

## New Mono-Quarternized Bis-*Cinchona* Alkaloid Ligands for Asymmetric Dihydroxylation of Olefins in Aqueous Medium: Unprecedented High Enantioselectivity and Recyclability

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**Abstract:** New mono-quaternized allyl bromide salts of bis-*Cinchona* alkaloid ligands, [(QD)<sub>2</sub>PHAL-Allyl]Br and [(QN)<sub>2</sub>PHAL-Allyl]Br, have been synthesized which can be converted into their highly water-soluble multihydroxylated derivatives under asymmetric dihydroxylation (AD) conditions and, thus, easily recovered by a simple extraction method after reaction and reused. These mono-quaternized ligands exhibited superior catalytic efficiency to their neutral counterparts such as (DHQD)<sub>2</sub>PHAL and (DHQ)<sub>2</sub>PHAL for the AD reactions of mono- and disubstituted styrenes under Upjohn conditions. Merely 0.1 mol % of osmium was enough to complete the reactions of mono- and disubstituted styrenes and, moreover, these ligands showed the highest enantioselectivities (e.g., for styrene, 97% *ee* with [(QD)<sub>2</sub>PHAL-Allyl]Br) among those ever achieved under Upjohn conditions.

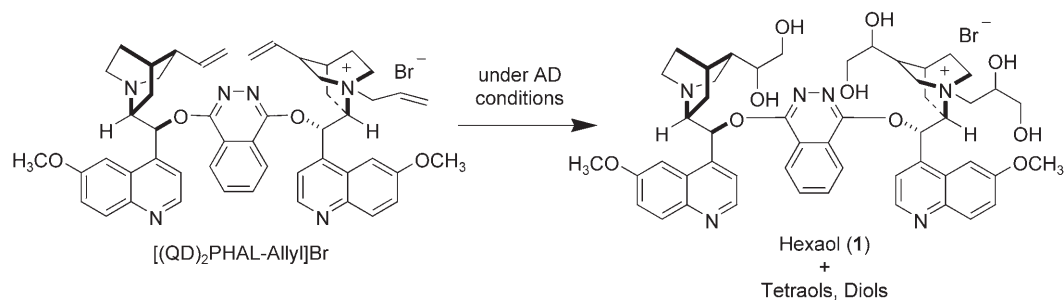
**Keywords:** aqueous phase catalysis; asymmetric dihydroxylation; catalyst recycling; mono-quaternized bis-*Cinchona* alkaloid ligands; unprecedented enantioselectivity

The international chemistry community is under increasing pressure to change current working practices and to find greener alternatives because of the increasingly stringent environmental regulations. This means that chemical manufacturers need to develop more environmentally sustainable processes that produce less waste and avoid, as much as possible, the use of toxic and/or hazardous reagents.

The Sharpless Os-catalyzed asymmetric dihydroxylation (AD) of olefins is undoubtedly one of the most

efficient methods of synthesizing chiral vicinal diols.<sup>[1]</sup> Although this reaction offers a number of processes that can be applied to the synthesis of chiral drugs, natural products and fine chemicals, etc., the cost, toxicity and contamination of products with osmium strongly restricts its use in industry. To address this issue, a great deal of effort has been directed at immobilizing the catalyst system, for example, by covalent attachment<sup>[2]</sup> of an alkaloid ligand to a soluble or insoluble support, by immobilizing the osmium catalyst itself, by the micro-encapsulation of OsO<sub>4</sub> in a dendrimer<sup>[3]</sup> or polymer matrix,<sup>[4]</sup> by use of various ion-exchange supports<sup>[5]</sup> or by fixation of osmium onto olefins covalently bound on silica<sup>[6]</sup> or on macroporous resins.<sup>[7]</sup> However, most examples of supported catalysts exhibit inferior catalytic properties to their homogeneous counterparts (1–5 mol % of osmium is usually needed to complete the reaction, whereas in homogeneous case 0.2 mol % of osmium is enough to complete most of the reactions) and require additional synthetic steps for their preparation that raises catalyst costs. Quite recently, an ionic liquid,<sup>[8]</sup> poly(ethylene glycol)<sup>[9]</sup> or fluorosolvents<sup>[10]</sup> have been used as reaction media as well as new immobilizing agents for the catalyst in AD reactions. The environmental impact of the use of ionic liquids, polyethylene glycol and fluorosolvents is, however, still unknown. Therefore, it would still be highly desirable to develop a more efficient and environmentally benign immobilization method for catalyst recycling.

We report herein a new catalyst recycling protocol for AD reactions using the new mono-quaternized bis-*Cinchona* alkaloid ligands, [(QD)<sub>2</sub>PHAL-Allyl]Br and [(QN)<sub>2</sub>PHAL-Allyl]Br, which are converted into their highly water-soluble multihydroxylated derivatives under AD conditions (Figure 1) and, thus, immobilized spontaneously in the aqueous phase after

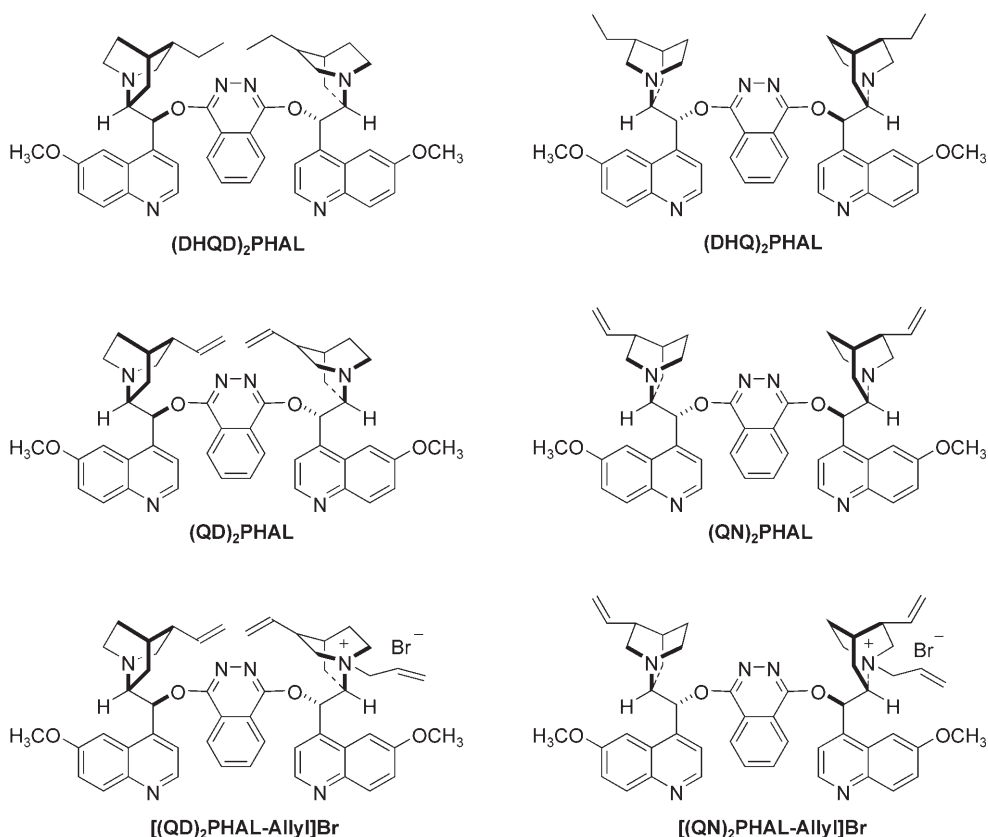


**Figure 1.** *In situ* generation of the highly water-soluble mutihydroxylated ligands such as **1** from  $[(QD)_2PHAL-Allyl]Br$  during AD reactions.

reaction. These ligands exhibited superior catalytic efficiency to their neutral counterparts such as  $(DHQD)_2PHAL$  and  $(DHQ)_2PHAL$  for the AD reactions of mono- and disubstituted styrene derivatives under Upjohn conditions.<sup>[11]</sup> Merely 0.1 mol% of osmium was enough to complete most reactions and, moreover, highly interestingly, the mono-quaternized ligands exhibited an unprecedented high enantioselectivity (e.g., for styrene, 97% *ee* with  $[(QD)_2PHAL-Allyl]Br$ ).

The mono-quaternized ligands,  $[(QD)_2PHAL-Allyl]Br$  and  $[(QN)_2PHAL-Allyl]Br$ , were simply prepared in moderate yield by the reaction of

$(QD)_2PHAL$ <sup>[12]</sup> and  $(QN)_2PHAL$ <sup>[12]</sup> with allyl bromide in THF, respectively. In order to compare the catalytic efficiency of the new ligands with the well-known neutral ligands,  $(DHQD)_2PHAL$ ,  $(DHQ)_2PHAL$ ,  $(QD)_2PHAL$  and  $(QN)_2PHAL$  (Figure 2), the AD reactions of styrene were initially carried out using 0.1 mol% of  $OsO_4$  under Upjohn conditions,<sup>[11]</sup> and the results are summarized in Table 1. The catalytic activity of the mono-quaternized ligands are comparable with the conventional neutral ligands. However, highly interestingly, the enantioselectivities of the mono-quaternized ligands,  $[(QD)_2PHAL-Allyl]Br$  and  $[(QN)_2PHAL-Allyl]Br$ ,



**Figure 2.** Chiral ligands used in this study.

**Table 1.** Asymmetric dihydroxylation of styrene.<sup>[a]</sup>

Entry	Ligand	Cooxidant	Time [h] <sup>[b]</sup>	Yield [%] <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	[(QD) <sub>2</sub> PHAL-Allyl]Br	NMO·H <sub>2</sub> O	20	93	97
2	[(QN) <sub>2</sub> PHAL-Allyl]Br	NMO·H <sub>2</sub> O	20	89	95
3	[(QD) <sub>2</sub> PHAL]	NMO·H <sub>2</sub> O	20	87	90
4	[(QN) <sub>2</sub> PHAL]	NMO·H <sub>2</sub> O	20	90	83
5	[(DHQD) <sub>2</sub> PHAL]	NMO·H <sub>2</sub> O	20	90	93
6	[(DHQN) <sub>2</sub> PHAL]	NMO·H <sub>2</sub> O	20	92	90

<sup>[a]</sup> All the reactions were carried out on a 3 mmol reaction scale of styrene using 0.1 mol % of OsO<sub>4</sub>, 2.5 mol % of ligand and 3.3 mmol of NMO·H<sub>2</sub>O in *t*-BuOH-H<sub>2</sub>O (v/v = 1 : 1, 30 mL) at 20 °C. Styrene was added using a syringe pump for 18 h.

<sup>[b]</sup> Reaction time includes the addition time (18 h) of olefin.

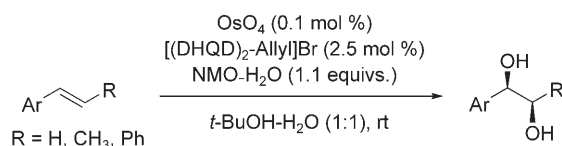
<sup>[c]</sup> Isolated yield.

<sup>[d]</sup> Determined by chiral HPLC.

were found to be higher (up to 97% *ee*) than those achieved with the conventional neutral ligands. To the best of our knowledge, this *ee* value is the highest one ever achieved with styrene under Upjohn conditions. In order to verify the versatility of this result, other mono- and disubstituted olefins were subjected to asymmetric dihydroxylation, and the results are summarized in Table 2. In all cases, the reactions were completed within 2 h after completion of adding olefin, affording the desired diols with higher *ees* than those obtained with the corresponding neutral ligands. One of the possible reasons for the improved enantioselectivity of the monoquaternized ligands might be attributed to highly polar hydroxy residues generated *in situ* during reaction which would greatly enhance the hydrophilic environment in the trioxo-Os(VIII) glycolate complex **2**. Under NMO condition, the

osmate ester **2** either can be hydrolyzed affording the free diol with high enantiomeric excess (enantioselective catalytic cycle) or can react with a second olefin, forming an Os(VI) bis-glycolate **3** which liberates a racemic diol by hydrolysis (non-enantioselective catalytic cycle).<sup>[13]</sup> However, the greatly enhanced hydrophilic environment in the trioxo-Os(VIII) glycolate **2** not only may accelerate glycolate hydrolysis, but also may result in the minimal concentration of hydrophobic olefins in the vicinity of the trioxo-Os(VIII) glycolate **2** and consequently in prevention of formation of Os(VI) bis-glycolate **3**.

Encouraged by the above-described results, we next performed catalyst recycling experiment as follows. When the reaction was complete, the product was extracted with hexane. The relative amounts of the chiral ligands [hexaol (**1**), tetraols and diols] dissolved

**Table 2.** Asymmetric dihydroxylation of olefins using [(QD)<sub>2</sub>PHAL-Allyl]Br.<sup>[a]</sup>

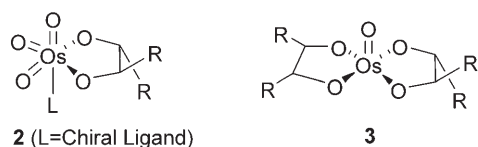
Entry	Substrate	Time [h] <sup>[b]</sup>	Yield [%] <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	styrene	20 h	88	97
2	<i>trans</i> -β-methylstyrene	20 h	92	97
3	4-bromostyrene	20 h	95	97
4	4-chlorostyrene	20 h	90	97
5	4-fluorostyrene	20 h	91	97
6	3-chlorostyrene	20 h	90	97
7	3-fluorostyrene	20 h	92	96
8	2-chlorostyrene	20 h	90	96
9	2-vinylnaphthalene	20 h	93	93

<sup>[a]</sup> All the reactions were carried out on a 3 mmol reaction scale of olefin using 0.1 mol % of OsO<sub>4</sub>, 2.5 mol % of [(QD)<sub>2</sub>PHAL-Allyl]Br and 3.3 mmol of NMO·H<sub>2</sub>O in *t*-BuOH-H<sub>2</sub>O (v/v = 1:1, 30 mL) at 20 °C. Olefins were added by a syringe pump for 18 h.

<sup>[b]</sup> Reaction time includes the addition time (18 h) of olefin.

<sup>[c]</sup> Isolated yield.

<sup>[d]</sup> Determined by chiral HPLC.



in the two layers were determined by LC-MS. As expected, >95 % of the ligand was immobilized in the aqueous phase and, thus, the aqueous layer was then recycled with a fresh batch of styrene and NMO without any addition of ligand (Figure 3). For example, when half the initial amount (0.05 mol %) of OsO<sub>4</sub> was added in each run to regenerate the reaction condition completely,<sup>[14]</sup> the recovered aqueous phase was reused for at least 5 times without any significant loss of activity and enantioselectivity (Table 3).

In summary, we have synthesized the new mono-quaternized bis-*Cinchona* alkaloid ligands, [(QD)<sub>2</sub>PHAL-Allyl]Br and [(QN)<sub>2</sub>PHAL-Allyl]Br, which are converted to the highly water-soluble hydroxylated derivatives such as **1** during reaction and, thus, easily recovered by a simple extraction method after reaction and reused. This new type of ligands exhibited superior catalytic efficiency to the conventional neutral ligands for the AD reactions of mono- and disubstituted styrene derivatives under Upjohn conditions. Merely 0.1 mol % of osmium was enough to complete most of reactions and, surprisingly, the mono-quaternized ligands showed an unprecedented high enantioselectivity (e.g., for styrene, 97 % *ee* with [(QD)<sub>2</sub>PHAL-Allyl]Br). Optimization of reaction

**Table 3.** Recycling experiments for AD reactions of styrene using (QD)<sub>2</sub>PHAL-allyl bromide salt.<sup>[a]</sup>

Run 1	Run 2	Run 3	Run 4	Run 5
93 %	92 %	94 %	90 %	92 %
97 % <i>ee</i>	95 % <i>ee</i>	95 % <i>ee</i>	95 % <i>ee</i>	95 % <i>ee</i>

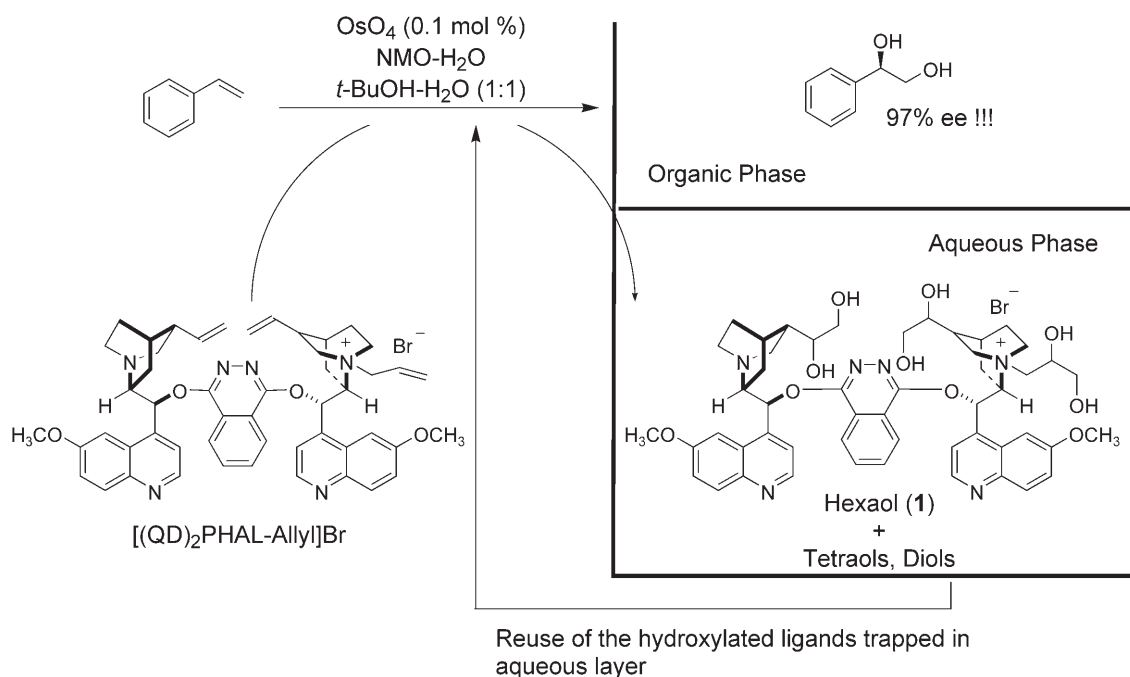
<sup>[a]</sup> The recycle experiments were carried out on a 3 mmol reaction scale of olefin using 0.1 mol % of OsO<sub>4</sub>, 2.5 mol % of [(QD)<sub>2</sub>PHAL-Allyl]Br and 3.3 mmol of NMO in *t*-BuOH-H<sub>2</sub>O (v/v=1:1, 30 mL) at 20 °C for 24 h. Styrene was added using a syringe pump for 18 h. From the second run, the reaction was carried out with aqueous phase recovered from the first run without further addition of [(QD)<sub>2</sub>PHAL-Allyl]Br. However, 0.05 mol % of OsO<sub>4</sub> was added in each run to regenerate reaction condition.

conditions, especially to minimize Os leaching into the organic layer, is currently underway by our group.

## Experimental Section

### Synthesis of [(QD)<sub>2</sub>PHAL-Allyl]Br

Allyl bromide (11.25 mL, 130 mmol) was added dropwise into a solution of (QD)<sub>2</sub>PHAL (20 g, 26 mmol) in EtOAc (800 mL) at 40 °C. The reaction mixture was stirred for 72 h. After completion of the reaction, the precipitate was filtered. The filtered solid was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) to give [(QD)<sub>2</sub>PHAL-Allyl]Br as a light yellow solid; yield: 11.2 g (48 %).



**Figure 3.**

### Synthesis of [(QN)<sub>2</sub>PHAL-Allyl]Br

Allyl bromide (11.25 mL, 130 mmol) was added dropwise into a solution of (QN)<sub>2</sub>PHAL (20 g, 26 mmol) in dry THF (700 mL) at 40 °C. The reaction mixture was further stirred for 72 h at the same temperature, and the solvent was removed under vacuum. The resulting residue was treated with 150 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with H<sub>2</sub>O twice. The organic layer was dried over anhydrous MgSO<sub>4</sub> and filtered. After concentration of the filtrate under vacuum, the resulting residue was purified by flash column chromatography (CHCl<sub>3</sub>/MeOH 9:1) to give [(QN)<sub>2</sub>PHAL-Allyl]Br as a light yellow solid; yield: 12.1 g (52 %).

### Typical Procedure for Asymmetric Dihydroxylation

A 100-mL flask was charged with *t*-BuOH-H<sub>2</sub>O (1:1, v/v, 30 mL), [(QD)<sub>2</sub>PHAL-Allyl]Br (67 mg, 0.075 mmol) and OsO<sub>4</sub> (72 µL, of 1.0 wt % of aqueous solution, 0.003 mmol, 0.1 mol %). After stirring for 15 min, NMO-H<sub>2</sub>O (*N*-methylmorpholine *N*-oxide monohydrate) (446 mg, 3.3 mmol, 1.1 equivs.) was added. Subsequently, styrene (344 µL, 3 mmol) was added by a syringe pump for 18 h and the reaction mixture was stirred at 20 °C. After completion of the reaction, the chiral diol and *N*-methylmorpholine produced during the reaction were successively extracted with hexane (1 × 20 mL) and hexane/THF (3 × 30 mL) from the reaction mixture. The recovered aqueous phase was recycled to the next run. The combined organic layer was evaporated and the crude product was purified by flash column chromatography on silica (EtOAc/hexane 1:2) to give pure 1-phenyl-1,2-ethanediol as a white solid.

In the recycling experiment, OsO<sub>4</sub> (36 µL, of 1.0 wt % of aqueous solution, 0.0015 mmol, 0.05 mol %), 446 mg (3.3 mmol) of NMO-H<sub>2</sub>O and 15 mL of *t*-BuOH were added to the aqueous phase recovered from the above experiment. After stirring for 5 min, styrene (344 µL, 3 mmol) was added by a syringe pump for 18 h. After completion of the reaction, the reaction mixture was worked up as described above.

### Acknowledgements

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### References

- [1] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, 94, 2483–2547; P. Dupau, R. Epple,

A. A. Thomas, V. V. Fokin, K. B. Sharpless, *Adv. Synth. Catal.* **2002**, 344, 412–433.

- [2] For reviews: a) C. E. Song, S.-g. Lee, *Chem. Rev.* **2002**, 102, 3495–3524; b) Q.-H. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, 102, 3385–3466.
- [3] W.-J. Tang, N.-F. Yang, B. Yi, G.-J. Deng, Y.-Y. Huang, Q.-H. Fan, *Chem. Commun.* **2004**, 1378–1379.
- [4] a) S. Nagayama, M. Endo, S. Kobayashi, *J. Org. Chem.* **1998**, 63, 6094–6905; b) S. Kobayashi, M. Endo, S. Nagayama, *J. Am. Chem. Soc.* **1999**, 121, 11229–11230; c) S. Kobayashi, T. Ishida, R. Akiyama, *Org. Lett.* **2001**, 3, 2649–2652.
- [5] a) B. M. Choudary, N. S. Chowdari, M. L. Kantam, K. V. Raghavan, *J. Am. Chem. Soc.* **2001**, 123, 9220–9221; b) B. M. Choudary, N. S. Chowdari, K. Jyothi, M. L. Kantam, *J. Am. Chem. Soc.* **2002**, 124, 5341–5349.
- [6] a) A. Severeys, D. E. De Vos, L. Fiermans, F. Verpoort, P. J. Grobet, P. A. Jacobs, *Angew. Chem. Int. Ed.* **2001**, 40, 586–589; b) A. Severeys, D. E. De Vos, P. A. Jacobs, *Green Chem.* **2002**, 4, 380–384.
- [7] a) J. W. Yang, H. Han, E. J. Roh, S.-g. Lee, C. E. Song, *Org. Lett.* **2002**, 4, 4685–4688; b) K. J. Kim, H. Y. Choi, S. H. Hwang, I. S. Park, E. K. Kwueon, D. S. Choi, C. E. Song, *Chem. Commun.* **2005**, 3337–3339; c) Y. S. Park, C. H. Jo, H. Y. Choi, E. K. Kwon, C. E. Song, *Bull. Korean Chem. Soc.* **2004**, 25, 1671–1675; d) C. H. Jo, S.-H. Han, J. W. Yang, E. J. Roh, U.-S. Shin, C. E. Song, *Chem. Commun.* **2003**, 1312–1313.
- [8] a) C. E. Song, D.-u. Jung, E. J. Roh, S.-g. Lee, D. Y. Chi, *Chem. Commun.* **2002**, 3038–3039; b) L. C. Branco, C. A. M. Afonso, *Chem. Commun.* **2002**, 3036–3037; c) L. C. Branco, C. A. M. Afonso, *J. Org. Chem.* **2004**, 69, 4381–4389; d) L. C. Branco, A. Servanovic, M. N. da Ponte, C. A. M. Afonso, *Chem. Commun.* **2005**, 107–109; e) Q. Yao, *Org. Lett.* **2002**, 4, 2197–2199; f) R. Yanada, Y. Takemoto, *Tetrahedron Lett.* **2002**, 43, 6849–6851.
- [9] S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana, N. R. Reddy, *Chem. Commun.* **2003**, 1716–1717.
- [10] Y. Huang, W.-D. Meng, F.-L. Qing, *Tetrahedron Lett.* **2004**, 45, 1965–1968.
- [11] V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, 23, 1973–1976.
- [12] C. E. Song, J. W. Yang, H. J. Ha, S.-g. Lee, *Tetrahedron: Asymmetry* **1996**, 7, 645–648.
- [13] J. S. M. Wai, I. Marko, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, 111, 1123–1125.
- [14] According to ICP analysis, ca. half the amount of Os used initially was leached into the product phase after the first run. Thus, to regenerate the reaction conditions completely, half the initial amount (0.05 mol %) of OsO<sub>4</sub> was added in each run.