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Enantioselective Carbonyl-Ene Reactions of Trifluoropyruvate in Ionic Liquid *via* a Recyclable Indium(III)-Pybox Complex

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Abstract: A highly enantioselective carbonyl-ene reaction of trifluoropyruvate catalyzed by a recyclable indium(III)-pybox complex in ionic liquid afforded trifluoromethyl-containing tertiary homoallylic alcohols with excellent yields (up to 98%) and enantioselectivities (up to 98% *ee*). Notably, this catalytic system can be recycled up to seven cycles.

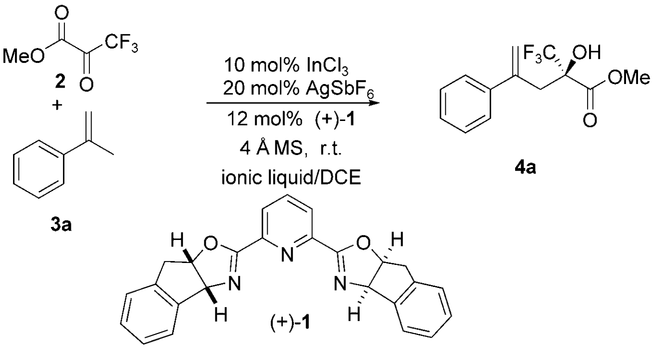
Keywords: asymmetric catalysis; carbonyl-ene reaction; indium; ionic liquids

Organofluorine compounds have attracted much attention in many scientific disciplines in view of the unique physical and biological properties of fluorine.[1] Among them, CF_3-containing compounds are of great interesting due to the unique properties, such as lipophilicity, stability, and strong electronegativity of the CF_3 group. Introduction of CF_3 groups often induces considerable changes in the chemical, physical, and physiological properties of the parent compounds.[2] Therefore, synthetic methods for introducing the trifluoromethyl group into an organic compound selectively have developed into an important field of chemistry.[3] The asymmetric carbonyl-ene reaction of trifluoropyruvate,[4] one type of ketone-ene reaction, is an effective methodology for constructing optically active tertiary homoallylic alcohols, containing a trifluoromethyl group, which are important building blocks for pharmaceuticals and agrochemicals. To our surprise, however, there are only few successful examples of asymmetric ketone-ene reactions[4,5] compared to the extensive studies of asymmetric aldehyde-ene reactions.[6] Thus far, the ketone-ene reaction still remains as a challenge. We have recently developed a highly enantioselective carbonyl-ene reaction of trifluoropyruvate catalyzed by a powerful In(III)-pybox complex, which was designed based on the counterion effect.[7] Regarding the practical, economical and environmental factors and biological importance of the products, we herein present the In(III)-pybox complex[8] catalyzed, highly enantioselective ketone-ene reactions of trifluoropyruvates by using ionic liquid as the solvent, which enable the easy recycle of the chiral catalyst.

Recently, our laboratory has been interested in using ionic liquid as an alternative to conventional organic solvent.[9] Employing ionic liquid as reaction medium has many advantages among which the most important one is the easy isolation of product by simple extraction, which enables recycling of the ionic liquid containing the chiral catalyst.[10] As far as we know, no asymmetric carbonyl-ene reaction of trifluoropyruvate in ionic liquid has been reported.[11] Considering the stability and recyclability of the In(III)-pybox complex in ionic liquid,[12] we attempted to carry out the ketone-ene reaction in ionic liquid. The catalyst was prepared by mixing indium(III) chloride, pybox (+)-**1** and 4 Å molecular sieves in a solution of 1,2-dichloroethane (DCE) and stirring for 20 min at room temperature. Then, $AgSbF_6$ was added to replace the anion of the parent In(III)-pybox complex. After stirring for another 20 min, ionic liquid [bmim]PF_6 was added, followed by sequential addition of α-methylstyrene and methyl trifluoropyruvate. To our delight, the carbonyl-ene reaction proceeded smoothly and afforded the enantioenriched tertiary allylic alcohol in 95% yield and 93% *ee* (Table 1, entry 1). Among the ionic liquids screened, [hmim]PF_6 proved to be the best choice of solvent (Table 1, entry 2).

We next examined the generality of this methodology and the results are summarized in Table 2. As shown in Table 2, the asymmetric ketone-ene reac-

Table 1. Optimization studies.[a]



Entry	Ionic liquid	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	[bmim]PF_6	1	95	93
2	[hmim]PF_6	1	96	96
3	[omim]PF_6	1	94	92
4	[hmim]BF_4	24	trace	–
5	[bmim]Br	24	trace	–
6[d]	[hmim]PF_6	1	95	96

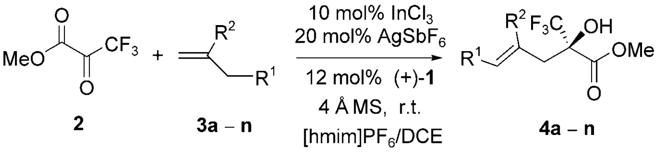
[a] Unless otherwise noted, reactions were carried out on a 0.3 mmol scale with 2 equiv. of trifluoropyruvate in a mixture of 0.5 mL of ionic liquid and 0.5 mL 1,2-dichloroethane (DCE) at room temperature.

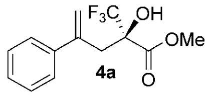
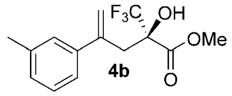
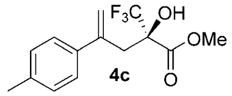
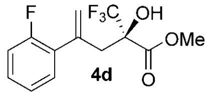
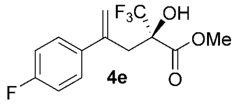
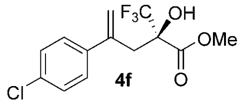
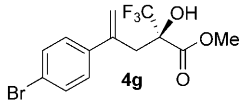
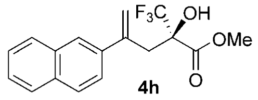
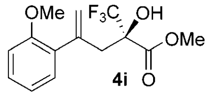
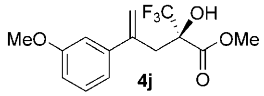
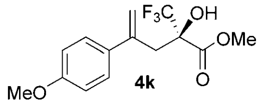
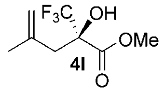
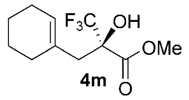
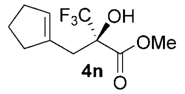
[b] Isolated yield.

[c] The *ee* values were determined by chiral-phase HPLC.

[d] DCE was removed before the addition of reactant.

Table 2. In(III)-pybox complex-catalyzed aymmetric carbonyl-ene reactions of methyl trifluoropyruvate with various olefins in ionic liquid.[a]



Entry	Product [**4a–n**]	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	 **4a**	1 (3)	95 (99)	96 (95)
2	 **4b**	1 (3)	92 (98)	95 (94)
3	 **4c**	1 (3)	93 (97)	94 (94)
4	 **4d**	162 (240)	90 (56)	97 (87)
5	 **4e**	5 (72)	91 (92)	97 (92)
6	 **4f**	4 (144)	91 (90)	97 (95)
7	 **4g**	7 (48)	97 (97)	98 (91)
8	 **4h**	4 (3)	80 (91)	96 (95)
9	 **4i**	72 (72)	74 (86)	80 (85)
10	 **4j**	20 (3)	91 (99)	97 (95)
11[d]	 **4k**	1 (2)	85 (99)	55 (64)
12[e]	 **4l**	3 (6)	78 (79)	98 (96)
13[f]	 **4m**	43 (48)	98 (95)	98 (98)
14	 **4n**	43 (3)	98 (94)	92 (98)

[a] Unless otherwise noted, reactions were carried out on a 0.3 mmol scale with 2 equiv. of trifluoropyruvate in a mixture of 0.5 mL [hmim]PF_6 and 0.5 mL 1,2-dichloroethane (DCE) at room temperature; the results in parentheses are for the reactions carried out in DCE.[7]

[b] Isolated yield.

[c] The *ee* values were determined by chiral-phase HPLC or GC analysis.

[d] 5 mol% of catalyst loading was used.

[e] Excess of isobutene was used.

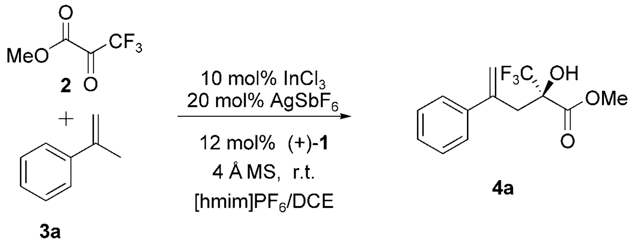
[f] This reaction was carried out at 0 °C.

tions of trifluoropyruvate proceeded smoothly to give the products with excellent yields and enantioselectivities. In addition, most of the reactions carried out in ionic liquid proceeded faster than those carried out in pure organic solvent with comparable or better yields and enantioselectivities. Similar to the reactions carried out in pure organic solvent, significant electronic and steric effects were also observed in this system. An electron-withdrawing group on the phenyl ring of substituted α-methylstyrene prolonged the reaction time (Table 2, entries 4–7). The position of the substituted group also has an effect on the reaction efficiency. Due to steric effect, either an electron-withdrawing or an electron-donating group at the *ortho* position led to lower yields and enantioselectivities (Table 2, entries 4 and 9). The lowest enantioselectivity observed in **4k** might be due to the more reactive nature of substrate **3k** (Table 2, entry 11).

In terms of cost-effectiveness, the recyclability of the chiral catalyst is a very important and a challenging task for industry. Therefore, we further investigated the recyclability of the In(III)-pybox complex by using the ketone-ene reaction of methyl trifluoropyruvate and α-methylstyrene as the model reaction and the results are listed in Table 3. After the reaction was completed, the reaction mixture was extracted with hexane (5×5 mL) to leave the ionic liquid [hmim]PF_6 containing the chiral In(III)-pybox complex, which can be used directly for the next cycle. It is noteworthy that this catalytic system can be reused for up to seven cycles with retention of excellent catalytic efficiency.

In summary, we have developed a chiral In(III)-pybox complex-catalyzed, highly enantioselective ketone-ene reaction of trifluoropyruvate in ionic liquid. This methodology has many advantages such as: (i) the moisture tolerant catalyst, which is easily prepared from commercially available chemicals, renders strict anhydrous conditions unnecessary; (ii) CF_3-containing homoallylic alcohols, important building blocks of pharmaceuticals and agrochemicals, can be obtained with excellent enantioselectivities and yields; (iii) the chiral In(III)-pybox complex in ionic liquid could be recycled up to seven times with retention of excellent catalytic efficiency; (iv) the operationally simple procedure will make this catalytic system more attractive for industrial as well as academic laboratories. Studies on further applications of this catalytic system to other organic transformations are underway in our laboratory.

Table 3. Recyclability study.[a]



Cycle	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	1	95	96
2	1	97	95
3	1	93	96
4	1	96	96
5	1	95	95
6	1.5	98	94
7	1.5	96	94

[a] Unless otherwise noted, reactions were carried out on a 0.3 mmol scale with 2 equiv. of trifluoropyruvate in a mixture of 0.5 mL [hmim]PF_6 and 0.5 mL 1,2-dichloroethane (DCE) at room temperature.

[b] Isolated yield.

[c] The *ee* values were determined by chiral-phase HPLC.

Experimental Section

General Procedure for Carbonyl-Ene Reactions of Alkenes with Trifluoromethylpyruvate Catalyzed by In(III)-Pybox complex in the Ionic Liquid [hmim]PF_6

In an oven-dried, 5-mL round-bottom flask equipped with a stirring bar, indium(III) chloride (6.66 mg, 0.03 mmol), pybox (+)-**1** (14.4 mg, 0.036 mmol) and 4 Å molecular sieves (100 mg) were stirred in a solution of DCE (0.5 mL) for 20 min at room temperature. To the above mixture, silver hexafluoroantimonate ($AgSbF_6$) (20.64 mg, 0.06 mmol) was added in one portion and stirred for another 20 min. To the pre-prepared catalyst in 1,2-dichloroethane (DCE), ionic liquid [hmim]PF_6 (0.5 mL) was added and stirred at room temperature for 10 min. Then the alkene (0.3 mmol, 1 equiv.) and trifluoromethylpyruvate (93.6 mg, 0.6 mmol, 2 equiv.) were added using a syringe. The mixture was stirred until the alkene had been consumed completely as indicated by TLC analysis. The crude product was loaded directly onto a silica gel column and purified by flash column chromatography to obtain the enantioenriched tertiary homoallylic alcohol.

Procedure for Recycle of In(III)-Pybox Complex in Ionic Liquid ([hmim]PF_6)

After the reaction in ionic liquid was completed, the reaction mixture was extracted with hexane (5×5 mL) to afford the crude ketone-ene product. 0.5 mL of DCE was added to the ionic liquid residue for the next run under identical reaction conditions. This catalytic system can be recycled for seven times and give the ketone-ene product in 96% yield and 94% *ee* for the last run.

Acknowledgements

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