

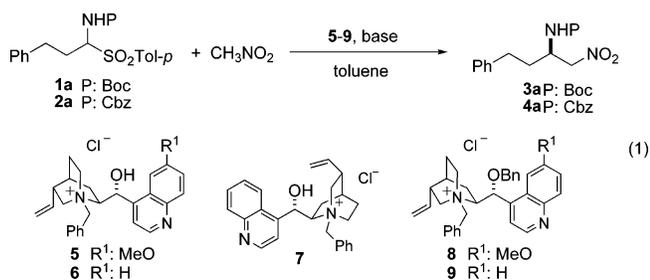
Catalytic Enantioselective Aza-Henry Reaction with Broad Substrate Scope

Claudio Palomo,* Mikel Oiarbide, Antonio Laso, and Rosa López

Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco, Apdo. 1072, 20080 San Sebastián, Spain

Received October 3, 2005; E-mail: qoppanic@sc.ehu.es

The reaction of nitrocompounds with azomethine functions to afford 1,2-nitroamines, the aza-Henry (or nitro-Mannich) reaction,¹ is a highly valuable C–C bond forming process. The resulting nitroamine adducts can either be reduced,² producing 1,2-diamines,³ or oxidized,⁴ affording α -amino acids. While the production of both families of target molecules in nonracemic form bears considerable interest, the use of the aza-Henry approach in that endeavor remains nearly unexplored because of the long-standing lack of (catalytic) asymmetric versions. Several groups have recently reported enantioselective aza-Henry protocols involving metallic⁵ as well as purely organic⁶ catalysts. Despite the remarkable levels of selectivity so far reported,^{5,6} these methods are restricted, with almost no exception, to non-enolizable aldehyde-derived azomethines.⁷ The availability of catalytic, enantioselective protocols also suitable for enolizable substrates would considerably expand the aza-Henry reaction. We have found recently that α -amido sulfones are appropriate in situ precursors of enolizable aldehyde-derived azomethine compounds in the context of the asymmetric Mannich reaction.⁸ In connection to our recent interest in the area,^{5g} we present here a new asymmetric aza-Henry technology with broad substrate scope based on the use of α -amido sulfone substrates⁹ and phase transfer catalysis (PTC).



Given that in situ generation of azomethines from α -amido sulfones requires stoichiometric base,¹⁰ the base-promoted, nonselective background aza-Henry reaction constitutes an initial obstacle.¹¹ It seemed that phase transfer conditions using chiral quaternary ammonium salts¹² in combination with a nonsoluble base would render the competitive undesired reaction marginal.

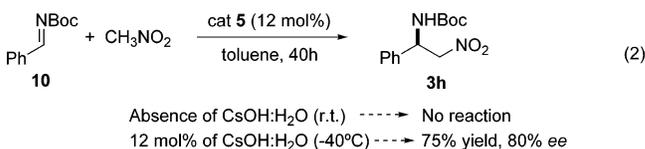
The initial screen of several commercially available chiral quaternary ammonium salts **5–7** and inorganic bases for the reaction of α -amido sulfone **1a** and nitromethane in toluene as solvent was informative (eq 1 and Table 1). After 44 h of stirring at $-40\text{ }^\circ\text{C}$, only $\text{CsOH}\cdot\text{H}_2\text{O}$ ¹³ exhibited, among the bases tested, nearly complete conversion; in all other cases, conversions remained below 40%. As is often customary, while quinine derivative **5** and cinchonidine derivative **6** provided products with *R* configuration, cinchoninium salt **7** afforded the products with opposite configuration.¹⁴ Good enantioselectivities were attained with all three salts when *N*-Boc sulfone **1a** was employed, but the reactions with the corresponding Cbz sulfone **2a** were less satisfactory.

Table 1. Screening of Bases and Quaternary Ammonium Salts in the Reaction of α -Amido Sulfones **1a/2a** with Nitromethane^a

substrate	salt	base	product	conv. (%) ^b	ee (%) ^c
1a	5	Cs_2CO_3	3a	33	82
1a	5	$\text{CsOH}\cdot\text{H}_2\text{O}$	3a	>95	90
2a	5	Cs_2CO_3	4a	23	65
2a	5	$\text{CsOH}\cdot\text{H}_2\text{O}$	4a	90	65
1a	5	K_2CO_3	3a	38	80
1a	5	KOH	3a	36	82
1a	6	Cs_2CO_3	3a	40	76
1a	6	$\text{CsOH}\cdot\text{H}_2\text{O}$	3a	>95	85
1a	7	Cs_2CO_3	ent- 3a	17	44
1a	7	$\text{CsOH}\cdot\text{H}_2\text{O}$	ent- 3a	90	84

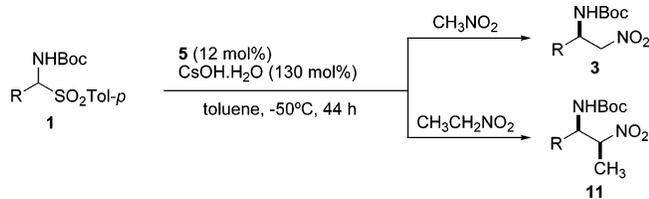
^a Reactions conducted at 0.5 mmol scale in 1.5 mL of toluene using a nitromethane:base:ammonium salt molar equivalent ratio of 5:3:1.2 at $-40\text{ }^\circ\text{C}$ for 40–44 h. ^b Determined by ¹H NMR. ^c Determined by HPLC.

In subsequent experiments, it was found that catalytic quantities of **5** in combination with $\text{CsOH}\cdot\text{H}_2\text{O}$ (120–150 mol %) sufficed for the reaction of nitromethane with a variety of α -amido sulfones **1**. As data in Table 2 show, the enantiomeric excesses are generally high for aryl-substituted α -amido sulfones (**1h–m**) irrespective of the electronic nature of the aromatic ring: heteroaromatic azomethines being also tolerated (**1n**). Most remarkably, the aza-Henry reaction with an array of enolizable aldehyde-derived azomethines gave enantiomeric excesses regularly above 94%. Hence, both linear as well as branched chain alkyl α -amido sulfones **1a–g**, which show uneven degrees of steric hindrance, gave the corresponding adduct **3** in good yields and enantiomeric excesses in the 94–98% range. Again, catalyst **5** performed slightly better than **6** (compare entries 1/2, 3/4, and 10/11).



Additional observations gave further insights on the requirements of and role played by the base and the catalyst. Thus, amine bases, such as DBU, also gave good conversions but at the expense of the enantioselectivity.¹⁵ The achiral amidinium nitronate, initially generated in this instance upon nitromethane-base proton transfer, may likely contribute to the racemic background process. On the other hand, as results in eq 2 show, catalyst **5** alone is not capable of promoting the reaction between **10** and nitromethane, and a scenario with the cinchona catalysts acting as concurrent acid and base¹⁶ can be ruled out in this system. Clearly, $\text{CsOH}\cdot\text{H}_2\text{O}$ does not merely act as the base for *N*-acyl imine formation but also intervenes during the subsequent aza-Henry reaction. In addition, the free hydroxyl group in catalysts **5–7** plays a key role in substrate activation since the corresponding catalysts **8** and **9**, whose alcohol group has been protected in the form of benzyl ether, showed

Table 2. Aza-Henry Reaction of Nitromethane and Nitroethane with Azomethines Generated from α -Amido Sulfones **1** under PTC^a



entry	compound	R	product	yield (%) ^b	ee (%) ^c
1	a	PhCH ₂ CH ₂	3	83	96 ^e
2				40 ^d	91
3	b	CH ₃ CH ₂	3	80	96
4				68 ^d	90
5	c	CH ₃ CH ₂ CH ₂	3	78	94
6	d	CH ₃ (CH ₂) ₄ CH ₂	3	78	98
7	e	(CH ₃) ₂ CHCH ₂	3	75	97
8	f	(CH ₃) ₂ CH	3	81	95
9	g	<i>c</i> -C ₆ H ₁₁	3	77	98
10	h	Ph	3	79	91
11				80 ^d	78
12	i	4-MeOC ₆ H ₄	3	82	91
13	j	4-ClC ₆ H ₄	3	79	80 (96)
14	k	4-F ₃ CC ₆ H ₄	3	80	82 (90)
15	l	3-NO ₂ C ₆ H ₄	3	72	83 (90)
16	m	1-naphthyl	3	81	90 (94)
17	n	2-furyl	3	72	84 ^f
18	a	PhCH ₂ CH ₂	11	85	91 (90:10) ^g
19	h	Ph	11	88	94 (93:7) ^g
20	i	4-MeOC ₆ H ₄	11	87	90 (95:5) ^g
21	j	4-ClC ₆ H ₄	11	88	98 (75:25) ^g

^a Reactions conducted at 0.5 mmol scale in dry toluene (1.5 mL) using **1**:CH₃NO₂:**5**:CsOH·H₂O in a 1:5:0.12:1.3 molar ratio. ^b Isolated yields after column chromatography. ^c Determined by HPLC (see the SI for details). The number in parentheses refers to the product after a single crystallization from hexane. ^d With cat **6** (conversions). ^e 89% ee at -20 °C. ^f Oil. ^g Ratio of *syn/anti* diastereomers in parentheses.

significantly lower efficiency (conversions typically <10%). This result contrasts with previous observations¹⁷ and suggests that the present catalysts exhibit dual functions;¹⁸ eventually, a hydrogen bond may be formed between the hydroxyl group and the nitro group's oxygen, facilitating nitronate formation, and/or between the hydroxyl and the azomethine's nitrogen, activating the electrophile and rigidifying transition structure.

The potential of this catalytic approach is further demonstrated by the reaction of azomethine precursors **1a,h–j** with nitroethane to afford adducts **11a,h–j** in *syn:anti* relationships up to 95:5 and enantiomeric excesses in the range of 90–98% for the major *syn* diastereomer. Finally, most products are crystalline, and essentially, enantiopure compounds can be obtained by direct crystallization of the crude nitroamines.¹⁹

In conclusion, a catalytic, highly enantioselective aza-Henry methodology is described, which works under PTC conditions. As salient features, the new method involves readily available α -amido sulfone substrates²⁰ and commercial catalysts, making it easily scalable. Most important, it is the first protocol amenable to enolizable aldehyde-derived azomethine substrates, thus considerably expanding the potential of the aza-Henry reaction in synthesis.

Acknowledgment. This work was financially supported by The University of the Basque Country (UPV/EHU), and Ministerio de Educación y Ciencia (MEC, Spain). A Ramón y Cajal contract to R.L. and a predoctoral grant to A.L., both from MEC, are acknowledged.

Supporting Information Available: Complete experimental procedures, ¹H and ¹³C spectra, HPLC chromatograms, and stereochemical assignments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For recent advances on this reaction, see: Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151–153.
- (2) See, for instance: O'Brien, P. H.; Sliskovic, D. R.; Blankley, C. J.; Roth, B.; Wilson, M. W.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L. *J. Med. Chem.* **1994**, *37*, 1810–1822.
- (3) For a review on 1,2-diamines, see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.
- (4) Reviews: (a) Pinnick, H. W. *Org. React.* **1990**, *38*, 655–792. (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.
- (5) (a) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504–3506. (b) Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980–982. (c) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843–5844. (d) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992–2995. (e) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362–1364. (f) Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665–5670. (g) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem., Int. Ed.* **2005**, *44*, in press; DOI: 10.1002/anie.200502674.
- (6) (a) Nugent, B. M.; Poder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419. (b) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627. (c) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466–468.
- (7) For one exception using preformed silylnitronates, see ref 5f.
- (8) (a) Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063–1065. (b) Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Martín-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 8637–8643.
- (9) Chiral α -amido sulfones as azomethine precursors in aza-Henry processes: (a) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *64*, 8970–8972. (b) Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275–4281. (c) Giri, N.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2004**, *69*, 7303–7308.
- (10) Aromatic *N*-acyl imines can be obtained as isolable, relatively stable compounds upon treatment with stoichiometric potassium carbonate. See: (a) ref 6a,c. (b) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238–1240. (c) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.
- (11) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449–4452.
- (12) For recent reviews, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. (b) O'Donnell, M. *J. Acc. Chem. Res.* **2004**, *37*, 506–517. (c) Lygo, B.; Andrews, P. I. *Acc. Chem. Res.* **2004**, *37*, 518–525. (d) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526–533.
- (13) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.
- (14) For further information, see: Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961–998.
- (15) For **3a**: 48% ee in toluene (90% conv.); 18% ee in trifluoromethylbenzene (60% conv.). The selectivity could be improved up to 70% ee in a 1:1 mixture of toluene and dichloromethane.
- (16) (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907. (b) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105–108. (c) Lou, S.; Taoka, B. M.; Jing, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256–11257 and references therein.
- (17) O-alkylation of cinchone derivatives has proven to provide more efficient catalysts for PTC: (a) ref 12. (b) ref 13. (c) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347–5350. (d) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257–4259. (e) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931–1934.
- (18) Other examples that support this assumption: (a) Nerinckx, W.; Vandewalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 265–276. (b) Perrad, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hébrault, D. *Org. Lett.* **2000**, *2*, 2959–2962. (c) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844–6845. (d) Ooi, T.; Ohara, D.; Fukumoto, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 3195–3197.
- (19) For assignment of the configuration of adducts **3** and **11**, see the Supporting Information.
- (20) For representative transformations eventually amenable for PTC, see the following. Alkynyl–metal additions: (a) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970–8972. Mannich reaction: (b) Nejman, M.; Sliwińska, Zwierzak, A. *Tetrahedron* **2005**, *61*, 8536–8541. (c) Schunk, S.; Enders, D. *Org. Lett.* **2001**, *3*, 3177–3180. (d) Enders, D.; Oberbörsch, S. *Synlett* **2002**, 471–473. Strecker reaction: (e) Banphavichit, V.; Chaleawertumporn, S.; Bhanthummavin, Vilaivan, T. *Synth. Commun.* **2004**, *34*, 3147–3160.

JA056594T