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SYNTHESIS OF HETEROCYCLES UTILIZING *N*-ALKOXYIMINES AND AMIDES

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Abstract – *N*-Alkoxyimines and amides are unique functional groups bearing adjacent N-O bonds. Alkynes having an *N*-alkoxyimine or amide group generate reactive vinylmetal species through activation by a transition metal catalyst to synthesize heterocycles. This approach, which allows various sequential reactions, can be expected to directly form a complex heterocycle from a simple starting material under mild conditions. Meanwhile, these kinds of reactions require chemoselectivity between the N- and O-atoms at the nucleophilic site and/or regioselectivity at the electrophilic alkyne moiety. This review introduces intramolecular nucleophilic addition of *N*-alkoxyimines/amides into an alkyne moiety, followed by various transformations to synthesize heterocycles.

CONTENTS

1. INTRODUCTION

Heterocycles play an important role in maintaining life activity, such as biosynthesis and metabolic processes in living things,[1] being included in various useful compounds such as pharmaceuticals,[2] pesticides,[3] dyes,[4] and functional materials.[5] Moreover, heterocycles are also useful building blocks for both cyclic and acyclic compounds. Therefore, the development of a new synthetic methodology for heterocycles is an important issue in organic synthetic chemistry. Various methods for the construction of heterocycles, which depends on the constituent elements and the size of the ring, have been developed.[1,6,7] In particular, an approach that takes advantage of heteronucleophilic addition to alkynes activated by transition metals has developed in recent years.[8] Since this method can produce a highly reactive intermediate containing a carbon-metal bond, sequential reactions such as rearrangement, insertion, elimination, cycloaddition, electrocyclization, and halogenation, allow the direct formation of a complex heterocycle from a simple starting material under mild conditions.

In general, functional groups with consecutive heteroatoms, like alkoxyamines, present unique properties such as the stabilization effect of radicals,[9] and labile nitrogen-oxygen bonds.[10] Recently, the chemistry of C-H activation using *N*-alkoxy groups as a directing group has been developed.[11] In addition, since alkoxyamines have higher nucleophilicity than simple amines due to the well-known α-effect,[12] various domino reactions initiated by nucleophilic addition into an alkyne moiety for synthesis of heterocycles have also been accomplished. In general, these kinds of reactions require chemoselectivity between the nitrogen and oxygen atoms at the nucleophilic site and/or regioselectivity at the electrophilic alkyne moiety (Figure 1). In this review, the intramolecular nucleophilic addition of *N*-alkoxyimines (i.e., oxime ethers) /*N*-alkoxyamides into an alkyne moiety followed by various transformations are described.

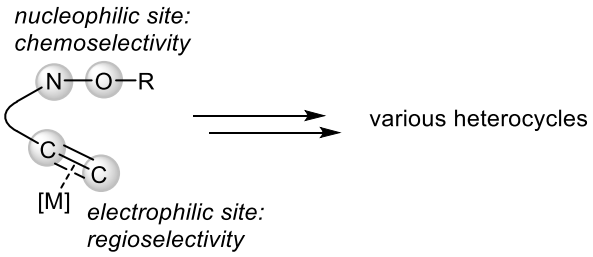


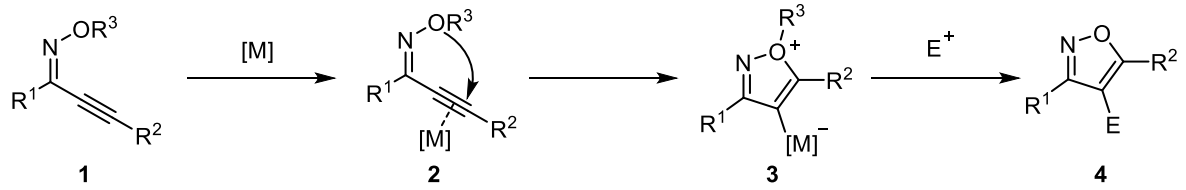
Figure 1. Intramolecular nucleophilic addition of *N*-alkoxy functional group

2. NUCLEOPHILIC ADDITION OF ALKOXY GROUP ON *N*-ALKOXYIMINES

2-1. Capture of Electrophile

As the simplest transformation, nucleophilic addition to an alkyne moiety followed by reaction with an electrophile has been developed for synthesis of isoxazoles. The *N*-alkoxyimine **1** is cyclized by activation with a transition metal catalyst in a 5-*endo*-*dig* fashion to produce a vinyl metal intermediate **3**,

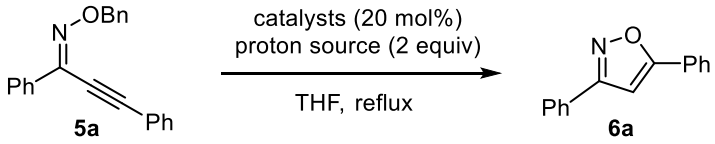
which traps an electrophile, and the substituent R^3 on an oxygen atom is eliminated simultaneously (Scheme 1).



Scheme 1. Cyclization followed by capture of electrophile

Our group reported the π-acidic transition metal-catalyzed cyclization of alkynyl *N*-benzyloxyimine **5a** followed by protonation and removal of the benzyl group to afford 3,5-disubstituted isoxazoles **6a**.[13] $AuCl_3$, $AuCl(PPh_3)$, $AgBF_4$, $AgSbF_6$ and $Cu(OTf)_2$ were tested in optimization studies, and $AgBF_4$ was found to accelerate the reaction (Table 1, entries 1-5). In addition, a weakly acidic proton source, such as PhOH, was also effective (entries 3, 6 and 7). Control experiments suggest that both the silver catalyst and the proton source are essential for this reaction (entries 8 and 9).

Table 1. Optimization of metal-catalyzed cyclization-protonation

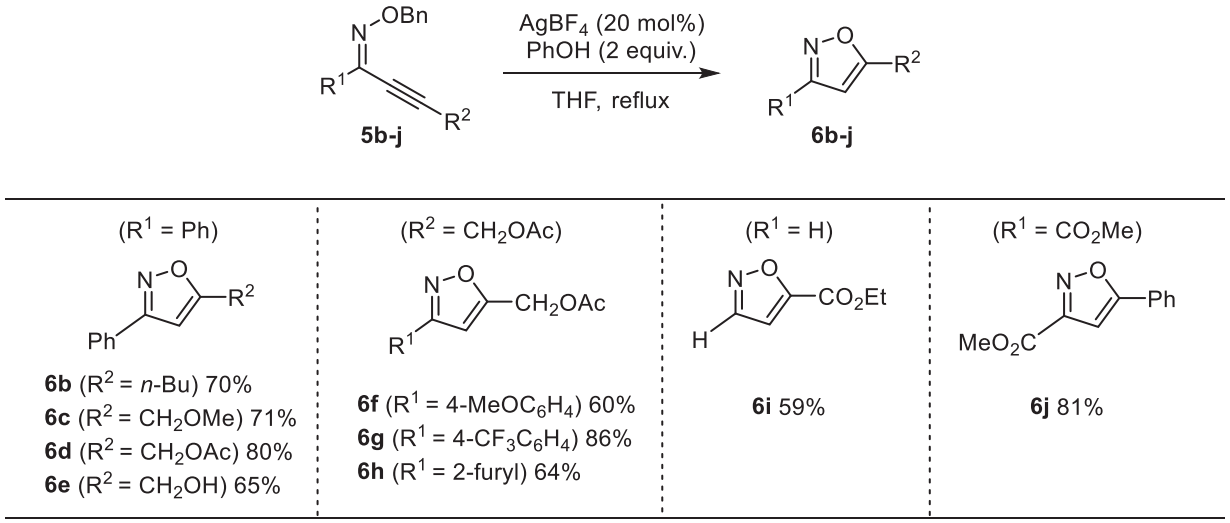


Entry	Catalyst	Proton source	Time (h)	Yield (%)
1	$AuCl_3$	PhOH	24	23
2	$AuCl(PPh_3)$	PhOH	24	9
3	$AgBF_4$	PhOH	6	80
4	$AgSbF_6$	PhOH	24	32
5	$Cu(OTf)_2$	PhOH	24	59
6	$AgBF_4$	MeOH	6	48 (50)
7	$AgBF_4$	AcOH	2	71
8	$AgBF_4$	none	6	NR
9	none	PhOH	6	NR

[a]Yield in parentheses is for the recovered starting material **5a**.

In this protocol, various substrates **5b–5j** could be transformed to disubstituted isoxazoles **6b–6j** in moderate to good yields (Scheme 2). The cyclization reaction of **5b**, which has an alkyl group on the triple bond terminus, proceeded to afford **6b** in good yield. **5c–5e**, which have an oxygen-containing functional group at the propargylic position, efficiently underwent cyclization to yield **6c–6e**, in which

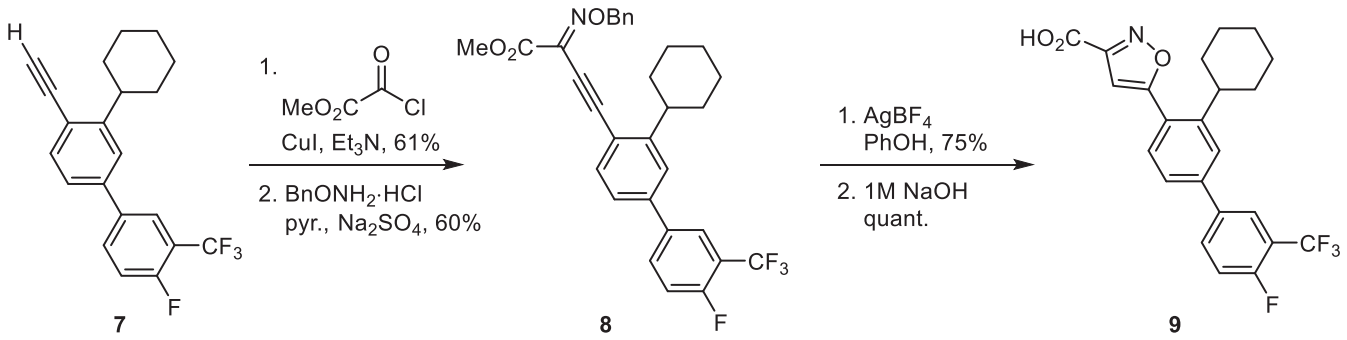
chelation of the oxygen atom may enhance the reactivity of catalyst. The unprotected hydroxy group did not prevent the course of the reaction (**6e**). Both the electron-rich and electron-poor aryl groups, and a hydrogen atom were readily accommodated, producing the disubstituted isoxazoles **6f–h** and the monosubstituted isoxazole **6i** in good yields, respectively.



Scheme 2. Ag(I)-Catalyzed cyclization-protonation

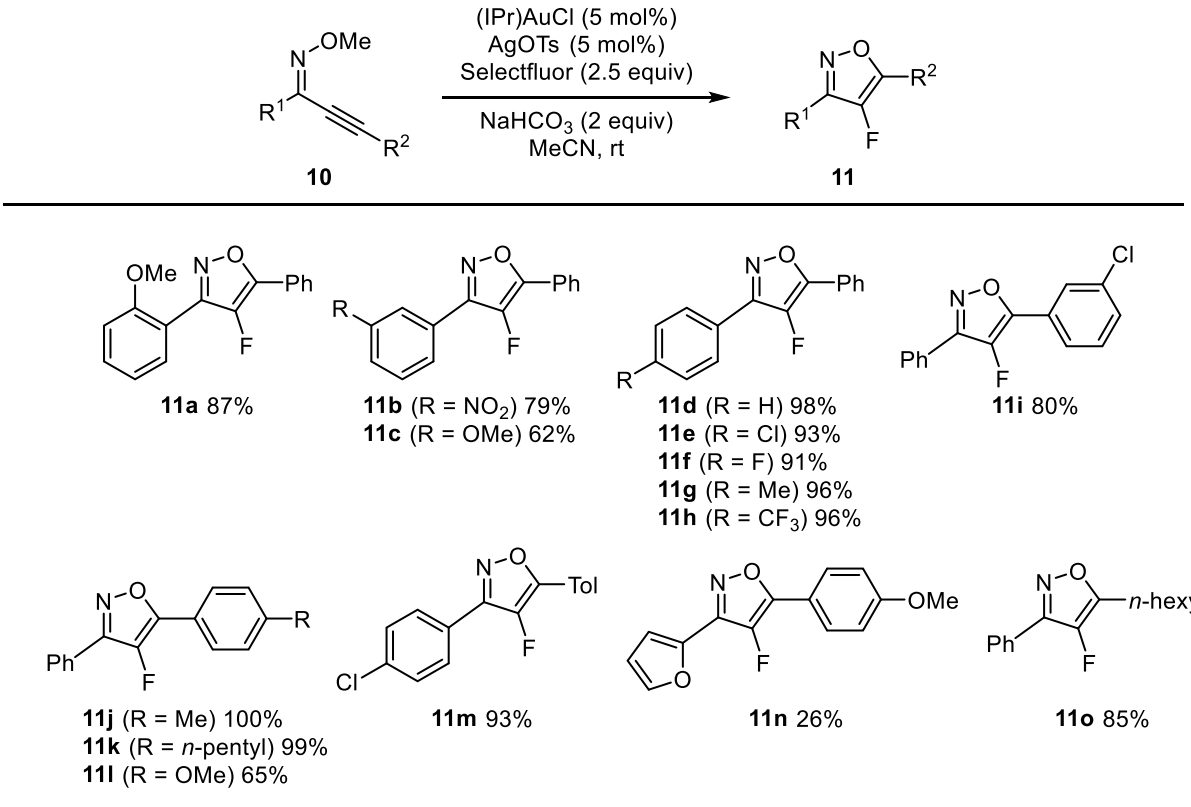
A notably high chemical yield was observed in the reaction of **5g**, which has a *p*-trifluoromethylphenyl group at R^1. An imino ester, **5j**, was also employed in this reaction, affording the isoxazole carboxylate **6j** in high yield.

This cyclization-protonation reaction was applied to the synthesis of the biologically active isoxazolecarboxylic acid **9**, which is known as a potent *Mycobacterium tuberculosis* phosphatase PtpB inhibitor (Scheme 3).[14] The cyclization of alkynyl benzyloxyimine **8**, which was readily prepared from alkyne **7**, afforded the desired isoxazolecarboxylate in 75% yield. Synthesis of the phosphatase PtpB inhibitor **9** was accomplished by hydrolysis of the ester with 1 M NaOH.



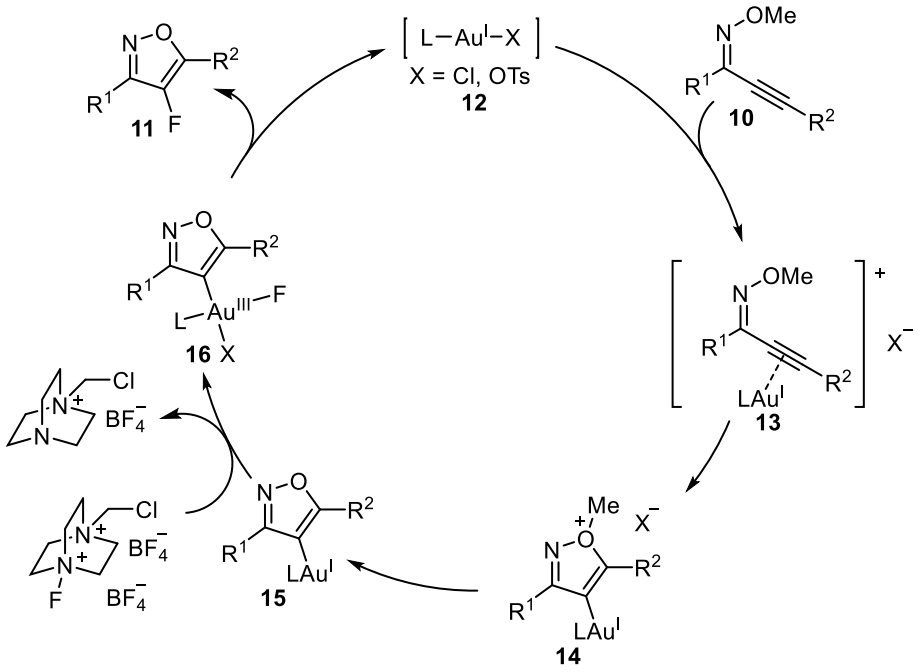
Scheme 3. Synthesis of phosphatase PtpB inhibitor

In 2014, Ryu reported Au(I)-catalyzed cascade cyclization-fluorination of (*Z*)-*N*-methoxyimine **10** to 4-fluoro-3,5-disubstituted isoxazoles **11** (Scheme 4).[15] In optimization studies, various ligands for the Au catalyst were investigated, and the IPr ligand was elected as the most effective ligand.[16] In control experiments, (*E*)-*N*-methoxyimine did not undergo the cascade reaction. Many *N*-methoxyimines displayed a broad substrate scope and functional group compatibility. Substrates **10a-10h,** bearing both electron-rich and poor R^1 groups, underwent the tandem reaction very well and provided the corresponding 4-fluoroisoxazoles. Similarly, both the electron-rich and poor substrates on the R^2 group **10i-10l** produced the corresponding isoxazoles **11i-11l** in good yields. Although both modifications to the R^1 and R^2 groups at the 1 and 3 positions did not influence the reactivity (**11m**), furan-substituted alkoxyimine **10n** was rather unstable under the reaction conditions, and afforded **11n** in lower yield. The domino reaction could also be applied to the synthesis of the aliphatic fluoroisoxazole **11o**.



Scheme 4. Au(I)-Catalyzed cascade cyclization-fluorination

A plausible mechanistic pathway was proposed for the Au(I)-catalyzed cyclization-fluorination of (*Z*)-*N*-methoxyimine **10** (Scheme 5). The initial coordination of the Au(I) catalyst **12** to the alkyne of *N*-methoxyimine **10** and subsequent cyclization lead to the Au(I) complex **14**. Then, demethylation and oxidation by Selectfluor gives the cationic Au(III) intermediate **16** having both isoxazole and fluoride; **16**

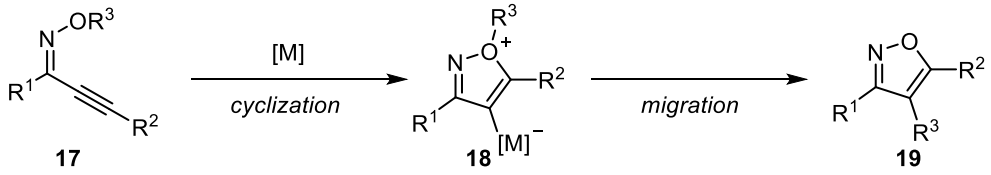


Scheme 5. Proposed mechanism of cascade cyclization-fluorination

readily decomposes to yield the cross-coupled fluoroisoxazole **11** and the cationic Au(I) catalyst **12** after reductive elimination. However, there may be also a possibility of Au(III)-mediated cyclization.

2-2. Cyclization/Rearrangement

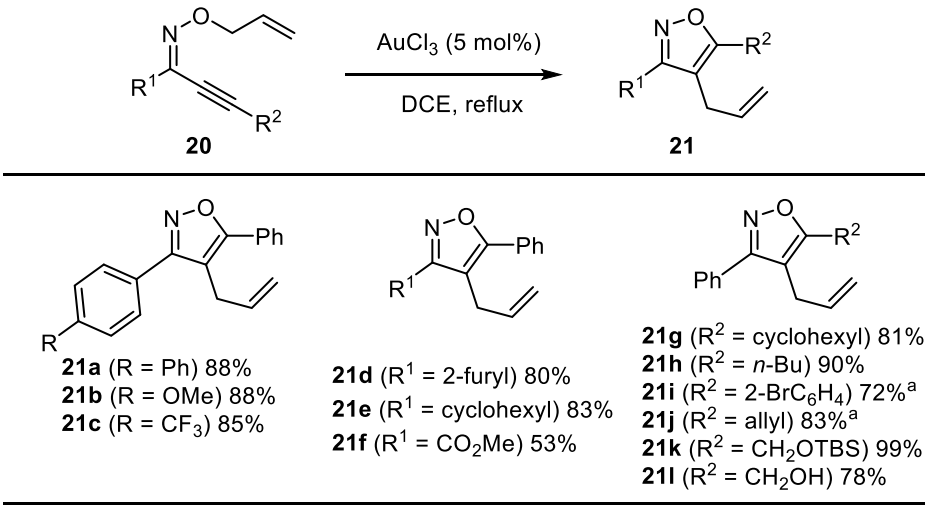
π-Acidic transition metal-catalyzed intramolecular addition of a heteroatom to an alkyne and subsequent migration of the substituent has been developed for heterocycle synthesis. Although these transformations have provided useful access to benzofurans, indoles, benzothiophenes, furans, pyrans, and pyrrolidine, less is known about the synthesis of isoxazoles. In recent years, our group reported transition metal-catalyzed cyclization of alkynyl *N*-alkoxyimines to produce the vinylmetal intermediate **18**, followed by rearrangement of the substituent R^3 into the C4 position to afford the trisubstituted isoxazole **19** (Scheme 6).[17]



Scheme 6. Transition metal-catalyzed cyclization-rearrangement of alkynyl *N*-alkoxyimines

The alkynyl *N*-allyloxyimines **20**, which are easily prepared by the condensation of ketones with an alkoxyamine, are easily transformed into 3,4,5-trisubstituted isoxazoles via cyclization and Claisen-type [3,3]-sigmatropic rearrangement by Au-catalyzed activation of the alkyne moiety in good to high yields. In optimization studies, $AgBF_4$, $AuCl(PPh_3)$, $PdCl_2(PPh_3)_2$, and $AuCl_3$ were examined, and $AuCl_3$ gave the desired isoxazole the most efficiently.

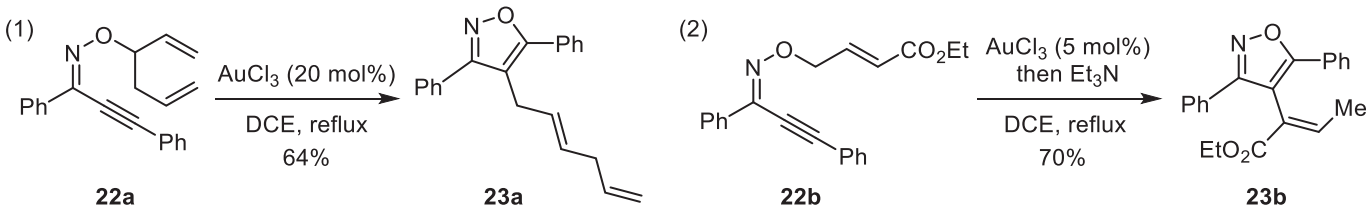
In substrate scope studies, electron-rich or electron-poor aryl groups and alkyl groups for R^1 were readily accommodated, producing the expected trisubstituted isoxazoles **21a**-**21e** (Scheme 7). The imino ester **20f** was also employed in this reaction although the yield slightly decreased. Variation of the substituent on the triple bond terminus was also tolerable (**21g**-**21l**). The unprotected hydroxy group did not affect the course of the reaction (**21l**).



[a]Reactions were carried out with $AuCl_3$ (20 mol%).

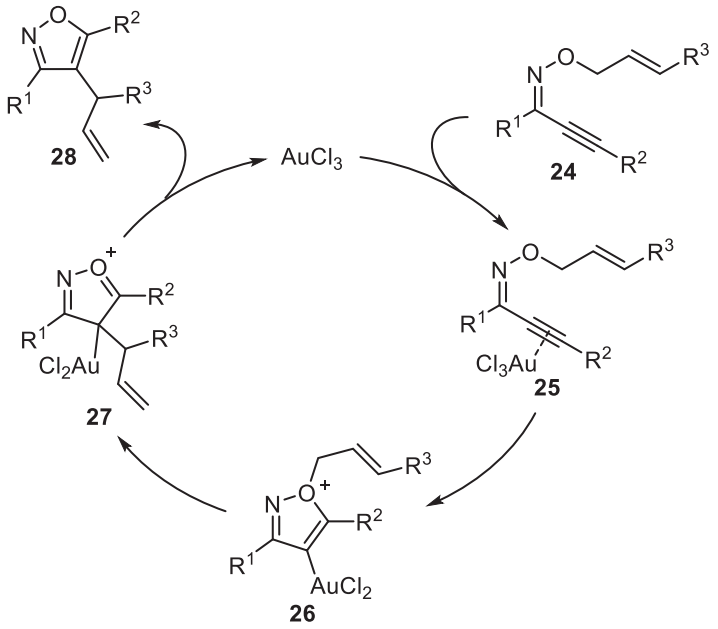
Scheme 7. Optimization of transition metal-catalyzed cyclization-rearrangement

The cyclization/rearrangement reaction could be applied to substrates bearing a substituted allyl group. Branched allyloxyimine **22a** furnished the skipped diene (*E*)-**23a** (Scheme 8, eq. 1). Additionally, the reaction of crotonate **22b** with 5 mol% of $AuCl_3$ followed by stereoselective isomerization by Et_3N afforded the functionalized isoxazole **23b** in 70% yield. These results suggest that a new carbon−carbon bond was generated predominantly at the γ-position in an S_N2' fashion, which indicated that the migration of the allyl moiety would not proceed through a shift of the allyl cation intermediate,[18] but rather through a Claisen-type [3,3]-sigmatropic rearrangement.



Scheme 8. Substitution effect on the allyl group

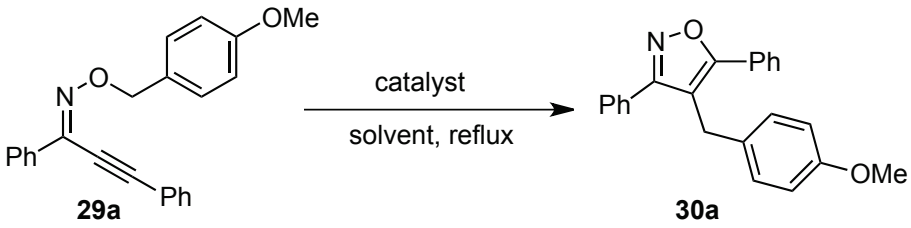
A proposed reaction pathway is shown in Scheme 9. The reaction commences with the addition of an O-atom to a Au(III)-activated C−C triple bond in a 5-*endo-dig* manner, generating an oxonium intermediate **26**, which undergoes Claisen-type rearrangement to form intermediate **27**. Subsequently, aromatization of **27** affords isoxazole **28** and liberates the gold catalyst.



Scheme 9. Possible reaction pathway

In 2012, our group reported that the process of cyclization/rearrangement could be also applicable to benzyloxyimine, in which not Claisen-type rearrangement but 1,3-migration of carbocation proceeded.[19] A series of alkynophilic catalysts were screened for their ability to catalyze the synthesis of the trisubstituted isoxazole **30a** from *N*-*p*-methoxybenzyloxyimine **29a** using dichloroethane (DCE) as a solvent at reflux (Table 2). As shown by the results, $Cu(OTf)_2$ overcame the other catalysts on the yield (entries 1-4). This reaction was found to be strongly temperature and/or solvent-dependent (entries 4-8).

Table 2. Optimization of cyclization-1,3-migration



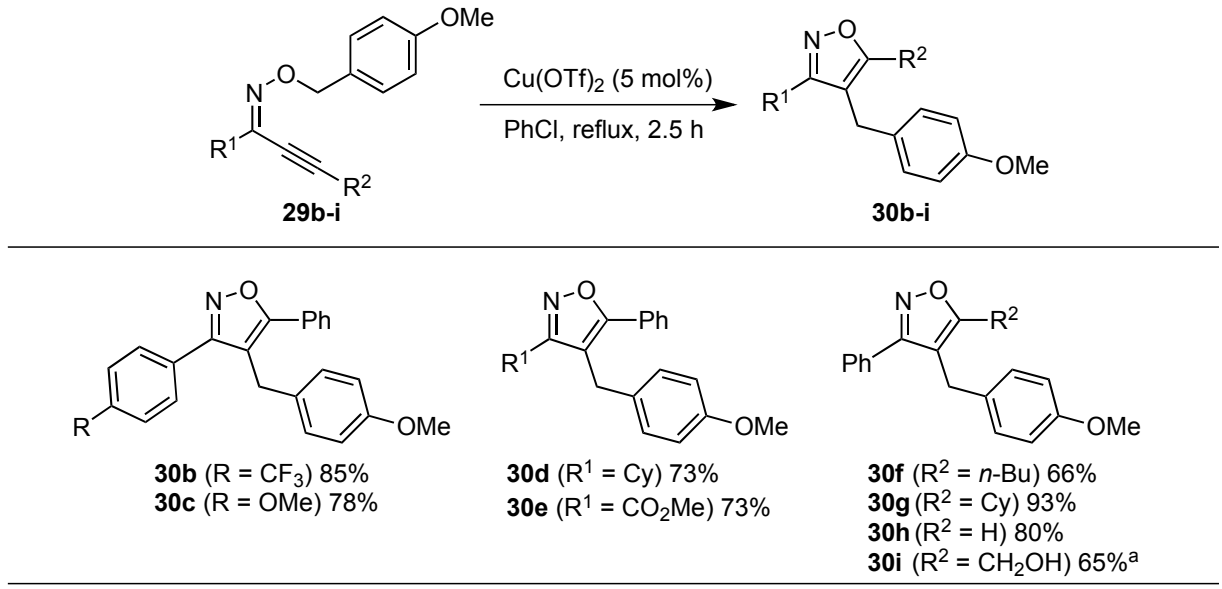
29a **30a**

Entry	Catalyst (mol%)	Solvent	Bp (°C)	Time	Yield
1	$AuCl_3$ (5)	DCE	83	10	29
2	$AgBF_4$ (5)	DCE	83	6	43
3	$CuCl_2$ (5)	DCE	83	10	NR
4	$Cu(OTf)_2$ (5)	DCE	83	2	57
5	$Cu(OTf)_2$ (5)	THF	65	2	NR
6	$Cu(OTf)_2$ (5)	toluene	110	2	47
7	$Cu(OTf)_2$ (5)	PhCl	132	2	70
8[a]	$Cu(OTf)_2$ (5)	*n*-BuOH	116	2	27

[a]*n*-Butyl *p*-methoxybenzyl ether was obtained in 11% yield.

n-Butyl *p*-methoxybenzyl ether was obtained as a byproduct when the reaction was carried out in the presence of *n*-BuOH (entry 8). This result suggests that the reaction proceeded via generation of the *p*-methoxybenzyl cation.

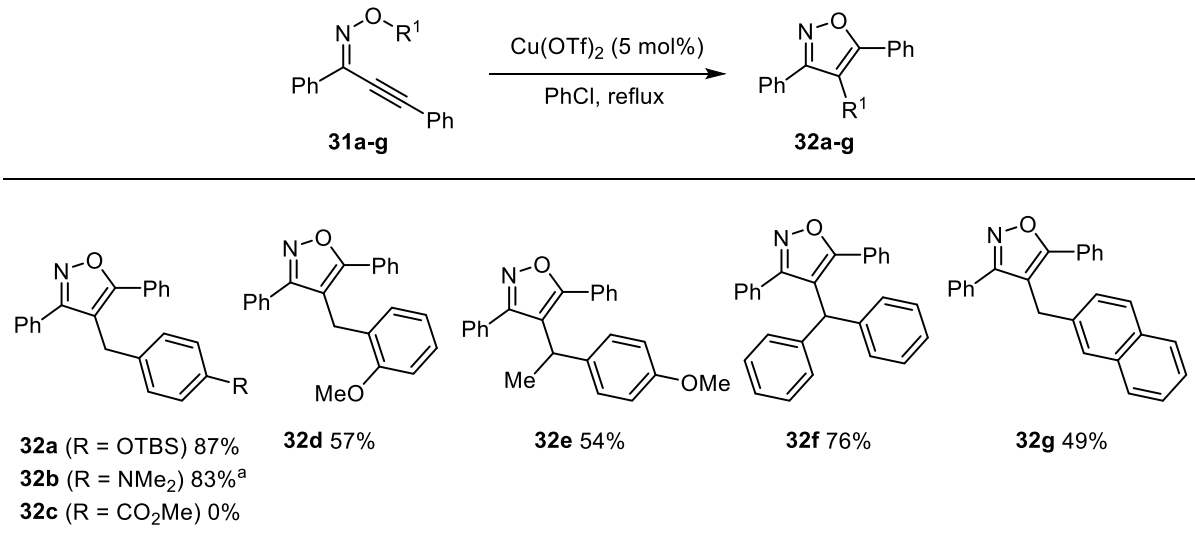
The substrate scope showed that a variety of different *N*-*p*-methoxybenzyloxy alkynylimines **29b–i** are applicable (Scheme 10). Electron-rich and electron-poor aryl groups and an alkyl group were well tolerated on the R^1 substituent, affording the corresponding trisubstituted isoxazoles **30b–d** in good yields. Moreover, the ester moiety on alkoxyimine **29e** was compatible with the reaction conditions, providing isoxazole carboxylate **30e** in good yield and demonstrating the mild nature of the transformation. The R^2 substituent on the alkyne terminus could also be varied without any problem under the optimized reaction conditions. Substrates **29f** and **29g** bearing aliphatic substituents performed well under the current reaction conditions, providing the desired trisubstituted isoxazoles in high yields. The acidic proton of the terminal alkyne **29h** did not have an adverse impact on the transformation, and the desired product was obtained in high yield. When the silyl-protected substrate **29i** was subjected to optimized conditions, partial desilylation was observed. Consequently, upon completion of the copper-catalyzed cyclization, the crude product was treated with tetra-*n*-butylammonium fluoride (TBAF) to afford 4-(hydroxymethyl)isoxazole **30i** in 65% yield.



[a]Silylated substrate (R^2= TBS) **29i** was employed in cyclization/1,3-migration and the crude product was treated with TBAF.

Scheme 10. Substrate scope of Cu(II)-catalyzed cyclization-1,3-migration

The substituent effect on the migrating group was investigated (Scheme 11). The *p*-silyloxybenzyl group in alkoxyimine **31a** successfully migrated to afford the corresponding trisubstituted isoxazole **32a** in high yield. The introduction of a dimethylamino group enhanced the efficiency of the domino reaction, which proceeded even at a lower temperature in refluxing DCE (**32b**). The substrate **31d** having an *o*-methoxy group at the *ortho*-position gave **32d** in relatively lower yield, probably because of steric repulsion. The introduction of an electron-withdrawing group, such as an ester moiety, completely prevented the

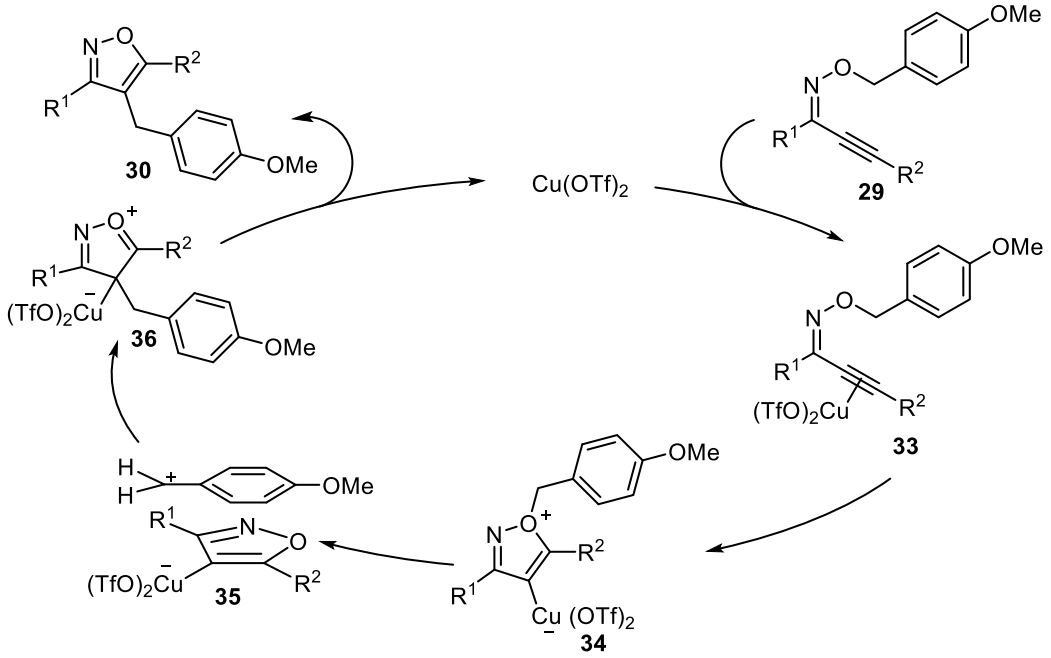


[a]DCE was employed instead of PhCl at 83 °C.

Scheme 11. Substitution effect of the migrating group

cyclization reaction and only alkoxyimine **31c** was recovered. This result indicates that the rate-determining step involved the generation of a benzyl cation by C–O bond cleavage. The substituted benzyl groups and 2-naphthylmethyl group in substrates **31e-g** were well tolerated under the current conditions to afford **32e-g** in moderate to good yields.

A possible reaction pathway is described in Scheme 12 according to crossover experiments which suggested intramolecular migration to be most likely. Initially, the O-atom of *N*-benzyloxyimine adds to the Cu(II)-activated C–C triple bond in a 5-*endo*-*dig* fashion to form an oxonium intermediate **34**. The irreversible generation and 1,3-migration of the benzyl cation via the formation of ion-pair **35** leads to the formation of intermediate **36**.[20] The interaction of the benzyl cation and the π-electron of the isoxazole core leads to intramolecular 1,3-migration. In the final step, aromatization of **36** affords the trisubstituted isoxazole **30** and liberates the copper catalyst.



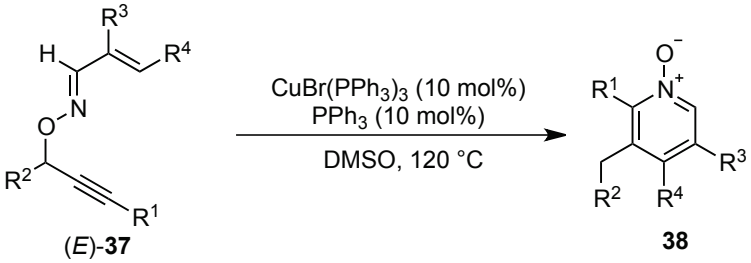
Scheme 12. Possible reaction pathway

3. NUCLEOPHILIC ADDITION OF N-ATOM ON *N*-ALKOXYIMINES

3-1. Cyclization/Rearrangement

During the past decade, a large number of nucleophilic additions of the N-atom on *N*-alkoxyimines followed by rearrangement reactions for synthesis of heterocycles have been reported. In 2010, Nakamura and Terada provided a breakthrough in nucleophilic addition to alkyne moiety-initiated tandem reactions, where Cu-catalyzed domino [2,3]-rearrangement and 6π-3-azatriene electrocyclization of

(*E*)-*O*-propargylic α,β-unsaturated oximes **37** proceeded to afford polysubstituted pyridine *N*-oxide **38** in moderate to high yields (Scheme 13).[21,22] According to the optimization studies, CuBr and PPh_3 were found essential for this transformation in heating condition. Alkyl and aryl substituents of α,β-unsaturated moiety (R^3 and R^4) could be tolerated in this tandem reaction (**38a**-**38f**). Electron-rich aryl or alkyl substituent provided high yield, while electron-deficient aryl substituent decreased. *N*-Propargyloxyimine **37m** bearing a *tert*-butyl substituent on alkyne terminus did not give any pyridine *N*-oxide. An electron density of substituents on propargylic position was important; *p*-anisyl group accelerated the reaction (**38n**), while *p*-trifluoromethylphenyl group did not give any product (**38o**). Also, primary and secondary alkyl group could be tolerated (**38p**, **38q**).



(*E*)-**37** → **38**

38a (R^4 = Ph) 75%
38b (R^4 = H) 84%
38c (R^4 = Me) 64%
38d (R^4 = *n*-Pr) 50%

38e 71%

38f 53%

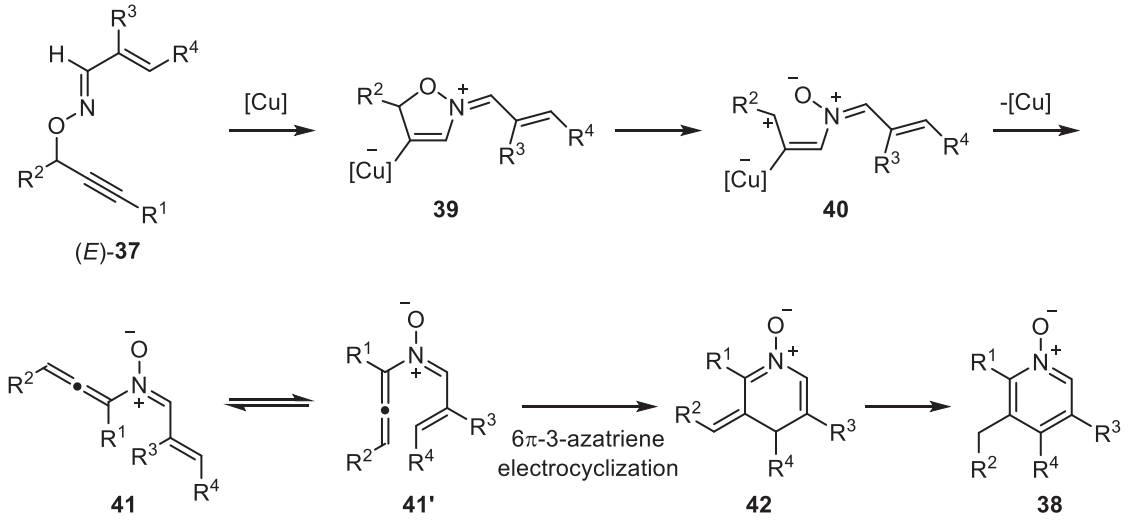
38g (R^1 = *p*-anisyl) 75%
38h (R^1 = *p*-$F_3CC_6H_4$) 52%
38i (R^1 = H) 80%
38j (R^1 = *n*-Pr) 87%
38k (R^1 = $(CH_2)_3OTBS$) 87%
38l (R^1 = Cy) 81%
38m (R^1 = *t*-Bu) 0%

38n (R^2 = *p*-anisyl) 86%
38o (R^2 = *p*-$F_3CC_6H_4$) 0%
38p (R^2 = *n*-Pr) 47%[a]
38q (R^2 = Cy) 44%[a]

[a]CuBr (10 mol%) and PPh_3 (20 mol%) were used.

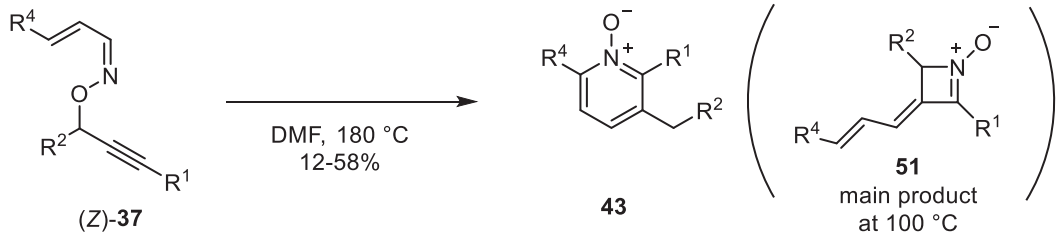
Scheme 13. Cu(I)-Catalyzed tandem [2,3]-rearrangement and 6π-3-azatriene electrocyclization

Based on some control experiments, the proposed reaction mechanism is described in Scheme 14. First, intramolecular nucleophilic addition of the N-atom to the alkyne moiety takes place, providing the cyclic coppervinyl intermediate **39**. Ionic cleavage of the C-O bond and subsequent elimination of the Cu catalyst leads to the *N*-allenylnitrone intermediate **41**. Its rotamer (**41'**) undergoes a 6π-3-azatriene electrocyclization to afford dihydropyridine **42**, which isomerizes to **38** under the reaction conditions.



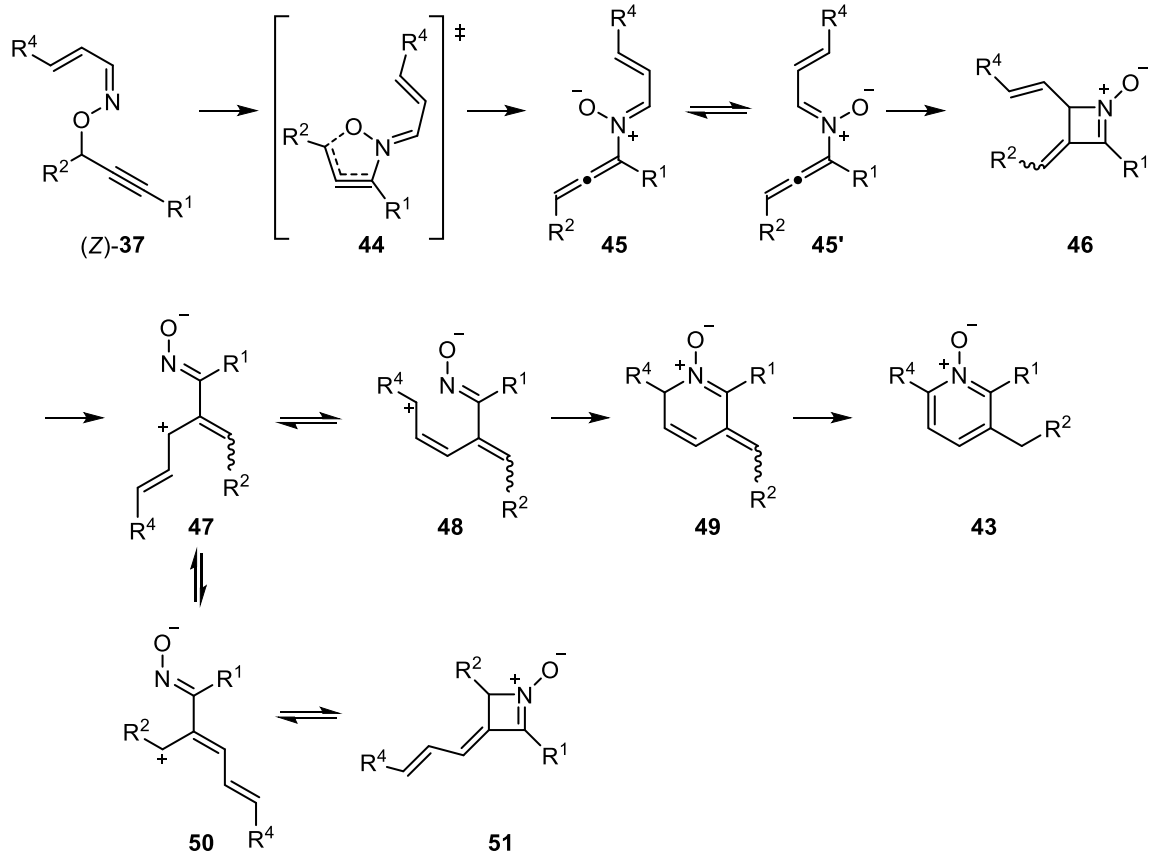
Scheme 14. Proposed mechanism

Meanwhile, (*Z*)-*O*-propargylic α,β-unsaturated aldoximes **37** furnished 2,3,6-substituted pyridine oxides **43** in moderate yields by thermally-induced skeletal rearrangement without a catalyst (Scheme 15).[23]



Scheme 15. Thermally-induced skeletal rearrangement of (*Z*)-*O*-propargylic α, β-unsaturated aldoxime

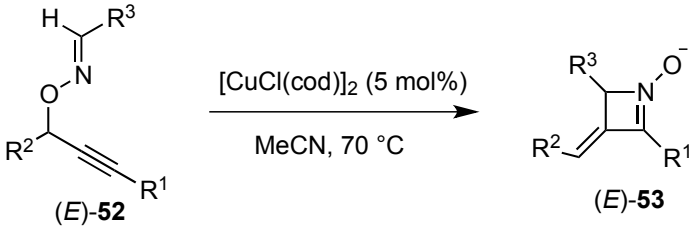
A proposed mechanism for the transformation is shown in Scheme 16. First, the thermal [2,3]-rearrangement of (*Z*)-**37** leads to the *N*-allenylnitrone intermediate **45** in a concerted manner in the absence of a catalyst.[24] Its rotamer **45'** undergoes 4π-electrocyclization to form a four-membered cyclic nitrone **46**.[25] The sp^3-carbon-nitrogen bond is cleaved to form zwitterionic species **47**. At a lower reaction temperature (100 °C), re-formation of the C-N bond takes place via zwitterionic intermediate **50**, and another cyclic nitrone **51** having a longer conjugated chain than does **46** is obtained as the



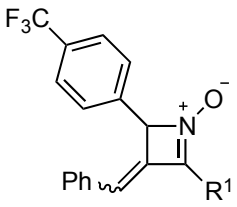
Scheme 16. Proposed mechanism

thermodynamic product. At a higher temperature (180 °C), re-formation of the sp^3-carbon-nitrogen bond occurs via intermediate **48**. The resulting dihydropyridine oxide **49** readily isomerizes to 2,3,6-trisubstituted pyridine oxide **43**.

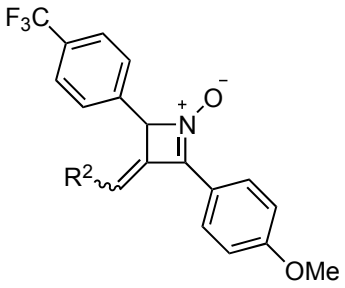
Following this report, copper-catalyzed skeletal rearrangement of (*E*)-*O*-propargylic arylaldoximes **52** was developed to produce the corresponding cyclic nitrones **53** with excellent regioselectivities by using $[CuCl(cod)]_2$ as catalysts (Scheme 17).[26] Both electron-rich and electron-deficient aryl groups, and alkyl groups can afford four-membered cyclic nitrones in the tandem reaction (**53a**-**53g**). In particular, bulky substituents at the alkyne terminus (R^1) resulted in high *E*/*Z* selectivity (**53b**, **53c**). Substrates **53h** and **53i**, which possess an alkyl group at the propargylic position (R^2), were transformed to the corresponding product in good yield, although it was necessary to raise the reaction temperature.



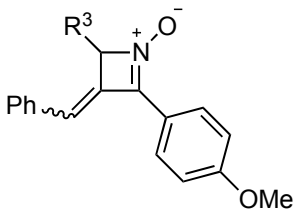
(*E*)-**52** (*E*)-**53**



53a (R^1 = 4-$MeOC_6H_4$) 90% (74:26)
53b (R^1 = 2-$MeOC_{10}H_6$) 78% (97:3)
53c (R^1 = 2,6-$(MeO)_2C_6H_3$) 90% (95:5)
53d (R^1 = Ph) 81% (73:27)
53e (R^1 = 4-$F_3CC_6H_4$) 81% (74:26)
53f (R^1 = *n*-Pr) 88% (73:27)
53g (R^1 = Cy) 88% (83:17)



53h (R^2 = *n*-Pr) 75% (73:27)[b]
53i (R^2 = *i*-Pr) 67% (74:26)[b]



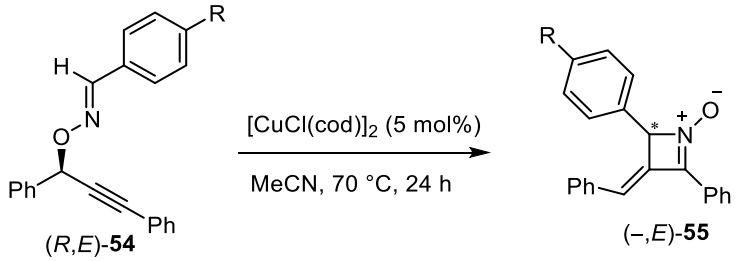
53j (R^3 = 2-naphthyl) 88% (74:26)

[a]*E*/*Z* ratios are described in parentheses. [b]Reactions were conducted at 100 °C.

Scheme 17. Cu(I)-Catalyzed rearrangement/4π-electrocyclization[a]

Optically active (*R*,*E*)-**54a** was subjected to the rearrangement reaction under optimal conditions (Table 3).[27] The resulting products (-,*E*)- and (+,*Z*)-**55a** were obtained in 77% ee and 80% ee, respectively, suggesting chirality transfer from the starting material to some extent (entry 1). Similarly, the chirality of substrates **54b** and **54c** was maintained during the formation of products **55b** and **55c** (entries 2 and 3).

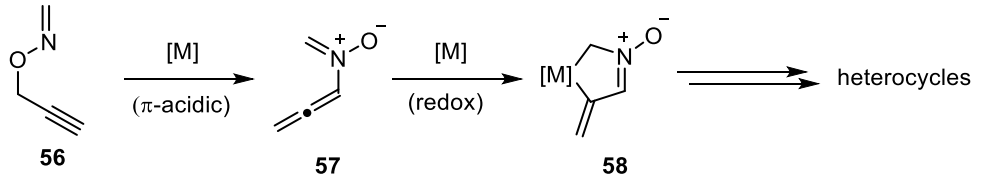
Table 3. Cyclization of chiral substrates



(*R*,*E*)-**54** (–,*E*)-**55**

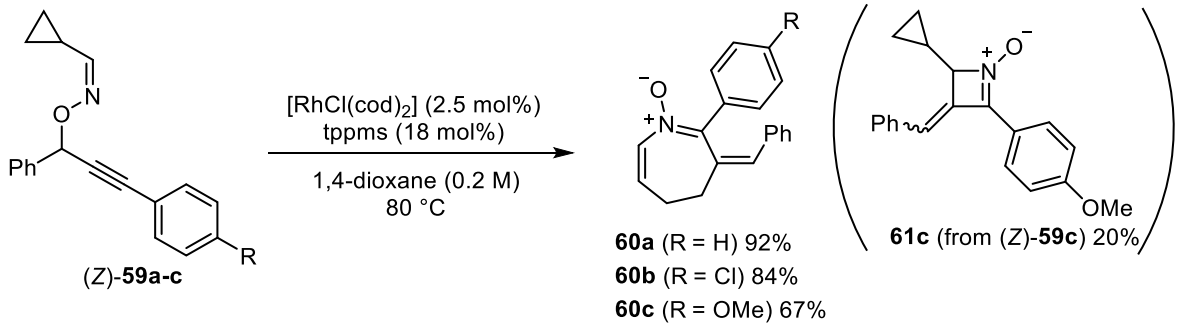
entry	SM	R	yield (%)	*E*/*Z*	ee (*E*/*Z*)
1	**54a**	H	88	72:28	77/80
2	**54b**	Br	90	72:28	81/85
3	**54c**	Me	87	>99:1	76/75

In 2012, Nakamura and Terada reported the aza-metallacyclization of *N*-allenylnitrone, in which rhodium complexes play a dual role as π-acidic and redox catalysts, to synthesize heterocycles (Scheme 18).[28]



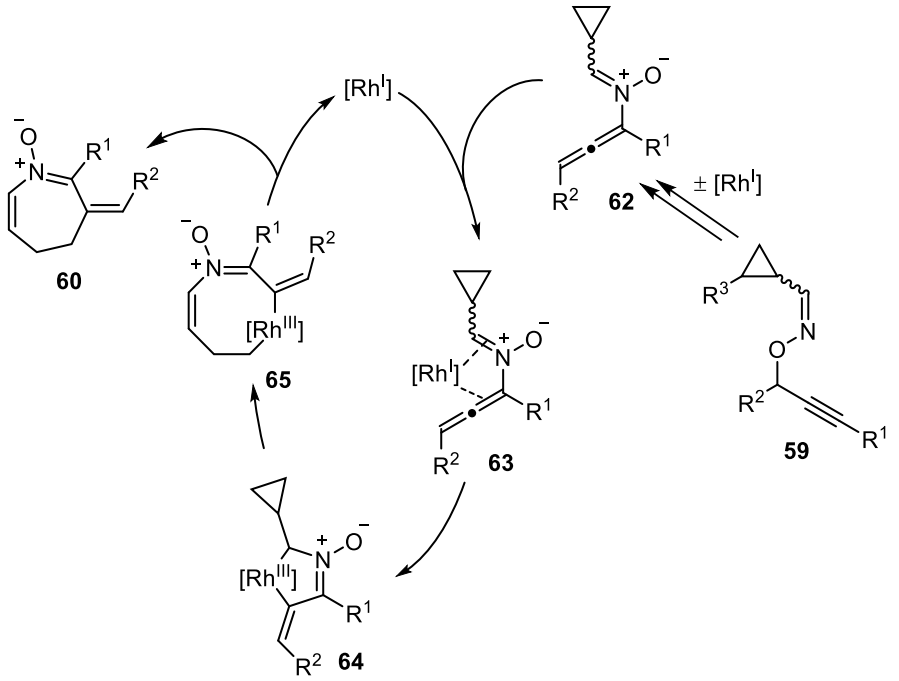
Scheme 18. Cyclization through metallacycle intermediates

(*Z*)-*O*-Propargylic cyclopropylcarbaldoxime **59a** was treated with [RhCl(cod)$_2$] and tppms (sodium diphenylphosphinobenzene-3-sulfonate), which is a polymer-bound and water-soluble phosphine ligand,[29] and afforded azepine oxide **60a** in high yield (Scheme 19). Substrate (*Z*)-**59b**, which possesses an electron-deficient aromatic ring at the alkyne terminus, was successfully converted into product **60b**, whereas substrate (*Z*)-**59c**, which bears an electron-rich *p*-anisyl group, gave the product in a lower yield, along with a considerable amount of the corresponding four-membered cyclic nitrone **61c** as a by-product.



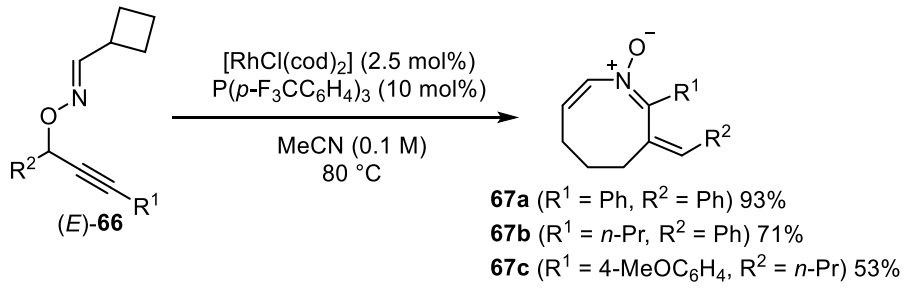
Scheme 19. Rh(I)-Catalyzed tandem reaction of (*Z*)-*O*-propargylic cyclopropylcarbaldoxime

In the proposed reaction mechanism, the *s-cis* form of *N*-allenylnitrone **62** allowed η^4-coordination to the Rh catalyst from the opposite side of R^2, as shown in intermediate **63** (Scheme 20). Then, the formation of aza-rhodacycle **64** and ring expansion involving the cleavage of carbon-carbon bond leads to an eight-membered aza-rhodacycle **65**.[30,31] Finally, reductive elimination of the Rh catalyst produces **60**.



Scheme 20. Proposed reaction mechanism

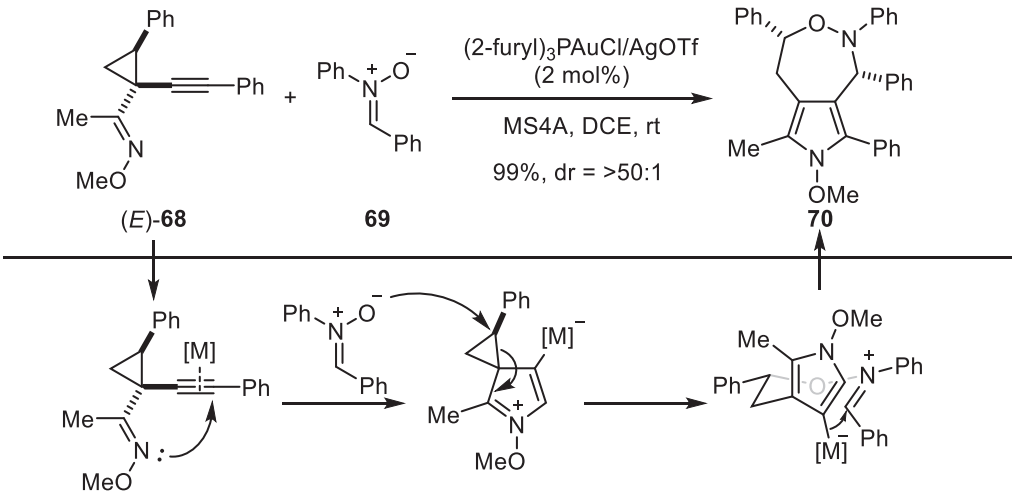
Later, the reaction was extended to *O*-propargylic cyclobutylcarbaldoxime **66**, where the use of an electron-deficient phosphine ligand was effective to produce azocine derivatives (Scheme 21).[32] Although the reaction of the terminal alkyne (R^1 = H) afforded unidentified byproducts, various substituents on the alkyne terminus successfully underwent the reaction (**67a**, **67b**). Alkyl substituents at the propargylic moiety also afforded the corresponding azocine **67c** in moderate yield. In addition, the reaction with the corresponding (*Z*)-**66a** also proceeded smoothly to give the azocine **67a** in almost the same yield.



Scheme 21. Rh(I)-Catalyzed cascade reaction to synthesize azocine derivatives

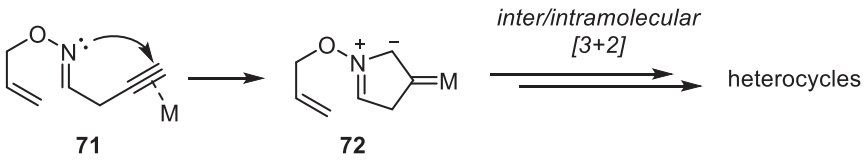
In 2012, Zhang developed Au(I)-catalyzed 1,3-dipolar cycloaddition of 1-(1-alkynyl)cyclopropyl oxime ether **68** with nitrone **69** to synthesize pyrrolo[3,4-*d*][1,2]oxazepine **70** (Scheme 22).[33] According to a previous report on corresponding ketone derivatives,[34] intramolecular cyclization of *N*-methoxyimines proceeds by Au(I)-catalyzed activation of the alkyne moiety, followed by nucleophilic attack of nitrone

on the cyclopropyl moiety and diastereoselective cyclization to afford product **70**. In this transformation, a complete chirality transfer was observed.



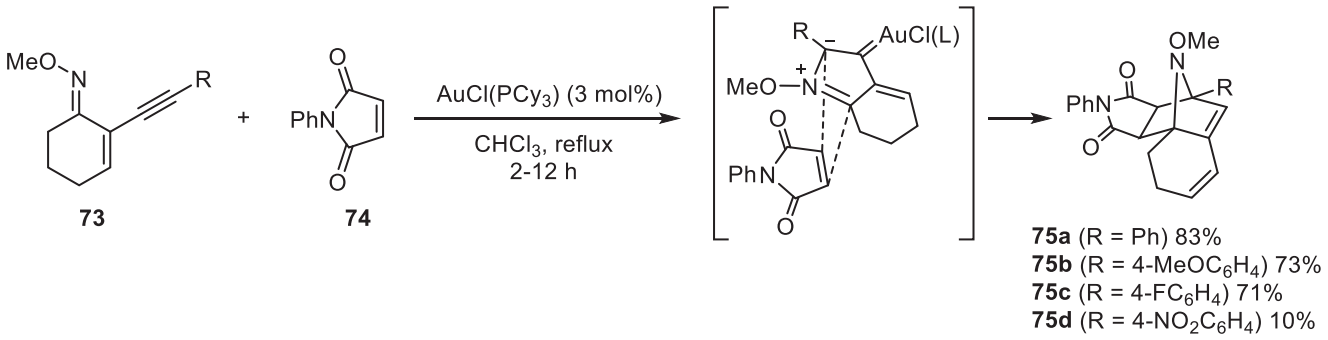
Scheme 22. Au(I)-Catalyzed 1,3-dipolar cycloaddition

In 2017, our group reported that *N*-alkoxyazomethine ylide **72**, which was generated by Au-catalyzed cyclization of *N*-alkoxyimine **71**, undergoes intermolecular or intramolecular [3+2] cycloaddition to afford various heterocycles (Scheme 23).[35]



Scheme 23. Cycloaddition cascade of *N*-alkoxyazomethine yilide

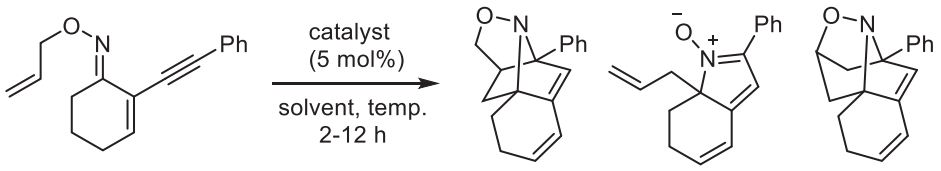
N-Methoxyimine **73** and maleimide **74** were employed as the substrates for investigation of intermolecular [3+2] cycloaddition.[36] AuCl(PCy$_3$), which has an electron-rich σ-donating ligand, was found to increase the stability of the gold carbenoid[37] and gave the highest chemical yield of 7-azabicyclo[2.2.1]heptane **75a** (Scheme 24). In the substrate scope studies, 4-methoxyphenyl and 4-fluorophenyl groups were found to be well tolerated at the terminus of the alkyne moiety, affording the corresponding products **75b** and **75c**, respectively. In contrast, *N*-methoxyimine **75d**, which bears a strong electron-withdrawing group at the alkyne terminus, gave a poor result, most likely because it is difficult for the π-acidic gold catalyst to coordinate to the electron-deficient alkyne.



Scheme 24. Au(I)-Catalyzed preparation of an azomethine ylide and its intermolecular cycloaddition

The treatment of the *N*-allyloxyimine **76a** with AuCl(PCy$_3$) in DCE at reflux resulted in the formation of the corresponding *N*-allyloxyazomethine ylide, with a subsequent intramolecular cycloaddition reaction to furnish 3,6-methanopyrrolo[1,2-*b*]isoxazole **77a** with a 63% yield, along with a 27% yield of the nitrone **78a**, which was generated by the retro-[3+2] cycloaddition of **77a** (Table 4, entry 1). Increasing the reaction temperature enabled the [3+2]/retro-[3+2]/[3+2] cascade to give the 2,6-methanopyrrolo[1,2-*b*]isoxazole **79a** (entry 2). A survey of several other gold catalysts, as well as silver, copper, and platinum catalysts revealed that (AuCl)$_2$dppm was optimum, giving **79a** in 90% yield (entry 3).

Table 4. Au(I)-Catalyzed intramolecular cycloaddition cascade



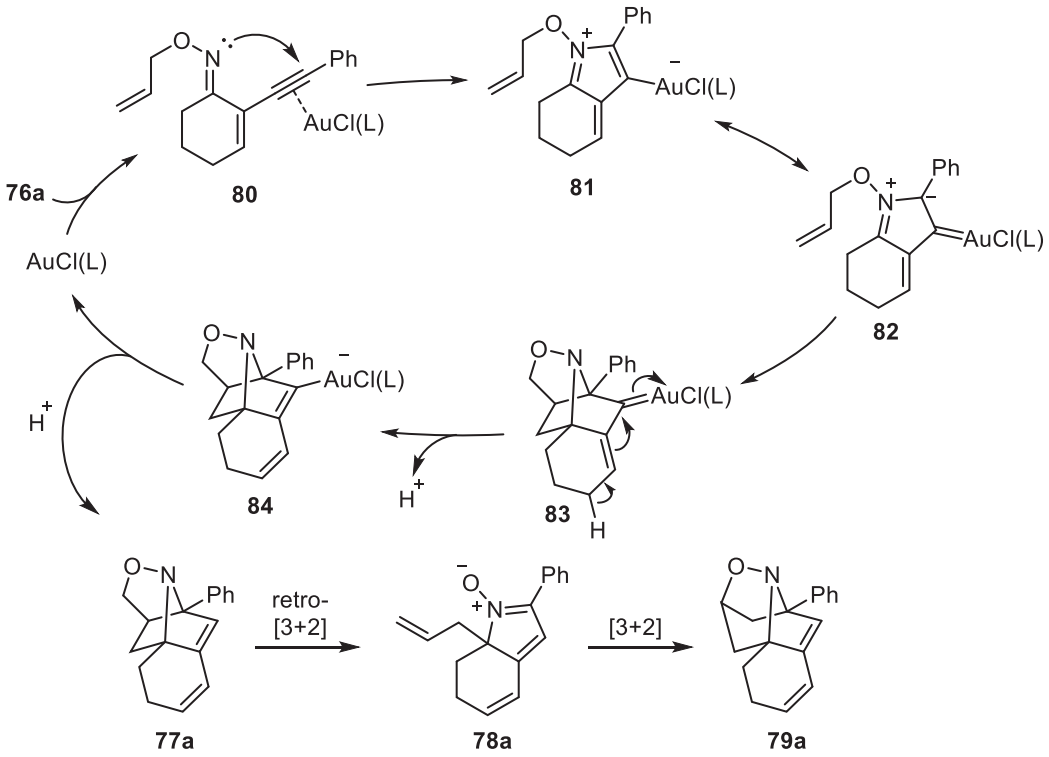
76a **77a** **78a** **79a**

entry	catalyst	solvent	temp. (°C)	Yield (%)		
				77a	**78a**	**79a**
1	AuCl(PCy$_3$)	DCE	83	63	27	–
2[a]	AuCl(PCy$_3$)	PhCl	160	–	–	64
3[a]	(AuCl)$_2$dppm	PhCl	160	–	–	90

[a]Reaction was carried out in a sealed tube.

A series of control experiments indicated that the pathway for the formation of **79a** was irreversible and that the Au catalyst was not involved in the retro-cycloaddition or nitrone cycloaddition. Based on the information, a proposed reaction mechanism is presented in Scheme 25. First, the Au catalyst coordinates to the C−C triple bond to form the activated intermediate **80**. Then, the N-atom of the alkoxyimine attacks

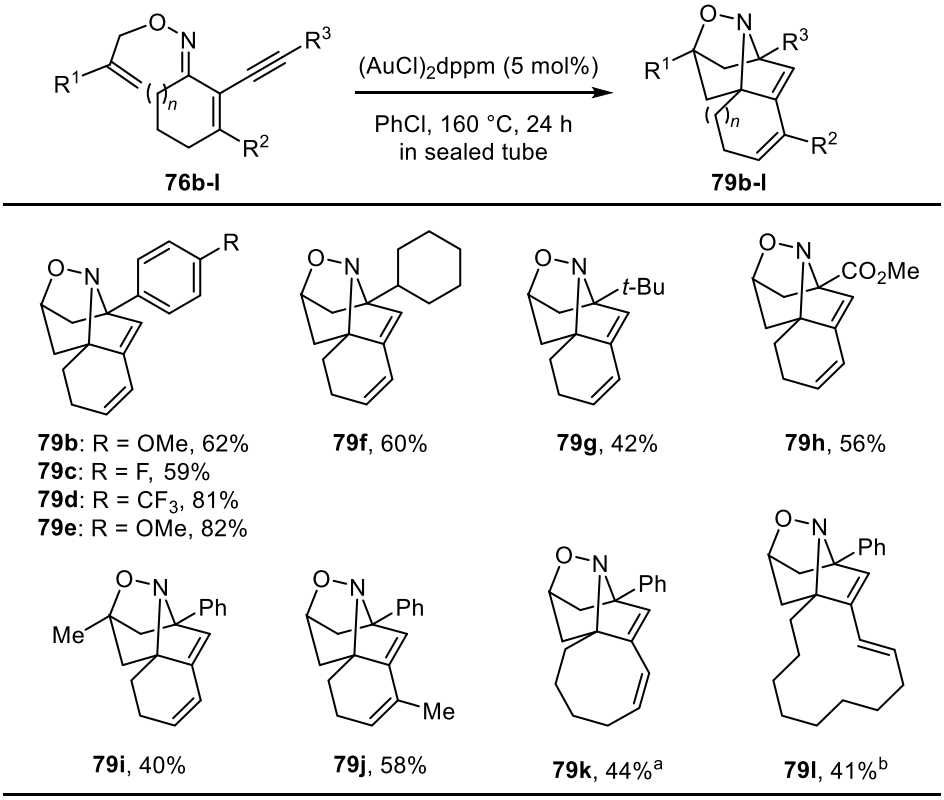
the Au-activated C−C triple bond, inducing a 5-*endo-dig* cyclization to produce intermediate **81**, which also exists as the corresponding resonance structure **82**. The Au-carbenoid-containing azomethine ylide **82** then undergoes an intramolecular cycloaddition to give **83**. Sequential double-bond migration and protodemetalation steps afford **77a** along with regeneration of the gold catalyst. Finally, the fused isoxazolidine **77a** undergoes a thermally induced ring-opening reaction to give **78a**, which subsequently undergoes an intramolecular cycloaddition to afford the highly fused isoxazolidine **79a**. This cascade reaction has a 100% atom economy and involves the formation of three C−C bonds, one C−O bond, one C−N bond, and one C−H bond, as well as the cleavage of one C−C bond, one C−O bond, and one C−H bond in a single operation. It is the first reported example of the domino reaction of an azomethine ylide involving a [3+2]/retro-[3+2]/[3+2] cycloaddition cascade.



Scheme 25. Proposed reaction mechanism

The substrate scope shows that the reactions of substrates bearing a *para*-substituted electron-rich or electron-deficient phenyl ring (R^3) proceeded smoothly under the optimal reaction conditions to give the corresponding bridged heterocycles (**79b-e**) in moderate to good yields (Scheme 26). An aliphatic cyclohexyl substituent was also well tolerated as R^3 to produce **79f** in moderate yield, while the introduction of a *tert*-butyl group at this position led to a low yield of the corresponding bridged heterocycle **79g** because of steric hindrance. A substrate having an ester moiety as part of R^3 reacted well under these reaction conditions to afford the desired product **79h** in 56% yield. Substrates that possess a

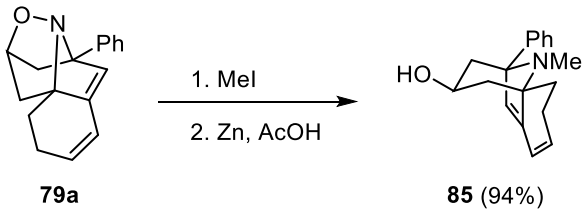
methyl substituent at either R^1 or R^2 also reacted to provide products **79i** and **79j** in moderate yields, respectively. Moreover, other cycloalkenes instead of the cyclohexenyl moiety were found to be amenable to the cascade reaction, with the corresponding cycloadducts **79k** and **79l** being formed.



[a]Reaction was carried out at 150 °C for 12 h. [b]Reaction was carried out at 170 °C.

Scheme 26. Substrate scope of Au(I)-catalyzed cascade cyclization

Cleavage of the N−O bond took place, as shown in Scheme 27. The methylation of **79a** with MeI, followed by treatment of the methylated product with zinc dust afforded the tropenol **85** with a 94% yield.[38]

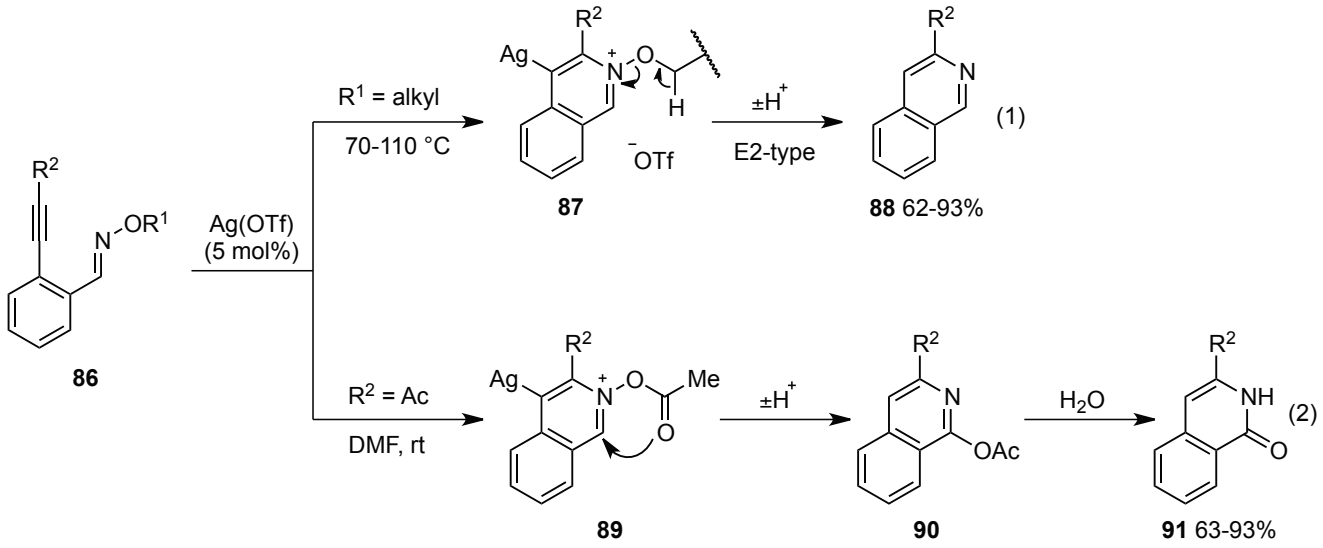


Scheme 27. Conversion of **79a** into the tropenol skeleton **85**

3-2. Cyclization/N-O Bond Cleavage

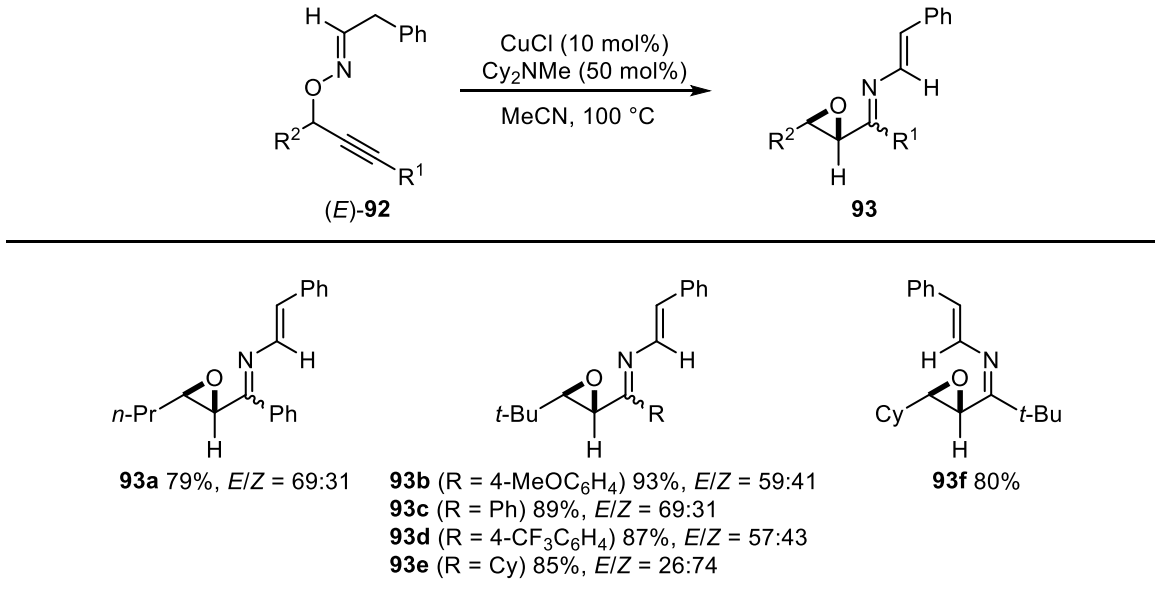
In 2009, Zhang reported Ag(I)-catalyzed 6-*endo*-selective cyclization of *N*-alkoxyimine **86** bearing an alkynyl group to synthesize pyridine **88** along with removal of the alkoxy group (Scheme 28, eq. 1).[39] In

the case of *N*-acetoxyimine as a substrate, intramolecular nucleophilic addition followed by 2,3-rearrangement was achieved (eq. 2). Almost at the same time, Shin reported that a Ag(I) and TfOH co-catalyst system was more effective in reactions where the bimolecular E2-type elimination mechanism was proposed (Scheme 28, eq. 1).[40]



Scheme 28. Ag(I)-Catalyzed cyclization for synthesis of isoquinoline or isoquinolinone

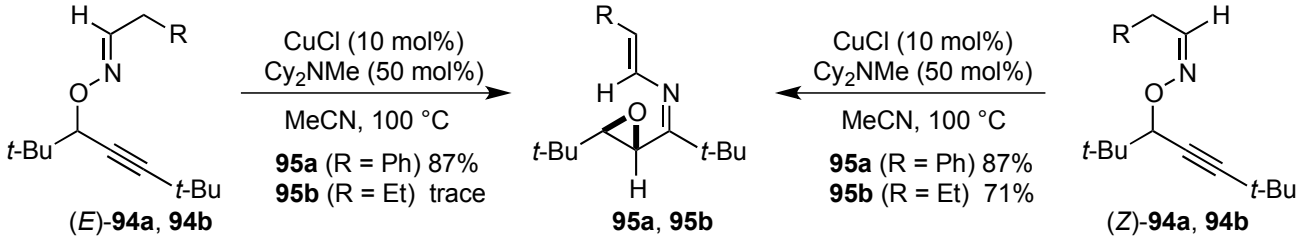
In 2012, Nakamura and Terada accomplished Cu-catalyzed cyclization/rearrangement via N-O bond cleavage.[41] (*E*)-Propargyloxyimine **92a** was treated with a catalytic amount of CuCl and Cy_2NMe in MeCN at reflux to afford the corresponding *N*-alkenyl oxiranylketimine **93a** successfully (Scheme 29).



Scheme 29. Cu(I)-Catalyzed skeletal rearrangement of (*E*)-propargyloxyimine

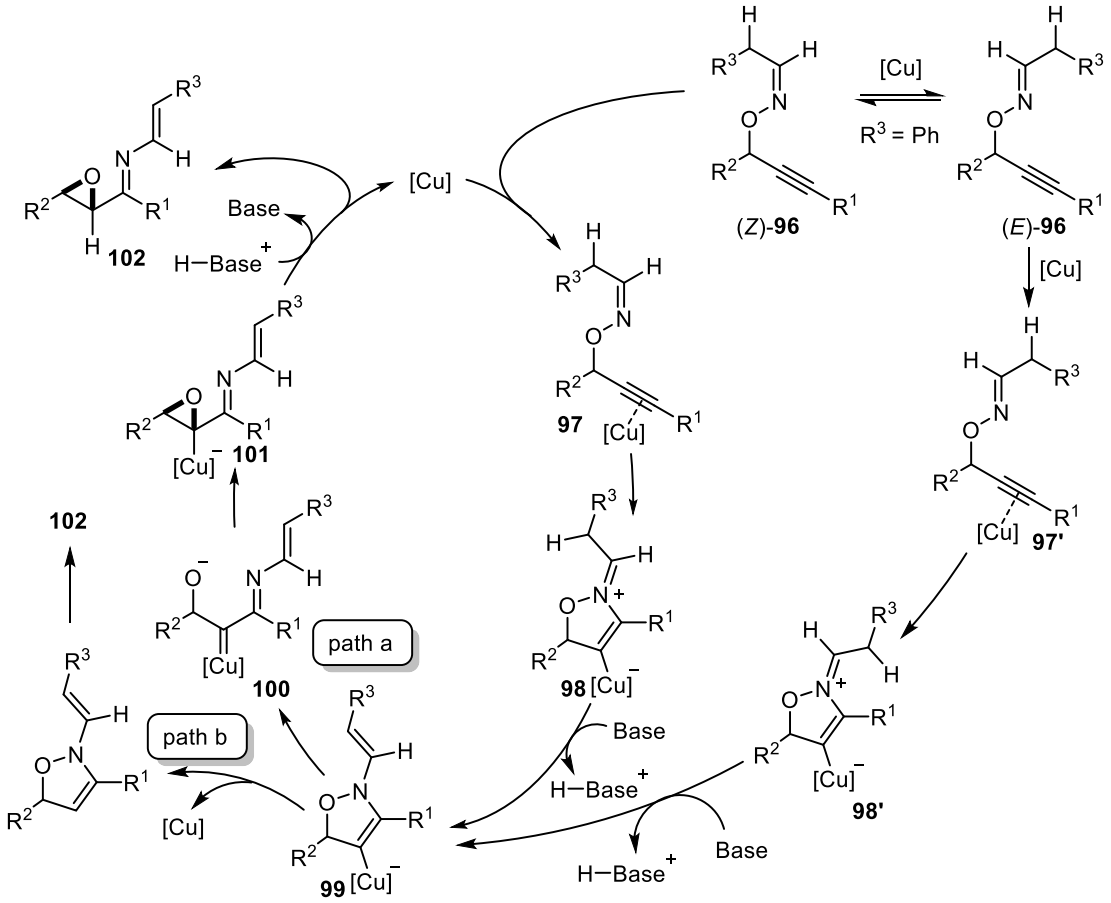
With respect to the substrate scope, both electron-rich and electron poor aromatic rings, and alkyl substituents at the alkyne terminus provided the corresponding oxiranylketimine in high yields (**93b**-**93e**). (*Z*)-**93f** was obtained as a single isomer via a bulky substituent at the alkyne terminus.

The reactivity of Cu(I)-catalyzed cyclization/isomerization was affected by the geometry of imine and the acidity of the α-proton of the alkoxyamine moiety. The reaction of benzylimine **94a**, which has a more acidic benzyl proton, did not depend on the *E*/*Z* isomer to afford epoxide **95a**, while the reaction with (*E*)-*n*-propylimine **94b** was sluggish to give a trace amount of product **95b** although the corresponding (*Z*)-**94b** led to **95b** in high yield (Scheme 30).



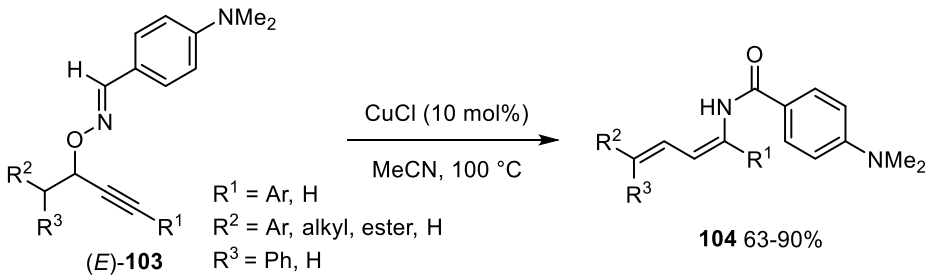
Scheme 30. Reactivity between *E*/*Z* isomers

A proposed reaction mechanism of the Cu(I)-catalyzed skeletal rearrangement is illustrated in Scheme 31. First, the Cu catalyst coordinates to the alkyne moiety of **96** to produce adducts **97** and **97'**. Next, a 5-*endo*-*dig* cyclization proceeds via nucleophilic attack of the alkoxyimine N-atom onto the activated triple bond to afford vinylcopper intermediates **98** or **98'**. The α-proton of *N*-alkoxyiminium is abstracted by the base to form the common enamine intermediate **99**, which rearranges to Cu-carbenoid **100** via cleavage of the N–O bond, assisted by the donation of electrons from the Cu atom in the original report (path a). Finally, the oxirane ring is then formed via nucleophilic attack of the oxygen anion onto the carbenoid carbon, followed by protodemetalation to afford the product **102**.[42] However, protodemetalation followed by [1,3]-oxygen rearrangement may proceed based on the recent related studies (path b).[22,43,49] In the case of R^3 = phenyl, the oxime (*E*)-**96** isomerizes to its (*Z*)-isomer prior to cyclization, presumably due to the higher acidity of the α-proton. In contrast, in the case of R^3 = alkyl, the reaction of the alkyl (*E*)-oxime ether was sluggish due to steric repulsion between the substituents R^3 on *N*-alkoxyimine and the alkyne terminus R^1 within the cyclized intermediate **98'** and the lower acidity of the α-proton. The experimental result indicates that decreased steric interactions allow for the successful reaction of the (*E*)-isomer. It is likely that Cy_2NMe serves not only as an electron-donating ligand to facilitate the donation of electrons from the Cu atom during the conversion from **99** to **100**, but also as a Brønsted base to facilitate the proton transfer processes as well as to trap any acid components, thus stabilizing the acid-sensitive product **102**.



Scheme 31. Proposed reaction mechanism

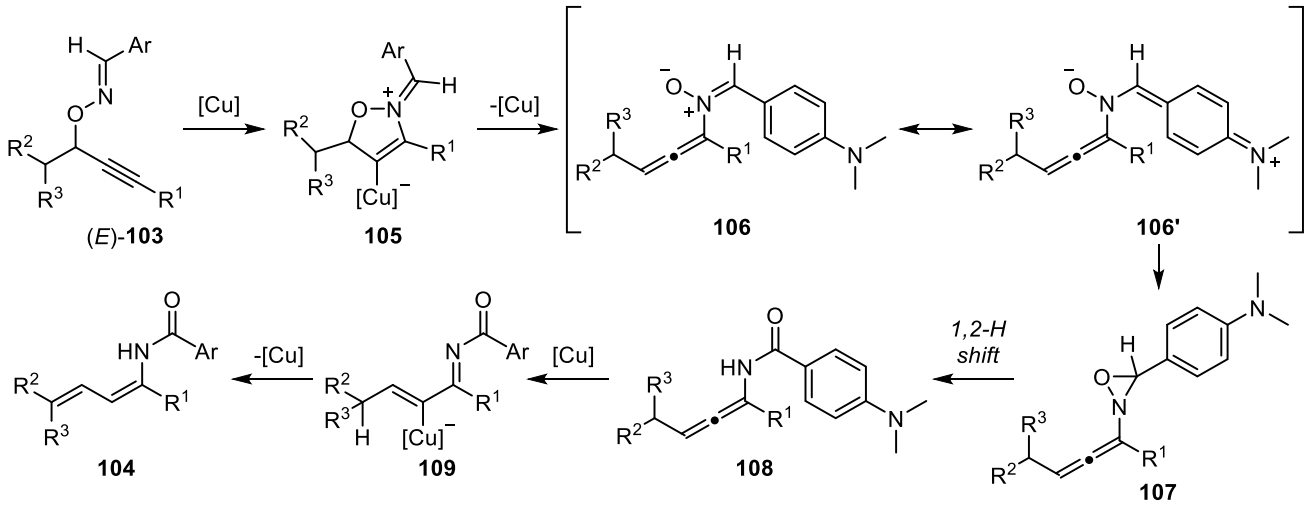
In the case of (*E*)-*O*-propargylic oximes **103** bearing the electron-rich *p*-(dimethylamino)phenyl group at the oxime moiety and an alkyl group at the propargylic position, 1-amidodienes **104** were obtained in moderate to high yields (Scheme 32).[44]



Scheme 32. Cu(I)-Catalyzed skeletal rearrangement of *O*-propargylic electron-rich arylaldoximes

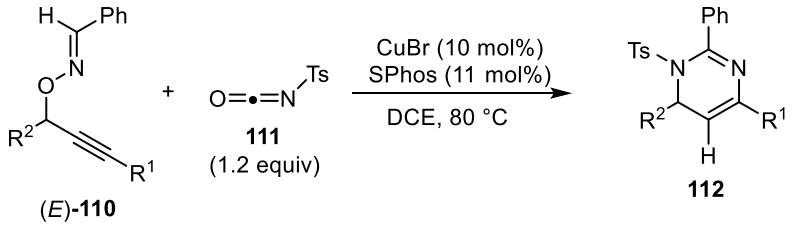
A plausible reaction mechanism is proposed in Scheme 33. First, the cyclized vinyl Cu species **105** is formed via nucleophilic attack on the alkyne moiety. Next, Cu catalyst is released to generate *N*-allenylnitrone **106**, followed by formation of oxaziridine **107**,[45] assisted by the electron-donating group. Immediately, a 1,2-hydrogen shift driven by the electron-donating dimethylaminophenyl group generates

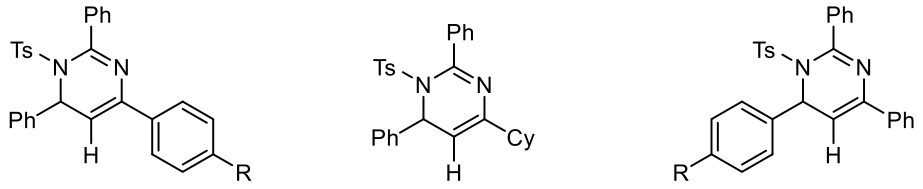
N-allenylamide **108**.[46] Finally, isomerization through a vinylcopper intermediate **109** provides 1-amidodiene **104**.[47]



Scheme 33. Proposed reaction mechanism

Following this report, [3+2] cycloaddition of *N*-allenylnitrone derived from propargylic oxime with isocyanate followed by decarboxylative ring opening involving a 1,4-hydrogen shift, and 6π-electrocyclization was developed.[48] As a result of optimization study, the combination of CuBr and SPhos was determined to give the best yield, where reactions between *O*-propargylic aldoximes **110** and isocyanate **111** provided 1,6-dihydropyrimidines **112** (Scheme 34). Investigation of the substitution effect showed that both electron-rich and electron-poor substituents on the propargylic moiety (R^2) and the alkyne terminus (R^1) gave the corresponding 1,6-dihydropyrimidines in moderate yield.





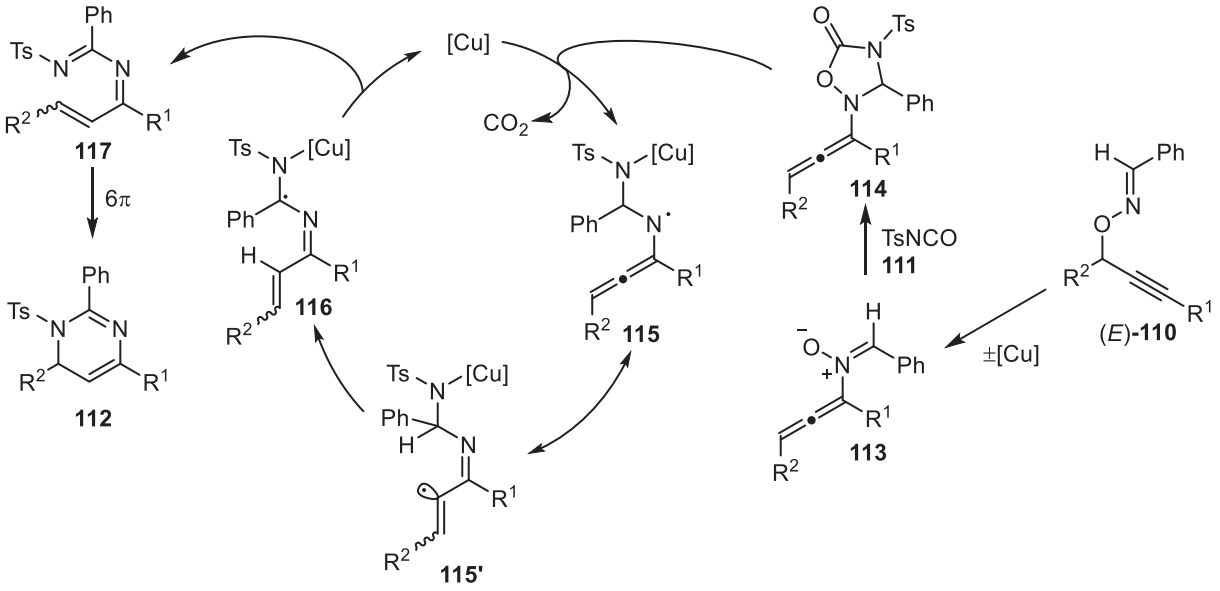
112a (R = OMe) 51%
112b (R = Cl) 45%
112c (R = CF_3) 48%

112d 55%

112e (R = OMe) 64%
112f (R = Me) 63%
112g (R = CF_3) 43%

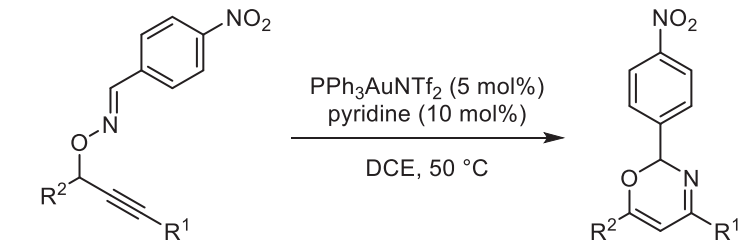
Scheme 34. Synthesis of 1,6-dihydropyrimidines via Cu(I)-catalyzed cascade reactions

Tandem rearrangement initiates coordination of the Cu catalyst to the triple bond of the alkyne **110** to form a π-complex, followed by cyclization and cleavage of the N-O bond to form *N*-allenylnitrone **113** (Scheme 35). Subsequently, [3+2] cycloaddition with isocyanate **111** proceeds to give 2-allenyl-1,2,4-oxadiazolin-5-one **114**. Cleavage of the N-O bond via single electron transfer from the Cu catalyst followed by decarboxylation produces the aminyl radical species **115**. Subsequently, 1,4-hydrogen migration and elimination of the Cu catalyst provide 1,3-diazatriene **117**, which undergoes a 6π-electrocyclization to afford 1,6-dihydropyrimidine **112**.



Scheme 35. Plausible mechanism

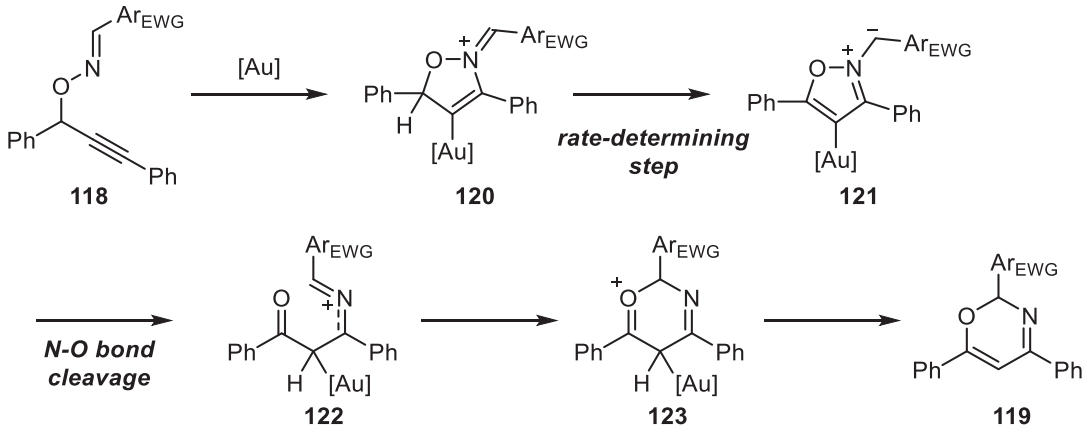
Recently, a novel synthetic method for *2H*-1,3-oxazine derivatives was reported,[49] wherein *O*-propargylic oximes **118** bearing an electron-withdrawing aryl group on the imine moiety undergo Au-catalyzed skeletal rearrangements via N-O bond cleavage to afford 2*H*-1,3-oxazine derivatives **119** in good to high yields (Scheme 36).



118a (R^1 = Ph, R^2 = Ph) (without pyridine) **119a** 93%
118b (R^1 = Ph, R^2 = Cy) **119b** 65%
118c (R^1 = *t*-Bu, R^2 = Ph) **119c** 75%

Scheme 36. Au-Catalyzed transformation into 2*H*-1,3-oxazine derivatives via N-O bond cleavage

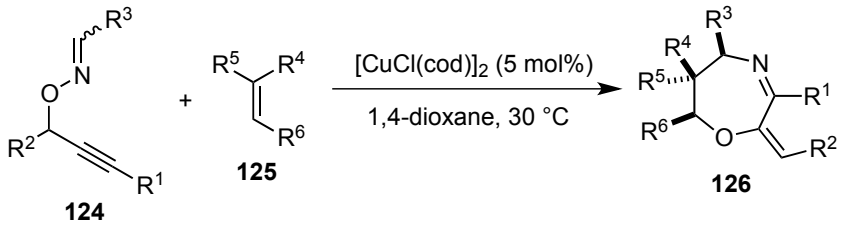
Density functional theory (DFT) calculations were conducted to elucidate the reaction pathway. The result led to the formulation of a possible reaction mechanism (Scheme 37). First, the vinyl Au intermediate **120** derived from *N*-propargyloxyimine **118** is deprotonated to generate the isoxazolium species **121**. The deprotonation is the rate-determining step according to calculation and mechanistic studies. Subsequently, protonation of the Au-bound carbon of **121** induces simultaneous ring-opening with cleavage of the N-O bond to form the cationic ketone **122** as a highly exergonic process. Finally, recyclization of **122** and release of the Au catalyst proceeds to give the 2*H*-1,3-oxazine derivative **119**.



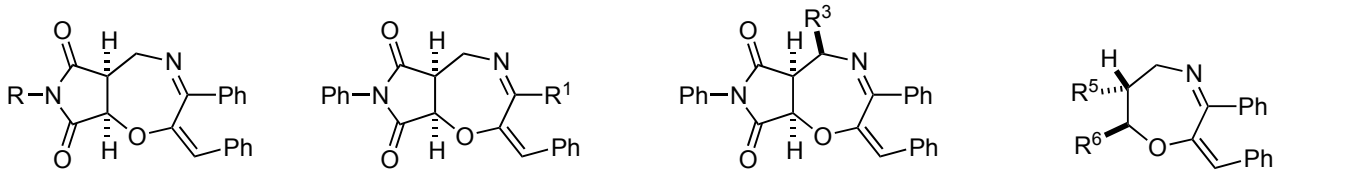
Scheme 37. Proposed reaction mechanism based on DFT calculations

3-3. Cyclization/Intermolecular C-C/C-N Bond Formation

N-Allenylnitrone was used as a 1,3-dipolar reagent to react with an electrophilic dipolarophile for the synthesis of oxazepane derivatives (Scheme 38).[50] Initially, the reaction between the formaldoxime **124a** and *N*-methylmaleimide was carried out in the presence of $[CuCl(cod)]_2$ to give **126a** with a 67% yield. Among the examined maleimides, *N*-phenylmaleimide gave the highest yield of **126c**. A *tert*-butyl group on the N-atom was tolerated (**126b**), and the nonprotected maleimide gave a lower chemical yield (**126d**). The substrate **124e**, with an aryl substituent at the alkyne terminus, was efficiently converted into the corresponding product **126e** in good yield. Although the reaction of **124g** (R^1 = cyclohexyl group) was highly effective, the reaction of **124f** (R^1 = *n*-propyl group) resulted in a low yield of the product **126f**. Arylaldoxime could also give the cyclized product **126h** with excellent diastereoselectivity. The reaction of **124a** (R^1 = R^2 = Ph, R^3 = H) with fumaric acid esters afforded the desired products **126i** and **126j**, respectively.



124 **125** **126**



126a (R = Me) 67%
126b (R = *t*-Bu) 61%
126c (R = Ph) 77%
126d (R = H) 39%

126e (R^1 = 4-$F_3CC_6H_4$) 76%
126f (R^1 = *n*-Pr) 41%
126g (R^1 = Cy) 91%

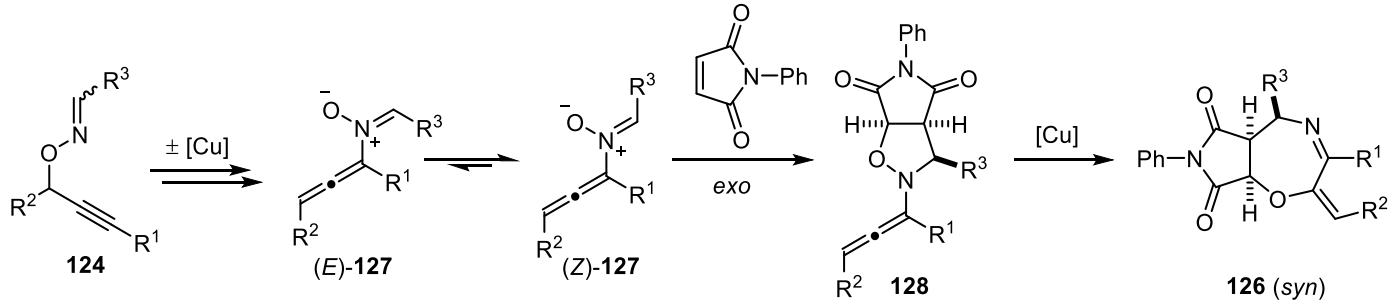
126h (R^3 = 4-$F_3CC_6H_4$) 71%[a,b]

126i (R^5 = R^6 = CO_2Me) 63%[a]
126j (R^5 = R^6 = CO_2*i*-Pr) 59%[a]

[a]MeCN was employed instead of 1,4-dioxane.[b]Reaction temperature was 50 °C.

Scheme 38. [3+2] Cycloaddition of *N*-allenylnitrone derived from *O*-propargylic oximes

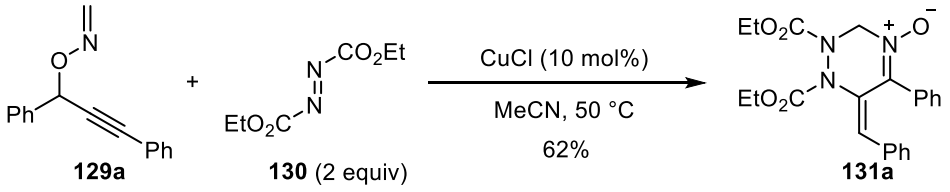
N-Allenylnitrone (*Z*)-**127**, which is generated from the *O*-propargylic oxime **124** by Cu-catalyzed intramolecular addition/[2,3]-rearrangement/isomerization or thermal [2,3]-rearrangement in a concerted manner, undergoes [3+2] cycloaddition with maleimide to give *N*-allenylisoxazolidine **128**, primarily in an *exo* manner (Scheme 39). Subsequently, 1,3-oxygen migration from the N-atom to the C-atom of the allene center produces the *syn*-product **126** as a major product.[51] Although the mechanism is not clear, the author proposed that the 1,3-oxygen migration process from **128** to **126** is also promoted by the Cu catalyst.



124 (*E*)-**127** (*Z*)-**127** **128** **126** (*syn*)

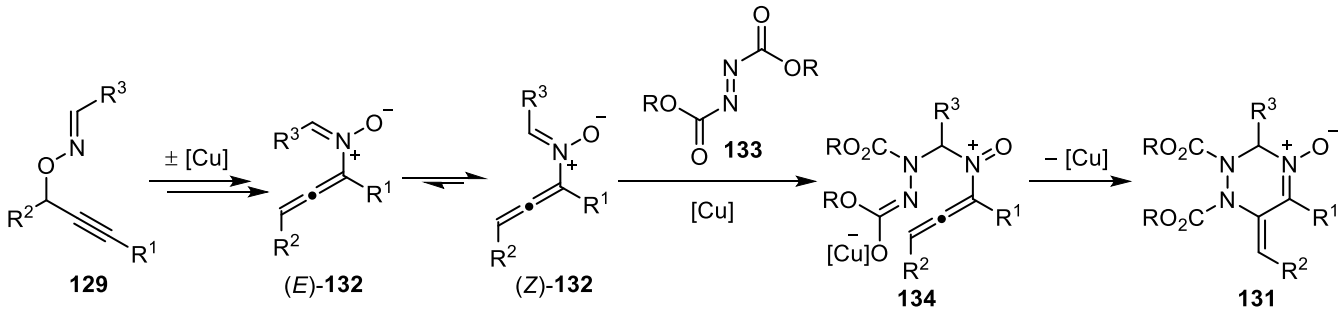
Scheme 39. Proposed reaction mechanism

N-Allenylnitrone can be used for Cu(I)-catalyzed [4+2] cycloaddition with diazene to provide 1,2,3,6-tetrahydro-1,2,4-triazine oxide.[52] *O*-Propargylic oxime **129a** and 2 equivalents of diazene **130** were treated with 10 mol% of CuCl in MeCN under optimal conditions, resulting in [4+2] cycloaddition to afford the corresponding triazine oxide **131a** in good yield (Scheme 40).



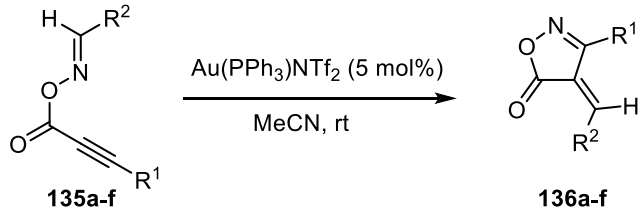
Scheme 40. Cu(I)-Catalyzed synthesis of 1,2,3,6-tetrahydro-1,2,4-triazine oxides

The proposed reaction mechanism is shown in Scheme 41. Initially, Cu(I)-catalyzed intramolecular nucleophilic addition/rearrangement leads to (*E*)-allenylnitrone **132**, which isomerizes to the more thermodynamically stable (*Z*)-isomer. The nucleophilic attack of the imino carbon of the key intermediate (*Z*)-**132** on the azodicarboxylate **133** activated by the Cu catalyst generates the zwitterionic species **134**. Finally, intramolecular addition of the Cu amidate to the C=C bond from the less hindered allene face produces **131** having an *exo*-*E*-olefin.[53]



Scheme 41. Proposed reaction mechanism

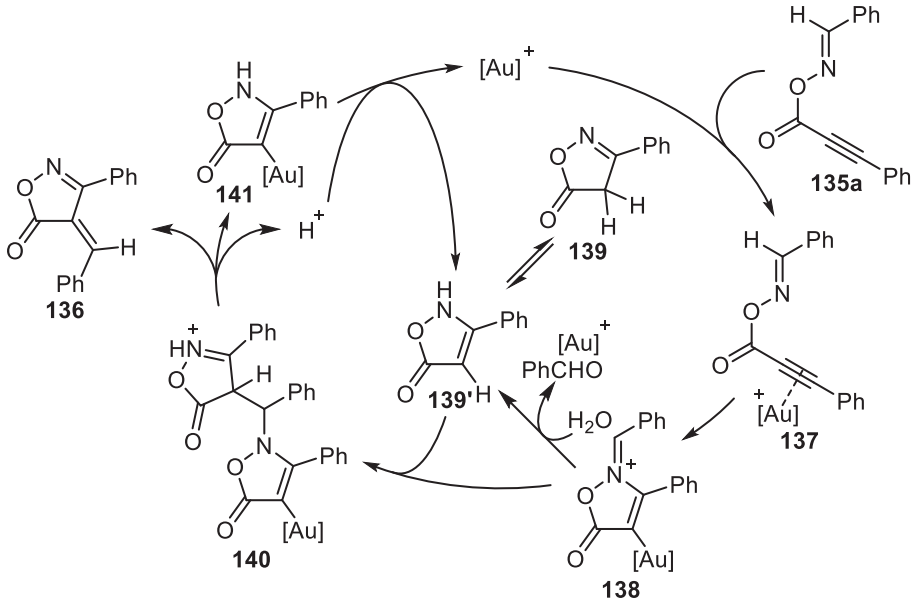
In 2010, Nakamura and Terada found that *O*-propioloyl oxime **135** undergoes arylidene transfer to afford 4-arylideneisoxazol-5(4*H*)-one **136** (Scheme 42).[54] For the alkyne terminus group (R^1), electron-rich, electron-poor, and bulky substituents could be applied without any problem (**136a**-**136d**). On the other hand, substituents on the oxime carbon (R^2) significantly affected the reaction: an electron-donating group (R^2 = *p*-anisyl) afforded **136e** in good yield, whereas an electron-withdrawing group (R^2= *p*-$CF_3C_6H_4$) decreased the yield of **136f** due to competitive decomposition of the starting materials.



136a (R^1 = Ph, R^2 = Ph) 90% (97:3)
136b (R^1 = *p*-anisyl, R^2 = Ph) 87% (97:3)
136c (R^1 = *p*-$F_3CC_6H_4$, R^2 = Ph) 81% (92:8)
136d (R^1 = *t*-Bu, R^2 = Ph) 90% (>99:1)
136e (R^1 = Ph, R^2 = *p*-anisyl) 88% (>99:1)
136f (R^1 = Ph, R^2 = *p*-$CF_3C_6H_4$) 50% (92:8)
(*E*/*Z* ratios are shown in parentheses)

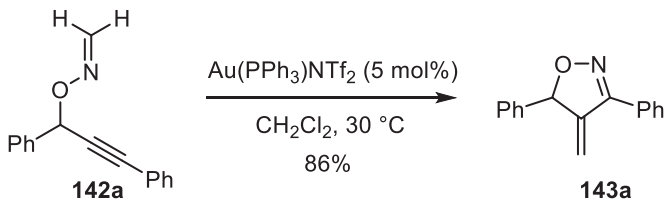
Scheme 42. Au(I)-Catalyzed cycloisomerization

The proposed reaction mechanism for this Au(I)-catalyzed cycloisomerization is shown in Scheme 43. Initially, a cyclized vinyl-Au(I) intermediate **138** is formed via nucleophilic attack by the N-atom of the imino group onto the electrophilic alkyne moiety of **135a**, which is coordinated to the π-acidic Au(I) catalyst. Subsequently, 5-isoxazolone **139** and its enamine tautomer **139'** are formed by hydrolysis of trace amounts of water.[55] Then, intermolecular nucleophilic attack by **139'** on the iminium moiety of another molecule of **138** forms the intermediate **140**. Finally, β-elimination and subsequent protodeauration give the product **136**, while the Au(I) catalyst and 5-isoxazolone **139'** are regenerated. Arylidene group transfer occurs via effective combination between the highly electrophilic iminium intermediate **138** and the highly nucleophilic isoxazolone species **139'**, which are generated *in situ* during the reaction.



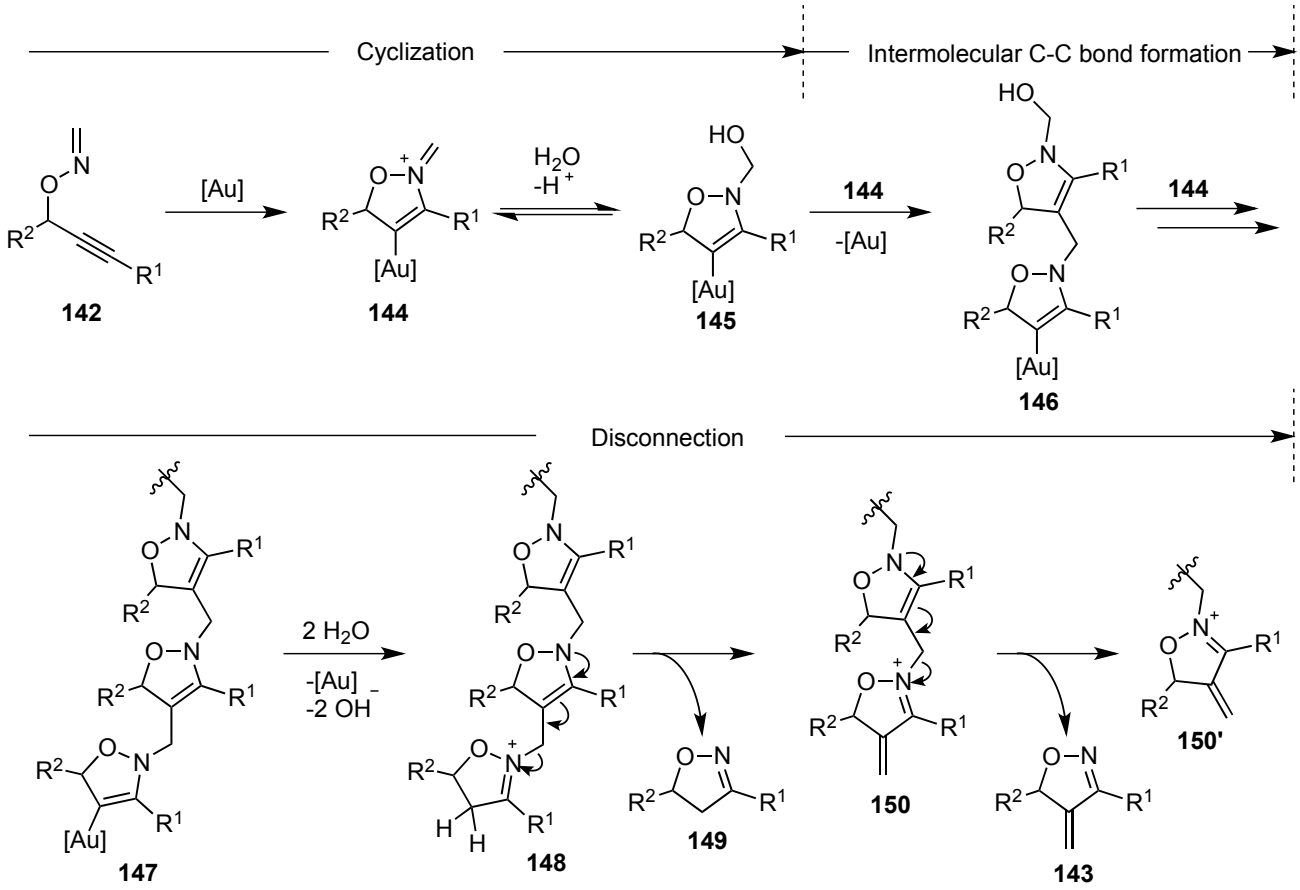
Scheme 43. Proposed reaction mechanism

Another type of cyclization/intermolecular C-C bond formation sequence, namely the Au(I)-catalyzed skeletal rearrangement of *O*-propargylic formaldoxime **142a** to synthesize 4-methylenated isooxazoline **143a**, has been developed (Scheme 44).[56]



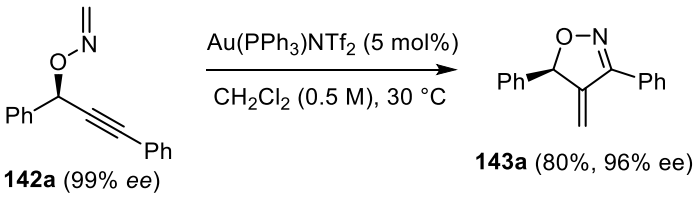
Scheme 44. Au(I)-Catalyzed cyclization/intermolecular methylene transfer cascade reaction

Based on several mechanistic studies, the reaction mechanism of a cyclization/intermolecular C-C bond formation/cleavage sequence is proposed in Scheme 45. Initially, Au catalyst-assisted intramolecular nucleophilic addition by the N-atom on the *N*-propargylic oxime provides a cyclized vinylgold intermediate **144**. The electrophilic iminium moiety of **144** reacts with the trace amount of water in the reaction mixture to form an enaminylgold species **145**. Then, the nucleophilic vinylgold moiety of **145** attacks the iminium moiety of another **144** molecule to form a C-C bond. Because the C-C bond formation takes place at the vinylgold terminus, the sequential process continuously generates another intermediate **147** molecule. Simultaneously, protonation at the nucleophilic vinylgold terminus of **147** leads to the iminium intermediate **148**. Subsequently, donation of electrons from the N-atom of the adjacent isooxazoline ring results in cleavage of the C-N bond and formation of an *exo* C=C bond to produce **150**, thus liberating the nonmethylenated isooxazoline **149**. Finally, electron donation from an adjacent isooxazoline ring continues and sequentially disconnects **143**.



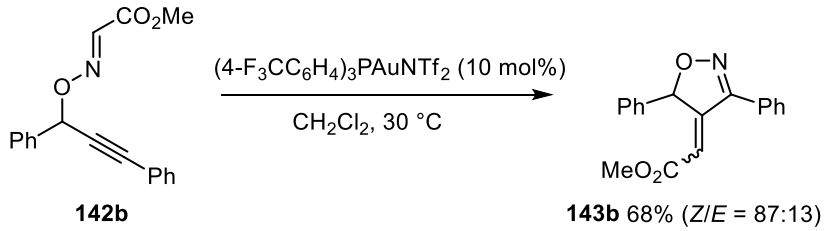
Scheme 45. Proposed reaction mechanism

Later, it was reported that the methylene-group transfer reaction can be applied to chirality transfer reactions (Scheme 46).[57]



Scheme 46. Chirality transfer on Au-catalyzed methylene-group transfer reaction

Recently, following consideration of the reaction mechanism, *O*-propargylic oxime **142b** derived from glyoxalate could also be applied to the Au-catalyzed methylene transfer reaction, where $(4\text{-}F_3CC_6H_4)_3PAuNTf_2$ gave the highest yield (Scheme 47).[58]



Scheme 47. Au-Catalyzed methylene transfer sequence of *O*-propargylic oxime derived from glyoxalate

4. TRANSITION METAL-CATALYZED CYCLIZATION OF *N*-ALKOXYAMIDE

Intramolecular nucleophilic addition of esters and amides to alkynes is a powerful method for synthesis of heterocycles. Although *N*-alkoxyamides, such as Weinreb amides, have been employed as electrophilic sites[59] or directing groups in C-H activation,[11,60] there have been few reports on reactions using *N*-alkoxyamides as nucleophilic sites. It should be noted that *N*-alkoxyamides have three nucleophilic sites: two oxygen atoms and a nitrogen atom (Figure 2). In such "multident" nucleophiles, it is necessary to control the selectivity of the nucleophilic site. In recent years, this issue has been addressed and will be introduced in this chapter.

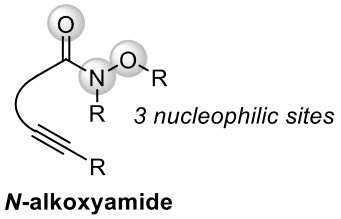
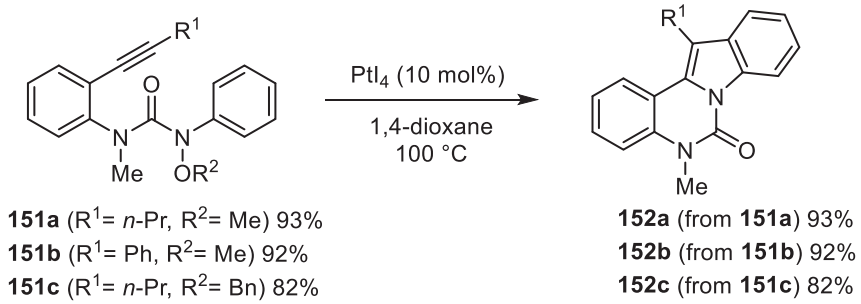


Figure 2. Properties of *N*-alkoxyamide

4-1. Nucleophilic Addition of N-Atom on *N*-Alkoxyamides

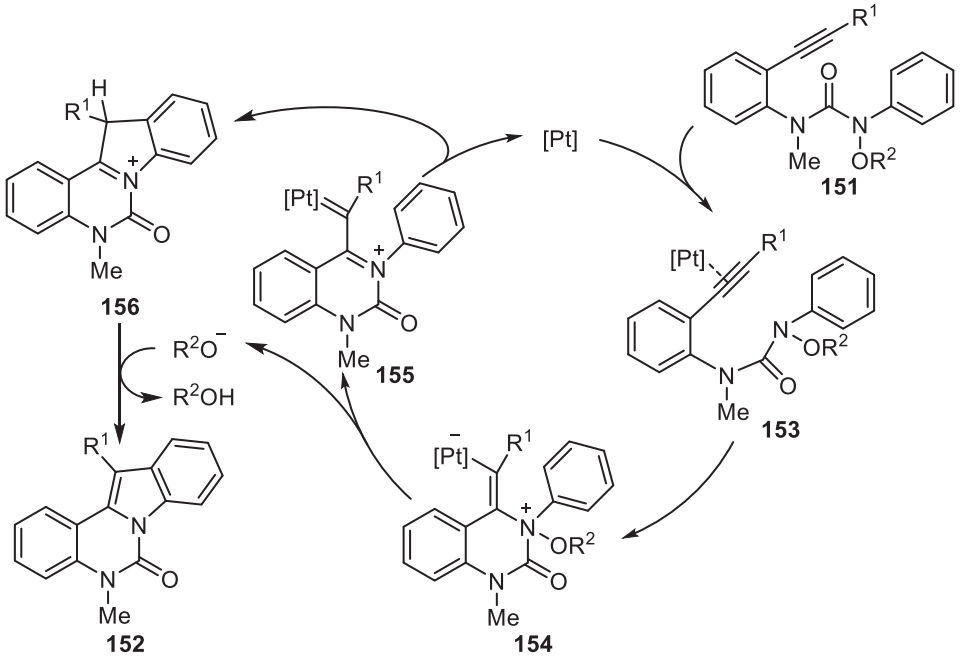
In 2009, Nakamura and Terada accomplished Pt-catalyzed cyclization of (*o*-alkynylphenyl)urea **151** accompanied by elimination of the alkoxy group, in which the N-atom on *N*-alkoxy urea worked as a

nucleophilic moiety (Scheme 48).[61] *N*-Methoxy-*N'*-methyl-*N'*-(2-(pent-1-ynyl)phenyl)-*N*-phenylurea **151a** with PtI_4 gave the corresponding N-containing tetracyclic compound **152a** in high yield. The cyclization of substrates bearing both alkyl and aryl groups on the alkyne terminus proceeded smoothly (**152a-c**). The reaction of **151c** having a benzyloxy group afforded **152c** in satisfactory yield.



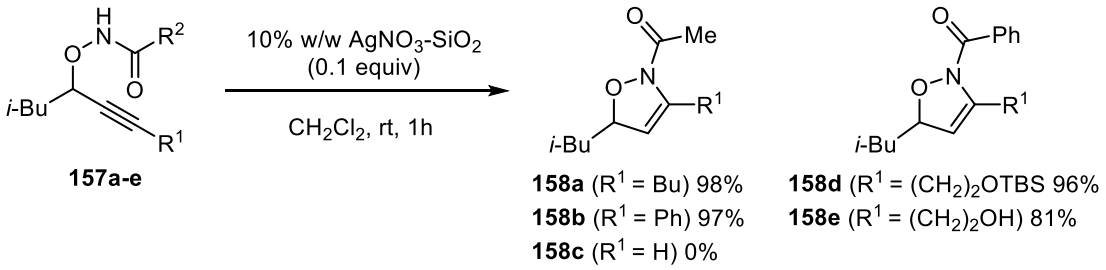
Scheme 48. PtI_4-Catalyzed dehydroxyalkoxylation-cyclization via N-O bond cleavage

As depicted in Scheme 49, the following reaction mechanism was proposed: first, the Lewis acidic Pt catalyst coordinates to the alkynyl moiety of **151** to form the π-complex **153**. Next, nucleophilic addition of the N-atom to the triple bond gives a vinylplatinum species **154**, followed by elimination of the alkoxy group to afford the iminium-bound Pt carbenoid **155**.[62] A C−H bond at the ortho-position of the phenyl group on the iminium N-atom inserts into the Pt carbenoid to give an iminium species **156**,[63] followed by the elimination of a proton to afford product **152**.



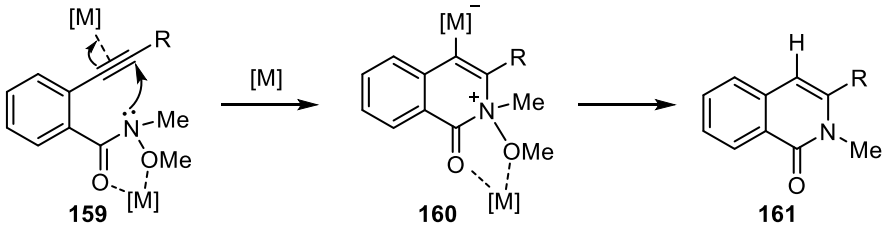
Scheme 49. Proposed reaction mechanism

In 2009, Knight reported the synthesis of 2,5-dihydroisoxazoles **157** from *N*-acylated hydroxylamines **158** where 5-*endo-dig* cyclization using silver(I) nitrate adsorbed on silica gel proceeded chemoselectively (Scheme 50).[64] Although a terminal alkyne could not be tolerated in this reaction, alkyl and aryl substituents on alkyne terminus were tolerated. Siloxy and hydroxy groups were also compatible with this reaction.



Scheme 50. Cyclization of *N*-acylated hydroxamines

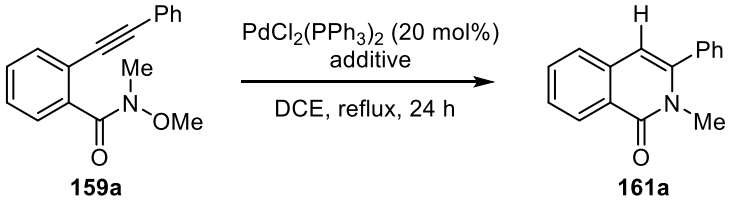
Our group reported the chemoselective synthesis of isoquinolinone **161** from *N*-alkoxy-*o*-alkynylbenzamide **159**.[65] It was envisaged that although *N*-alkoxyamide has three nucleophilic sites, the N-atom would react with the alkyne predominantly to produce a lactam because the lone pair of two O atoms coordinates to the transition metal. (Scheme 51).



Scheme 51. Chemoselective synthesis of isoquinolinone

In an investigation of the reaction, the treatment of *N*-alkoxy-*o*-alkynylbenzamide **159a** with $PdCl_2(PPh_3)_2$ in refluxing DCE led to the formation of the cyclized product *N*-methylisoquinolin-1-one **161a** via cyclization, elimination of the methoxy group, and protonation at the 4-position, albeit in low yield (Table 5, entry 1). A catalyst survey revealed that $PdCl_2(PPh_3)_2$ was superior to other catalysts, such as $PdBr_2(PPh_3)_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $FeCl_3$, $FeCl_2$, $ZnCl_2$, $Zn(OTf)_2$, $InCl_3$, $PtCl_2$, and $AuCl_3$. The addition of benzoquinone to the catalytic reaction led to a significant improvement in the chemical yield (entry 2).[66] The reaction was conducted in the presence of isopropyl alcohol and provided the desired product in an 81% yield (entry 4). Moreover, the reaction was found to be tolerant to an atmosphere of molecular oxygen, with these conditions providing a slightly enhanced yield of **161a** (entry 5).

Table 5. Optimization of Pd(II)-catalyzed cyclization of *N*-alkoxy-*o*-alkynylbenzamide



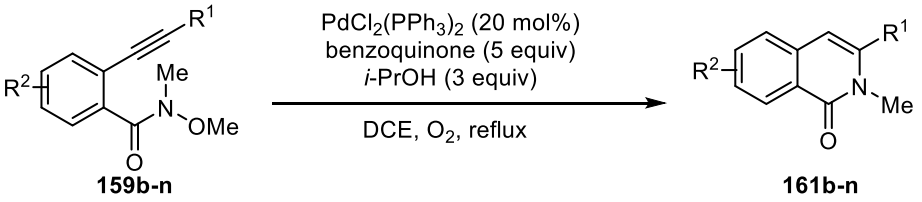
159a **161a**

Entry	Additive (equiv)	Yield (%)
1	–	28
2	benzoquinone (5)	66
3[a]	benzoquinone (5)	–
4	benzoquinone (5), *i*-PrOH (3)	81
5[b]	benzoquinone (5), *i*-PrOH (3)	85

[a]Without $PdCl_2(PPh_3)_2$

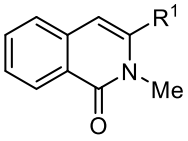
[b]Reaction was carried out under an O_2 atmosphere.

In an investigation of substrate scope, as shown in Scheme 52, the cyclization reaction of the Weinreb amide **159b** which possesses a *p*-fluorophenyl group at an alkyne terminus gave isoquinolinone **161b** with a 89% yield, whereas the introduction of an electron-donating group to the phenyl ring afforded the products **161c**, **161d** in lower yields. Although aliphatic substituents were well tolerated under the optimized conditions, a higher temperature was needed in the case of the cyclohexyl substituent, probably



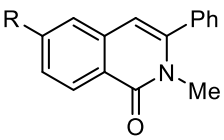
159b-n **161b-n**

(R^2 = H)

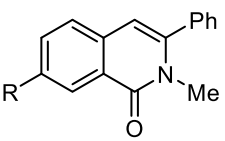


161b (R^1 = 4-FC_6H_4) 89%
161c (R^1 = 4-MeC_6H_4) 54%
161d (R^1 = 4-$MeOC_6H_4$) 62%
161e (R^1 = *n*-Bu) 46%[a]
161f (R^1 = Cy) 45%[a]

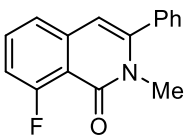
(R^1 = Ph)



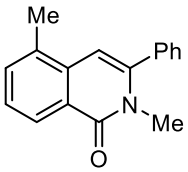
161g (R = F) 94%
161h (R =Cl) 91%



161i (R = OMe) 60%
161j (R =Me) 62%
161k (R = F) 76%
161l (R =Cl) 79%



161m 70%



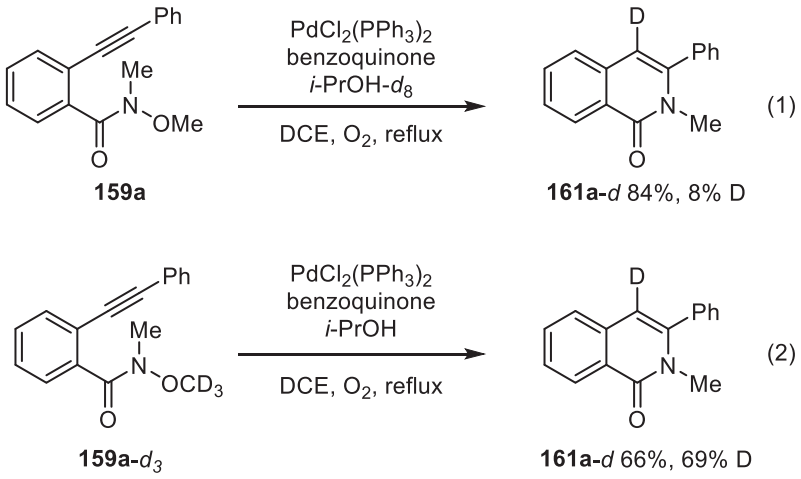
161n[a] 31%

[a]PhCl was used as a solvent instead of DCE.

Scheme 52. Substrate scope

due to steric hindrance (**161e**, **161f**). This Pd(II)-catalyzed cyclization protocol was also tolerant of substrates bearing halogen groups, such as fluoro and chloro groups, on the benzene ring at the *para* and *meta* positions to provide the cyclized products **161g**, **161h**, **161k**, and **161l**, respectively. Similarly, substrate **159m** bearing a fluoro group *ortho* to the carbonyl group produced **161m** in good yield. When substrates containing electron-rich aromatic rings were subjected to the cyclization conditions, the desired isoquinolinones **161i**, **161j** and **161n** were obtained in relatively lower yields, which indicates the preference of the reaction for electron-deficient ring systems.

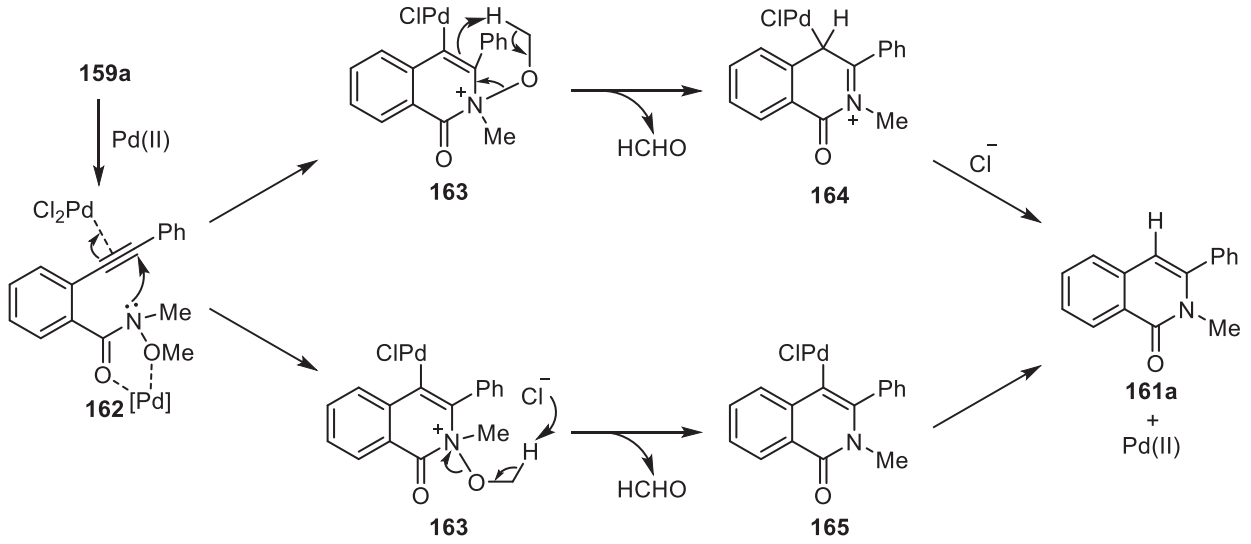
When the reaction of **159a** was conducted with deuterated isopropyl alcohol, the product **161a**-*d* was isolated containing only 8% of deuterium at the 4-position (Scheme 53, eq. 1). Compound **159a**-d_3 containing a deuterium-labeled methoxy group was subjected to palladium-catalyzed cyclization in the presence of isopropyl alcohol (eq. 2). This reaction resulted in 69% deuterium incorporation at the 4-position of isoquinolinone **161a**-*d*. These results imply that the hydrogen atom at the 4-position was derived predominantly by an intramolecular hydrogen shift from the methoxy group.



Scheme 53. Deuterium experiments

Based on the experimental results, a plausible mechanism for the transformation was proposed (Scheme 54). The alkyne moiety of *N*-methoxy-*N*-methyl-2-(2-phenylethynyl)benzamide (**159a**) is activated by the palladium catalyst to form a π-complex **162**. Subsequently, intramolecular nucleophilic attack by the N-atom of the Weinreb amide onto the triple bond occurs in a 6-*endo*-*dig* manner to generate intermediate **163**, which undergoes a 1,5-hydrogen shift to generate **164** with the concomitant formation of formaldehyde. Then, liberation of the catalyst provides isoquinolinone **161a**. Alternatively, chloride anion mediated N–O bond cleavage occurs to generate a vinylpalladium intermediate **165**, which subsequently undergoes protodepalladation to give **161a** as a minor pathway. Although the roles of benzoquinone and

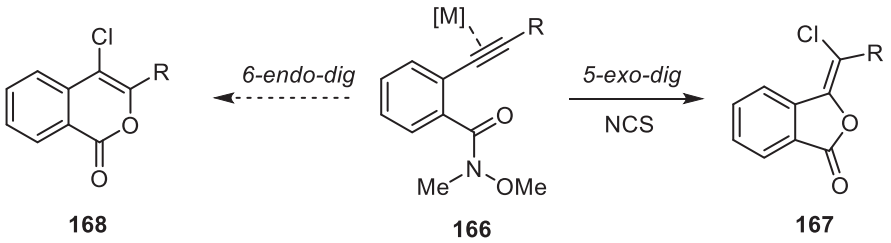
molecular oxygen are unclear, benzoquinone is thought to act as ligand for the palladium catalyst.[66]



Scheme 54. Proposed mechanism for the cyclization of the 2-alkynylbenzamides

4-2. Nucleophilic Addition of Carbonyl O-Atom on *N*-Alkoxyamides

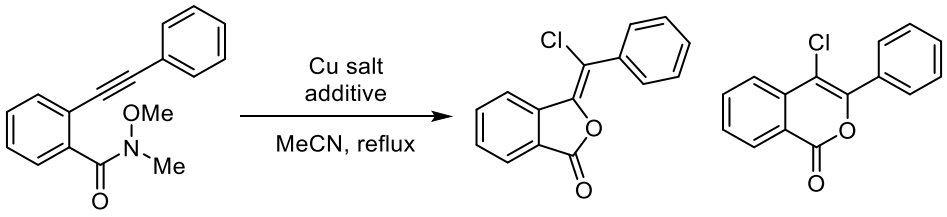
In 2011, our group developed transition metal-mediated 5-*exo*-selective chlorocyclization of *N*-alkoxy-*o*-alkynylbenzamide **166** to synthesize 3-(chloromethylene)isobenzofuran-1-ones **167** (Scheme 55).[67]



Scheme 55. Transition metal-mediated chlorocyclization of *N*-alkoxy-*o*-alkynylbenzamide **166**

In optimization studies, (chlorobenzylidene)isobenzofuran-1-one **167a** was exclusively obtained in 57% yield via regioselective cyclization, when *N*-methoxy-*o*-alkynylbenzamide **166a** was treated with 2.5 equivalents of $CuCl_2$ in MeCN at reflux (Table 6, entry 1). The cyclization proceeded smoothly in the presence of 2 equivalents of *N*-chlorosuccinimide (NCS) to produce **167a** as a pure (*E*)-isomer in 90% yield (entry 2). Using only NCS predominantly generated the six-membered-ring product **168a** in moderate yield (entry 3). These results indicated that $CuCl_2$ plays a pivotal role in the selective formation of five-membered-rings and that chlorocyclization is activated by NCS.

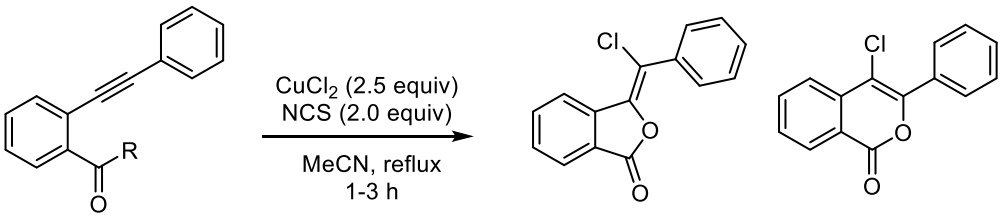
Table 6. Optimization of chlorocyclization of *N*-alkoxy-*o*-alkynylbenzamide



166a **167a** **168a**

entry	Cu salt (equiv.)	additive (equiv.)	yield	
			159a	**160a**
1	$CuCl_2$ (2.5)	none	57	–
2	$CuCl_2$ (2.5)	NCS (2)	90	–
3	none	NCS (2)	7	41

When the other carbonyl derivatives were examined, chlorocyclization of primary, secondary and tertiary amides **169-172** produced a mixture of products **167a** and **168a** in low to moderate yields (Scheme 56). In contrast, the exclusive formation of isocoumarin **168a** was observed when methyl ester **172** was subjected to the cyclization reaction.[68] These results indicate that a component of the Weinreb amides plays an important role in selective 5-*exo*-*dig* cyclization.



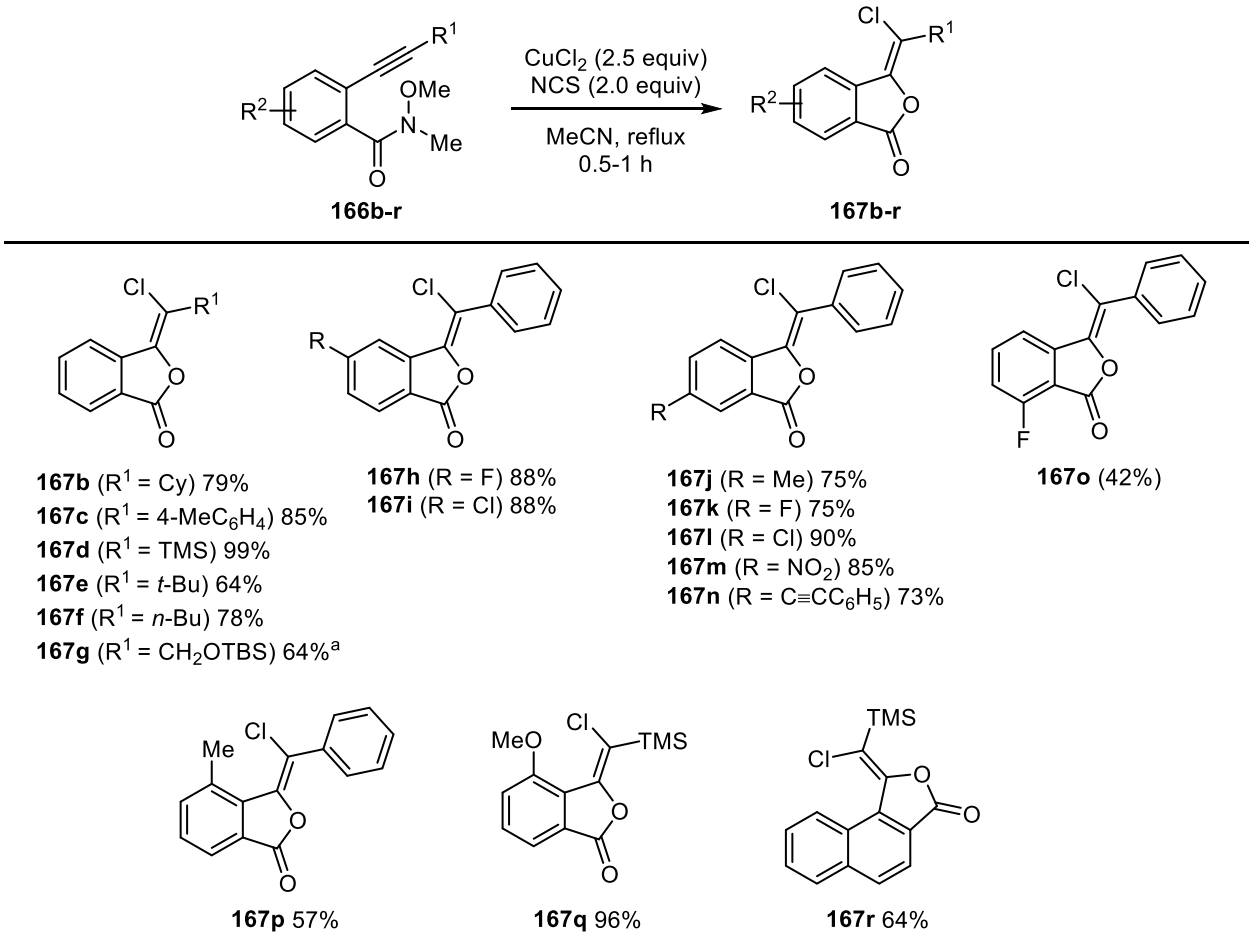
166a, **169-172** **167a** **168a**

166a (R = N(OMe)Me)	90%	–
169 (R = NMe_2)	14%	trace
170 (R = NHPh)	42%	trace
171 (R = NH_2)	22%	7%
172 (R = OMe)	–	88%

Scheme 56. Cyclization of substrates

The substrate scope is illustrated in Scheme 57. The reaction of various acetylenic substrates with $CuCl_2$/NCS resulted in broad substrate capability and the reaction could be well tolerate in a range of substituents on the acetylenic unit carrying a cyclic or acyclic moiety. An excellent chemical yield was observed in the reaction of TMS-substituted alkyne **166d**, albeit a relatively lower yield being obtained in the reaction of *tert*-butyl substituted alkyne **166e**. Substrates **166b** and **166f** having aliphatic substituents also worked well. Alkyne **166g**, which possesses a silyloxymethyl group underwent chlorolactonization

and then desilylation to yield the allylic alcohol **167g** in moderate yield. The manipulation of the benzamide bearing a halogen substituent, such as a fluoro or chloro atom, *para* or *meta* to the carbonyl group lead to very good yields (**167h**, **167i**, **167k**, **167l**). On the other hand, the substrate having an *ortho*-fluoro group to the carbonyl group afforded **167o** in lower yield. **166n** bearing an additional alkyne moiety gave **167n** as a sole product without suppression of the desired reaction. Alternatively, substrates bearing electron-rich or electron-deficient substituents performed well (**167j**, **167m**, **167p**).



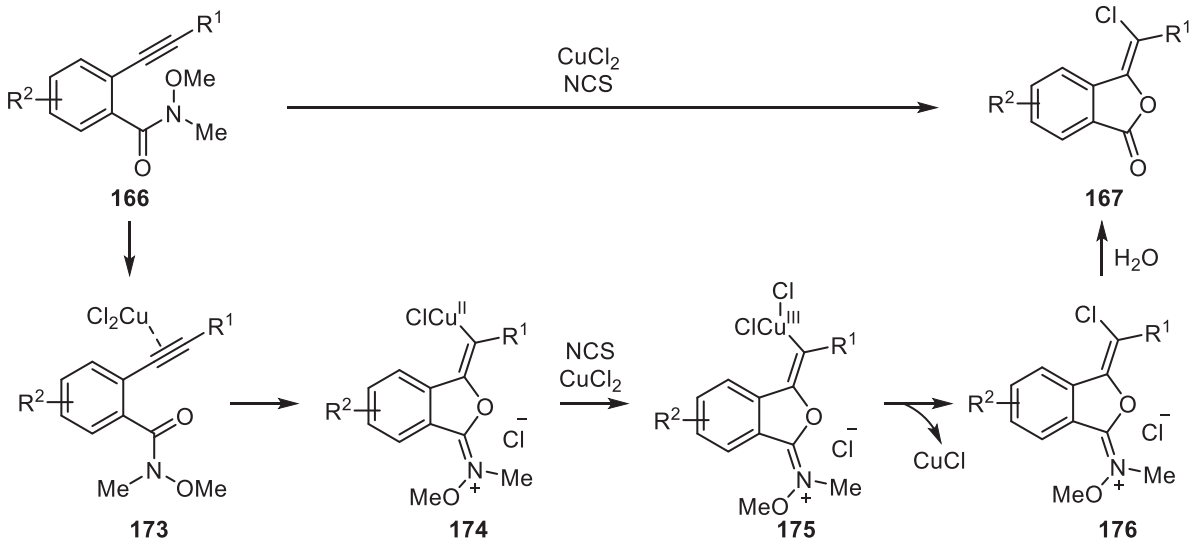
[a]The yield of a siloxy group-removed derivative is shown.

Scheme 57. Substrate scope

The cyclization proceeded well to give **167q** in 96% yield when the substrate contained a methoxy group *ortho* to the alkyne. Moreover, the naphthyl substrate was also demonstrated to afford **167r** in 64% yield.

A proposed reaction pathway is shown in Scheme 58. The activation of an alkyne moiety of **166** by $CuCl_2$ followed by the nucleophilic addition of the carbonyl oxygen proceeds to form an intermediate **174** via 5-*exo*-*dig* cyclization. The Cu(II) species is oxidized by another equivalent of $CuCl_2$ to give Cu(III)

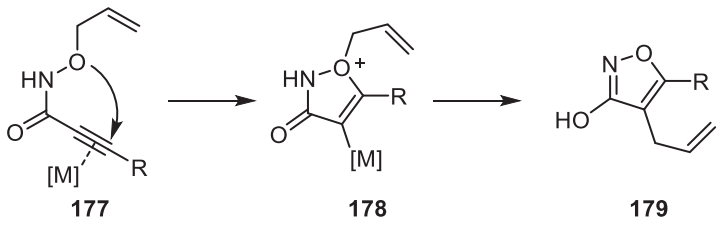
species **175**.[69] After chlorination at the copper atom by NCS, reductive elimination affords **176**. Finally, the work-up process leads to product **167** from intermediate **176**.



Scheme 58. Plausible reaction pathway

4-3. Nucleophilic Addition of Alkoxy O-Atom on *N*-Alkoxyamides

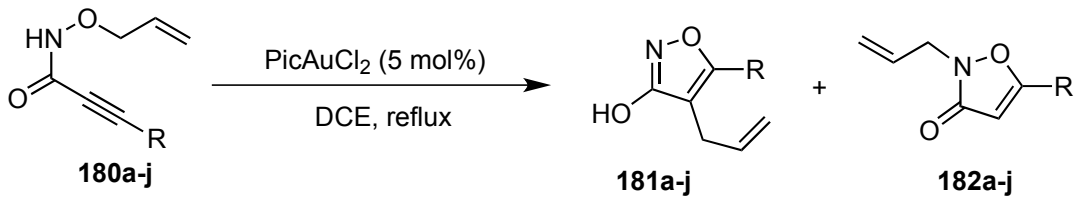
In 2016, our group reported that the transition metal-catalyzed cyclization of *N*-allyloxypropiolamide **177** provides access to the corresponding 4-allyl-3-hydroxyisoxazole **179** via migration of the allyl group (Scheme 59).[70]



Scheme 59. Nucleophilic addition of alkoxy O-atom on *N*-alkoxyamides

The investigation of various transition metal catalysts showed $PicAuCl_2$ to be an optimal catalyst. The scope of this reaction was explored by varying the nature of the substituent at the alkyne terminus (Table 7). Substrates having an electron-rich/deficient aryl group were well tolerated to afford the corresponding 3-hydroxyisoxazoles **181** in good yields along with a small amount of *N*-allylisoxazolone **182** (entries 1-4). Although various aliphatic substituents were well tolerated at the terminal position of the alkyne under these conditions (entries 5-8, 10), substrate **180i** bearing a *tert*-butyl group gave **181i** in a lower yield due to steric repulsion (entry 9).

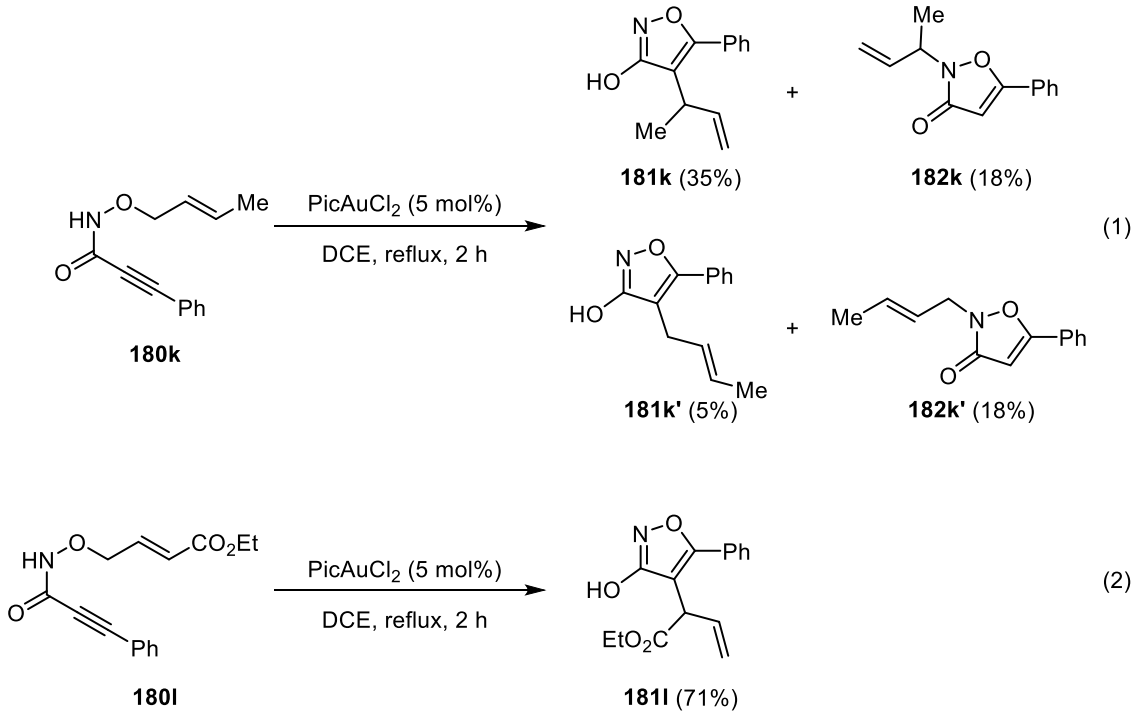
Table 7. Substituent effect at alkyne terminus



180a-j **181a-j** **182a-j**

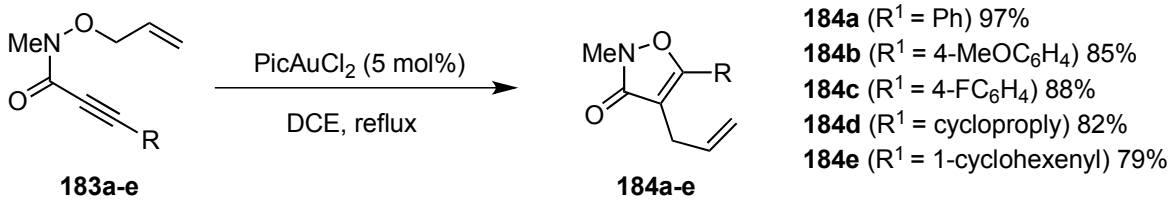
entry	substrate	R	yield (%)	
			181	**182**
1	**180a**	Ph	86	8
2	**180b**	4-$MeOC_6H_4$	78	9
3	**180c**	4-$CF_3C_6H_4$	75	5
4	**180d**	4-FC_6H_4	88	6
5	**180e**	Me	65	-
6	**180f**	*n*-Bu	74	11
7	**180g**	Cy	75	11
8	**180h**	cyclopropyl	72	-
9	**180i**	*t*-Bu	52	15
10	**180j**	1-cyclohexenyl	90	3

The reaction of *O*-crotyl hydroxamate **180k** gave isoxazole **181k** bearing a branched allyl group as a major product, although small amounts of a linear allylated isoxazole **181k'** and branched/linear *N*-allylated isoxazolones **182k** and **182k'** were formed (Scheme 60). The formation of the branched 4-(1-methylallyl)-3-hydroxyisoxazole **181k** as a major product suggests that the rearrangement of the allyl moiety to the C4 position of the isoxazole skeleton mainly proceeds via a [3,3]-sigmatropic rearrangement rather than an allyl cation shift, while the migration of the allyl group onto the N atom proceeds via a [2,3]-sigmatropic rearrangement or cation shift. Moreover, these results indicate that the substituent on the alkene terminus can suppress the formation of the six-membered ring transition state for the [3,3]-sigmatropic rearrangement by steric hindrance, resulting in a lower chemical yield of the desired 3-hydroxyisoxazole. However, the use of an ester moiety allowed to overcome this drawback, as exemplified by the reaction of the α,β-unsaturated ester **180l**, which afforded the corresponding 3-hydroxyisoxazole **181l** in high yield.



Scheme 60. Effect of substituents on the allyl group

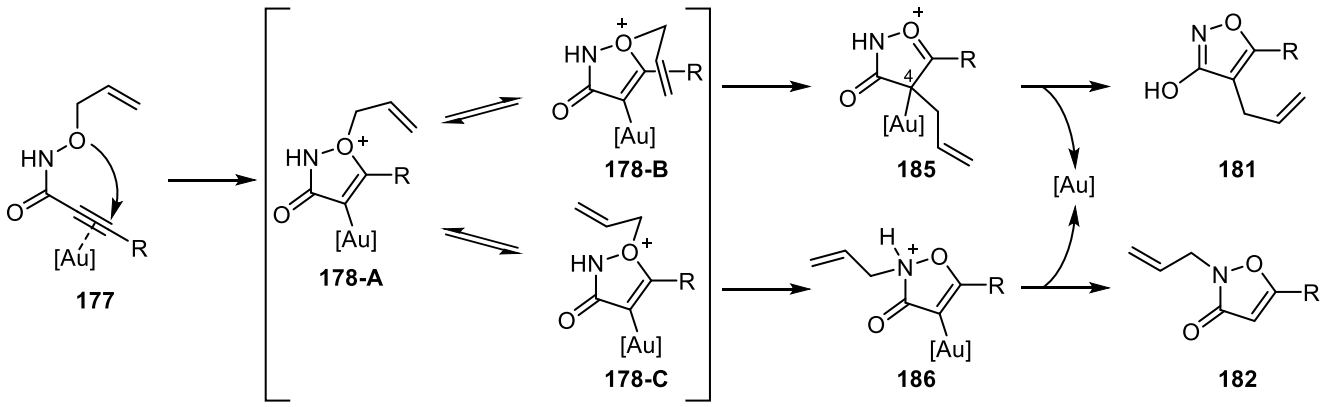
The use of *N*-methylated hydroxamate **183a** as a substrate gave the corresponding isoxazolone **184a** in excellent yield (Scheme 61). Aryl and alkyl groups were both well tolerated at the alkyne terminal of these substrates under these conditions, with the corresponding isoxazolones **184b–e** being isolated in good yields.



Scheme 61. Substrate scope of *N*-methylhydroxamate **183a-e**

A proposed reaction mechanism for the reaction is shown in Scheme 62. Initially, intramolecular addition of the hydroxamate O-atom to the Au(III)-activated alkyne moiety occurs in a 5-*endo-dig* fashion to give an oxonium intermediate **178-A**. Subsequently, [3,3]-sigmatropic rearrangement of the allyl group to the C-4 carbon proceeds via conformation **178-B** to give intermediate **185**, which undergoes an aromatization process to give the 3-hydroxyisoxazole **181**. In contrast, the rearrangement via conformation **178-C** leads to the formation of intermediate **186**, which undergoes aromatization to afford the undesired *N*-allylisoxazolone **182**. Substrates having a bulky substituent at the terminal position of their alkyne (e.g.,

180i) are subject to severe steric repulsion in conformation **178-B** between the bulky R substituent and the allyl moiety. The lower yield of **180i** compared with **180h** is accounted for by the steric repulsion, with the reaction being forced to proceed via conformation **178-C** to give the *N*-allylated product **182**.



Scheme 62. Plausible reaction pathway

5. CONCLUSION

In this review, cyclization reactions of alkynes initiated by the addition of heteroatoms into a C-C triple bond were introduced, with a focus on the nucleophilic site of the nitrogen-oxygen bond. This methodology could be used to synthesize various heterocycles, as shown in Figure 3. The product diversity is associated with the highly reactive organometallic intermediates generated by nucleophilic addition, which undergo various transformation, depending on the metal species and substitution pattern. Moreover, the nitrogen-oxygen bond does not only have high nucleophilicity, but is also easily cleaved. Notably, most of these reactions proceeds in an atom-economical manner and thereby are environmentally friendly. These promising properties will pioneer further novel chemistry to synthesize unidentified heterocycles. Therefore, in addition to nitrogen-oxygen bonds, the chemistry of adjacent heteroatoms, such as nitrogen-nitrogen bonds, will be further developed.

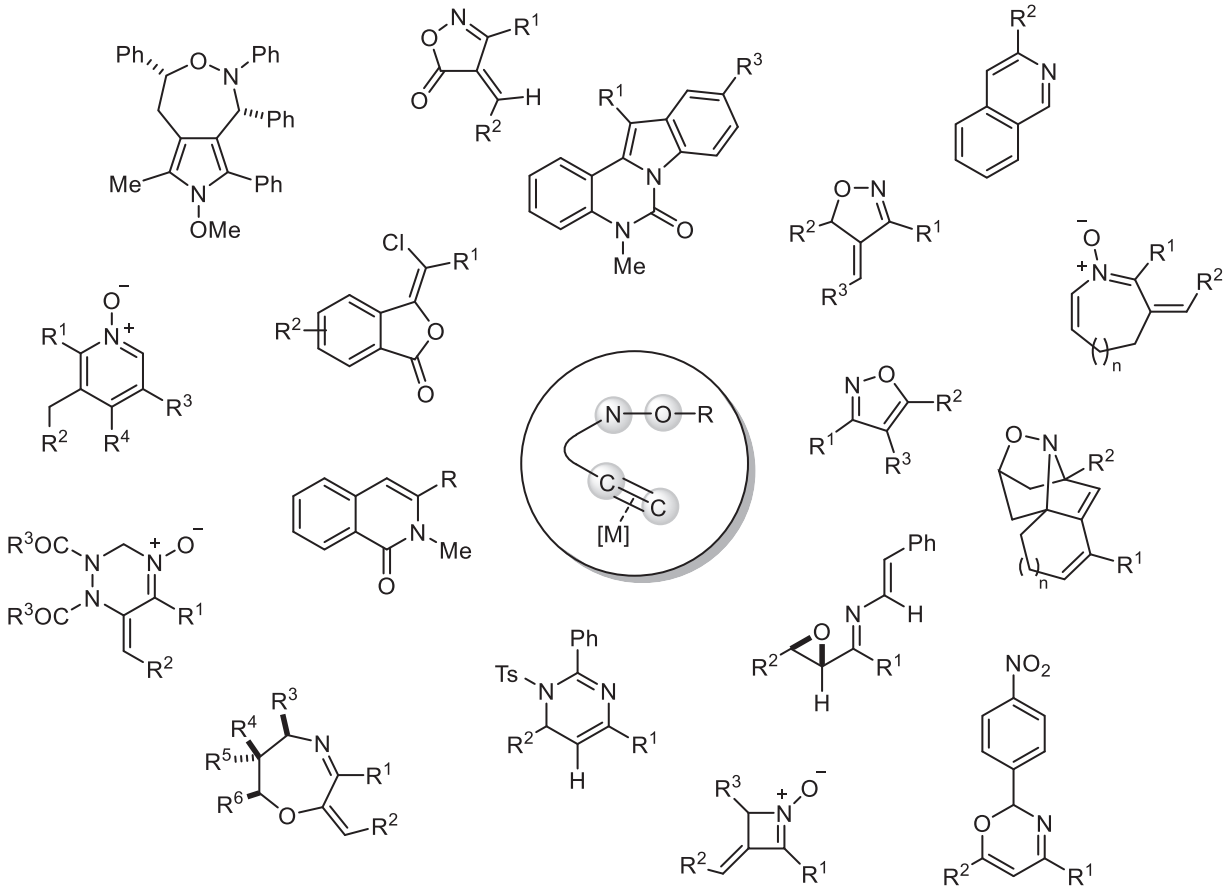


Figure 3. Summary for synthesis of heterocycles utilizing *N*-alkoxyimines and *N*-alkoxyamides

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