Manganese(III)-Catalyzed Formal [3+2] Annulation of Vinyl Azides and β-Keto Acids for Synthesis of Pyrroles

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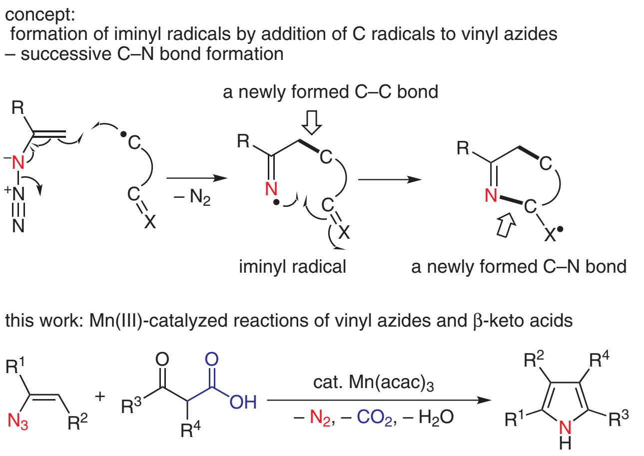
Abstract: Manganese(III)-catalyzed formal [3+2] annnulation of vinyl azides and β-keto acids has been developed for the synthesis of substituted NH pyrroles with a wide range of substituents.

Key words: manganese(III) catalysts, radical reactions, vinyl azides, β-keto acids, pyrroles

Pyrroles are one of the most prevalent heterocyclic compounds, being present as the basic cores in a lot of natural products,[1] potent pharmaceutical compounds,[2] and various kinds of functional materials.[3] Although diverse approaches toward the synthesis of pyrroles have been developed,[4,5] versatile and flexible methodologies to construct pyrroles with selective control of substitution patterns using readily accessible building blocks are still needed.

We have recently been interested in the application of vinyl azides as a three-atom unit including one nitrogen to synthesize azaheterocycles. One of our reaction designs involves the addition of a carbon radical to the C=C bond of a vinyl azide to provide a new C–C bond with generation of an iminyl radical.[6] The iminyl radical then intramolecularly forms a C–N bond by the cyclization with an unsaturated bond (Scheme 1).[7,8] Our current study has focused on the use of 1,3-dicarbonyl compounds as a precursor/equivalent of α-carbonyl radicals and on the investigation of their addition reactions toward vinyl azides. We recently succeeded in the manganese(III)-catalyzed formal [3+2] annulation by the combined use of vinyl azides and 1,3-dicarbonyl compounds such as β-keto esters and 1,3-diketones, where manganese(III) acetate [$Mn(OAc)_3 \cdot 2H_2O$] and manganese(III) tris(2-pyridinecarboxylate) [$Mn(pic)_3$] were respectively utilized to prepare densely functionalized pyrroles.[8b]



Scheme 1 A concept for the synthesis of azaheterocycles from vinyl azides

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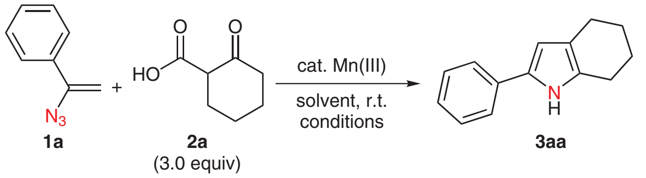
β-Keto acids have been utilized as an equivalent of either α-carbonyl anions[9] or radicals[10] with elimination of carbon dioxide. As it was found that vinyl azides exhibited good reactivity toward the α-carbonyl radicals derived from β-keto esters and 1,3-diketones with manganese(III) catalysts, we intended to study the reaction of vinyl azides and β-keto acids. In this communication, we report a reaction of vinyl azides and β-keto acids for the synthesis of substituted pyrroles catalyzed by manganese(III) acetylacetonate [$Mn(acac)_3$].

Firstly, a suitable catalytic system was explored using α-azidostyrene (**1a**) and β-keto acid **2a** with manganese(III) complexes (Table 1). The reaction with 10 mol% of $Mn(OAc)_3 \cdot 2H_2O$ required long reaction time (30 h) to consume vinyl azide **1a**, affording the desired bicyclic pyrrole (4,5,6,7-tetrahydro-1*H*-indole) **3aa** in 51% yield (Table 1, entry 1). Although utilization of $Mn(pic)_3$ accel-

Table 1 Reactions of Vinyl Azide **1a** with β-Keto Acid **2a** Using Manganese(III) Complexes[a]



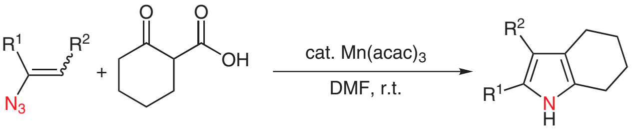
Entry	Mn(III) (equiv)	Solvent	Time (h)	Yield (%)[b]
1	$Mn(OAc)_3 \cdot 2H_2O$ (0.1)	DMF	30	51
2	$Mn(pic)_3$ (0.2)	DMF	1	59
3	$Mn(acac)_3$ (0.1)	DMF	5	83
4	$Mn(acac)_3$ (0.1)	MeOH	17	0
5	$Mn(acac)_3$ (0.1)	MeCN	36	76

[a] Reactions were performed under N_2 atmosphere using 0.3 mmol of **1a**.
[b] Isolated yield.

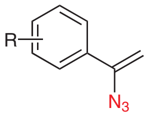
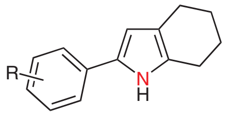
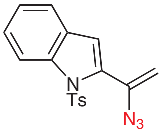
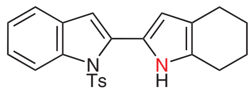
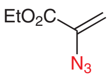
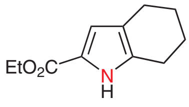
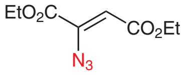
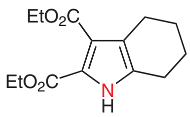
erated the reaction (entry 2), the yield of **3aa** was comparable with that obtained with $Mn(OAc)_3·2H_2O$ (entry 1). The yield of pyrrole **3aa** was further improved to 83% by employing $Mn(acac)_3$ (entry 3).[11] It was noted that the choice of solvent was crucial to this reaction. No reaction was observed in methanol, which gave the best results in the $Mn(OAc)_3·2H_2O$- and $Mn(pic)_3$-catalyzed pyrrole formation with β-keto esters and 1,3-diketones, respectively (entry 4).[8b] The reaction in acetonitrile needed longer reaction time, while providing the desired pyrrole **3aa** in good yield (entry 5).

With the optimized reaction conditions in hand, the generality of this reaction was investigated by employing a range of vinyl azides **1** and β-keto acids **2** with $Mn(acac)_3$ as a catalyst. The reactions of various vinyl azides **1** with β-keto acid **2a** are summarized in Table 2. The reaction of α-aryl vinyl azides with **2a** provided the desired bicyclic pyrroles in good yields (entries 1–5). Notably, the reaction of vinyl azide **1f** possessing an α-indole substituent led to the formation of an interesting 2,2′-bisindole derivative **3fa** (entry 6). Moreover, α-ethoxycarbonyl vinyl azides **1g** and **1h** also could be applied to this reaction, giving the corresponding bicyclic pyrroles **3ga** and **3ha** in good yields (entries 7 and 8). In the case of vinyl azide **1h**, the presence of ethoxycarbonyl at the β-position did not retard the reaction, providing tetrasubstituted pyrrole **3ha** in 74% yield (entry 8).

Table 2 Substrate Scope on Vinyl Azides[a,b]

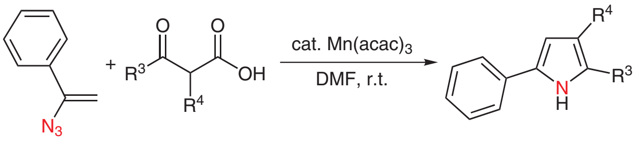


1 2a (1.5–3 equiv) 3

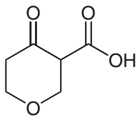
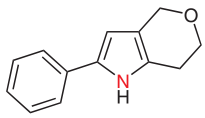
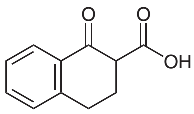
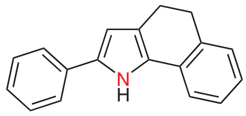
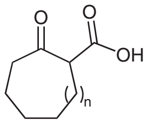
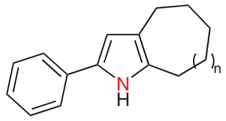
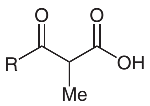
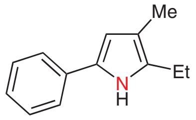
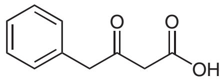
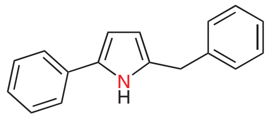
Entry	Vinyl azide **1**	Pyrrole **3**/yield (%)
		
1	**1a** (R = H)	**3aa** (83)[c]
2	**1b** (R = 4-Br)	**3ba** (92)[d]
3	**1c** (R = 4-CO_2Me)	**3ca** (68)[d]
4	**1d** (R = 2-MeO)	**3da** (91)[d]
5	**1e** (R = 4-MeO)	**3ea** (87)[d]
6	 **1f**	 **3fa** (76)[c]
7	 **1g**	 **3ga** (68)[c]
8	 **1h**	 **3ha** (74)[c]

[a] Reactions were performed in DMF at r.t. with 1.5–3.0 equiv of β-keto acids **2** under N_2 atmosphere.
[b] Isolated yields were noted above.
[c] $Mn(acac)_3$ used: 10 mol%.
[d] $Mn(acac)_3$ used: 20 mol%.

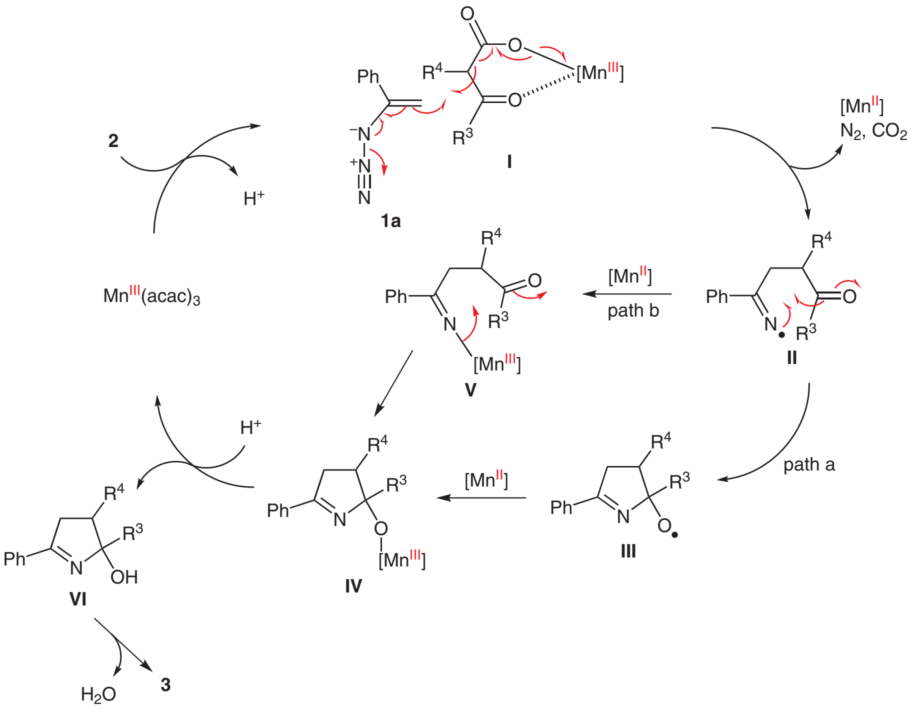
Table 3 Substrate Scope on β-Keto Acids[a,b]



1a 2 (1.5–3 equiv) 3

Entry	β-Keto acid **2**	Pyrrole **3**/yield (%)
1	 **2b**	 **3ab** (70)[c]
2	 **2c**	 **3ac** (65)[d]
		
3	**2d** (n = 1)	**3ad** (81)[e]
4	**2e** (n = 2)	**3ae** (82)[e]
		
5	**2f** (R = Et)	**3af** (84)[e]
6	**2g** (R = Ph)	**3ag** (82)[e]
7	 **2h**	 **3ah** (23)[f]

[a] Reactions were performed in DMF at r.t. with 1.5–3.0 equiv of β-keto acid **2** under N_2.
[b] Isolated yields were noted above.
[c] $Mn(acac)_3$ used: 30 mol%.
[d] $Mn(acac)_3$ used: 40 mol%; β-keto acid **2c** was added through a syringe pump over 1 h.
[e] $Mn(acac)_3$ used: 20 mol%.
[f] $Mn(pic)_3$ used: 1 equiv. Utilization of $Mn(acac)_3$ (1 equiv) afforded pyrrole **3ah** in only 10% yield.



Scheme 2 A proposed catalytic cycle.

Next, the scope of β-keto acids **2** was investigated with vinyl azide **1a** (Table 3). Tetrahydropyrano[4,3-*b*]pyrrole **3ab** and 4,5-dihydro-1*H*-benzo[*g*]indole **3ac** were assembled in good yields by employing β-keto acids **2b** and **2c**, respectively (entries 1 and 2). As the β-keto acid **2c** was labile in such oxidative conditions, the slow addition of **2c** through a syringe pump was required (entry 2). Bicyclic pyrroles bearing larger carbocycles **3ad** and **3ae** could be obtained by treatment with β-keto acids **2d** and **2e** (entries 3 and 4). In addition, the reactions of linear β-keto acids **2f** and **2g** proceeded, affording the trisubstituted pyrroles **3af** and **3ag**, respectively, in good yields, (entries 5 and 6). However, β-keto acid **2h**, which could generate a primary α-carbonyl radical, was not viable for the reaction, delivering only 23% yield of the desired pyrrole **3ah** even by using a stoichiometric amount of the manganese(III) complexes (entry 7).

This catalytic reaction may be initiated by addition of manganese(III) carboxylate **I** to vinyl azide **1a** via a radical pathway,[12] giving iminyl radical **II** with release of manganese(II) species, N_2, and CO_2 (Scheme 2). The resulting iminyl radical **II** undergoes intramolecular addition to a carbonyl group to give alkoxy radical **III**. Reduction of this alkoxy radical **III** by manganese(II) species gives manganese(III) alkoxide **IV** (path a). Alternatively, the reaction of iminyl radical **II** with manganese(II) species affords iminylmanganese(III) **V**, which attacks a carbonyl group to yield the addition intermediate **IV** (path b).[13] Finally, protonation of **IV** followed by dehydration produces pyrrole **3** along with regeneration of manganese(III).

In summary, Mn(acac)$_3$-catalyzed formal [3+2] annulation of vinyl azides and β-keto acids was successfully developed for the synthesis of N–H pyrroles with a variety of substituents.[14] Further investigation to explore other modes of annulation reactions of vinyl azides to prepare azaheterocycles is in progress.

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References and Notes

(1) For recent reviews, see: (a) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (b) Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582. (c) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753.

(2) (a) Hall, A.; Atkinson, S.; Brown, S. H.; Chessell, I. P.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Healy, M. P.; Jandu, K. S.; Johnson, M. R.; Michel, A. D.; Naylor, A.; Sweeting, J. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1200. (b) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. (c) Micheli, F.; Di Fabio, R.; Benedetti, R.; Capelli, A. M.; Cavallini, P.; Cavanni, P.; Davalli, S.; Donati, D.; Feriani, A.; Gehanne, S.; Hamdan, M.; Maffeis, M.; Sabbatini, F. M.; Tranquillini, M. E.; Viziano, M. V. A. *Farmaco* **2004**, *59*, 175. (d) Huffman, J. W. *Curr. Med. Chem.* **1999**, *6*, 705. (e) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 357.

(3) (a) Plitt, P.; Gross, D. E.; Lynch, V. M.; Sessler, J. L. *Chem. Eur. J.* **2007**, *13*, 1374. (b) Zhao, W.; Carreira, E. M. *Chem.*

Eur. J. **2006**, *12*, 7254. (c) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465. (d) Nadeau, J. M.; Swager, T. M. *Tetrahedron* **2004**, *60*, 7141. (e) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17. (f) Yoon, D. W.; Hwang, H.; Lee, C. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1757. (g) Seidel, D.; Lynch, V.; Sessler, J. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 1422. (h) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem. Int. Ed.* **2000**, *39*, 1777. (i) Depraetere, S.; Smet, M.; Dehaen, W. *Angew. Chem. Int. Ed.* **1999**, *38*, 3359.

(4) For recent reviews on the synthesis of pyrroles, see: (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (b) Ferreira, V. F.; de Souza, M.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411. (c) Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238. (d) Joshi, U.; Pipelier, M.; Naud, S.; Dubreuil, D. *Curr. Org. Chem.* **2005**, *9*, 261. (e) Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, *(x)*, 121. (f) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095.

(5) For recent selected reports on the synthesis of polysubstituted pyrroles, see: (a) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (b) Morin, M. A. T.; St-Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2010**, *12*, 4916. (c) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290. (d) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372. (e) Zhao, X.; Zhang, E.; Tu, Y.-Q.; Zhang, Y.-Q.; Yuan, D.-Y.; Cao, K.; Fan, C.-A.; Zhang, F.-M. *Org. Lett.* **2009**, *11*, 4002. (f) Fu, X.; Chen, J.; Li, G.; Liu, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 5500. (g) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2009**, *12*, 372. (h) Lu, Y.; Arndtsen, B. A. *Org. Lett.* **2009**, *11*, 1369. (i) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2009**, *12*, 312. (j) Kiren, S.; Hong, X.; Leverett, C. A.; Padwa, A. *Org. Lett.* **2009**, *11*, 1233. (k) Fontaine, P.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 1555. (l) Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293. (m) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624. (n) Mizuno, A.; Kusama, H.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 8318. (o) Ackermann, L.; Sandmann, R.; Kaspar, L. T. *Org. Lett.* **2009**, *11*, 2031. (p) Lu, Y.; Arndtsen, B. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 5430. (q) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629. (r) Attanasi, O. A.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Spinelli, D. *Org. Lett.* **2008**, *10*, 1983. (s) St. Cyr, D. J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366. (t) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem. Eur. J.* **2007**, *13*, 9973. (u) Su, S.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (v) Martín, R.; Rodríguez Rivero, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079. (w) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006**, *8*, 5837. (x) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349. (y) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (z) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260.

(6) For prior studies on iminyl radical formation from vinyl azides, see: (a) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *J. Org. Chem.* **1997**, *62*, 5846. (b) Bamford, A. F.; Cook, M. D.; Roberts, B. P. *Tetrahedron Lett.* **1983**, *24*, 3779.

(7) For reviews of synthesis of azaheterocycles using iminyl radicals, see: (a) Stella, L. In *Radicals in Organic Synthesis*, Vol. 2; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**, 407–426. (b) Mikami, T.; Narasaka, K. In *Advances in Free Radical Chemistry*, Vol. 2; Zard, S. Z., Ed.; JAI: Greenwich, **1999**, 45–88. (c) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (d) Zard, S. Z. *Synlett* **1996**, 1148.

(8) For our previous communications based on this concept for the synthesis of azaheterocycles, see: (a) Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570. (b) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019.

(9) Fortner, K. C.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 1032.

(10) Narasaka, K.; Miyoshi, N.; Iwakura, K.; Okauchi, T. *Chem. Lett.* **1989**, *18*, 2169.

(11) Mn(OAc)$_3$, Mn(pic)$_3$, and Mn(acac)$_3$ possess different redox potentials, see: Richert, S. A.; Tsang, P. K. S.; Sawyer, D. T. *Inorg. Chem.* **1988**, *27*, 1814.

(12) For the addition of manganese(III) enolate to alkenes to give alkyl radicals, see: Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137.

(13) For an example of addition of aminyl radicals to carbonyl groups, see: Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328.

(14) **General Procedure for Mn(acac)$_3$-Catalyzed Pyrrole Formation from Vinyl Azides and β-Keto Acids**: To a solution of α-azido styrene (**1a**; 52.8 mg, 0.364 mmol) and 2-oxocyclohexanecarboxylic acid (**2a**; 155.2 mg, 1.09 mmol) in DMF (3.6 mL) was added Mn(acac)$_3$ (12.8 mg, 0.0364 mmol) and the mixture was stirred for 5 h. The reaction mixture was quenched with a pH 9 ammonium buffer, and then extracted with Et$_2$O (2 ×). The combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated. Purification of the crude product by flash column chromatography (florisil; hexane–EtOAc = 97:3) afforded **3aa** (59.5 mg, 0.302 mmol) in 83% yield.