ORGANIC LETTERS

2007
Vol. 9, No. 10
1927−1929

Synthesis of a Fluorous Ligand and Its Application for Asymmetric Addition of Dimethylzinc to Aldehydes

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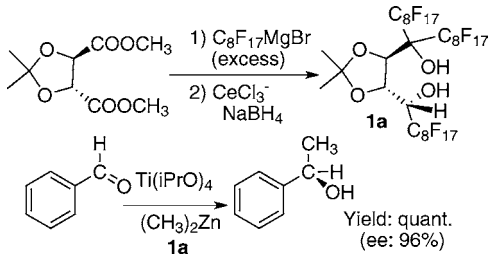
Received February 22, 2007

ABSTRACT



A new fluorous ligand was synthesized from the acetonide of dimethyl tartarate, which showed excellent asymmetric induction on the addition of dimethylzinc to aldehydes. This ligand will be useful for synthesis of bioactive compounds with a methyl carbinol moiety. It could be recycled without using a fluorous solvent or a fluorous column.

Although there are a great number of biologically active compounds containing a chiral methyl carbinol moiety,[1] only a small number of studies on the asymmetric addition of dimethylzinc to aldehydes[2] have been reported probably due to the lower reactivity of dimethylzinc than those of its higher homologues.[3] Therefore, the development of a high enantioselective methodology for the addition of a methyl group to a carbonyl group is strongly desired.

On the other hand, tartaric acid has attracted attention as a chiral pool for synthesis of asymmetric ligands for a long time due to its high availability of both enantiomers and its easy derivatization to many ligands.

TADDOL is one of the excellent chiral ligands derived from tartaric acid.[4]

In this paper, we would like to describe the synthesis of a new fluorous ligand **1a** (see Figure 1) derived from tartaric acid, which shows a high efficiency for asymmetric addition of dimethylzinc to aldehydes.

On the other hand, we have reported the synthesis of perfluoroalkylated chiral ligands.[5] We had expected that large

(1) Examples of the total synthesis of natural products having a chiral methylcarbinol moiety: (a) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2604−2608. (b) Pattenden, G.; Critcher, D. J.; Remuinan, M. *Can. J. Chem.* **2004**, *82*, 353−365. (c) Scott, M. S.; Luckhurst, C. A.; Dixon, D. J. *Org. Lett.* **2005**, *7*, 5813−5816. (d) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Oxford, 1983. (e) Jones, G. B.; Guzel, M.; Chapman, J. *Tetrahedron: Asymmetry* **1998**, *9*, 901−905. (f) Sabitha, G.; Reddy, C.; Yadaf, J. S. *Tetrahedron Lett.* **2006**, *47*, 4513−4516.

(2) For enantioselective addition of Me_2Zn, see: (a) Blay, G.; Fernàndez, I.; Hernandez-Olmos, V.; Marco-Aleixandre, A.; Pedro, J. R. *Tetrahedron: Asymmetry* **2005**, *16*, 1953−1958. (b) Cozzi, P. G.; Kotrusz, P. *J. Am. Chem. Soc.* **2006**, *128*, 4940−4941. (c) Garcia-Delgado, N.; Fontes, M.; Pericàs, M. A.; Riera, A.; Verdaguer, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2085−2090. (d) Sprout, C. M.; Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2004**, *69*, 6666−6673. (e) Cozzi, P. G.; Locatelli, M. *Lett. Org. Chem.* **2004**, *1*, 208−211. (f) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072. (g) A unique example for Me_2Zn addition to ketones: García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971. (h) Addition of Me_2Zn to ketoesters: Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 15453−15456.

(3) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036.

(4) For the use of TADDOL as a chiral ligand, please see: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92−138.

10.1021/ol070466n CCC: $37.00
Published on Web 04/11/2007

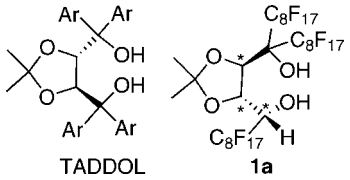


Figure 1. TADDOL and our ligand **1a**.

perfluoroalkyl groups would be sterically large enough to induce high ee and that their electronic effect would increase the Lewis acidity of the metal coordinated and hence increase the activity of the complex. These expectations were confirmed by the synthesis of a few perfluoroalkylated ligands.[5] As the extension of these works, we designed a new chiral ligand (**1a**).

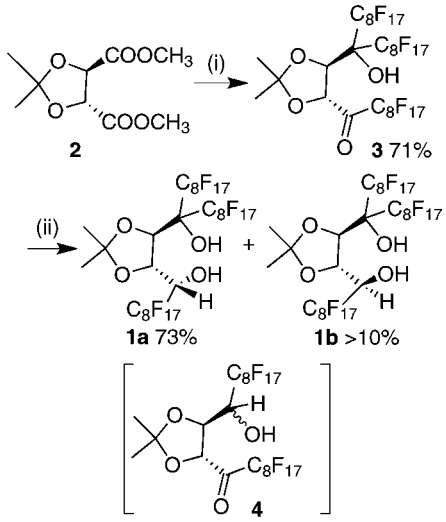
The ligand **1a** has two different types of OH groups and hence different coordination strengths that may help the formation of a more effective metal complex with a fixed electronic and steric environment.[2a] Perfluoroalkyl groups would make the neighboring hydroxy group less sensitive to elimination and/or oxidation than common alkyl groups due to their high electronegativity[5] and make **1a** very stable. Further, the high content of fluorine would make the ligand recoverable by fluorous technology.[6]

The ligand **1a** was synthesized according to Scheme 1.

Treatment of dimethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (**2**) with a perfluorooctyl Grignard reagent gave a keto alcohol (**3**). This reaction was highly sensitive to temperature. At low temperature, the main product was a keto alcohol (**4**), which must be formed by reduction of a dicarbonyl intermediate with methoxymagnesium halide via the same mechanism as that on the reduction of perfluoroalkyl ketone with lithium alkoxide.[7] On the other hand, at a higher temperature, the Grignard reagent was decomposed. A part of these difficulties was due to the low solubility of highly fluorinated compounds in common solvents. After several trials, we found that the optimum condition is to use a high dilution condition and a temperature range between −65 and −30 °C. The Grignard reagent was formed at −65 °C. Then the mixture was warmed rapidly to −40 °C, and the diester **2** was added. The reaction mixture was stirred below −30 °C for 4 h.

The reduction of the keto alcohol **3** using $LiAlH_4$ or other common reducing agents afforded a mixture of two possible isomers, **1a** and **1b**, with low selectivity. We had the best

Scheme 1

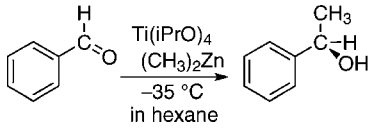


(i) $C_8F_{17}MgBr$ 4 equiv, Et_2O, –78 - –30 °C.
(ii) $CeCl_3 \cdot 7H_2O$ 2 equiv, $NaBH_4$ 4 equiv, Et_2O, MeOH, rt.

results using a mixture of excess $NaBH_4/CeCl_3$. This reagent gave a good selectivity (**1a**/**1b** = 10:1) and high conversion. The isomer **1a** was obtained as crystals by crystallization of the mixture from chloroform, whereas **1b** was obtained as an oil contaminated with 30% (estimated by GLC) of **1a** after concentration of the filtrate. We determined the structure of **1a** by single-crystal X-ray analysis. Thus, we could obtain **1a** effectively.

We estimated the activity of asymmetric induction of the isomers on the addition of diethylzinc to benzaldehyde. Ligand **1a** was found to be highly effective in the level of 3 mol % giving (*R*)-1-phenylpropanol in a quantitative yield with 98% ee, whereas **1b** gave the (*S*) isomer in only 40% yield with 20% ee. These results showed that we obtained the active isomer predominantly. This result encouraged us to try the addition of dimethylzinc in the presence of **1a** (Scheme 2).

Scheme 2



1a 3 mol % Y: quant. ee: (80%)
6 mol % Y: quant. ee: (96%)

A portion of 3 mol % of **1a** gave the product in a quantitative yield with 80% ee. Increasing the amount of **1a** to 6 mol % afforded 96% ee. Solvents other than hexane were shown to be noneffective. The reaction was completed within only 3 h, which is unusually short for the addition of dimethylzinc to aldehydes.

These results encouraged us to apply this reaction to other aromatic aldehydes, including the ortho-substituted ones,

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(6) Omote, M.; Nishimura, Y.; Sato, K.; Ando, A.; Kumadaki, I. *Tetrahedron* **2006**, *62*, 1886−1894, and references therein.

(7) Sokeirik, Y. S.; Omote, M.; Sato, K.; Kumadaki, I.; Ando, A. *J. Fluorine Chem.* **2006**, *127*, 150−152. Concerning the reduction of perfluoroalkyl ketones with alkoxymagnesium: Yamazaki, T.; Terajima, T. unpublished data.

aliphatic aldehydes, and heterocyclic ones, most of which were reported to give low ee's even in the reaction of diethylzinc.[8] The results are shown in Table 1.

Table 1. Methylation of Various Aldehydes in the Presence of **1a**

entry	RCHO (R)	time (h)	yield (%)[a]	ee (%)[b]
1	C_6H_5	3	99	96
2	p-$CH_3OC_6H_4$−	3	95	92
3	p-$CF_3C_6H_4$−	4	96	>99
4	2-naphthyl	2	99	95
5	o-FC_6H_4−	3	97	89
6	o-ClC_6H_4−	3	97	91
7	n-C_7H_{15}−	2	98	91[c]
8	$PhCH_2CH_2$−	3	92	88
9	cyclohexyl	4	78	84[c]
10	PhCH=CH−	3	93	92
11	n-$C_5H_{11}C{\equiv}C$−	3	95	98[c]
12	2-furyl	1.5	98	>99
13	benzofuran-2-yl	1	99	84

[a] Isolated yields. [b]Determined by an HPLC OD-H column. Absolute configurations are established by signs of the optical rotation reported. All are *R* configuration. [c]Determined by chiral HPLC analysis of the dinitrobenzoate.

The ligand gave excellent yields in every entry except cyclohexanecarbaldehyde. The enantioselectivities were very good to excellent. Aromatic aldehydes gave excellent yields and ee's, especially in the case of an electron-withdrawing group which gave up to 99% ee (Table 1 entry 3), whereas an aldehyde with an electron-donating group gave a little lower ee of 92% (entry 2). Bulky aromatic aldehydes such as 2-naphthaldehyde also gave excellent ee up to 95%. With ortho-substituted aldehydes (entries 5 and 6), which were reported to give low yields and ee's even in the addition of diethylzinc using TADDOL, we got an excellent chemical yield up to 97% with very good to excellent ee. Furfural gave an excellent result (entry 12), and the more bulky derivative showed a lower ee of 84% (entry 13).

Next, we tried aliphatic aldehydes including linear, cyclic, and α,β-unsaturated aldehydes (entries 7−11). Saturated linear aldehydes gave excellent results. Thus, the ee was very good with hydrocinnamaldehyde (88%) and excellent with octanal (91%) but a little lower than those of the aromatic aldehydes. Cyclohexanecarbaldehyde (Table 1, entry 9) gave lower yield and ee. α,β-Unsaturated aldehydes gave excellent results especially in the case of 2-octynal (98% ee).

Next, we examined the recycling of the catalyst. We found an economical way, taking advantage of the very low solubility of the ligand in cold toluene. Our procedure was as follows: the crude mixture obtained by concentrating the extract from the reaction of dimethylzinc and benzaldehyde was treated with cold toluene, in which the ligand is practically insoluble. By simple filtration, we could separate the ligand from the products. The recovered ligand was used without purification. By this simple method, we could recycle the ligand several times. The recycling data are shown in Table 2.

Table 2. Recycling of the Ligand

		product	
cycle	ligand recovered(%)	yield (%)[a]	ee (%)[b]
1		100	95
2	100	100	96
3	93	100	93
4	90	96	91
5	89	99	85
6	80	100	83

[a] Determined by GLC. [b]Determined by HPLC.

We observed that the yield was not affected through the whole recycling process, whereas the ee decreased slightly. The recycling of the ligand was not accompanied by epimerization. The reason for the slight decrease of enantiomeric excess is under investigation.

In conclusion, we have synthesized a new ligand based on fluorous technology which showed an excellent asymmetric induction on the addition of dimethylzinc to aldehydes. The high yield and ee and the short reaction time will make it one of the best ligands ever made. This ligand can be recycled without using expensive fluorous solvents or fluorous columns.

Supporting Information Available: General procedures of experimental and spectral data including NMR, HPLC, and X-ray analysis and NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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