Angewandte Chemie

Aldol Reaction

Asymmetric Direct Aldol Reaction Assisted by Water and a Proline-Derived Tetrazole Catalyst**

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Optically active 1,1,1-trichloro-2-alkanol groups are versatile tools in the preparation of compounds with various functional groups[1] including α-hydroxy- and α-amino acids. Obviously a suitable approach to access such pivotal fragments would be the asymmetric aldol reaction.[2–4] Unfortunately, however, both reactive aldehydes, including chloral, that have a high affinity to water resulting in the corresponding hydrates, and water-soluble aldehydes have been considered unsuitable for asymmetric syntheses to date.[3h] In this report, the proline-derived tetrazole catalyst **1**[5,6] displayed even greater catalytic

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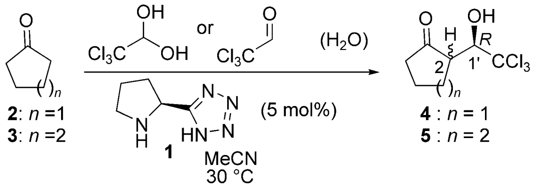
activity and efficiency, which widened the substrate scope in the water-assisted direct aldol reaction.

Spectacular improvement has been made recently in the asymmetric direct aldol reaction with proline as a catalyst described by List, Barbas III, and Lerner.[3] During our continuous research on chiral diamine/protonic acid catalysts,[7] we discovered that the acidity of protonic acids plays a critical role in enhancing reactivity, catalyst efficiency, and to an even great extent, enantioselectivity. A solution of chloral in MeCN (≈ 10 ppm water) at room temperature was treated with cyclopentanone (**2**), and then the tetrazole catalyst **1** (5 mol %) and water (100 mol %) were added (Scheme 1).



Scheme 1. Direct aldol reaction of cyclic ketones catalyzed by **1**.

The mixture was stirred at 30 °C for 50 h under air to give the aldol product **4** in 85 % yield with 84 % *ee* and 80 % *de* (remarkably, the major product was the *syn* isomer). In marked contrast, without water, the reaction was far from complete (< 1 % conversion) even after 60 h. More interesting is the fact that the addition of more than 100 mol % of water led to similar acceleration effects. The greater the amount of water (200 and 500 mol %), the greater the enantioselectivity of the reaction (92 % *ee* and 94 % *ee*, respectively), and the less the diastereoselectivity (67 % *de* and 52 % *de*, respectively, *syn* major). The *ee* of the *anti* product was also exceedingly high (> 98 % *ee*). In contrast, catalytic amounts of water (20 or 50 mol %) uniformly disabled the catalytic cycle (≈ 5 % conversion). When chloral was replaced by its monohydrate, the reaction proceeded smoothly without water with a similar level of productivity (83 %) and selectivity (82 % *ee*; 76 % *de*, *syn* major). When proline (5 mol %) was used instead of **1** with either chloral or its monohydrate in $CHCl_3$ or MeCN, the reactions were sluggish (**4**: ≈ 10 % after 46 h). In general, lower catalyst and ketone loading is possible with **1**.[8]

For the purpose of better understanding these findings, we determined the kinetic profile of each reaction course (Figure 1). The reaction was obviously initiated and accelerated at the point where water participated. The yield gradually increased after the addition of water at a rate comparable to that exhibited in the reaction with chloral monohydrate. Although moderate, rate acceleration was also seen in the reaction of cyclohexanone (**3**) with the monohydrate in MeCN in the presence of **1** (5 mol %) to give (2*S*, 1′*R*)-**5** in 78 % yield with 98 % *ee* and 92 % *de* (*anti* major). The result is superior in all respects to that with anhydrous chloral (72 % yield; 79 % ee; 76 % *de* (*anti* major)).

Although water effects that shift the aldehyde–iminium ion equilibrium to the formation of aldehydes by decomposition of iminium ions might be possible, we were unable to identify any ^{1}H NMR peaks corresponding to the formation of the iminium ion during the reaction. We also could not exclude the following additional role of water. The generation of the hydrate form might prevent the formation of the iminium ion from **1** and chloral. In fact, a catalytic amount of water (20 or 50 mol %) totally disabled the catalytic cycle, indicating that the remaining chloral poisoned the catalyst activity.[10] In contrast, addition of 100 mol % of water markedly improved the catalysis, as mentioned above. In addition, the following and other[9a] investigations support the involvement of the monohydrate in the catalysis: *N*-(1-cyclopentenyl)pyrrolidine was subjected to the reaction with either chloral or its monohydrate at 30 °C for approximately 50 h. With chloral almost no reaction took place, but with the monohydrate the product was obtained in ≈ 36 % yield, which indicates the importance of the hydrogen bonding between the nitrogen and the hydroxy group. In any event, the identical 1′*R* configuration[11] at the chloral moiety predominated owing to a tight conformation in the transition structure through hydrogen-bond networks. It should be emphasized that a simple Zimmerman–Traxler model cannot explain the present diasterochemical reversal, because in this model, *syn* and *anti* selectivities arise from the *Z* and *E* enolates, respectively.[12]

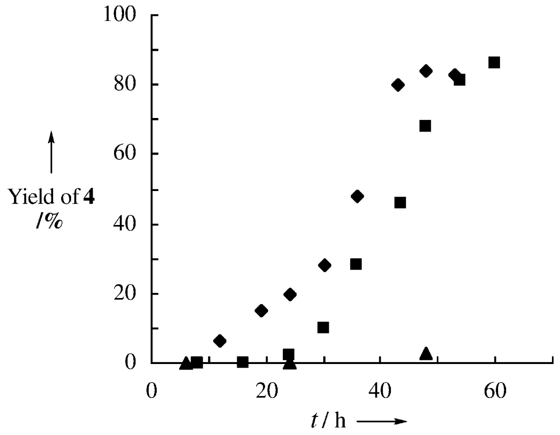
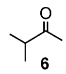
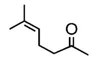
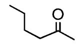
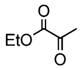
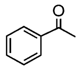
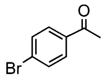
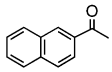


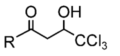
Figure 1. Reaction of **2** (2 equiv) in the presence of catalyst **1** (5 mol %) in MeCN. ◆: chloral monohydrate; ■: anhydrous chloral, then water (100 mol %) was added after 24 h; ▲: anhydrous chloral.

Other ketones were tested to expand the substrate scope of this reaction; for operational simplicity the monohydrates were used (Table 1). In the reaction of **6** (entries 1 and 2) no regioisomers nor dehydration products were detected by ^{1}H NMR analysis, indicating **7** to be the sole product (97 % *ee*). Other examples are listed in (Table 1), which shows the characteristic nature of the reaction. 1) Methyl and aromatic ketones, which showed scant reactivity in aldol reactions with with catalytic amounts of proline,[3c,d] exhibited sufficient reactivity and gave high enantioselectivities (82–97 % *ee*). 2) In general, reactions of aliphatic ketones are better with chloral than with its monohydrate in terms of both reactivity and selectivity (entries 1–6). By contrast, the reactions of aromatic ketones showed higher selectivity and reactivity in reactions with the monohydrate (entries 9–12). 3) Although prone to self-dimerization[4f] the pyruvate afforded the crossed-aldol product in 86 % *ee* (entries 7 and 8).

Table 1: Reaction of various ketones with chloral monohydrate in the presence of **1**.[a]

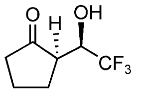
Entry	Ketone	Cond. [°C, h]	Prod.	Yield [%][b]	Sel. [% *ee*][c]	Method[d]
1[e]	 6	40, 24	**7**	79	97	A
2		40, 24	**7**	35	97	A
3[e]		30, 24	**8**	93	82	B
4		30, 26	**8**	73	67	B
5[e,f]		30, 36	**9**	91	82	B
6[f]		30, 66	**9**	88	81	B
7		30, 24	**10**	55	86	C
8		30, 24	**10**	39	86	C
9		40, 48	**11**	72	88 (*R*)	B
10		40, 48	**11**	75	92 (*R*)	B
11		40, 96	**12**	76	91	D
12		40, 96	**13**	83	91	D

[a] Unless otherwise specified, reactions were carried out using ketone, chloral monohydrate, and **1** (10 mol%) in MeCN. [b] Of isolated, purified products. [c] Determined by chiral HPLC analysis. The absolute configurations are not determined except for entries 9 and 10. [d] Method A: ketone (0.5 mL), monohydrate (0.5 mmol); method B: ketone (0.5 mL), monohydrate (0.5 mmol), MeCN = 1 mL; method C: ketone (0.5 mmol), monohydrate (0.75 mmol), MeCN = 1 mL; method D: ketone (2.5 mmol), monohydrate (0.5 mmol), MeCN = 1 mL. [e] Chloral was used instead of its monohydrate. [f] **1** (20 mol%) was used.



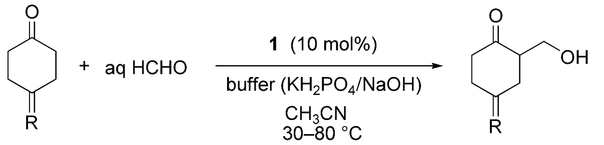
7 : R = $CHMe_2$
8 : R = $(CH_2)_2$-CH=CMe_2
9 : R = $(CH_2)_3Me$
10 : R = (C=O)-OEt
11 : R = Ph
12 : R = (C_6H_4)-*p*-Br
13 : R = 2-naphthyl

This method was further extended to other aldehydes having a high affinity to water. The monohydrate and ethanol hemiacetal of trifluoroacetaldehyde[9b] were both subjected to the catalytic cycle to give the identical product **14** in ≈65% yields (with 5 mol% **1**) and with high enantio- (94% and 92% *ee*, respectively) and diastereoselectivities (> 95% *de*, *syn* major). Even more striking is the level of enantioselectivity (99% *ee*) obtained in the reaction of aqueous formaldehyde, though the turnover number is still modest (Scheme 2).[13] The absolute configuration of product **16a** is consistent with that of the α-carbon of **5**, suggestive of the favorable creation of the two stereogenic centers by doubling the effects of enantio- and diastereofacial control.



14

In summary, we have demonstrated that the tetrazole catalyst **1** functions as a highly efficient catalyst when the overall reaction conditions are precisely adjusted. The present experimental results strongly suggest that other ketones may have potential to participate in the asymmetric intermolecular direct aldol reaction occurring by means of a keto–enamine mechanism.[10] The exploitation of more efficient catalysts, which in the transition state make better positioned hydrogen bonds, is now in progress in our laboratory.



3 : R = H, H
15 : R = -O(CH₂)₂O-

16a : R = H, H : 40% yield, 99% *ee* (*S*)
16b : R = -O(CH₂)₂O- : 37% yield, 99% *ee*

Scheme 2. Asymmetric direct aldol reaction with aqueous formaldehyde.

Experimental Section

The reaction with cyclopentanone in the presence of tetrazole catalyst **1** is representative: To a mixture of tetrazole **1** (3.5 mg, 0.025 mmol) in MeCN (1.0 mL) was added cyclopentanone (**2**) (88.5 μL, 1.0 mmol) and chloral monohydrate (82.7 mg, 0.5 mmol) at 23 °C under air in a closed system. The reaction mixture was stirred at 30 °C for 48 h. The reaction mixture was quenched with aq NaCl. The organic layer was extracted with EtOAc, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/Et_2O, 4:1) to give product **4** in 83% yield. (2*R*,1′*R*)-2-(1′-Hydroxy-2′,2′,2′-trichloroethyl) cyclopentan-1-one ((2*R*,1′*R*)-*syn*-**4**): IR (KBr): $\tilde{\nu} = 3372$, 2974, 2895, 2689, 1728, 1423, 1329, 1259, 1145, 1041, 925, 808 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$): $\delta = 4.75$ (1H, dd, $J = 5.4$, 1.2 Hz, C*H*O), 3.22 (1H, brs), 2.85 (1H, t, $J = 9.9$ Hz), 2.44–2.06 (5H, m), 1.88–1.72 ppm (1H, m); typical chemical shifts of the *anti* product: $\delta = 5.55$ (1H, d, $J = 5.7$ Hz, -OH), 4.23 (1H, t, $J = 5.7$ Hz, C*H*-O), 2.75–1.80 ppm (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 217.9, 103.0, 80.6, 50.9, 37.6, 23.1, 20.7 ppm; Elemental analysis calcd (%) for $C_7H_9Cl_3O_2$: C 36.32, H 3.92; found: C 36.25, H 3.94. $[\alpha]_D^{20} = +69.9$ ($c = 1.01$, $CHCl_3$, for the *syn* product of 99% *ee*), The chiral HPLC analytical data (column AD-H): retention times: $t_R =$ 24.98 min ((2*S*,1′*S*): *syn*, minor enantiomer) and $t_R = 34.90$ min ((2*R*,1′*R*): *syn*, major enantiomer) using *i*PrOH/hexane (1/50) as eluent at a flow rate of 1.0 mL min^{-1}; $t_R = 22.86$ (*anti*, major enantiomer) and $t_R = 30.05$ (*anti*, minor enantiomer).

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[1] For example, see: a) E. J. Corey, J. O. Link, *J. Am. Chem. Soc.* **1992**, *114*, 1906; b) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1993**, *34*, 5227; c) E. J. Corey, J. O. Link, Y. Shao, *Tetrahedron Lett.* **1992**, *33*, 3435; d) T. Fujisawa, T. Ito, K. Fujimoto, M. Shimizu, H. Wynberg, E. G. J. Staring, *Tetrahedron Lett.* **1997**, *38*, 1593; e) T. Fujisawa, T. Ito, S. Nishiura, M. Shimizu, *Tetrahedron Lett.* **1998**, *39*, 9735; f) Z. Muljiani, S. R. Gadre, S. Modak, N. Pathan, R. B. Mitra, *Tetrahedron: Asymmetry* **1991**, *2*, 239; g) C. E. Song, J. K. Lee, S. H. Lee, S. Lee, *Tetrahedron: Asymmetry* **1995**, *6*, 1063; h) J. P. Benner, G. B. Gill, S. J. Parrot, B. Wallace, *J. Chem. Soc. Perkin Trans. 1* **1984**, 291; i) H. Wynberg, E. G. Staring, *J. Chem. Soc. Chem. Commun.* **1984**, 1181; j) C. E. Hatch III, J. S. Baum, T. Takashima, K. Kondo, *J. Org. Chem.* **1980**, *45*, 3281; k) T. J. Donohoe, P. M. Guyo, *J. Org. Chem.* **1996**, *61*, 7664; l) R. L. Tennyson, G. S. Cortez, H. J. Galicia, C. R. Kreiman, C. M. Thompson, D. Romo, *Org. Lett.* **2002**, *4*, 533; m) E. Kiehlmann, P.-W. Loo, B. C. Menon, N. McGillivray, *Can. J. Chem.* **1971**, *49*, 2964.

[2] For recent reviews, see: a) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357; b) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352;

c) P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917; d) S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432.

[3] This work is based on the landmark contribution by List, Lerner, and Barbas III. See: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2396; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386; c) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260. For reviews, see: d) B. List, *Synlett* **2001**, 1675; e) B. List, *Tetrahedron* **2002**, *58*, 5573; f) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573; g) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301; h) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3204.

[4] For other asymmetric direct aldol reaction, see: a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871; b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168; c) S. Matsnaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.* **2002**, *344*, 1; d) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003; e) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466, and references therein. f) K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Commun.* **2000**, 2211; g) T. Suzuki, N. Yamagiwa, Y. Matsuo, S. Sakamoto, K. Yamaguchi, M. Shibasaki, R. Noyori, *Tetrahedron Lett.* **2001**, *42*, 4669; h) K. Watanabe, Y. Yamada, K. Goto, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1401; i) Y. Yamada, K. Watanabe, H. Yasuda, *Utsunomiya Daigaku Kyoikugakubu Kiyo Dai-2-bu* **1989**, *39*, 25, and references therein; j) N. Yoshikawa, N. Kumagami, S. Matsunaga, G. Moll, T. Oshima, T. Suzuki, M. Shibasaki, *Org. Lett.* **2001**, *3*, 1539; k) B. M. Trost H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367; l) B. M. Trost, E. R. Silcoff, H. Ito, *Org. Lett.* **2001**, *3*, 2497, and references therein; m) T. Suzuki, N. Yamagiwa, Y. Matsuo, S. Sakamoto, K. Yamaguchi, M. Shibasaki, R. Noyori, *Tetrahedron Lett.* **2001**, *42*, 4669; n) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798. For recent examples of the catalytic direct aldol reactions, see: o) R. Mahrwald, B. Gundogan, *J. Am. Chem. Soc.* **1998**, *120*, 413; p) C. M. Mascarenhas, M. O. Duffey, S.-Y. Liu, J. P. Morken, *Org. Lett.* **1999**, *1*, 1427; q) T.-P. Loh, L.-L. Wei, Feng, L.-C. *Synlett* **1999**, 1059; r) S. J. Taylor, M. O. Duffey, J. P. Morken, *J. Am. Chem. Soc.* **2000**, *122*, 4528; s) D. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2002**, *124*, 392; t) T. J. Dickerson, K. M. Janda, *J. Am. Chem. Soc.* **2002**, *124*, 3220.

[5] Prepared as in the literature: R. G. Almquist, W.-R. Chao, C. J. White, *J. Med. Chem.* **1985**, *28*, 1067.

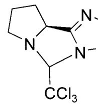
[6] N-Unsubstituted tetrazoles are moderately strong acids; the $\mathrm{p}K_\mathrm{a}$ values in water of tetrazoles lie in the range of -0.8 to about 6 depending on the electronic properties of the substituent at position 5 of the tetrazole ring, see: A. A. A. Boraei, *J. Chem. Eng. Data* **2001**, *46*, 939.

[7] a) S. Saito, M. Nakadai, H. Yamamoto, *Synlett* **2001**, 1245; b) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167; For the preliminary report on the present communication, see: c) The 83th (Spring) Annual Meeting of the Chemical Society of Japan, **2003**, Abstract II, p. 1186.

[8] In some respects, our results compare well with the proline-catalyzed reactions.[3] However, what is different from proline is enhanced reactivity leading to a lower catalyst (5–10 mol %) and ketone (1–8 equiv) loading, and even more expanded substrate scope regarding the ketone component. See also the Supporting Information for comparison experiments with proline.

[9] After we finished this work, the following important papers were published, which also support our mechanism, see: a) K. Funabiki, N. Honma, W. Hashimoto, M. Matsui, *Org. Lett.* **2003**, *5*, 2059; b) K. Funabiki, K. Matsunaga, M. Nojiri, W. Hashimoto, H. Yamamoto, K. Shibata, M. Matsui, *J. Org. Chem.* **2003**, *68*, 2853.

[10] One referee suggested that **17** might be formed from **1** and chloral, deteriorating the catalytic activity of **1**. However, we were unable to detect any ^{1}H NMR peaks corresponding to this during the aldol reaction but a very small, doublet peak at $\delta = 5.91$ ppm ($J = 2.1$ Hz) when **1** and chloral were mixed in a 1:1 ratio without **2** in CD$_3$CN or MeOD at room temperature for one day.



17

[11] The absolute configuration of **4** and **5** was determined by X-ray single-crystal analysis. See the Supporting Information.

[12] a) C. H. Heathcock in *Asymmetric Synthesis*, *Vol. 3* (Ed.: J. D. Morrison), Academic Press, San Diego, **1984**, p. 111. Ab initio calculation of proline- or amine-catalyzed aldol reactions, see: b) K. N. Rankin, J. W. Gauld, R. J. Boyd, *J. Phys. Chem. A* **2002**, *106*, 5155; c) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273; d) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 12911.

[13] This enantioselective hydroxymethylation is now under investigation with other carbonyl compounds, and the results will appear in a full account.