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Catalytic Asymmetric Synthesis of Quaternary α-Hydroxy Trifluoromethyl Phosphonate via Chiral Aluminum(III) Catalyzed Hydrophosphonylation of Trifluoromethyl Ketones

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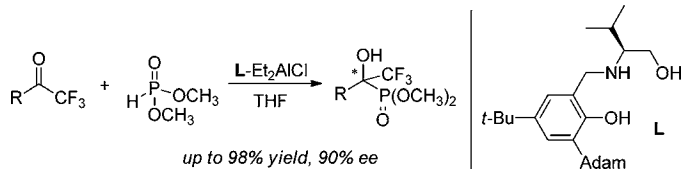
ABSTRACT



The chiral hydrogenated tridentate Schiff base−aluminum(III) complex has been first applied in the catalytic enantioselective hydrophosphonylation of trifluoromethyl ketones. The side reactions related to phospha-Brook rearrangement were completely avoided, and the corresponding quaternary α-hydroxy trifluoromethyl phosphonates have been first synthesized in good yields with high enantioselectivities (up to 90% ee).

As mimics of α-hydroxy acids, the chiral α-hydroxy phosphonates exhibited intriguing biological activities[1] and have found widespread use as biophosphate mimics,[2] antibiotics,[3] antiviral,[4] and antitumor agents.[5] Particularly, the quaternary α-hydroxy phosphonates are of considerable value because they may potentially increase rigidity and resistance to protease enzymes and enhance bioactivity. On the other hand, α-trifluoromethyl alcohols have attracted significant attention owing to their biological activities and their applications in the pharmaceutical area.[6,7] Thus, it is suspected that quaternary α-hydroxy trifluoromethyl phosphonates, in which the CF_3 and $PO(OR)_2$ moieties are located at a stereogenic tetrasubstituted carbon atom, potentially have some unique

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bioactivities. The increased importance of unnatural α-hydroxy acids in modification of natural and unnatural products to improve bioactivity and stability makes the synthesis of α-hydroxy phosphonates a significant subject. However, the synthesis of quaternary α-hydroxy trifluoromethyl phosphonates has been scarcely investigated. The strong electron-withdrawing CF_3 group could supply considerable carbanion stabilization to provide **3**, which facilitated the phospha-Brook rearrangement and related reactions. Therefore, the previous efforts, such as the addition reactions of nucleophilic CF_3TMS to benzoyl phosphonates[8] and the traditional base catalyzed hydrophosphonylations of trifluoromethyl ketones,[9] were all aborted, and α-aryldifluoroethenyl phosphates and α-trifluoromethyl phosphates were obtained with moderate to high yields, respectively (Figure 1). Furthermore, the asymmetric construction of carbon quaternary stereocenters represents a very interesting and challenging area in organic synthesis.[10] We envisioned that a suitable chiral Lewis acid[11] could not only effectively promote the enantioselective hydrophosphonylation of trifluoromethyl ketones to successfully synthesize the chiral quaternary α-hydroxy trifluoromethyl phosphonates[12] but also potentially suppress or avoid the phospha-Brook rearrangement and related side reactions.[13] Herein, we describe the first enantioselective hydrophosphonylation of trifluoromethyl ketones using chiral hydrogenated tridentate Schiff base−aluminum(III) complex as the catalyst, and the corresponding quaternary α-hydroxy trifluoromethyl phosphonates were first synthesized with high yields and ee.

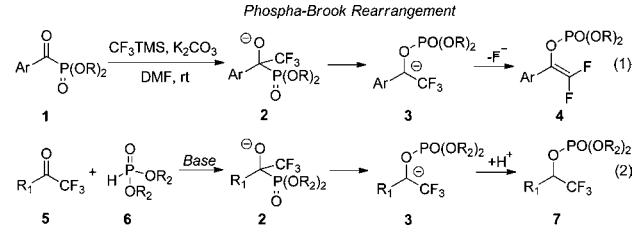

Figure 1. Addition reaction of CF_3TMS to ketone **1** and base catalyzed hydrophosphonylation of trifluoromethyl ketone.

Preliminary survey revealed that chiral hydrogenated tridentate Schiff base−aluminum(III) complex could efficiently catalyze the enantioselective hydrophosphonylation of trifluoromethyl ketone, and no side reaction was observed.[12b] To obtain the most effective ligand structure, various hydrogenated tridentate Schiff bases were complexed in situ with Et_2AlCl to catalyze the reaction. As shown in Table 1, the chiral backbone of the hydrogenated tridentate

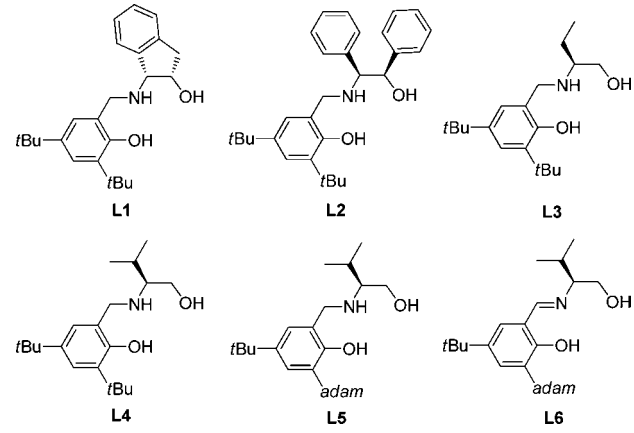

Figure 2. Ligands evaluated in the catalytic enantioselective hydrophosphonylation of trifluoromethyl ketones.

Schiff base showed a crucial effect on the enantioselectivity of the reaction. L-Valinol derived **L4** was superior to the

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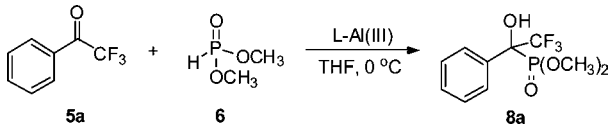
(12) (a) Lewis acid $Ti(OiPr)_4$ has been successfully applied in the hydrophosphonylation of ketones for the synthesis of quaternary α-hydroxy phosphonates, see: Zhou, X.; Liu, Y. L.; Chang, L.; Zhao, J. N.; Shang, D. J.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Adv. Synth. Catal.* **2009**, *351*, 2567. (b) $Ti(OiPr)_4$ catalyzed the hydrophosphonylation of trifluoromethyl ketone smoothly, giving the corresponding quaternary α-hydroxy trifluoromethyl phosphonates with 70% yield. However, the phospha-Brook rearrangement also occurred, and 23% yield of α-trifluoromethyl phosphate was obtained.

other ligands (Table 1, entries 1−4). Racemic products were obtained with **L1** (derived from (1*R*,2*S*)-1-amino-2-indanol) and **L2** (derived from (1*R*,2*S*)-2-amino-1,2-diphenylethanol) (Figure 2). Meanwhile, ligands with bulkier *ortho* groups, such as adamantanyl, on the phenol moiety could achieve higher enantioselectivity (up to 85% ee) (Table 1, entry 5 vs 4). Despite that ligands **L5** and **L6** had the same absolute backbone configuration, the tridentate Schiff base **L6** only afforded the product with poor ee value (Table 1, entry 5 vs 6). The counterions of **L5**−Al(III) complexes had significant impact on the enantioselectivity. **L5**−Et_2AlCl complex catalyzed the reaction smoothly, giving the desired product with 85% ee, while product with low ee was obtained in the presence of **L5**−$AlEt_3$ and **L5**−Al(O*i*Pr)$_3$ (Table 1, entry 5 vs entries 7 and 8). The disparate results were probably caused by the different properties of counterions (Cl, Et, and O*i*Pr), which showed different action in the catalytic cycles.[11e] By lowering the reaction temperature to −15 °C, the enantioselectivity was further improved to 89% ee (Table 1, entry 9).

Table 1. Catalytic Asymmetric Hydrophosphonylation of Trifluoromethyl Ketone under the Indicated Conditions[a]



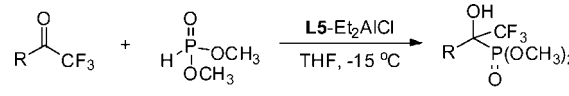
5a **6** **8a**

entry	ligand	metal	yield (%)[b]	ee (%)[c]
1	**L1**	Et_2AlCl	80	0
2	**L2**	Et_2AlCl	83	0
3	**L3**	Et_2AlCl	86	24
4	**L4**	Et_2AlCl	89	41
5	**L5**	Et_2AlCl	90	85
6	**L6**	Et_2AlCl	78	14
7	**L5**	$AlEt_3$	87	22
8	**L5**	Al(O*i*Pr)$_3$	85	30
9[d]	**L5**	Et_2AlCl	99	89

[a] Reactions were carried out with ligand (10 mol %), metal (10 mol %), **5a** (0.2 mmol), **6** (0.24 mmol) in THF (1.0 mL) at 0 °C within 12 h. [b] Isolated yield. [c] Determined by HPLC using chiral AS-H column. [d] The reaction was performed at −15 °C for 40 h.

Under the optimized reaction conditions, the substrate scope of the hydrophosphonylation of trifluoromethyl ketones was investigated, and the corresponding quaternary α-hydroxy trifluoromethyl phosphonates were obtained in good yields with high enantioselectivities. It is noteworthy that the present process completely avoided the phospha-Brook rearrangement and related side reactions. As shown in Table 2, the electronic property of the *para*-substituent on the aromatic ring had no obvious effect on the enantioselectivity of the reaction, while the ones with electron-donating groups showed a slightly lower reactivity (Table 2, entries 1−6). 2,2,2,3′-Tetrafluoroacetophenone underwent the reaction smoothly, but the enantioselectivity was slightly reduced (Table 2, entry 7). Moreover, the heteroaromatic trifluoromethyl ketone **5h** also proved to be an excellent substrate with respect to enantioselectivity and yield of the reaction (Table 2, entry 8).[14]

Table 2. Substrate Scope for the Catalytic Asymmetric Hydrophosphonylation of Trifluoromethyl Ketones[a]



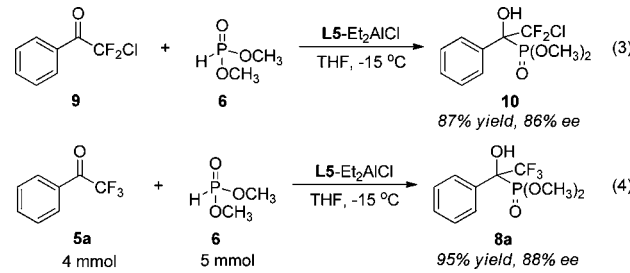
5 **6** **8**

entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph	**8a**	99	89
2	4-$CH_3C_6H_4$	**8b**	82	87
3	4-$CH_3OC_6H_4$	**8c**	85	90
4	4-BrC_6H_4	**8d**	87	85
5	4-ClC_6H_4	**8e**	96	85
6	4-FC_6H_4	**8f**	93	86
7	3-FC_6H_4	**8g**	95	74
8	2-C_4H_3S	**8h**	86	85

[a] Unless otherwise noted, reactions were carried out with **L5** (10 mol %), Et_2AlCl (10 mol %), **5** (0.2 mmol), **6** (0.24 mmol) in THF (1.0 mL) at −15 °C for 40 h. [b] Isolated yield. [c] Determined by HPLC using commercial chiral columns.

To expand the application of the present synthetic strategy, catalytic asymmetric hydrophosphonylation of 2,2-difluoro-2-chloroacetophenone was performed,[15] and the corresponding product was obtained with 86% ee. Furthermore, a scale-up version of the catalytic asymmetric hydrophosphonylation of trifluoromethyl ketone **5a** was also performed to test the synthetic potential. By treatment of 4 mmol of trifluoroacetophenone **5a** under the optimal reaction conditions, the desired product was produced without obvious loss of reactivity or enantioselectivity (Scheme 1).

Scheme 1. Chiral Aluminum(III) Catalyzed Reactions



In conclusion, we have developed the first highly enantioselective hydrophosphonylation of trifluoromethyl ketones using

(13) The intermediate of the phospha-Brook rearrangement may potentially react with other electrophiles. See: (a) Demir, A. S.; Reis, Ö.; Iğdir, A. C.; Esiringüe, İ.; Eymur, S. *J. Org. Chem.* **2005**, *70*, 10584. (b) Demir, A. S.; Eymur, S. *J. Org. Chem.* **2007**, *72*, 8527. (c) Demir, A. S.; Esiringüe, İ.; Göllü, M.; Reis, Ö. *J. Org. Chem.* **2009**, *74*, 2197.

(14) 1,1,1-Trifluoro-3-phenylpropan-2-one was also tested in the catalytic hydrophosphonylation, though the reaction performed smoothly, only racemic product was obtained.

chiral hydrogenated tridentate Schiff base−aluminum(III) complex as the catalyst. The reaction performed smoothly under mild conditions, and the corresponding quaternary α-hydroxy trifluoromethyl phosphonates were obtained with excellent yields and high enantioselectivities. The present approach completely avoided the phospha-Brook rearrangement and related side reactions and provided a potential for large scale synthesis of the chiral quaternary α-hydroxy trifluoromethyl phosphonates. Further studies of the reaction mechanism are in progress.[16]

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

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(15) Selected example for the hydrolysis of α-hydroxy phosphonates: (a) Kolodyazhnaya, A. O.; Kukhar, V. P.; Kolodyazhnyi, O. I. *Russ. J. Gen. Chem.* **2008**, *78*, 2043. (b) McGeary, R. P.; Vella, P.; Mak, J. Y.W.; Guddat, L. W.; Schenk, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 163. (c) See also ref 11i. (d) 2,2-Difluoroacetophenone underwent the catalytic asymmetric hydrophosphonylation slowly, and the corresponding product was obtained with 63% yield and 70% ee. It is suspected that the strong electron-withdrawing property and large steric effect of the trifluoromethyl group was responsible for the high reactivity and enantioselectivity of the catalytic asymmetric hydrophosphonylation of trifluoromethyl ketones.

(16) The relationship between the enantiomeric excess of the chiral ligand **L5** and the product **8a** was investigated. Linear effect was observed, which implied that the reaction was performed in the presence of monomeric aluminum species.