Chiral Benzoquinones as a New Class of Ligands for Asymmetric Catalysis: Synthesis and Application to the Palladium(II)-Catalyzed 1,4-Dialkoxylation of 1,3-Dienes

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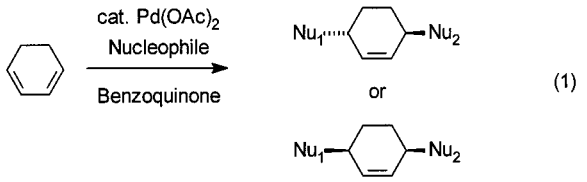
Chiral C_2-symmetric 2,5-bisamide hydroquinone ligands, with β-amino alcohols as chiral building units, were synthesized in excellent overall yields. The ligands gave up to 54.4% ee in the palladium-catalyzed 1,4-dialkoxylation of 1,3-dienes. These findings demonstrate the potential of asymmetric induction utilizing chiral benzoquinones as ligands in palladium(II) catalysis, albeit with modest enantiomeric excesses. Weakly coordinating hydroxyl groups of the ligand appear to be crucial for the success of the reaction. Mechanistic aspects and the origin of enantioselectivity are also discussed.

Introduction

The molecular design of enantiomerically pure chiral auxiliaries and ligands for use in asymmetric reactions is arguably one of the most important issues in modern organic chemistry.[1] Chiral ligands with phosphine and nitrogen functionalities constitute successful classes of compounds for achieving a high degree of asymmetric induction.[2] However, there are transition metal-catalyzed reactions where the ordinary chiral ligands cannot be used because of their low catalytic activity toward a desired reaction pathway. For example, the 1,4-oxidations of 1,3-dienes catalyzed by the palladium(II)−benzoquinone system (eq 1) developed in our laboratory



(1)

are among such reactions.[3] Although a number of natural products were synthesized using this methodology, we had to rely on an enzymatic transformation to make enantiomerically enriched final products.[4] Among asymmetric reactions, the most desirable and the most challenging is catalytic asymmetric synthesis. Therefore, new types of chiral ligands were called for in order to realize a catalytic asymmetric 1,4-oxidation of 1,3-dienes. Since *p*-benzoquinone is known to be an essential ligand for inducing nucleophilic attack[3,5] in the palladium(II)-catalyzed 1,4-oxidations of 1,3-dienes, chiral benzoquinones are potential ligands in the asymmetric version of these reactions.[6]

We have recently reported our preliminary results[7] on the palladium(II)-catalyzed asymmetric 1,4-diacetoxylation of 2-phenyl-1,3-cyclohexadiene, utilizing chiral sulfoxide and amide-substituted benzoquinones as ligands, which indicated that a coordinating group in the side chain of the benzoquinone is required. Since amides are known to be good ligands to palladium(II),[8] we decided to explore the use of 1,4-benzoquinones with chiral amides in the 2- and 5-positions. In this paper, we report on a general methodology for the synthesis of chiral C_2-symmetric 2,5-bis-amide hydroquinone ligands and our preliminary results on the use of these ligands in the palladium(II)-catalyzed asymmetric 1,4-dialkoxylation of 1,3-dienes.

Result and Discussion

A. Synthesis of Chiral C_2-Symmetric 2,5-Bis-amide Hydroquinone Ligands. Chiral benzoquinones of general motive were designed where the use of chiral 2,5-bis-amide units would create the C_2 symmetry, and in addition, the chiral portion of the ligands could be easily varied by appropriate choice of β-amino alcohols (Figure 1). The advantage of using β-amino alcohols as chiral building units is apparent, as they are readily

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(1) (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York, 1995. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994. (c) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993.

(2) For a review: Brunner, H. *Top Stereochem.* **1988**, *18*, 129.

(3) (a) Bäckvall, J. E. Palladium-Catalyzed 1,4-Additions to Conjugated Dienes. Review in *Metal-catalyzed Cross Coupling Reactions*; Stang, P., Diederich, F., Eds.; Wiley-VCH: Weinheim, 1998; pp 339−385. (b) Bäckvall, J. E.; Byström, S. E.; Norberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.

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(8) (a) Sigel, H.; Martin, R. B. *Chem. Rev.* **1982**, *82*, 385. (b) Conti, F.; Donati, M.; Pregaglia, G. F.; Ugo, R. *J. Organomet. Chem.* **1971**, *30*, 421.

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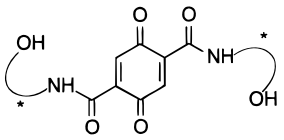
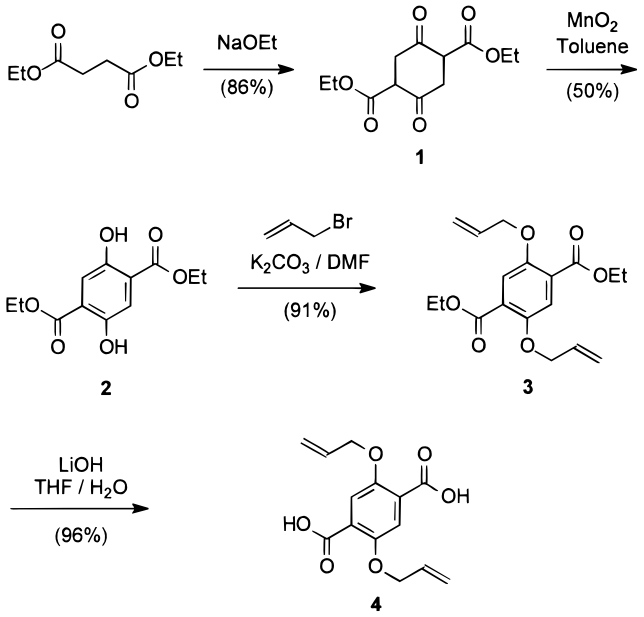


Figure 1. Symmetric 2,5-bisamide benzoquinone ligands.

Scheme 1



available in enantiomerically pure form either from natural sources[9] or by asymmetric synthesis.[9−13] The synthesis of the benzoquinone scaffold is shown in Scheme 1. Aldol condensation of ethyl succinate according to the description by Nielsen[14] furnished the cyclohexanedione **1**, which was then oxidized to hydroquinone **2** in 50% yield utilizing freshly prepared manganese dioxide.[15] Having a suitable benzoquinone core in hand, a hydroxyl protection was required during the transformation of the bis-acid chloride to chiral bis-amide. After many attempts, it was found that the allyl protecting group was a good choice due to its easy and selective deprotection.[16] Thus, treating hydroquinone **2** in DMF with allyl bromide and K_2CO_3 afforded the protected product **3** in 91% yield. The ethyl ester groups were then removed by basic hydrolysis with LiOH in THF, and the bis acid **4**[17] was isolated in 91% yield as a tan solid.

The bis acid **4** was utilized as a common intermediate for the preparation of all the ligands. Syntheses of the desired chiral C_2-symmetric 2,5-bis-amide hydroquinone ligands are depicted in Table 1. The bis acid chloride generated by refluxing the bis acid **4** in $SOCl_2$ was allowed to react with the appropriate amino alcohol to give the allyl-protected 2,5-bis-amide hydroquinones **5** in excellent yields. The allyl group was subsequently removed by the $Pd(PPh_3)_4/NaBH_4$ system[18] to give the chiral C_2-symmetric 2,5-bis-amide hydroquinones **6a**−**f** in good overall yields. In the present study, the in situ oxidation of hydroquinones **6** to the corresponding C_2-symmetric chiral benzoquinones by molecular oxygen, activated by iron phthalocyanine (Fe(Pc)),[5,7,19] was employed. This allows the use of hydroquinone ligands **6** in catalytic amounts in the 1,4-oxidation of 1,3-dienes.

B. Palladium(II)-Catalyzed Asymmetric 1,4-Dialkoxylation of 1,3-Dienes. An evaluation of ligand architecture was done by application to the palladium(II)-catalyzed 1,4-dialkoxylation[20] of 2-phenyl-1,3-cyclohexadiene **7**. The reactions were carried out in EtOH at room temperature using 10 mol % of $Pd(OAc)_2$, 10 mol % of ligand **6**, 20 mol % of $MeSO_3H$, and 3 mol % of Fe(Pc) under an oxygen atmosphere. The results are depicted in Table 2. Unfortunately, ligands **6a**,**b** were found to be totally ineffective in terms of asymmetric induction giving racemic product (entries 1 and 2). We next examined the ligands without any substituents in the β-position of the amides (entries 3−5). Ligand **6c** having benzyl groups at the α-position of the amides provided **8** in 30.9% ee and in 41% yield. Increasing the steric bulk of the α-substituent employing *i*-Pr (**6d**) and *t*-Bu (**6e**) groups had beneficial effects in enantioselectivities, 36.3% and 41.2% ee, respectively. Conformationally fixed ligand **6f**, on the other hand, provided **8** in a lower ee (24.8%). During the studies of the controlling factors in this reaction, it was observed that the use of solvents, other than the nucleophile itself, affects the enantioselectivities of the reaction. Several different solvents were examined for the reaction using **6d** as a ligand, and the results are given in Table 3. Most of the nonpolar solvents[21] gave higher enantioselectivities than EtOH. Among them, CH_2Cl_2 was found to provide the best result (54.4% ee). It is interesting to note that the observed enantioselectivities correlate with the polarity of the solvent employed. Other reaction parameters were also examined, but the effects were not as dramatic as those of the solvent.

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(10) Asymmetric aminohydroxylation of alkenes: (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810. (c) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813. (d) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483.

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(13) Asymmetric aldol and Mannich-type reactions: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Shibasaki, M.; Sasai, H. *Pure Appl. Chem.* **1996**, *68*, 523. (c) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.

(14) Nielsen, A. T.; Carpenter, W. R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 288.

(15) (a) Fatiadi, A. J. *Synthesis* **1976**, 65. (b) No reaction with commercial MnO_2.

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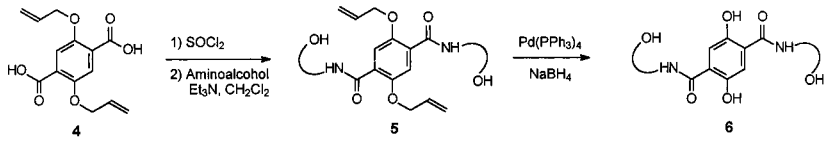
(18) (a) For a review see: Giubé, F. *Tetrahedron* **1997**, 53, 13509. (b) Dessolin, M.; Guillerez, M. G.; Thieriet, N. Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *32*, 5741. (c) Four, P.; Guibé, F. *Tetrahedron Lett.* **1982**, *23*, 1825. (d) Beugelmans, R. Bourdet, S.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 4349.

(19) (a) Bäckvall, J. E.; Hopkins, R. B.; Grennberg, H.; Mader, M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160. (b) Bäckvall, J. E.; Awasthi, A. K.; Renko, Z. D. *J. Am. Chem. Soc.* **1987**, *109*, 4750.

(20) (a) Bäckvall, J. E.; Vågberg, J. O. *J. Org. Chem.* **1988**, *53*, 5695. (b) Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 6374. (c) Itami, K.; Palmgren, A.; Bäckvall, J. E. *Tetrahedron Lett.* **1998**, *39*, 1223.

(21) Employment of polar solvent such as CH_3CN did not give the product.

Table 1. Synthesis of Chiral C_2-Symmetric 2,5-Bisamide Hydroquinone Ligands



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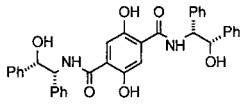
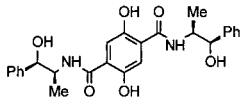
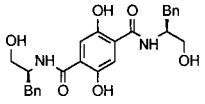
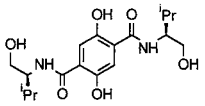
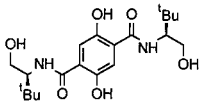
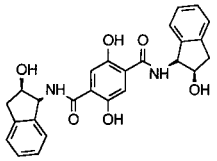
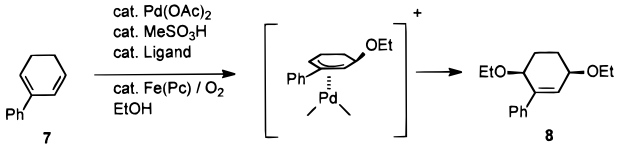
entry	amino alcohol	yield (**5**, %)	yield (**6**, %)	ligand
1		93	78	 **6a**
2		89	96	 **6b**
3		99	90	 **6c**
4		98	91	 **6d**
5		100	87	 **6e**
6		99	93	 **6f**

Table 2. Palladium-Catalyzed Asymmetric 1,4-Dialkoxylation[a]



7 8

entry	ligand	yield[b] (%)	% ee of **8**[c]
1	**6a**	51	0
2	**6b**	42	0
3	**6c**	41	30.9
4	**6d**	57	36.3
5	**6e**	32	41.2
6	**6f**	31	24.8

[a] All reactions were run at room temperature using 10 mol % of $Pd(OAc)_2$, 20 mol % of $MeSO_3H$, 10 mol % of chiral ligand, and 3 mol % of Fe(Pc) in EtOH under an oxygen atmosphere. [b] Isolated yield by column chromatography. [c] Determined by HPLC analysis.

Table 3. Effect of Solvent[a]

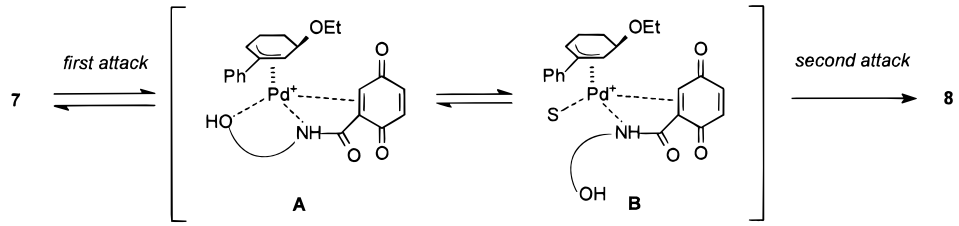
entry	solvent	yield[b] (%)	% ee of **8**[c]
1	EtOH	57	36.3
2	acetone	47	31.2
3	DME	42	41.4
4	CCl_4	46	41.7
5	$CHCl_3$	50	47.2
6	CH_2Cl_2	45	54.4
7	toluene	28	51.9

[a] All reactions were run at room temperature using 10 mol % of $Pd(OAc)_2$, 20 mol % of $MeSO_3H$, 10 mol % of **6d**, 3 mol % of Fe(Pc), and EtOH in solvent (EtOH/solvent = 1:4) under an oxygen atmosphere. [b] Isolated yield by column chromatography. [c] Determined by HPLC analysis.

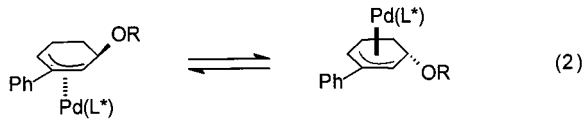
C. Mechanistic Considerations and Origin of Enantioselectivity. Enantioselectivity in a multistep asymmetric reaction is not necessarily determined by the initial enantiodifferentiating event, but rather by the relative energy difference of the diastereomeric transition states of the first irreversible step.[22] In the 1,4-dialkoxylation, there are two stereocenter-creating steps (i.e., first and second nucleophilic attack). The catalyst may differentiate the enantiotopic faces of **7** leading preferentially to (π-allyl)palladium complex **9** or **10** (eq 2). However, the two diastereomeric (π-allyl)palladium complexes **9** and **10** are in equilibrium[23] with one another

(22) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. For an exception, see: Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425.

Scheme 2



via the (η^4-diene)palladium complex, and the enantiodifferentiation most likely occurs by preferential second nucleophilic attack on either **9** or **10**.

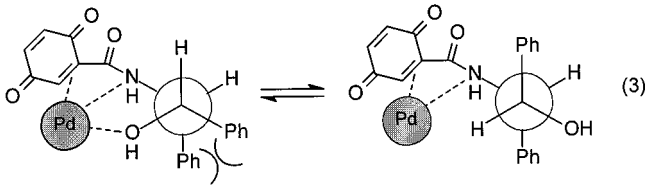


(2)

9 **10**

A tentative rationalization of our results in the palladium(II)-catalyzed 1,4-dialkoxylation of **7** is given in Scheme 2. Since benzoquinones are rate-accelerating ligands in the second nucleophilic attack,[24] the most important intermediates to be considered are (π-allyl)-palladium complexes **A** and **B** resulting from the first nucleophilic attack on 1,3-diene. We hypothesized that the hydroxyl group is coordinating[25] to the palladium (intermediate **A**), therefore bringing the sterically demanding group at the α-position of the amide in closer proximity to the π-allyl group. Besides, the noncoordinated complex **B** should result in a less efficient asymmetric induction.

Some insight about the coordination was available from the disappointing results of ligands **6a**,**b**. These led us to examine the configuration of the coordinated ligand (eq 3). In the case of **6a**, the equilibrium of eq 3 is shifted

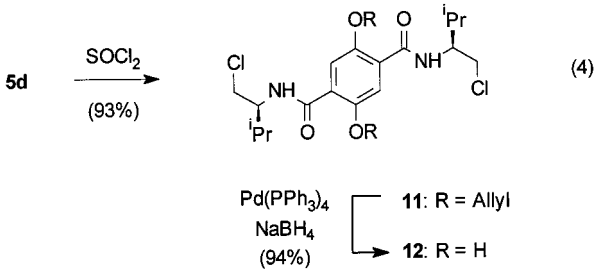


(3)

to the right (noncoordinated complex, type **B**) due to the steric repulsion. On the other hand, in the case of **6c**−**e**, the equilibrium is expected to be shifted to the left (coordinated complex, type **A**) due to the absence of substituents at α to the hydroxyl group on the amino alcohol moiety, which should make a gauche conformation between the nitrogen and oxygen function more likely. In agreement with these assumptions, ligand **6f**, in which the configuration is fixed to give a gauche conformation between the amide and the alcohol, did provide **8** in 24.8% ee, despite having a substituent similar to that of ligand **6a** in the α-position.

The effect of solvent is also in line with the suggested mechanism. Employment of a polar solvent such as EtOH would shift the equilibrium in Scheme 2 toward complex **B**. On the other hand, the use of nonpolar solvent, such as CH_2Cl_2, might help the intramolecular coordination of the hydroxyl groups to palladium, therefore giving rise to a larger bias in the enantioselection.

However, there is still the unavoidable question to be addressed of whether the hydroxyl group is coordinated to the palladium or not. Therefore, ligand **12** having no additional coordinating groups[26] at the β-position of the amides was synthesized according to eq 4. When subsequently subjected to the 1,4-dialkoxylation of diene **7**, it gave **8** as a racemate in 35% yield. We believe that this pronounced difference between **6d** and **12** supports our hypothesis about the requirement of a hydroxyl group coordination for asymmetric induction. Thus, the hydroxyl group on the ligand appears to be essential in order to obtain a fixed conformation (intermediate **A**), thereby achieving more efficient chirality transmission from the ligand.



(4)

Conclusion

A methodology for the synthesis of a new type of chiral 2,5-disubstituted 1,4-hydroquinones was developed, employing β-amino alcohols as chiral building units. The ligands gave up to 54.4% ee in the palladium(II)-catalyzed 1,4-dialkoxylation of 1,3-dienes. These findings demonstrate the potential of asymmetric induction utilizing chiral benzoquinones as ligands in palladium(II) catalysis, albeit with modest enantiomeric excesses. We further demonstrated that asymmetric induction for palladium(II)-catalyzed 1,4-dialkoxylation can only be achieved by the use of ligands with appropriately placed hemilabile coordinating groups. It is noteworthy that such a control element has not been exploited extensively in asymmetric catalysis.[27] Moreover, it is noteworthy that asymmetric induction in the palladium(II)-catalyzed 1,4-dialkoxylation of 1,3-dienes is a difficult task because the chiral ligand is located far from both reactive sites of the substrate. Since palladium(II)-catalyzed asym-

(23) Thorarensen, A.; Palmgren, A.; Bäckvall, J. E. Unpublished results. See also: Szabó, K. J. *Chem. Eur. J.* **1997**, *3*, 592.

(24) The complexation of the benzoquinone or the subsequent second nucleophilic attack is believed to be the rate-determining step of the process.[4b]

(25) (a) An example of hydroxyl group coordination to (π-allyl)-palladium complex: Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604. (b) The hydroxyl group is also used as a directing group for diastereo- and enantioselective hydrogenation; see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307 and references therein.

(26) Several attempts to introduce alkoxy groups into the β-position of the amides met with no success.

(27) Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459.

metric reactions lag far behind those of palladium(0), this study opens up a new frontier for the development of asymmetric palladium(II) chemistry.[7,28] The design and the preparation of a new generation of ligands as well as their application to other reactions are currently under investigation.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity-400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer in $CDCl_3$, CD_3OD, THF-d_8, and acetone-d_6 with internal standards as follows: $CDCl_3$ (7.26 ppm ^{1}H, 77.0 ppm ^{13}C), CD_3OD (4.78, 3.30 ppm ^{1}H, 49.0 ppm ^{13}C), THF-d_8 (3.58, 1.73 ppm ^{1}H, 67.4, 25.3 ppm ^{13}C), and acetone-d_6 (2.04 ppm ^{1}H, 206.0, 29.8 ppm ^{13}C). Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer, and the samples were examined as KBr plates. Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Column chromatography was performed with 230−400 mesh silica gel (Woelm). Melting points (mp) were determined on a hot-stage capillary melting point apparatus and are uncorrected. Analytical high-pressure liquid chromatography (HPLC) was performed on a Waters liquid chromatograph using a Daicel Chiralcel OD-H column. Optical rotations were obtained on a Perkin-Elmer 241 Polarimeter and are reported as follows $[\alpha]^{\text{temperature}}_{\text{wavelength}}$, concentration ($c$ = g/100 mL), and solvent. Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany.

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF), and diethyl ether (Et_2O) were freshly distilled from sodium benzophenone ketyl prior to use. Toluene was distilled from sodium, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. $Pd(PPh_3)_4$ was prepared according to the literature method.[29] 2-Phenyl-1,3-cyclohexadiene **7** was prepared by procedures recently developed in our laboratory.[30] Cyclohexanedione **1** was obtained according to the procedure described by Nielsen.[14]

Diethyl 1,4-Dihydroxy-2,5-benzenedicarboxylate (2). To a solution of the cyclohexanedione **1**[14] (10.28 g, 40 mmol) in toluene (200 mL) was added freshly prepared MnO_2 (14.0 g, 160 mmol), and the resulting brown suspension was stirred for 17 h under reflux. The reaction mixture was cooled to room temperature and filtered through Celite, followed by washing with EtOAc (100 mL). The combined organic phases were concentrated under reduced pressure to afford 5.1 g (50%) of **2** as yellow crystals: mp 125−127 °C; ^{1}H NMR ($CDCl_3$) δ 10.14 (s, 2H), 7.47 (s, 2H), 4.42 (q, J = 7.2 Hz, 4H), 1.42 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 169.1, 152.9, 118.5, 117.7, 62.0, 14.1; IR (KBr) 1687 cm^{-1}.

Diethyl 1,4-Diallyloxy-2,5-benzenedicarboxylate (3). To a suspension of **2** (4.88 g, 19.2 mmol) and K_2CO_3 (7.95 g, 57.6 mmol) in DMF (45 mL) was added allyl bromide (5.0 mL, 57.6 mmol), and the reaction mixture was stirred at room temperature for 13 h. The mixture was diluted with CH_2Cl_2 and then washed with H_2O and brine. The organic layer was dried over $MgSO_4$. Removal of solvent under reduced pressure followed by silica gel chromatography (pentane/EtOAc 8/1−2/1) afforded 5.83 g (91%) of **3** as white crystals: mp 50−52 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 2H), 6.10−6.00 (m, 2H), 5.48 (ddd, J = 17.3, 2.7, 1.7 Hz, 2H), 5.30−5.27 (m, 2H), 4.58 (dt, J = 4.9, 1.4 Hz, 4H), 4.37 (q, J = 7.2 Hz, 4H), 1.38 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 165.6, 151.5, 132.7, 125.0, 117.6, 117.3, 70.6, 61.4, 14.2; IR (KBr) 1708 cm^{-1}.

1,4-Diallyloxy-2,5-benzenedicarboxylic Acid (4). To a solution of **3** (5.66 g, 16.9 mmol) in THF (100 mL) was added LiOH (2.49 g, 50.7 mmol) in H_2O (25 mL). The mixture was stirred for 5 h under reflux and then allowed to cool to room temperature. The reaction mixture was acidified with 2 N HCl and then concentrated under reduced pressure to ca. 20 mL followed by filtration to afford 4.54 g (96%) of **4** as a beige solid: mp 173−174 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 2H), 6.11−6.01 (m, 2H), 5.46 (ddd, J = 17.2, 3.5, 1.7 Hz, 2H), 5.26 (ddd, J = 10.6, 3.1, 1.5 Hz, 2H), 4.63 (dt, J = 5.1, 1.6 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 168.6, 152.6, 134.2, 126.4, 118.1, 118.0, 71.5; IR (KBr) 1673 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.55; H, 5.13.

(+)-*N*-[(1*R*,2*S*)-1,2-Diphenyl-2-hydroxyethyl]-1,4-diallyloxy-2,5-benzenedicarboxamide (5a). General Procedure. The bis acid **4** (593 mg, 2.13 mmol) was stirred for 3 h under reflux in $SOCl_2$ (6 mL). After the acid was cooled to room temperature, the solvent was removed under reduced pressure. Azeotropical removal of residual $SOCl_2$ with toluene (5 mL × 2) under reduced pressure afforded bis acid chloride as a brown solid. To a solution of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (1.00 g, 4.69 mmol) and Et_3N (1.5 mL, 10.65 mmol) in CH_2Cl_2 (15 mL) was slowly added a solution of bis acid chloride in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. The mixture was diluted with $CHCl_3$ (50 mL) and washed with H_2O (50 mL), 2 N HCl (50 mL), and brine (50 mL). Drying over $MgSO_4$ followed by removal of solvent afforded 1.32 g (93%) of **5a** as a white solid: mp 237 °C; $[\alpha]^{25}_D$ +138.1° (*c* 1.00, THF); ^{1}H NMR ($CDCl_3$) δ 8.99 (d, J = 8.0 Hz, 2H), 7.86 (s, 2H), 7.25−7.18 (m, 12H), 7.10−7.03 (m, 8H), 6.00−5.88 (m, 2H), 5.59 (dd, J = 8.0, 3.6 Hz, 2H), 5.40 (d, J = 17.6 Hz, 2H), 5.33 (d, J = 10.4 Hz, 2H), 5.22 (d, J = 3.6 Hz, 2H), 4.72−4.60 (m, 4H), 3.24 (br, 2H); ^{13}C NMR ($CDCl_3$) δ 164.3, 150.8, 139.8, 137.2, 131.9, 128.1, 128.0, 127.9, 127.74, 127.69, 126.8, 124.6, 120.2, 116.6, 77.2, 70.9, 60.4; IR (KBr) 1639, 1531 cm^{-1}.

(+)-*N*-[(1*S*,2*R*)-1-Methyl-2-phenyl-2-hydroxyethyl]-1,4-diallyloxy-2,5-benzenedicarboxamide (5b). According to the procedure given for the preparation of **5a**, **5b** (89% based on **4**) was obtained from (1*R*,2*S*)-(−)-norephedrine as a white solid: mp 135 °C; $[\alpha]^{25}_D$ +37.3° (*c* 1.63, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 7.2 Hz, 2H), 7.44 (d, J = 7.2 Hz, 4H), 7.35−7.23 (m, 8H), 6.01−5.90 (m, 2H), 5.47 (d, J = 17.2 Hz, 2H), 5.32−5.28 (m, 4H), 5.27 (d, J = 10.8 Hz, 2H), 4.56−4.38 (m, 4H), 4.37−4.30 (m, 2H), 1.02 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 163.3, 149.7, 141.5, 131.4, 127.8, 126.7, 125.9, 123.7, 119.1, 115.3, 73.4, 70.0, 51.9, 12.2; IR (KBr) 1634, 1532 cm^{-1}.

(−)-*N*-[(*S*)-1-Benzyl-2-hydroxyethyl]-1,4-diallyloxy-2,5-benzenedicarboxamide (5c). According to the procedure given for the preparation of **5a**, **5c** (99% based on **4**) was obtained from L-phenylalaninol as a white solid: mp 161 °C; $[\alpha]^{25}_D$ −103.3° (*c* 1.61, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.39 (d, J = 7.2 Hz, 2H), 7.71 (s, 2H), 7.32−7.16 (m, 10H), 5.99−5.86 (m, 2H), 5.38 (d, J = 17.2 Hz, 2H), 5.31 (d, J = 10.4 Hz, 2H), 4.65−4.52 (m, 4H), 4.45−4.34 (m, 2H), 3.88−3.82 (m, 2H), 3.64 (dd, J = 11.2, 5.6 Hz, 2H), 3.02−2.86 (m, 2H), 2.94 (d, J = 7.2 Hz, 4H);); ^{13}C NMR ($CDCl_3$) δ 164.4, 150.6, 137.7, 131.9, 129.3, 128.5, 126.6, 124.5, 119.4, 116.6, 70.6, 64.2, 53.6, 37.3; IR (KBr) 1634, 1540 cm^{-1}.

(−)-*N*-[(*S*)-1-(Hydroxymethyl)-2-methylpropyl]-1,4-diallyloxy-2,5-benzenedicarboxamide (5d). According to the procedure given for the preparation of **5a**, **5d** (98% based on **4**) was obtained from L-valinol as a white solid: mp 172−175 °C; $[\alpha]^{20}_D$ −35.2° (*c* 0.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.38 (d, J = 7.8 Hz, 2H), 7.80 (s, 2H), 6.15−6.06 (m, 2H), 5.49 (d, J = 16.1 Hz, 2H), 5.40 (d, J = 10.4 Hz, 2H), 4.76−4.66 (m, 4H), 4.07−4.01 (m, 2H), 3.88 (dd, J = 11.3, 3.2 Hz, 2H), 3.71 (dd, J = 11.3, 7.3 Hz, 2H), 2.91 (s, 2H), 1.98 (m, 2H), 1.01 (d, J = 6.7 Hz, 6H), 0.99 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 165.1, 150.6, 131.8, 124.4, 120.2, 116.5, 70.8, 64.5, 58.1, 29.5, 19.6, 18.5; IR (KBr) 1617, 1552 cm^{-1}. Anal. Calcd for $C_{24}H_{36}N_2O_6$: C, 64.26; H, 8.09. Found: C, 64.01; H, 7.91.

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(+)-*N*-[(*S*)-2,2-Dimethyl-1-(hydroxymethyl)propyl]-1,4-diallyloxy-2,5-benzenedicarboxamide (5e). According to the procedure given for the preparation of **5a**, **5e** (100% based on **4**) was obtained from (*S*)-*tert*-leucinol as a white solid: mp 83−85 °C; $[\alpha]^{25}_D$ +4.8° (*c* 1.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.33 (d, *J* = 9.6 Hz, 2H), 7.59 (s, 2H), 6.12−5.99 (m, 2H), 5.45 (d, *J* = 17.2 Hz, 2H), 5.33 (d, *J* = 10.4 Hz, 2H), 4.71 (dd, *J* = 12.0, 5.2 Hz, 2H), 4.56 (dd, *J* = 12.0, 6.0 Hz, 2H), 4.35 (br, 2H), 4.07−3.96 (m, 4H), 3.60−3.50 (m, 2H), 0.92 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 164.8, 150.2, 131.9, 123.9, 119.9, 116.5, 70.7, 62.4, 60.4, 33.9, 26.8; IR (KBr) 1644, 1538 cm^{-1}.

(+)-*N*-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]-1,4-diallyloxy-2,5-benzenedicarboxamide (5f). According to the procedure given for the preparation of **5a**, **5f** (99% based on **4**) was obtained from (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol as a white solid: mp 330 °C; $[\alpha]^{25}_D$ +76.5° (*c* 1.56, THF); ^{1}H NMR (THF-d_8) δ 8.91 (d, *J* = 7.6 Hz, trace of amide proton), 7.97 (s, 2H), 7.33 (d, *J* = 6.8 Hz, 2H), 7.22−7.08 (m, 6H), 6.15−6.03 (m, 2H), 5.52 (d, *J* = 4.8 Hz, 2H), 5.35 (d, *J* = 17.2 Hz, 2H), 5.14 (d, *J* = 10.4 Hz, 2H), 4.75−4.67 (m, 4H), 4.64−4.58 (m, 2H), 4.48 (d, *J* = 5.2 Hz, 2H), 3.17 (dd, *J* = 16.4, 5.2 Hz, 2H), 2.92 (d, *J* = 16.4 Hz, 2H); ^{13}C NMR (THF-d_8) δ 164.3, 151.8, 143.7, 141.5, 134.1, 128.1, 127.2, 126.3, 125.7, 125.5, 118.6, 117.7, 73.7, 71.6, 59.0, 41.1; IR (KBr) 1631, 1540 cm^{-1}.

(+)-*N*-[(1*R*,2*S*)-1,2-Diphenyl-2-hydroxyethyl]-1,4-dihydroxy-2,5-benzenedicarboxamide (6a. General Procedure. A suspension of **5a** (1.30 g, 1.94 mmol), $Pd(PPh_3)_4$ (280 mg, 0.16 mmol), and $NaBH_4$ (378 mg, 10.0 mmol) in Et_2O (30 mL) was stirred at room temperature for 14 h under an argon atmosphere. The reaction was quenched with MeOH (20 mL), and the mixture was acidified with 2 N HCl. After concentration under reduced pressure, the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH, 100/0−19/1) to afford 886.3 mg (78%) of **6a** as a cream-colored solid: mp 266 °C; $[\alpha]^{25}_D$ +69.2° (*c* 1.00, THF); ^{1}H NMR (CD_3OD) δ 7.46 (s, 2H), 7.22−7.16 (m, 12H), 7.14−7.09 (m, 8H), 5.39 (d, *J* = 5.2 Hz, 2H), 5.10 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (CD_3OD) δ 166.6, 150.6, 142.1, 140.0, 129.2, 128.84, 128.82, 128.5, 128.2, 128.0, 123.6, 118.9, 77.2, 61.1; IR (KBr) 1617, 1541 cm^{-1}.

(+)-*N*-[(1*S*,2*R*)-1-Methyl-2-phenyl-2-hydroxyethyl]-1,4-dihydroxy-2,5-benzenedicarboxamide (6b). According to the procedure given for the preparation of **6a**, **6b** (96%) was obtained from **5b** as a white solid: mp 105−108 °C; $[\alpha]^{25}_D$ +60.6° (*c* 1.08, MeOH); ^{1}H NMR (CD_3OD) δ 8.70 (d, *J* = 8.0 Hz, trace of amide proton), 7.39−7.33 (m, 6H), 7.29−7.22 (m, 4H), 7.20−7.14 (m, 2H), 4.82−4.78 (m, 2H), 4.38−4.26 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (CD_3OD) δ 167.8, 150.6, 143.4, 128.9, 128.2, 127.0, 122.7, 118.1, 72.1, 62.4, 58.7; IR (KBr) 1627, 1539 cm^{-1}.

(+)-*N*-[(*S*)-1-Benzyl-2-hydroxyethyl]-1,4-dihydroxy-2,5-benzenedicarboxamide (6c). According to the procedure given for the preparation of **6a**, **6c** (90%) was obtained from **5c** as a white solid: mp 204−206 °C; $[\alpha]^{25}_D$ +41.8° (*c* 2.02, THF); ^{1}H NMR (CD_3OD) δ 7.35 (s, 2H), 7.26 (s, 4H), 7.26−7.22 (m, 4H), 7.20−7.13 (m, 2H), 4.36−4.28 (m, 2H), 3.61 (d, *J* = 5.2 Hz, 4H), 2.98 (dd, *J* = 13.6, 6.4 Hz, 2H), 2.88 (dd, *J* = 13.6, 8.0 Hz, 2H); ^{13}C NMR (CD_3OD) δ 168.4, 151.6, 139.6, 130.4, 129.4, 127.4, 122.6, 117.7, 63.7, 54.6, 38.0; IR (KBr) 1626, 1548 cm^{-1}. Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.23; H, 6.08. Found: C, 67.36; H, 5.96.

(−)-*N*-[(*S*)-1-(Hydroxymethyl)-2-methylpropyl]-1,4-dihydroxy-2,5-benzenedicarboxamide (6d). According to the procedure given for the preparation of **6a**, **6d** (91%) was obtained from **5d** as a white solid: mp 233−234 °C; $[\alpha]^{20}_D$ −62.6° (*c* 0.27, MeOH); ^{1}H NMR (CD_3OD) δ 7.48 (s, 2H), 3.94 (dd, *J* = 11.8, 5.1 Hz, 2H), 3.72−3.64 (m, 4H), 2.02 (m, 2H), 1.01 (d, *J* = 6.9 Hz, 6H), 0.98 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (CD_3OD) δ 168.3, 151.2, 123.1, 118.3, 63.0, 58.2, 30.0, 20.2, 18.8; IR (KBr) 1621, 1559 cm^{-1}. Anal. Calcd for $C_{18}H_{28}N_2O_6$: C, 58.68; H, 7.66. Found: C, 58.50; H, 7.64.

(+)-*N*-[(*S*)-2,2-Dimethyl-1-(hydroxymethyl)propyl]-1,4-dihydroxy-2,5-benzenedicarboxamide (6e). According to the procedure given for the preparation of **6a**, **6e** (87%) was obtained from **5e** as a white solid: mp 266−269 °C; $[\alpha]^{25}_D$ +5.4° (*c* 0.41, MeOH); ^{1}H NMR (CD_3OD) δ 7.52 (s, 2H), 4.01 (dd, *J* = 7.2, 3.6 Hz, 2H), 3.84 (dd, *J* = 11.6, 3.6 Hz, 2H), 3.62 (dd, *J* = 11.6, 7.2 Hz, 2H), 1.01 (s, 18H); ^{13}C NMR (CD_3OD) δ 168.3, 150.9, 123.5, 118.6, 62.6, 61.0, 35.1, 27.4; IR (KBr) 1622 cm^{-1}.

(+)-*N*-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]-1,4-dihydroxy-2,5-benzenedicarboxamide (6f). According to the procedure given for the preparation of **6a**, **6f** (93%) was obtained from **5e** as a white solid: mp 152−154 °C; $[\alpha]^{25}_D$ +64.6° (*c* 1.51, THF); ^{1}H NMR (CD_3OD) δ 9.26 (d, *J* = 7.8 Hz, trace of amide proton), 7.61 (s, 2H), 7.31−7.14 (m, 8H), 5.53 (d, *J* = 4.4 Hz, 2H), 4.65 (dd, *J* = 4.8, 4.4 Hz, 2H), 3.18 (dd, *J* = 16.4, 4.8 Hz, 2H), 2.96 (d, *J* = 16.4 Hz, 2H); ^{13}C NMR (CD_3OD) δ 167.7, 150.9, 142.5, 141.6, 128.9, 127.9, 126.2, 125.2, 123.4, 118.9, 74.1, 59.3, 40.8; IR (KBr) 1629, 1522 cm^{-1}.

(−)-*N*-[(*S*)-1-(Chloromethyl)-2-methyl-propyl]-1,4-diallyloxy-2,5-benzenedicarboxamide (11). To a solution of **5d** (1.00 g, 2.22 mmol) in CH_2Cl_2 (20 mL) was added $SOCl_2$ (0.81 mL, 11.1 mmol) at 0 °C. The mixture was allowed to warm to room temperature over 17 h. After removal of solvent under reduced pressure, the residue was subjected to silica gel chromatography (pentane/EtOAc 4/1−1/1) to afford 1.00 g (93%) of **11** as a white solid: mp 148−149 °C; $[\alpha]^{20}_D$ −59.2° (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.40 (d, *J* = 8.7 Hz, 2H), 7.92 (s, 2H), 6.17−6.08 (m, 2H), 5.49 (d, *J* = 17.2 Hz, 2H), 5.40 (d, *J* = 10.3 Hz, 2H), 4.75 (d, *J* = 5.9 Hz, 4H), 4.23 (m, 2H), 3.81 (dd, *J* = 11.3, 3.7 Hz, 2H), 3.75 (dd, *J* = 11.3, 4.2 Hz, 2H), 2.12−2.03 (m, 2H), 1.05 (d, *J* = 6.7 Hz, 6H), 1.01 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 163.9, 150.8, 131.9, 124.7, 120.1, 116.8, 70.9, 55.5, 46.4, 29.3, 19.4, 18.7; IR (KBr) 1628 cm^{-1}.

(+)-*N*-[(*S*)-1-(Chloromethyl)-2-methylpropyl]-1,4-dihydroxy-2,5-benzenedicarboxamide (12). According to the procedure given for the preparation of **6a**, **12** (94%) was obtained from **11** as a white solid: mp 264−268 °C; $[\alpha]^{25}_D$ +6.2° (*c* 1.63, acetone); ^{1}H NMR (acetone-d_6) δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.41 (s, 2H), 4.26−4.17 (m, 2H), 3.92−3.82 (m, 4H), 2.18−2.06 (m, 2H), 1.03 (d, *J* = 6.4 Hz, 6H), 1.02 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (acetone-d_6) δ 170.0, 153.6, 120.1, 115.7, 57.3, 46.4, 30.8, 19.6, 18.9; IR (KBr) 1622, 1558 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_4Cl_2$: C, 53.34; H, 6.47. Found: C, 53.50; H, 6.42.

***cis*-1,4-Diethoxy-2-phenyl-2-cyclohexene (8. General Procedure.** To a solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), ligand **6d** (18.4 mg, 0.05 mmol), Fe(Pc) (8.5 mg, 0.015 mmol), and EtOH (0.5 mL, 8.5 mmol) in CH_2Cl_2 (2 mL) was added $MeSO_3H$ (9.6 mg, 0.1 mmol) followed by 2-phenyl-1,3-cyclohexadiene **7** (78.1 mg, 0.5 mmol). The mixture was stirred for 24 h at room temperature under an oxygen atmosphere. The reaction mixture was filtered through a short silica gel column with Et_2O as eluent. Evaporation of the solvent and subsequent purification by silica gel chromatography (pentane/Et_2O 9/1) afforded **8** (55.4 mg, 0.23 mmol, 45%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.50−7.45 (m, 2H), 7.35−7.22 (m, 3H), 6.18 (d, *J* = 2.4 Hz, 1H), 4.21 (t, *J* = 3.2 Hz, 1H), 4.04−3.98 (m, 1H), 3.67−3.55 (m, 3H), 3.48−3.38 (m, 1H), 2.22−2.12 (m, 1H), 1.95−1.82 (m, 2H), 1.70−1.58 (m, 1H), 1.25 (t, *J* = 6.8 Hz, 3H), 1.13 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 140.4, 139.7, 129.9, 128.0, 127.1, 126.2, 74.5, 72.6, 64.2, 63.0, 25.2, 23.6, 15.7, 15.6. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.80; H, 9.02. The product was found to be of 54.4% ee as determined by HPLC analysis using a Chiralcel OD-H column (flow rate 0.5 mL/min, 98/2 hexane/2-propanol): t_R(minor) = 9.6 min; t_R(major) = 15.6 min.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **5a**−**c**,**e**,**f**, **6a**,**b**,**e**,**f**, and **11** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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