DOI: 10.1002/adsc.200800798

Use of the Chiral Pool – Practical Asymmetric Organocatalytic Strecker Reaction with Quinine

Rüdiger Reingruber,[a,b] Thomas Baumann,[c] Stefan Dahmen,[c,d,*] and Stefan Bräse[a,b,*]

[a] Institute of Organic Chemistry, University of Karlsruhe (TH), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
Fax: (+49)-721-608-8581; phone: (+49)-721-608-2902; e-mail: stefan.braese@kit.edu
[b] Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany
[c] cynora GmbH, Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany
[d] New address: BASF SE, ED/DN, 67056 Ludwigshafen, Germany

Received: December 21, 2008; Revised: March 23, 2009; Published online: May 5, 2009

Dedicated to Armin de Meijere on the occasion of his 70th birthday.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800798.

Abstract: An efficient, organocatalytic enantioselective synthesis of *N*-arylsulfonyl α-amino nitriles from the corresponding α-amido sulfones has been developed. This quinine-catalyzed Strecker reaction provides the corresponding cyanated products in good yields and enantioselectivities.

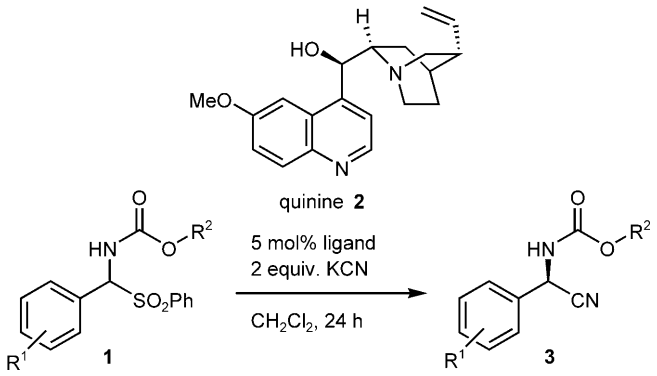
Keywords: asymmetric cyanation; chiral pool; organocatalysis; potassium cyanide; quinines; Strecker reaction

The catalytic asymmetric cyanation of imines, the so-called Strecker reaction,[1] is one of the most powerful and efficient strategies for the synthesis of chiral α-amino acids and their derivatives. In the last decade, both metal-catalyzed[2] processes and organocatalytic approaches[3,4] have been developed for this purpose and a large number of highly successful and efficient protocols, providing a reliable access to a wide range of optically active α-amino nitriles, have been reported.[5] However, more efforts are still needed in this area, because the highly efficient cyanation of imines to afford the precursors of pharmaceutically important α-amino acids is always prevailing and the quest for a universal and powerful organocatalytic system which avoids the use of hazardous and expensive cyanation agents like TMSCN or HCN still remains a challenge.

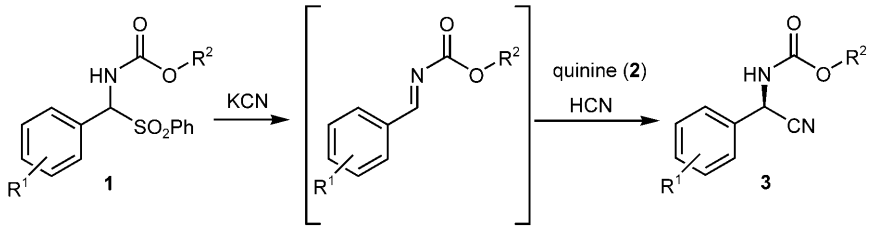
Herein, we present an enantioselective cyanation of several *N*-carbamoyl aldimines, *in situ* generated from α-amido sulfones **1**,[6] promoted by the powerful and naturally occurring alkaloid quinine (**2**)[4] using potassium cyanide (KCN) as a safe and convenient cyanating agent (Scheme 1).

The required *N*-carbamoyl α-amido sulfone **1**, a synthetic precursor of the corresponding aldimines, can be readily prepared from aldehydes and the corresponding carbamate following known protocols in the literature, and easily purified by recrystallization.[7]

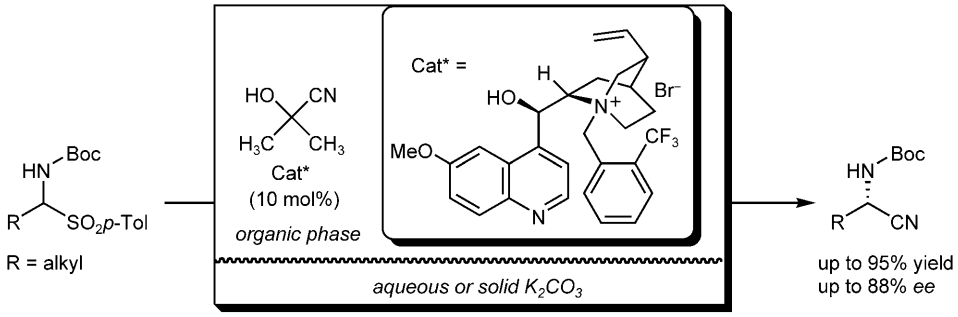
As a model reaction, we investigated the reactivity of the representative substrate **1a**, which can easily be synthesized from benzaldehyde, *tert*-butyl carbamate and $NaSO_2Ph$. To avoid the highly toxic and volatile HCN, we used potassium cyanide (KCN), a more convenient cyanation reagent, which is easier to handle. In this process, KCN plays two roles. It first acts as a base, liberating the free *N*-carbamoyl imine by deprotonation of precursor **1** and subsequent elimination of



Scheme 1. Organocatalytic Strecker reaction with quinine.



Scheme 2. *In situ* formation of the *N*-carbamoyl imine.



Scheme 3. Phase-transfer-catalyzed enantioselective Strecker reactions of α-amido sulfones with cyanohydrins.[4]

the sulfinate. The intermediately formed HCN then acts as the cyanating agent giving enantioenriched product **3** in the presence of suitable chiral catalysts (Scheme 2).

A screening of various catalysts revealed readily available commercial alkaloids as the best choice for further optimization of the selectivity of the catalytic system (Table 1 and Table 2).

In a publication from 2006, Ricci et al. have described a phase-transfer-catalyzed Strecker reaction that is related to the described process (Scheme 3).[4] They applied a quaternary ammonium salt of quinine as catalyst in a biphasic system containing potassium carbonate as a base and cyanohydrin as a cyanide source. Using an electron-deficient benzylic substituent on the quinine catalyst, they successfully achieved the Strecker reaction with aliphatic substrates.

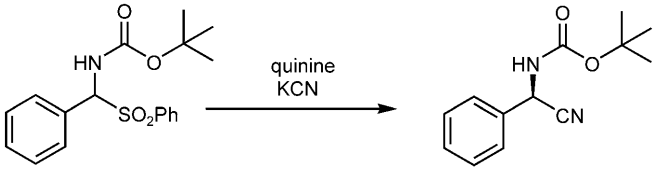
In contrast to the work of Ricci, however, it was found that chiral phase-transfer catalysts did not show any activity on our system. The use of other cyanating agents like NaCN, TMSCN or acetone cyanohydrin (even in presence of a base) did not show any significant improvement and led to depletion of yield and/or selectivity.

From screening various solvents, it was found that the polarity of the solvent had a significant effect on the outcome of the reaction (Table 1, entries 1–4).

Thus, CH_2Cl_2 and toluene were proven to be superior to any other solvents. While polar, non coordinating solvents like CH_2Cl_2 improve reaction yield by enabling sufficient solubility of substrate as well as KCN salt, polar, coordination solvents like diethyl ether drastically diminish enantioselectivity.

Trying to find the ideal temperature (Table 1, entries 5–7), it is important to mention that the selectivity dropped significantly when we performed the reaction at room temperature and that there was no reac-

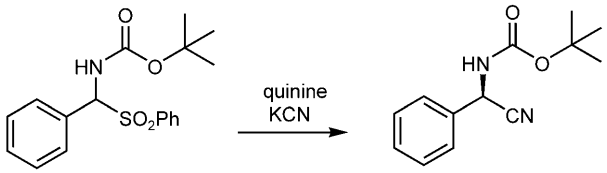
Table 1. Screening of reaction conditions for the organocatalytic Strecker reaction.[a]



Entry	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	0	67	50 (*R*)[d]
2	$CHCl_3$	0	88	37 (*R*)
3	toluene	0	30	43 (*R*)
4	Et_2O	0	40	5 (*S*)
5	CH_2Cl_2	+25	80	19 (*R*)
6	CH_2Cl_2	−10	82	57 (*R*)
7	CH_2Cl_2	−40	NR	–
8	0.5 mL CH_2Cl_2	0	88	33 (*R*)
9	10 mL CH_2Cl_2	0	NR	–

[a] Reactions were performed on 250 μmol scale using 10 mol% of quinine (**2**) and 2.0 equiv. of KCN in 1.0 mL of the specified solvent at the stated temperature for 24 h.
[b] Isolated yields after purification.
[c] Determined by HPLC analysis on chiral stationary phase.
[d] Determined by comparison with literature values of the optical rotation.[8]

Table 2. Catalyst and additive screening for the organocatalytic Strecker reaction. Selected examples.[a]



1a **3a**

Entry	Catalyst	Additive	Yield [%][b]	*ee* [%][c]
1	10 mol% cinchonidine	–	46	10 (*R*)[e]
2	30 mol% *N*-methylephedrine	–	48	16 (*S*)
3	5 mol% *O*-benzoylquinine	–	58	37 (*S*)
4[d]	5 mol% quinidinium sulfate	–	92	32 (*S*)
5	5 mol% quinine *N*-oxide	–	51	25 (*R*)
6	10 mol% quinine	1 mL heptane	76	49 (*R*)
7	10 mol% quinine	1 mL H_2O	95	27 (*R*)
8	5 mol% quinine	10 μL AcOH	57	40 (*R*)
9	5 mol% quinine	6 μL H_3PO_4	62	46 (*R*)

[a] Reactions were performed on 250 μmol scale using 2.0 equiv. KCN in 1.0 mL CH_2Cl_2 at −10 °C for 24 h.
[b] Isolated yields after purification.
[c] Determined by HPLC analysis on chiral stationary phase.
[d] 2.0 equiv. NaCN as cyanation reagent.
[e] Determined by comparison with literature values of the optical rotation.[8]

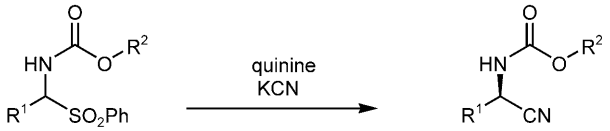
tion at all (even after 3 days), when we went down to −40 °C. According to this observation the optimal temperature to achieve high yield and selectivity turned out to be −10 °C (Table 1, entry 6). We assume that the main influence of the temperature comes about by carefully balancing the amounts of free dissolved reactive intermediates *N*-carbamoyl imine and KCN/HCN in the reaction mixture.

The appropriate amount of catalyst used for the described reaction was found to be 5–10 mol% as there was no further improvement when using more than 10 mol%. Looking at the ideal concentration while performing the reaction, we found that the selectivity dropped when the mixture was too concentrated and no reaction took place when it was too highly diluted (Table 1, entries 8–9). The use of other catalysts such as cinchonidine, *N*-methylephedrine or quinine derivatives (Table 2, entries 1–5) showed only minor catalytic activity. Thus, the naturally occurring quinine itself was proven to be the most effective catalyst for the reaction, both in terms of efficiency and enantioselectivity (Table 1, entry 6).

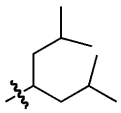
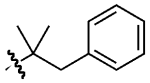
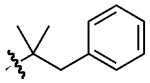
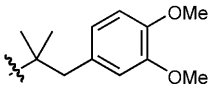
In order to further improve the reaction outcome, various additives were tested but no overall improvement could be observed (Table 2, entries 6–9). However, there are several striking features of this reaction that shed some light on a possible reaction mechanism. While trying to optimize the catalyst structure, we screened various N,O ligands in this reaction. It turned out that all structural features of quinine are necessary to obtain optimal reactivity and selectivity. Primary and secondary amino alcohols give poor turnover, blocking the free OH group of quinine drastically reduces activity as well as selectivity, even removal of the aromatic methoxy group (e.g., with free cinchonidine) leads to drastically diminished results. At this point we began to assume that the deprotonation of the substrate as well as the addition of cyanide proceed *via* a proton shuttle process facilitated by the catalyst. Further evidence are the facts that water is tolerated to a high amount (Table 2, entry 7, biphasic system) and even the addition of acids does not negatively impact the enantioselectivity (Table 2, entries 8 and 9). Especially the latter in combination with the fact that quinidinium sulfate as catalyst (Table 2, entry 4) still resulted in reasonable enantioselectivity and that the addition of Li salts dramatically diminishes the *ee* gives strong evidence that the enantio-discriminating step involves an *N*-protonated catalyst intermediate.

Aliphatic imine substrates bearing active alpha hydrogens like the ones applied by Ricci et al. are usually less reactive than aromatic substrates. This also manifests in the finding that aliphatic sustrates are prone to undergo enamine side reactions when applied in (metal-) catalyzed addition reactions.[6d] In our experience, aromatic substrates tend to be more reactive but also more sensitive to hydrolysis. Although mechanistic details for both processes are still elusive, we assume that the inherent differences in the reaction mechanism explain why Ricci only reported the use of aliphatic substrates while our system gives rise to aromatic products. While the enantioselective step in the Ricci reaction would have to include a

Table 3. Generality and scope of the asymmetric organocatalytic Strecker reaction with quinine (**2**).[a]



1 **3**

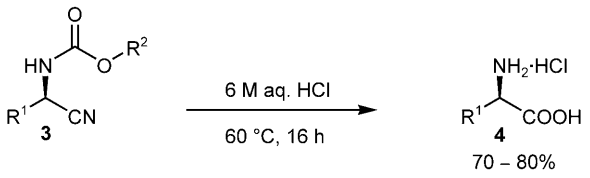
Entry	R^1	R^2	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	Ph	*t*-Bu	−10	82	57 (*R*)[d]
2	4-MeC_6H_4	*t*-Bu	−10	99	61 (*R*)
3	3-MeC_6H_4	*t*-Bu	−10	99	74 (*R*)
4	2-MeC_6H_4	*t*-Bu	−15	95	62 (*R*)
5	3-$MeOC_6H_4$	*t*-Bu	−10	35	62 (*S*)
6	1-naphthyl	*t*-Bu	−10	95	79 (*R*)
7	Ph		−10	34	62 (*R*)
8	Ph		−10	68	60 (*S*)
9	Ph		−10	95	56 (*R*)
10	Ph		0	53	64 (*S*)
11	1-naphthyl		−10	98	80 (*S*)
12	Ph		−10	25	54 (*S*)
13	3-ClC_6H_4	*t*-Bu	−10	80	34 (*S*)
14	2,6-di-ClC_6H_3	*t*-Bu	−10	91	48 (*R*)
15	1-furyl	*t*-Bu	−10	94	43 (*R*)

[a] Reactions were performed on 500 μmol scale using 5 mol% of quinine (**2**) and 2.0 equiv. of KCN in 1.0 mL of CH_2Cl_2 at the stated temperature for 24 h.
[b] Isolated yields after purification.
[c] Determined by HPLC analysis on chiral stationary phase.
[d] Determined by comparison with literature values of the optical rotation.[8]

'hard' anionic PTC-bound cyanide giving rise to a fast addition step, our system likely includes a 'soft' hydrogen cyanide bound to a proton-shuttle catalyst. Additionally, we would expect the phase-transfer deprotonation step in the Ricci variant to be the rate-determining step, while in our case deprotonation and addition are both strongly influenced by the catalyst and are estimated to be both equally fast under the chosen reaction conditions.

Having established the optimum conditions for the reaction (Scheme 1), we proceeded to investigate its generality and scope. As demonstrated in Table 3, a series of optically active α-amino nitriles bearing bulky substituents at the aromatic core as well as at the carbamoyl group result from the Strecker reaction in good yield and selectivity. Although the selectivity dropped down significantly when using electron-poor imine precursors, the corresponding nitriles could still be obtained in synthetically useful yields (Table 3, entries 13 and 14). As far as aliphatic substrates concerned, we tested a pivalaldehyde derivative which, however, could not be converted into the corresponding nitrile. This finding also strengthens our hypothesis about the reaction mechanism as discussed above.

The resulting *N*-carbamoyl-α-aminonitriles **3** can be converted to the corresponding amino acids by refluxing with aqueous HCl as described in the literature.[6a,9] The amino acid hydrochlorides **4** were obtained by evaporation of the solvent and recrystallizing the residue with water (Scheme 4).



Scheme 4. Hydrolysis of the *N*-carbamoyl-α-aminonitriles **3**.

In summary, we have demonstrated an organocatalytic enantioselective Strecker reaction making use of the chiral pool and α-amido sulfones.[10] The overall process is highly efficient, encompasses a broad substrate scope and was accomplished by making use of the powerful and naturally occurring catalyst quinine (**2**) and KCN as a less hazardous cyanide source. In the presence of 5–10 mol% catalyst, excellent yields up to 99% and reasonable enantioselectivities up to 80% *ee* were achieved for many substrates. Thus the reported method provides a convenient route to unnatural amino acids that may find an application in medicinal chemistry.

Experimental Section

General Procedure for the Preparation of *N*-Carbamoyl-α-(phenylsulfonyl)amines 1 (Method A)

A mixture of the carbamate (1.00 equiv.) and benzenesulfinic acid salt (2.00 equiv.) was suspended in a solution of methanol in water (1:2). Afterwards, the specific aldehyde (1.50 equiv.) was added in one portion, followed by formic acid (98%, 2.00 equiv.). The resulting mixture was allowed to stir for 24 h at 25 °C. The resulting white precipitate was filtered off and washed with water and diethyl ether. The precipitate was then recrystallized from CH_2Cl_2/hexane to obtain the title compound as a crystalline material.

General Procedure for the Preparation of *N*-Carbamoyl-α-(phenylsulfonyl)amines 1 (Method B)

A mixture of the carbamate (2.00 equiv.) and benzenesulfinic acid salt (1.50 equiv.) was suspended in a mixture of toluene/acetonitrile (1:1). Afterwards, the specific aldehyde (1.00 equiv.) was added in one portion, followed by formic acid (98%, 1.50 equiv.) and TMSCl (1.10 equiv.). The resulting mixture was allowed to stir for 24 h at 50 °C. After completion, the mixture was cooled down to 0 °C and treated with water. The resulting solution was extracted with diethyl ether, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The resulting precipitate was filtered off and washed with water and diethyl ether. The precipitate was then recrystallized from CH_2Cl_2/hexane to obtain the title compound as a crystalline material.

General Procedure for the Strecker Reaction of *N*-Carbamoyl-α-(phenylsulfonyl)amines 1

A 0.5 M solution of the *N*-carbamoyl-α-(phenylsulfonyl)-amine (500 μmol, 1.00 equiv.) and quinine (**2**) (5 mol%) in CH_2Cl_2 (1.0 mL) was cooled to −10 °C under argon. At this temperature KCN (1.00 mmol, 2.00 equiv.) was added and the reaction mixture was stirred vigorously for 24 h at −10 °C. After completion, the mixture was quenched with saturated aqueous $NaHCO_3$ (1.00 mL), extracted with CH_2Cl_2 (2×5 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting residue was further purified by column chromatography to give the pure title compounds. The enantiomeric excess (*ee*) of each product was determined by HPLC analysis on chiral stationary phase.

Acknowledgements

We thank the BMBF (Wing – QuatCat) for financial support. R. R. is a fellow of the Landesgraduiertenförderung Baden-Württemberg.

References

[1] A. Strecker, *Ann. Chem. Pharm.* **1850**, *75*, 27.
[2] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315; b) C. A. Krueger, K. W. Kuntz, C. W. Dzierba, W. G. Wirschun, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284; c) J. R. Porter, G. Wirschun, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 2657; d) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem.* **1998**, *110*, 3369; *Angew. Chem. Int. Ed.* **1998**, *37*, 3186; e) H. Ishitani, S. Komiyama, Y. Hasegawa, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 762; f) M. Chavarot, J. J. Byrne, P.-Y. Chavant, Y. Vallée, *Tetrahedron: Asymmetry* **2001**, *12*, 1147; g) S. Masumoto, H. Usuda, M. Suzuki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5634; h) N. Kato, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2004**, *45*, 3147; i) S. Wünnemann, R. Fröhlich, D. Hoppe, *Eur. J. Org. Chem.* **2008**, 684; j) A. Berkessel, S. Mukherjee, J. Lex, *Synlett* **2006**, 41; k) J. Huang, X. Liu, Y. Wen, B. Quin, X. Feng, *J. Org. Chem.* **2007**, *72*, 204; l) J. Wang, X. Hu, J. Jiang, S. Gou, H. Huang, X. Liu, X. Feng, *Angew. Chem.* **2007**, *119*, 8620; *Angew. Chem. Int. Ed.* **2007**, *46*, 8468.
[3] a) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; b) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157; c) J. Huang, E. J. Corey, *Org. Lett.* **2004**, *6*, 5027; d) M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910; e) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; f) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336; *Angew. Chem. Int. Ed.* **2000**, *39*, 1279; g) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; h) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012; i) M. Rueping, E. Sugiono, S. A.

Moreth, *Adv. Synth. Catal.* **2007**, *349*, 759; j) T. Ooi, Y. Uematsu, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2548; k) T. Ooi, Y. Uematsu, J. Fujimoto, K. Fukumoto, K. Maruoka, *Tetrahedron Lett.* **2007**, *48*, 1337; l) M. Negru, D. Schollmeyer, H. Kunz, *Angew. Chem.* **2007**, *119*, 9500; *Angew. Chem. Int. Ed.* **2007**, *46*, 9339; m) S. C. Pan, B. List, *Chem. Asian J.* **2008**, *3*, 430; n) S. C. Pan, J. Zhou, B. List, *Angew. Chem.* **2007**, *119*, 618; *Angew. Chem. Int. Ed.* **2007**, *46*, 612.

[4] R. P. Herrera, V. Sgarzani, L. Bernardi, F. Fini, D. Pettersen, A. Ricci, *J. Org. Chem.* **2006**, *71*, 9869.

[5] For recent reviews, see: a) H. Gröger, *Chem. Rev.* **2003**, *103*, 2795; b) C. Spino, *Angew. Chem.* **2004**, *116*, 1796; *Angew. Chem. Int. Ed.* **2004**, *43*, 1764; c) L. Yet, *Angew. Chem.* **2001**, *113*, 900; *Angew. Chem. Int. Ed.* **2001**, *40*, 875; d) D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359; e) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; f) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; g) S. J. Connon, *Angew. Chem.* **2008**, *120*, 1194; *Angew. Chem. Int. Ed.* **2008**, *47*, 1176.

[6] For a racemic synthesis of α-amino nitriles see: a) V. Banphavichit, S. Chaleawlertumpon, W. Bhanthumnavin, T. Vilaivan, *Synth. Commun.* **2004**, *34*, 3147; b) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964; c) T. Ooi, in: *Asymmetric Phase Transfer Catalysis*, (Ed.: K. Maruoka), Wiley-VCH, Weinheim, **2008**, pp 9–33; d) for a recent review on the utility of α-amido sulfones as precursors of *N*-acylimino derivatives, see: M. Petrini, *Chem. Rev.* **2005**, *105*, 3949.

[7] a) W. H. Pearson, A. C. Lindbeck, J. W. Kampf, *J. Am. Chem. Soc.* **1993**, *115*, 2622; b) H. Buschmann, C. Pütz, D. Enders, S. Oberbörsch, *PCT Int. Appl.* **2003** *WO/03/068734*, 35.

[8] a) D. Subhas Bose, B. Jayalakshmi, *J. Org. Chem.* **1999**, *64*, 1713; b) F. Effenberger, A. Kremser, U. Stelzer, *Tetrahedron: Asymmetry* **1996**, *7*, 607.

[9] a) I. Jaafar, G. Francis, R. Danion-Bougot, D. Danion, *Synthesis* **1994**, 56; b) C. Cativiela, M. D. Diaz-de-Villegas, J. A. Galvez, Y. Lapena, *Tetrahedron* **1997**, *53*, 5891; c) C. P. Decicco, P. Grover, *Synlett* **1997**, 529.

[10] For the use of sulfones **1** in asymmetric reactions with zinc reagents: a) S. Dahmen, S. Bräse, *J. Am. Chem. Soc.* **2002**, *124*, 5940; b) N. Hermanns, S. Dahmen, C. Bolm, S. Bräse, *Angew. Chem.* **2002**, *114*, 3844; c) Accounts: S. Bräse, S. Dahmen, S. Höfener, F. Lauterwasser, M. Kreis, R. E. Ziegert, *Synlett* **2004**, 2647; d) S. Bräse, T. Baumann, S. Dahmen, H. Vogt, *Chem. Commun.* **2007**, 1881.

