A Novel Cleavage for Polystyrene-Supported Selenium Resins: An Efficient Route to 3,5-Disubstituted Isoxazolines and Their Derivatives

Wei-Ming Xu,[a,b] Yu-Guang Wang,[a] Mao-Zhong Miao,[a] Xian Huang*[a]

[a] Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, 310028, P. R. China
Fax +86(571)88807077; E-mail: huangx@mail.hz.zj.cn

[b] Center of Analysis and Measurement, Zhejiang University, Hangzhou, 310028, P. R. China

Received 28 February 2005; revised 22 March 2005

Abstract: We report here a novel cleavage method for polystyrene-supported selenium resin using CH_3I–NaI under mild conditions to prepare 3,5-disubstituted isoxazolines. The polymer selenium resins can be reused without further transformation.

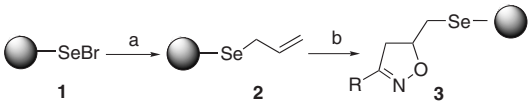
Keywords: heterocycles, selenium, cycloadditions, isoxazolines, solid-phase synthesis

The preparation of diverse libraries of organic compounds is an important facet of modern drug discovery programs. One of the most commonly employed methods in library production is solid-phase organic synthesis (SPOS).[1] Experience has shown that compounds with biological activity are often derived from heterocyclic structures. 1,3-Dipolar cycloaddition reactions are among the most important synthetic manipulations allowing the construction of five-membered ring heterocycles.[2] Nitrile oxides have been shown to be effective 1,3-dipoles and they undergo smooth reactions with substituted alkynes and alkenes to give substituted isoxazoles and isoxazolines, respectively.

Isoxazole and isoxazoline moieties represent two classes of unique pharmacophores that are observed in many therapeutic agents[3] and are versatile intermediates for the synthesis of complex natural products.[4] It is therefore not surprising that these structures have received special attention in combinatorial synthesis and several methods for their preparation have been transferred to the solid phase.[5]

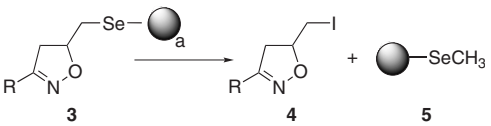
Since the first organoselenium resin[6] was reported in 1976, several groups have developed organoselenium resins as convenient linkers.[7,8] Recently, our research group has been interested in the application of organic selenium resins in organic synthesis.[9] We wish to report here a novel cleavage method, using CH_3I–NaI in DMF under mild conditions, for the isoxazoline supported selenium resin which is prepared from nitrile oxides and polystyrene-supported allyl selenide to afford 3-substituted 5-(iodomethyl)isoxazolines. Evident advantages of this reaction are easy operations, odorlessness, and high purity of the products. And also the resins can be reused without further transformation.

We began our efforts from polystyrene-supported selenenyl bromide [7] (resin **1**) (Br: 0.99 mmol/g), which was treated with $NaBH_4$ and allyl bromide to give the corresponding pale-yellow resin **2** almost quantitatively (FTIR: 1631 cm^{-1} and Br was undetectable). Resin **2** reacted smoothly with nitrile oxides to furnish isoxazoline-supported selenium resin **3** and in this process we found that it was necessary to add Et_3N dropwise over 24 hours to avoid the dimerization of the nitrile oxides (Scheme 1).



Scheme 1 (a) (1) $NaBH_4$, THF, DMF, 40 °C, 8 h; (2) allyl bromide, THF, r.t., 3 h; (b) RCH=NOH, NCS, CH_2Cl_2, Et_3N, r.t., 24 h

Common cleavage protocols of selenium linkers[10] have been reported using two strategies: selenoxide *syn*-elimination and radical hydride transfer. Although a β-H exists in the molecule, selenoxide *syn*-elimination did not occur when we treated resin **3** with H_2O_2 even when we raised the temperature to 50 °C in THF. *n*-Bu_3SnH could be used here as a good radical hydride transfer reagent but it was too toxic. Here we report a new cleavage protocol using CH_3I–NaI in DMF under mild conditions followed by the method that we[11] recently devised under solution conditions (Scheme 2). It shows that 3-substituted 5-(iodomethyl)isoxazolines **4** can be obtained in moderate to good yields with good purity. Results are described in Table 1.



Scheme 2 (a) CH_3I, NaI, DMF, 80 °C, 24 h

It is noteworthy that polystyrene-supported methyl selenide was regenerated after the cleavage stage without further transformation. The regenerated polystyrene-supported methyl selenide[7] could be reused as a starting material and recycled in the same reaction for several times without the loss of purity of the products but with a slight decrease in yield. Results are described in Table 2.

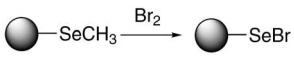
SYNTHESIS 2005, No. 13, pp 2143–2146
Advanced online publication: 24.06.2005
DOI: 10.1055/s-2005-869971; Art ID: F04505SS

Table 1 Synthesis of 3,5-Disubstituted Isoxazolines

Products	R	Yield (%)[a]	Purity [b]
4a	4-FC_6H_4	77	96
4b	4-$NO_2C_6H_4$	71	89
4c	4- BrC_6H_4	78	97
4d	4-ClC_6H_4	82	95
4e	4-$CH_3C_6H_4$	80	98
4f	COOEt	87	98
4g	Ph	78	95

[a] Yield of the crude product based on the loading of the resin **1**.
[b] Determined by HPLC.

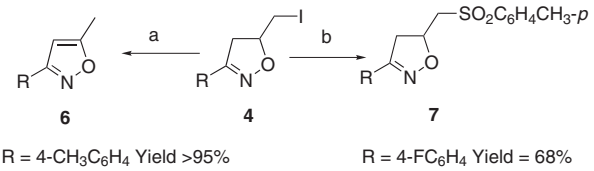
Table 2 Recycling of the Polymer Selenium Resin



Products	Times	Yield (%)[a]	Purity [b]
4e	1	78	98
4e	2	77	96
4e	3	75	96
4e	4	73	96

[a] Yield of the crude product based on the original loading of the resin **1**.
[b] Determined by HPLC.

An outstanding feature of this cleavage reaction is that a new functional group (iodine) is introduced during the cleavage stage, which has versatile reactivities in organic synthesis. 3-Substituted 5-(iodomethyl)isoxazolines **4** reacted with an organic base (DBU) or an inorganic base (NaCN) to afford 3-substituted 5-methylisoxazole **6** almost quantitatively and also they reacted with *p*-$MeC_6H_4SO_2Na$ to afford 3,5-disubstituted isoxazoline **7** in moderate yield (Scheme 3).



Scheme 3 (a) DBU or NaCN, DMF, 80 °C, 12 h; (b) $PhSO_2Na$, DMF, 130 °C, 16 h

In conclusion, we have developed a method for the preparation of 3,5-disubstituted isoxazoles through a novel cleavage protocol of selenium resin. It is noteworthy that the polymer selenium resins used here can be recycled without further transformation.

Starting materials were obtained from commercial suppliers and used without further purification. DMF was distilled from calcium hydride and THF was distilled from sodium–benzophenone immediately prior to use. Polystyrene (H 1000, 100-200 mesh, cross-linked with 1% divinylbenzene) was purchased from commercial sources. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. MS (EI, 70eV) were recorded on a HP5989B mass spectrometer. IR spectra were recorded on a Shimadzu IR-408 spectrometer. Elemental analyses were performed on a Flash EA1112 instrument. HPLC was performed on an Agilernt 1100 high performance liquid chromatograph.

Polystyrene-Supported Selenenyl Bromide 1; Typical Procedure[7]

To a suspension of swollen polystyrene-supported methyl selenide (Se: 1.08 mmol/g) (2.5 g) in anhyd CH_2Cl_2 (40 mL) was dropwise added Br_2 (2.7 mmol in 10 mL anyhyd CH_2Cl_2) under nitrogen atmosphere at 0 °C. After stirring at 0 °C for 30 min, the resin was collected by filtration, washed with CH_2Cl_2 (20 mL × 2) and EtOH (20 mL × 2), and reswelled in EtOH (50 mL). The mixture was stirred at 65 °C for 1 h. After the reaction, the resin **1** was collected by filtration and dried under vacuum.

Preparation of Isoxazoline-Supported Selenium Resin 3; Typical Procedure

To a suspension of the swollen polystyrene-supported selenenyl bromide (Br: 0.99 mmol/g) resin **1** (2.5 g) in anhyd THF–DMF (5:1; 30 mL) was added $NaBH_4$ (5 mmol) under a nitrogen atmosphere at 40 °C. After stirring for 8 h at 40 °C, allyl bromide (5.5 mmol) was added dropwise under a nitrogen atmosphere, and stirring was continued for another 3 h. The resin **2** was collected by filtration, washed with THF (20 mL × 2), THF–H_2O (3:1; 20 mL × 2), H_2O (20 mL × 2), THF (20 mL × 2), and CH_2Cl_2 (20 mL × 2), and dried under vacuum. To a suspension of the swollen resin **2** (2.5 g) in CH_2Cl_2 was added a mixture of hydroximoyl halide (7.5 mmol) in CH_2Cl_2 (10 mL; prepared from 7.5 mmol of aldoxime and 7.5 mmol of NCS stirring at r.t. for about 3 h before use). A mixture of Et_3N (9 mmol) in CH_2Cl_2 (15 mL) was slowly added dropwise in 3 portions every 8 h (each time 3 mmol in 5 mL anhyd CH_2Cl_2 was added). After stirring for 24 h at r.t., the resin **3** was collected by filtration, washed with THF (20 mL × 2), Et_2O (20 mL × 2), THF–H_2O (3:1) (20 mL × 2), THF (20 mL × 2), benzene (20 mL × 2), MeOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2), and dried under vacuum.

Preparation of 3-Substituted 5-Iodomethyl Isoxazolines; General Procedure

To a suspension of the swollen resin **3** (0.5 g) in anhyd DMF (5 mL), was added NaI (1.0 g) and CH_3I (1.0 mL) under nitrogen. The suspension was stirred at 80 °C for 24 h. The mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL × 3). The filtrate was washed successively with sat. aq $NaHCO_3$ (30 mL), sat. aq $Na_2S_2O_3$ (30 mL) and H_2O (30 mL × 3), dried ($MgSO_4$), and evaporated to dryness under vacuum.

3-(4-Fluorophenyl)-5-iodomethylisoxazoline (4a)

White solid; mp; 88–89 °C.

IR: 1630, 1599, 1492, 897, 819, 540 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.70–7.66 (2 H, m), 7.12 (2 H, t, J = 8.8 Hz), 4.96–4.92 (1 H, m), 3.52 (1 H, dd, J_1 = 10.4, J_2 = 16.8 Hz), 3.44 (1 H, dd, J_1 = 4.0, J_2 = 10.4 Hz), 3.28–3.19 (2 H, m).

^{13}C NMR ($CDCl_3$): δ = 163.9 (J = 249.6 Hz), 154.8, 126.7 (J = 8.4 Hz), 125.4 (J = 5.8 Hz), 115.9 (J = 22.3 Hz), 80.5, 41.1, 7.3.

MS: m/z = 178 (40), 305 (100, M^+)

Anal. Calcd for $C_{10}H_9FINO$: C, 39.25; H, 2.87; N, 4.68. Found: C, 39.37; H, 2.97; N, 4.59.

3-(4-Nitrophenyl)-5-iodomethylisoxazoline (4b)
White solid; mp 123–124 °C.

IR: 1630, 1598, 1511, 1340, 1319, 909, 751, 690 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.26 (2 H, d, J = 8.0 Hz), 7.82 (2 H, d, J = 8.0 Hz), 4.99–4.90 (1 H, m), 3.53 (1 H, dd, J_1 = 10.8, J_2 = 17.2 Hz), 3.43 (1 H, dd, J_1 = 4.0, J_2 = 10.0 Hz), 3.28–3.20 (2 H, m).

^{13}C NMR ($CDCl_3$): δ = 154.2, 135.1, 127.4, 126.0, 124.0, 81.3, 40.5, 6.8.

MS: m/z = 332 (100, M^+).

Anal. Calcd for $C_{10}H_9IN_2O_3$: C, 36.29; H, 2.79; N, 8.36. Found: C, 36.17; H, 2.73; N, 8.44.

3-(4-Bromophenyl)-5-iodomethylisoxazoline (4c)
White solid; mp 116–117 °C.

^1H NMR ($CDCl_3$): δ = 7.54 (4 H, s), 4.96–4.92 (1 H, m), 3.49 (1 H, dd, J_1 = 10.8, J_2 = 16.8 Hz), 3.44 (1 H, dd, J_1 = 4.0, J_2 = 10.0 Hz), 3.26–3.17 (2 H, m).

^{13}C NMR ($CDCl_3$): δ = 155.0, 132.0, 128.2, 124.7, 80.7, 40.8, 7.3.

MS: m/z = 75 (100), 365 (82, M^+).

IR: 1629, 1598, 1493, 1102, 896, 821 cm^{-1}.

Anal. Calcd for $C_{10}H_9BrINO$: C, 32.93; H, 2.57; N, 3.78. Found C, 32.82; H, 2.48; N, 3.83.

3-(4-Chlorophenyl)-5-iodomethylisoxazoline (4d)
White solid; mp 91–91.5 °C.

IR: 1631, 1596, 1495, 1098, 892, 826, 612, 543 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.67 (2 H, d, J = 8.4 Hz), 7.45 (2 H, d, J = 8.4 Hz), 5.02–4.96 (1 H, m), 3.57 (1 H, dd, J_1 = 10.4, J_2 = 16.8 Hz), 3.48 (1 H, dd, J_1 = 4.0, J_2 = 10.0 Hz), 3.32–3.23 (2 H, m).

^{13}C NMR ($CDCl_3$): δ = 154.8, 136.3, 129.0, 127.9, 127.6, 80.6, 40.9, 7.2.

MS: m/z = 152 (100), 321 (99, M^+).

Anal. Calcd for $C_{10}H_9ClINO$: C, 37.26; H, 2.88; N, 4.28. Found C, 37.35; H, 2.82; N, 4.36.

3-(4-Methylphenyl)-5-iodomethylisoxazoline (4e)
White solid; mp 86–87 °C.

IR: 1632, 1599, 1580, 1495, 1377, 898, 816 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.56 (2 H, d, J = 8.0 Hz), 7.22 (2 H, d, J = 8.0 Hz), 4.92–4.90 (1 H, m), 3.50 (1 H, dd, J_1 = 10.4, J_2 = 16.8 Hz), 3.42 (1 H, dd, J_1 = 4.0, J_2 = 10.0 Hz), 3.25–3.19 (2 H, m), 2.38 (3 H, s).

^{13}C NMR ($CDCl_3$): δ = 155.7, 140.6, 129.4, 126.7, 126.3, 80.3, 41.1, 21.4, 7.5.

MS: m/z = 91 (100), 301 (74, M^+).

Anal. Calcd for $C_{11}H_{12}INO$: C, 43.99; H, 3.94; N, 4.58. Found: C, 43.87; H, 4.02; N, 4.65.

3-Ethoxycarbonyl-5-iodomethylisoxazoline (4f)
White solid; mp; 77–78 °C.

IR: 1720, 1631, 1591, 1259, 930, 862, 617 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.97–4.93 (1 H, m), 4.36 (2 H, q, J = 7.2 Hz), 3.41–3.34 (2 H, m), 3.22 (1 H, t, J = 9.2 Hz), 3.09 (1 H, dd, J_1 = 7.2, J_2 = 18.2 Hz), 1.38 (3 H, d, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 160.3, 150.8, 82.6, 62.2, 39.7, 14.1, 6.0.

MS: m/z = 91 (100), 283 (74, M^+).

Anal. Calcd for $C_7H_{10}INO_3$: C, 29.81; H, 3.61; N, 4.88. Found: C, 29.70; H, 3.56; N, 4.95.

3-Phenyl-5-iodomethylisoxazoline (4g)
Low-melting solid.

IR: 1631, 1600, 1495, 1108, 892, 758, 693, 540 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.69–7.67 (2 H, m), 7.43–7.41 (3 H, m), 4.97–4.90 (1 H, m), 3.53 (1 H, dd, J_1 = 10.0, J_2 = 16.8 Hz), 3.43 (1 H, dd, J_1 = 4.0, J_2 = 10.0 Hz), 3.27–3.21 (2 H, m).

^{13}C NMR ($CDCl_3$): δ = 155.0, 132.0, 128.6, 128.2, 124.7, 80.7, 40.8, 7.3.

MS: m/z = 91 (100), 287 (89, M^+).

Anal. Calcd for $C_{10}H_{10}INO$: C, 41.93; H, 3.44; N, 4.95. Found: C, 41.83; H, 3.51; N, 4.88.

3-(4-Methylphenyl)-5-methylisoxazole (6)
3-(4-Methylphenyl)-5-iodomethylisoxazoline (0.3 mmol) was dissolved in DMF–THF (5 mL; 2:3), and to the mixture DBU (0.5 mmol) was added. The mixture was stirred at 90 °C for 10 h. After the reaction, CH_2Cl_2 (20 mL) was added. The mixture was washed with sat. aq $NaHCO_3$ (20 mL) and H_2O (15 mL × 3) and dried ($MgSO_4$). Drying without further purification gave **6** as a single product.

White solid; 50.9 mg; mp 57–59 °C.

IR: 3058, 1622, 1599, 1378, 1222, 829 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.62 (2 H, d, J = 8.0 Hz), 7.21 (2 H, d, J = 8.0 Hz), 6.26 (1 H, s), 2.41 (3 H, s), 2.35 (3 H, s).

^{13}C NMR ($CDCl_3$): δ = 169.6, 162.5, 140.0, 129.5, 126.6, 126.5, 99.6, 21.3, 12.3.

MS: m/z = 173 (100, M^+).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.39; H, 6.49; N, 7.97.

3-(4-Fluorophenyl)-5-*para*-toluenesulfonylmethylisoxazoline (7)
3-(4-Fluorophenyl)-5-iodomethylisoxazoline (0.3 mmol) was dissolved in DMF (5 mL), and to the mixture p-$MeC_6H_4SO_2Na$ (0.9 mmol) was added. The mixture was stirred at 130 °C for 10 h. After the reaction, CH_2Cl_2 (20 mL) was added. The mixture was washed with sat. aq $NaHCO_3$ (20 mL) and H_2O (15 mL × 3) and dried ($MgSO_4$). Drying followed by purification via flash chromatography (*n*-hexanes–EtOAc, 4:1) gave **7**.

White solid; 67.9 mg; mp 147–148 °C.

IR: 1627, 1599, 1495, 1319, 1146, 891, 822 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.72 (2 H, d, J = 8.0 Hz), 7.57–7.53 (2 H, m), 7.30 (2 H, d, J = 8.0 Hz), 7.00 (2 H, t, J = 7.6 Hz), 5.02–4.97 (1 H, m), 3.54–3.40 (2 H, m), 3.37 (1 H, dd, J_1 = 6.4, J_2 = 17.6 Hz), 3.26 (1 H, dd, J_1 = 10.4, J_2 = 13.2 Hz), 2.38 (3 H, s).

MS: m/z = 164 (100), 333 (M^+).

Anal. Calcd for $C_{17}H_{16}FNO_3S$: C, 61.38; H, 4.89; N, 4.11. Found: C, 61.25; H, 4.84; N, 4.20.

Acknowledgement

We are grateful to the Natural Science Foundation of China (Project No.20332060 and 20272050) and the CAS Academician Foundation of Zhejiang Province.

References

(1) (a) Guilliier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091. (b) James, I. W. *Tetrahedron* **1999**, *55*, 4855. (c) Sammelson, R. E.; Kurth, M. *J. Chem. Rev.* **2001**, 137. (d) Czarnik, A. W. *Solid-Phase Organic Synthesis*, Vol. 1; Wiley: New York, **2001**. (e) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of Combinatorial Chemistry*; Wiley-VCH: Weinheim, **2002**. (f) Dolle, R. E. *J. Comb. Chem.* **2004**, *6*, 623.

(2) For reviews, see the following: (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, **1984**. (b) Torsell, K. G. B. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, **1988**. (c) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products,* In *The Chemistry of Heterocyclic Compounds*, Vol. 5; Wiley: New York, **2002**.

(3) (a) Rowley, M.; Broughton, H. B.; Collins, I.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Freedman, S. B.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1943. (b) Simoni, D.; Roberti, M.; Invidiata, F. P.; Rondanin, R.; Baruchello, R.; Malagutti, C.; Mazzali, A.; Rossi, M.; Grimaudo, S.; Capone, F.; Dusonchet, L.; Meli, M.; Raimondi, M. V.; Landino, M.; D'Allesandro, N.; Tolomeo, M.; Arindam, D.; Lu, S.; Benbrook, D. M. *J. Med. Chem.* **2001**, *44*, 2308. (c) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, A. E.; Wang, S.; Jiang, B.; Ma, P.; Mousa, S. A.; Olson, R. E.; Wexler, R. R. *J. Med. Chem.* **1997**, *40*, 50.

(4) Koiowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

(5) (a) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195. (b) Dowald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, **2002**, Chap. 15.

(6) Michels, R.; Kato, M.; Heitz, W. *Makromol. Chem.* **1976**, *177*, 2311.

(7) Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, 1947.

(8) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (b) Ruhland, T.; Andersen, K.; Pedersen, H. *J. Org. Chem.* **1998**, *63*, 9204. (c) Zaragoza, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2077. (d) Fujita, K.; Taka, H.; Oishi, A.; Ikeda, Y.; Taguchi, Y.; Fujie, K.; Saeki, T.; Sakuma, M. *Synlett* **2000**, 1509.

(9) (a) Huang, X.; Xu, W. M. *Tetrahedron Lett.* **2002**, *43*, 5495. (b) Xu, W. M.; Tang, E.; Huang, X. *Synthesis* **2004**, 2094. (c) Tang, E.; Huang, X.; Xu, W. M. *Tetrahedron* **2004**, *60*, 9963. (d) Huang, X.; Xu, W. M. *Org. Lett.* **2003**, *5*, 4649.

(10) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G. Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807.

(11) Xu, W. M.; Tang, E.; Huang, X. *Tetrahedron* **2005**, *61*, 501.