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

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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). Moreover, nucleophilic amination reactions such as combinations of nitrogen nucleophiles and carbon nucleophiles are also known, and both chloroamine and hydroxylamine derivatives have been used as nitrogen electrophiles. 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 nitriilium 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 sp² 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 S₂N₂ 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 S₂N₂ 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-Bu₄N]ReO₄) and p-toluensulfonic acid. As

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shown in Scheme 1, an allyl alcohol produces a perhenic 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 the formation of the rearrangement product (Scheme 1).§

We therefore considered it possible to catalytically induce a Beckmann Rearrangement when \( n\)-Bu4NReO4 and sulfonic acid were reacted with different oximes, resulting in the generation of various perhenic acid esters of oximes. Indeed, the Beckmann Rearrangement occurred, and amides were produced when oximes were reacted with \( n\)-Bu4NReO4 and trifluoromethanesulfonic acid (TfOH, CF3SO3H) in a highly polar solvent such as nitromethane (Scheme 2). Since syn- and anti-geometric isomers 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.5

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).§ 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.7

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.8
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 \( \text{Bu}_{4}\text{NReO}_4 \) 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 product dihydroquinoline. Furthermore, when an equimolar amount of \( \text{Bu}_{4}\text{NReO}_4 \) and TfOH, 20 mol% were rearranged. Therefore, these results suggested that for oximes with \( \text{meta} \)-substituted compounds were used, there were no quinolines produced at all, whose \( \text{ipso} \)-cyclic compounds were rearranged. Therefore, these results suggested that for oximes with \( \text{meta} \)-substitute groups, direct cyclization might occur at the \( \text{ortho} \)- or \( \text{para} \)-positions.

Based on the cyclization products of \( \text{meta} \) or \( \text{para} \)-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 \( \text{para} \)-positions (1,4), cyclization took place first at the \( \text{ipso} \) 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 \( \text{meta} \)-substituted compounds were used, there were no quinolines produced at all, whose \( \text{ipso} \)-cyclic compounds were rearranged. Therefore, these results suggested that for oximes with \( \text{meta} \)-substitute groups, direct cyclization might occur at the \( \text{ortho} \)- or \( \text{para} \)-positions.

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 \( \text{S}_2 \) 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 \( \text{S}_2 \) nucleophilic substitution reaction does not occur on \( \text{sp}^2 \) atoms”. In order to determine whether an \( \text{S}_2 \) 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 \( \text{S}_2 \) 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 $S_N 2$ 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 $S_N 2$ type substitution reaction may occur, with the phenyl groups acting as nucleophiles.

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$_3$SO$_2$H 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). 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 $sp^2$ carbanionic 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 $S_N 2$ 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 $S_N 2$ type nucleophilic substitution reaction could take place on the $sp^2$ nitrogen atoms of oximes, its applications were now exploited in various aspects.

![Scheme 11.](image)

![Scheme 12.](image)

![Figure 3. Transition state and activation energy for $S_N 2$ type reaction and Beckmann Rearrangement.](image)
1.2 Synthesis of Cyclic Imines Using Nucleophilic Substitution Reaction of Oximes.

When \( \text{(E)-O-methylsulfonyloximes} \) 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).\(^{12}\) 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.

![Scheme 13.](image)

Similarly, Scheme 14 shows synthesis of spiro[indolin-3,2-pyrrolidine] derivatives using the substitution reaction.\(^{13}\) 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.

![Scheme 14.](image)

1.3 Isomerization of \( O \)-Substituted Oximes and Intramolecular Nucleophilic Substitution Reactions on the Nitrogen Atoms.

As described in the previous section, only \( \text{anti-isomers} \) can be employed for the applications of \( S_N^2 \) type nucleophilic substitution of \( O \)-substituted oximes.\(^{8} \) Although oximes alone can be easily syner\text{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 \( S_N^2 \) type reaction with simultaneous isomerization as shown in the cyclization reactions using \( \text{n-Bu}_4\text{ReO}_4 \), we speculate that both stereo isomers could be used for cyclization (Figure 4).

![Figure 4.](image)

Therefore, we next investigated isomerization of \( O \)-substituted oximes (Table 1).\(^{12} \) It was noted that methyl phenethyl ketone oxime could be easily isomerized, when it was treated with trifluoromethanesulfonic acid (\( \text{CF}_3\text{SO}_2\text{H} \)). 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 \( O \)-methyl oxime was found to be isomerized by the treatment with \( \text{CF}_3\text{SO}_2\text{H} \) 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 \( O \)-acyloxyimine was very slowly but gradually isomerized when it was reacted with benzoic acid (run 4). On the other hand, \( O \)-acyloxyimines, which had active acyl moieties such as trifluoroacetyl group, could be isomerized at room temperature when treated with trifluoroacetic acid (\( \text{CF}_3\text{CO}_2\text{H} \)) (run 5).

![Table 1. Isomerization of oximes.](image)

\[
\begin{array}{c|c|c|c}
\text{run} & \text{OR} & \text{conditions} & \text{anti: syn} \\
\hline
1 & \text{OH} & \text{CF}_3\text{SO}_2\text{H} (2.0), \text{CH}_2\text{Cl}_2, \text{rt}, \text{<20 min} & 2 : 1^a \\
2 & \text{OMe} & \text{CF}_3\text{SO}_2\text{H} (2.0), \text{CH}_2\text{Cl}_2, \text{rt}, \text{12 h} & >98 : <1 \\
3 & \text{OMe} & \text{CF}_3\text{SO}_2\text{H} (2.0), \text{CD}_2\text{OD} (2.0), \text{CH}_2\text{Cl}_2, \text{rt}, \text{<20 min} & 2 : 1^b \\
4 & \text{OAc} & \text{PhCO}_2\text{H}, \text{toluene}, \text{80 °C}, \text{6 h} & 3 : 1^c \\
5 & \text{OCOCF}_3 & \text{CF}_3\text{CO}_2\text{H}, \text{CDCl}_3, \text{rt}, \text{28 h} & 3 : 1^c \\
\end{array}
\]

\( a \) 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 \textit{o}-methoxyphenethyl ketone oxime \textsuperscript{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 \textsuperscript{7} was used in the same reaction above, the cyclization occurred smoothly as expected. Thus, we have successfully achieved the cyclization of \textit{syn} and \textit{anti} phenethyl ketone oximes accompanied with their simultaneous isomerization. 

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

It is known that alkenes can act as nucleophiles. Therefore, \textit{\gamma,\delta}-unsaturated \textit{o}-methoxyacetyl oxime 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.

\textbf{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 \textit{N} atoms indicates that \textit{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 \textit{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). \textsuperscript{15} In this method, large excess amounts of Grignard reagents were required to make the reaction take place. Moreover, mono \textit{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 \textit{N}-alkylimines formed by monoalkylation are far more easily susceptible to addition reactions than \textit{O}-methylsulfonyl oxime. There was another report of a case in which \textit{O}-sulfonyloxime was alkynylated with an alkynylcopper reagent (Scheme 19). \textsuperscript{16,17} It was found that a substitution reaction occurred in this example, although the yield was poor. Thus, we first attempted to perform \textit{N}-alkylation of oxime derivatives using organocopper compounds.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme15.png}
\caption{Scheme 15.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme16.png}
\caption{Scheme 16.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme17.png}
\caption{Scheme 17.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme18.png}
\caption{Scheme 18.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme19.png}
\caption{Scheme 19.}
\end{figure}
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. 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).

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-methylsulfonyl oxime 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). 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 ureas and carbonates in detail, and demonstrated that oxime 10, a cyclic carbonate ester, could be an excellent amination reagent for Grignard reagents. 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-Quinolinol 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-quinolinol and its tetrahydro derivative were formed when m-hydroxyphenyl ketone O-2,4-dinitrophenyloxime was treated with sodium hydride (NaH). However, it was also found that no 6-quinolinol, 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).
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 phenethylketone \(O\)-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 phenethylketone (Scheme 25). It was postulated that both azines and phenethylketones could be generated via the intermediates such as alkylidene-aminyl 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.\(^{23}\) 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).\(^{23}\) To obtain tetrahydroquinolinol, \(O\)-2,4-dinitrophenyl oxime was treated with NaH in the presence of NaBH\(_3\)CN as a reducing agent of the intermediate dihydroquinoline to give tetrahydro-8-quinolinol in high yield (Scheme 27).\(^{23,24}\)
2.2 Synthesis of Cyclic Imines.

Forrester et al. have demonstrated that alkylidene-aminyl radicals are produced by oxidation of O-hydroxy-carbonylmethyl oximes, and have successfully synthesized quinolines (Schemes 28). 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). However, both reactions have some problems in the generality and the operation procedure. In order to more effectively use alkylideneaminyl radicals as active species for organic synthesis, we initiated the development of methods to synthesize cyclic imines from γ,δ-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 γ,δ-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-2H-pyrroles were obtained in a good yield (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 dihydropyrole from γ,δ-unsaturated ketone O-aclyloxime by an S₈₂ 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 oxime, or α-keto oxime, or α-keto ester oxime (Scheme 32). This radical cyclization occurs using β-alkynyl ketone oximes, which gives the corresponding pyrroles (Scheme 33)

Radical cyclization of γ,δ-unsaturated ketone O-aclyloxime can be complementarily used in electrophilic cyclization under acidic conditions. That is, dihydropyroles 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.

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.

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 cyclc compounds are obtained from the oxime having an electron deficient alkene moiety, aryl ketone oxime, or α-keto ester oxime (Scheme 32). This radical cyclization occurs using β-alkynyl ketone oximes, which gives the corresponding pyrroles (Scheme 33)

Radical cyclization of γ,δ-unsaturated ketone O-aclyloxime can be complementarily used in electrophilic cyclization under acidic conditions. That is, dihydropyroles 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.29 Dihydropyroles can be synthesized by treatment of γ,δ-unsaturated ketone O-methoxycarbonyloximes or O-pentafluorobenzoyloximes with copper (I) complexs or copper powder (Scheme 34). Moreover, α-carboline derivatives can be prepared when β-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.
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$_3$)$_4$, 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. $^{30}$

Although we have not yet achieved the isolation of 16, Pombeiro et al. $^{31}$ and Tillaart et al. $^{32}$ 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. $^{33}$ That is, (E)-γ,δ-unsaturated ketone $O$-pentafluorobenzoyloxime 18 was treated with a catalytic amount of Pd(PPh$_3$)$_4$ in the presence of triethylamine in DMF, resulting in cyclization of the oxime and the production of 2H-3,4-dihydropyrrole 20. When 2H-3,4-dihydroarylpurroles 20 was further reacted with chlorotrimethylsilane, it facilitated isomerization, yielding 85% of pyrrole 21 (Scheme 38). $^{30}$ 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-endo cyclization proceeds, isoquinoline can be synthesized. In this case, the yield can be improved when tetrabutylammonium chloride is added to the reaction (Scheme 39).$^{34}$

Cyclic amines such as aza-spiro compound 35, azaatulene 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.

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[Scheme 36]

[Scheme 37]

[Scheme 38]

[Scheme 39]

[Scheme 40]

[Scheme 41]

[Scheme 42]
Thus, many types of azaheterocycles can be synthesized from their corresponding ketoamines by amino-Heck reactions. However, aldoximes and ketoamines with alkyl groups at the α-position cannot be used for this reaction because they undergo the Beckmann cleavage. Furthermore, when an alkyl ketone oxime was used, nitriles were formed by a β-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).37

CONCLUSION:

Here, we briefly reviewed the novel methods that we recently developed for the synthesis of nitrogen-containing heterocyclic compounds and amiation reactions using oximes. It is started from isolation of by-products with the catalytic Beckmann reaction, and we could expand development of amiation 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_N_2-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_N_2) and S_N_V mechanisms even of simple vinyl halides. This method also would provide unique processes to synthesize various kinds of cyclic compounds.38

REFERENCES

4. Definition of syn and anti geometric isomers in this study: When a nucleophilic site and a leaving group on the nitrogen atom of oxime are oriented in the same direction and the opposing directions, the isomers are defined as syn and anti, respectively.
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Optically Active Ketoiminato Co(II) Complexes for Enantioselective Borohydride Reduction

The ketoiminato cobalt(II) complexes 1 and 2 developed by Mukaiyama, Yamada and co-workers are utilized for catalytic asymmetric reductions. The asymmetric reduction using 1 and 2 can use sodium borohydride, a widely used reducing agent. Therefore, this method is receiving much attention as it is likely to become a popular, convenient and economical method for obtaining optically active alcohols, amines, 1,3-diols, 3-hydroxycarbonyl compounds, β-substituted amides and so forth.

References
1) Applications of MPAC
2) Applications of AMAC

Reviews
Katsuki \textit{et al.} have reported that the chiral salen-Mn(III) complex \textbf{1} is useful as a catalyst for enantioselective epoxidation of conjugated \textit{cis}-olefins. \textbf{1} is oxidized with iodosobenzene as co-oxidant to generate oxo(salen)-Mn(V) complex \textbf{2}, which then reacts with conjugated \textit{cis}-olefins to yield chiral epoxides \textbf{3} with high enantioselectivity.

References

1) Highly enantioselective epoxidation


Compound \textbf{1} is a salen-Ru complex which was developed by Katsuki \textit{et al.} and is activated under visible light irradiation. When used as a catalyst, primary alcohols are selectively oxidized to aldehydes under aerobic conditions. \textsuperscript{1} When a 1,\textit{n}-diol, which has both primary and secondary hydroxyl groups, is oxidized in an atmosphere with 20\% molecular oxygen, the corresponding lactols can be obtained. \textsuperscript{1b} Compound \textbf{1} can even use molecular oxygen at room temperature and therefore is not only an excellent catalyst in terms of atomic efficiency, but is also environmentally friendly.

References

1) Chemoselective aerobic oxidation of primary alcohols


Minimal Artificial Acylase for the Kinetic Resolution of Racemic Alcohols

Recently, Ishihara and co-workers have studied minimal artificial enzymes to overcome various problems of enzymatic reactions. One of the research achievements, L-histidine-derived minimal artificial catalyst 1 was developed. Ishihara and co-workers reported 1 was a highly effective catalyst in the kinetic resolution of racemic alcohols with acylation. For example, the kinetic resolution of (±)-cis-1-(N-pyrrolidinocarbonyloxy)-2-cyclopentanol 2 was achieved by asymmetric acylation with isobutyric anhydride induced by 1 to obtain (1R,2S)-3 and (1S,2R)-2 in high optical purity \( S\left(\frac{k_{\text{fast}}}{k_{\text{slow}}}\right) = 93 \). Moreover, S value was increased to 132 if this reaction is done at -20 °C. Isobutyric anhydride is effective as the acylating agent.

Moreover, 1 can also be used as catalyst for the kinetic resolution of chain 1,2-diols, \( \beta \)-hydroxycarboxylic acids, and 2-amino alcohols after the suitable derivatization. In any case, acylation progresses by adding 0.5 equivalent molar of isobutyric anhydride to racemic alcohols, and achieves the conversion near 50%. Therefore, atom efficiency is extremely high.

The molecular weight of acylase is well over 10,000. On the other hand, the molecular weight of 1 is far small with 660, and 1 has only one chiral carbon atom of the histidine origin as chiral source. 1 has imidazole base of catalytic active center and sulfonamide proton which is required for the selective capture of substrates through the chiral carbon atom in the molecule. These are comprehensively at work, the kinetic resolution can be done effectively. Usually 1 is enough in the use of 5 mol% or less, in the kinetic resolution of 1 mmol of racemic alcohol, 1 have only to be used 0.05 mmol (33 mg) or less.

Reference
Highly Potent Chiral Derivatizing Reagents

A1657 (1R,2R)-2-(Anthracene-2,3-dicarboximido)cyclohexanecarboxylic Acid (1a) 100mg
A1658 (1S,2S)-2-(Anthracene-2,3-dicarboximido)cyclohexanecarboxylic Acid (1b) 100mg
N0713 (1R,2R)-2-(Naphthalene-2,3-dicarboximido)cyclohexanecarboxylic Acid (2a) 100mg
N0714 (1S,2S)-2-(Naphthalene-2,3-dicarboximido)cyclohexanecarboxylic Acid (2b) 100mg

In the recent development in pharmaceuticals, agrochemicals and functional materials including liquid crystals, the importance of chiral compounds is increasingly emphasized, and discrimination of enantiomers is considered to be a more and more important subjects. One of the most common enantiomeric discrimination methods utilizes diastereomer which are obtained from the reaction of the enantiomers and chiral derivatizing reagents, and many excellent chiral derivatizing reagents have been developed. This method utilizing chiral derivatizing reagents, however, has a problem in that it is very difficult to discriminate derivatized diastereomers having chiral centers more than four carbon atoms away from derivatization site.

Fig. Configuration model, 1 ester of 10-methyldodecanol. 1a: (1R,2R)-2ACyclo-COO-, 1b: (1S,2S)-2ACyclo-COO-.
Recently, Ohrui and co-workers have developed highly sensitive chiral derivatizing reagents 1 and 2 that overcome this problem, and have reported on their efficiency. For instance, 1 reacts with a long-chain alcohol to form esters 3 and 4, where the aromatic ring of the chiral derivatizing reagent and the methylene chain of the alcohol are in a gauche configuration. Thus, these esters exhibit only one helical structure (clockwise or counterclockwise) based on the absolute configuration of the chiral derivatizing reagents. In cases where a long chain alcohol have a chirality, the esters 3 and 4 has both an asymmetric helical configuration and a chiral center. Moreover, if this alcohol is racemic form, it forms diastereoisomers. These diastereomers can be discriminated by HPLC and NMR.

1 and 2 can be easily discriminated when their chiral centers are far away from the hydroxyl group of an alcohol. However, in HPLC analysis, 1 is effective for the discrimination of an chiral center more than 11 carbon atoms away from the hydroxyl group, while 2 is effective for discrimination of an chiral center less than 10 carbon atoms away from the hydroxyl group. In particular, since 1 possesses potent fluorescence derived from its anthracene moiety, determination can be done at a femto molar (10^{-15} M) level. Moreover, these reagents can discriminate the chirality of a secondary hydroxyl group, thus, it is also possible to separate steroisomers of branched secondary alcohols by HPLC.

Mori and co-workers have determined the optical purity of synthetic intermediate (6S,19S)-6-hydroxy-19-methylnonaicosadecane in the synthesis of a sex pheromone extracted from female Spiral Uji fly (Screwworm fly) using reagent 1. The reagents 1 and 2 developed by Ohrui and co-wokers can be discriminated of chiral centers far away from hydroxyl groups, which used to be impossible by the diastereomer methods. Thus, these reagents are highly expected to be useful for many applications in practical use including determination of the absolute configuration and optical purity of natural products.

References
1) Highly potent chiral derivatizing reagents

2) The synthesis of N-containing fused ring compounds
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