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Mn(III)-Mediated Formal [3+3]-Annulation of Vinyl Azides and Cyclopropanols: A Divergent Synthesis of Azaheterocycles

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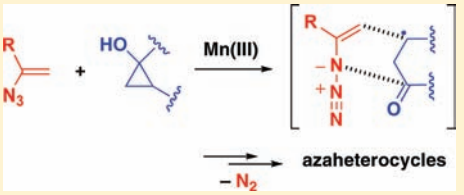
Supporting Information

ABSTRACT: Mn(III)-mediated formal [3+3]-annulation has been developed using readily available vinyl azides and cyclopropanols with a wide range of substituents. Vinyl azides were successfully applied as a three-atom unit including one nitrogen to prepare pyridines and δ-lactams by the reactions with monocyclic cyclopropanols as well as to construct 2-azabicyclo[3.3.1] and 2-azabicyclo[4.3.1] frameworks with bicyclic cyclopropanols, bicyclo[3.1.0]hexan-1-ols, and bicyclo-[4.1.0]heptan-1-ols. These reactions were initiated by a radical addition of β-carbonyl radicals, generated by the one-electron oxidation of cyclopropanols with Mn(III), to vinyl azides to give iminyl radicals, which cyclized with the intramolecular carbonyl groups. In addition, application of the present methodology to a synthesis of the quaternary indole alkaloid, melinonine-E, was accomplished.



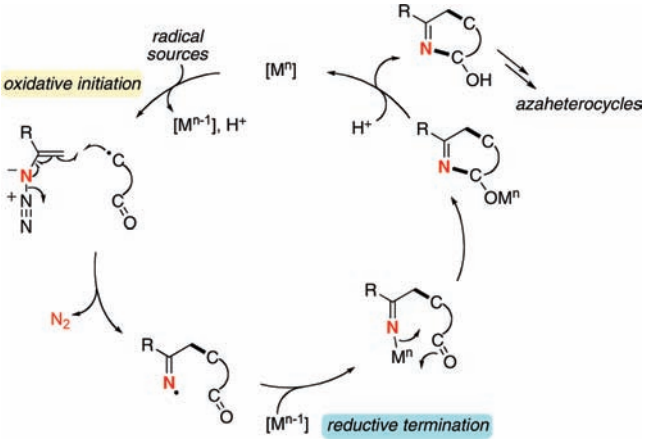
INTRODUCTION

Nitrogen-containing heterocyclic compounds (azaheterocycles) are essential components 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.

Intermolecular annulation reactions allow for rapid and selective construction of complex cyclic molecules in a one-pot manner from relatively simple building blocks, which is an ideal process in organic synthesis from atom-[2] and step-economical[3] points of view. 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.[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 an iminyl radical.[5] The iminyl radical then intramolecularly forms a C−N bond by cyclization with the C=O bond, leading to various azaheterocycles (Scheme 1).[6−9] This process could potentially be achieved via a redox catalytic manner featuring two key redox steps: (1) oxidative generation of the radical species by the reaction of radical sources with metal oxidant [M^n] (to become [M^{n-1}]) (oxidative initiation) and (2) reduction of the resulting iminyl radical by [M^{n-1}] followed by cyclization and protonation to afford azaheterocycles along with regeneration of metal oxidant [M^n] (reductive termination).

Our current study has focused on the use of cyclopropanols as a precursor/equivalent of β-carbonyl radicals and the investigation of their addition reactions toward vinyl azides followed by C−N bond formation (formal [3+3]-annulation).[10] This article is a full account of the Mn(III)-mediated/catalyzed reactions of vinyl azides with cyclopropanols for a divergent synthesis of azaheterocycles with broad evaluation of the mechanisms, scope, and limitations (Scheme 2), where we disclose (1) Mn(III)-mediated/catalyzed synthesis of multisubstituted pyridines from vinyl azides and monocyclic cyclopropanols; (2) synthesis of δ-lactams by Mn(III)-catalyzed reactions of vinyl azides and 1-ethoxycyclopropanol followed by $NaBH_3CN$ reduction; (3) Mn(III)-catalyzed construction of 2-azabicyclo[*n*.3.1] systems

Scheme 1. Concept for New Catalytic Annulation: Formation of Iminyl Radicals by Addition of C-Radicals to Vinyl Azides and Successive C−N Bond Formation in a Redox Catalytic Manner



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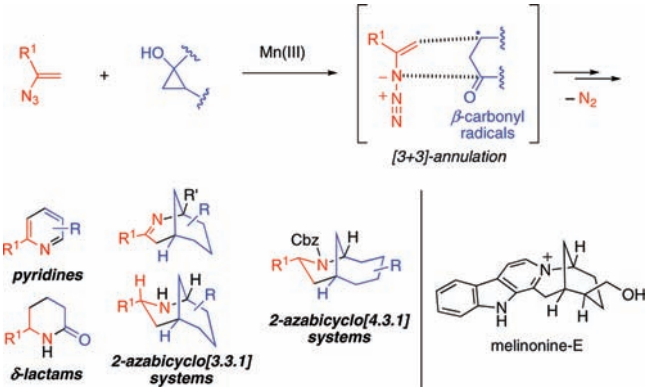
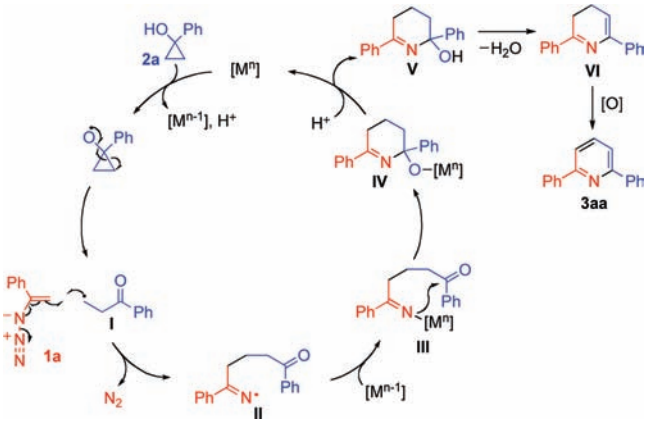
Scheme 2. Mn(III)-Mediated Formal [3+3]-Annulation of Vinyl Azides and Cyclopropanols



Scheme 3. Proposed Pathway for Pyridine Formation



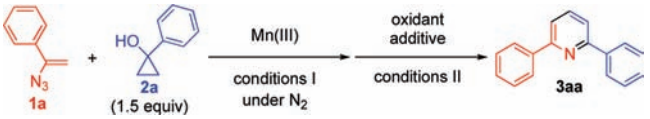
(n = 3 and 4) from vinyl azides and bicyclic cyclopropanols and their facile chemical transformation; and (4) a synthesis of the quaternary indole alkaloid, melinonine-E.

RESULTS AND DISCUSSION

Mn(III)-Mediated Synthesis of Pyridine Derivatives from Vinyl Azides and Cyclopropanols. We embarked on an investigation of the reaction of α-azidostyrene (**1a**) and 1-phenylcyclopropanol (**2a**) to target 2,6-diphenylpyridines (**3aa**).[11,12] A proposed reaction pathway for the pyridine formation is illustrated in Scheme 3. The reaction is initiated by the addition of β-keto radical **I**, generated by one-electron oxidation of **2a** by the metal oxidant [M^n], to vinyl azide **1a**, affording iminyl radical **II** with elimination of dinitrogen. The reaction of **II** with [M^{n-1}] affords iminyl metal species **III**, nucleophilic attack of which to a carbonyl group yields addition intermediate **IV**.[13] Subsequent protonation affords tetrahydropyridine **V** along with regeneration of [M^n]. Dehydration of **V** forms dihydropyridine **VI**, which is oxidized to afford the desired pyridine **3aa**.

The study on the pyridine formation commenced utilizing a stoichiometric amount of Mn(III) complexes for oxidation of cyclopropanol **2a** as well as dihydropyridine **VI** (Table 1, entries 1–4). Treatment of a mixture of vinyl azide **1a** and **2a** (1.5 equiv) with 1.7 equiv of Mn(III) acetate [$Mn(OAc)_3 \cdot 2H_2O$] in MeOH led to rapid consumption of **1a** within 5 min at room temperature (entry 1). Stirring further 1 h with subsequent addition of AcOH (2 equiv) afforded 2,6-diphenylpyridine (**3aa**) in 57% yield. In the case of Mn(III) tris(2-pyridinecarboxylate) [$Mn(pic)_3$][14] as an oxidant, the reaction was conducted in acetonitrile at 40 °C without any additive for 5 h, and the yield of **3aa** was 58% yield (entry 2). The longer reaction time might be due to low solubility of $Mn(pic)_3$ in acetonitrile. Utilization of Mn(III) acetylacetonate [$Mn(acac)_3$] was found to be essential in rendering this process synthetically useful (entries 3 and 4). Addition of $Mn(acac)_3$ to a mixture of **1a** and **2a** led to rapid consumption of **1a** within 5 min, providing **3aa** in 74% yield after additional heating at 40 °C for 3 h (entry 3). Addition of AcOH (2 equiv) after consumption of **1a** could accelerate the reaction, affording **3aa** in 84% yield within 1 h at room temperature (entry 4). Other metal oxidants such as Ag(I),[15] Fe(III),[16] or Cu(II)[17] complexes, which could work as one-electron oxidants for the oxidative generation of β-carbonyl radicals from cyclopropanols or cyclopropyl silyl ethers, were not viable for this transformation. Next, we intended to use a catalytic amount of $Mn(acac)_3$ with another stoichiometric oxidant for aromatization of dihydropyridine **VI** to **3aa** (see Scheme 3). A brief study revealed that treatment of a mixture of **1a** and **2a** with a catalytic amount of $Mn(acac)_3$ (0.2 equiv) in MeOH also consumed **1a** within 5 min at room temperature, and the subsequent addition of an oxidant (O_2 as an atmosphere or DDQ) and AcOH (2 equiv) provided the desired pyridine **3aa**, although the yield of **3aa** was moderate

Table 1. Optimization of Reaction Conditions for Pyridine Formation[a]



entry	Mn(III) (equiv)	conditions I	oxidant (equiv)	additive (equiv)	conditions II	yield/%[b]
1	$Mn(OAc)_3 \cdot 2H_2O$	MeOH (1.7) rt, 5 min	—	AcOH (2.0)	rt, 1 h	57
2	$Mn(pic)_3$ (1.2)	CH_3CN 40 °C, 5 h	—	—	—	58
3	$Mn(acac)_3$ (1.7)	MeOH 40 °C, 3 h	—	—	—	74
4	**$Mn(acac)_3$ (1.7)**	**MeOH rt, 5 min**	—	**AcOH (2.0)**	**rt, 1 h**	**84**
5	$Mn(acac)_3$ (0.2)	MeOH rt, 5 min	DDQ (1.5)	AcOH (2.0)	rt, 1 h	53
6	$Mn(acac)_3$ (0.2)	MeOH rt, 5 min	O_2 (1 atm)	AcOH (2.0)	rt, 1 h	59
7	**$Mn(acac)_3$(0.1)**	**MeOH rt, 5 min**	**O_2 (1atm)**	**HCl (2.0)**	**40 °C, 1 h**	**80**

[a] The reactions were carried out using vinyl azide **1a** (0.3 mmol) and cyclopropanol **2a** (1.5 equiv). [b] Isolated yields.

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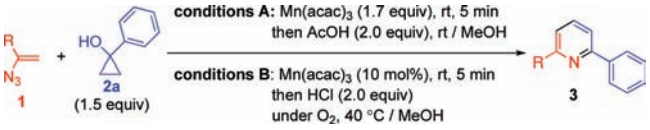
Table 2. Mn(III)-Mediated Pyridine Formation from Vinyl Azides 1 and Cyclopropanols 2a[a]



entry	vinyl azides 1	pyridines 3	yield/%[b] condition A	condition B
1	**1a**: R = H	**3aa**	84%	80%
2	**1b**: R = 4-Me	**3ba**	84%	
3	**1c**: R = 2-OMe	**3ca**	71%	70%
4	**1d**: R = 4-OMe	**3da**	70%	
5	**1e**: R = 2-Br	**3ea**	47%[c]	
6	**1f** : R = 4-Br	**3fa**	70%	
7	**1g**: R = 4-CO_2Me	**3ga**	70%	
8	**1h**	**3ha**	75%	72%
9[d]	**1i**	**3ia**	70%	
10[d]	**1j**	**3ja**	66%	50%
11	**1k**: R_2 = H	**3ka**	51%	
12[e]	**1l** : R_2 = Ph	**3la**	30%	
13[e]	**1m**	**3ma**	45%	
14[e]	**1n**	**3na**	52%	

[a] Unless otherwise noted, the reactions were carried out under either conditions A or B. Conditions A: treatment of a mixture of vinyl azides **1** (0.3 mmol) and cyclopropanol **2a** (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). Conditions B: treatment of a mixture of **1** (0.3 mmol) and **2a** (1.5 equiv) with $Mn(acac)_3$ (0.1 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min followed by addition of HCl (3 M in MeOH, 2 equiv). [b] Isolated yields. [c] Vinyl azide **1e** was recovered in 30% yield. [d] A solution of **2a** and AcOH in MeOH was added to vinyl azides **1** and $Mn(acac)_3$ by a syringe pump over 1 h. [e] The reactions were run using $Mn(pic)_3$ (1.7 equiv) and AcOH (2 equiv) in CH_3CN at 40 °C at room temperature.

(entries 5 and 6). It was noteworthy that addition of HCl (3 M in MeOH, 2 equiv) instead of AcOH could improve the yield of **3aa** to 80% with 0.1 equiv of $Mn(acac)_3$ (entry 7).

With the optimized reaction conditions for the stoichiometric use of $Mn(acac)_3$ (Table 1, entry 4) as well as the catalytic manner with molecular oxygen (Table 1, entry 7), the scope of this Mn(III)-mediated/catalyzed pyridine formation was investigated utilizing various vinyl azides **1** (Table 2). By applying $Mn(acac)_3$ as the stoichiometric oxidant (conditions A), reactions of a range of α-aryl vinyl azides with cyclopropanol **2a** afforded 2,6-diarylpyridines in good to moderate yields (entries 1−10). Especially, heteroaryl motifs such as pyrrolyl and indolyl were successfully incorporated (entries 9 and 10). The reaction of electron-deficient azido acrylate **1k** provided pyridine **3ka** in 51% yield (entry 11). When the reactions of trisubstituted vinyl azides (**1l**, **1m**, and **1n**) were performed by using $Mn(acac)_3$ in MeOH, the generated β-carbonyl radicals underwent self-coupling or hydrogen abstraction preferentially, leading to the desired pyridines in only a trace amount.[18] This indicated that the addition of the β-carbonyl radicals to **1l**−**1n** was extremely slow due to the steric hindrance of the β-substituents on the vinyl azides. Interestingly, the reactions with Mn(III) tris(2-pyridinecarboxylate) [$Mn(pic)_3$] in acetonitrile provided 2,3,6-trisubstituted pyridines in moderate yields, probably due to the low solubility of $Mn(pic)_3$ in acetonitrile which could keep the concentration of the generated β-carbonyl radicals low, preventing their side reactions (entries 12−14).

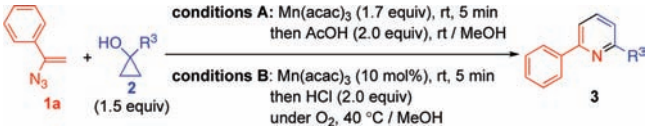
Using vinyl azides **1a**, **1c**, **1h**, and **1j**, pyridine formation under the catalytic conditions (condition B) was examined (entries 1, 3, 8, and 10). The yields of the corresponding pyridines **3** were almost comparable with those obtained under stoichiometric conditions A.

The generality of cyclopropanols **2** was then surveyed using α-azidostyrene (**1a**) under both the stoichiometric and catalytic reaction conditions (conditions A and B), as shown in Table 3. 1-Arylcyclopropanols were converted to the corresponding 2,6-diarylpyridines **3** in good yields (entries 1−3). Moreover, some alkyl groups (entries 4−7), including strained cycloalkyls (**3af**, **3ag**) as well as a piperidine moiety (**3ah**), could be installed at C(2) of the pyridine ring. Introduction of alkenyl and alkynyl groups on the pyridine ring was also a particular feature of this method (entries 8 and 9). This method allowed for the installation of alkoxycarbonyl groups as well as a phenyldimethylsilyl moiety (entries 10 and 11). The catalytic reaction (conditions B) provided comparable results for most of the substrates, except for pyridines **3ah** (entry 7) and **3aj** (entry 9).

On the other hand, the reaction of vinyl azide **1a** and 1,2-disubstituted cyclopropanols (**2m**, **2n**) with $Mn(pic)_3$ afforded not only the desired 2,4,6-trisubstituted pyridines (**3am**, **3an**) but also dihydropyrroles (**4am**, **4an**) as minor products (Scheme 4). The formation of dihydropyrroles might commence with the conversion of iminyl radical **III** to α-carbonyl radical **IV** through a 1,5-hydrogen shift,[19] followed by cyclization of the α-carbonyl radical with *N*−H imine to afford a new C−N bond with a tertiary radical **V**. Further oxidation of this tertiary radical **V** to carbocation **VI** by the Mn(III) complex and subsequent deprotonation could lead to dihydropyrroles **4**. In these reactions, secondary β-keto radicals **II** were found to be formed predominantly via oxidative ring-opening of **2m** and **2n** via cyclopropoxy radicals **I**, judging from the substituted patterns of the products.

One-Pot Synthesis of δ-Lactams from Vinyl Azides and 1-Ethoxycyclopropanol. Based on the finding that Mn(III) complexes could promote the reaction of vinyl azides **1** and monocyclic cyclopropanols **2** to produce substituted pyridines **3**, we planned to broaden the reaction scope by utilizing the other types of cyclopropanols. One-electron oxidation of

Table 3. Mn(III)-Mediated Pyridine Formation from Vinyl Azides 1a and Cyclopropanols 2[a]

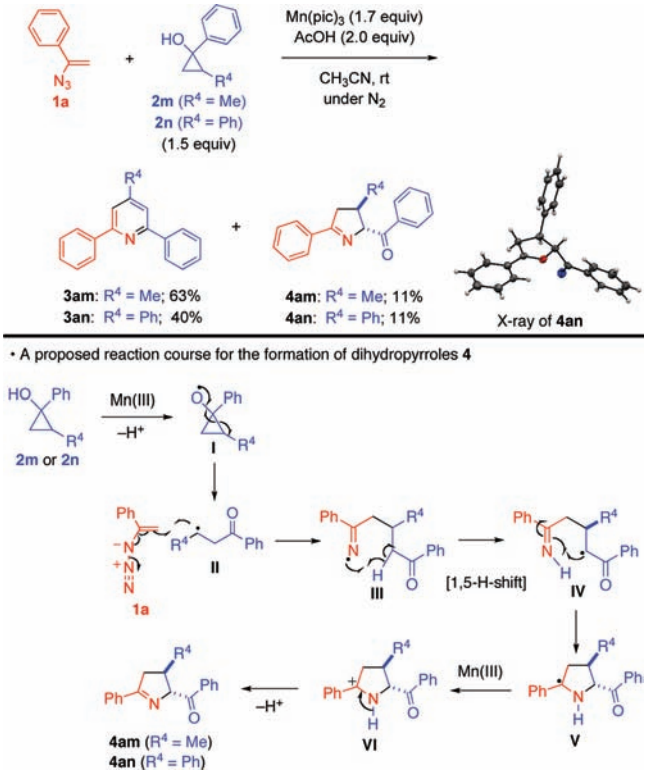


entry	cyclopropanols 2	pyridines 3	yield/%[b] condition A	condition B
1	**2b**: R = 2-Br	**3ab**	70%	
2	**2c**: R = 4-Br	**3ac**	81%	82%
3	**2d**: R = 4-C_6H_5	**3ad**	66%	
4	**2e**	**3ae**	80%	70%
5	**2f**	**3af**	73%	70%
6	**2g**	**3ag**	78%	70%
7	**2h**	**3ah**	82%	45%
8	**2i**	**3ai**	54%	51%
9	**2j**	**3aj**	55%	21%
10	**2k**: R^3 = CO_2Me	**3ak**	33%	
11[c]	**2l** : R^3 = $SiMe_2Ph$	**3al**	45%	

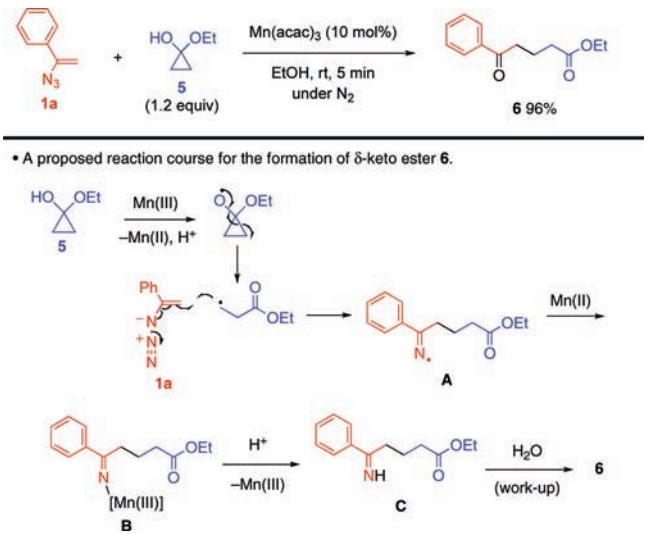
[a] Unless otherwise noted, the reactions were carried out under either conditions A or B. Conditions A: treatment of a mixture of vinyl azide **1a** (0.3 mmol) and cyclopropanols **2** (1.5 equiv) with $Mn(acac)_3$ (1.7 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min, followed by addition of AcOH (2 equiv). Conditions B: treatment of a mixture of **1a** (0.3 mmol) and cyclopropanols **2** (1.5 equiv) with $Mn(acac)_3$ (0.1 equiv) in MeOH at room temperature under N_2 atmosphere for 5 min, followed by addition of HCl (3 M in MeOH, 2 equiv). [b] Isolated yields. [c] The reaction was run using $Mn(pic)_3$ (1.7 equiv) in CH_3CN at room temperature.

1-alkoxycyclopropanols could generate β-alkoxycarbonyl radicals, which were also expected to add to viny azides. Actually, a reaction of vinyl azide **1a** and 1-ethoxycyclopropanol (**5**) proceeded smoothly and rapidly (within 5 min) using 10 mol % of $Mn(acac)_3$ in EtOH at room temperature, giving δ-keto ester **6** in 96% yield (Scheme 5).[20] In this case, the generated iminyl radical **A** was reduced by the resulting Mn(II) species to afford iminyl-manganese(III) **B**, which could not cyclize with an ethoxycarbonyl group. The subsequent protonation would lead to regeneration of Mn(III) species and to give *N*−H imine **C** that was hydrolyzed to δ-keto ester **6** during the workup process.

Scheme 4. Reactions of 1,2-Disubstituted Cyclopropanols 2m and 2n



Scheme 5. $Mn(acac)_3$-Catalyzed Formation of δ-Keto Ester 6



In order to keep a nitrogen atom of the putative *N*−H imine **C** in the final product, we tried reduction of the generated *N*−H imine **C** to amine, which could readily undergo lactamization to provide δ-lactam **7a**.[21] Upon consumption of vinyl azide **1a** by the reaction with 1-ethyoxycyclopropanol (**5**) in the presence of $Mn(acac)_3$ as the catalyst, $NaBH_4$ (2 equiv) was subsequently

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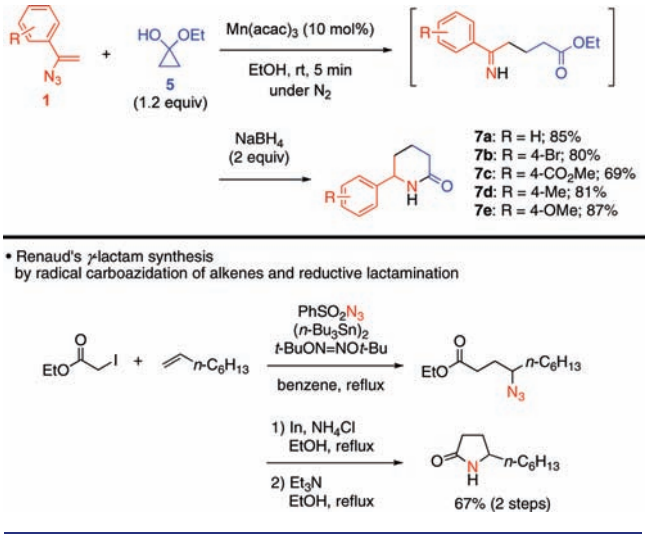
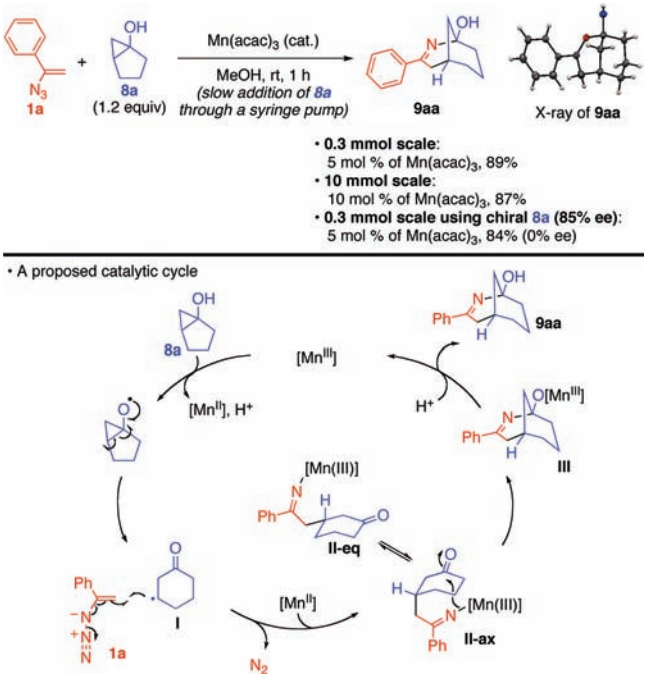
Scheme 6. One-Pot Synthesis of δ-Lactams 7 from Vinyl Azides 1 and 1-Ethoxycyclopropanol 5



Scheme 7. Formation of 2-Azabicyclo[3.3.1]non-2-en-1-ol 9aa



added to the reaction mixture. Expectedly, **7a** was isolated in 85% yield (Scheme 6). A series of α-aryl vinyl azides possessing both electron-withdrawing and electron-donating groups were transformed to α-aryl-δ-lactams **7** in good yields. The Renaud group has developed an elegant procedure for synthesis of a series of γ-lactams and their derivatives by radical carboazidation of alkenes followed by reduction of azides and subsequent lactam formation.[22,23] These two-step processes are contrasting manners to construct δ- and γ-lactams, respectively, via radical processes involving organic azides.

Mn(acac)$_3$-Catalyzed Synthesis of 2-Azabicyclo[3.3.1]-non-2-en-1-ols from Vinyl Azides and Bicyclo[3.1.0]hexan-1-ols. Next, we envisioned utilizing bicyclic cyclopropanols such as bicyclo[3.1.0]hexan-1-ol (**8a**) as a source of β-carbonyl radicals. Interestingly, an unusual 2-azabicyclo[3.3.1]non-2-en-1-ol (**9aa**) was isolated in 89% yield by the reaction with vinyl azide **1a** using only a catalytic amount of Mn(acac)$_3$ (5 mol %), although slow addition of **8a** through a syringe pump to a mixture of **1a** and the catalyst over 1 h was required to complete the reaction (Scheme 7). A gram scale preparation of **9aa** was also accomplished in good yield. It is noteworthy that treatment of chiral bicyclic cyclopropanol **8a** (85% ee)[24] with **1a** afforded racemic **9aa**. The absence of transmission of the chirality of **8a** to **9aa** would suggest that generation of achiral ring-expanded β-carbonyl radical **I**[25] from **8a** followed by its radical addition to **1a** is most likely involved in the reaction mechanism, forming iminyl manganese(III) compounds **II-*eq*** and **II-*ax***, placing an iminyl tether in the equatorial- and axial-like positions, respectively. Conformational inversion of **II-*eq*** to **II-*ax*** should be indispensable to achieve 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 **9aa**.

With the Mn(III)-catalyzed method to construct a 2-azabicyclo[3.3.1]non-2-en-1-ol structure in hand, the substrate scope was next investigated (Table 4). A variety of 3-aryl-2-azabicyclo[3.3.1]non-2-en-1-ols were prepared in good to excellent yields. Heteroaryl moieties such as pyrrolyl and indolyl were successfully incorporated, even though higher catalyst loading (20 mol %) was needed to complete the reaction (entries 8 and 9). The reaction of trisubstituted vinyl azide **1m** with **8a** furnished the desired **9ma** in only 28% yield, along with recovery of **1m** (68%), even in the presence of 40 mol % of the catalyst, probably due to the steric hindrance of the β-methyl group of **1m** in the addition of β-carbonyl radical to **1h**. Introduction of some substituents, including alkyl, vinyl, and phenyl groups, at C-4 of bicyclic cyclopropanols **8** did not retard the reactions, providing the corresponding 2-azabicyclo[3.3.1]non-2-en-1-ols **9** in high yields and diastereoselectivities (83:17 to 94:6 *exo*-selective) (entries 11−15). In these cases, the addition of β-carbonyl radicals to vinyl azide **1a** in the C−C bond formation occurred preferentially in an *anti* manner to the adjacent C-4 substituents to minimize 1,2-steric repulsion.

Interestingly, for the reaction of 3-phenylbicyclo[3.1.0]hexan-1-ol (**8g**), 2-azabicyclo[3.3.1]non-2-en-1-ol (**9ag**) was obtained in 40% yield, along with 1,5-diketone **10ag**[26] in 28% yield (Scheme 8). Both of the products **9ag** and **10ag** were obtained as single diastereoisomers. The reaction of β-carbonyl radical **I** generated from **8g** could provide two diastereomers of iminyl manganese complexes (or iminyl radicals) bearing the iminyl tether in axial- and equatorial-like positions (**II-*ax*** and **II-*eq***, respectively). From **II-*ax***, the cyclization occurred smoothly to give **9ag**, while **II-*eq*** needed ring-inversion for cyclization, which might be disfavored due to 1,3-diaxial repulsion between the iminyl radical moiety and the phenyl group. Noncyclized compound **10ag** was thus exclusively formed from **II-*eq*** via hydrolysis.

Transformations of 2-Azabicyclo[3.3.1]non-2-en-1-ols 9. Having developed a method for preparation of 2-azabicyclo-[3.3.1]non-2-en-1-ols **9**, we then explored their transformations

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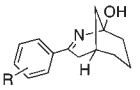
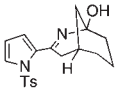
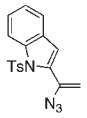
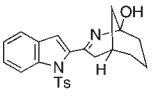
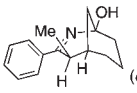
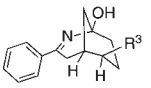
Table 4. Mn(III)-Catalyzed Synthesis of 2-Azabicyclo-[3.3.1]non-2-en-1-ols 9[a]

entry	vinyl azides **1**	cyclopropanols **8**	products **9**	yield/%[b]
				
1	**1a**: R = H	**8a**	**9aa**	89%[c]
2	**1b**: R = 4-Me	**8a**	**9ba**	95%
3	**1c**: R = 2-OMe	**8a**	**9ca**	88%
4	**1d**: R = 4-OMe	**8a**	**9da**	93%
5	**1e**: R = 2-Br	**8a**	**9ea**	70%
6	**1f** : R = 4-Br	**8a**	**9fa**	83%
7	**1g**: R = 4-CO_2Me	**8a**	**9ga**	75%
8	 **1i**	**8a**		**9ia** 83%[c]
9[d]	 **1j**	**8a**		**9ja** 77%[c]
10[d]	 **1m**	**8a**		**9ma** 28%[d,e] (*exo*:*endo* = 85:15)[f,g]
				
11	**1a**	**8b**: R^3 = $CH(CH_3)_2$	**9ab**: 90% (*exo*:*endo* = 85:15)[f]	
12	**1a**	**8c**: R^3 = $CH=CH_2$	**9ac**: 82% (*exo*:*endo* = 83:17)[f,g]	
13	**1a**	**8d**: R^3 = $CH_2CH=CH_2$	**9ad**: 86% (*exo*:*endo* = 86:14)[f,h]	
14	**1a**	**8e**: R^3 = Ph	**9ae**: 91% (*exo*:*endo* = 94:6)[f,g]	
15	**1a**	**8f**: R^3 = CH_2OMOM	**9af**: 74% (*exo*:*endo* = 85:15)[f]	

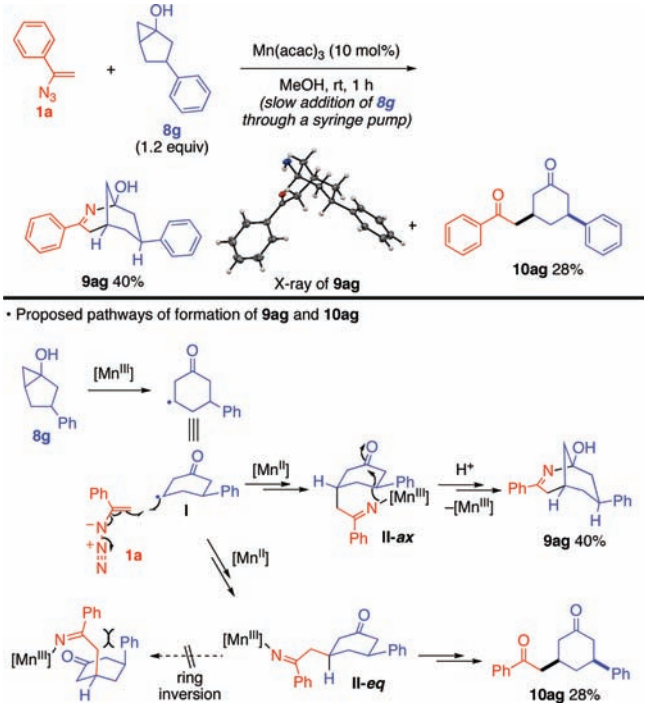
[a] Unless otherwise noted, the reactions were carried out by addition of a solution of cyclopropanols **8** (1.2 equiv) in MeOH via a syringe pump over 1 h to a solution of vinyl azides **1** (0.3 mmol) and $Mn(acac)_3$ (10 mol %) under N_2 atmosphere at room temperature (see Supporting Information). [b] Isolated yields. [c] 5 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 *exo*-isomer was shown above. [g] The structures of *exo*-isomers of **9ma**, **9ac**, and **9ae** were secured by X-ray crystallographic analyses; see Supporting Information. [h] NMR yield using $Cl_2CHCHCl_2$ as internal standard due to the instability of **9ad**, which could be isolated as its acetate in 73% yield by treatment of the crude mixture of **9ad** with Ac_2O (8.0 equiv), Et_3N (2.0 equiv), and DMAP (0.1 equiv) in CH_2Cl_2 at rooom temperature for 8 h.

to 2-azabicyclo[3.3.1]nonane (morphan)[27] or 2-azabicyclo[3.3.1]-non-2-ene frameworks, which are prevalent in some alkaloids as well as pharmacologically valuable molecules.[28]

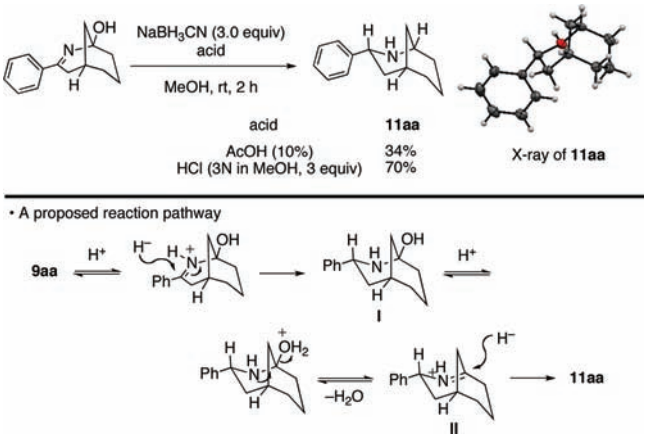
Treatment of **9aa** with $NaBH_3CN$ in the presence of an acid induced the double hydride reduction of the C═N and C−O bonds, affording 2-azabicyclo[3.3.1]nonane (**11aa**) stereoselectively, where reduction using HCl afforded **11aa** in 70% yield (Scheme 9). The first hydride approached the C═N bond entirely from the less hindered *exo*-face to give aminal **I**. Subsequent dehydration of **I** gave the bridgehead iminium species **II**, which could be reduced to afford **11aa**.

It was found that a one-pot conversion starting from the reaction of vinyl azide **1a** and cyclopropanol **8a** using $Mn(acac)_3$ as a catalyst followed by treatment with $NaBH_3CN$ (3 equiv) and HCl (3 equiv) could produce **11aa** in good yield

Scheme 8. Reaction of Vinyl Azide 1a and Cyclopropanol 8g



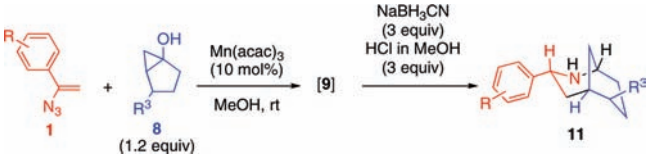
Scheme 9. Double Hydride Reduction of 9aa



without isolation of 2-azabicyclo[3.3.1]non-2-en-1-ol (**9aa**). This two-step process represented a particularly straightforward methodology to construct the morphan framework from readily available vinyl azides **1** and bicyclic cyclopropanols **8** (Table 5).

Further methods for reduction of the C−O bond at the bridgehead position were explored utilizing acetate **12** prepared from **9aa** as depicted in Scheme 10. Interestingly, it was found that reduction of acetate **12** with Et_3SiH in the presence of $TiCl_4$ induced selective C−O bond cleavage, affording 2-azabicyclo[3.3.1]non-2-ene (**13**) in excellent yield, keeping the C═N bond intact. Similarly, treatment with allyltrimethylsilane−$TiCl_4$ or Me_3Al provided a new quaternary carbon center[29] at the bridgehead position (**14** and **15**). In order to elucidate the mechanism of these chemoselective reductions,

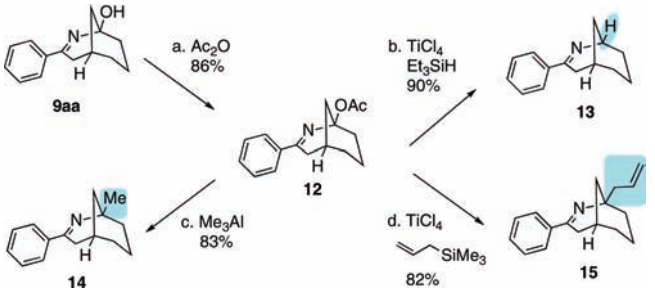
Table 5. One-Pot Synthesis of 2-Azabicyclo[3.3.1]nonanes 11[a]



entry	vinyl azides 1	cyclopropanols 8	products 11	yield/%[b]
1	**1a**: R = H	**8a**	**11aa**	70%
2	**1b**: R = 4-Me	**8a**	**11ba**	68%
3	**1d**: R = 4-OMe	**8a**	**11da**	58%
4	**1f** : R = 4-Br	**8a**	**11fa**	76%
5	**1a**	**8b**: $R^3 = CH(CH_3)_2$	**11ab** 70% (*exo*:*endo* = 85:15)[c]	
6	**1a**	**8c**: $R^3 = CH{=}CH_2$	**11ac** 67% (*exo*:*endo* = 81:19)[c]	
7	**1a**	**8d**: $R^3 = CH_2CH{=}CH_2$	**11ad** 80% (*exo*:*endo* = 81:19)[c]	
8	**1a**	**8e**: R^3 = Ph	**11ae** 56% (*exo*:*endo* = 90:10)[c]	

[a] The reactions were carried out by addition of a solution of cyclopropanols **8** (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, followed by treatment with $NaBH_3CN$ (3 equiv) and HCl (3 M in MeOH, 3 equiv) for 3 h. [b] Isolated yiels. [c] The ratio was determined by ^1H NMR, and the major *exo*-isomer is shown above.

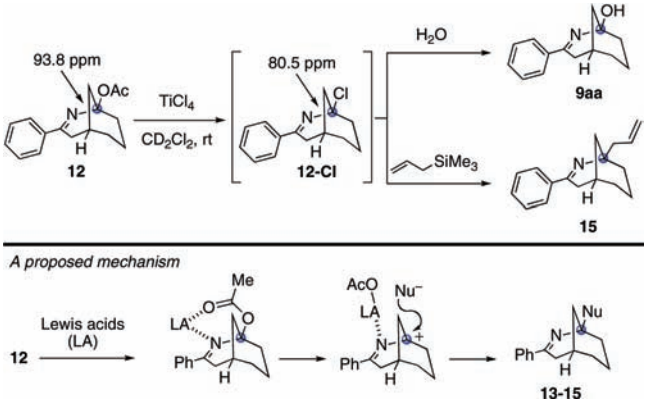
Scheme 10. Transformations of 2-Azabicyclo[3.3.1]non-2-en-1-ol (9aa)[a]



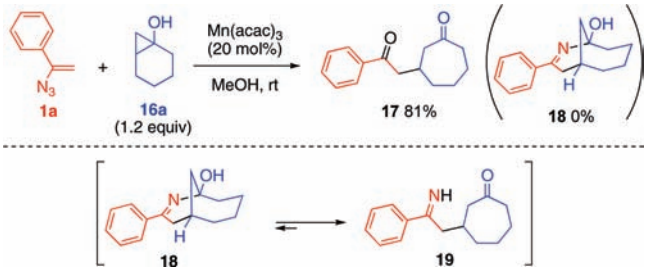
[a] Reagents and conditions: (a) Ac_2O (8.0 equiv), Et_3N (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 3 h, 86%; (b) $TiCl_4$ (1.5 equiv), Et_3SiH (2.0 equiv), CH_2Cl_2, rt, 3 h, 90%; (c) Me_3Al (4.0 equiv), $CHCl_3$, rt, 1 h, 83%; (d) $TiCl_4$ (1.5 equiv), $CH_2{=}CHCH_2SiMe_3$ (2.0 equiv), CH_2Cl_2,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

the reaction of acetate **12** with $TiCl_4$ in the absence of nucleophiles was monitored by ^1H NMR and ^{13}C NMR in CD_2Cl_2 (Scheme 11). Acetate **12** disappeared immediately upon treatment with $TiCl_4$ to give chloride **12-Cl**. The chemical shift of the bridgehead carbon was shifted to higher field, from 93.8 ppm (for acetate **12**) to 80.5 ppm (for chloride **12-Cl**). The formation of **12-Cl** occurred presumably via coordination of $TiCl_4$ to the imino nitrogen and the acetate carbonyl oxygen, followed by cleavage of the bridgehead C−O bond to generate a bridgehead carbocation,[30] which

Scheme 11. Elucidation of the Reaction Mechanism



Scheme 12. $Mn(acac)_3$-Catalyzed Reaction of Vinyl Azide 1a with Bicyclo[4.1.0]heptan-1-ol (16a)



was then immediately trapped by a chloride ion. It was confirmed that subsequent treatments of a mixture including **12-Cl** with water or allyltrimethylsilane led to the formation of **9aa** or **15**, respectively. Likewise, in the presence of nucleophiles such as hydrosilane, allyltrimethylsilane, and Me_3Al, the bridgehead carbocation could immediately be trapped to produce the desired bridgehead-substituted products **13**−**15**.

Synthesis of 2-Azabicyclo[4.3.1]decane Derivatives from Vinyl Azides and Bicyclo[4.1.0]heptan-1-ols. The promising protocol to access 2-azabicyclo[3.3.1]non-2-en-1-ols **9** encouraged us to explore further methods to construct another azabicyclic framework, 2-azabicyclo[4.3.1]dec-2-en-1-ol, from vinyl azide **1a** and bicyclo[4.1.0]heptan-1-ol **16a** (Scheme 12). However, treatment of **1a** and **16a** with $Mn(acac)_3$ (20 mol %) afforded 1,5-diketone **17** exclusively in 81% yield, without formation of desired 2-azabicyclo[4.3.1]dec-2-en-1-ol (**18**).

It was envisioned that there might be an equilibrium between the desired 2-azabicyclo[4.3.1]dec-2-en-1-ol **18** and ring-opened N−H imine **19**, which should be driven to the imine **19** side. Stimulated by the one-pot process developed to prepare 2-azabicyclo[3.3.1]nonanes **11** without isolation of 2-azabicyclo[3.3.1]non-2-en-1-ols **9** (Table 5), the same procedure was employed to the reaction of **1a** and **16a** to synthesize 2-azabicyclo[4.3.1]decane derivatives. To our delight, 2-azabicyclo[4.3.1]decane **20aa** was obtained as a single diastereoisomer via double hydride reductions of the C=N and C−O

dx.doi.org/10.1021/ja200879w | *J. Am. Chem. Soc.* 2011, 133, 6411–6421

Scheme 13. One-Pot Synthesis of 2-Azabicyclo[4.3.1]-decanes

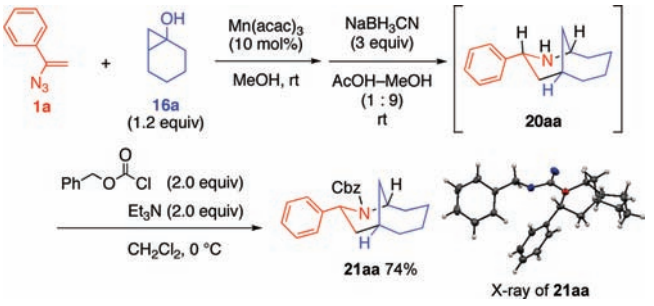


Table 6. Construction of 2-Azabicyclo[4.3.1]decane Frameworks from Vinyl Azides 1 and Bicyclo[4.1.0]heptan-1-ols 16[a]

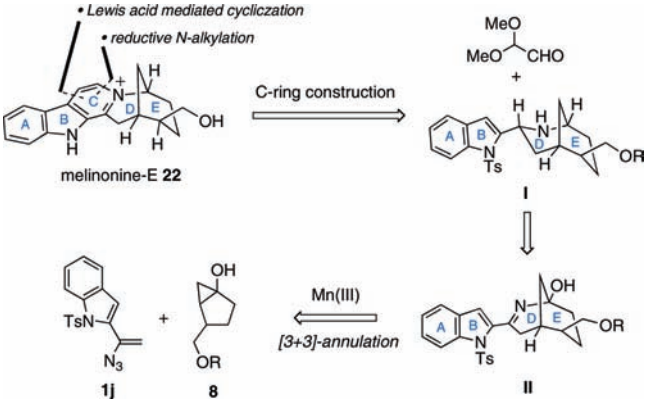
entry	vinyl azides 1	cyclopropanols 16	products 21	yield/%[b]
1	**1a**: R = H	**16a**	**21aa**	74%
2	**1d**: R = 4-OMe	**16a**	**21da**	58%
3[c]	**1g**: R = 4-CO_2Me	**16a**	**21ga**	62%
4	**1a**	**16b**: R^4 = Ph	**21ab** 74% (*exo*:*endo* = >99:1)[d]	
5	**1a**	**16c**: R^4 = $CH_2CH{=}CH_2$	**21ac** 83% (*exo*:*endo* = 84:16)[d]	
6	**1a**	**16d**	**21ad** 74% (*exo*:*endo* = >99:1)[d,e]	
7	**1a**	**16e**	**20ae**	46%[f]

[a] Unless otherwise noted, the reactions were carried out by addition of $Mn(acac)_3$ (10 mol %) in one portion to a solution of vinyl azides **1** and cyclopropanols **16**. After 5 min, $NaBH_3CN$ (3.0 equiv) and AcOH were added, and then the mixture was kept stirring overnight. After simple workup of the reaction mixture, the crude products were treated with benzyl chloroformate (3.0 equiv) and Et_3N (2.0 equiv) in CH_2Cl_2 for 1 h. [b] Isolated yields. [c] 15 mol % $Mn(acac)_3$ was used, and **16a** was added via a syringe pump over 1 h. [d] The ratio was determined by GC and GC-MS, and the major *exo*-isomer is shown above. [e] The structure was secured by X-ray crystallographic analysis; see Supporting Information. [f] **20ae** was isolated without protection as the N-Cbz derivative.

bonds of 2-azabicyclo[4.3.1]dec-2-en-1-ol (**18**). Subsequent protection of N−H amine with Cbz-Cl provided the *N*-benzyloxycarbonyl derivative **21aa** in 74% yield from vinyl azide **1a** (Scheme 13).

The reactions of α-aryl-substituted vinyl azides **1d** and **1g** proceeded smoothly to afford *N*-benzyloxycarbonyl-7-azabicyclo-[4.3.1]decanes **21da** and **21ga** in moderate yields (Table 6, entries 2 and 3). Introduction of a phenyl group at C-4 (**16b**) or even at C-5 (**16d**) of the bicyclic cyclopropanol led to the

Scheme 14. Synthetic Plan of Melinoline E



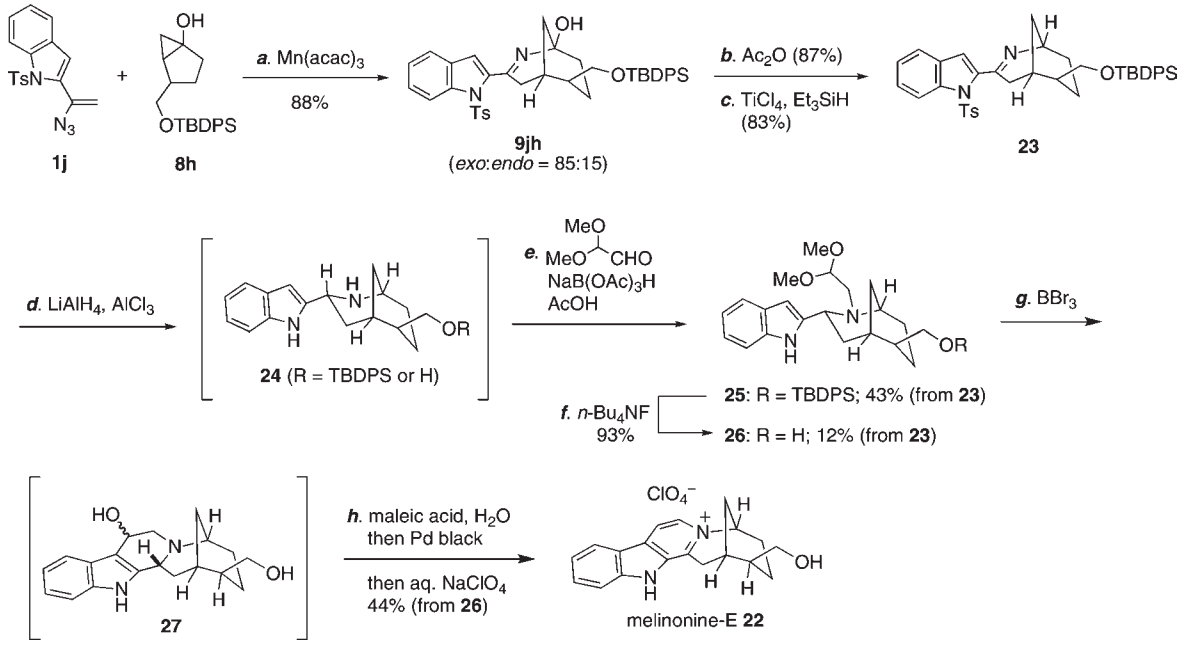
azabicyclic compounds **21ab** and **21ad** as single diastereoisomers (entries 4 and 6), while cyclopropanol **16c**, bearing a less hindered allyl group at C-4, provided **21ac** in 83% yield with slightly lower diastereoselectivity (entry 5, *exo*:*endo* = 84:16). The reaction with benzene-bridged cyclopropanol **16e** also afforded 7-azabicyclo[4.3.1]decane **20ae**, but the yield was moderate (entry 7).

Synthesis of (±)-Melinonine-E. Melinonine-E (**22**) was originally isolated from the bark of *Strychnos melinoniana*,[31] and its structure was characterized by a unique pentacyclic ring system including indolo[2,3-*a*]quinolizidine and 2-azabicyclo-[3.3.1]nonane (morphan) frameworks.[32] The first synthesis of (±)-melinonine-E was achieved by the Bonjoch group.[33] We envisioned that the 2-azabicyclo[3.3.1]nonane moiety of melinonine-E would be readily constructed by Mn(III)-mediated annulation of vinyl azide **1j** and cyclopropanol **8**, bearing a hydroxymethyl tether, followed by reduction of the C═N and bridgehead C−O bonds (see **II** → **I** in Scheme 14). Reductive *N*-alkylation with dimethoxyacetaldehyde followed by Lewis acid-mediated cyclization of the acetal moiety at the C(3) position of the indole ring would generate the C-ring at a later stage.

[3+3]-Annulation of α-indolylvinyl azide **1j** and bicyclic cyclopropanol **8h** afforded azabicyclic compound **9jh** in 88% yield on a 2 g scale with good diastereoselectivity (*exo*:*endo* = 85:15), while 1.6 equiv of $Mn(acac)_3$ were necessary to complete the reaction (Scheme 15). The two diastereoisomers of **9jh** could be separated by silica gel column chromatography. After conversion of **9jh** into its acetate, the bridgehead C−O bond was reduced by the $Et_3SiH-TiCl_4$ protocol to give cyclic imine **23**.[34] Subsequent reduction of the C═N bond of **23** with $LiAlH_4-AlCl_3$[35] leading to not only the complete 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 **24** with dimethoxyacetaldehyde in the presence of $NaBH(OAc)_3$ provided **25** and **26** in 43% and 12% yield, respectively. The remaining TBDPS group of **25** was removed with *n*-Bu_4NF. BBr_3-induced cyclization of **26** took place cleanly to afford the cyclic alcohol **27**, which further underwent dehydration with maleic acid in water followed by dehydrogenation with palladium black in one-pot fashion,[36,37] affording (±)-melinonine-E (**22**) as a perchlorate salt in 44% yield from **26**. The ^1H and ^{13}C NMR data of the synthetic

dx.doi.org/10.1021/ja200879w |*J. Am. Chem. Soc.* 2011, 133, 6411–6421

Scheme 15. Synthesis of (±)-Melinonine-E[a]



[a] Reagents and conditions: (a) **8h** (3.0 equiv, added by a syringe pump), $Mn(acac)_3$ (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) $(MeO)_2CHCHO$ (1.5 equiv), $NaB(OAc)_3H$ (1.5 equiv), CH_2Cl_2, 0 °C, 30 min, **25** (43% from **23**) + **26** (12% from **23**); (f) *n*-Bu_4NF (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 **26**).

(±)-melinonine-E perchlorate were identical to the reported ones.

CONCLUSION

In summary, we have developed a divergent synthetic route to construct azaheterocycles from readily available vinyl azides and cyclopropanols via formal [3+3]-annulation using Mn(III) complexes. A series of azaheterocycles such as pyridines, δ-lactams, and azabicyclic compounds have been successfully prepared by utilizing this promising strategy. Further investigation to explore other modes of annulation reactions of vinyl azides to prepare azaheterocycles is currently underway.

ASSOCIATED CONTENT

Supporting Information. 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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REFERENCES

(1) For recent reviews, see: (a) *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Oxford, 2008; Vol. 20 and others in this series. (b) *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon: Oxford, 2008. (c) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon: Oxford, 2008. (d) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon: Oxford, 1996 and references therein. (e) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003.

(2) (a) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259. (b) Trost, B. M. *Science* **1991**, *254*, 1471.

(3) (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (b) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505.

(4) For our recent reports on synthesis of pyrroles from vinyl azides and 1,3-dicarbonyl compounds, see: (a) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019. (b) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313.

(5) 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*, 5864. (b) Bamford, A. F.; Cook, M. D.; Roberts, B. P. *Tetrahedron Lett.* **1983**, *24*, 3779.

(6) For reviews on construction of organic frameworks by radical cascade reactions, see: (a) Godineau, E.; Landais, Y. *Chem. Eur. J.* **2009**, *15*, 3044. (b) Ihara, M. *Arkivoc* **2006**, 416. (c) Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. *Chem. Eur. J.* **2004**, *10*, 3606. (d) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**,

40, 2225. (e) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 3215.

(7) For reviews on synthesis of azaheterocycles using iminyl radicals, see: (a) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 407. (b) Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603. (c) Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 539.(d) Mikami, T.; Narasaka, K. In *Advances in Free Radical Chemistry*; Zard, S. Z., Ed.; JAI: Stamford, CT, 1999; Vol. 2, p 45. (e) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (f) Zard, S. Z. *Synlett* **1996**, 1148.

(8) For recent reports on generation of iminyl radicals from *N*-substituted imine derivatives, see: (a) Portela-Cubillo, F.; Surgenor, B. A.; Aitken, R. A.; Walton, J. C. *J. Org. Chem.* **2008**, *73*, 8124. (b) Portela-Cubillo, F.; Lymer, J.; Scanlan, E. M.; Scott, J. S.; Walton, J. C. *Tetrahedron* **2008**, *64*, 11908. (c) Alonso, R.; Campos, P. J.; Garcia, B.; Rodriguez, M. A. *Org. Lett.* **2006**, *8*, 3521. (d) Yoshida, M.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2003. (e) Yoshida, M.; Kitamura, M.; Narasaka, K. *Chem. Lett.* **2002**, 144. (f) Lin, X.; Artman, G. D.; Stien, D.; Weinreb, S. M. *Tetrahedron* **2001**, *57*, 8779. (g) Lin, X.; Stien, D.; Weinreb, S. M. *Org. Lett.* **1999**, *1*, 637.

(9) For recent reports on generation of iminyl and amidinyl radicals from nitriles and cyanamides, respectively, see: (a) Larraufie, M.-H.; Courillon, C.; Ollivier, C.; Lacôte, E.; Malacria, M.; Fensterbank, L. *J. Am. Chem. Soc.* **2010**, *132*, 4381. (b) Larraufie, M.-H.; Ollivier, C.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 2178. (c) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 576. (d) Bowman, W. R.; Cloonan, M. O.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.* **2005**, *3*, 1460. (e) Bowman, W. R.; Cloonan, M. O.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.* **2005**, *3*, 146. (f) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 58. (g) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765.

(10) For our preliminary communication on this concept, see: Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570.

(11) For recent reviews on synthesis of pyridines, see: (a) Hill, M. D. *Chem. Eur. J.* **2010**, *16*, 12052. (b) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459. (c) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (d) Ciufolini, M. A.; Chan, B. K. *Heterocycles* **2007**, *74*, 101. (e) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (f) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787.

(12) For recent selected reports on synthesis of pyridines, see: (a) Nakamura, I.; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2010**, *132*, 7884. (b) Chiba, S.; Xu, Y.-J.; Wang, Y.-F. *J. Am. Chem. Soc.* **2009**, *131*, 12886. (c) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602. (d) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602. (e) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (g) Barluenga, J.; Fernández-Rodriguez, M. A.; García-García, P.; Aguilar, E. *J. Am. Chem. Soc.* **2008**, *130*, 2764. (h) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325. (i) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (j) Dash, J.; Lechel, T.; Reissig, H.-U. *Org. Lett.* **2007**, *9*, 5541. (k) Trost, B. M.; Gutierrez, A. C. *Org. Lett.* **2007**, *9*, 1473. (l) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem. Eur. J.* **2006**, *12*, 5618. (m) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592. (n) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774. (o) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030.

(13) Alternatively, it could be proposed that consecutive cyclization of iminyl radical **II** to an intramolecular carbonyl group gives an alkoxyl radical that can be reduced by $[M^{n-1}]$ to afford **IV**.

(14) For oxidative generation of β-carbonyl radicals from cyclopropanols by using $Mn(pic)_3$, see: (a) Iwasawa, N.; Hayakawa, S.; Funahashi, M.; Isobe, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 819. (b) Iwasawa, N.; Hayakawa, S.; Isobe, K.; Narasaka, K. *Chem. Lett.* **1991**, 1193.

(15) Chiba, S.; Cao, Z. Y.; El Bialy, S. A. A.; Narasaka, K. *Chem. Lett.* **2006**, *35*, 18.

(16) (a) Hasegawa, E.; Tsuchida, H.; Tamura, M. *Chem. Lett.* **2005**, *34*, 688. (b) Booker-Milburn, K. I.; Jones, J. L.; Sibley, G. E. M.; Cox, R.; Meadows, J. *Org. Lett.* **2003**, *5*, 1107. (c) Booker-Milburn, K. I.; Barker, A.; Brailsford, W.; Cox, B.; Mansley, T. E. *Tetrahedron* **1998**, *54*, 15321.

(17) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1992**, *57*, 2399.

(18) When the reaction of trisubstituted vinyl azides **1k**, **1l**, and **1m** was performed by using $Mn(acac)_3$ in MeOH, the generated β-carbonyl radicals underwent self-coupling or hydrogen abstraction preferentially, leading to the desired pyridines in very low yield. Moreover, even though $Mn(acac)_3$ was added to the reaction mixture by a syringe pump, which could keep the concentration of $Mn(acac)_3$ low, the yield of product could not be improved greatly.

(19) (a) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568. (b) Fujitani, M.; Tsuchiya, M.; Okano, K.; Takasu, K.; Ihara, M.; Tokuyama, H. *Synlett* **2010**, 822. (c) Robertson, M.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825. (d) Murakami, M.; Hayashi, M.; Ito, Y. *Appl. Organomet. Chem.* **1995**, *9*, 385. (e) Williams, L.; Booth, S. E.; Undheim, K. *Tetrahedron* **1994**, *50*, 13697. (f) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896.

(20) For reports on synthesis of δ-keto esters by the reaction of 1-ethyoxycyclopropanol with silyl enol ethers in the presence of 2 equiv of $Mn(pic)_3$, see ref 13.

(21) For selected reports on preparation of δ-lactams, see: (a) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828. (b) Patil, N. T.; Huo, Z.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 3612. (c) Taylor, P. J. M.; Bull, S. D.; Andrews, P. C. *Synlett* **2006**, 1347. (d) Hu, T.; Li., C. *Org. Lett.* **2005**, *7*, 2035.

(22) (a) Lapointe, G.; Schenk, K.; Renaud, P. *Chem. Eur. J.* **2011**, *17*, 3207. (b) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755. (c) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3460.

(23) For generation of amidyl radicals and their cyclization with an alkene to prepare lactam derivatives, see: (a) Lu, H.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 5983. (b) Moutrille, C.; Zard, S. Z. *Chem. Commun.* **2004**, 1848. (c) Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 2707. (d) Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333. (e) Clark, A. J.; Deeth, R. J.; Samuel, C. J.; Wongtap, H. *Synlett* **1999**, *4*, 444. (f) Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Synlett* **1999**, *4*, 441. (g) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 2463. (h) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 8791. (i) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517. (j) Callier, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 6109. (k) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779. (l) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877. (m) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933.

(24) Du, H.; Long, J.; Shi, Y. *Org. Lett.* **2006**, *8*, 2827.

(25) For discussion on racemization of cyclohexyl radicals, see: (a) Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386. (b) Roberts, B. P.; Steel, A. J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2025 and references therein.

(26) The stereochemistry of **10ag** was assigned by 2D NMR; see Supporting Information.

(27) For a review on the construction of the morphan structure, see: Bosch, J.; Bonjoch, J. *Heterocycles* **1980**, *14*, 505. For recent synthetic reports, see: (a) Ieda, S.; Kan, T.; Fukuyama, T. *Tetrahedron Lett.* **2010**, *51*, 4027. (b) Ieda, S.; Asoh, Y.; Fujimoto, T.; Kitaoka, H.; Kan, T.; Fukuyama, T. *Heterocycles* **2009**, *79*, 721. (c) Zou, W.; Vembaiyan, K.; Bhasin, M.; Williams, D. T. *Carbohydr. Res.* **2009**, *344*, 2144. (d) Patir, S.; Uludag, N. *Tetrahedron* **2009**, *65*, 115. (e) Simila, S. T. M.; Martin, S. F. *J. Org. Chem.* **2007**, *72*, 5342. (f) Aurrecoechea, J. M.; Gorgojo, J. M.; Saornil, C. *J. Org. Chem.* **2005**, *70*, 9640. (g) Brummond, K. M.; Hong, S.-p. *J. Org. Chem.* **2004**, *70*, 907. (h) Bonjoch, J.; Diaba, F.; Puigb, G.; Peidr, E.; Sol, D. *Tetrahedron Lett.* **2003**, *44*, 8387. (i) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353. (j) Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347. (k) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225.

(28) For recent selected reports, see: (a) Thomas, J. B.; Zhang, L.; Navarro, H. A.; Carroll, F. I. *J. Med. Chem.* **2006**, *49*, 5597. (b) Pluotno, A.; Carmeli, S. *Tetrahedron* **2005**, *61*, 575. (c) Kim, I. J.; Dersch, C. M.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *Bioorg. Med. Chem.* **2004**, *12*, 4543.

(29) For a report on C−C bond formation at bridgehead iminium cations to prepare 1-alkylated 2-azabicyclo[3.3.1]nonanes, see: Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280.

(30) Kraus, G. A.; Hon, Y.-S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* **1989**, *89*, 1591.

(31) Bächli, E.; Vamvacas, C.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1957**, *40*, 1167.

(32) Borris, R. P.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 455.

(33) (a) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968. (b) Quirante, J.; Escolano, C.; Bosch, J.; Bonjoch, J. *J. Chem. Soc., Chem. Commun.* **1995**, 2141.

(34) The double hydride reduction of the C=N bond and the C−O bond of **9jh** or its acetate by $NaBH_3CN$ was not successful under the reaction conditions in Scheme 9, since the indole moiety could also be reduced in these conditions. For an example of reduction of the indole moiety by $NaBH_3CN$, see: Ketcha, D. M.; Lieurance, B. A. *Tetrahedron Lett.* **1989**, *30*, 6833 and references therein.

(35) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.

(36) Fujii, T.; Ohba, M.; Ohashi, T. *Tetrahedron* **1993**, *49*, 1879.

(37) A range of oxidants such as molecular oxygen, DDQ, $Pb(OAc)_4$, and $Hg(OAc)_2$ were examined for this dehydrogenation; they resulted in a mixture of the final product and an unidentified side product.