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Oxime ethers as versatile precursors in organic synthesis: A review

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Abstract

This review is a survey of the literature describing synthetic applications of oxime ethers. The cyclization and metal-catalyzed cross-coupling reactions of oxime ethers in recent years are also highlighted.

1. Introduction

Compounds bearing oxime ether group are valued not only for their rich and varied chemistry, but also for many important biological properties. The oxime ether moiety (Figure 1) is a privileged group in chemistry due to its presence in a large number of medicinal scaffolds that exhibit a broad range of biological and pharmaceutical properties, such as antifungal,[1] antibacterial,[2] anti-enteroviral,[3] anti-protozoan,[4] anti-inflammatory,[5] anticonvulsant,[6] anticancer,[7] antitumor[8] activities. Overall, both aldoxime (**a**) and ketoxime *O*-ethers (**b**) are most important and versatile intermediates in organic synthesis. They are attractive starting materials for the synthesis of nitrogen containing compounds including amines, 1,2-aminoalcohols, α- and β-amino acids, nitriles, lactams and 3- to 8-membered ring nitrogen heterocycles.[9]

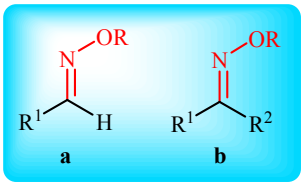


Figure 1. General structure of aldoxime (a) and ketoxime *O*-ethers (b)

To the best of our knowledge, the significance of oxime ethers and their polyfunctional derivatives as useful building blocks in organic syntheses has not been reviewed. This review includes available information on using these compounds for preparation of a board range of useful compounds. We have classified the applications of oxime ethers in organic synthesis based on type of the reaction (e.g.

cyclization, and metal-catalyzed cross coupling reactions) and the desired reaction products (e.g. amines, nitriles and hydroxylamines). The most detailed discussion will be focused on cyclization and metal-catalyzed cross coupling reactions of titled compounds. Some of the important synthetic compounds derived from oxime ethers are summarized in Figure 2.

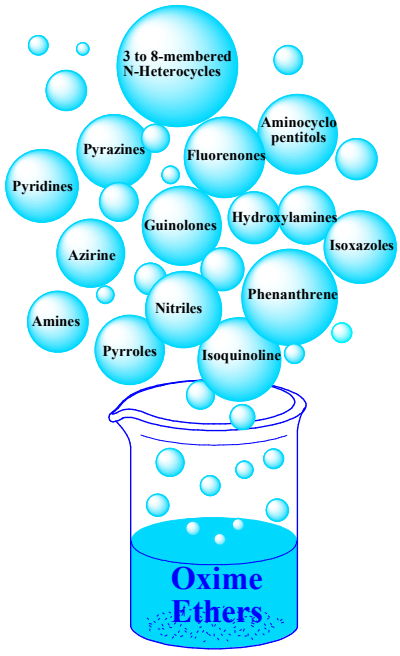
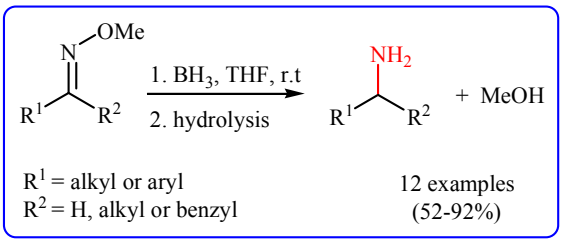


Figure 2. Some important synthetic compounds derived from oxime ethers

2. Amine and hydroxylamine formation from oxime ethers

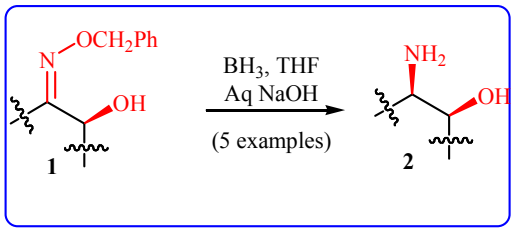
Amines are a very important family of compounds in chemistry and biology. They constitute a major class of naturally occurring compounds and are widely used in the production of pharmaceuticals.[10] There are several papers on the preparation of amines from oxime ethers. A report of the successful formation of amines *via* reduction of oxime ethers has been published by Feuer and Braunstein in 1969 (Scheme 1).[11] This reduction is an attractive route for the efficient conversion of aldehydes and ketones into amines at room temperature in the presence of diborane, and gives the corresponding amines in good to high yields.



Scheme 1. Formation of amines *via* reduction of oxime ethers

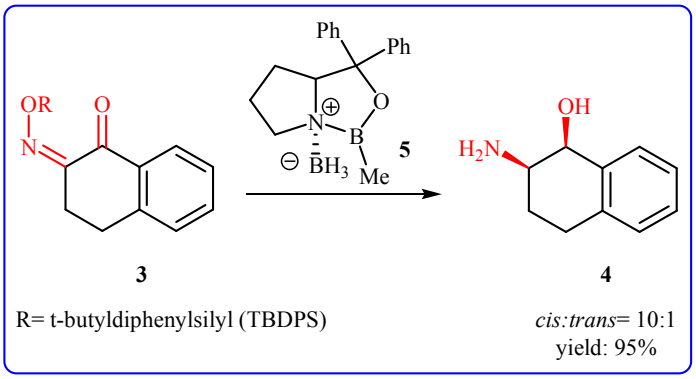
Following this work, Sakito's group in 1988, has investigated the enantioselective reduction of oxime ethers using borane and chiral auxiliary of norephedrine in THF at -30 to 20 ^{o}C and primary amines were achieved in good to high enantiomeric excess (79-92% ee).[12]

The *cis*-1,2-amino alcohols are important structural elements in a wide variety of biologically important molecules.[13] A robust method for the synthesis of cyclic *cis*-1,2-amino alcohols **2** *via* reduction of α-hydroxy oxime ethers **1** has been reported by Ghosh and co-workers (Scheme 2).[14] The borane/THF/Aq NaOH system was found to be optimal for this reaction. The mechanism for the selective formation of *cis*- 1,2-amino alcohols involves the reaction of borane with α-hydroxy oxime to generate the alkoxy borinate and subsequent reduction of oxime occurs from the less hindered side away from the bulky borinate to give the titled products in high yields.



Scheme 2. Synthesis of cyclic *cis*-1,2-amino alcohols *via* reduction of α-hydroxy oxime ethers

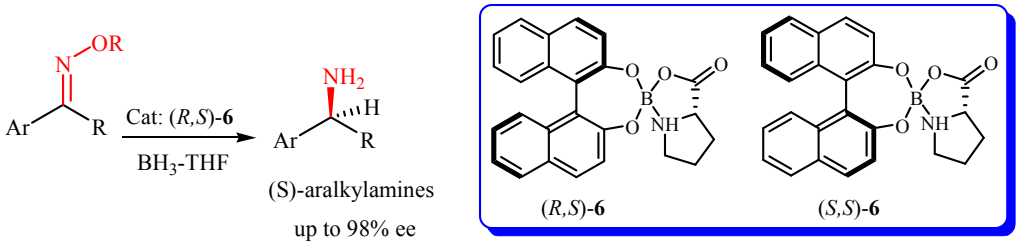
Four years later, an efficient method for synthesis of cyclic (1*S*, 2*R*)-*cis* amino alcohols **4** from α-keto oxime ethers **3** *via* catalytic asymmetric reduction using oxazaborolidine-borane complex **5** was contributed by Tillyer's research team (Scheme 3). The reaction involves the reduction of C=O, C=N, and N-O bonds, respectively. The *O*-protecting groups have a vital effect on the reduction of N-O bond. The unprotected keto oxime undergoes almost non-stereoselective reduction while the reduction of *t*-butyldiphenylsilyl (TBDPS) -protected α-keto oxime ether **3** led to formation of **4** with excellent enantio- and diastereoselectivity.[15]



Scheme 3. Synthesis of cyclic (1*S*, 2*R*)-*cis* amino alcohols **4** from N-protected keto oxime ether **3**

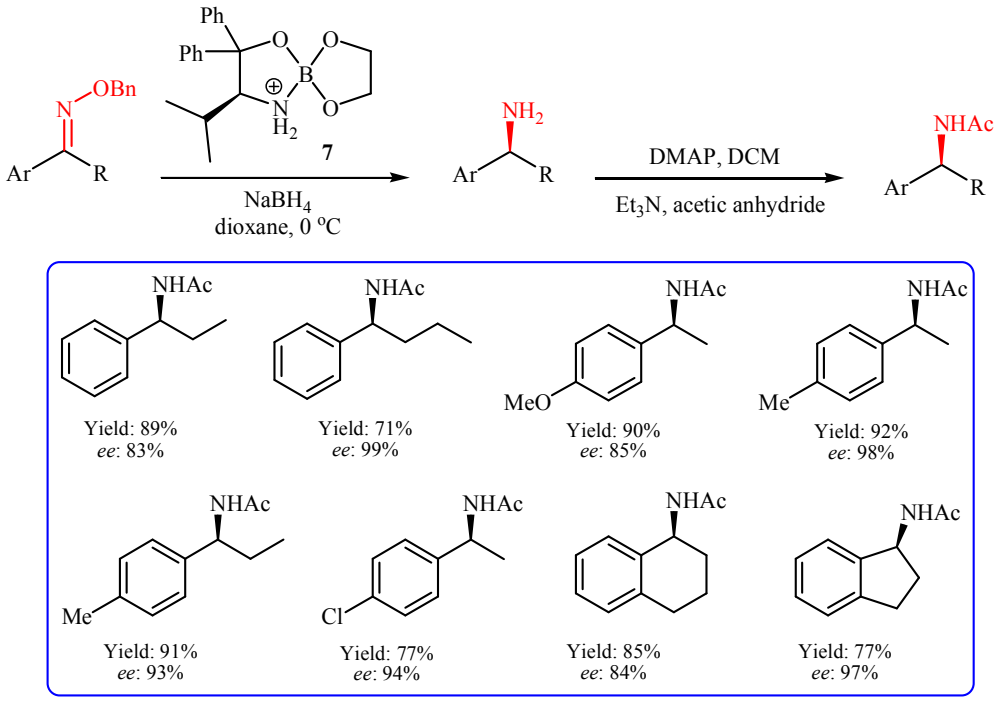
Itsuno *et al.* further expanded the efficiency of this method by using the polymer-supported oxazaborolidine catalyst. This catalyst was used in the efficient enantioselective borane reduction of oxime ethers to enantioenriched primary amines.[16]

In an effort towards the development of a more effective methodology for enantioselective synthesis of primary amines *via* asymmetric reduction of oxime ethers, Shan's research team reported a new chiral promoter for borane reduction of prochiral aryl alkyl ketoxime ethers.[17] Asymmetric reduction of aryl alkyl ketoxime ethers by borane-THF in the presence of chiral spiroborate ester (*R,S*)-**6**, at 0-5 °C gave (*S*)-aryl alkylamines in high yields (76-97%) and excellent enantiomeric excess up to 98% ee (Scheme 4).



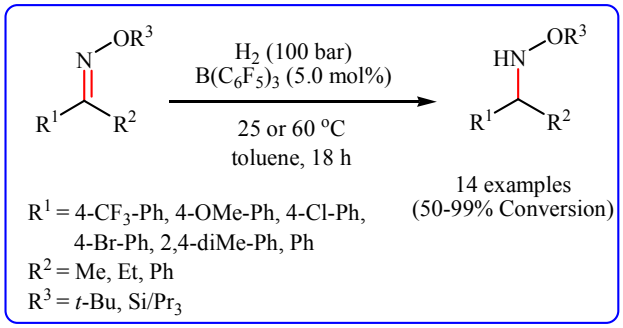
Scheme 4. Asymmetric reduction of aryl alkyloxime ethers by Chiral Spiroborate Esters **6**

A very similar approach for enantioselective synthesis of amines using spiroborate ester **7** as a chiral promoter, $NaBH_4$ as a borane stabilizer, and dioxane as solvent at 0 °C was reported by Ortiz-Marciales and co-workers (Scheme 5).[18]



Scheme 5. Asymmetric reduction of oxime benzyl ethers catalyzed by **7**

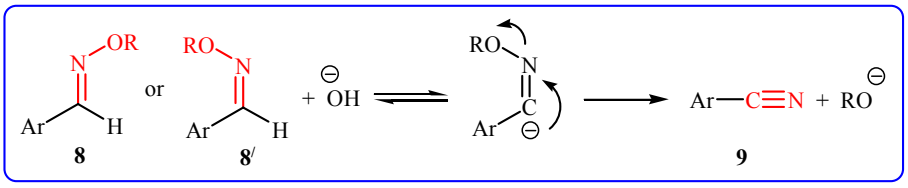
More recently, an interesting and high efficiency triarylborane Lewis acid catalyzed chemoselective hydrogenation of oxime ethers was reported by Oestreich and Mohr.[19] The commercially available $B(C_6F_5)_3$ (tris(pentafluorophenyl)borane) was found to be an optimal catalyst for this reaction. The reaction worked well at elevated or even room temperature under 100 bar hydrogen pressure for a broad range of oxime ethers (Scheme 6). Notably, the reaction conditions were compatible with functional groups such as halogens and ethers which are useful for further synthetic transformations. Previously Kawase and Kikugawa reported the same reaction for reduction of *O*-methyl oximes to hydroxylamines in high to excellent yields (83-98%) by using pyridine/BH_3/acid system.[20]



Scheme 6. Hydrogenation of oxime ethers to hydroxyl amines

3. Nitrile formation from dehydration of aldoxime ethers

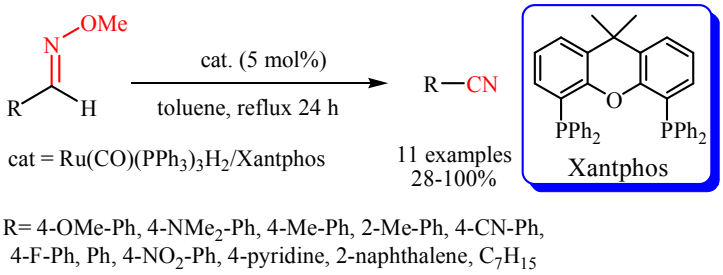
Dehydration of oxime ethers is a reaction which permits the transformation of an aldehyde to the corresponding nitrile under mild conditions. The oxime ethers **8** and **8′** undergo base-catalyzed elimination to form benzonitriles **9** in water /dioxane (4:1) (Scheme 7). The electronic characters of Ar and OR had remarkably important effect on the facility of this reaction. Overall, the electron poor aldoxime ethers worked well under this reaction condition. The *Z*-isomer **8′** reacts 70-fold more rapidly than the corresponding *E*-isomer. These results are interpreted in terms of a central E_2 elimination, with appreciable C-H and N-O bond cleavage in the transition state.[21]



Scheme 7. Formation of nitriles from aldoxime ethers

In 2002, Yonezawa *et al.* reported the metal catalyzed dehydration of alkyl aromatic aldoxime ethers to form nitriles. They tested several catalysts, and the system $NiCl_2$/Zn/*p*-xylene was found to be superior. They proposed that the reaction proceed *via* coordination of oxygen of ether to low- valent metal species. Under optimized conditions, the reaction tolerates electron-donating –OR substituents at

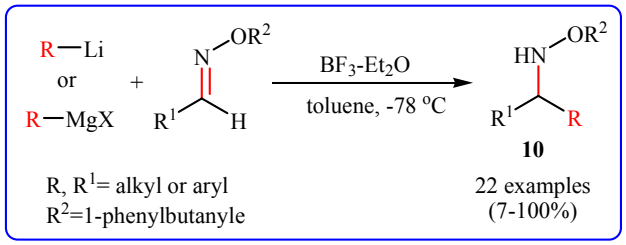
ortho positions of aryl moiety and gave corresponding nitriles in good yields, but it could not be extended to sterically hindered *ortho*-substituted aryl moiety. It is due to the difficulty of interaction of the sterically hindered oxygen atom with metal.[22] Following this work, Williams research team developed more efficient method for this reaction using $Ru(CO)(PPh_3)_3H_2$/Xantphos/toluene system (Scheme 8). The result reveals that oxime ethers can be converted into nitriles using similar catalyst system which is effective for the conversion of the parent oximes into amides.[23]



Scheme 8. Synthesis of nitriles from oxime ethers catalyzed by Ru catalyst

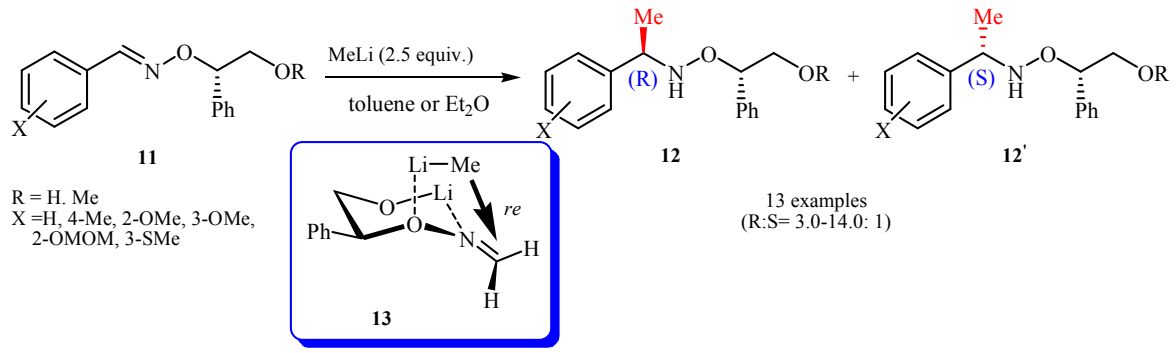
4. Hydroxylamines formation by electrophilic reactions of aldoxime ethers

Addition of carbanions to aldoxime ethers is an efficient route for synthesis of hydroxyl amines, which are key reagents for preparation of α-amino acids.[24, 25] Early reports of the successful formation of hydroxylamines **10** from oxime ethers in the presence of organolithium and borontrifluoride etherate in THF showed that this method complemented the existing literature in a number of ways.[26] The reaction does not work well with Grignard reagents in THF but toluene was found to be optimal solvent for this reaction[27, 28]. The presence of $BF_3.Et_2O$ was crucial to do the reaction (Scheme 9).[29] Notably, the oxime ethers derived from heteroaromatic aldehydes gave very poor results under aforementioned conditions.[27]



Scheme 9. Addition reaction of carbanions to aldoxime ethers

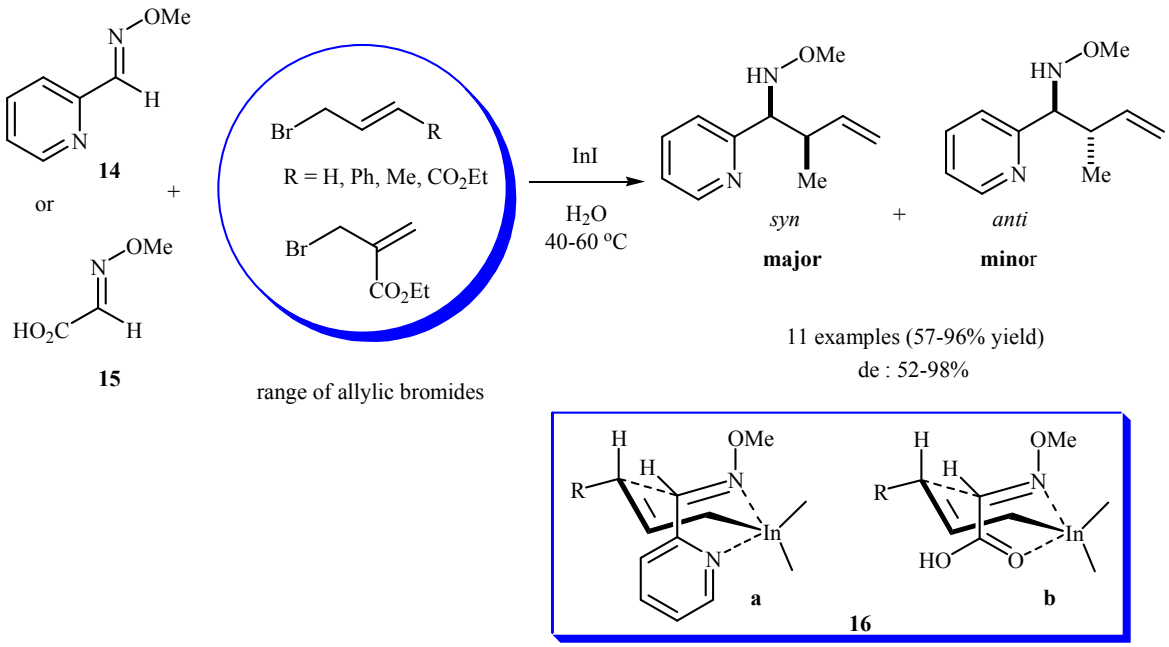
Kibayashi *et al.* demonstrated that a series of (*E*)-aryl aldehyde oxime ethers **11** could be reacted with methyl lithium in toluene or Et_2O to produce diasteromerically enriched *O*-alkyl hydroxamine *via* six-membered ring lithium chelation **13**, which activates the substrate for addition, leading to 1.4-asymmetric induction (Scheme 10).



Scheme 10. Nucleophilic addition of methyl lithium to chiral oxime ethers

This methodology has been applied to the enantioselective synthesis of a new type of aryl alkyl amine calcimimetics (R)-(+)-NPS R-568 and its thio analogue which can be used for the treatment of primary and secondary hyperparathyroidism.[30] Moody and co-workers employed this strategy for the asymmetric synthesis of chiral primary r-ferrocenyl alkyl amines which are used in the preparation of chiral redox-active receptors.[31] It should be noted that the treatment of aldoxime ethers with alkyllithium compounds or Grignard reagents followed by hydrolysis afford ketones in high yields.[32]

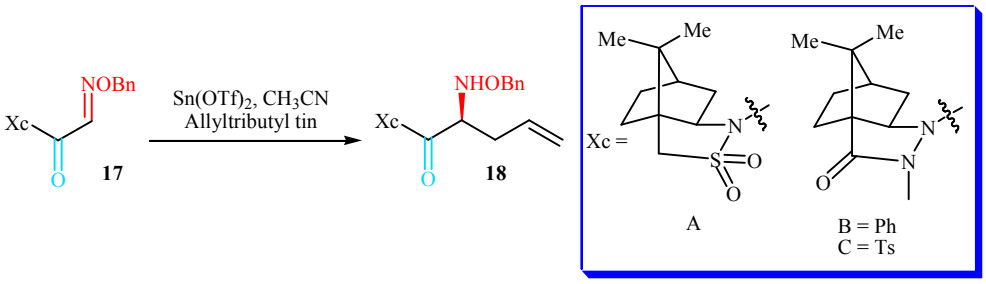
In 2002, Ricci *et al*. highlighted that oxime ethers **14** and **15** derived from 2-pyridinecarboxaldehyde and glyoxylic acid, respectively, can be effectively allylated in water with a range of allylic bromides in the presence of indium iodide. Six-membered ring indium chelation **16 (a,b)** activated the substrate for addition, and led to 1,2-asymmetric induction. Indeed, chelation affects both reactivity and diastereoselectivity (Scheme 11).[33] Takemoto *et al.* extended the utility of this method using a catalytic amount of palladium complex ($Pd(PPh_3)_4$) for allylation of glyoxylic oxime ether with a broad range of allylic reagents in the presence of InI in THF at 20 ^oC. Excellent diastereoselectivities were achieved in the presence of water. The level of yields and diastereoselectivity of the eight listed examples in THF/ H_2O with ratio of 10/1, lies in the range of 88-96% and 91-94%, respectively. Excellent diastereoselectivities were achieved in water. Although the role of water was unclear, these observations would be explained by the reversibility of allylation reaction. To develop a practical method for the propargylation of oxime ethers, $Pd(OAc)_2$**.**PPh_3/InI was chosen as an effective catalytic system by the same authors. Anhydrous THF was the best solvent for propargylation and addition of LiBr or LiCl was found to be necessary for efficiency of the reaction.[34, 35]



Scheme 11. Indium-mediated allylation reaction of oxime ethers in aqueous media

A beautiful diastereoselective nucleophilic allylation of camphor derived glyoxylic oxime ether **17** with Lewis acids was reported by Kulkarni and Chen.[36] Various allylmetal reagents, Lewis acids and solvents were examined and the allyltributyltin/$Sn(OTf)_2$/CH_3CN system was found to be optimal for this reaction. Under optimized conditions, the corresponding allylated products **18** were obtained in good to high yields and diastereoselectivity (Table 1). A plausible mechanism for asymmetric allylation is depicted in Figure 3. As shown, the reaction proceeds *via* an ionic mechanism and allyl radical species are not generated. Following this work, the same group in 2007 has investigated the allylation of various chiral glyoxylic oxime ethers with allyltributyltin and triallyl aluminum and high yields and diastereoselectivity of the desired products were observed.[37]

Table 1. Diastereoselective allylation of glyoxylic oxime ethers using allyltributyltin in the presence of $Sn(OTf)_2$.



Entry	Xc	T (°C)	t (min)	Yield (%)	de (%)	Abs. conf.
1	A	rt.	30	92	56	S
2	A	0	60	90	74	S
3	A	-25	60	91	78	S

4	A	-40	60	90	91	S
5	A	-40	60	88	89	S
6	B	-40	60	92	>99	S
7	C	-40	60	94	>99	S

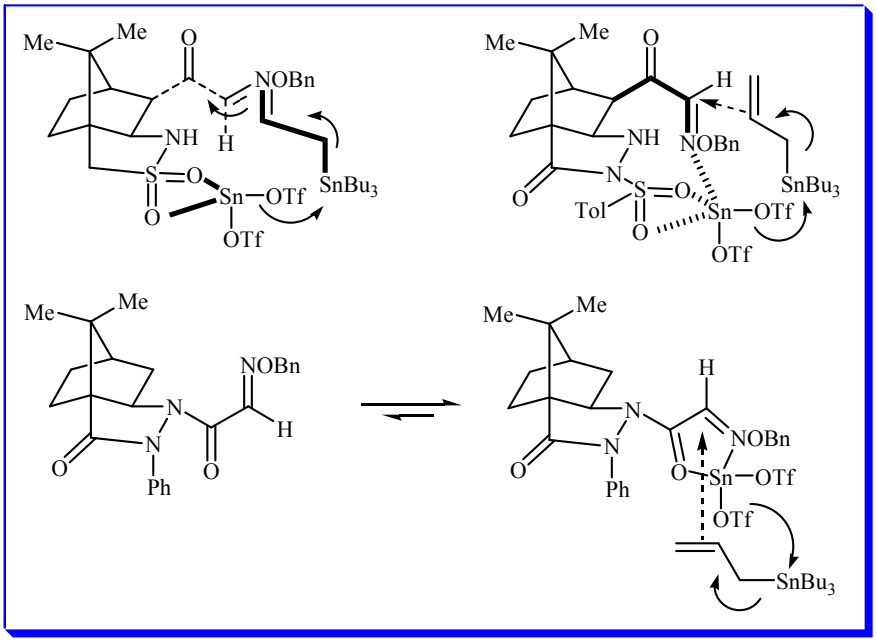
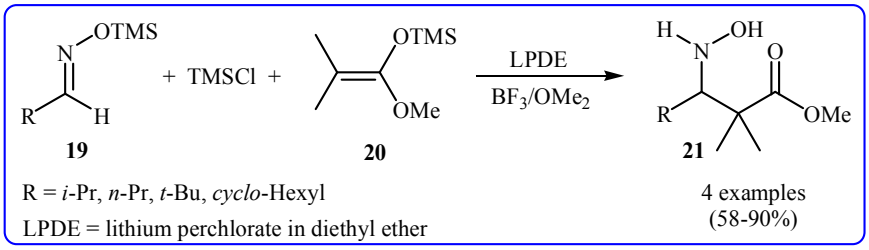


Figure 3. Proposed mechanism of the asymmetric allylation of oxime ether **17**

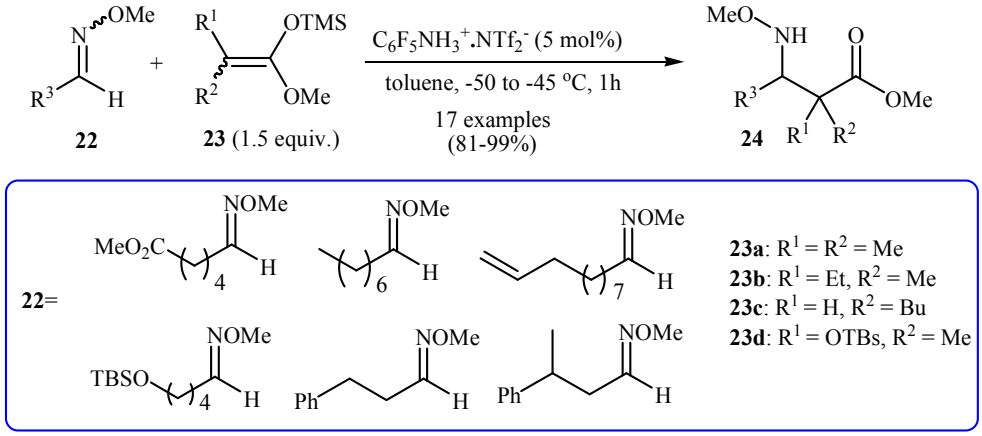
The synthesis of substituted hydroxylamines **21** from oxime ethers **19** has been described by Tavakol *et al* In 2007. *O*-trimethylsilyl oxime ethers **19** condensed with ketene acetal **20**/TMSCl in the presence of LPDE as Lewis acid in BF_3/OMe_2 and gave corresponding substituted hydroxylamines in good to high yields (Scheme 12).[38]



Scheme 12. Synthesis of substituted hydroxylamines

Following this work, a more robust and versatile method for preparation of β-alkoxyamino esters **24** from oxime ethers **22** was reported by Tanabe and co-workers in 2010. Oxime ethers **22** were found to undergo Mannich reaction with ketene silyl acetals **23** in the presence of pentaflouro phenyl ammonium trifluoro methane sulfonimide ($C_6F_5NH_3^+ \cdot NTf_2^-$) as catalyst in high to excellent yields with good functional group tolerance (such as Br, TBSO, and MeO_2C) (Scheme 13). However, the

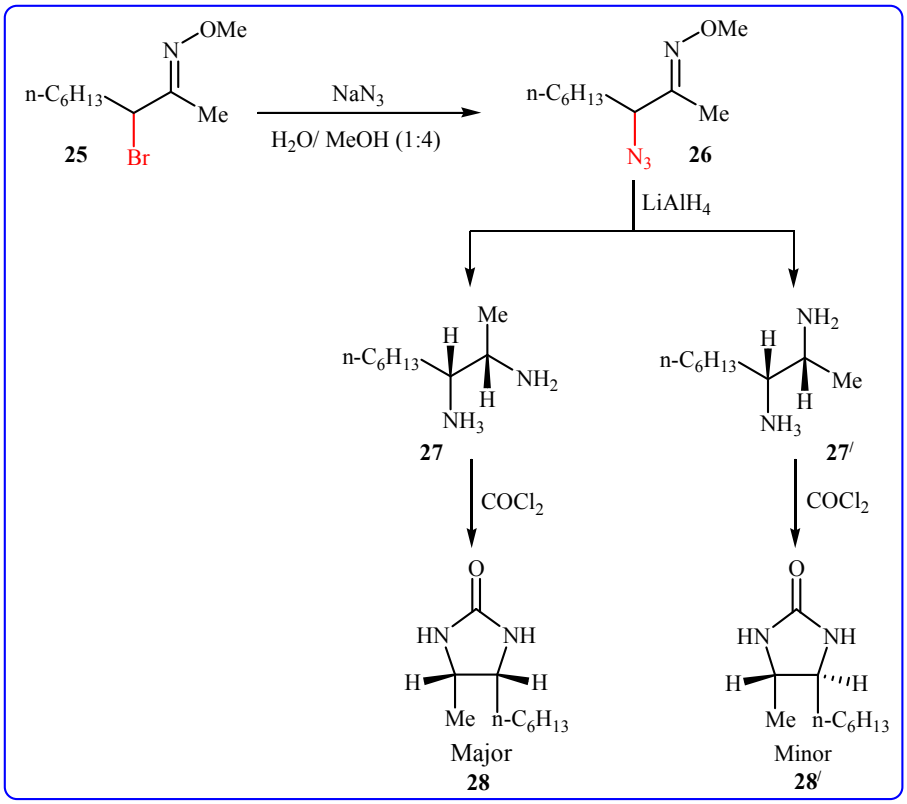
syn/*anti* selectivity was poor to moderate. It is noted that this method provides a new avenue for the natural product synthesis and process chemistry.[39]



Scheme 13. $C_6F_5NH_3^+ \cdot NTf_2^-$-promoted Mannich reaction between KSAs **23** and oxime ethers **22**

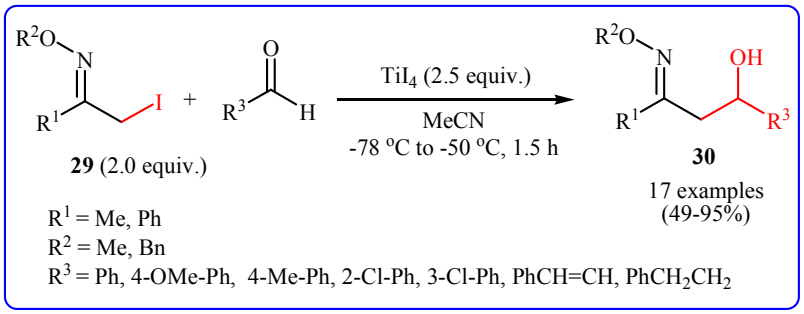
5. Regio- and stereoselective carbon–carbon (heteroatom) bond formation

Substitution reactions are the fundamental reactions in chemistry. Halides and sulfonates are the most frequently used as leaving groups because of their good nucleofugal properties and favorable rate of reactions.[40] α-Halo oxime ethers in the reaction with a nucleophile have two electrophilic sites (C=N and C-X). Because of the inductive effect of the C=N group, polarity of C-X bond increases, making the carbon atom more electropositive. So α-halo oxime ethers readily react with various nucleophiles.[41-44] Shatzmiller and Bercovici synthesized 1,2-diamines **28** and **28′** from α-bromo oxime ether **25** (Scheme 14).[45] The reaction involves: 1) treatment of the bromide **25** with sodium azide in water: methanol (1:4), which produced α-azido oxime ether **26** in good yield (85%); 2) reduction of **26** with $LiAlH_4$ gave a mixture of diamines **27** and **27′** (1:5); 3) the reaction of **27** and **27′** with $COCl_2$ in toluene obtained a mixture of diastereomeric 2-imidazolidone in 87% yield.



Scheme 14. Synthesis of 1,2-diamines **28** and **28′** from α-bromo oxime ether

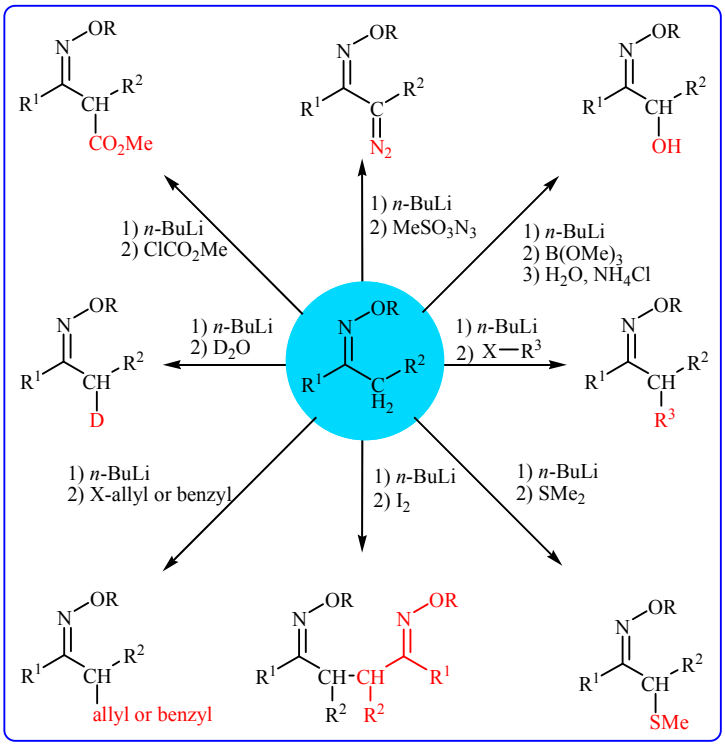
It's interesting to note that α-iodo oxime ethers **29** are excellent precursors of aza-enolates. Titanium tetraiodide promotes an aza-Reformatsky-type reaction of **29** with aldehydes to give β-hydroxy ketone *O*-alkyl oximes **30** in good yields (Scheme 15).[46] When R^3 is an alkyl group, such as isopropyl or n-hexyl, the desired product was not observed. Further reduction of the products afforded an easy access to new chiral β-amino alcohols.



Scheme 15. Reaction of a-iodomethyl ketone *O*-alkyl oximes **29** with aldehydes in the presence of TiI_4

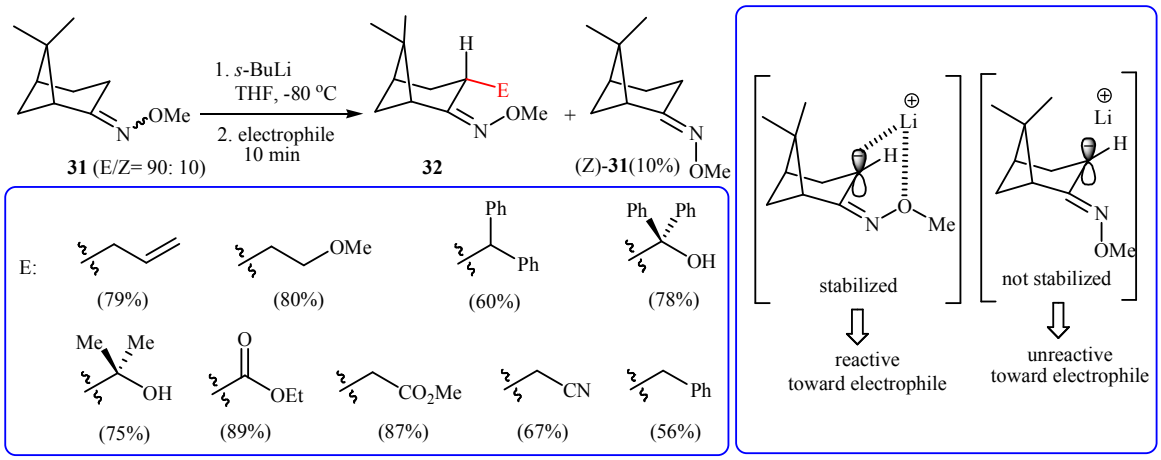
The substitution reaction of the lithium salts of oxime ethers has been the subject of a number of studies, and has been used in a number of synthetic reactions such as α-halogenation, α-alkylation, and oxidative coupling reactions (Scheme 16). Deprotonation of oxime ethers by using a strong base such

as butyl lithium, and subsequent reaction with a range of electrophiles elaborated the desired product in good yields.[47-55]



Scheme 16. Some synthetic application of lithium salts of oxime ethers.

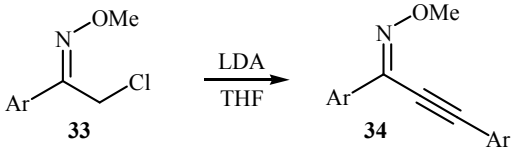
One of the beautiful examples of α-alkylation of oxime ethers has been reported by Caille *et al.* They showed that treatment of (+)-nopinone oxime methyl ether **31** with a wide range of electrophiles in the presence of *s*-BuLi in THF at -80 °C for 10 min gave the corresponding stereoselectively α-alkylated oxime ether **32** in good to high yields. As shown in Scheme 17, due to the stabilization of the carbanion intermediate with the oxygen lone pair of the oxime function, only the E-isomer of **31** able to react through a syn-alkylation process. Reduction of the products **32** afforded new chiral γ-and δ-amino alcohols of high interest for catalysis and asymmetric synthesis.[56] Previously, this type of thermodynamically unfavored reaction of oxime ethers with organolithium compounds has been also reported by Shatzmiller et al.[57]



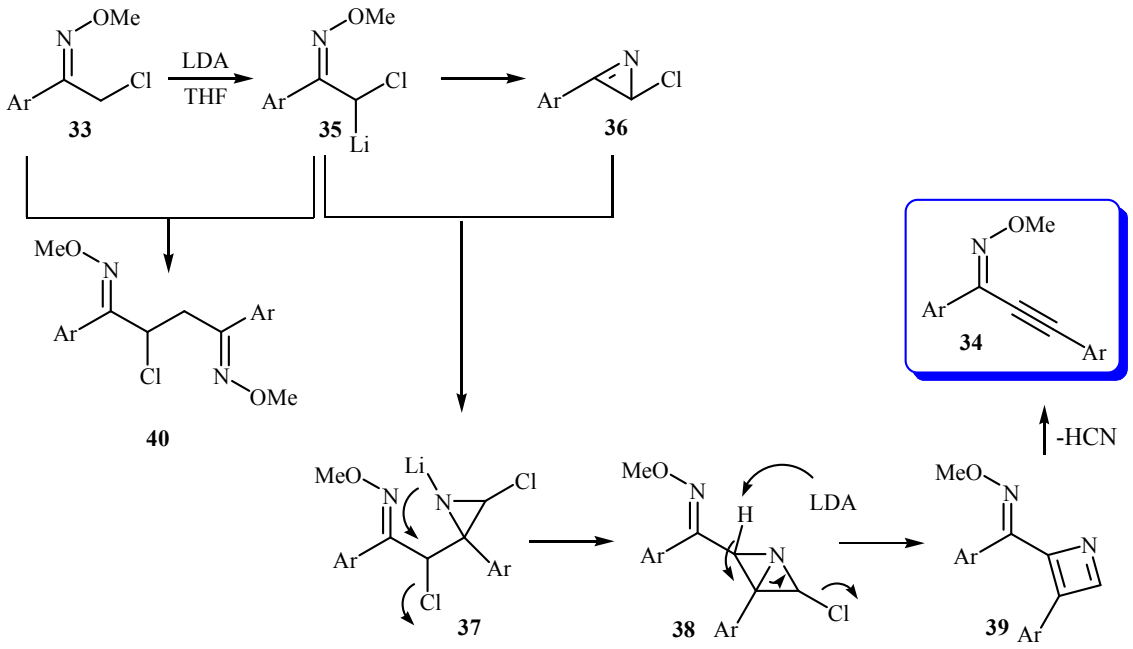
Scheme 17. Stereoselective α-alkylation of (+)-nopinone oxime methyl ether **31**

In an effort towards the self-condensation of α-chloro oxime ethers **33** with lithium diisopropyl amine (LDA) in THF to generate **40**, Shinokubo's research group showed an unusual conversion of **33** into alkynes **34** in good yields (Table 2 and Scheme 18). The authors proposed that the reaction involves 1) Deprotonation of α-chloro ether **33** with LDA, following by Neber-type cyclization to provide the highly reactive azirine **36**; 2) reaction of **36** with lithium salt **35** to give **37**, which undergoes internal cyclization to yield 1-aza-2-chlorobicyclo[1.1.0]-butane **38**; 3) removal of an α-proton of **38** to give the highly unstable azacyclo butadiene **39**; 4) the retro [2+2] cyclization of **39** affords the alkynyl oxime ether **34** (Scheme 18).[58]

Table 2. Self-condensation of α -chloro oxime ethers



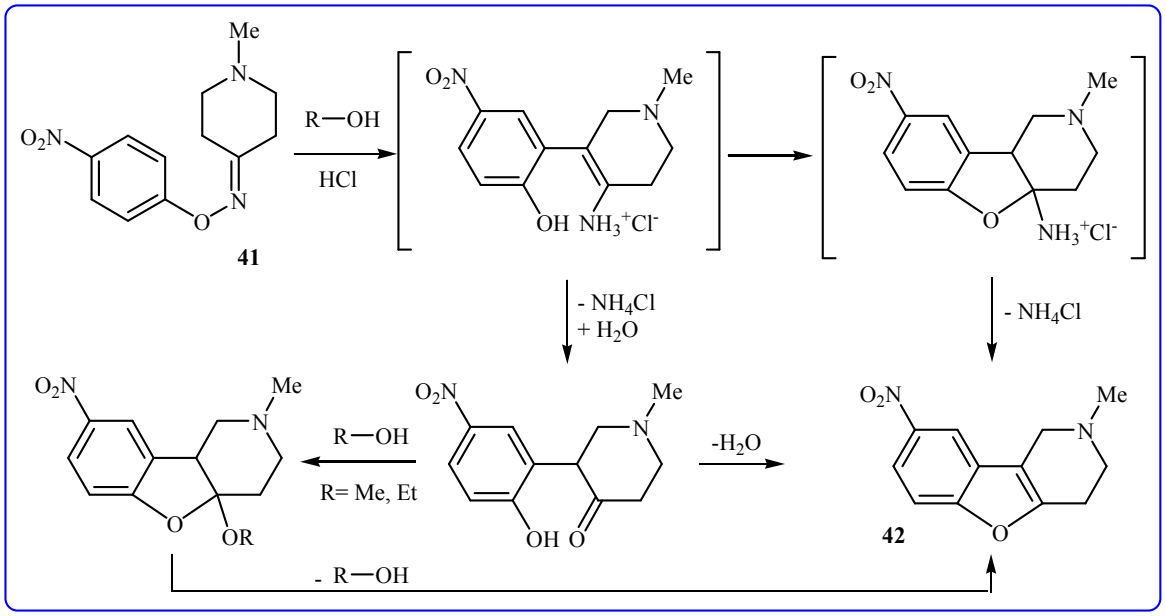
Entry	Ar	Yield (%)	Z/E
1	Ph	76	> 95/5
2	4-MeO-Ph	81	> 95/5
3	4-Cl-Ph	19	> 95/5
4	4-Cl-Ph	70	95/5
5	4-Br-Ph	65	94/6
6	2-naphthyl	67	> 95/5



Scheme 18. Proposed reaction pathway for generation of **34** from **33**

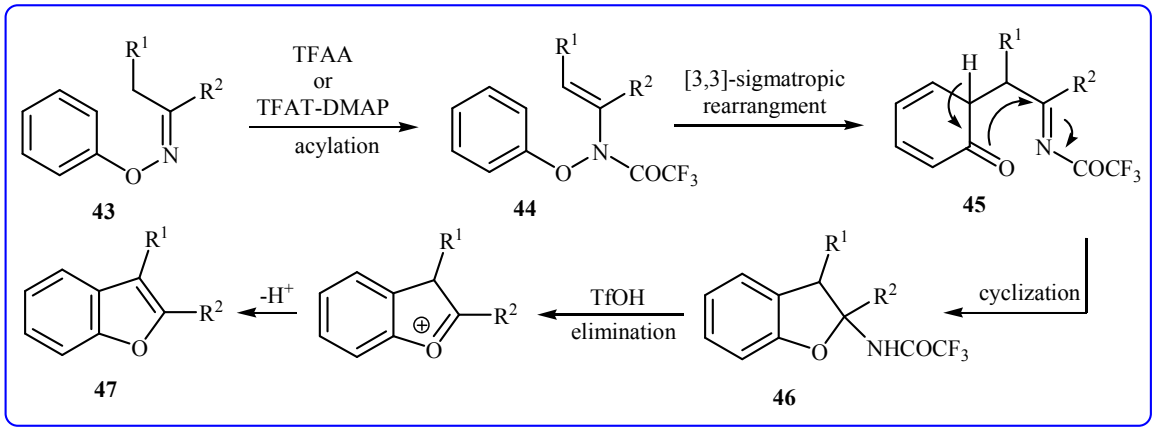
6. Cyclization reactions of oxime ethers for formation of heteroaromatics

Cyclization reactions of oxime ethers provide powerful and flexible protocols for preparation of a wide range of heterocyclic compounds. These reactions have been abundantly used for synthesis of special hetero aromatic compounds. One of the earliest reports of the applicability of these reactions, has been reported by Sharkova and co-workers in 1971, when oxime ether **41** underwent a cyclization reaction in the presence of HCl in MeOH or EtOH to form benzofurans **42** (Scheme 19).[59]



Scheme 19. Synthesis of benzofurans **42** from oxime ether **41**

An interesting reaction for generation of benzofurans **47** by sequential acylation, rearrangement and cyclization of oxime ethers **43,** under mild conditions, has been reported by Naito *et al* (Scheme 20).[60] The authors proposed that this reaction involves: 1) acylation of starting oxime ethers **43** by trifluoroacetic anhydride (TFAA) or trifluoroacetyl triflate/4-dimethylaminopyridine (TFA-DMPA) which resulted *N*-trifluoroacetyl-ene-hydroxylamines **44**; 2) the [3,3]-sigmatropic rearrangement of **44** lead to acylimine **45**; 3) the intramolecular cyclization of **45** to form **46**; 4) the elimination of trifluoroacetamido group of **46** in the presence of TfOH, followed by deprotonation led to **47**. This reaction can be applied for the synthesis of a major class of naturally occurring benzofuran compounds and pharmaceuticals without protection of the hydroxyl group. Stemofuran A, Eupomatenoid 6 and Coumestan were synthesized by using aforementioned method in the key steps of reactions, in yields of 72, 53, and 55%, respectively (Figure 4).



Scheme 20. Possible reaction pathway for conversion of **43** to **47**

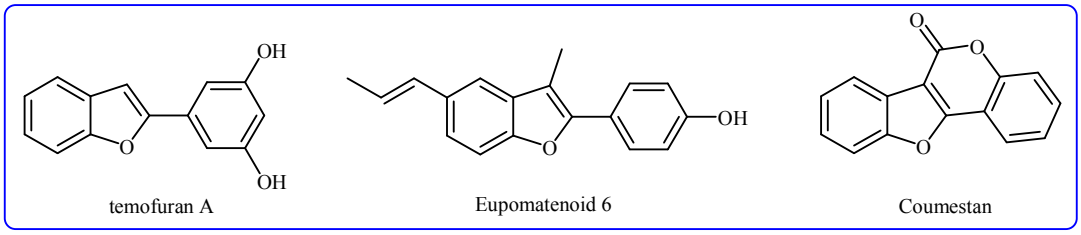
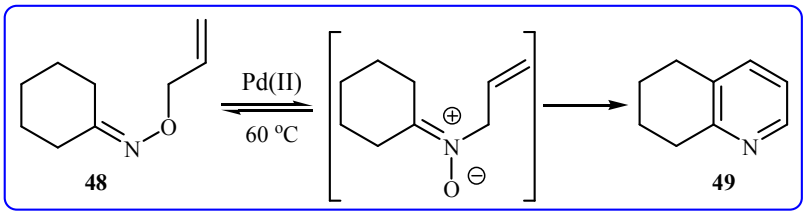


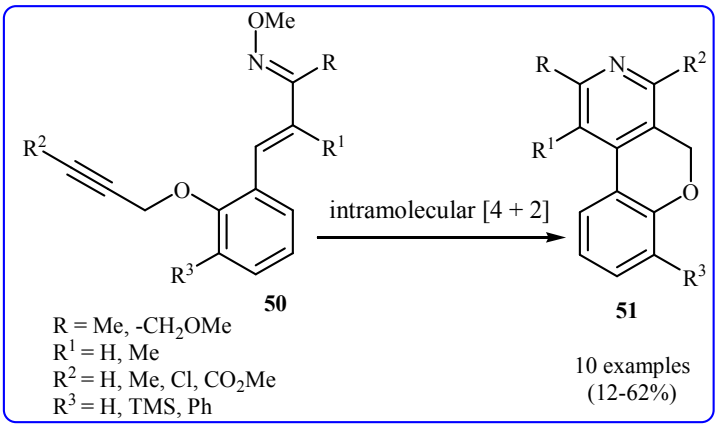
Figure 4: Benzofurans prepared from O-aryl oximes.

One of the interesting applications of oxime ethers for generation of heterocycles appears in the synthesis of pyridines. Allylic oxime ether **48** can be converted to the corresponding *N*-oxide in the presence of air at 180 ^{o}C, followed by [2,3]-sigmatropic shift to provide pyridine **49** in moderate yields (Scheme 21).[61-64]



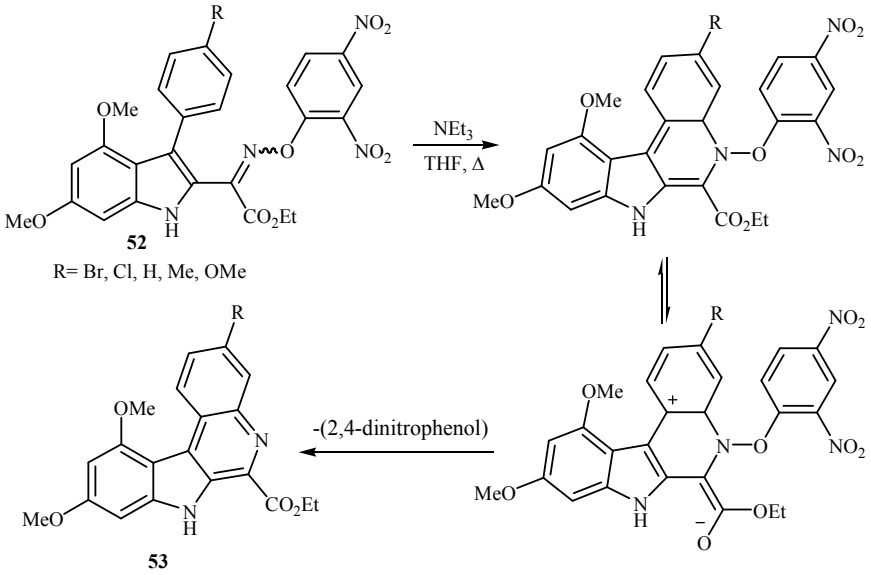
Scheme 21. Synthesis of pyridine **49** *via* thermolysis of Oxime Ethers

Heating vinyl oxime ethers **50** to 180 °C in xylene gave the desired [c]-annulated pyridines **51** by intramolecular hetero-Diels-Alder reaction (Scheme 22).[65] The electronic characters of the substituents on acetylenes had a large effect on the facility of this reaction. The reaction works well with electron-poor acetylene in accordance with the likely frontier orbital interactions (HOMO diene/ LUMO dienophile), but it could not be extended to electron-rich acetylenes. Previously, Boger and Zhu used this protocol for generation of 5,6-dihydrocyclopenta[c]pyridin-7-one systems.[66]

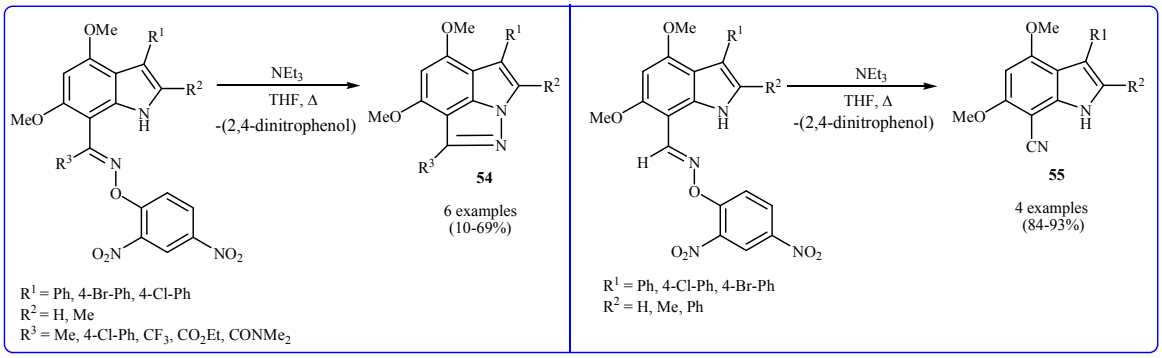


Scheme 22. Intramolecular hetero Diels-Alder reactions of α, β-unsaturated oxime ethers

Heating of the oxime ethers **52** with THF/NEt_3 for 24 hours gave the aromatic tetracycles **53** in good yields (Scheme 23). The cyclization occurs through an electrocyclic mechanism, which proceeds through an intermediate containing a dinitrophenoxide moiety, followed by the elimination of 2,4-dinitrophenol to give indolo[3,2-c]quinolones. It should be noted that the presence of an electron donating substituent (R) at 4″ position increases the rate of cyclization due to stabilization of the resonance.[67, 68] This protocol also has been used by the same group for the generation of indazoles **54** and indoles **55** (Scheme 24).[69, 70]

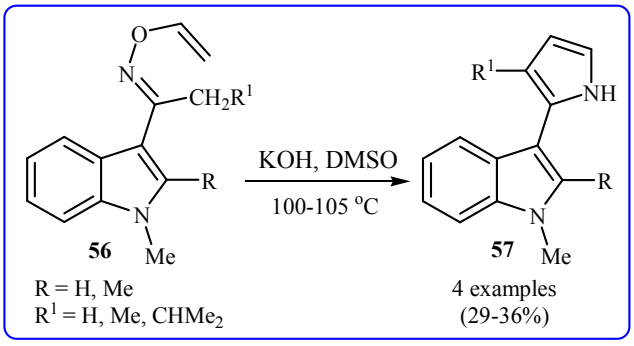


Scheme 23. Cyclization of **52a–e**



Scheme 24. Generation of indazoles **54** and indoles **55** from oxime ether **52**

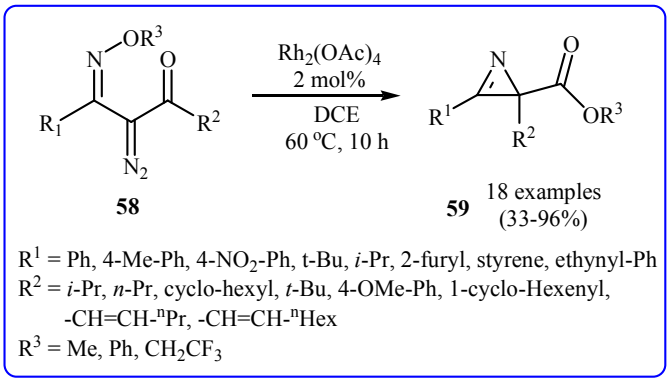
Pyrroles are important building blocks for a number of biologically and pharmaceutically active compounds.[71] Oxime ethers are versatile precursors for the synthesis of this heterocycle. *O*-vinyl oxime ethers **56** in a basic medium (KOH/DMSO) at 100-105 ^{o}C underwent [3, 3]-sigmatropic shift and gave pyrroles **57** in moderate yields (Scheme 25).[72]



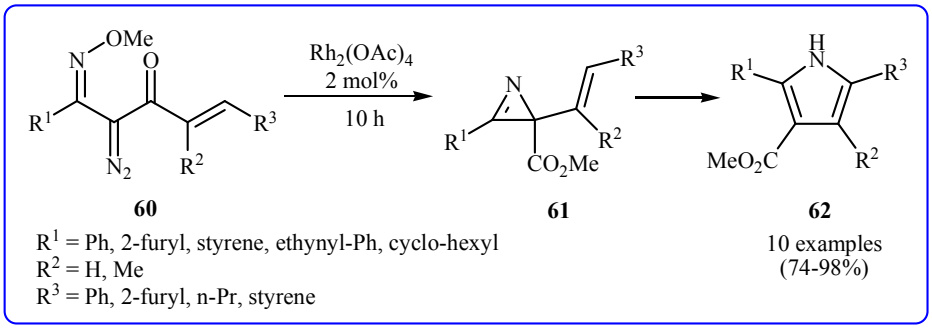
Scheme 25. Synthesis of pyrrole derivatives from *O*-vinyl oximes

In 2012, Park *et al*. reported an efficient and elegant rhodium-mediated cascade rearrangement of α-diazo oxime ethers **58** to 2H-azirine-2-carboxylic esters **59** (Scheme 26). Moreover, the presence of a

vinyl group on starting α-diazo oxime ethers by further rearrangement led to pyrroles **62** in good to high yields (Scheme 27).

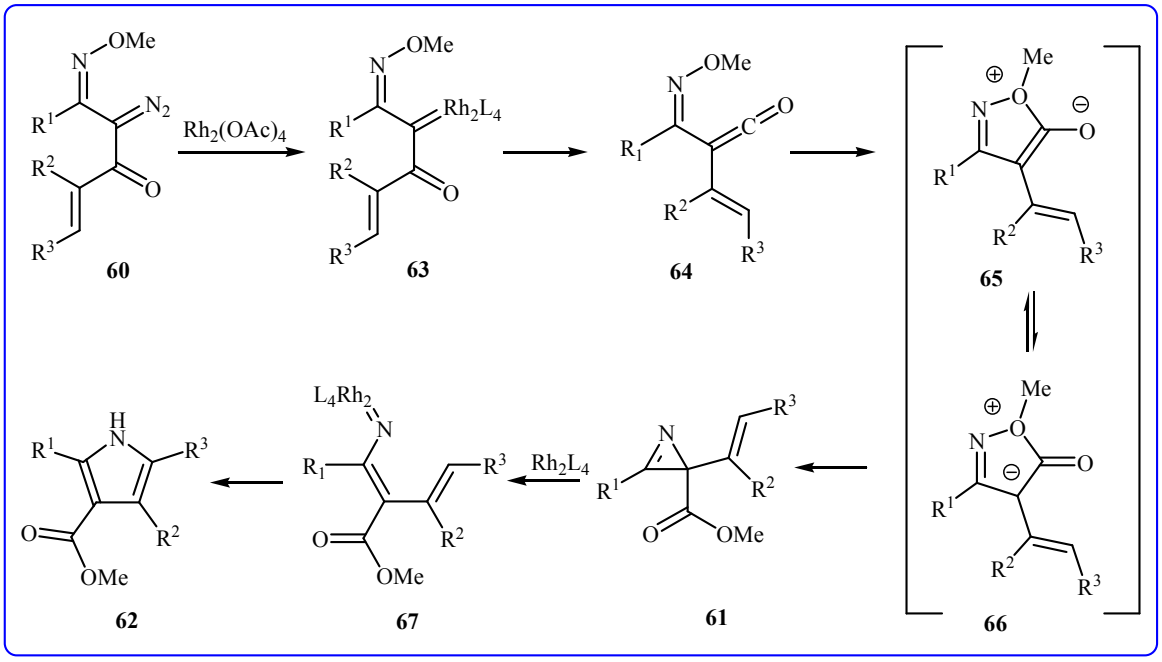


Scheme 26. Synthesis of 2H-azirine-2-carboxylic esters from α-diazo oxime ethers



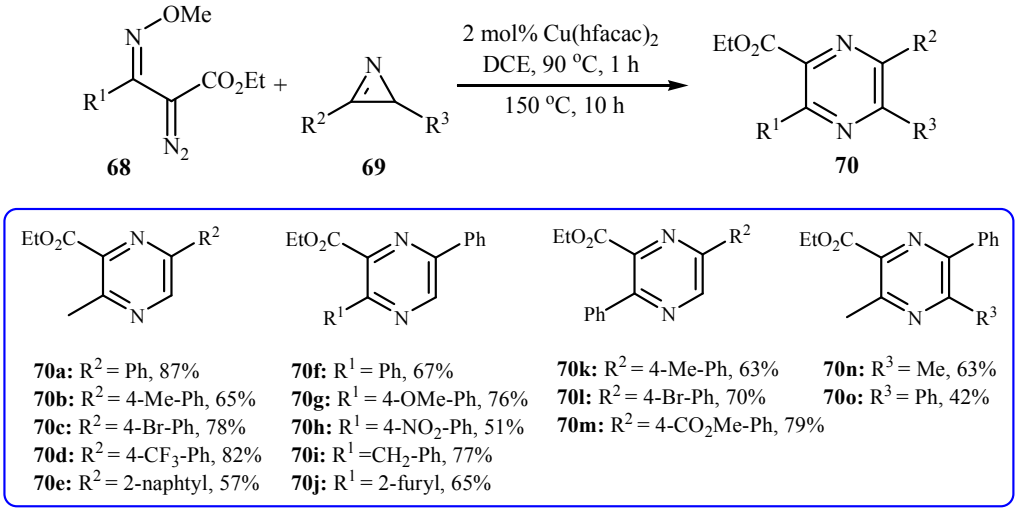
Scheme 27. Synthesis of pyrroles *via* tandem reaction of α-diazo oxime ethers

The plausible mechanism for this cyclization is presented in scheme 28. Rhodium catalyzed formation of carbenoid **63** promoted migration of the vinyl substituent to the carbenoid center, resulting in ketene **64**. Nucleophilic attack of the oxygen atom of the oxime ether moiety on the ketene led to formation of the intermediates **65** and **66** that rearrange to 2H-azirine-2-carboxylic ester **61**. Rhodium−nitrene complex **67** formed *via* ring-opening of **61**, followed by C−H insertion affords pyrrole **62**.[73]



Scheme 28. Accounted Mechanism for synthesis of pyrroles **62**

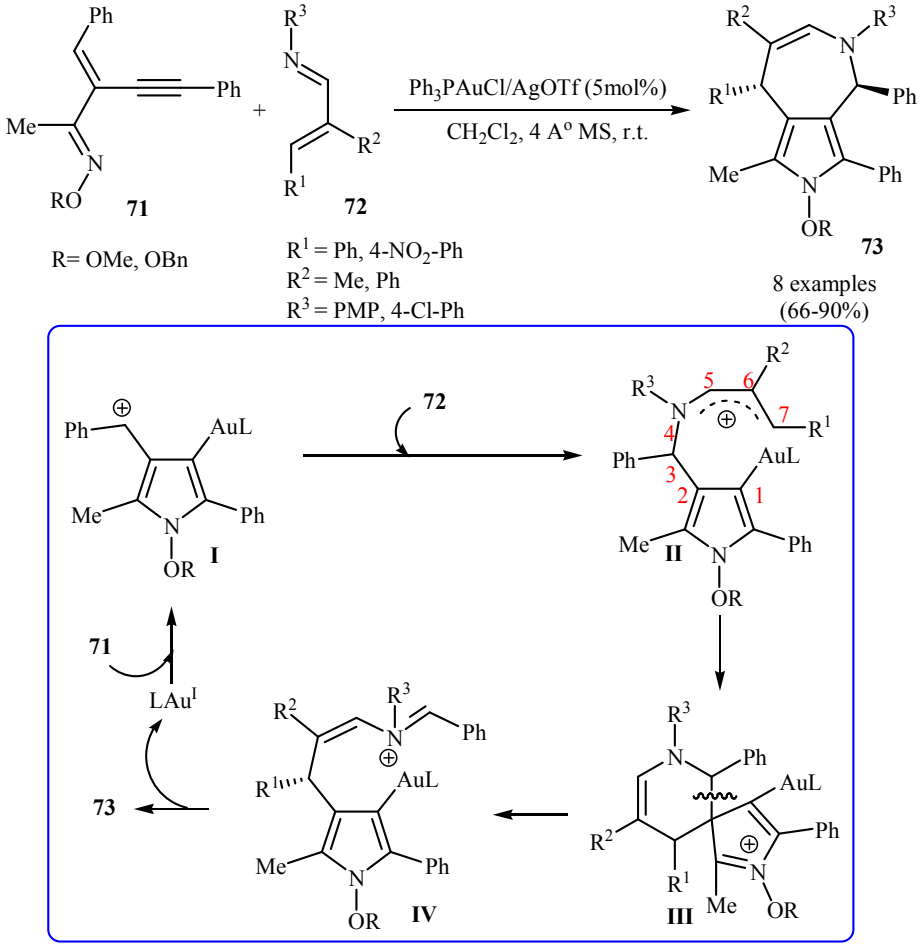
In 2015, this protocol has been utilized for synthesis of pyrazines by the same group.[74] The treatment of **68**, the ester analogues of **58,** with 2H-azirines in the presence of Cu(hfacac)$_2$ at 105 ^{o}C, led to highly substituted pyrazines in moderate to good yields (Scheme 29).



Scheme 29. Synthesis of high substituted pyrazines

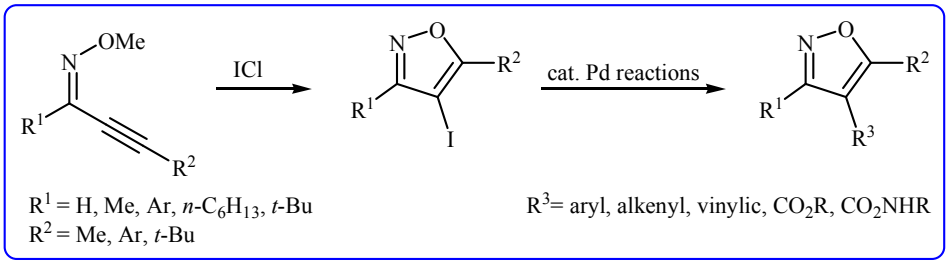
Recently Zhang reported a facile route to highly substituted pyrrolo[3,4-c]azepines by intermolecular diastereoselective [4+3] cyclization of 2-(1-alkynyl)alk-2-en-1-one oxime ethers **71** with α, β-unsaturated imines **72**, followed by 1,2-alkyl migration in the presence of gold (I) as catalyst, under mild reaction conditions. Several catalysts and solvents were tested, and the system $Ph_3PAuCl/AgOTf/CH_2Cl_2$ was found to be superior. It is worth noting that the electronic character of substrates had little effect on the facility of reaction. Under optimized conditions, the reaction tolerates

electron-donating and electron-withdrawing substituents and gave the corresponding highly substituted pyrroles **73** in good to high yields (Scheme 30).[75]



Scheme 30. Gold(I)-catalyzed diastereoselective domino reactions of oxime ethers **71** with **72**

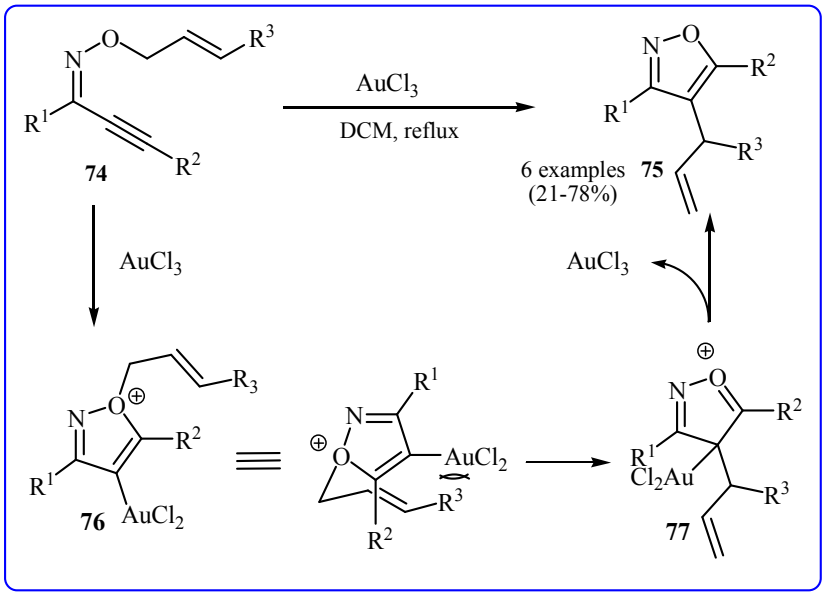
The isoxazole nucleus is a versatile and valuable building block for number of biologically and pharmaceutically active compounds.[76] Larock *et al*. demonstrated that a series of *O*-methyl alkynyl oxime ethers could be condensed with ICl, I_2, Br_2, or PhSeBr through an electrophilic cyclization and subsequent metal-catalyzed coupling reaction of the resulting 4-haloisoxazole, produce isoxazoles in high to excellent yields (Scheme 31).[77-79]



Scheme 31. Efficient synthesis of 4-haloisoxazole using oxime ethers

In 2010, Miyata and co-workers reported a direct and efficient protocol for generation of trisubstituted isoxazoles **75** from alkynyl oxime ethers **74** by gold-catalyzed domino reaction involving cyclization

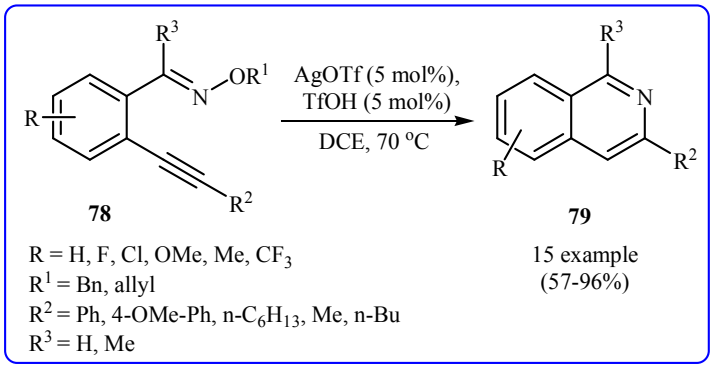
and Claisen-type rearrangement.[80] The addition of oxygen atom to Au(III)-activated C-C triplet bond which resulted oxonium intermediate **76,** subsequently Claisen-type rearrangement of **75** gave intermediate **77.** The aromatization of **77** afforded isoxazole **75** and liberated the catalytic gold species. It should be mentioned that the substitution on C-C double bond decreased the yield of products due to steric repulsion between the substitution and the gold moiety (Scheme 32). In a later investigation by the same research team, they showed that by changing the $AuCl_3$/DCM system to $AgBF_4$/PhOH/THF, because of increased catalytic activity, the desired products were obtained in good to high yields.[81]



Scheme 32. Possible reaction pathway for generation of isoxazoles **75** from oxime ethers **74.**

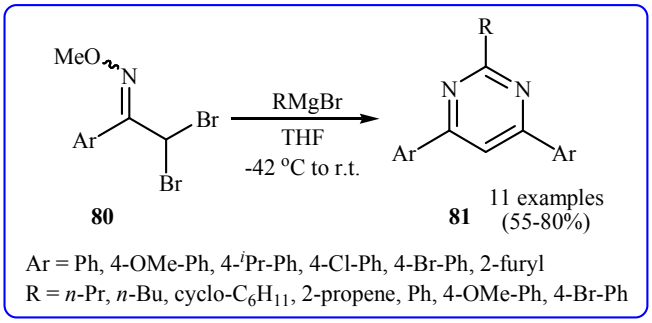
A very efficient method for synthesis of isoquinolines *via* redox reactions of oxime ethers was reported by Shin *et al*.[82] *O*-alkyl *ortho*-alkynylbenzaldoxime derivatives **78** in the presence of AgOTf (5 mol %) as catalyst and TfOH (5 mol %) as co-catalyst in DCE at 70 ^{o}C, afforded isoquinolines **79** in good to excellent yields (Scheme 33). TfOH was crucial to the reaction, due to the facile proto-demetallation in the turnover step. Presumably, the reaction proceeds through 6-endo-dig addition of the nitrogen atom of oxime on the Ag-activated alkyne, followed by N–O cleavage. Subsequent E_2-type elimination gave the isoquinoline derivatives **79**. Some important information of the reaction is listed below: 1) the *O*-benzyl substrate on the oxime ethers reacted faster than *O*-allyl substrate; 2) the oxime ethers with electron-rich aryl group at R_2 are more reactive than those with electron-poor aryl groups; 3) the oxime ethers bearing an alkenyl or a long alkyl group at R_2 underwent sluggish reaction; 4) the electronic character of the substituents in the aromatic ring has little effect on the facility of reaction; 5) the reaction of ketoximes occurs much faster than that of aldoximes; 6) (*Z*)-ketoxime

derivatives failed to react. It is noted that oximes produced isoquinoline-*N*-oxides in good to excellent yields under the same reaction conditions.[83]

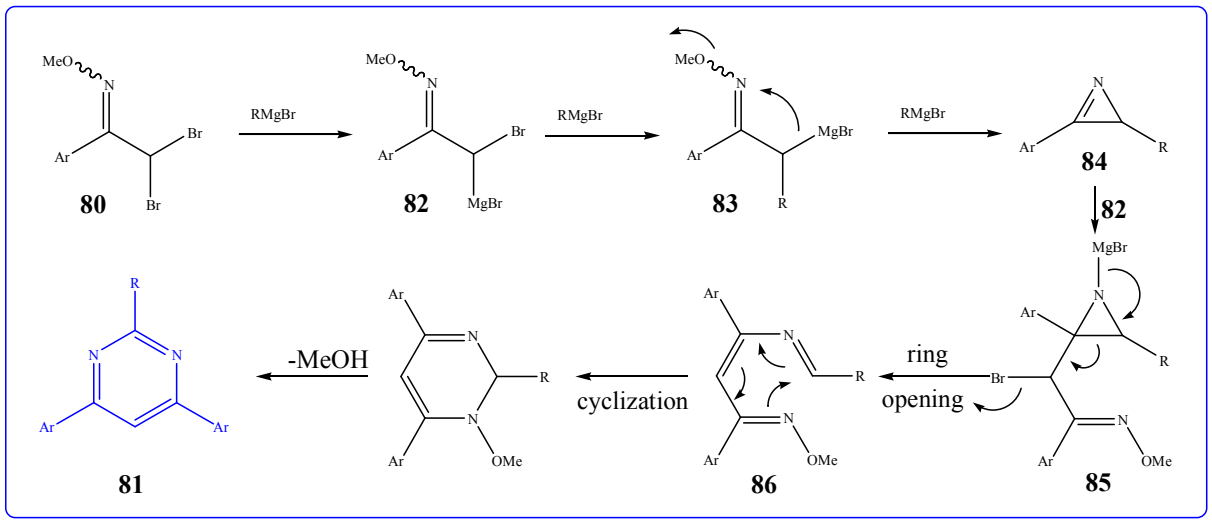


Scheme 33. Redox-mediated isoquinolines synthesis.

An efficient protocol for synthesis of pyrimidines **81**, *via* treatment of α,α-dibromo oxime ethers **80** with Grignard reagents, has been reported by Shinokubo and co-workers (Scheme 34).[84] The reaction tolerated both alkyl and aryl Grignard reagents with electron-donating and electron-withdrawing substituents and gave the corresponding pyrimidines in good to high yields. Notably, allyl Grignard reagents don't work in this protocol. Mechanistically, this reaction involves 1) bromine-magnesium exchange which results carbenoid **82**; 2) alkylation of **82** at α-position with Grignard reagent to form **83**; 3) the Neber-type cyclization of **83** gave the highly reactive azirine **84**; 4) the reaction of azirine **84** with **82** to afford **85**; 5) ring opening of **85**, followed by an electrocyclization and subsequent elimination of methanol to provide pyrimidine **81** (Scheme 35).[84]

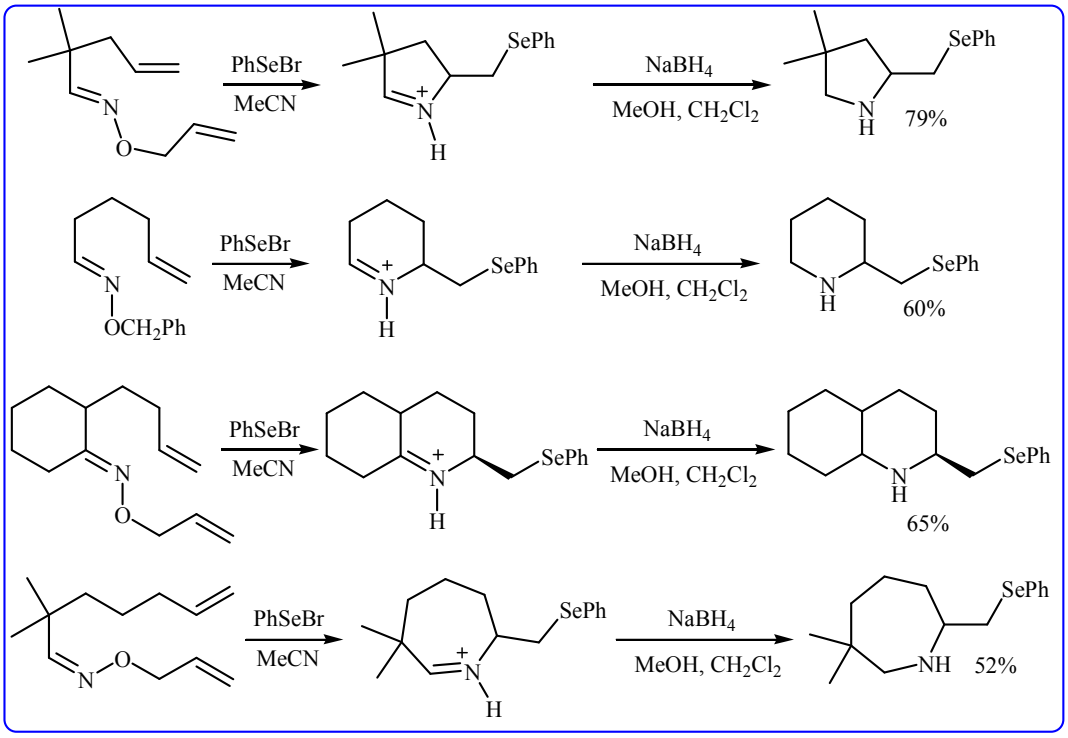


Scheme 34. Synthesis of pyrimidines from dibromo oxime ethers



Scheme 35. Possible reaction pathway for generation of pyrimidines from dibromo oxime ethers

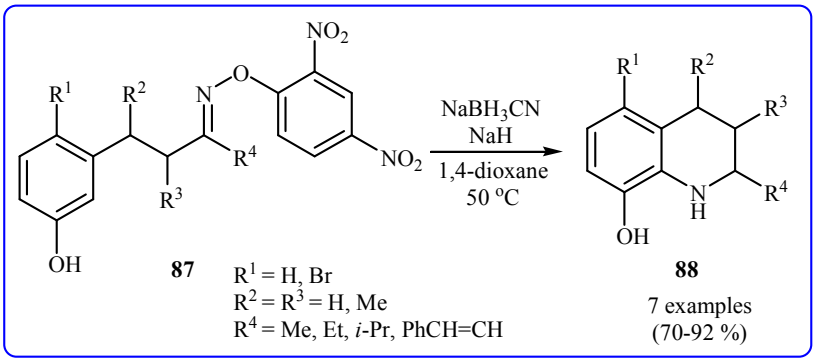
The γ- and δ-unsaturated aldoxime and ketoxime *O*-allyl and *O*-benzyl ethers reacted with phenylselenyl bromide in acetonitrile at room temperature to give cyclic iminium ions. The key steps of the reaction involve cyclization, followed by elimination of *O*-allyl and *O*-benzyl moiety on nitrogen atom. Reduction of cyclic imines with sodium borohydride gave pyrrolidines, piperidines, tetrahydroisoquinolines or related compounds in good yields (Scheme 36).[85, 86]



Scheme 36. Synthesis of 5-7 membered *N*-heterocycles

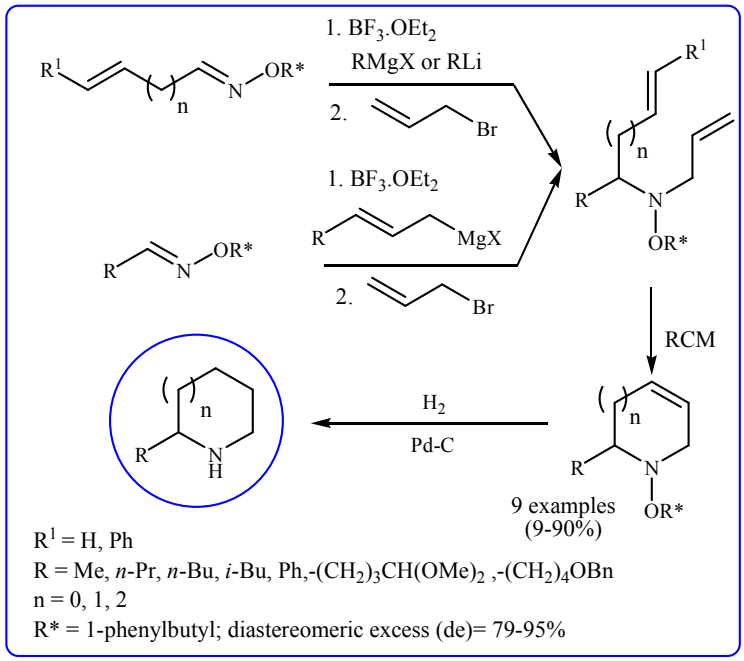
One of the interesting applications of oxime ether in the generation of *N*-heterocyclic compounds appears in the synthesis of 8-hydroxytetrahydroquinolines **88**. The treatment of *m*-hydroxy phenethyl

ketone *O*-2,4-dinitrophenyloximes **87** with sodium hydride and sodium cyanoborohydride in 1,4-dioxane at 50 ^{o}C afforded **88** in good to high yields (Scheme 37). Under these conditions the Beckmann rearrangement product quinolones or other regioisomers were not obtained.[87]



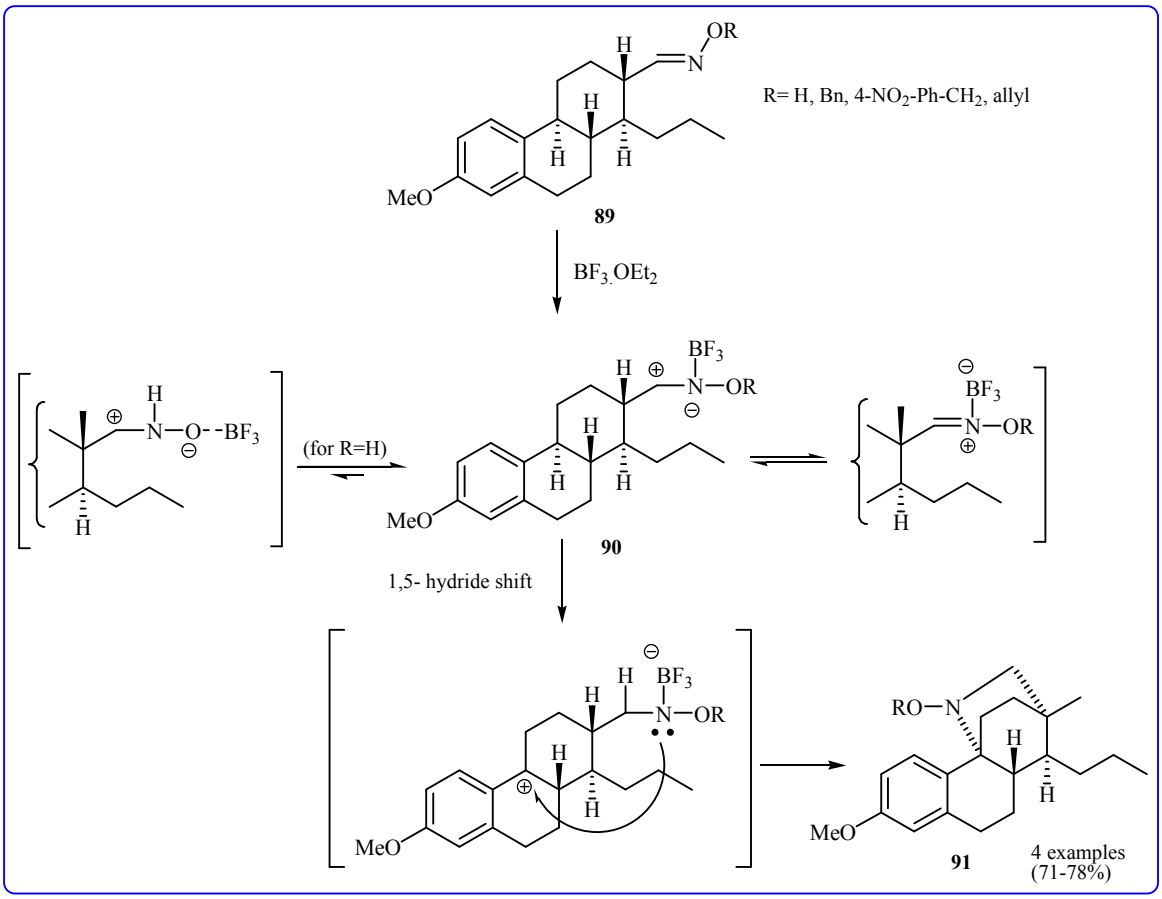
Scheme 37. Cyclization of *O*-2,4-dinitrophenyloximes **87**

The ring-closing metathesis reaction of oxime ethers is a powerful route for the synthesis of *N*-heterocycles (Scheme 38). Moody and co-workers explained this reaction in details .[88]



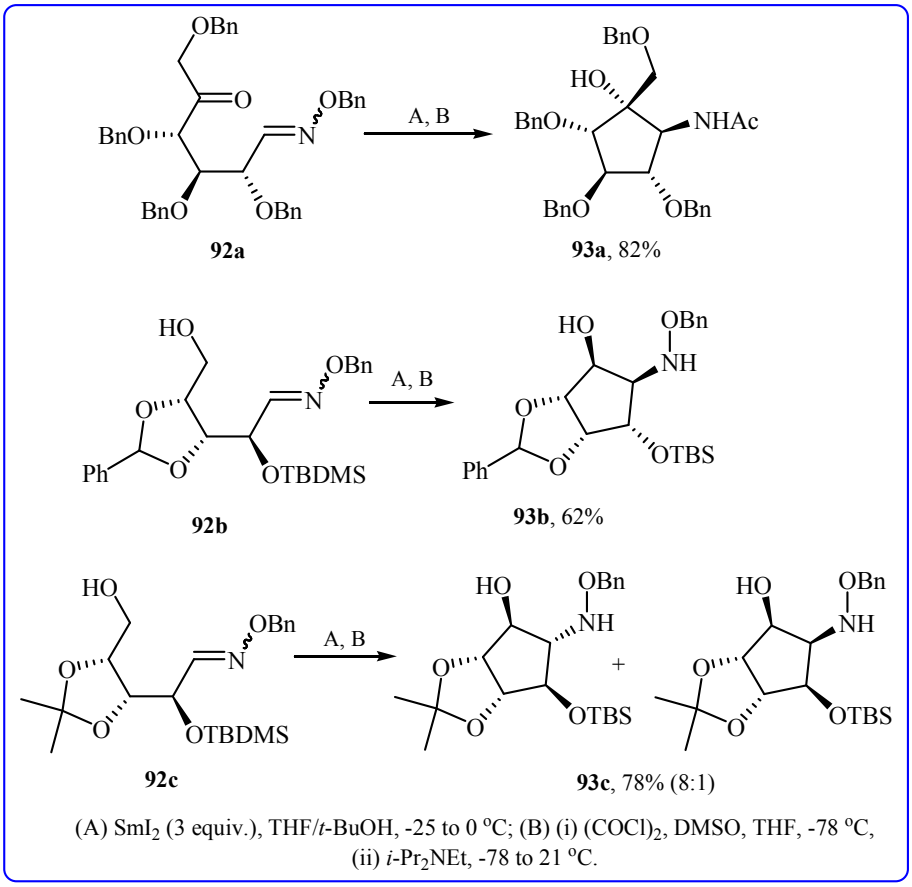
Scheme 38. Synthesis of *N*-heterocycles *via* combination of the addition reactions and ring-closing metathesis (RCM) reaction

In 2009, Frank *et al*. reported an efficient reaction for synthesis of *D*-Secoestrone isoquinuclidines **91** from oxime ethers **89** *via* direct transformation of benzylic C-H bond into a C-N bond in the presence of a stoichiometric amount of BF_3**.**OEt_2 (Scheme 39).[89] Mechanistically, the reaction proceeds through an oxyiminium intermediate **90**, followed by an intramolecular domino 1,5-hydride transfer/cyclization sequence.



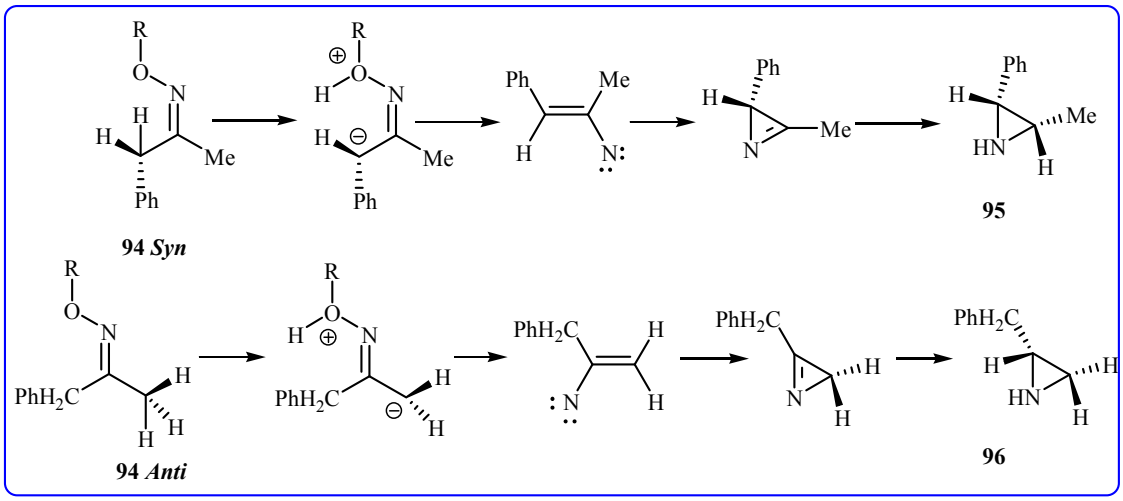
Scheme 39. $BF_3 \cdot OEt_2$-promoted *N*-alkylation of oxime ethers.

Intramolecular reductive coupling of carbonyl-tethered oxime ethers **92a-c** in the presence of samarium diiodide as one-electron reducing agent, gave the corresponding aminocyclopentitols **93a-c** in good yields and diastereoselectivity (Scheme 40).[90]



Scheme 40. Intramolecular reductive coupling of carbonyl-tethered oxime ethers

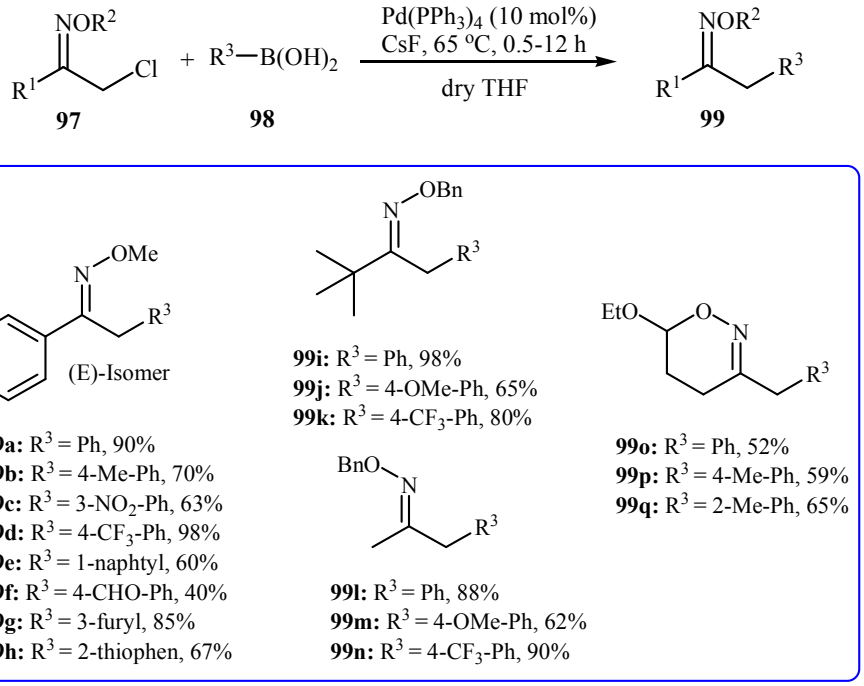
A useful method for synthesis of aziridines from oxime ethers has been reported by Landor and co-workers.[91] As depicted in Scheme 41, reduction of *anti*- and *syn*-forms of oxime ethers **94** with lithium aluminium hydride through formation of a niterene intermediate gave mainly aziridines **95** and **96** *via* deprotonation and ring closure on the same side of oxygen atom of oxime ethers. Notably, the solvent has a dramatic effect on the yield of products. THF and diglyme were found to be optimal for this reaction. Amines were obtained as main products in high yields in other solvents.



Scheme 41. Possible reaction pathway for synthesis of aziridines from oxime ethers

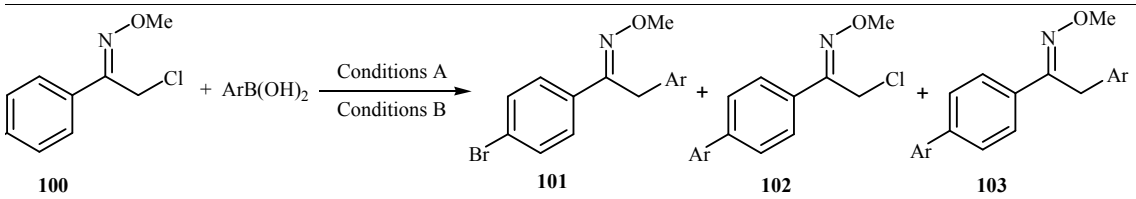
7. Transition-metal catalyzed cross coupling reactions of oxime ethers

The transition-metal catalyzed cross-coupling reactions such as Suzuki-Miyaura, Negishi, Hiyama, Sonogashira, Stille and Heck reactions have a unique ability to form carbon-carbon bonds. These reactions have been abundantly used in other coupling reactions such as carbon-hetroatom coupling, α-arylation, direct arylation by C-H activation, and decarboxylative coupling. These reactions have been successfully applied in academic, pharmaceutical, agrochemical, and industrials research. The Suzuki-Miyaura palladium-catalyzed cross-coupling reactions between arylboronic acids and organic halides or triflates, provide an effective and general synthetic route to biaryls. This methodology is one of the most useful tools to create new carbon-carbon bonds.[40] In 2013, Medio-Simón *et al*. investigated the Suzuki-Miyaura reaction of α-chloromethyl oxime ethers **97** with a wide range of boronic acids **98** in the presence of some palladium catalysts. They examined several catalysts and bases, and the system $Pd(PPh_3)_4$/CsF/THF was found to be superior (Scheme 42). (*Z*)-α-halomethyl oxime ethers are most suitable substrates for this reaction and gave the corresponding α-methyl-substituted oxime ethers in good yields. This *syn*-orientation allows the *O*-Pd interaction between the oxygen of ether and palladium in the intermediate oxidative addition complex, and (*Z*)-α-halomethyl oxime ethers become privileged substrates for the α-coupled products. It is interesting to note that the dihalo oxime ethers containing Csp^2- and C-sp^3-halogen bonds **97** underwent different coupling reactions by using different catalyst. $Pd(PPh_3)_4$ is most effective for regioselective coupling reaction of C-sp^3-halogen bond and $Pd(dba)_2$/P(*o*-tolyl)$_3$ is superior for C-sp^2-halogen bond (Table 3).[92]

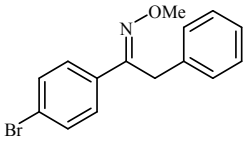
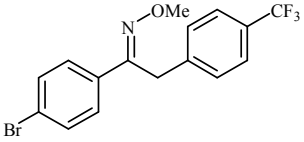
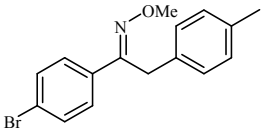
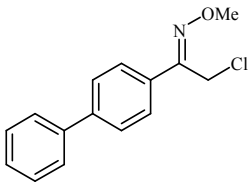
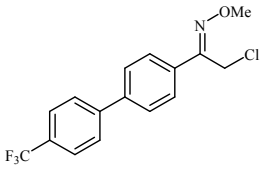
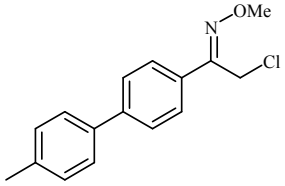


Scheme 42. Palladium-catalyzed cross-coupling reactions of oxime ethers **97** with boronic acids **98**

Table 3. Regioselective arylation of (*Z*)-**100**



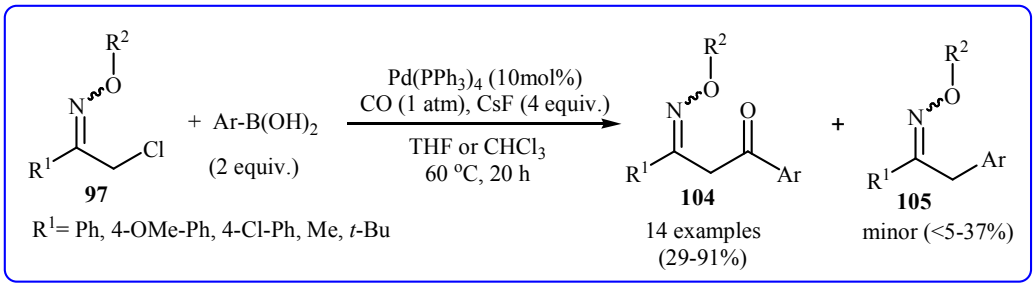
100 **101** **102** **103**

Run	Conditions[a]	Product	Yield (%)	Conv. (%)	**99:100:101**
1	A		68	77	95:1:4
2	A		58	65	100:0:0
3	A		60	64	100:0:0
4	B		88	100	0:91:9
5	B		71	73	0:100:0
6	B		87	100	0:92:8

[a] A = Pd (PPh_3)$_4$ (10 mol%), **100** (1 equiv.), **98** (1 equiv.), CsF (2 equiv.), THF, 65 °C, 1 h; B = Pd(dba)$_2$ (10 mol%), P(*o*-tolyl)$_3$ (10 mol%), **100** (1 equiv.), **98** (1.5 equiv.), CsF (3 equiv.), THF, 65°C, 1 h.

One year later the same group reported the three-component Suzuki–Miyaura cross-coupling reaction of α-chloro methyl oxime ethers, boronic acids and carbon monoxide in the presence of Pd(PPh_3)$_4$ as catalyst, for preparation of unsymmetrical β-alkoxyimino carbonyl compounds **104**. The reaction showed remarkable flexibility and desired products were formed in high yields with both electron rich and electron poor arylboronic acids, but it could not be extended to *ortho*-substituted arylboronic acids. It should be mentioned that low yields of direct coupling products **105** were also observed (Scheme 43) .[93] Changing of arylboronic acids to alcohols or amines as nucleophiles, in the presence

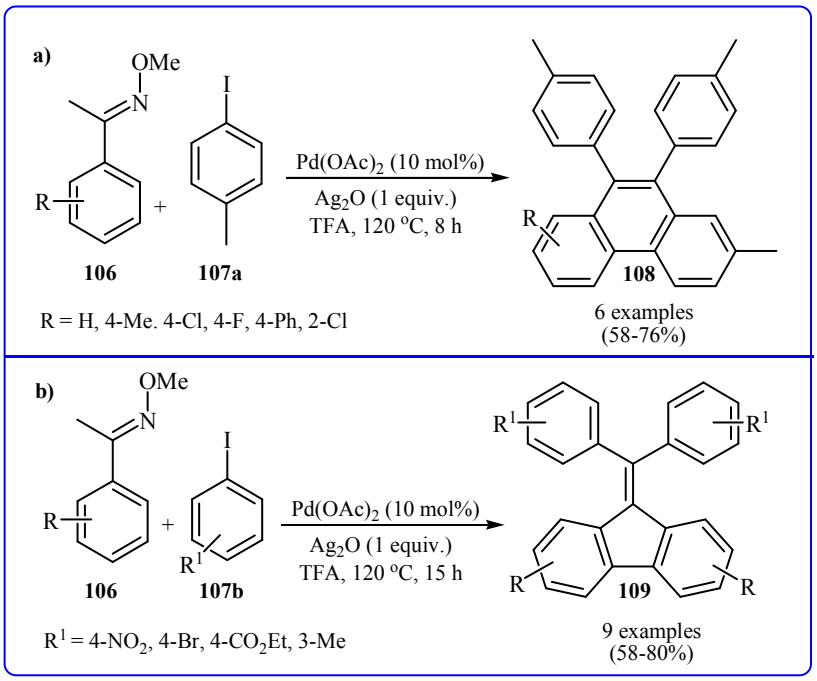
of $Pd(OAc)_2$/Xantphos, afforded 1,3-alkoxyimino esters and 1,3-alkoxyimino amides, respectively in high yields.[94]



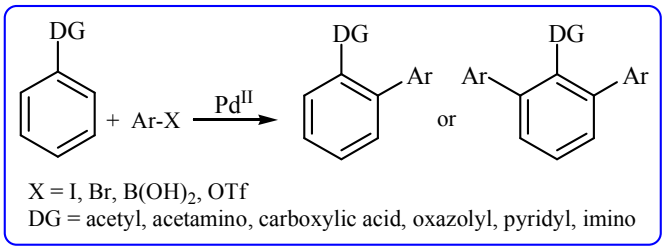
Scheme 43. Pd-catalyzed three-component Suzuki–Miyaura cross-coupling reaction of oxime ethers **97** with boronic acids

The Oxime ethers as an elegant directing-group for activation of aromatic or vinylic C-H bonds for construction of new C-O, C-X and C-N bonds, by metal-catalyzed cross-coupling reactions, has been the subject of a number of papers.[95-100]

In 2010, Cheng and co-worker reported a beautiful route for construction of substituted phenanthrenes **108** and diarylmethylidenefluorenes **109** from the reaction of aryl-alkyl ketoxime ethers **106** and aryl iodides **107a,b** through a palladium-catalyzed multiple C-H activation, and C-C bond formation strategy in good to high yields. The treatment of one equivalent of **106** and three equivalent of 4-methyliodobenzene **107a** with 10 mol% of $Pd(OAc)_2$ and one equivalent of Ag_2O in trifluoroacetic acid at 120 ^oC gave the diphenylphenanthrenes derivatives **108** in good yields (Scheme 44 a). When the aryl iodide containing an electron-withdrawing substituent was used, the reaction at aforementioned conditions, afforded diarylmethylidenefluorene derivatives **109** in good to high yields (Scheme 44 b). However, the aryl iodides containing strong electron donating groups, work in neither of the reactions. It is worth noting that other directing group generally gave only mono- or diarylated products at the *ortho*-position (Scheme 45).[101]

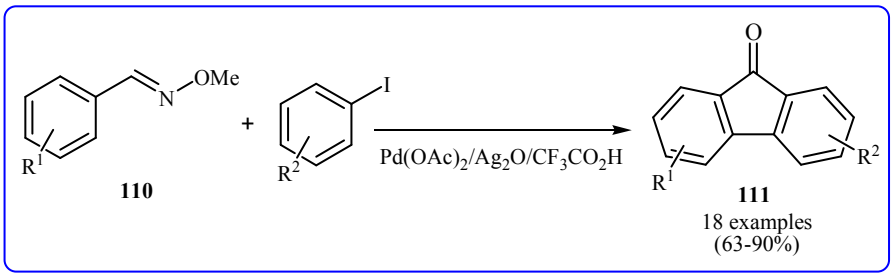


Scheme 44. a) Synthesis of diphenylphenanthrene derivatives; b) Synthesis of diarylmethylidenefluorene derivatives

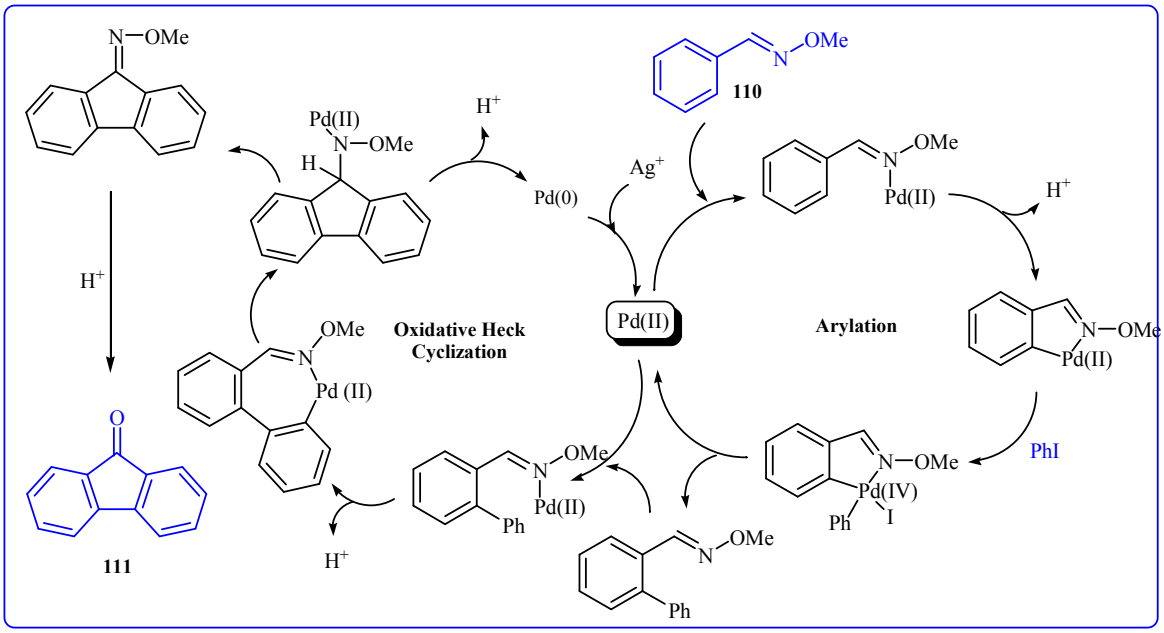


Scheme 45. Palladium-catalyzed arylation of ortho aromatic C-H bonds

Previously, the same group reported an efficient rout for synthesis of functionalized 9-fluorenone derivatives **111** *via* the reaction of aromatic aldoxime ethers **110** with aryl iodide in the presence of Pd(II) catalyst (Scheme 46). The system $Pd(OAc)_2/Ag_2O/CF_3CO_2H$ was found to be optimal for this reaction and the presence of silver salt is vital for the reaction. The reaction involves two distinct steps in one pot: arylation and oxidative Heck cyclization. A plausible catalytic cycle is depicted in scheme 47.[102] Heck cyclization of oxime ethers is a well-known reaction and has been the subject of some papers.[103, 104]

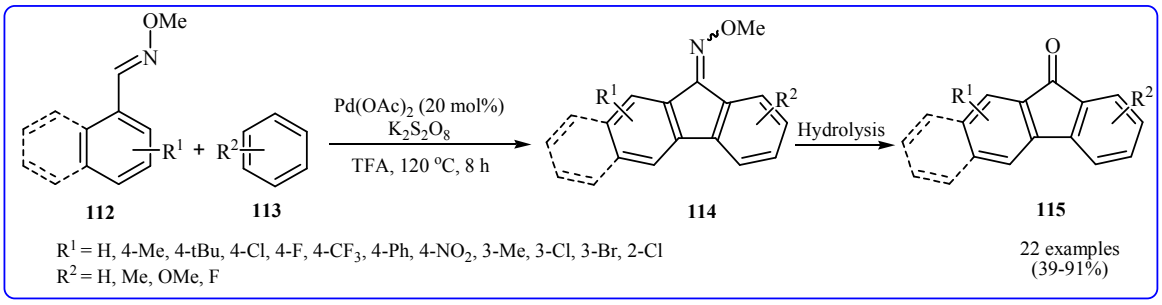


Scheme 46. Palladium-catalyzed synthesis of functionalized 9-fluorenone derivatives **111**



Scheme 47. Proposed mechanism for the reaction of benzaldoxime ethers with phenyl iodide

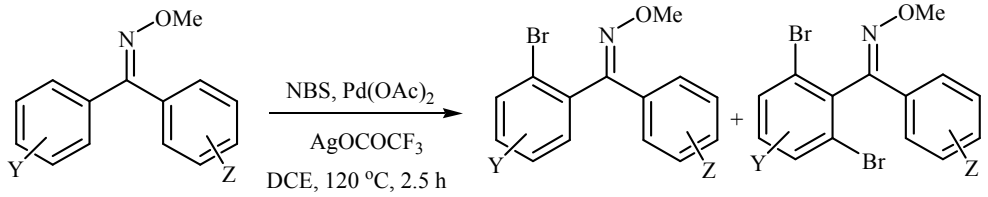
The authors extended their methodology to the direct arylation of oxime ethers, using arenes instead of aryl iodides.[105] Treatment of aromatic aldoxime ethers **112** and arenes **113** with $Pd(OAc)_2$ (20 mol%) and $K_2S_2O_8$ in TFA at 120 °C afforded fluorenone oxime ethers **114** in good yields. Hydrolysis of **114** in aqueous HCl, gave fluorenones **115** in high yields (Scheme 48). However, this method for synthesis of fluorenones is problematic, due to the requirement of high catalyst loading (20 mol%).



Scheme 48. Reaction of aromatic aldoxime ethers with arenes

The possibility of the palladium-catalyzed *ortho* monobromination and iodination of diaryl ketoxime ethers [$Ar^1C(Ar^2)$= N–OCH_3] was demonstrated by Dolliver and co-workers. By using $Pd(OAc)_2$/NBS/DCE/$AgOCOCF_3$ system, corresponding *ortho* mono brominated products were obtained in high yields (69-97%) after 2.5 h at 120 °C. However, a minor amount of *di-ortho*-bromo as a side product is produced in this reaction (up to 11%) (Table 4). The single example of corresponding *ortho* mono-iodinated products was also obtained in high yields (82%). It should be mentioned that the electron-withdrawing substituents on either ring, decrease reaction rate and diminish the amount of *di-ortho*- brominated side product. Notably, *ortho*-halogenation reaction undergoes only on the aromatic ring which is *trans* to the –OCH_3 group, and the oxime ether moiety does not isomerize under the optimized conditions.[106]

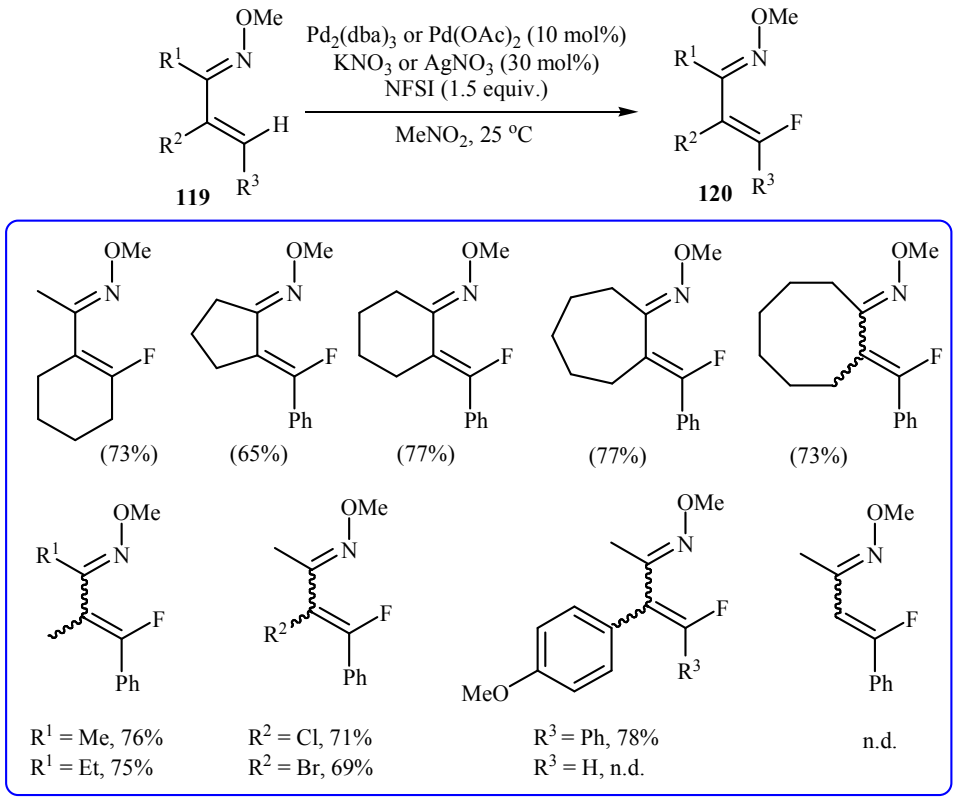
Table 4. The palladium-catalyzed ortho mono bromination of diaryl ketoxime ethers



116 **117** **118**

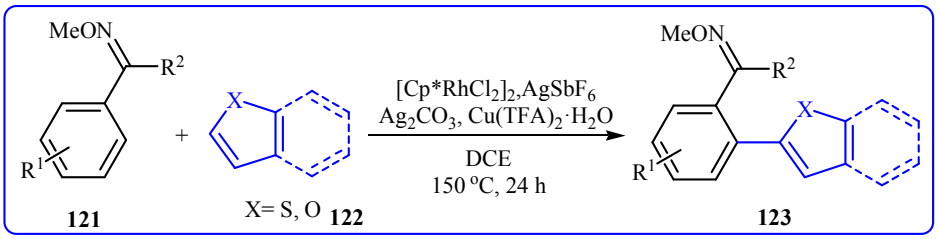
Entry	Y	Z	unreacted oxime ether **116** (%)	Mono/di **117**/ **118** (%)
1	4-Me	H	1	88:11
2	H	4-Me	2	87:10
3	H	4-NO_2	20	80:0
4	H	4-OMe	1	93:6
5	4-OMe	H	6	86:8
6	H	4-Cl	6	92:2
7	4-Cl	H	17	82:1
8	H	3-NO_2	30	69:1
9	H	3-NO_2	9	91:0
10	H	3-NO_2	3	97:0

An elegant method for the palladium-catalyzed *mono*-fluorination of Csp^2-H bond of oxime ethers, promoted by nitrate, was reported by Xu *et al.*[107] All of the 27 reported aryl-alkyl ketoxime ethers gave the corresponding *mono*-fluorinated products in high yield (71-87%). This methodology was successfully applied to mono-fluorination of benzylic C-H bonds in high yields and good tolerance was observed with a variety of substituents (Scheme 49).



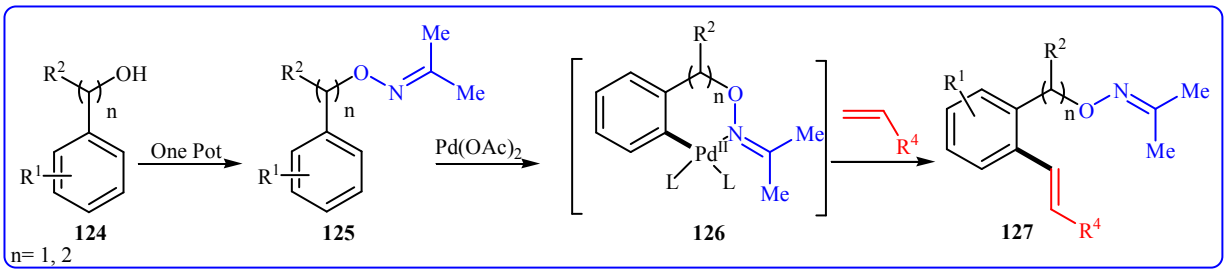
Scheme 49. Mild fluorination of aromatic C-H bonds

A Rh(III)-catalyzed C-H/C-H cross-coupling reaction of aryl-alkyl ketoxime ethers with heteroarens was reported by Gao and co-workers (Scheme 50).[108] The reaction was carried out in DCE under an inert atmosphere (150 °C, 24 h) using $[Cp^*RhCl_2]_2/AgSbF_6/Ag_2CO_3/Cu(TFA)_2{\cdot}H_2O$ system as the catalyst and the desired products was obtained in yields of 40-78%.



Scheme 50. Rh(III)-catalyzed oxime ether-directed heteroarylation of arene through oxidative C–H/C–H cross-coupling

Following these works, Zhao's research team demonstrated the direct *ortho*-C-H olefination of aromatic alcohols *via* a six- or seven-membered exo-acetone oxime ether palladacycle (Scheme 51).[109] The reaction was carried out by using $Pd(OAc)_2$/Ac-Val-OH/AgOAc/1,4-dioxane system and a broad range of oxime ethers and olefins with various functional groups, such as alkyl, Cl, F, CF_3, NO_2, SMe, CN, SO_2Ph, CO_2Et, CO_2H. The desired products are obtained in yields of 46-95%.



Scheme 51. Direct *ortho*-C−H functionalization of aromatic alcohols masked by acetone oxime ether *via exo*-palladacycle

8. Conclusion

The application of oxime ethers in organic synthesis has provided high efficiency methods for a wide array of organic reactions, many of which are staples of synthetic organic chemistry. In many cases, the use of these compounds provides milder conditions and simpler procedures than previously reported examples. This research area has still further possibilities for growth and we believe that the highly versatile and extremely effective and novel procedures for the synthesis of these compounds will be attainable in the near future.

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Oxime ethers as versatile precursors in organic synthesis: A review

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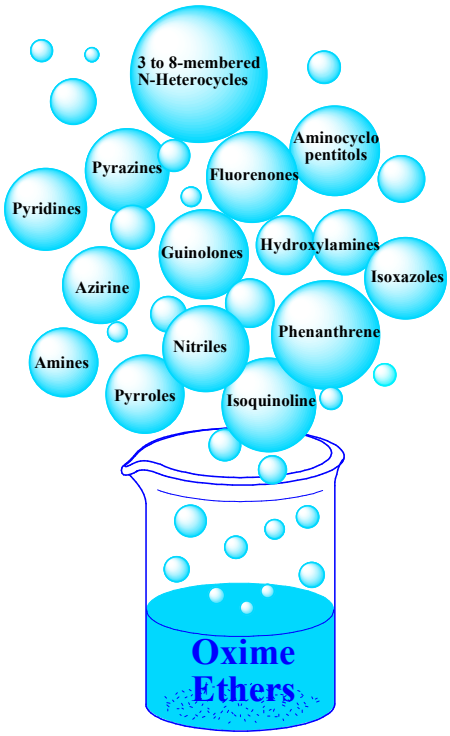

This review is a survey of the literature describing synthetic applications of oxime ethers. The cyclization and metal-catalyzed cross-coupling reactions of oxime ethers in recent years are also highlighted.