Thieme Chemistry Journal Awardees – Where are They Now? Regio- and Stereoselective Radical Additions of Thiols to Ynamides

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Abstract: Regioselective and stereoselective radical additions of arenethiols to various ynamides have been developed. Mixing ynamides and arenethiols in the presence of a catalytic amount of triethylborane affords the corresponding adducts, (*Z*)-1-amino-2-thio-1-alkenes, in excellent yields with high selectivities. The products can be reduced by means of trifluoroacetic acid and triethylsilane to yield 1-amino-2-thioalkanes.

Key words: radical, hydrothiolation, ynamide, hydrogenation

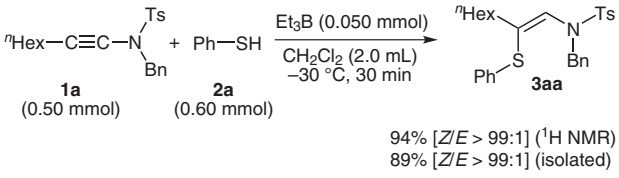
Because of the high importance of organosulfur compounds, development of new reactions to introduce sulfur atoms to organic molecules is indispensable.[1] Radical addition of thiols to unsaturated bonds is one of the most basic and concise methods to achieve the purpose.[2,3] Although radical additions of thiols to terminal alkynes are well known, examples of additions to internal alkynes are limited.[2c,4] Furthermore, additions to heteroatom-substituted internal alkynes have scarcely been reported.[5]

We have focused on *N*-alkynylamides (ynamides),[6] as heteroatom-substituted internal alkynes in the radical addition reaction. Here we report radical hydrothiolation of ynamides,[7,8] which yields synthetically useful (*Z*)-1-amino-2-thio-1-alkene derivatives[9] regio- and stereoselectively.[10]

Under air, a catalytic amount of triethylborane[11] was added to a solution of *N*-benzyl-*N*-(1-octynyl)-*p*-toluenesulfonamide[12] (**1a**) and benzenethiol (**2a**, 1.2 equiv) in dichloromethane at –30 °C. After the mixture was stirred for 30 minutes at the same temperature, the mixture was concentrated. NMR analysis of the crude mixture indicated the formation of *N*-benzyl-*N*-(2-phenylthio-1-octenyl)-*p*-toluenesulfonamide (**3aa**, 94%, *Z*/*E* > 99/1). We confirmed by NOE experiments that the *Z*-isomer was exclusively formed. Silica gel column chromatography afforded **3aa** in 89% yield (Scheme 1).[13]

Hideki Yorimitsu was born in Kochi, Japan, in 1975. He graduated from Kyoto University in 1997 and obtained Ph.D. under the supervision of Koichiro Oshima in 2002. He served as a JSPS postdoctoral fellow, working with Professor Eiichi Nakamura at the University of Tokyo from 2002 to 2003. He then became an Assistant Professor at Kyoto University. He has been an Associate Professor since 2008. His research program focuses on the development of new organic reactions useful for synthesizing biologically interesting compounds, novel coordinating structures, and organometallic compounds.

This reaction would proceed as follows (Scheme 2). Initially, an ethyl radical, generated from triethylborane with a trace amount of molecular oxygen, abstracts hydrogen atom from benzenethiol to form thiyl radical **4**. The electron-deficient radical[14] immediately reacts with ynamide **1a**, an electron-rich alkyne, to furnish vinyl radical **5**. The carbon–sulfur bond formation occurs regioselectively at the 2-position of ynamide **1a**, where the higher electron density resides. The *Z*-isomer of vinyl radical **5** selectively abstracts hydrogen atom from benzenethiol.[15] Product **3aa** is thus formed, and thiyl radical **4** is regenerated to complete the radical chain.



Scheme 1 Triethylborane-initiated hydrothiolation of ynamide **1a**

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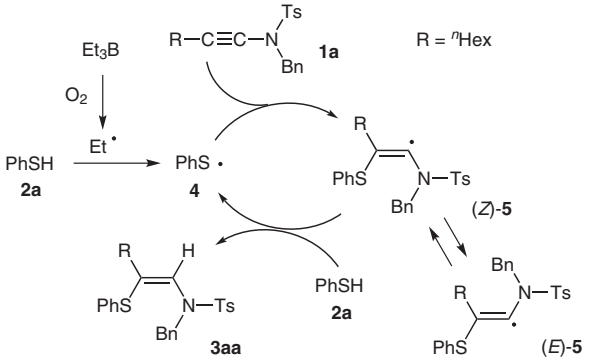
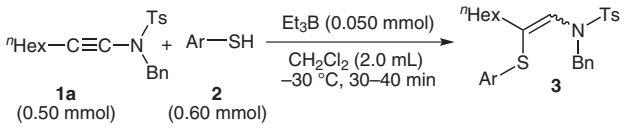


Scheme 2 Plausible reaction mechanism

Electron-deficient arenethiol participated smoothly in this radical reaction (Table 1, entries 2 and 3). On the other hand, additions of electron-rich arenethiols were not efficient (entries 4–6). These poor yields would be due to the low reactivity of the electrophilic thiyl radicals that are stabilized by electron-donating aryl groups. Addition of a catalytic amount of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) to the reaction system or the absence of triethylborane almost prevented the reaction (entries 7 and 8). These results strongly support that the reaction would proceed via the radical chain mechanism.

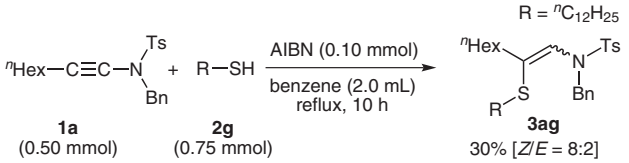
Table 1 Hydrothiolation of **1a** with Various Arenethiols



Entry	Ar	Product	Isolated yield (%) [*Z*/*E*]
1	Ph (**2a**)	**3aa**	89 [>99:1]
2	*p*-BrC_6H_4 (**2b**)	**3ab**	88 [>99:1]
3	C_6F_5 (**2c**)	**3ac**	93 [>99:1]
4	*o*-MeC_6H_4 (**2d**)	**3ad**	31[a] [n.d.[b]]
5	*p*-MeC_6H_4 (**2e**)	**3ae**	23[a] [n.d.[b]]
6[c]	*p*-$MeOC_6H_4$ (**2f**)	**3af**	35 [>99:1]
7[d]	Ph (**2a**)	**3aa**	6[a] [59:41]
8[e]	Ph (**2a**)	**3aa**	<2[a] [n.d.[b]]

[a] NMR yield.
[b] Not determined.
[c] The reaction was performed at r.t.
[d] The reaction was performed with TEMPO (0.10 mmol).
[e] The reaction was performed without triethylborane.

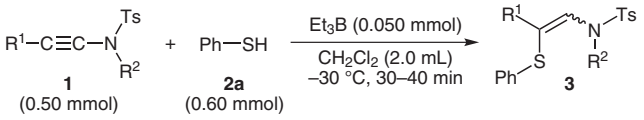
The addition of dodecanethiol (**2g**) to ynamide **1a** did not proceed at –30 °C. The reaction in boiling benzene with AIBN [2,2′-azobis(isobutyronitrile)] instead of triethylborane proceeded, although the yield and stereoselectivity were unsatisfactory (Scheme 3).



Scheme 3 Hydrothiolation of **1a** with dodecanethiol

A wide range of ynamides were subjected to the radical addition of benzenethiol (**2a**; Table 2). Not only **1a** but also ynamides bearing an acid-sensitive THP ether moiety and a base-sensitive ester moiety underwent the addition reactions without loss of the functional groups (entries 2 and 3). Benzenethiol added to ynamide **1d** substituted with a secondary alkyl group in lower yield with slightly lower selectivity (entry 4). Ynamide **1e** having a tertiary alkyl group resisted the addition reaction (entry 5).[16] Replacement of the benzyl group of **1a** by a methyl group slightly decreased the regioselectivity of the reaction (entry 1 vs. entry 6). The allyl group of **1g** remained unchanged under the reaction conditions (entry 7). *N*-Phenyl ynamide **1h** was less reactive than the *N*-benzyl analogue **1a** (entry 8). Not only *p*-toluenesulfonamides **1a–h** but also camphorsulfonamides **1i** and **1j** and Boc-protected ynamide **1k** underwent the radical addition smoothly (Scheme 4).

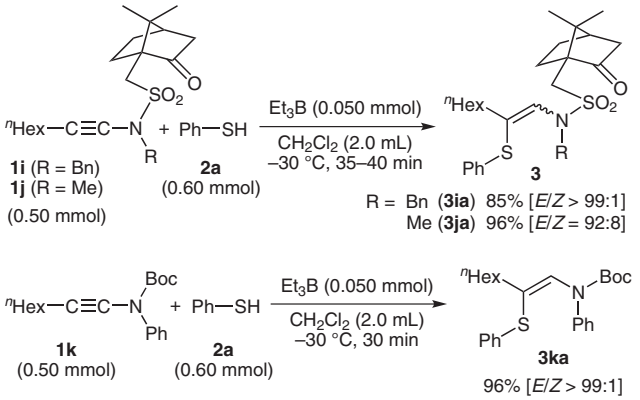
Table 2 Radical Hydrothiolation of *p*-Toluenesulfonyl-Substituted Ynamides with Benzenethiol



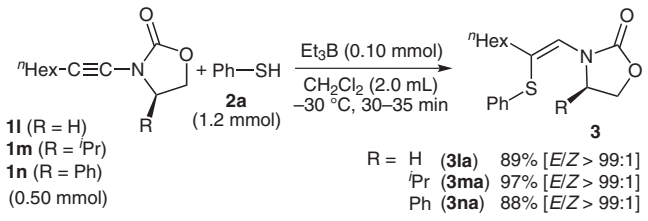
Entry	R^1	R^2	1	Product	Isolated yield (%) [*Z*/*E*]
1	*n*-C_6H_{13}	Bn	**1a**	**3aa**	89 [>99:1]
2	$THPOCH_2$	Bn	**1b**	**3ba**	90 [>99:1]
3	$EtO_2C(CH_2)_4$	Bn	**1c**	**3ca**	97 [>99:1]
4	*c*-C_6H_{11}	Bn	**1d**	**3da**	73 [97:3]
5	*t*-Bu	Bn	**1e**	**3ea**	15[a] [n.d.[b]]
6	*n*-C_6H_{13}	Me	**1f**	**3fa**	97 [96:4]
7	*n*-C_6H_{13}	allyl	**1g**	**3ga**	84 [>99:1]
8	*n*-C_6H_{13}	Ph	**1h**	**3ha**	60 [>99:1]

[a] NMR yield.
[b] Not determined.

The addition reactions to *N*-(1-alkynyl)oxazolidinones led to the exclusive formation of the corresponding *Z* adducts in excellent yields (Scheme 5). In these cases, 2.4 equivalents of benzenethiol and a larger amount of triethylborane were needed.



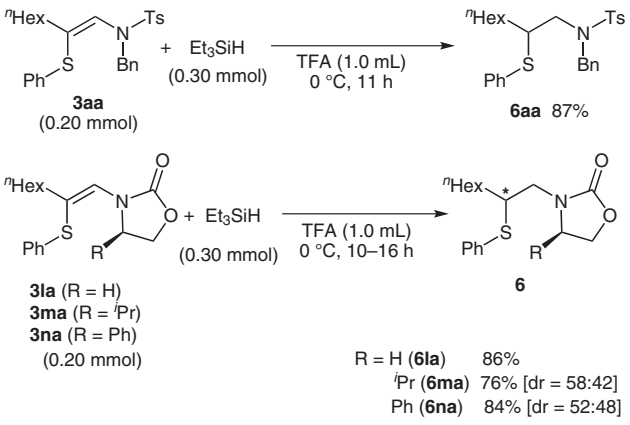
Scheme 4 Radical hydrothiolation of various ynamides with benzenethiol



Scheme 5 Radical hydrothiolation of *N*-(1-alkynyl)oxazolidinone with benzenethiol

Hydrogenation of the double bonds of adducts **3** could provide interesting structures having a phenylthiolated chiral center. We hence tried to reduce alkenylamides **3**. Many attempts to reduce the double of **3aa** in the presence of various transition metal complexes under hydrogen atmosphere resulted in failure, suffering from no conversions.

On the other hand, treatment of **3aa** with triethylsilane in trifluoroacetic acid reduced the alkene moiety[17] to afford the desired *N*-(2-phenylthioalkyl)amide **6aa** in good yield (Scheme 6).[18] Unfortunately, attempted diastereoselective reduction of chiral *N*-(1-alkenyl)oxazolidinones **3ma** and **3na** resulted in the formation of 1:1 mixtures of diastereomers. However, the diastereomers were separable from each other by flash column chromatography on silica gel.



Scheme 6 Reduction of double bonds of adducts **3**

In summary, we have developed a concise method to synthesize (*Z*)-1-amino-2-thio-1-alkene derivatives in high yields with excellent regio- and stereoselectivity. The products can be hydrogenated by the action of triethylsilane in trifluoroacetic acid. Since reduced products **6** have asymmetric carbons, they can be useful as chiral building blocks[19] and chiral bidentate N,S-ligands of transition metal catalysts.[20]

Acknowledgment

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References and Notes

(1) (a) Page, P. *Organosulfur Chemistry*; Academic Press: London, **1995**. (b) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (c) Arisawa, M.; Yamaguchi, M. *Pure Appl. Chem.* **2008**, *80*, 993.

(2) (a) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*, Vol. 2; Wiley-VCH: Weinheim, **2001**, Chapter 5.5.3. (b) Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273. (c) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J.-L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, *16*, 1647. (d) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1035. (e) Chatgilialoglu, C.; Ferreri, C. *Acc. Chem. Res.* **2005**, *38*, 441.

(3) For recent studies including radical hydrothiolations of alkynes, see: (a) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1963. (b) Miyata, O.; Nakajima, E.; Naito, T. *Chem. Pharm. Bull.* **2001**, *49*, 213. (c) Friestad, G. K.; Jiang, T.; Fioromi, G. M. *Tetrahedron: Asymmetry* **2003**, *14*, 2853. (d) Beaufils, F.; Dénès, F.; Renaud, P. *Org. Lett.* **2004**, *6*, 2563. (e) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *Synlett* **2004**, 987. (f) Beaufils, F.; Dénès, F.; Becattini, B.; Renaud, P.; Schenk, K. *Adv. Synth. Catal.* **2005**, *347*, 1587. (g) Yasuda, H.; Uenoyama, Y.; Nobuta, O.; Kobayashi, S.; Ryu, I. *Tetrahedron Lett.* **2008**, *49*, 367. (h) Bencivenni, G.; Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *Org. Lett.* **2008**, *10*, 1127.

(4) (a) Wadsworth, D. H.; Detty, M. R. *J. Org. Chem.* **1980**, *45*, 4611. (b) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2103. (c) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Eur. J. Org. Chem.* **1998**, 1219; and references cited therein. (d) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Tetrahedron* **1998**, *54*, 8207. (e) Fernández-Gonzáles, M.; Alonso, R. *J. Org. Chem.* **2006**, *71*, 6767.

(5) For boron-substituted alkynes, see: (a) Matteson, D. S.; Peacock, K. *J. Org. Chem.* **1963**, *28*, 369. (b) Lhermitte, F.; Carboni, B. *Synlett* **1996**, 377. (c) For sulfur-substituted alkynes, see: Melandri, D.; Montevecchi, P. C.; Navacchia, M. L. *Tetrahedron* **1999**, *55*, 12227.

(6) (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379.

(7) For the first example of a radical reaction involving ynamides, see: Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095.

(8) Our group has reported the hydrothiolation of ynamides with dithiophosphinic acid via cationic intermediates: Kanemura, S.; Kondoh, A.; Yasui, H.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 506.

(9) For examples of the synthesis of (*Z*)-1-amino-2-thio-1-alkene derivatives, see: (a) Apparao, S.; Schmidt, R. R. *Synthesis* **1987**, 896. (b) Kondo, T.; Baba, A.; Nishi, Y.; Mitsudo, T. *Tetrahedron Lett.* **2004**, *45*, 1469.

(10) For hydrothiolations under transition-metal catalysis, see: (a) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108. (b) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614. (c) Ananikov, V. P.; Malyshev, D. A.; Beletskaya, I. P.; Aleksandorov, G. G.; Eremenko, I. L. *Adv. Synth. Catal.* **2005**, *347*, 1993; and references cited therein.

(11) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3465.

(12) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.

(13) **Typical Experimental Procedure for Radical Hydrothiolation of Ynamides**: Under air, Et_3B (1.0 M hexane solution, 0.050 mL, 0.050 mmol) was added to a solution of *N*-benzyl-*N*-(1-octynyl)-*p*-toluenesulfonamide (**1a**, 0.18 g, 0.50 mmol) and benzenethiol (**2a**, 0.062 mL, 0.60 mmol) in CH_2Cl_2 (2.0 mL) at –30 °C. The solution was stirred for 30 min at the same temperature and concentrated in vacuo. ^{1}H NMR analysis of the crude mixture showed a 94% yield of the adduct (*Z*/*E* >99:1). Silica gel column chromatography (hexane–EtOAc = 10:1 → 5:1) afforded *N*-benzyl-*N*-[(*Z*)-2-phenylthio-1-octenyl]-*p*-toluenesulfonamide (**3aa**) as a white solid in 89% yield (0.21 g, 0.45 mmol).
3aa: IR (Nujol): 2925, 1456, 1351, 1339, 1161, 1089, 1024, 741, 661 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.83 (t, *J* = 7.5 Hz, 3 H), 1.02–1.15 (m, 4 H), 1.16–1.35 (m, 4 H), 1.89 (t, *J* = 7.0 Hz, 2 H), 2.45 (s, 3 H), 4.46 (s, 2 H), 5.64 (s, 1 H), 6.90–6.94 (m, 2 H), 7.13–7.21 (m, 3 H), 7.26–7.35 (m, 5 H), 7.36–7.41 (m, 2 H), 7.76–7.80 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 14.04, 21.57, 22.50, 28.09, 28.25, 31.40, 33.36, 54.15, 124.26, 127.14, 127.62, 127.67, 128.32, 128.58, 128.77, 129.60, 132.31, 133.10, 135.63, 135.83, 142.86, 143.59. Anal. Calcd for $C_{28}H_{33}NO_2S_2$: C, 70.11; H, 6.93. Found: C, 70.00; H, 6.94.

(14) It was reported that arylthiyl radicals behave as electron-deficient radicals: Ito, O.; Fleming, M. D. C. M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 689.

(15) The diastereoselectivity can be explained by steric effect. In reference 4b, Montevecci and Spagnolo insisted that primary alkyl groups are bulkier than a phenylthio group. We thus assume that vinyl radical **5** would exist almost as a *Z*-form to prevent the steric repulsion between the bulky amide moiety and the alkyl group. The *Z*-form abstracts hydrogen from benzenethiol selectively. On the other hand, Montevecci et al. also insisted that a methyl group is smaller than a phenylthio group. Indeed, the reaction of *N*-methyl-*N*-(1-propenyl)-*p*-toluenesulfonamide with benzenethiol resulted in favorable formation of the corresponding *Z*-adduct (*E*/*Z* = 2:3).

(16) The addition reaction of phenyl-substituted ynamide PhC≡CNTs(Bn) led to a mixture of stereo- and regioisomers.

(17) Alkenes and ketones can be reduced under these conditions. See: Kursaniov, D. N.; Parnes, Z. N.; Bassova, G. L.; Loim, N. M.; Zdanovich, V. I. *Tetrahedron* **1967**, *23*, 2235.

(18) **Typical Experimental Procedure for Hydrogenations of the Double Bonds of Enamides**: Under an argon atmosphere, Et_3SiH (0.048 mL, 0.30 mmol) was added to a solution of **3aa** (0.096 g, 0.20 mmol) in TFA (1.0 mL, 13.5 mmol) at 0 °C. The solution was stirred for 11 h at the same temperature. Then the reaction was quenched with a sat. $NaHCO_3$ solution and extracted with EtOAc (2 × 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Silica gel column chromatography (hexane–EtOAc, 20:1) afforded *N*-benzyl-*N*-[2-(phenylthio)-octyl]-*p*-toluenesulfonamide (**6aa**) as a colorless oil in 87% yield (0.084 g, 0.17 mmol).
6aa: IR (neat): 2926, 2855, 1599, 1456, 1439, 1342, 1162, 1092, 737, 654 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 7.5 Hz, 3 H), 1.02–1.31 (m, 8 H), 1.34–1.46 (m, 1 H), 1.65–1.75 (m, 1 H), 2.42 (s, 3 H), 2.95–3.05 (m, 2 H), 3.26–3.34 (m, 1 H), 4.05 (d, *J* = 14.5 Hz, 1 H), 4.31 (d, *J* = 14.5 Hz, 1 H), 7.17–7.32 (m, 12 H), 7.57–7.61 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 14.07, 21.49, 22.58, 26.62, 28.94, 30.82, 31.64, 47.40, 53.96, 54.26, 126.75, 127.30, 127.96, 128.58, 128.62, 128.83, 129.69, 131.62, 134.66, 135.82, 136.21, 143.37. Anal. Calcd for $C_{28}H_{35}NO_2S_2$: C, 69.81; H, 7.32. Found: C, 70.03; H, 7.38.

(19) Markgren, P.-O.; Schaal, W.; Hämäläinen, M.; Karlén, A.; Hallberg, A.; Samuelsson, B.; Danielson, U. H. *J. Med. Chem.* **2002**, *45*, 5430.

(20) Chiral *vic*-aminothio compounds serve as ligands in enantioselective reactions. See: (a) Vargas, F.; Sehnem, J. A.; Galetto, F. Z.; Braga, A. L. *Tetrahedron* **2008**, *64*, 392; and references cited therein. (b) Jin, M.-J.; Sarkar, S. M.; Lee, D.-H.; Qiu, H. *Org. Lett.* **2008**, *10*, 1235; and references cited therein.