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Synthesis of azaheterocycles from oxime derivatives*

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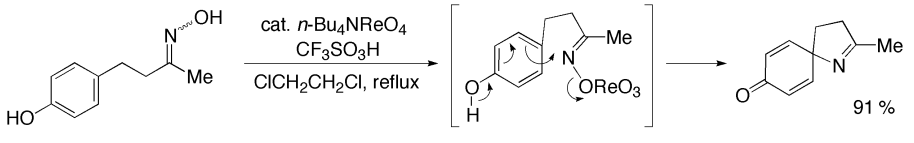
Abstract: Electrophilic amination of Grignard reagents has been accomplished by using *O*-sulfonyloximes as amination reagents. Benzophenone *O*-sulfonyloxime derivatives react with Grignard reagents on sp^2 nitrogen, yielding primary amines by successive hydrolysis of the resulting *N*-alkylimines.

Various cyclic imines are synthesized by Pd-catalyzed reaction from olefinic oxime derivatives. That is, treatment of *O*-pentafluorobenzoyloximes of olefinic ketones with a catalytic amount of $Pd(PPh_3)_4$ and triethylamine affords nitrogen-containing heterocycles, such as pyrroles, pyridines, isoquinolines, spiro-imines, and aza-azulenes. This reaction proceeds via the initial formation of alkylideneaminopalladium(II) species generated by oxidative addition of the oximes to the Pd(0) complex, and the following intramolecular amination on the olefinic moiety.

Cyclic imines are prepared from γ,δ-unsaturated *O*-acetyloximes by treatment with acetic acid and 1,4-cyclohexadiene in the presence of a catalytic amount of 1,5-naphthalenediol. γ,δ-Unsaturated ketone *O*-methoxycarbonyloximes are transformed to 2-bromomethyl-3,4-dihydro-2*H*-pyrroles by the action of a catalytic amount of Cu(I) bromide dimethyl sulfide complex and lithium bromide.

INTRODUCTION

During the course of study on the catalytic Beckmann rearrangement of oximes by the use of tetrabutylammonium perrhenate and trifluoromethanesulfonic acid [1], we found that S_N2-type substitution proceeded on the nitrogen atom of phenethyl ketone oximes in a nonpolar solvent instead of the Beckmann reaction (eq. 1) [2]. In addition, S_N2-type cyclization was observed in the reaction of *O*-sulfonyloxime having an active methine group at γ- or δ-position with DBU as shown in the following equation [3]. This reaction proceeded in a stereospecific manner: The *anti* oximes cyclized to five- and six-membered cyclic imines (eq. 2), while the *syn* isomers did not give any such cyclization products [4].



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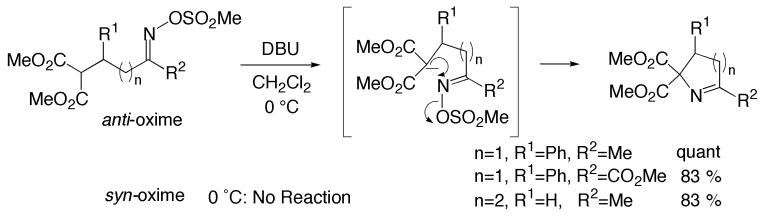
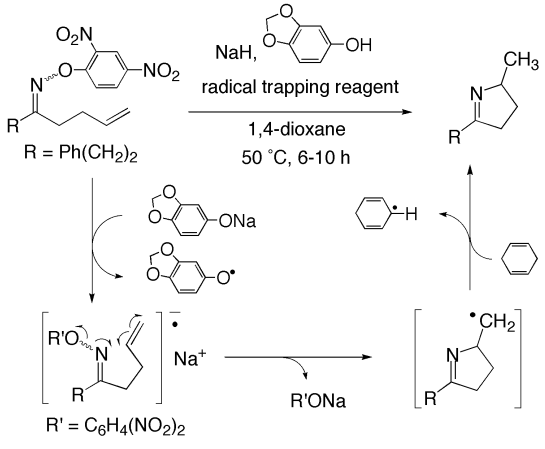
*Lecture presented at the 14th International Conference on Organic Synthesis (ICOS-14), Christchurch, New Zealand, 14–18 July 2002. Other presentations are published in this issue, pp. 1–70.



(2)

On the contrary, it was found that both of the *syn* and *anti* isomers cyclized into cyclic imines when γ,δ-unsaturated ketone *O*-2,4-dinitrophenyloximes were treated with reducing agents in the presence of radical trapping reagents [5]. The reaction proceeded via one-electron reduction of *O*-2,4-dinitrophenyloximes with sodium hydride and 3,4-methylenedioxyphenol, followed by radical cyclization with eliminating 2,4-dinitrophenoxide (Scheme 1).



Scheme 1 One-electron reduction of *O*-2,4-dinitrophenyloxime.

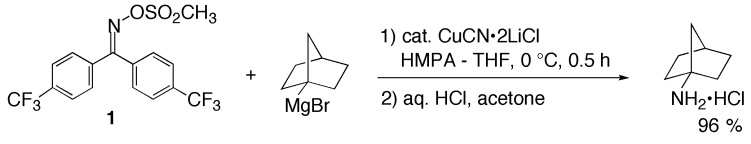
These results imply that oxime derivatives could be utilized for amination reagents. However, the above procedures have some drawbacks as synthetic methods. Due to the stereospecificity of the S_N2-type cyclization, only the *anti* isomer can be employed for the intramolecular reaction. In the electron-transfer reaction, it is needed to use large excess amounts of sodium hydride and to introduce a bulky leaving group such as 2,4-dinitrophenoxy group. Hence, we have been studying the improvement of the above carbon–nitrogen bond-forming reactions for the synthesis of nitrogen-containing compounds. The following points should be realized to use oxime derivatives for amination reactions: (1) suppressing the Beckmann reaction, (2) overcoming *syn*/*anti* stereospecificity of the S_N2-type reaction, (3) use of simple oxime derivatives, and (4) designing catalytic process.

PREPARATION OF PRIMARY AMINES FROM *O*-SULFONYLOXIMES AND GRIGNARD REAGENTS

In general, primary amines are prepared by the reduction of the compounds bearing a nitrogen function such as nitro and azide groups or the Gabriel-type nucleophilic amination reactions. Although electrophilic amination is another method to prepare primary amines, it has been rarely employed in organic synthesis [6]. As mentioned in the above S_N2-type reaction, oxime derivatives were found to behave as electrophilic amination reagents. On the basis of the findings, the reaction of oxime derivatives and organometallic reagents was examined. There have been reported reactions of this type. Hagopian prepared primary arylamines by the reaction of tetraphenylcyclopentadienone *O*-sulfonyloxime with large

excess amounts of arylmagnesium and lithium compounds, whereas dialkylation occurred with alkylmetals [7]. Erik reported the reaction of acetone *O*-sulfonyloxime with Grignard reagents, which gave primary amines in moderate-to-low yield [8].

For amination reagents, we chose 4,4′-bis(trifluoromethyl)benzophenone *O*-methylsulfonyloxime (**1**) and 3,3′,5,5′-tetrakis(trifluoromethyl)benzophenone *O*-*p*-tolylsulfonyloxime (**2**), which have no acidic hydrogen at α position and have electron-withdrawing groups on the phenyl group to suppress the Beckmann rearrangement [9]. Although bis(trifluoromethyl) *O*-sulfonyloxime **1** reacted with alkyl Grignard reagents in low yield, CuCN·2LiCl catalyzed the amination in a mixed solvent of tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) (eq. 3). Primary-, secondary-, and tertiary-alkyl primary amines are synthesized in high yields by this Cu-catalyzed electrophilic amination, whereas this method cannot be applied to the preparation of aniline derivatives from aryl Grignard reagents due to the formation of biphenyl derivatives.



(3)

In the absence of the copper catalyst, a marked solvent effect was observed in the reaction of 3,3′,5,5′-tetrakis(trifluoromethyl)benzophenone *O*-*p*-tolylsulfonyloxime **2** and phenyl Grignard reagent. Treatment of **2** in toluene with phenylmagnesium bromide generated in THF afforded benzanilide in 15 % yield with the recovery of the starting material **2** (eq. 4). The same reaction with the Grignard reagent prepared in ether provided benzanilide in 96 % yield. Even a sterically hindered Grignard reagent, 2,6-dimethylphenylmagnesium bromide, reacted smoothly with **2** to yield 2,6-dimethylanilide in 98 % yield (Table 1). In addition to aniline formation, this method found the application to prepare primary- and secondary-alkyl primary amines, while the amination of tertiary-alkyl Grignard reagent produced a low yield of the product.

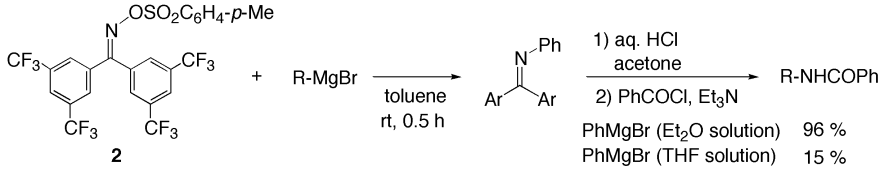


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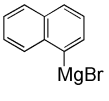
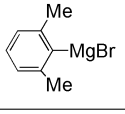
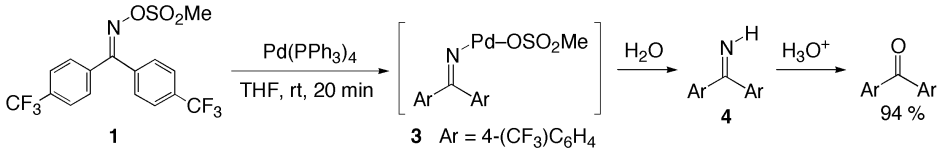
Table 1 Amination of Grignard reagent with benzophenone oxime **2**.

R-MgX	Yield/%	R-MgX	Yield/%
MeO–C6H4–MgBr	98		96
F3C–C6H4–MgBr	71	Et-MgBr	87
	98	cyclo-C_6H_{11}-MgCl	87
		t-C_4H_9-MgCl	35

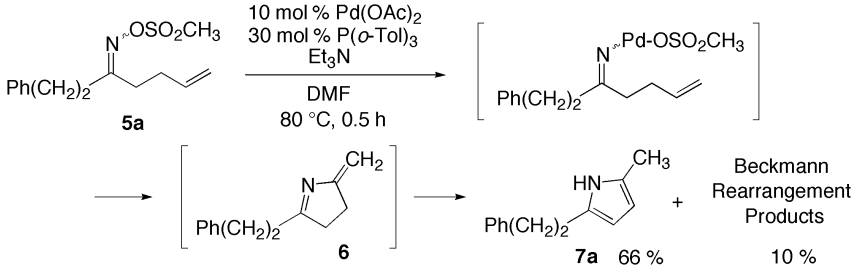
PREPARATION OF AZAHETEROCYCLES BY Pd-CATALYZED CYCLIZATION OF OLEFINIC OXIMES

Due to their electron-donor property of lower-valent transition-metal compounds, Pd(0) complexes were expected to react with oxime derivatives to generate oxidative addition products, alkylideneamino-palladium complexes. In fact, when 4,4′-bis(trifluoromethyl)benzophenone *O*-methylsulfonyloxime (**1**) was treated with an equimolar amount of $Pd(PPh_3)_4$, benzophenone imine **4** was isolated quantitatively after hydrolysis (eq. 5).



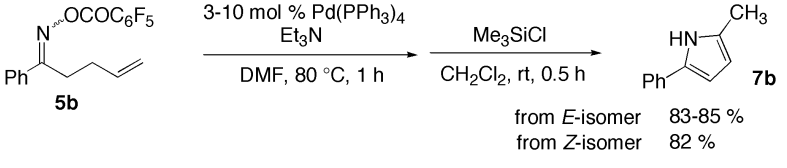
(5)

This results suggested that *O*-sulfonyloxime readily underwent oxidative addition to Pd(0) complex to generate alkylideneaminopalladium(II) species **3**, which was then hydrolyzed to imine **4**. Although this oxidative addition species has not been successfully isolated, the generation of such an intermediate may be reliable, because a similar oxidative addition of oxime to Re(I) complex was reported recently [10]. To utilize this aminopalladium species for organic synthesis, the intramolecular amino-Heck reaction was investigated on γ,δ-unsaturated ketone *O*-sulfonyloxime **5a** [11]. In fact, 3-methyl-5-phenethylpyrrole (**7a**), which is an isomerization product of the initially formed 4-methylidene-2-phenethyl-3,4-dihydro-2*H*-pyrrole (**6**), was obtained in 66 % yield by a catalytic use of $Pd(OAc)_2/P(o\text{-Tol})_3$ and triethylamine, whereas the Beckmann rearrangement was also observed (eq. 6).



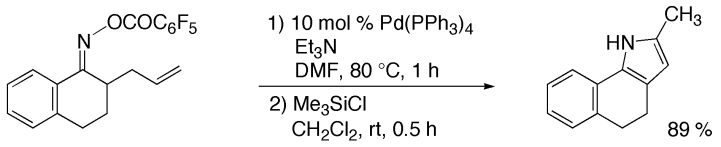
(6)

To avoid the rearrangement, *O*-pentafluorobenzoyloxime was found to be suitable for this cyclization reaction. *O*-Pentafluorobenzoyloxime **5b** was converted to pyrrole **7b** in good yield by the amino-Heck cyclization followed by isomerization of the crude products with trimethylsilyl chloride without the Beckmann rearrangement (eq. 7). It is noteworthy that the stereochemistry of the oximes exhibited no significant influence on the cyclization.



(7)

This amino-Heck reaction can be widely applied to prepare pyrrole derivatives. Various γ,δ-unsaturated ketone oximes having terminal methylene group and monosubstituted methylene group cyclized to pyrroles smoothly (eqs. 8 and 9).



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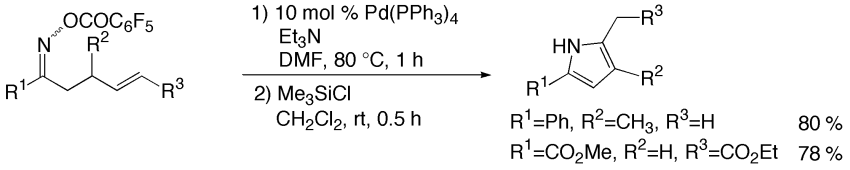
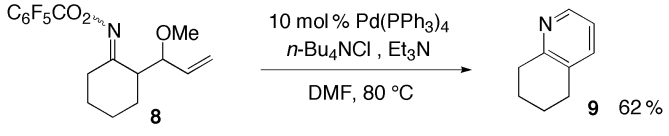


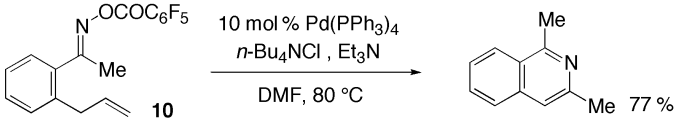
(9)

Thus, the 5-*exo* mode cyclization proceeds in γ,δ-unsaturated ketone *O*-pentafluorobenzoyloximes via alkylideneaminopalladium species, while the 6-*endo* mode of cyclization was observed in the reaction of γ,δ-unsaturated ketone oximes **8** having β-methoxy group. Particularly in the presence of tetrabutylammonium chloride, pyridine derivatives **9** were obtained in reasonable yields (eq. 10) [12]. The reaction pathway of this 6-*endo* mode cyclization has been not clear, but the reaction is certainly initiated by the oxidative addition of the oximes.



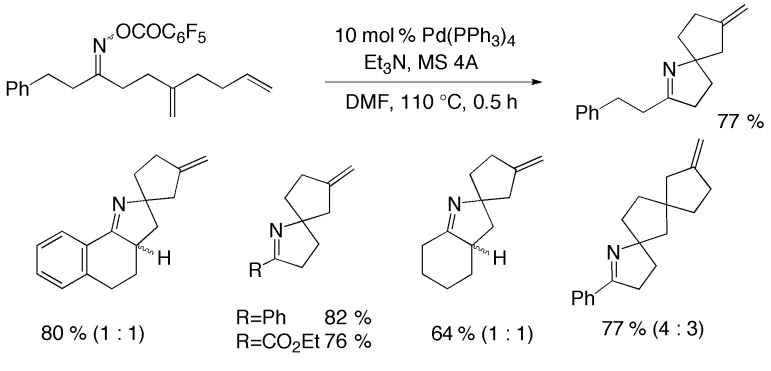
(10)

Under these reaction conditions, *ortho*-allylphenyl ketone *O*-pentafluorobenzoyloxime **10** also cyclized to give various isoquinoline derivatives in the mode of 6-*exo* mode cyclization (eq. 11).



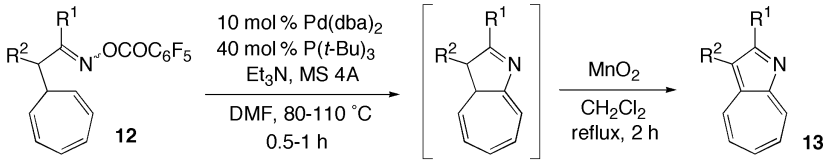
(11)

Various methods have been developed towards the construction of 1-azaspiro[4.4]nonane skeleton, including a recent metal-catalyzed allylation reaction [13]. This amino-Heck reaction provides another metal-catalyzed method for the synthesis of 1-azaspiro[4.4]nonane derivatives. Bicyclic and tricyclic imines could be prepared in domino cyclization from dienyl and trienyl ketone oximes (eq. 12).



(12)

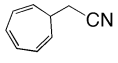
A straightforward method is developed for the synthesis of aza-azulenes. 1-Aza-azulenes **13** were obtained by treatment of cycloheptatrienylmethyl ketone *O*-pentafluorobenzoyloximes **12** with $Pd(dba)_2/P(t\text{-}Bu)_3$ and triethylamine and the successive oxidation of the crude mixture with MnO_2 (eq. 13, Table 2) [14].



(13)

Table 2 Preparation of 1-aza-azulenes **13**.

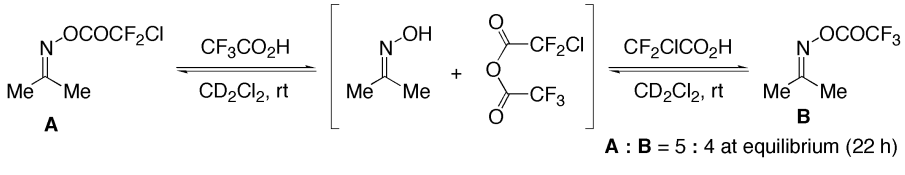
R^1	R^2	Yield/%	R^1	R^2	Yield/%
Ph	H	78	Ph	Me	52
t-Bu	H	84	Ph	Ph	84
i-Pr	H	62	Et	Me	42
	H	63	Ph	H	0*
Ph	H	68			
Me	H	27			

*  89 %

CYCLIZATION OF γ,δ-UNSATURATED KETONE *O*-ACYLOXIMES

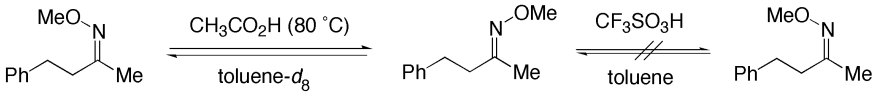
Although oximes themselves readily isomerize by treatment with acid, isomerization of *O*-substituted oximes hardly occurs under acidic conditions. This makes the application of S_N2-type cyclization to cyclic imine preparation difficult, because it is hard to synthesize *E* or *Z* oximes in a stereoselective manner. In order to apply the S_N2-type substitution, therefore, we have investigated some isomerization of *O*-substituted oximes under mild conditions.

When *O*-chlorodifluoroacetyloxime was treated with trifluoroacetic acid at room temperature (rt), formation of *O*-trifluoroacetyloxime was observed and the reaction came up to be in equilibrium after 22 h (eq. 14). Thus, *O*-acyloximes have the possibility of *syn/anti* isomerization, presumably due to the formation of free oximes as intermediates.



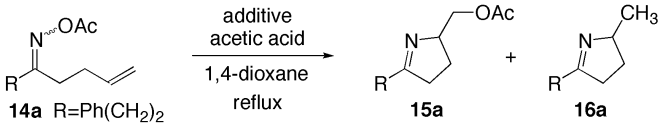
(14)

Syn/anti isomerization of a 1:1 mixture of *E* and Z *O*-methyloximes did not occur with a non-nucleophilic acid such as trifluoromethanesulfonic acid, while *O*-methyloximes isomerized by treatment with acetic acid at 80 ºC, although the isomerization proceeded very slowly (eq. 15). The isomerization was found to be accelerated by the addition of a catalytic amount of phenol derivatives like 1,4-hydroquinone and 1,5-naphthalenediol. After 2 h at 80 ºC, the *syn/anti* isomers attained to the equilibrium.



(15)

Cyclization of γ,δ-unsaturated *O*-acetyloxime **14a** was tried by treatment with 2 molar amounts of acetic acid and a catalytic amount of 1,5-naphthalenediol in refluxing 1,4-dioxane (eq. 16, Table 3) [15]. The desired cyclization product **15a** was obtained in about 23 % yield, with 43 % yield of unexpected 2-methyl-5-phenethyl-3,4-dihydro-2*H*-pyrrole (**16a**) (Run 1). When the reaction was carried out in the presence of 1,4-cyclohexadiene, the total yield of **15a** and **16a** increased to 86 % (Run 3). Without the naphthalenediol, the reaction proceeded very slowly, and the total yield was low (Runs 2 and 4).

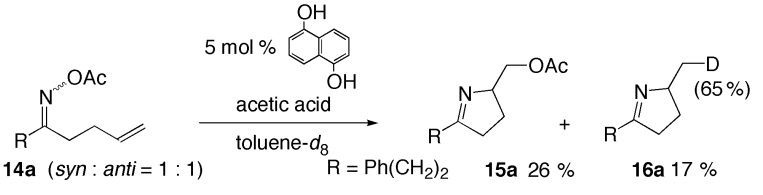


(16)

Table 3 Cyclization of *O*-acetyloxime **14a**.

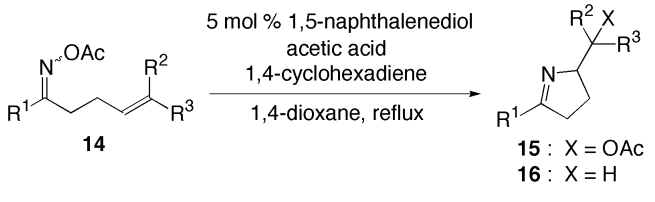
Run	Additive 1 (5 mol %)	Additive 2 (1000 mol %)	Time	Yield/% **15a**	Yield/% **16a**
1	1,5-naphthalenediol	none	6 h	23	43
2	none	none	24 h	19	20
3	1,5-naphthalenediol	1,4-cyclohexadiene	6 h	34	52
4	none	1,4-cyclohexadiene	24 h	12	29

The formation of the unexpected product **16a** could not be explained by the S_N2-type mechanism, but was considered to stem from a radical process [16]. Actually, by the reaction in toluene-d_8 without 1,4-cyclohexadiene, the cyclic imine **16a** was obtained in 17 % yield with 65 % deuterium content in the methyl group along with 26 % yield of **15a** (eq. 17).



(17)

By the reaction of *O*-acetyloxime **14b** having an electron-rich olefinic moiety, acetoxymethyl imine **15b** was yielded as a major product. In contrast, only radical cyclization products **16c** and **16d** were obtained from oximes having electron-deficient olefinic moieties. Radical cyclization product **16e** was obtained exclusively from *O*-acetyloxime of phenyl ketone. Presumably, the steric repulsion between phenyl and acetoxy group gives rise to the preferential formation of the *syn* isomer, which prevents the nucleophilic substitution with the intramolecular alkenyl group. *O*-Pivaloyloxime of α-keto ester also gave only methylimino ester **16f** in 61 % yield (eq. 18, Table 4).



(18)

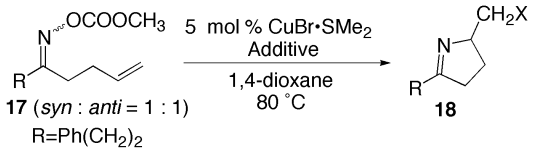
Table 4 Cyclization of *O*-acetyloxime **14**[a].

Run	R^1	R^2	R^3	Time/h	Yield/%			
1	$PhCH_2Ch_2$[b]	H	H	6	**15a**	34	**16a**	52
2	$PhCH_2Ch_2$[b]	Me	Me	6	**15b**	72	**16b**	5
3	$PhCH_2Ch_2$[c]	H	CN	12	**15c**	0	**16c**	69
4	$PhCH_2Ch_2$[b]	H	CO_2Et	12	**15d**	0	**16d**	72
5	Ph[d]	H	H	8	**15e**	0	**16e**	75
6	$Ph(CH_2)_3O_2C$[d,e]	H	H	6	**15f**	0	**16f**	61

[a]Cyclization was carried out under the following conditions; 1,5-naphthalenediol (5 mol %), acetic acid (2 molar amounts), 1,4-cyclohexadiene (10 molar amounts).
[b]*syn/anti* = 1:1.
[c]*syn/anti* = 1:2.
[d]Only *syn* isomer was used.
[e]*O*-Pivaloyloxime was used instead of *O*-acetyloxime.

As mentioned in the introductory section, one-electron reduction activates *O*-2,4-dinitrophenyloxime derivatives to react with intramolecular phenyl and alkenyl moieties via a radical process. It was expected that one-electron reduction of oxime derivatives would proceed by the action of low-valent transition-metal compounds. Such an example was reported by Zard. That is, the treatment of γ,δ-unsaturated *O*-acetyloximes with nickel powder and acetic acid in 2-propanol leads to the cyclization to dihydropyrroles [17]. This reaction, however, requires large excess amounts of nickel powder, and it is desirable to conduct such a transformation in a catalytic manner.

By using copper compounds as metal catalysts [18], we examined the cyclization of various γ,δ-unsaturated oximes. After screening, the substituents on the oxime nitrogen atom (vide infra), *O*-methoxycarbonyloximes were found to be suitable for the transformation of γ,δ-unsaturated oximes to dihydropyrroles. The reaction of a *syn/anti* (1:1) mixture of *O*-methoxycarbonyloxime **17** with 5 mol % of $CuBr{\cdot}SMe_2$ in 1,4-dioxane 80 °C, cyclic imine **18a** was obtained in 39 % yield (eq. 19, Table 5, Run 1). Thus, the reaction proceeded catalytically, though the yield was not good. The yield was much improved to 86 % by the addition of LiBr (Run 4).



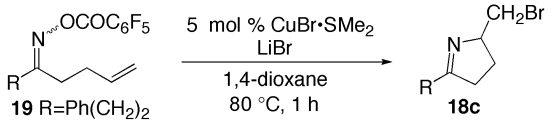
(19)

Table 5 Cu-catalyzed cyclization of **17**[a].

Run	Additive	Time	X	Yield/%	
1	none	1 h	H	**18a**	39
2	$(Me_3Si)_3SiH$	1 h	H	**18a**	49
3	PhSSPh	3 h	SPh	**18b**	41[b]
4	LiBr	1 h	Br	**18c**	86
5	LiCl[c]	1 h	Cl	**18d**	57[d]

[a]Oxime **17**:Cu cat.:additive = 1.0:0.05:3.0.
[b]**18a** was obtained in 14 % yield.
[c]CuCl was used instead of $CuBr{\cdot}Sme_2$.
[e]**18a** was obtained in 18 % yield.

In addition to *O*-methoxycarbonyloxime **17**, *O*-pentafluorobenzoyloxime **19** was transformed into **18c** in high yield, but the corresponding *O*-2,4-dinitrophenyl and *O*-acetyloxime were not appropriate for the CuBr•LiBr-catalyzed cyclization. The cyclization proceeds irrespective of the stereochemistry of *O*-pentafluorobenzoyloxime **19**. The cyclization product **18c** was obtained in 86 % and 91 % yield from the *syn* and *anti* isomers **19**, respectively (eq. 20).

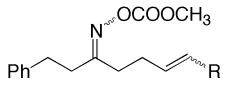
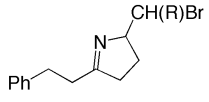
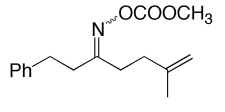
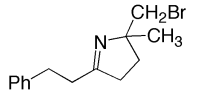
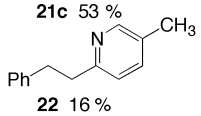
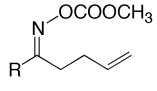
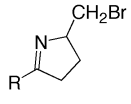


from *syn*-**19** 86 %
from *anti*-**19** 91 %

(20)

As listed in Table 6, the catalytic system of CuBr•SMe_2•LiBr was applied to the cyclization of various γ,δ-unsaturated ketone *O*-methoxycarbonyloximes. Cyclization of **20a** and **20b** having disubstituted olefin moiety proceeded to give cyclic imines **21a** and **21b** in 85 % and 74 % yield, respectively (Table 6, Runs 1 and 2). 5,5-Disubstituted dihydropyrrole **21c** was obtained in 53 % yield from γ-methyl substituted oxime **20c** along with 16 % yield of disubstituted pyridine **22** (Run 3) [19]. Oxime derivatives of phenyl ketone **20d** and keto ester **20e** were smoothly transformed into 2-phenyl and 2-ethoxycarbonyl dihydropyrroles **21d** and **21e**, respectively (Runs 4 and 5).

Table 6 Cu-catalyzed cyclization of **20**[a].

Run	Oxime **20**	Product
		
1	**20a** (R = CH_3[b]; *syn* : *anti* = 1 : 1)	**21a** 85 % (4 : 1)[c]
2	**20b** (R = Ph[d]; *syn* : *anti* = 1 : 1)	**21b** 74 % (20 : 1)[c]
		
3	**20c** (*syn* : *anti* = 1 : 1)	**21c** 53 %  **22** 16 %
		
4	**20d** (R = Ph)	**21d** 83 %
5	**20e** (R = CO_2Et)	**21e** 53 %

[a]Oxime **20** : Cu cat. : LiBr = 1.0 : 0.05 : 3.0. [b]The stereochemistry of olefin moiety was *E* : *Z* = 3 : 1. [c]Diastereomer ratio. [d]The stereochemistry of olefin moiety was *E*.

Very recently, a Cu-catalyzed radical cyclization of unsaturated *N*-benzoyloxyamines to pyrrolidines was reported [20]. Totally, various dihydropyrrols and pyrrolidines can be prepared by Cu-catalyzed radical cyclization processes.

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