

Mn(III)-Catalyzed Radical Reactions of 1,3-Dicarbonyl Compounds and Cyclopropanols with Vinyl Azides for Divergent Synthesis of Azaheterocycles

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Abstract: Mn(III)-catalyzed formal [3+2]- and [3+3]-annulations have been developed using readily available vinyl azides with 1,3-dicarbonyl compounds and cyclopropanols. Vinyl azides were successfully applied as a three-atom unit including one nitrogen to prepare various azaheterocycles *via* Mn(III)-catalyzed radical reactions.

Keywords: Azaheterocycles · Cyclopropanols · 1,3-Dicarbonyl compounds · Manganese · Radicals · Vinyl azides

1. Introduction

Azaheterocycles are an omnipresent component of numerous natural alkaloids and potent pharmaceutical drugs.^[1] Although diverse synthetic approaches toward azaheterocycles have been exploited,^[2] there remains a need for conceptually novel and versatile methodologies for chemical synthesis of azaheterocycles from readily available building blocks. Intermolecular annulation reactions allow rapid and selective construction of complex cyclic molecules in a one-pot manner from relatively simple building blocks, which is one of the most ideal processes in organic synthesis from atom-^[3] and step-^[4] economical point of views. Guided by these views, we have recently been interested in application of vinyl azides as a three-atom unit including one nitrogen to develop new types of annulation reactions for synthesis of azaheterocycles. This review mainly focuses on the Mn(III)-catalyzed radical

reactions of 1,3-dicarbonyl compounds and cyclopropanols with vinyl azides for a divergent synthesis of azaheterocycles, which have been recently developed in our research group at Nanyang Technological University, Singapore.^[5]

2. Backgrounds of Vinyl Azides and Mn(III)-Mediated Oxidative Radical Reactions

Vinyl azides are readily prepared from commercially available starting materials in several ways, and generally stable/easy to handle.^[6] The application of vinyl azides to synthetic organic reactions have been exclusively relied on their thermal denitrogenative decomposition to vinyl nitrenes, which could be converted into highly reactive strained three-membered ring, 2*H*-azirines (Scheme 1).^[7] Heating of azido cinnamates in aprotic solvents (for example, xylene at 140 °C) gave indoles *via* aromatic C–H amination of putative 2*H*-azirine intermediates, which have been widely utilized for synthesis of indole alkaloids and potent pharmaceutical drugs bearing indole cores.^[8,9]

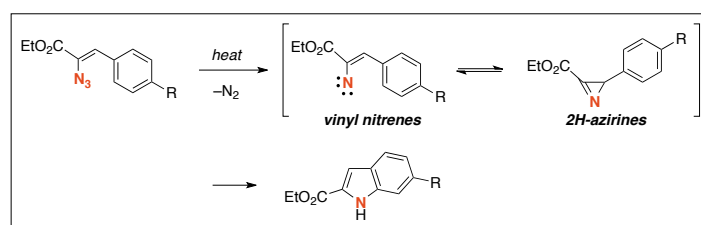
We planned to use the C=C bond of vinyl azides for initiation of the reactions. Although such attempts have been extremely scarce, we could get two key hints

from the following literature precedents to implement our research projects with a radical strategy.

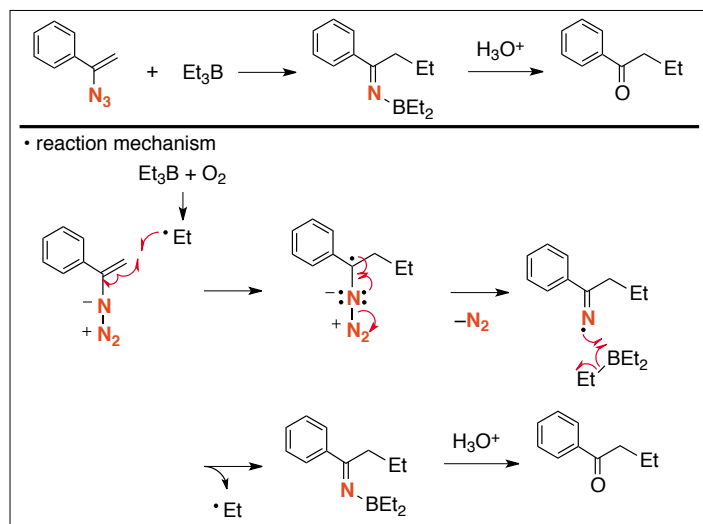
The 1st key: In 1975, Suzuki reported the reaction of α -azido styrene with triethylborane, which provided butyrophenone after aqueous workup (Scheme 2).^[10] In 1983, Roberts had clarified the reaction mechanism of this C–C bond forming reaction,^[11] which included a free radical process. An ethyl radical generated from triethylborane with molecular oxygen adds to the C=C bond of α -azido styrene to give the α -azido radical, which undergoes quick denitrogenation to afford an iminyl radical. The reaction of the resulting iminyl radical reacts with triethylborane to generate an ethyl radical that maintains the radical chain. The resulting iminylborane is hydrolyzed under work-up to give butyrophenone.

The 2nd key: Manganese(III)-mediated oxidative radical reactions have been extensively studied to construct new C–C bonds since the pioneering reactions of acetic acid with alkenes mediated by Mn(III) acetate were reported in 1968.^[12] Especially, this Mn(III)-mediated oxidative radical strategy has been applied for the reactions of 1,3-dicarbonyl compounds with various carbon–carbon unsaturated bonds in both inter- and intramolecular manners, leading to highly functionalized

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Scheme 1.



Scheme 2. Reaction of vinyl azides with trialkylboranes via free radical pathway.

an iminyl radical. The iminyl radical then intramolecularly forms a C–N bond by the cyclization with the C=O bond, leading to various azaheterocycles (Scheme 4). This process could potentially be achieved via a redox catalytic manner featured by the two key redox steps: i) oxidative generation of the radical species by the reaction of radical sources with metal oxidant [Mn^{III}] (to be [Mn^{II}]) (oxidative initiation) and ii) reduction of the resulting iminyl radical by [Mn^{II}] followed by cyclization and protonation to afford azaheterocycles along with regeneration of metal oxidant [Mn^{III}] (reductive termination). This review focuses on this Mn(III)-catalyzed radical reactions of vinyl azides for synthesis of nitrogen-containing heterocycles.

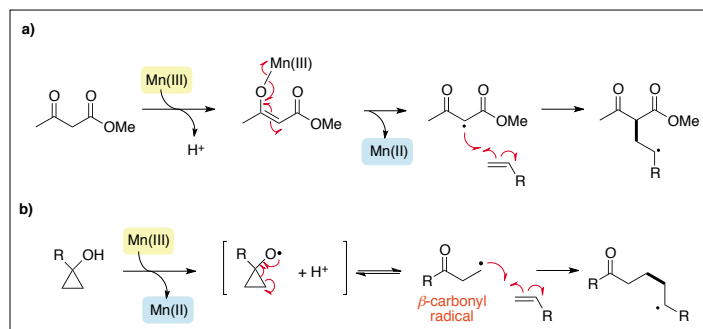
organic molecules (Scheme 3).^[13] From a mechanistic point of view, initially formed Mn(III)-enolates undergo rapid loss of Mn(II) to give α -carbonyl radicals, which form a new C–C bond with alkenes or alkynes. Similarly, this Mn(III)-mediated oxidative manner can be served for generation of β -carbonyl radicals from cyclopropanols.^[14] However, these strategies basically need superstoichiometric amounts of Mn(III) complexes to complete the reactions because the resulting carbon radicals should be terminated by some oxidative manners (*i.e.* further oxidation to carbocations) under the reaction conditions.

3. Design of Mn(III)-Catalyzed Radical Reactions with Vinyl Azides

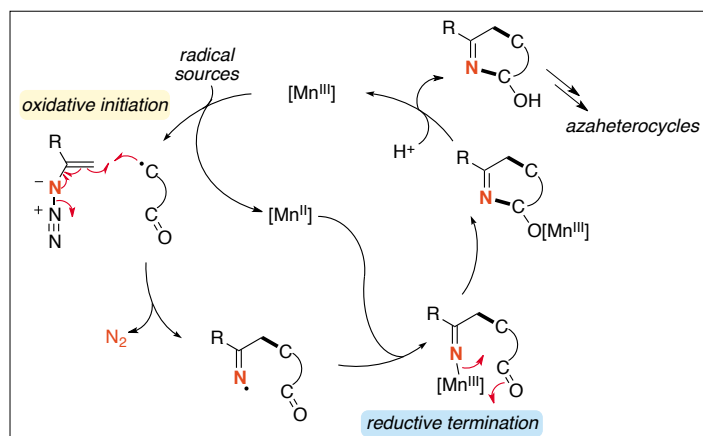
We speculated that the combination of the two above-mentioned radical concepts, namely, i) addition of carbon radicals onto vinyl azides and ii) Mn(III)-mediated oxidative radical reactions using 1,3-dicarbonyl compounds or cyclopropanols, could lead to unique *Mn(III)-catalyzed radical reactions* (Scheme 4). Our reaction design involves the addition of a carbon radical bearing a carbonyl group to the C=C bond of a vinyl azide to provide a new C–C bond with generation of

3.1 Mn(III)-Catalyzed Radical Reactions of Vinyl Azides and 1,3-Dicarbonyl Compounds

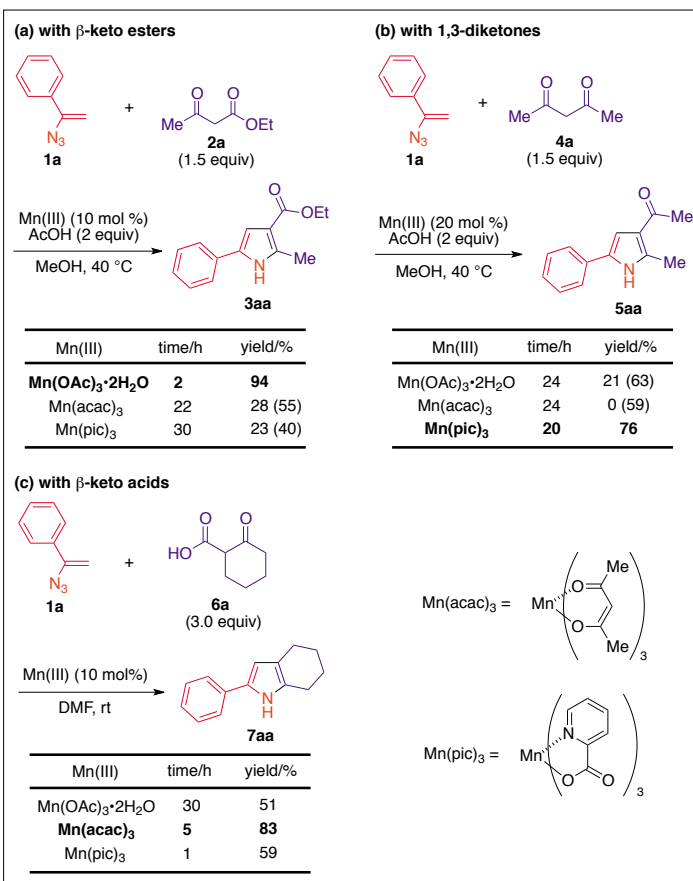
Based on the hypothesis, we have succeeded in developing Mn(III)-catalyzed reactions of vinyl azides with 1,3-dicarbonyl compounds for synthesis of multi-substituted pyrroles, that could be characterized as a formal [3+2]-annulation process.^[15] The reactions of α -azido styrene with β -keto ester, 1,3-diketone, and β -keto acid using Mn(III) catalysts are shown in Scheme 5. Interestingly, for each kind of 1,3-dicarbonyl compounds, the preferential Mn(III)-catalyst is varied,



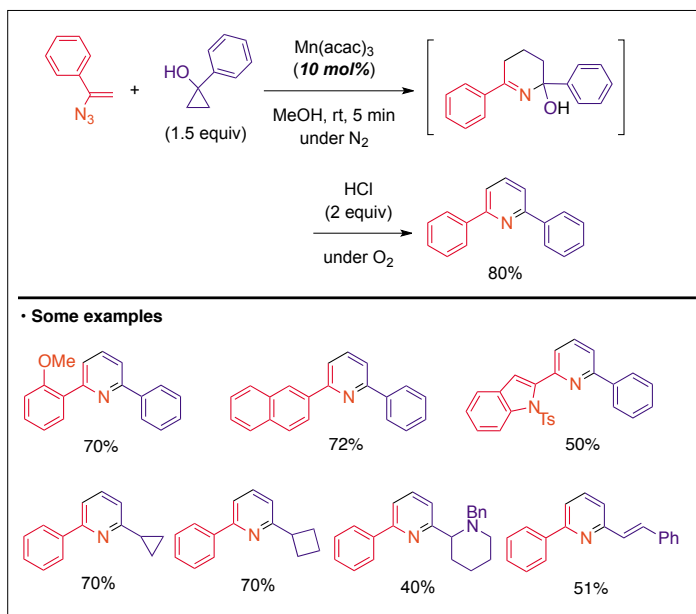
Scheme 3. a) One-electron oxidation of 1,3-dicarbonyls: generation of α -carbonyl radical. b) One-electron oxidation of cyclopropanols: Generation of β -carbonyl radicals.



Scheme 4.



Scheme 5.



Scheme 6.

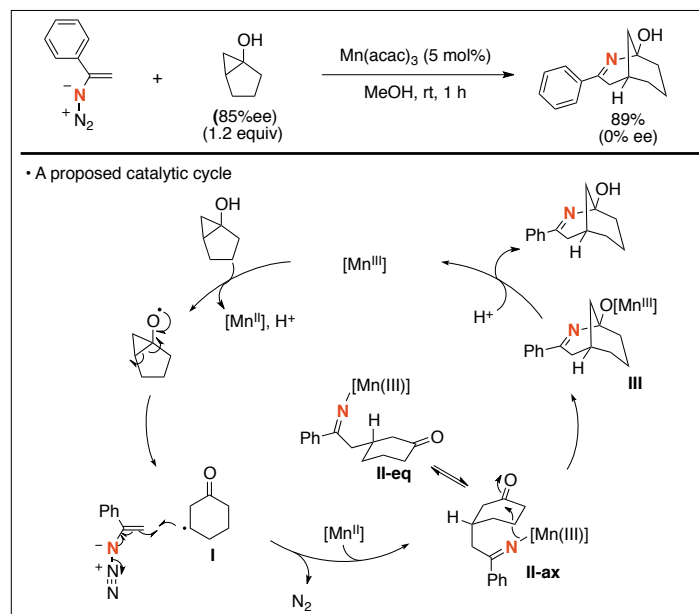
depending on the nature of 1,3-dicarbonyl compounds as well as the redox potentials of Mn(III) catalysts.^[16] As a consequence, Mn(OAc)₃·2H₂O was an effective catalyst for the reactions of vinyl azides and β-keto esters, while a stronger oxidant, Mn(pic)₃, is required for the reactions with 1,3-diketones. On the other hand, Mn(acac)₃ was preferred for the reactions of vinyl azides and β-keto acids. These [3+2]-annulation strategies have a general and wide scope on substituents of both vinyl azides and 1,3-dicarbonyl compounds to give a variety of pyrroles in good yields.

3.2 Mn(III)-Catalyzed Radical Reactions of Vinyl Azides and Cyclopropanols^[17]

We next focused on the use of cyclopropanols as a precursor of β-carbonyl radicals and investigated their addition reactions toward vinyl azides followed by C–N bond formation (formal [3+3]-annulation). The reactions of α-azidostyrene and 1-phenylcyclopropanol were investigated to target 2,6-diphenylpyridine

(Scheme 6). It was revealed that treatment of a mixture of vinyl azide and cyclopropanol with a catalytic amount of Mn(acac)₃ (10 mol%) in MeOH consumed vinyl azide within 5 min at room temperature, and the subsequent addition of oxygen (1 atm O₂ as an atmosphere) and HCl (2 equiv.) provided the desired 2,6-diphenylpyridine in 80% yield. A wide scope was shown in the substituents of vinyl azides as well as cyclopropanols, and some representative examples were described below.

Next, we envisioned utilizing bicyclic cyclopropanols such as bicyclo[3.1.0]hexan-1-ol as a source of β-carbonyl radicals (Scheme 7). Interestingly, an unusual 2-azabicyclo[3.3.1]non-2-en-1-ol was isolated in 89% yield by the reaction with α-azidostyrene using only a catalytic amount of Mn(acac)₃ (5 mol%). It is noteworthy that treatment of optically active cyclopropanol (85% ee)^[18] with α-azidostyrene afforded the racemic product. No transmission of the chirality of cyclopropanol would suggest that generation of achiral ring-expanded β-carbonyl radical

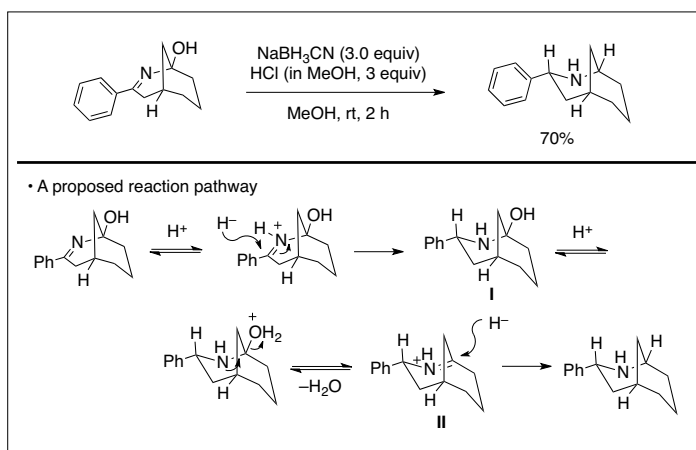


Scheme 7.

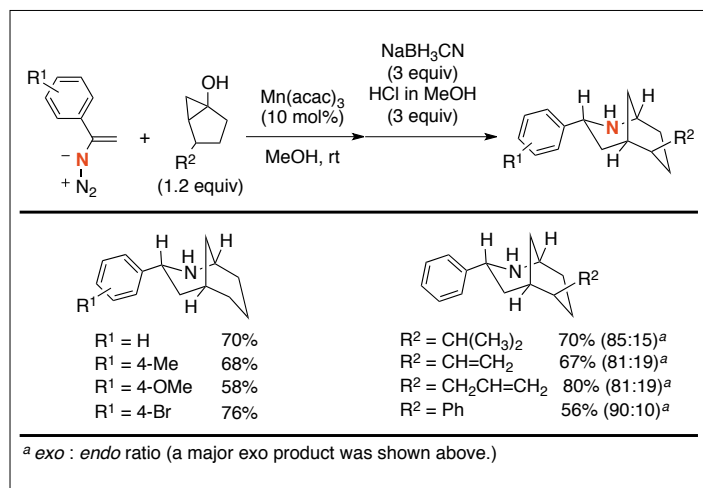
I^[19] followed by its radical addition to vinyl azide is involved in the reaction mechanism, forming iminyl manganese(III) **II-eq** and **II-ax** placing an iminyl tether in the equatorial- and axial-like position, respectively. Conformational inversion of **II-eq** to **II-ax** should be indispensable to achieve the further cyclization of the iminyl manganese **II-ax** with the carbonyl group to give alkoxy manganese(III) species **III** that could be protonated to afford 2-azabicyclo[3.3.1]non-2-en-1-ol.

With the preparation method for 2-azabicyclo[3.3.1]non-2-en-1-ol, we then explored their transformations to 2-azabicyclo[3.3.1]nonane (morphane) or 2-azabicyclo[3.3.1]non-2-ene frameworks, which are prevalent in several natural alkaloids as well as biologically active molecules.^[20] Treatment of 2-azabicyclo[3.3.1]non-2-en-1-ol with NaBH₃CN in the presence of HCl induced the double hydride reduction of the C=N and C–O bonds, affording 2-azabicyclo[3.3.1]nonane stereoselectively in 70% yield (Scheme 8). The first hydride attacked to the C=N bond entirely from the less hindered *exo*-face to form amination **I**. Subsequent dehydration of **I** gave the bridgehead iminium species **II**, which could be reduced by one more hydride to afford 2-azabicyclo[3.3.1]non-2-en-1-ol.

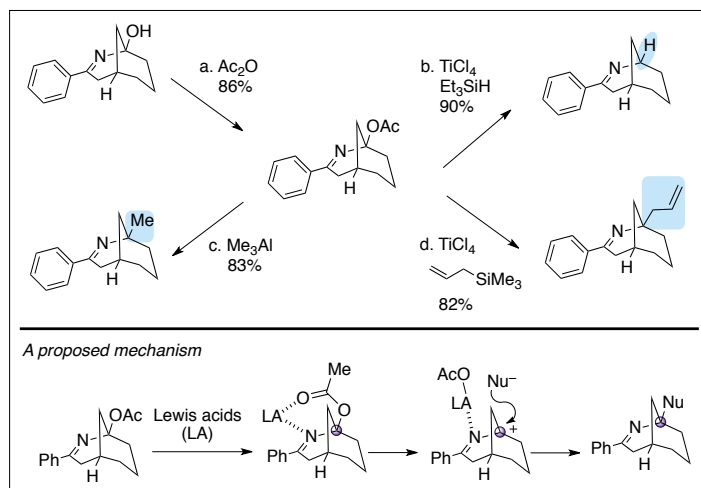
It was found that a one-pot conversion could be achieved starting from the reaction of vinyl azides and cyclopropanols using Mn(acac)₃ as a catalyst followed by treatment with NaBH₃CN (3 equiv.) with HCl (3 equiv.), producing 2-azabicyclo[3.3.1]nonanes in good yields without isolation of 2-azabicyclo[3.3.1]non-2-en-1-ols (Scheme 9). This one-pot/two-step process represented a straightforward procedure for construction of the morphane



Scheme 8.



Scheme 9.



Scheme 10.

framework from readily available vinyl azides and bicyclic cyclopropanols.

Further methods for reduction of the C–O bond at the bridgehead position were explored using acetate prepared from 2-azabicyclo[3.3.1]non-2-en-1-ol (Scheme 10). Interestingly, TiCl₄-mediated reduction of acetate with Et₃SiH induced selective C–O bond cleavage, affording 2-azabicyclo[3.3.1]non-2-ene in 90% yield keeping the C=N bond intact. Similarly, treatment with allyltrimethylsilane-TiCl₄ or Me₃Al provided a new quaternary carbon center at the bridgehead position. These transformations might proceed *via* a bridgehead carbocation, which was then immediately trapped by present nucleophiles.

Stimulated by the one-pot process developed to prepare 2-azabicyclo[3.3.1]nonanes (Scheme 9), the same procedure was employed to the reaction of α -azidostyrenes and bicyclo[4.1.0]heptan-

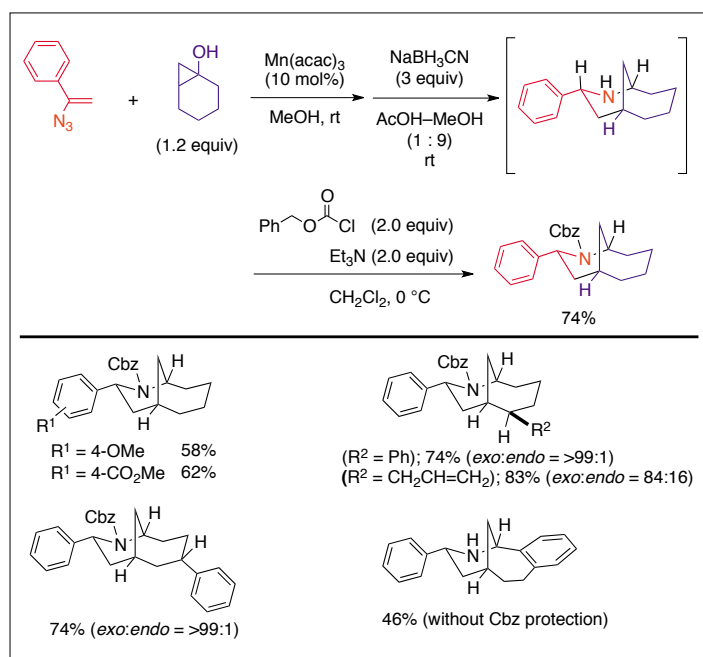
1-ol to synthesize 2-azabicyclo[4.3.1]decane derivatives. To our delight, 2-azabicyclo[4.3.1]decanes were obtained as a single diastereoisomer *via* double hydride reductions of the C=N and C–O bonds of the resulting 2-azabicyclo[4.3.1]dec-2-en-1-ols. Subsequent protection of N–H amine with Cbz-Cl provided *N*-benzyloxycarbonyl derivatives in good yields from vinyl azides (Scheme 11).

Melinonine-E (**1**) was isolated from the bark of *Strychnos melinoniana*,^[21] and its structure was characterized by a unique pentacyclic ring system including indolo[2,3-*a*]quinolizidine and morphan frameworks.^[22] The first synthesis of (\pm)-melinonine-E was accomplished by Bonjoch.^[23] We envisioned that the 2-azabicyclo[3.3.1]nonane moiety of melinonine-E would be constructed by Mn(III)-mediated [3+3]-annulation of α -indolyl vinyl azide **2** and bicyclic cyclopropanol **3**

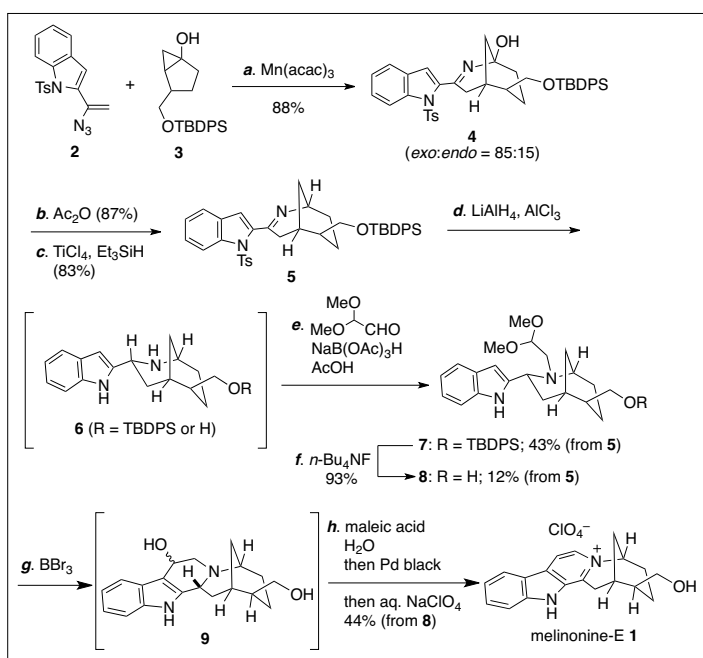
bearing a hydroxymethyl tether followed by reduction of the C=N and bridgehead C–O bonds. [3+3]-Annulation of α -indolyl vinyl azide **2** and bicyclic cyclopropanol **3** afforded azabicyclic compound **4** in 88% yield in a 2 g scale in a diastereoselective manner (*exo:endo* = 85:15), although it needed 1.6 equiv. of Mn(acac)₃ to complete the reaction (Scheme 12). After conversion of **4** into its acetate, the bridgehead C–O bond was reduced by the Et₃SiH-TiCl₄ protocol to afford cyclic imine **5**. Subsequent reduction of the C=N bond of **5** with AlH₃ prepared from LiAlH₄-AlCl₃, leading to not only the entire reduction of imine and *N*-tosyl moieties but also partial deprotection of the TBDPS group. Reductive *N*-alkylation of the resulting *N*-H amines of **6** with dimethoxyacetaldehyde in the presence of NaBH(OAc)₃ provided **7** and **8** in 43% and 12% yield, respectively. The remaining TBDPS group of **7** was removed with *n*-Bu₄NF. BBr₃-induced cyclization of **8** proceeded cleanly to afford the cyclic alcohol **9**, which further underwent dehydration with palladium black in one-pot manner, affording (\pm)-melinonine-E (**1**) as a perchlorate salt in 44% yield from **8**. The ¹H and ¹³C NMR data of the synthetic (\pm)-melinonine-E perchlorate were identical to those of the reported ones.

4. Conclusions

We have developed a divergent synthetic route to construct azaheterocycles from readily available vinyl azides and 1,3-dicarbonyl compounds/cyclopropanols *via* formal [3+2]- or [3+3]-annulation using Mn(III) complexes. A series of azaheterocycles such as pyrroles, pyridines, and azabicyclic compounds have been successfully prepared by utilizing this promising strategy. Further investigation to explore



Scheme 11.



Scheme 12. Reagents and conditions: (a) **3** (3.0 equiv, added by a syringe pump), $\text{Mn}(\text{acac})_3$ (1.6 equiv), MeOH, rt, 8 h, 88%; (b) Ac_2O (8.0 equiv), Et_3N (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2 , rt, 12 h, 87%; (c) TiCl_4 (1.5 equiv), Et_3SiH (2.0 equiv), CH_2Cl_2 , rt, 4 h, 83%; (d) AlCl_3 (5.0 equiv), LiAlH_4 (15.0 equiv), rt, 30 h; (e) $(\text{MeO})_2\text{CHCHO}$ (1.5 equiv), $\text{NaB}(\text{OAc})_3\text{H}$ (1.5 equiv), CH_2Cl_2 , 0 °C, 30 min, **7** (43% from **5**) + **8** (12% from **5**); (f) $n\text{-Bu}_4\text{NF}$ (1.5 equiv), THF, rt, 36 h, 93%; (g) BBr_3 (8.0 equiv), CH_2Cl_2 , -78 °C, 3 h; (h) maleic acid (6.0 equiv), H_2O , rt, overnight, then Pd black (excess), reflux, 50 h; aqueous NaClO_4 (3.0 equiv), rt, 44% (from **8**).

other modes of annulation reactions of vinyl azides to prepare azaheterocycles is currently underway.

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- [1] For recent reviews, see: a) G. L. Thomas, C. W. Johannes, *Curr. Opin. Chem. Biol.* **2011**, *15*, 516; b) R. Tohme, N. Darwiche, H. Gali-Muhtasib, *Molecules* **2011**, *16*, 9665; c) S. Dandapani, L. A. Marcaurrelle, *Curr. Opin. Chem. Biol.* **2010**, *14*, 362; d) M. E. Welsch, S.

- A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347; e) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337.
- [2] a) J. A. Joule, K. Mills, 'Heterocyclic Chemistry', 5th edition, Wiley-Blackwell, **2010**; b) 'Progress in Heterocyclic Chemistry', Eds. G. W. Gribble, J. A. Joule, Elsevier: Oxford, **2008**; Vol. 20 and others in this series; c) 'Comprehensive Heterocyclic Chemistry III', Eds. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, Pergamon: Oxford, **2008**; d) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, **2003**.
- [3] a) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259; b) B. M. Trost, *Science* **1991**, *254*, 1471.
- [4] a) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40. b) P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505.
- [5] For a prior account on our azide chemistry, see S. Chiba, *Synlett* **2012**, 23, 21.
- [6] For a review, see: K. Banert, in 'Organic Azides: Syntheses and Applications', Eds. S. Bräse, K. Banert, Wiley, **2010**; p. 115.

- [7] For our recent works on heterocycle synthesis using 2H-azirines generated from vinyl azides, see: a) E. P. J. Ng, Y.-F. Wang, B. W.-Q. Hui, G. Lapointe, S. Chiba, *Tetrahedron* **2011**, *67*, 7728. b) S. Chiba, Y.-F. Wang, G. Lapointe, K. Narasaka, *Org. Lett.* **2008**, *10*, 313.
- [8] a) C. J. Moody, in 'Comprehensive Organic Synthesis', Eds. B. M. Trost, I. Fleming, S. Ley, Pergamon: Oxford, 1991; Vol. 7, p 21; b) G. Smolinsky, C. A. Pryde, *J. Org. Chem.* **1968**, *33*, 2411; c) G. L'abbe, *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 775; d) H. Hemetsberger, D. Knittl, H. Weidmann, *Monatsh. Chem.* **1970**, *101*, 161; e) A. R. MacKenzie, C. J. Moody, C. W. Rees, *J. Chem. Soc., Chem. Commun.* **1983**, 1372; f) R. E. Bolton, C. J. Moody, M. Pass, C. W. Rees, G. Tojo, *J. Chem. Soc., Perkin Trans. 1* **1988**, 2491.
- [9] Fe(II)- and Rh(II)-catalyzed indole formation from azidocinnamates was reported, see: a) J. Bonnamour, C. Bolm, *Org. Lett.* **2011**, *13*, 2012; b) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, T. G. Driver, *J. Am. Chem. Soc.* **2007**, *129*, 7500.
- [10] A. Suzuki, *Tetrahedron Lett.* **1975**, 2195.
- [11] B. P. Roberts, *Tetrahedron Lett.* **1983**, *24*, 3779.
- [12] a) J. B. Bush, Jr., H. Finkbeiner, *J. Am. Chem. Soc.* **1968**, *90*, 5903; b) E. I. Heiba, R. M. Sessau, W. J. Koehl, Jr. *J. Am. Chem. Soc.* **1968**, *90*, 5905.
- [13] For selected reviews, see: a) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339; b) B. B. Snider, in 'Radicals in Organic Synthesis', Vol. 1, Eds. P. Renaud, M. P. Sibi, Wiley-VCH, Weinheim, **2001**, p. 198.
- [14] a) N. Iwasawa, S. Hayakawa, M. Funahashi, K. Isobe, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 819; b) N. Iwasawa, S. Hayakawa, K. Isobe, K. Narasaka, *Chem. Lett.* **1991**, 1193.
- [15] a) E. P. J. Ng, Y.-F. Wang, S. Chiba, *Synlett* **2011**, 783; b) Y.-F. Wang, K. K. Toh, S. Chiba, K. Narasaka, *Org. Lett.* **2008**, *10*, 5019.
- [16] S. A. Richert, P. K. S. Tsang, D. T. Sawyer, *Inorg. Chem.* **1988**, *27*, 1814.
- [17] a) Y.-F. Wang, K. K. Toh, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 6411; b) Y.-F. Wang, S. Chiba, *J. Am. Chem. Soc.* **2009**, *131*, 12570.
- [18] H. Du, J. Long, Y. Shi, *Org. Lett.* **2006**, *8*, 2827.
- [19] For discussion on racemization of cyclohexyl radicals, see: a) A. J. Buckmelter, A. I. Kim, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2000**, *122*, 9386; b) B. P. Roberts, A. J. Steel, *J. Chem. Soc., Perkin Trans. II* **1992**, 2025, and references therein.
- [20] For a review on synthesis of 2-azabicyclo[3.3.1]nonanes, see: J. Bonjoch, F. Diaba, B. Bradshaw, *Synthesis* **2011**, 993.
- [21] E. Bächli, C. Vamvacas, H. Schmid, P. Karrer, *Helv. Chim. Acta* **1957**, *40*, 1167.
- [22] R. P. Borris, A. Guggisberg, M. Hesse, *Helv. Chim. Acta* **1984**, *67*, 455.
- [23] a) J. Quirante, C. Escolano, A. Merino, J. Bonjoch, *J. Org. Chem.* **1998**, *63*, 968; b) J. Quirante, C. Escolano, J. Bosch, J. Bonjoch, *J. Chem. Soc., Chem. Commun.* **1995**, 2141.