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Highly Enantioselective Ketone-Ene Reactions of Trifluoropyruvate: Significant Counterion Effect of the In(III)−PyBox Complex

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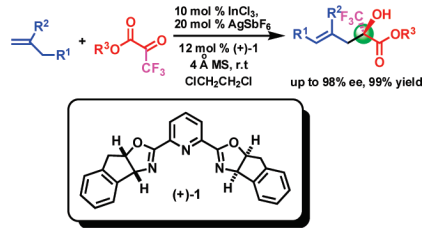
ABSTRACT



A chiral indium(III)−pybox complex catalyzed asymmetric ketone-ene reaction of trifluoropyruvate is described. Both aromatic and aliphatic 1,1-disubstituted alkenes reacted smoothly to give the enantioenriched tertiary homoallylic alcohols in good to excellent yields (up to 99%) and with excellent enantioselectivities (up to 98% ee).

Designing effective catalysts to control relative and absolute stereochemistries as well as to speed up reactions is an important driving force for the development of organic synthesis. Accordingly, many chiral Lewis acid complexes[1] and Brønsted acids[2] have been developed in recent years. Among the Lewis acid complexes, indium(III) complexes[3] have emerged as a popular choice due to their versatile utility in effecting various organic transformations. Our group[4] and others[5] have developed several chiral indium(III) complexes which could be used as chiral catalysts for a series of asymmetric reactions.

Unlike other chiral metal complex catalyzed reactions which must be carried out under strictly anhydrous condi-

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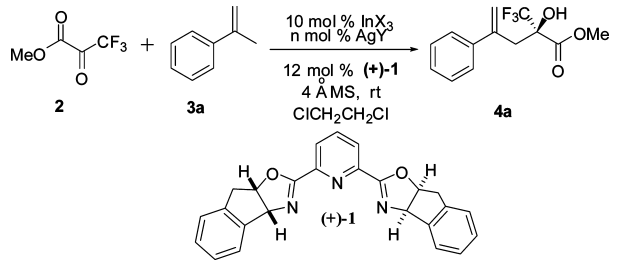
tions, chiral indium(III) complexes are water-tolerant catalysts. However, existing chiral indium(III) complexes are not reactive enough, and their applications are limited. Therefore, one of the major challenges in this field is to design more reactive chiral indium(III) complexes which can substantially expand their utility. In this paper, we showed that the chiral In(III)−pybox complex designed based on counterion effect is much more reactive than the corresponding parent complex. With the catalysis of this more powerful chiral indium(III) complex, the less reactive asymmetric ketone-ene reactions[6] of trifluoropyruvates proceeded smoothly under mild conditions to afford the biologically important enantioenriched tertiary homoallylic alcohols with excellent enantioselectivities and yields.

We have recently demonstrated that the indium(III)−pybox complex is an effective catalyst for asymmetric carbonyl-ene reactions of glyoxylates.[4a] Unfortunately, long reaction times (4−6 days) were required for completing the reactions. Furthermore, this catalyst system is too mild to catalyze the less reactive ketone-ene reaction (Table 1, entry 1). Counterion effects had been shown as an efficient strategy for improving the catalytic efficiency of chiral metallic Lewis acid complexes.[7] However, most of these successful examples are focused on transition metal complexes. We hypothesized that replacing the counteranion of the parent indium(III)−pybox complex with a stronger electronegative anion will lead to a more reactive indium(III)−pybox complex which derived from a main group metal.

Table 1. Optimization Studies[a]



entry	InX_3	AgY (mol %)	time (h)	yield[b] (%)	ee[c] (%)
1	$In(OTf)_3$	−	144	33	8
2	$In(OTf)_3$	$AgSbF_6$ (20%)	18	63	57
3	$InBr_3$	$AgSbF_6$ (20%)	3	94	95
4	**$InCl_3$**	**$AgSbF_6$ (20%)**	**3**	**99**	**95**
5	$InCl_3$	$AgSbF_6$ (10%)	22	99	92
6	$InCl_3$	$AgSbF_6$ (30%)	3	93	92
7	$InCl_3$	$AgPF_6$ (20%)	48	80	62
8	$InCl_3$	$AgBF_4$ (20%)	48	59	90
9	$InCl_3$	$AgClO_4$ (20%)	48	53	85
10[d]	$InCl_3$	$AgSbF_6$ (20%)	3	95	95
11[e]	$InCl_3$	$AgSbF_6$ (10%)	48	92	94
12	−	$AgSbF_6$ (20%)	24	−	−

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of trifluoropyruvate in 4.0 mL of 1,2-dichloroethane (DCE) 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.[6e] [d] Ethyl trifluoropyruvate was used. [e] 5 mol % of $InCl_3$ and 6 mol % of (+)-**1** were used.

To test this idea, we started with the highly electronegative "noncoordinating" anion SbF_6^-, which is usually used. Initially, the ketone-ene reaction of methyl trifluoropyruvate and α-methylstyrene was carried out in the presence of chiral indium(III) complex, which was formed in situ from 12 mol % pybox **1** and 10 mol % $InCl_3$. There was only a trace amount of product formed after stirring at room temperature for two days (monitored by TLC). When 30 mol % of silver hexafluoroantimonate ($AgSbF_6$) was added in one portion, the reaction was completed after 3 h and furnished the ketone-ene product quantitatively with excellent enantioselectivity (92% ee). Encouraged by this result, we investigated the counterion effect systematically, and the results are summarized in Table 1. The corresponding cationic indium(III)−pybox complexes with various counteranions were prepared by treatment of chloro or bromo indium(III)−pybox complex with the corresponding silver salts. A significant counterion effect was observed in the indium(III)−pybox complex, and the catalyst efficiency is positively correlated to the acidity of the conjugated acid of these counteranions (Table 1, entries 4, 7, 8, and 9). Interestingly, the catalytic efficiency was also affected by the amount of silver salt (Table 1, entries 4−6). Control experiments indicated that the chiral indium complex is the real catalyst (Table 1, entry 12). Finally, we found that in the presence of 4 Å molecular sieves 10 mol % $InCl_3$, 12 mol % pybox (+)-**1**, and 20 mol % $AgSbF_6$ provided the best results in terms of yield, reaction time, and enantioselectivity (Table 1, entry 4). The catalyst loading could be lowered to 5 mol % with no detrimental effect on yield and enantioselectivity, albeit a longer reaction time was required (Table 1, entry 11).

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Table 2. Indium(III)−PyBox Complex-Catalyzed Asymmetric Ketone-Ene Reactions of Methyl Trifluoropyruvate with Various Olefins[a]

2 3a-n 4a-n

entry	ene	product	time (h)	yield (%)[b]	ee (%)[c]
1	3a	4a	3	99	95
2	3b	4b	3	99	94
3	3c	4c	3	99	94
4	3d	4d	240	56	87
5	3e	4e	72	92	92
6	3f	4f	144	90	95
7	3g	4g	48	97	91
8	3h	4h	3	91	95
9	3i	4i	72	86	85
10	3j	4j	3	99	95
11[d]	3k	4k	2	99	64
12[e]	3l	4l	6	79	96
13[f]	3m	4m	48	95	98
14	3n	4n	3	94	98

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of methyl trifluoropyruvate in 4.0 mL of DCE at room temperature, 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 X-ray analysis[9] of **4f** and **4g** and comparing HPLC with the literature. [d] 5 mol % of catalyst loading was used. [e] Excess of isobutene was used. [f] This reaction was carried out at 0 °C.

With this promising result in hand,[8] we next evaluated the substrate scope of this ketone-ene reaction, and the results are listed in Table 2. As shown in Table 2, both aromatic and aliphatic alkenes afforded the expected enantioenriched tertiary homoallylic alcohols, containing a trifluoromethyl group, in good to excellent yields and excellent enantioselectivities. Significant electronic and steric effects were observed in the ketone-ene reaction of aromatic alkenes. This might be due to the positive charge built up in the process of the carbonyl-ene reaction.[10] The presence of an electron-withdrawing group decreases the reactivity of the alkene significantly, and a longer reaction time was required (Table 2, entries 4−7). On the contrary, an electron-donating group increases the reactivity of the alkene a little. 4-Methoxy-α-methyl styrene is too reactive to give satisfactory enantioselectivity (Table 2, entry 11) due to the strong electron-donating ability of the 4-methoxy group. It was found that the position of the substituents on the phenyl ring of the aromatic alkene also has some subtle effects on the reaction efficiency. For example, the yield and the enantioselectivity were both significantly sacrificed when the substituent, either an electron-withdrawing or -donating group, was at the *ortho* position (Table 2, entries 4 and 9).[11] This is presumably due to steric hindrance in the transition state.

In summary, we have successfully developed highly enantioselective indium(III)−pybox catalyzed ketone-ene reactions of trifluoropyruvate. This operationally trivial protocol provides facile access to the enantioenriched homoallylic alcohols, containing a trifluoromethyl group and a quaternary carbon center, which are important building blocks of pharmaceuticals and agrochemicals. The bench stable catalyst is easily prepared from commercially available $InCl_3$, pybox (+)-**1**, and $AgSbF_6$. The increased activity of the indium(III)−pybox complex, upon taking advantage of counterion effect, will expand the application of this catalyst. Efforts to apply this catalyst to other kinds of asymmetric transformations are ongoing in our laboratory.

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Supporting Information Available: Additional experimental procedures, spectral data for all the compounds, and CIF files for **4f** (CCDC 748910) and **4g** (CCDC 748911). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Because similar results were obtained when the AgX salt was filtered from the reaction system, AgX salt was not precipitated in this work.

(9) CCDC 748910 (**4f**) and 748911 (**4g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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(11) There was only a trace amount of product obtained after 2 days when *ortho*-methyl α-methyl styrene was used as substrate.