

## Contribution

### A Novel Method for the formation of C-N Bonds Using Oxime Derivatives

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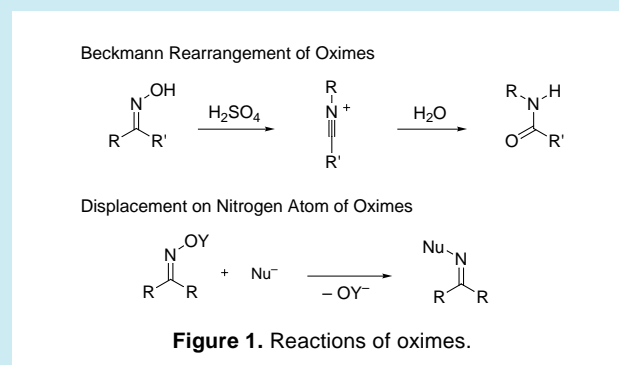
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#### INTRODUCTION: Amination Reactions

Many amino compounds show biologically interesting activities and have been synthesized using a variety of synthetic methods. In general, there are several methods widely used to synthesize amines, which include 1) reduction of nitrogen-containing functional groups such as nitro or cyano groups, and 2) nucleophilic amination, by which carbon electrophiles are reacted with nitrogen nucleophiles (Gabriel type Reaction).<sup>1</sup> Moreover, electrophilic amination reactions such as combinations of nitrogen electrophiles and carbon nucleophiles are also known, and both chloroamine and hydroxylamine derivatives have been used as nitrogen electrophiles.<sup>2</sup> However, the latter has almost never been efficiently used as a method of synthesizing amino compounds because it lacks general applicability, but has recently recovered attention as an amination method.

Oximes can be easily synthesized from the corresponding carbonyl compounds and hydroxylamine derivatives. Furthermore, oximes are more stable, more resistant to hydrolysis and much easier to handle as compared to their relatives, imines, which possess nitrogen-carbon double bonds. However, because electrophilicity of the carbon atom of the imino group of oximes is very poor, addition of nucleophilic reagents to oximes is a difficult process. The Beckman rearrangement is well known as the most characteristic reaction of oxime derivatives, and using this reaction, amides are produced when oximes or their derivatives react with either acid or base (Figure 1). This rearrangement reaction is used not only for synthesis of amides but also for synthesis of various heterocyclic compounds using *N*-alkyl nitrilium ion intermediates. Thus, substitution on the nitrogen atom of the oxime can be easily achieved via the Beckman rearrangement, while almost no examples have been reported so far regarding direct displacement taking place on the sp<sup>2</sup> nitrogen atom

of oxime derivatives. We have recently found that such a direct displacement reaction generally occurs, and have demonstrated that oxime derivatives can be widely used as electrophilic amination reagents for syntheses of amines and heterocyclic compounds containing nitrogen atoms.



In the current study, we introduce the following three reactions: 1) a substitution reaction on the nitrogen atom of oxime by an S<sub>N</sub>2 nucleophilic substitution reaction, 2) radical cyclization of oximes by single electron reduction, and 3) oxidative addition reaction of oximes to a palladium catalyst.

#### 1. Substitution on Oxime Nitrogen Atoms by S<sub>N</sub>2 Type Nucleophilic Reaction

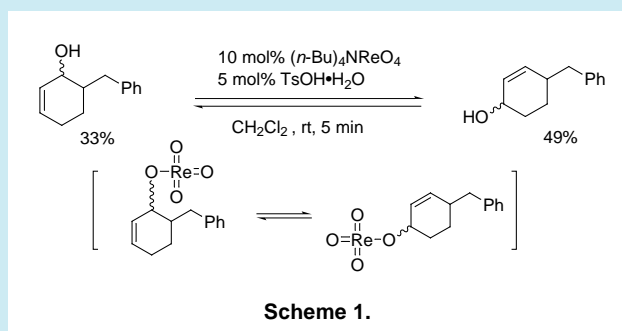
##### 1.1 Conversion of Phenethyl Ketone Oximes to Quinolines using a Rhenium Reagent.

Allyl rearrangement occurs when an allyl alcohol is treated with a catalytic amount of tetra-*n*-butylammonium perrhenate (*n*-Bu<sub>4</sub>NReO<sub>4</sub>) and *p*-toluenesulfonic acid. As

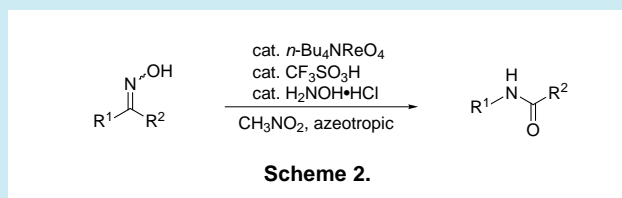
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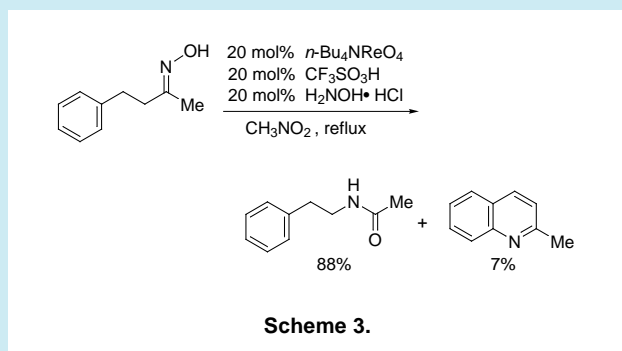
shown in Scheme 1, an allyl alcohol produces a perrhenic acid ester, which in turn leads either to a [3,3]sigmatropic rearrangement or to generation of allyl cations by elimination of perrhenate ions, resulting in the formation of the rearrangement product (Scheme 1).<sup>3</sup>



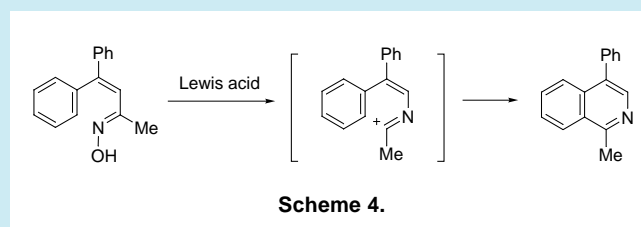
We therefore considered it possible to catalytically induce a Beckmann Rearrangement when *n*-Bu<sub>4</sub>NReO<sub>4</sub> and sulfonic acid were reacted with different oximes, resulting in the generation of various perrhenic acid esters of oximes. Indeed, the Beckmann Rearrangement occurred, and amides were produced when oximes were reacted with *n*-Bu<sub>4</sub>NReO<sub>4</sub> and trifluoromethanesulfonic acid (TfOH, CF<sub>3</sub>SO<sub>3</sub>H) in a highly polar solvent such as nitromethane (Scheme 2). Since *syn*- and *anti*-geometric isomers<sup>4</sup> of oximes undergoes rapid isomerization by treatment with TfOH, uniform amides were produced by the selective rearrangement even when mixtures of *syn* and *anti* isomers of unsymmetrical ketone oximes were used as the starting materials, in which one isomer that could be more easily rearranged into the other one.<sup>5</sup>



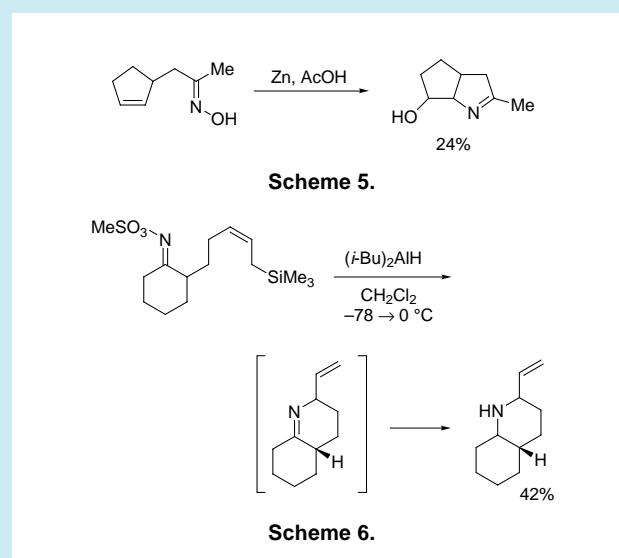
However, it was found that in the reaction of 4-phenyl-2-butanone oximes, 2-methylquinoline was also produced as a by-product (7%) in addition to the major product of the Beckmann Rearrangement (Scheme 3).



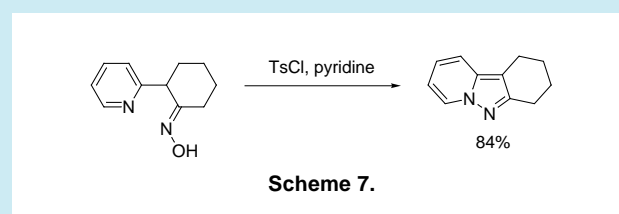
This reaction to produce the quinoline was totally unexpected. That is, a nitrilium ion intermediate is generated via the Beckmann rearrangement of an analogue of phenethyl ketone oxime, followed by an intramolecular cyclization of the intermediate, which gives an isoquinoline derivative (Scheme 4).<sup>6</sup> However, when a rhenium reagent was used in the reaction, 2-methylquinoline was produced, indicating that intramolecular cyclization of the nitrogen atom of the oxime with the phenyl ring would occur without mediating through a Beckmann Rearrangement.



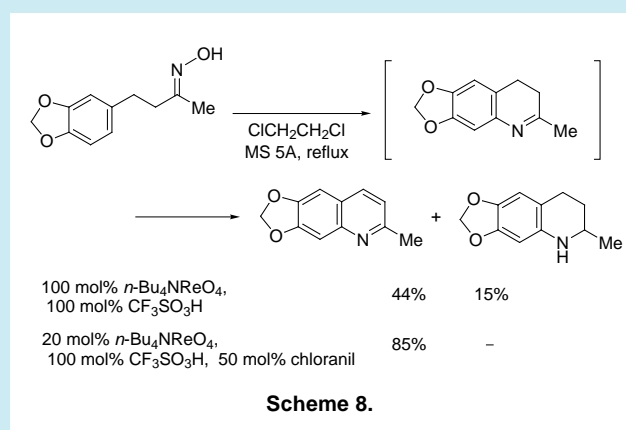
In the past, there was a report that cyclization occurred on the nitrogen atom of oximes possessing alkenyl groups (Scheme 5 and 6), as an example of C-N bond formation on the nitrogen atoms of oxime derivatives. However, in these reports, none were further investigated for general utility and reaction mechanisms.<sup>7</sup>



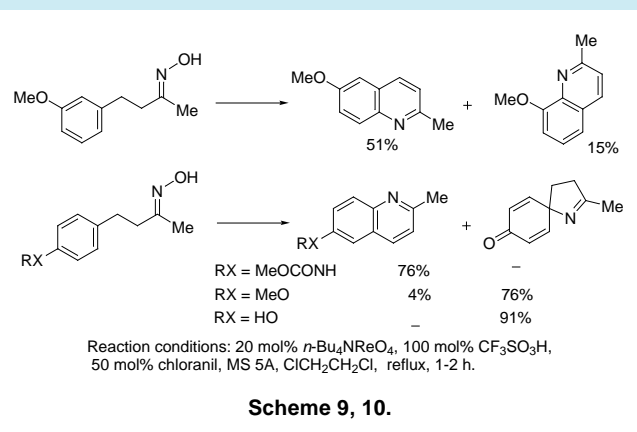
On the other hand, there are several reports in which N-N or N-S bond formation took place at the nitrogen atom of oxime. For instance, it has been reported that when an oxime having pyridyl group was reacted with tosyl chloride and pyridine (Scheme 7), a cyclic compound was produced from *anti*-isomer of the oxime, while no cyclization occurred when the *syn*-isomer was used.<sup>8</sup>



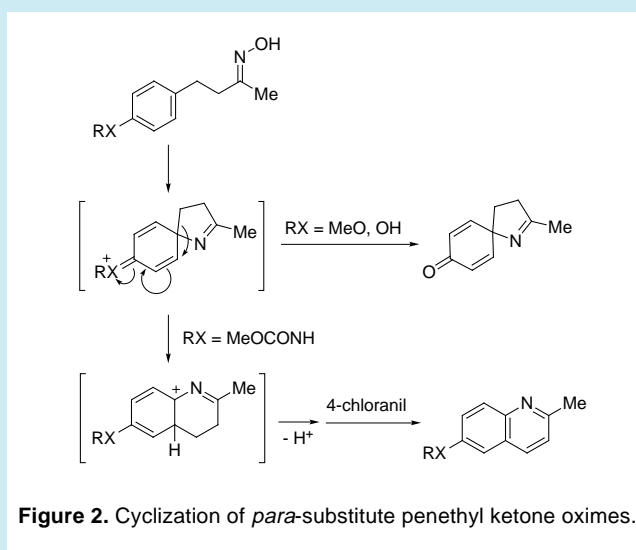
Thus, since it is extremely unusual that a C-N bond were formed on the nitrogen atom of oxime and its reaction mechanism is still unknown, our interest focused on the production of quinolines using the rhenium reagents. It was required to use polar solvents such as nitromethane for the catalytic Beckmann rearrangement. However, it was found that only quinolines were produced when a non-polar solvent such as 1,2-dichloroethane was used in this reaction. Furthermore, when an equimolar amount of  $n\text{-Bu}_4\text{NReO}_4$  was used in the reaction, the yield was only approximately 60%. It was demonstrated later that this low yield was due to reduction of perrhenic acid by the first product dihydroquinoline. Accordingly, the reaction was processed in the presence of chloranil as an oxidant, a high yield of quinoline was obtained even after reducing the amount of  $n\text{-Bu}_4\text{NReO}_4$  to 20 mol% (Scheme 8).<sup>9</sup>



When phenethyl ketone oximes containing electron donating groups at the *meta*-position were cyclized using a catalytic cyclization reaction with  $n\text{-Bu}_4\text{NReO}_4$  and TfOH, quinoline derivatives that were cyclized at the *ortho*- and *para*- positions were obtained (Scheme 9). On the other hand, when *p*-substituted phenethyl ketone oximes were cyclized, the following products were obtained (Scheme 10). That is, *p*-methoxy carbonylamino (RX = MeOCONH) substituted phenethyl ketone oximes yielded quinoline as a product, in which the two substituents originally present at the 1 and 4 positions were shifted to the 1 and 3 positions in the resultant quinolines. Moreover, when *p*-methoxy or hydroxyl substituted phenethyl ketone oximes (RX = MeO, HO) were used, spirocyclic compounds were obtained instead of quinolines as reaction products.

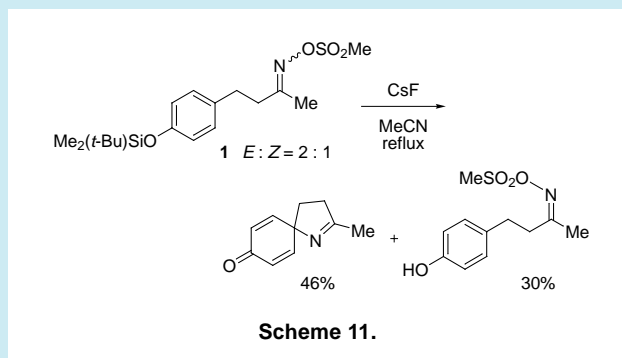


Based on the cyclization products of *meta*- or *para*-substituted phenethyl ketone oximes, it could be predicted by which pathways quinolines were produced. As shown in Figure 2, when the substituents were at the *para*-positions (1,4), cyclization took place first at the *ipso* position, where spiro-cyclic compounds were produced when R-X bonds could be easily cleaved. In the case when R-X bonds could not be easily cleaved, cyclohexadienone-phenol rearrangement occurred and alkyl side chains were rearranged to obtain quinolines. On the other hand, when *meta*-substituted compounds were used, there were no quinolines produced at all, whose *ipso*-cyclic compounds were rearranged. Therefore, these results suggested that for oximes with *meta*-substitute groups, direct cyclization might occur at the *ortho*- or *para*-positions.<sup>10</sup>



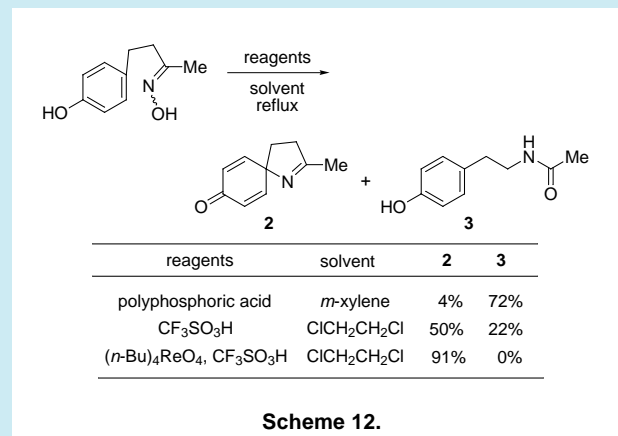
In the catalysis reaction described above, it was thought that oximes reacted with perrhenic acid to produce esters as well as they did in the Beckmann Rearrangement. However, as for the mechanism of cyclization, various possibilities including addition and elimination reactions, electron transfer reactions, and nucleophilic substitution reactions were considered, and we could not be clearly determined the mechanism how this catalysis reaction was undertaken. As we describe later in detail, after examining these substitution reactions under various conditions, we reached a final conclusion that perrhenic acid anions acted as a leaving group for  $\text{S}_{\text{N}}2$  type nucleophilic substitution at the nitrogen atoms. This means that bimolecular nucleophilic substitution reactions occur at the  $\text{sp}^2$  nitrogen atoms of oximes, and is against the conventional rule of organic chemistry, that "the  $\text{S}_{\text{N}}2$  nucleophilic substitution reaction does not occur on  $\text{sp}^2$  atoms". In order to determine whether an  $\text{S}_{\text{N}}2$  type substitution was actually occurring, we need to investigate whether inversion of the steric configuration occurs on the nitrogen atom of oxime (corresponding to Walden inversion of an  $\text{sp}^3$  carbon atom in a typical  $\text{S}_{\text{N}}2$  reaction) during the substitution reactions. However, since oximes are geometrically *E/Z* isomerized in the presence of TfOH, it was impossible to determine the stereospecificity of the cyclization reaction under these reaction conditions.

If it is true that this reaction occurs in an  $S_N2$  type reaction, similar reactions should occur not only under acidic conditions but also under neutral or basic conditions. Accordingly, we synthesized *p*-silyloxyphenethyl ketone *O*-methylsulfonyl oxime **1**, and examined whether cyclization of this oxime **1** occurred (Scheme 11). When a mixture of *E*- or *Z*-isomers of oxime **1** was treated with cesium fluoride (CsF), the *E*-isomer cyclized and yielded spirocyclic compounds, whereas *Z*-isomers remained intact without reacting. This result strongly suggests a possibility that an  $S_N2$  type substitution reaction may occur, with the phenyl groups acting as nucleophiles.



As described later, some other stereospecific cyclizations at oxime nitrogen, similar to the reaction mentioned above, were observed. Thus, it was highly likely that cyclization took place at the  $sp^2$  nitrogen atoms of oximes by the  $S_N2$  type mechanism. When we looked at a transition state of the Beckmann Rearrangement, in which *anti* substituents to the hydroxy group always migrate onto the oxime nitrogen atoms. This could be considered to be an intramolecular  $S_N2$  type reaction to a broad degree. Therefore, we carried out the following model experiments to ran molecular orbital calculations.<sup>11</sup> The results from the experiments in which a phenethyl ketone oxime with a hydroxyl group at the *para*-position was reacted with various acids are shown in Scheme 12. When polyphosphoric acid, which is often used for Beckmann Rearrangement, was reacted with *p*-OH oximes **3** was produced as a result of the Beckmann Rearrangement. However, when trifluoromethanesulfonic acid ( $CF_3SO_3H$ ) was used, spirocyclic compound **2** was obtained as a main product with the Beckmann product. Reaction of the oxime with  $n-Bu_4NReO_4$  and  $CF_3SO_3H$  yielded only spirocyclic

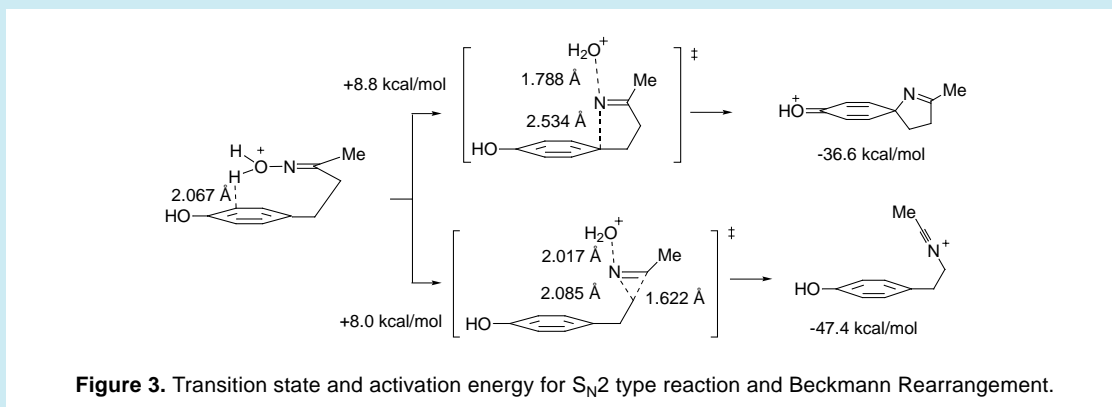
compound **2**. These results indicate that either the Beckmann rearrangement or cyclization may occur based on a very subtle difference in the reaction conditions.



Next, given that a starting material was the oxime whose hydroxyl group was protonated, molecular orbital calculations were run for the transition states of the cyclization and the Beckmann Rearrangement, and for the activation energies. The reaction conditions corresponded to that in which  $CF_3SO_3H$  was used in a solvent of 1,2-dichloroethane in Scheme 12. As a result of these calculations, it was found that the activation energies for both of the reactions were almost the same (8.0 and 8.8 kcal/mol, respectively, Figure 3).<sup>11</sup>

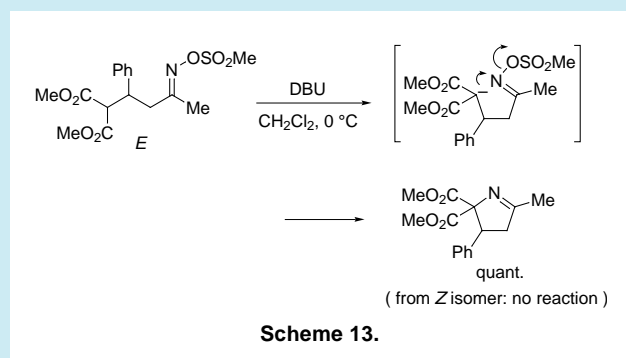
The Beckmann Rearrangement dominates in a polar solvent or when a highly nucleophilic acid such as polyphosphoric acid is used for the reaction. This is considered to be probably because the  $sp^2$  carbocationic species, which are gradually formed upon the rearrangement, are nucleophilically solvated or attacked by such a polar solvent or a nucleophilic acid, resulting in the stabilization of cationic transition state. On the other hand, the  $S_N2$  type nucleophilic substitution can easily take place when only the phenyl group acts as a nucleophile in the absence of other nucleophilic reagents (polar solvents or nucleophilic acids, in the reaction described here).

Thus, since it was found that the  $S_N2$  type nucleophilic substitution reaction could take place on the  $sp^2$  nitrogen atoms of oximes, its applications were now exploited in various aspects.

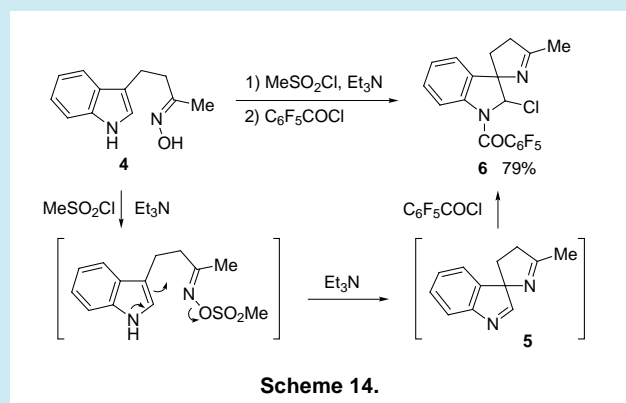


## 1.2 Synthesis of Cyclic Imines Using Nucleophilic Substitution Reaction of Oximes.

When (*E*)-*O*-methylsulfonyloximes of ketones having active methylene moieties at the  $\gamma$  and  $\delta$  positions, were treated with DBU, an intramolecular nucleophilic substitution took place, resulting in the quantitative production of five- and six-membered cyclic imines (Scheme 13).<sup>12</sup> However, when the corresponding *Z*-isomers were used, no cyclic compounds were obtained at all. Moreover, when reaction conditions were set for being more restricted, various reaction products such as Neber reaction products were yielded.



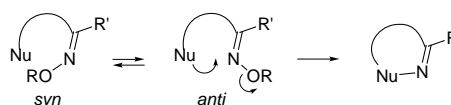
Similarly, Scheme 14 shows synthesis of spiro[indolin-3,2-pyrolidine] derivatives using the substitution reaction.<sup>13</sup> When  $\beta$ -indolyl ketone oxime **4** was mesylated under basic conditions, the reaction underwent cyclization to yield the corresponding spiroimine **5**. Spiroimine **5** is too polar to be isolated, but can be converted to *N*-pentafluorobenzoyl spiroimine **6**, which is quite stable and easily isolated.



## 1.3 Isomerization of *O*-Substituted Oximes and Intramolecular Nucleophilic Substitution Reactions on the Nitrogen Atoms.

As described in the previous section, only *anti*-isomers can be employed for the applications of  $S_N2$  type nucleophilic substitution of *O*-substituted oximes.<sup>4</sup> Although oximes alone can be easily *syn/anti*-isomerized under acidic conditions, it is generally difficult to isomerize *O*-substituted oximes such as *O*-alkyl or *O*-acyl oximes. However, if by any means we could make *O*-substituted oximes undergo

the  $S_N2$  type reaction with simultaneous isomerization as shown in the cyclization reactions using  $n\text{-Bu}_4\text{NReO}_4$ , we speculate that both stereo isomers could be used for cyclization (Figure 4).



**Figure 4.** Intramolecular cyclization of *syn*- and *anti*-isomers of oximes.

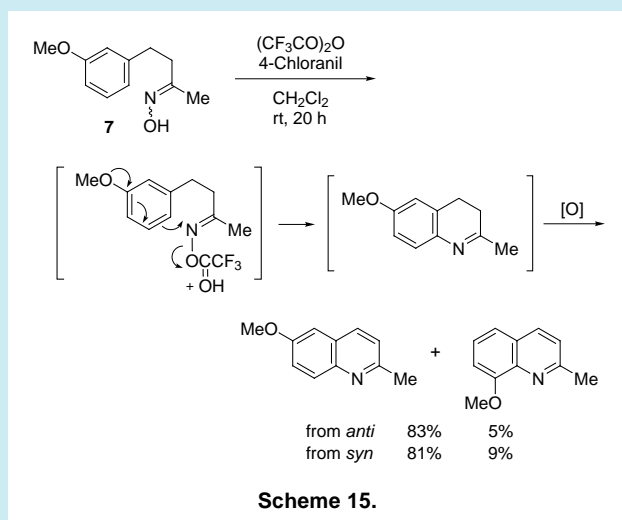
Therefore, we next investigated isomerization of *O*-substituted oximes (Table 1).<sup>14</sup> It was noted that methyl phenethyl ketone oxime could be easily isomerized, when it was treated with trifluoromethanesulfonic acid ( $\text{CF}_3\text{SO}_3\text{H}$ ). However, the *O*-substituted oximes could not be isomerized under the same conditions, indicating that *N*-protonation alone could not isomerize the oximes (**runs 1, 2**). However, the *O*-methyloxime was found to be isomerized by the treatment with  $\text{CF}_3\text{SO}_3\text{H}$  in the presence of nucleophiles such as methanol (**run 3**). We speculate that this isomerization may be induced by protonation on the oxime N atom and an addition-elimination reaction of methanol. Moreover, it was shown that *O*-acetyloxime was very slowly but gradually isomerized when it was reacted with benzoic acid (**run 4**). On the other hand, *O*-acyloximes, which had active acyl moieties such as a trifluoroacetyl group, could be isomerized at room temperature when treated with trifluoroacetic acid ( $\text{CF}_3\text{CO}_2\text{H}$ ) (**run 5**). In order to understand the mechanism for this isomerization of *O*-trifluoroacetyloxime, acetone *O*-chlorodifluoroacetyloxime was treated with  $\text{CF}_3\text{CO}_2\text{H}$ , and this resulted in a mixture of *O*-trifluoroacetyloxime and *O*-chlorodifluoroacetyloxime. Therefore, there may be some other mechanisms in addition to the *N*-protonation and addition/elimination mechanism for this isomerization of oximes with active acyl moieties. And the possible mechanism may include a substitution reaction at the oxime N atoms by carboxylic acid or the formation of mixed acid anhydrides and free oximes by the attack of acids to the labile acyl moieties.

**Table 1.** Isomerization of oximes.

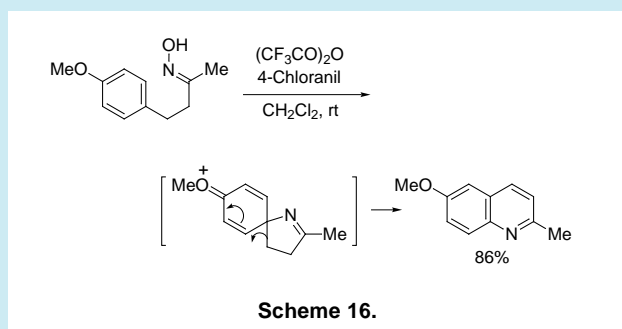
run	OR	conditions	<i>anti</i> : <i>syn</i>
1	OH	$\text{CF}_3\text{SO}_3\text{H}$ (2.0), $\text{CH}_2\text{Cl}_2$ , rt, <20 min	2 : 1 <sup>a</sup>
2	OMe	$\text{CF}_3\text{SO}_3\text{H}$ (2.0), $\text{CH}_2\text{Cl}_2$ , rt, 12 h	>99 : <1
3	OMe	$\text{CF}_3\text{SO}_3\text{H}$ (2.0), $\text{CD}_3\text{OD}$ (2.0), $\text{CH}_2\text{Cl}_2$ , rt, 20 min	2 : 1 <sup>a</sup>
4	OAc	$\text{PhCO}_2\text{H}$ , toluene, 80 °C, 6 h	3 : 1 <sup>a</sup>
5	OCOCF <sub>3</sub>	$\text{CF}_3\text{CO}_2\text{H}$ , $\text{CDCl}_3$ , rt, 28 h	3 : 1 <sup>a</sup>

a) At equilibrium.

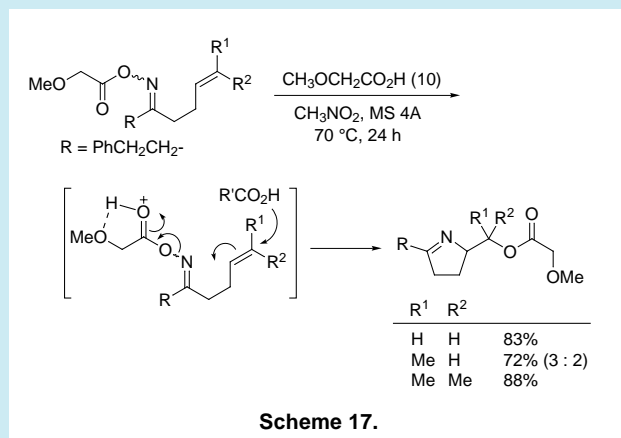
Based on these findings described above regarding isomerization mechanisms of oximes, we attempted to develop a simple method for intramolecular cyclization of oxime *syn/anti* isomers. First, we focused on transformation from phenethyl ketone oximes to quinolines. When the *anti*-isomer of *o*-methoxyphenethyl ketone oxime **7** was treated with trifluoroacetic anhydride in the presence of 4-chloranil at room temperature, quinolines were obtained in a high total yield (Scheme 15). Next, when the corresponding *syn*-isomer of **7** was used in the same reaction above, the cyclization occurred smoothly as expected. Thus, we have successfully achieved the cyclization of *syn* and *anti* phenethyl ketone oximes accompanied with their simultaneous isomerization.



A similar cyclization could occur using various *syn-anti* mixtures of *p*-substituted phenethyl ketone oximes (Scheme 16).

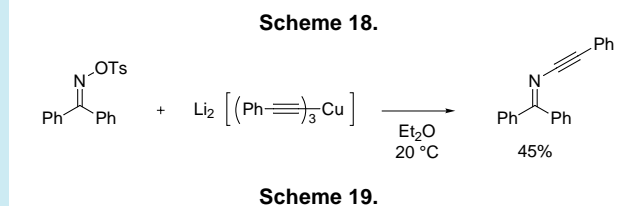
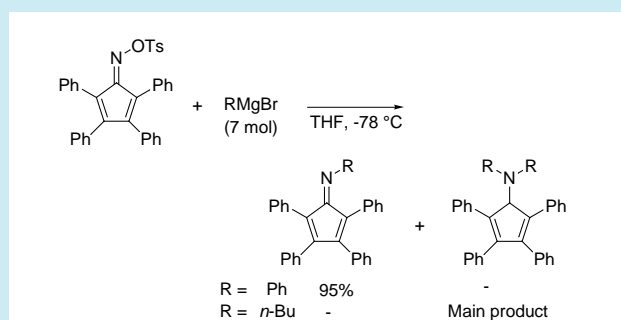


It is known that alkenes can act as nucleophiles. Therefore,  $\gamma,\delta$ -unsaturated *O*-methoxyacetyloxime was treated with methoxyacetic acid in nitromethane at 70 °C. This, as expected, resulted in the formation of cyclization compounds, dihydropyrroles (Scheme 17). This cyclization reaction can be applied to oximes with various electron abundant alkenes.

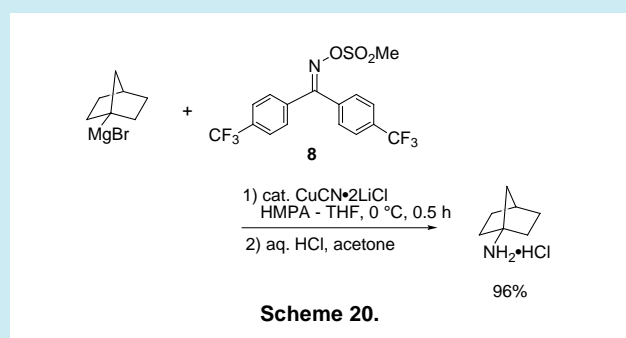


#### 1.4 Alkylation of Oxime Derivatives by Grignard Reagents: Synthesis of the Primary Amines.

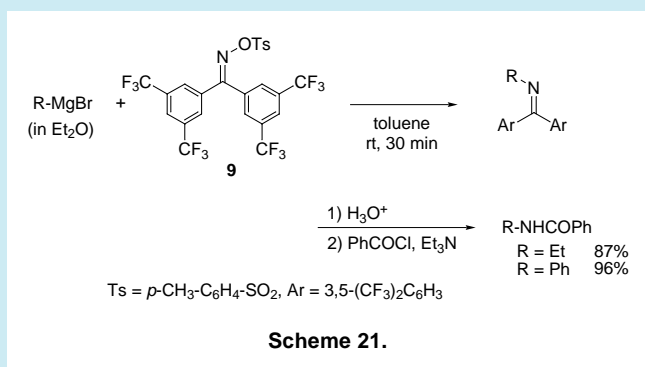
Our present finding that nucleophilic species can attack on the oxime N atoms indicates that *N*-alkylation can be undertaken by organometallic compounds using oxime derivatives that rarely undergo the Beckmann Rearrangement. We found a report, in which a similar attempt was made using *O*-tolylsulfonyl oxime derived from tetraphenylcyclopentadienone as described below. However, it was reported that the reaction mechanism was through addition/elimination but not substitution reactions (Scheme 18).<sup>15</sup> In this method, large excess amounts of Grignard reagents were required to make the reaction take place. Moreover, mono *N*-alkylation could dominantly occur only when an aromatic Grignard reagent was used, while dialkylated compound was a major reaction product in cases involving an alkyl Grignard reagent. This is because *N*-alkylimines formed by monoalkylation are far more easily susceptible to addition reactions than *O*-methylsulfonyl oxime. There was another report of a case in which *O*-sulfonyloxime was alkylated with an alkynylcopper reagent (Scheme 19).<sup>16,17</sup> It was found that a substitution reaction occurred in this example, although the yield was poor. Thus, we first attempted to perform *N*-alkylation of oxime derivatives using organocopper compounds.



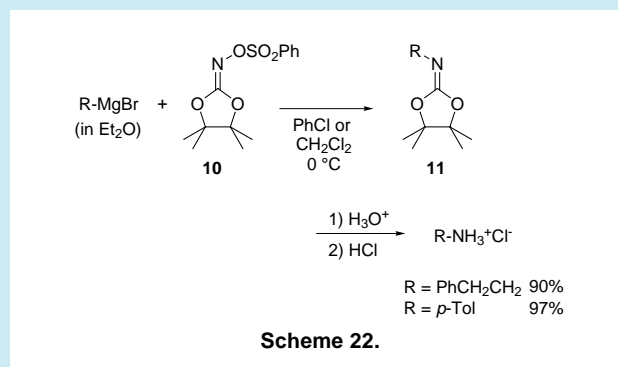
In order to suppress the Beckmann Rearrangement and the Neber reaction, benzophenone *O*-methylsulfonyloxime **8** was first prepared by introducing trifluoromethyl group as an electron withdrawing group at the *p*-position, and was then used as an amination reagent. In fact, *N*-alkylimine was obtained in a high yield when a catalytic amount of copper cyanide and a slight excess of a Grignard reagent were added to oxime **8**. Primary, secondary and tertiary alkyl Grignard reagents were reacted with **8** to produce the corresponding imines in high yield, and primary amines could be obtained by hydrolysis of these imines.<sup>18</sup> For instance, it is difficult to carry out amination of norbornyl bromide by usual methods, but 1-norbornylamine can be synthesized in a high yield using the present method (Scheme 20).<sup>19</sup>



Unfortunately, it was demonstrated that synthesis of aniline derivatives was difficult by this method. That is, biphenyls were significant byproducts when aryl Grignard reagents were used. Accordingly, we searched for another oxime derivative that could be applied to the synthesis of aniline derivatives. We found that arylation occurred without addition of a copper catalyst and a good yield of an *N*-arylimine was obtained, when 3,3',5,5'-tetrakis-(trifluoromethyl)benzophenone *O*-methylsulfonyloxime was reacted in toluene with aryl Grignard reagents prepared in ether. A high yield of amines was obtained even when primary and secondary alkyl Grignard reagents were used (Scheme 21).<sup>19</sup> Although it was found that these benzophenone oximes were very useful for amination of carbanions such as Grignard reagents, it was recommended that the structure of oxime **9** should be improved by altering the bulky substituents such as substituted phenyl groups.



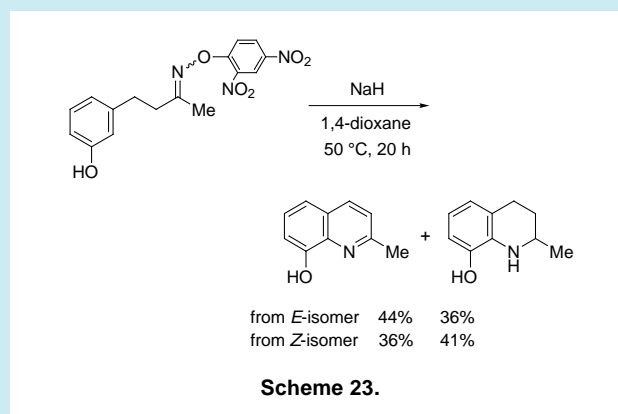
Next, we further investigated properties of oxime derivatives of cyclic ureaes and carbonates in detail,<sup>20</sup> and demonstrated that oxime **10**, a cyclic carbonate ester, could be an excellent amination reagent for Grignard reagents.<sup>21</sup> It was found that oxime **10** reacted with various aryl and alkyl Grignard reagents without a catalyst in non-polar solvents to yield the corresponding imines **11**. When these imines **11** were readily hydrolyzed under acidic conditions, primary amines were obtained (Scheme 22). This *O*-sulfonyloxime **10** worked as an excellent electrophilic amination reagent to exhibit a wide generality in the reactions with various kind of Grignard reagents.



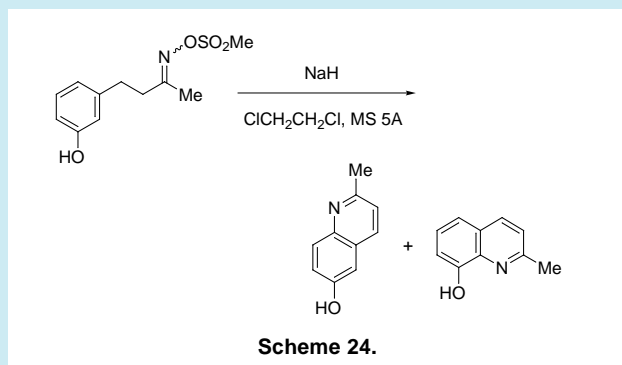
## 2. Radical Cyclization Reaction of Oximes by One Electron Reduction

### 2.1 Synthesis of 8-Quinololinol Derivatives.

In the nucleophilic substitution reactions described above, it was considered to be important to maintain a good balance between nucleophiles and leaving groups on the oxime N atoms. Therefore, we attempted substitution using oxime derivatives possessing various leaving groups. During this process, we found that 8-quinololinol and its tetrahydro derivative were formed when *m*-hydroxyphenethyl ketone *O*-2,4-dinitrophenyloxime was treated with sodium hydride (NaH). However, it was also found that no 6-quinololinol, one of the position isomers, was produced at all. Moreover, it was also demonstrated that both *E*- and *Z*-isomers of *O*-2,4-dinitrophenyloximes exerted a similar reactivity (Scheme 23).<sup>22</sup>

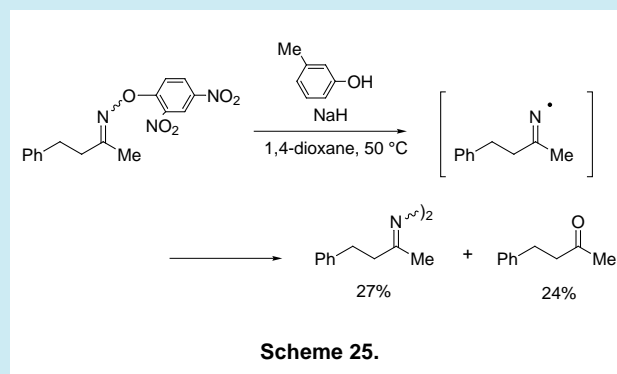


These results are quite different from those of the  $S_N2$  type cyclization of *O*-sulfonyloximes described earlier. For example, both 8- and 6-quinolinols were produced when the *m*-hydroxyphenethyl ketone *O*-methylsulfonyloxime was reacted with NaH (Scheme 24). Thus the properties that the both stereoisomers are cyclized smoothly and that 8-quinolinol is regioselectively formed were observed only in the reaction of *O*-2,4-dinitrophenyl derivatives (Scheme 23).



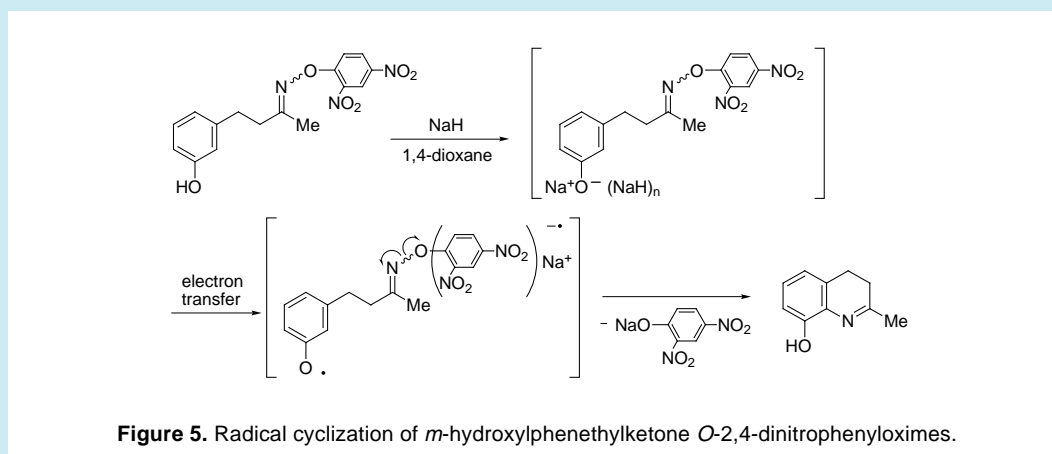
As one of the reasons that both *E* and *Z* isomers were cyclized in the reaction of *O*-2,4-dinitrophenyl oximes (Scheme 23), it was considered that the *Z*-isomers might be isomerized under these reaction conditions and cyclized via  $S_N2$  type displacement reaction. Therefore, in order to determine whether the isomerization occurred in the process, we synthesized a model compound of phenethyl ketone *O*-2,4-dinitrophenyloxime, which did not have the hydroxyl group on the phenyl ring. This model compound was treated with *m*-cresol and an excess amount of NaH, and the presence or absence of isomerization was investigated. Although we could not demonstrate actual isomerization, it was found that a part of oxime reacted under these reaction conditions, resulting in the formation of azine and phenethyl ketone (Scheme 25). It was postulated that both azines and phenethyl ketones could be generated via the intermediates such as alkylidene-aminyll radicals or their equivalents, followed by the successive dimerization and the hydrolysis of imine which was formed by hydrogen abstraction. Thus, it was

suggested that this reaction should occur via a radical mechanism.



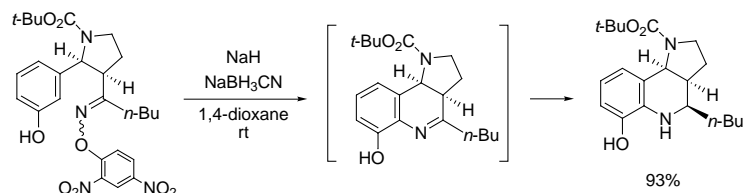
We further investigated other possible mechanisms for the cyclization and hypothesize that the cyclization may occur by the mechanism shown in Figure 5. First, sodium phenoxide generated by NaH forms a complex with excess NaH, and with this complex as a reducing agent, one electron transfer occurs to the *O*-2,4-dinitrophenyl group. Here, coupling occurs between phenoxide radicals and nitrogen atoms, accompanied by elimination of *O*-2,4-dinitrophenoxide ions.<sup>23</sup> The reason why 8-quinolinol was regioselectively obtained is considered to be due to the chelate formation of a sodium ion between phenoxide ion and oxime N atoms.

In the cyclization of the above *O*-2,4-dinitrophenyl-oxime, quinolinol and its tetrahydro derivative were produced. When considering from the viewpoint of its use as a synthetic method, it was necessary to develop a system in which only single reactants could be produced. Therefore, in order to produce only 8-quinolinol, *O*-2,4-dinitrophenyloxime was first treated with NaH to cyclize it. After cyclization, the reaction mixture was treated successively with acetic acid and DDQ, yielding only 8-quinolinol as a final product (Scheme 26).<sup>23</sup> To obtain tetrahydroquinolinol, *O*-2,4-dinitrophenyl oxime was treated with NaH in the presence of  $\text{NaBH}_3\text{CN}$  as a reducing agent of the intermediate dihydroquinolinol to give tetrahydro-8-quinolinol in high yield (Scheme 27).<sup>23,24</sup>





**Scheme 26.**

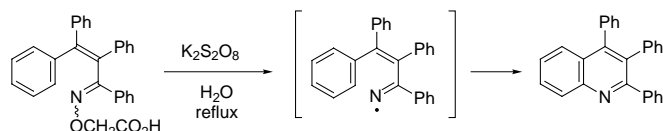


**Scheme 27.**

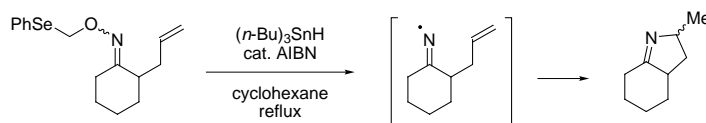
## 2.2 Synthesis of Cyclic Imines.

Forrester *et al.* have demonstrated that alkylideneaminyll radicals are produced by oxidation of *O*-hydroxycarbonylmethyl oximes, and have successfully synthesized quinolines (Scheme 28).<sup>25</sup> Moreover, Zard *et al.* have been investigating *N*-radical formation by reactions of oxime derivatives with stannane or nickel powder and their addition reactions to intramolecular alkenes. (Scheme 29).<sup>26</sup> However, both reactions have some problems in the generality and the operation procedure. In order to more effectively use alkylideneaminyll radicals as active species for organic synthesis, we initiated the development of methods to synthesize cyclic imines from  $\gamma,\delta$ -unsaturated *O*-2,4-dinitrophenyl oximes using a reductive radical generation method that we found in this study.

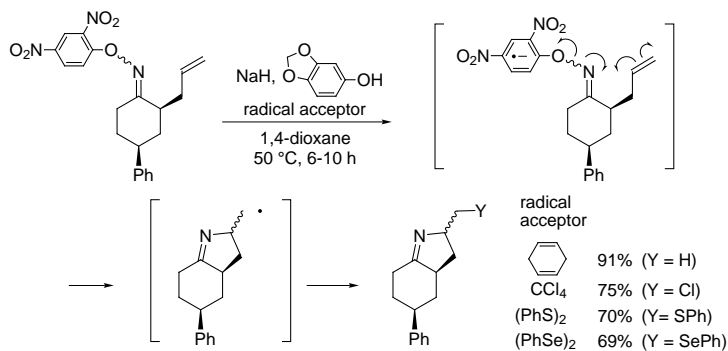
In the reductive aminyl radical generation we have developed, electron transfer to the *O*-2,4-dinitrophenyl groups from an electron donor part was essential. We speculated that one electron transfer to the *O*-2,4-dinitrophenyloximes could easily occur even intermolecularly, if we added excellent electron donors. We performed an experiment in which a  $\gamma,\delta$ -unsaturated *O*-2,4-dinitrophenyloxime was treated with a mixture of NaH and 3,4-methylene-dioxyphenol (Sesamol; as an electron donor) in the presence of 1,4-cyclohexadiene or diphenyl disulfide as a radical scavenger, and found that 3,4-dihydro-2*H*-pyrroles were obtained in a good yield (Scheme 30).<sup>27</sup>



**Scheme 28.**



**Scheme 29.**

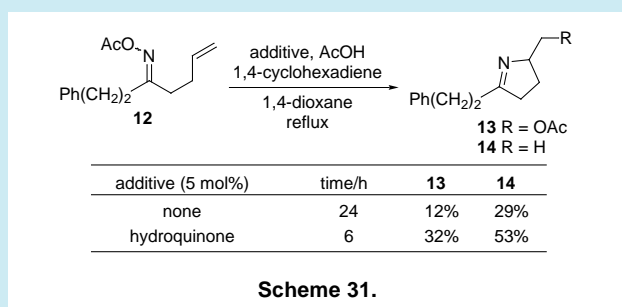


**Scheme 30.**

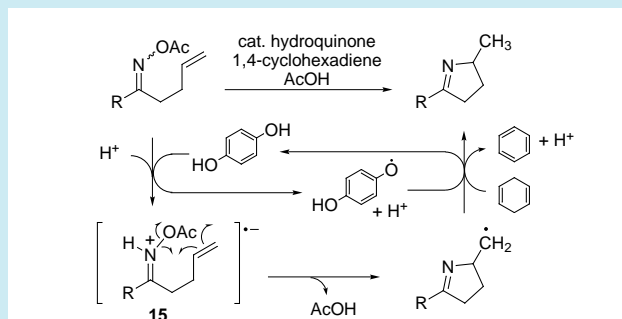
### 2.3 Catalytic Radical Cyclization Reaction of Oxime Derivatives.

Thus, we found oxime derivatives could be used as iminyl radical equivalents, when they were reduced by electron donors. Based on this observation, we investigated to develop a catalytic system for radical cyclization.

While we were further investigating synthesis of dihydropyrrole from  $\gamma,\delta$ -unsaturated ketone *O*-acyloxime by an  $S_N2$  type nucleophilic substitution (Scheme 17), we found that the reaction could be markedly modified based on the presence or absence of hydroquinone. That is, when oxime **12** was treated with acetic acid in the presence of 1,4-cyclohexadiene to yield an acetoxy substituted dihydropyrrole **13** as a product of the nucleophilic substitution reaction, and its hydrogenated compound **14** were produced in 12% and 29% yields, respectively (Scheme 31).<sup>28</sup> When a catalytic amount of hydroquinone was added to the above reaction, the reaction was accelerated to result in an increase in yields of both compounds to 32% and 53% for **13** and **14**, respectively. A similar result was obtained when 1,5-naphthalenediol was used instead of hydroquinone.



It was confirmed that hydrogenated compound **14** was produced by a radical mechanism from experiments using a deuterated solvent. The putative reaction mechanism is shown in Figure 6. One electron transfer occurs from hydroquinone to a protonated oxime, resulting in the formation of anion radical **15**. Following this, radical cyclization takes place. It is speculated that one electron transfer to oximes effectively happens because the *N*-protonation by acetic acid decrease the *O*-acyl oxime electron deficient.

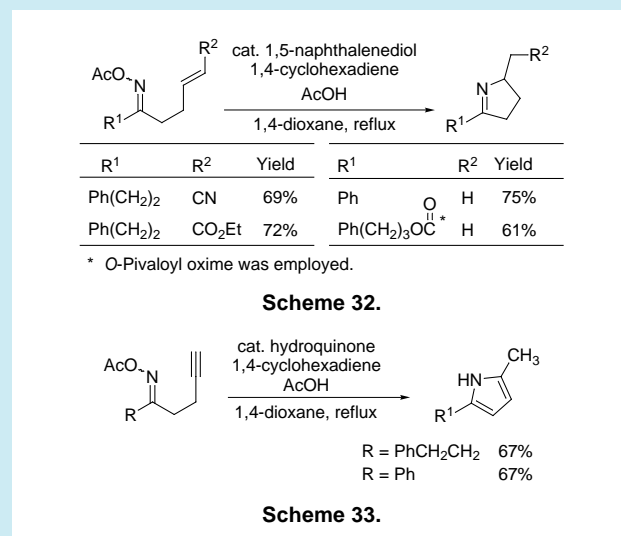


**Figure 6.** Radical cyclization of  $\gamma,\delta$ -unsaturated ketone *O*-acetyloxime by hydroquinone catalysis.

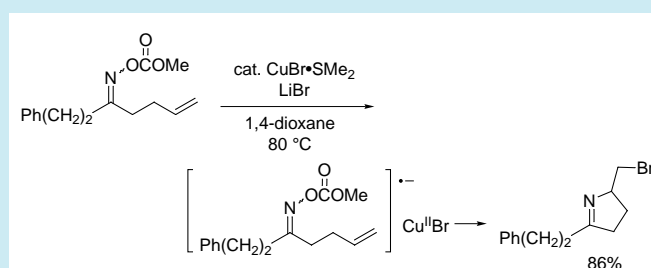
In this radical cyclization, nucleophilic substitution reaction products are also formed as by-products, when a

radical acceptor is an electron rich alkene, while only radical cyclic compounds are obtained from the oxime having an electron deficient alkene moiety, aryl ketone oxime, or  $\alpha$ -keto ester oxime (Scheme 32). This radical cyclization occurs using  $\beta$ -alkynyl ketone oximes, which gives the corresponding pyrroles (Scheme 33)

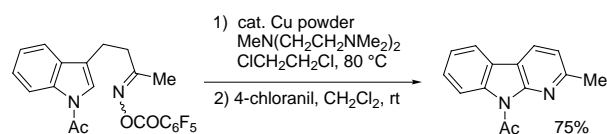
Radical cyclization of  $\gamma,\delta$ -unsaturated ketone *O*-acyloxime can be complementarily used in electrophilic cyclization under acidic conditions. That is, dihydropyrroles can be obtained as expected using either nucleophilic substitution (Scheme 17) for oximes with electron rich alkenes or radical cyclization for oximes with electron deficient alkenes.



We also examined the aminyl radical generation method using metal compounds as redox catalysts, and demonstrated that copper compounds could be good catalysts for the reaction.<sup>29</sup> Dihydropyrroles can be synthesized by treatment of  $\gamma,\delta$ -unsaturated ketone *O*-methoxycarbonyloximes or *O*-pentafluorobenzoyloximes with copper (I) complexes or copper powder (Scheme 34). Moreover,  $\alpha$ -carboline derivatives can be prepared when  $\beta$ -3-indolyl ketone *O*-pentafluorobenzoyloxime is reacted with copper powder (0) in 1,2-dichloroethane (Scheme 35). Since in general copper powder (0) very gradually reacts with dichloroethane, it is suggested that the actual catalyst in this reaction may be mono-valent copper ions.



**Scheme 34.**

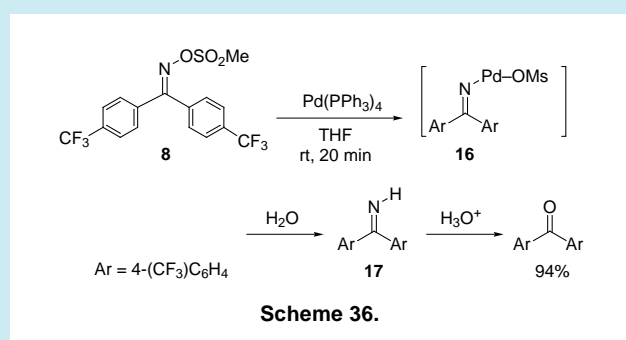


**Scheme 35.**

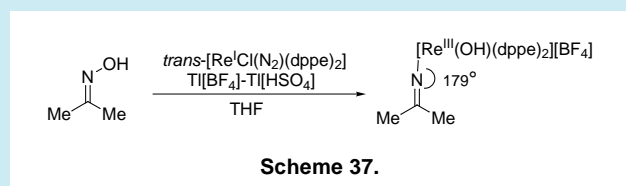
### 3. Oxidative Addition Reaction of Oximes to Palladium Catalysts

#### 3.1 Oxidative Addition Reaction of Oximes.

Since low valent transition metal complexes are good electron donors, it was expected that alkylideneamino metal complexes can be formed when *O*-substituted oximes are oxidatively added to low valent transition metal complexes. In fact, when benzophenone *O*-mesyloxime was reacted with an equimolar amount of Pd(PPh<sub>3</sub>)<sub>4</sub>, followed by addition of water to the reaction mixture, imine **17** was quantitatively obtained (Scheme 36). This result showed that an alkylideneaminopalladium complex **16** was formed as an intermediate.<sup>30</sup>



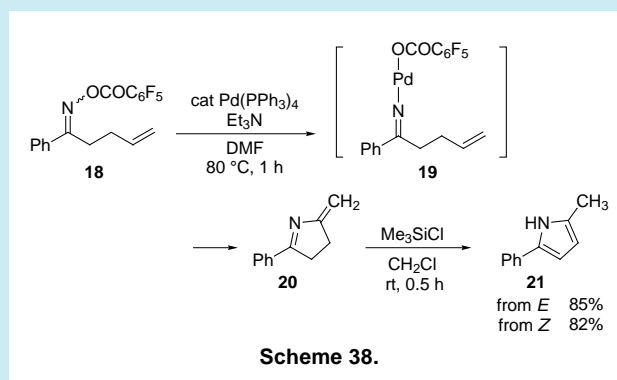
Although we have not yet achieved the isolation of **16**, Pombeiro *et al.*<sup>31</sup> and Tillact *et al.*<sup>32</sup> reported successful oxidative addition of oximes almost at the same time when we reported this study (Scheme 37), in which X-ray crystallography of the oxidative addition reaction products was performed. The angle produced by the oxime carbon, nitrogen, and oxidative metal ( $\angle CNM$ ) was shown to be close to 180 degrees and almost linear.



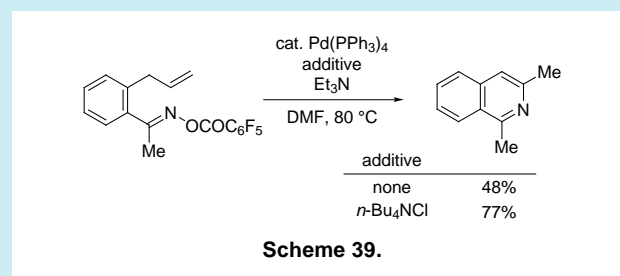
#### 3.2 Catalytic Amino-Heck Reactions.

Thus, we next attempted to run intramolecular Mizoroki-Heck type reaction (Amino-Heck reaction) using alkylideneamino metal species produced by oxidative addition reactions of oximes.<sup>33</sup> That is, (*E*)- $\gamma,\delta$ -unsaturated ketone *O*-pentafluorobenzoyloxime **18** was treated with a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> in the presence of triethylamine in DMF, resulting in cyclization of the oxime and the production of 2*H*-3,4-dihydropyrrole **20**. When 2*H*-3,4-dihydropyrroles **20** was further reacted with chlorotrimethylsilane, it facilitated isomerization, yielding 85% of pyrrole **21** (Scheme 38).<sup>30</sup> It was found that *Z*-isomer oximes exhibited a similar reactivity. It was considered that the palladium complexes generated from both of the *Z*-oximes and *E*-oximes could be easily

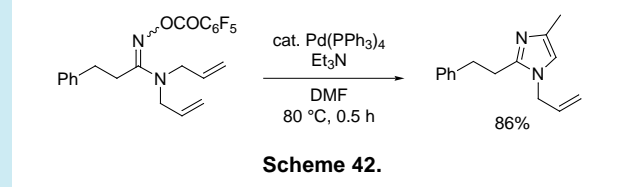
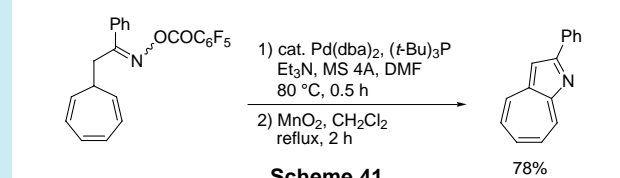
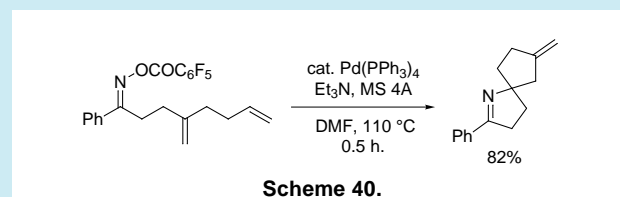
isomerized probably because the intermediate alkylideneamino metal complexes were almost linear as shown in Scheme 37. Furthermore, when *O*-sulfonyloxime was used, a Beckmann Rearrangement simultaneously took place as well as a similar cyclization occurred.



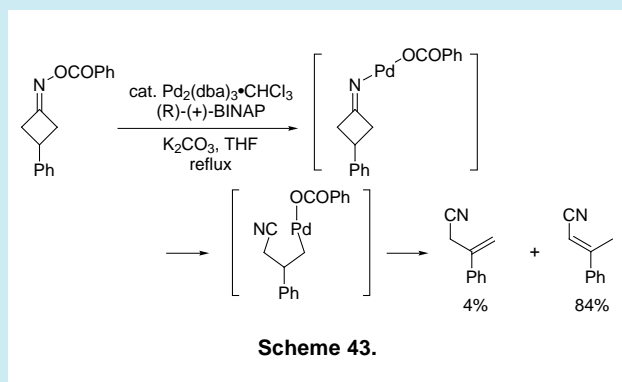
As a catalytic 6-*exo* cyclization proceeds, isoquinoline can be synthesized. In this case, the yield can be improved when tetrabutylammonium chloride is added to the reaction (Scheme 39).<sup>34</sup>



Cyclic amines such as aza-spiro compound **35**, azaazulene **36**, imidazoles and indoles, other than pyrroles and isoquinolines, were synthesized by an intramolecular amino-Heck reaction where various unsaturated *O*-pentafluorobenzoyloximes reacted with a Pd (0) catalyst.



Thus, many types of azaheterocycles can be synthesized from their corresponding ketoximes by amino-Heck reactions. However, aldoximes and ketoximes with alkoyl groups at the  $\alpha$ -position cannot be used for this reaction because they undergo the Beckmann cleavage. Furthermore, when an alkynyl ketone oxime was used, nitoriles were formed by a  $\beta$ -alkyl elimination (C-C bond cleavage) from an intermediate amino-palladium. As a related reaction, Uemura *et al.* reported a ring opening of cyclobutanone oximes using palladium catalyst (Scheme 43).<sup>37</sup>



## CONCLUSION:

Here, we briefly reviewed the novel methods that we recently developed for the synthesis of nitrogen-containing heterocyclic compounds and amination reactions using oximes. It is started from isolation of by-products with the catalytic Beckmann reaction, and we could expand development of amination using oximes. Since oximes are compounds that possess different element types such as oxygen, nitrogen and carbon linked to each other, we believe that oximes definitely possess many useful properties that we do not yet know how to fully exploit.

Concerning the  $S_N2$ -type substitution reactions at  $sp^2$  hybridized atoms, we discussed only the examples of substitution at oxime nitrogens. We are continuously studying further development on this topics. Now, it is successful to carry out the concerted substitution ( $S_NV\sigma$  and  $S_NV\pi$  mechanisms) even of simple vinyl halides. This method also would provide unique processes to synthesize various kinds of cyclic compounds.<sup>38</sup>

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