several lanthanides¹¹ had also been used to mediate the asymmetric carbonyl-ene reaction. Most recently, Terada¹² and Rueping¹³ have independently reported the organo-catalyzed 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 complex¹⁴ catalyzed highly enantioselective carbonyl-ene reactions.

Preliminary studies¹⁵ demonstrated that the chiral indium complex, formed in situ from commercially available 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).

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

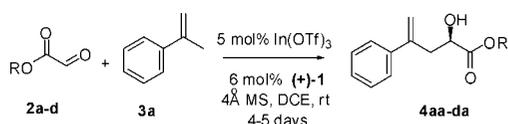
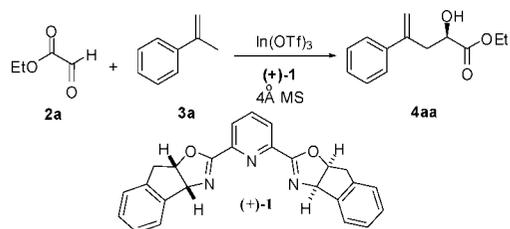


Table 1. Optimization Studies^a



entry	catalyst (mol %)	solvent	time (day)	yield (%) ^b	ee (%) ^c
1	20	CH ₂ Cl ₂	1	97	83
2	20	CH ₃ CN	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.

entry	R	product	yield (%) ^b	ee (%) ^c
1	Et 2a		93	94
2	Me 2b		95	93
3	<i>i</i> -Pr 2c		80	92
4	<i>n</i> -Bu 2d		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

Table 3. In(III)–PyBox Complex-Catalyzed Asymmetric Carbonyl-ene Reactions of Ethyl Glyoxylate with Various Olefins^a

entry	ene	product	yield (%) ^b	ee (%) ^c
1			96	95
2			96	94
3			90	95
4			83	89
5			95	90
6			60	97
7			80	90
8			20	91
9			96	96
10			18	76
11			75	95
12			96	95
13			97	90
14 ^d			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-methylsulfonyl- 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 available 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.

Acknowledgment. We gratefully acknowledge the Nanyang Technological University and Singapore Ministry of Education Academic Research Fund Tier 2 (No. T206B1221 and T207B1220RS) for the funding of this research.

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>.

References

- (1) For a general review of the ene reaction, see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050. (b) Berrisford, D. J.; Bolm, C. *Angew. Chem., Int. Ed.* **1995**, *34*, 1717–1719. (c) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255–265. (d) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639–644.
- (2) (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701–3704. (b) Hornberger, K. R.; Hamblet, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894–12895. (c) Felpin, F. X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192–9199.
- (3) Maruoka, K.; Hoshino, Y.; Shirasaka, Y. H.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967–3970.
- (4) (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940–1941. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039–7040. (d) Mikami, K.; Yajima, T.; Terada, M.; Kato, E.; Maruta, M. *Tetrahedron: Asymmetry* **1994**, *6*, 1087–1090. (e) Mikami, K.; Tomoko, Y.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimar, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85–98.
- (5) (a) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824–5825. (b) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936–7943. (c) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133–2143.
- (6) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006–8007.
- (7) (a) Kezuka, S.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 1937–1939. (b) Hutson, G. E.; Dave, A. H.; Rawal, V. H. *Org. Lett.* **2007**, *9*, 3869–3872.
- (8) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059–4062. (b) Aikawa, K.; Kainuma, S.; Hatano, M.; Mikami, K. *Tetrahedron Lett.* **2004**, *45*, 183–185. (c) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704–4705. (d) Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, *129*, 12950–12951.
- (9) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233–1236.
- (10) (a) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882–2883. (b) Ruck, R. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 4771–4774. (c) Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1469–1472.
- (11) Qian, C.; Wang, L. *Tetrahedron: Asymmetry* **2000**, *11*, 2347–2357.
- (12) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122–4125.
- (13) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798–6801.
- (14) (a) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739–2749. (b) Lu, J.; Hong, M. L.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 1010–1012. (c) Lu, J.; Hong, M. L.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Chem. Commun.* **2005**, 4217–4218. (d) Lu, J.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 2345–2347. (e) Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 159–161. (f) Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, 1318–1320. (g) Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2539–2541. (h) Teo, Y. C.; Goh, J. D.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2743–2745. (i) Fu, F.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2006**, *8*, 5999–6001. (j) Fu, F.; Teo, Y. C.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 4267–4269.
- (15) For screening of chiral ligands and indium salts, see Supporting Information.

JA807501A