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Enantioselective Chemoenzymatic Synthesis of *cis*- and *trans*-2,5-Disubstituted Morpholines

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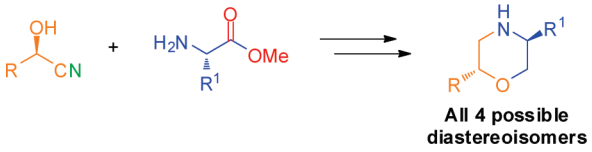

A versatile synthesis of enantiomerically pure *cis*- and *trans*-2,5-disubstituted morpholines is described. Hydroxynitrile lyase-mediated cyanide addition onto aldehydes provided cyanohydrins in virtually quantitative yield and excellent enantioselectivity. Subsequent formation of diastereomerically pure amino esters via a three-step, one-pot reduction−transimination−reduction sequence followed by reduction and simultaneous protection provided cyclization precursors. Finally, cyclization and SmI_2-mediated reductive detosylation completed the synthesis of *cis*- and *trans*-2,5-disubstituted morpholines in good yields and excellent diastereoselectivities.

Substituted morpholines have attracted considerable interest due to their presence in a vast number of therapeutically and biologically active compounds.[1] For instance, reboxetine, a potent antidepressant drug, selectively inhibits the norepinephrine reuptake and is widely studied for its pharmacological properties.[2] Aprepitant has recently been approved in combination with other agents as an effective treatment for preventing acute and delayed chemotherapy-induced nausea and vomiting (CINV) resulting from highly emetogenic chemotherapy in adults.[3] The morpholine skeleton is also of importance for the construction of a large class of agrochemical fungicides and bactericides. Fenpropimorph and tridemorph, for example, both ergosterol biosynthesis inhibitors, are used as agricultural fungicides in cereals.[4] Furthermore, morpholines have been applied as chiral auxiliaries in asymmetric synthesis,[5] although that general application is somewhat limited due to restricted access to stereoselective entries into these kinds of molecules. Despite their importance, applications in organic synthesis are most frequently restricted to simple bases or *N*-alkylating agents. Less attention has been devoted to the synthesis of *C*-funtionalized morpholine derivatives, a compound class that may have important applications in the ongoing search to new pharmaceutically active compounds. As a consequence, the development of efficient synthetic routes to *C*-funtionalized morpholines has been an important subject of investigation over the past decades. Various classes of chiral *C*-functionalized disubstituted morpholine derivatives have been synthesized.[1,5,6] To the best of our knowledge, only two enantioselective synthetic routes to *trans*-2,5-disubstituted morpholines exist,[1b,7] and only one that provides access to both *cis*- and *trans*-2,5-disubstituted morpholines.[8] However, all three strategies are rather limited in their substitution pattern or produce the target morpholines with modest diastereoselectivity.

We recently reported a concise asymmetric synthesis of 2,3-disubstituted *trans*-aziridines starting from enantiomerically pure cyanohydrins.[9] Considering the general value of morpholines, we felt that a similar cyanohydrin-based strategy could be applied to the construction of both *cis*- and *trans*-2,5-disubstituted morpholines. The retrosynthetic plan is outlined in Scheme 1. We envisioned obtaining the morpholines **1** in enantiopure form starting from cyanohydrins **4** and amino esters as building blocks, which are readily available in both enantiomeric forms. The target molecules **1** could arise via ring-closure of the amino diols **2**, followed by deprotection under mild reductive conditions. The intermediates **2**, in turn, might be accessed by coupling amino acid methyl esters with cyanohydrins **4** in a transimination reaction. Finally, chemoenzymatic cyanohydrin formation was envisioned to provide the starting compounds **4** with high enantioselectivity using aldehydes as substrates.

The synthesis commenced with the preparation of enantiomerically pure cyanohydrins. Hydroxynitrile lyases (HNL)

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SCHEME 1. Retrosynthetic Route to Chiral Morpholines

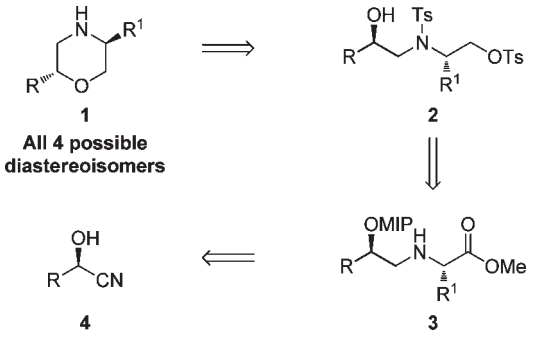
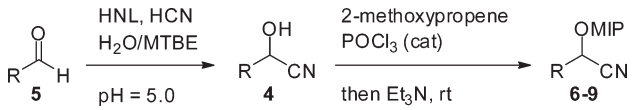


TABLE 1. HNL-Mediated Cyanohydrin Formation and Protection

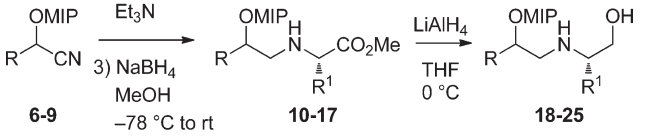


entry	R	enzyme	product	yield[a] (%)	ee (%)	config
1	Ph	(*R*)-HNL	**6**	99	>99[b]	(*R*)
2	2-furanyl	(*S*)-HNL	**7**	90	>99[b]	(*R*)[d]
3	4-BrC_6H_4	(*S*)-HNL	**8**	99	>99[b]	(*S*)
4	4-butenyl	(*S*)-HNL	**9**	99	>99[c]	(*S*)

[a]Isolated yield after chromatography. [b]Determined by HPLC analysis of the free cyanohydrins **4**. [c]Determined by derivatization with Mosher's acid chloride and comparison with the diastereomeric esters prepared from their racemic counterparts. [d]The stereochemical arrangement is as expected for the (*S*)-HNL: however, due to priority changes following the Cahn–Ingold–Prelog rules, the product has the (*R*)-configuration.

are enzymes that in nature convert cyanohydrins into the corresponding aldehydes and hydrogen cyanide. Using a biphasic aqueous–organic solvent system consisting of citrate buffer (pH 5) and methyl *tert*-butyl ether (MTBE) combined with a large excess of KCN, however, the equilibria can be directed to the cyanohydrins.[10] Starting from four different aldehydes and using (*R*)-selective HNL from *Prunus amygdalus* (*Pa*HNL)[11] and (*S*)-selective HNL from *Hevea brasiliensis* (*Hb*HNL)[12] as catalysts, the corresponding cyanohydrins **4** were obtained as crude products. Subsequent protection of the hydroxyl group (MIP protecting group), mandatory in order to prevent racemization via an equilibrium with the aldehyde, afforded the cyanohydrins **6**–**9** (Table 1) in virtually quantitative yield and excellent enantiomeric access.

TABLE 2. Three-Step, One-Pot Coupling and Reduction



entry	s.m.	R^1	methyl ester	yield[a] (%)	amino alcohol	yield[a] (%)	config
1	**6**	H	**10**	48	**18**	80	(*R*)
2	**6**	Me	**11**	32	**19**	92	(*R*,*S*)
3	**6**	Bn	**12**	44	**20**	89	(*R*,*S*)
4	**6**	Allyl	**13**	34	**21**	95	(*R*,*S*)
5	**7**	Bn	**14**	10	**22**	88	(*R*,*S*)
6	**8**	Me	**15**	35	**23**	87	(*S*,*S*)
7	**8**	Bn	**16**	34	**24**	92	(*S*,*S*)
8	**9**	Allyl	**17**	47	**25**	97	(*S*,*S*)

[a]Isolated yield after chromatography.

Inspired by results from Van der Gen et al.,[13] cyanohydrin **6** was reacted in a three-step, one-pot reduction–transimination–reduction sequence to prepare the *N*-substituted *β*-amino ester **10**. Treatment with a 5-fold excess of DIBALH at −78 °C followed by protonation of the resulting imine–aluminum complex with dry methanol afforded the intermediate primary imine. Subsequent transimination with an excess of glycine methyl ester and Et_3N led to rapid formation of the more stable secondary imine upon loss of NH_3. Finally, the transimination product was reduced in situ with sodium borohydride at 0 °C furnishing **10** in 48% overall yield (entry 1, Table 2). The somewhat moderate yield for this reaction sequence can be mainly explained by over-reduction of the intermediate metallo-imine to the corresponding amine with DIBALH as was shown by mass spectrometry analysis. Optimizing the conditions to keep this side reaction to a minimum proved to be difficult. Changing the addition speed or lowering the amount of DIBALH gave lower conversions, while longer exposure of the starting material under these conditions resulted in increased formation of the corresponding amine. In the course of determining the optimal conditions, we noticed that the use of the MIP protective group turned out to be critical. When the same sequence was carried out using a TBS protective group, considerable side-product formation was observed due to reductive cleavage of the TBS ether by DIBALH.[14] Furthermore, we encountered severe difficulties in deprotecting the hydroxyl group in a later stage of the synthesis. In contrast, the MIP protective group could be readily removed under mildly acidic conditions. Pleased with these results, we applied the one-pot reaction sequence on cyanohydrins **7**–**9** using various commercially available (*S*)-amino acid methyl esters. Gratifyingly, the desired amino esters could be isolated in fair to moderate yields for the three-step sequence. In case of entry 5, only 10% yield was obtained, apparently as a result of increased reactivity of the 2-furanyl moiety toward DIBALH.

Reduction of methyl esters **10**–**17** under standard conditions ($LiAlH_4$ in THF, 0 °C) proceeded in all cases to give the corresponding amino alcohols in high yields. Alternatively, these amino alcohols might be directly obtained by coupling

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SCHEME 2. Synthesis of *N*-Tosyl-Protected 2-Phenylmorpholine

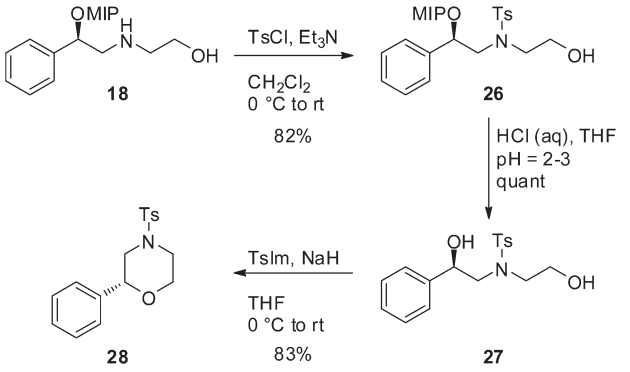
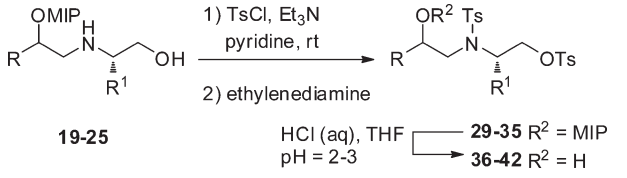


TABLE 3. Simultaneous Sulfonylation and Deprotection



entry	s.m.	R	R^1	product	yield[a] (%)	product	yield[a] (%)
1	**19**	Ph	Me	**29**	80	**36**	90
2	**20**	Ph	Bn	**30**	74	**37**	98
3	**21**	Ph	allyl	**31**	85	**38**	95
4	**22**	2-furanyl	Bn	**32**	70	**39**	92
5	**23**	4-BrC_6H_4	Me	**33**	88	**40**	100
6	**24**	4-BrC_6H_4	Bn	**34**	n.d.[b]	**41**	96[c]
7	**25**	4-butenyl	Allyl	**35**	n.d.[b]	**42**	80[c]

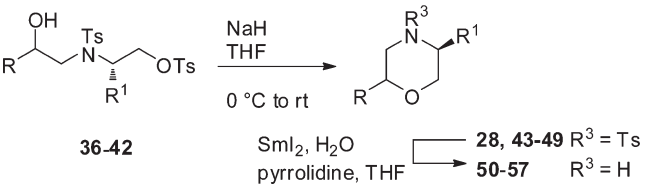
[a]Isolated yield after chromatography. [b]n.d. = not determined. [c]Yield over two steps.

the cyanohydrins with the appropriate enantiopure β-amino alcohols. However, such attempts resulted in considerably decreased product formation (10−15%) so that we decided to focus on the amino acid methyl esters.

Exposure of amino alcohol **18** to an excess of *o*-nitrobenzenesulfonyl chloride (NsCl) to simultaneously react the primary alcohol and the secondary nitrogen provided the desired product in only 35% yield. In contrast, subjection of **18** to *p*-toluenesulfonyl chloride (1.1 equiv) and triethylamine (2.0 equiv) in dichloromethane at 0 °C afforded selectively the *N*-tosylated amino alcohol **26** in 82% yield (Scheme 2). This product was MIP-deprotected under mild acidic conditions (pH 2−3) and then cyclized in one step via selective tosylation of the primary alcohol involving excess sodium hydride in THF, followed by *p*-toluenesulfonyl imidazole at 0 °C. Fortunately, this provided *N*-tosylmorpholine derivative **28** in 83% yield.

Although the sequence summarized in Scheme 2 was highly efficient, attempts to apply the same sequence to prepare 2,5-disubstituted morpholines (R^1 = methyl, benzyl, allyl; compounds **19**−**25**, Table 3) only provided selective *O*-tosylation, apparently as a result of increased steric hindrance of the amino group. A more rewarding result was obtained by stirring compounds **19**−**25** in the presence of *p*-toluenesulfonyl chloride (4.0 equiv) in pyridine containing triethylamine, thereby providing **29**−**35** as summarized in Table 3.[1b] To facilitate purification of the products, ethylenediamine was added to scavenge the excess of *p*-toluenesulfonyl chloride. Moreover, in some cases under these circumstances cleavage of the MIP protective group took place also (entries 6 and 7). In other cases, subsequent deprotection of the hydroxyl group proceeded smoothly in high yields, and the crude morpholine precursors **36**−**42** were used without further purification for the next step.

TABLE 4. Ring Closure and SmI_2-Mediated Deprotection



entry	s.m.	R	R^1	product	yield[a] (%)	product	yield[a] (%)	config
1		Ph	H	**28**		**50**	80	(*R*)
2	**36**	Ph	Me	**43**	96	**51**	92	*trans*
3	**37**	Ph	Bn	**44**	99	**52**	83	*trans*
4	**38**	Ph	allyl	**45**	97	**53**	86	*trans*
5	**39**	2-furanyl	Bn	**46**	73	**54**	82	*trans*
6	**40**	4-BrC_6H_4	Me	**47**	94	**55**	50	*cis*
7	**41**	4-BrC_6H_4	Bn	**48**	93	**56**	56	*cis*
8	**42**	4-butenyl	allyl	**49**	83	**57**	86	*cis*

[a]Isolated yield after chromatography.

Subsequent cyclization under the influence of NaH in THF at 0 °C successfully provided the *N*-tosyl-protected morpholines **28** and **43**−**49** in high yields (Table 4). Finally, deprotection completed the synthesis of unprotected *cis*- and *trans*-2,5-disubstituted morpholines **50**−**57**. Generally, the robustness of sulfonamides can be problematic in the deprotection to the free amines. Traditional deprotection methods involving single electron donors such as lithium or sodium are often too harsh for these systems. Upon application of recent methodology developed by Ankner et al.,[15] we found that by using a combination of $SmI_2/Et_3N/H_2O$, the *N*-tosyl-protected morpholines **28** and **43**−**49** underwent clean and instantaneous deprotection. Unfortunately, in the case of entries 6 and 7, lower yields were obtained. Mass spectrometry of the reaction mixture showed that under these reductive conditions partial dehalogenation of the aromatic ring had occurred.

In summary, we have described a synthetic route that effectively provides access to diastereomerically pure *cis*- and *trans*-2,5-disubstituted morpholines. Key steps involve HNL-catalyzed cyanohydrin formation, a three-step, one-pot coupling sequence, and a SmI_2-mediated detosylation. Important advantages of this sequence are the ready availability of the two chiral precursors from either simple aldehydes or commercially available amino acids and the relatively mild character of the route which, in principle, allows for introduction of various functional groups.

Experimental Section

Methyl (*S*)-2[[(*R*)-2-[(2-methoxypropan-2-yl)oxy]-2-phenylethyl]-amino]propanoate (11). A solution of **6** (500 mg, 2.44 mmol) in dry Et_2O (75 mL) was cooled to −78 °C, and DIBALH (12.2 mL of a 1.0 M solution in hexane, 12.2 mmol, 5.0 equiv) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min.

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After the mixture was quenched with dry MeOH (70 mL), (*S*)-alanine methyl ester hydrochloride (850 mg, 2.5 equiv) and Et_3N (850 μL, 2.5 equiv) were added. The reaction mixture was allowed to warm to rt and stirred for another 2 h. Then the mixture was cooled to 0 °C, and $NaBH_4$ (370 mg, 4.0 equiv) was added. After 2 h at 0 °C, the mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the product was extracted with EtOAc (3 × 60 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:2 → 1:1) to afford **11** (233 mg, 32% yield) as a colorless oil: R_f 0.76 (EtOAc/heptane, 1:1); $[\alpha]_D$ −96.2 (*c* 1.21, CH_2Cl_2); IR (ATR) 2984, 2360, 1738, 1206 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.21 (m, 5H), 4.81 (dd, J = 4.5, 8.1 Hz, 1H), 3.69 (s, 3H), 3.34 (q, J = 6.9 Hz, 1H), 3.14 (s, 3H), 2.85 (dd, J = 8.1, 11.9 Hz, 2H), 2.61 (dd, J = 4.5, 11.9 Hz, 2H), 1.85 (br s, 1H), 1.42, (s, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.14, (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8, 143.2, 128.1, 127.1, 126.4, 101.1, 73.2, 56.4, 55.1, 51.6, 49.2, 26.0, 25.1, 18.7; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{25}NO_4$ $(M + H)^+$ 296.1862, found 296.1849.

(*S*)-2-[[(*R*)-2-[(2-Methoxypropan-2-yl)oxy]-2-phenylethyl]amino]-propan-1-ol (19). A suspension of $LiALH_4$ (36 mg, 2.0 equiv) in dry THF (9 mL) was cooled to 0 °C, and a solution of **11** (0.14 g, 0.47 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. After being quenched with water (42 μL, 5.0 equiv), the mixture was concentrated in vacuo and purified by column chromatography (CH_2Cl_2/MeOH, 0.99:0.01 → 0.90:0.10) to afford **19** (0.12 g, 92% yield) as a colorless oil: R_f 0.76 (CH_2Cl_2/MeOH, 0.9:0.1); $[\alpha]_D$ −47.4 (*c* 1.10, CH_2Cl_2); IR (ATR) 3304, 2920, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.30 (m, 4H), 7.27−7.23 (m, 1H), 4.81 (dd, J = 6.3, 6.3 Hz, 1H), 3.53 (dd, J = 4.1, 10.6 Hz, 1H), 3.20 (dd, J = 7.2, 10.6 Hz, 1H), 3.13 (s, 3H), 2.93 (dd, J = 5.6, 12.0 Hz, 1H), 2.82−2.75 (m, 2H), 2.07 (br s, 1H), 1.42 (s, 3H), 1.15 (s, 3H), 1.00 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.0, 128.2, 127.2, 126.5, 101.2, 72.7, 65.2, 54.1, 53.5, 49.3, 25.8, 25.1, 16.9; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{25}NO_3$ $(M + H)^+$ 268.1913, found 268.1909.

(2*R*,5*S*)-5-Methyl-4-(4-methylbenzenesulfonyl)-2-phenylmorpholine (43). A solution of **36** (48 mg, 0.10 mmol) in THF (5 mL) was cooled to 0 °C, and NaH (3.4 mg of 60% NaH in oil, 1.5 equiv) was added. The resulting mixture was allowed to warm to rt and stirred for 1 h. The mixture was cooled to 0 °C and quenched by the dropwise addition of saturated aqueous NH_4Cl (1 mL). The resulting solution was diluted with EtOAc (30 mL) and washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and brine (2 × 20 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:2) to afford **43** (32 mg, 96% yield) as a colorless oil: R_f 0.44 (EtOAc/heptane, 1:1); $[\alpha]_D$ −88.2 (*c* 1.45, CH_2Cl_2); IR (ATR) 2855, 1349, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65−7.63 (m, 2H), 7.35−7.25 (m, 7H), 4.69 (dd J = 2.3, 9.1 Hz, 1H), 3.94 (dd, J = 2.6, 12.1 Hz, 1H), 3.81 (dd, J = 3.2, 11.7 Hz, 1H), 3.47 (dd, J = 9.0, 11.6 Hz, 1H), 2.92−2.84 (m, 1H), 2.66 (dd, J = 9.2, 12.0 Hz, 1H), 2.43 (s, 3H), 1.36 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.7, 138.4, 133.7, 129.7, 128.4, 128.1, 127.6, 126.1, 77.1, 71.7, 52.3, 51.9, 21.4, 16.1; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{21}NO_3S$ $(M + H)^+$ 332.1320, found 332.1309.

(2*R*,5*S*)-5-Methyl-2-phenylmorpholine (51). A solution of SmI_2 (8.8 mL of a 0.1 M solution in THF, 0.88 mmol, 10 equiv) and water (47 μL, 30 equiv) was added to **43** (29 mg, 0.088 mmol) under an argon atmosphere. Pyrrolidine (0.15 mL, 20 equiv) was subsequently added. The reaction mixture turned white instantaneously upon addition of amine. The resulting mixture was quenched by blowing air through the mixture. The mixture was concentrated in vacuo and purified by column chromatography (CH_2Cl_2/MeOH, 0.99:0.01 → 0.96:0.04) to afford **51** (14 mg, 92% yield) as a colorless oil: R_f 0.65 (CH_2Cl_2/MeOH, 0.9:0.1); $[\alpha]_D$ −7.9 (*c* 0.75, CH_2Cl_2); IR (ATR) 3434, 2920, 2353, 1453, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.32 (m, 5H), 5.98 (br s, 1H), 5.00 (dd, J = 2.2, 11.1 Hz, 1H), 4.10 (dd, J = 3.6, 12.6 Hz, 1H), 3.90 (dd, J = 11.0, 12.4 Hz, 1H), 3.58−3.50 (m, 1H), 3.46 (dd, J = 2.2, 12.7 Hz, 1H), 3.00 (dd, J = 11.2, 12.7 Hz, 1H), 1.47 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.2, 128.6, 126.0, 75.2, 70.4, 51.0, 49.4, 14.8; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{15}NO$ $(M + H)^+$ 178.1232, found 178.1232.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.