Synthesis and characterization of new chiral azolinium salts, precursors to *N*-heterocyclic carbenes, derived from L-proline

Amélia Thomasset, Lucie Bouchardy, Chloée Bournaud, Martial Toffano and Giang Vo-Thanh*

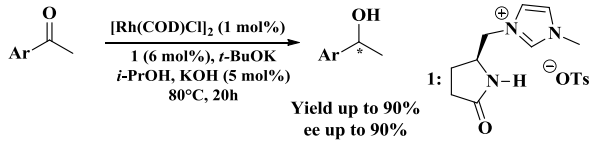
Laboratoire de Catalyse Moléculaire, Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), UMR CNRS 8182, Université Paris-Sud, 91405 Orsay Cedex, France

Email: giang.vo-thanh@u-psud.fr

Abstract: A short and flexible procedure for the preparation of 7 chiral azolinium and 5 functionalized chiral azolinium salts, precursors to *N*-heterocyclic carbenes, derived from L-proline has been developed. Moderate to good overall yields were obtained. Some NHC dimers and thiones were isolated. X-ray structure determinations of two [Rh-NHC] complexes were also reported.

Key words: azolinium salts, *N*-heterocyclic carbene, L-proline, microwave activation.

As part of our own program of studies, we have recently described the rhodium-catalyzed asymmetric transfer hydrogenation of aromatic ketones using chiral NHC ligands derived from (*S*)-pyroglutamic acid. Good yields and enantioselectivities (up to 94% yield and 90% ee) were observed (Scheme 1).[5] Here, we report the synthesis and characterization of novel functionalized chiral azolinium salts, precursors to NHCs, derived from L-proline, a naturally available product.



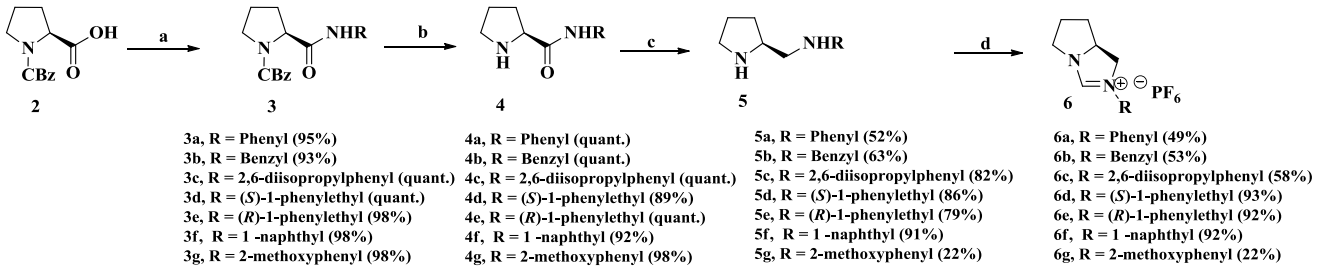
Scheme 1 Asymmetric transfer hydrogenation of aromatic ketones

As reported, azolium and azolinium salts are often used as precursors to metal-NHC complexes[1-4], but they have also found applications on their own as organocatalysts[6] and ionic liquids.[7] These research areas are currently well investigating because of their importance for developing 'greening' chemical processes.

The useful method for the preparation of azolinium salts containing a saturated backbone is a condensation of a *N,N'*-disubstituted alkanediamine and an inorganic ammonium salt with a trialkylorthoester using both as reagent and solvent, in the presence of a catalytic amount of acid.[8] Several modifications of the experimental reaction conditions of this method have been reported in literature.[9] In all cases, long reaction time (from few hours to some days) along with a prolonged reflux heating conditions are required for obtaining good conversions. In 2008, Delaude *et al*. described a facile microwave-assisted synthesis of cyclic amidinium salts. The transformation is highly compatible with a wide range of substituents and counter ions.[10]

For our synthesis, we chose *N*-CBz protected-L-proline ((*S*)-*N*-(benzyloxycarbonyl)-proline) **2** which is commercially available as starting material.

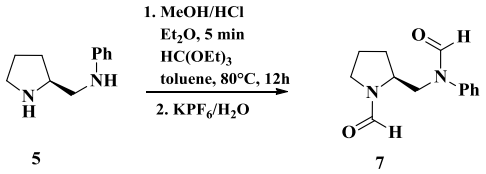
The synthetic route for the chiral azolinium salts **6** is summarized in Scheme 2.



Scheme 2 Synthesis of chiral azolinium salts **6**.

Reagents and conditions: a) *N*-methylmorpholine, $ClCO_2Et$, RNH_2, AcOEt, 0°C to rt, 15h. b) Pd/C, H_2, rt, 15h. c) $LiAlH_4$, THF reflux, 15h. d) $HC(OEt)_3$, NH_4PF_6, MW, 145°C, 5 min.

Our synthesis was initiated by transforming (*S*)-*N*-(benzyloxycarbonyl)-proline **2** into corresponding amides **3** by treatment with ethyl chloroformate in the presence of *N*-methylmorpholine and a variety of amines. The cleavage of *N*-CBz protective group of **3** by hydrogenolysis under hydrogen atmosphere at ordinary pressure in the presence of 5% Pd/C catalyst followed by the reduction of amide function using $LiAlH_4$ afforded the disubstituted alkanediamines **5** in moderate to good yields. Subsequently, the diamines **5** were converted to the azolinium salts **6** by heating with a large excess of triethylorthoformate along with an equivalent of KPF_6 at 80°C for 12h according to the protocol reported in literature.[11] However, after many repeated experiments, no desired product was detected. Only the diamide **7** was isolated and its structure was determined by NMR and MS analysis methods (Scheme 3).

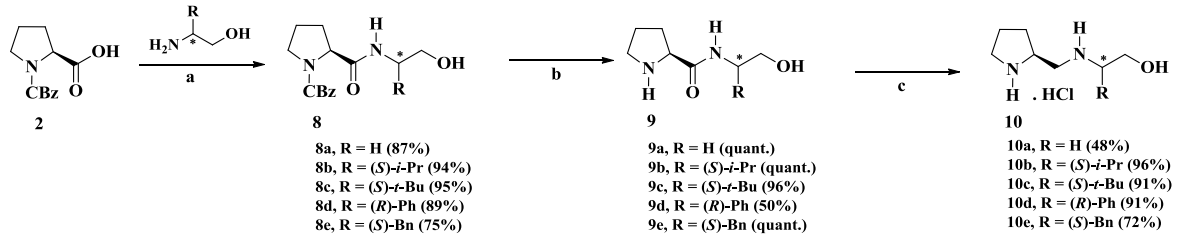


Scheme 3 Formation of diamide **7**.

We turned our attention to the use of microwave irradiation. This technique was widely developed in our Laboratory and in other research groups.[12] The combination of solvent-free synthesis conditions and MW irradiation considerably reduces reaction time, enhances conversions as well as selectivity and sometimes enables the preparation of molecules which are impossible to synthesize in classical heating conditions.[13]

So, the cyclisation was carried out in 'one-pot' reaction using amines **5**, triethylorthoformate and NH_4PF_6 under microwave irradiation conditions at 145°C for 5 min. Generally speaking, azolinium salts **6** were isolated in moderate to good yields (Scheme 2). Under identical reaction conditions (same temperature, same reaction time,…) using a thermostated oil bath (conventional heating), only traces of desired products were detected. Using this experimental protocol, 7 new chiral azolinium salts were synthesized in 4 steps from (*S*)-*N*-(benzyloxycarbonyl)-proline **2** in 5-75% overall yields..

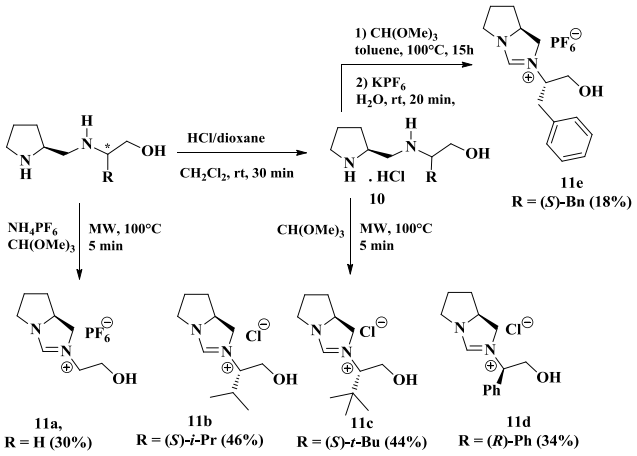
We then proceeded to synthesize the functionalized chiral azolinium salts **11** possessing not only a hydroxyl function but also a supplementary stereogene center on the alkyl chain in order to study their effects on prospective applications of these chiral salts as precursors to NHCs in asymmetric catalysis. Thus, functionalized chiral azolinium salts **11** were synthesized from diamines **10** which were easily obtained in good overall yields (41% to 90%) in 3 steps from *N*-CBz protected-L-proline **2** (Scheme 4).



Scheme 4 Synthesis of chiral diamines **10**.

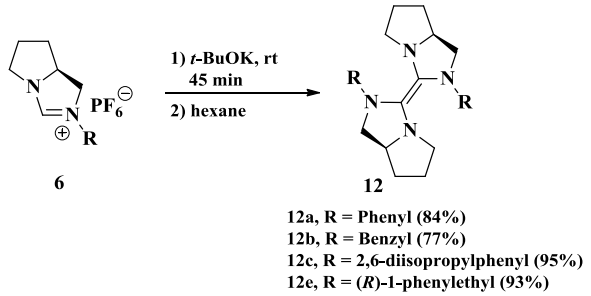
Reagents and conditions: a) *N*-methylmorpholine, $ClCO_2Et$, AcOEt, -15°C to rt, 15h. b) Pd/C, H_2, rt, 15h. c) 1. BH_3.THF reflux, 15h. 2. HCl, dioxane, CH_2Cl_2, rt, 30 min.

Using the same strategy previously described in Scheme 2, functionalized chiral azolinium salts **11a-d** were isolated in moderate yields after purification by flash chromatography on silica gel. On the other hand, owing to the degradation under MW irradiation, the chiral azolinium salt **11e** was synthesized by treatment of the diamine **10** with a large excess of trimethylorthoformate followed by an anion exchange with KPF_6. Scheme 5 summarizes the synthesis of these functionalized chiral azolinium salts **11**.



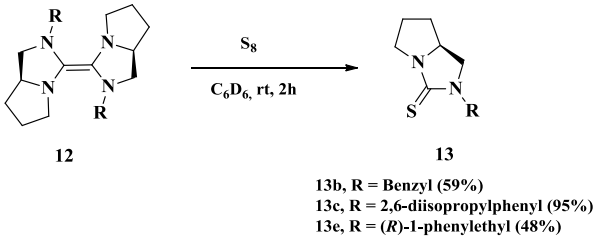
Scheme 5 Synthesis of functionalized chiral azolinium salts **11**.

Next, we were interested in characterizing our NHCs. Some azolinium salts were selected for this study. Treatment of the chiral azolinium salts **6a-c** and **6e** with *t*-BuOK in THF at room temperature led to the formation of corresponding NHC dimers **12**, and not free NHCs, in good yields. These NHC dimers are quite stable in keeping in the glove box and their structures were confirmed by NMR analysis (Scheme 6).



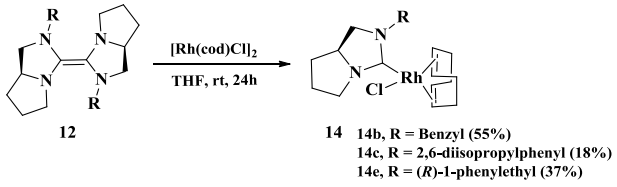
Scheme 6 Formation of NHC dimers **12**.

To characterize the unstable free NHCs, the useful method is to transform directly a free NHC to its derivative by reaction with sulfur or selenium.[14] These adducts are very stable and could be characterized by different analysis methods. Thus, treatment of NHC dimers **12b**, **12c** and **12e** with S_8 in the presence of C_6D_6 at room temperature for 2h conducted to the formation of thiones **13** in moderate to good yields. Their structures were confirmed by NMR and ESI analyses. The ^{13}C NMR signals for C=S appear at δ = 186.2, 187.6, and 185.4 ppm for **13b**, **13c** and **13e** respectively (Scheme 7).



Scheme 7 Formation of thiones **13**.

Finally, the ability of the NHC dimers to the formation of transition metal complexes was also evaluated. The reaction of **12b**, **12c** and **12e** with $[Rh(COD)Cl]_2$ in THF at room temperature for 24h led to the formation of the expected [Rh-NHC] complexes **14b**, **14c** and **14e** which were isolated, after purification by flash chromatography on silica gel, in 18-55% yields as air-stable yellow solids (Scheme 8). NMR and ESI analyses and especially the X-ray diffraction (for **14b** and **14e**) (Figures 1 and 2) confirmed the formation of these [Rh-NHC] complexes.



Scheme 8 Formation of [Rh-NHC] complexes **14**.

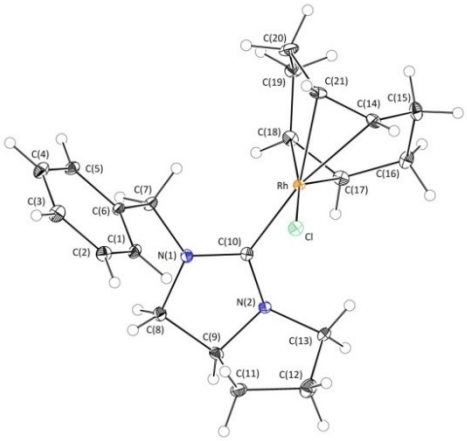


Figure 1 ORTEP drawing representation of the molecular structure of **14b**. Ellipsoids are drawn at the 30 % probability level. Selected bond distances (Å) and angles (deg): Rh-Cl=2.3754(7) Å; Rh-C(10)=1.994(2) Å; Rh-C(14)=2.229(3) Å; Rh-C(21)=2.191(3) Å; Rh-C(17)=2.095(3) Å; Rh-C(18)=2.131(3) Å; C(10)-N(1)= 1.338(3) Å; C(10)-N(2)= 1.354(3) Å; N(1)-C(10)-N(2)= 108.6(2)°.

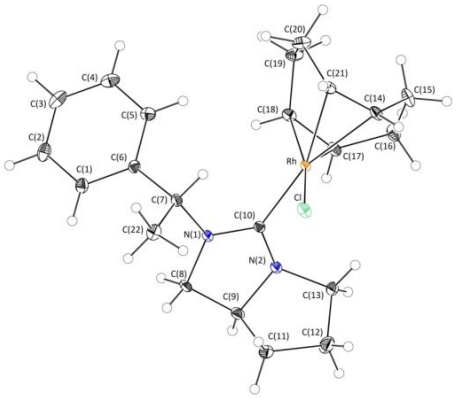


Figure 2 ORTEP drawing representation of the molecular structure of **14e**. Ellipsoids are drawn at the 30 % probability level. Selected bond distances (Å) and angles (deg):Rh-Cl=2.3761(3) Å ; Rh-C(10)= 2.0021(13) Å ; Rh-C(14)= 2.2342(13) Å ; Rh-C(21)=2.2055(12) Å ; Rh-C(17)=2.1032(13) Å; Rh-C(18)=2.1202(13) Å; C(10)-N(1)= 1.3385(17) Å; C(10)-N(2)= 1.3564(17) Å; N(1)-C(10)-N(2)= 108.57(11)°.

In summary, we have developed a short and flexible procedure for the synthesis of 7 chiral azolinium salts, and 5 functionalized chiral azolinium salts, precursors to *N*-heterocyclic carbene, derived from L-proline. Moderate to good overall yields were obtained in all cases. The structures of some NHC dimers, thiones and two [Rh-NHC] complexes were confirmed by different analysis methods in particular the X-ray diffraction analysis. The efficiency of these NHC ligands has been evaluated in asymmetric allylic substitution and in conjugate addition of Grignard reagent to α,β-unsaturated ketones. The results of these studies will be communicated in due course.

References

(1) (a) Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361. (b) Fröhlich, N.; Pidun, U.; Stahl, M.; Frenking, G. *Organometallics* **1997**, *16*, 442. (c) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290. (d) Hahn, F. E. *Angew. Chew. Int. Ed*. **2006**, *45*, 1348. (e) Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L. *Coordination Chem. Rev.* **2009**, *253*, 687. (f) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev*. **2009**, *109*, 3612. (g) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev*. **2009**, *109*, 3708.

(2) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.
(3) (a) Lee, H. M.; Lee, C. C.; Cheng, P. J. *Curr. Org. Chem.* **2007**, *11*, 1491. (b) Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed*. **2010**, *49*, 6940. (c) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev*. **2011**, *111*, 2705.
(4) (a) Zinner, S. C.; Herrmann, W. A.; Kuhn, F. E. *J. Organomet. Chem.* **2008**, *693*, 1543. (b) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951. (c) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619. (d) Glorius, F. *N-Heterocyclic Carbenes in Transition Metal Catalysis*. Springer: Berlin, **2007**.
(5) Aupoix, A.; Bournaud, C.; Vo-Thanh, G. *Eur. J. Org. Chem*. **2011**, 2772.
(6) Dalko, P.; Moisan, L. *Angew. Chem. Int. Ed*. **2004**, *43*, 5138.
(7) (a) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed*. **2000**, *39*, 3772. (b) Dupont, J.; De Souza, R. F.; Suarez, P. A. *Chem. Rev*. **2002**, *102*, 3667. (c) Wasserscheid, P.; Welton, T. *Ionic liquids in synthesis*, 2nd ed., Wiley-VCH, Weinheim, **2008**. (d) Deetlefs, M.; Seddon, K. S. *Green Chem.* **2003**, 5, 181. (e) Lévêque, J. M.; Estager, J.; Draye, M.; Cravotto, G.; Boffa, L.; Bonrath, W. *Monatsh. Chem*. **2007**, 138, 1103. (f) Aupoix, A.; Pégot, B.; Vo-Thanh, G. *Tetrahedron* **2010**, *66*, 1352. (g) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev*. **2007**, *107*, 2615. (h) Van Rantwijk, F.; Sheldon, R. A. *Chem. Rev*. **2007**, *107*, 2757. (i) Greaves, T. L.; Drummond, C. J.*Chem. Rev*. **2008**, *108*, 206. (j) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. *Chem. Rev*. **2008**, *108*, 2015. (k) Aupoix, A.; Vo-Thanh, G. *Synlett*, **2009**, *12*, 1915.
(8) Saba, S.; Brescia, A.; Kaloustian, M. A. *Tetrahedron Lett*. **1991**, *32*, 5031.
(9) (a) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523. (b) Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett*. **2003**, *5*, 3317. (c) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2006**, *128*, 1840. (d) Alder, R. W.; Blake, M. E.; Bufali, S.; Butts, C. P.; Orpen, A. G.; Schütz, J.; Williams, S. J. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1586. (e) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2003**, *125*, 12502.
(10) Aidouni, A.; Bendahou, S.; Demonceau, A.; Delaude, L. *J. Comb. Chem*. **2008**, *10*, 886.
(11) Rix, D.; Labat, S.;Toupet, L.; Crévisy, C. ; Mauduit, M. *Eur. J. Inorg. Chem*. **2009**, 1989.
(12) (a) Vo-Thanh, G.; Pégot, B.; Loupy, A. *Eur. J. Org. Chem*. **2004**, *5*, 1112. (b) Varma, R. S.; Namboodiri, V. V. *Chem. Commun*. **2001**, 643. (c) Varma, R. S.; Namboodiri, V. V.*Pure Appl. Chem*. **2001**, *73*, 1309. (d) Khadilkar, B. M.; Rebeiro, G. L. *Org. Proc. Res. & Develop*. **2002**, *6*, 826. (e) Law, M. C.; Wong, K. Y.; Chan, T. H. *Green Chem*. **2002**, *4***,** 328. (f) Varma, R. S.; Namboodiri, V. V. *Chem. Commun*. **2002**, 342. (g) Dubreuil, J. F.; Famelart, M. H.; Bazureau, J. P. *Org. Proc. Res. & Develop.* **2002**, *6*, 374. (h) Cravotto, G.; Calcio-Gaudino, E.; Boffa, L.; Lévêque, J. M.; Estager, J.; Bonrath, W. *Molecules* **2008**, *13*, 149.
(13) For reviews on microwave chemistry, see: (a) Perreux, L.; Loupy, A.; *Tetrahedron* **2001**, *57*, 9199. (b) Lidström, P.; Tierney, J.; Wathey, P.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light* **2002,** CEM Publishing, Matthews, NC. (d) Loupy; A. *Microwaves in Organic Synthesis* **2006**, Wiley-VCH, Weinheim. (e) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry* **2005**, Wiley-VCH, Weinheim. (f) Polshettiwar, V.; Varma, R. S. *Acc. of Chem. Res*. **2008**, *41*, 629. (g) Truong, T. K. T.; Nguyen Van Buu, O.; Pégot, B.; Aupoix, A.; Vo-Thanh, G. *Curr. Org. Synth*. **2012**, *1*, 53.
(14) (a) Zhang, J.; Qin, X.; Fu, J.; Wang, X.; Su, X.; Hu, F.; Jiao, J.; Shi, M. *Organometallics* **2012**, *31*, 8275. (b) Makhloufi, A.; Wahl, M.; Frank, W.; Ganter, C. *Organometallics* **2013**, *32*, 854.
(15) (a) Xu, J.; Fu, X.; Wu, C.; Hu, X. *Tetrahedron: Asymmetry* **2011**, *22*, 840. (b) Held, I.; Larionov, E.; Bozler, C.; Wagner, F.; Zipse, H. *Synthesis* **2009**, *13*, 2267. (c) Kikuchi, M.; Inagaki, T.; Nishimaya, H. *Synlett* **2007**, *7*, 1075. (d) Fuentes de Arriba, A. L.; Simon, L.; Raposo, C.; Alcazar, V.; Moran, J. R. *Tetrahedron* **2009**, *65*, 4841. (e) Kelleher, F.; Kelly, S.; Watts, J.; McKee, V. *Tetrahedron* **2010**, *66*, 3525. (f) Carmona, A.; Corma, A.; Iglesias, M.; San José, A.; Sanchez, F. *J. Organomet. Chem*. **1995**, *492*, 11. (g) Clapham, B.; Wilson, N. S.; Michmerhuizen, M. J.; Blanchard, D. P.; Dingle, D. M.; Nemcek, T. A.; Pan, J. Y.; Sauer, D. R *J. Comb. Chem.* **2008**, *10*, 88. (h) Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1978**, *51*, 1869. (i) Amedjkouh, M.; Ahlberg, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2229. (j) Miao, S.; Bai, J.; Yang, J.; Zhang, Y. *Chirality* **2010**, *22*, 855.
(16) (a) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci*. **2004**, *101*, 5755. (b) Almaşi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nagel, Y.; Nájera, C. *Eur. J. Org. Chem*. **2007**, 2328.
(17) CEM Discover S class reactor, see www.cem.com