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Recent Methodologies toward the Synthesis of Valdecoxib: A Potential 3,4-diarylisoxazolyl COX-2 Inhibitor

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Abstract

Non-steroidal anti-inflammatory drugs are widely used therapeutic agents in the treatment of inflammation, pain and fever. Cyclooxygenase catalyzes the initial step of biotransformation of arachidonic acid to prostanoids, and exist as three distinct isozymes; COX-I, COX-II and COX-III. Selective COX-II inhibitors are a class of potential anti-inflammatory, analgesic, and antipyretic drugs with reduced gastrointestinal (GI) side effects compared to nonselective inhibitors. 3,4-diarylisoxazole scaffold is recurrently found in a wide variety of NSAIDs, protein kinase inhibitors, hypertensive agents, and estrogen receptor (ER) modulators. In the present review, we document on the recent synthetic strategies of 3,4-diarylisoxazolyl scaffolds of valdecoxib and its relevant structural analogues.

Keywords

Isoxazoles; Valdecoxib; Nitrile oxides; Heterocycles; Regioselectivity and Cycloaddition

1. Introduction

The classical non-steroidal anti-inflammatory drugs (NSAIDs) are therapeutic agents widely used in the treatment of inflammation, pain and fever.[1,2,3] These compounds are primarily used in the inhibition of cyclooxygenase (COX), normally referred to as prostaglandin synthase.[3,4] Prostaglandins are lipid derived fatty acids virtually present in all human tissues and produced by most of the cells in the body.[3] Cyclooxygenase (COX) catalyzes the first step in the biotransformation of arachidonic acid to prostanoids,[5–7] and usually exist in three distinct isoforms: COX-I, COX-II, COX-III,[8–11] as well as two smaller COX-I derived proteins (partial COX-1 or PCOX-I proteins).[11,12] While COX-I is expressed in all healthy tissues reconciling physiological responses, COX-II is induced by inflammatory stimuli,[13–15] and is responsible for the conversion of arachindonic acid to prostaglandin H_2, a potential key mediator for the inflammation.[16] Further COX-III and PCOX-Ia protein are derived from the COX-I which retain intron one and has a frameshift mutation.[12] Selective inhibition of COX-II provided a potential class of anti-inflammatory, analgesic, and antipyretic drugs with reduced gastrointestinal (GI) side effects compared to nonselective inhibitors.[5,17–20] Recent studies also indicated that inhibiting COX-II is not only a key approach for the treatment of several types of cancers,[21] and also can be used to postpone

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the clinical manifestation of Alzheimer's disease.[22] 3,4-diarylisoxazole scaffold[23] is one of the frequently found pharmacophore in a wide variety of NSAIDs,[24–26] protein kinase inhibitors,[27] and hypertensive agents.[28] One of the most familiar examples of 3,4-diarylisoxazoles is Valdecoxib (4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide), commercialized under the brand name Bextra. The phenylsulfonamide group located at the *para*- position is known to interact effectively with the COX-II side pocket through slow tight-binding kinetics.[29–31] The syntheses of isoxazoles usually involve the 1,3-dipolar cycloaddition of nitrile oxides with alkynes[32,33] or alkyne surrogates,[34] or through Suzuki cross coupling reaction.[21] In the present review, we document on the recent synthetic methodologies to access these diarylisoxazolyl derivatives of valdecoxib **1** in the context of recent applications to organic synthesis and methodology.

2.1 Coupling & Electrophilic Cyclization reactions

3,4-diarylisoxazoles are popular examples known for high COX-II selectivity and potency, and are represented by 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide moiety. Although several literature reports exist to synthesize substituted isoxazoles,[34–36] and selectivity in synthesizing 3,4-diarylisoxazoles are restricted and subjected to the availability of the starting materials.[37–39]

Toyokuni and co-workers[23] reported the synthesis of 3,4-diarylisoxazoles (**9**, **11** and **12)** through Suzuki cross coupling arylation of the C-4 position of the 3-arylisoxazoles.[40,41] Reaction of substituted phenyl-ethanone oxime **5** in presence of *n*-BuLi generated the enolate, which on subsequent condensation with EtOAc followed by dehydration, furnished the 3-aryl-5-methylisoxazole **6**.[42–44] Electrophilic bromination followed by Suzuki coupling reaction of 4-bromoisoxazole **7** with arylboronic acids **8** led to the formation of the 3,4-diarylisoxazoles **9**.

In addition, the treatment of 4-bromoisoxazole **7** with triisopropyl borate provided the corresponding isoxazole boronic acids **10**. Reaction of isoxazole boronic acids **10** with several arylbromides (bearing sulfonamide or 4-methylsulfonyl groups) and 5-bromopyrimidine proceeded successfully and furnished valdecoxib and analogues (**11** and **12**). However, poor yields were observed for arylbromides substituted with *vicinal* nitro and sulfonamide groups. The nitro and sulfonamide residues functioned as bidentate chelating ligand for Pd and interfered the catalytic cycle (scheme 2).[21]

Krogsgaard-Larsen and his group documented the synthesis of 4-aryl and 4-heteroaryl substituted 3-alkoxyisoxazoles as immediate precursors for the synthesis of pharmacologically interesting 3-isoxazolyl containing aminoacids.[40] Reaction of 3-ethoxy-5-methylisoxazole[45] **13** in presence of Br_2 in CCl_4 (or ICl/AcOH) generated the 4-halosubsituted isoxazoles **14** (**15**) (Scheme 3).

Suzuki-Miyaura coupling reaction of 4-substituted isoxazoles (**14** and **15**) with phenylboronic acid catalyzed by $Pd(PPh_3)_2Cl_2$ afforded the corresponding 3-ethoxy-5-methyl-4-phenylisoxazole **16**. In addition the reaction with 4-bromoisoxazole **14** was partially complete and the starting materials were isolated in the 1:2 ratio (Scheme 4).

However, when $Pd(PPh_3)_2Cl_2$ was replaced with $Ni(PPh_3)_2Cl_2$, it failed to undergo completion and resulted in the isolation of the 3-ethoxy-5-methyl-4-phenylisoxazole **16** along with **15**. Additional Suzuki-Miyaura and Stille cross-coupling reactions of 3-ethoxy-5-methyl-4-iodoisoxazole **15** with phenylboronic acids and tributyltin reagents furnished the desired coupling products (**17** and **18**) in moderate to excellent yields (Scheme 5).[40]

Heck coupling reactions of 3-ethoxy-5-methyl-4-iodoisoxazole **15** were further attempted to study the arylation and vinylation of alkyne and olefine derivatives (Scheme 6).

Finally, attempts to incorporate different functionalities with alkyllithium reagents primarily resulted in the deprotonation of methyl group of 3,5-disubsituted isoxazole **13**.[46] To avoid the undesired deprotonation, 4-iodoisoxazole **15** was converted into the Grignard intermediate **21** using *i*-PrMgBr,[47] later followed by transmetallation **22** and Pd-coupling reaction furnished the desired coupling product **23**. Similar reactions of the intermediate heteromagnesium bromide were smoothly converted to the final products (**24** and **25**) following treatment with benzaldehyde and benzoylchloride, respectively (Scheme 7).[40]

Larock and co-workers reported an efficient methodology toward the construction of several isoxazoles through electrophilic cyclization of 2-alkyn-1-one *O*-methyl oximes.[48,49] The reaction protocol involved the ICl promoted cyclization of methyl oximes, which was successfully employed for the synthesis of 4-iodoisoxazoles. The ynones **26** required for the synthesis of *O*-methyl oximes **31** were prepared by coupling of the terminal acetylene **27** with an acid chloride or an aryl iodide, or by the reaction of an acetylide **28** with aldehyde followed by oxidation of the alcohol, or by the treatment of silylated acetylene **29** with an acid chloride in the presence of $AlCl_3$ (Scheme 8).

The reaction of ynone **26** with methoxylamine hydrochloride, pyridine, and Na_2SO_4 (or $MgSO_4$/MeOH) provided the *O*-methyl oxime **30**.[50] When **30** is unsubstituted or substituted with a methyl group (R= H, Me), 2-alkyn-1-one *O*-methyl oxime tend to isomerize to **31** when passed through silica gel and often resulted in a mixture of *E/Z* isomers in 1:1 ratio. However, with increase of the size of the R group, the *Z* isomer was predominantly the major isolated product (Scheme 9).[49]

The ICl promoted electrophilic cyclizations of *Z*-*O*-methyl oximes (**32**/**33**) were performed with a wide variety of aryl and alkyl substitutions or substituted heteroaromatic systems. The desired 4-iodoisoxazoles (**34**/**35**) were isolated in very good to excellent yields depending on the nature of the substituent. Substitution of alkynyl moiety with aliphatic and aryl substituents had a little effect on the yield of the reaction. Further, the electron-deficient and electron-rich substituents at the *para*-position did not significantly alter the yields. On the other hand, insertion of thiophene heterocycle at the alkynyl unit slightly lowered the yield (Scheme 10).[49]

Similarly, the effect of the substituents attached to the imine carbon of the 2-alkyn-1-one O-methyl oximes (**36**/**37**) was also investigated. The *para*-substituted electron-deficient groups provided the isoxazoles in excellent yields (**38**/**39**). The electron-rich NMe_2 group in *para* position required extended reaction times and an excess of ICl to achieve excellent yield. Other alkyl and heteroaryl substituents of the 1-alkynone were quite successful and the products were isolated in excellent yields irrespective of the size (Scheme 11).[49]

Additional attempts to examine the effect of steric hindrance exerted by the introduction of bulky substituents (**40**/**41**) proved to be negligible on product formation and the desired isoxazoles (**42**/**43**) were isolated in good to excellent yields (Scheme 12).

The readily synthesized 4-iodoisoxazoles (**35** and **39**) are useful precursors to synthesize valdecoxib **1** through Suzuki cross-coupling with the corresponding boronic acid ester. Reaction of 4-iodoisoxazole **46** with boronic ester **47** under mild Suzuki conditions (5 mol % $PdCl_2$ catalyst, 1.4 equiv of $KHCO_3$; DMF:H_2O (4:1), 85°C) afforded the valdecoxib **1** in 74% yield. Similar reaction of 4-iodoisoxazole **38** in catalytic amounts of $Pd(OAc)_2$, ferrocene, carbon monoxide, in DMF:MeOH (4:1) gave the isoxazole methyl ester **48** (Scheme 13).[48,49]

Further, the 4-iodo-5-methyl-3-phenylisoxazole **46** was converted to the corresponding phenethylamide **49** by using catalytic amounts of $PdCl_2(PPh_3)_2$, carbon monoxide, and 2-phenethyl amine.[50] Additional Heck[51] and Sonogashira[52] coupling reactions of 4-iodo-5-methyl-3-phenylisoxazole **46** with phenyl acetylene **50** and *N*-acryloylmorpholine **51** provided the desired 4-acetlyated isoxazole **52** and α,β-unsaturated amide **53** in high yields (Scheme 14).

However, the carbonylative cyclization catalyzed in presence of palladium furnished the reduced isoxazole product than expected cyclized product **54** (Scheme 15).[49]

2.3 Condensation reactions

Talley *et al*[38] reported the initial synthesis of valdecoxib **1** and its hydroxymethyl analogue **59**, and the concise route to access **1** is outlined in scheme 14. Treatment of deoxybenzoin **55** with hydroxylamine hydrochloride in presence of sodium acetate furnished the desired oxime. Deprotonation of the oxime with *n*-BuLi followed by condensation with ethyl acetate afforded the intermediate isoxazoline **56**. Reaction of the isoxazoline **56** with chlorosulfonic acid followed by the reaction with ammonium hydroxide afforded the valdecoxib **1** (Scheme 16).

Similarly, the hydroxymethyl analogue of valdecoxib **59** was synthesized following the same protocol. Condensation of dianion of the deoxybenzoin with methyl chloroacetate provided the isoxazoline derivative **57**. Chlorosulfonation and treatment of the isoxazoline **57** with sulfonyl chloride with aqueous ammonia afforded the sulfonamide derivative **58**. Final treatment of sulfonamide derivative with formic acid in presence of triethylamine followed by hydrolysis with aqueous NaOH[53] furnished the hydroxymethyl analogue of valdecoxib **59** (Scheme 17).[38]

In another report, Talley and his coworkers reported the synthesis of parecoxib sodium **2**, a water soluble prodrug of valdecoxib.[17] Parecoxib sodium was identified as a highly potent and selective inhibitor of prostaglandins from COX-2. Acylation of the valdecoxib sulfonamide **1** with acid anhydride in presence of triethylamine afforded the desired sodium salt of the isoxazole derivative **2** (Scheme 18).

Syntheses of radiolabelled COX-II inhibitors with short lived positron emission are attractive targets for synthesis and find several applications in imaging techniques. Positron emission tomography abbreviated as PET is a powerful non-invasive, molecular imaging technique that found extensive biomedical applications.[54] Toyokuni *et al* reported the synthesis of fluoroalkyl and fluroaryl analogues of valdecoxib as a potential PET imaging probe for COX-II.[8] The non radioactive fluoroalkyl analogues of valdecoxib **61** and **62** were synthesized by direct fluorination of the corresponding hydroxy analogue **60** with DAST (diethylaminosulfur trifluoride) and other relevant fluoroaryl analogues (**63** and **64**) were synthesized by earlier reports (Scheme 19).[23,37,38]

The radiosynthesis of the [^{18}F]fluoromethyl analogue **1-^{18}F** (**68**) of valdecoxib was accomplished as shown in Scheme 18. The sulfonamide group of the hydroxymethyl isoxazole **65** was selectively protected using 4,4'-dimethoxytrityl (DMTr) group **66**. The hydroxyl group was tosylated with tosylic anhydride to give the tosylated isoxazole **67**. The tosyl group was substituted with fluorine and following deprotection under acidic conditions furnished the desired **1-^{18}F** (**68**; Scheme 20).[8]

2.3 1,3-Dipolar Cycloadditions

Scilimati and his group[31] reported the synthesis of a series of 3,4-diarylisoxazoles analogues of valdecoxib (Fig. 2). The synthetic protocol involved the generation of a thermodynamically stable enolate **71** from phenylacetone **70** in presence of LDA at 0°C.[55] The readily formed **71**, reacted with a wide variety of substituted arylnitrile oxides and afforded the intermediate 3-aryl-5-hydroxy-5-methyl-4-phenyl-2-isoxazoline diastereomer **74**. The hydroxyisoxazoline underwent aromatization to the analogous isoxazole **75** through dehydration process.[31,56] However, the reaction of mesityl and 5-chloro-2-furyl substituted nitrile oxides with enolate **71** provided unstable isoxazolines, which on partial dehydration (or silica gel separation) furnished the isoxazoles **75**. The readily synthesized 5-methyl-3,4-diphenylisoxazole **75** or the intermediate hydroxyl-isoxazoline **74** under $ClSO_3H/NH_4OH$ conditions provided the valdecoxib analogues **1** (Scheme 21).[57]

Similarly, other potential analogues of valdecoxib **1** were synthesized by adopting the same protocol. While analogues (Ar = Ph, 5-chloro-2furyl) were synthesized in high to excellent yields, analogue **77a** (Ar = 3-Cl-2,4,6-$(OCH_3)_3$Ph) was isolated in low yields. Further, in case of mesityl substituted analogue **79**, $ClSO_3H/NH_4OH$ reaction took place at the mesityl ring **80** and **81**, due to the activation of electron rich methyl groups on the phenyl ring. However, in case of **81** the reaction wasn't exclusive and also occurred at the C-4 phenyl ring of the isoxazole (Scheme 22).[31].

Erdélyi *et al*[3] reported the synthesis and pharmacological evaluation of an active metabolite *N*-hydroxyvaldecoxib. Chlorosulfonation of 5-methyl-3,4-diphenylisoxazole[38] gave a mixture of *ortho*- and *para*-chlorosulfonylisoxazoles (**83** and **84**), which following recrystallization and treatment with hydroxylamine hydrochloride gave the unstable *para*-substituted *N*-Hydroxy-4-(5-methyl-3-phenyl-isoxazol-4-yl)-benzenesulfonamide isomer **85**. The intermediate **85** was transformed into a more stable monohydrate form **86** and recrystallized from L-ascorbic acid in aqueous ethanol (Scheme 23).[3]

Organoboron reagents[58] are the most sought synthetic intermediates[59] primarily used in the construction of C-C bond via Pd-catalyzed cross coupling reactions under relatively mild conditions.[60] Harrity and his coworkers documented the regiochemistry of boron containing alkynes by investigating the 1,3-dipolar cycloaddition reactions of nitrile oxides with various alkynylboronates.[61–63] 1,3-Dipolar cycloaddition reaction of alkynylboronate **87** with mesitylcarbonitrile oxide **88** proceeded smoothly and furnished a mixture of isoxazoleboronates **89** and **90**. In addition, 1,3-dipolar reaction of mesitylcarbonitrile oxide **88** with methyl substituted alkynylboronate (**87**; R= Me) resulted in complete reversal of regioselectivity and isolated **90** as single regioisomer. Similar reactions of mesitylcarbonitrile oxide **88** with substituted alkynylboronates **91** provided the isoxazole-4-boronic esters **92** regioselectively (Scheme 24).[63]

The application of alkyl **93** and substituted arylnitrile oxides **94** also provided the 4-substituted boronic esters **95**/**96** with excellent regioselectivity.[32,64] This regioselective 1,3-dipolar reaction toward the synthesis of 3,4,5-trisubstituted isoxazoles can selectively be used to incorporate the boronates at C-4 with excellent levels of regioselectivity by permitting a reasonable variety of substituents to be introduced at C-5 position of the isoxazole (Scheme 25).[63]

In efforts to promote the dipolarophile cycloaddition over competiting dimerization of nitrile oxides,[65] the reaction conditions of the 1,3-dipolar reaction were optimized ($KHCO_3$/DME suspension) by decreasing the relative solubility to aid in slow generation of nitrile oxides.[66] 1,3-dipolar reaction of aryl and alkyl nitrile oxides **97** under either set of conditions with substituted ethynylboronate **98**/**100** proceeded smoothly and furnished isoxazole-4-

boronates as a single regioisomers **99**/**101**. However, attempted similar cycloadditions using triethylamine with aryl and alkyl nitrile oxides **97** resulted in a low yield of isoxazoles **101** (Scheme 26).[63]

The reaction scope was further broadened by extending the cycloadditions reactions with halonitrile oxides **102** generated in situ from the corresponding dihaloformaldoximes. The formations of the 3-haloisoxazoles **104**/**106** were found to be more efficient in $KHCO_3$/DME suspension than compared to triethylamine conditions. After the efficient optimization of the cycloadditions in presence of mild bases, the reaction scope was further tested in acidic conditions. Reaction of TMS substituted alkyne **107** with acetylnitrile oxide **108**[67] provided a 6:1 mixture of 3-acetylisoxazole regioisomers **109** and **110** (Scheme 27).[63]

The readily prepared isoxazoleboronates **111** are useful precursors for the Suzuki coupling reactions. Isoxazoleboronic ester **111** underwent Pd-catalysed coupling with bromobenzene and allyl bromides efficiently to yield the coupling products **112** and **113** in excellent yields. This efficient two step route is of great significance for the regioselective construction of an array of highly substituted isoxazoles (Scheme 28).[61,63]

The scope of this reaction methodology[63] was explored to a significant extent toward the synthesis of nonsteroidal antinflammatory drug; valdecoxib **1** and relevant analogues **114**. Valdecoxib **1** and its mesityl-substituted analogue **114** were synthesized by the cycloaddition of alkyne **113** with benzo- and mesitonitrile oxides **94** to afford intermediate isoxazole-4-boronates **95**.[62] These isoxazole-4-boronates **95** when subjected to Suzuki coupling reaction with *p*bromobenzene sulfonamide furnished the targeted drug valdecoxib **1** and its mesityl-substituted analogue **114** in excellent yields (Scheme 29). The reaction protocol is of greater significance in the synthesis of valdecoxib analogues (especially **114**) compared to earlier report,[31] where the reaction suffered from undesired chlorosulfonation, steric effects, and low product formation.

Bourbeau *et al*[68] reported the synthesis of 4-alkyl-5-aminisoxazoles through nucleophilic addition of lithiated alkyl nitriles to hydroximoyl chlorides. The hydroximoyl chlorides are highly electrophilic and can easily react with lithiated nitriles at low temperature reaction conditions. α-Chlorobenzaldoxime **115** reacted with a variety of lithiated nitriles to provide the desired 5-aminoisoxazoles **116** (Scheme 30).[69,70]

Similarly lithiated propionitrile was treated with an array of substituted hydroximoyl chlorides **117**/**118** to examine the effect of substitution on the rate of reaction.[68] All the reactions proceeded smoothly and furnished the desired aminoisoxazoles **119**/**120** in moderate to high yields (Scheme 31). The plausible reaction mechanism involved the addition of lithiated nitrile to in situ generated nitrile oxides, followed by cyclization to afford the 5-aminoisoxazoles (or) involve a concerted pathway analogous to oxime chlorides and alkynes.[70]

Conclusions

In summary, the review provided a compact overview of different synthetic methodologies to synthesize diarylisoxazole derivatives of valdecoxib and synthetic analogues. The chemistry of isoxazoles[8,23,32,34,38] is of great interest for synthetic organic and medicinal chemists over several decades. Of the several existing protocols, (a) 1,3-dipolar cycloaddition reactions of sydnones offered excellent regio-control to synthesize valdecoxib and analogues.[61–63] This methodology has the advantage of avoiding the issues associated with undesired chlorosulfonation, steric effects, and low product yield;[31] (b) in addition to the cycloadditions, electrophilic cyclizations[48,49] and cross-coupling reactions[23,40] are equally important and serve as alternative approaches for the synthesis of diarylisoxazoles.

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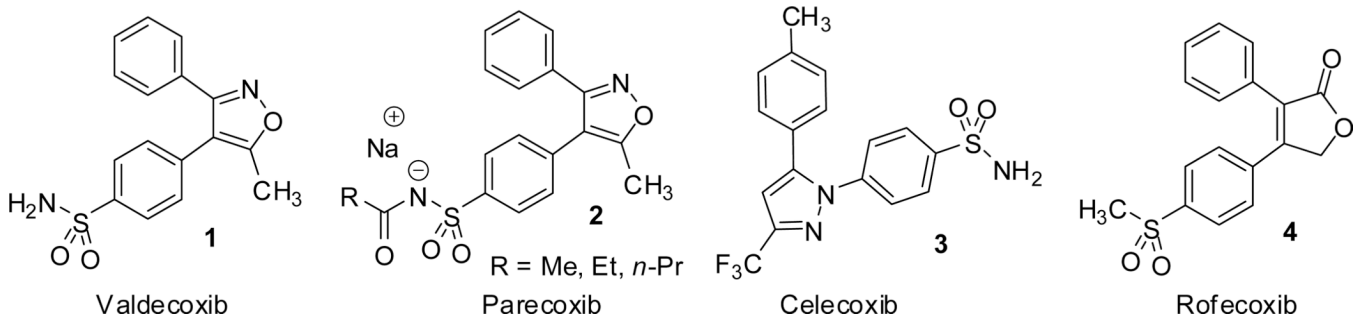


Figure 1.
Examples of pharmaceutically relevant diaryl heterocycle scaffolds

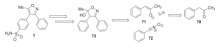
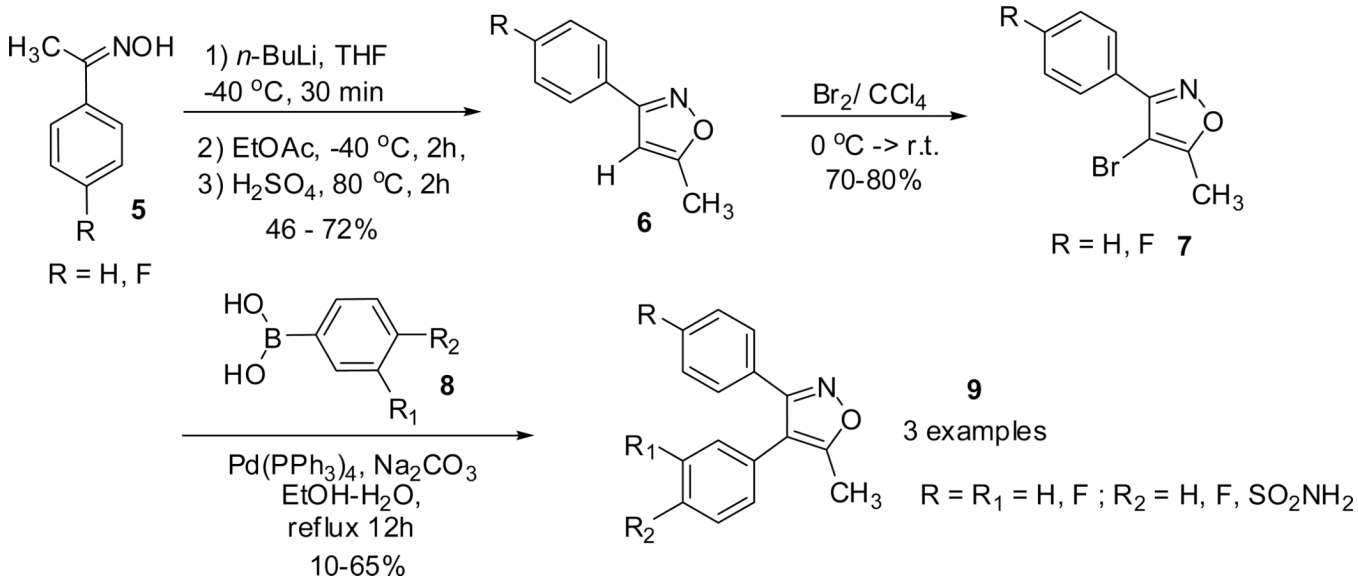
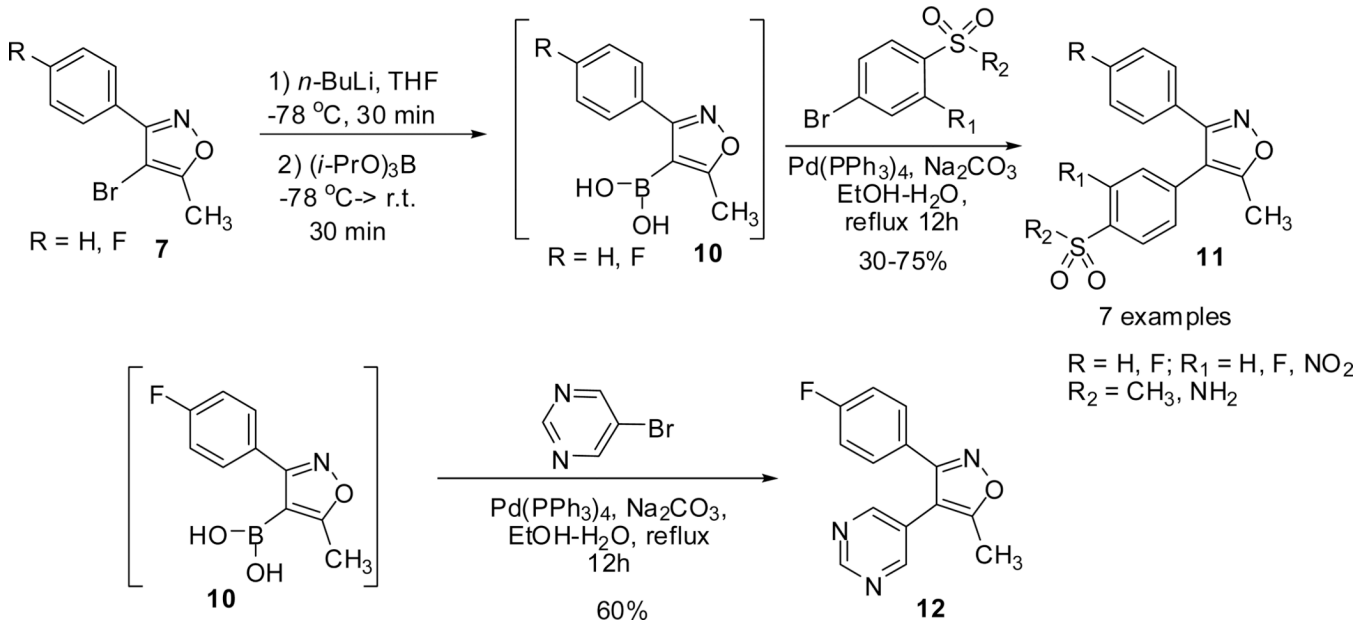


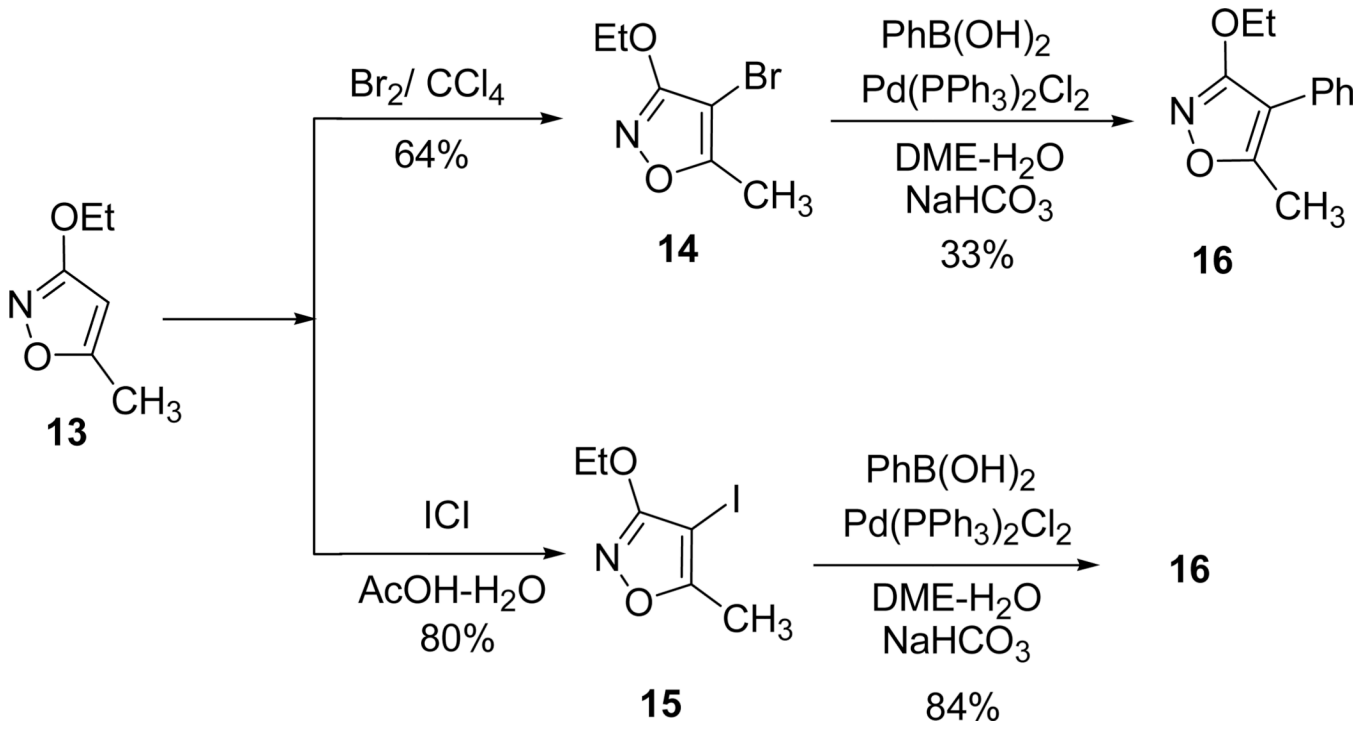
Figure 2.



Scheme 1.



Scheme 2.



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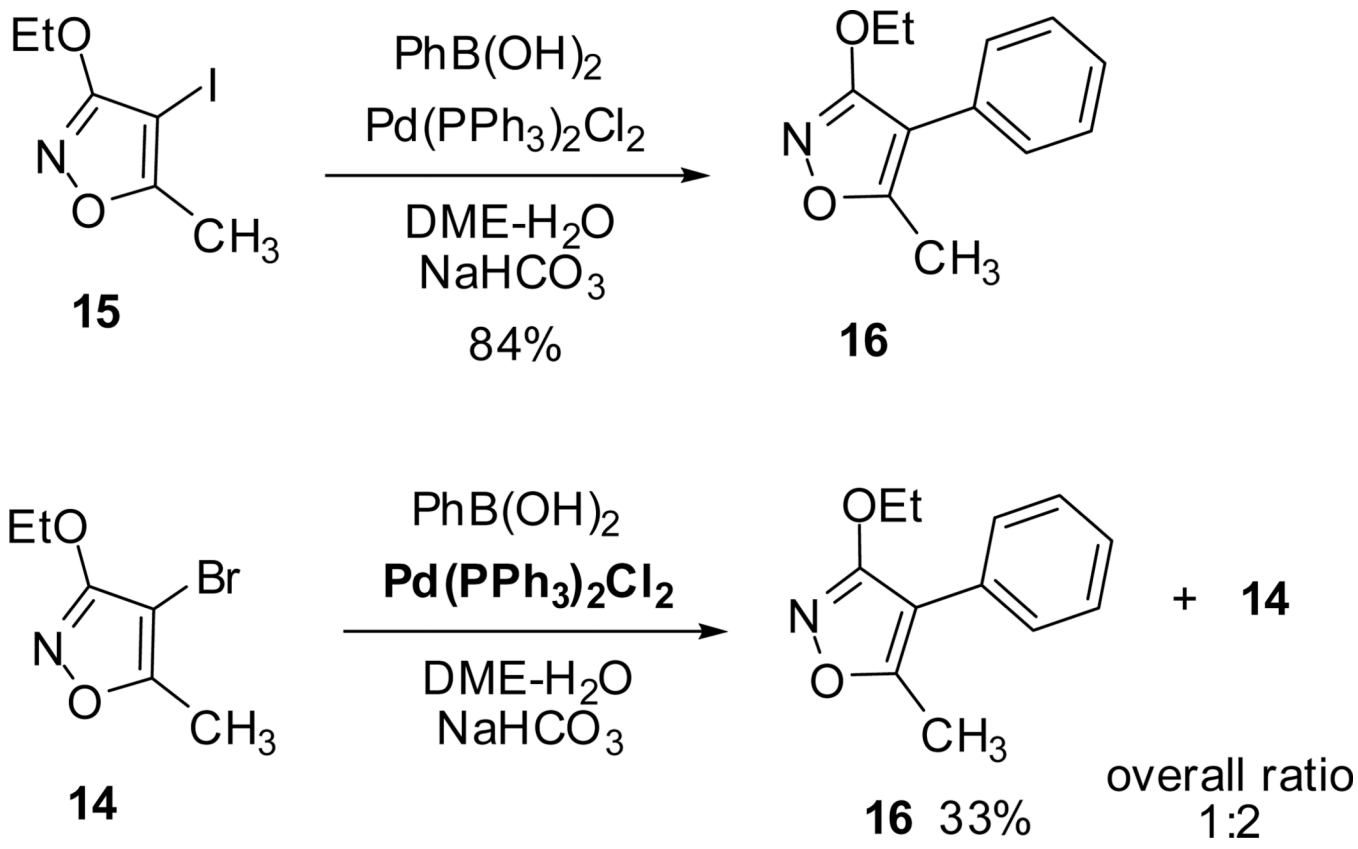

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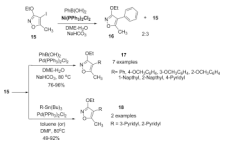

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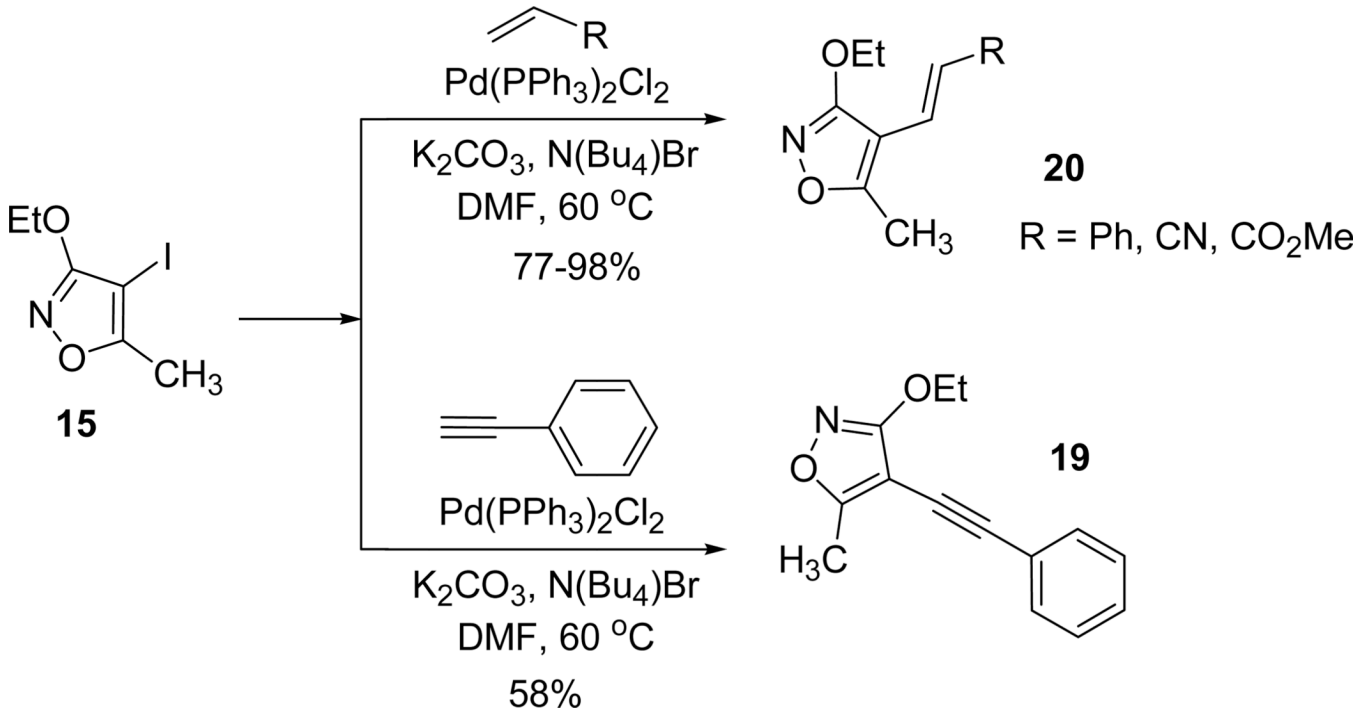

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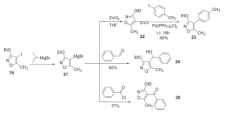

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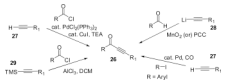
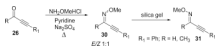


Scheme 8:[49]



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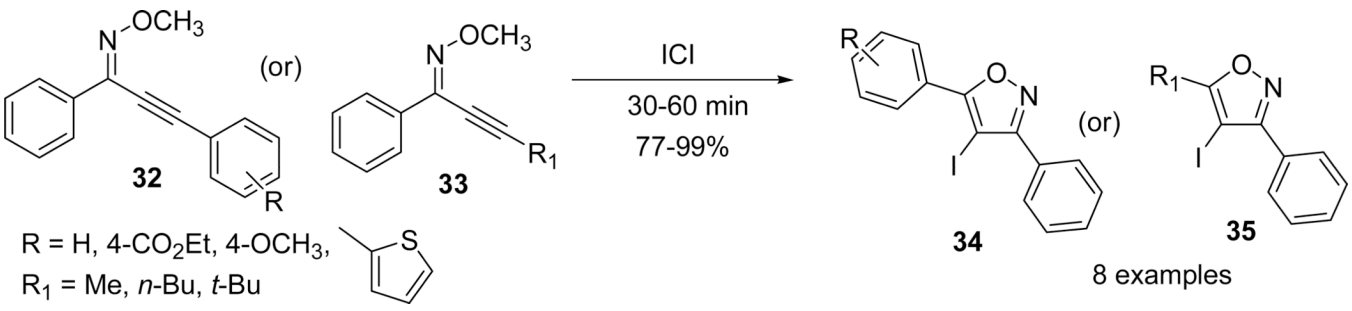
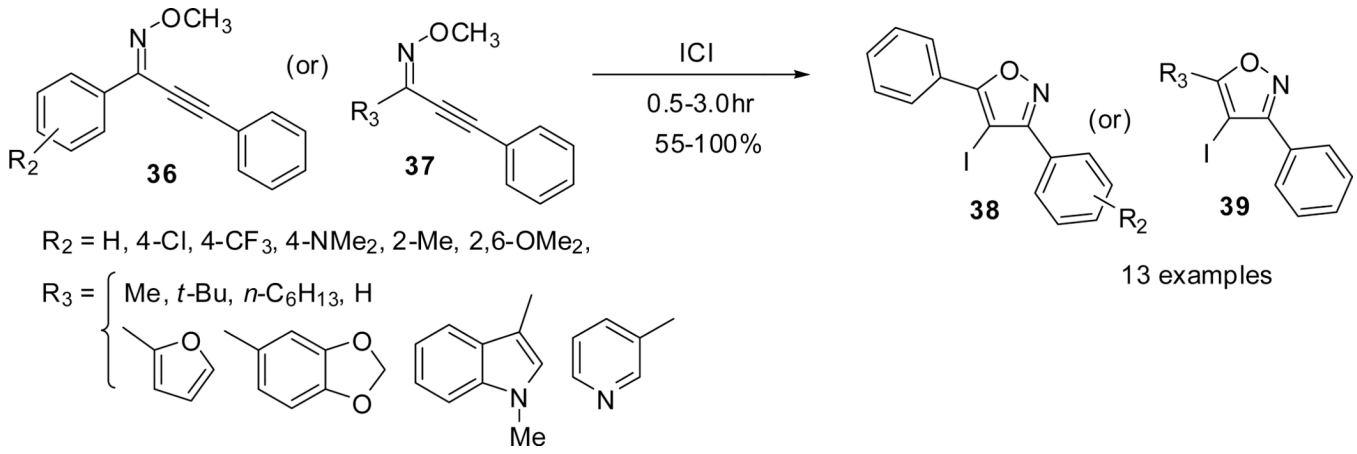
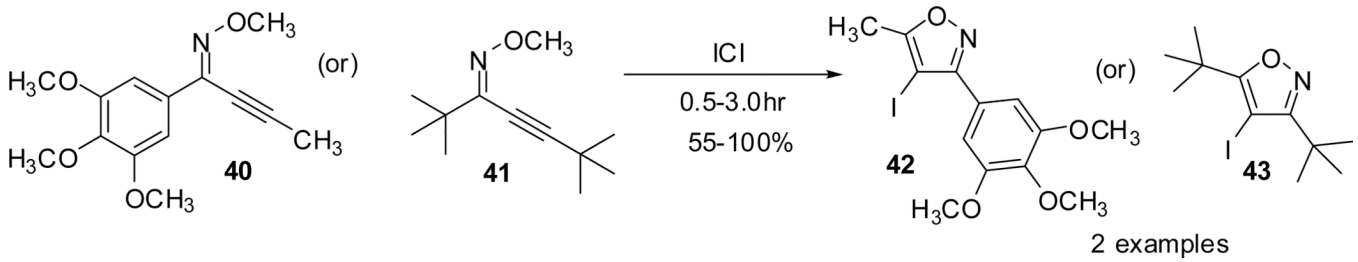


Scheme 10.



Scheme 11.



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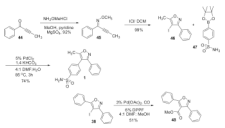
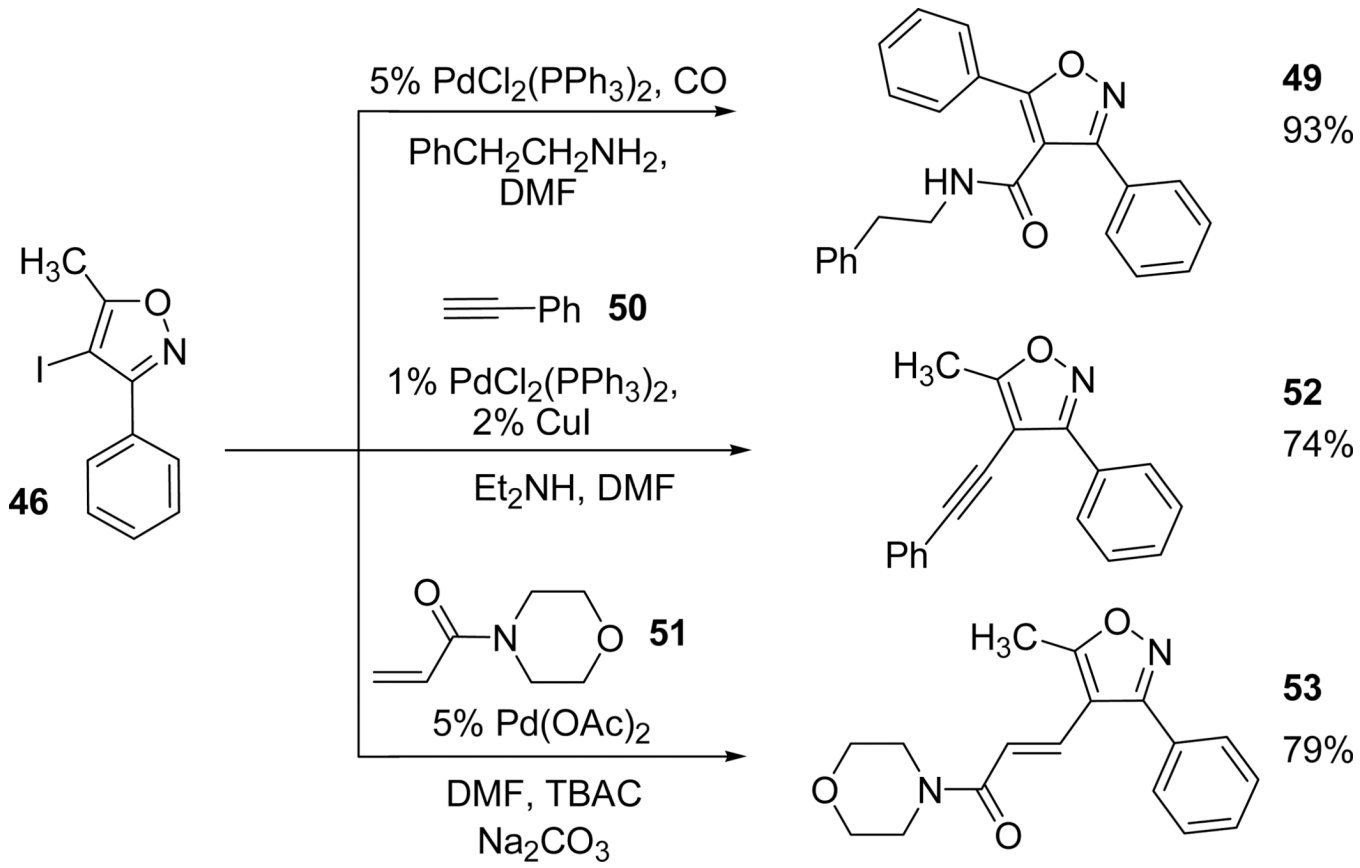
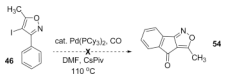


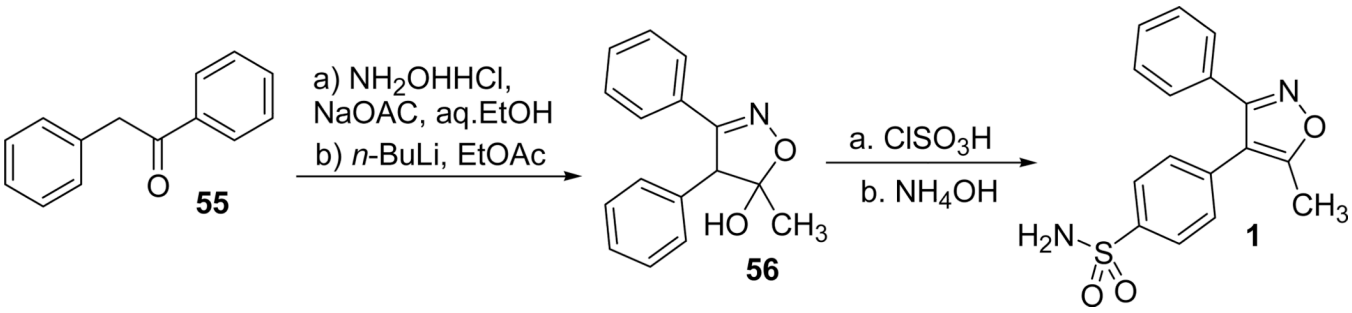
Scheme 13.



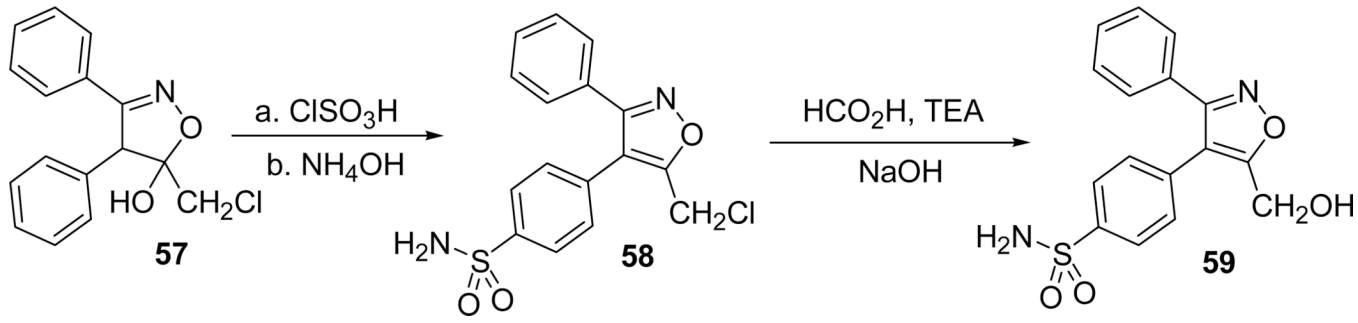
Scheme 14.



Scheme 15.



Scheme 16.



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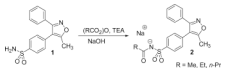

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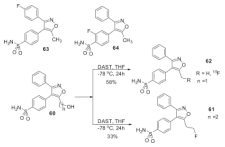

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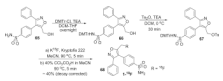

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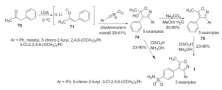

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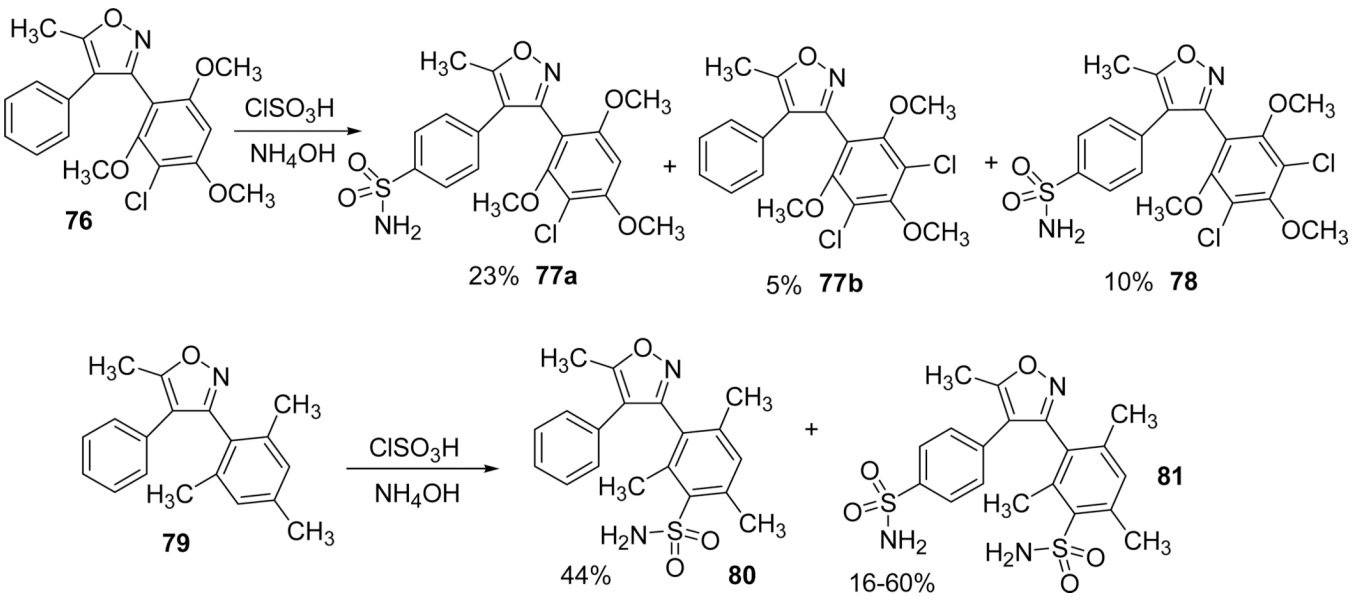

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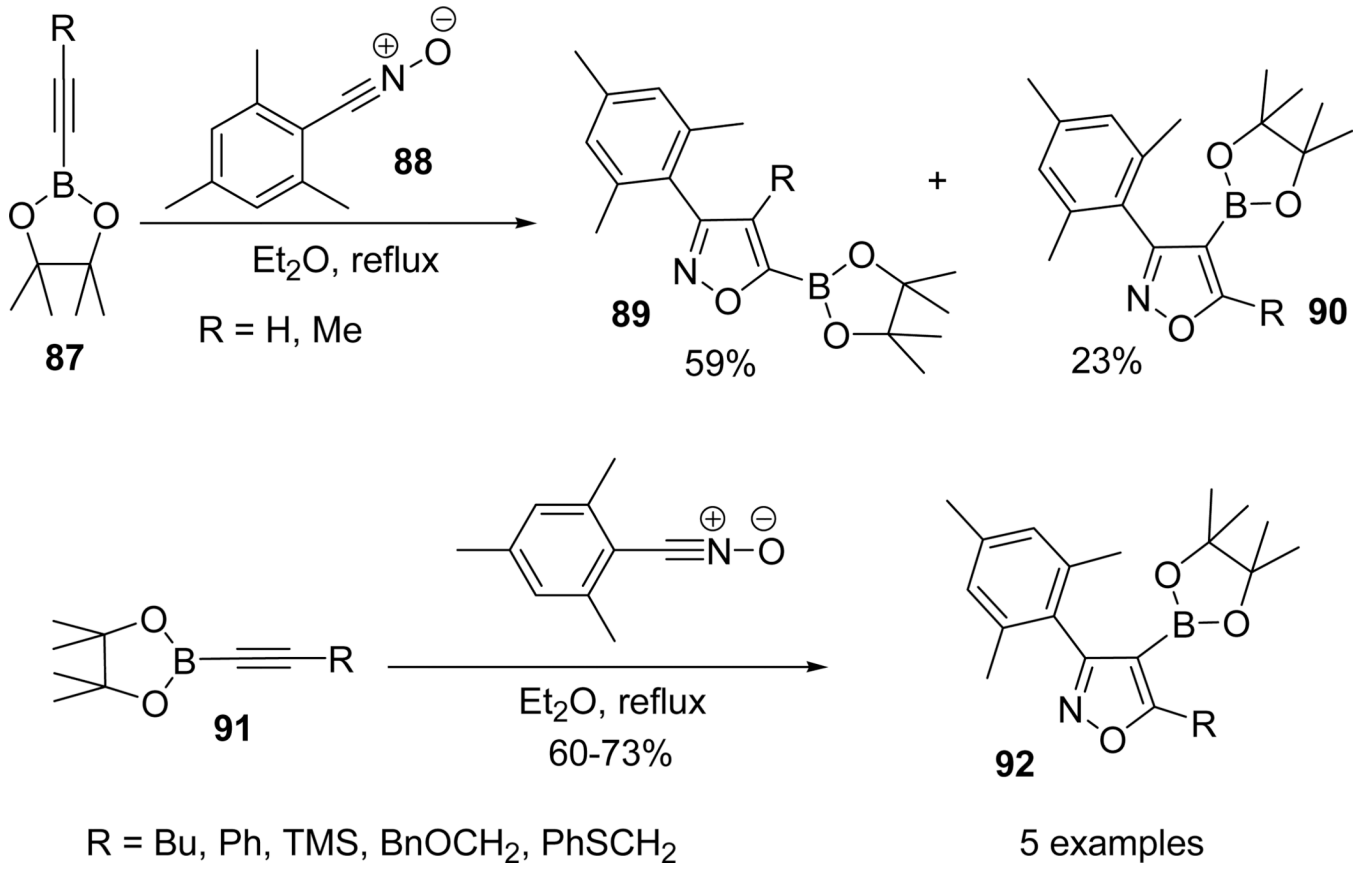
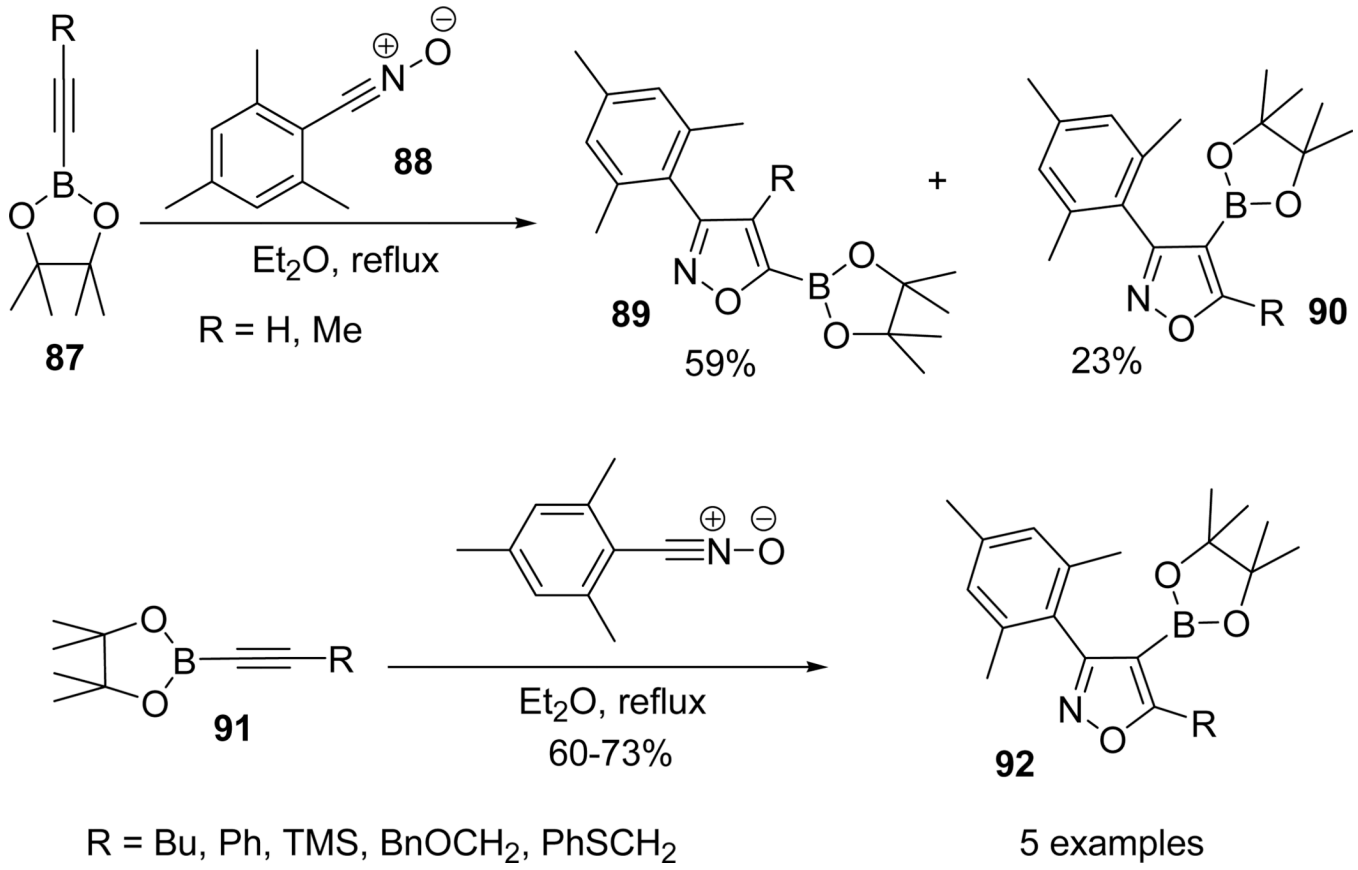
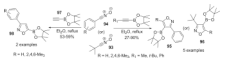


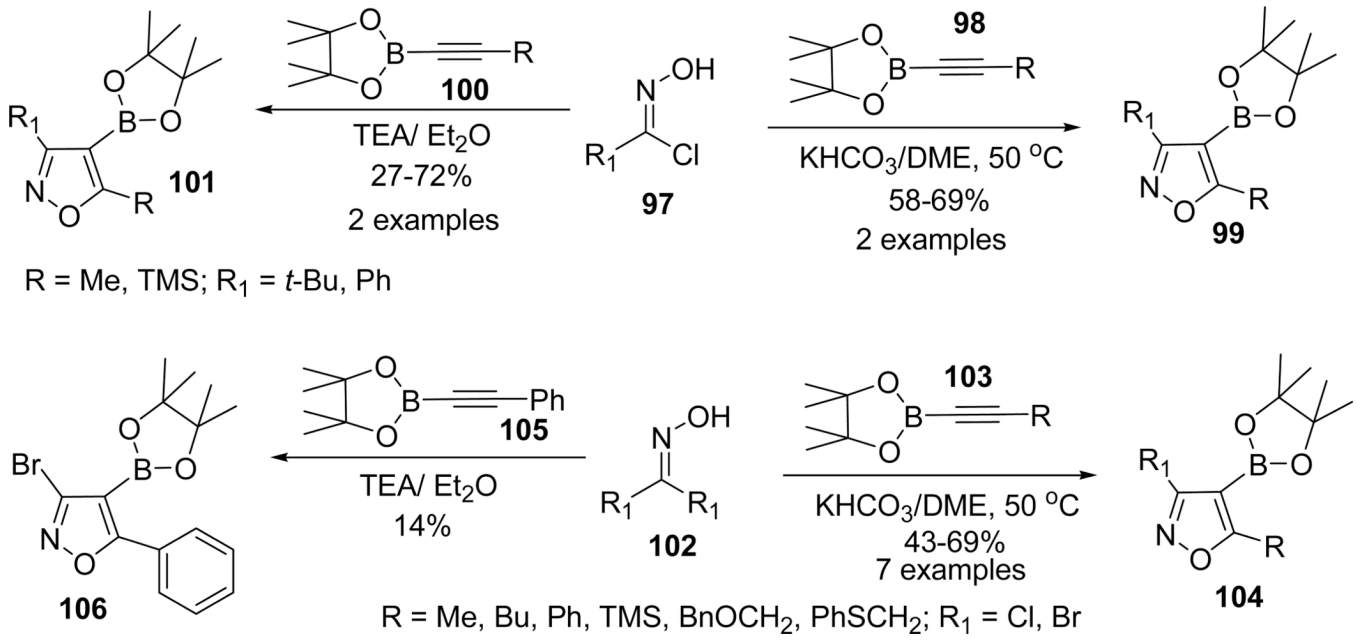
Scheme 23.



Scheme 24.



Scheme 25.



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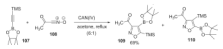
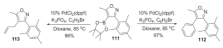


Scheme 27.



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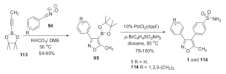

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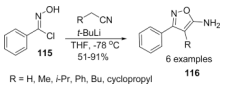

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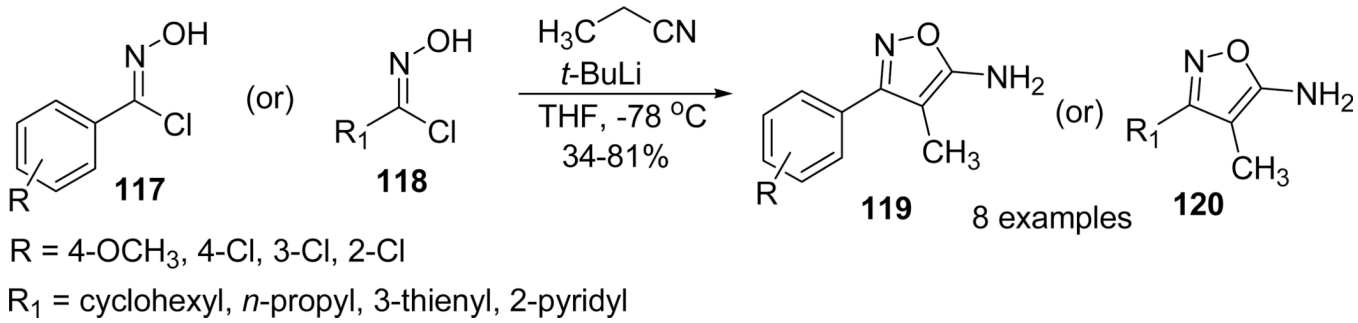

Scheme 31.