Pergamon

Tetrahedron Letters 42 (2001) 199–201

TETRAHEDRON LETTERS

Amine-catalyzed direct asymmetric Mannich-type reactions

Wolfgang Notz, Kandasamy Sakthivel, Tommy Bui, Guofu Zhong and Carlos F. Barbas, III*

The Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Received 23 October 2000; accepted 27 October 2000

Abstract—Three chiral cyclic secondary amines are shown to be catalysts for the direct asymmetric Mannich-type reaction of acetone with a variety of preformed aldimines derived from *o*-anisidine. A simple one-pot three-component reaction procedure consisting of aldehyde, acetone, *p*-anisidine and an amine catalyst provides the corresponding β-amino ketones with 50–89% ee under very mild conditions. © 2000 Published by Elsevier Science Ltd.

Optically active β-amino ketones, esters, and alcohols are versatile synthons that may be employed in the construction of a wide variety of nitrogen containing natural products. One classic route to 1,3-amino ketones and esters involves Mannich-type reactions.[1] Asymmetric Mannich-type reactions have typically involved addition of enolates to chiral aldimines[2] or hydrazones[3] wherein the chiral controller of the reaction is used in stoichiometric amounts. Recently, asymmetric Mannich-type reactions that employ chiral Lewis acids to catalyze the reaction of preformed enolate equivalents (e.g. silyl enol ethers) with aldimines[4] and an example of a direct asymmetric Mannich-type reaction[5] have been reported.

For the past few years we have devoted considerable effort to the development of catalytic asymmetric aldol and related reactions that are facilitated by amine-based mechanisms.[6] These studies, originally founded in the area of catalytic antibodies, have resulted in the development of simple amine catalysts for these types of reactions. We have reported amine-catalyzed direct asymmetric aldol reactions[7] and a Robinson annulation reaction.[8] Herein we explore catalysis of the aza-variant of the aldol reaction and disclose the development of chiral amine-based catalysis of direct asymmetric Mannich-type reactions.

During the course of screening studies for aldol and Robinson annulation catalysts, various chiral amines and thiazolidine carboxylic acids were identified as promising Mannich catalysts[8,9] and diamine salt **1**, L-proline **2**, and the penicillamine derivative L-5,5-dimethylthiazolidine-4-carboxylic acid **3** (DMTC) are among the most promising (Table 1a).

In order to further test their utility in directing the addition of acetone to imines, reactions of preformed aldimine **4c** in DMSO/acetone (4:1) at room temperature were studied in the presence of 20 mol% of catalysts **1**, **2** and **3**, (entry 3, Table 1a). Within 48 h, all of the chiral amines employed catalyzed the addition of acetone to imine **4c** resulting in the formation of β-amino ketone **5c** with comparable yield, albeit with varying degrees of enantioselectivity. In particular, the reaction using penicillamine derivative DMTC **3** provided the desired product in 80% ee.

In additional comparative studies of these catalysts, aldimines derived from the reaction of *o*-anisidine with benzaldehyde, *p*-acetamido benzaldehyde, and 1-naphthaldehyde (entries 1, 2, 4, Table 1a) were reacted in DMSO/acetone (4:1) with 20 mol% catalyst at room temperature Based on these results, we judged DMTC **3** to be the most promising catalyst for further investigations. In all reactions, the condensation product was observed as a side-product and was the main product when using preformed aldimines derived from *o*-aminophenol. This side-product does not form by deamination of the Mannich products since, upon treatment of racemic **5a** with DMTC **3** for 5 days under the standard reaction conditions, neither the elimination product nor any resolution of the racemate was detected.

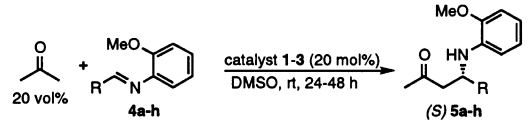
Next, we attempted to extend our studies to the non-aromatic aldimines derived from cyclohexanecarboxaldehyde and isobutyraldehyde. In these cases we were

* Corresponding author.

0040-4039/01/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01908-0

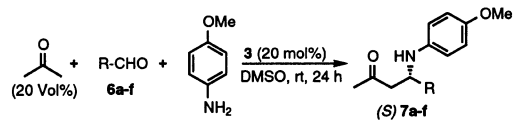
Table 1.

(a) β-Amino ketones obtained from the reaction of acetone with preformed aldimines **4a-h**



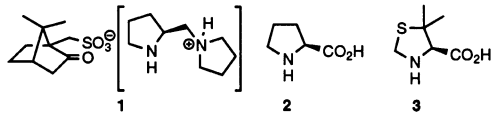
Entry	4; R	Catalyst	Yield of 5[a]	ee[b]
(1)	a	1	43 %	2 %
		3	45 %	16 %
(2)	b	1	50 %	67 %[c]
		2	48 %	51 %
		3	48 %	60 %
(3)	c	1	40 %	55 %[c]
		2	50 %	40 %
		3	48 %	80 %
(4)	d	1	32 %	25 %[c]
		2	42 %	86 %
		3	56 %	88 %
(5)	h	3	47 %	75 %

(b) β-Amino ketones obtained from the one-pot three-component reaction



Entry	6; R	Yield of 7[a]	ee[b]
(1)	a	45 %	86 %
(2)	b	52 %	89 %
(3)	c	46 %	70 %
(4)	d	58 %	51 %
(5)	e	38 %	62 %
(6)	f	45 %	50 %

[a]Isolated yield after column chromatography. [b]Determined by chiral-phase HPLC analysis. [c]Reverse stereochemistry obtained.



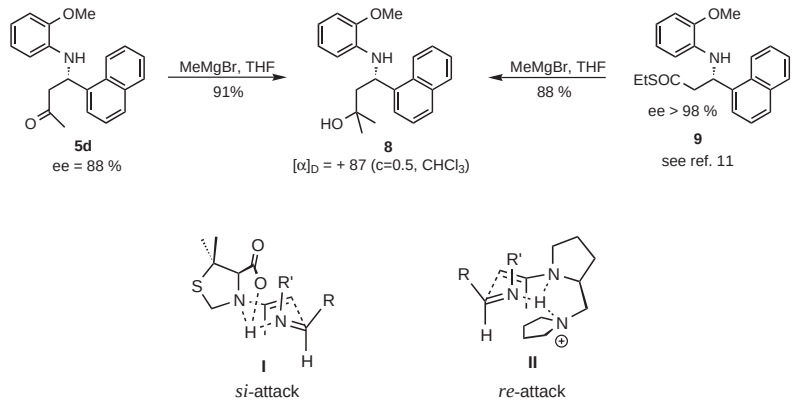
unable to prepare the *o*-anisidine derived aldimines in pure form. Alternatively, we have studied one-pot three-component reactions (Table 1b) and found that the reaction of a 1:1-mixture of aldehyde and *p*-anisidine proceeded smoothly in DMSO/acetone (4:1) at room temperature for 24 h in the presence of catalyst **3** to give the corresponding Mannich products **7a**–**f** (Table 1b). However, studies with aromatic aldehydes in one-pot reactions with *o*-anisidine did not furnish the desired Mannich products. Removal of the *N*-protective groups used here is readily achieved by treatment with cerium ammonium nitrate (CAN).[10]

Like the analogous aldol reaction, these reactions are assumed to proceed via an enamine mechanism. The absolute stereochemistry of the new stereogenic center formed by the catalysis of amines **2** and **3** has been determined by comparison of the optical rotation and chiral-phase HPLC data of derivative **8**, which were identical to those of **8** obtained after derivatization of **9** (Scheme 1) obtained via Kobayashi's methodology.[10] Catalysis mediated by diamine salt **1** yields products of the opposite absolute configuration of those provided by **2** and **3**. The stereochemistry observed can be rationalized by transition state geometries **I** and **II** (Scheme 1).[11] Note that the facial selectivity in these Mannich-type reactions is opposite that which we have observed for the corresponding aldol reactions using these catalysts.[7,9]

In summary, we have achieved direct catalytic enantioselective Mannich-type reactions of both aliphatic and aromatic aldimines with acetone by using simple chiral amines **1**–**3** as catalysts providing the corresponding β-amino ketones with high enantiomeric excesses. Further, chiral β-amino ketones **7a**–**f** can be synthesized in a one-pot three-component reaction consisting of aldehyde, *p*-anisidine, acetone, and catalyst in DMSO. Our best catalysts, L-proline **2** and penicillamine derivative **3**, are nontoxic, relatively inexpensive, and readily available in both enantiomeric forms. This methodology represents advantages in terms of reaction conditions, catalyst stability, cost, and optical yield and extends the scope of organocatalysis using chiral amines. During the course of our studies, a report regarding proline-catalyzed Mannich-type reactions analogous to those described here was published.[12]

Acknowledgements

This study was supported by the NIH (CA27489) and the Skaggs Institute for Chemical Biology.



Scheme 1. Determination of absolute configuration of Mannich-product **5d** and potential transition states **I** and **II**.

References

1. For reviews, see: (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp. 893–951. (b) Hart, D. J.; Ha, D.-C. *Chem. Rev*. **1989**, *89*, 1447. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed*. **1998**, *37*, 1044. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069.
2. (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **1999**, *64*, 12. (b) Müller, R.; Goesmann, H.; Waldmann, H. *Angew. Chem., Int. Ed*. **1999**, *38*, 184. (c) *Enantioselective Synthesis of β-Amino Acids*; Juraisti, E., Ed.; Wiley-VCH: New York, 1997. (d) Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem*. **1996**, *61*, 2222. (e) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett*. **1991**, *32*, 5287. (f) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc*. **1994**, *116*, 10520. (g) Kambara, T.; Hussein, A.; Fujieda, H.; Iida, A.; Tomioka, K. *Tetrahedron Lett*. **1998**, *39*, 9055.
3. Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed*. **1996**, *35*, 981. See also: Risch, N.; Esser, A. *Liebigs Ann. Chem*. **1992**, 233.
4. (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc*. **1997**, *119*, 2060. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc*. **1997**, *119*, 7153. (c) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc*. **1998**, *120*, 2472. (d) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc*. **1998**, *120*, 4548. (e) Ferraris, D.; Young, B.; Cox, C.; Drury III, W. J.; Dudding, T.; Lectka, T. *J. Org. Chem*. **1998**, *63*, 6090. (f) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc*. **1998**, *120*, 431. (g) Ishihara, K.; Miyata, M.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc*. **1994**, *116*, 10520.
5. (a) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857. (b) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed*. **1999**, *38*, 3504.
6. (a) Wagner, J.; Lerner, R. A.; Barbas, III, C. F. *Science* **1995**, *270*, 1797. (b) Björnestedt, R.; Zhong, G.; Lerner, R. A.; Barbas, III, C. F. *J. Am. Chem. Soc*. **1996**, *118*, 11720. (c) Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas, III, C. F. *J. Am. Chem. Soc*. **1997**, *119*, 8131. (d) Hoffmann, T.; Zhong, G.; Last, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, III, C. F. *J. Am. Chem. Soc*. **1998**, *120*, 2768. (e) Zhong, G.; Lerner, R. A.; Barbas, III, C. F. *Angew. Chem., Int. Ed*. **1999**, *38*, 3738.
7. (a) List, B.; Lerner, R. A.; Barbas, III, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395; (b) Notz, W.; List, B. *J. Am. Chem. Soc*. **2000**, *122*, 7386.
8. Bui, T.; Barbas, III, C.F. *Tetrahedron Lett*. **2000**, *41*, 6951.
9. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, III, C. F., submitted for publication.
10. Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc*. **2000**, *122*, 8180.
11. A (*Z*)-imine has been proposed earlier for this type of reaction. See: Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett*. **1991**, *39*, 5287.
12. List, B. *J. Am. Chem. Soc*. **2000**, *122*, 9337.