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Mn(III)-Mediated Reactions of Cyclopropanols with Vinyl Azides: Synthesis of Pyridine and 2-Azabicyclo[3.3.1]non-2-en-1-ol Derivatives

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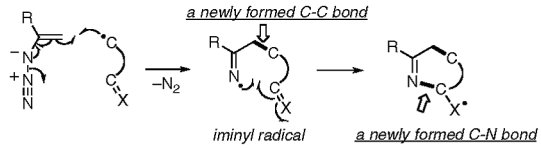
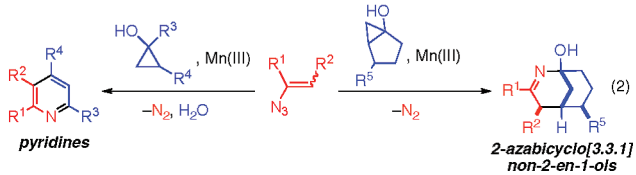
Nitrogen-containing heterocycles (azaheterocycles) are one of the most prevalent compounds in numerous natural products, potent pharmaceutical drugs, and various kinds of functional materials. Although diverse synthetic approaches toward azaheterocycles have been developed,[1] versatile and flexible methodologies to construct azaheterocycles 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.[2] 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.[3,4] The iminyl radical then intramolecularly forms a C−N bond by cyclization with an unsaturated bond (eq 1). The current study focuses on the use of cyclopropanols as a precursor of β-carbonyl radicals and the investigation of their addition reactions toward vinyl azides.[5] Herein, we wish to report a Mn(III)-mediated synthesis of substituted pyridines and 2-azabicyclo[3.3.1]non-2-en-1-ol derivatives from vinyl azides and cyclopropanols (eq 2).

• Concept: Formation of iminyl radicals by addition of C radicals to vinyl azides–Successive C-N bond formation



(1)

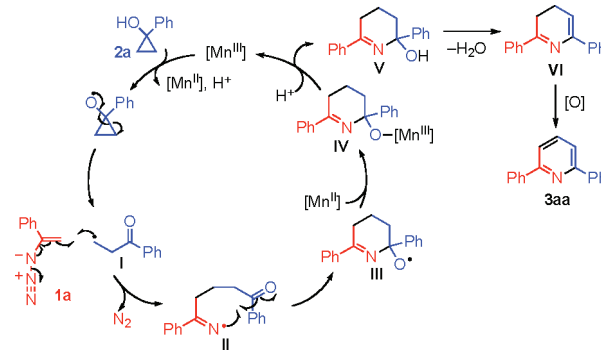
• This work: Mn(III)-induced reactions of vinyl azides and cyclopropanols



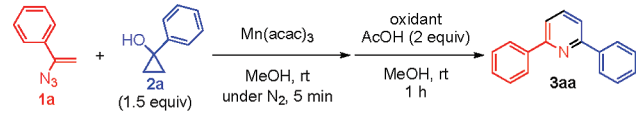
(2)

We began our investigation of the synthesis of pyridines[6,7] by the reaction of α-azidostyrene (**1a**) and 1-phenylcyclopropanol (**2a**). A proposed reaction pathway for the pyridine formation is illustrated in Scheme 1. The reaction might be initiated by the addition of β-keto radical **I**, generated by one-electron oxidation of **2a** by Mn(III), to vinyl azide **1a**, affording iminyl radical **II** with elimination of dinitrogen. Consecutive cyclization of iminyl radical **II** to an intramolecular carbonyl group would give alkoxyl radical **III**, which can be reduced by Mn(II) and subsequently protonated to afford tetrahydropyridine **V** and regenerate Mn(III) species. Dehydration of **V** and further oxidation of generated dihydropyridine **VI** would afford the desired pyridine **3aa**. A brief study revealed that treatment of a mixture of vinyl azide **1a** and cyclopropanol **2a** (1.5 equiv) with a catalytic amount of Mn(III) acetylacetonate [Mn(acac)$_3$] (0.2 equiv) in MeOH led to rapid consumption of **1a** within 5 min at room temperature, and the subsequent addition of oxidant (O_2 or DDQ) and AcOH (2 equiv) provided the desired pyridine **3aa**, although the yield of **3aa** was moderate (Scheme 2). Ultimately, utilization of 1.7 equiv of Mn(acac)$_3$ was found to be essential in rendering this process synthetically useful (84% of **3aa**), in which Mn(acac)$_3$ might play a dual role for oxidation of cyclopropanol **2a** and dihydropyridine **VI**.[8]

Scheme 1. A Proposed Pathway of Pyridine Formation



Scheme 2. Optimization of Mn(III)-Mediated Pyridine Formation



Mn(acac)$_3$/equiv	oxidant	
0.2	O_2	59%
0.2	DDQ (1.5 equiv)	53%
1.7	—	84%

With the optimized reaction conditions at hand, the scope of this Mn(III)-mediated pyridine formation was investigated (Table 1). Various 2,6-diarylpyridines were provided in good yields. Especially, heteroaryl motifs such as pyrrole (**3fa**) and indole (**3ga**) were successfully incorporated. Introduction of alkenyl and alkynyl groups (**3ai**, **3aj**) on the pyridine ring is also a particular feature of this method. For the reaction of trisubstituted vinyl azides (**1h**, **1i**, and **1j**) with **2a**, Mn(III) 2-pyridinecarboxylate [Mn(pic)$_3$][9] was used as an oxidant in CH_3CN, providing 2,3,6-trisubstituted pyridines (**3ha**, **3ia**, **3ja**). Some alkyl groups including strained cycloalkyls (**3ae**, **3af**, **3ag**) as well as a piperidine moiety (**3ah**) could be compatible with the reaction conditions. This method allowed for the installation of alkoxycarbonyl groups (**3ja**, **3ka**, **3ak**) as well as a phenyldimethylsilyl moiety (**3al**) on the pyridine ring. On the other hand, the reaction of vinyl azide **1a** with 1,2-disubstituted cyclopropanols (**2m**, **2n**) afforded not only the desired 2,4,6-trisubsituted pyridines (**3am**, **3an**) but also dihydropyrroles (**4am**, **4an**)[10,11] as minor products. In these reactions, secondary β-keto

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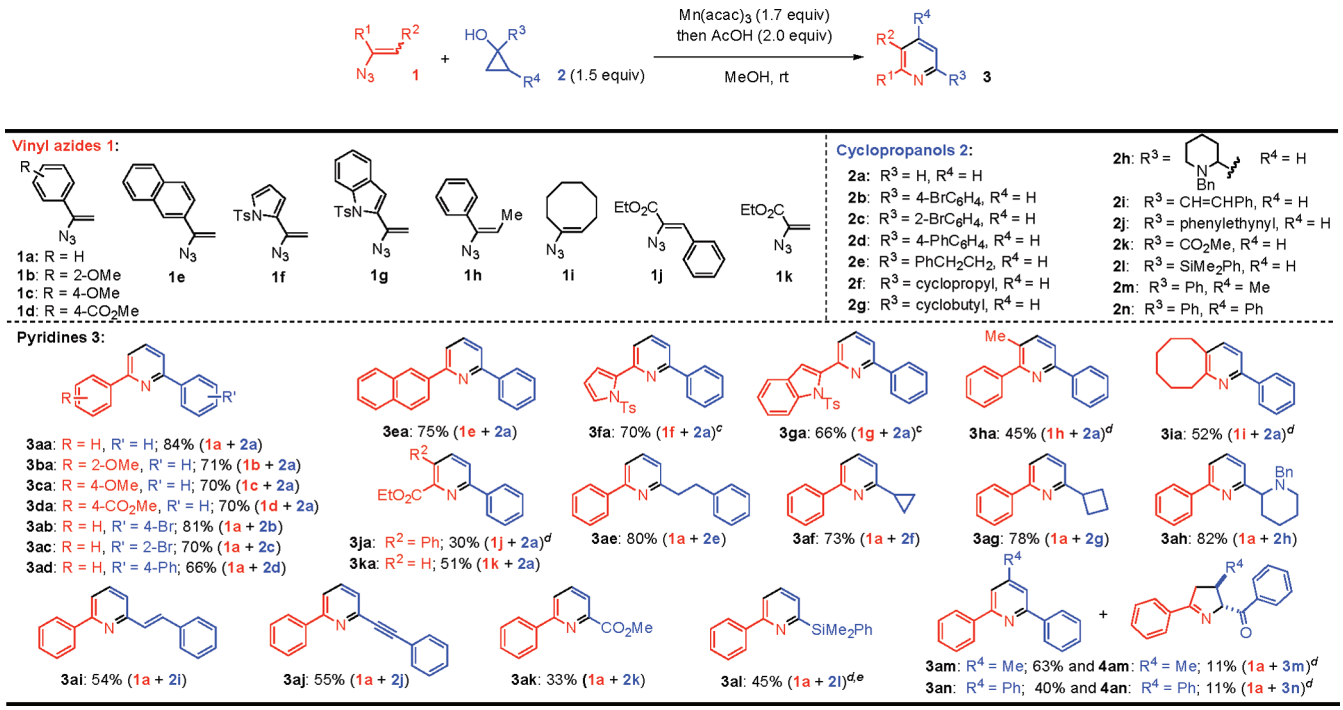
Table 1. Mn(III)-Mediated Synthesis of Pyridine **3** from Vinyl Azides **1** and Cyclopropanols **2**[a,b]



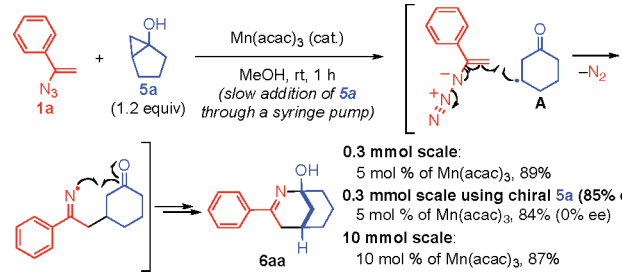
[a] Unless otherwise noted, the reactions were carried out by treatment of a mixture of vinyl azides **1** (0.3 mmol) and cyclopropanols (1.5 equiv) with $Mn(acac)_3$ (1.7 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min followed by addition of AcOH (2 equiv) (see Supporting Information). [b] Isolated yield was noted above. [c] A solution of cyclopropanol **2** and AcOH in MeOH was added to vinyl azide **1** and $Mn(acac)_3$ by a syringe pump over 1 h. [d] The reactions were run using $Mn(pic)_3$ (1.7 equiv) and AcOH (2 equiv) in CH_3CN. [e] The reaction was performed in the absence of AcOH.

radicals were found to be formed predominantly via oxidative ring opening of **2m** and **2n**, judging from the substituted patterns of the products.

Upon finding that Mn(III) complexes could promote the reaction of vinyl azides **1** and monocyclic cyclopropanols **2** to produce substituted pyridines **3**, we broadened our search to apply bicyclic cyclopropanols **5**. In the case of the reaction of vinyl azide **1a** with bicyclo[3.1.0]hexan-1-ol (**5a**), an iminyl radical addition product, 2-azabicyclo[3.3.1]non-2-en-1-ol **6aa** was isolated in 89% yield by using only a catalytic amount of $Mn(acac)_3$ (5 mol %), although slow addition of **5a** through a syringe pump to a mixture of vinyl azide **1a** and the catalyst over 1 h was required to complete the reaction (Scheme 3). Interestingly, treatment of chiral bicyclic cyclopropanol **5a** (85% ee) with **1a** afforded racemic **6aa**. No transmission of the chirality of cyclopropanol **5a** to **6aa** would suggest that generation of ring-expanded β-keto radical **A** from **5a** followed by radical addition of **A** to vinyl azide **1a** is most likely involved in the reaction mechanism. A gram scale preparation of **6aa** was also achieved in good yield.

It was found that this reaction has a broad scope, and a range of 2-azabicyclo[3.3.1]non-2-en-1-ol derivatives have been synthesized using a catalytic amount of $Mn(acac)_3$ (Table 2). Treatment of vinyl azides **1f** and **1g** bearing pyrrole and indole units with **5a** led into the formation of **6fa** and **6ga** in good yields. The reaction of trisubstituted vinyl azide **1h** with **5a** furnished the desired **6ha** only in 28% yield along with recovery of **1h** (68%) even in the presence of 40 mol % of the catalyst, probably due to the steric hindrance of the β-methyl group of **1h** in the addition of β-keto radical **A** to **1h**. Notably, introduction of some substituents at C-4 of bicyclic cyclopropanols (**5b**, **5c**, and **5d**) did not retard the reactions, providing the corresponding 2-azabicyclo[3.3.1]non-2-en-1-ols **6** in high yields and diastereoselectivities.

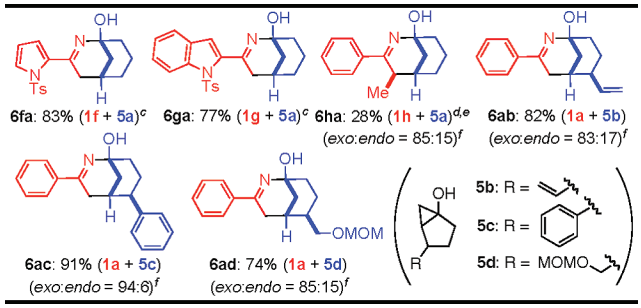
Scheme 3. Formation of 2-Azabicyclo[3.3.1]non-2-en-1-ol **6aa**



Having developed a preparation method for 2-azabicyclo[3.3.1]non-2-en-1-ols **6**, we finally explored their transformations to 2-azabicyclo[3.3.1]nonane (morphan) or 2-azabicyclo[3.3.1]non-2-ene frameworks, which are prevalent in some alkaloids[12] as well as pharmacologically valuable molecules.[13] Facile methods were developed using acetate **7** prepared from **6aa** as depicted in Scheme 4. When acetate **7** was treated with $NaBH(OAc)_3$ in the presence of AcOH, double hydride reductions of the C═N and C—O bonds proceeded smoothly to give 2-azabicyclo[3.3.1]nonane **8** as a single stereoisomer. Alternatively, the reduction of **7** with Et_3SiH in the presence of $TiCl_4$ induced selective C—O bond cleavage, affording 2-azabicyclo[3.3.1]non-2-ene **9**. It is noteworthy that treatment with Me_3Al or allyltrimethylsilane-$TiCl_4$ provided a new quaternary carbon center at C-1 with keeping the C═N bond intact (**10** an **11**).[14]

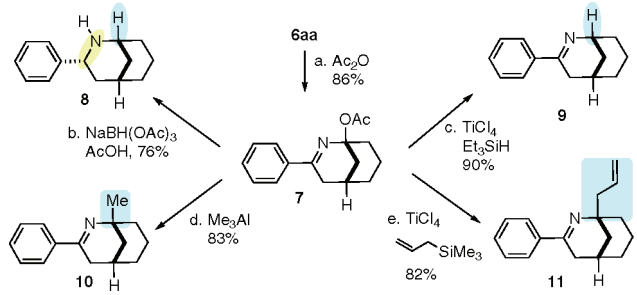
In summary, we have developed a Mn(III)-mediated divergent synthesis of substituted pyridines and 2-azabicyclo[3.3.1]non-2-en-1-ol derivatives from readily available vinyl azides and cyclopropanols with a range of substituents. In addition, versatile transformations of 2-azabicyclo[3.3.1]non-2-en-1-ol to 2-

Table 2. Mn(III)-Catalyzed Synthesis of 2-Azabicyclo[3.3.1]non-2-en-1-ols **6**[a,b]



[a] Unless otherwise noted, the reactions were carried out by addition of a solution of cyclopropanols **5** (1.2 equiv) in MeOH via a syringe pump over 1 h to a solution of vinyl azides **1** (0.3 mmol) and $Mn(acac)_3$ (10 mol %) under N_2 atmosphere at room temperature (see Supporting Information). [b] Isolated yield was noted above. [c] 20 mol % of $Mn(acac)_3$ was used. [d] 40 mol % of $Mn(acac)_3$ was used. [e] Vinyl azide **1h** was recovered in 68% yield. [f] The ratio was determined by ^1H NMR, and the major exoisomer was shown above.

Scheme 4. Transformations of 2-Azabicyclo[3.3.1]non-2-en-1-ol **6aa**[a]



[a] Reagents and conditions: (a) Ac_2O (8.0 equiv), Et_3N (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 3 h, 86%; (b) $NaBH(OAc)_3$ (3.0 equiv), $AcOH—CH_2Cl_2$ (1:2), 5 h, 76%; (c) $TiCl_4$ (1.5 equiv), Et_3SiH (2.0 equiv), CH_2Cl_2, rt, 3 h, 90%; (d) Me_3Al (4.0 equiv), $CHCl_3$, rt, 1 h, 83%; (e) $TiCl_4$ (1.5 equiv), $CH_2{=}CHCH_2SiMe_3$ (2.0 equiv), CH_2Cl_2, rt, 3 h, then 1 N HCl, THF, 0.5 h, 82%

azabicyclo[3.3.1]nonane or -non-2-ene frameworks were exploited. Further investigation of the scope and synthetic application of these reactions are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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