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Copper-Mediated Oxidative Transformation of N-Allyl Enamine Carboxylates toward Synthesis of Azaheterocycles

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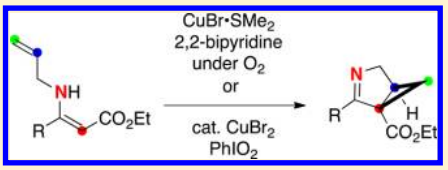
Supporting Information

ABSTRACT: A method for synthesis of 3-azabicyclo[3.1.0]hex-2-enes has been developed by intramolecular cyclopropanation of readily available N-allyl enamine carboxylates. Two complementary reaction conditions, CuBr-mediated aerobic and $CuBr_2$-catalyzed-$PhIO_2$-mediated systems effectively induced stepwise cyclopropanation via carbocupration of alkenes. Oxidative cyclopropane ring-opening of 5-substituted 3-azabicyclo[3.1.0]hex-2-enes was also developed for synthesis of highly substituted pyridines. In addition, diastereoselective reduction of 3-azabicyclo[3.1.0]hex-2-enes to 3-azabicyclo[3.1.0]hexanes was achieved using $NaBH_3CN$ in the presence of acetic acid.



INTRODUCTION

The 3-azabicyclo[3.1.0]hexane motif is an important azaheterocyclic framework from the medicinal chemistry perspective. This scaffold is prevalent in biologically active molecules, showing various potent pharmacological activities such as bicifadine for treatment of acute and chronic pain,[1] indolizomycin as a bioengineered antibiotic,[2] boceprevir as a protease inhibitor for hepatitis C treatment,[3] and naturally occurring *anti*-tumor alkaloids like (+)-duocarmycin A (Figure 1).[4]

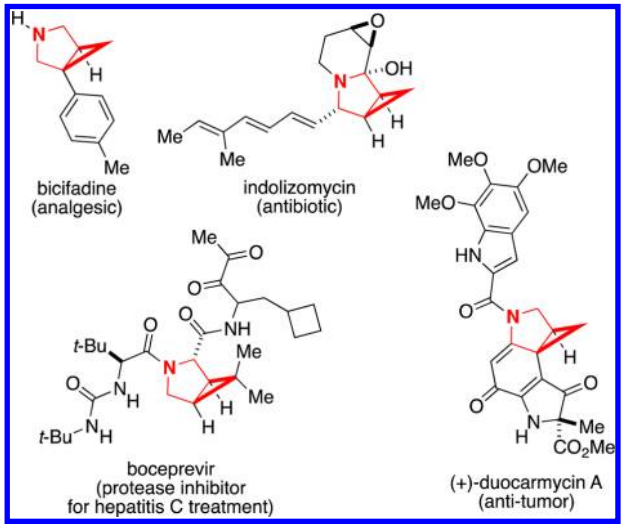
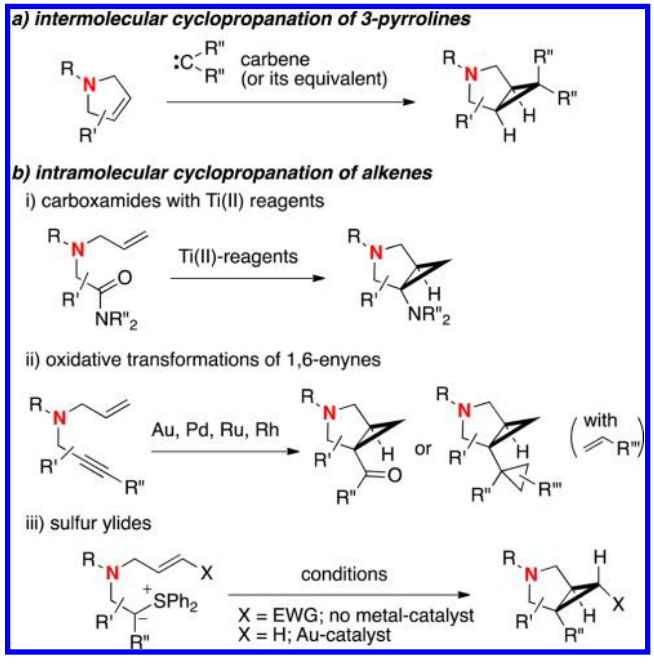


Figure 1. Selected examples of pharmacologically active 3-azabicyclo[3.1.0]hexanes.

The chemical synthesis of 3-azabicyclo[3.1.0]hexane scaffolds has therefore evoked considerable interests, resulting in development of a variety of strategies to construct them. Although these motifs have commonly been constructed either by intermolecular cyclopropanation of 3-pyrroline derivatives (Scheme 1a)[5] or intramolecular cyclopropanation of alkenes with carboxamides using Ti(II) reagents (Scheme 1b-i),[6] these methods limit the substituent compatibility on the available 3-azabicyclo[3.1.0]hexanes. Robust variants of intramolecular alkene cyclopropanation have recently been exploited using nitrogen-tethered 1,5- or 1,6-enynes with transition-metal catalysts such as Au,[7] Pd,[8,9] Ru,[10] and Rh[11] (Scheme 1b-ii).

Scheme 1. Construction of 3-Azabicyclo[3.1.0]hexane Scaffolds



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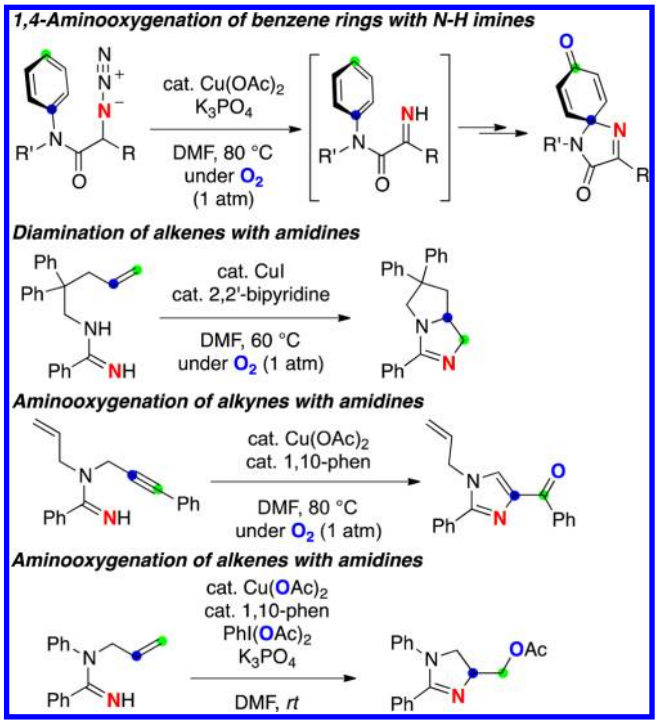
Cyclopropanation with sulfur ylides has also been developed (Scheme 1b-iii).[12] However, these existing strategies require long routes for the starting material preparation or the need to use expensive noble transition metals.[13] It is therefore of great significance to develop concise and versatile methodology to construct the 3-azabicyclo[3.1.0] frameworks from readily available building blocks with step-, atom-, and cost-economical fashion.

We have recently developed oxidative functionalization of carbon−carbon unsaturated bonds triggered by Cu-catalyzed reactions of N-H imines and amidines for synthesis of highly functionalized azaheterocycles (Scheme 2).[14−16]

Scheme 2. Cu-Catalyzed Oxidative Functionalization of C−C Unsaturated Bonds with N-H Imines and Amidines

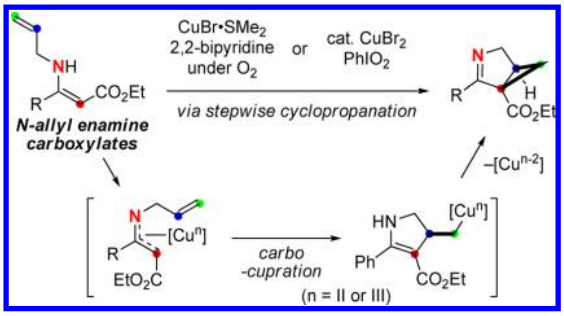


In this context, we have also studied Cu-catalyzed oxidative transformation of N-unsaturated enamine carboxylates, which are easily prepared by acid-mediated condensation of the corresponding primary amines with β-keto esters or by conjugate addition of the amines to acetylene carboxylates.[17] We envisioned that oxidative functionalization of the pendant C−C unsaturataed bond installed on the enamine nitrogen could occur through carbocupration with putative copper-azaenolates.[18,19] This article describes the full account of copper-mediated aerobic and copper-catalyzed-$PhIO_2$-mediated alkene cyclopropanation of N-allyl enamine carboxylates for synthesis of 3-azabicyclo[3.1.0]hex-2-enes with broad evaluation in scope, limitations, and reaction mechanisms (Scheme 3). Facile oxidative transformations of the resulting 3-azabicyclo[3.1.0]hex-2-enes to highly substituted pyridines as well as diastereoselective reduction of them to 3-azabicyclo[3.1.0]hexanes are also presented.

RESULTS AND DISCUSSION

Optimization of Reaction Conditions. Our studies began with copper-mediated aerobic reactions of ethyl 3-allylamino-3-phenyl acrylate (**1a**) (Table 1). When **1a** was treated with 3.0 equiv of $CuBr{\cdot}SMe_2$ in DMSO at 60 °C under an O_2

Scheme 3. Cu-Mediated Cyclopropanation of N-Allylenamine Carboxylates (this work)



atmosphere, 3-azabicyclo[3.1.0]hex-2-enes **2a** was formed in 67% through intramolecular cyclopropanation (entry 1). The examples of direct alkene cyclopropanation with nucleophilic carbons have been limited.[12,20] This discovery therefore inspired us to optimize the reaction conditions. The yields were improved by addition of nitrogen-ligands (2.0 equiv) to $CuBr{\cdot}SMe_2$ (entries 2−4), in which the highest yield of **2a** (93%) was obtained using 2,2′-bipyridine (entry 4). A comparable yield of **2a** was obtained with 1.1 equiv of $CuBr{\cdot}SMe_2$ and 2,2′-bipyridine (entry 5). Use of molecular oxygen as an atmosphere was essential as the reaction became sluggish under an inert atmosphere (entry 6). Other types of copper(I) such as CuCl could also mediate the reaction, albeit in a slightly lower yield and longer reaction time (entry 7). Interestingly, this aerobic cyclopropanation is only amenable for copper(I) complexes, as $CuBr_2$ failed to provide the desired product (entry 8). The oxidation state of the Cu species during these reaction courses is discussed in detail in the Mechanistic Discussion section.

We next examined the reaction conditions to achieve the catalytic conversion of this cyclopropanation. The attempts under an O_2 atmosphere gave only unsatisfactory results (entries 9 and 10), in which the best result was 44% yield of **2a** using 20 mol % of $CuBr{\cdot}SMe_2$ in the presence of 5 equiv of DABCO (entry 10). We thus turned our attention to use hypervalent iodine reagents as stoichiometric oxidants to achieve the catalytic turnover.[21] The hypervalent iodine(III) reagent, $PhIO$[22] was first tested with 20 mol % of $CuBr_2$ (entries 11 and 12). It was found that use of 1.5 equiv of PhIO produced **2a** in 50% yield along with 29% recovery of **1a** even after stirring for 24 h (entry 11). An excess amount of PhIO (2.5 equiv) was required to complete the reaction, giving **2a** in 73% yield (entry 12). It is known that PhIO undergoes disproportionation upon heating or extended storage to give PhI and iodine(V) species, iodylbenzene ($PhIO_2$).[21f] We wondered whether $PhIO_2$ could be the active oxidant rather than PhIO. Indeed, the reaction with $PhIO_2$ (0.75 equiv) was completed within 3.5 h to deliver 87% yield of **2a** (entry 13).[23,24] The catalytic loading of $CuBr_2$ could also be reduced to 15 mol % (entry 14), while 10 mol % of $CuBr_2$ lowered the yield of **2a** to 65% (entry 15). Other Cu(II) salts such as $CuCl_2$ and $Cu(OAc)_2$ worked to give **2a** in acceptable yields in spite of slower reaction rate (entries 16 and 17). The reaction with $Cu(OTf)_2$, on the other hand, resulted in formation of complex mixtures (entry 18). In this catalytic variant, $CuBr{\cdot}SMe_2$ could also be utilized, giving slightly lower yield of **2a** (74% yield) in 8 h (entry 19). The reaction with only $PhIO_2$ yielded 13% of **2a** (entry 20),[25] and the reaction with 2 equiv of $CuBr_2$ in the

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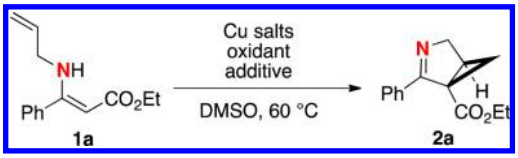
Table 1. Optimization of Reaction Conditions[a]



entry	Cu salts [equiv]	oxidants [equiv]	additive [equiv]	time [h]	yield [%][b]
Reactions with a Stoichiometric Amount of Copper Salts					
1	$CuBr{\cdot}SMe_2$ (3.0)	O_2 (1 atm)	–	1.5	67
2	$CuBr{\cdot}SMe_2$ (2.1)	O_2 (1 atm)	DABCO (2.0)	0.7	50[c]
3	$CuBr{\cdot}SMe_2$ (2.1)	O_2 (1 atm)	DMAP (2.0)	1.5	83
4	$CuBr{\cdot}SMe_2$ (2.1)	O_2 (1 atm)	2,2′-bipyridine (2.0)	1.5	93
5	**$CuBr{\cdot}SMe_2$ (1.1)**	**O_2 (1 atm)**	**2,2′-bipyridine (1.1)**	**3**	**89**
6	$CuBr{\cdot}SMe_2$ (1.1)	–[d]	2,2′-bipyridine (1.1)	12	10[c] (75)[e]
7	CuCl (1.1)	O_2 (1 atm)	2,2′-bipyridine (1.1)	25	67[c]
8	$CuBr_2$ (1.1)	O_2 (1 atm)	2,2′-bipyridine (1.1)	48	0
Reactions with a Catalytic Amount of Copper Salts					
9	$CuBr{\cdot}SMe_2$ (0.2)	O_2 (1 atm)	2,2′-bipyridine (2.0)	12	17[c] (40)[e]
10	$CuBr{\cdot}SMe_2$ (0.2)	O_2 (1 atm)	DABCO (5.0)	2	44[f]
11[d]	$CuBr_2$ (0.2)	PhIO (1.5)	MS 4A	24	50 (29)[e]
12[d]	$CuBr_2$ (0.2)	PhIO (2.5)	MS 4A	3	73
13[d]	**$CuBr_2$ (0.2)**	**$PhIO_2$ (0.75)**	–	**3.5**	**87**
14[d]	$CuBr_2$ (0.15)	$PhIO_2$ (0.75)	–	5	88
15[d]	$CuBr_2$ (0.1)	$PhIO_2$ (0.75)	–	6	65
16[d]	$CuCl_2$ (0.2)	$PhIO_2$ (0.75)	–	7.5	72[c]
17[d]	$Cu(OAc)_2$ (0.2)	$PhIO_2$ (0.75)	–	20	65[c]
18[d]	$Cu(OTf)_2$ (0.2)	$PhIO_2$ (0.75)	–	20	14[c]
19[d]	$CuBr{\cdot}SMe_2$ (0.2)	$PhIO_2$ (0.75)	–	8	74[c]
20[d]	–	$PhIO_2$ (0.75)	–	24	13
21[d]	$CuBr_2$ (2.0)	–	–	3	0

[a]The reactions were carried out using 0.3 mmol of N-allyl enamine carboxylate **1a** in DMSO at 60 °C unless otherwise stated. [b]Isolated yields. [c]^{1}H NMR yields. [d]The reaction was carried out under an Ar or N_2 atmosphere. [e]Recovery of **1a**. [f]12% of ethyl 4-formyl-2-phenyl-1H-pyrrole-3-carboxylate was also obtained. DABCO = 1,4-diazabicyclo-[2.2.2]octane; DMAP = 4-dimethylaminopyridine.

absence of $PhIO_2$ did not give **2a** at all (entry 21). These results suggested that the combination of copper salts and $PhIO_2$ is indispensable in this catalytic cyclopropanation.

Scope and Limitation. With the optimized reaction conditions for the stoichiometric $CuBr{\cdot}SMe_2/O_2$ system (Table 1, entry 5) as well as the catalytic $CuBr_2/PhIO_2$ system (Table 1, entry 13), the scope of this oxidative synthesis of 3-azabicyclo[3.1.0]hex-2-enes **2** was investigated (Table 2). Both the $CuBr{\cdot}SMe_2/O_2$ and $CuBr_2/PhIO_2$ systems performed comparably when R^1 of the N-allyl enamines **1** was varied. The reactions could install both electron-donating (MeO, entries 1 and 2) and electron-withdrawing groups (CF_3, entry 3) on the benzene ring. In addition, a C–Br bond was kept untouched in the present process (entries 4 and 5). Naphthyl (entries 6 and 7), benzofuranyl (entry 8), and thienyl (entry 9) as well as alkyl groups (entries 10–12) could be introduced as R^1 under both the $CuBr{\cdot}SMe_2/O_2$ and $CuBr_2/PhIO_2$ conditions, while the Cu(II)/$PhIO_2$ system furnished poor yields of **2l** and **2m** when isopropyl and butenyl groups were utilized as R^1 (entries 12 and 13). Of particular importance is the observation that N-allyl enamine **1m** bearing an additional pendant alkene on R^1 cyclized exclusively with the alkene tethered to the nitrogen atom, providing 3-azabicyclo[3.1.0]hex-2-enes **2m** in 77% and 30% under the $CuBr{\cdot}SMe_2/O_2$ and $CuBr_2/PhIO_2$ systems, respectively. The finding highlights the pronounced degree of chemoselectivity inherent in these present methods. The ethoxy carbonyl group on R^2 could be replaced with a cyano group, giving **2n** in 60–62% yields for the both systems (entry 13). However, enamine **1o** bearing a benzoyl group as R^2 did not work well to afford **2o** only in 15% and 45% yields under the $CuBr{\cdot}SMe_2/O_2$ and the $CuBr_2/PhIO_2$ conditions, respectively (entry 14).

Next, the effects of the substituents on the alkene tether were investigated (Table 3). The reactions of both (*Z*)- and (*E*)-*N*-3-phenylallyl derivatives **1p** under the $CuBr{\cdot}SMe_2/O_2$ conditions afforded nearly 50:50 diastereo-mixtures of **2p** and **2p′** (entries 1 and 2). In contrast, the $CuBr_2/PhIO_2$ system delivered the product **2p** as the major product (**2p**:**2p′** = 85:15) regardless of the original stereochemistry of enamine **1p** along with the formation of 4-benzoylpyrrole **3p** as a side product. The present cyclopropanation likely proceeds via the stepwise C–C bond formation as the stereochemistry of the double bond was not retained in both of the reactions. However, the structure of the intermediates involved in the cyclopropanation might be different under the $CuBr{\cdot}SMe_2/O_2$ and the $CuBr_2/PhIO_2$ conditions, resulting in the dissimilar diastereoselectivity (see Scheme 7 for more details). The present methods are capable of constructing the C–C bond between quaternary carbons starting from *N*-3,3-disubstituted allyl enamines **1q** and **1r**, in which the $CuBr{\cdot}SMe_2/O_2$ conditions performed better (entries 3 and 4). The reaction of *N*-3,3-dimethylallyl enamine **1q** under the $CuBr{\cdot}SMe_2/O_2$ conditions (entry 3) afforded the corresponding azabicyclo[3.1.0]-hexene **2q** in 36% yield along with the formation of bromomethyl dihydropyrrole **4q-Br** (X = Br) in 13% yield. Using CuCl as a copper source with 2,2′-bipyridine provided **2q** and **4q-Cl** (X = Cl) in 58% and 23% yields, respectively. Using DMAP as an additive improved the yield of **2q** to 63% yield with minimizing the formation of **4q-Br** to less than 5%. Putting a substituent on the α-position of the enamine nitrogen (for **1s** and **1t**) rendered the process diasteroselective in both of the reaction conditions, affording the corresponding α-**2s** and α-**2t** as the major products, respectively (entries 5 and 6). The present cyclopropanation is robust to construct highly strained fused azatricyclic cyclopropane compounds **2u** and **2v** by the reactions of cyclic N-allyl enamines **1u** and **1v**, respectively, although **2v** could not be accessed under the $CuBr_2/PhIO_2$ conditions (entries 7 and 8). *N*-Butenyl enamine carboxylate **1w** showed poor reactivity toward the present cyclopropanation, in which only the $CuBr_2/PhIO_2$ conditions could construct the desired azabicyclic cyclopropane **2w** albeit in low yield (entry 9).

Mechanistic Discussion. On the basis that the present cyclopropanation under the $CuBr{\cdot}SMe_2/O_2$ system could only be mediated by Cu(I) complexes (see Table 1, entries 8),[26] we postulated that Cu(II)-O_2 complexes play a vital role to realize the process.[27] On the contrary, only a trace amount of **2a** was observed using 2.0 equiv of $CuBr_2$ without $PhIO_2$ (Table 1, entry 21), indicating that the $CuBr_2/PhIO_2$ system likely involves a higher oxidation state copper(III) species.

To gain more detailed mechanistic information for the present cyclopropanation, the reactions of tetrasubstituted enamine **1x**, which is not able to form the cyclopropane ring, were tested under the present reaction conditions (Scheme 4). The reaction of **1x** under the $CuBr{\cdot}SMe_2/O_2$ system afforded bromomethyl dihydropyrrole **4x** and azabicyclic lactone **5x** in 30% and 11% yields, respectively (Scheme 4a). Similarly, the $CuBr_2$–$PhIO_2$ system delivered **4x** and **5x** in 7% and 20% yields, respectively, while another azaheterocycle **6x** having

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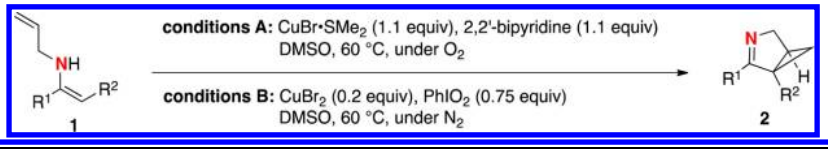
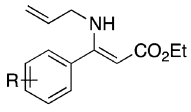
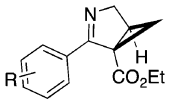
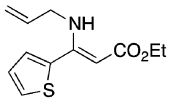
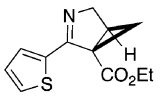
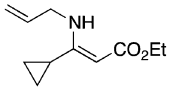
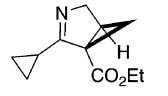
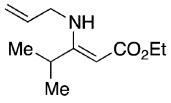
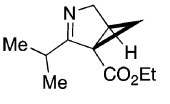
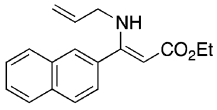
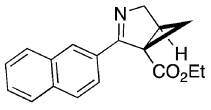
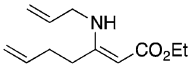
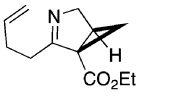
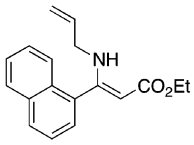
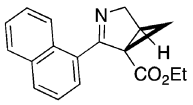
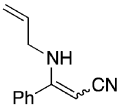
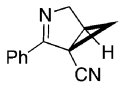
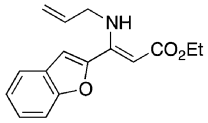
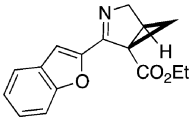
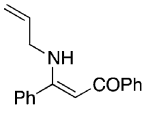
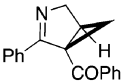
Table 2. Scope of the Synthesis of 3-Azabicyclo[3.1.0]hex-2-enes 2: Substituents on the Alkene[a]



entry	enamines 1	products 2/yield with conditions A or B[b]	entry	enamines 1	products 2/yield with conditions A or B[b]
			9	 1j	 2j **A**: 84% **B**: 82%
1	**1b** (R = 4-MeO)	**2b A:** 90% **B:** 89%	10	 1k	 2k **A**: 85% **B**: 82%
2	**1c** (R = 2-MeO)	**2c A:** 73% **B:** 70%			
3	**1d** (R = 4-CF_3)	**2d A:** 85% **B:** 81%			
4	**1e** (R = 2-Br)	**2e A:** 62%[c] **B:** 82%	11	 1l	 2l **A**: 84% **B**: 16%
5	**1f** (R = 3-Br)	**2f A:** 87% **B:** 88%			
6	 1g	 2g **A**: 89% **B**: 93%	12	 1m	 2m **A**: 77% **B**: 30%
7	 1h	 2h **A**: 70%[c] **B**: 83%	13	 1n	 2n **A**: 60% **B**: 62%
8	 1i	 2i **A**: 80% **B**: 84%	14	 1o	 2o **A**: 15% **B**: 45%

[a]Unless otherwise stated, the reactions were carried out under either condition A or B. Condition A: 0.5 mmol of N-allyl enamine carboxylate **1** with 1.1 equiv of CuBr·SMe_2 and 1.1 equiv of 2,2′-bipyridine in DMSO at 60 °C under O_2 atmosphere. Condition B: 0.3 mmol of N-allyl enamine carboxylate **1** with 0.2 equiv of $CuBr_2$, 0.75 equiv of $PhIO_2$ in DMSO at 60 °C under N_2 atmosphere. [b]Isolated yields. [c]The reaction was run using 1.1 equiv of CuBr·SMe_2 and 1.1 equiv of DMAP.

tetrahydro-1*H*-benzo[*f*]isoindole skeleton was also isolated in 17% yield (Scheme 4b).

The formation of these azaheterocyles **4x**−**6x** suggested the presence of organocopper intermediates **B**/**B**′ (as a diastereomeric mixture), which are formed presumably via carbocupration of the putative copper-azaenolates **A**/**A**′ onto the tethered alkene (Scheme 5a). As shown in Scheme 5b, the C−Cu bond of **B**/**B**′ is substituted by a present bromide anion to give bromomethyl dihydropyrrole **4x** (ionic path). Alternatively, bromination via a carbon-radical intermediate generated via homolytic cleavage of the C−Cu bond is not ruled out (radical path).[28] The intermediate **B** bearing the ethoxycarbonyl group at the same side with the organocopper tether undergoes intramolecular C−O bond forming ionic cyclization,[29] followed by de-ethylation to afford azabicyclic lactone **5x** (Scheme 5c). On the other hand, diastereomer **B**′ having the benzyl moiety and organocopper tether in *cis*-orientation undergoes cyclization to deliver **6x** either via ionic or radical pathway (Scheme 5d).

Based on these observations, the proposed mechanistic possibilities of the present cyclopropanation are illustrated in Schemes 6 and 7, which are categorized according to the substitution patterns of alkenes of enamines **1**. The cyclopropanation of terminal alkene (for the reactions of enamines **1a**−**o**, **1s**, **1t**, and **1w**) involves the first C−C-bond-forming intramolecular carbocupration[30] (formation of the imine **C**/enamine **D** mixture) followed by the second C−C bond formation via a intramolecular S_N2-type substitution reaction of organocopper with enamine moiety **D** (Scheme 6a). On the other hand, carbocupration of enamines **1q** and **1r** bearing the 3,3-disubstituted allylic tether provides the tertiary organocopper moieties (**E** and **F**), which might not undergo an S_N2-type substitution reaction. Instead, prior elimination of Cu^{n-2}

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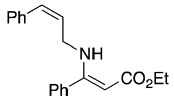
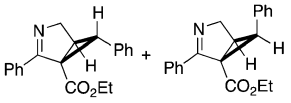
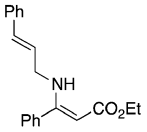
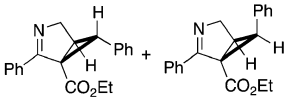
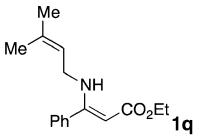
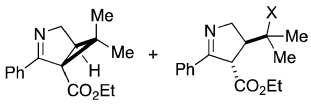
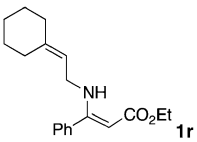
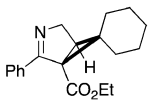
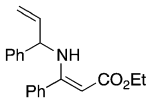
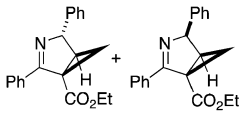
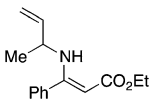
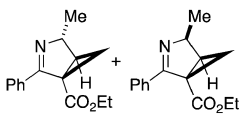
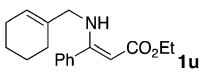
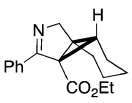
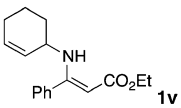
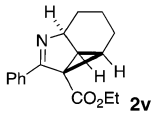
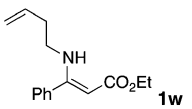
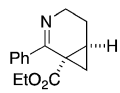
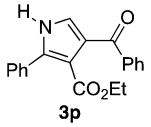
Table 3. Scope of the Synthesis of 3-Azabicyclo[3.1.0]hex-2-enes 2: Substituents on the Allyl Group[a]

entry	enamines 1	products	yield[b] A: CuBr•SMe$_2$/O$_2$	yield[b] B: cat. CuBr$_2$/PhIO$_2$
1	 **(*Z*)-1p**	 **2p** **2p'**	60%[d] (**2p**:**2p'** = 55:45)	52% (**2p**:**2p'** = 85:15) with pyrrole **3p**[c] 10%
2	 **(*E*)-1p**	 **2p** **2p'**	68% (**2p**:**2p'** = 50:50)	54% (**2p**:**2p'** = 85:15) with pyrrole **3p**[c] 14%
3	 **1q**	 **2q** **4q**	**2q** 36%; **4q-Br** (X = Br) 13%[d] **2q** 58%; **4q-Cl** (X = Cl) 23%[e] **2q** 63%; **4q-Br** (X = Br) <5%[d,f]	**2q** 49% (no **4q**)
4	 **1r**	 **2r**	41%[f]	33%
5	 **1s**	 **2s-α** **2s-β**	82% (**2s-α**:**2s-β** = 94:6)	65% (**2s-α**:**2s-β** = 95:5)
6	 **1t**	 **2t-α** **2t-β**	56% (**2t-α**:**2t-β** = 83:17)	72% (**2t-α**:**2t-β** = 83:17)
7	 **1u**	 **2u**	56%	88%
8	 **1v**	 **2v**	65%	0%
9	 **1w**	 **2w**	0%	26% (**1w**: 20%)

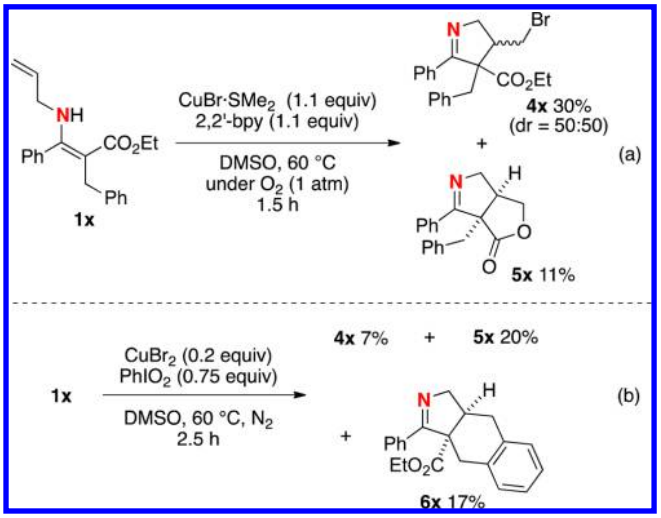
[a]Unless otherwise stated, the reactions were carried out under either conditions A or B. Condition A: 0.5 mmol of N-allyl enamine carboxylate 1 with 1.1 equiv of CuBr·SMe$_2$ and 1.1 equiv of 2,2′-bipyridine in DMSO at 60 °C under O$_2$ atmosphere. Condition B: 0.3 mmol of N-allyl enamine carboxylate 1 with 0.2 equiv of CuBr$_2$, 0.75 equiv of PhIO$_2$ in DMSO at 60 °C under N$_2$ atmosphere. [b]Isolated yields. [c]Ethyl 4-benzoyl-2-phenyl-1*H*-pyrrole-3-carboxylate **3p** was formed as a coproduct (see the figure below). [d]^{1}H NMR yields. [e]CuCl (2.1 equiv) was used instead of CuBr·SMe$_2$. [f]The reaction was run using 1.1 equiv of CuBr·SMe$_2$ and 1.1 equiv of DMAP.


3p

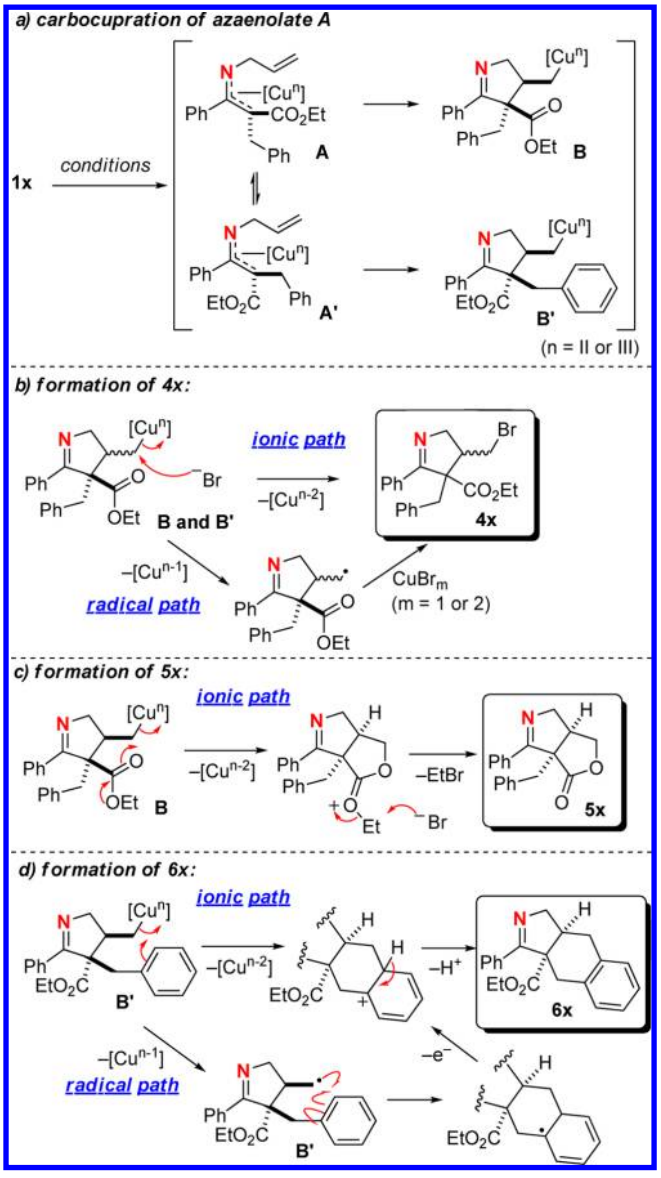
species generates stable tertiary carbocation **G**,[31] which is readily trapped by the enamine moiety to give **2q** and **2r** (Scheme 6b). Subjection of chloromethyl dihydropyrrole **4q-Cl** (Table 3, entry 3) to the CuBr·SMe$_2$/O$_2$ conditions resulted in formation of cyclopropane **2q** only in 13% yield along with a complex mixture of unidentified products. The reaction of

dx.doi.org/10.1021/ja500382c | *J. Am. Chem. Soc.* 2014, 136, 6011−6020

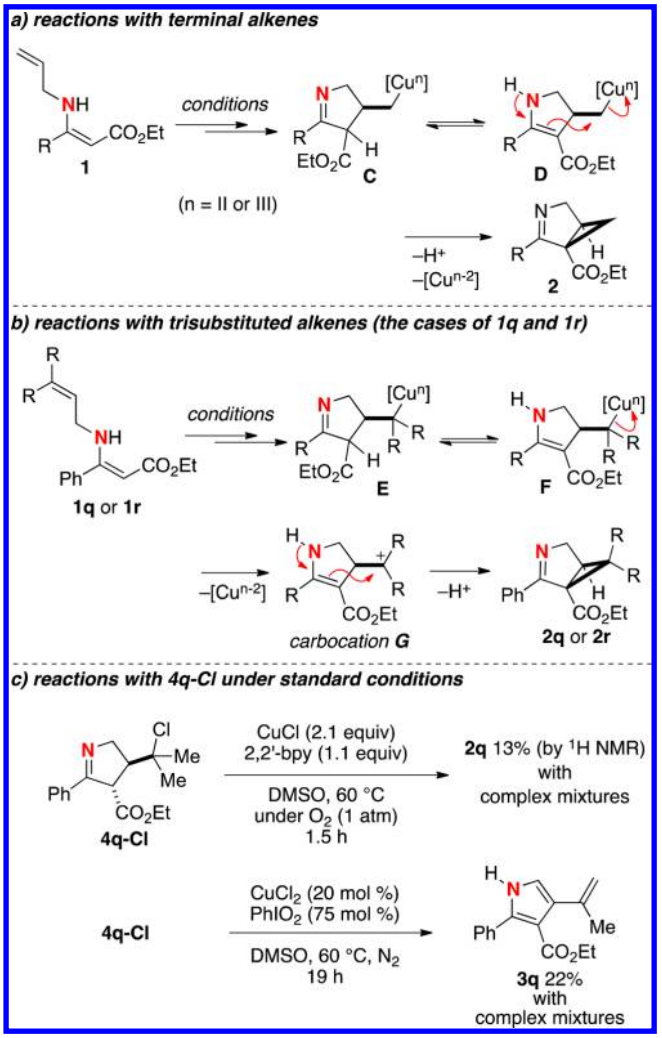
Scheme 4. Reactions of Enamine 1x



Scheme 5. Proposed Mechanisms for the Formation of Compounds 4x–6x



Scheme 6. Proposed Mechanisms for the Cyclopropanation

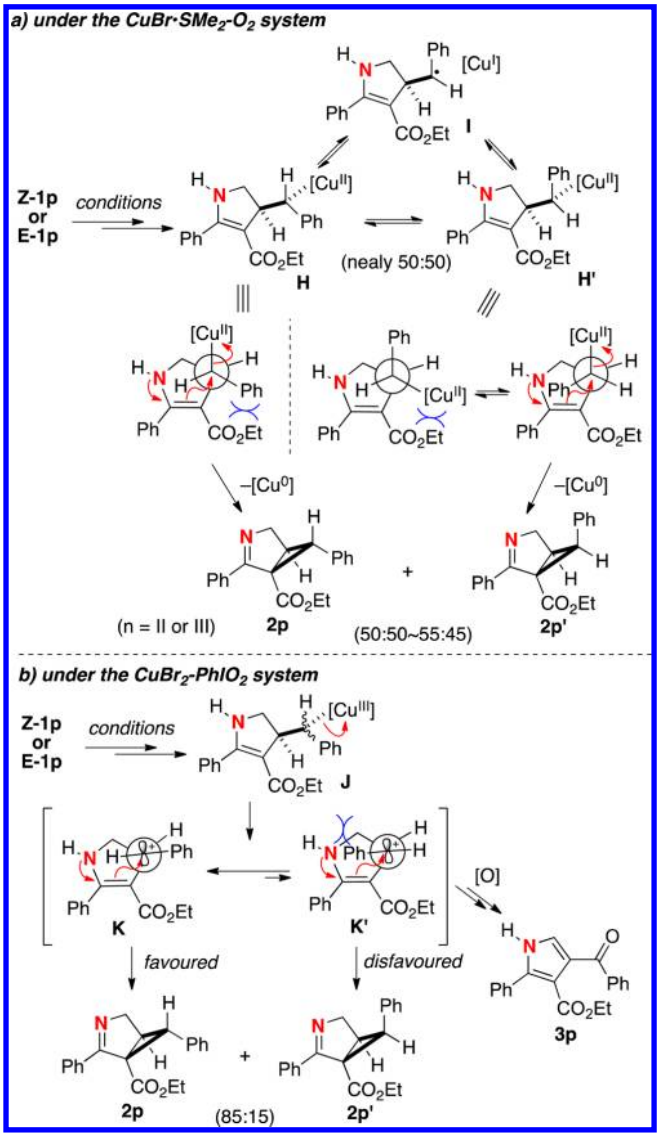


4q-Cl under the $CuCl_2/PhIO_2$ system did not provide cyclopropane **2q** but generates 4-propenylpyrrole **3q** in 22% yield (Scheme 6-c). These results indicate that halomethyl dihydropyrroles **4** are not likely involved in the second C–C bond forming step of the cyclopropanation. Nonetheless, the possibility of the reaction pathway including electrophilic activation of the alkene with halonium ions is ruled out as the reactions could be performed in the absence of halide anions (i.e., the reactions with $Cu(OAc)_2$ in Table 1, entry 17).

In the reactions of 3-phenylallyl enamines (*Z*)- and (*E*)-**1p**, the reaction conditions interestingly varied the diastereoselectivity of the cyclopropanation, in which the $CuBr{\cdot}SMe_2/O_2$ conditions provided almost 50:50 ratio of **2p** and **2p′**, whereas the $CuBr_2/PhIO_2$ system rendered the reaction more selective for the formation of **2p** (**2p**:**2p′** = 85:15) (Table 3, entries 1 and 2). The $CuBr{\cdot}SMe_2/O_2$ system generates a diastereomeric mixture of organocopper(II) intermediates **H** and **H′**, which are likely under equilibrium through homolytic dissociation and recombination of the C-radical **I** and Cu(I) species (Scheme 7-a).[32] These organocopper(II) intermediates **H** and **H′** might keep covalent-bond character through the C–Cu bond, resulting in the formation of them in nearly 50:50 ratio due to the steric repulsion between the phenyl group with the ethoxy carbonyl part for **H** and between the copper moiety ([Cu]) with the ethyoxy carbonyl part for **H′** (see the Newman projections).

dx.doi.org/10.1021/ja500382c | J. Am. Chem. Soc. 2014, 136, 6011–6020

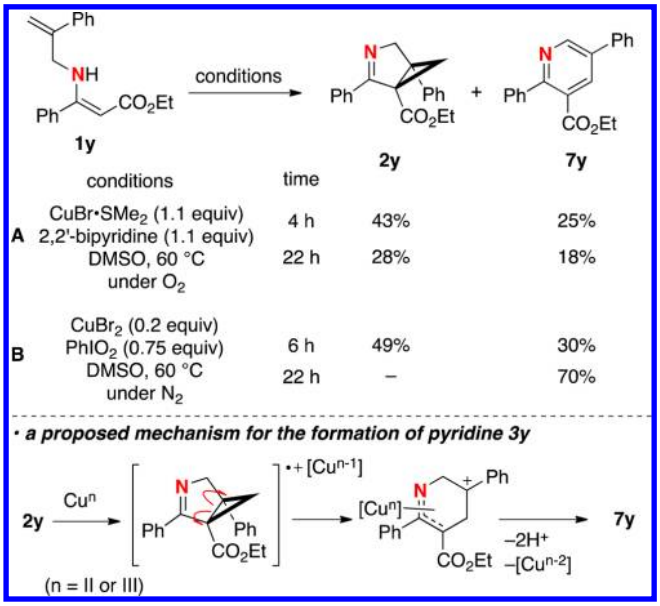
Scheme 7. Proposed Mechanisms for Enamine 1p



Presumably, successive intramolecular nucleophilic substitution of **H** and **H**′ produces **2p** and **2p**′, respectively. On the other hand, in the $CuBr_2/PhIO_2$ system, the higher valent organocopper(III) intermediate **J** bearing more ionic C−Cu(III) bond is likely involved, that is readily converted into benzylic carbocation species **K** and **K**′ by elimination of copper(I) species (Scheme 7-b). The steric repulsion between the phenyl group on the tethered carbocation and the dihydropyrrole ring rendered the carbocation **K** more stable, resulting in the selective formation of **2p**. The presence of benzylic carbocation **K** and **K**′ could be supported by the formation of 4-benzoylpyrrole **3p** that was generated presumably by oxygenation of **K** and **K**′ with the DMSO solvent.[33] The cyclopropanation reactions under the $CuBr·SMe_2/O_2$ conditions should generate Cu(0) species along with formation of the products, that might render it difficult to realize the catalytic process with molecular oxygene (see Table 1, entries 9 and 10).

Pyridine Formation. The generality of this copper-mediated/catalyzed synthesis of 3-azabicyclo[3.1.0]hex-2-enes **2** was further explored using 2-phenylallyl enamine **1y** (Scheme 8). The reaction under the $CuBr·SMe_2/O_2$ system for 4 h yielded not

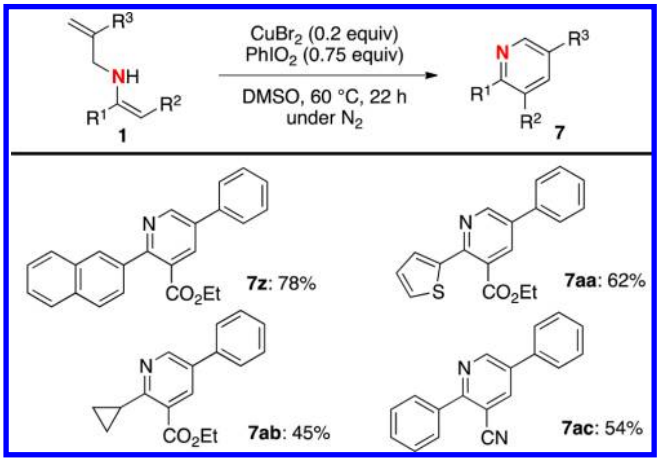
Scheme 8. Reactions of 2-Phenylallyl Enamine 1y



only 3-azabicyclo[3.1.0]hex-2-ene **2y** but also trisubstituted pyridine **7y** in 43% and 25% yields, respectively, while prolonging the reaction time to 22 h lowered the mass balance. Similarly, the reaction of **1y** under the $CuBr_2/PhIO_2$ system for 6 h provided both **2y** and **7y** in 49% and 30% yields, respectively. In contrast, the longer reaction time (for 22 h) provided pyridine **7y** as a single product in 70% yield. This implied that 3-azabicyclo[3.1.0]hex-2-ene **2y** is oxidatively transformed into pyridine **7y** during the reaction course.[34] It is proposed that single-electron oxidation of **2y** by the higher valent copper species [Cu^n] generates cation radical, that undergoes ring-expansion via C−C bond homolytic cleavage of the cyclopropane ring followed by oxidative aromatization to afford **7y**.

We next examined the scope and limitation of the direct oxidative conversion of N-2-phenylallyl enamines **1** to pyridines **7** under the $CuBr_2$−$PhIO_2$ conditions.[35] Various 2-phenylallyl enamines **1** were transformed to the corresponding pyridines **7**

Scheme 9. Scope of Oxidative Synthesis of Trisubstituted Pyridines 7 from 2-Phenylallyl Enamines 1[a,b]



[a]The reactions were carried out using 0.2 mmol of 2-phenylallyl enamine carboxylate **1** with 0.2 equiv of $CuBr_2$ and 0.75 equiv of $PhIO_2$ in DMSO at 60 °C under a N_2 atmosphere. [b]Isolated yields were reported.

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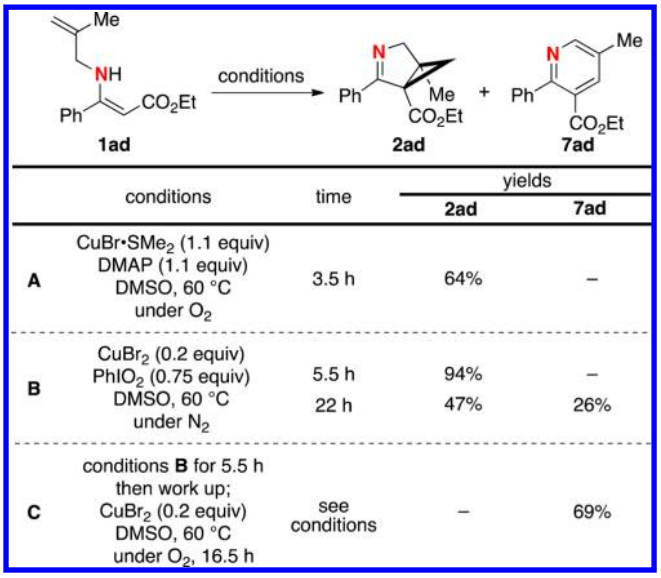
by stirring the reaction mixture for 22 h (Scheme 9). Enamines **1** bearing naphthyl and thienyl groups as R^1 worked smoothly to give the corresponding pyridines **7z** and **7aa** in good yields, while installation of a cyclopropyl group as R^1 (for **7ab**) and replacement of an ethoxycarbonyl group to cyano group (for **7ac**) resulted in moderate yields.

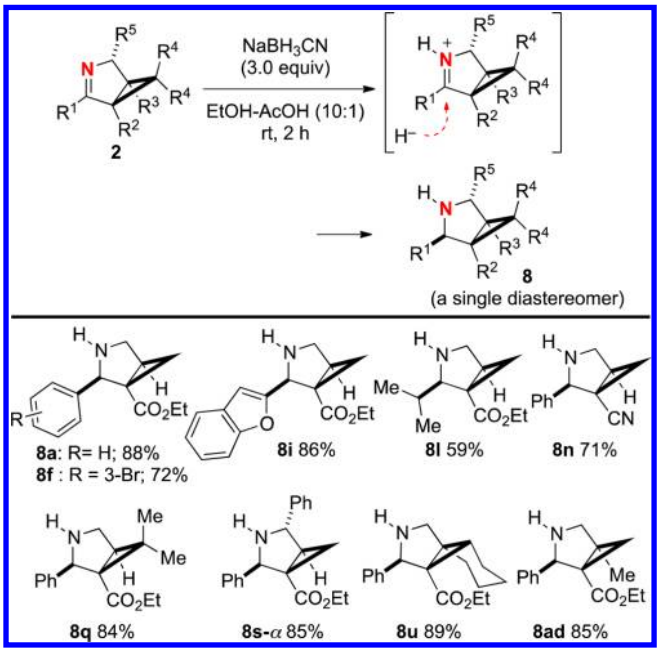
This oxidative pyridine synthesis was then investigated using 2-methallyl enamine **1ad** that provided exclusively 3-azabicyclo-[3.1.0]hex-2-ene **2ad** under both of the reaction conditions A and B in shorter reaction time (3.5−5.5 h) (Scheme 10).

Scheme 10. Reactions of 2-Methallyl Enamine 1ad



	conditions	time	yields 2ad	yields 7ad
A	$CuBr{\cdot}SMe_2$ (1.1 equiv) DMAP (1.1 equiv) DMSO, 60 °C under O_2	3.5 h	64%	–
B	$CuBr_2$ (0.2 equiv) $PhIO_2$ (0.75 equiv) DMSO, 60 °C under N_2	5.5 h 22 h	94% 47%	– 26%
C	conditions **B** for 5.5 h then work up; $CuBr_2$ (0.2 equiv) DMSO, 60 °C under O_2, 16.5 h	see conditions	–	69%

Scheme 11. Diastereoselective Reduction of 3-Azabicyclo[3.1.0]hex-2-enes 2[a,b]



[a]The reactions were carried out using 0.1−0.3 mmol of **2** with 3 equiv of $NaBH_3CN$ in EtOH-AcOH (10:1) at rt under a N_2 atmosphere. [b]Isolated yields were recorded.

Extending the reaction time to 22 h under the Cu(II)/$PhIO_2$ system gave only a mixture of **2ad** and pyridine **7ad** in 47% and 26% yields, respectively. Further screening of the reaction conditions (see the Supporting Information) revealed that successive treatment of the crude mixture of 3-azabicyclo[3.1.0]hex-2-ene **2ad** with $CuBr_2$ under an O_2 atmosphere in DMSO at 60 °C could complete the conversion to afford pyridine **7ad** in 69% yield as two-step yield from enamine **1ad** (condition C).

Diastereoselective C═N Reduction. Finally, we investigated reduction of the imine C═N bond of 3-azabicyclo[3.1.0]hex-2-enes **2** for synthesis of saturated 3-azabicyclo[3.1.0]hexanes **8**.[36] Assuming that a hydride approaches the C═N bond from the opposite side of the cyclopropane ring, diastereoselective reduction is anticipated (Scheme 11). As expected, reduction of **2a** with $NaBH_3CN$ in the presence of acetic acid provided 3-azabicyclo[3.1.0]hexane **8a** in 88% yield as a single stereoisomer.[37] This stereoselective reduction could be applied to a range of substrates **2** with different substitutents on R^1−R^5 to give the corresponding 3-azabicyclo[3.1.0]hexanes **8** in good to excellent yields.

CONCLUSION

In summary, we have successfully established a novel cyclopropanation protocol for accessing 3-azabicyclo[3.1.0]-hex-2-enes from readily available N-allyl enamine derivatives. Two complementary reaction conditions, CuBr-mediated aerobic and $CuBr_2$-catalyzed-$PhIO_2$-mediated systems, effectively induced cyclopropanation for a variety of N-allyl enamines. Oxidative cyclopropane ring-opening of 5-substituted 3-azabicyclo[3.1.0]hex-2-enes to form highly substituted pyridines was also developed. In addition, diastereoselective reduction of 3-azabicyclo[3.1.0]hex-2-enes to 3-azabicyclo[3.1.0]hexanes was achieved using $NaBH_3CN$ in the presence of acetic acid. We anticipate that the present molecular transformation of N-allyl enamine carboxylates is capable of offering a new synthetic approach to biologically and medicinally important azaheterocycles.

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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Notes

The authors declare no competing financial interest.

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(30) We are not certain as to the mechanism of the alkene carbocupration, either in concerted manner or stepwise radical pathway (generation of radical and its addition onto alkene followed by recombination). It is noted that the reaction with chiral *N,N′*-ligands could not generate chirality in the present cyclopropanation. We have also examined the reactions of enamine having a cyclopropyl moiety on the alkene for the radical clock experiment, although a complex mixture with unidentified compounds was obtained. See the Supporting Information for more details.

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(37) **8a** was converted into the corresponding *N*-tosylate **9a**, the structure of which was confirmed by X-ray crystallographic analysis, see the Supporting Information for more details.