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# TADDOL-Derived Phosphites and Phosphoramidites for Efficient Rhodium-Catalyzed Asymmetric Hydroboration

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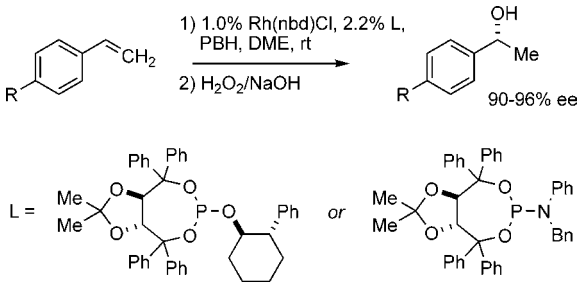
## ABSTRACT




**Two simple TADDOL-derived monodentate ligands, the (1*R*,2*S*)-2-phenylcyclohexanol-derived phosphite and the *N*,*N*-(phenylbenzyl)-phosphoramidite, give comparably high levels of enantioselectivity (90–96% ee) in the rhodium-catalyzed hydroborations of substituted styrenes bearing either electron-donating or electron-withdrawing substituents. Rhodium(I) chloride and tetrafluoroborate catalyst precursors give comparable results. Pinacolborane is superior to catecholborane in these reactions.**

Rhodium-catalyzed hydroboration has attracted much interest, in part, because it proceeds with complementary regio- and diastereoselectivity in certain substrates.[1,2] The novel regiocontrol is exemplified by the rhodium-catalyzed hydroboration of styrene which, in contrast to the noncatalyzed reaction, introduces boron at the benzylic position yielding, after oxidation, predominately the α-aryl alcohol, 1-phenylethanol.

The asymmetric reaction has advanced considerably since Hayashi's seminal paper describing the BINAP/$[Rh(cod)_2]$-$BF_4$-catalyzed reaction in 1989.[3] The best ligands for the reaction of styrene and related vinylarene derivatives include the chiral bidentate *P*,*P*-ligands BINAP (91%, >95% α, 96% ee) and Josiphos,[4] as well as, more recently, the *P*,*N*-ligands QUINAP,[5] PYPHOS,[6] and the ferrocenylpyrazole derivative **1** (Figure 1).[7] Nonetheless, substrate scope and catalyst tunability remain rather limited. For example, QUINAP gives 91.5% ee for styrene but only 78% ee for 4-chlorostyrene.

(1) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878−879.

(2) Recent reviews: (a) Carroll, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609−631. (b) Vogels, C. M.; Westcott, S. A. *Curr. Org. Chem.* **2005**, *9*, 687−699. (c) Guiry, P. J.; Saunders: C. P. *Adv. Synth. Catal.* **2004**, *346*, 497−537. (d) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695−4712.

(3) (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426−3428. (b) Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 601−612.

(4) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062−4066.

(5) (a) Brown, J. M.; Hulmes, D. I.; Layzell, T. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1673−1674. (b) Doucet, H.; Fernandez, E.; Layzell, T. P.; Brown, J. M. *Chem. Eur. J.* **1999**, *5*, 1320−1330.

(6) Kwong, F. Y.; Yang, Q.; Mak, T. C. W.; Chan, A. S. C.; Chan, K. S. *J. Org. Chem.* **2002**, *67*, 2769−2777.

(7) (a) Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 931−933. (b) Kollner, C.; Togni, A. *Can. J. Chem.* **2001**, *79*, 1762−1774.

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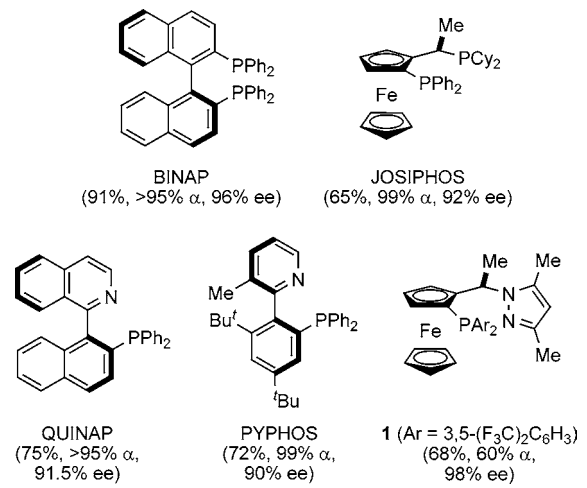
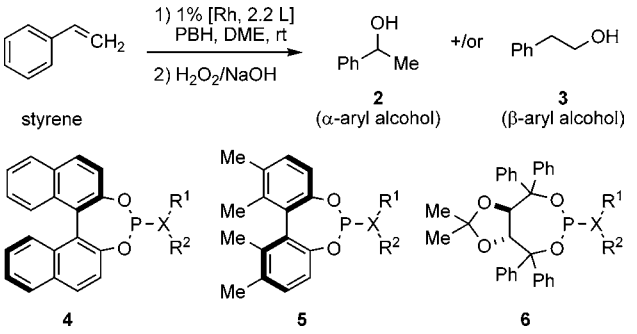



**Figure 1.** Successful chiral ligands for the rhodium-catalyzed asymmetric hydroboration of styrene; yield, percent α-isomer, and its percent enantiomeric excess are given in parentheses.

Chiral monophosphites and phosphoramidites can offer attractive alternatives to chiral diphosphines and related chelating ligands as demonstrated, for example, in asymmetric hydrogenations.[8] As part of our studies into chiral catalyst design,[9] we explored their use in rhodium-catalyzed asymmetric hydroboration.[10,11] Our initial studies employed chiral phosphites and phosphoramidites derived from BINOL (**4**), biaryl derivative **5**,[12] and TADDOL (**6**) in the catalyzed hydroboration of styrene with pinacol borane (PBH) (Table 1). Neither axially chiral scaffold proves very successful (entries 1−6). However, a promising result is obtained with (TADDOL)POPh (**6a**); it affords the branched product in high yield (95%, 89% α) and good enantioselectivity (84% ee, *S*) (entry 7). The presence of coordinating or noncoordinating counterions in the catalyst precursor has little effect (entries 7−10), a surprising observation in light of mechanistic studies indicating the counterion can play a significant role.[13] The TADDOL-benzyl phosphite **6b** (entry 11) and the *N*,*N*-dibenzylphosphoramidite **6c** are much less effective (entries 12−15).

**Table 1.** Comparing Chiral Phosphites and Phosphoramidites in the Rhodium-Catalyzed Asymmetric Hydroboration of Styrene[a]




| entry | Rh catalyst | L | X | $R^1$ | $R^2$ | yield (%) | % α | ee (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | $[Rh(cod)Cl]_2$ | **4a** | O | Ph | | 13 | 65 | 5 |
| 2 | $[Rh(cod)Cl]_2$ | **4b** | O | Bn | | 54 | 72 | 17 |
| 3 | $[Rh(cod)Cl]_2$ | **4c** | N | Bn | Bn | 21 | 83 | 40 |
| 4 | $[Rh(nbd)Cl]_2$ | **5a** | O | Ph | | 21 | 44 | 11 |
| 5 | $[Rh(nbd)Cl]_2$ | **5b** | O | Bn | | 61 | 59 | 18 |
| 6 | $[Rh(cod)Cl]_2$ | **5c** | N | Bn | Bn | 18 | 66 | 15 |
| 7 | $[Rh(cod)Cl]_2$ | **6a** | O | Ph | | 95 | 89 | 84 |
| 8 | $[Rh(nbd)Cl]_2$ | **6a** | O | Ph | | 95 | 87 | 84 |
| 9 | $Rh(nbd)_2BF_4$ | **6a** | O | Ph | | 95 | 83 | 81 |
| 10 | $Rh(cod)_2SbF_6$ | **6a** | O | Ph | | 94 | 78 | 75 |
| 11 | $[Rh(cod)Cl]_2$ | **6b** | O | Bn | | 38 | 50 | 0 |
| 12 | $[Rh(cod)Cl]_2$ | **6c** | N | Bn | Bn | 62 | 74 | 25 |
| 13 | $[Rh(nbd)Cl]_2$ | **6c** | N | Bn | Bn | 66 | 64 | 0 |
| 14 | $Rh(nbd)_2BF_4$ | **6c** | N | Bn | Bn | 95 | 73 | 7 |
| 15 | $Rh(cod)_2SbF_6$ | **6c** | N | Bn | Bn | 95 | 73 | 7 |

[a] Reactions were run in DME at ambient temperature (17 h) in the presence of powdered 4A molecular sieves using a Rh/L/styrene/PBH ratio of 1:2.2:100: 120 and followed by oxidation with basic hydrogen peroxide. The yield, isomer ratio, and enantioselectivity are determined by chiral GC (cyclosil *β*) using an internal standard.

In light of the promising results obtained with **6a**, a more extensive library of TADDOL-derived phosphites and phosphoramidites was prepared. Several vinyl arene substrates were screened using these ligands;[14] the data obtained for 4-chlorostyrene are summarized in Table 2. The yield and regioselectivity vary widely with no apparent trend favoring phosphites or phosphoramidites. Regioselectivity in the catalyzed reaction has been attributed to a variety of influences, including the nature of the hydroborating reagent[15] and the electronic and steric nature of the ligands.[16] Sterics apparently play an important role in our study; for example, the 1- and 2-naphthyl phosphites **14** and **15** differ greatly, giving 77% and 8% of the α-product, respectively (entries 8 and 9).

In terms of enantioselectivity, the methyl and benzyl phosphites (entries 1 and 2) are unsatisfactory. The (1*S*,2*R*)-

(8) Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943−951 and references therein.

(9) (a) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494−4495. (b) Takacs, J. M.; Chaiseeda, K.; Moteki, S. A.; Reddy, D. S.; Wu, D.; Chandra, K. *Pure Appl. Chem.* **2006**, *78*, 501−509.

(10) During the course of our work, Alexakis and Micouin reported promising results using phosphoramidite ligands in the asymmetric iridium-catalyzed hydroboration of meso-bicyclic hydrazines; see: Alexakis, A.; Polet, D.; Bournaud, C.; Bonin, M.; Micouin, L. *Tetrahedron: Asymmetry* **2005**, *16*, 3672−3675.

(11) (a) Seebach reported the TADDOL-derived methyl phosphinite, (TADDOL)PMe, gives 20% ee in the rhodium-catalyzed hydroboration of styrene; see: Sakaki, J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2654−2665. (b) Mixed bidentate ligands combining diphenylphosphine and TADDOL-derived phosphites subunits have been used with success; see: Blume, F.; Zemolka, S.; Fey, T.; Kranich, R.; Schmalz, H.-G. *Adv. Synth. Catal.* **2002**, *344*, 868−883.

(12) Hua, Z.; Vassar, V. C.; Choi, H.; Ojima, I. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5411−5416.

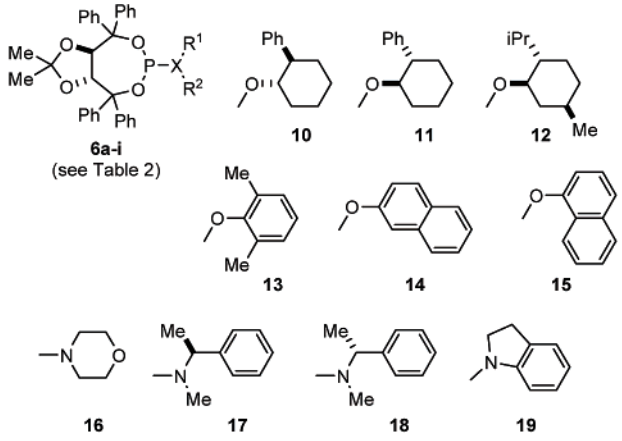
(13) Segarra, A. M.; Daura-Oller, E.; Claver, C.; Poblet, J. M.; Bo, C.; Fernandez, E. *Chem. Eur. J.* **2004**, *10*, 6456−6467.

(14) Screening combinatorial mixtures of chiral monodentate ligands has recently attracted much attention. See: (a) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790−793. (b) Pena, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087−1089. (c) Hartwig, J. *Nature* **2005**, *437*, 487−488. No heterocombination of ligands **6a**−**i** and **10**−**19** gives significantly higher ee than the corresponding homocombinations shown in Table 2.

(15) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 9200−9201.

(16) Daura-Oller, E.; Segarra, A. M.; Poblet, J. M.; Claver, C.; Fernandez, E.; Bo, C. *J. Org. Chem.* **2004**, *69*, 2669−2680.

**Table 2.** [Rh(nbd)Cl]$_2$-Catalyzed Hydroboration of 4-Chlorostyrene Using TADDOL-Phosphite and Phosphoramidite Ligands, L[a]




| entry | L | X | $R^1$ | $R^2$ | yield | % α | % ee |
|---|---|---|---|---|---|---|---|
| 1 | **6d** | O | Me | - | 66 | 25 | 35 |
| 2 | **6b** | O | Bn | - | 80 | 67 | -17 |
| 3 | **10** | O | (1*S*,2*R*) Ph-cyclohexyl | - | 68 | 51 | 42 |
| 4 | **11** | O | (1*R*,2*S*) Ph-cyclohexyl | - | 99 | 74 | 91 |
| 5 | **12** | O | L-menthyl | - | 59 | 82 | 31 |
| 6 | **6a** | O | Ph | - | 97 | 86 | 75 |
| 7 | **13** | O | 2,6-$Me_2C_6H_3$ | - | 80 | 16 | 0 |
| 8 | **14** | O | 2-naphthyl | - | 84 | 77 | 40 |
| 9 | **15** | O | 1-naphthyl | - | 67 | 8 | 65 |
| 10 | **16** | N | -$CH_2CH_2OCH_2CH_2$- | | 44 | 61 | -19 |
| 11 | **6e** | N | Me | Me | 67 | 74 | 51 |
| 12 | **6f** | N | Bn | Me | 54 | 69 | 17 |
| 13 | **17** | N | (*S*) phenethyl | Me | 84 | 68 | -33 |
| 14 | **18** | N | (*R*) phenethyl | Me | 72 | 61 | -11 |
| 15 | **6c** | N | Bn | Bn | 77 | 71 | -3 |
| 16 | **6g** | N | Bn | Ph | 86 | 75 | 94 |
| 17 | **6h** | N | Me | Ph | 98 | 52 | 85 |
| 18 | **6i** | N | Ph | Ph | 92 | 12 | 45 |
| 19 | **19** | N | indolinyl | | 58 | 85 | 41 |

[a] See Table 1, footnote a, for the reaction conditions employed; + values for the % ee correspond to the *S* enantiomer predominating.

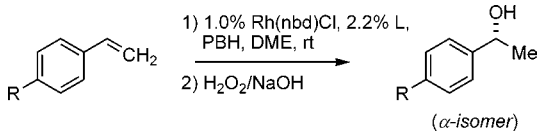
2-phenylcyclohexanol-derived TADDOL phosphite[17] gives a modest result (**10**, entry 3, 42% ee), but its (1*R*,2*S*) diastereomer **11** affords a high level of asymmetric induction (entry 4, 91% ee). In contrast, phosphite **12**, prepared from L-menthol and thus bearing an isopropyl substituent in the favored (2*S*)-orientation, is much less successful (entry 5, 31% ee). With the exception of the phenyl derivative **6a** (entry 6, 75% ee), aryl phosphite derivatives generally give poor enantioselectivity.

Having identified the successful phosphite **11**, it was somewhat surprising to find a comparably successful phosphoramidite, ligand **6g** (entry 16). The latter bears benzyl and phenyl substituents on nitrogen and affords 94% ee in the catalyzed reaction, the highest level yet reported for 4-chlorostyrene.[3] In contrast, neither the $NBn_2$ (entry 15, 3% ee) nor the $NPh_2$ (entry 18, 45% ee) derivatives are effective.

(17) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; Van den Heuvel, A.; Leveque, J.-M.; Maze, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011−4027.

Styrene derivatives bearing electron-withdrawing substituents are generally reported to give lower enantioselectivity than those bearing electron-donating substituents.[5,6] Nonetheless, **11** and **6g** afford 90−96% ee in preparative reactions for a series of 4-substituted styrenes (Table 3); both electron-donating and electron-withdrawing substituents are tolerated. The enantioselectivities obtained with ligands **6g** and **11** are higher than those reported for any other single catalyst system with this series of substrates and are comparable to, or better than, the most successful catalyst systems reported for each case individually. For example, the most successful catalyst previously reported for the $CF_3$-substituted styrene gives only 74% ee.[5] The results obtained with ligands **6g** and **11** are essentially unchanged using $Rh(nbd)_2BF_4$ as the catalyst precursor (Figure 2). However, the level of enantioselectivity

**Table 3.** Preparative Reactions for a Series of 4-Substituted Styrenes Using Monodentate Ligands **11** and **6g**[a]




| | **11** | | | **6g** | | |
|---|---|---|---|---|---|---|
| R | yield (%) | % α | ee (%) | yield (%) | % α | ee (%) |
| OMe | 96 | 71 | 93 | 96 | 67 | 94 |
| $CH_3$ | 94 | 62 | 92 | 91 | 60 | 93 |
| H | 96 | 78 | 95 | 96 | 82 | 96 |
| $CF_3$ | 96 | 63 | 90 | 92 | 62 | 90 |
| Cl | 94 | 77 | 91 | 95 | 77 | 94 |
| F | 95 | 79 | 95 | 95 | 72 | 95 |

[a] Reactions run using 4.8 mmol of the indicated styrene. See Table 1, footnote a, for the reaction conditions employed.

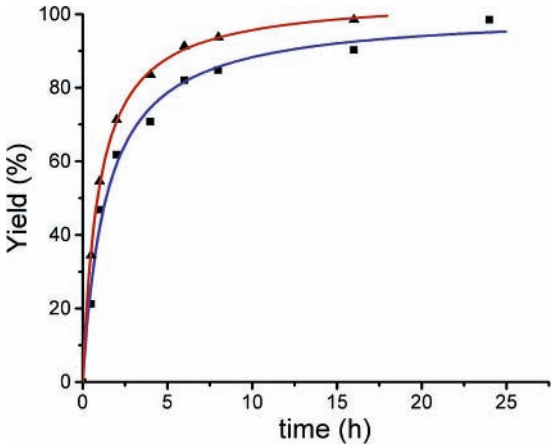



**Figure 2.** Comparison of the phosphite **11** and phosphoramidite **6g** modified rhodium-catalyzed hydroboration of 4-chlorostyrene using $[Rh(nbd)Cl]_2$ and PBH.

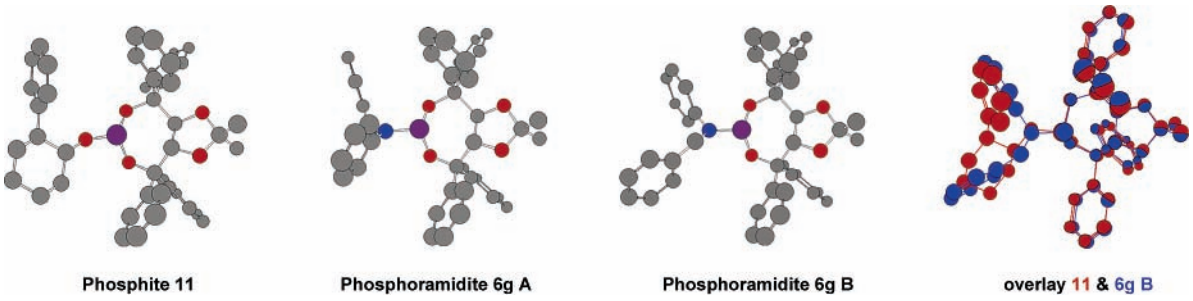



**Figure 3.** Low energy conformers of **11** and **6g** (**A** and **B**) obtained via molecular modeling and the overlay of **11** (red) and **6g B** (blue).

drops to ca. 40% ee using catecholborane, although the *S* enantiomer still predominates.[15]

Since the two ligands give the same sense and essentially the same degree of enantioselectivity in the reaction, several lines of experimentation were carried out to further explore their somewhat puzzling similarity. The two catalysts exhibit very similar rates in the catalyzed hydroboration of 4-chlorostyrene; the phosphite is somewhat faster (Figure 3). In each case, the observed levels of regioselectivity and enantioselectivity remain constant throughout the course of the reaction.

It is perhaps tempting to suggest that the bicyclic (TADDOL)P core, common to both ligands, is the element most responsible for stereoinduction. However, it is clear from the data in Table 2 that the nature of the $X(R^1)R^2$ moiety has a major influence. We therefore asked whether the two substituents, *O*-(1*R*,2*S*)-2-phenylcyclohexyl and *N*-benzyl-*N*-phenyl, naturally adopt conformations that coincidentally define a similar topography. Preliminary modeling studies using AM1 suggest this may be the case.

Figure 3 shows the low energy conformer for phosphite **11** and two closely related low energy conformers of phosphoramidite **6g**; the latter two differ in structure by rotation about the P−N bond and in energy by less than 0.1 kcal/mol. There are of course very significant differences in the phosphite and phosphoramidite structures, but the overlay of **11** (in red) with **6g** conformer **B** (in blue) shows that the two phenyl substituents occupy similar regions of space as do the cyclohexyl and benzyl groups.

Given the similarities of phosphite **11** and phosphoramidite **6g**, it seemed conceivable that the heterocombination of these two monodentate ligands, that is, employing 1 equiv of each, should generate an effective mixed catalyst. However, the heterocombination proves far inferior to either homocombination. In contrast to the results shown in Table 3, the heterocombination (**11** + **6g**) gives only 46% ee for the reaction of 4-chlorostyrene (91% yield, 52% α-isomer). While we have no data on the relative abundance of homo- and heterocombination rhodium complexes present under the conditions of catalysis, the result suggests that the heterocombination is a competent and competitive catalyst for the reaction, but not as selective.

In summary, two simple TADDOL-derived monodentate ligands, phosphite **11** and phosphoramidite **6g**, afford comparably high levels of enantioselectivity in the room-temperature rhodium-catalyzed asymmetric hydroborations of styrenes. Compared to some chiral catalysts systems employing chiral bidentate ligands, a wider range of donor- and acceptor-substituted styrenes are tolerated, rhodium(I) chloride and tetrafluoroborate catalyst precursors give similar results, and while pinacol- and catecholborane give the same sense of asymmetric induction, the results obtained with pinacolborane are superior. Further studies into the utility of these catalyst systems and into the origin of the enantioselectivity are in progress.

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**Supporting Information Available:** Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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