Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5699–5701

TETRAHEDRON LETTERS

The direct aldol reaction using bifunctional catalysts

Michael A. Calter* and Robert K. Orr

Department of Chemistry, University of Rochester, Rochester, NY 14627-0216, USA

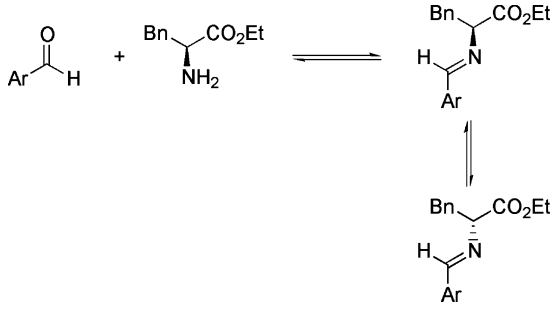
Received 14 May 2003; accepted 29 May 2003

Abstract—In this paper, we describe an approach to the direct aldol reaction using a bifunctional catalyst containing Lewis acidic and basic functional groups. To achieve this novel means of catalysis we have developed new tertiary amine–zinc catalysts, which perform the aldol reaction between acetone and *p*-nitrobenzaldehyde.

In recent years, the direct aldol reaction has received the attention of a number of synthetic groups.[1] Inspired by nature, two different approaches have evolved for the construction of aldol adducts from unactivated ketones and aldehydes. Based on the class I aldolases, several researchers have utilized proline to perform the direct aldol reaction.[2] The class II aldolases have stimulated work with lanthanide–binapthoxide complexes[3] and zinc-alkoxides.[4] We report here an approach that closely mimics the class II aldolase, using a complex containing a triaza binding pocket for Zn(II), along with a leaving group that can serve as both a weakly bound ligand and a base.[5]

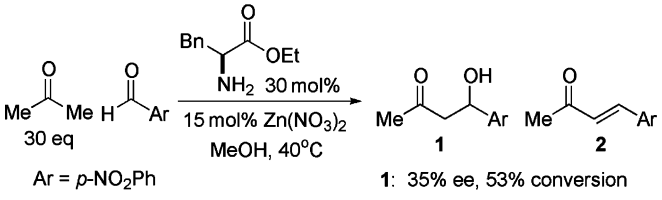
At the onset of this project, only two examples of a direct aldol reaction were known.[6] Initially, we choose to explore the reaction described by Watanabe and co-workers (Scheme 1). This Zn(II)-amino ester-catalyzed reaction was reported to give modest conversions and enantioselectivities.

The Watanabe reaction appeared to provide an easy entry point into the relatively unexplored direct aldol reaction. However, the reaction proved to be irreproducible. While the aldol adduct was formed, although in much lower conversion than reported, the product was always racemic. Investigation revealed that the amine condensed with the aldehyde to afford a Schiff base, in which the acidity of α-proton of the ester is increased (Scheme 2). Furthermore, the chiral ligand epimerized during the course of the reaction at a rate higher than that for the aldol reaction. The use of Zn(II)-dimethyl-α-amino-ester complexes as catalysts for the reaction also failed to afford any enantioselectivity.



Scheme 2.

Given these results, we decided that a more thorough study of the reaction parameters was necessary. Thus, a variety of tertiary amines were screened as ligands for zinc following Watanabe's general procedure (Eq. 1).[7] This series consisted of triethylamine, tetramethylethylenediamine **3**, pentamethyldiethylenetriamine **4**, and hexamethyltriethylenetetraamine **5** (Fig. 1). In the case of triethylamine, very little aldol product was observed after 24 h, using metal to ligand ratios ranging from 1:1 to 1:4 (entry 1, Table 1). With the chelating ligands **3**–**5**, the aldol reactions were success

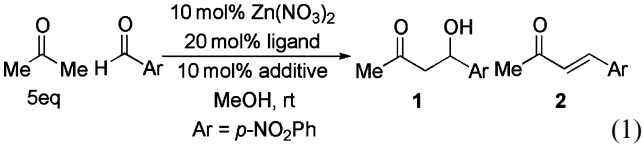


Scheme 1.

* Corresponding author. Tel.: +1-585-275-1626; fax: +1-585-506-0205; e-mail: calter@chem.rochester.edu

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01332-7

ful, the conversion of the reactions decreased as an additional amino group was added to the chain of the ligand (entries 2–4). The amount of condensation product also decreased with increasing number of amino groups on the ligand. This decrease could either be attributed to the decreasing amount of free-amine in solution or to the degree of saturation of the Lewis acid. To test this hypothesis, 10 mol% of triethylamine was added to the reaction mixture of **5** (entry 5). The reaction proceeded to give more aldol adduct than without base, albeit at lower conversion rates than reactions employing **3** and **4**.



(1)

We then turned our attention to the use of cyclic tetra-amines, such as the tripodal ligand trimethyl-triazacyclononane (Me_3TACN, **6**), as well as the closely related trimethyltriazacyclododecane (**7**), and tetramethyl-tetraazacyclododecane (**8**). In the case of Me_3TACN **6** (entry 6, Table 1), the reaction with zinc nitrate in methanol failed to give any products, even after several days. The lack of reactivity perhaps stems from the stability of the Zn(II)-TACN complex, as free

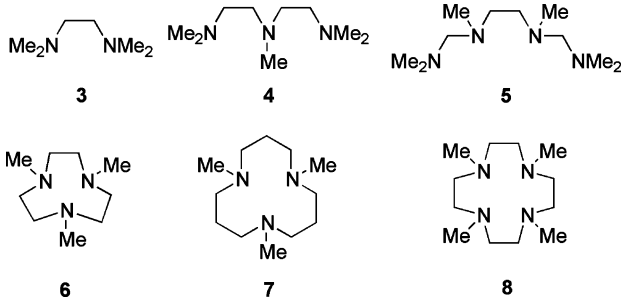
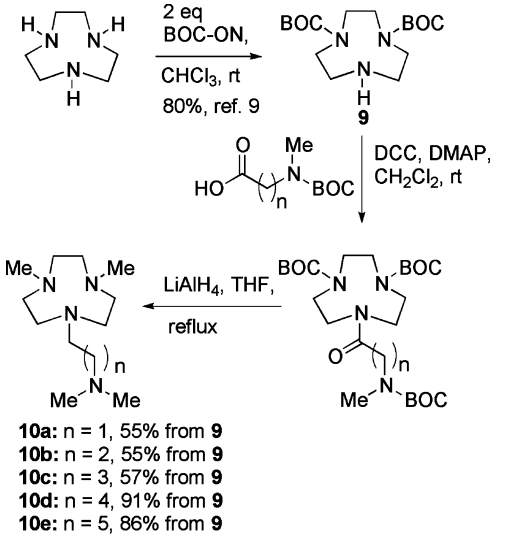


Figure 1. Achiral polyamine ligands.

Table 1. Achiral ligands for direct aldol reaction with $Zn(NO_3)_2$[a]

Entry	Ligand[b]	Additive	Time	% **1**[c]	% **2**[c]
1[d]	None	Et_3N	24	5	0
2	**3**	None	6	72	20
3	**4**	None	6	66	14
4	**5**	None	42	8	0
5	**5**	Et_3N	24	42	0
6	**6**	None	42	8	0
7	**6**	Et_3N	6	64	24
8	**6**	Pyridine	24	0	0
9	**6**	NaOAc	24	0	0
10	**7**	Et_3N	24	0	0
11	**8**	Et_3N	24	12	0

[a] See Eq. (1) for reaction conditions.
[b] Ligands **3** and **4** were used as 2:1 complexes with zinc nitrate. All others were used as 1:1 complexes unless noted.
[c] Conversion by ^{1}H NMR.
[d] Reaction run with Et_3N:$Zn(NO_3)_2$ = 4:1.



Scheme 3.

Me_3TACN would potentially act as a base.[8] Upon the addition of Et_3N, the reaction occurred rapidly (entry 7), suggesting a bifunctional mechanism. Weaker bases such as sodium acetate and pyridine failed to give aldol products with this metal and ligand. The other two cyclic ligands were ineffective in the aldol reaction (entries 10 and 11).

Encouraged by the results with Me_3TACN, **6**, we decided to synthesize a series of TACN complexes bearing a tethered base (**10a–e**). We hoped that the preorganization of a TACN-tethered base would further accelerate the reaction. These compounds were synthesized by the following sequence (Scheme 3): the commercially available TACN is first bis-acylated with 2 equiv. of the reactive agent BOC-ON (2-(*t*-butoxycarboyloxyimino)-2-phenylacetonitrile)[9] to yield **9**, and then acylated with the *N*,*N*-Boc,Me-amino acids[10] using DCC/DMAP.[11] Finally, tetraamines **10a–e** were prepared by reduction with $LiAlH_4$.[12]

The catalytic activity of the Zn(II)-tetraamine complexes varied with the length of the tether (Table 2). The reaction catalyzed by the complex of **10a** did not afford any products after several days. Reactions with the same complex and external base gave minimal conversion after 24 h (entries 1 and 2). While the

Table 2. Aldol reaction with TACN tethered base[a]

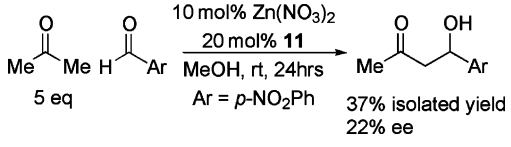
Entry	Ligand[b]	*n*	Additive	Time (h)	% **1**[c]	% **2**[c]
1	**10a**	2	None	24	0	0
2	**10a**	2	Et_3N	24	12	0
3	**10b**	3	None	24	30	0
4	**10c**	4	None	24	24	0
5	**10d**	5	None	24	66	0
6	**10e**	6	None	24	36	0

[a] See Eq. (1) for the reaction conditions.
[b] Reactions run with $Zn(NO_3)_2$:ligand = 1:1.
[c] Conversion by ^{1}H NMR.

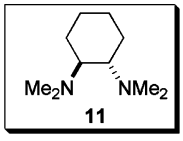
reactions catalyzed by compounds containing three and four carbon tethers, **10b** and **10c**, did furnish some aldol adduct (entries 3 and 4), the conversion of the aldol reaction peaked with the five carbon tether, and then decreased at six (entries 5 and 6).

Contrary to our original hypothesis, the reactions of the tethered amines were slower than that of the simple TACN and Et_3N system. Sterics may have been the cause of this rate reduction. This trend has also been observed using TACN derivatives bearing larger but non-chelating groups pendant to the TACN nitrogens.

Our most recent endeavors have been in the development of an enantioselective version of this reaction using chiral tertiary amine catalysts. Unfortunately, we have found that none of the TACN-derived complexes synthesized thus far afforded any asymmetric induction. A variety of achiral di- and triamines were also screened. Our best results were with tetramethyldiaminocyclohexane, **11** (Eq. (2)).



(2)



In conclusion, we have shown the pitfalls of using α-aminoesters in the direct aldol reaction. We have also explored a variety of new tertiary amine ligands for the direct aldol reaction with acetone and *p*-nitrobenzaldehyde. Both tetramethylethylenediamine- and triazacyclononane-derived ligands accelerate the reaction efficiently. In the case of the TACN ligands, it has been demonstrated that additional base is necessary to perform the reaction, supporting a bifunctional mechanism. Excellent selectivity for the aldol adduct versus the aldol condensate can be achieved by using base-tethered TACN derivatives.

Acknowledgements

The authors thank the Chemistry Departments of Virginia Tech and the University of Rochester for funding this work.

References

1. For recent advances in the direct aldol reaction, see: Lalic, G. L.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852–2853; (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177.
2. (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; (c) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16–17; (d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.
3. (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178; (b) Kumagai, N.; Matasunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178.
4. (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004; (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368.
5. Dreyer, M. K.; Schulz, G. E. *J. Mol. Biol.* **1996**, 458–466.
6. (a) Nakagawa, M.; Nakao, H.; Watanabe, K. *Chem. Lett.* **1985**, 391–394; (b) Watanabe, K.; Yamada, Y.; Goto, K. *Bull. Chem. Soc. Jpn.* **1985**, *55*, 1401–1406; (c) Yumada, Y.; Watanabe, K.; Yasuda, H. *Usonomiya Daiguku Kyoikugabubu Kiyo* **1989**, *39*, 25–31; (d) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.
7. *Procedure*: To a solution of ligand (0.2 equiv.) in MeOH (0.1 M with respect to the aldehyde) at room temperature was added zinc nitrate hexahydrate (0.1 equiv.). To the complex was then added *p*-nitrobenzaldehyde (1 equiv.) and acetone (5 equiv.). The solution was then stirred under nitrogen atmosphere overnight. Conversion was determined by ^1H NMR of concentrated aliquots.
8. Fry, F. H.; Fallon, G. D.; Spiccia, L. *Inorg. Chim. Acta* **2003**, 57–66.
9. Zoltan, K.; Sherry, A. D. *Tetrahedron Lett.* **1995**, *36*, 9269–9272.
10. *N*,*N*-BOC,Me-amino acids were prepared via BOC protection of the parent amino acid. The BOC protected compounds were then treated with NaH and MeI (3 and 5 equiv., respectively) in THF overnight. The solvent was removed, water was added to the resulting solid, and the mixture was acidified and extracted with CH_2Cl_2. The organic extract was concentrated and chromatographed (silica gel, EtOAc/hexanes) to yield the *N*,*N*-BOC,Me-amino acids.
11. To a 0.1 M solution of Bis-BOC-TACN in CH_2Cl_2 was added the *N*,*N*-BOC,Me-amino acid (1.2 equiv.), then DCC (1.5 equiv.), and DMAP (0.1 equiv.). The reaction was stirred overnight, filtered through a cotton plug, and the volume was reduced in vacuo. The product was then purified by chromatography (silica gel, EtOAc/hexanes). The tris-BOC compound was then refluxed overnight in THF (0.1 M) with excess $LiAlH_4$ (10 equiv., *n* grams). To the reaction mixture was added *n* mL of H_2O, *n* mL of 15% NaOH, and, after 10 min, 3*n* mL of H_2O. The solid formed was washed with CH_2Cl_2 and EtOAc. The combined organic washes were evaporated to give the tetramines, which were used directly in the aldol reaction.
12. All new compounds gave satisfactory analytical and spectral data.