JOC Article

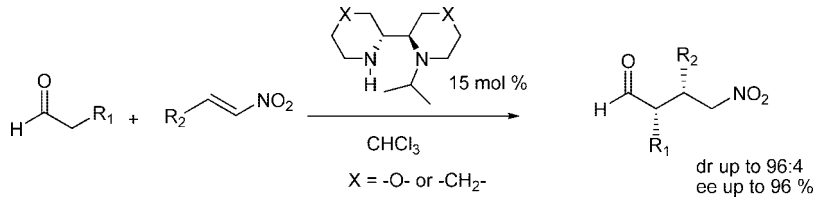
Enantioselective Organocatalytic Michael Addition of Aldehydes to β-Nitrostyrenes

Marju Laars, Kerti Ausmees, Merle Uudsemaa, Toomas Tamm, Tõnis Kanger,* and Margus Lopp

Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia

kanger@chemnet.ee

Received February 13, 2009



The utility of C_2-symmetric bipiperidine and bimorpholine derivatives as organocatalysts in the Michael addition of enamine intermediates formed from aldehydes to nitroolefins has been demonstrated. The best results were obtained when the reaction was run in the presence of (2*R*,2′*R*)-*N*-iPr-bipiperidine. The products were formed via an enamine intermediate with high diastereo- and enantioselectivity with relatively short reaction times.

Introduction

In recent years, organocatalysis has developed intensively, and a variety of carbon−carbon and carbon−heteroatom bond-forming reactions have been carried out by using organic molecules as catalysts.[1] Organocatalysis has become the third main branch in catalytic asymmetric synthesis together with enzymatic and organometallic catalysis.[2] The key to success lies in the nature of catalysts—they are generally insensitive to oxygen and moisture and, therefore, easy to handle. In addition, they are typically nontoxic and environmentally friendly. A variety of them are available from natural biological sources, and they are readily accessible in a wide range of quantities.

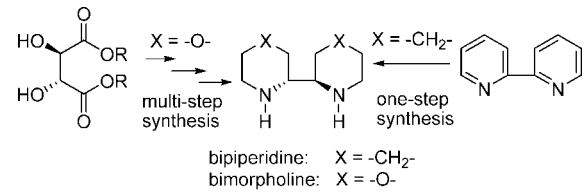


FIGURE 1. Principal scheme of the synthesis of catalysts.

Michael addition of nucleophiles formed from aldehydes to nitroolefins is one of the reactions that is catalyzed by simple chiral amines.[3] The nitro group is a versatile functionality due to its easy transformation into amine, nitrile oxide, ketone, carbocylic acid, hydrogen, etc.[4]

We have previously shown that bimorpholine derivatives catalyze Michael addition of enamine intermediates formed from aldehydes to nitroolefins with dr up to 95:5 and ee up to 90%.[5] Although the synthesis of chiral C_2-symmetric bimorpholine is simple,[6] seven synthetic steps make it laborious. The search for a comparable but inexpensive organocatalyst led us to 2,2′-bipiperidine (BP), which has a skeleton very similar to bimorpholine (Figure 1).

(1) For selected reviews on organocatalysis, see: (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) List, B. *Chem. Commun.* **2006**, 819. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (f) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (g) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed* **2007**, *46*, 1570. (h) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (i) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (j) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (k) Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (l) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638.

(2) MacMillan, D. W. *C Nature* **2008**, *455*, 304.

(3) For selected reviews and recent examples, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Almaşi, D.; Alonso, D. D.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (c) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722. (d) Wang, J.; Ma, A.; Ma, D. *Org. Lett.* **2008**, *10*, 5425. (e) Zhu, Q.; Cheng, L.; Lu, Y. *Chem. Commun.* **2008**, *47*, 6315. (f) Gao, P.; Wang, C.; Wu, Y.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2008**, *27*, 4563. (g) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539.

(4) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

(5) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559.

(6) (a) Kanger, T.; Laars, M.; Kriis, K.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synthesis* **2006**, 1853. (b) Sulzer-Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Synthesis* **2007**, 1729.

10.1021/jo900322h CCC: $40.75
Published on Web 04/09/2009

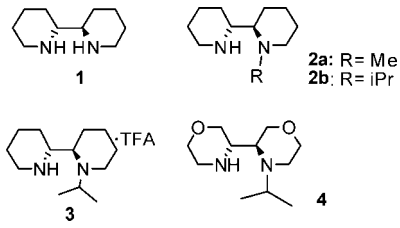


FIGURE 2. Organocatalysts **1**−**4**.

The only difference in the structures of these catalysts lies in the β-position of the bridging bond between two heterocycles: there is an oxygen atom in bimorpholine and a methylene group in bipiperidine in that position. However, this subtle change in the structure of the catalyst makes the synthesis of BP easy and straightforward from commercial 2,2′-dipyridyl in one step.[7]

Results and Discussion

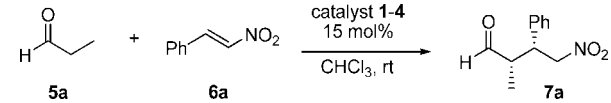
Herein, we present the results of Michael addition of aldehydes to nitroolefins catalyzed by (2*R*,2′*R*)-bipiperidine derivatives **1**−**3** and bimorpholine derivative **4** (Figure 2).

We have reported the preparation of *N*-iPr-BP **2b**.[8] The same methodology based on the aminal formation with formaldehyde and its reduction with sodium borohydride was applied to the synthesis of Me-BP **2a** in the present study. In order to establish the most reactive and selective catalyst, we studied 2,2′-bipiperidine **1** as well as its three derivatives (**2a**, **2b**, **3**) in the Michael addition of the enamine intermediates formed from propionaldehyde to *trans*-β-nitrostyrene (Table 1). Two *N*-monosubstituted piperidines—sterically less demanding methyl compound (**2a**) and bulkier isopropyl compound (**2b**)—were used and compared with *N*-iPr-bimorpholine **4**.

The reaction was conducted in the presence of 15 mol % of the catalyst in chloroform at room temperature. Methyl-substituted bipiperidine **2a** showed high reactivity but moderate selectivity, and the reaction was complete in 2 h (Table 1, entry 2). The bulkier iPr group at the nitrogen atom made the catalyst **2b** more selective and more reactive (Table 1, entry 3). It was found that catalyst **2b** was more efficient than the corresponding bimorpholine derivative **4** (Table 1, entry 5).[5] It is known that Brønsted acid additive has a substantial influence on the selectivity of Michael addition to nitrostyrenes.[9] Therefore, monosalt **3** was synthesized from trifluoroacetic acid and *N*-iPr-BP **2b**, and it turned out to be quite a selective catalyst, although a very unreactive one. The reaction time increased up to 9 days, affording the product with only a moderate yield (Table 1, entry 4). Thus, *N*-iPr-BP **2b** was the catalyst of choice for investigating the addition of different aldehydes to β-nitrostyrene (Table 2).

The smallest, less sterically hindered propionaldehyde was the most reactive substrate toward Michael addition, resulting in a product of a high yield in just 1 h at room temperature (Table 2, entry 1) with 91% ee. The high reactivity of the catalyst allowed us to investigate the reaction at lower temperature in an attempt to increase enantio- and diastereoselectivity.

TABLE 1. Michael Addition of Propionaldehyde 5a to *trans*-β-Nitrostyrene 6a Catalyzed by 2,2′-Bipiperidine Derivatives 1−3 and 3,3′-Bimorpholine 4



entry	catalyst	time	yield[a] (%)	dr (syn/anti)[b]	ee[b] (syn) (%)
1	BP (**1**)	32 h	45	60:40	70
2[c]	MeBP (**2a**)	2 h	94	76:24	−59
3	iPrBP (**2b**)	1 h	91	91:9	91
4	iPrBP TFA (**3**)	9 d	52	85:15	84
5[d]	iPrBM (**4**)	24 h	90	82:18	74

[a] Isolated yield after purification by column chromatography on silica gel. [b] Determined by chiral HPLC. Relative (syn) and absolute configurations determined by comparison with literature data. [c] (2*S*,2′*S*)-MeBP was used. [d] Reference 5.

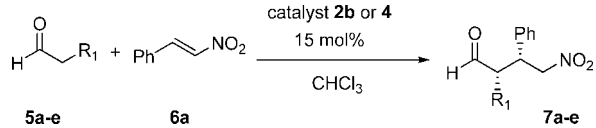
Indeed, the decrease of temperature to 0 °C increased enantioselectivity to 93% (Table 2, entry 2), and at −25 °C, we observed the highest ee, 96% (Table 2, entry 3). Furthermore, the diastereoselectivity of the reaction showed the same trend. Even though the catalyst loading was decreased to 5 mol % the product formed in 4 h with no change in enantioselectivity (Table 2, entry 4). The reactivity and stereoselectivity of the catalyst **2b** were much higher than in the case of the corresponding *N*-iPr-bimorpholine **4** (Table 2, entry 5). Michael addition with moderately sterically hindered aldehydes, like valeraldehyde (Table 2, entry 6) and isovaleraldehyde (Table 2, entry 8), proceeded with good ee and dr. Phenylacetaldehyde was quite reactive but afforded a product with low selectivity (dr 62:38 and ee 37%) (Table 2, entry 10). A clear dependence between reactivity and steric hindrance was observed—a bulky isobutyraldehyde afforded only 14% yield after a 7 day reaction with low enantioselectivity (Table 2, entry 11). There is a drastic difference in the reactivities of bimorpholine and bipiperidine catalysts. The reaction time needed to obtain a comparable conversion of the starting material was several times longer when using the morpholine derivative than the piperidine derivative (Table 2, entries 6, 7 and 8, 9). The enamine intermediate derived from BP is clearly more nucleophilic[10] and reacts faster. The scope of the carbonyl compounds in this reaction was limited to aldehydes. Cyclohexanone gave only traces of the product after 9 days when the reaction was run at an elevated temperature (60 °C).

To complete the study, we investigated several Michael acceptors in the reaction with propionaldehyde in the presence of a more reactive and selective catalyst **2b** (Table 3). The electron-donating methoxy group in the para position of the phenyl ring made the double bond less reactive (Table 3, entry 2). Nitrostyrene with the unsubstituted phenyl ring as well as the phenyl rings with electronegative substituents (4-Br and 4-CF_3O group) showed high reactivity in the presence of *N*-iPrBP and afforded products in a very high yield (>90%, Table 3, entries 1, 3, and 4). The substituents on the phenyl ring did not influence substantially enantio- or diastereoselectivity of the reaction: ee ranged from 88 to 91%, dr 84:16 to 91:9. The decrease in the temperature did not improve the stereoselectivity (Table 3, entry 5).

(7) Krumholz, P. *J. Am. Chem. Soc.* **1953**, *75*, 2163.
(8) Laars, M.; Kriis, K.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron: Asymmetry* **2008**, *19*, 641.
(9) (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966. (b) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624. (c) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (e) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758. (f) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.

(10) (a) Kempf, B; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9*, 2209. (b) Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584.

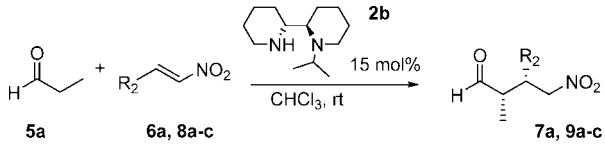
TABLE 2. Michael Addition of Aldehydes 5a−e to *trans*-β-Nitrostyrene



entry	aldehyde **5**	catalyst	conditions, yield[a]	dr[b] syn/anti	ee (syn)[b] (%)	product
1	**a**: R_1 = Me	**2b**	1 h, rt, 91%	91:9	91	**7a**
2	**a**: R_1 = Me	**2b**	2 h, 0 °C, 85%	90:10	93	**7a**
3	**a**: R_1 = Me	**2b**	23 h, −25 °C, 82%	94:6	96	**7a**
4[c]	**a**: R_1 = Me	**2b**	4 h, rt, 86%	92:8	91	**7a**
5[d]	**a**: R_1 = Me	**4**	24 h, rt, 90%	82:18	74	**7a**
6	**b**: R_1 = Pr	**2b**	8 h, rt, 96%	89:11	88	**7b**
7[d]	**b**: R_1 = Pr	**4**	3 d, rt, 88%	87:13	89	**7b**
8	**c**: R_1 = iPr	**2b**	8 h, rt, 85%	96:4	89	**7c**
9[d]	**c**: R_1 = iPr	**4**	8 d, rt, 68%	95:5	91	**7c**
10	**d**: R_1 = Ph	**2b**	3 h, rt, 76%	62:38	37	**7d**
11	**e**: R_1 = Me, Me	**2b**	7 d, rt, 14%		41	**7e**

[a] Isolated yield after purification by column chromatography on silica gel. [b] Determined by chiral HPLC. Relative (syn) and absolute configurations determined by comparison with literature data. [c] 5 mol % of the catalyst was used. [d] Reference 5.

TABLE 3. Michael Addition of Propionaldehyde 5a to Nitroolefins Catalyzed by *N*-iPr-BP 2b



entry	R_2	time (h)	yield[a] (%)	dr,[b] syn/anti	ee (syn)[b] (%)	product
1	Ph	1	91	91:9	91	**7a**
2	4-MeOPh	6	82	87:13	88	**9a**
3	4-BrPh	1	99	87:13	90	**9b**
4	4-CF_3OPh	1	90	84:16	89	**9c**
5[c]	4-CF_3OPh	30	78	87:13	89	**9c**

[a] Isolated yield after purification by column chromatography on silica gel. [b] Determined by chiral HPLC. Relative (syn) and absolute configurations determined by comparison with literature data. [c] Reaction temperature −20 °C.

The stereochemical outcome of Michael addition to nitrostyrenes can be rationalized empirically[11] or by theoretical calculations.[12] According to Seebach's topological rule,[13] a preferential synclinal transition state leads to a syn product. We have previously shown that the conformation of the catalyst and reaction intermediates strongly influenced the stereoselectivity of the aldol reaction.[14]

Here, the conformational analysis of enamine derived from *N*-iPr-BP and propionaldehyde in $CHCl_3$ was carried out by DFT calculations. It was found that the lowest energy conformer has 91% Boltzmann probability. In this conformation both piperidine rings are in the chair conformation and the central C−C−bond is in equatorial relation to both rings (Figure 3).

Nitrogen atoms are located opposite to each other (N−C−C−N dihedral angle near 180°), and enamine is in an anti conformation (double bond is oriented away from iPr-substituted piperidine ring). *Si*-face of the enamine is efficiently shielded by the *N*-substituted piperidine ring and the nucleophilic attack comes preferentially from the *Re*-face of enamine. *Re*-face of the Michael acceptor is preferable due to the electrostatic interaction between the nitrogen atoms of nitro the group and the piperidine ring leading to a syn product with (2*S*,3*R*) absolute configuration (Figure 4).

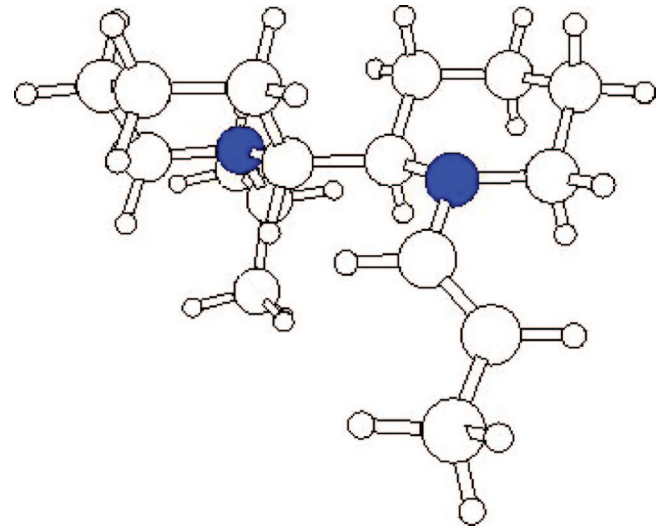


FIGURE 3. Calculated conformation of enamine intermediate derived from *N*-iPr-BP and propionaldehyde.

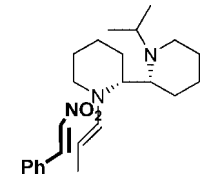


FIGURE 4. Proposed transition state.

Conclusions

We have shown that iPr-bipiperidine is a selective and efficient catalyst for Michael addition of aldehydes to nitroolefins, affording products in high diastereo- and enatioselectivities in short reaction times. This new catalyst has several advantages over bimorpholine-based catalysts. It has a higher reactivity and

(11) (a) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(12) (a) Shinisha, C. B.; Sunoj, R. B. *Org. Biomol. Chem.* **2008**, *6*, 3921. (b) Patil, M. P.; Sunoj, R. B. *Chem. Eur. J.* **2008**, *14*, 10472. (c) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321.

(13) (a) Blare, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 3086. (b) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(14) Uudsemaa, M.; Laars, M.; Kriis, K.; Tamm, T.; Lopp, M.; Kanger, T. *Chem. Phys. Lett.* **2009**, *471*, 92.

a better selectivity in Michael addition and is obtained in a one-step synthesis from commercial 2,2′-dipyridyl. These features make bipiperidine an attractive organocatalyst. The C_2-symmetry of the bipiperidine enables its easy derivatization affording monosubstituted diamines.

Experimental Section

(2*S*,2′*S*)-*N*-Me-2,2′-bipiperidine (2a). To a solution of (2*S*,2′*S*)-bipiperidine **1** (0.89 mmol) in diethyl ether (3.6 mL) were added 4 Å molecular sieves (∼ 0.4 g) and aqueous formaldehyde 40% (0.98 mmol). The reaction mixture was stirred for 2.5 h, K_2CO_3 was added, and the mixture was stirred for an additional 1 h and filtered. The solvent was removed to give the crude aminal (144 mg), which was dissolved in MeOH (5 mL). $NaCNBH_3$ (1.01 mmol) was added to the solution in portions followed by addition of CF_3COOH (2.68 mmol) at 0 °C. The reaction was complete after 1.5 h. After the addition of 30% aqueous NaOH (3 mL) and water (3 mL), methanol was removed, and the residue was extracted with diethyl ether (10 × 3 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography on silica gel (10:1:0.2 CH_2Cl_2/MeOH/17% NH_3 in MeOH) afforded a yellow oil (92 mg, 75%). $[\alpha]^{20}_D = -74.5$ (*c* 3.8, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 −3.06 (m, 1H), 2.92−2.83 (m, 1H), 2.74−2.66 (m, 1H), 2.65−2.56 (m, 1H), 2.33− 2.25 (m, 4H), 2.04−1.97 (m, 1H), 1.86−1.78 (m, 1H), 1.77−1.53 (m, 5H), 1.53−1.44 (m, 2H), 1.44−1.22 (m, 4H), 1.16−1.03 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 67.0 (CH), 57.0 (CH), 55.8 (CH_2), 47.6 (CH_2), 40.9(CH_3), 27.2 (CH_2), 27.0 (CH_2), 25.1 (CH_2), 24.0 (CH_2), 23.1 (CH_2), 22.6 (CH_2). MS (EI): *m*/*z* 99 (9), 98 (100), 84 (12), 70 (11), 56 (4), 42 (6). IR: ν = 3330, 2933, 2853, 2780, 1441, 1119, 1026, 767 cm^{-1}. HRMS: calc for $C_6H_{12}N^-$ [*m*/*z* = 98] 98.0975, found 98.0970.

General Procedure for the Organocatalytic Addition of Aldehydes to Nitroolefins. To a solution of catalyst **1**−**4** (0.05 mmol, 15 mol %) in chloroform (3 mL) were added nitrostyrene (0.34 mmol) and aldehyde (3.4 mmol) at the indicated temperature. The reaction was monitored by TLC. After completion of the reaction, 1 N HCl was added, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL), dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography on silica gel using a mixture of petroleum ether and ethyl acetate.

(2*S*,3*R*)-2-Methyl-4 nitro-3-phenylbutyraldehyde 7a. To a solution of *N*-iPr-BP **2b** (11 mg, 0.05 mmol) in chloroform (3 mL) were added nitrostyrene (50 mg, 0.34 mmol) and aldehyde (242 μL, 3.4 mmol). The mixture was stirred at room temperature for 1 h. HCl (1 N) was added, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL), dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography on silica gel using a 15:1 mixture of petroleum ether and ethyl acetate, affording the compound **7a** (63 mg, 91%). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex/iPrOH 8:2, UV 254 nm, 1 mL/min, syn: t_R = 14.09 (major) and t_R = 20.85 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.7, 1H), 7.38 - 7.26 (m, 3H), 7.18−7.16 (m, 2H), 4.81 (dd, *J* = 5.5, 12.7, 1H), 4.69 (dd, *J* = 9.3, 12.7, 1H), 3.82 (td, *J* = 5.5, 9.2, 1H), 2.84−2.72 (m, 1H), 1.01 (d, *J* = 7.3, 3H).

Acknowledgment. We thank the Estonian Science Foundation (Grant No. 6662 and 7135), the Estonian Ministry of Education and Research (Grant No. 0142725s06), and the EU European Regional Development Fund (3.2.0101.08-0017) for financial support.

Supporting Information Available: Experimental procedures and characterizations, NMR, chiral phase HPLC data, computational aspects, optimized structures for calculated species. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900322H