Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1337–1340

Advantage of in situ generation of *N*-arylsulfonyl imines from α-amide sulfones in the phase-transfer-catalyzed asymmetric Strecker reaction

Takashi Ooi,* Yukitaka Uematsu, Jun Fujimoto, Kazuhiro Fukumoto and Keiji Maruoka*

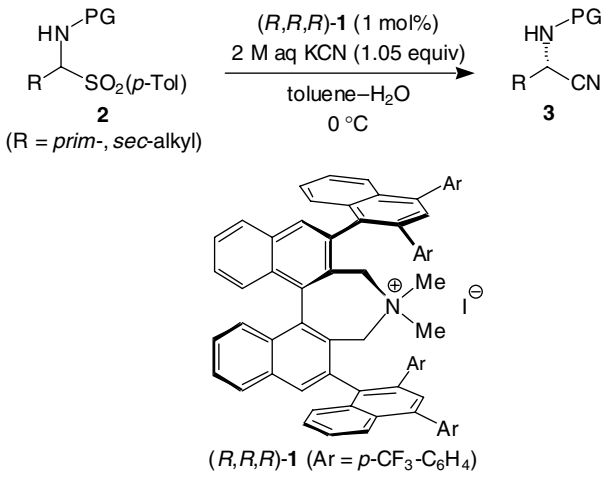
Department of Chemistry, Graduate School of Science, Kyoto University Sakyo, Kyoto 606-8502, Japan

Received 21 November 2006; revised 18 December 2006; accepted 21 December 2006
Available online 23 December 2006

Abstract—Highly efficient, catalytic enantioselective synthesis of *N*-arylsulfonyl α-amino nitriles from the corresponding α-amido sulfones has been achieved under toluene–aqueous potassium cyanide biphasic conditions using chiral quaternary ammonium iodide (*R*,*R*,*R*)-**1** as an effective phase-transfer catalyst. This Strecker synthesis involving the in situ generation of the reactive *N*-sulfonyl imines is advantageous for the cyanation of the substrates having primary and secondary alkyl substituents.

Stereochemical control in the Strecker reaction, cyanation of imines, has been the focus of extensive study primarily due to the importance of optically active α-amino acids, obtained through hydrolysis of α-amino nitriles, in various fields of science. For the last decade, enormous efforts have been devoted to the development of chiral catalysts to effect the enantioselective Strecker reaction of aldimines and ketimines.[1–3] In this context, we have recently devised the phase-transfer-catalyzed asymmetric cyanation of *N*-arylsulfonyl aldimines using aqueous potassium cyanide (KCN) as a cyanide source through the molecular design of a chiral quaternary ammonium salt (*R*,*R*,*R*)-**1** bearing a stereochemically defined tetranaphthyl backbone.[4] Although this new asymmetric Strecker protocol nicely accommodates a wide range of aliphatic aldimines, the chemical yield and enantioselectivity were still insufficient in the reactions with secondary and, particularly, primary alkyl aldimines compared to tertiary alkyl ones. This could be ascribed to the partial imine hydrolysis and uncatalyzed cyanation under biphasic conditions. To overcome these problems associated with the direct use of the reactive imines, we sought to employ *N*-arylsulfonyl α-amido sulfones as a suitable starting substrate for the in situ generation of the imine under similar liquid–liquid phase-transfer conditions.[5–7] Herein, we report the highly enantioselective synthesis of N-protected α-amino nitriles from the corresponding α-amido sulfones with remarkable efficiency, featuring its distinct practical advantages (Scheme 1).

The requisite *N*-mesitylenesulfonyl (Mts)[8] α-amido sulfone, a synthetic precursor of the corresponding



Scheme 1.

Keywords: α-Amido sulfones; α-Amino nitriles; Chiral quaternary ammonium iodide; Potassium cyanide; Strecker synthesis.
* Corresponding authors at present address: Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya, 464-8603 Japan (T.O.). Tel./fax: +81 75 753 4041 (K.M.); e-mail addresses: tooi@apchem.nagoya-u.ac.jp; tooi@kuchem.kyoto-u.ac.jp; maruoka@kuchem.kyoto-u.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.122

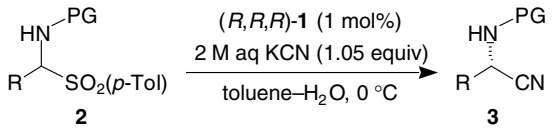
aldimines, can be readily prepared from aldehydes and mesitylenesulfonamide as we previously reported,[4] and easily purified by recrystallization. With cyclohexanecarboxaldehyde-derived α-amido sulfone **2a** as a representative substrate, we first attempted the exposure of **2a** to our original biphasic conditions using (*R*,*R*,*R*)-**1** as a catalyst. Thus, a mixture of **2a**, 1.5 equiv of 2 M KCN aqueous solution and 1 mol % of **1** in toluene–H_2O (volume ratio = 1:3) was stirred vigorously at 0 °C. Complete consumption of **2a** was confirmed after 1.5 h, and the desired *N*-Mts α-amino nitrile **3a** was produced in a quantitative yield with 97% ee (entry 1 in Table 1). The considerable improvement of the chemical yield and the enhanced enantioselectivity compared to the case with the imine as substrate clearly indicates that the intervention of imine hydrolysis and background cyanation is minimized, thereby releasing the full potential of the chiral phase-transfer catalysis of **1**. It should be emphasized that reducing the amount of KCN to 1.05 equiv did not afford any detrimental effect on the reaction efficiency, thus solidifying the practical aspect of the present system (entry 2).

Other selected examples are summarized in Table 1. With a variety of α-amido sulfones derived from α-branched and α-unbranched aldehydes including a highly enolizable one, the reaction proceeded rapidly and cleanly in the presence of 1 mol % of (*R*,*R*,*R*)-**1** and 1.05 equiv of aqueous KCN, and the corresponding α-amino nitriles **3** were obtained in excellent chemical yields and always with higher enantioselectivities. In particular, this method is quite effective for the asymmetric synthesis of an α-amino nitrile possessing a secondary alkyl α-substituent as represented by the cyanation starting from the substrate with *N*-benzyloxycarbonyl-4-piperidinyl group, where the target product **3d** was isolated quantitatively in an essentially enantiomerically pure form (entry 5).

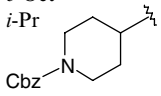
To strengthen this approach further with respect to the stereoselectivity in the reactions with α-primary-alkyl α-amido sulfones, the effect of substituents on the *N*-arylsulfonyl moiety was evaluated, fortunately revealing that the use of the 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr) group[8,9] proved to be beneficial. The *N*-Mtr α-amido sulfones was assembled from aldehydes and Mtr-NH_2 (**7**), which was conveniently derivatized from commercially available 2,3,5-trimethylphenol (**4**) as illustrated in Scheme 2. After methylation of **4**, the resulting 2,3,5-trimethylanisole (**5**) was converted to 4-methoxy-2,3,6-trimethylbenzene-sulfonyl chloride (**6**, Mtr-Cl) according to the procedure reported by Fujino.[9a] Subsequent treatment with aqueous ammonia furnished **7**.

As included in Table 1, subjection of *N*-Mtr α-amido sulfones to the phase-transfer cyanation with 2 M KCN aqueous solution under the influence of (*R*,*R*,*R*)-**1** led to formation of the corresponding *N*-Mtr α-amino nitriles with uniformly improved enantioselectivities (entries 10–13 vs entries 6–9 in Table 1).[10] A notable enhancement of the selectivity was attained with unbranched, α-heptyl-substituted α-amido sulfone (entry 12 vs entry 8). Unfortunately, however, chemical

Table 1. Phase-transfer-catalyzed asymmetric Strecker reaction with α-amido sulfones **2** as a starting substrate[a]



2 **3**

Entry	α-Amido sulfone **2** (R)	PG	Time (h)	Yield[b] (%)	ee[c] (%)	Product
1[d,e]	*c*-Hex (**2a**)	Mts	1.5	99 (89)	97[f] (95)	**3a**
2	*c*-Hex (**2a**)	Mts	1.5	99	97[f]	**3a**
3[e]	*c*-Oct	Mts	2	99 (88)	98 (97)	**3b**
4[e]	*i*-Pr	Mts	1.5	99 (85)	97 (93)	**3c**
5		Mts	1	99	99	**3d**
6[e]	$Ph(CH_2)_2$	Mts	1	99 (81)	94 (90)	**3e**
7[e]	$(CH_3)_2CHCH_2$	Mts	1	96 (82)	91 (88)	**3f**
8	$CH_3(CH_2)_5CH_2$	Mts	1	96	84	**3g**
9	$PhCH_2$	Mts	1	93	85	**3h**
10	$Ph(CH_2)_2$	Mtr	1	98	96	**3i**
11	$(CH_3)_2CHCH_2$	Mtr	1	99	93	**3j**
12	$CH_3(CH_2)_5CH_2$	Mtr	1	96	89	**3k**
13	$PhCH_2$	Mtr	1	86	86	**3l**

[a] Unless otherwise specified, the reaction was conducted with 1.05 equiv of 2 M KCN aqueous solution in the presence of 1 mol % of (*R*,*R*,*R*)-**1** in toluene–H_2O (volume ratio = 1:3) at 0 °C for the given reaction time.

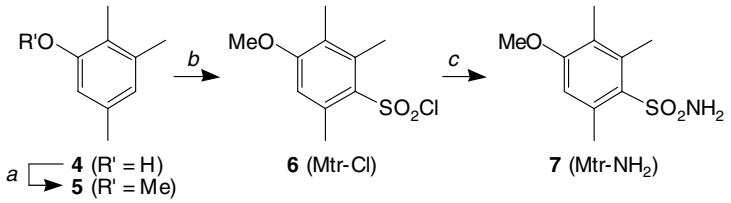
[b] Isolated yield.

[c] Enantiopurity of **3** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H or Chiralcel OD-H) with hexane–2-propanol as solvent. For detail, see the Supplementary data.

[d] With 1.5 equiv of 2 M KCN.

[e] The results with the corresponding aldimine as a starting substrate using 1.5 equiv of 2 M KCN are shown in the parenthesis.

[f] Absolute configuration of **3a** was assigned to be *S* by comparison of the HPLC retention time with the reported value.[4]



Scheme 2. Reagents and conditions: (a) NaH, MeI, THF, 0 °C, 92%; (b) chlorosulfonic acid (3 M solution in CH_2Cl_2), CH_2Cl_2, 0 °C; (c) 25% NH_3 aqueous solution, THF, 0 °C, 71% (two steps).

yield was sacrificed in the reaction involving the generation of the imine with α-protons of high acidity (entry 13 vs entry 9).

In conclusion, highly efficient, enantioselective synthesis of *N*-Mts and *N*-Mtr α-amino nitriles from the corresponding α-amido sulfones has been accomplished under toluene–aqueous KCN biphasic conditions by the utilization of phase-transfer catalysis of chiral quaternary ammonium iodide (*R*,*R*,*R*)-**1**. This asymmetric Strecker synthesis has the following characteristics: (1) *N*-arylsulfonyl α-amido sulfones can be used directly as a starting substrate, thus obviating the preformation of the reactive *N*-arylsulfonyl aldimines having primary or secondary alkyl α-substituents; (2) 1.05 equiv of KCN are sufficient for the smooth reaction, which is completed within 2 h at 0 °C; (3) the products are isolated with excellent levels of chemical yield and enantioselectivity. We believe these salient features should be greatly appreciated in the large-scale industrial applications, underscoring the practical advantage of our approach.

Synthesis of *N*-Mts α-amido sulfone [*N*-(Mts)-α-(*p*-toluenesulfonyl)cyclohexylmethylamine (**2a**)]:[4] A mixture of cyclohexanecarboxaldehyde (363 μL, 3.0 mmol), mesitylenesulfonamide (598 mg, 3.0 mmol) and sodium *p*-toluenesulfinate (481 mg, 3.0 mmol) in HCO_2H (4.5 mL) and H_2O (4.5 mL) was stirred for 12 h at room temperature. The resulting white precipitate was filtered off, washed with H_2O and hexane. The precipitate was then recrystallized from EtOAc/hexane to obtain **2a** (301 mg, 2.01 mmol, 67%) as a crystalline material; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, $J = 8.3$ Hz, ArH), 7.03 (2H, d, $J = 8.3$ Hz, ArH), 6.81 (2H, s, ArH), 5.27 (1H, d, $J = 10.7$ Hz, NH), 4.53 (1H, dd, $J = 3.0$, 10.7 Hz, NHC*H*), 2.50–2.40 (1H, m, C*H*$(CH_2)_2$), 2.42 (6H, s, $ArCH_3$), 2.34 (3H, s, $ArCH_3$), 2.29 (3H, s, $ArCH_3$), 2.11 (1H, d, $J = 12.3$ Hz, CH_2), 1.81–1.60 (4H, m, CH_2), 1.38–1.28 (2H, m, CH_2), 1.19–1.02 (3H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 141.7, 137.5, 135.7, 134.2, 131.6, 129.3, 128.3, 77.5, 37.5, 30.7, 27.2, 26.2, 25.8, 25.7, 22.9, 21.7, 21.0 ppm; IR (thin film) 3401, 3285, 3028, 2928, 2855, 1599, 1566, 1450, 1331, 1302, 1155, 1123, 1082, 903, 853, 814, 733 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{31}NO_4S_2Na$ ($[M+Na]^+$): 472.1575, found: 472.1587.

Typical experimental procedure is as follows (entry 2 in Table 1): A mixture of *N*-(Mts)-α-(*p*-toluenesulfonyl)cyclohexylmethylamine (**2a**, 89.9 mg, 0.20 mmol) and chiral quaternary ammonium iodide (*R*,*R*,*R*)-**1** (2.6 mg, 0.002 mmol) in toluene (1 mL) and H_2O (3 mL) was cooled to 0 °C and a 2 M KCN aqueous solution (105 μL, 0.210 mmol) was added dropwise. The reaction mixture was stirred vigorously for 1.5 h at this temperature. Then, saturated NH_4Cl aqueous solution was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the crude products by flash column chromatography on silica gel (EtOAc/hexane = 1:4 as eluent) gave *N*-(Mts)-α-(cyano)cyclohexylmethylamine (**3a**, 64.1 mg, 0.2 mmol, >99%); HPLC analysis: DAICEL Chiralpak AD-H, 2-propanol/hexane = 1:10, flow rate = 0.5 mL/min, $\lambda = 254$ nm, retention time; 13.3 min (*R*) and 14.7 min (*S*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (2H, s, ArH), 5.37 (1H, d, $J = 9.1$ Hz, NH), 3.92 (1H, dd, $J = 6.7$, 9.1 Hz, NHC*H*), 2.65 (6H, s, $ArCH_3$), 2.31 (3H, s, $ArCH_3$), 1.86–1.67 (6H, m, CH and CH_2), 1.29–1.06 (5H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 139.0, 132.7, 132.1, 116.5, 49.5, 41.2, 29.0, 28.4, 25.7, 25.4, 25.3, 23.0, 21.1 ppm; IR (thin film) 3275, 3028, 2930, 2855, 2253, 1602, 1566, 1450, 1330, 1157, 1091, 1057, 904, 852, 731 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{24}N_2O_2SNa$ ($[M+Na]^+$): 343.1454, found: 343.1451.

Acknowledgements

This work was partially supported by the Shorai Foundation for Science and Technology and a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformation of Carbon Resources' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.122.

References and notes

1. For reviews, see: (a) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875; (b) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795; (c) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764; (d) Vachal, P.; Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004; p 117.

2. Aldimines: (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910; (b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901; (c) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315; (d) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186; (e) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157; (f) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284; (g) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762; (h) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279; (i) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650; (j) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657; (k) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327; (l) Su, J. T.; Vachal, P.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 197; (m) Liu, B.; Feng, X.-M.; Chen, F.-X.; Zhang, G.-L.; Cui, X.; Jiang, Y.-Z. *Synlett* **2001**, 1551; (n) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801; (o) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784; (p) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594; (q) Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron Lett.* **2003**, *44*, 3805; (r) Jiao, Z.-G.; Feng, X.-M.; Liu, B.; Chen, F.-X.; Zhang, G.-L.; Jiang, Y.-Z. *Eur. J. Org. Chem.* **2003**, 3818; (s) Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1513; (t) Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027; (u) Banphavichit, V.; Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron* **2004**, *60*, 10559.
3. Ketimines: (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867; (b) Byrne, J. J.; Chavarot, M.; Chavant, P.-Y.; Vallee, Y. *Tetrahedron Lett.* **2000**, *41*, 873; (c) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallee, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147; (d) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012; (e) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634; (f) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147; (g) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153.
4. Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548.
5. For recent excellent review on the utility of α-amido sulfones as precursors of *N*-acylimino derivatives, see: Petrini, M. *Chem. Rev.* **2005**, *105*, 3949.
6. For pioneering study on the synthesis of N-protected α-amino nitriles from α-amide sulfones under phase-transfer conditions, see: Banphavichit, V.; Chaleawlertumpon, S.; Bhanthumnavin, W.; Vilaivan, T. *Synth. Commun.* **2004**, *34*, 3147; For a recent approach toward the asymmetric version, see: Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 9869.
7. For in situ generation of *N*-carbamoyl imines from α-amido sulfones in the phase-transfer-catalyzed asymmetric aza-Henry reaction, see: (a) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975; (b) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622.
8. For this type of abbreviation for multi-substituted benzenesulfonyl groups, see, for example: Ramage, R.; Green, J.; Blake, A. J. *Tetrahedron* **1991**, *47*, 6353.
9. (a) Fujino, M.; Wakimasu, M.; Kitada, C. *Chem. Pharm. Bull.* **1981**, *29*, 2825; (b) Fujino, M.; Wakimasu, M.; Kitada, C. *Chem. Commun.* **1982**, 445.
10. Deprotection of the Mtr group can be readily performed under exactly the same conditions reported for that of Mts group.[4,11]
11. Costanzo, M. J.; Yabut, S. C.; Almond, H. R., Jr.; Andrade-Gordon, P.; Corcoran, T. W.; de Garavilla, L.; Kauffman, J. A.; Abraham, W. M.; Recacha, R.; Chattopadhyay, D.; Maryanoff, B. E. *J. Med. Chem.* **2003**, *46*, 3865.