ORGANIC LETTERS
2010
Vol. 12, No. 17
3930−3933

Cu-Catalyzed Double S-Alkenylation of Potassium Sulfide: A Highly Efficient Method for the Synthesis of Various Thiophenes

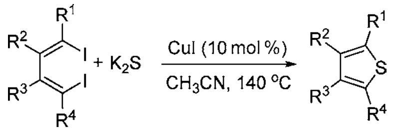
Wei You, Xiaoyu Yan, Qian Liao, and Chanjuan Xi*

Key Lab of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Department of Chemistry, Tsinghua University, Beijing 100084, China, and China State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

cjxi@tsinghua.edu.cn

Received July 14, 2010

ABSTRACT



An efficient synthetic approach to variously substituted thiophenes has been developed through copper-catalyzed tandem *S*-alkenylation of potassium sulfide with 1,4-diiodo-1,3-dienes.

Substituted thiophenes have emerged as a class of important heterocycles because of their presence in a broad spectrum of natural and synthetic molecules with diverse biological properties,[1−4] material characteristics,[5] and utility in organic synthesis as versatile intermediates.[6,7] The general synthetic approaches to such thia-heterocycles involve either the functionalization in the α- and β-position of the preconstructed thiophene skeleton[8,9] or the construction of the thiophene ring from appropriately substituted open chain

---

(1) (a) Gronowitz, S. *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Gronowitz, S., Ed.; Wiley: New York, 1991; Vol. 44,Part 3, Chapter 2. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocyclic*; Wiley-VCH: New York, 2003; Chapter 5, Section 5.6.

(2) (a) Modica, M.; Santagati, M.; Guccione, S.; Russo, F.; Cagnotto, A.; Goegan, M.; Mennini, T. *Eur. J. Med. Chem.* **2000**, *35*, 1065. (b) Wu, C.; Decker, E. R.; Blok, N.; Bui, H.; You, T. J.; Wang, J.; Bourgoyne, A. R.; Knowles, V.; Berens, K. L.; Holland, G. W.; Brock, T. A.; Dixon, R. A. F. *J. Med. Chem.* **2004**, *47*, 1969.

(3) (a) Lisowski, V.; Enguehard, C.; Lancelot, J.-C.; Caignard, D.-H.; Lambel, S.; Leonce, S.; Pierre, A.; Atassi, G.; Renard, P.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2205. (b) Doré, K.; Dubus, S.; Ho, H. A.; Lévesque, I.; Brunette, M.; Corbeil, G.; Boissinot, M.; Boivin, G.; Bergeron, M. G.; Boudreau, D.; Leclerc, M. *J. Am. Chem. Soc.* **2004**, *126*, 4240.

(4) (a) Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197. (b) Ramos, A. C.; Pelaez, R.; Lopez, J. L.; Caballero, E.; Medarde, M.; Feliciano, A. S. *Tetrahedron* **2001**, *57*, 3963.

(5) (a) Funahashi, M.; Zhang, F.; Tamaoki, N. *Adv. Mater.* **2007**, *19*, 353. (b) Koumura, N.; Wang, Z.-S.; Mori, S.; Miyashita, M.; Suzuki, E.; Hara, K. *J. Am. Chem. Soc.* **2006**, *128*, 14256. (c) Yasuda, S.; Yoshida, S.; Sasaki, J.; Okutsu, Y.; Nakamura, T.; Taninaka, A.; Takeuchi, O.; Shigekawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 7746. (d) Murphy, A. R.; Liu, J.; Luscombe, C.; Kavulak, D.; Fréchet, J. M. J.; Kline, R. J.; McGehee, M. D. *Chem. Mater.* **2005**, *17*, 4892.

(6) For reviews, see: (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109.

(7) For representative papers, see: (a) Zambianchi, M.; Maria, F. D.; Cazzato, A.; Gigli, G.; Piacenza, M.; Sala, F. D.; Barbarella, G. *J. Am. Chem. Soc.* **2009**, *131*, 10892. (b) Arai, N.; Miyaoku, T.; Teruya, S.; Mori, A. *Tetrahedron Lett.* **2008**, *49*, 1000. (d) Yu, H.; Pullen, A. E.; Büschel, M. G.; Swager, T. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3700. (e) Vriezema, D. M.; Hoogboom, J.; Velonia, K.; Takazawa, K.; Christianen, P. C. M.; Maan, J. C.; Rowan, A. E.; Nolte, R. J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 772.

(8) For books, see: Blicke, F. F. In *The Chemistry of Heterocyclic Compounds: Thiophenes and its Derivatives*; Hartough, H. D., Ed.; Interscience Publishers: New York, 1952; Chapter 2.

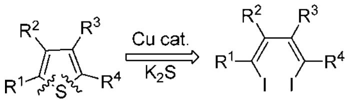
(9) For representative papers, see: (a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (b) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron* **2005**, *61*, 4779. (c) Katritzky, A. R.; Serdyuk, L.; Xie, L.; Ghiviriga, I. *J. Org. Chem.* **1997**, *62*, 6215. (d) Amb, C. M.; Rasmussen, S. C. *Eur. J. Org. Chem.* **2008**, 801.

10.1021/ol101619s

precursors.[10−12] Each of these approaches represents an important advance toward the objective of a general method for the synthesis of substituted thiophenes; each of them, however, suffers from significant limitations in terms of harsh conditions, low yields, expensive catalyst, or difficult purification. Thus, new and efficient methodologies for the construction of substituted thiophenes are still desirable.

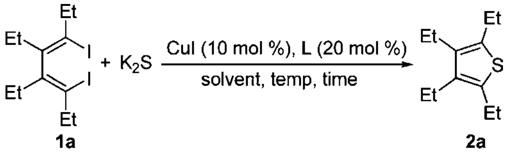
Metal-catalyzed C−S bond formations have played an important role in organosulfur chemistry.[13] With the renaissance of Ullmann coupling in the past few years,[14] the copper-catalyzed cross-coupling reactions of thiols and aryl halides have been demonstrated to be a powerful tool in the formation of aryl C−S bonds.[15] More recently, this methodology was successfully extended to the synthesis of vinyl sulfides by coupling of thiols with vinyl halides either in intermolecular or intramolecular manner.[16,17] It could be envisioned that if a tandem vinylation could proceed between an inorganic sulfide and a 1,4-dihalo-1,3-diene via an intermolecular/intramolecular process, it might provide a straightforward route for the synthesis of thiophene derivatives. However, vinyl C−S cross-coupling reactions with inorganic sulfides have rarely been reported,[18] to the best of our knowledge, despite one of the principal methods of forming C-heteroatom bonds. These results have led us to investigate the participation of K_2S in C−S cross-coupling reactions. Herein we would like to describe a copper-catalyzed double alkenyl C−S bond formation by the reaction of (1*Z*,3*Z*)-1,4-diiodo-1,3-dienes with potassium sulfide, thereby allowing for the synthesis of a wide range of structurally diverse thiophenes including alkyl-substituted electron-rich thiophenes and silyl-substituted thiophenes (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Thiophene Core



1,4-Diiodo-1,3-diene **1a**, which was readily prepared in a one-pot procedure from the coupling of two alkynes with a low-valent metal complex followed by diiodonation,[19a] was used as the model substrate for the optimization of reaction conditions (Scheme 2). The results are summarized in Table 1. Substrate **1a** was first subjected to the following typical conditions for Ullmann coupling: 10 mol % of CuI, 20 mol % of 1,10-phenanthroline (**A**), toluene as solvent, at 110 °C for 24 h. No reaction occurred (entry 1). When the reaction was carried out in acetonitrile, at 110 °C for 24 h, the expected coupling product **2a** was achieved in 70% yield along with 22% of **1a** remained (entry 2). Prolonging the reaction time to 48 h did not help (entry 3). However, when the reaction was carried out in acetonitrile at 140 °C for 24 h, the expected coupling product **2a** was achieved in 99% yield (entry 11). We screened several ligands. Surprisingly, all of the ligands screened (**A**−**H**) (Figure 1) gave similar results (entries 2, 4−10). These results let us suspect that the ligands

Scheme 2. Cu-Catalyzed Tandem C−S Bond-Forming Reactions of 1,4-Dihalo-1,3-dienes **1a**



---

(10) (a) Paal, C. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367. (b) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 299. (c) Tronchet, J. M. J.; Bonenfant, A. P. *Helv. Chim. Acta* **1981**, *64*, 2322. (d) Barton, T. J.; Zika, R. G. *J. Org. Chem.* **1970**, *35*, 1279.

(11) (a) Gewald, K. *Angew. Chem.* **1961**, *73*, 114. (b) Mckibben, B. P.; Cartwright, C. H.; Castelhano, A. L. *Tetrahedron Lett.* **1999**, *40*, 5471. (c) Castanedo, G. M.; Sutherlin, D. P. *Tetrahedron Lett.* **2001**, *42*, 7181. (d) Hoener, A. P. F.; Henkel, B.; Gauvin, J.-C. *Synlett* **2003**, 63. (e) Zhang, H.; Yang, G.; Chen, J.; Chen, Z. *Synthesis* **2004**, 3055.

(12) (a) Wang, Y.; Huang, J.; Chai, Y.; Liu, Q.; Liang, Y.; Dong, D. *J. Comb. Chem.* **2008**, *10*, 511. (b) Wang, Y.; Dong, D.; Yang, Y.; Huang, J.; Ouyang, Y.; Liu, Q. *Tetrahedron* **2007**, *63*, 2724. (c) Kaleta, Z.; Makowski, B. T.; Soos, T.; Dembinski, R. *Org. Lett.* **2006**, *8*, 1625. (d) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (e) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277. (f) Moghaddam, F. M.; Bionee, H. Z. *Tetrahedron* **2004**, *60*, 6085. (g) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351. (h) Fazio, A.; Gabriele, B.; Salerno, G.; Destri, S. *Tetrahedron* **1999**, *55*, 485. (i) Ong, C. W.; Chen, C. M.; Wang, L. F.; Shieh, P. C. *Tetrahedron Lett.* **1998**, *39*, 9191. (j) Stephensen, H.; Zaragoza, F. *J. Org. Chem.* **1997**, *62*, 6096. (k) Chen, J.; Song, Q.; Xi, Z. *Tetrahedron Lett.* **2002**, *43*, 3533.

(13) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205.

(14) For reviews, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973. (d) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153. (e) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(15) (a) Xu, H.-J.; Zhao, X.-Y.; Deng, J.; Fu, Y.; Feng, Y.-S. *Tetrahedron Lett.* **2009**, *50*, 434. (b) Sperotto, E.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *J. Org. Chem.* **2008**, *73*, 5625. (c) Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2008**, 640. (d) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583. (e) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem.—Eur. J.* **2007**, *13*, 5100. (f) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (g) Kumar Verma, A.; Singh, J.; Chaudhary, R. *Tetrahedron Lett.* **2007**, *48*, 7199. (h) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609. (i) Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, 1254. (j) Naus, P.; Leseticky, L.; Smrcek, S.; Tislerova, I.; Sticha, M. *Synlett* **2003**, 2117. (m) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (n) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (o) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283. (p) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986. (q) Pinchart, A.; Dallaire, C.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 543.

(16) Intercoupling of thiols with vinyl halides. Cu-catalyzed, see: (a) Jiang, B.; Tian, H.; Huang, Z.-G.; Xu, M. *Org. Lett.* **2008**, *10*, 2737. (b) Kabir, M. S.; Linn, M. L. V.; Monte, A.; Cook, J. M. *Org. Lett.* **2008**, *10*, 3363. (c) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005. (d) Wang, Z.; Mo, H.; Bao, W. *Synlett* **2007**, 91. (e) Zheng, Y.; Du, X.; Bao, W. *Tetrahedron Lett.* **2006**, *47*, 1217. Pd-catalyzed, see: (f) Lee, J.-Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 7413. (g) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643. (h) Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.-i.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408. Ni-catalyzed, see: (j) Cristau, H. J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *J. Org. Chem.* **1986**, *51*, 875.

(17) Intracoupling of thiols with vinyl halides. Cu-catalyzed, see: (a) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459. Pd-catalyzed, see: (b) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064.

(18) Braye, E. H.; Hübel, W.; Caplier, I. *J. Am. Chem. Soc.* **1961**, *83*, 4406.

Table 1. Optimization of Reaction Conditions for the Formation of **2a**

entry	ligand	solvent	temp (°C)	time (h)	yield (%)[b]
1	A	toluene	110	24	trace
2	A	MeCN	110	24	70
3	A	MeCN	110	48	73
4	B	MeCN	110	24	60
5	C	MeCN	110	24	59
6	D	MeCN	110	24	58
7	E	MeCN	110	24	55
8	F	MeCN	110	24	66
9	G	MeCN	110	24	63
10	H	MeCN	110	24	63
11	A	MeCN	140	24	99 (79)
12	none	MeCN	140	24	99
13[c]	none	MeCN	140	48	0

[a] Reactions were performed with 1a (1.0 mmol), K_2S (3.0 mmol), CuI (0.10 mmol), solvent (5 mL), ligand (0.2 mmol). [b] GC yield, isolated was given in parentheses. [c] No CuI was used.

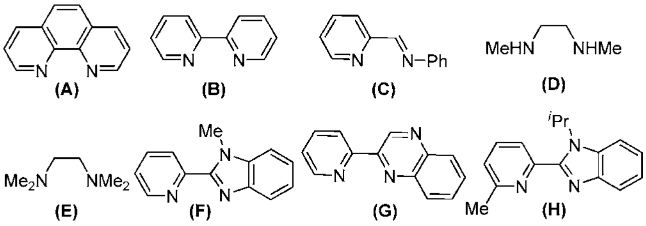
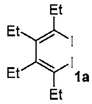
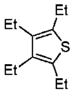
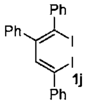
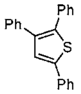
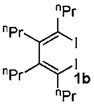
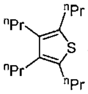
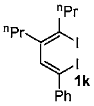
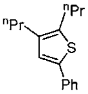
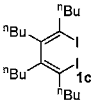
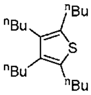
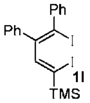
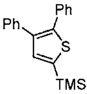
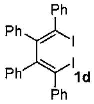
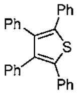
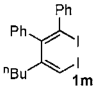
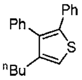
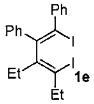
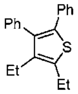
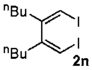
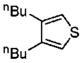
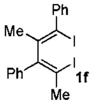
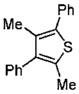
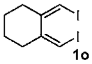
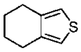
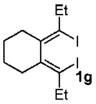
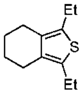
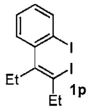
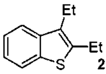
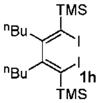
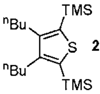
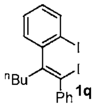
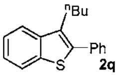
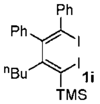
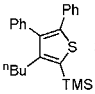
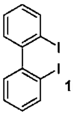
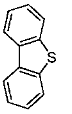


Figure 1. Structure of ligands.

might not participate in the coupling reaction at all because dramatically different effects of ligands are usually observed in Ullmann coupling. Indeed, we were pleased to find that, in the absence of a ligand, the C−S coupling proceeded smoothly, and the thiophene **2a** formed also in excellent yield (entry 12). On the other hand, without CuI, no thiophene could be obtained (entries 13).

Having established an effective catalytic system for the coupling reactions, we next synthesized a variety of diiododienes[19] to explore the scope of double alkenylation under the optimized conditions (10 mol % of CuI, CH_3CN as solvent, at 140 °C). The results are summarized in Table 2. The transformation described herein allows the synthesis of di-, tri-, and tetrasubstituted thiophenes. At the beginning, alkyl-substituted dienyl diiodides were examined, and alkyl-substituted electron-rich thiophenes formed in excellent yields (entries 1−3). Besides alkyl-substituted dienyl diiodides, aryl-substituted dienyl diiodides were also suitable substrates.

Table 2. Scope of the Cu-Catalyzed Tandem C−S Bond-Forming Reactions of 1,4-Diiodo-1,3-diene **1**

entry	substrate 1	product	yield[b] (%)	entry	substrate 1	product	yield[b] (%)
1	 **1a**	 **2a**	79	10	 **1j**	 **2j**	83
2	 **1b**	 **2b**	82	11	 **1k**	 **2k**	80
3	 **1c**	 **2c**	75	12	 **1l**	 **2l**	81
4	 **1d**	 **2d**	93	13	 **1m**	 **2m**	76
5	 **1e**	 **2e**	84	14	 **2n**	 **2n**	79
6	 **1f**	 **2f**	83[c]	15	 **1o**	 **2o**	72
7	 **1g**	 **2g**	77	16	 **1p**	 **2p**	82
8	 **1h**	 **2h**	75	17	 **1q**	 **2q**	78
9	 **1i**	 **2i**	82	18	 **1r**	 **2r**	89

[a] Reactions were performed with substrate 1 (1.0 mmol), K_2S (3.0 mmol), CuI (0.10 mmol). [b] Isolated yield. [c] Combined yield of 2,4-dimethyl-3,5-diphenylthiophene and 3,4-dimethyl-2,5-diphenylthio-phene, which could not be separated from the corresponding isomer.

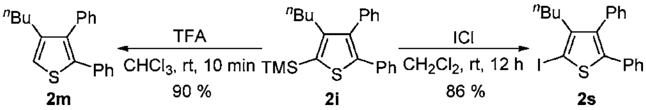
Moreover, silyl-substituted dienyl diiodides were also suitable substrates. The corresponding products were formed in high yields in all cases. When a diiododiene fused with a six-membered ring (**1g** and **1o)** was used, the reactions smoothly occurred to afford bicyclic thiophene **2g** and **2o** in high yields, respectively (entries 7 and 15). Furthermore, reactions of (*Z*)-1-iodo-2-(2-iodovinyl)benzenes were also examined, and benzothiophenes were obtained in excellent yields (entries 16 and 17). 2,2′-Diiodobiphenyl **1r** was also achieved smoothly in the conditions to afford dibenzothiophene **2r** in satisfying yield (entry 18).

In addition to acting as a directing group in the metal-mediated cross-coupling of alkynes, the silyl group also provides a convenient functional handle for further manipulation (Scheme 3). Protodesilylation of **2i** was near quantitative with trifluoroacetic acid (TFA), thus allowing access to other substitution patterns on the thiophene core. More

---

(19) (a) Xi, C.; Huo, S.; Afifi, T. H.; Hara, R.; Takashashi, T. *Tetrahedron Lett.* **1997**, *38*, 4099. (b) Takahashi, T.; Sun, W.-H.; Xi, C.; Ubayama, H.; Xi, Z. *Tetrahedron* **1998**, *54*, 715. (c) Ubayama, H.; Sun, W.-H.; Takahashi, T.; Xi, Z. *Chem. Commun.* **1998**, 1931. (d) Xi, Z.; Liu, X.; Lu, J.; Bao, F.; Fan, H.; Li, Z.; Takahashi, T. *J. Org. Chem.* **2004**, *69*, 854. (e) Xi, Z.; Song, Z.; Liu, G.; Liu, X.; Takahashi, T. *J. Org. Chem.* **2006**, *71*, 3154. (f) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870. (g) Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342.

Scheme 3. Silyl-Substituted Thiophenes As Versatile Intermediates



importantly, the reaction of **2i** with ICl at room temperature cleanly delivered 2-iodothiophene **2s** in 86% isolated yield.

In summary, we have described an efficient copper-catalyzed double vinylation of potassium sulfide with dienyl diiodides. This methodology provided a facile route for the synthesis of di-, tri-, and tetrasubstituted thiophenes in excellent yields. The transformation is distinguished by simplicity, low cost, and tolerance of a wide variety of substituted groups in a range of substitution patterns. Further application of the system to the synthesis of various heterocycles is in progress.

Acknowledgment. We thank the National Natural Science Foundation of China (20872076, 20972085) and the Doctoral Program of Higher Education (200800030072) for financial support.

Supporting Information Available: Experimental procedures and full characterization including ^{1}H NMR and ^{13}C NMR data for compounds **2a**−**2s**; NMR spectra for **2a**−**2s**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101619S