Letter

L-Proline catalyzed asymmetric aldol reactions of protected hydroxyacetone

Huawei Liu, Lizeng Peng, Tao Zhang and Yulin Li*

National Laboratory of Applied Organic Chemistry, Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China. E-mail: liyl@lzu.edu.cn; Fax: +86 931 891 2283

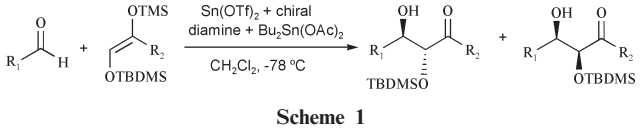
Received (in Montpellier, France) 9th April 2003, Accepted 27th May 2003
First published as an Advance Article on the web 11th July 2003

We extended the proline-catalyzed asymmetric direct aldol reactions to the TBDMS protected hydroxyacetone. This important donor provides a ready access to optically active monoprotected 1,2-diol units simultaneously accompanied by stereoselective carbon-carbon bond formation in 40–90% yield and in up to 95% *ee*.

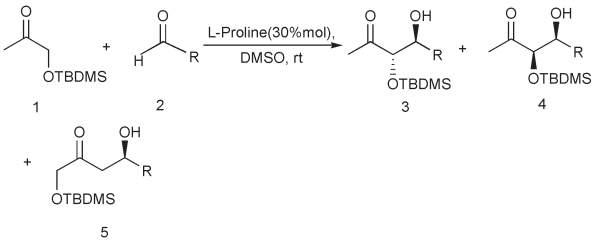
The construction of C–C bonds with complete control of the stereochemical course of a reaction is of utmost importance in organic synthesis. Study of the catalytic asymmetric aldol reaction, which efficiently and effectively transfers chirality information, has become a major effort in synthetic organic chemistry.[1] Mukaiyama and cowaorkers[2] have shown that aldehydes and ketene silyl acetals prepared from either esters or thioesters afford the corresponding aldol adduct with high *ee* values using chiral tin(II) complexes (Scheme 1). In recent years, the groups of Shibasaki,[3] Trost[4] and List[5,6] have reported catalytic asymmetric direct aldol reactions of aldehydes with unmodified ketones using a heterobimetallic, a chiral semi-crown Zn complex or L-proline as the chiral catalyst to give *anti*-1,2-diols in excellent diastereo- and enantioselectivities.

We became interested in investigating the asymmetric direct aldol reactions between the TBDMS protected hydroxyacetone **1** and aldehydes **2** using L-proline as the catalyst (Scheme 2). Similarly to catalytic asymmetric aldol reactions using hydroxyacetone,[5c] this aldol reaction does not require the pregeneration of enolates or enolate equivalents. Most importantly, the optically active monoprotected 1,2-diol units allow easy manipulation of the functional groups in the subsequent chemical transformations of the aldol adducts. Due to its simplicity and its mild reaction conditions, this reaction will find wide applications in organic synthesis.

We initiated our study on the proline catalyzed asymmetric direct aldol reactions using TBDMS protected hydroxyacetone **1** and *p*-nitrophenyl aldehyde (entry 7). This was challenging work since three different regio- and diastereomeric products and their enantiomers were obtained. The corresponding *anti*-aldol product was obtained in 77% yield, with a diastereomeic ratio (dr) of $>10:1$ and in 90% *ee*. With the success of the above reaction, we continued our study by exploring the aldol reaction with nine different aldehydes (Table 1). The aldol products were prepared in good yields (except for entry 10) and the *ee* were moderate. In all cases, formation of regioisomeric products was observed with yields ranging from 5% to 10% (except for entry 10) and with *ee* values of around 10%. Some of the reactions listed in Table 1 provided high enantioselectivity of $>90\%$ *ee* for the electron-withdrawing aromatic (*e.g.*, entry 7) and aliphatic (*e.g.*, entry 9) aldehydes. It is important to note that the regioisomeric product **5** was the primary aldol product in the reaction of the TBDMS protected hydroxyacetone with unsaturated aldehydes (entries 10–12).[7]

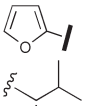
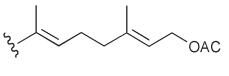
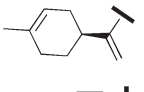
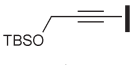


Scheme 1



Scheme 2

Table 1 Aldol reaction of **1** with various aldehydes catalyzed by L-proline

Entry	R	% Yield[a]	**3** : **4** : **5**	% *ee*[b] (**3**/**4**)
1	C_6H_5	90	75 : 20 : 5	40/41
2	*p*-CH_3–C_6H_4	82	83 : 15 : 2	56/45
3	*p*-CH_3O–C_6H_4	84	62 : 32 : 6	28/41
4	*m*-CH_3O–C_6H_4	74	67 : 27 : 6	65/65
5	*o*-CH_3O–C_6H_4	80	60 : 30 : 10	62/72
6	*p*-Cl–C_6H_4	77	53 : 40 : 7	72/48
7	*p*-NO_2–C_6H_4	86	90 : 7 : 3	90/15
8		68	80 : 15 : 5	84/75
9		60	80 : 10 : 10	95/95
10		40	0 : 0 : 100	<10[c]
11		54	12 : 8 : 80	95[c]
12		83	20 : 10 : 70	43[c]
13		No reaction	–	–
14		No reaction	–	–

[a] The yield was estimated by weighing or/and HPLC analysis. [b] The *ee* was determined by chiral-phase HPLC analysis using Chiralpak OD columns (Daicel Chemical Industries, Ltd.) with 10% 2-propanol–hexane mixture as eluent. [c] The ee value of **5** was measured by 400 MHz ^{1}H NMR analysis of its MTPA ester.

Unfortunately, other unsaturated aldehydes including *trans*-crotonaldehyde (entry 13) and geranial (entry 14) failed in these reactions.

In summary, we have demonstrated that L-proline catalyzes the direct aldol reaction between the TBDMS protected hydroxyacetone **1** and various aldehydes to give the monoprotected 1,2-diol units in good yield and regioselectivities. Although the diastereomeric ratios are not always very high, we believe that this reaction will find wide applications in organic synthesis on the basis of its operational simplicity, good yields, and high regioselectivities. Furthermore, the monoprotected 1,2-diols allow easy manipulations of functional groups in the following chemical transformations of the aldol adducts. This distinguishes our procedure from that reported in the literature

Experimental

To a solution of **1** (1 mL) in anhydrous DMSO (4 mL) and) was added *p*-methylbenzaldehyde aldehyde (60 mg, 0.5 mmol), followed by L-proline (17 mg, 30% mol). The resultant mixture was stirred at room temperature for 12 h. The reaction was quenched with a saturated ammonium chloride solution, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 7% EtOAc in hexane) to give (3*R*, 4*S*)-3-(*t*-butyldimethylsiloxy)-4-hydroxy-4-(4′-methylphenyl)-butan-2-one (*syn*-**4**, 19 mg, 12%) and (3*S*, 4*S*)-3-(*t*-butyldimethyl-siloxy)-4-hydroxy-4-(4′-methylphenyl)-butan-2-one (*anti*-**3**, 106 mg, 68%) (entry 2, Table 1).

syn-**4**: $[\alpha]_D^{20}$ −14 (*c* 1.0, $CHCl_3$); IR (film): 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, $J = 8.4$ Hz, 1 H), 7.16 (d, $J = 8.4$ Hz, 1 H), 4.87 (dd, $J = 8.0$, 3.0 Hz, 1 H), 4.12 (d, $J = 3.0$ Hz, 1 H), 2.93 (d, $J = 8.0$ Hz, 1 H), 2.33 (s, 3 H), 2.17 (s, 3 H), 0.89 (s, 9 H), −0.04 (s, 3 H), −0.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 137.4, 137.2, 128.9, 125.9, 82.7, 75.2, 27.3, 25.7, 21.1, −5.3, −5.8; EI-MS *m*/*z* 308 (M^+, 5), 188 (100); anal. calcd for $C_{17}H_{28}O_3Si$: C, 66.19; H, 9.15; found: C, 66.18; H, 9.14.

anti-**3**: $[\alpha]_D^{20}$ +7 (*c* 1.0, $CHCl_3$); IR (film): 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, $J = 8.0$ Hz, 1 H), 7.15 (d, $J = 8.0$ Hz, 1 H), 4.74 (dd, $J = 6.0$, 3.6 Hz, 1 H), 4.12 (d, $J = 6.0$ Hz, 1 H), 2.56 (d, $J = 3.6$ Hz, 1 H), 2.35 (s, 3 H), 2.07 (s, 3 H), 0.87 (s, 9 H), −0.03 (s, 3 H), −0.17 (s, 3 H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 201.5, 137.9, 136.6, 128.9, 126.9, 82.4, 75.6, 26.4, 25.7, 21.1, −5.2, −5.5; EI-MS *m*/*z* 308 (M^+, 6), 188 (100); anal. calcd for $C_{17}H_{28}O_3Si$: C, 66.19; H, 9.15; found: C, 66.15; H, 9.16.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Grant No. 20072012) and the Special Research Grant for Doctoral Sites in Chinese Universities (Grant No. 20010730001).

References

1 (*a*) T. D. Machajewski and C. H. Wong, *Angew. Chem., Int. Ed.*, 2000, **39**, 1352; (*b*) H. Gröger, E. M. Vogl and M. Shibasaki, *Chem.-Eur. J.*, 1998, **4**, 1137; (*c*) S. G. Nelson, *Tetrahedron: Asymmetry*, 1998, **9**, 357.

2 (*a*) T. Mukaiyama and S. Kobayashi, in *Stereocontrolled Organic Synthesis*, ed. B. M. Trost, Blackwell, London, 1994, p. 34; (*b*) S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, 1989, 297; (*c*) T. Mukaiyama, H. Uchiro, I. Shiina and S. Kobayashi, *Chem. Lett.*, 1990, 1019; (*d*) S. Kobayashi and M. Horibe, *Chem.-Eur. J.*, 1997, **3**, 1472; (*e*) T. Mukaiyama, I. Shiina, H. Uchiro and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1708.

3 (*a*) Y. M. A. Yamada and M. Shibasaki, *Angew. Chem., Int. Ed.*, 1997, **36**, 1871; (*b*) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 2169; (*c*) N. Yoshikawa and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 2466; (*d*) N. Yoshikawa and M. Shibasaki, *J. Am. Chem. Soc.*, 1999, **121**, 4168; (*e*) Y. M. A. Yamada and M. Shibasaki, *Tetrahedron Lett.*, 1998, **39**, 5561.

4 (*a*) B. M. Trost and H. Ito, *J. Am. Chem. Soc.*, 2001, **123**, 3367; (*b*) B. M. Trost and H. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 12 003.

5 (*a*) B. List, P. Pojarliev, W. T. Biller and H. J. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 827; (*b*) B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395; (*c*) W. Notz and B. List, *J. Am. Chem. Soc.*, 2000, **122**, 7386; (*d*) B. List, P. Pojarliev and C. Castello, *Org. Lett.*, 2001, **3**, 573; (*e*) B. List, *Tetrahedron*, 2002, **58**, 10 450; (*f*) B. List, *Synlett.*, 2001, **11**, 1675.

6 For reviews and highlights of the proline catalyzed asymmetric direct aldol reaction in various contexts, see: (*a*) H. Gröger and J. Wilken, *Angew. Chem., Int. Ed.*, 2001, **40**, 529; (*b*) C. Palomo, M. Oiarbide and J. M. Garcia, *Chem.-Eur. J.*, 2001, **8**, 37; (*c*) B. Alcaide and P. Almendros, *Eur. J. Org. Chem.*, 2002, 1595; (*d*) M. Movassaghi and E. N. Jacobsen, *Science*, 2002, **298**, 1904.

7 The phenomenon that the regioisomeric product was the primary aldol product in the L-proline catalyzed aldol reaction was not reported in previous papers.