ORGANIC LETTERS

2008
Vol. 10, No. 9
1731−1734

Brønsted-Acid-Catalyzed Activation of Nitroalkanes: A Direct Enantioselective Aza-Henry Reaction

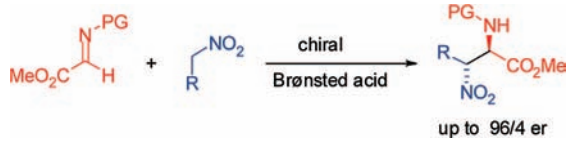
Magnus Rueping* and Andrey P. Antonchick

Degussa Endowed Professorship, Institute of Organic Chemistry and Chemical Biology, University Frankfurt, Max-von-Laue Strasse 7, 60438 Frankfurt am Main, Germany

M.rueping@chemie.unifrankfurt.de

Received February 17, 2008

ABSTRACT



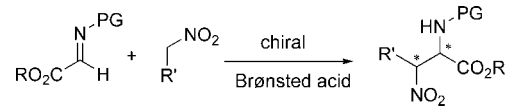
A direct asymmetric organocatalytic aza-Henry reaction has been developed in which a new bifuctional Brønsted-acid-catalyzed activation of nitroalkanes provides an efficient access to α,β-diamino acids with high dia- and enantioselectivities under mild and base-free reaction conditions.

The addition of nitroalkanes to aldimines, the aza-Henry reaction, represents an important C−C coupling reaction which can result in the formation of two neighboring, nitrogen containing, stereocenters.[1] These valuable reactions represent not only a simple route to numerous chiral synthetic building blocks but also provide efficient access to vicinal diamines[2] and α-carbonyl compounds.[3]

Attempts to achieve asymmetric variants of the nitro-Mannich reaction have previously been made using chiral metal complexes[4] or metal free catalysts[5] in combination with various aromatic aldimines and α-amidosulfones which gave the corresponding 2-nitroamines with good yields and selectivities.

However, despite these interesting results it is surprising that an asymmetric organocatalytic aza-Henry reaction of nitroalkanes with α-iminoesters has not previously been described although the corresponding α,β-diamino acids are of great biological significance and are the basis for numerous natural products.[6] This is often due to the reaction conditions being too basic resulting in the loss of enantio- and diastereoselectivity.

On the basis of these facts we decided to examine a direct Brønsted-acid-catalyzed enantioselective aza-Henry reaction (eq 1).



(1)

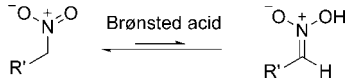
This would not only be the first example of such a reaction but it would also be a conceptionally new approach insofar

(1) (a) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.
(2) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2581.
(3) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.
(4) (a) Metal-catalyzed asymmetric aza-Henry reaktions with ytterbium: Yamada, K.; Harwood, S. J.; Gröger H., Shibasaki; M, *Angew. Chem., Int. Ed.* **1999**, *38*, 3504. (b) Aluminium: Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980. (c) Copper: Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (d) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992.
(5) (a) Metal-free enantioselective variants with thiourea: Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y *Org. Lett.* **2004**, *6*, 625. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466. (c) With chincona alcaloids: Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (d) Robak, M. T.; Trincado, M.; Ellman, J. A *J. Am. Chem. Soc.* **2007**, *129*, 15110. (e) With amidines: Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (f) Hess, A. S.; Yoder, R. A.; Johnston, J. N. *Synlett* **2006**, 147. (g) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N *J. Am. Chem. Soc.* **2007**, *129*, 3466. (h) The nitro-Mannich reaction in neat nitropropane (pK_a (propane-nitronic acid) = 4.6) was accelerated by the addition of substoichiometric amounts of AcOH (pK_a = 4.7) : Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549.

10.1021/ol8003589 CCC: $40.75
Published on Web 04/08/2008

as a direct enantioselective acid-catalyzed activation of nitroalkanes had not previously been described.

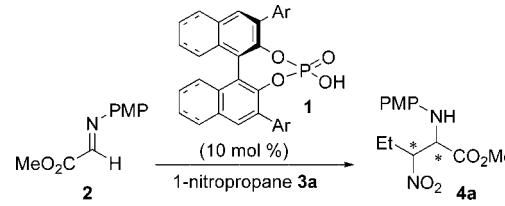
Given that Brønsted acids are able to catalyze aldol reactions we assumed that a chiral BINOL phosphate **1** could play a bifunctional role in that it not only protonates the aldimine but also accelerates the adjustment of the equilibrium between the nitroalkane and nitronate (eq 2)



(2)

Furthermore, in comparison to previously described methods, under these nonbasic conditions the corresponding products should be configurationally stable. Hence, this new, direct Brønsted-acid-catalyzed aza-Henry reaction would enable, for the first time, simple yet efficient access to the valuable β-nitro-α-amino acid esters. On the basis of our earlier work regarding chiral ion pair catalysis, as well as asymmetric Brønsted acid activation of imines[7] and carbonyl compounds,[8] we started our experiments with the BINOL phosphoric acid[7–9] catalyzed nitro-Mannich reaction of α-iminoester **2** and 1-nitropropane **3a** (Table 1). It was shown that the different substituted BINOL-phosphates **1a**−**f** as well as the corresponding octahydro derivatives **1g**−**i** did indeed catalyze the aza-Henry reaction and provided the amino acid esters **4a** in good diastereo- and enantiomeric ratios.

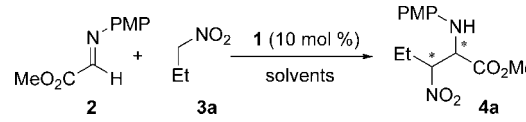
Table 1. Evaluation of Chiral Brønsted Acids in the Direct Enantioselective Aza-Henry Reaction



entry[a]		aryl	yield (%)	time (h)	dr[b]	er[c]
1	**1a**	phenyl	4	168	6/1	56/44
2	**1b**	4-biphenyl	15	168	10/1	80/20
3	**1c**	1-naphthyl	44	144	6/1	41/59
4	**1d**	2-naphthyl	19	168	8/1	53/47
5	**1e**	3,5-(t-Bu)$_2$-PMP	13	168	5/1	91/9
6	**1f**	9-phenanthryl	65	120	6/1	82/18
7	**1g**	[H]$_8$ Ph_3Si	72	18	9/1	82/18
8	**1h**	[H]$_8$ 9-phenanthryl	62	120	8/1	85/15
9	**1i**	[H]$_8$ 4-phenoxyphenyl	20	120	8/1	47/53

[a] Reactions were performed at ambient temperature, using catalyst **1** (10 mol %) in 1-nitropropane (0.15 M). [b] Anti/syn ratio was determined by ^{1}H NMR. [c] The enantiomeric ratio of the anti diastereomer was determined by HPLC analysis.

Table 2. Influence of the Solvent on the Brønsted-Acid-Catalyzed Direct Enantioselective Aza-Henry Reaction



entry[a]	solvent	catalyst	yield (%)	dr[b]	er[c]
1	toluene	**1h**	10	5/1	75/25
2	toluene	**1f**	12	5/1	89/11
3	toluene	**1g**	42	12/1	95/5
4	benzene	**1g**	45	13/1	95.5/4.5
5	CH_2Cl_2	**1g**	35	12/1	88/12
6	$CHCl_3$	**1g**	12	13/1	80/20
7	(n-Bu)$_2$O	**1g**	47	11/1	91/9
8	AcOEt	**1g**	33	8/1	91/9

[a] Reactions were performed at ambient temperature, using catalyst **1** (10 mol %), 10 equivalents of 1-nitropropane in solvent (0.05 M). [b] *Anti*/*syn* ratio was determined by ^{1}H NMR. [c] The enantiomeric ratio of the *anti*-diastereomer was determined by HPLC analysis.

The best enantioselectivities were achieved with the BINOL-phosphate **1e** (Table 1, entry 5); however, the sterically demanding triphenylsilyl-substituted Brønsted acid **1g** gave not only the best diastereoselectivity but also exhibited increased reactivity compared to all the other catalysts tested (Table 1, entry 7).

To further optimize the reaction, the imino ester protecting group, the temperature, the catalyst loading, the concentration, and the solvent were varied. Thus, it was observed that the reactivity, enantio-, and diastereoselectivity of the Brøn-

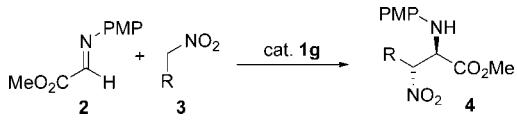
(6) Viso, A.; de la Pradilla, R. F.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.

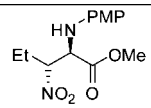
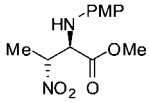
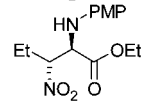
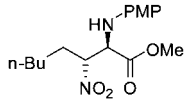
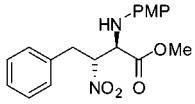
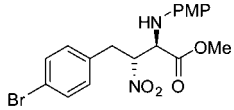
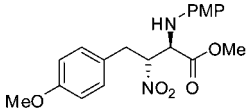
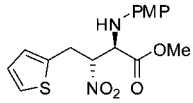
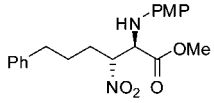
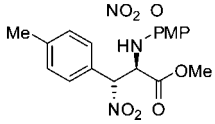
(7) (a) Rueping, M.; Azap, C.; Sugiono, E.; Theissmann, T. *Synlett* **2005**, 2367. (b) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (c) Rueping, M.; Theissmann, T.; Antonchick, A. P. *Synlett* **2006**, 1071. (d) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (e) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (f) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617. (g) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832. (h) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Köckritz, A.; Pews Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065. (i) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2007**, 1441. (j) Rueping, M.; Sugiono, E.; Moreth, S. A. *Adv. Synth. Catal.* **2007**, *349*, 759. (k) Rueping, M.; Antonchick, A.; P, *Angew. Chem., Int. Ed.* **2007**, *46*, 4562. (l) Rueping, M.; Antonchick, A. P.; Brinkmann., C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903.

(8) (a) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097. (b) Rueping, M.; Nachtsheim, B. J.; Moreth, S. M.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593.

(9) Reviews:(a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Applications: Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (e) Hofmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (f) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (g) Terada, M; Sorimachi, K.; Uraguchi, D. *Synlett* **2006**, 13. (h) Terada, M.; Machiok, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (i) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193. (j) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796. (k) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (l) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074. (m) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368. (n) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (o) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802. (p) Liu, H.; Cun, L.-F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Org. Lett.* **2006**, *8*, 6023. (q) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (r) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. (s) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. (t) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498. (u) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (v) Rowland, E. B.; Roland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084.

Table 3. Scope of the Enantioselective Brønsted-Acid-Catalyzed Direct Enantioselective Aza-Henry Reaction



product[a]		yield (%)	dr[b]	er[c]
	**4a**	64	9/1	96/4
	**4b**	61	10/1	96/4
	**4c**	74	11/1	92/8
	**4d**	65	9/1	96/4
	**4e**	93	13/1	94/6
	**4f**	84	11/1	93/7
	**4g**	73	13/1	94/6
	**4h**	69	13/1	92/8
	**4i**	57	7/1	96/4
	**4j**	64	2/1	92/8

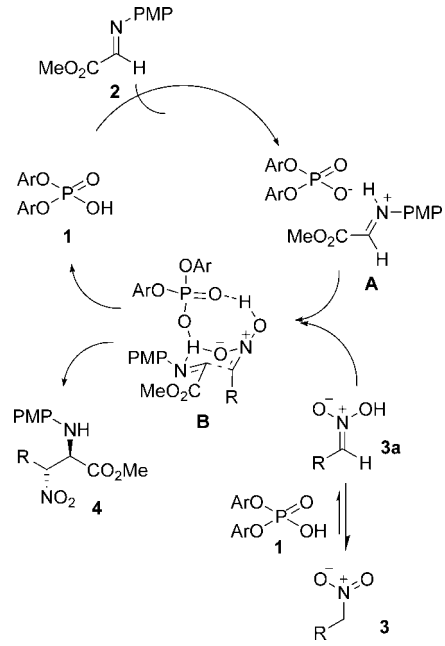
[a] Reactions were performed at 30°C, using catalyst **1g** (10 mol %), 10 equiv of nitroalkane in benzene (0.10 M) for 12−166 h. Isolated yield after purification by column chromatography. [b] Anti/syn ratio was determined by ^{1}H-NMR. [c] The enantiomeric ratios of the anti diastereomers was determined by HPLC analysis.

sted-acid-catalyzed aza-Henry reaction are profoundly dependent on the solvent employed (Table 2).

In solvents such as THF, acetonitrile and dioxane almost no transformation occurred. However, the reactions in halogenated and aromatic solvents (Table 2, entry 1−6) provided the enantiomerically enriched amino acid ester **4a**.

The best enantio- and diastereoselectivities were achieved in benzene and toluene and, thereby, the nitro-Mannich reaction of iminoester **2** and nitroalkane **3a** in the presence of catalytic amounts **1g** gave the desired amino acid ester **4a** in an enantiomeric ratio of 96/4 er and in a diastereomeric

Scheme 1. Proposed Reaction Mechanism for the Brønsted-Acid-Catalyzed Aza-Henry Reaction



ratio of 13/1. Under these optimized conditions we tested different nitroalkanes in the BINOL-phosphate catalyzed, enantio- and diastereoselective aza-Henry reaction (Table 3).[10] In general, it was possible to successfully apply various aliphatic and aromatic nitromethanes, whereby, the new amino acid esters **4a**−**j** were isolated for the first time in good yields as well as very good diastereo- and enantioselectivities.

With regard to the reaction mechanism we assume that the chiral Brønsted acid **1** plays a bifunctional role (Scheme 1). On the one hand the α-iminoester **2** is activated by the protonation of **1** which results in the formation of the chiral ion pair **A**. On the other hand it can be assumed that the adjustment of the nitroalkane/nitronate equilibrium is also accelerated by **1**. The addition of the nitronate **3a** to the activated imino ester **A** probably then occurs via the intermediate **B** in which the chiral bifunctional BINOL-phosphate acts simultaneously as a Brønsted acid and as a Lewis base and which then results in the desired amino acid ester **4**.

In summary we report here for the first time the development of a new direct Brønsted acid catalyzed diastereo- and enantioselective nitro-Mannich reaction of α-imino esters with diverse nitroalkanes providing valuable *β*-nitro-α-amino acid esters.[11] Prior activation of the nitroalkane *via* transformation to silyl nitronates, as often previously reported, is in our newly developed direct aza-Henry reaction no longer necessary. Furthermore, the dual activation mode of the BINOL-phosphate allows the reaction to be performed under mild and strong base-free reaction conditions.

In addition, the reaction described here represents the first example of the direct enantioselective Brønsted-acid-catalyzed activation of nitroalkanes and allows the desired

amino acid esters to be isolated in good yields, excellent enantioselectivities (up to 96/4 er) and with the widest substrate scope to date. The concept of mild Brønsted-acid-catalyzed activation of nitroalkanes as well as the bifunctional activation through BINOL-phosphates is promising with regard to the development of other enantioselective transformations and is the focus of ongoing research.

(10) Detailed experimental information as well as the assignment of the absolute configuration is provided in the Supporting Information.

Acknowledgment. The authors acknowledge Evonik-Degussa GmbH and the DFG (Schwerpunktprogramm Organokatalyse) for financial support.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8003589

(11) The β-nitro-α-amino acid esters can be readily transferred into the corresponding diamino acid, which has been demonstrated by Jørgense et al., ref 4d.