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Catalytic Enantioselective Mannich-Type Reaction with β-Phenyl Sulfonyl Acetonitrile

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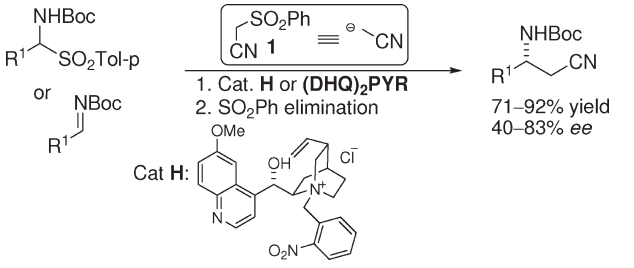
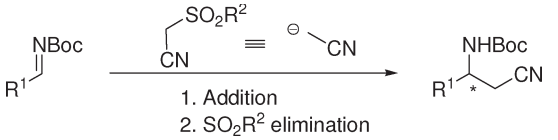


The organocatalytic addition of β-phenyl sulfonyl acetonitrile **1** to either *N*-Boc-protected α-amido sulfones or imines allowed the synthesis of enantioenriched α-unsubstituted β-amino nitriles through a Mannich-type reaction.

Chiral β-amino nitriles are interesting building blocks because they are readily transformed into optically active β-amino acids and 1,3-diamines useful for the preparation of optically active ligands, peptides, and some natural products. Among the most direct methods to prepare β-amino nitriles, the addition of α-cyanoalkyl moieties to imines is very attractive since concomitant to the carbon−carbon bond formation up to two contiguous stereocenters may be generated in a single operation. However, very few enantioselective versions for this transformation have been reported.[1,2] During the past decade, there have been considerable advances in the catalytic generation and the enantioselective addition of carbon nucleophiles (i.e., nitroalkanes, malonates, ketoesters) to azomethine derivatives.[3] Nevertheless, the addition of alkylnitriles, a unique class of carbon nucleophiles, represents an exception.[4] From the synthetic point of view, alkylnitriles constitute a versatile synthon with wide functional potency and the same oxidation state as carboxylic acids. There have been few attempts to catalytically generate nucleophiles from alkylnitriles probably because of its poor acidity (pK_a 31.3 in DMSO, 28.9 in H_2O).[5] The use of strong bases may cause undesirable reactions, whereas weak bases fail deprotonation.[6] The direct activation through cooperative amine bases and soft Lewis acids has been, so far, the most efficient procedure for the catalytic addition of acetonitrile to imines.[7] Here, we describe our attempts in developing an effective method to overcome the above problems that consist of the enantioselective addition of 2-(phenylsulfonyl)acetonitrile (**1**)[8] as a synthetic equivalent of acetonitrile to *N*-Boc-protected imines (Scheme 1). It was argued that the presence of the sulfonyl group would increase acidity enough to catalytically allow the carbon nucleophile generation upon treatment with mild bases under asymmetric conditions. The subsequent easy removal of the sulfonyl moiety would render the corresponding optically active β-amino nitriles.

SCHEME 1. Addition of Formal Acetonitrile Anions to *N*-Boc-Protected Imines



We have recently disclosed a highly efficient method for the enantioselective aza-Henry reaction of α-amido sulfones and nitroalkanes employing commercially avavilable cinchone-derived ammonium salts as phase transfer catalysts.[9] By analogy to this reaction, we decided to evaluate similar reaction conditions in the addition of 2-(phenylsulfonyl)acetonitrile (**1**) to aryl

(1) For addition to chiral imines, see: (a) Mukaiyama, T.; Michida, M. *Chem. Lett.* **2007**, *36*, 1244–1245. (b) Nemoto, H.; Moriguchi, H.; Ma, R.; Kawamura, T.; Kamiya, M.; Shibuya, M. *Tetrahedron: Asymmetry* **2007**, *18*, 383–389.

(2) A method for the catalytic and enantioselective synthesis of optically active β-aminonitriles has been reported that consists of the asymmetric ring opening of arylmethylated *N*-nosylazidirines with TMSCN: Minakata, S; Murakami, Y.; Satake, M.; Hidaka, I.; Okada, Y.; Komatsu, M. *Org. Biomol. Chem.* **2009**, *7*, 641–643.

(3) (a) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569. (b) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315–1392. For metal-based asymmetric-catalyzed Mannich reactions, see: (c) Kobayashi, S.; Veno, M. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004; pp 143−150. (d) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089–2100. For metal-free, see: (e) Verkade, J. M. M.; van Hermert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41. (f) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797–5815.

(4) For a decarboxylative Mannich-type reaction, see: (a) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610–9611. For Mannich reactions involving cyanoacetates, see: (b) Paulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896–2899. (c) Santoro, S.; Paulsen, T. B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 5155–5157. For Mannich reactions invoving α-cyanoketones, see: (d) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 5630–5631. (e) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3799–3784.

(5) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. (b) Richard, J. P.; Williamns, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715–726.

(6) For exceptions, see the use of $P(RNCH_2CH_2)_3N$: (a) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090–3094. (b) Matsukawa, S.; Kitzaki, E. *Tetrahedron Lett.* **2008**, *49*, 2982–2984.

(7) (a) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632–13633. (b) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 8598–8608. (c) Aydin, J.; Conrad, C. S.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 5175–5178.

(8) For the use of other synthetic equivalents of acetonitrile, such as $TMSCH_2CN$, see: (a) Palomo, C.; Aizpurua, J. M.; López, M. C.; Lecea, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1692–1694. (b) See ref 1.

(9) (a) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622–17623. (b) Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955–7966. Also, see: Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975–7978.

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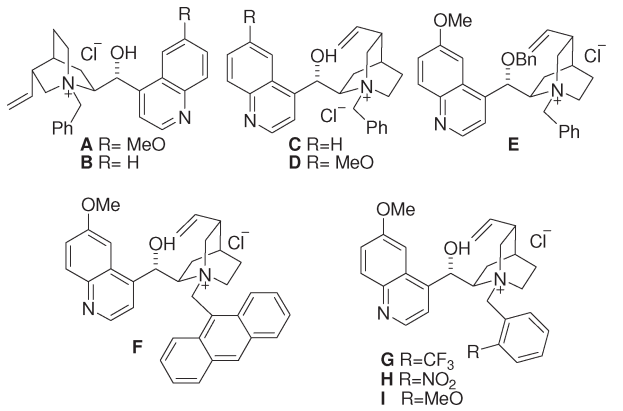
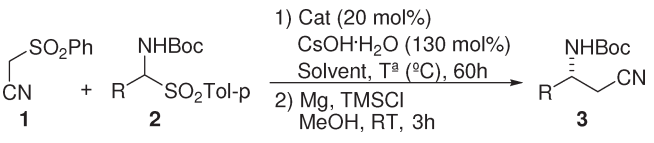


FIGURE 1. Phase transfer catalysts employed in this study.

TABLE 1. Screening of Reaction Conditions for the PT-Catalyzed Reaction[a]



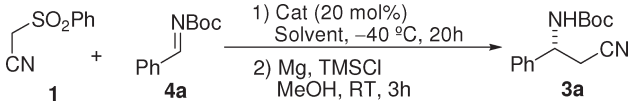
entry	R	catalyst	solvent	T (°C)	conv (%)[b]	ee (%)[c]
1	4-Cl-Ph	A	toluene	−30	>90	0
2		B	toluene	−30	>90	5
3		C	toluene	−30	>90	0
4		D	toluene	−30	>90	35
5		D	CH_2Cl_2	−40	>90	25
6		E	toluene	−30	>90	7
7		F	toluene	−30	>90	15
8	Ph	D	toluene	−30	>90	38
9		G	toluene	−40	>90	61
10		H	toluene	−40	70	65
11		I	toluene	−40	>90	55
12		H	toluene	−70	30	72
13		H	Tol/CH_2Cl_2 (9:1)	−70	>90	76

[a]Reactions were carried out at 0.5 mmol scale in 1.5 mL of solvent. [b]Conversion determined by ^{1}H NMR. [c]Determined by HPLC.

α-amidosulfones (**2**).[10] The initial screen was carried out employing commercially available chiral quaternary ammonium salts (Figure 1) and $CsOH \cdot H_2O$ as inorganic base in toluene (Table 1).

After 60 h of stirring at −30 °C, and subsequent sulfone elimination under standard conditions, nearly complete conversions and rather poor enantiomeric excesses were obtained (Table 1, entries 1−4). Variation in the reaction conditions, employing catalyst **D**, such us the use of more polar solvents (entry 5), other inorganic bases, different *N*-protection in the α-amido sulfone, and modifications on the phenyl group in **1**, resulted in diminished enantioselectivities.[11] Nevertheless, ammonium salts derived from quinidine featuring an *ortho*-substituted benzyl group (**G**−**I**)[12,13] had a positive impact on the stereocontrol (entries 9−11), which was further improved by decreasing the reaction temperature from −40 to −70 °C (entry 12). The best reaction conditions were a mixture of toluene and a small amount of methylene chloride at −70 °C, which produced adduct **3a** (R = Ph) in 72% isolated yield and 76% ee (entry 13).[14] In parallel experiments, carried out in the absence of the chiral phase transfer catalyst at −50 °C, a high conversion into products **3** (70−90%) was also obtained. This observation confirmed the easy transfer of the cesium salt of **1** to the organic phase even at low temperatures, thus increasing the racemic reaction pathway.[15]

TABLE 2. Screening of Cinchone-Derived Catalysts[a]



entry	catalyst	solvent	conv (%)[b]	ee (%)[c]
1	quinine	CH_2Cl_2	85	−11
2	quinidine	CH_2Cl_2	>90	4
3	cinchonine	CH_2Cl_2	60	65
4	cinchonidine	CH_2Cl_2	>90	−42
5	$(CN)_2$PYR	CH_2Cl_2	50	5
6	$(DHQD)_2$PYR	CH_2Cl_2	60	60
7	$(DHQD)_2$AQN	CH_2Cl_2	60	33
8	$(DHQ)_2$PHAL	CH_2Cl_2	65	5
9	$(DHQ)_2$PYR	CH_2Cl_2	>90	73
10	$(DHQ)_2$PYR	$CHCl_3$	>90	74
11	$(DHQ)_2$PYR	CH_3CN	53	5
12	$(DHQ)_2$PYR	THF	>90	10
13	$(DHQ)_2$PYR	MeOH	0	
14	$(DHQ)_2$PYR	toluene	10	*d*

[a]Reactions were carried out at 0.5 mmol scale in 1.5 mL of solvent. [b]Conversion determined by ^{1}H NMR. [c]Determined by HPLC. [d]Not determined.

Trying to overcome this problem, we decided to explore the use of chiral Brønsted bases as an alternative approach for the addition of 2-(phenylsulfonyl)acetonitrile (**1**) to *N*-Boc imines (**4**). For the initial screening of catalysts, the addition of **1** to *N*-Boc imine **4a** was explored employing commercially available cinchona-derived bases in methylene chloride at −40 °C (Table 2).

Among the bases tested, $(DHQ)_2$PYR produced the highest transformation and enantiomeric excess after 20 h (entry 9). Attempts to improve enantioselectivity by decreasing reaction temperature were unsuccessful because irreproducible results, probably due to an increased heterogeneity in the reaction media, were obtained. Among the solvents, methylene chloride and chloroform gave the best results. No reaction was observed in protic solvents such as methanol, while in acetonitrile, tetrahydrofuran, and toluene, either low transformations or ee values were produced.

Although the enantiomeric excesses obtained, employing either chiral salt H or Brønsted base $(DHQ)_2$PYR as catalysts, were moderated, we decided to explore the validity of 2-(phenylsulfonyl)acetonitrile (**1**) as a synthetic equivalent of acetonitrile in this Mannich-type reaction and applied the best reaction conditions obtained for each methodology to a variety of differently substituted α-amidosulfones (**2**) and

(10) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949–3077.
(11) See Supporting Information for details.
(12) This type of catalyst has shown previously its efficiency in Mannich reactions: Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem.—Eur. J.* **2007**, *13*, 8338–8351.
(13) 2,6-Disubstitution in the benzylic residue of the catalysts decreased enantiomeric excesses.
(14) Determination of the absolute configuration was made by comparison with published data. See Supporting Information.
(15) This result is in contrast with our previous observations for the phase transfer catalyzed aza-Henry reaction in which no racemic transformation was detected. For more details on this subject, see ref 9b.

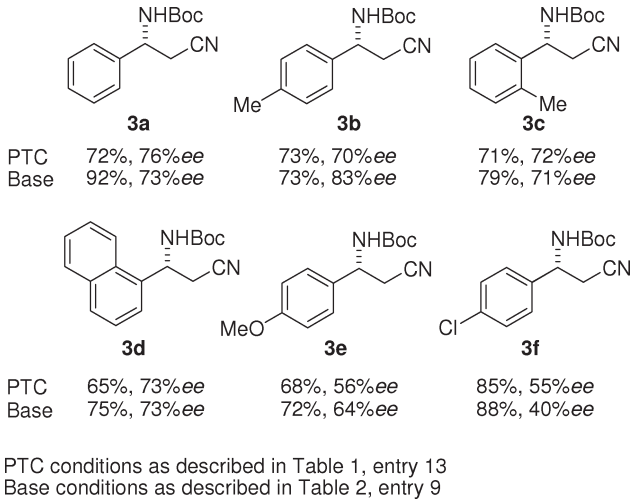


FIGURE 2. Enantioenriched β-amino nitriles obtained in this work.

N-Boc-protected imines (**4**) (Figure 2). Both methodologies afforded similar results, in terms of chemical efficiency and enantioselectivity, for each substrate, being the highest enantiomeric excesses obtained for adducts **3a**−**3d**. The products are usually solid compounds, and a single crystallization allows ee to increase, an aspect which is of practical interest. For example, adducts **3a**, **3c**, **3d**, and **3f** were enantiomerically enriched up to 90−98% ee and isolated in 37−50% yield after recrystallization.[11]

In summary, the methodologies described constitute convenient procedures for access to enantioenriched β-amino nitriles and set the basis for further development.

Experimental Section

General Procedure for the PT-Catalyzed Reaction. To a mixture of the corresponding α-amido sulfone **1** (0.5 mmol, 1 equiv), catalyst H (0.06 mmol, 0.12 equiv, 0.028 g), and the α-cyano sulfone **2** (0.65 mmol, 1.3 equiv, 0.118 g) in toluene/CH_2Cl_2 (9:1, 2 mL) at −70 °C was added $CsOH \cdot H_2O$ (0.65 mmol, 1.3 equiv, 0.109 g) under a nitrogen atmosphere. After stirring at the same temperature for 60 h, the reaction mixture was treated with HCl (0.1 N) and extracted with CH_2Cl_2. The organic layers were combined, washed with HCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in methanol (1.5 mL) and added to a suspension of Mg (powder), 1,2-dibromoethane (1 drop), and TMSCl (1 drop) in methanol (1.5 mL) at 0 °C. After 3 h at room temperature, the reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The organic layers were combined and washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using mixtures of ethyl acetate/hexane as the eluent.

3a: 0.089 g (72%); white solid; mp 109−113 °C; $[\alpha]^{25}_D$ = +25.4 (*c* 0.45, EtOH); IR (KBr) ν 2249, 1701, 1516, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 5H), 5.17−4.92 (m, 2H), 3.11−2.85 (m, 2H), 1.50 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 154.8, 138.5, 129.2, 128.7, 126.2, 116.9, 80.6, 51.3, 28.2, 25.2; chiral HPLC (Chiralpak IA column; hexane/*i*PrOH 95:5; 0.5 mL/min, 210 nm) t_R (major) = 30 min, t_R (minor) = 34 min; 76% ee; after recrystallization from a mixture of toluene/hexane, 94% ee; $[\alpha]^{25}_D$ = +41.0 (*c* 0.45, EtOH); HRMS (EI) for $C_{14}H_{18}N_2O_2$ (M^+) calcd 246.1368, found 246.1404.

General Procedure for the $(DHQ)_2PYR$-Catalyzed Reaction. To a mixture of the corresponding imine **4** (0.5 mmol, 1 equiv), $(DHQ)_2PYR$ (0.1 mmol, 0.2 equiv, 0.088 g) in dry CH_2Cl_2 (2 mL) was added the α-cyano sulfone **2** (0.65 mmol, 1.3 equiv, 0.118 g) at −50 °C under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 18 h, then quenched with HCl (0.1 N) and extracted with CH_2Cl_2. The organic layer was washed with HCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was then exposed to the same reaction conditions described above.

3b: 0.095 g (73%); white solid; mp 107−110 °C; $[\alpha]^{25}_D$ +20.2 (*c* 0.5, EtOH); IR (film) 2252, 1680, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 4H), 5.23−4.85 (m, 2H), 2.91 (m, 2H), 2.39 (s, 3H), 1.49 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 154.8, 138.5, 135.6, 129.8, 126.1, 117.1, 80.5, 51.1, 28.3, 25.2, 21.1; chiral HPLC (Chiralpak IB column; hexane/*i*PrOH 90:10; 0.5 mL/min, 210 nm) t_R (major) = 18 min, t_R (minor) = 23 min; 83% ee; HRMS (EI) for $C_{15}H_{20}N_2O_2$ (M^+) calcd 260.1525, found 260.1534

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Supporting Information Available: Complete experimental procedures, ^1H and ^{13}C spectra, and HPLC chromatograms for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.