

# Synthesis of Polysubstituted *N*-H Pyrroles from Vinyl Azides and 1,3-Dicarbonyl Compounds

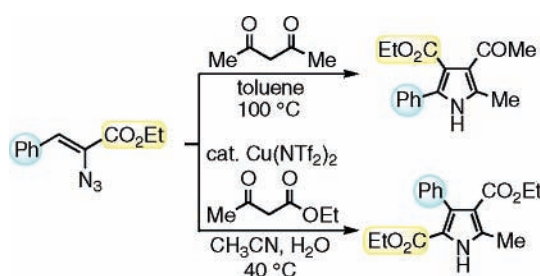
Shunsuke Chiba,\* Yi-Feng Wang, Guillaume Lapointe,<sup>†</sup> and Koichi Narasaka\*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

shunsuke@ntu.edu.sg; narasaka@ntu.edu.sg

Received November 10, 2007

## ABSTRACT



Two synthetic methods for tetra- and trisubstituted *N*-H pyrroles are presented: (i) the thermal pyrrole formation by the reaction of vinyl azides with 1,3-dicarbonyl compounds via the 1,2-addition of 1,3-dicarbonyl compounds to 2*H*-azirine intermediates generated in situ from vinyl azides; (ii) the Cu(II)-catalyzed synthesis of pyrroles from  $\alpha$ -ethoxycarbonyl vinyl azides and ethyl acetoacetate through the 1,4-addition reaction of the acetoacetate to the vinyl azides. By applying these two methods, regioisomeric pyrroles can be prepared selectively starting from the same vinyl azides.

Pyrroles are an important class of compounds in the pharmaceutical<sup>1</sup> and material sciences.<sup>2</sup> Although there have been reported many methods for the synthesis pyrroles,<sup>3</sup> it is still challenging to prepare polysubstituted pyrroles with various substituents directly from readily available building blocks. In this communication, we present two synthetic methods for tetra- and trisubstituted *N*-H pyrroles from vinyl azides and 1,3-dicarbonyl compounds, which give regioisomeric pyrroles selectively.

During the course of our study on the reactions of 2*H*-azirine derivatives with various transition metals,<sup>4</sup> we found that the reaction of 2*H*-azirine **1a** with Cu(acac)<sub>2</sub> in 1,2-dichloroethane gave tetrasubstituted pyrrole **2a** in 94% yield. The reaction with acetylacetone instead of Cu(acac)<sub>2</sub> also provided pyrrole **2a** in quantitative yield (Scheme 1).

<sup>†</sup> Current address: Department für Chemie und Biochemie, Universität Bern, Freiestrasse 3, CH-3012, Switzerland.

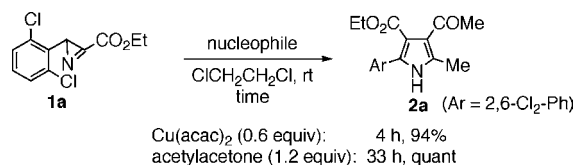
(1) (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, UK, 1996; Vol. 2, p 207. (b) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. *Nat. Prod. Rep.* **2006**, *23*, 517. (c) Huffman, J. W. *Curr. Med. Chem.* **1999**, *6*, 705.

(2) (a) Lee, C. F.; Yang, L. M.; Hwu, T. Y.; Feng, A. S.; Tseng, J. C.; Luh, T. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992. (b) Novak, P.; Müller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev.* **1997**, *97*, 207.

(3) For recent reports on the synthesis of polysubstituted pyrroles, see: (a) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (b) Shindo, M.; Yoshimura, Y.; Hayashi, M.; Soejima, H.; Yoshikawa, T.; Matsumoto, K.; Shishido, K. *Org. Lett.* **2007**, *9*, 1963. (c) Rodríguez Rivero, M.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (d) Cyr, D. J. S.; Martin, N.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 449. (e) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (f) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (g) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465. (h) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (i) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (j) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.

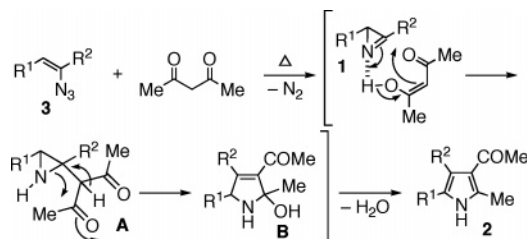
(4) Chiba, S.; Hattori, G.; Narasaka, K. *Chem. Lett.* **2007**, 36, 52.

### Scheme 1. Pyrrole Formation from 2*H*-Azirine **1a**



Although the reaction of 2*H*-azirine **1a** with acetylacetone in THF has been reported, the yield of pyrrole **2a** was low.<sup>5</sup> The high yield of **2a** in the above reaction prompted us to study the pyrrole formation in detail. The reaction may proceed through the addition of acetylacetone to the imino carbon of **1a**,<sup>6</sup> followed by the intramolecular nucleophilic attack of the nitrogen of the resulting aziridine to a carbonyl group with the ring opening of the strained three-membered ring as reported in the reactions with ketone enolates or enamines.<sup>7</sup> Although this reaction seemed to be useful to synthesize pyrroles, most 2*H*-azirines were found to be difficult to prepare and to handle due to their instability.<sup>8</sup> Accordingly, we planned to use vinyl azides as precursors of 2*H*-azirines, which can be easily synthesized<sup>8,9</sup> and are known to be transformed to the corresponding 2*H*-azirines in situ by thermal elimination of dinitrogen (Scheme 2).<sup>8</sup>

### Scheme 2. Synthesis of Pyrroles from Vinyl Azides and 1,3-Dicarbonyl Compounds



As expected, when a mixture of vinyl azide **3a** and acetylacetone was heated in toluene at 100 °C, pyrrole **2a** was obtained in 86% yield (Table 1, entry 1). Various  $\alpha$ -aryl pyrroles ( $R^1$  = aryl) were prepared not only with phenyl substituents possessing both electron-donating and -with-

(5) Alves, M. J.; Gilchrist, T. L.; Sousa, J. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1305.

(6) (a) Alves, M. J.; Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Gilchrist, T. L. *Tetrahedron Lett.* **2000**, 41, 4991. (b) Carlson, R. M.; Lee, S. Y. *Tetrahedron Lett.* **1969**, 10, 4001. (c) Leonard, N. J.; Zwanenburg, B. *J. Am. Chem. Soc.* **1967**, 89, 4456.

(7) (a) Law, K. W.; Lai, T. F.; Sammes, M. P.; Katritzky, A. R.; Mak, T. C. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 111. (b) Laurent, A.; Mison, P.; Nafti, A.; Pellissier, N. *Tetrahedron* **1979**, 35, 2285. (c) Padwa, A.; Kulkarni, Y. *Tetrahedron Lett.* **1979**, 20, 107. (d) Faria dos Santos Filho, P.; Schuchardt, U. *Angew. Chem., Int. Ed. Engl.* **1977**, 16, 647.

(8) (a) Timén, Á. S.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2003**, 44, 5339. (b) Söderberg, B. C. G. *Curr. Org. Chem.* **2000**, 4, 727. (c) Knittel, D. *Synthesis* **1985**, 186.

(9) (a) Nair, V.; George, T. G. *Tetrahedron Lett.* **2000**, 41, 3199. (b) Gilchrist, T. L.; Mendonça, R. *Synlett* **2000**, 1843. (c) Palacios, F.; Aparicio, D.; de los Santos, J. M.; Perez de Heredia, I.; Rubiales, G. *Org. Prep. Proced. Int.* **1995**, 27, 171.

Table 1. Reaction of Vinyl Azides **3** with Acetylacetone<sup>a</sup>

entry	vinyl azide <b>3</b>	R <sub>1</sub>	R <sub>2</sub>	pyrrole <b>2</b>	yield/% <sup>b</sup>
1	<b>3a</b>	2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	CO <sub>2</sub> Et	<b>2a</b>	86
2	<b>3b</b>	Ph	CO <sub>2</sub> Et	<b>2b</b>	93
3	<b>3c</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>2c</b>	90
4	<b>3d</b>	2-Me-C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>2d</b>	89
5	<b>3e</b>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>2e</b>	96
6	<b>3f</b>	4-Br-C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>2f</b>	90
7	<b>3g</b>	4-NC-C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>2g</b>	87
8 <sup>c</sup>	<b>3h</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>2h</b>	81
9	<b>3i</b>	3-pyridyl	CO <sub>2</sub> Et	<b>2i</b>	94
10 <sup>d</sup>	<b>3j</b>	Ph	COMe	<b>2j</b>	74
11	<b>3k</b>	Ph	CONMe <sub>2</sub>	<b>2k</b>	quant
12	<b>3l<sup>e</sup></b>	Ph	H	<b>2l</b>	75
13	<b>3m<sup>f</sup></b>	EtO <sub>2</sub> C	CO <sub>2</sub> Et	<b>2m</b>	82
14 <sup>g</sup>	<b>3n</b>	PhCH <sub>2</sub>	CO <sub>2</sub> Et	<b>2n</b>	96
15	<b>3o</b>	H	CO <sub>2</sub> CH <sub>2</sub> Ph	<b>2o</b>	77
16 <sup>h</sup>	<b>3p</b>	H	Ph	<b>2p</b>	85

<sup>a</sup> 1.2 equiv of acetylacetone was used. <sup>b</sup> Isolated yield. <sup>c</sup> The reaction was performed at 85 °C for 16 h. <sup>d</sup> The reaction was performed at 85 °C for 20 h in the presence of 2 equiv of acetyl acetone. <sup>e</sup> *E:Z* = 1:1. <sup>f</sup> *Z*-isomer. <sup>g</sup> The reaction was performed at reflux for 5 h. <sup>h</sup> The reaction was performed at 100 °C for 24 h.

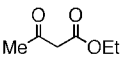
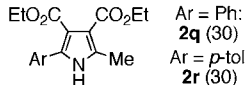
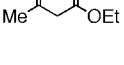
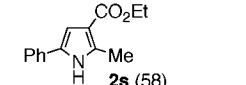
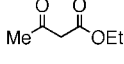
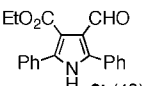
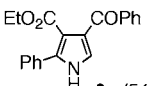
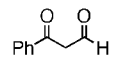
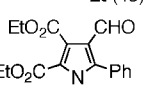
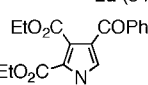
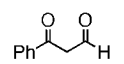
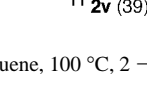
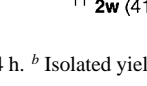
drawing groups (entries 2–8) but also with a pyridyl moiety (entry 9). Instead of  $\alpha$ -ethoxycarbonyl vinyl azides,  $\alpha$ -acetyl (entry 10) and *N,N*-dimethylaminocarbonyl (entry 11) vinyl azides **3j** and **3k** could be employed to give the corresponding pyrroles ( $R^2$  = COCH<sub>3</sub> or CONMe<sub>2</sub>). The reaction of  $\beta$ -azidostyrene (**3l**) gave trisubstituted pyrrole **2l** in good yield (entry 12). It is known that the pyrolysis of  $\beta$ -aryl vinyl azides results in the formation of indoles via intramolecular C–H amination,<sup>10,11</sup> while the reaction with acetylacetone gave pyrroles selectively without any indole formation (entries 2–12). For the  $\beta$ -substituents of vinyl azides ( $R^1$ ), ethoxycarbonyl (**3m**), alkyl (**3n**), and hydrogen (**3o**, **3p**) could be introduced, giving the corresponding pyrroles in good yield (entries 13–16).

Treatment of vinyl azides **3b**, **3c**, and **3l** with a  $\beta$ -keto ester, ethyl acetoacetate, also gave pyrroles **2q**, **2r**, and **2s** in 30, 30, and 58% yield, respectively (Table 2, entries 1–3). A  $\beta$ -oxo aldehyde reacted smoothly with vinyl azides (entries 4 and 5), whereas tri- and tetrasubstituted pyrroles were obtained in almost 1:1 ratio via the nucleophilic attack of the nitrogen atom to both carbonyl groups (Scheme 2, **A**→**B**).

(10) (a) Moody, C. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 21. (b) Smolinsky, G.; Pryde, C. A. *J. Org. Chem.* **1968**, 33, 2411. (c) L'abbé, G. *Angew. Chem., Int. Ed. Engl.* **1975**, 14, 775. (d) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1970**, 101, 161. (e) MacKenzie, A. R.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1983**, 1372. (f) Bolton, R. E.; Moody, C. J.; Pass, M.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2491.

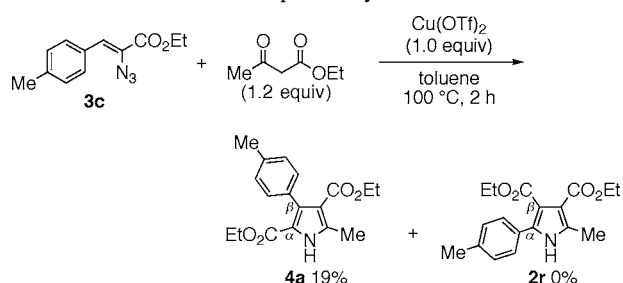
(11) Recently, Rh(II)-catalyzed indole formation from azidocinnamates was reported, see: Stokes, B. J.; Dong, H.; Lesile, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, 129, 7500.

**Table 2.** Reaction of Vinyl Azides with  $\beta$ -keto Ester and Aldehyde<sup>a</sup>

entry	azide <b>3</b>	1,3-dicarbonyl	pyrrole <b>2</b> (yield / %) <sup>b</sup>
1	<b>3b</b>		 Ar = Ph: <b>2q</b> (30) Ar = <i>p</i> -tol: <b>2r</b> (30)
2	<b>3c</b>		 <b>2s</b> (58)
3	<b>3l</b>		 <b>2t</b> (43)  <b>2u</b> (54)
4	<b>3a</b>		 <b>2v</b> (39)  <b>2w</b> (41)
5	<b>3m</b>		 <b>2v</b> (39)  <b>2w</b> (41)

<sup>a</sup> 1.2 equiv of 1,3-dicarbonyls, toluene, 100 °C, 2 – 4 h. <sup>b</sup> Isolated yield.

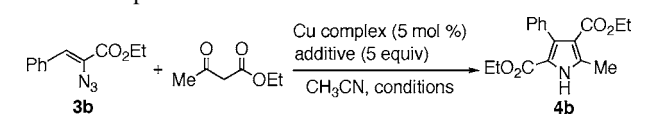
The use of any additives such as acids, bases, etc.<sup>12</sup> could not improve the yield of the reaction of azide **3c** with ethyl acetoacetate, whereas the reaction in the presence of a stoichiometric amount of Cu(OTf)<sub>2</sub> gave an unexpected pyrrole **4a**,<sup>13</sup> which has a reverse substitution pattern ( $\alpha$ -ethoxycarbonyl,  $\beta$ -*p*-tolyl) compared with that of the expected **2r** ( $\alpha$ -*p*-tolyl,  $\beta$ -ethoxycarbonyl) (Scheme 3).

**Scheme 3.** Unexpected Pyrrole Formation

Even by the catalytic use (5 mol %) of Cu(OTf)<sub>2</sub>, the reaction of azide **3b** with ethyl acetoacetate proceeded smoothly in CH<sub>3</sub>CN at 60 °C, giving pyrrole **4b** in 34% yield (Table 3, entry 1). The addition of 5 equiv of water and the use of 3 equiv of ethyl acetoacetate increased the yield of **4b** to 78% (entry 3). Cu(NTF<sub>2</sub>)<sub>2</sub><sup>14</sup> exhibited the catalytic activity for this pyrrole formation as well as Cu(OTf)<sub>2</sub> (entry 4), whereas Cu(PF<sub>6</sub>)(MeCN)<sub>4</sub> afforded **4b** in moderate yield (entry 5).

(12) We examined the following additives; AcOH, PPTS, TfOH, MgBr<sub>2</sub>, Mg(OTf)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, CuCO<sub>3</sub>, DABCO, H<sub>2</sub>O, and MS 4Å.

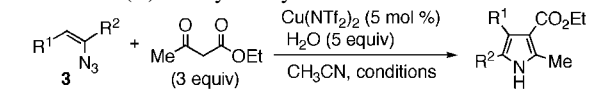
(13) The structure of **4a** was secured by X-ray crystallographic analysis. CCDC-295066 contains the supplementary crystallographic data for compound **4a**. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21 EZ, UK; fax: (+44)1223-336-033; or e-mail deposit@cdc.cam.ac.uk). See Supporting Information.

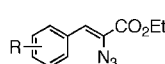
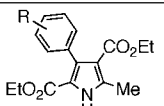
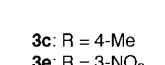
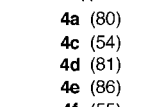
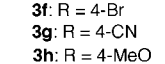
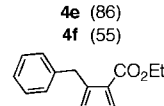
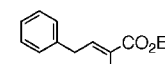
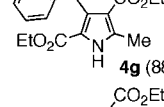
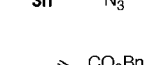
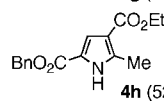
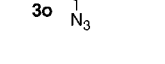
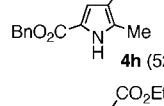
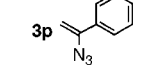
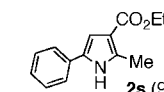
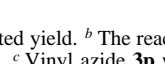
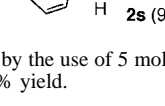
**Table 3.** Optimization of Reaction Conditions


entry	$\beta$ -keto ester (equiv)	Cu cat.	additive	conditions	yield/% <sup>a</sup>
1	1.2	Cu(OTf) <sub>2</sub>	—	60 °C, 16 h	34
2	1.2	Cu(OTf) <sub>2</sub>	H <sub>2</sub> O	60 °C, 18 h	55
3	3.0	Cu(OTf) <sub>2</sub>	H <sub>2</sub> O	40 °C, 30 h	78
4	3.0	Cu(NTF <sub>2</sub> ) <sub>2</sub>	H <sub>2</sub> O	40 °C, 24 h	80
5	3.0	Cu(PF <sub>6</sub> )(CH <sub>3</sub> CN) <sub>4</sub>	H <sub>2</sub> O	40 °C, 24 h	44 (46)

<sup>a</sup> Isolated yield. <sup>b</sup> Recovery of vinyl azide **3b**.

Vinyl azides **3c,e–h,n,o** having an ethoxycarbonyl group at the  $\alpha$ -position were transformed to pyrroles **4** in good to moderate yield (Table 4, entries 1–7). The reaction of vinyl

**Table 4.** Cu(II)-Catalyzed Pyrrole Formation


entry	vinyl azides <b>3</b>	conditions	pyrroles (yield / %) <sup>a</sup>
1		40 °C, 24 h	 <b>4a</b> (80)
2		40 °C, 24 h	 <b>4c</b> (54)
3		40 °C, 24 h	 <b>4d</b> (81)
4		40 °C, 24 h	 <b>4e</b> (86)
5		40 °C, 24 h	 <b>4f</b> (55)
6		60 °C, 20 h	 <b>4g</b> (88)
7		40 °C, 24 h	 <b>4h</b> (52)
8 <sup>b</sup>		60 °C, 24 h	 <b>2s</b> (9) <sup>c</sup>

<sup>a</sup> Isolated yield. <sup>b</sup> The reaction was performed by the use of 5 mol % of Cu(OTf)<sub>2</sub>. <sup>c</sup> Vinyl azide **3p** was recovered in 43% yield.

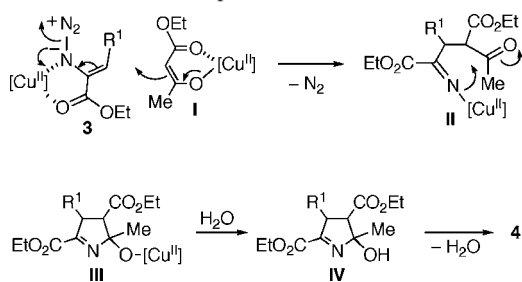
azide **3p** with an  $\alpha$ -phenyl group, however, gave the corresponding pyrrole **2s** in only 9% yield (entry 8).

Since the Cu-catalytic reaction was performed at 40–60 °C, a 2*H*-azirine intermediate is unlikely to be on the reaction course.<sup>15</sup> The reaction may be initiated by the 1,4-addition of copper enolate **I** to vinyl azide **3**, the internal nitrogen of which coordinates to copper (Scheme 4).<sup>16</sup>

(14) Earle, M. J.; Hakala, U.; McAuley, B. J.; Nieuwenhuyzen, M.; Ramani, A.; Seddon, K. R. *Chem. Commun.* **2004**, 1368.

(15) No reaction was observed by the treatment of vinyl azide **3b** with a stoichiometric amount of Cu(OTf)<sub>2</sub> and Cu(NTF<sub>2</sub>)<sub>2</sub> in CH<sub>3</sub>CN at 40–60 °C.

**Scheme 4.** Proposed Reaction Mechanism



Simultaneous elimination of dinitrogen affords alkylidene-aminocopper **II**, which undergoes intramolecular nucleophilic attack to the carbonyl group, affording pyrrole with the elimination of water.

The radical pathway via the generation of iminyl radical<sup>17</sup> is not completely excluded due to the formation of pyrrole

(16) (a) For a report on the coordination of the internal nitrogen of an organic azide with a Cu(II) complex, see: Barz, M.; Herdweck, E.; Thiel, W. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2262. (b) For a review on the coordination of organic azides with transition metals: Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, *250*, 1234.

**2s** from  $\alpha$ -azido styrene (**3p**) in spite of the quite low yield (entry 8). Further studies on the scope, mechanism, and synthetic applications of this reaction are in progress.

**Acknowledgment.** This paper is dedicated to the late Professor Yoshihiko Ito for his outstanding contribution to synthetic organic chemistry. We acknowledge the Nanyang Technological University for funding of this research. We thank Dr. Junji Kobayashi (Department of Chemistry, Graduate School of Science, The University of Tokyo) for assistance with the X-ray crystallographic analysis.

**Supporting Information Available:** Experimental procedures, characterization of new compounds, and CIF files giving crystallographic data for **4a** (CCDC-656009). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL70272J

(17) For prior studies on the iminyl radical formation from vinyl azides, see: (a) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *J. Org. Chem.* **1997**, *62*, 5864. (b) Bamford, A. F.; Cook, M. D.; Roberts, B. P. *Tetrahedron Lett.* **1983**, *24*, 3779.