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Chiral Phosphoric Acid Catalyzed Enantioselective Synthesis of β-Amino-α, α-difluoro Carbonyl Compounds

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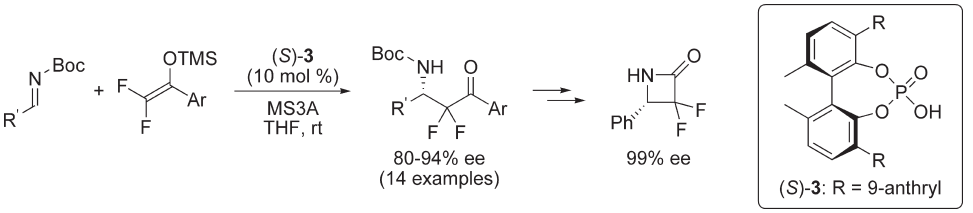
ABSTRACT



A biphenol-based chiral phosphoric acid bearing a 9-anthryl group at each of the 3,3′-positions catalyzed the asymmetric Mannich-type reaction of *N*-Boc imine with difluoroenol silyl ethers in the presence of MS3A in THF to afford β-amino-α,α-difluoroketones in good yields and with excellent enantioselectivities. Optically pure 3,3-difluoroazetidin-2-one was readily synthesized from the Mannich-adduct.

The incorporation of fluorine atoms into a target organic molecule often dramatically changes the physical, chemical, and biological properties of the molecule and affects its application in various areas, including pharmaceutical, agrochemical, and material sciences.[1] Among them, β-amino-α,α-difluoro carbonyl compounds, which are valuable intermediates for and targets of drug design, have attracted much attention due to their unique biological properties.[2] For example, some of the difluoro docetaxel compounds[2c] showed activities that were comparable or superior to that of docetaxel. A β-amino-α,α-difluoro carbonyl unit containing a rhodopeptin derivative[2d] exhibited improved physical and biological properties, such as acute toxicity and solubility, while retaining its antifungal activity (Figure 1). The *gem*-difluoromethylene group not only increases the acidity of its neighboring group but also significantly improves lipophilicity, because of its strong electron-withdrawing effect.[3] Furthermore, the *gem*-difluoromethylene group also increases the electrophilicity of the neighboring carbonyl group. The α,α-difluoro carbonyl compounds form stable hydrates or hemiketals that mimic tetrahedral intermediates involved in the enzymatic cleavage of peptide bonds, and inhibit the activity of a number of hydrolytic enzymes.[4] The development of a method for the preparation of β-amino-α,α-difluoro carbonyl compounds in an optically pure form is extremely important from a synthetic point of view. Three methods are available for the asymmetric synthesis of β-amino-α,α-difluoro carbonyl compounds: (1) deoxydifluorination of β-keto carbonyl compound using diethylaminosulfur trifluoride (DAST),[5] (2) the

(1) (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U. K., 2006. (b) Dolbier, W. R. *J. Fluorine Chem.* **2005**, *126*, 157–163. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (d) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (f) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369. (g) Zhang, W.; Cai, C. *Chem. Commun.* **2008**, 5686–5694.

(2) For a review on gem-difluoromethylene compounds, see: (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619–8683. For examples on the utility of β-amino-α,α-difluoro carbonyl compounds, also see:(b) Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Turner, S. R. *J. Med. Chem.* **1987**, *30*, 1837–1842. (c) Uoto, K.; Ohsuki, S.; Takenoshita, H.; Ishiyama, T.; Iimura, S.; Hirota, Y.; Mitsui, I.; Terasawa, H.; Soga, T. *Chem. Pharm. Bull.* **1997**, *45*, 1793–1804. (d) Nakayama, K.; Kawato, H. C.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett.* **2000**, *2*, 977–980.

(3) (a) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589. (b) Pesenti, C.; Viani, F. *ChemBioChem* **2004**, *5*, 590–613. (c) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643.

(4) (a) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813–1817. (b) Gelb, M. H. *J. Am. Chem. Soc.* **1986**, *108*, 3146–3147. (c) Damon, D. B.; Hoover, D. J. *J. Am. Chem. Soc.* **1990**, *112*, 6439–6442.

(5) Hook, D. F.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBioChem* **2004**, *5*, 691–706.

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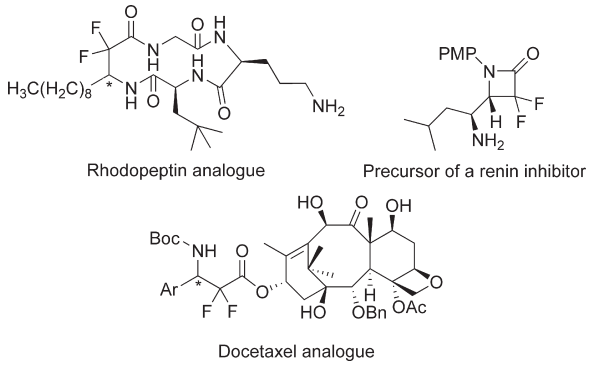


Figure 1. Examples of optically active β-amino-α,α-difluoro carbonyl compounds.

Reformatsky reaction of α-bromo-α,α-difluoroacetate with aldimines,[6] and (3) the Mannich-type reaction of difluorinated silyl enol ether with aldimines.[7] A highly diastereoselective Reformatsky reaction was reported and moderate diastereoselectivity was observed in the Mannich-type reaction. The catalytic enantioselective variant of these processes leading to β-amino-α,α-difluoro carbonyl compounds, however, remains elusive.

As part of our ongoing work to develop chiral phosphoric acid (Figure 2)[8,9] catalyzed reactions, we started a program to study the chiral phosphoric acid catalyzed Mannich-type reaction[10] of aldimines with difluorinated enol silyl ethers. This substrate is readily available from a trifluoroacetophenone derivative.[11] We wish to report herein the first catalytic enantioselective synthesis of β-amino-α,α-difluoro carbonyl compounds. The Mannich-type reaction of difluoroenol silyl ethers with aldimines catalyzed by a chiral phosphoric acid furnished β-amino-α,α-difluoro carbonyl compounds with high to excellent enantionselectivities.

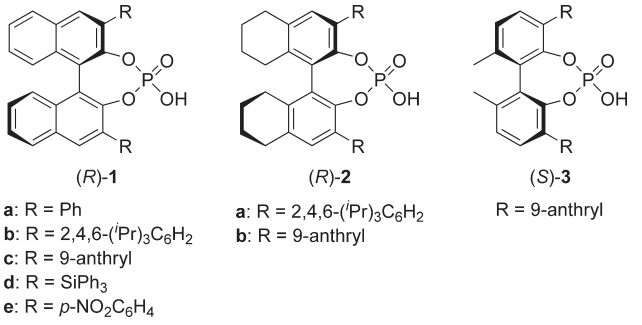
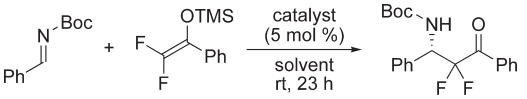


Figure 2. Chiral phosphoric acids.

At the outset, the effect of the catalyst was investigated on the reaction of *N*-*tert*-butoxycarbonyl (Boc) imines **4a** with difluoroenol silyl ethers **5a**, and the results are summarized in Table 1. On treatment of **4a** and **5a** with (*R*)-**1a** (5 mol %) in toluene at room temperature for 23 h, the corresponding β-amino-α,α-difluoroketone **6a** was obtained in 35% yield with 63% ee (entry 1, Table 1). Whereas the use of catalysts (*R*)-**1b** and **1c** bearing a bulky substituent, such as 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$ and 9-anthryl groups, slightly improved the enantioselectivity (entries 2 and 3), whereas the use of **1d** with $SiPh_3$ groups resulted in low enantioselectivity (entry 4). We found that the chiral phosphoric acid scaffold affected both yield and ee, and

Table 1. Effect of Catalyst and Solvent in the Mannich-type Reaction of *N*-Boc Imine with Difluoroenol Silyl Ether[a]



entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	(*R*)-**1a**	Toluene	35	63
2	(*R*)-**1b**	Toluene	9	89
3	(*R*)-**1c**	Toluene	36	84
4	(*R*)-**1d**	Toluene	11	29
5	(*R*)-**1e**	Toluene	38	64
6	(*R*)-**2a**	Toluene	16	75
7	(*R*)-**2b**	Toluene	24	93
8	(*S*)-**3**	Toluene	44	92
9	(*S*)-**3** (10 mol %)	Toluene	58	93
10[d]	(*S*)-**3** (10 mol %)	Toluene	60	93
11[d]	(*S*)-**3** (10 mol %)	THF	89	94 (>99)[e]

[a] Reactions were performed with **4a** (0.2 mmol, 1.0 equiv) and **5a** (0.3 mmol, 1.5 equiv) in the presence of 5 mol % chiral phosphoric acid in 2 mL of toluene at rt (23 h). [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] MS3A (100 wt %) was added. [e] Values in parentheses are the ee values after one recrystallization from EtOH.

(6) (a) Vidal, A.; Nefzi, A.; Houghten, R. A. *J. Org. Chem.* **2001**, *66*, 8268–8272. (b) Soloshonok, V. A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett.* **2002**, *43*, 5445–5448. (c) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.; Fujii, N. *Org. Lett.* **2006**, *8*, 613–616. (d) Christianson, C. V.; Montavon, T. J.; Festin, G. M.; Cooke, H. A.; Shen, B.; Bruner, S. D. *J. Am. Chem. Soc.* **2007**, *129*, 15744–15745. (e) Oishi, S.; Kamitani, H.; Kodera, Y.; Watanabe, K.; Kobayashi, K.; Narumi, T.; Tomita, K.; Ohno, H.; Naito, T.; Kodama, E.; Matsuoka, M.; Fujii, N. *Org. Biomol. Chem.* **2009**, *7*, 2872–2877.

(7) Jonet, S.; Cherouvrier, F.; Brigaud, T.; Portella, C. *Eur. J. Org. Chem.* **2005**, 4304–4312.

(8) For reviews, see:(a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (c) Terada, M. *Chem. Commun.* **2008**, 4097–4112. (d) Terada, M. *Synthesis* **2010**, 1929–1982. (e) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262–5276.

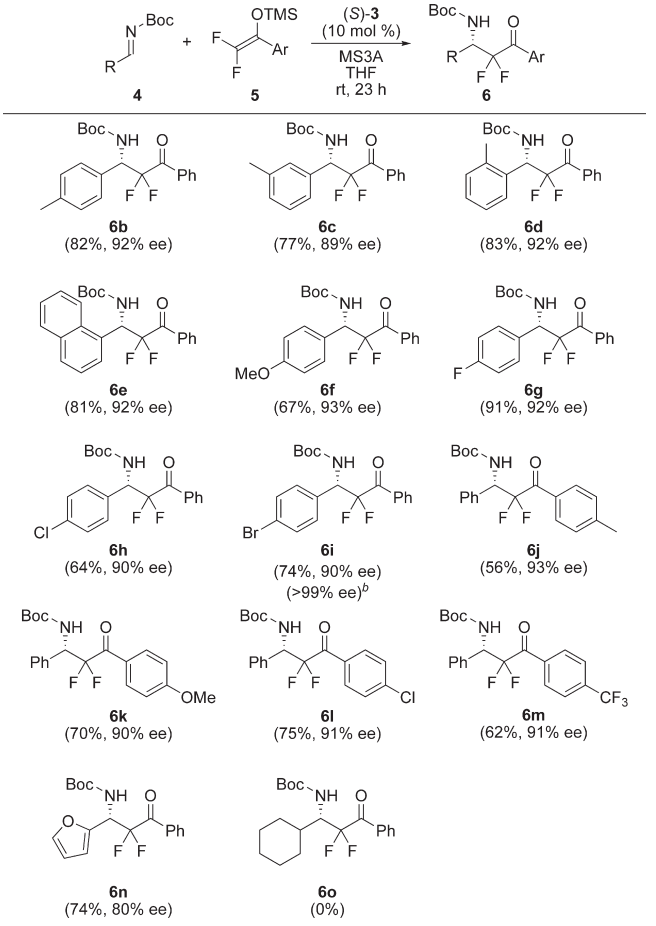
(9) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

(10) (a) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523–1526. (b) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764. (c) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631–3634. (d) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399–402. (e) Giera, D. S.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10*, 4259–4262. (f) Itoh, J.; Fuchibe, K.; Akiyama, T. *Synthesis* **2008**, 1319–1322. (g) Akiyama, T.; Katoh, T.; Mori, K.; Kanno, K. *Synlett* **2009**, 1664–1666. (h) Giera, D. S.; Sickert, M.; Schneider, C. *Synthesis* **2009**, 3797–3802. (i) Sickert, M.; Abels, F.; Lang, M.; Sieler, J.; Birkemeyer, C.; Schneider, C. *Chem.—Eur. J.* **2010**, *16*, 2806–2818.

(11) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323–1324.

that (*S*)-**3**, derived from biphenol[10g,12] bearing a 9-anthryl group at each of the 3,3′-positions, was the optimal catalyst (entries 7 and 8). It was also found that the addition of MS3A to the reaction system in THF significantly improved the yield (entry 11).

Scheme 1. Results of the Mannich-type Reaction of *N*-Boc Imine with Difluoroenol Silyl Ether Catalyzed by (*S*)-**3**[a]



[a] Reactions were performed with **4** (0.2 mmol, 1.0 equiv) and **5** (0.3 mmol, 1.5 equiv) in the presence of 10 mol % (*S*)-**3** and 100 wt % MS3A in 2 mL of THF at rt (23 h). [b] Result was obtained after one recrystallization from EtOH.

Having established the optimal reaction conditions (entry 11, Table 1), we studied the Mannich-type reaction of a range of aldimines **4** with various difluoroenol silyl ethers **5** and found that the reaction proceeded successfully with excellent enantioselectivities and in good to high yields (Scheme 1). A substrate bearing a bulky group, such as 1-naphthyl, on R underwent the reaction smoothly to give addition product **6e** in 81% isolated yield with 92% ee. Both electron-withdrawing and electron-donating substituents on R or Ar were well tolerated in the reaction. A heteroaromatic aldimine bearing a 2-furyl group also afforded addition product **6n** in good enantioselectivity. An aldimine derived from aliphatic aldehyde did not give the corresponding adduct **6o**.

The absolute configuration of **6i** was established to be *S* by X-ray crystallographic analysis of **8** (Figure 3). **6i** was readily transformed into **8** in two steps: the removal of the Boc group and the introduction of a benzoyl group. The absolute stereochemistry of the other adducts was surmised by analogy.

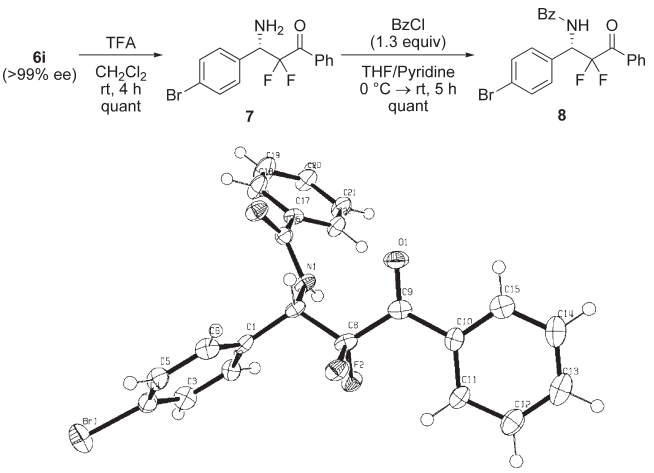
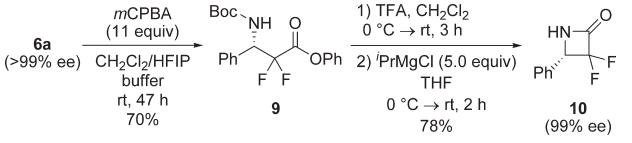


Figure 3. X-ray crystal structure of **8**.

To demonstrate the synthetic utility of the Mannich-type reaction, we investigated a practical route for the synthesis of enantiopure 3,3-difluoroazetidin-2-one, which is a pharmaceutically important target as well as a useful synthetic building block.[2b,c,13] Treatment of **6a** (>99% ee after one recrystallization) with *m*CPBA in CH_2Cl_2/HFIP in the presence of aqueous phosphate buffer (pH 7.6)[14] furnished corresponding ester **9** without loss of enantioselectivity. Ester **9** was converted into 3,3-difluoroazetidin-2-one **10** in two steps *via* the removal of the Boc group and the subsequent base-promoted cyclization (Scheme 2).

Scheme 2. Preparation of 3,3-Difluoroazetidin-2-one



To disclose the effect of a fluorine substituent, we tried to perform the Mannich-type reaction of nonfluorinated enol silyl ether **11** with **4a**. We compared the reactivity of **5a** and its defluorinated analogue **11**. Although we expected that **5a** would be less reactive than **11** due to the −I effect and

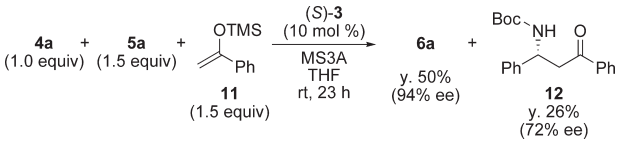
(12) Takai, M.; Urata, H.; Takahashi, T. Japan Patent JP 2004189696A, 2004.

(13) For a recent review, see: Tarui, A.; Sato, K.; Omote, M.; Kumadaki, I. *Adv. Synth. Catal.* **2010**, *352*, 2733–2744.

(14) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron* **2003**, *59*, 1547–1552.

the $+I\pi$ effect of fluorine,[1a,15] competitive experiments with **5a** and **11** revealed that the reaction of **5a** with **4a** was approximately twice as fast as that of **11** with **4a**. The ee of **6a** was also higher than that of **12** (Scheme 3).[16]

Scheme 3. Comparison of Reactivity of Difluoroenol Silyl Ether and Nonfluorinated Enol Silyl Ether



Although the reaction of *N*-*p*-methoxyphenyl (PMP) imine **14** with **5a** in the presence of (*S*)-**3** yielded a product with an extremely low ee in comparison with *N*-Boc imine **4a**,[17] the enantioselectivity was improved to 76% ee when the reaction was carried out in the presence of (*S*)-**13** instead of (*S*)-**3** and in the absence of MS3A. Resulting addition product **15** was obtained in an optically pure form after recrystallization. Interestingly, these modified reaction conditions exhibited opposite enantioselectivity for the Mannich-type reaction of **4** to afford (*R*)-**15**. The removal of PMP and Boc groups readily proceeded under mild conditions to afford (*R*)-**16** and (*S*)-**16**, respectively, without racemization (Scheme 4).

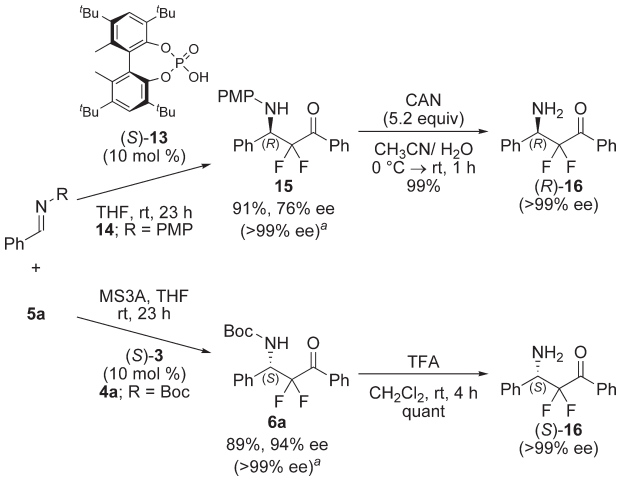
In summary, we have developed catalytic enantioselective Mannich-type reactions of aldimine with difluoroenol silyl ether by employing biphenol-derived chiral phosphoric acid. The reaction proceeded with good to excellent enantioselectivities (up to 94% ee). The resulting Mannich adduct could be readily transformed into versatile 3,3-difluoroazetidin-2-one in three steps without loss of optical purity. Furthermore, both enantiomers of β-amino-α,α-difluoroketone could be prepared using the catalyst derived from (*S*)-biphenol.

(15) (a) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271–10280. (b) Kloetzing, R. J.; Thaler, T.; Knochel, P. *Org. Lett.* **2006**, *8*, 1125–1128. (c) Guo, Y.; Shreeve, J. M. *Chem. Commun.* **2007**, 3583–3585. (d) Yue, X.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 73–76.

(16) The absolute stereochemistry of **12** was assigned by comparison of optical rotation with literature data: Tillman, A. L.; Dixon, D. J. *Org. Biomol. Chem.* **2007**, *5*, 606–609.

(17) **15** was obtained in 91% yield with 14% ee (*S*).

Scheme 4. Enantioselective Synthesis of (*R*)- or (*S*)- β-Amino-α, α-difluoroketone



[a] Values in parentheses are the ee values after recrystallization from EtOH for **6a** and hexane-CH_2Cl_2 for **15**, respectively.

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Supporting Information Available. Synthetic procedures, CIF file of compound **8**, together with characterization and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.