Asymmetric transfer hydrogenation of aromatic ketones using rhodium complexes of chiral *N*-heterocyclic carbenes derived from (*S*)-pyroglutamic acid.

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Abstract: A new and flexible procedure for the preparation of chiral azolium salts derived from (S)-pyroglutamic acid has been developed. The efficiency of these ligands has been evaluated in the metal-catalyzed asymmetric transfer hydrogenation of aromatic ketones in iso-propanol. Good enantioselectivities up to 90% ee were observed.

Keywords: Asymmetric transfer hydrogenation / N-heterocyclic carbene / Aromatic ketones / (S)-pyroglutamic acid/ Azolium salts.

Introduction:

The reduction of carbonyl compounds to the corresponding alcohols is one of the most fundamental and useful reactions that are important in the pharmaceutical and chemical industry. The asymmetric transfer hydrogenation (ATH) of ketones has recently emerged as a highly efficient method for the synthesis of enantiomerically enriched secondary alcohols that are key intermediates for the manufacture of a variety of molecules and molecular scaffolds of biological and therapeutic interest.[1] Transition metal-catalyzed asymmetric transfer hydrogenation of prochiral ketones provides a powerful alternative to asymmetric hydrogenation due to its ease of handling, the easy availability of hydrogen sources, lower cost and safety.[2] Many chiral ligands and transition metals have been developed and applied to this reaction. The common catalysts are rhodium, ruthenium and iridium complexes with chiral phosphine and chiral diamine ligands.[3]

N-Heterocyclic carbenes (NHCs) have attracted increasing attention as they have been proven to act as efficient ligands in coordination chemistry and homogeneous catalysis.[4] In many cases, NHC complexes show higher thermal stability and catalytic activities than their phosphine counterparts partially owing to the strong metal–NHC bonds and the high σ-donating ability of NHC ligands.[5] The incorporation of the carbene functionality into ligand systems offers great opportunities for ligand design and the discovery of new efficient catalysts.[6] Chiral *N*-Heterocyclic carbenes are well established as efficient alternatives to chiral phosphine ligands in asymmetric synthesis processes.[7] However, transition metal-catalyzed asymmetric transfer hydrogenation of prochiral ketones using chiral NHCs as ligands has been limited so far and only a few examples have been reported. In general, moderate to good conversions were obtained but with very poor enantioselectivities.[8-10]

Recently, in 2009, Douthwaite *et al*. reported the synthesis of iridium NHC-phenoxyimine and rhodium and iridium NHC-amine complexes. These complexes were investigated their

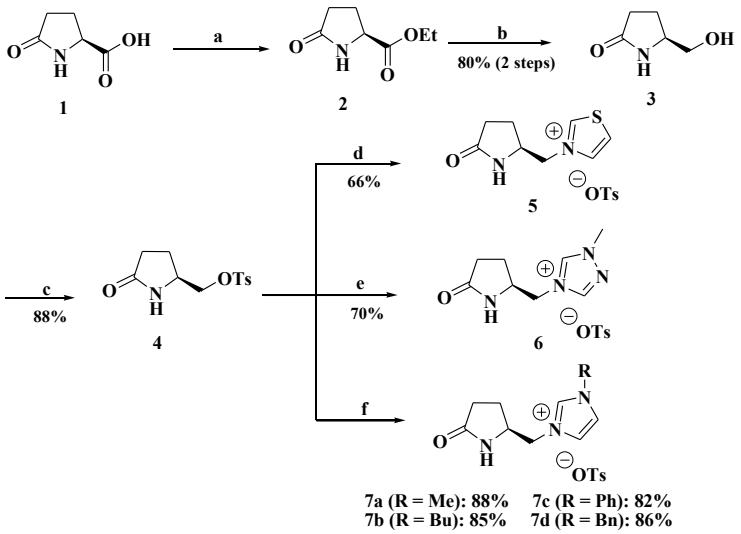
catalytic application to enantioselective transfer hydrogenation of acetophenone and derivatives. The highest ee of 56% was obtained with 3-chloroacetophenone.[11] In the same year, Kuang *et al*. applied a chelated ferrocene-based planar chiral NHC-rhodium (I) complex to the asymmetric transfer hydrogenation of acetophenone and cyclohexylphenylketone affording corresponding secondary alcohols with 60% ee and 67% ee, respectively.[12] It should be noted that was the highest enantioselectivities that have been reported in the literature. Therefore, the development of more efficient chiral NHC ligands remains a challenge for ATH.

As a part of our own program of studies, we have recently described the ruthenium-catalyzed asymmetric transfer hydrogenation of acetophenone using aminoalcohol ligands derived from isosorbide.[13] Here, we report the synthesis of novel chiral azolium salts, precursors to NHCs, derived from (*S*)-pyroglutamic acid and investigate their application to the enantioselective transfer hydrogenation of aromatic ketones.

Results and Discussion

Synthesis of chiral azolium salts precursor to NHC ligands derived from (*S*)-pyroglutamic acid.

The synthetic route for the chiral azolium salts **5**, **6**, **7** is summarized in Scheme 1.



Scheme 1: Synthesis of azolium salts **5**, **6**, **7a-d**.

Reagents and conditions : a) $SOCl_2$, EtOH, 3h, rt. b) $NaBH_4$, EtOH, 48h, rt. c) TsCl, Et_3N, CH_2Cl_2, DMAP, 20h, rt. d) thiazole, MW, 130°C, 2h. e) 1-methyl-1,2,4-triazole, MW, 130°C, 2h. f) 1-R-imidazole, MW, 130°C, 1.5h.

Our synthesis was initiated by esterification of (*S*)-pyroglutamic acid followed by reduction using $NaBH_4$ to afford the alcohol **3** in 80% yield.[14] The hydroxyl group was then activated as its tosylate.[15] Subsequently, the tosylate **4** was converted to the thiazolium **5** by heating with a large excess of thiazole at 80°C.[16] However, no product was detected even after 2 days.

We turned out our attention to the use of microwave irradiation. This technique was widely developed in our Laboratory and in other research groups.[17] The combination of solvent-free 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 conditions.[18]

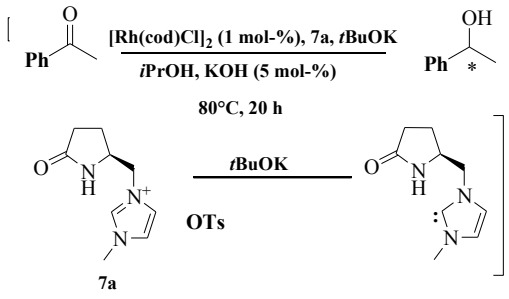
Many experiments were carried out by varying the number of equivalents of thiazole, the temperature and the reaction time using solvent-free MW reaction conditions. The best result was obtained when performing the reaction of tosylate **4** with 5 equivalents of thiazole at 130°C for 2h. Purification by flash chromatography on silica gel afforded the desired thiazolium salt **5** in 66% yield. Using the same strategy, but with only 2 equivalents of reagent, the triazolium salt **6** and a series of 1-substituted imidazolium salts **7** were isolated in 70% and 82-88% yields, respectively.

Asymmetric reduction of aromatic ketones by transfer hydrogenation reaction

After achieving the synthesis of these azolium salts containing a chiral moiety, we were interested in testing their potential as precursor to NHC ligands for asymmetric catalysis.

The reduction of acetophenone to 1-phenylethanol was chosen as a model reaction to explore the catalytic behaviours of complexes using *i*PrOH as the hydrogen donor in the presence of KOH as promoter. From a practical point of view, the application of *in situ* prepared catalysts has significant advantages. Thus, a small library of chiral azolium salts (Scheme 1, compounds **5**, **6**, **7**) as carbene precursors and $[Rh(cod)Cl]_2$ as catalyst precursor were tested. The complex formation conditions are described in detail in the experimental section.

We have first screened the effect of ligand to metal (L/M) ratio and the substrate concentration ([C]) on catalytic activity and asymmetric induction of the transfer hydrogenation. The catalytic trials were carried out using acetophenone (1.0 mmol), $[Rh(cod)Cl]_2$ catalyst precursor (1 mol%), KOH (5 mol%), and *i*PrOH at 80°C for 20 h. The methylimidazolium salt **7a** was used for these experiments. The reaction conversion was monitored by ^{1}H NMR and the enantiomeric excess was determined by chiral HPLC analysis. Some significant results are presented in Table 1.



Scheme 2: Asymmetric transfer hydrogenation of acetophenone.

Table 1: Screening of ligand / metal (L / M) and substrate concentration [C] for ATH of acetophenone.

Entry	L/M	[C] (M)	T [°C]	Time [h]	Conv.[a] [%]	ee[b] [%]
1	1	0.4	80	20	65	0
2	2	0.4	80	20	63	38
3	3	0.4	80	20	71	60
4	3	0.2[c]	80	20	82	80
5	3	0.1	80	20	63	76
6	3	0.2	65	72	59	84
7	3	0.2	50	72	33	90

Reaction conditions: acetophenone (1 mmol), $[Rh(cod)Cl]_2$ 1 mol-%, KOH 5 mol-%. [a] Determined by ^1H NMR. [b] Determined by chiral HPLC analysis using Chiralcel OD-H column. [c] [acetophenone]= 0.2M in *i*PrOH.

Initial investigations showed a crucial effect on reactivity and especially on asymmetric induction by varying ligand/metal (L/M) ratio. The best conversion and enantioselectivity were obtained at L/M 3 and at 0.2M concentration of the substrate (Table 1, entry 4). Noteworthy, there is a significant temperature effect on the reaction rate and enantiomeric excess. The highest ee of 90% was obtained when performing the reaction at 50°C. However, only 33% conversion was observed after 3 days (Table 1, entry 7).

It is well-known that transfer hydrogenations are sensitive to the nature of the base. Thus, the influence of potassium *tert*-butylate, sodium hydroxide and potassium hydroxide, used as promotor, on selectivity and conversion was investigated. In all cases, good conversion (> 72%) was observed. The best conversion and enantioselectivity were obtained in the presence of 2 mol% potassium hydroxide, one of the most common bases for transfer hydrogenation (Table 2, entry 4). By increasing the amount of base up to 8 mol%, the same reaction rate is recorded, while a drop in ee was observed (Table 2, entry 6).

Table 2: Influence of nature of the base co-catalyst on the reduction of acetophenone by transfer hydrogenation

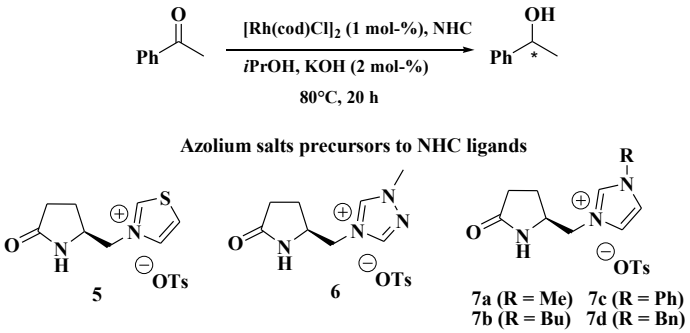
Entry	Base nature	Base [mol-%]	Conv.[a] [%]	ee[b] [%]
1	*t*BuOK	5	72	58
2	NaOH	5	74	73
3	KOH	5	82	80
4	KOH	2	90	80
5	KOH	1	76	80
6	KOH	8	87	64

Reaction conditions: acetophenone (1 mmol), $[Rh(cod)Cl]_2$ 1 mol-%, L/M = 3, [C] = 0.2M, T = 80°C, t = 20h. [a] Determined by ^1H NMR. [b] Determined by chiral HPLC analysis using Chiralcel OD-H column.

Next, the influence of the ligand nature was investigated. As shown in Table 3, we examined 6 examples out of the growing number of carbene precursors (**5**–**7**) under the previously optimized conditions for the transfer hydrogenation of acetophenone. Very low activity or no

conversion was observed when using, respectively, triazolium salt **6** or thiazolium salt **5** as precursor to NHC ligands (Table 3, entries 1 and 2). Summarizing the activities of imidazolium salts **7**, a crucial influence was observed by variation of substituents at the nitrogen atoms of the imidazolium salts. The best conversion and enantioselectivity were obtained when performing the transfer hydrogenation of acetophenone using imidazolium **7a** (R = Me). The same conversion but lower ee were recorded with **7b** (R = Bu). Very surprisingly, the reaction did not proceed at all with **7c** (R = Ph) or **7d** (R = Bn) (Table 3, entries 5 and 6).

Table 3: Variation of azolium salts in the ATH of acetophenone

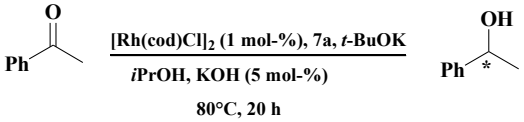


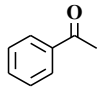
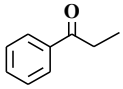
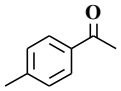
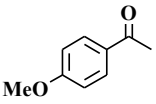
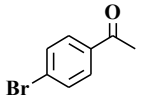
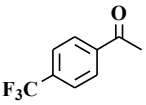
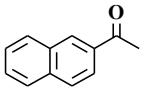
Entry	Azolium salt	Conv.[a] [%]	ee[b] [%]
1	**5**	0	0
2	**6**	15	nd[c]
3	**7a**	90	80
4	**7b**	90	46
5	**7c**	0	0
6	**7d**	0	0

Reaction conditions: acetophenone (1 mmol), $[Rh(cod)Cl]_2$ 1 mol-%, L/M = 3, [C] = 0.2M, T = 80°C, t = 20h. [a] Determined by ^{1}HNMR. [b] Determined by chiral HPLC analysis using Chiralcel OD-H column. [c] Not determined.

In order to demonstrate the usefulness of the catalysts in a more general manner, we employed the catalyst system $[Rh(cod)Cl]_2$/ NHC in the transfer hydrogenation of eight aromatic ketones (Table 4). Since the imidazolium salt **7a** displayed the highest activity and asymmetric induction for the transfer hydrogenation of acetophenone, we tested this NHC precursor with some functionalized acetophenones which are more difficult to hydrogenate. The substrates were selected so as to have either electron-donating or electron-withdrawing moieties on the phenyl ring. According to the literature, no decomposition or side reactions of these substituted ketones in transfer hydrogenation has been detected.[19]

Table 4: ATH of aromatic ketones



Entry	Ketone	Isolated yield [%]	ee[a][%]
1		90	80
2		58	50
3		56	74
4		36	71
5		90	76
6		94	51
7		81	70
8		38	50

Reaction conditions: acetophenone (1 mmol), $[Rh(cod)Cl]_2$ 1 mol-%, L/M = 3, [C] = 0.2M, T = 80°C, t = 20h. [a] Determined by chiral HPLC or GC (see experimental section).

As shown in Table 4, these ketones can be transformed to the corresponding secondary alcohols under the optimized reaction conditions for acetophenone. The steric and electronic properties of substrates affected considerably on the chemical yield and enantioselectivity. The more electron rich the substrates are, like methoxy or methyl, the slower the reaction with the catalyst system $[Rh(cod)Cl]_2$/ NHC is (Entries 3 and 4). Introduction of an electron-withdrawing group, however, led to much lower enantioselectivity, but higher yield (Entry 6). On the other hand, a slight negative effect on yield and enantioselectivity was observed when performing the ATH with acetonaphthone in lieu of acetophenone, presumably due to increased substrate bulk (Entries 7 and 1). This was confirmed when increasing the bulkiness of the R group, next to the active center, very low activity and enantioselectivity were recorded (Entries 2 and 8).

Conclusions

In summary, we have developed a new and flexible procedure for the synthesis of chiral azolium salts, precursors to *N*-heterocyclic carbene, derived from (*S*)-pyroglutamic. We have also demonstrated the successful application of rhodium catalysts containing chiral NHC ligands in the asymmetric transfer hydrogenation of aromatic ketones. Good yield and enantioselectivity were observed for acetophenone as the substrate. Although the results are certainly still quite modest with respect to what can be achieved using well developed asymmetric transfer hydrogenation catalysts, this represents the highest enantioselectivity to date for a transfer hydrogenation catalysts incorporating a chiral NHC ligand. Attempts to

identify the NHC-rhodium complex structures as well as the catalytic species of the procedure are currently underway in our Laboratory.

References

[1] For recent selected examples, see: a) A. Schlatter, M. K. Kundu, W.-D. Woggon, *Angew. Chem. Int. Ed*. **2004**, *43*, 6731-6734; b) D. Xue, Y.-C. Chen, X. Cui, Q.-W. Wang, J. Zhu, J.-G. Deng, *J. Org. Chem*. **2005**, *70*, 3584-3591; c) X. Wu, X. Li, F. King, J. Xiao, *Angew. Chem. Int. Ed*. **2005**, *44*, 3407-3411; d) A. M. Hayes, D. J. Morris, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2005**, *127*, 7318-7319; e) W. Baratta, G. Chelucci, S. Gladiali, K. Siega, M. Toniutti, M. Zanette, E. Zangrando, P. Rigo, *Angew. Chem. Int. Ed*. **2005**, *44*, 6214-6219; f) S. Enthaler, R. Jackstell, B. Hagemann, K. Junge, G. Erre, M. Beller, *J. Organomet. Chem*. **2006**, *691*, 4652-4659; g) M. T. Reetz, X. Li, *J. Am. Chem. Soc***. 2006**, *128*, 1044-1045.

[2] a) T. Ohkuma, R. Noyori, *Comprehensive Asymmetric Catalysis Supplement* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto). Springer: Berlin, **2004**, Vol. 1, p. 43; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev*. **2006**, 35, 226-236; c) T. Ikariya, A. J. Blacker, *Acc. Chem. Res*. **2007**, *40*, 1300-1308; d) C. Wang, X. Wu, J. Xiao, *Chem. Asian J*. **2008**, *3*, 1750-1770; e) P. Paloma, D. Josefina, M. P. Gamasa, *Organometallics* **2008**, *27*, 2597-2607.

[3] a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res*. **1997**, *30*, 97-102; b) M. Kitamura, R. Noyori, *Ruthenium in Organic Synthesis* (Ed.: S.-I. Murahashi).Wiley-VCH: Weinheim, **2004**, p. 3; c) W. He, P. Liu, B. L. Zhang, X. L. Sun, S. Y. Zhang, *Appl. Organometal. Chem.* **2006**, *20*, 328-334; d) W. Baratta, P. Rigo, *Eur. J. Inorg. Chem*. **2008**, *26*, 4041-4053.

[4] a) A. J. Arduengo, III, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, **1991**, *113*, 361-363; b) F. E. Hahn, *Angew. Chew. Int. Ed.*, **2006**, *45*, 1348-1352; c) W. A. Herrmann, *Angew. Chem. Int. Ed.*, **2002**, *41*, 1290-1309; d) W. A. Herrmann and C. Köcher, *Angew. Chem. Int. Ed.*, **1997**, *36,* 2162-2187; e) N. Fröhlich, U. Pidun, M. Stahl and G. Frenking, *Organometallics*, **1997**, *16*, 442-448; f) H. Jacobsen, A. Correa, A. Poater, C. Costabile, L. Cavallo, *Coordination Chem. Rev.*, **2009**, *253*, 687-703.

[5] D. Bourissou, O. Guerret, F. P. Gabbaï and G. Bertrand, *Chem. Rev.*, **2000**, *100*, 39-92.

[6] H. M. Lee, C.-C. Lee and P.-Y. Cheng, *Curr. Org. Chem.*, **2007**, *11*, 1491-1524.

[7] a) S. C. Zinner, W. A. Herrmann, F. E. Kuhn, *J. Organomet. Chem.* **2008**, *693*, 1543-1546; b) M. C. Perry, K. Burgess, *Tetrahedron: Asymmetry* **2003**, *14*, 951-961; c) V. César, S. B. Laponnaz, L. H. Gade, *Chem. Soc. Rev.* **2004**, *33*, 619-636; d) F. Glorius, *N-Heterocyclic Carbenes in Transition Metal Catalysis*. Springer: Berlin, **2007**.

[8] H. Seo, B. Y. Kim, J. H. Lee, H. J. Park, H. U. Son, Y. K. Chung, *Organometallics* **2003**, *22*, 4783-4791.

[9] R. Hodgson, R. E. Douthwaite, *J. Organomet. Chem.* **2005**, *690*, 5822-5831.

[10] W. A. Herrmann, D. Baskakov, E. Herdtweck, S. D. Hoffmann, T. Bunlaksananusorn, F. Rampf, L. Rodefeld, *Organometallics* **2006**, *25*, 2449-2456.

[11] G. Dyson, J.-C. Frison, A. C. Whitwood, R. E. Douthwaite, *Dalton Trans*. **2009**, 7141-7151.

[12] R. Jiang, X. Sun, W. He, H. Chen, Y. Kuang, *Appl. Organometal. Chem*. **2009**, *23*, 179-182.

[13] D. Huynh-Khanh, H. Ibrahim, M. Toffano, G. Vo-Thanh, *Tetrahedron: Asymmetry*, **2010**, *21*, 1542-1548.

[14] a) J. Ackermann, M. Matthes, C. Tamm, *Helv. Chim. Acta* **1990**, *73*, 122-132; b) C. M. Acevedo,E. F. Kogut, M. A. Lipton, *Tetrahedron* **2001**, *57*, 6353-6359.

[15] a) G. D. Williams, C. E. Wade, G. J. Clarkson, M. Wills, *Tetrahedron: Asymmetry* **2007**, *18*, 664-670; b) M. B. Smith, B. T. Dembofsky, Y. C. Son, *J. Org. Chem.* **1994**, *59*, 1719-1725.

[16] a) R. Tamion, F. Marsais, P. Ribereau, G. Queguiner, D. Abenhaim, A. Loupy, L. Munnier, *Tetrahedron: Asymmetry,* 1**993**, *4*, 1879-1890; b) S. Kuma, U. Ramachandra, *Tetrahedron,* **2005**, *61*, 4141-4148.

[17] a) G. Vo-Thanh, B. Pégot, A. Loupy, *Eur. J. Org. Chem*., **2004**, *5*, 1112-1116; b) R. S. Varma, V. V. Namboodiri, *Chem. Commun*., **2001**, 643-644; c) R. S. Varma, V. V. Namboodiri, *Pure Appl. Chem*., **2001**, *73*, 1309-1313; d) B. M. Khadilkar, G. L. Rebeiro, *Org. Proc. Res. & Develop.,* **2002**, *6*, 826-828; e) M. C. Law, K. Y. Wong, T. H. Chan, *Green Chem*., **2002**, *4***,** 328-330; f) R. S. Varma, V. V. Namboodiri, *Chem. Commun*., **2002**, 342-343; g) J. F. Dubreuil, M. H. Famelart, J. P. Bazureau, *Org. Proc. Res. & Develop.,* **2002**, *6*, 374-378; h) R. S.Varma, V. V. Namboodiri, *Tetrahedron Lett*., **2002**, *43*, 5381-5383; i) M. Deetlefs, K. . Seddon, *Green Chem*., **2003**, *5*, 181-186; j) J. M. Lévêque , J. Estager, M. Draye, L. Boffa, G. Cravotto, W. Bonrath, *Monatshe. Chem*., **2007**, *138*, 1103-1113; k) G. Cravotto, E. Calcio-Gaudino, L. Boffa, J.M. Lévêque, J. Estager, W. Bonrath, *Molecules,* **2008**, *13*, 149-156; l) A. Aupoix, B. Pégot, G. Vo-Thanh, *Tetrahedron*, **2010**, *66*, 1352-1356.

[18] For recent reviews on microwave chemistry, see: a) A. De la Hoz, A. Diaz-Ortis, A. Moreno, F. Langa, *Eur. J. Org. Chem*., **2000**, *22*, 3659-3673; b) M. Alterman, A. Hallberg, *J. Org. Chem*., **2000**, *65*, 7984-7989; c) L. Perreux, A. Loupy, *Tetrahedron,* **2001**, *57*, 9199-9223, d) P. Lidström, J. Tierney, P. Wathey, J. Westman, *Tetrahedron,* **2001**, *57*, 9225-9283; e) B. L. Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*, **2002,** CEM Publishing, Matthews, NC. f) A. Loupy; *Microwaves in Organic Synthesis*, **2006**, Wiley-VCH, Weinheim. g) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, **2005**, Wiley-VCH, Weinheim; (h) V. Polshettiwar, R. S. Varma, *Acc. of Chem. Res*., **2008**, *41*, 629-639.

[19] *a*) M. Bressan, N. d'Allessandro, L. Liberatore, A. Morvillo, *Coord. Chem. Rev.*, **1999**, *185-186*, 385-402; *b*) S. Inoue, K. Nomura, S. Hashiguchi, R. Noyori, Y. Izawa, *Chem. Lett.*, **1997**, 957-958.

[20] CEM Discover S class reactor, see www.cem.com