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# Significant counterion effect of the In(III)–pybox complex in highly enantioselective carbonyl-ene reactions of ethyl glyoxylate

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ABSTRACT

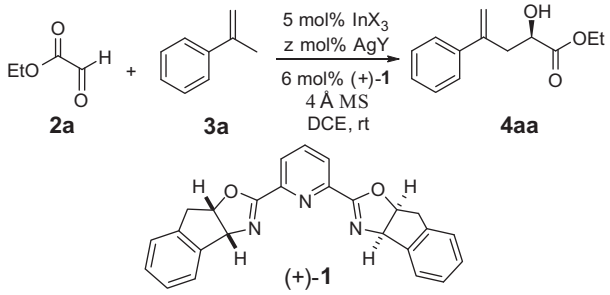
A highly efficient enantioselective carbonyl-ene reaction of ethyl glyoxylate catalyzed by an In(III)–pybox complex, which is designed based on the counterion effect, is reported. Reactions of both aliphatic and aromatic 1,1-disubstituted olefins proceed smoothly to give enantioenriched homoallylic alcohols with excellent yields and enantioselectivities. In addition, electron-withdrawing as well as donating groups on the phenyl ring of α-methyl styrenes are tolerated in this reaction.



The carbonyl-ene reaction is an important reaction in C–C bond formation.[1] The asymmetric carbonyl-ene reaction has attracted much attention as it offers convenient access to enantioenriched homoallylic alcohols, which are the versatile building blocks and intermediates of pharmaceutical and agricultural compounds.[2] Very recently, our group developed an efficient catalytic system for the asymmetric carbonyl-ene reaction of glyoxylates under mild conditions.[3] Under the catalysis of an In(III)–pybox complex, formed in situ from commercially available $In(OTf)_3$ and pybox (+)-**1**, the enantioselective carbonyl-ene reactions of 1,1-disubstituted and 1,1,2-trisubstituted olefins, including aromatic and aliphatic olefins, proceeded smoothly to give the enantioenriched homoallylic alcohols in good to excellent yields and enantioselectivities. However, the obvious disadvantage of this methodology is that the reaction rate is relatively slow requiring 4-6 days to complete the reaction. Moreover, the reaction must be carried out at 0 °C to obtain excellent and reproducible enantioselectivities. With regard to practicality, more reactive catalysts are needed. In a parallel study of asymmetric ketone-ene reactions of trifluoropyruvate, we developed a more powerful In(III)–pybox complex by taking advantage of the counterion effect.[4] Herein, we report an improved version of the highly enantioselective carbonyl-ene reactions of ethyl glyoxylate, catalyzed by the more active In(III)–pybox complex, at room temperature within several hours.

The counterion effect had been demonstrated as an efficient strategy to increase the catalytic activity of chiral metallic Lewis acid complexes.[5] It is also notable that the counterion effect of the In(III)–pybox complex improved the catalytic efficiency of the parent complex significantly.[4] The new generation In(III)–pybox complex is efficient enough to catalyze the ketone-ene reaction of trifluoropyruvate to give enantioenriched homoallylic alcohols containing a trifluoromethyl group in excellent yields and enantioselectivities at room temperature within an acceptable reaction time. We

**Table 1**
Optimization studies[a]




| Entry | $InX_3$ | AgY (mol %) | Time/h | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1[d] | $In(OTf)_3$ | — | 24 | 63 | 94 |
| 2 | $InCl_3$ | — | 24 | Trace | nd |
| 3 | $InBr_3$ | — | 24 | Trace | nd |
| 4 | $InBr_3$ | $AgSbF_6$ (15) | 8 | 95 | 81 |
| 5 | $InCl_3$ | $AgSbF_6$ (15) | 8 | 96 | 92 |
| **6** | **$InCl_3$** | **$AgSbF_6$ (10)** | **15** | **98** | **95** |
| 7 | $InCl_3$ | $AgSbF_6$ (5) | 24 | 96 | 94 |
| 8 | $InCl_3$ | $AgBF_4$ (10) | 30 | 94 | 94 |
| 9 | $InCl_3$ | $AgPF_6$ (10) | 24 | 87 | 90 |
| 10 | $InCl_3$ | $AgClO_4$ (10) | 24 | 98 | 90 |
| 11 | — | $AgSbF_6$ (10) | 24 | — | — |

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of α-methylstyrene in 4.0 mL of solvent at room temperature, unless otherwise noted.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analysis and the absolute configuration of the major products was *R*, assigned by comparison with the literature.
[d] Reaction not complete.

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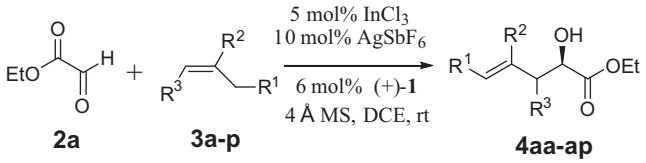
**Table 2**
In(III)–pybox complex-catalyzed asymmetric carbonyl-ene reactions of ethyl glyoxylate with various olefins[a]




**2a** **3a-p** **4aa-ap**

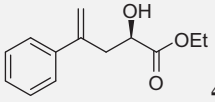
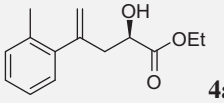
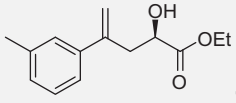
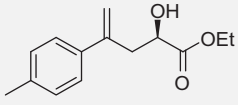
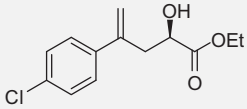
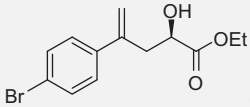
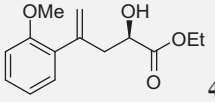
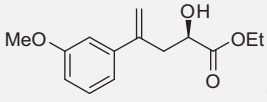
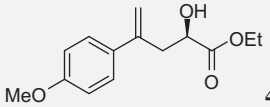
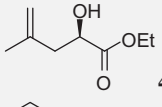
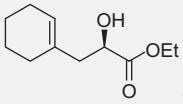
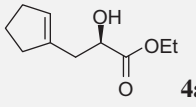
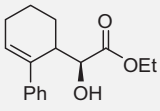
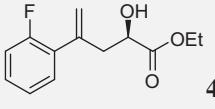
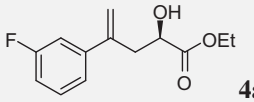
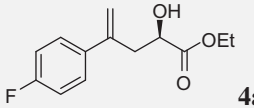
| Entry | Product | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 |  **4aa** | 15 | 98 | 95 |
| 2 |  **4ab** | 16 | 97 | 91 |
| 3 |  **4ac** | 16 | 98 | 93 |
| 4 |  **4ad** | 16 | 98 | 89 |
| 5 |  **4ae** | 16 | 88 | 93 |
| 6 |  **4af** | 16 | 98 | 92 |
| 7 |  **4ag** | 16 | 96 | 95 |
| 8 |  **4ah** | 16 | 97 | 96 |
| 9 |  **4ai** | 16 | 92 | 90 |
| 10 |  **4aj** | 16 | 98 | 92 |
| 11 |  **4ak** | 16 | 89 | 90 |
| 12 |  **4al** | 16 | 98 | 90 |
| 13[d] |  **4am** | 20 | 72 | 99 |
| 14 |  **4an** | 20 | 62 | 93 |

**Table 2** (*continued*)

| Entry | Product | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 15 |  **4ao** | 20 | 73 | 93 |
| 16 |  **4ap** | 16 | 98 | 93 |

[a] Reactions were carried out on 0.5 mmol scale with 2 equiv of the olefin in 4.0 mL of DCE at room temperature.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analysis or GC; the absolute (*R*)-configuration of the major products was assigned by comparison with the literature.
[d] Diastereoselectivity was >99:1.

attempted to use this strategy to improve the efficiency of the In(III)–pybox complex-catalyzed carbonyl-ene reaction of glyoxylates, which exhibited sluggish reaction rates previously (Table 1, entry 1).[3] The asymmetric carbonyl-ene reaction of ethyl glyoxylate (**2a**) and α-methylstyrene (**3a**) was chosen as a model reaction to evaluate the counterion effect of the In(III)–pybox complex. To the chiral In(III)–pybox complex, formed in situ from 6 mol % of pybox (+)-**1** and 5 mol % of $InCl_3$ in 1,2-dichloroethane (DCE), was added 15 mol % of $AgSbF_6$ in one portion. After stirring for 30 min at room temperature, ethyl glyoxylate and α-methylstyrene were added sequentially. The reaction mixture was stirred at room temperature and monitored by thin layer chromatography (TLC). The results summarized in Table 1 show that the reaction efficiency is related to the species as well as the scale of the counter anion of the In(III)–pybox complex. We were delighted to find that the newly formed In(III)–pybox complexes, based on the counterion effect, were more efficient than the parent complexes in catalyzing the asymmetric carbonyl-ene reactions of ethyl glyoxylate (Table 1, entries 4–10). The reaction rate was increased significantly, and excellent yields and enantioselectivities were obtained. The combination of 5 mol % of $InCl_3$, 6 mol % of pybox (+)-**1,** and 10 mol % of $AgSbF_6$ provided the best results in terms of yield, reaction time, and enantioselectivity (Table 1, entry 6).

To test the generality of this methodology, various 1,1-disubstituted and 1,1,2-trisubstituted olefins and ethyl glyoxylate were reacted under the optimized conditions and the results are listed in Table 2. In most cases, the new generation In(III)–pybox complex afforded better yields and enantioselectivities than the parent In(III)–pybox complex (Table 2). Notably, compared to the long reaction times (4–6 days) reported previously at 0 °C,[3] the reaction time was decreased significantly to 15–20 h at room temperature with the new generation In(III)–pybox complex. Both aromatic and aliphatic olefins afforded the expected enantioenriched homoallylic alcohols in better or comparable yields and enantioselectivities compared to the previous results. Unlike in the previous case,[3] and in the case of trifluoromethyl pyruvate,[4] in which significant electronic effects had been demonstrated, electronic discrimination in the asymmetric carbonyl-ene reaction decreased when the new generation In(III)–pybox complex was used as the catalyst. In addition, the counterion effects were amplified when electron-withdrawing groups were present on the olefins (Table 2, entries 5, 6 and 14–16). In contrast to the previous case,[3] in which the presence of a methoxy group, a strong electron-donating group, at either *ortho* or *para* positions led to very poor yields and enantioselectivities, in this case a methoxy group at the *ortho* or *para* position had no detrimental effect on the reaction efficiency (Table 2, entries 7–9).

In summary, we have developed a new version of the highly enantioselective carbonyl-ene reaction catalyzed by an In(III)–pybox complex, which is designed based on the counterion effect. Compared to the previous case,[3] the new version has many advantages including: (1) the reaction rate was increased significantly while retaining the excellent yields and enantioselectivities; (2) the reaction can be carried out at room temperature rather than at 0 °C making it more practical, convenient, and energy efficient; (3) the increased tolerance toward the strong electron-withdrawing and donating groups expands the substrate scope of this system; (4) this reaction could be carried out on a large scale (up to 5 mmol). All of these features should make this method more attractive for the preparation of enantioenriched homoallylic alcohols in industrial applications as well as basic research.

## Acknowledgment

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.066.

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