## Asymmetric Synthesis

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## Phase-Transfer-Catalyzed Asymmetric Aza-Henry Reaction Using *N*-Carbamoyl Imines Generated In Situ from α-Amido Sulfones\*\*

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Nucleophilic addition to the C=N bond of imine derivatives is of paramount importance in organic chemistry for the synthesis of functionalized amines and related nitrogencontaining compounds.<sup>[1]</sup> In this transformation, the substituent on the nitrogen atom of the imine often plays a crucial role, thus strongly affecting the electrophilicity.<sup>[2]</sup> In principle, as well as guaranteeing sufficient reactivity, this N-substituent should be easily removable after the reaction has taken place. Both requirements are fulfilled by carbamoyl groups, such as *tert*-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz).<sup>[3]</sup> However, because of their inherent high reactivity, Ncarbamoyl imines are rather sensitive to moisture, their purification (though often not necessary) is rather troublesome, and their storage requires some precautions. Furthermore, the isolation of N-carbamoyl imines derived from aliphatic enolizable aldehydes has not been reported, as they readily tautomerize to the corresponding ene carbamate,<sup>[4]</sup> thus resulting in a considerable limitation to the generality of their applications. A possible way to overcome these drawbacks is the in situ generation of the imine through the use of carbamates with a good leaving group at the carbon atom  $\alpha$  to the nitrogen atom. Among the suitable imine precursors available,  $\alpha$ -amido sulfones 1 are particularly attractive as they are bench-stable solids and can be very easily obtained by the condensation of a carbamate and a sodium aryl sulfinate with the appropriate aldehyde.<sup>[5]</sup> As  $\alpha$ -amido

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sulfones **1** furnish the corresponding imine when treated with a base,<sup>[6]</sup> they have been widely used in combination with hard organometallic reagents or metal-stabilized enolates.<sup>[7]</sup> The formation of the imine in situ can also be achieved by using a phase-transfer catalyst in combination with an inorganic base. Despite the considerable benefits of the latter approach, which combines the operational simplicity and the mild reaction conditions typical of phase-transfer catalysis (PTC)<sup>[8]</sup> with the convenience and the generality of the use of  $\alpha$ -amido sulfones **1** as imine surrogates, this reaction has been only occasionally reported.<sup>[9]</sup>

Bearing in mind the impressive applications of PTC in enantioselective transformations,<sup>[8]</sup> we decided to employ this strategy in the catalytic asymmetric nucleophilic addition of nitromethane to N-carbamoyl imines (aza-Henry reaction) generated in situ from  $\alpha$ -amido sulfones  $\mathbf{1}^{[10]}$  using cinchonaderived quaternary ammonium salts as catalysts.<sup>[11]</sup> The aza-Henry reaction,<sup>[12]</sup> and especially its catalytic asymmetric variants.<sup>[13]</sup> has received a lot of attention in recent years, the resulting  $\beta$ -nitroamines being readily converted into highly valuable chiral compounds, such as  $\alpha$ -amino acids and vicinal diamines. After the first pioneering reports on metal-catalyzed asymmetric aza-Henry reactions,<sup>[14]</sup> a few organocatalytic protocols have been reported.<sup>[15]</sup> Despite the remarkable results in terms of enantioselectivity and catalytic efficiency, all methods show a considerable limitation in the variability of the imine partner because preformed imines are employed. We felt that our approach could significantly extend the scope of the reaction, besides providing a new and convenient protocol for this asymmetric transformation.<sup>[16]</sup>

To test the feasibility of our approach, we thought it convenient to first explore the capability of phase-transfer catalysts derived from cinchona alkaloids to impart an

appreciable asymmetric induction in the addition of nitromethane to N-carbamoyl imines. For this purpose, N-Boc imine 2a was treated in the presence of catalytic amounts of several cinchona-derived quaternary ammonium salts and KF as a base under the solid-liquid PTC conditions used for the enantioselective addition of nitromethane to chalcones and for the Henry reaction (Scheme 1).<sup>[17]</sup> Among the catalysts tested (see the Supporting Information), the commercially available N-benzyl quininium chloride 4 proved to be the most effective, thus furnishing the corresponding  $\beta$ -nitroamine **3a** after 18 h in good yield of isolated product and with moderate, but promising, enantiomeric excess (Scheme 1). Encouraged by this result, we turned our attention to the possibility of using 1a directly in the reaction with nitromethane. After a thorough screening of different



Scheme 1. PTC aza-Henry reaction using imine 2 and  $\alpha\text{-amido sulfone 1 a.}$ 

reaction conditions (see the Supporting Information), we found that the reaction proceeded smoothly even at low temperature when a stronger base, such as solid KOH, was used, thus furnishing the product 3a directly from 1a at -45 °C in good yield and with useful enantiomeric excess (Scheme 1).

We next investigated the generality of this new catalytic enantioselective addition of nitromethane to *N*-carbamoyl imines generated in situ from **1** by varying both the substituent of the starting compound **1** and the protecting group (PG) on the nitrogen atom (Table 1). A few  $\alpha$ -amido sulfones **1a**-e derived from aromatic and heteroaromatic

**Table 1:** Catalytic asymmetric addition of nitromethane to *N*-carbamoyl imines generated in situ from  $\alpha$ -amido sulfones **1** a–I under PTC.<sup>[a]</sup>

	$\begin{array}{c} \text{FG}_{\text{NH}} & \text{KOH} & \text{FG}_{\text{NH}} \\ \text{R} \xrightarrow{\text{ISO}_2\text{Ar}} & \text{ICH}_3\text{NO}_2 & \xrightarrow{\text{Ioluene, } -45 \ ^\circ\text{C}} & \text{R} \xrightarrow{\text{Ioluene, } -45 \ ^\circ\text{C}} \\ \textbf{1a-e: } \text{Ar} = \text{Ph} & \textbf{3a-l} \\ \text{f-l: } \text{Ar} = p\text{-tol} & \textbf{3a-l} \end{array}$						
Entry	1	R group	PG	3	<i>t</i> [h]	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	la	Ph	Вос	3 a	40	95	84 (>99) <sup>[e]</sup>
2	1 b	o-BrC <sub>6</sub> H <sub>4</sub>	Boc	3 b	64	70	76
3	1c	<i>p</i> -MeOC <sub>6</sub> H₄	Boc	3 c	60	75 <sup>[d]</sup>	88 (>99) <sup>[e]</sup>
4	٦d	1-naphtyl	Boc	3 d	44	95	84
5	le	2-furyl	Boc	3 e	25	81	75
6	1 f	PhCH <sub>2</sub> CH <sub>2</sub>	Boc	3 f	40	98	95
7	1g	Су	Boc	3 g	42	84	98
8	1ĥ	iPr	Boc	3 ĥ	40	95	95
9	1i	Et	Boc	3 i	40	92	94
10	1j	Me	Boc	3 j	43	86	92
11	1 k	Ph	Cbz	3 k	44	53 <sup>[f]</sup>	73
12	11	Су	Cbz	31	40	96 <sup>[f]</sup>	93

[a] Experimental conditions: finely ground KOH (0.5 mmol) was added to a cooled mixture (-45 °C) of 1 (0.1 mmol), 4 (0.01 mmol), and CH<sub>3</sub>NO<sub>2</sub> (0.5 mmol) in toluene (1 mL), and the reaction mixture vigorously stirred for the stated time. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral stationary-phase HPLC. [d] aqueous KOH (50% w/w) was used in the reaction. [e] After a single crystallization. [f] A mixture of toluene/CH<sub>2</sub>Cl<sub>2</sub> (1:1) was used as the solvent. Cy = cyclohexyl.

aldehydes were treated with nitromethane under the optimized reaction conditions, thus furnishing the corresponding optically active N-Boc  $\beta$ -nitroamines **3a**–e in fairly good yield and enantiomeric excess (entries 1-5). It is noteworthy that 3a and 3c could be obtained in essentially enantiopure form after a single crystallization (entries 1 and 3). Moreover, we found that this new strategy for the catalytic enantioselective aza-Henry reaction was particularly effective for the synthesis of N-Boc  $\alpha$ -alkyl  $\beta$ -nitroamines, which cannot be obtained by the previously reported methods. As a matter of fact, 1 f-j, derived from both linear and branched aliphatic aldehydes, all gave the corresponding  $\beta$ -nitroamines **3 f**-**j** in very good yields and enantioselectivities (entries 6-10). The efficiency of the present method for this class of substrates is well accounted for by the high enantiofacial discrimination in the imine derived from 1j (entry 10) bearing a proton and a small methyl group. Variation of the protecting group on the nitrogen atom was then shortly investigated using 1k and 1l bearing a Cbz moiety (entries 11 and 12), thus demonstrating that the present method is not restricted to obtaining N-Bocprotected  $\beta$ -nitroamines. Also in this case, **11**, derived from an aliphatic aldehyde, gave better results with respect to 1k.

The absolute configuration of the products was determined by comparison of the HPLC retention time and optical rotation of **3a** with reported values<sup>[15b,c]</sup> and by reduction of **3h** (see the Supporting Information) to the known diamine derivative.<sup>[18]</sup> Attack on the *Si* face of the intermediate imine by the nitronate and quininium ion pair accounts for the *R* configuration at the stereogenic centre observed in both cases.

In summary, we have developed a new catalytic enantioselective approach to the asymmetric nucleophilic addition of nitromethane to *N*-carbamoyl imines generated in situ from  $\alpha$ -amido sulfones. The chiral phase-transfer catalyst acts in a dual fashion,<sup>[19]</sup> first promoting the formation of the imine under mild reaction conditions and then activating the nucleophile for asymmetric addition. The potential of this approach was demonstrated in the reaction of nitromethane with  $\alpha$ -amido sulfones, which could be efficiently catalyzed by a simple and commercially available quininium salt. Besides the mild reaction conditions and the operational simplicity, this new method allows *N*-carbamoyl imines derived from enolizable aldehydes in a catalytic asymmetric aza-Henry reaction to be used for the first time, thus extending the generality of this asymmetric transformation.

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Ishitani, *Chem. Rev.* **1999**, *99*, 1069; e) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102.

- [2] S. M. Weinreb, Top. Curr. Chem. 1997, 190, 131.
- [3] a) H. A. Zuagg, Synthesis 1984, 85; b) H. A. Zuagg, Synthesis
  1984, 181; for recent applications of N-carbamoyl and N-acyl imines, see for example; c) A. M. Kanazawa, J.-N. Denis, A. E. Greene, J. Org. Chem. 1994, 59, 1238; d) A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, Angew. Chem. 2005, 117, 4640; Angew. Chem. Int. Ed. 2005, 44, 4564; e) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, Angew. Chem. 2005, 117, 2956; Angew. Chem. Int. Ed. 2005, 44, 2896; f) D. Uraguchi, K. Sorimachi, M. Terada, J. Am. Chem. Soc. 2004, 126, 11804; g) R. Matsubara, Y. Nakamura, S. Kobayashi, Angew. Chem. 2004, 116, 1711; Angew. Chem. Int. Ed. 2004, 43, 1679; h) A. G. Wenzel, E. N. Jacobsen, J. Am. Chem. Soc. 2002, 124, 12964.
- [4] T. Mecozzi, M. Petrini, Synlett 2000, 73.
- [5] a) J. B. F. N. Engberts, J. Strating, *Recl. Trav. Chim. Pys-Bas* 1965, 84, 942; b) W. H. Pearson, A. C. Lindbeck, J. W. Kampf, J. *Am. Chem. Soc.* 1993, 115, 2622.
- [6] A method for the synthesis of aromatic *N*-Boc imines involves the treatment of  $\alpha$ -amido sulfones with K<sub>2</sub>CO<sub>3</sub> in THF at reflux for several hours; see reference [3c].
- [7] a) J. Morton, A. Rahim, E. R. H. Walker, *Tetrahedron Lett.* 1982, 23, 4122; b) N. Hermanns, S. Dahmen, C. Bolm, S. Bräse, Angew. Chem. 2002, 114, 3844; Angew. Chem. Int. Ed. 2002, 41, 3692; c) D. Enders, S. Oberbörsch, Synlett 2002, 471; d) C. Palomo, M. Oiarbide, A. Landa, M. C. González-Rego, J. M. García, A. González, J. M. Odriozola, M. Martin-Pastor, A. Linden, J. Am. Chem. Soc. 2002, 124, 8637; e) C. Palomo, M. Oiarbide, C. González-Rego, A. K. Sharma, J. M. García, A. González, C. Landa, A. Linden, Angew. Chem. 2000, 112, 1105; Angew. Chem. Int. Ed. 2000, 39, 1063; f) M. Petrini, R. Profeta, P. Righi, J. Org. Chem. 2002, 67, 4530; g) N. Giri, M. Petrini, R. Profeta, J. Org. Chem. 2004, 69, 7303, and references therein.
- [8] For recent reviews, see: a) A. Nelson, Angew. Chem. 1999, 111, 1685; Angew. Chem. Int. Ed. 1999, 38, 1583; b) K. Maruoka, T. Ooi, Chem. Rev. 2003, 103, 3013; c) B. Lygo, B. I. Andrews, Acc. Chem. Res. 2004, 37, 518; d) M. J. O'Donnell, Acc. Chem. Res. 2004, 37, 506.
- [9] a) R. Kimura, T. Nagano, H. Kinoshita, Bull. Chem. Soc. Jpn. 2002, 75, 2517; b) V. Banphavichit, S. Chaleawlertumpon, W. Bhanthumnavin, T. Vilaivan, Synth. Commun. 2004, 34, 3147.
- [10] For a reaction of nitromethane with α-amido sulfones, see: a) R. Ballini, M. Petrini, *Tetrahedron Lett.* **1999**, 40, 4449; b) E. Foresti, G. Palmieri, M. Petrini, R. Profeta, *Org. Biomol. Chem.* **2003**, *1*, 4275.
- [11] a) H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87; b) K. Kacprzak, J. Gawroñski, *Synthesis* **2001**, 961.
- [12] a) H. Adams, J. C. Anderson, S. Peace, A. M. K. Pennell, *J. Org. Chem.* **1998**, *63*, 9932; b) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672; c) J. C. Anderson, A. J. Blake, J. P. Howell, C. Wilson, *J. Org. Chem.* **2005**, *70*, 549; d) L. Bernardi, B. F. Bonini, E. Capitò, M. Comes-Franchini, G. Dessole, M. Fochi, A. Ricci, *J. Org. Chem.* **2004**, *69*, 8168, and references therein.
- [13] For an overview, see: B. Westermann, Angew. Chem. 2003, 115, 161; Angew. Chem. Int. Ed. 2003, 42, 151.
- [14] a) K.-i. Yamada, S. J. Harwood, H. Gröger, M. Shibasaki, Angew. Chem. 1999, 111, 3713; Angew. Chem. Int. Ed. 1999, 38, 3504; b) K.-i. Yamada, G. Moll, M. Shibasaki, Synlett 2001, 980; c) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K. A. Jørgensen, Angew. Chem. 2001, 113, 3080; Angew. Chem. Int. Ed. 2001, 40, 2992; d) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, J. Am. Chem. Soc. 2001, 123, 5843.
- [15] a) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, Org. Lett. 2004, 6, 625; b) B. M. Nugent, R. A. Yoder, J. N. Johnston, J. Am.

For recent reviews, see: a) R. A. Volkmann, Nucleophilic Addition to Imines and Imine Derivatives in Comprehensive Organic Synthesis, Vol. I (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), 1st ed., Pergamon, Oxford, 1991, p. 355; b) D. Enders, U. Reinhold, Tetrahedron: Asymmetry 1997, 1895; c) R. Bloch, Chem. Rev. 1998, 98, 1407; d) S. Kobayashi, H.

## Communications

*Chem. Soc.* **2004**, *126*, 3418; c) T. P. Yoon, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 470; *Angew. Chem. Int. Ed.* **2005**, *44*, 466; d) L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani, *Tetrahedron*, in press DOI: 10.1016/j.tet.2005.09.076.

- [16] Very recently, an asymmetric aza-Henry reaction of two aliphatic *N-para*-methoxyphenyl imines with preformed *O*-silyl propionitronate, which makes use of a chiral Cu<sup>II</sup> complex as a catalyst, has been reported: J. C. Anderson, G. P. Howell, R. M. Lawrence, C. S. Wilson, *J. Org. Chem.* **2005**, *70*, 5665.
- [17] a) S. Colonna, H. Hiemstra, H. Wynberg, J. Chem. Soc. Chem. Commun. 1978, 238; b) E. J. Corey, F.-Y. Zhang, Org. Lett. 2000, 2, 4257; c) E. J. Corey, F.-Y. Zhang, Angew. Chem. 1999, 111, 2057; Angew. Chem. Int. Ed. 1999, 38, 1931.
- [18] D. Enders, J. Wiedemann, Synthesis 1996, 1443.
- [19] For another example of two sequential processes carried out using a cinchona-derived phase-transfer catalyst, see: B. Lygo, D. C. M. To, *Chem. Commun.* 2002, 2360.