Asymmetric Hydrogenation

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Asymmetric Hydrogenation of Quinolines and Isoquinolines Activated by Chloroformates**

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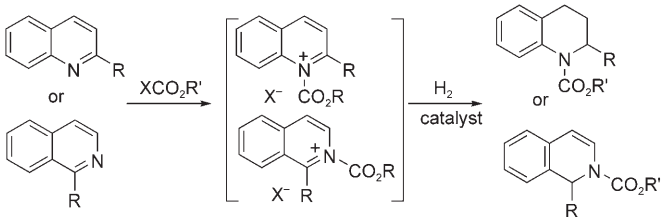
Despite significant progress in the area of asymmetric hydrogenation,[1] the enantioselective hydrogenation of aromatic and heteroaromatic compounds still remains a major challenge. Only a few examples with moderate enantioselectivity, which rely on unique catalyst systems and suffer from a limited scope of suitable substrates, have been described so far.[2] There are several reasons that might explain this situation. First, heteroaromatic compounds have a resonance stability that might impede enantioselective reduction with hydrogen.[3] Second, heteroaromatic compounds containing nitrogen and sulfur atoms may poison the catalyst. Third, little attention has been directed to these challenging substrates relative to alkenes, ketones, and imines. The low activity of aromatic compounds may be the main reason. In spite of these difficulties, the search for an effective asymmetric hydrogenation of heteroaromatic compounds continues because of the usefulness and importance of a method for the preparation of optically active heteroaromatic compounds.

Recently, we developed the first asymmetric hydrogenation of quinolines using [{IrCl(cod)}$_2$]/MeO-biphep/I$_2$ (cod = 1,5-cyclooctadiene; MeO-biphep = (2,2′-dimethoxybiphenyl-6,6′-diyl)bis(diphenylphosphine) as the catalyst system.[2f,g] It was found that the substrate scope was limited to quinoline derivatives and that the hydrogenation reaction cannot proceed for isoquinolines under standard conditions. As tetrahydroquinolines and tetrahydroisoquinolines are important structural units in naturally occurring alkaloids and biologically active compounds,[4] we are interested in exploring a general strategy for the asymmetric hydrogenation of aromatic compounds containing nitrogen. By analysis of the possible mechanism of the reported hydrogenation of aromatic compounds, we envisioned that the key factor for such reactions is to find a way to activate the substrate, and we selected chloroformates as the activating reagent[5] for the following reasons: 1) the aromaticity should be partially destroyed by the formation of quinolinium and isoquinolinium salts; 2) bonding of the activating reagent to the N atom may avoid poisoning of the catalyst; and 3) the attached CO_2R group is probably important for coordination between substrate and catalyst, and thus is beneficial to the control of enantioselectivity. Herein, we present our preliminary results on the asymmetric hydrogenation of quinolines and isoquinolines by this strategy (Scheme 1).



Scheme 1. Hydrogenation of quinolines and isoquinolines.

In our previous research work, iodine was necessary for full conversion and high enantioselectivity. Without iodine, the reaction only proceeded with very low conversion (< 5%).[2f] Herein, we tried to hydrogenate 2-methylquinoline (**1a**) in the absence of iodine using [{IrCl(cod)}$_2$]/*rac*-MeO-biphep as the catalyst and benzyl chloroformate as the activating reagent. When the reaction was performed in toluene under hydrogen (600 psi) at room temperature, only

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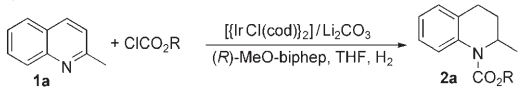
moderate conversion (55%) into 2-methyl-3,4-dihydro-2*H*-quinolin-1-carboxylic acid benzyl ester (**2a**) was obtained. Analysis of the mechanism and the experimental result indicated that the hydrogen chloride produced might block the reaction by the formation of the hydrogen chloride salt of quinoline. Therefore, the addition of base to neutralize hydrogen chloride is necessary for full conversion. A survey of bases and solvents revealed that organic bases, such as Et_3N and iPr_2NEt, are ineffective because of their strong coordinative ability. When using Li_2CO_3 as a base, the reaction in THF could proceed completely to give the desired product **2a**.

The effects of various activating reagents on enantioselectivity and conversion were examined with (*R*)-MeO-biphep (1 mol%) as the chiral ligand. As shown in Table 1

Table 1: Optimization of the reaction conditions for hydrogenation of 2-methylquinoline **1a**.[a]



Entry	Activator	*T* [°C]	H_2 [psi]	Conversion [%][b]	*ee* [%][c] (configuration)
1	$ClCO_2Bn$	25	600	>95	82 (*R*)
2	$ClCO_2Me$	25	600	>95	83 (*R*)
3	$ClCO_2Et$	25	600	>95	83 (*R*)
4	$ClCO_2Ph$	25	600	>95	82 (*R*)
5	ClCOPh	25	600	<5	–
6	$BrCOCH_3$	25	600	<5	–
7	Ac_2O	25	600	<5	–
8[d]	$ClCO_2Bn$	25	600	17	−44 (*S*)
9	$ClCO_2Bn$	25	900	>95	82 (*R*)
10	$ClCO_2Bn$	25	300	69	82 (*R*)
11	$ClCO_2Bn$	3	600	47	83 (*R*)
12	$ClCO_2Bn$	50	600	>95	81 (*R*)

[a] See the Experimental Section for details. [b] Determined by ^1H NMR spectroscopic analysis. [c] Determined by HPLC with an AS-H column. [d] 4-Å molecular sieves (60 mg) were added.

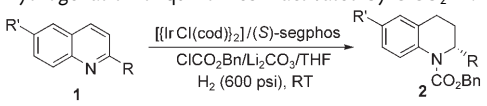
(entries 1–4), the hydrogenation of **1a** activated by other chloroformates (R = Me, Et, Ph) proceeds smoothly to afford the corresponding products in high conversion with similar enantioselectivity. Other reagents, such as ClCOPh, $BrCOCH_3$, and Ac_2O, were ineffective (Table 1, entries 5–7). Considering the easy deprotection of Cbz-protected groups (Cbz = carbobenzyloxy), we chose benzyl chloroformate as the activating reagent throughout the following reactions. The effect of the water produced in the reaction was also investigated. Unexpectedly, by adding 4-Å molecular sieves, the conversion decreased greatly and the configuration of the product was reversed (Table 1, entry 8), which demonstrates that water might be important for the conversion and enantioselectivity. The reason is unclear and awaits further study. A change in hydrogenation pressure and reaction temperature had no clear effect on enantioselectivity, but conversion was decreased under lower pressure and temperature (Table 1, entries 9–12).

To further improve the reaction, the amounts of Li_2CO_3 and the substrate concentration were investigated. Concentrations of Li_2CO_3 of 0.6–3.0 equivalents gave products of similar conversion and enantioselectivity. The substrate concentration had almost no effect on the conversion and enantioselectivity.

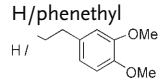
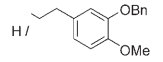
Other commercially available chiral ligands were also tested under the optimal conditions. It was shown that bisphosphine ligands with a biphenyl motif gave a higher enantioselectivity than those with binaphthyl structures: (5,5′-dichloro-6,6′-dimethoxybiphenyl-2,2′-bis(diphenylphosphino)1,1′-biphenyl (90% *ee*), (4,4′-bi-1,3-benzodioxole-5,5′-diyl)bis(diphenylphosphine) (segphos, 90% *ee*), (2,3,2′,3′-tetrahydro-5,5′-bis(1,4-benzodioxin)-6,6′-diyl)bis(diphenylphosphine) (synphos, 83% *ee*), (2,2′-(1,6-dioxahexano)biphenyl-6,6′-diyl)bis(diphenylphosphine) (C4-tunaphos, 84% *ee*), 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphine) (binap, 72% *ee*), 3,5-xylyl-binap (67% *ee*); other electron-rich bisphosphine ligands gave poor results (1,2-bis(2,5-dimethylphospholano)benzene (Me-duphos): <5% conversion; 2,3-*O*-isopropylidene-2,3-dihydroxy-l,4-bis(diphenylphosphanylbutane (diop): 15% conversion, 39% *ee*); monophosphine ligand 2-diphenylphosphanyl-2′-methoxy-1,1′-binaphthalene (mop) and N,P ligands gave less than 10% conversion. Thus, the best ligand for the reaction is segphos.

A variety of substituted quinoline derivatives were hydrogenated under the optimized conditions with the Ir/(*S*)-segphos/Li_2CO_3/$ClCO_2Bn$/THF catalyst system. Several 2-alkyl-substituted quinolines were hydrogenated with high enantioselectivities regardless of the length of the chain (Table 2, entries 1–5). The reaction is not very sensitive to the substituent at the 6-position (Table 2, entries 6–8). Lower conversion and enantioselectivity were obtained with 2-phenyl-substituted quinoline (Table 2, entry 9), which is probably attributable to the steric bulkiness of the phenyl

Table 2: Hydrogenation of quinolines **1** activated by $ClCO_2Bn$.[a]



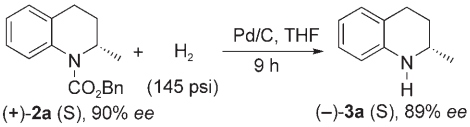
1 2

Entry	**1/2**	R′/R	Yield [%][b]	*ee* [%][c] (configuration)[d]
1	**a**	H/Me	90	90 (*S*)
2	**b**	H/Et	85	90 (*S*)
3	**c**	H/*n*Pr	80	90 (*S*)
4	**d**	H/*n*Bu	88	89 (*S*)
5	**e**	H/*n*-pentyl	91	89 (*S*)
6	**f**	Me/Me	90	89 (*S*)
7	**g**	F/Me	83	89 (*S*)
8	**h**	MeO/Me	92	90 (*S*)[e]
9	**i**	H/Ph	41	80 (*R*)
10	**j**	H/phenethyl	86	90 (*S*)
11	**k**		80	90 (*S*)
12	**l**		88	88 (*S*)

[a] See the Experimental Section for details. [b] Yields of the isolated products based on quinolines. [c] Determined by HPLC analysis with chiral column. [d] Determined by the described procedure; other products determined by analogy with **2a** or comparison with reported data. [e] Reaction at 50°C.

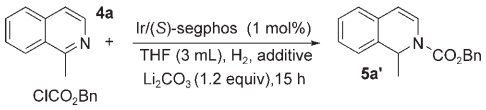
group. 2-Arenethyl-substituted quinolines also gave good asymmetric induction (Table 2, entries 10–12).

The absolute configuration of the quinoline hydrogenation product was determined by the following chemical transformation. Compound (+)-**2a** was converted iinto the known (−)-**3a**[2f] with H_2/Pd/C in THF [Eq. (1)]. On the basis of the sign of optical rotation and absolute configuration (*S*) of (−)-**3a**, (+)-**2a** was assigned as *S*. The configurations of the other compounds are assumed by analogy with **2a**.



(1)

Gratifyingly, we found that the reaction worked well when the substrate was extended from quinolines to isoquinolines. In the case of 1-methylisoquinoline (**4a**), only the partially hydrogenated product dihydroisoquinoline (**5a′**) was obtained in 87% yield with 76% *ee* under the above conditions [Eq. (2)]. The reaction did not occur without benzyl chloroformate.



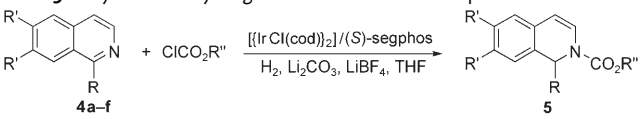
(2)

To improve the enantioselectivity, the effects of solvent, base, activating reagent, and chiral ligand were investigated. The results indicated that THF/Li_2CO_3/$ClCO_2Bn$/segphos is the best combination in our screened conditions. An equivalent amount of LiCl was produced during this reaction, and hence the effect of lithium salts with different counterions on the enantioselectivity was investigated.[6] Lithium salts influenced the reaction: when 1.0 equivalent of $LiSO_3CF_3$ or $LiBF_4$ was used, the *ee* increased from 76 to 83% (see the Supporting Information).

The results for the reaction of some isoquinolines under optimal conditions are summarized in Table 3. 1-Alkyl-substituted isoquinolines were hydrogenated with moderate to good enantioselectivities regardless of the length of the chain (Table 3, entries 1–4, 8, and 9). For 1-phenylisoquinoline, 82% *ee* (**5e**, $ClCO_2Me$ as the activating reagent) and 83% *ee* (**5e′**, $ClCO_2Bn$ as the activating reagent) can be obtained, but the conversions are moderate, which might be a result of the steric effect of the bulky phenyl group. A low enantioselectivity of 10% *ee* was obtained for 1-benzylisoquinoline (Table 3, entry 5); the reason is not yet clear. Notably, to the best of our knowledge, this is the first example of the asymmetric hydrogenation of isoquinoline derivatives.

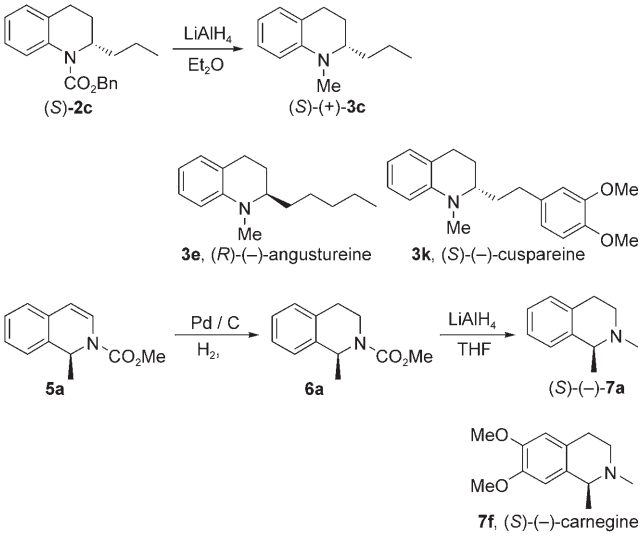
The application of the present method to the enantioselective synthesis of several biologically active compounds proved its utility. For example, the reduction of **2c**, **2e**, and **2k** with $LiAlH_4$ in Et_2O gives the N-methylation[7] products in high yield (Scheme 2), which are the naturally occurring tetrahydroquinoline alkaloids **3c**,[8] angustureine (**3e**),[4c,8] and cuspareine (**3k**),[4e,8] respectively. Similarly, the naturally occurring tetrahydroisoquinoline alkaloids **7a**[4d,9] and carnegine (**7f**)[10] were also synthesized in three steps starting from isoquinolines.

Table 3: Asymmetric hydrogenation of activated isoquinolines **4**.[a]



Entry	R′/R	R″	Product	Yield [%][b]	*ee* [%][c] (configuration)[d]
1	H/Me	Me	**5a**	85	80 (*S*)
2	H/Me	Bn	**5a′**	87	83 (*S*)
3	H/Et	Me	**5b**	85	62 (*S*)[e]
4	H/*n*Bu	Me	**5c**	87	60 (*S*)[e]
5	H/Bn	Me	**5d**	83	10 (*S*)[e]
6	H/Ph	Me	**5e**	57	82 (*S*)
7	H/Ph	Bn	**5e′**	49	83 (*S*)
8	MeO/Me	Me	**5f**	57	63 (*S*)
9	MeO/Me	Bn	**5f′**	46	65 (*S*)[f]

[a] See the Experimental Section for details. [b] Yields of the isolated products based on isoquinolines. [c] Determined by HPLC analysis with a chiral column. [d] Determined by comparison of rotation sign with reported data or by analogy. [e] Determined by conversion into tetrahydroisoquinoline; see the Supporting Information for details. [f] Without $LiBF_4$.



Scheme 2. Application of the enantioselective hydrogenation of quinolines and isoquinolines in the synthesis of naturally occuring alkaloids.

In conclusion, a new strategy for the asymmetric hydrogenation of quinolines and isoquinolines has been developed by using chloroformates as activating agents, thus providing a new avenue for the hydrogenation of heteroaromatic compounds. This method has been successfully applied to the asymmetric synthesis of several naturally occurring alkaloids. Further work will be directed toward the development of the hydrogenation of other heteroaromatic compounds.

Experimental Section

In a glove box, THF (3 mL) was added to a mixture of [{IrCl(cod)}$_2$] (3.4 mg, 0.005 mmol) and (*S*)-segphos (6.8 mg, 0.011 mmol). Similarly, THF (2 mL) was added to a mixture of Li_2CO_3 (79 mg, 1.2 mmol) and substrate **1a** (1.0 mmol). Both mixtures were stirred at room temperature for 10 min, then benzyl chloroformate (1.1 mmol) was added to the solution of Li_2CO_3 and substrate. Next, the in situ prepared catalyst solution was added with a syringe. The hydrogenation was performed at room temperature under H_2 (600 psi) for 12–15 h. After carefully releasing the hydrogen, the reaction mixture was diluted with diethyl ether (20 mL), and saturated sodium carbonate aqueous solution (10 mL) was added. After stirring for 15 min, the aqueous layer was extracted with diethyl ether (3 × 15 mL), dried over sodium sulfate, and concentrated to afford the crude product **2a**. Clean up was performed on a column of silica gel eluted with hexane/EtOAc (10:1) to give the pure product. The enantiomeric excesses were determined by chiral HPLC with AS-H columns. Yield 90%, 90% *ee*, $[\alpha]_D^8 = +105.2$ ($c = 0.98$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.18$ (d, $J = 6.4$ Hz, 3H), 1.52 (m, 1H), 2.22 (m, 1H), 2.66 (m, 2H), 4.65 (m, 1H), 5.16, 5.29 (AB system, $J = 12.6$ Hz, 2H), 7.02–7.15 (m, 3H), 7.31–7.37 (m, 5H), 7.56 ppm (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.2$, 25.8, 31.7, 50.3, 68.0, 125.0, 126.1, 126.7, 128.4, 128.5, 128.6, 129.2, 132.5, 137.2, 155.3 ppm; HRMS for $C_{18}H_{20}NO_2$ [*M*+1]: *m*/*z* calcd 282.1489, found 282.1476; HPLC (AS-H, eluent: hexane/*i*PrOH 95:5, detector: 254 nm, flow rate: 0.5 mL min^{-1}): (*S*) $t_1 = 5.5$ min, (*R*) $t_2 = 6.2$ min.

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[1] For reviews, see: a) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, Weinheim, **1999**; b) *Asymmetric Catalysis in Organic Synthesis* (Ed.: R. Noyori), Wiley, New York, **1994**; c) *Comprehensive Asymmetric Catalysis*, *Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] For some examples of asymmetric hydrogenation of heteroaromatic compounds, see: a) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614–7615; b) C. Bianchini, P. Barbaro, G. Scapacci, *J. Organomet. Chem.* **2001**, *621*, 26–33; c) M. Studer, C. Wedemeyer-Exl, F. Spindler, H. U. Blaser, *Monatsh. Chem.* **2000**, *131*, 1335–1343; d) S. Murata, T. Sugimoto, S. Matsuura, *Heterocycles* **1987**, *26*, 763–766; e) J. P. Henschke, M. J. Burk, C. G. Malan, D. Herzberg, J. A. Peterson, A. J. Wildsmith, C. J. Cobley, G. Casy, *Adv. Synth. Catal.* **2003**, *345*, 300–307; f) W. B. Wang, S. M. Lu, P. Y. Yang, X. W. Han, Y. G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537; g) S. M. Lu, X. W. Han, Y. G. Zhou, *Adv. Synth. Catal.* **2004**, *346*, 909–912; h) R. Kuwano, K. Kaneda, T. Ito, K. Sato, T. Kurokawa, Y. Ito, *Org. Lett.* **2004**, *6*, 2213–2215; i) C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti, M. Graziani, *Organometallics* **1998**, *17*, 3308–3310; j) C. J. Cobley, J. P. Henschke, *Adv. Synth. Catal.* **2003**, *345*, 195–201; k) L. J. Xu, K. H. Lam, J. X. Ji, Q.-H. Fan, W.-H. Lo, A. S. C. Chan, *Chem. Commun.* **2005**, 1390–1393; l) S. A. Raynor, J. M. Thomas, R. Raja, B. F. G. Johnson, R. G. Belle, M. D. Mantle, *Chem. Commun.* **2002**, 1925–1926; m) H. U. Blaser, H. Hornig, M. Studer, C. Wedemeyer-Exl, *J. Mol. Catal. A* **1999**, *139*, 253–257; for efficient chiral-auxiliary-based hydrogenation reactions, see: n) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann. *Angew. Chem.* **2004**, *116*, 2910–2913; *Angew. Chem. Int. Ed.* **2004**, *43*, 2850–2852; o) B. Scheiper, F. Glorius, A. Leitner, A. Furster, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11960–11965. During preparation of this manuscript, the Ir-catalyzed asymmetric hydrogenation of *N*-iminopyridinium ylides with high enantioselectivity was reported: p) C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966–8967.

[3] C. W. Bird, *Tetrahedron* **1992**, *48*, 335–340.

[4] a) J. D. Keay in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 579–601; b) *Comprehensive Natural Products Chemistry*, *Vols. 1–9* (Eds.: D. H. R. Barton, K. Nakanishi, O. Meth-Cohn), Elsevier, Oxford, **1999**; c) I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, *Phytochemistry* **1999**, *51*, 1167–1169; d) J. H. Rokotoson, N. Fabre, I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, *Planta Med.* **1998**, *64*, 760–762; e) P. J. Houghton, T. Z. Woldemariam, Y. Watanabe, M. Yates, *Planta Med.* **1999**, *65*, 250–254; f) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370.

[5] For some recent reactions based on activation by chloroformates, see: a) S. H. Lee, Y. S. Park, M. H. Nam, C. M. Yoon, *Org. Biomol. Chem.* **2004**, *2*, 2170–2172; b) C. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2003**, *125*, 6360–6361; c) E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 11808–11809; d) F. Amiot, L. Cointeaux, E. J. Silve, A. Alexakis, *Tetrahedron* **2004**, *60*, 8221–8231, and references therein.

[6] For reviews on the additive effect, see: a) E. M. Vogl, H. Groger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 1672–1680; *Angew. Chem. Int. Ed.* **1999**, *38*, 1570–1577; b) K. Fagnou, M. Lautens, *Angew. Chem.* **2002**, *114*, 26–29; *Angew. Chem. Int. Ed.* **2002**, *41*, 26–47.

[7] a) A. Alexakis, F. Amiot, *Tetrahedron: Asymmetry* **2002**, *13*, 2117–2122; b) K. Soai, A. Ookawam, T. Kaba, K. Ogawa, *J. Am. Chem. Soc.* **1987**, *109*, 7111–7115; c) C. L. Gibson, *Tetrahedron: Asymmetry* **1999**, *10*, 1551–1561.

[8] I. Jacquemond-Collet, J. M. Bessiere, S. Hannedouche, C. Bertrand, I. Fouraste, C. Moulis, *Phytochem. Anal.* **2001**, *12*, 312–319.

[9] T. Shinohara, A. Takeda, J. Toda, T. Sano, *Chem. Pharm. Bull.* **1998**, *46*, 430–433.

[10] a) S. G. Pyne, P. Bloem, S. L. Chapman, C. E. Dixon, R. Griffith, *J. Org. Chem.* **1990**, *55*, 1086–1093; b) K. Ito, S. Akashi, B. Saito, T. Katsuki, *Synlett* **2003**, 1809–1812; c) T. S. Kaufman, *Tetrahedron: Asymmetry* **2004**, *15*, 1203–1237.

