

REVIEW

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Scope and advances in the catalytic propargylic substitution reaction

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Nucleophilic displacement of the propargylic alcohol is one of the sought-after methods in the current scenario. The highly nucleophilic alkyne functional moiety along with its considerably acidic terminal hydrogen atom allows the propargylic unit to play a crucial role in organic synthesis by offering a handle for further synthetic transformations. Until 2000, the most fundamental propargylic substitution reaction was the Nicolas reaction, a multi-step transformation, developed in 1972, which involved cobalt as a stoichiometric promoter. Therefore, the direct catalytic substitution of propargylic alcohols was a highly desirable method for development. The pioneering work on the Ru-catalyzed propargylic substitution reaction in 2000 encouraged many researchers to develop several novel catalytic propargylic substitution reactions, which have made rapid progress since then. The purpose of this review is to emphasise the involvement of diverse types of Lewis acid, transition metal and Brønsted acid catalysts in the propargylic substitution reaction and provide an updated summary of the recent developments in this field. The selected examples presented here are the most significant and relevant ones and we believe that this will help the readers to comprehend the scope of the propargylic substitution reaction with diverse types of catalysts and will envisage the scientific community for the future developments in this field.

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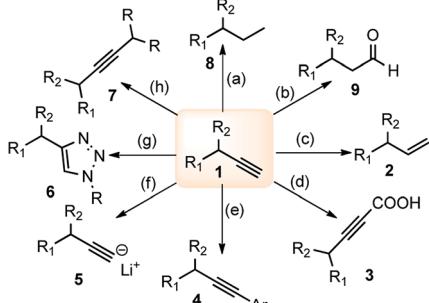
1. Introduction

Direct nucleophilic displacement of the alpha-hydroxy of the propargylic alcohol is one of the desirable methods in the current scenario. The highly nucleophilic alkyne functional moiety along with the considerable acidic terminal hydrogen atom **1** allows the propargylic unit to play a crucial role in organic synthesis by providing access to saturated products by catalytic hydrogenation, as well as offering a handle for further synthetic transformations, Scheme 1.¹

Apart from the versatile applicability of the alkyne synthon in chemical transformations,² many natural products,³ fine chemicals⁴ and synthetic pharmaceuticals⁵ are reported to possess the propargylic subunit as their structural component, Fig. 1.

Until 2000, there were only a few intermittent reports of nucleophilic propargylic substitution reactions. The most fundamental being the Nicolas reaction, developed in 1972, involving a stoichiometric cobalt complex, $\text{Co}_2(\text{CO})_8$ as the promoter for the reaction between a propargyl ether **15** and any nucleophile (Nu), Scheme 2.⁶⁻⁸

The reaction proceeds *via* the hexacarbonylcobalt, $\text{Co}_2(\text{CO})_6$ stabilized carbocationic pathway, prior to the encounter with the nucleophile. Subsequent oxidative demetallation gives the substitution product. Despite the broad scope



(a) $\text{H}_2/\text{Pd-C}$; (b) $\text{H}_2\text{O}, \text{HgSO}_4, \text{H}_2\text{SO}_4$; (c) Na, NH_3 ; (d) $n\text{-BuLi}, \text{CO}_2/\text{HCl}$
(e) $\text{Ar-X}, \text{Pd-cat}, \text{Cul}$; (f) $n\text{-BuLi}/\text{THF}$; (g) $\text{Cu-salt}, \text{RN}_3$; (h) $\text{Fe}(\text{acac})_2, \text{K}_2\text{CO}_3$

Scheme 1 Various synthetic transformations of the alkyne moiety.

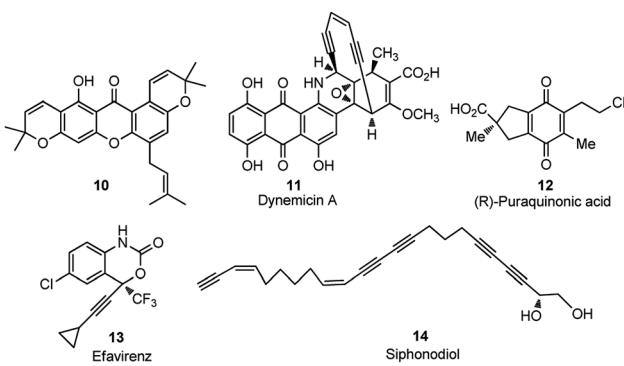
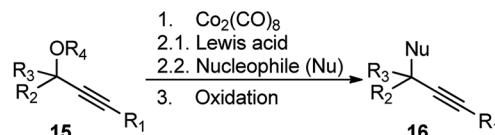
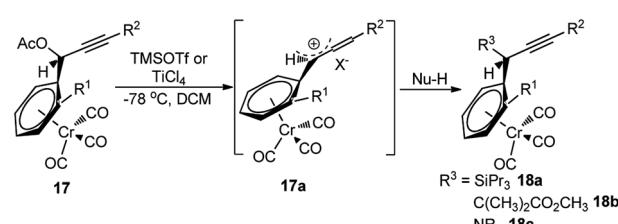


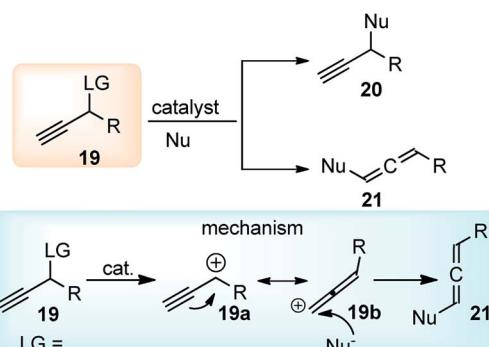
Fig. 1 Some bioactive molecules with propargylic subunit.



Scheme 2 Propargylic substitution by Nicolas reaction.



Scheme 3 Stoichiometric propargylic substitution reaction.



Scheme 4 Formation of allene derivative during propargylic substitution reaction.

of nucleophiles, this reaction did not gain popularity in the scientific community, due to the involvement of stoichiometric amount of $\text{Co}_2(\text{CO})_8$ and multistep process. Another stoichiometric method, reported by Müller and Netz, for the propargylic substitution, uses *ortho*-substituted (arene) $\text{Cr}(\text{CO})_3$ **17** in conjunction with Lewis acid like TiCl_4 or TMSOTf , also has limited applicability, Scheme 3.⁹

Therefore, the urge to develop an efficient catalytic propargylic substitution reaction become an inexorable task for the synthetic community. But unlike the catalytic allylic substitution reactions, propargylic substitution reactions are quite arduous due to the predominant formation of allene derivatives, thereby making the propargylic substitution difficult, Scheme 4.

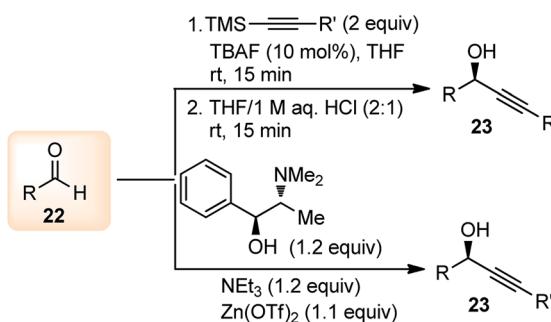
The hydroxy being a poor leaving group is generally transformed into more reactive substituents in propargylic alcohol like halide, carboxylate, carbonate, phosphonate, sulfonate, *etc.* to facilitate the propargylic substitution reaction. However, this process unavoidably involves multiple reaction steps and bound to produce stoichiometric amounts of waste on the release of environmentally unfriendly leaving groups. Therefore, the direct catalytic substitution of propargylic alcohols is an appropriate method for development.



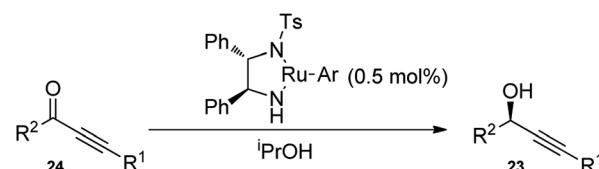
Essentially it was evident that apart from selecting the proper catalysts, several other factors including the nature of the nucleophiles, propargylic substrates and prior activation of the hydroxyl group, demands fine-tuning to selectively substitute the α -position of the propargylic moiety. Classical propargylic substitution reaction has had a great set-back until the Ru-catalyzed propargylic substitution reaction discovered in 2000 (ref. 10) which was instrumental in the rapid development in this area. Several pioneering works on transition-metal catalyzed propargylic substitution reactions have been reported by the groups of Toste,¹¹ Campagne,¹² Nishibayashi,¹³ and van Maarseveen¹⁴ involving rhenium, direhnium, gold, and copper-catalyzed nucleophilic substitution of propargylic alcohols, respectively. The very early review in this area mainly on the role of ruthenium-allenylidene complexes in propargylic substitution reaction was reported by Nishibayashi in 2006 (ref. 15) followed by another review in 2009 by van Maarseveen. Van Maarseveen gathered the early examples of catalytic propargylic substitution reaction that was focused on the role of diverse catalysts involved in the propargylic substitution reaction and early examples of enantioselective propargylic substitution reactions.¹⁶ In the same year 2009, Nishibayashi also summarized the advances in catalytic propargylic substitution reactions in terms of catalyst used, the mechanism involved and substrate scope.¹⁷ Ding and Hou in 2011 presented a review discussing the asymmetric propargylic substitution exemplified by selected enantioselective transformations using carbon and heteroatom nucleophiles.¹⁸ A detailed review on the copper-catalyzed propargylic substitution was published by Hu in 2015.¹⁹ Besides these reviews, Sakata and Nishibayashi recently reported a review in 2017 discussing the mechanism and reactivity of transition metal catalyzed propargylic substitution reactions from a theoretical perspective.²⁰ Nishibayashi in 2011 presented a review describing the series of heterobimetallic complexes consisting of group IV metallocenyl diphosphines and Ru as catalysts for propargylic substitution reaction.²¹

2. Synthesis of propargylic alcohols

The propargylation reaction is one of the most fundamental reactions in organic synthesis featuring mild reaction conditions, diverse functional group tolerance leading to the easy construction of C–C bond. It can be easily accessed by the



Scheme 5 Different methods for the synthesis of propargylic alcohol.

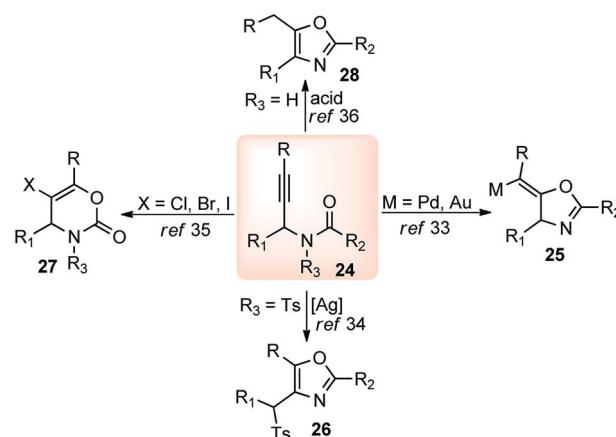


Scheme 6 Different methods for the synthesis of propargylic alcohol.

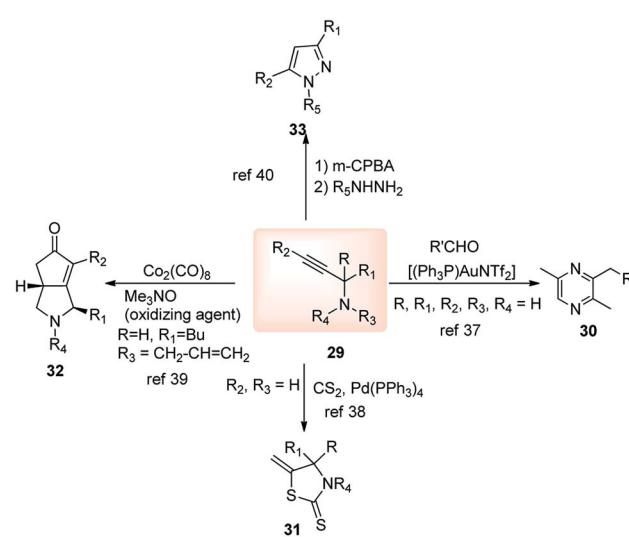
simple reaction between the corresponding aldehydes with *in situ* generated alkynyl lithium obtained from monosubstituted acetylene derivatives and *n*-BuLi. Several other practiced methods for the synthesis of propargyl alcohol are highlighted in the Scheme 5 and Scheme 6.^{22–30}

3. Structural modifications of the propargyl derivatives

The high electron density of the propargyl alcohols and their derivatives renders them exceptionally versatile synthetic



Scheme 7 Synthesis of different heterocyclic building blocks from propargyl unit.



Scheme 8 Synthesis of various heterocycles from propargylamine.



intermediates.^{31,32} The π -nucleophilic character of the triple bond makes it a well-designed unit for further chemical transformations. Transition metal/Brønsted acid catalyzed intramolecular cycloisomerization of propargylic sub-unit offers a new dimension for the synthesis of extremely useful building blocks for organic synthesis as highlighted in Scheme 7 and Scheme 8.^{33–40} The nature of the catalysts and the structure of propargyl derivatives have great influences on the cyclization modes. These cyclization reactions, due to their ability to rapidly assemble into structurally complex molecules and good functional group compatibility, have emerged as an outstanding method for the synthesis of N-containing heterocycles.

4. The scope of this review

Since Nishibayashi and van Maarseveen's major review on the advances of catalytic propargylic substitution published in 2009, there has been a phenomenal development on catalytic propargylic substitution reactions. The reasons for the rapid progress of propargylic substitution reaction can be attributed to the development in the concept and in-depth knowledge of catalysis and design methodology. The assiduous interest in this domain of research is because of several reasons as highlighted below: (i) commercially available starting materials or easy availability of the starting materials; (ii) non-toxic H_2O as the only side product; (iii) the synthetic utility of the propargyl subunits for further functional group transformations; (iv) involvement of mild reaction conditions. The gargantuan extent of work has been done in the last few years with diverse types of catalyst demands necessary documentation of different methods in a systematic manner.

This review describes the latest developments on the synthetic methodologies of propargylic substitution reaction which has become a subject of burgeoning interest. Thus, the aim of this review is to provide an updated summary of the recent advancements in the catalytic propargylic substitution reaction with an emphasis on the role of different Lewis acid,

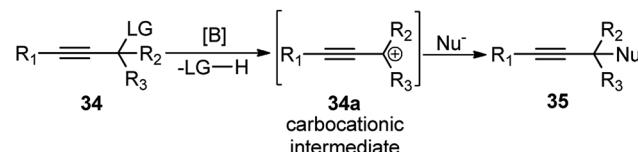
transition metal catalysts as well as Brønsted acid catalysts in the propargylic substitution reaction and scope for further development. Initial attempts in early 2000 using ruthenium and soon after with copper as transition metal catalysts were consequently followed by a multitude of new methods employing a variety of Lewis- and Brønsted acids will be discussed systematically in terms of the use of catalysts, reaction conditions, substrates and mechanistic insights as we move across the periodic table, Fig. 2.

We hope this will help readers to grasp a general but in-depth impression of catalytic propargylic substitution reaction and will satisfy the expectations of readers who are interested in the advancement of the field and looking for an up-to-date. The selected examples presented here mostly are the significant and recent ones which will allow the readers to visualize the gradual progress in this field.

5. Different catalysts used in propargylic substitution reactions

5.1. Boron derived catalysts

Boron trihalides are electron deficient species acting as Lewis acids. The tendency to form back bonding is maximum with BF_3 and falls rapidly on passing from BCl_3 to BBr_3 due to the increase in the size of the halogen 2p orbital. Use of boron halides as Lewis acid catalyst is well documented⁴¹ and several propargylic substitution reactions have also been carried out involving boron trihalide as a catalyst where propargylic



Scheme 9 Propargylic substitution reaction via propargylic carbocationic intermediate.

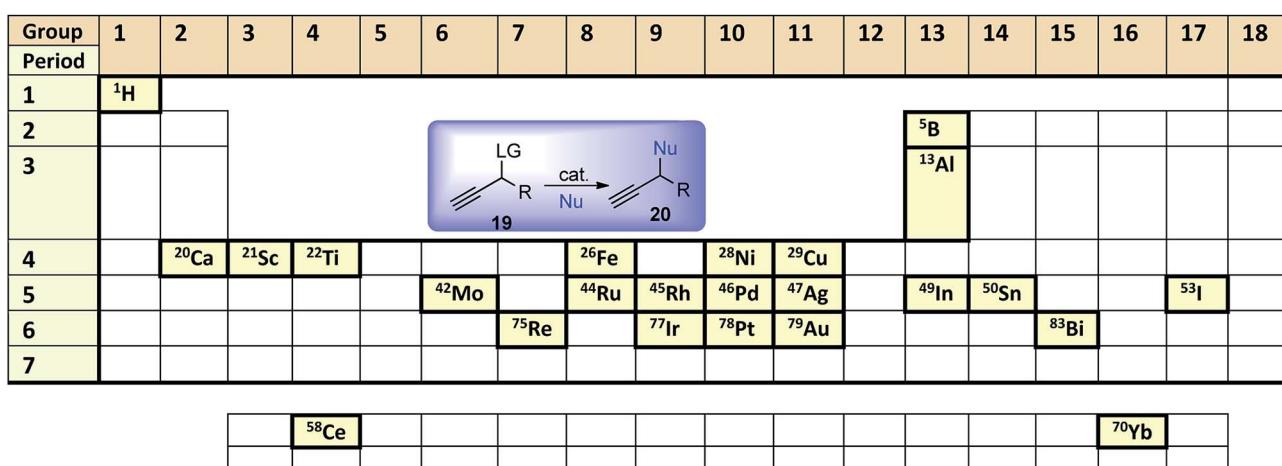
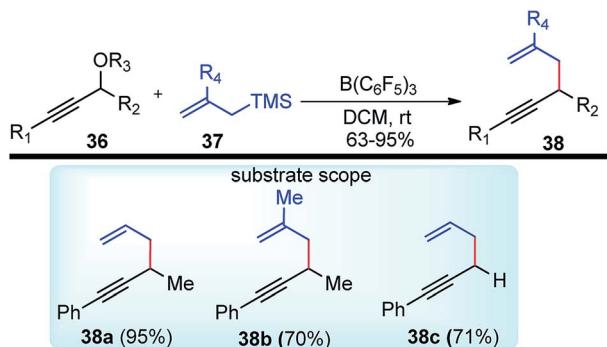
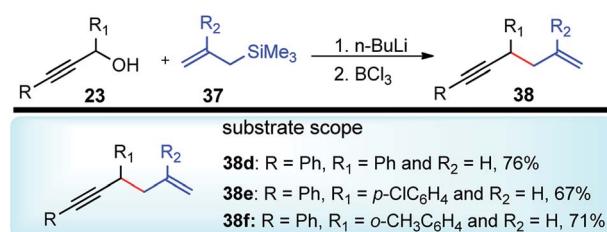


Fig. 2 Frequently used elements as catalysts for catalytic propargylic substitution reaction in the periodic table.



Scheme 10 Allylation of propargylic alcohol derivatives with $B(C_6F_5)_3$.Scheme 11 Regioselective allylation of propargyl alcohols with BCl_3 .

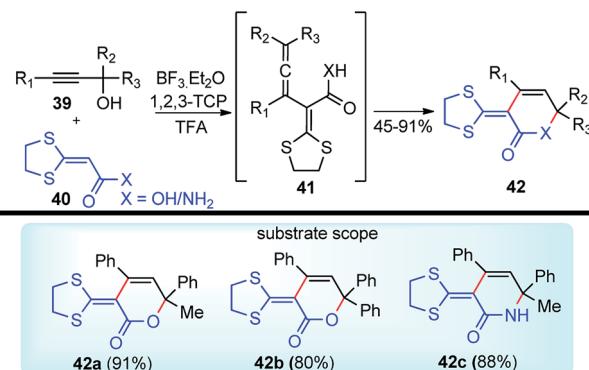
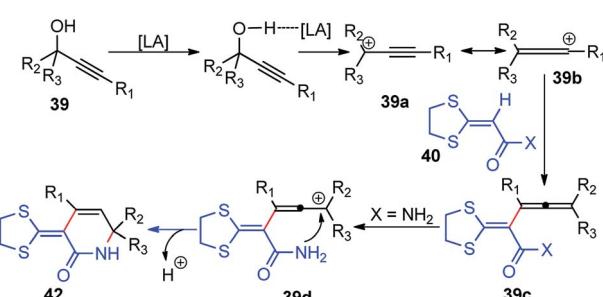
carbocation **34a** is formed as the reactive intermediate as shown in Scheme 9.

Back in early 2000, the urge for the development of propargylic allylation using inexpensive reagents encouraged many researchers to develop several catalytic systems for this reaction. The use of $B(C_6F_5)_3$ towards the coupling of allylsilanes with benzylic alcohols was first demonstrated by the group of Gevorgyan in the year 2001.⁴² The same group in the year 2004 described yet another application of $B(C_6F_5)_3$ in the catalytic reaction of secondary propargylic alcohol derivatives **36** with allylsilane **37** in DCM at room temperature, Scheme 10.⁴³

The reaction on optimization with respect to several leaving groups like OH, OTMS, $OCOCH_3$, $OCOC(CH_3)_3$, $OCOCl_3$, $OCOCH_2Cl$, OCO_2Ph revealed that OH and OTMS were inefficient as leaving whereas $OCOC(CH_3)_3$, $OCOCl_3$, $OCOCH_2Cl$, OCO_2Ph , and $OCOCH_3$ with average reaction time ranging from 1 h to 5 days. With $OCOCH_2Cl$, the reaction was completed within 1 h furnishing products in excellent yield. The product outcome is highly dependent on catalyst loading and typically 5 mol% catalyst loading was found optimum for this reaction.

Kabalka and co-workers in the year 2006 demonstrated yet another efficient allylation procedure with *in situ* generated lithium propargyl oxide using inexpensive and commercially available boron trichloride, Scheme 11.⁴⁴

The allylated products **38** were obtained in very high yield and excellent regioselectivity which is apparently due to the absence of Brønsted acids in the reaction medium which was known to reduce the regioselectivity. The mechanistic investigation revealed the role of steric hindrance between the

Scheme 12 $BF_3 \cdot Et_2O$ catalyzed propargylic substitution and synthesis of δ -lactone thereof.Scheme 13 Mechanism for the formation of δ -lactam involving propargylic substitution as the key step using $BF_3 \cdot Et_2O$ as the catalyst.

substituents in the R group and chloride, as well as the high electronegativity of chlorine, are the two prime reasons for the weakening of the C–O bond and its subsequent cleavage.

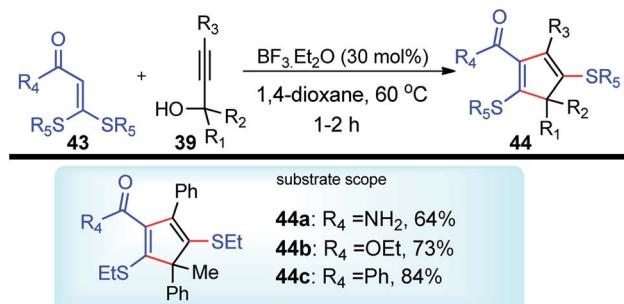
Bi and co-workers in 2013 demonstrated an efficient and inexpensive approach for the synthesis of R-(1,3-dithiolan-2-ylidene) δ -lactam **42c** and δ -lactone rings **42** using $BF_3 \cdot Et_2O$ as the catalyst, involving propargylic substitution as the key step, Scheme 12.⁴⁵

The maximum product yield of 93% was achieved in 1,2,3-trichloropropane (1,2,3-TCP) within 20 min in the presence of $BF_3 \cdot Et_2O$ as a catalyst. A thorough solvent screening disclosed that other solvents like DMSO, 1,4-dioxane, and CH_3CN were incapable of this transformation. The proposed mechanistic detail for this reaction is outlined in Scheme 13.

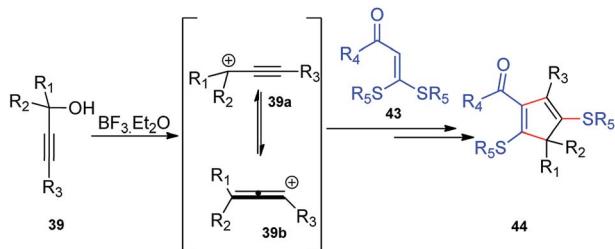
The OH of the propargylic alcohol **39** on polarization by the Lewis acid, $BF_3 \cdot Et_2O$, generates the incipient propargylic carbocation **39a** by the loss of H_2O followed by the attack of the α -carbon of ketene dithioacetal **40** and intramolecular nucleophilic addition to the tertiary carbocation to produce the δ -lactams **42**. Particularly, cyclization did not occur with 4 equivalents of $BF_3 \cdot Et_2O$ and TFA were essential for the final cyclization step. So, a dual catalytic system furnishes the delta-lactam **42** in high yield from propargylic alcohol and ketene dithioacetal.

$BF_3 \cdot Et_2O$ was again used as a catalyst by Bi and co-workers in the year 2014 for the synthesis of substituted 2,5-dialkylthiocyclopentadienes **44** in excellent yields. Regiospecific [3 + 2]





Scheme 14 $\text{BF}_3\cdot\text{Et}_2\text{O}$ catalyzed propargylation and the synthesis of substituted 2,5-dialkylthiocyclopentadienes thereof.



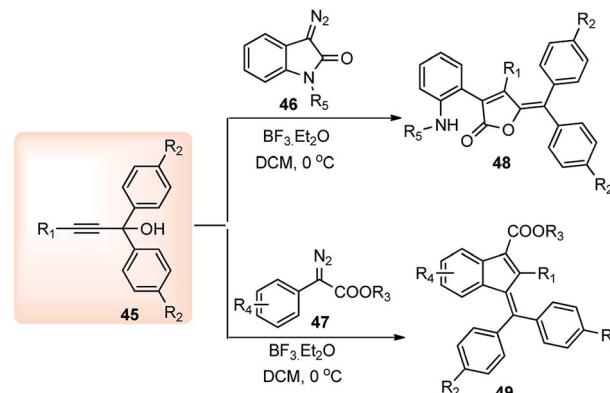
Scheme 15 Mechanism of the propargylation of propargylic alcohols catalyzed by $\text{BF}_3\cdot\text{Et}_2\text{O}$.

cycloaddition of propargylic alcohols **39** and α -oxo ketene dithioacetals **43** in the presence of $\text{BF}_3\cdot\text{Et}_2\text{O}$ generates 2,5-dialkylthiocyclopentadienes **44** in good yields, Scheme 14.⁴⁶

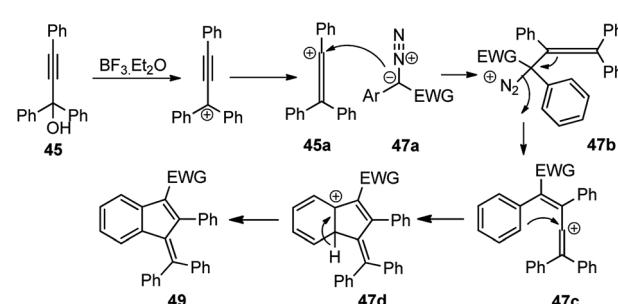
As detailed in the mechanism, the catalyst $\text{BF}_3\cdot\text{Et}_2\text{O}$ initiates the formation of propargylic carbocation **39a** by the loss of the OH species from the propargylic alcohol **39** which isomerizes to the less sterically hindered allenic carbocation **39b**. The preferable nucleophilic attack on the allenic carbocation **39b** by the α -oxo ketene dithioacetals **43**, followed by the cyclization, affords five-membered carbocycle, along with allylic carbocation. A subsequent attack of the sulfur atom to the allylic carbocation followed by the 1,4-alkylthio shift, elimination of a proton and cleavage of the C-S bond produces cyclopentadiene **44** in good yield, Scheme 15. The key step is the $\text{BF}_3\cdot\text{Et}_2\text{O}$ catalyzed generation of the propargylic cation.

Several other Lewis acid catalysts like FeCl_3 , TiCl_4 , and SnCl_4 in different non-polar, polar and polar protic solvents like toluene, CH_3CN and polar-protic (MeOH) were screened. Other than $\text{BF}_3\cdot\text{Et}_2\text{O}$, all other catalysts afforded either trace amount of the desired product or no product in 1,4-dioxane. The reaction did not proceed in other solvents. Interestingly $\text{CF}_3\text{SO}_3\text{H}$ was found efficient in catalyzing the reaction albeit with reduced yield. The reaction has a wide substrate scope and tolerates a variety of electron-donating and withdrawing (hetero)-aryl, fused aryl, alkyl, and ether amino, alkoxy, aryl, and styryl functional groups.

$\text{BF}_3\cdot\text{Et}_2\text{O}$ yet again proved to be an efficient catalyst in the propargylic substitution reaction for the facile synthesis of highly substituted furanone **48** and indene **49** systems. Muthusamy and co-workers in 2014 described a $\text{BF}_3\cdot\text{Et}_2\text{O}$



Scheme 16 $\text{BF}_3\cdot\text{Et}_2\text{O}$ catalyzed synthesis of substituted indene/furanone from propargyl alcohols.



Scheme 17 Mechanism for the indene formation catalyzed by $\text{BF}_3\cdot\text{Et}_2\text{O}$.

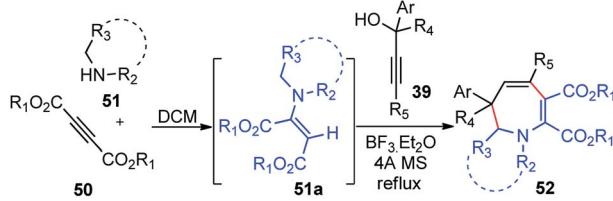
catalyzed tandem reaction of amides **46** and α -diazo-esters **47**, and propargyl alcohols **39** towards the synthesis of substituted furanone **48** and indene **49**, in high yield under mild conditions, Scheme 16.⁴⁷

An equimolar mixture of α -diazoester **47** and propargyl alcohol **45** in presence of 10 mol% of $\text{BF}_3\cdot\text{Et}_2\text{O}$ at 0 °C afforded the product **49** in high yield within 10 min. Diminished product yield was observed when the reaction was carried out in DCE, hexane, THF and using catalysts like AlCl_3 , CuOTf , TfOH , $\text{Yb}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, FeCl_3 , or InCl_3 . The proposed mechanistic pathway for the above reaction is outlined in Scheme 17.

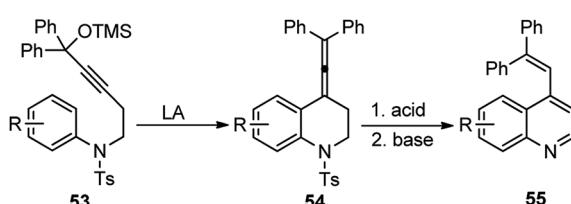
In the above-depicted mechanism, $\text{BF}_3\cdot\text{Et}_2\text{O}$ catalyzes the formation of allene carbocation **45b** via Meyer-Schuster rearrangement from propargyl carbocation followed by the nucleophilic attack of the diazo compound to generate aryl allene **47b** followed by the extrusion of nitrogen to produce the vinylic cationic species **47c**. Electrocyclic ring closure of the vinylic cationic species **47c** furnishes the desired product **49** after proton elimination. The reaction is independent of the nature of the substituents on both α -diazoesters **47** and propargyl alcohols **45** and offered the highly substituted and conjugated indene **49** in excellent yields with both electrons donating and withdrawing groups as substituents.

The use of $\text{BF}_3\cdot\text{Et}_2\text{O}$ as a Lewis acid catalyst for propargylic substitution was again demonstrated by Wang and co-workers in the year 2011 for the synthesis of functionalized

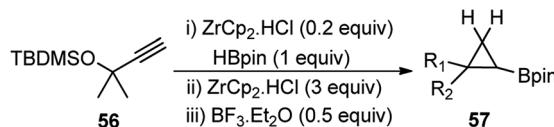




Scheme 18 $\text{BF}_3\text{-Et}_2\text{O}$ catalyzed synthesis of functionalized dihydroazepines from propargyl alcohols.



Scheme 19 $\text{BF}_3\text{-Et}_2\text{O}$ catalyzed synthesis of quinoline derivatives from propargyl alcohol.



Scheme 20 $\text{BF}_3\text{-Et}_2\text{O}$ catalyzed synthesis of cyclopropylboronic acid pinacol esters from propargyl silyl ethers.

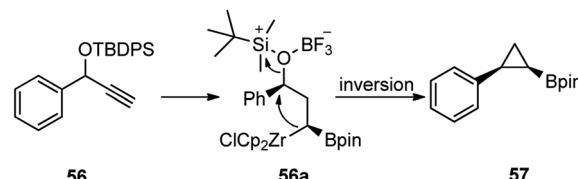
dihydroazepines 52 by a three-component reaction between propargylic alcohols 39, 2-butyne-1,4-dioates 50 and secondary amines 51, Scheme 18.⁴⁸

The key step is ascribed to the reaction of the *in situ* generated enamine 51a with allenic intermediate formed from the propargylic alcohol. Several catalysts like ZnCl_2 , FeCl_3 , or I_2 were tested and $\text{BF}_3\text{-Et}_2\text{O}$ gave the best result yield among all the catalysts. Changing the solvent from DCM to toluene, CH_3CN , THF or DMF diminished the product yield. Enhancing the reaction temperature and exclusion of moisture from the reaction mixture by addition of molecular sieves had a positive effect on the reaction yield.

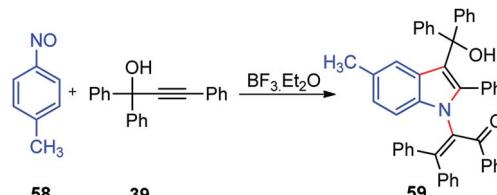
A novel catalytic method using $\text{BF}_3\text{-Et}_2\text{O}$ to synthesize a quinoline 55 backbone by uniting a propargylic alcohol unit across an electron-rich aromatic center to undergo intramolecular propargylic substitution reaction was described by Saito and co-workers in the year 2004, Scheme 19.⁴⁹

The key step is the intramolecular Friedel-Crafts alkylation of the electron-rich aromatics to the *in situ* generated allenyl cation generated from the propargyl unit under the action of a catalytic amount of Lewis acid $\text{BF}_3\text{-Et}_2\text{O}$.

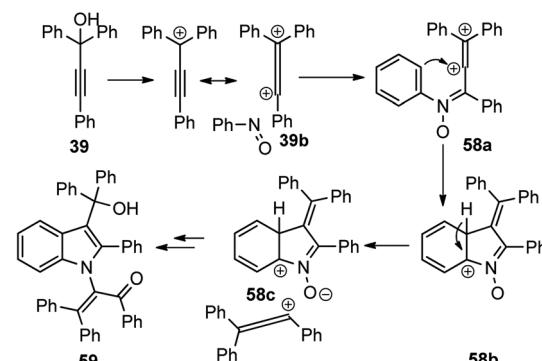
Talbot and co-workers in the year 2017 reported an efficient one-pot procedure for the conversion of propargylic silyl ethers 56 to cyclopropylboronic acid pinacol esters 57 using $\text{BF}_3\text{-Et}_2\text{O}$ as a catalyst, Scheme 20.⁵⁰



Scheme 21 Mechanism for the $\text{BF}_3\text{-Et}_2\text{O}$ mediated synthesis of cyclopropylboronic acid pinacol esters.



Scheme 22 $\text{BF}_3\text{-Et}_2\text{O}$ catalyzed synthesis of highly-substituted indole-3-carbinols from propargylic alcohols.



Scheme 23 Mechanism for the $\text{BF}_3\text{-Et}_2\text{O}$ mediated synthesis of substituted indole-3-carbinols.

The mechanistic pathway is illustrated in Scheme 21 where Schwartz's reagent (ZrCp_2HCl) catalyzes the hydroboration of the terminal acetylenes followed by further addition of Schwartz's reagent and subsequent cyclization leading to a range of cyclopropylboronic acid pinacol ester 57.

Muthusamy and co-workers in the year 2018 described the synthesis of highly-substituted indole-3-carbinols 60 in good yields by from 1 equiv. of nitrosobenzene 58 and 2 equiv. of propargylic alcohols 39 in the presence of $\text{BF}_3\text{-Et}_2\text{O}$ as a catalyst, Scheme 22.⁵¹

The mechanism for the propargylation is highlighted in Scheme 23. The key step is the formation of allenyl carbocation 39b under the influence of the Lewis acid catalyst, $\text{BF}_3\text{-Et}_2\text{O}$. Subsequent addition of the nitrosobenzene 58 to the allenyl carbocation intermediate followed by the Friedel-Crafts cyclization generates 3-alkylidene-3*H*-indole *N*-oxides 58b. Indole *N*-oxide 58c on reaction with the second equivalent of allenyl carbocation followed by the addition of water and concomitant *N*-O bond cleavage leads to the formation of indole-3-carbinols 59 in good yield.

Several other Lewis acids catalysts like AlCl_3 , FeCl_3 , InCl_3 , and SnCl_4 , did not furnish the desired product in good yield. Even Brønsted acids like *p*-TSA were found inefficient. Apart from DCM, poor product yield was obtained when investigated with other organic solvents, such as dichloroethane, 1,4-dioxane, and toluene. The reaction has a wide substrate scope and its operational simplicity allows for scaling up.

5.2. Aluminium derived catalysts

Propargylic and benzyl alcohols are known to form stabilized carbocations in the presence of Lewis acids like aluminium and gallium triflate salts. Especially, aluminium triflate is a highly active yet selective catalyst for a diverse set of reactions. Importantly, it tolerates protic conditions and so can be readily recycled by simply extracting it in water and recovered by subsequent removal of the water.⁵²

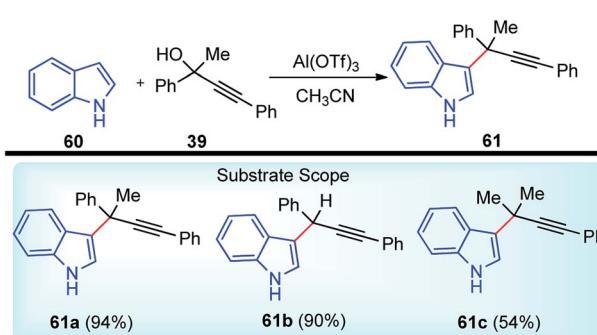
A water-tolerant reusable $\text{Al}(\text{OTf})_3$ Lewis acid catalyst for the propargylation of indoles **61** in refluxing acetonitrile was reported by Bezuidenhoudt and co-workers in the year 2012, Scheme 24.⁵³

From the environmental point of view, water-tolerant Lewis acids are quite attractive due to their recyclability and reusability attributes and the by-product from the reaction is also non-hazardous H_2O . The catalyst was recycled and reused with minimum loss of activity over three consecutive cycles. This methodology has a wide substrate scope and was successfully applied to both 2° and 3° propargylic alcohols for the preparation of propargylated indoles in a very high yield. The reaction is believed to pass through propargylic carbocationic species followed by a nucleophilic attack on the propargyl carbocation.

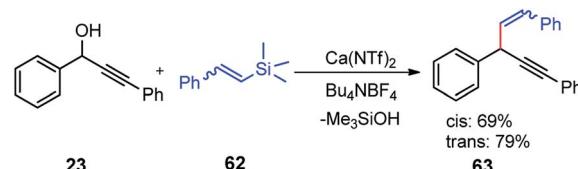
Use of $\text{Al}(\text{OTf})_3$ in the direct nucleophilic displacement of OH in 'activated' systems with several nucleophiles were reported by Williams and co-workers in 2017.⁵⁴ This efficient process allows the ready synthesis of a wide range of benzylic and allylic substituted products in very high yields with water as the only by-product.

5.3. Calcium derived catalysts

Use of precious metals in homogeneously catalyzed reactions becomes increasingly expensive as we continuously deplete the earth's natural resources.⁵⁵ The potential application of early main group metals as catalysts has remained a widely



Scheme 24 $\text{Al}(\text{OTf})_3$ catalyzed propargylation of indoles.



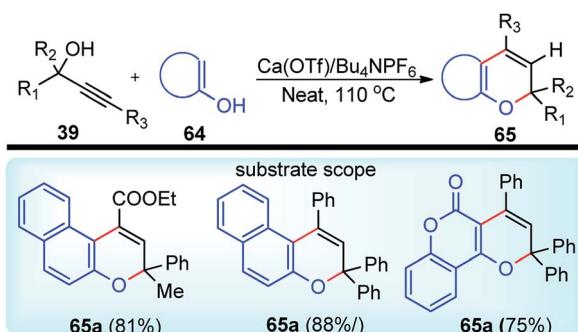
Scheme 25 Calcium-catalyzed direct substitution of π -activated alcohols with allyltrimethylsilane.

underexplored research field, despite the apparent ecological and economic benefits. Among other alkaline earth metals, calcium is an ideal main group metal catalyst, essentially free of toxicity, very cheap, and the fifth most abundant element of the earth crust. Recently, calcium-based Lewis acid catalyst has been used by the group of Niggemann for the nucleophilic substitution of benzylic and allylic alcohols under very mild reaction conditions.^{56,57}

In further pursuit towards the cost-effective methodology for propargylic substitution reaction avoiding costly transition metals, Niggemann and co-workers in the year 2011 developed an efficient calcium-catalyzed allylation of π -activated alcohols **23** with diverse silyl-based carbanions **63** under very mild reaction conditions, Scheme 25.⁵⁸

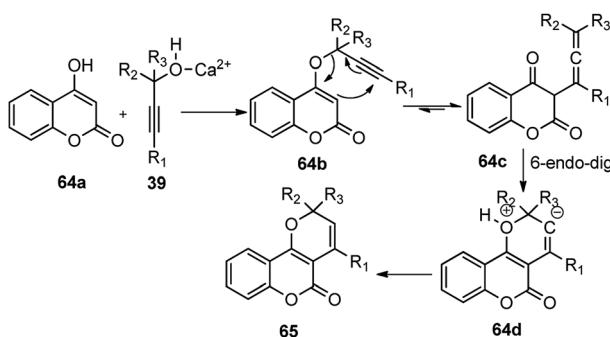
The reaction of propargylic alcohols **23** and allyltrimethylsilane **63** in presence of 5 mol% each of $\text{Ca}(\text{NTf}_2)_2$ and Bu_4NPF_6 proceeded smoothly at room temperature in dichloromethane to give the desired allylated product **64** after 1 h as a 2.7 : 1 mixture of allylated regioisomers in good yield. Incomplete transformation was observed with strongly coordinating solvents like ether, THF whereas dichloromethane was found to be the most suitable solvent for the allylation of propargyl alcohols. Toluene could replace DCM as a solvent although with slightly poorer product yield. Typical reactions proceed at room temperature, with no added strong acids or bases, and special precautions for the exclusion of moisture or air are not necessary.

Yaragorla and co-workers in the year 2017 described a highly regioselective annulation reaction between propargyl alcohols **39** and several enols **65** using calcium triflate catalyst, under a solvent-free condition at 110 °C, Scheme 26.⁵⁹

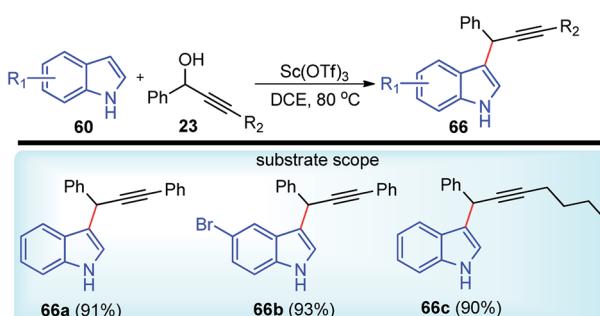


Scheme 26 Calcium triflate catalyst synthesis of 2H-chromene from propargylic alcohols.





Scheme 27 Mechanism for the Ca-catalyzed synthesis of 2H-chromenes from propargylic alcohols.



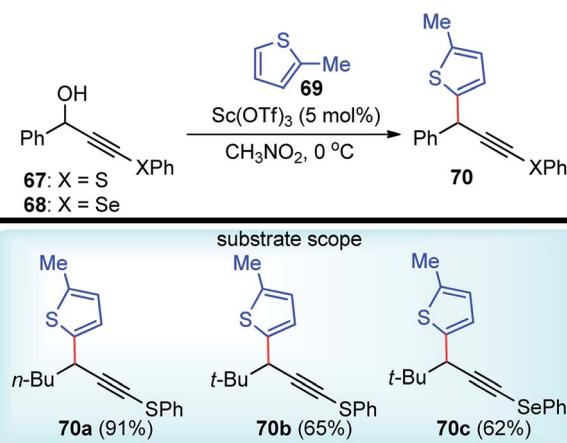
Scheme 28 $\text{Sc}(\text{OTf})_3$ catalyzed propargylation of indoles.

The propargyl alcohol **39** and 2-naphthol **65** in the presence of 10 mol% of $\text{Ca}(\text{OTf})_2$, 10 mol% of Bu_4NPF_6 when heated at 110 °C furnished the desired product in good yield. The temperature had a pronounced effect on the reaction yield. Lowering the temperature reduced the product yield and the presence of additive like Bu_4NPF_6 enhanced the product yield possibly due to the formation of $\text{Ca}[(\text{OTf})(\text{PF}_6)]$ by ligand metathesis which has an enhanced Lewis acidity. Other additives like KPF_6 , NH_4BF_4 , and Bu_4NF provided moderate yields with $\text{Ca}(\text{OTf})_2$. Moderate yields of the product were achieved with metal catalysts, such as $\text{Mg}(\text{OTf})_2$ and FeCl_3 . The reaction did not occur in water as well as in other protic solvents and gave poor yield in aprotic non-polar solvents. The reaction proceeds *via* a cascade annulation between propargyl alcohols **39** and 4-hydroxy coumarin **64a** involving a calcium promoted vinyl-propargyl ether **64b** formation followed by [3,3]-Claisen type rearrangement to furnish the allene **64c**. Subsequent 6-endo regioselective cyclization furnishes the desired product **65**, Scheme 27.

5.4. Scandium derived catalysts

Scandium chemistry is almost completely dominated by the trivalent ion, $\text{Sc}(\text{III})$. The chemical properties of scandium ions have more in common with yttrium ions than with aluminium ions but have been rarely used as a catalyst in the propargylic substitution reaction.

In pursuit of the catalytic uses of scandium salts as water-tolerant and recyclable Lewis acid catalyst, Yadav and co-



Scheme 29 Scandium catalyzed propargylic substitution reaction.

workers in the year 2007 reported a scandium triflate catalyzed efficient alkylation of indoles **60** with propargylic alcohols **23**, Scheme 28.⁶⁰

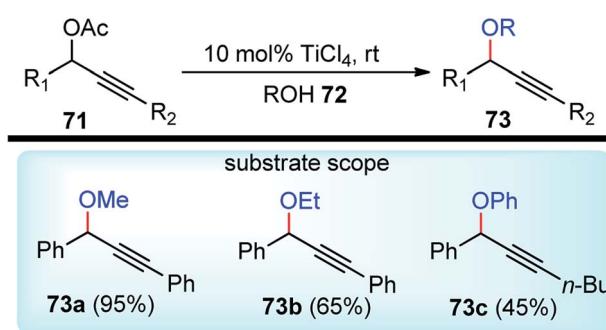
Within a short time-span, the hydroxyl group was replaced by the indole in an S_N2 manner to furnish products in more than 90% yield. However, in absence of scandium triflate, no product was observed. Reaction in dichloroethane provided the best yield among several other solvents screened. The reaction is equally competent with several other Lewis acids like $\text{Bi}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, $\text{Sm}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$.

$\text{Sc}(\text{OTf})_3$ was yet again used for the regioselective propargylic substitution reactions of the phenylsulfanyl and phenylselanyl propargyl alcohols **67/68** in very high yields by Yoshimatsu and co-workers in the year 2008, Scheme 29.⁶¹

A thorough screening of various Lewis acids like $\text{Yb}(\text{OTf})_3$, $\text{La}(\text{OTf})_3$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, as well as the solvent (e.g., dichloromethane, 1,2-dichloroethane, DMF, and THF), disclosed scandium triflate-nitromethane as the ideal combination for the highly regioselective substitution reaction.

5.5. Titanium derived catalysts

The relevance of $\text{Ti}(\text{IV})$ Lewis acidity is due to low-lying empty d orbitals which are responsible to play a crucial role in



Scheme 30 TiCl_4 catalyzed propargylic substitution with diverse oxygen-centered nucleophiles.

catalysis. But not much has been explored in the domain of propargylic substitution reaction.

TiCl_4 has been utilized as an efficient Lewis acid catalyst by Mahrwaid and co-workers in the year 1999 for the direct displacement of propargylic esters **71** with diverse oxygen-centered nucleophiles, Scheme 30.⁶²

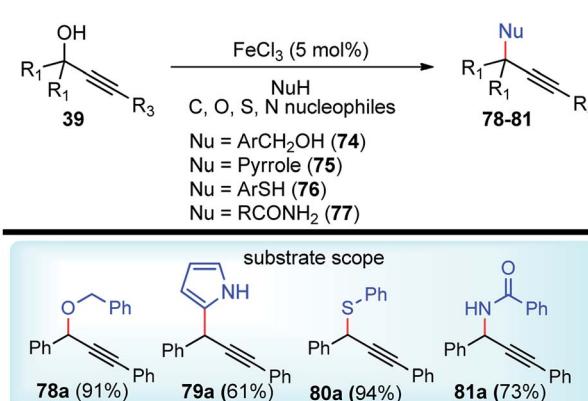
Alcoholic solvents like MeOH , EtOH , $^1\text{PrOH}$, $^2\text{BuOH}$ resulted in decreased product yield with concomitant formation of hydrolyzed products. Even with aliphatic substituents hydrolyzed products were mainly obtained probably due to the decreasing stabilization of the formed cation during the reaction. The challenge was overcome by using catalytic amounts of trifluoromethane sulfonates as a Lewis-acid catalyst. By using 10 mol% of trimethylsilyl triflate, the propargylic methyl ether was obtained in about 40% yield for deactivated propargylic esters.

5.6. Iron derived catalysts

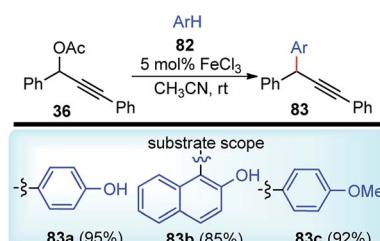
Transition metal catalyzed methods for organic synthesis often use expensive and transition metals such as platinum, palladium, gold, nickel, and mercury has led to significant concern about possible metal residues in the final product and waste, especially in pharmaceuticals and food additives. This, in turn, will increase the expenses in the process and waste management. In comparison with cobalt, rhenium, ruthenium, and gold complexes, which are usually used to catalyze the nucleophilic substitution of propargylic alcohols, FeCl_3 as the catalyst offers several relevant advantages including cheapness and commercial availability, broad scope, and mild reaction conditions of this transformation.⁶³ Partly due to these reasons, iron has only recently received growing interest in the field of catalysis. On the one hand, it often suffers from poor reactivity or selectivity in comparison to the more "noble" metals.

Zhan and co-workers in 2006 reported an efficient FeCl_3 -catalyzed propargylic substitution reaction of propargylic alcohols **39** with various carbon and heteroatom-centered nucleophiles, Scheme 31.⁶⁴

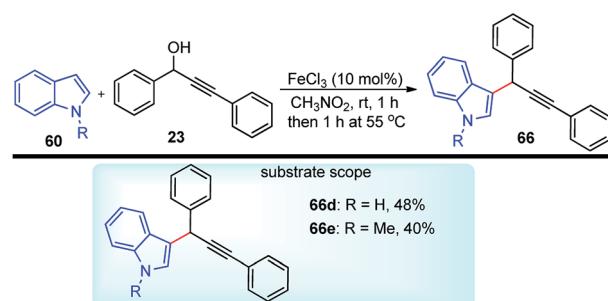
The following methodology provides an easy access to the construction of C-S bonds by the nucleophilic substitution of



Scheme 31 FeCl_3 -catalyzed propargylic substitution reaction of propargylic alcohols.



Scheme 32 FeCl_3 catalyzed propargylic substitution reaction of electron-rich aromatics.



Scheme 33 Propargylic substitution of indoles with FeCl_3 catalyst.

propargylic alcohols with a series of nucleophiles. Transition metal-catalyzed substitution of propargylic alcohols with thiols has been considered difficult to achieve, probably due to the reason of the strong co-ordinating ability of sulfur which causes catalyst poisoning.

The experimental results suggest that the mechanism proceeds *via* the formation of propargylic cation intermediate. Both electron-rich and electron-poor aromatic substrates reacted efficiently to afford the corresponding products in high yield. The primary aliphatic alcohol 3-phenylprop-2-yn-1-ol failed to furnish propargylated product. Instability of the propargylic cation intermediate clearly made the substitution reaction less favorable.

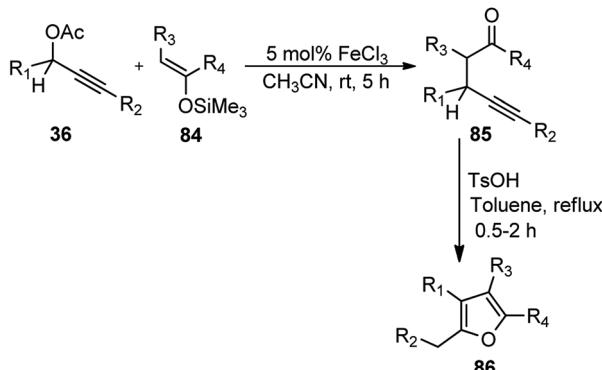
A new method for the Friedel-Crafts propargylation of several electron-rich aromatics **82** catalyzed by FeCl_3 was developed by Zhan and co-workers in the year 2006, Scheme 32.⁶⁵

A facile aromatic electrophilic substitution of the electron-rich aromatics at room temperature in acetonitrile without exclusion of moisture or air resulted in substituted products with high yield and excellent regioselectivity.

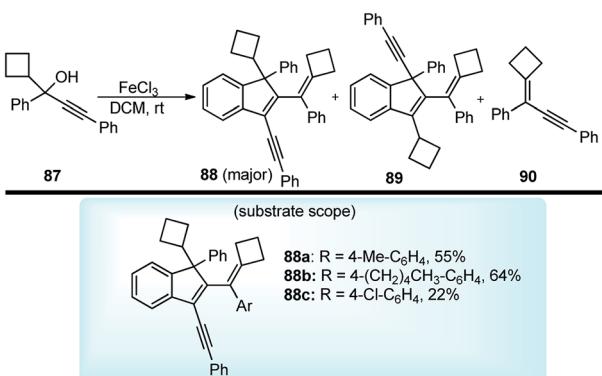
Jana and co-workers in the year 2007 have developed an efficient and atom economical method for the direct alkylation of indoles **60** with various propargyl alcohols **23** in the presence of the inexpensive and non-toxic FeCl_3 , under mild conditions, Scheme 33.⁶⁶

The authors found that the reaction proceeded in the presence of FeCl_3 (10 mol%) at room temperature in nitromethane affording the propargylated product in moderate yield. Other solvents didn't afford the product in good yield. The reaction was clean and furnished the C3-substitution product with high





Scheme 34 FeCl_3 catalyzed synthesis of γ -alkynyl ketones from propargylic acetates with enoxysilanes.



Scheme 35 Synthesis of highly conjugated indenes by iron(III) chloride-catalyzed dimerization of trisubstituted propargylic alcohols.

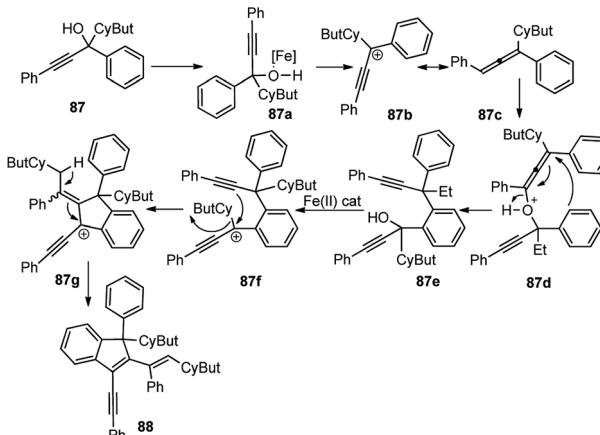
regioselectivity within 2 h without the need for an inert atmosphere.

Zhan and co-workers in the year 2007 developed an efficient method for the synthesis of γ -alkynyl ketones 85 in high yield via FeCl_3 -catalyzed substitution reaction of propargylic acetates 36 with enoxysilanes 84 under mild conditions. Subsequent cyclization by $p\text{-TsOH}$ without purification of the γ -alkynyl ketone intermediates resulted into tri- or tetra substituted furans 86 in high yield, Scheme 34.⁶⁷

The reaction proceeded smoothly without exclusion of moisture or air from the reaction mixture. Both electron-donating and electron-withdrawing aromatic substrates reacted smoothly with enoxysilane 84 affording the corresponding alkylated products in high yields. Additionally, the methodology provided a straight forward access to polysubstituted furans 86 starting from easily available starting materials utilizing cheap catalysts in an open atmosphere.

Chan and co-workers in the year 2010 described an efficient method to prepare highly conjugated indenes 88 by iron(III) chloride-catalyzed dimerization of trisubstituted propargylic alcohols 87 under very mild conditions at room temperature, Scheme 35.⁶⁸

After careful screening of the reaction conditions, the best result was observed with 5 mol% of FeCl_3 and 4 \AA MS at room temperature in DCM. Products with reasonably good yield were

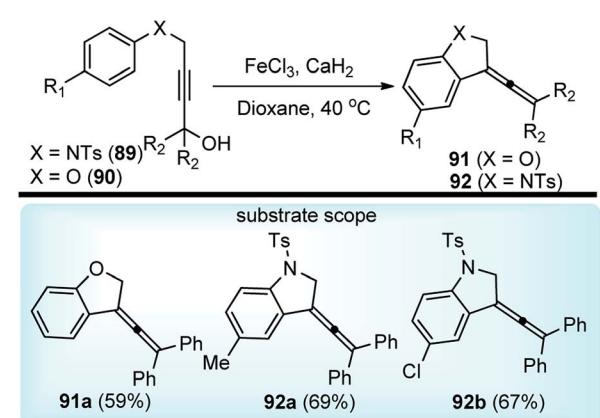


Scheme 36 Mechanism for the formation of highly conjugated indenes by iron(III) chloride-catalyzed dimerization of trisubstituted propargylic alcohols.

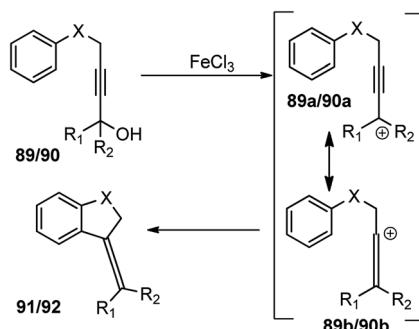
also achieved with catalysts like ZnCl_2 and AuCl_3 . However, in the absence of a catalyst, or switching to the metal triflates like $\text{Cu}(\text{OTf})_2$ and $\text{Yb}(\text{OTf})_3$, or Brønsted acids like $p\text{-TsOH}$ and TfOH , or changing the substitution pattern in the propargyl derivatives did not furnish any product or resulted in products with low chemo and regioselectivity. The mechanism outlined in Scheme 36 involves the activation of the alcohol substrate 87 through coordination of the hydroxyl group to the FeCl_3 catalyst resulting in the formation of a $\text{Fe}(\text{III})$ -coordinated intermediate 87a which on the elimination of water furnishes the alkenyl cation 87b or its resonance analogue allenic cation 87c. Alkoxylation of carbocation 87c at the sterically less hindered carbon center by another molecule of the propargyl alcohol followed by the intramolecular Friedel-Crafts reaction affords the dimer 88.

Xu and co-workers in the year 2014 developed a FeCl_3 catalyzed intermolecular Friedel-Crafts alkylations of aryloxy and arylamino-substituted propargylic alcohols 89/90 towards the synthesis of dihydrobenzofurans 91 and dihydroindolets 92 in high yields, Scheme 37.⁶⁹

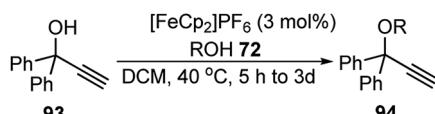
This transformation provides a versatile and direct strategy for the construction of dihydrobenzofurans 91 (when $\text{X} = \text{O}$)



Scheme 37 FeCl_3 catalyzed intermolecular Friedel-Crafts cyclizations of aryloxy and arylamino-substituted propargylic alcohols.



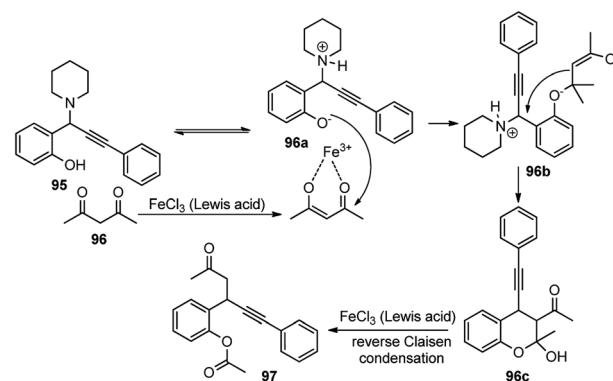
Scheme 38 Mechanism of FeCl_3 catalyzed synthesis of dihydrobenzofurans and dihydroindoles from propargylic alcohols.



Scheme 39 Ferrocenium hexafluorophosphate ($[\text{FeCp}_2]\text{PF}_6$) catalyzed etherification of the terminal, tertiary propargylic alcohols.

and dihydroindoles **92** (when $\text{X} = \text{NTs}$) from easily accessible starting materials. The reaction was optimized by screening several Lewis acid catalysts like TiCl_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, AlCl_3 , $\text{Sc}(\text{OTf})_3$, ZnBr_2 and Brønsted acids, such as *p*-TsOH and TFA. Unfortunately, none of them furnished product in good yield. Desiccants had a role on reaction yield, as higher efficiency was observed with CaH_2 compared to MgSO_4 when tested in solvents like MeNO_2 , toluene, MeCN , and DCM. Catalyst loading significantly influenced the reaction yield. The product yield reduced to only 14% when 20 mol% catalyst was used. The probable mechanistic pathway depicted in Scheme 38 portrays that propargyl alcohol is first converted into the allenyl cations **89b/90b** in the presence of Lewis acid FeCl_3 via a Meyer-Schuster rearrangement followed by an intramolecular Friedel-Crafts type alkylation to trap the cation and form the corresponding dihydrobenzofuran **91** and dihydroindole derivatives **92**.

Substituents have a definite role to play in the reactivity. No product was observed for substrates having aliphatic



Scheme 41 Mechanism of the $\text{Fe}(\text{III})$ -catalyzed propargylation of propargyl amines.

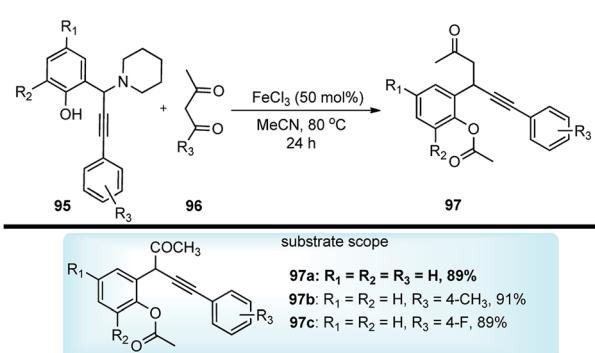
substituents, probably due to the lesser stabilization of the formed carbocation **89a/90a**. Further, a mixture of unidentified side-products was obtained for propargylic alcohol bearing *p*-Me group, while the *p*-Cl substituted propargylic alcohol afforded product in 34% yield only.

Bauer and co-workers in 2015 reported an efficient protocol for the propargyl etherification of the terminal, tertiary propargylic alcohols **93** with primary and secondary alcohols **72** under ambient temperature in CH_2Cl_2 using commercial ferrocenium hexafluorophosphate ($[\text{FeCp}_2]\text{PF}_6$), Scheme 39.⁷⁰

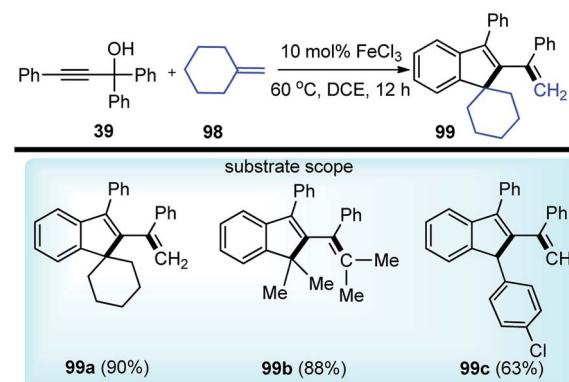
Shang and co-workers in 2015 described a FeCl_3 -catalyzed domino reaction of *N*-cyclohexyl propargylamines **95** with 1,3-diketones **96** towards the synthesis of β -alkynyl ketones **97** in good to excellent yields, Scheme 40.⁷¹

Several Lewis acid catalysts like CuBr_2 , CuI , $\text{Sc}(\text{OTf})_3$ and Brønsted acid like H_2SO_4 were tested but the highest yield was achieved using FeCl_3 . Even altering the catalyst loading did not have any positive impact on the reaction yield. Further solvent screening revealed that solvents like CH_2Cl_2 , THF, DMF, DMSO, H_2O , and 1,4-dioxane were inappropriate for this reaction. The highest yield was achieved when the reaction was carried out with 50 mol% catalyst FeCl_3 in CH_3CN at 80°C for 24 h. The mechanistic detail of this process is highlighted in Scheme 41.

The reaction initiates with the proton transfer from the hydroxyl group of phenol to the nitrogen of the piperidine

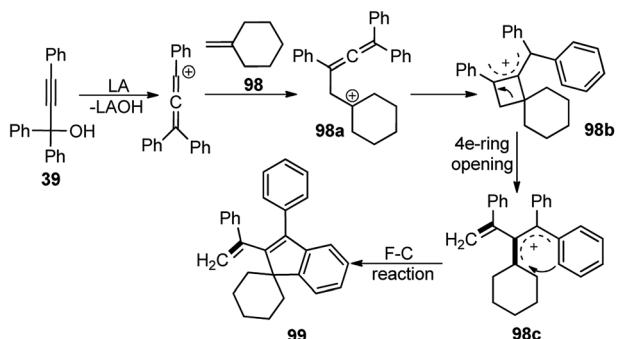


Scheme 40 Iron-catalyzed domino reaction of *N*-cyclohexyl propargyl amines and 1,3-diketones.



Scheme 42 FeCl_3 catalyzed indene-based polycyclic compounds.





Scheme 43 A proposed mechanism for the FeCl_3 -catalyzed synthesis of indenes.

resulting in the formation of phenoxide intermediate **96a** under the influence of FeCl_3 catalyst. Subsequently, phenoxide **96a** attacks the 1,3-dicarbonyl compound to form the β -keto ester **96b** followed by the propargylic substitution reaction to release piperidine and eventually cyclizes to form **96c**. Finally, a reverse Claisen condensation reaction of intermediate **96c** in the presence of FeCl_3 , followed by a proton transfer process, generates the desired product **97** in good yield.

Chen and co-workers in the year 2018 developed a FeCl_3 catalyzed straightforward protocol to synthesize complex indene-based polycyclic compounds **99** via the cascade cyclization of propargylic alcohols **39** with alkenes **98**, Scheme 42.⁷²

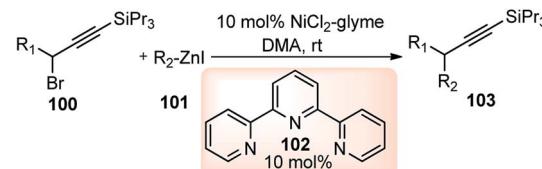
The authors investigated a series of Lewis acids and observed that except for AgSbF_6 , InCl_3 or $\text{Cu}(\text{OTf})_2$ all other catalysts like $\text{Zn}(\text{OTf})_2$, $\text{Sc}(\text{OTf})_3$, and FeCl_3 were effective for the formation of the desired product and FeCl_3 was the best among them in terms of yield and selectivity. Solvent screening revealed that better result was achieved in DCE. The mechanism for this reaction is highlighted in Scheme 43.

The starting material gets converted into the triphenylallenyl cation **39a** under the influence of FeCl_3 , which underwent a stepwise [2 + 2]-cycloaddition to form the intermediate **98a**. Subsequent ring opening and intramolecular Friedel-Crafts reaction delivered the product **99** in good yield.

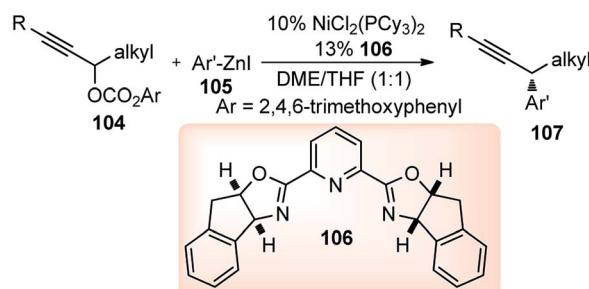
5.7. Nickel derived catalysts

Nickel lies just above palladium in the periodic table and can perform many of the same elementary reactions as palladium or platinum. Practically speaking, the cost of nickel in its elemental form is roughly 2000 times lower than palladium and 10 000 times lower than platinum on a mole for mole basis which tremendously appeals as a catalyst. As a first-row transition metal, nickel has a small atomic radius, and Ni-ligand bond lengths are often relatively short. The field of nickel catalysis has made tremendous advances in the past decade.⁷³ NiCl_2 and its hydrate are occasionally useful in organic synthesis mainly as a mild Lewis acid. Researchers have taken the advantages of all the above features to develop nickel catalyzed propargylic substitution reaction apart from several other reactions.

Fu and co-workers in the year 2008 reported the nickel catalyzed Negishi cross-coupling reactions of propargylic



Scheme 44 The nickel catalyzed propargylic substitution reaction.



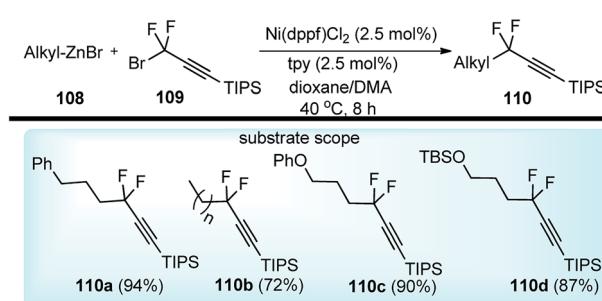
Scheme 45 Nickel catalyzed enantioselective propargylic substitution reaction.

electrophile with secondary alkyl and aryl nucleophiles, Scheme 44.⁷⁴ Later, asymmetric version of this reaction was also reported, Scheme 45.⁷⁵

This methodology disclosed a base free novel approach for the coupling of propargylic halides **100** with alkylzinc reagents **101** under mild reaction conditions at room temperature. The authors have observed that both propargylic bromides and propargylic chlorides were equally compatible with the reaction. Alkylzincs were readily coupled with R-bromoesters, 1-haloindanes, and allylic chlorides in good yield and ee but the identical reaction condition was inefficient in furnishing the desired product when propargylic halides were reacted with alkyl zinc reagent.⁷⁶

In the year 2012, Fu and co-workers developed a method that can utilize oxygen leaving groups for the nickel catalyzed asymmetric Negishi reactions of racemic propargylic carbonates **104** with aryl electrophiles **105**, Scheme 45.⁷⁵

The development of a versatile nickel-catalyzed enantioselective cross-coupling process for electrophiles that bear a leaving group other than a halide adds a new dimension to the scope of nickel-catalyzed propargylic substitution reaction.



Scheme 46 Nickel catalyzed substitution of propargyl bromides with deactivated alkyl zinc compounds.

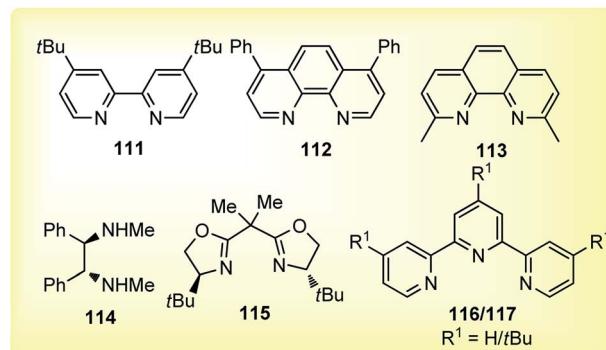


Fig. 3 Conventional ligands used in the nickel catalyzed reaction.

Zhang and co-workers in the year 2017 described an efficient nickel-catalyzed cross-coupling of deactivated alkylzinc reagents **108** with *gem*-difluoropropargyl bromides **109**, Scheme 46.⁷⁷

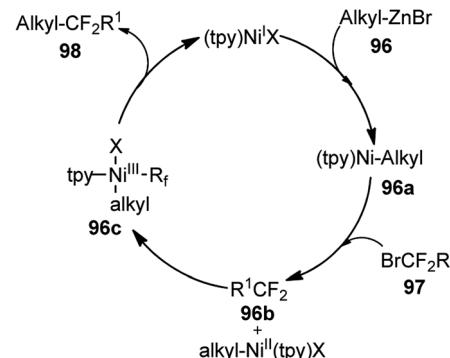
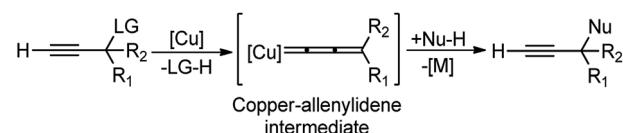
The reaction proceeded under mild reaction conditions with high efficiency and excellent regioselectivity. Low yields were only observed when other conventional diamine ligands (**111**–**117**) were used along with the nickel catalyst, Fig. 3.

Triamine ligand (tpy) significantly improved the product yield without any observable formation of an allenic side product. The reaction was independent of the nature of nickel catalysts and among all the screened nickel salts, $\text{Ni}(\text{dppf})\text{Cl}_2$ (2.5 mol%) performed best, providing product in 94% yield. No product was obtained in the absence of nickel catalyst and only 9% yield of product was produced when the reaction was carried out in absence of ligand. A plausible reaction mechanism involving a $\text{Ni}(\text{i}/\text{m})$ catalytic cycle is shown in Scheme 47.

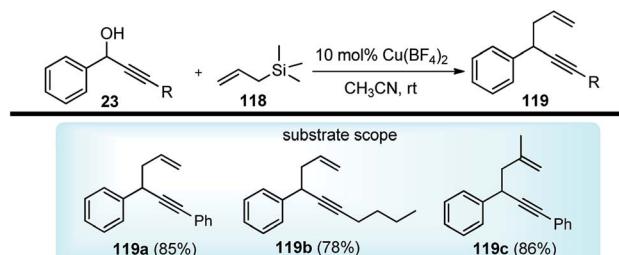
Preliminary mechanistic studies revealed that the reaction was initiated by the transmetalation reaction between $\text{Ni}(\text{i})$ and alkylzinc to generate alkyl nickel complex $[\text{alkylNi}(\text{tpy})]$ **96a** followed by a $\text{Ni}(\text{i}/\text{m})$ catalytic cycle. The proposed mechanism is different from that of the reported nickel-catalyzed Negishi arylation of propargyl bromides, which has been suggested through a bimetallic pathway.

5.8. Copper derived catalysts

The copper-catalyzed propargylic substitution reaction has become a powerful synthetic method to prepare the compounds containing the propargylic subunit. Compared with the other transition-metals applied in the propargylic substitution, copper has many obvious advantages, such as much more inexpensive, easier to handle, milder reaction condition, and higher selectivity which has resulted in to the development of several Cu-catalyzed propargylic substitution reactions, Scheme 48.¹⁹ The astounding progress of the Cu-catalyzed propargylic substitution reaction itself deserves an individual account and Hu has extensively reviewed the progress of the Cu catalyzed propargylic substitution reaction till 2014.¹⁹ Significant advances have been achieved in the copper-catalyzed propargylic substitutions after 2014. The Cu-catalyzed propargylic substitution, especially its asymmetric version, which was in a dormant stage, has bloomed to the fullest. Diverse

Scheme 47 $\text{Ni}(\text{i}/\text{ii})$ catalytic cycle for the nickel catalyzed substitution of propargyl bromides with alkylzinc compounds.

Scheme 48 General mechanism for the copper-catalyzed propargylic substitution reaction.

Scheme 49 Allylation of propargylic alcohols catalyzed by $\text{Cu}(\text{BF}_4)_2$ catalyst.

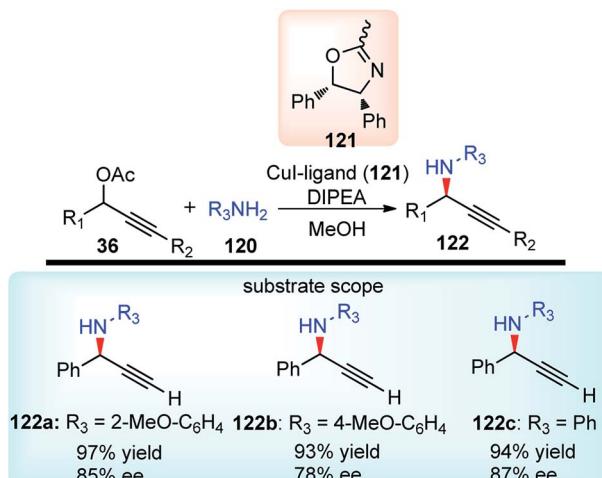
nucleophiles such as nitrogen, carbon, oxygen, sulfur nucleophiles have been successfully applied in the reaction. Many kinds of propargylic compounds have been prepared in satisfactory yields, regioselectivities, and enantioselectivities under very mild conditions. The general pathway for the copper-catalyzed propargylic substitution reaction is highlighted in Scheme 48.

A novel approach for the propargylic allylation of propargyl alcohols with allylsilanes to afford corresponding 1,5-enynes **119** was demonstrated by Yadav and co-workers in 2008 using copper(II) tetrafluoroborate as the catalyst, Scheme 49.⁷⁸

This method is compatible with halides, aryl alkyl ethers, alkynes, and alkenes present in the molecule. Among the various copper(II) salts such as $\text{Cu}(\text{BF}_4)_2$, $\text{Cu}(\text{OTf})_2$, $\text{Cu}(\text{acac})_2$, and $\text{Cu}(\text{ClO}_4)_2$ screened for this transformation, $\text{Cu}(\text{BF}_4)_2$ was found to be most effective. The reaction has a broad substrate scope and works well with both electron donating and electron withdrawing substituents.

With the rapid attractiveness of the catalytic propargylic substitution reactions over the Nicholas reaction, several



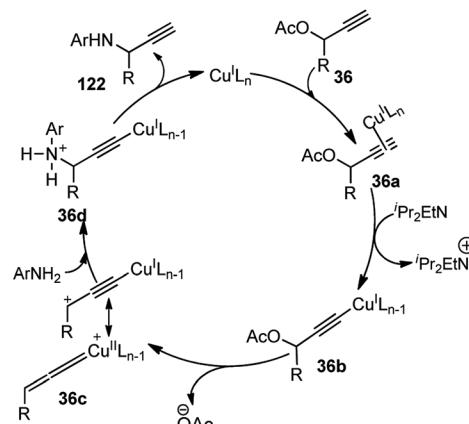


Scheme 50 Propargylic amination of various propargylic acetates.

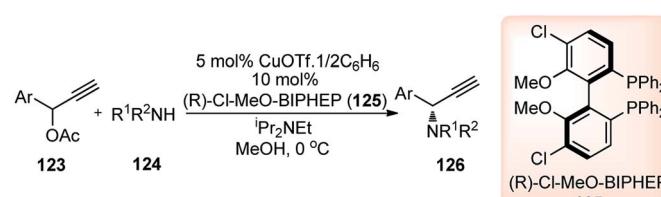
examples of propargylic substitution reaction have appeared. As an expansion of these studies, their asymmetric versions were also studied and the first examples of enantioselective copper-catalyzed propargylic amination reactions were described by both van Maarseveen's¹⁴ and Nishibayashi's⁷⁹ groups independently in 2008. Maarseveen's group has reported the propargylic substitutions from a variety of readily available propargylic acetates **36** using optically active 2,6-bis(oxazolinyl)pyridines (pybox) as chiral ligands in very high yield and high optical purity, Scheme 50.¹⁴

The optimization study revealed the superiority of CuI over other copper salts, such as $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$, CuOTf-benzene, and $\text{Cu}(\text{OAc})_2$, in terms of yield and selectivity. High enantioselectivity and a high reaction rate were only observed in polar protic solvents, especially in methanol. The addition of a base seemed to have a positive impact on both the yield as well as enantioselectivity of the reaction. However, both the yield and enantioselectivity decreased in presence of stronger bases, like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or cesium carbonate. The best results were achieved with tertiary amines, such as diisopropylethylamine (DIPEA). At lower temperature, there was further enhancement of the enantioselectivity although at the expense of an increased reaction time. The reaction has a wide substrate scope except for aliphatic substrates, where low enantioselectivities were observed. The mechanistic pathway for this reaction as illustrated in Scheme 51 was in accordance to Nishibayashi and co-workers postulated mechanism. The very first step is the formation of the pi-complex between Cu-catalyst and the alkyne followed by the formation of Cu-allenylidene complex **36b** with the concomitant removal of the OAc group. The amine nucleophile then attacks the Cu-allenylidene complex **36b**. Selective blocking of one side of the cationic intermediate by the copper-pybox complex directs the amine to selectively attack from one face. After proteolysis, the product **122** is released to complete the catalytic cycle.

Nishibayashi and co-workers on the other hand, described the reaction between 1-phenyl-2-propynyl acetate and *N*-methyl aniline to form the substituted product *N*-methyl-*N*-(1-phenyl-



Scheme 51 Mechanism for the propargylic amination of propargyl alcohols.



Scheme 52 Copper-catalyzed enantioselective propargylic amination of propargylic esters.

2-propynyl) aniline with good enantioselectivity using $\text{Cu}(\text{OTf})_2 \cdot 1/2\text{C}_6\text{H}_6$ and (R)-Cl-MeO-BIPHEP ligand under basic condition.⁷⁹

Followed by the seminal work by Maarseveen's and Nishibayashi's groups, in the year 2010, Nishibayashi and co-workers have reported a copper-catalyzed enantioselective propargylic amination of propargylic esters **123** with various secondary amines **124** using optically active diphosphines such as BINAP and BIPHEP as chiral ligands, Scheme 52.⁸⁰

The reaction is believed to pass through a copper-allenylidene complex followed by the attack of the amine. A transition state consisting of copper-allenylidene complex bearing a chiral ligand BIPHEP was proposed to account for the high enantioselectivity of the product, Fig. 4.

The re-facial attack of the *N*-methyl aniline, due to the edge-to-face aromatic interaction between the two phenyl groups is

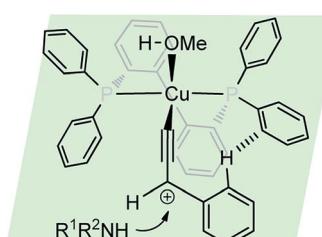
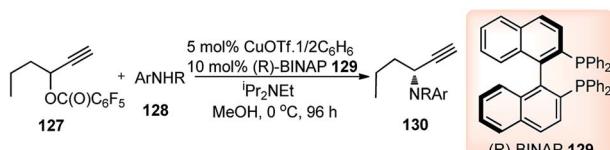
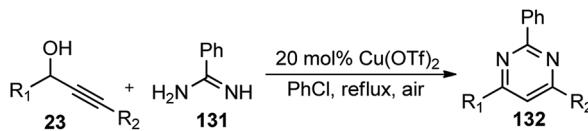


Fig. 4 Probable transition state for the copper-catalyzed propargylic substitution reaction.



Scheme 53 Copper catalyzed propargylic amination of propargylic esters.



Scheme 54 $\text{Cu}(\text{OTf})_2$ catalyzed synthesis of 2,4,6-trisubstituted pyrimidines from propargylic alcohols.

considered to play a significant role in achieving the high enantioselectivity.⁸¹

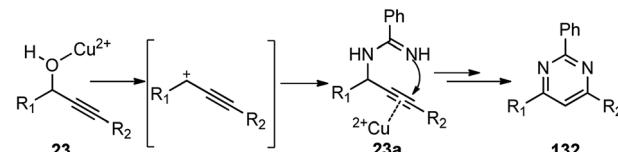
Introduction of a better leaving group than acetate, in the propargylic system, might promote the propargylic amination of propargylic esters bearing an alkyl group at the propargylic position. With this hypothesis, Nishibayashi and co-workers in 2011 reported the propargylic amination of propargylic penta-fluorobenzoates **127** with amines **128** in the presence of catalytic amounts of a copper complex and *(R)*-BINAP in good yields and high enantioselectivity, Scheme 53.⁸²

Like all other Cu-catalyzed propargylic reaction the above propargylic amination proceeded *via* copper-allenylidene complexes as the key intermediate.

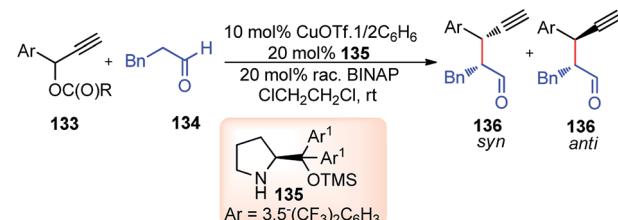
Rapid assembly of structural complexity for the synthesis of N-containing heterocycles *via* intramolecular cycloisomerization emerged as an exceptionally powerful tool for the synthesis of various heterocyclic structures. To achieve such tandem methodologies, Zhan and co-workers in the year 2011 developed a $\text{Cu}(\text{OTf})_2$ catalyzed synthesis of 2,4,6-trisubstituted pyrimidines **132** from propargylic alcohols **23** with amidine **131**, Scheme 54.⁸³

Several other catalysts were tested, like, BiCl_3 , InCl_3 , FeCl_3 , $\text{Bi}(\text{OTf})_3$, $\text{Zn}(\text{OTf})_2$, and AgOTf . Regrettably, all of them were found either inefficient or inferior as compared to $\text{Cu}(\text{OTf})_2$. Solvents like acetonitrile, 1,2-dichloroethane, nitromethane, and toluene were also tested and were found to facilitate the reaction. However, the best result was achieved with chlorobenzene. Surprisingly, dichloromethane failed to promote this reaction which clearly implied that the reaction rate was influenced by the boiling point and polarity of the solvent used. The proposed mechanism for the pyrimidine ring **132** formation *via* a propargylation–cyclization–oxidation tandem sequence is represented in Scheme 55.

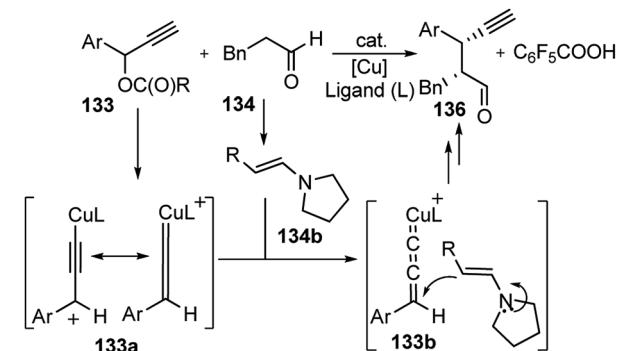
$\text{Cu}(\text{OTf})_2$ acts as a bifunctional catalyst, by promoting an $\text{S}_{\text{N}}1$ substitution of propargylic alcohol **23** by the amidine **131**, followed by facile intramolecular cyclization *via* 6-*endo*-dig process *via* the triple bond activation to produce cyclic dihydropyrimidine intermediate. Subsequent air oxidation and aromatization of the cyclic dihydropyrimidine intermediate leads to the pyrimidine **132**.



Scheme 55 Mechanism for the $\text{Cu}(\text{OTf})_2$ catalyzed synthesis of 2,4,6-trisubstituted pyrimidines from propargylic alcohols.



Scheme 56 Propargylic substitution employing cooperative catalysis.



Scheme 57 Mechanism for the propargylation of aldehydes by cooperative catalysis.

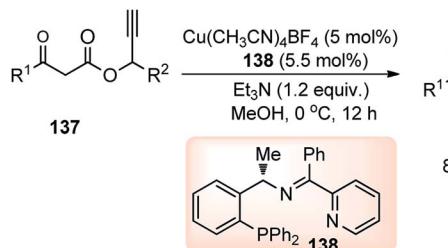
Cooperative catalysis using organocatalysts and transition metals has become a new tool to access compounds with excellent enantioselectivities which were otherwise difficult to prepare and therefore has gained significant interest in the chemical community in the recent years.^{84,85}

Nishibayashi and co-workers in 2011 described an enantioselective propargylic substitution reaction of propargyl acetates **133** with α -branched aldehydes **134**, using both the transition metal catalyst (copper complex) and organocatalyst (secondary amine), Scheme 56.⁸⁶

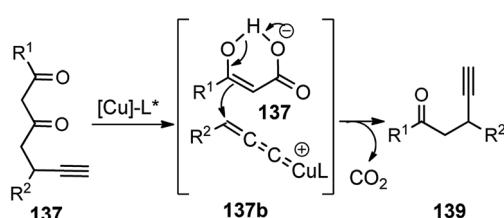
It was envisioned that both the copper complex and organocatalyst will simultaneously activate the propargylic ester **133** and aldehyde **134** to promote the enantioselective propargylic alkylation. In fact, the authors have found that reactions of propargylic esters **133** with aldehydes **134** in the presence of a copper complex bearing racemic diphosphine and an optically active secondary amine **135** as co-catalysts furnished the corresponding propargylic alkylated products **136** in good yields as a mixture of two diastereomers with a high enantioselectivity.

A proposed reaction pathway is presented in Scheme 57. The initial step is the formation of a copper-allenylidene complex





Scheme 58 Copper-catalyzed decarboxylative propargylic alkylation of propargyl β -ketoesters.



Scheme 59 Mechanism for the copper-catalyzed decarboxylative propargylic alkylation of propargyl β -ketoesters.

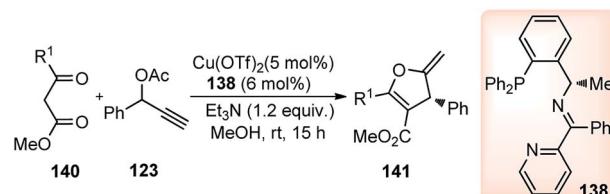
133a followed by the attack of an enamine, generated *in situ* from aldehyde and chiral amine 135, resulting in the formation of alkyne complex 133b *via* an acetylidyne complex. Subsequent ligand exchange with another propargylic ester furnishes the desired alkylated product 136.

In 2014, Hu and co-workers developed a facile approach for the synthesis of β -ethynyl ketones 139 in a highly enantioenriched form by copper-catalyzed decarboxylative propargylic alkylation of propargyl β -ketoesters 137, Scheme 58.⁸⁷

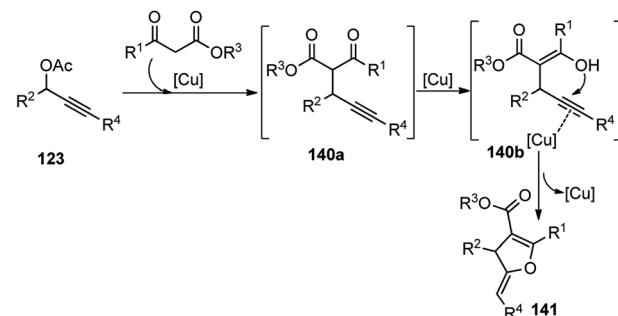
A new chiral tridentate ketimine P,N,N-ligand was designed to provide a facile access to a variety of β -ethynyl ketones 139 in good yields and with high enantioselectivities. Careful evaluation of several ligands and copper catalysts disclosed chiral tridentate P,N,N-ligand in conjunction with $[\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4]$ as the most promising combination. A reaction pathway is highlighted in Scheme 59 where asymmetric decarboxylative propargylic alkylation occurs when propargyl β -ketoesters 137, containing propargyl moiety and a nucleophile together with an ester functional group, is subjected to a chiral copper catalyst.

A broad range of 1-phenyl-2-propynyl 3-oxo-3-arylpropanoates 137 worked efficiently to provide the desired β -ethynyl ketones in good to excellent yields and with very high enantioselectivities. Electron-donating and electron-withdrawing substituents in the *para* or *meta* position of the phenyl ring were compatible with this transformation. The reaction works well even for heteroaromatic and aliphatic β -ketoesters although with a higher catalyst loading to reach complete conversion. However, the stereoselectivity reduces for substrates having a substituent at the *ortho* position of the phenyl ring.

Hu and co-workers in the year 2014 utilized their newly designed tridentate P,N,N ligand in conjunction with $\text{Cu}(\text{OTf})_2$ catalyst for the enantioselective synthesis of highly



Scheme 60 Enantioselective synthesis of highly functionalized dihydofurans from propargyl acetates and β -ketoesters.

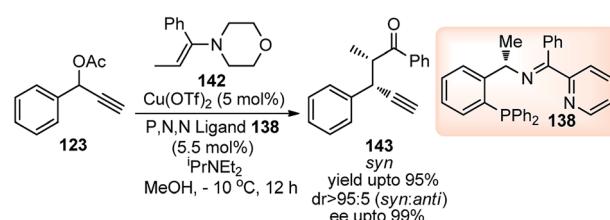


Scheme 61 Mechanism for the synthesis of highly functionalized dihydrofurans from propargyl acetates and β -ketoesters.

functionalized dihydrofurans 141 by a [3 + 2] cycloaddition of β -ketoesters 140 with propargylic ester 123, Scheme 60.⁸⁸

Through ligand and copper salts screening identified chiral tridentate P,N,N ligand and $\text{Cu}(\text{OTf})_2$ as the best combination, furnishing the product in 90% yield with 95% ee. No reaction occurred in the absence of a base and interestingly poor regioselectivity was observed when iPr_2NEt was used in place of Et_3N . Among the solvents that were tested, MeOH was the only suitable one, and no reaction occurred in DCM and toluene. The reaction proceeds *via* catalytic sequential propargylation/cycloisomerization reactions of propargylic alcohols 123 with 1,3-dicarbonyl compounds 140 in presence of a chiral copper catalyst and ligand 138, Scheme 61.

Bulky and structurally rigid tridentate ketimine-type P,N,N ligand was responsible for the high stereoinduction during the propargylation step. The reaction has a wide substrate scope and tolerates all kinds of electron donating and withdrawing groups. This method allows obtaining optically active 2,3-dihydrofurans bearing an exocyclic C=C bond in high yield and enantioselectivity.



Scheme 62 Copper catalyzed propargylic alkylation of enamines derived from acyclic ketones with propargylic esters.

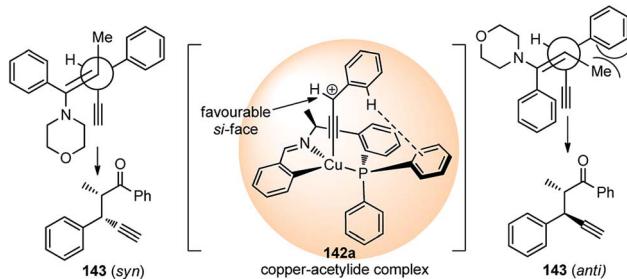


Fig. 5 Proposed transition state for the Cu-catalyzed substitution of propargylic esters with enamines.

Hou and co-workers in 2009 demonstrated the use of enamines as a source of carbon nucleophiles for the first time in the copper-catalyzed enantioselective propargylic substitution reactions of propargylic acetates to afford ethynyl-substituted ketones in high yield and excellent enantioselectivities.⁸⁹

Followed by their initial work on the Cu-catalyzed substitution of propargylic esters with enamines, Hu and co-workers in the year 2014 once again demonstrated the use of chiral P,N,N ligand in the copper-catalyzed propargylic alkylation of enamines derived from acyclic ketones **142** with propargylic esters **123** in excellent enantio- and diastereoselectivities, Scheme 62.⁹⁰

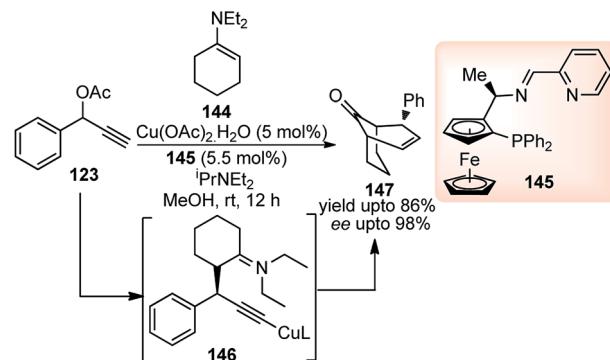
High diastereo and enantioselectivities observed is probably due to the interaction of the Cu-allenylidene complex with the chiral P,N,N-ligand shown in the transition state, Fig. 5. The edge-to-face aromatic interaction⁸¹ and the steric hindrance directs the attack of the enamine at the propargylic cation favorably from the *si*-face.

The final cyclization step leading to the alkylation products in the above methodology is greatly suppressed by the morpholine-derived cyclic enamines because of the increased stability of the resulting morpholinium ions.⁹⁰ This observation encouraged the authors to extend the application of the above-mentioned transformation towards ketone enamines.

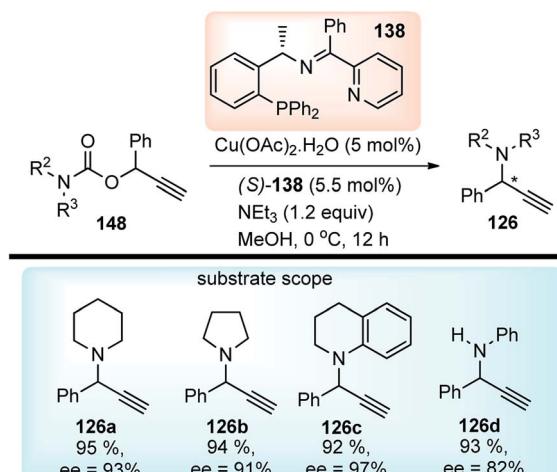
The same group have developed a Cu-catalyzed [3 + 3] cycloaddition of propargylic acetates **123** with cyclic *N,N*-diethyl-1-enamines **144** for the facile access of optically active bicyclo[n.3.1] frameworks **147** bearing three stereocenters with highly diastereo- and enantioselectivity, Scheme 63.⁹¹

Among various other ligands screened, ferrocenyl ligand displayed the best performance, affording the cycloadduct **147** in good yield (86%) with high enantioselectivity. The reaction proceeds *via* the formation of Cu-allenylidene complex as a key intermediate. Subsequent nucleophilic attack of the enamine furnishes the corresponding Cu-acetylidyne complex which is the key step for the stereoselection. It was further observed by the authors that the presence of cyclic enamine, derived from morpholine, greatly reduced the selectivity for cycloaddition and predominantly formed the alkylation product.

Analogous to the above-reported work, Hu in 2016 has developed a highly diastereo- and enantioselective copper-catalyzed propargylic alkylation of propargylic acetates with morpholine-derived cyclic enamines for the synthesis of two



Scheme 63 Cu-catalyzed [3 + 3] cycloaddition of propargylic acetates with cyclic *N,N*-diethyl-1-enamines.



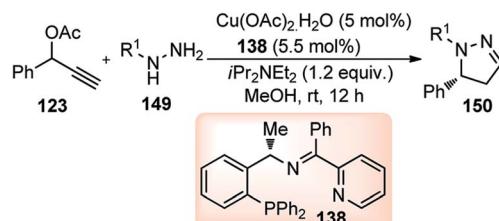
Scheme 64 Copper catalyzed propargylic amination of propargyl carbamates.

vicinal tertiary stereocenters.⁹² Using chiral 1-phenylethylamine-derived tridentate P,N,N-ligand, good to excellent diastereo- and enantioselectivities were achieved for a wide range of substrates. Less sterically hindered P,N,N-ligand showed better performance in the propargylic alkylation of cyclic enamines compared to the acyclic enamines in terms of chemoselectivity, because of its lower reactivity which suppressed the cyclization step.

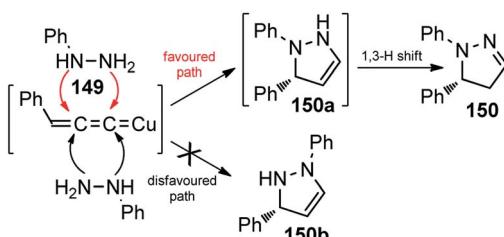
In 2014 Hu and co-workers reported the first enantioselective Cu-catalyzed propargylic amination of propargylic carbamates **148** through decarboxylation in presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and a chiral ketimine ligand **138**, Scheme 64.⁹³

Other copper salts like CuI , CuCl , $\text{Cu}(\text{OTf})_2$, $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$, $\text{Cu}(\text{CH}_3\text{CN})_4\text{ClO}_4$, in combination with bases like NEt_3 , DBU , iPr_2NEt were not efficient in terms of product yields and selectivity. The polarity of the solvent had a significant impact on the reaction outcome as the use of solvents like THF and toluene furnished only 10% and 15% ee respectively although with superior product yield. The transition state consisting of copper-allenylidene complex bearing a ketimine ligand **138** like the earlier reported TS (Fig. 5) was proposed to account for the





Scheme 65 Cu-catalyzed [3 + 2] cycloaddition of propargylic acetates with monosubstituted hydrazines.



Scheme 66 Competitive pathway for the Cu-catalyzed [3 + 2] cycloaddition of propargylic acetates with monosubstituted hydrazines.

high enantioselectivity of the product. The reaction has a broad substrate scope and tolerates tertiary as well as secondary carbamates and with the substitutions in the propargyl moiety.

With the advent of Cu-catalyzed enantioselective propargylic substitution reaction, it was realized that phenyl hydrazine could be an interesting substrate to access N-containing heterocycles by intramolecular tandem cycloaddition. Since both the nitrogen atoms of hydrazines are suitable nucleophiles, one major concern in the implementation of this cycloaddition was the possible formation of two regioisomeric cycloadducts *via* the competitive attack of N-atoms of hydrazines at the C γ -atom of Cu-allenylidene complex. Hu and co-workers in the year 2015 have reported a highly regio- and enantioselective Cu-catalyzed [3 + 2] cycloaddition of propargylic acetates **123** with monosubstituted hydrazines **149**, followed by a spontaneous 1,3-proton migration, for the stereoselective construction of optically active 2-pyrazolines, Scheme 65.⁹⁴

Interestingly, instead of the expected 3-pyrazoline the thermodynamically more stable 2-pyrazoline **131** was obtained, suggesting a cycloaddition *via* "pathway-a" took place, followed by a spontaneous 1,3-proton shift under the reaction condition, Scheme 66.

Tridentate P,N,N-ligand was reported to furnish regioselectively 2-pyrazoline derivatives in high yields (90%) and with excellent enantioselectivity (94% ee) irrespective of the electronic property of the phenyl ring. However, the reaction was sensitive to the substitution pattern on the phenyl ring in the hydrazine. The reaction with the substrates bearing an *ortho*-substituent resulted in the significantly decreased yield presumably due to the steric hindrance. Remarkably, non-aromatic hydrazine also turned out to be a suitable reaction

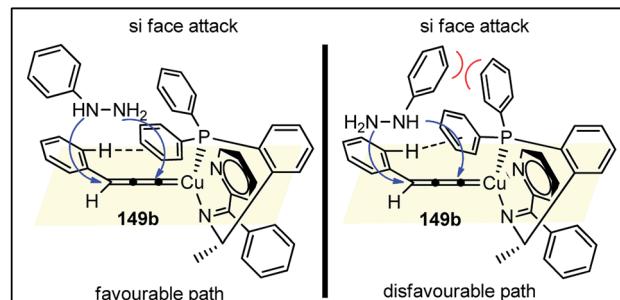
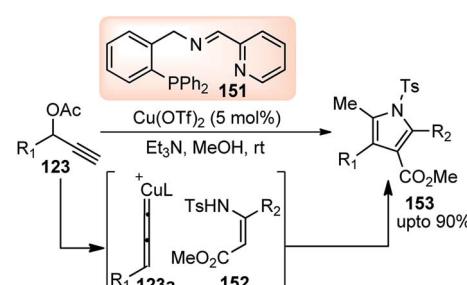


Fig. 6 Proposed transition state for the Cu-catalyzed [3 + 2] cycloaddition of propargylic acetates with monosubstituted hydrazines showing favoured and disfavoured cycloaddition pathway.



Scheme 67 Cu-catalyzed [3 + 2] cycloaddition of propargylic esters with β -enamino esters.

partner, providing the cycloadduct in 70% yield and with 92% ee. However, unsubstituted hydrazine did not furnish any desired product but resulted in the decomposition of the starting material.

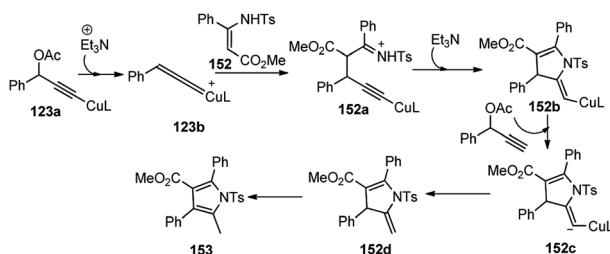
The high regio- and enantioselectivity was rationalized *via* the favoured si-facial attack of the hydrazine to the Cu-allenylidene complex with chiral P,N,N ligand as represented in the transition state structure in Fig. 6. The combined effects of edge-to-face aromatic interaction as well as the steric hindrance of ligand directs the approach of phenylhydrazine **149** from the si-face, thus facilitating the formation of (*R*)-cycloadduct.

The methodology represented a novel strategy for the stereoselective access to enantioenriched 2-pyrazolines **150** without a substituent at the 3-position.

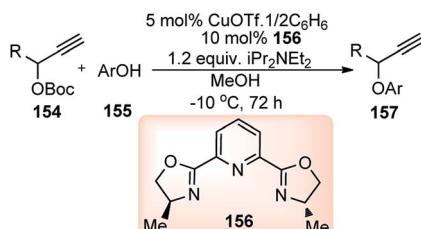
Based on the proficiency on the copper-catalyzed propargylic transformation for the synthesis of heterocyclic compounds, Hu and co-workers envisioned that copper catalyzed cyclization of propargylic carbonates with β -enamino esters should also be a suitable approach to construct fully substituted pyrroles which were earlier reported by Yoshida and co-workers using costly palladium.⁹⁵

Therefore, Hu and co-workers in the year 2015 developed the Cu-catalyzed [3 + 2] cycloaddition of propargylic esters **123** with β -enamino esters **152** for the synthesis of highly functionalized pyrroles **153**, Scheme 67.⁹⁶

Except for the P,N,N-ligands all other ligands like DPPF, DPPP, and BINAP, as well as bidentate nitrogen ligands such as biPy and 1,10-phenanthroline yielded the [3 + 2] cycloaddition



Scheme 68 Plausible mechanism for the Cu-catalyzed [3 + 2] cycloaddition of propargylic esters with β -enamino esters.



Scheme 69 Enantioselective propargylic etherification of propargylic esters with aliphatic alcohols.

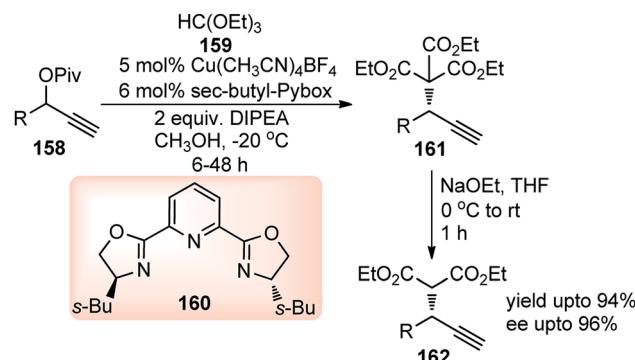
product 153 in moderate yield. Among several copper salts tested, $\text{Cu}(\text{OTf})_2$ proved to be the best choice, which gave the corresponding product in 87% yield. The reaction outcome was highly dependent on the presence and nature of the base. No reaction occurred in the absence of base and Et_3N provided a better result than $\text{i-Pr}_2\text{NEt}$ and DBU. Among different solvents tested, MeOH was only found to be suitable. The plausible mechanism for the formation of the product is depicted in Scheme 68. The key step is the formation of the Cu-allenylidene complex from the propargyl acetate which was subsequently attacked by the β -enamino ester 152 to generate Cu-acetylidyne complex. Then, intramolecular nucleophilic attack of N at the $\text{C}\beta$ atom of 152a would, at last, afford the 2,3-dihydropyrrole 153 bearing an exocyclic double bond at the 2-position.

Wu and co-workers in the year 2014 demonstrated the use of pybox as a ligand in the copper-catalyzed reaction between 2-substituted benzofuran-3(2H)-one and propargyl acetate for the highly diastereoselective and enantioselective synthesis of 2,2-disubstituted benzofuran-3(2H)-one.⁹⁸

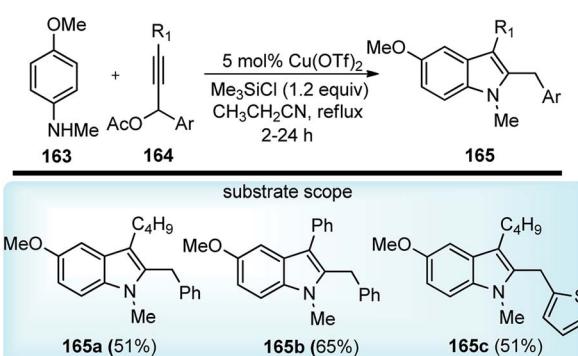
Nishibayashi and co-workers in the year 2015, developed first transition-metal catalyzed enantioselective propargylic etherification of propargylic esters 154 with aliphatic alcohols 155 as well as phenols in the presence of a catalytic amount of copper-pybox complex 156 in high yields with excellent enantioselectivity, up to 99% ee, Scheme 69.⁹⁸

After careful screening, MePybox was found to be the best chiral ligand and the copper-catalyzed enantioselective propargylic etherification of propargylic carbonates works efficiently not only with simple alcohols but also with phenols also.

Hu and co-workers in 2014 reported for the first time an efficient copper-catalyzed propargylic substitution of propargylic acetates with a variety of β -dicarbonyl compounds in moderate yield and excellent enantioselectivities using



Scheme 70 Enantioselective propargylation of trialkyl methanetricarboxylate with propargylic alcohol derivatives.



Scheme 71 Synthesis of 2,3-disubstituted indole derivatives from propargylic acetates and anilines using a copper catalyst.

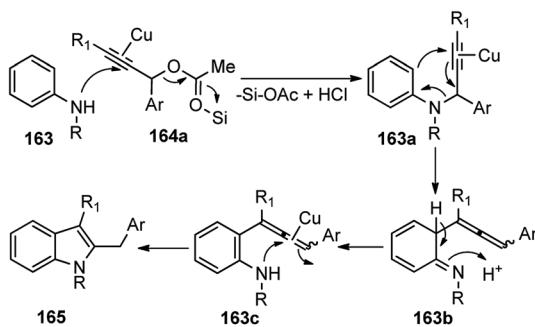
ketamine P,N,N ligand.⁹⁹ The same reaction was also reported by the research group of Maarseveen employing a Cu-Pybox complex as the catalyst affording the desired product in moderate yield and low ee.¹⁰⁰ Unfortunately, the reaction of propargylic acetates with dimethyl malonate resulted in a mixture of unidentified products.

In the search for a suitable malonate surrogate for this type of reaction, trialkyl methanetricarboxylate, with $\text{p}K_a$ approximately equals that of Meldrum's acid (*ca.* 7.3) provided an impressive solution. The success of copper-Pybox complexes for enantioselective propargylic substitution reactions prompted Wu and co-workers in the year 2015 for the first time developed enantioselective propargylation of trialkyl methane tricarboxylate 159 with propargylic alcohol derivatives 158, using pybox ligand 160, Scheme 70.¹⁰¹

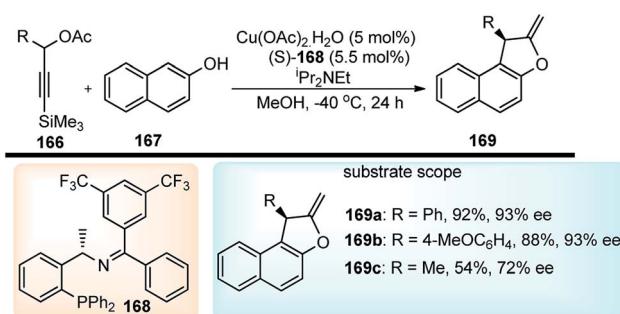
The reaction proceeded *via* the formation of copper allenylidene complexes as key intermediates following the attack of the trialkyl methane tricarboxylate. The temperature shift from room temperature to 0 °C drastically improved the enantioselectivity from 31% ee to 68% ee. The ee further improved to 76%, when the reaction was performed at -20 °C although required a longer reaction time for completion.

Sakai and co-workers in the year 2016 developed novel preparation of 2,3-disubstituted indole derivatives 165 form propargylic acetates 164 and anilines 163 using a co-operative





Scheme 72 Mechanism for the synthesis of 2,3-disubstituted indole derivatives from propargylic acetates and anilines using cooperative catalysis.



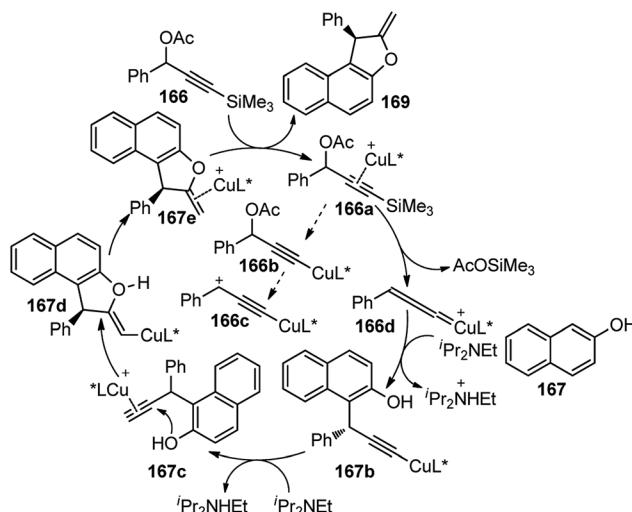
Scheme 73 Copper-catalyzed [3 + 2] cycloaddition of 3-trimethylsilylpropargylic acetates with either β -naphthols or electron rich phenols.

catalytic system composed of $\text{Cu}(\text{OTf})_2$ and Me_3SiCl *via* a [3 + 2] annulation reaction, Scheme 71.¹⁰²

Several Lewis acids, when tested for the coupling of *N*-methyl-*p*-anisidine **163** and propargylic acetate **164** and the screening, revealed that 20 mol% of either AlCl_3 , $\text{Cu}(\text{OTf})_2$ and ZnCl_2 doped with Me_3SiCl would furnish products in good yield. Catalysts like CuCl and InBr_3 were reported to reduce the chemical yield. Interestingly 5 mol% of $\text{Cu}(\text{OTf})_2$ preserved the catalytic activity, producing the corresponding indole in a 90% isolated yield. Control experiment clearly pointed out the role of a cooperative catalytic system composed of $\text{Cu}(\text{OTf})_2$ and Me_3SiCl to promote the annulation of anilines with propargylic acetates. The plausible reaction pathway for the formation of 2,3-disubstituted indoles is shown in Scheme 72.

Attack of the amino group on the propargylic carbon center generates the propargylic amine intermediate **163a**. Then further transformation *via* an aza-Claisen rearrangement through activation of the alkyne **163a** by the copper catalyst produces allene intermediate **163b**. Subsequent aromatization, followed by the intramolecular cyclization produces indole derivative **165**.

Hu and co-workers in the year 2016, have reported a highly enantioselective copper-catalyzed formal [3 + 2] cycloaddition of 3-trimethylsilyl propargylic acetates **164** with either β -naphthols **145**, Scheme 73.¹⁰³



Scheme 74 Mechanism for the copper-catalyzed formal [3 + 2] cycloaddition of 3-trimethylsilylpropargylic acetates with either β -naphthols.

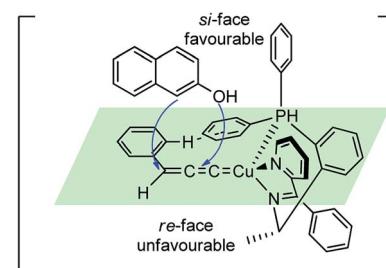


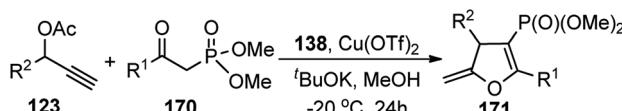
Fig. 7 Probable transition state structure for the copper-catalyzed enantioselective synthesis of benzofurans.

Benzofurans were obtained in good yields and with high enantioselectivities under the influence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and ketimine $\text{P},\text{N},\text{N}$ -ligand. The reaction proceeds *via* a desilylation followed by the nucleophilic attack by the naphthol, as highlighted in Scheme 74.

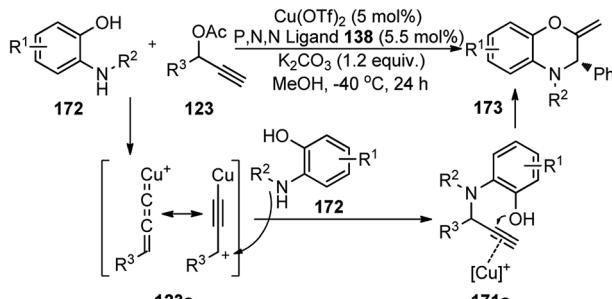
The reaction has a wide substrate scope and represented the first example of a catalytic propargylic transformation *via* desilylation strategy where copper allenylidene complex was efficiently generated from 3-trimethylsilyl propargylic esters by a copper promoted Si-C(sp) bond cleavage. The high enantioselectivity of the products was explained probably due to the favorable *si*-face attack by the β -naphthol to the gamma carbon of the Cu-allenylidene complexes, as shown in the transition state diagram, Fig. 7.

In 2016, Hu *et al.* has reported an interesting synthesis of chiral phosphorylated 2,3-dihydrofurans **171** with good enantioselectivity using copper triflate and chiral $\text{P},\text{N},\text{N}$ ligand **138** *via* a [3 + 2] cycloaddition pathway, Scheme 75.¹⁰⁴

Hu and co-workers in the year 2016 disclosed the first copper-catalyzed asymmetric formal [4 + 2] cycloaddition reaction *o*-aminophenol derivatives **172** and propargylic esters **123** to generate the chiral 2,3,4-trisubstituted 2*H*-1,4-benzoxazines



Scheme 75 Copper catalyzed synthesis of chiral phosphonylated 2,3-dihydrofurans.



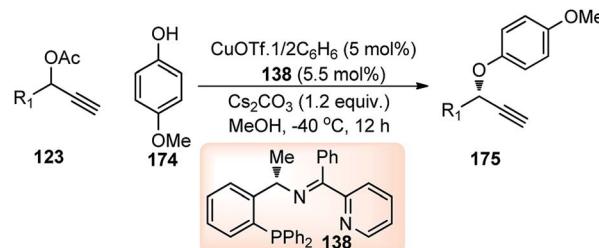
Scheme 76 Copper-catalyzed asymmetric synthesis of 2,3,4-trisubstituted 2H-1,4-benzoxazines via formal [4 + 2] cycloaddition reaction.

173 in high yields and good to excellent enantioselectivities, Scheme 76.¹⁰⁵

A wide range of *ortho*-aminophenol derivatives and propargylic esters efficiently reacted to generate the chiral 2,3,4-trisubstituted 2H-1,4-benzoxazines 173 in high yields and good to excellent enantioselectivities. The reaction mechanism is believed to proceed *via* the sequential propargylic alkylation/intramolecular hydroalkoxylation process, leading to highly functionalized chiral 3,4-dihydro-2H-1,4-benzoxazines 173 using a structurally rigid and finely modified ketimine P,N,N-ligand. The electronic property of the substituents at the *para*-position of the phenyl ring also affected the reaction outcome. The decrease in the reactivity and enantioselectivity were observed with the 4-CF₃-substituted substrate as well as with heteroaromatic propargylic ester. Very low conversions were observed with aliphatic substrates also.

In 2015, Nishibayashi *et al.* reported the first copper-catalyzed asymmetric propargylic etherification of propargylic carbonates with not only alcohols but also with phenols as oxygen nucleophiles to generate the corresponding propargylic ethers 175 in good to high yields with a high to excellent enantioselectivity.⁹⁸ However, only propargylic carbonates bearing an alkyl substituent at the propargylic position served as suitable substrates for the reaction. In search of an alternate catalytic system with broad substrate scope, Hu and co-workers in the year 2016 developed an efficient and highly enantioselective copper-catalyzed propargylic etherification of both aliphatic and aromatic propargylic esters with phenols 174 as oxygen nucleophiles, Scheme 77.¹⁰⁶

Addition of Cs₂CO₃ was found to significantly promote the reaction rate as well as enhance the enantioselectivity of the reaction. With the use of structurally rigid tridentate ketimine P,N,N-ligand 138 variety of aryl propargylic ethers 175 could be prepared in good to high yields and excellent enantioselectivities.



Scheme 77 Highly enantioselective copper-catalyzed propargylic etherification of both aliphatic and aromatic propargylic esters with phenols.

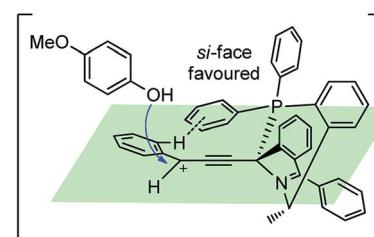
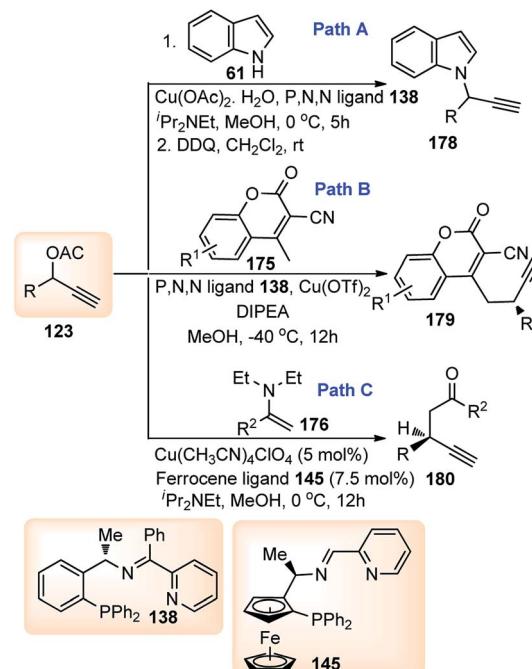


Fig. 8 Probable transition state for the copper-catalyzed enantioselective propargylic etherification reaction.



Scheme 78 Copper catalyzed propargylation of indoles, coumarin derivatives, and enamines.

Based on the commonly explained edge-to-face aromatic interaction a transition state model was proposed between the Cu-acetylide complex with chiral P,N,N-ligand to explain the observed stereochemistry, Fig. 8. Due to the steric hindrance of the ligand, the attack of the γ -carbon atom by the oxygen atom of hydroxy group happened favorably from the *si*-face.



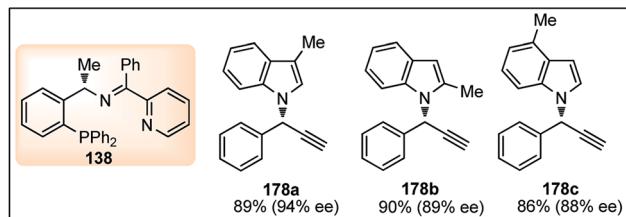


Fig. 9 Structures of P,N,N ligand and propargylated indoles with corresponding yield and enantioselectivities.

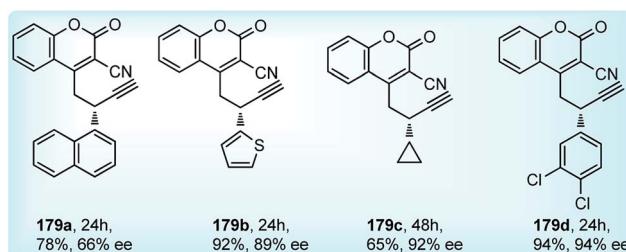
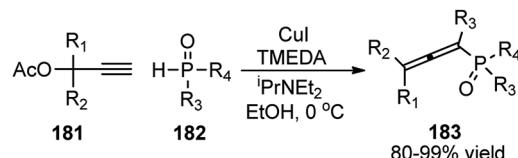


Fig. 10 Structures of propargylated coumarins with corresponding yields and enantioselectivities.

Hu and co-workers in 2015 have further extended their Cu catalyzed enantioselective nucleophilic propargylic substitutions methodology for the synthesis of N-substituted indoles **178** started from propargylic acetates **123**, Scheme 78 (Path A).¹⁰⁷

Optimization of the reaction conditions revealed that $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in presence of chiral ketimine P,N,N-ligand **138** and $^i\text{Pr}_2\text{NEt}$ was the best reagent system for the chiral induction. Other bases like NEt_3 even K_2CO_3 were also equally effective for this reaction. However, the reaction is very much solvent selective, and the reaction did not work well in CH_2Cl_2 , DMSO, DMF, toluene, and THF. The methodology worked well with a variety of substituted indolines like 2-, 3-, 4-methyl indolines, 6-fluoro indolines *etc.* and the enantioselectivity was found to be substrate dependent. Chloro substitution at the C-2 position in the phenyl ring of the propargylic acetate gave poor yield and decreased enantioselectivity. However, 3-Cl or 4-Cl substitution in the same ring gave products with good yields and higher selectivity.

A few examples of products obtained by changing the propargylic side chains and by changing the coumarin rings are shown in Fig. 9.



Scheme 79 Copper catalyzed substitution reaction of propargyl acetates with P(O)H compounds.

Antonchick and Waldmann's group has carried out an asymmetric vinylogous propargylation of substituted coumarins **174** using $\text{Cu}(\text{OTf})_2$ -**138** catalyst system, in 2017, Scheme 78 (Path B).¹⁰⁸

Screening of various chiral ligands like Cl-MeO-BIPHEP, ^iPr -PyBOX, Fesulphos, ^iPr -PHOX along with a copper catalyst gave poor yields and insignificant enantioselectivity. Finally, (*S*)-**138**- $\text{Cu}(\text{OTf})_2$ catalyst combination in DIPEA medium at $-40\text{ }^\circ\text{C}$ gave the excellent yields and good enantioselectivity. A few examples of products obtained using the above methodology are shown in Fig. 10.

Propargylic esters having aliphatic substitution containing a heteroatom underwent smooth reaction, however; tertiary-butyl substituted propargylic ester resulted in sluggish reaction with only 32% yields. Poor enantioselectivity was found with alkynyl substitution in the propargylic substrate (91% yield, 41% ee).

Guo and co-workers in the year 2014 have introduced a chiral tridentate ferrocenyl P,N,N-ligand **145** along with a copper catalyst for the enantioselective propargylic substitution of propargylic acetates, Scheme 78, (Path C).¹⁰⁹ Enamines were selected as the nucleophiles to deliver optically active propargylic ketones. Initially, ferrocenyl ligand **145** was combined with a copper salts such as $\text{Cu}(\text{OAc})_2$, $\text{Cu}(\text{OTf})_2$, CuCl , CuI , CuClO_4 , $\text{Cu}(\text{CH}_3\text{CN})_4\text{ClO}_4$ *etc.* in either MeOH, THF, toluene, CH_2Cl_2 , acetone or CH_3CN medium to pursue the substitution reaction. However, $\text{Cu}(\text{CH}_3\text{CN})_4\text{ClO}_4$ -**145** reagent system in the methanolic medium at room temperature turned out to be the best with the product yield 75% and 93% ee. Next, the same reaction when carried out by lowering the temperature to $0\text{ }^\circ\text{C}$ both yield and enantioselectivity increased to 90% and 97% respectively. Subsequent study was carried out with several substituted acetates and enamines to obtain highly functionalized propargylic ketones with excellent yields and enantioselective purity as shown in Fig. 11.

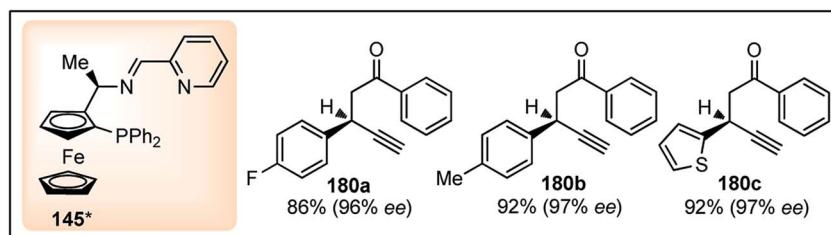
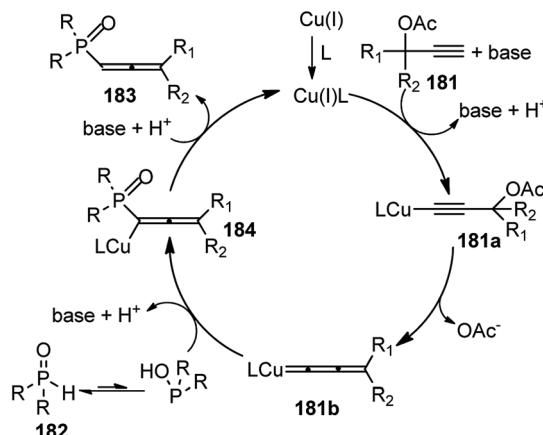
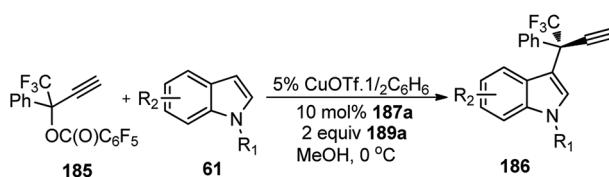


Fig. 11 Structures of propargylated enamines with corresponding yields and enantioselectivities.





Scheme 80 Mechanism for the novel Cu-catalysed substitution reaction of propargyl acetates with P(O)H compounds.



Scheme 81 Copper-catalyzed enantioselective propargylation of indoles with propargylic esters.

Han and co-workers in the year 2016 developed a novel Cu-catalysed substitution reaction of propargyl acetates **181** with P(O)H compounds **182** to afford allenylphosphoryl compounds **183** via C-P bond coupling in high yields under mild conditions, Scheme 79.¹¹⁰

Several bidentate N,N-ligands such as bpy, 1,10-Phen, and ethylenediamine, N,P-ligands like 2-(2-(diphenylphosphino)ethyl)pyridine and P,P-ligand dppe were evaluated and all were proved to be less effective except TMEDA. Screening of the catalysts revealed that CuBr, CuCl, and Cu(MeCN)₄PF₆ were all equally efficient catalysts, giving the product with comparable yields and selectivity. However, other metal salts such as CoCl₂, FeCl₃, RuCl₃ and Pd(OAc)₂ showed no reactivity. A proposed mechanistic pathway is shown in Scheme 80.

The active Cu(I) species generated from the reaction of the copper salt with TMEDA in presence of base reacted first with the propargyl acetate to produce the copper acetylidyne complex which then generates the allenylidene complex **181b** with the loss of ester group. The nucleophilic reaction of allenylidene complex **181b** with P(O)H compounds **182** produce an allenylcopper intermediate **181c**, the protonation of which gives the product **183** and regenerates the catalyst, Scheme 80.

Nishibayashi and co-workers in the year 2016 developed a copper-catalyzed enantioselective propargylation of indoles **61** with propargylic esters **185**, Scheme 81.¹¹¹

Treatment of 1,1,1-trifluoro-2-phenylbut-3-yn-2-yl perfluorobenzoate **185** with indole **61** in the presence of 5 mol% of CuOTf·1/2C₆H₆ and 10 mol% of (4S,5R)-diPh-Pybox **187a** and

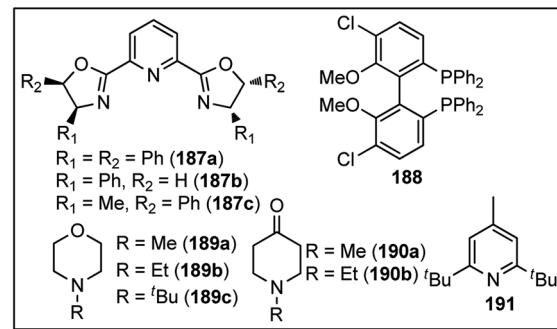
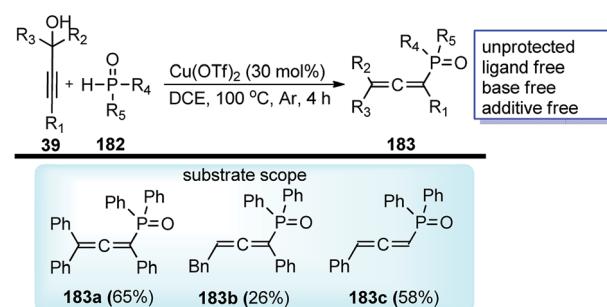


Fig. 12 Structures of different ligands and additives screened in the copper-catalyzed enantioselective propargylation of indoles with propargylic esters.

N,N-diisopropylethylamine in methanol at room temperature for 1 hour furnished the desired propargyl substituted product **186** in 41% yield with 47% ee. Propargylic esters such as acetate and *tert*-butyl carbonate were unable to react under this reaction condition. The base had a pronounced effect on both the reactivity and enantioselectivity and it was observed that cyclic amines like 4-methyl morpholine worked as more effective bases to promote the catalytic reactions smoothly. The previously known ligands for the copper-catalyzed enantioselective propargylic amination and etherification like (*S*)-Ph-Pybox, (*S*)-Me-Pybox, and (*R*)-Cl-MeO-BIPHEP were found unsatisfactory (Fig. 12). Lowering the reaction temperature to 0 °C improved the yield and enantioselectivity drastically. Also, it was observed that using a larger amount of base was effective in leading to the reaction completion in a shorter reaction time. Reactions of other propargylic perfluorobenzoates having substituents like fluoro, chloro, bromo, methoxy, phenyl, and a methyl group at the *para*-position of the benzene ring of the propargylic perfluorobenzoates were also equally efficient. Unfortunately, no reaction occurred at all with the *ortho*-methyl-substituted benzene ring.

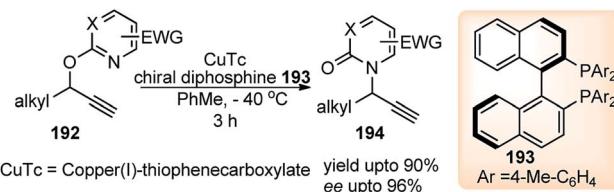
The propargylated product can be efficiently converted to chiral triarylmethanes, bearing a quaternary carbon center, with high to excellent enantioselectivities via sequential Huisgen cycloaddition with azides.

In the year 2016, Gao and co-workers also successfully developed similar Cu-catalyzed direct coupling of the



Scheme 82 Cu-catalyzed direct coupling of the unprotected terminal and internal propargylic alcohols with P(O)H compounds.





Scheme 83 Enantioselective Cu-catalyzed rearrangement of electron-deficient 2-propargyloxy-pyridines.

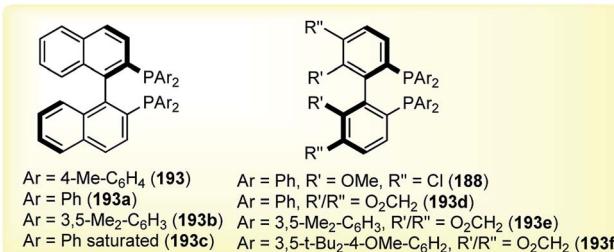


Fig. 13 Structures of the ligands used for the copper-catalyzed propargylic substitution reaction.

unprotected terminal and internal propargylic alcohols **39** with P(O)H compounds **182**, Scheme 82.¹¹²

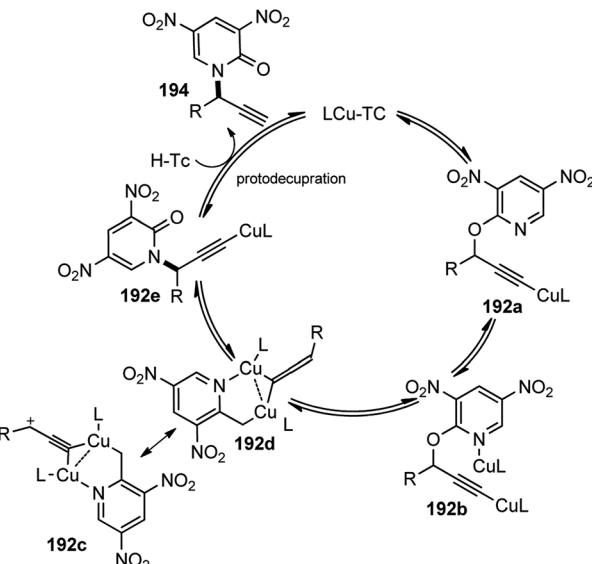
The reaction does not require any base, ligand, or an additive and proceeds only in presence of catalytic amount of Cu(OTf)₂. Additionally, the use of inexpensive Cu(OTf)₂ as a catalyst, H₂O as the only by-product, remarkable functional group tolerance, and the high atom-economy associated with this method makes it a highly prospective methodology for the construction of important allenylphosphoryl frameworks in organic synthesis and pharmaceutical research.

Cordier and co-workers in the year 2017 have developed the first enantioselective Cu-catalyzed rearrangement of electron-deficient 2-propargyloxy-pyridines **192** in high enantioselectivity within a brief time, Scheme 83.¹¹³

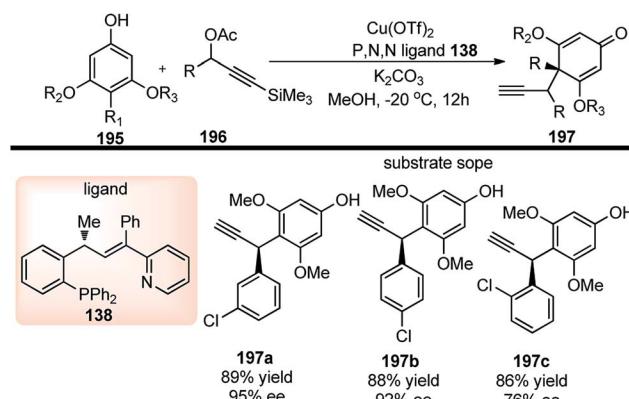
The nature of copper catalyst had a strong influence on both conversion and enantioselectivity. Ligands like diphenyl- and di-4-methylphenyl-phosphines (**188**, **193**, **193a-f**) Fig. 13, resulted in high conversion and stereoinduction. However, under the identical conditions, bis-3,5-dimethylphenyl analogs led to low product enantiomeric ratios and the highly bulky ligand **183f** resulted in no conversion. Performing the transformation in THF offered results like toluene. The authors noted that base is not required for this process. Employing lower catalyst loading did not impact enantioselectivity but did influence yield and reaction time. Significantly, the rearrangement was complete in less than 10 minutes at ambient temperature.

A proposed mechanistic pathway is shown in Scheme 84. Bimetallic intermediate is involved, and it was speculated that the Cu-coordination to the pyridyl nitrogen is responsible for the C–O bond cleavage.

Hu and co-workers in the year 2017 developed a copper-catalyzed intermolecular propargylic dearomatization of phenol derivatives **195**, with the support of a sterically hindered



Scheme 84 Mechanism for the enantioselective Cu-catalyzed rearrangement of electron-deficient 2-propargyloxy-pyridines.



Scheme 85 Propargylic dearomatization of phenols.

ketimine P,N,N-ligand leading to optically active cyclohexadienone derivatives **197** in high yield and excellent enantioselectivities with up to 99% ee, Scheme 85.¹¹⁴

Screening of the ligand structure showed their considerable influence on the reactivity and enantioselectivity. Chiral tridentate ketimine P,N,N-ligand was identified as the most promising ligand in terms of yield and enantioselectivity. Base additives proved to be crucial for the reaction since no dearomatization product was detected in its absence. The best base additive was Et₃N, which furnished products in 59% yield and 95% ee. Subsequent screening of Cu salts identified Cu(OTf)/C₆H₆ as the best choice. The solvent screening disclosed that the protic solvent was favorable for the reaction, and MeOH proved to be the best one, presumably facilitating the formation of Cu-allenylidene intermediates.

Lowering the reaction temperature significantly inhibits the competitive Friedel–Crafts reactions, thereby dramatically improving the reaction yield and enantioselectivity. Replacing



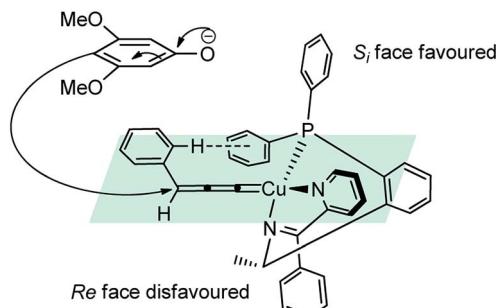
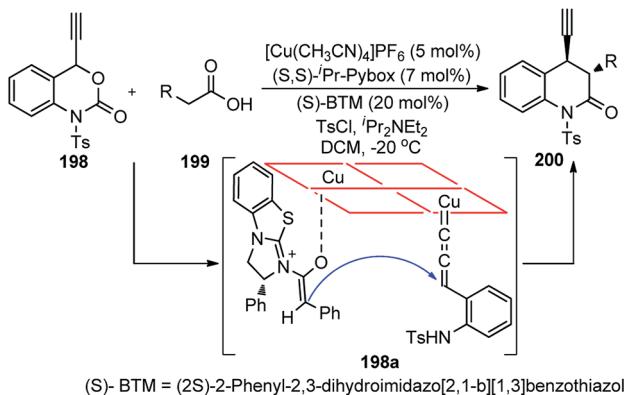


Fig. 14 Probable transition state structure for the copper-catalyzed Propargylic dearomatization of phenols.



Scheme 86 Decarboxylative [4 + 2] annulation of 4-ethynyl dihydrobenzoxazinones and carboxylic acids via cooperative catalysis.

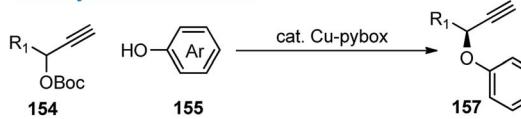
the OAc group with OCOCF_3 or TMS didn't result in the dearomatization product. A plausible transition state of the Cu-allenylidene complex with ligand 138 is shown in Fig. 14 to account for the observed stereochemistry.

Unlike the dearomatization reaction, nucleophilic attack preferably occurs from the si-face due to the steric hindrance surrounding the re-face. It was also observed that, unsubstituted phenol predominantly produced *O*-alkylated product instead of the desired Friedel–Crafts product. Also, *meta*-methoxy phenol gave the desired product with only 13% yields. However, 3,5-dimethoxy phenol with various propargylic esters furnished the Friedel–Crafts products in reasonably good to excellent yields.

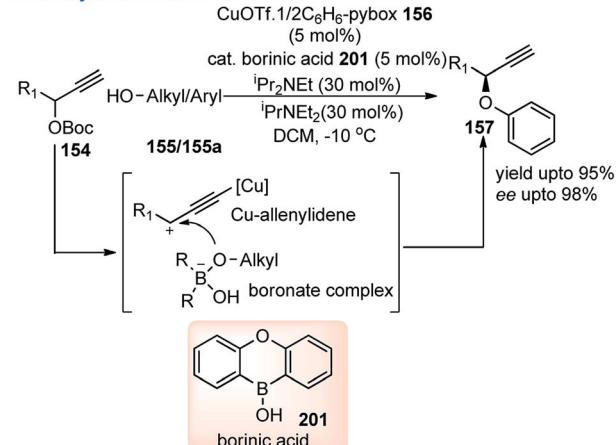
An asymmetric catalytic decarboxylative [4 + 2] annulation of 4-ethynyl dihydrobenzoxazinones 196 and carboxylic acids 197 was established by Gong and co-workers in 2017 using cooperative copper and nucleophilic Lewis base catalysis, Scheme 86.¹¹⁵

Substituted benzoxazinones were also excellent reaction partners affording products with excellent enantioselectivities ranging from 94 to 99% ee. Furthermore, excellent enantioselectivities ranging from 95–99% ee were achieved with both electron-donating and electron-withdrawing substituents. The dinuclear copper complex plays a dual role by participating in the decarboxylation process to generate the copper-allenylidene complex of 196 and acting as a counter ion to bind the

Nishibayashi's work in 2015



Nishibayashi's work in 2018



Scheme 87 Copper catalyzed propargylic etherification reaction.

ammonium *Z*-enolate. Following the activation of the reacting partners, propargylation proceeds *via* nucleophilic attack to the *si*-face of the copper-allenylidene complex followed by lactonization to furnish the (*R,R*) product 198 as the major isomer, Scheme 86.

Despite the enthusiastic studies by several groups, enantioselective propargylic substitution reactions with alcohols as nucleophiles seemed to be elusive till 2015. Nishibayashi's group reported the first successful example of the enantioselective propargylic etherification with the use of copper-pybox system.⁹⁸

Nishibayashi and co-workers in the year 2018 developed a copper- and borinic acid-catalyzed propargylic etherification strategy with aliphatic alcohols as nucleophiles in good yields with excellent enantioselectivities, Scheme 87.¹¹⁶ However, the nucleophiles were limited to phenol derivatives. Initial investigations were carried out with *tert*-butyl 1-phenyl-2-propyn-1-yl carbonate 154 and benzyl alcohol 155/155a as typical substrates. Under the optimized condition employing copper(I) trifluoromethanesulfonate benzene complex, (*S*)-Ph-pybox ligand 156 (10 mol%), 3,5-bis(trifluoromethyl)phenylboronic acid (5 mol%), and Hünig's base (30 mol%) the desired product was obtained in 68% yield with 89% ee. Other boron compounds listed in Fig. 15 were also screened but none of them offered products with better enantioselectivity than dibenzo-1,4-oxaborine-derived borinic acid 201. Several other pybox ligands like (*S*)-Me-pybox, diPh-pybox were tested and the best result was achieved by (*S*)-Ph-pybox ligand.

Propargylic carbonates bearing electron donating as well as withdrawing substituents at the *para*-position of the benzene ring were successfully transformed into the corresponding propargylic etherified products in moderate to high yields with an excellent enantioselectivity.





Fig. 15 Structures of the different borinic acid used.

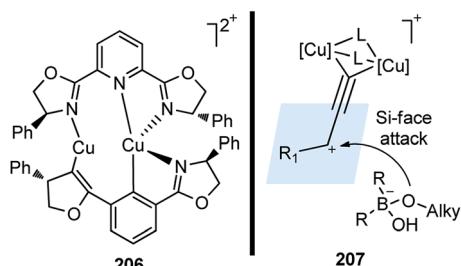
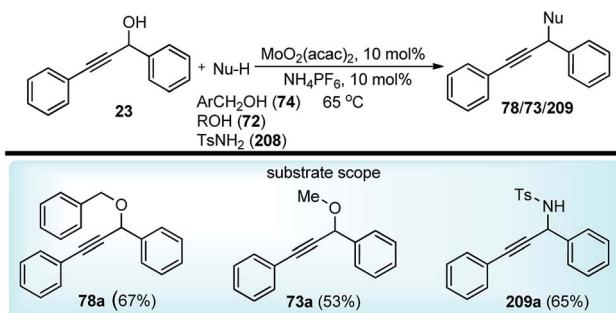


Fig. 16 Transition state structure for the copper-catalyzed propargylic etherification reaction.



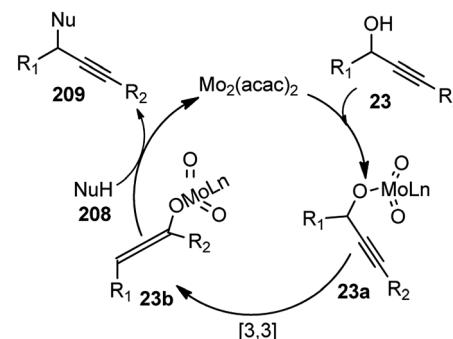
Scheme 88 Direct substitution of propargylic alcohol with oxygen, nitrogen, and carbon nucleophiles catalyzed by molybdenum.

The present etherification proceeds *via* a nucleophilic attack of an alcohol toward a dimetallic copper-allenylidene complex from si-face of the allenylidene ligand, Fig. 16.⁹⁸

A similar report of copper and borinic acid-catalyzed propargylic etherification reactions was also independently carried out by the group of Niu in 2017.^{117,118} But the substrate scope is limited and has been limited to diols and polyols, which may coordinate the boron center in a bidentate fashion.

5.9. Molybdenum derived catalysts

Molybdenum although falls under the category of 'heavy metal' its properties are very different from those of the typical heavy metals like mercury, thallium, and lead. It is much less toxic than these and other heavy metals which makes it an attractive substitute for several other toxic heavy metals. The oxidation states ranging from (–II) to (VI), coordination numbers expanding from 4 to 8 and their ability to form compounds with most inorganic and organic ligands makes the chemistry of molybdenum extremely versatile.^{119,120}



Scheme 89 Molybdenum(vi) catalyzed direct substitution of propargylic alcohols.

Molybdenum(vi) was first used as a catalyst for the direct substitution of propargylic alcohol 23 with several O, N and C-centered nucleophiles by Zhu and co-workers in the year 2010, Scheme 88.¹²¹

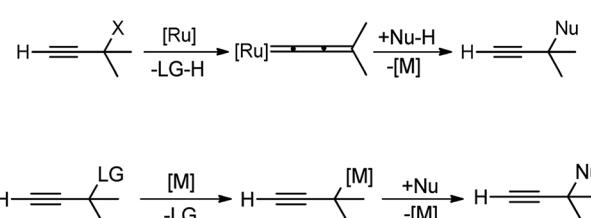
When 1,3-diphenylprop-2-yn-1-ol 23 was treated with an excess of phenylmethanol 74 or other nucleophiles like alcohol 72 or tosylamine 208 in the presence of 10 mol% of $\text{MoO}_2(\text{acac})_2$ and 10 mol% of NH_4PF_6 in acetonitrile at 65 °C for 6 h the desired product (3-(benzyloxy)prop-1-yn-1,3-diy) dibenzene 73/78/209 was obtained in good yield. Reduced yield was obtained when NH_4PF_6 was not used as an additive, whereas NH_4PF_6 alone showed no catalytic activity.

The presence of air and moisture did not have any role in the reaction outcome. The reaction is solvent dependent and yields considerably reduced when the reaction was carried out in toluene, nitromethane, dioxane or DMF. The mechanistic pathway for this Mo catalyzed reaction is illustrated in Scheme 89.

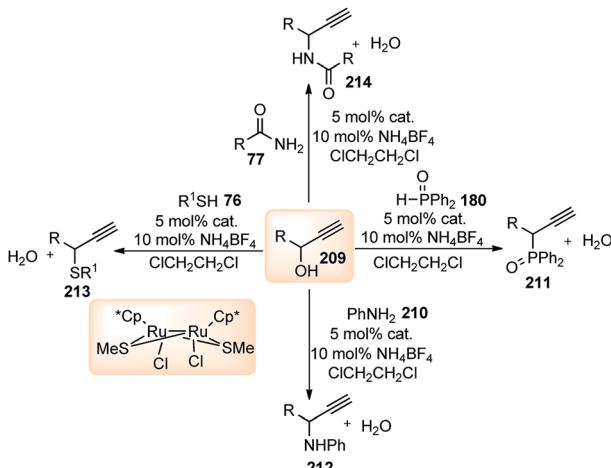
It was proposed that the transition state involves propargyl alcohol combined with molybdenum complex to form intermediate, which was followed by [3,3] rearrangement to form allenolate intermediate 23b. Subsequent nucleophilic attack by 206 on allenolate 23b delivered the desired product 198.

5.10. Ruthenium derived catalysts

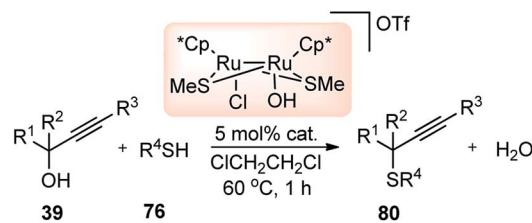
Ruthenium can exist in various valences (0 to 8 valence) and is not so expensive transition metal which prompted the scientific community to explore ruthenium for various useful catalytic reactions. Various substrates bearing heteroatoms are activated by these catalysts and undergo reactions with either



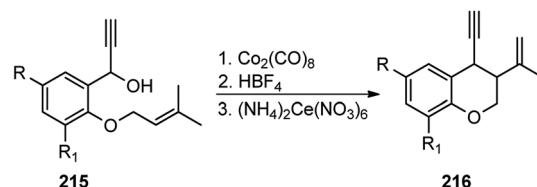
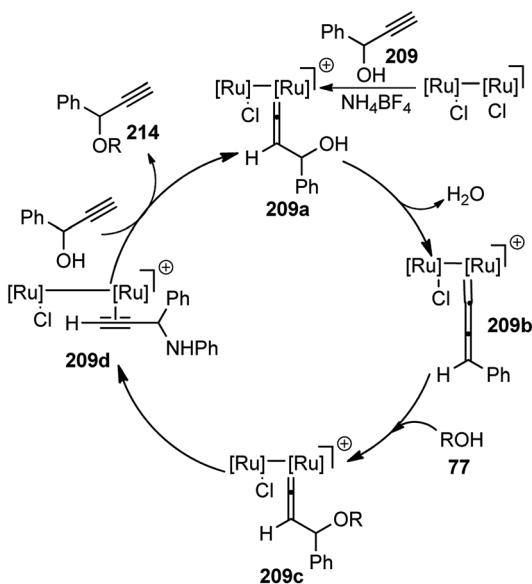
Scheme 90 General mechanism for the ruthenium catalyzed propargylic substitution reaction.



Scheme 91 Ruthenium catalyzed propargylic substitution reaction.



Scheme 93 Cationic diruthenium complex catalyzed propargylic thio-etherification reaction.

Scheme 94 $\text{Co}_2(\text{CO})_8$ catalyzed propargylic substitution reaction of deactivated alkenes.

Scheme 92 Mechanism for the ruthenium catalyzed propargylic substitution reaction.

nucleophiles or electrophiles under neutral conditions. Ruthenium catalysts react with propargyl alcohols to generate metal allenylidene complexes, which have attracted a great deal of attention in recent years as a new type of organometallic intermediate. The $\text{C}\alpha$ and $\text{C}\gamma$ carbon atoms of allenylidene ligands are electrophilic centers, while the $\text{C}\beta$ carbon atom is nucleophilic. In general, reactions of catalytic allenylidene ruthenium complexes with a variety of nucleophiles proceed *via* the nucleophilic attack either at the $\text{C}\beta$ or $\text{C}\gamma$ carbon atom in allenylidene complex. Only a few examples have been reported where propargylation occurs *via* the coordination of the alkyne bond, thereby enhancing the nucleofugacity of the hydroxide, Scheme 90.

Hidai and co-workers in the year 2000 described a series of novel propargylic substitution reactions catalyzed by thiolate-

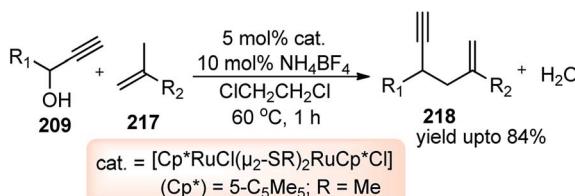
bridged diruthenium complexes, Scheme 91.¹⁰ They have demonstrated the facile ruthenium-catalyzed substitution reactions of propargyl alcohol with various nucleophiles like amine, amides, thiophenols, and diphenylphosphines to produce the corresponding propargylic derivatives 211–214 in high yields with complete regioselectivity.

A mechanism for this novel catalytic reaction is highlighted in Scheme 92. The initial step is the formation of a vinylidene complex 209a in the presence of NH_4BF_4 followed by conversion of vinylidene complex into an allenylidene complex 209b. Subsequent nucleophilic attack of an alcohol on the $\text{C}\gamma$ atom in the allenylidene ligand resulted in the formation of another vinylidene complex 209c. The complex 209c is then transformed into the η^2 -coordinated propargylic ether tautomer 209d, which furnishes propargylic ether by reaction with a propargylic alcohol to regenerate the complex.

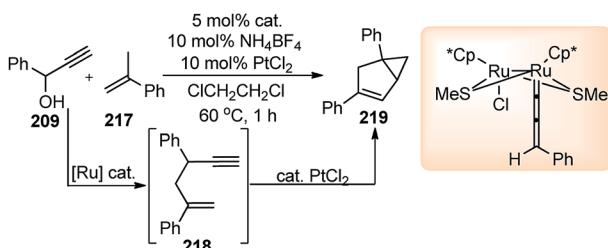
Until 2002, the most reliable method for the propargylic substitution was the Nicholas reaction. However, there were only a few studies on the substitution by thiols by the Nicholas reaction and the preparative methods for propargylic sulfides by other methods were quite limited. So, to devise propargylic substitution reactions with thiols, Uemura and co-workers in the year 2002 reported a highly selective and efficient propargylic substitution reaction of propargylic alcohols 39 with thiols 76 catalyzed by the cationic diruthenium complex, Scheme 93. That was the initiation of the subsequent propargylic reactions carried using diruthenium complex.¹²²

Tyrrell and co-workers in the year 1997 described a series of intramolecular cyclisation reactions of trisubstituted alkene 215 promoted by dicobalt hexacarbonyl complex, Scheme 94. Although a variety of activated carbon nucleophiles have been used to quench a dicobalt hexacarbonyl stabilized cation in the Nicholas reaction the use of deactivated alkenes has received little or no attention in the chemistry literature.¹²³

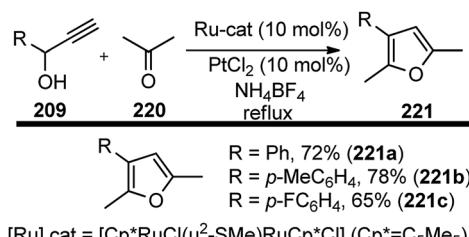




Scheme 95 Ruthenium-catalyzed inter- and intramolecular carbon–carbon bond forming reactions between propargylic alcohols and alkenes.



Scheme 96 Mechanism for the ruthenium catalyzed synthesis of fused polycyclic compounds.



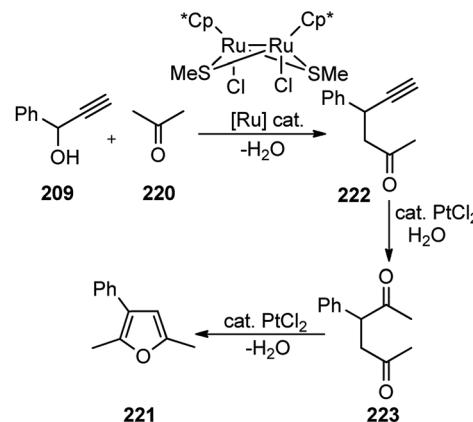
Scheme 97 Ruthenium- and platinum-catalyzed sequential reactions towards the synthesis of substituted furans from propargylic alcohols and ketones.

Although the intramolecular cyclization reaction of the trisubstituted alkene was accomplished to afford a series of benzopyran derivatives **216**, the reaction suffered from a serious drawback of involving stoichiometric amount of dicobalt hexacarbonyl complex. This limitation prompted researchers to develop new methodologies in the subsequent years.

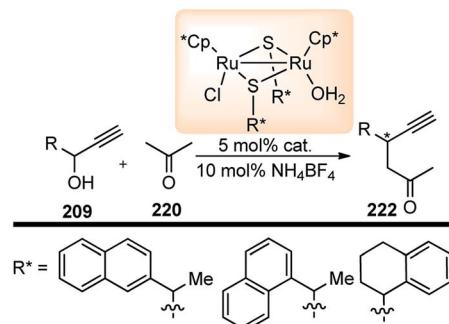
To devise a new methodology to construct C–C bond, Hidai, and Uemura in the year 2003 reported a ruthenium-catalyzed inter- and intramolecular carbon–carbon bond forming reactions between propargylic alcohols **209** and alkenes **217** *via* an allenylidene-ene type pathway, Scheme 95.¹²⁴

The authors have developed a simple method involving both Ru and Pt catalyst for the preparation of fused polycyclic compounds by an intramolecular cyclization of propargylic alcohols bearing an alkene moiety **218** at a suitable position, Scheme 96.¹²⁵

This one-pot efficient synthetic method provides a new type of skeleton of fused polycyclic compounds with a potential for biological activity. The thiolate-bridged diruthenium complexes promoted the catalytic propargylic substitution reaction



Scheme 98 The mechanism for the ruthenium- and platinum-catalyzed sequential reactions towards the synthesis of substituted furans from propargylic alcohols and ketones.



Scheme 99 Ruthenium catalyzed enantioselective propargylic alkylation of propargylic alcohols with acetone.

between propargylic alcohols and alkenes in the first step, while PtCl₂ catalyzed the cycloisomerization of the enynes in the same medium in the second step.

Hidai and Uemura in the year 2003 have found a combination of ruthenium- and platinum-catalyzed sequential reactions to afford the corresponding tri- and tetra-substituted furans or pyrroles from propargylic alcohols **209** with ketones **220** and anilines **221**, respectively, in moderate to good yields with high regioselectivities, Scheme 97.¹²⁶

Treatment of 1-phenyl-2-propyn-1-ol **209** in acetone **220** in the presence of Ru-catalyst, NH₄BF₄ (20 mol%), and PtCl₂ (20 mol%) at reflux temperature for 36 h afforded 2,5-dimethyl-3-phenylfuran **221** in 75% yield. The reaction proceeded even in the presence of smaller quantities of Ru-cat (5 mol%) and PtCl₂. Other transition-metal complexes, such as Pd(OAc)₂, [PdCl₂(MeCN)]₂ and PdCl₂ were found inefficient. Although AuCl₃ was found to furnish the desired product, an intermediate diketone was also formed. The reaction has a wide substrate scope and the use of various propargylic alcohols resulted in the formation of the corresponding 3-aryl and 3-alkenyl substituted 2,5-dimethylfurans in moderate to high yields with a complete regioselectivity.

The mechanistic pathway for this reaction is highlighted in Scheme 98.

At first, under the influence of Ru-catalyst **209** is transformed rapidly into γ -ketoalkyne **222**. Then, hydration of the alkyne moiety slowly delivers the 1,4-diketone **223**, under the influence of PtCl_2 . Intramolecular cyclization of the produced diketone resulted in the formation of the furan **221**, catalyzed by PtCl_2 .

In 2003, Nishibayashi and co-workers reported catalytic enantioselective propargylic alkylation of propargylic alcohols **209** with acetone **220**, using diruthenium complex in good yields, but only with moderate enantioselectivity (up to 35% ee), Scheme 99.¹²⁷

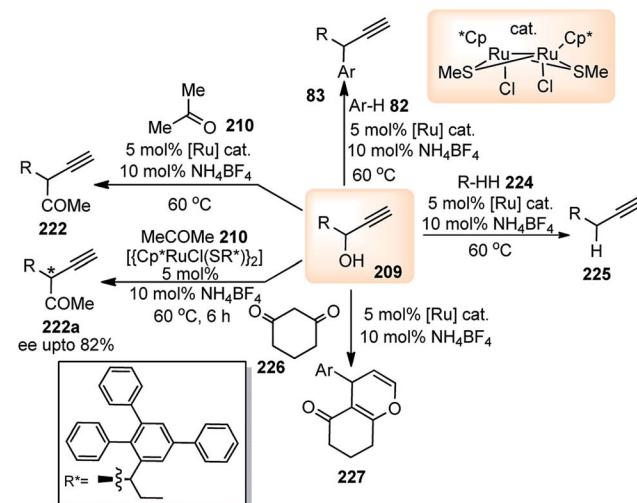
The authors envisaged that edge to face steric repulsion between substrates and chiral ligands would not be enough to achieve high enantioselectivity. Therefore, a new type of chiral ligands with a phenyl ring that might interact with a phenyl ring of ruthenium-allenylidene complexes by π - π interaction was designed.¹²⁸ Also the chiral thiolate-bridged ligands work to control the chiral environment around the diruthenium site.

Nucleophilic attack at the $\text{C}\gamma$ atom of the allenylidene ligand from the less hindered side accounts for the high enantioselectivity. Here, π - π interaction of phenyl rings between the ligand and allenylidene moieties is considered to play a crucial role in achieving such a high selectivity.^{129,130} The method reported was the first of its kind compared to the so-far-known highly diastereoselective and enantioselective propargylic substitution reaction methods, which used a stoichiometric amount of transition metal complexes,^{131–133} for the enantioselective reactions with a ketone.

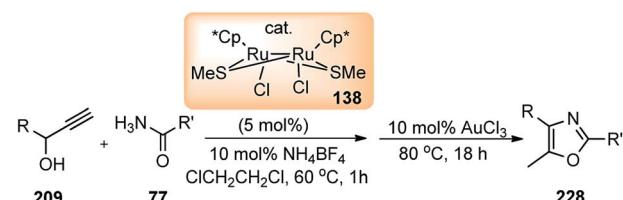
Reactions of allenylidene complexes with various heteroatom and carbon-centered nucleophiles at the α - and γ -carbons were already known but the direct reaction of the allenylidene ligand with aromatic compounds was not explored. This prompted several research groups to investigate the catalytic reaction of aromatic compounds with propargylic alcohols in the presence of the thiolate-bridged diruthenium complex $[\text{Cp}^*\text{RuCl}(\mu^2\text{-SMe})_2\text{-RuCp}^*\text{Cl}]$ as a catalyst.

Nishibayashi and Uemura in between 2004 and 2005 have found several interesting ruthenium-catalyzed reactions between propargylic alcohols and cyclic 1,3-dicarbonyl compounds¹³⁴ aromatic compounds^{135,136} and ketones^{134,137} and 1,3-dicarbonyls^{134a,138} to afford the corresponding chromen-5-ones and pyran-5-ones, propargylated aromatic products and related products respectively in high to excellent yields with high regioselectivity, Scheme 100. Although the ruthenium-catalyzed propargylic alkylation of propargylic alcohols with ketones **210** was disclosed in 2001 by Nishibayashi and co-workers¹³⁴ but the highly enantioselective propargylic substitution reaction of propargylic alcohols with acetone with up to 82% ee was reported only in 2005.¹³⁷ The diruthenium complex with a new class of chiral disulfides acted as catalyst where the π - π interaction of phenyl rings between the ligand and allenylidene moieties played a crucial role in achieving high selectivity.

The mechanistic studies indicated that the catalytic cycloaddition proceeds via allenylidene intermediate.¹³⁹ The electrophilic aromatic substitution reaction occurs at the γ -carbon of an allenylidene ligand.



Scheme 100 Ruthenium catalyzed propargylic substitution reaction of ketones and arynes.



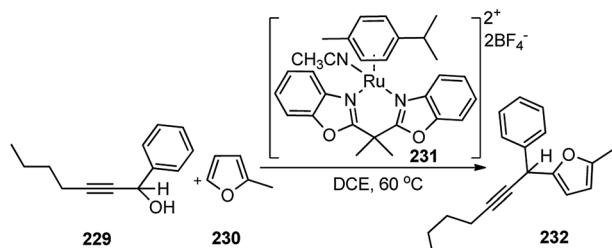
Scheme 101 Ruthenium and gold catalyzed synthesis of substituted oxazoles from propargyl alcohols with terminal alkyne moiety with amides.

Nishibayashi and Uemura in the year 2004 developed a convenient and straightforward methodology for the synthesis of substituted oxazoles **228** in good yields with a complete regioselectivity, Scheme 101.¹⁴⁰ The reaction proceeds *via* a one-pot reaction of propargylic alcohols bearing a terminal alkyne moiety **209** with amides **77** by the sequential action of ruthenium and gold catalysts.

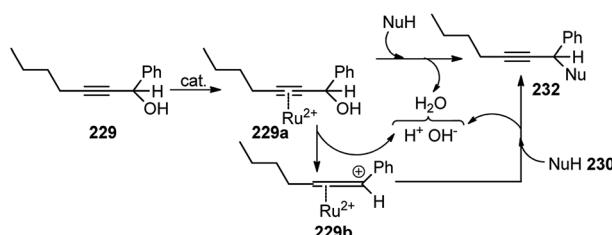
When PtCl_2 and PdCl_2 were used separately in the presence of methane thiolate-bridged diruthenium complex and NH_4BF_4 (10 mol%) in 1,2-dichloroethane ($\text{ClCH}_2\text{CH}_2\text{Cl}$) at 80 °C for 18 h, the reaction of 1-phenyl-2-propyn-1-ol **209** with acetamide did not afford any desired product. Interestingly, improved yield of the product was observed when AuCl_3 (10 mol%) was used as a catalyst in place of PtCl_2 . Marginal improvement in the product yield was observed when the amount of AuCl_3 was increased to 20 mol% whereas the reduction of the amount of ruthenium catalyst (2.5 mol%) improved the product yield. Also prolonging the reaction time did not improve the yield under the same reaction conditions.

The best result was obtained with 5 mol% of Ru catalyst and NH_4BF_4 (10 mol%) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ at 60 °C for 1 h followed by the addition of AuCl_3 (10 mol%). Reactions of a variety of propargylic alcohols with various amides were carried out by the stepwise addition of diruthenium complex **2a** (5 mol%) and





Scheme 102 Ruthenium(II)-catalysed direct propargylation of furan and arene with propargyl alcohols.



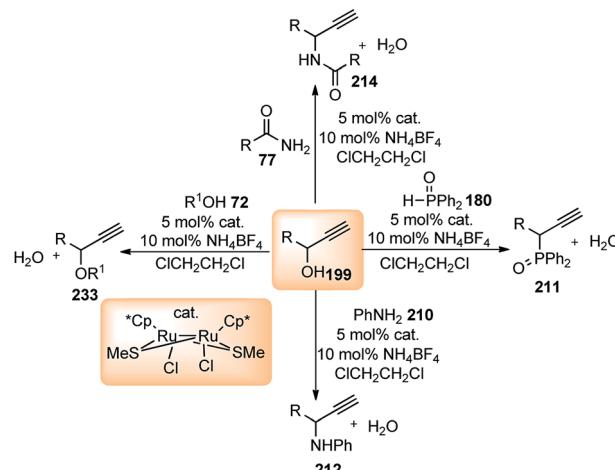
Scheme 103 Mechanism for the ruthenium(II)-catalysed direct propargylation reaction.

AuCl_3 (10 mol%) which furnished the expected 2-isopropyl-5-methyloxazoles in good to high isolated yields. Unfortunately, no reaction of alkyl-substituted propargylic alcohols proceeded at all. As expected, no reaction occurred when *N*-methylacetamide, 2-pyrrolidone, and methanesulfonamide were used as substrates. An elegant route for the synthesis of a variety of substituted oxazoles 228 in good yields with a complete regioselectivity was achieved by the sequential action of ruthenium and gold catalysts from simple and readily available starting materials such as propargylic alcohols and amides.

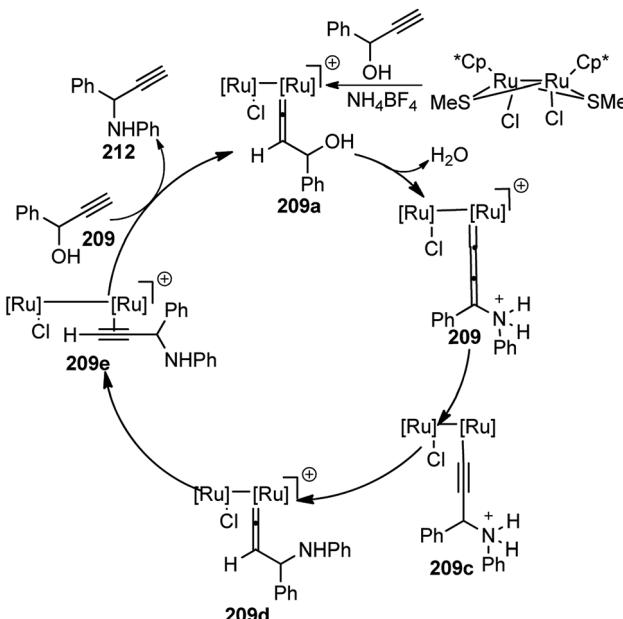
Dixneuf and co-workers in 2005 have earlier demonstrated the role of bisoxazoline-ruthenium complex precursors in the direct propargylation of weak nucleophiles with propargyl alcohols.¹⁴¹ Thereafter the same group reported that a mononuclear (bisoxazoline)(arene)ruthenium(II) complex catalyses the direct propargylation of furan 230 by propargyl alcohols 229 with C–C bond formation in moderate yields, Scheme 102.¹⁴²

Although the yields were modest the scope to modify the bisoxazolidine ligand by steric and electronic modifications to provide higher catalytic activity and play a crucial role in enantioselective catalysis was encouraging. A mechanistic detail was proposed for the above reaction, Scheme 100, where propargylation took place *via* coordinating the C=C bond, thereby enhancing the nucleofugality of the hydroxide leading to the stabilization of the resulting a carbonium ion and allowing further nucleophilic addition at the α -carbon of the coordinated C=C bond, (Scheme 103).

Nishibayashi in the year 2005 described a general procedure for the catalytic propargylic substitution reactions of propargylic alcohols 209 with heteroatom-centered nucleophiles like alcohols 72, amines 210, amides 77, and phosphine oxide 180 using di-ruthenium catalyst, Scheme 104.¹⁴³



Scheme 104 Ruthenium catalyzed propargylic substitution reaction with diverse nucleophiles.

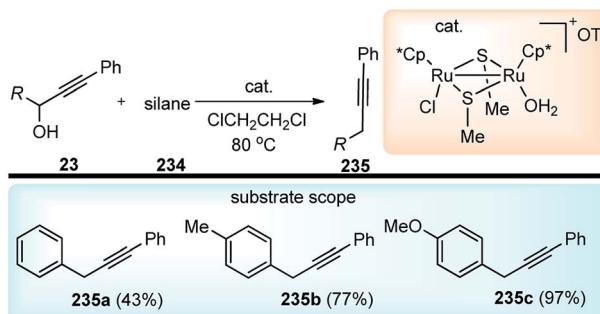


Scheme 105 Mechanism for the ruthenium catalyzed propargylic substitution reaction.

The catalytic cycle for the propargylic substitution reaction is illustrated in Scheme 105 which proceeds *via* the allenylidene intermediate. The attack of nucleophiles to the $\text{C}\gamma$ atom of the allenylidene complex is the key step for the formation of the propargylated product.

Nishibayashi and co-workers in the year 2006 developed a novel method for the reduction of propargylic alcohols 23 with triethylsilane 234 using ruthenium catalyst in good to high yields and complete selectivity, Scheme 106.¹⁴⁴

5 mol% of di-ruthenium complex in $\text{ClCH}_2\text{CH}_2\text{Cl}$ at 80 °C was enough to afford the reduced product 235 in 77% yield. Although, there were several reports of gold-catalyzed



Scheme 106 Ruthenium-catalyzed propargylic reduction of propargylic alcohols with triethylsilane.

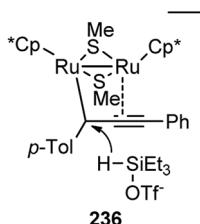


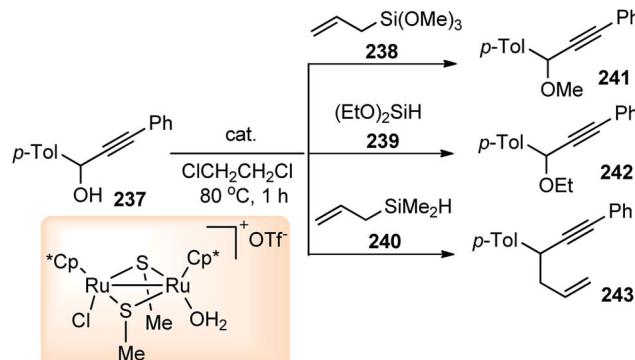
Fig. 17 Proposed reactive intermediate for the propargylic reduction with triethylsilane.

propargylic substitution reactions¹⁴⁵ but AuCl_3 was inefficient in catalyzing the propargylic reduction.

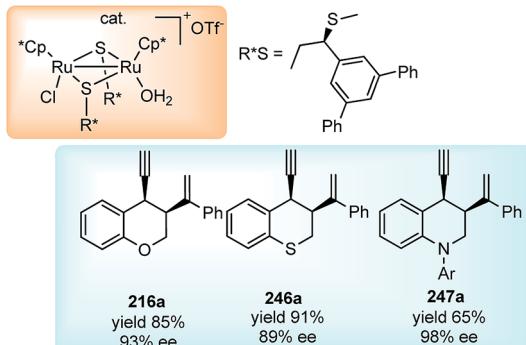
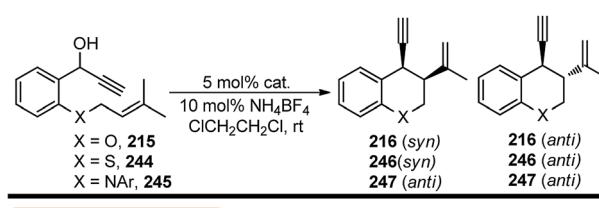
Several other silanes such as *tert*-butyldimethylsilane, dimethylphenylsilane, and triisopropylsilane performed well as reducing agents but triphenylsilane, diphenylsilane, methylphenylsilane, phenylsilane, and poly(methylhydrosiloxane) were not effective. Effect of the substituent on the phenyl ring had a marked influence on the reaction yield. Higher product yield was observed in the presence of an electron-donating group whereas electron withdrawing groups resulted in reduced yield suggesting the involvement of propargylic cation as the reactive intermediate. The proposed reactive intermediate is shown in Fig. 17 where the alkyne moiety interacts with the ruthenium centers of the thiolate diruthenium complex followed by a nucleophilic attack of hydride from the triflate-activated silane to furnish the corresponding reduction product.

Analogous to this reaction, etherification of propargylic alcohols was reported using ruthenium catalyst.¹⁴⁶ Furthermore, the authors have also investigated the ruthenium-catalyzed reactions of propargylic alcohols 237 with organosilicon compounds 238–240 other than trialkylsilanes under the same reaction conditions. Interestingly, the reactions with allyltrimethoxysilane 238 and triethoxysilane 239 proceeded to the corresponding propargylic ethers whereas allyldimethylsilyl hydride provided the corresponding allylated products in high yield at 80 °C within one hour, Scheme 107.¹⁴⁴

Nishibayashi and co-workers in 2008 have extended the application of Ru catalyzed propargylic substitution reaction for the preparation of a variety of optically active heterocycles like chromanes 216, thiochromanes 246, and 1,2,3,4-



Scheme 107 Ru-catalyzed propargylic substitution with different nucleophiles.



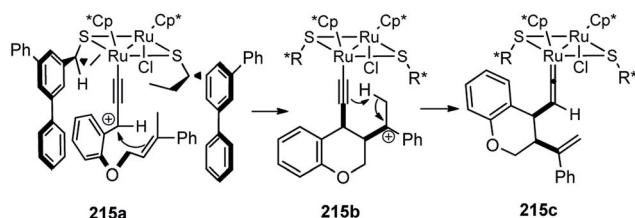
Scheme 108 Intramolecular cyclization of propargylic alcohols towards the synthesis of chiral chromanes, thiochromanes, and 1,2,3,4-tetrahydroquinolines.

tetrahydroquinolines 247 in good to high yields with up to 99% ee, Scheme 108.¹⁴⁷

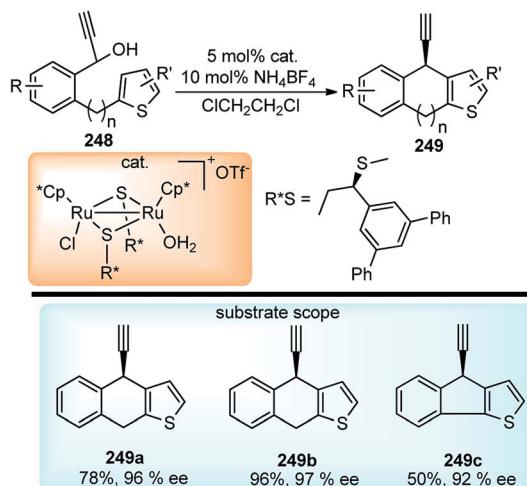
The reaction occurs *via* a ruthenium catalyzed intramolecular cyclization of propargylic alcohols 215 bearing an alkene moiety at a suitable position. Probable mechanistic pathway for the reaction is represented in Scheme 109. The intramolecular attack of an alkene on the cationic γ -carbon of the intermediate occurs from the *si*-face to provide the corresponding alkynyl complex 215b, followed by the facile proton transfer into the alkynyl moiety to give the corresponding vinylidene complex 215c.

Nishibayashi and co-workers in the year 2009 developed a ruthenium-catalyzed enantioselective cyclization of propargylic alcohols 248 bearing a thiophene moiety to afford the corresponding propargylated thiophenes 249 in good to high yields with a high enantioselectivity (up to 97% ee), Scheme 110.¹⁴⁸

The reaction proceeds *via* ruthenium–allenylidene complexes as key intermediates where the thiophene intermolecularly



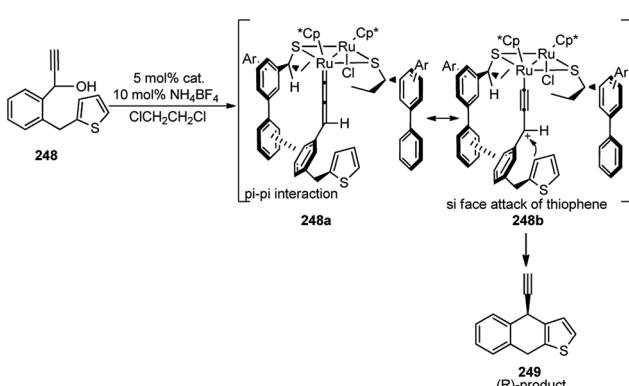
Scheme 109 Probable mechanistic pathway and transition state structure for the ruthenium-catalyzed intramolecular cyclization of propargylic alcohols bearing an alkene moiety.



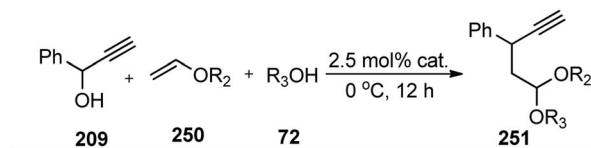
Scheme 110 Ruthenium-catalyzed enantioselective cyclization of propargylic alcohols bearing a thiophene.

attacks the alkynyl complex selectively from the *si*-face because of the π - π interaction between the chiral ligand and allenylidene complex as depicted in Scheme 111. The π - π interaction of the phenyl rings between the chiral ligand and allenylidene moieties was instrumental in achieving high enantioselectivity.

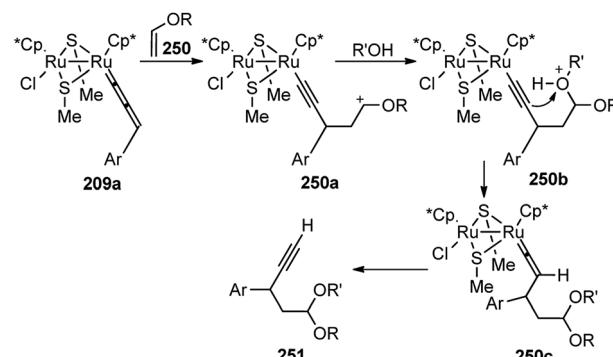
Nishibayashi and co-workers in the year 2009 developed a ruthenium-catalyzed oxypropargylation of alkenes **250** with



Scheme 111 Mechanistic pathway for the ruthenium-catalyzed enantioselective cyclization of propargylic alcohols bearing a thiophene.



Scheme 112 Ruthenium-catalyzed oxypropargylation of alkenes with propargylic alcohols.



Scheme 113 Mechanism for the ruthenium-catalyzed oxypropargylation of alkenes with propargylic alcohols.

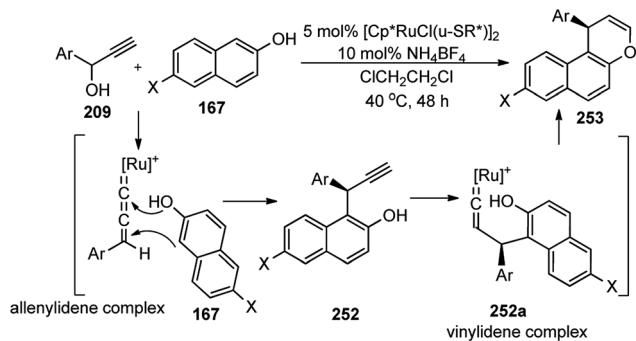
propargylic alcohols **209** and simple alcohols **72** using Ru-catalyst, Scheme 112.¹⁴⁹

A proposed reaction pathway is shown in Scheme 108. The propargylic alcohol gets converted to the ruthenium-allenylidene complexes under the influence of the ruthenium catalyst. Subsequent attack of a vinyl ether on the electron-deficient γ -carbon of ruthenium-allenylidene complexes generated the corresponding alkynyl complex **250a**, followed by the attack of an alcohol on the cationic-carbon to afford the corresponding oxypropargylated product *via* the ruthenium vinylidene complex **250c**, Scheme 113.

Nishibayashi and co-workers in the year 2010 reported a ruthenium-catalyzed enantioselective [3 + 3] cycloaddition of propargylic alcohols **209** with 2-naphthols **167** to afford the corresponding naphthopyran derivatives **253** in moderate to good yields with excellent enantioselectivity up to 99% ee, Scheme 111.¹⁵⁰

This cycloaddition reaction proceeds *via* stepwise reactions of propargylation and intramolecular cyclization, where ruthenium-allenylidene and vinylidene complexes work as key reactive intermediates, as highlighted in Scheme 114.

In 2010, Nishibayashi and co-workers reported an enantioselective propargylic alkylation of propargylic alcohols **209** with aldehydes **255** in the presence of a thiolate-bridged diruthenium complex and chiral secondary amine **258** as the co-



Scheme 114 Ruthenium-catalyzed enantioselective synthesis of naphthopyrans by $[3 + 3]$ cycloaddition of propargylic alcohols with 2-naphthols.

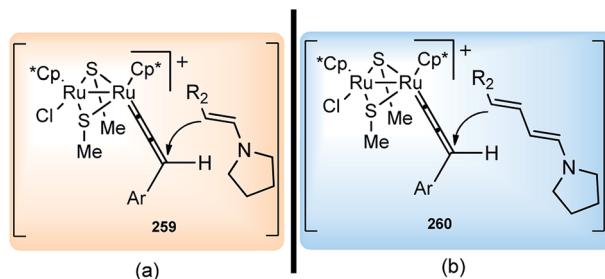
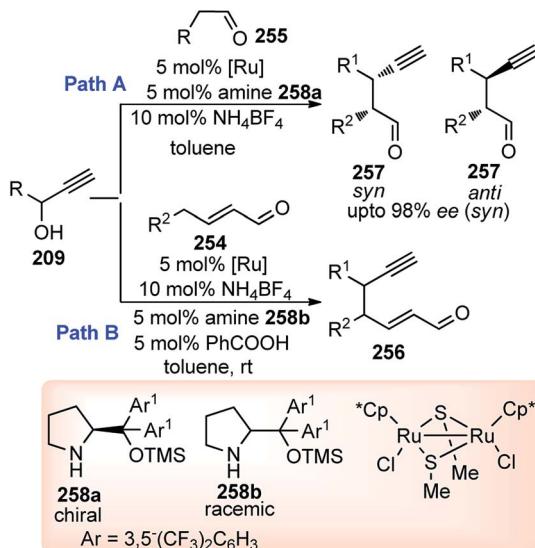


Fig. 18 (a) The key step for the α -propargylation of aldehydes with propargyl alcohols (Path A); (b) the key step for the gamma propargylation of α,β -unsaturated aldehydes with propargylic alcohols (Path B).



Scheme 115 Ruthenium catalyzed enantioselective alpha-propargylation of aldehydes (Path A) and gamma-propargylation of α,β -unsaturated aldehydes (Path B) by cooperative catalysis.

catalysts to give the corresponding propargylic alkylated products in excellent yield and enantioselectivity (up to 98% ee) as a mixture of two diastereoisomers, (Path B) Scheme 115.¹⁵¹ This catalytic reaction developed was a new type of enantioselective propargylic substitution reaction, wherein the enamines generated *in situ* from aldehydes stereoselectively attack the ruthenium-allenylidene complexes. In the present reaction system, both the transition metal catalyst (ruthenium complex) and organocatalyst (secondary amine) activated propargylic alcohols and aldehydes, respectively, and cooperatively work to promote the enantioselective propargylic alkylation.

In the year 2012, Nishibayashi and co-workers further extended the scope of cooperative catalysis. They reported a propargylic alkylation of propargylic alcohols **209** with α,β -unsaturated aldehydes **254** in the presence of the same thiolate-bridged diruthenium complex and racemic secondary amine **247** as co-catalysts to furnish the corresponding propargylic alkylated products **256**, (Path B) Scheme 115, where the γ -

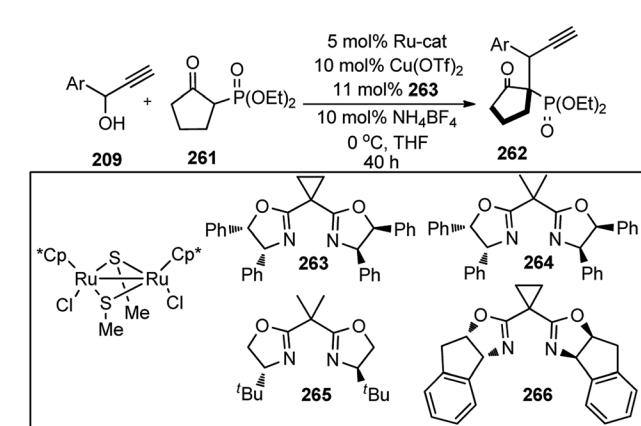
propargylation occurred selectively at α,β -unsaturated aldehydes, in moderate to high yields as a mixture of two diastereoisomers.¹⁵² The reaction system worked *via* a co-operative catalytic system where both the catalysts simultaneously worked together to promote the propargylic allylation.¹⁵²

The initial step for the reaction is the formation of the allenylidene complex. Subsequent attack of the enamine **E** generated *in situ* from aldehyde **254/255** and amine **258** resulted in the formation of the vinylidene complex followed by ligand exchange to generate the alkylate product. The key step followed by both the reactions (Path A and Path B) are shown in Fig. 18.

Combination of ruthenium and copper as catalyst leads to the propargylic alkylated products from propargylic alcohols and β -keto esters in high yields with excellent enantioselectivities.

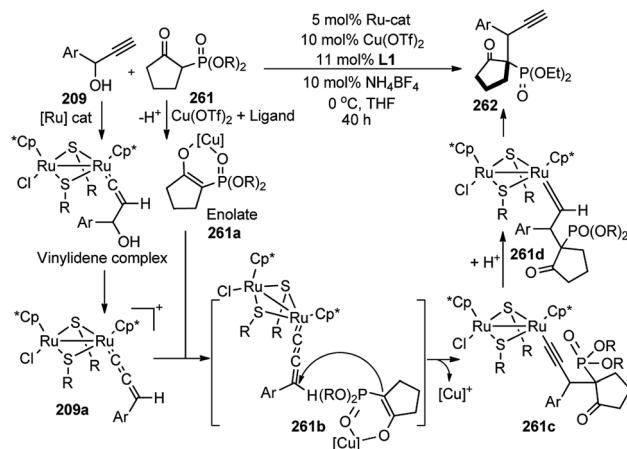
Nishibayashi and co-workers in the year 2012 developed the enantioselective propargylic alkylation of propargylic alcohols with β -keto phosphonates in the presence of a thiolate-bridged diruthenium complex and a copper complex as co-catalyst in excellent yields with high diastereo- and enantioselectivities, Scheme 116.¹⁵³

Treatment of propargyl alcohol **209** with 3 equiv. of diethyl 2-oxocyclopentylphosphonate **261** in the presence of catalytic



Scheme 116 Ruthenium and copper-catalyzed enantioselective propargylic alkylation of propargylic alcohols with β -keto phosphonates.





Scheme 117 Mechanistic pathway for the ruthenium and copper-catalyzed enantioselective propargylic alkylation of propargylic alcohols with β -keto phosphonates.

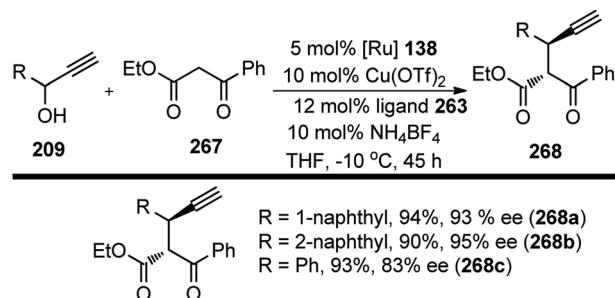
amounts of the ruthenium catalyst, $\text{Cu}(\text{OTf})_2$, (*4R,4'R,5S,5'S*)-2,2'-(cyclopropane-1,1-diyl)bis(4,5-diphenyl-4,5-dihydrooxazole) 263 and NH_4BF_4 in tetrahydrofuran (THF) at room temperature for 40 h furnished the desired product in 63% isolated yield as a mixture of two diastereoisomers (*anti/syn* = 15/1) with 89% ee of the major diastereomer. Unsatisfactory yields were received when the reaction was carried out in other solvents like dichloromethane, 1,4-dioxane, diethyl ether, and toluene. With ligands like bis(oxazoline) was used although yields were good but the diastereoselectivity as well as enantioselectivity deteriorated. Other diruthenium complexes such as the complex bearing the sterically more demanding S^iPr moiety [$\text{Cp}^*\text{RuCl}(\mu^2-\text{S}^i\text{Pr})_2$] exhibited a lower enantioselectivity. Also, the use of only ruthenium catalyst or copper complex did not promote the propargylic alkylation which indicates that both ruthenium catalyst and copper complex worked cooperatively as catalysts to promote the catalytic reaction enantioselectively.

A proposed reaction pathway is highlighted in Scheme 117. The initial step is the formation of an allenylidene complex 209a by the reaction of propargylic alcohol 209 with 261 *via* a vinylidene complex. Subsequent attack of an enolate 261a, on the γ carbon of 209a resulted in the formation of another vinylidene complex. After transformation of the vinylidene complex into the corresponding π -alkyne complex, the alkylated product 262 is formed by ligand exchange with another molecule of propargylic alcohol 209.

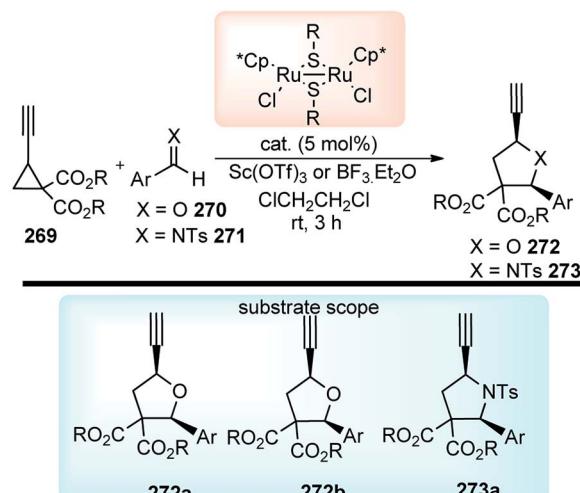
Both ruthenium complex and copper complex activate propargylic alcohols and β -keto phosphonates, respectively, and both catalysts cooperatively and simultaneously work to promote the propargylic alkylation with high stereoselectivity.

Nishibayashi and co-workers in the year 2012 developed an efficient enantioselective propargylic alkylation of propargylic alcohols 209 with β -ketoesters 267 in the presence of a thiolate-bridged diruthenium complex 138 and a copper complex as co-catalyst in high enantioselectivity, Scheme 118.¹⁵⁴

In the present reaction system, the transition metal catalysts (ruthenium and copper complexes) activate propargylic



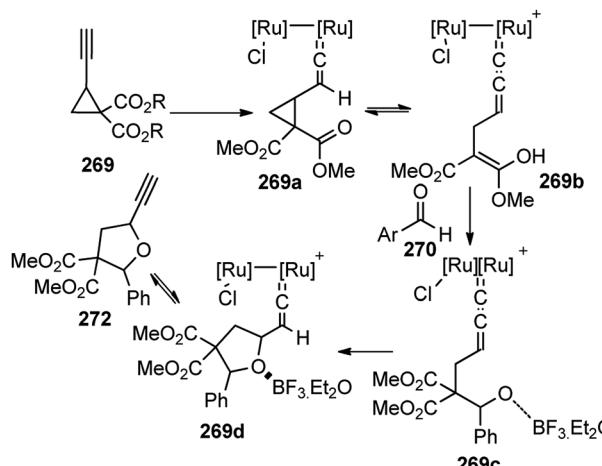
Scheme 118 Ruthenium and copper-catalyzed enantioselective propargylic alkylation of propargylic alcohols with β -ketoesters.



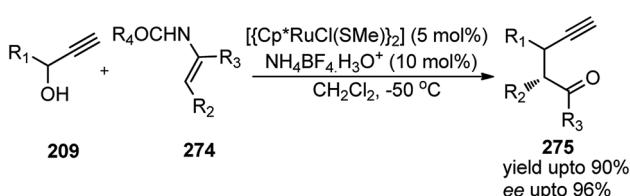
Scheme 119 Ruthenium-catalyzed [3 + 2] cycloaddition of ethynylcyclopropanes.

alcohols and β -ketoesters, respectively, thereby cooperatively promoting the propargylic alkylation enantioselectively. Treatment of 1-(1-naphthyl)-2-propyn-1-ol with three equivalents of ethyl 3-oxo-3-phenylpropanoate in the presence of catalytic amounts of thiolate-bridged diruthenium complex, $\text{Cu}(\text{OTf})_2$ with (*4R,4'R,5S,5'S*)-2,2'-(cyclopropane-1,1-diyl)bis(4,5-diphenyl-4,5-dihydrooxazole) 263, and NH_4BF_4 in THF at room temperature for 120 h gave ethyl 2-benzoyl-3-(naphthalen-1-yl)-4-pentenoate 268 in 96% isolated yield as a mixture of two diastereoisomers (*anti/syn* = 4 : 1) with 86% ee of the major diastereomer. Other bis(oxazoline) ligands were not efficient in terms of product selectivity. Use of either ruthenium catalyst or the copper complex alone did not promote the propargylic alkylation which indicated that both the catalysts acted cooperatively as catalysts to promote the catalytic reaction enantioselectively. The reaction has a wide substrate scope and a wide variety of propargylic alcohols efficiently reacted under the optimized conditions.

Nishibayashi and co-workers in the year 2013 described ruthenium-catalyzed [3 + 2] cycloaddition of ethynylcyclopropanes 269, bearing two carboxy groups at the homopropargylic position, with aldehydes 270 and aldimines 271 leading to the



Scheme 120 Mechanism for the ruthenium-catalyzed [3 + 2] cycloaddition of ethynylcyclopropanes.



Scheme 121 Highly diastereo- and enantioselective propargylic alkylation of propargylic alcohols with *E*-enecarbamates.

corresponding 2-ethynyltetrahydrofurans 272 and pyrrolidines 273 in high to excellent yields, Scheme 119.¹⁵⁵

2-Ethynyltetrahydrofurans 272 and pyrrolidines 273 were also achieved in high to excellent yields using different cocatalysts like $\text{BF}_3 \cdot \text{OEt}_2$ and $\text{Sc}(\text{OTf})_3$. But when $\text{BF}_3 \cdot \text{OEt}_2$ was used in place of $\text{Sc}(\text{OTf})_3$, the yield of pyrrolidine decreased dramatically, probably due to the difference in the coordination ability of BF_3 over $\text{Sc}(\text{OTf})_3$. A plausible reaction pathway is shown in Scheme 120.

The initial step is the formation of the ruthenium vinylidene complex 269a followed by the formation of allenylidene complex bearing an enol moiety 269b. Allenylidene complex bearing an enol moiety, on activation by $\text{BF}_3 \cdot \text{OEt}_2$, afford a new allenylidene complex 269c by the nucleophilic attack to the corresponding aldehyde followed by intramolecular cyclization to give a vinylidene complex 269d. Finally, a ligand exchange reaction furnishes the corresponding cycloaddition product 272.

Nishibayashi and co-workers in the year 2015 have reported a highly diastereo and enantioselective propargylic alkylation of propargylic alcohols 209 with *E*-ene-carbamates 274 in the presence of a catalytic amount of a thiolate-bridged diruthenium complex, bearing an optically active phosphoramido moiety, Scheme 121.¹⁵⁶

The authors have designed a hybrid catalyst consisting of a thiolate-bridged diruthenium complex tagged with (*R*)-BINOL based phosphoramido moiety with the rationale that the

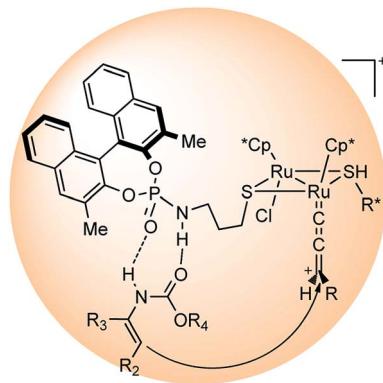
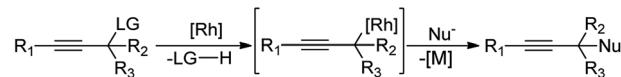


Fig. 19 Probable transition state structure for the highly diastereo and enantioselective propargylic alkylation of propargylic alcohols with *E*-ene-carbamates.



Scheme 122 General mechanistic pathway for the rhodium catalyzed propargylic substitution reaction.

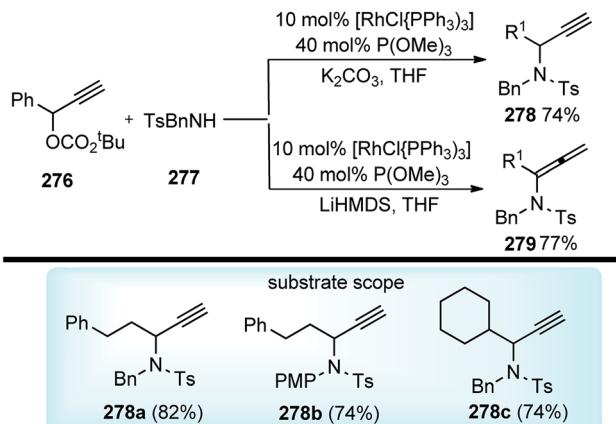
ruthenium complex will activate the allenediene intermediate and the phosphoramido will guide the ene-carbamate to control the nucleophilic attack, Fig. 19. The phosphoramido moiety (NH) was found to be essential for achieving high enantioselectivity and the introduction of two methyl groups at the 3,3'-positions of the naphthyl moiety in the chiral ligand dramatically increased the enantioselectivity of the product. However, the introduction of more bulky substituents at the 3,3' position had a negative effect on the reaction selectivity. The reaction proceeded *via* ruthenium-allenylidene complex and the probable transition state is depicted in Fig. 19.

It was also observed that phosphoramido catalyst added externally did not work as an effective organocatalyst; the intramolecular phosphoramido moiety in the ruthenium complex played an essential role in promoting the propargylic alkylation with high diastereo- and enantioselectivities.

5.11. Rhodium derived catalysts

Compared to the commonly used nickel, palladium, and platinum catalysts, rhodium presents the chemist with new and interesting catalytic possibilities.¹⁵⁷ Generally nickel, palladium, and platinum typically operate within catalytic cycles shuttling between the (0) and (II) oxidation states whereas rhodium typically shuttles between the (I) and (III) oxidation states. As a consequence, transmetalation can theoretically occur at two points in the catalytic cycle and opened up immense opportunity in catalysis.¹⁵⁸ But rhodium has rarely been utilized as a catalyst for the propargylic substitution reaction. A general mechanistic pathway followed by rhodium catalyzed propargylic substitution reaction is illustrated in Scheme 122.





Scheme 123 Rhodium-catalyzed propargylic amination of propargylic carbonates.

Rhodium-catalyzed propargylic amination of propargylic carbonates **276** with sulphonamides **277** was reported by Evans and Lawler in 2006, Scheme 123.¹⁵⁹

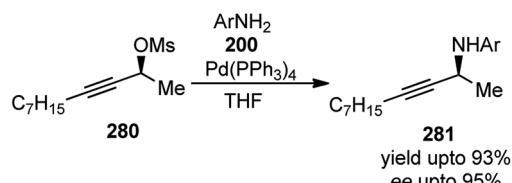
A range of alkyl-substituted propargylic carbonates reacted smoothly with sulfonamides in the presence of catalytic amounts of $[\text{RhCl}(\text{PPh}_3)_2]$ and $\text{P}(\text{OMe})_3$ to furnish the corresponding propargylated amides in good yields. The base has a pronounced effect on the regioselectivity of the reaction. When a powerful base was used, the propargylic sulphonamide **278** isomerized to the corresponding allenyl compounds **279**. Unfortunately, this rhodium-catalyzed reaction did not allow chirality transfer.

5.12. Palladium derived catalysts

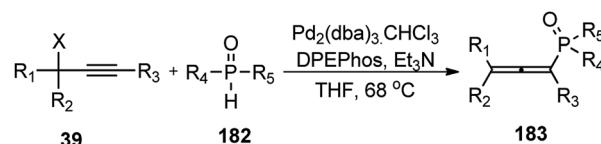
The earliest example of palladium-catalyzed propargylic substitution reaction was the hydrogenolysis of propargylic substrates with triethylammonium formate reported by Dixneuf and co-workers, in which the reduction at the propargylic position occurred in the presence of a combination of $\text{Pd}(\text{dba})$ and PnBu_3 as a catalyst.¹⁶⁰

But no systematic studies were carried out till the report by Marshall and Wolf in 1996 on the palladium-catalyzed propargylic amination which they accidentally discovered during the attempted amidocarbonylation of the racemic mesylate with diethylamine, in the presence of CO and catalytic $\text{Pd}(\text{PPh}_3)_4$, Scheme 124.¹⁶¹

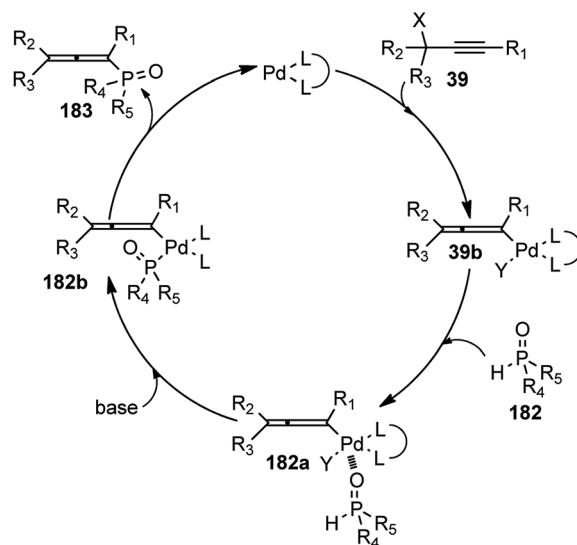
Desired propargylated amines were obtained in higher ratio when the more nucleophilic amines were used and *vice versa*. In



Scheme 124 Palladium catalyzed enantioselective propargylic amination reaction.



Scheme 125 Palladium-catalyzed synthesis of allenylphosphonates from propargylic derivatives.



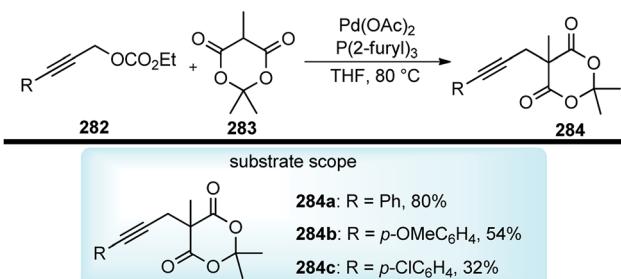
Scheme 126 Catalytic cycle for the palladium-catalyzed synthesis of allenyl phosphonates from propargylic derivatives.

the absence of CO , amines were obtained from the nonracemic propargyl mesylate **275** as the sole products of high enantioselectivity. Treatment of propargyl mesylate with aniline in the absence of Pd-catalyst afforded the propargylamine of opposite configuration to that of amine which provided a direct evidence that the $\text{Pd}(0)$ -catalyzed aminations proceed with retention of configuration.

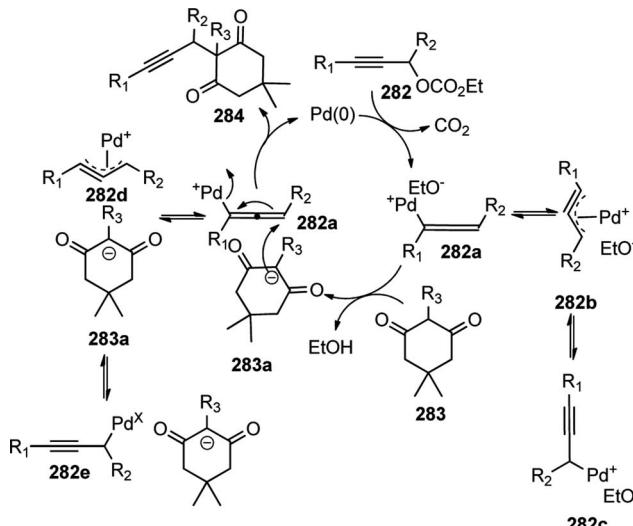
A novel approach for the synthesis of allenylphosphonates **183** and related compounds from the reaction between propargylic derivatives **39** with H-phosphonate **182**, H-phosphonothioate, H-phosphonoselenoate, and H-phosphinate esters utilizing palladium(0) as catalyst catalyzed was reported by Stawinski and co-workers in the year 2010, Scheme 125.^{162,163}

Ligand screening revealed that bidentate ligands like DPEPhos with large bite angles were able to promote the conversion into the allenylphosphonate. Several catalytic systems were evaluated, and the most efficient combination was found to consist of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ as a palladium source and bis(2-diphenylphosphino)diphenyl ether (DPEPhos) as a supporting ligand. A mechanistic pathway for the Pd-catalyzed synthesis of allenylphosphonates from propargyl alcohol is illustrated in Scheme 126.

Iazzetti and co-workers in 2015 designed a palladium-catalyzed reaction of propargylic carbonates **282** with Meldrum's acid derivatives **283** to give the substitution products **284** in very good yield and high regioselectivity, Scheme 127.¹⁶⁴



Scheme 127 Palladium-catalyzed reaction of propargylic carbonates with Meldrum's acid derivatives.



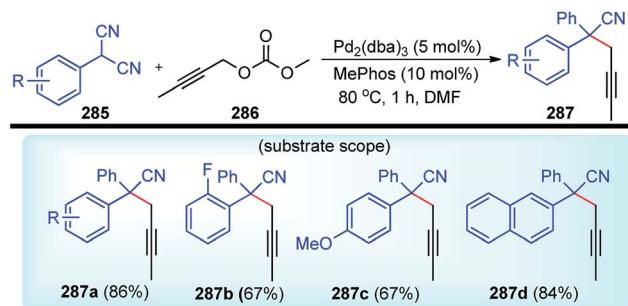
Scheme 128 Mechanistic pathway for the palladium-catalyzed reaction of propargylic carbonates with Meldrum's acid derivatives.

The reaction of propargylic carbonates with Meldrum's acid derivatives proceeded smoothly in the presence of $\text{Pd}(\text{OAc})_2$ and $\text{P}(2\text{-furyl})_3$ in THF at $80\text{ }^\circ\text{C}$ to offer the propargyl substitution products in good yields.

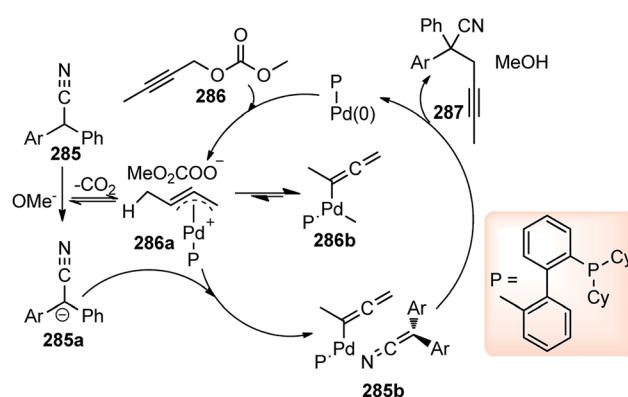
Among the several other palladium catalysts screened, $\text{Pd}(\text{OAc})_2$ appeared to be the best in terms of reaction yield. The methodology has wide functional group tolerance and tolerates a variety of functional groups like ester, keto, ether, amido, and chloro substituents. The reaction is highly dependent on the nature of the phosphine ligand as well as the basicity/polarizability of the anion derived from the 1,3-dicarbonyl compound. The reaction mechanism is outlined in Scheme 128.

Lattenzi's report in 2015 about the propargylic alkylation using propargylic carbonates was limited to highly stabilized Meldrum's acid-like nucleophiles. Tunge and co-workers in the year 2016 reported a regioselective substitution of diaryl acetonitrile pronucleophiles **285** to propargylic carbonates **286** in good yields, Scheme 129.¹⁶⁵

The method described by the authors has expanded the scope of palladium-catalyzed propargylation to weakly acidic α,α -diarylacetonitrile motifs that resulted into the functionalized quaternary diarylmethane products. The reaction course is controlled by



Scheme 129 Palladium catalyzed regioselective substitution of diaryl acetonitrile to propargylic carbonates.



Scheme 130 Mechanistic pathway for the palladium-catalyzed regioselective substitution of diaryl acetonitrile to propargylic carbonates.

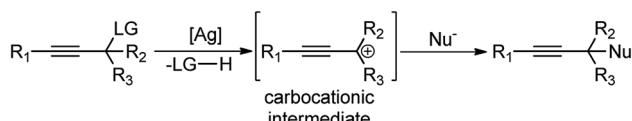
the nature of the ligand. With bidentate ligand like dppe, substitution of methyl propargyl carbonate with α,α -diarylacetonitrile resulted in 1,3-dienyl products whereas using a monodentate ligand like MePhos leads to the formation of propargyl isomer under identical reaction conditions. Regioselective nucleophilic substitution occurs *via* the inner sphere and outer sphere mechanism that is controlled by the denticity of the ligand. Bidentate ligands blocked the coordination of the nitrile nucleophile, favoring outer-sphere mechanism, leading to dienylation. Whereas, a monodentate ligand allowed coordination of the nucleophile to palladium, resulting in propargylation through an inner sphere nucleophilic attack as illustrated in Scheme 130.

5.13. Silver derived catalysts

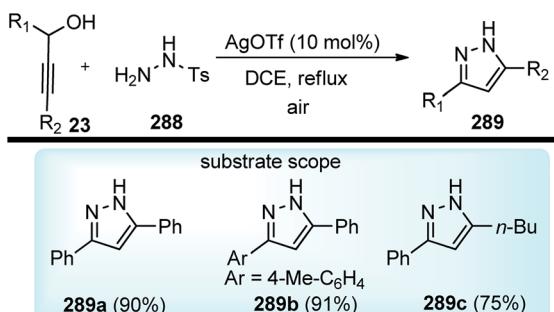
Silver(i) salts have been used in several organic transformations. The high oxidation potentials associated with Ag⁺ ions allowed silver catalysis, complexes, and ligands to enjoy significant importance in chemical synthesis. The mechanistic pathway for the silver catalyzed propargylic substitution reaction is illustrated in Scheme 131 where the silver salt polarizes the hydroxy group sufficiently to generate the propargylic carbocation intermediate, which was subsequently attacked by the approaching nucleophile.

A AgOTf catalyzed cascade and chemoselective approach towards the synthesis of 3,5/1,3-disubstituted pyrazoles **289**





Scheme 131 General mechanism for the silver catalyzed propargylic substitution reaction.



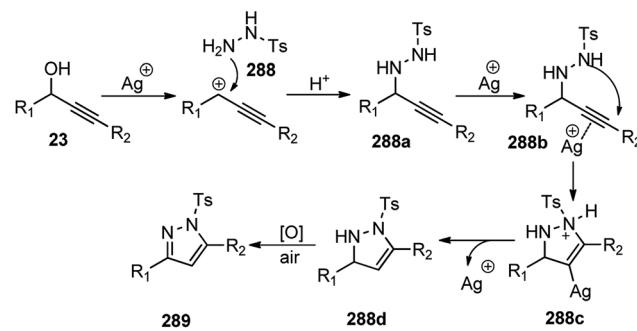
Scheme 132 AgOTf-catalyzed chemoselective approach to 3,5/1,3-disubstituted pyrazoles from propargylic alcohols.

from propargylic alcohols **23** and *para*-tolylsulfonylhydrazide **288** was reported by Zhan and co-workers in the year 2013, Scheme 132.¹⁶⁶

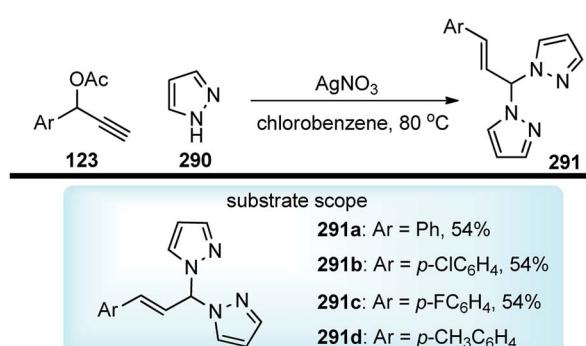
Several other catalysts like FeCl_3 , AgOTf , AgBF_4 , InCl_3 , $\text{In}(\text{OTf})_3$, $\text{Zn}(\text{OTf})_2$, $\text{Cu}(\text{OTf})_2$, BiCl_3 were also tested for this reaction but the best result in terms of yield was achieved with AgOTf . Solvent study evaluation revealed that the reaction, when performed in 1,2-dichloroethane at reflux, afforded the product in highest yield. With other silver catalysts like AgOAc and AgBF_4 , reaction yield decreased significantly clearly indicating the role of counter anion to facilitate this cascade reaction. Even no desired product was observed when the reaction was carried out under a Brønsted acid condition which clearly ruled out the effect of “hidden of Brønsted acid” as proposed by several other research groups.¹⁶⁷ It was further observed that other substituted hydrazines under standard conditions did not furnish the products due to the suppression of the catalytic activity of the AgOTf by the stronger alkalinity of those substituted hydrazines. Electron-donating functional groups were found to enhance the reaction rate and furnished products in good yields whereas electron-withdrawing substituents slowed down the transformation.

A plausible mechanistic pathway is illustrated in Scheme 133 involved the formation of propargylic cation intermediate under the influence of silver catalyst followed by the regioselective attack of the terminal nitrogen atom, resulting in the substituted product **288a**. Then, a series of reactions involving 5-*endo*-dig cyclization, proton exchange, and aromatization finally leads to the desired product **289**, Scheme 133.

Sahoo and co-workers in the year 2013 reported a silver(I) catalyzed propargylation of pyrazole **290** with propargyl acetates **123** towards the synthesis of (*E*)-allyl-*gem*-dipyrazoles **291**, Scheme 134.¹⁶⁸



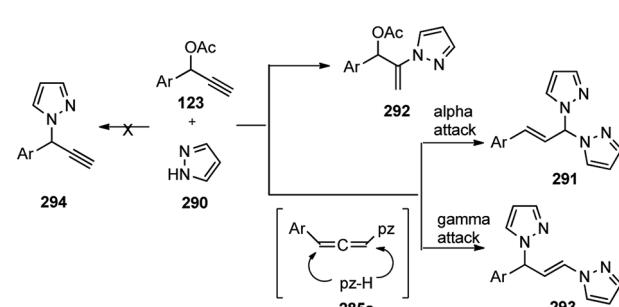
Scheme 133 Mechanism for the AgOTf -catalyzed synthesis of 3,5/1,3-disubstituted pyrazoles from propargylic alcohols.



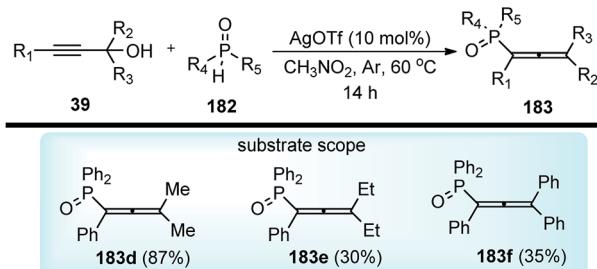
Scheme 134 Silver(I) catalyzed propargylation of pyrazole with propargyl acetates.

Several catalysts were tested in different solvents like chlorobenzene, THF, CH_3CN , DMF, DCE. Incomplete consumption of the starting material, complex reaction mixture and poor overall yield of the products were noticed when $\text{Cu}(\text{OTf})_2$, $\text{In}(\text{OTf})_3$, and $\text{CuNO}_3 \cdot \text{H}_2\text{O}$, AuCl_3 , AgNO_3 , AgCl , Ag_2CO_3 , AgNO_3 , AgBF_4 were independently employed. AgNO_3 was found to be the most effective among the various Ag-salts examined. Surprisingly, the reaction was incomplete in polar aprotic solvents like THF, CH_3CN , and DMF. The product yield in DCE was poor. The probable mechanism for the propargylation reaction is shown below, Scheme 135.

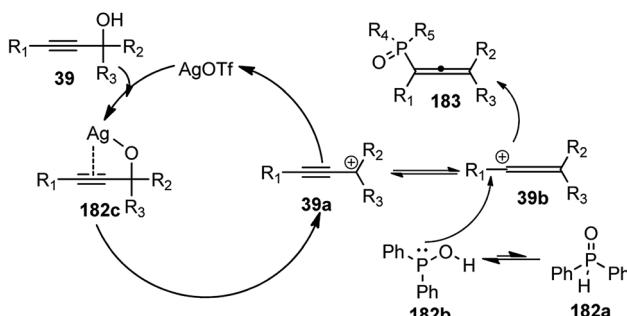
The above methodology provided a quick access to a wide array of (*E*)-allyl-*gem*-dipyrazoles (**ADPs**) derivatives **291**, whose



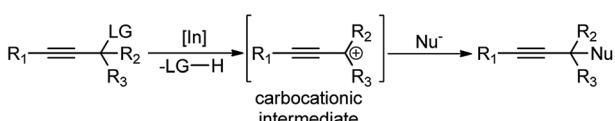
Scheme 135 Probable mechanistic pathway for the silver(I) catalyzed propargylation of pyrazole with propargyl acetates.



Scheme 136 Silver catalyzed synthesis of synthesis of allenylphosphoryl compounds from propargylic alcohol.



Scheme 137 Silver catalyzed synthesis of allenyl-phosphoryl compounds from propargylic alcohol.



Scheme 138 General mechanism for the indium catalyzed propargylic substitution reaction.

two adjacent N atoms offered a strong chelating ability to the metal. Their capability to act as the bidentate ligand was nicely demonstrated in the well-known Suzuki–Miyaura biaryl cross-

coupling reaction. Both the electron-rich, electron poor as well as sterically hindered, and heteroaryl iodides were effectively coupled with $\text{PhB}(\text{OH})_2$ under the influence of 0.1 mol% of catalyst in aqueous K_2CO_3 at 80 °C.

Yang and co-workers in the year 2013 reported a silver-catalyzed direct phosphorylation of propargyl alcohols 39 with readily available and stable $\text{P}(\text{O})\text{H}$ compounds 182 in an efficient manner, Scheme 136.¹⁶⁹

The desired product was obtained in a moderately low yield in the presence of 10 mol% of AgOTf as a catalyst in DCE at 60 °C for 14 h under an argon atmosphere. Product yield did not improve when other catalysts like $\text{Cu}(\text{OTf})_2$, LiOTf , CuOTf , $\text{Sm}(\text{OTf})_3$, AgNTf_2 , $\text{Cu}(\text{ClO}_4)_2$ and $\text{Ni}(\text{OAc})_2$ were used. Subsequently, the effect of different solvents such as CH_3NO_2 , MeCN, and THF was tested and it was found that CH_3NO_2 was the optimal solvent and could enhance the yield up to 47%.

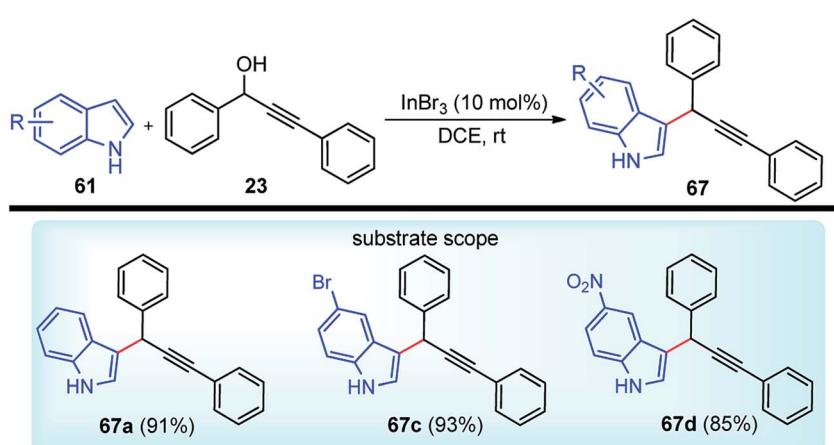
A proposed reaction mechanism is shown in Scheme 137. The OH is polarized by the coordination of the AgOTf with the alkyne resulting in the formation of propargylic carbocation intermediate which is resonance stabilized to the allenylidene intermediate 39b. Consequent attack by the nucleophile furnishes the product 183 with the concomitant loss of H^+ .

5.14. Indium derived catalysts

Recently, indium(III) salts have received a great deal of attention due to its water-tolerant green Lewis acid for performing chemo and regioselective organic transformations.¹⁷⁰ Compared to conventional Lewis acids, it has the advantages of water stability, recyclability, operational simplicity and strong functional group tolerance. In general, indium catalyzed propargylic substitution reaction using indium catalyst proceeds *via* propargylic carbocation intermediate formed by the loss of water, Scheme 138.

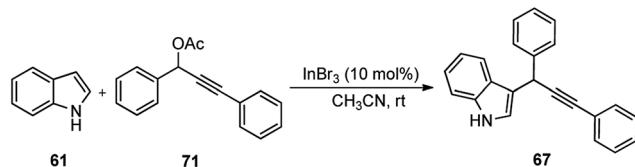
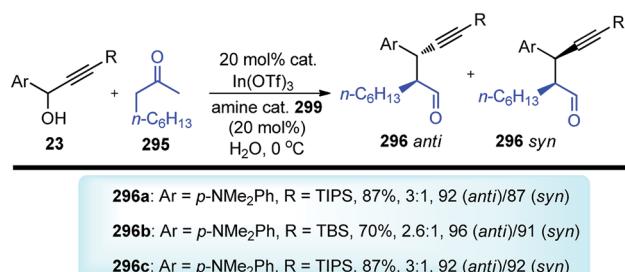
Yadav and co-workers in the year 2007 described propargylation of heteroaromatic systems 61 in high yields and high selectivity by propargylic alcohols 23 within a short reaction time using indium(III) bromide as a catalyst, Scheme 139.¹⁷¹

The reaction proceeded under the influence of the catalytic amount of InBr_3 and a wide range of heteroaromatic



Scheme 139 InBr_3 catalyzed C3-propargylation of indoles.



Scheme 140 InBr_3 catalyzed C3-propargylation of indoles.Scheme 141 $\text{In}(\text{OTf})_3$ catalyzed the stereoselective addition of aldehydes to propargylic alcohols.

compounds such as indole, carbazole, pyrrole, and furan underwent facile reaction under mild reaction conditions. No product was obtained in the absence of indium(III) bromide. This methodology has a wide substrate scope and tolerates functional groups like alkenyl, alkynyl, halo, nitro, cyano, and free amino groups as well as acid sensitive substrates like pyrrole and furan.

In the same year 2007, Chen and co-workers, demonstrated a similar propargylic substitution reaction of propargylic acetates **71** with indoles **61** utilizing InCl_3 as the catalyst, Scheme 140.¹⁷²

Catalyst screening revealed that indium(III) chloride was the most efficient Lewis acid catalyst for the reaction. The methodology has a wide substrate scope and tolerates both electrons rich and electron-poor substrates.

Recently, the concept of combining organocatalysis with transition metal complexes has led to exciting strategies for the development of dual catalysis for several innovative transformations.^{173–175} Nishibayashi in the recent past has described highly enantioselective propargylation of aldehydes by combining the Hayashi–Jørgensen organocatalyst with a ruthenium complex.¹⁵³ The possibility to induce the formation of carbenium ion in the presence of water by merging an organocatalytic process with a Lewis acid was believed to open several new opportunities in the field of organocatalysis.

Cozzi and co-workers in the year 2011 described the first catalytic stereoselective addition of aldehydes **295** to propargylic alcohols **23**, promoted by a combination of an organocatalyst and indium triflate, Scheme 141.¹⁷⁶

Indium(III)triflate is known to generate less stabilized carbocations from secondary alcohols and are not deactivated by aldehydes, secondary amines or water. Therefore, the authors have selected alcohol as model substrates and performed the reaction in the presence of different MacMillan catalysts **297–301**, Fig. 20.

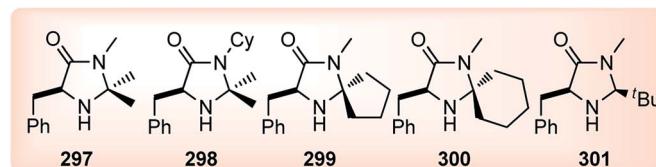


Fig. 20 Different organocatalysts screened.

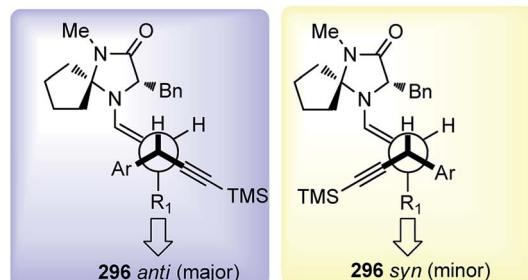
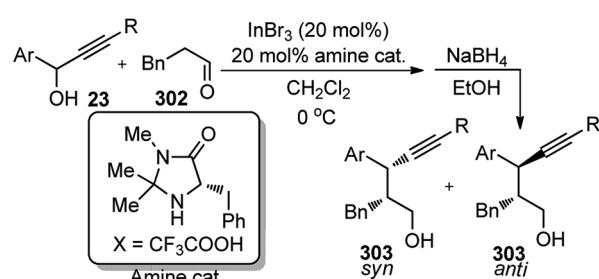


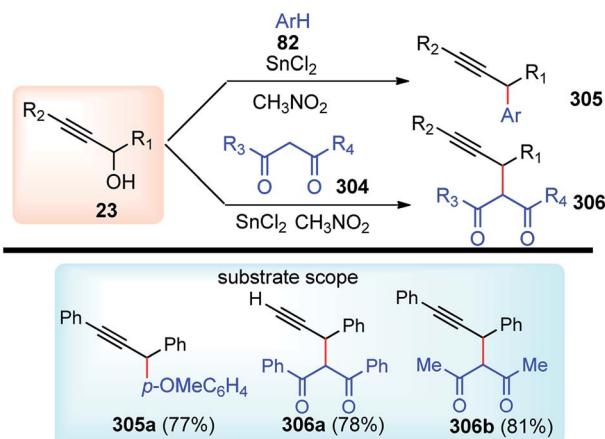
Fig. 21 Probable transition state for the stereoselective addition of aldehydes to propargylic alcohols.

Propargylic alcohol which can form a stabilized carbocation did not furnish any product in the absence of indium salts. Quite remarkably, the reaction tolerated a wide range of functional groups including thio, amides, silyl ether, and even acetals in the alkyne moiety. The probable mechanistic pathway along with the transition state for this dual catalytic enantioselective propargylic substitution reaction is shown in Fig. 21.

Nishibayashi and co-workers in the year 2011 developed the enantioselective propargylic alkylation of propargylic alcohols bearing an internal alkyne moiety with aldehydes in the presence of InBr_3 and an optically active secondary amine in excellent yields and high enantioselectivity (up to 98% ee), Scheme 142.¹⁷⁷

This catalytic reaction provided a new type of enantioselective propargylic substitution reaction, where the enamines generated *in situ* from the aldehydes enantioselectively attacked the propargylic cations as reactive intermediates. In the present reaction system, both the Lewis acid catalyst (InBr_3 or FeCl_3) and the organocatalyst (secondary amine) activate the

303a: Ar = 4-MeOC₆H₄, R = Ph, 89%, 1.1:1, 94%:88% ee (*syn:anti*)
 303b: Ar = 4-Me₂NC₆H₄, R = Ph, 92%, 1:1.6, 95%:96% ee (*syn:anti*)Scheme 142 Enantioselective propargylic alkylation of propargylic alcohols with aldehydes in the presence of InBr_3 and an optically active secondary amine.



Scheme 143 Tin(II) chloride as an efficient catalyst for the propargylic substitution of secondary propargylic alcohols.

propargylic alcohols **23** and aldehydes **302**, respectively, and both catalysts cooperatively and simultaneously work to promote the propargylic alkylation enantioselectively.

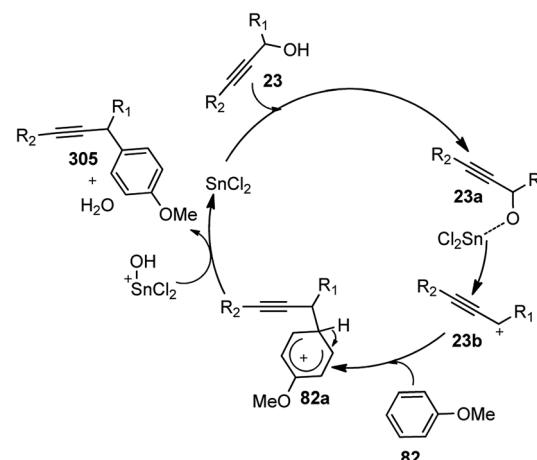
Similar product yield was also achieved when InCl_3 was used as the Lewis acid. The catalytic reaction did not proceed smoothly in the presence of a catalytic amount of BiCl_3 as well as TsOH did not work at all as a catalyst for the cooperative catalytic reaction. A longer reaction time was necessary when the amounts of InBr_3 (10 mol%) and secondary amine catalyst (10 mol%) were decreased under the same reaction conditions. It was also observed that the use of only InBr_3 or the secondary amine catalyst did not promote the propargylic alkylation. The reaction has a wide substrate scope and furnished products with various substituents in good yields and enantioselectivities.

5.15. Stannous derived catalysts

Stannous chloride is known to be an inexpensive mild Lewis acid has been used in various organic synthetic operations and has recently expanded the scope of its applications in organic synthesis.¹⁷⁸

Masuyama's group in 2013 demonstrated the use of weak Lewis acid, tin(II) chloride as an efficient catalyst for the propargylic substitution of secondary propargylic alcohols **23** with different carbon nucleophiles **82/304**, Scheme 143.¹⁷⁹

Different electron-rich arenes, heteroarenes, 1,3-dicarbonyl compounds and nitrogen nucleophiles, like sulfonamides, carbamates, and carboxamides easily underwent propargylic substitution reaction at 40–80 °C in CH_3NO_2 solvent under air in presence of catalytic amount of SnCl_2 . The authors optimized the reaction condition by screening several other Lewis acid catalysts like tin(II) bromide, tin(II) iodide, tin(II) fluoride in different solvents like 1,2-dichloroethane, toluene, acetonitrile, THF, and DMF. Nitromethane was found superior to other solvents such as 1,2-dichloroethane, toluene, and acetonitrile. No reaction was observed either in THF or DMF and even in the absence of a catalyst. Tin(II) chloride exhibited a higher catalytic activity in CH_3NO_2 than other tin halides like tin(II) bromide or



Scheme 144 Mechanistic pathway for the SnCl_2 catalyzed propargylic substitution of propargylic alcohols.



Scheme 145 Synthesis of 1,5-ene-yne using catalytic amounts of SnCl_4 and ZnCl_2 .

tin(II) iodide. With tin(II) fluoride no propargylic substitution reaction occurred because of the extremely low solubility of tin(II) fluoride in CH_3NO_2 . The temperature did have a positive impact on the rate of the reaction but furnishes products with lower yield due to by-product formation. A probable mechanism for the tin(II) chloride catalyzed propargylic substitution is described in Scheme 144.

Another example of Sn-catalyzed propargylic substitution for the synthesis of 1,5-ene-yne derivative was disclosed by Mukaiyama and co-workers in the year 1987, Scheme 138. When propargylic ether was treated with allyltrimethylsilane **118** in the presence of catalytic amounts of SnCl_4 and ZnCl_2 , 1,5-ene-yne derivative **287** was obtained in a reasonably good yield, Scheme 145.¹⁸⁰

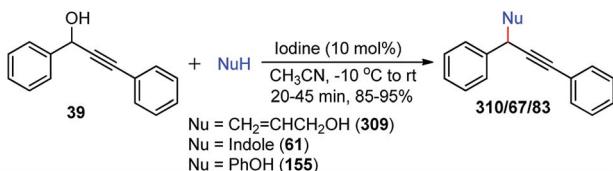
5.16. Iodine derived catalysts

Recently, molecular iodine has gained a huge interest in organic synthesis because of its low cost and ready availability. The mild Lewis acidity associated with iodine has enhanced its use in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts which are able to activate the hydroxyl group.¹⁸¹

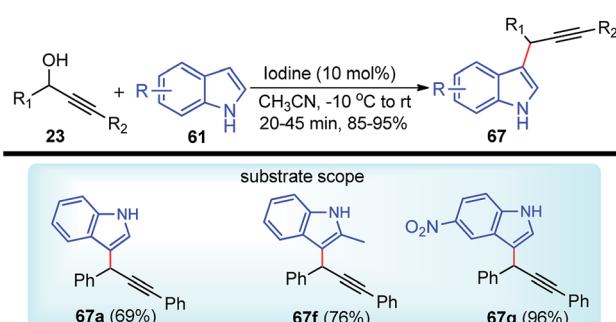
Srihari and co-workers in 2007 demonstrated the role of elemental iodine as a catalyst in mediating the nucleophilic propargylic substitution reactions, Scheme 146.¹⁸²

The reaction was screened with varied concentrations of iodine and it was observed that the reaction progressed well





Scheme 146 Iodine mediated propargylic substitution reaction.



Scheme 147 Iodine mediated propargylic substitution reaction.

with even 1 mol% of the catalyst. But the highest yield was achieved with 5% iodine. The reaction proceeds *via* direct displacement of the hydroxy group with nucleophiles. Substrates with electron donating groups on the aromatic ring underwent the reaction much faster than unsubstituted aryl propargylmethanols.

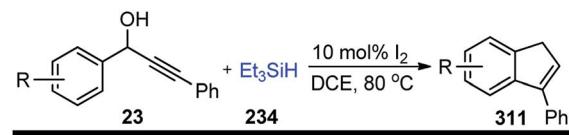
Chen and co-workers in the year 2007 reported a similar type of iodine catalyzed efficient propargylation of indoles **61** under a mild condition in high regioselectivity and excellent yields, Scheme 147.¹⁸³

Operational simplicity, excellent yields, and chemoselectivity are major advantages of this protocol compared to other catalyzed propargylic substitution reactions reported in the literature.

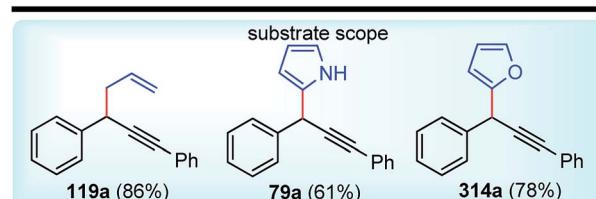
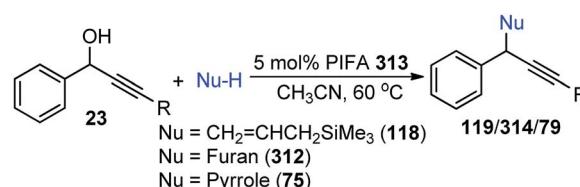
Subba Reddy and co-workers in the year 2010 developed a novel and efficient catalytic process for the synthesis of substituted indenes **311** from aryl-substituted propargylic alcohols **23** by means of a series of cascade reactions involving tandem isomerization of the propargylic cations, reduction followed by intramolecular Friedel-Crafts type cyclization, Scheme 148.¹⁸⁴

The catalytic efficiency of various Lewis acids such as BiCl_3 , ZnCl_2 , and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ was tested and none of them were found efficient. Among the several solvents screened, dichloroethane appeared to give the best results.

Hypervalent iodine acting as Lewis acid catalyst in the absence of an extra oxidant or other acidic activator have been developed and received much attention in recent years.¹⁸⁵ PIFA



Scheme 148 Iodine mediated propargylic substitution reaction.

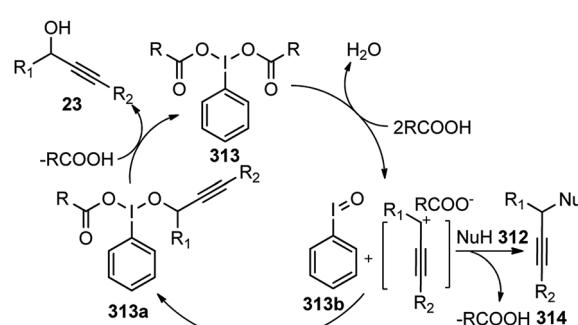


Scheme 149 PIFA catalyzed propargylic substitution reaction.

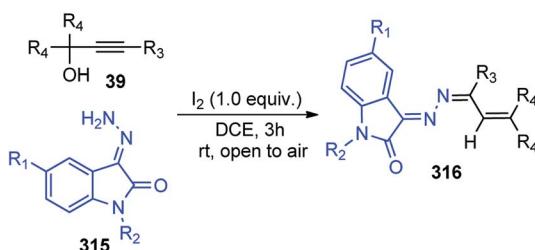
is known to behave as a Lewis acid and its utility towards the propargylic substitution reactions in absence of any acid activator or oxidants has been nicely demonstrated by Weng and co-workers.¹⁸⁶

Weng and co-workers in the year 2015 reported $\text{PhI}(\text{OCOCF}_3)_2$ as an efficient catalyst for the reaction of propargyl alcohols **23** with allyl trimethylsilane **118** and several electron-rich arenes **75/312** in very good yield, Scheme 149.¹⁸⁶

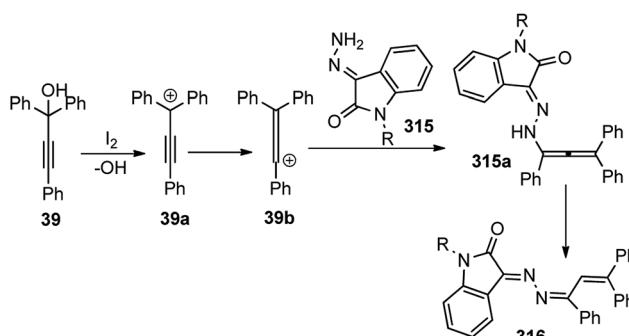
The methodology is highly substrate dependent and electron donating substrates furnished products in higher yield compared to electron withdrawing substrates. Even, trimethylsilyl substituted and terminal propargyl alcohols were also



Scheme 150 Mechanism for the hypervalent iodine mediated propargylic substitution reaction.



Scheme 151 Iodine mediated reaction of propargyl alcohols and isatin hydrazones for the synthesis of azines.



Scheme 152 Mechanism for the iodine mediated synthesis of azines from propargyl alcohols and isatin hydrazones.

well tolerated although with longer reaction time and reduced yields. Sterically hindered substrates were also found to reduce the reaction rate. The mechanism for the reaction is demonstrated in Scheme 150.

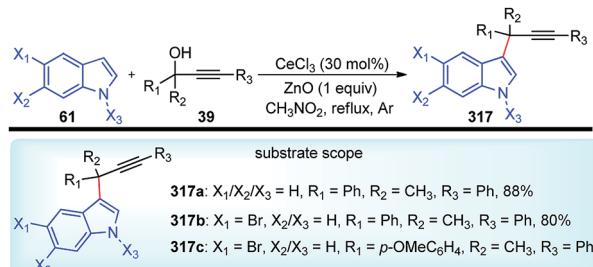
Muthusamy and co-workers in the year 2016 reported a iodine mediated reaction of propargyl alcohols **39** and isatin hydrazones **315** under open air condition to synthesize highly substituted as well as conjugated unsymmetrical azines **316** in good yield, Scheme 151.¹⁸⁷

Several other Lewis acids like $\text{BF}_3 \cdot \text{OEt}_2$, $\text{Yb}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, FeCl_3 and InCl_3 , were found inefficient in catalyzing the reaction. Surprisingly, only DCE was found to be the suitable solvent, among several other solvents screened, for this reaction. A mechanistic detail of the formation of unsymmetrical azines is shown in Scheme 152.

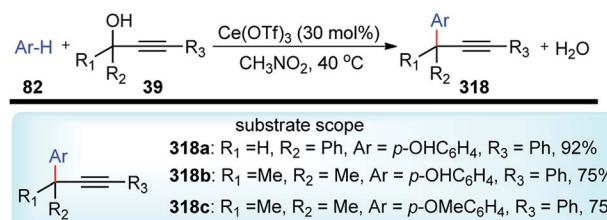
Under the influence of iodine, the propargylic alcohol is converted to the allene carbocation intermediate **39b** which is subsequently trapped by isatinhydrazones followed by a [1,3]-shift of the N-group through aza-Meyer-Schuster rearrangement resulting into an allene intermediate **315a**. Isomerization of the allene intermediate **315a** furnished the unsymmetrical azines **316**.

5.17. Cerium derived catalysts

Lanthanide salts are often employed as catalysts in organic synthesis, mainly due to their low toxicity, affordability, stability, and ease of handling. Cerium(III) chloride has emerged as a very useful Lewis acid imparting high regio- and



Scheme 153 CeCl_3 catalyzed propargylic substitution reaction.



Scheme 154 $\text{Ce}(\text{OTf})_3$ catalyzed propargylic substitution reaction.

chemoselectivity in various chemical transformations over the past few years. It is an inexpensive, nontoxic and water-tolerant catalyst and has been used in several different forms, alone as heptahydrate, anhydrous, and in combination with NaI . The salt has also been used in solid supports which modify their reactivity. Even organocerium compounds also found extensive applications in organic synthesis.¹⁸⁸

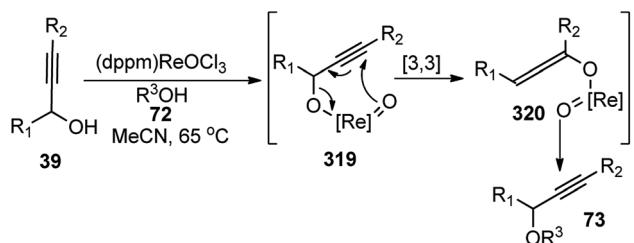
Silveira and co-workers in the year 2010 employed anhydrous CeCl_3 as a catalyst for the propargylation of indoles **61** in good yield and high regioselectivity Scheme 153.¹⁸⁹

The authors found that stirring propargylic alcohols and indole with 30 mol% of CeCl_3 in CH_3NO_2 under reflux condition furnished 3-propargyl indole in 60% yield. Other solvents such as glycerine, DMA, $^i\text{PrOH}$ were also employed but the best yield was achieved with MeNO_2 . The use of larger amounts of CeCl_3 neither improved the reaction yield nor reduced the reaction time. However, when 0.1 equiv. of anhydrous CeCl_3 was used, product yield reduced to 25%. Replacing anhydrous CeCl_3 with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, gave no desired product. The reported method was simple, general and the products were obtained in good yields.

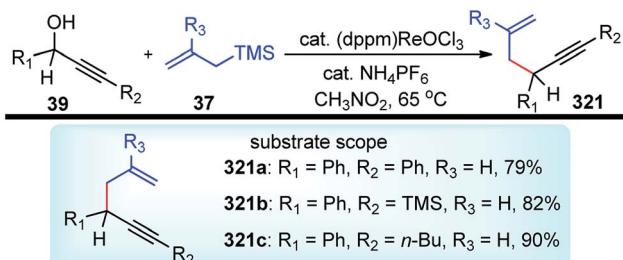
Silveira and co-workers in the year 2012 demonstrated that $\text{Ce}(\text{OTf})_3$ could be successfully employed as a catalyst for the propargylation of aromatic compounds **82**, Scheme 154.¹⁹⁰

The effect of solvent, the amount of catalyst, and reaction temperature were thoroughly screened, and the best condition was established with 30 mol% of $\text{Ce}(\text{OTf})_3$ in nitromethane at 40 °C. Other solvents like CH_3CN , MeNO_2 , glycerol, DMA, and 2-propanol were found inefficient in furnishing products in good yield. When the reaction was carried out at 80 °C, a decrease in selectivity was observed. The protocol demonstrated the application of CeCl_3 a useful alternative to triflic acid and other usual catalysts for the propargylation reaction.





Scheme 155 Mechanism for the Re-catalyzed etherification of propargylic alcohols.



Scheme 156 Re-catalyzed propargylic substitution with allyl trimethylsilane.

5.18. Rhenium catalyzed reactions

Rhenium(v) is known to form a variety of stable octahedral complexes with multiple bonds to oxygen.¹⁹¹

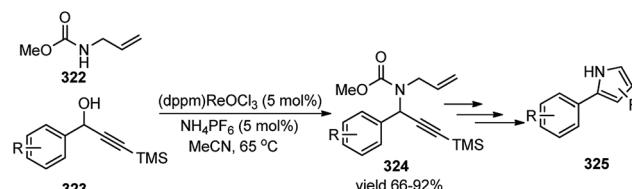
Re-catalyzed methodologies remained mostly overlooked as a tool for organic transformations. Recently, high oxidation-state Re complexes have been employed in a variety of organic transformations. 2Re-oxo complexes offer several advantages in metal-mediated catalysis, because of the (1) high stability against moisture due to the high oxidation state of the metal and (2) mild conditions which allow for the activation of sensitive substrates.

Toste and co-workers in the year 2003 have reported the formation of propargylic ethers 73 by the coupling of simple alcohols 72 and propargyl alcohols 39 using a robust air- and moisture-tolerant rhenium(v)-oxo complex, Scheme 155.¹⁹²

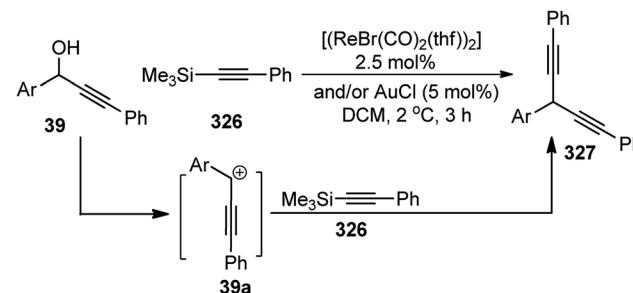
Following their discovery, the same group in 2003 described the application of that catalyst system to the formation of C–C bonds by the coupling of allylsilanes 37 and propargyl alcohols 39, Scheme 156.¹⁹³

The reaction was even carried out with lower catalyst loadings without any significant deterioration in yield by increasing the reaction temperature to 80 °C. The reaction tolerated a wide range of electron donating and electron withdrawing substrates. The catalyst being both air and moisture stable was easily recovered and reused several times which exemplifies its obvious advantages in organic transformations.

Toste and co-workers in the year 2005 reported the use of air and moisture-tolerant rhenium-oxo complex for the regioselective synthesis of propargylamine derivatives 324 from propargyl alcohols 323 and carbamates 322, Scheme 157.¹⁹⁴



Scheme 157 Rhenium catalyzed propargylic substitution reaction.

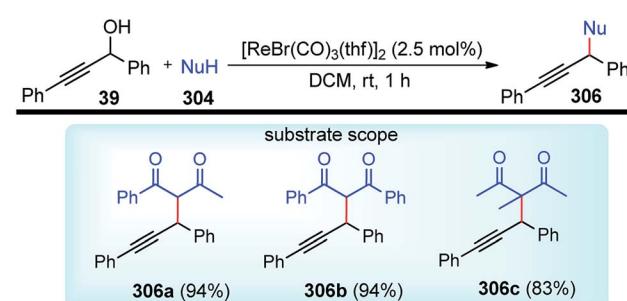


Scheme 158 Rhenium-and gold-catalyzed synthesis of diethynylmethanes by reactions of propargylic alcohols with trimethyl(phenylethynyl)silane.

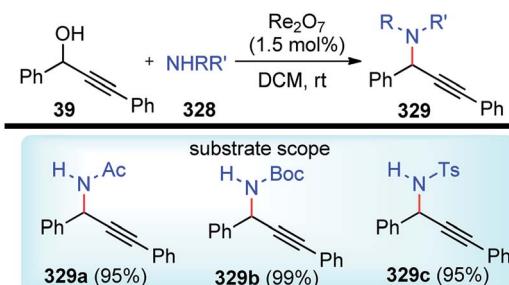
The reaction has a wide substrate scope and interestingly, both sterically hindered *ortho*-disubstituted and heteroaromatic substrates furnished products in good yield. The substrate scope, mild reaction conditions, and operational simplicity have made it a valuable method for construction of C–N bonds.

Recently, dual catalysis has received considerable attention because they lead to products that cannot be synthesized with a single catalyst in one-pot. Takai and co-workers in 2007 report rhenium-and gold-catalyzed synthesis of diethynylmethanes 327 by reactions of propargylic alcohols 39 with trimethyl(phenylethynyl)silane 326, Scheme 158.¹⁹⁵

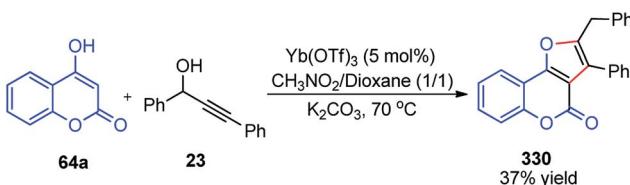
The authors have demonstrated the rhenium-catalyzed transformations of propargyl and benzyl alcohols using organosilanes, as well as the rhenium- and gold-catalyzed synthesis of diethynylmethanes. This reaction proceeded *via* propargylic carbocation as a reactive intermediate. A combination of the rhenium and gold complexes promoted the first ethynylation step, and the rhenium complex accelerated the second ethynylation ultimately producing the desired product.



Scheme 159 Rhenium catalyzed propargylic substitution reaction.



Scheme 160 Synthesis of various π -activated amines from propargylic alcohols.



Scheme 161 $\text{Yb}(\text{OTf})_3$ catalyzed propargylic substitution of 1,3-dicarbonyls and 4-hydroxycoumarin.

Kuninobu and co-workers in the year 2008, described rhodium-catalyzed coupling reactions between 2-propynyl alcohols **39** and several 1,3-diketone nucleophiles **304** to construct C–C bond efficiently, Scheme 159.¹⁹⁶

The dehydrative coupling reactions between 2-propynylalcohol and several carbon and heteroatom nucleophiles furnished substituted propargylic derivatives **306** efficiently. The reaction mechanism proceeds *via* the formation of a 2-propynyl cation *via* dihydroxylation followed by a nucleophilic attack on the propargyl cation and finally deprotonation to produce the desired product **285**.

Ghorai and co-workers in the year 2012 described the direct catalytic amination of π -activated alcohols **39**, producing water as the only by-product using Re_2O_7 as a catalyst, Scheme 160.¹⁹⁷

Propargylic substituted products **329** were observed with high regioselectivity. Optically active propargylic alcohol with 50% ee, when reacted under this reaction condition, resulted in

racemic product formation suggesting that the substitution probably proceeded through an $\text{S}_{\text{N}}1$ -like mechanism.

5.19. Ytterbium derived catalysts

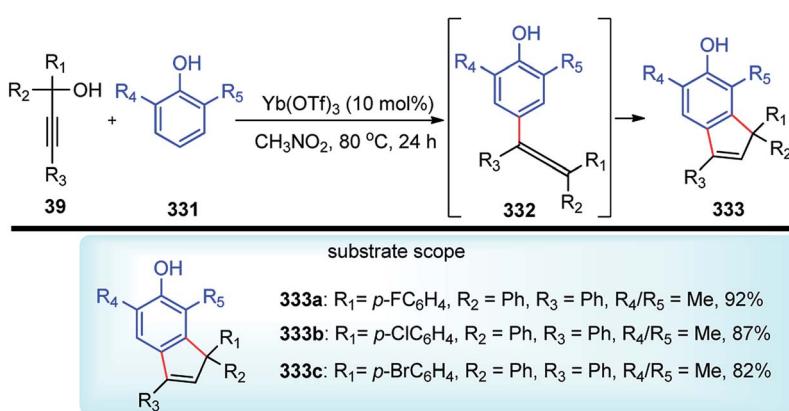
Ytterbium belongs to a low cost and commercially available metal salt family of the lanthanide series that has a high tolerance to air and moisture. These salts have been shown to be versatile in mediating a wide variety of organic transformations that make use of alcohol pro-electrophiles in excellent yields and with high selectivity. Taking account of the versatile reactivity of the ytterbium, several interesting propargylic substitution reactions have been carried out.

Zhou and co-workers in the year 2007 developed a highly efficient coupling reaction of 1,3-dicarbonyl compounds **304** and 4-hydroxycoumarins **64a** with propargylic alcohols **23** in presence mildly Lewis acidic $\text{Yb}(\text{OTf})_3$, Scheme 161.¹⁹⁸

The reaction mechanism proceeds *via* the propargylic carbocationic intermediate. Broad scope, mild conditions, and easy handling are the advantages of this method. This method provided a mild and straightforward route to multi-substituted furocoumarin.

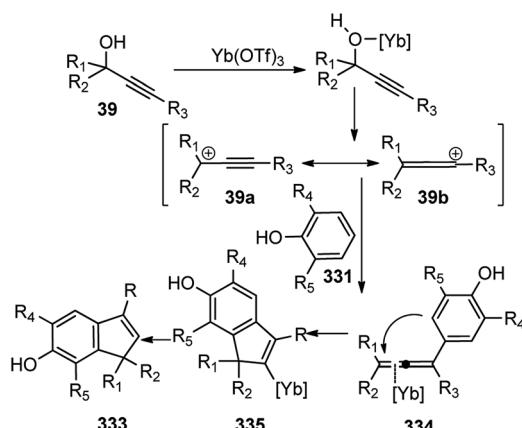
Different methodologies to synthesize indenes employing environmentally benign Lewis acid catalysts from propargylic alcohols have been reported recently.^{199–201} Following those work, Chan and co-workers in the year 2009 developed a method to prepare indenols **333** efficiently by ytterbium(III) triflate catalyzed tandem Friedel–Crafts alkylation/hydroarylation of propargylic alcohols **39** with phenols **331**, Scheme 162.²⁰²

The reaction furnished products in moderate to excellent yields with high regioselectivity under mild conditions. It offered a straightforward and convenient one-step access to bioactive indenols and its derivatives. Different Lewis acid catalysts like $\text{Yb}(\text{OTf})_3$, $\text{Cu}(\text{OTf})_2$, InCl_3 , $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, AlCl_3 , AuBr_3 , PtCl_2 and even Brønsted acid like TfOH were tested to establish the reaction conditions. AuBr_3 and PtCl_2 were found to be equally effective as catalyst whereas $\text{Cu}(\text{OTf})_2$, InCl_3 and AlCl_3 furnished products with diminished yield. Both electrons donating and electron withdrawing substituents on the carbinol or alkyne carbon delivered the desired indenols **333** in good to



Scheme 162 Yb-catalyzed synthesis of 3-phenyl-1H-indenes from propargyl alcohols.





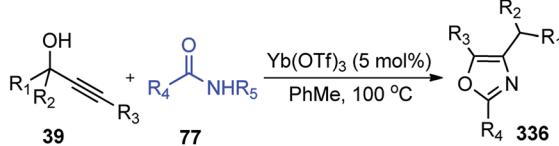
Scheme 163 Mechanism for the synthesis of 3-phenyl-1*H*-indenes from propargyl alcohols promoted by Yb-catalyst.

excellent yields. For aliphatic substituents, longer reaction time and lower yields were obtained. The reaction is believed to proceed by a mechanism outlined in Scheme 163, involving the activation of the alcohol substrate through coordination of the ytterbium triflate followed by the Friedel-Crafts type reaction at the alenic carbocation center to generate the intermediate 334. Subsequent Yb(III)-mediated intramolecular hydroarylation, re-aromatization and protodemetalation deliver the desired product 333 in good yield.

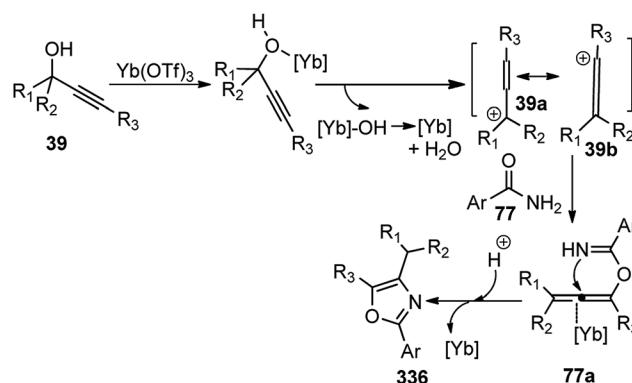
Constructing aromatic heterocycle remains the continuous pursuit of several research groups using more efficient and flexible approaches. Uemura and co-workers first reported the synthesis of oxazole by employing a dual diruthenium (II,III) and gold(III) catalytic system.^{140,203}

Following this work, Liu and Kumar demonstrated a dual ruthenium(III) and zinc(II) catalyst combination could also mediate the cyclization of propargylic alcohols with amides that afforded the oxazole product in excellent yields.²⁰⁴ More recently, Zhan and co-workers described a Brønsted acid-mediated synthesis of oxazole that could be achieved in the presence of a stoichiometric amount of *p*-TsOH·H₂O.²⁰⁵ Although both these methodologies were shown to be highly efficient, the need for two metal catalysts is a serious limitation. In addition to this, the cost of the catalysts and the limited substrate scope restricted to terminal propargylic alcohols poses a serious challenge to this reported method.

Chan and co-workers in the year 2011 reported a Yb(OTf)₃ catalyzed cyclization of trisubstituted propargylic alcohols 39 with aryl amides 77 towards the synthesis of di- and trisubstituted 2-aryloxazoles 336, Scheme 164.²⁰³



Scheme 164 Yb(OTf)₃ catalyzed efficient method for the synthesis of di- and trisubstituted 2-aryloxazoles from propargylic alcohols.



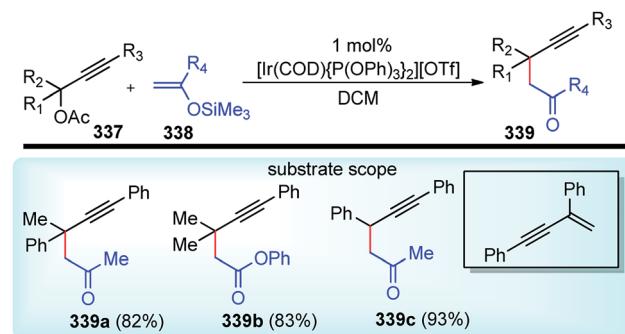
Scheme 165 Mechanism for the Yb(OTf)₃ catalyzed synthesis of di- and trisubstituted 2-aryloxazoles from propargylic alcohols.

Moderate to excellent product yields were obtained along with complete regioselectivity. Both toluene and 1,2-dichloroethane were found to be equally competent for this reaction. Lower product yields were obtained when the reaction was carried out in MeCN or MeNO₂ as well as on switching the catalyst from Yb(OTf)₃ to either AgOTf, CuBr or FeCl₃·6H₂O. The mechanism highlighted in Scheme 165 involves the activation of the starting alcohol by the metal catalyst that resulted in its ionization. Subsequent cyclization of this newly generated carbocationic species 39b with the aryl amide 77 finally afforded the oxazole 336, Scheme 165.

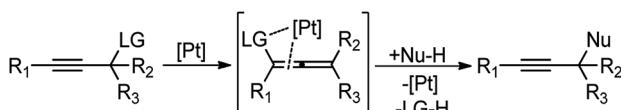
In view of the mild reaction conditions along with the low cost, commercially availability of Yb(OTf)₃ and its high tolerance to air and moisture, the above synthetic approach offered an operationally simplistic and convenient approach for the synthesis of oxazole derivatives.

5.20. Iridium derived catalysts

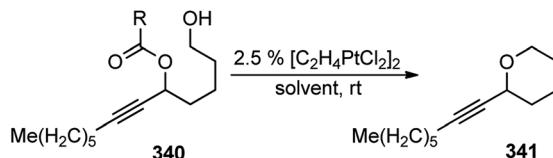
Iridium has been rarely used as a catalyst for the propargylic substitution reaction. In one of the early examples, Matsuda and co-workers reported [Ir(cod)(PR)]OTf modified by H₂ as an active catalyst for the Mukaiyama-type aldol reaction, Michael addition, and the allylic substitution reaction. It was concluded that enoxysilane behaved as a nucleophile in all these reactions.²⁰⁶



Scheme 166 Iridium catalyzed propargylic substitution with enoxysilane.



Scheme 167 General mechanism for the platinum catalyzed propargylic substitution reaction.



Scheme 168 Pt-catalyzed synthesis of tetrahydrofurans from a propargylic ester by an intramolecular substitution reaction.

Subsequently, Matsuda and co-workers in the year 2002 reported the use of Ir-catalyst for the substitution reactions of a propargylic-type alcohol 337 with an enoxysilane 338, Scheme 166.²⁰⁷

The authors found that enoxysilanes worked as a good nucleophile to form β -alkynyl carbonyl compounds in the presence of a catalytic amount of Ir catalyst. Other cationic complexes such as $[\text{Ir}(\text{cod})(\text{PPh}_3)_2]\text{OTf}$ and $[\text{Ir}(\text{cod})(\text{binap})]\text{OTf}$, were also effective without any change in regioselectivity for this substitution product, except that they required a longer reaction time.

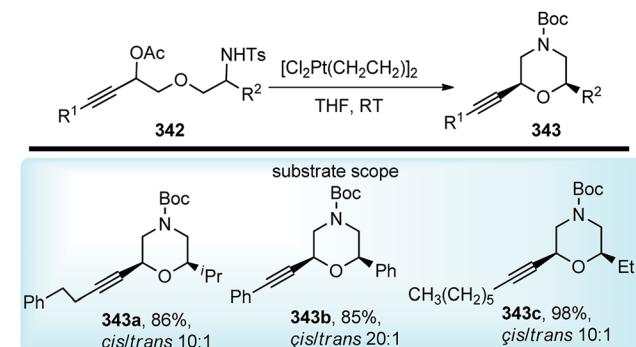
5.21. Platinum derived catalysts

Platinum has also been used, although not so extensively, as catalyst for the propargylic substitution reaction. The reaction proceeds *via* the Pt-allene intermediate where the nucleophile normally attacks in an S_N2 fashion to furnish the product, Scheme 167.

Brabander and co-workers in the year 2008 reported a platinum-catalyzed propargylic substitution of ω -hydroxy 2-propargylic esters 340 to furnish substituted tetrahydropyrans 341 in good yield, Scheme 168.²⁰⁸

Use of Zeise's dimer ω - $[(\text{CH}_2\text{CH}_2\text{PtCl}_2)_2]$ did not induce cycloisomerization but instead catalyzed the propargylic substitution pathway. Various control experiments ruled out the mechanism *via* propargylic carbocation intermediates. Strong Lewis acids (cat. or equivalent TiCl_4 , $\text{BF}_3\cdot\text{OEt}_2$, FeCl_3) did not furnish the product. Also, sterically hindered substrates that prevent coordination to the alkyne but not the ester did not furnish the desired products. Overall, the authors reported a novel platinum-catalyzed propargylic substitution reaction that functions with internal alkynes lacking a carbocation-stabilizing substituent.

Platinum-catalyzed nucleophilic propargylic substitutions are relatively rare. One classic example reported in 2008 was Zeise's dimer $[(\text{CH}_2\text{CH}_2\text{Cl}_2\text{Pt})_2]$ catalyzed intramolecular cyclization of ω -substituted propargylic acetates to furnish heterocycles.²⁰⁹ Despite the therapeutic importance of the *cis*-2,6-disubstituted morpholines there are only a few synthetic methodologies available for them.



Scheme 169 Pt-catalyzed synthesis of *cis*-2,6-disubstituted morpholines.

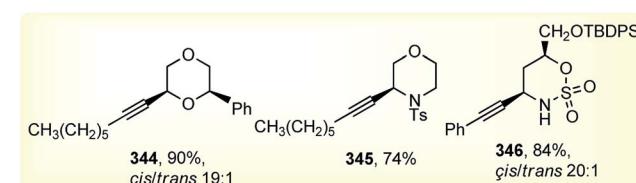
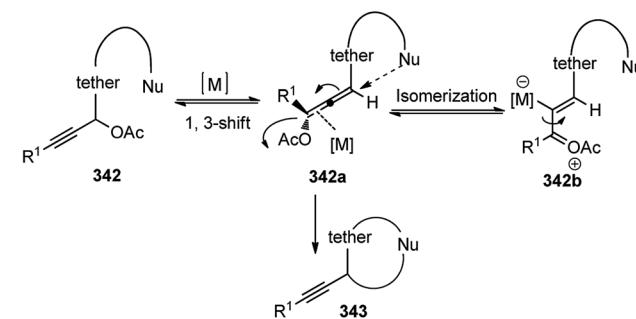


Fig. 22 Representative examples of disubstituted-1,4-dioxanes, 3-disubstituted morpholines, and cyclic sulfamates.

Brabander and co-workers in 2011 demonstrated that ω -hydroxy propargylic acetates 342 with a side chain containing Boc-protected nitrogen atom underwent intramolecular substitution in presence of 2.5 mol% Zeise's dimer in THF medium to form 2,6-disubstituted morpholines 343 with the predominance of the *cis*-isomer in good yields at room temperature, Scheme 169.²⁰⁹

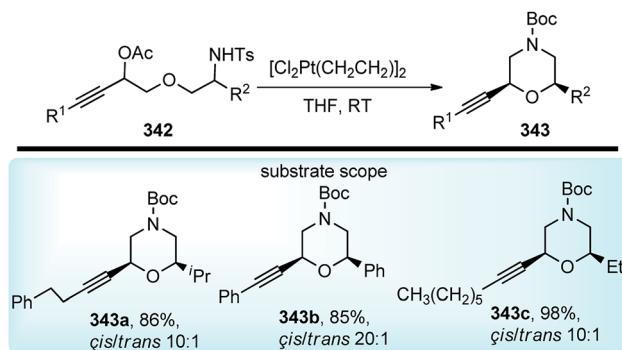
The methodology has been extended to synthesize *cis*-2,6-disubstituted-1,4-dioxanes 344 from oxygen tethered ω -hydroxy propargylic acetates under similar reaction conditions in good yield and high diastereoselectivity. Other classes of molecules synthesized using this methodology included 3-substituted morpholines 345 and cyclic sulfamates 346 from various heteroatom tethered propargylic acetates, Fig. 22.

An S_N2' kind of mechanism was proposed for the intramolecular cyclization of the propargylic acetates. In the reaction mechanism, [1,3] shift or double [1,2] shift of the acetate group followed by the metal complex coordination resulted in the

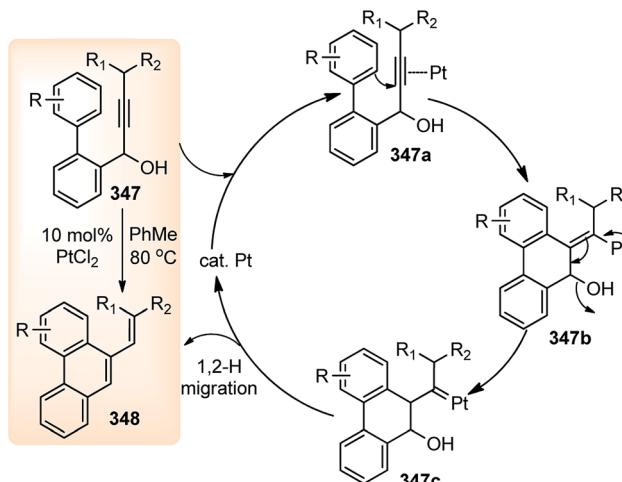


Scheme 170 Proposed mechanism for the intramolecular cyclization.





Scheme 171 Pt(II)-catalyzed synthesis of phenanthrenes from propargylic alcohols.



Scheme 172 Mechanism of the Pt-catalyzed synthesis of phenanthrenes from propargylic alcohols.

formation of intermediate **342a**. Finally, intramolecular attack from the nucleophilic residue in an S_N2' manner furnished the desired heterocycle with the liberation of acetate, Scheme 170.

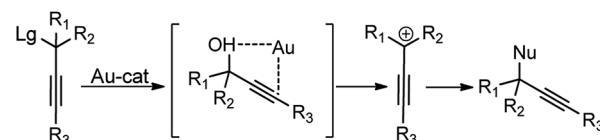
Kim and co-workers in the year 2014 developed a Pt(II)-catalyzed synthesis of phenanthrenes **348** from readily accessible biaryl propargyl alcohol substrates **347**, Scheme 171.²¹⁰

The reaction tolerated a wide range of functional groups and afforded products in excellent yields. Catalysts like $\text{Pd}(\text{OAc})_2$, Ru complex, InCl_3 , and AgOTf were found ineffective in promoting the reaction, apart from PtCl_2 , other Pt salts, such as PtCl_4 and PtBr_2 , although afforded the desired product, but were less efficient than PtCl_2 in terms of reaction yield and selectivity. The mechanism for the synthesis of substituted vinyl phenanthrenes is shown in Scheme 172.

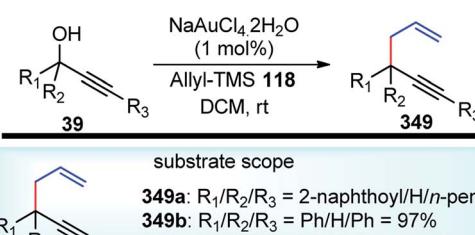
In the presence of a catalytic amount of PtCl_2 , intramolecular cyclization and subsequent dehydration resulted into phenanthrene with a carbene functional group which rapidly underwent 1,2-H migration to afford a vinylphenanthrene system **348**.

5.22. Gold derived catalysts

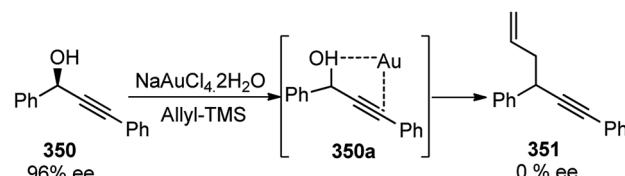
Gold catalysis has gained huge popularity and becomes an efficient tool to activate triple bonds for various nucleophilic



Scheme 173 Gold-catalyzed propargylic substitution reaction.



Scheme 174 Au-catalyzed allylation of propargylic alcohols.



Scheme 175 Mechanism of the gold-catalyzed propargylic substitution reaction.

addition reactions.²¹¹ Gold stands out among the other conventional Lewis acids since it possesses a unique hard/soft Lewis acid nature which allows the simultaneous activation of both alcohols and π -bonds that could possibly take the advantage to perform new domino processes, Scheme 173.²¹²

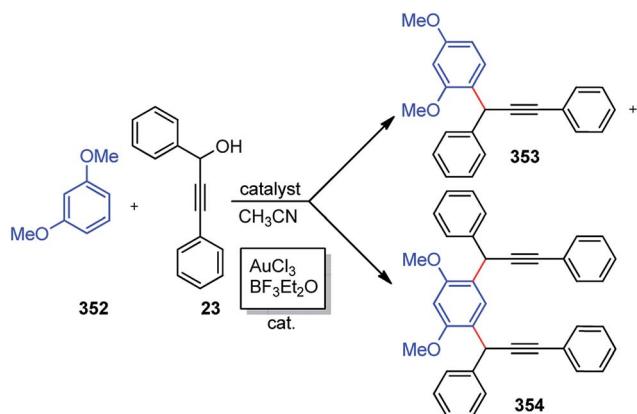
Campagne and co-workers described an excellent methodology for the gold-catalyzed allylation of propargylic alcohols **39** at room temperature, Scheme 174²¹³

The reaction was found to furnish products in moderate to good yield in the range of 30–68% with several catalysts like AuBr_3 , AuCl_3 , $\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$, and AuCl . Whereas no product formation was observed with Ph_3PAuCl , $\text{PdCl}_2(\text{PhCN})_2$, PtCl_2 . The reaction displayed a wide substrate scope and the reaction found equally efficient with both electron-rich and moderately electron-poor aromatic substrates.

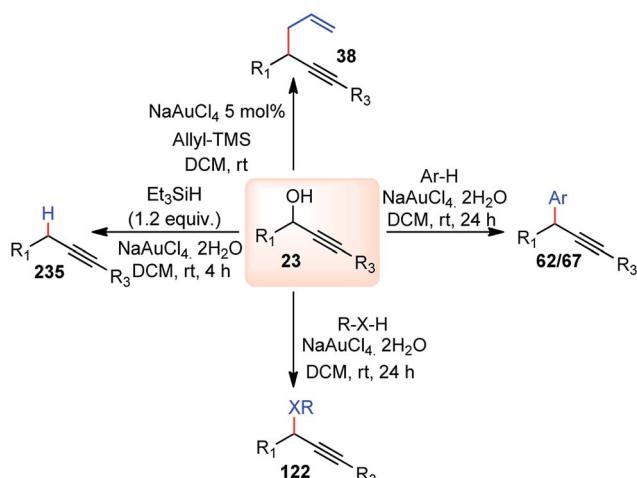
Allylation of optically pure propargylic alcohol (96% ee) resulted in the formation of the racemic product, Scheme 175, suggesting the reaction mechanism proceeded *via* a carbocationic intermediate.

Dyker and co-workers in the year 2006, demonstrated the powerful strategy for the Friedel–Crafts propargylation of electron rich arenes **352** using gold chloride catalyst, Scheme 176.²¹⁴

In the process of evaluating the catalytic activities and selectivities for the multi-fold Friedel–Crafts propargylation of electron rich arenes, the authors compared the reactivities of gold(III) chloride with the classical Friedel–Crafts catalyst, *i.e.* $\text{BF}_3 \cdot \text{Et}_2\text{O}$.



Scheme 176 Au-catalyzed propargylation of electron rich arenes.

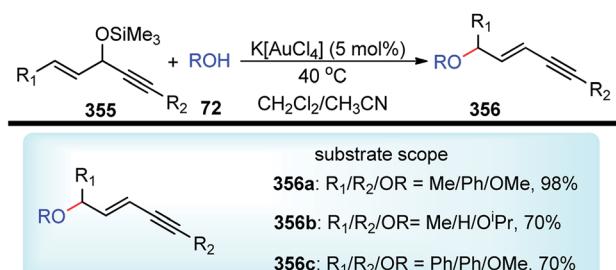


Scheme 177 Au-catalyzed propargylic substitution reactions.

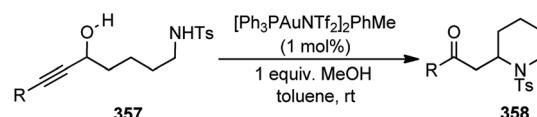
Several electron-rich arenes like 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene and azulene when tested with just 0.3 to 1% of the gold catalyst, monosubstituted products were obtained in 96% isolated yield. Whereas, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ resulted in either the mono- or the dipropargylated product proving that gold chloride is a very mild, yet highly reactive Friedel-Crafts catalyst, which works at rather low concentration and ensures a high selectivity for propargylation reactions.

Campagne and co-workers in the year 2009, described a gold(III)-catalyzed direct nucleophilic substitution of propargylic alcohols 23 with various nucleophiles like allylsilane and electron-rich aromatics like alcohols/thiols/hydrides/1,3-dicarbonyl derivatives/sulphonamides in DCM at room temperature, Scheme 177.¹²

Disappointing results were obtained when Au(I) catalysts were used. Even PtCl_2 and $\text{PdCl}_2(\text{PhCN})_2$ catalysts were found inefficient with no observable product formation. An excellent result was achieved when Au(III) catalysts were used at room temperature in DCM solvent. Mechanistic investigations by the authors suggested a mechanism through a carbocationic intermediate.



Scheme 178 Gold(III)-catalyzed regioselective nucleophilic substitution reaction.



Scheme 179 Facile synthesis of 2-substituted piperidines from propargylic alcohols.

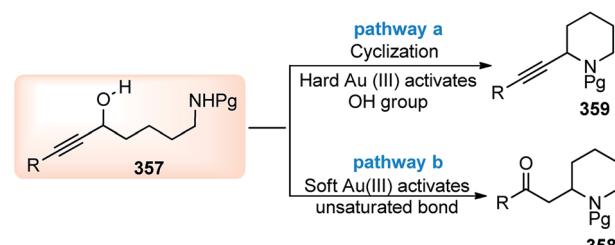
Kirsch and co-workers in the year 2009, developed a gold(III)-catalyzed regioselective nucleophilic substitution reaction of propargylic enol silyl ether 355 with alcohols 72, Scheme 178.²¹⁵

Gold(III) complex acted as a pre-catalyst to activate propargyl silyl ether. An extensive catalyst screening with various gold(I) and gold(III) catalysts revealed $\text{K}[\text{AuCl}_4]$ to be the best choice for the conversion of 3-trimethylsilyloxy-1-phenylhex-4-en-1-yne 355 into (5-methoxyhex-3-en-1-ynyl)benzene 356. Other gold catalysts such as $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$, AuCl , and $[(\text{Me}_3\text{P})\text{AuSbF}_6]$ resulted in markedly reduced product yield. Interestingly, Brønsted and Lewis-acid catalysts like $\text{Bi}(\text{OTf})_3$ (67%), $p\text{-TsOH}$ (61%), and HBF_4 (52%) furnished products in moderate yield.

Morita and co-workers in the year 2015 purposefully used hard gold(III) and soft gold(I) catalysts for the facile access of two types of 2-substituted piperidines 358 from propargylic alcohols 357, Scheme 179 and Scheme 180.²¹⁶

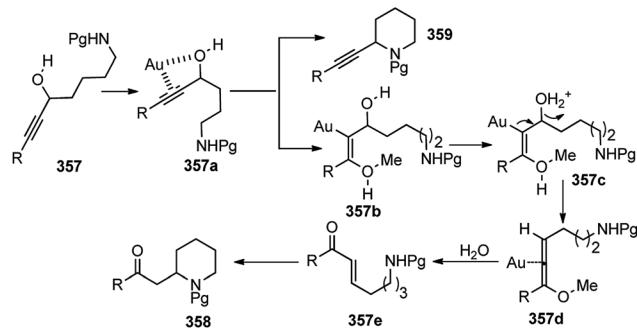
Screening of the reaction with different catalyst combinations like AuCl (15 mol%), Ph_3PAuCl (15 mol%) or Ph_3PAuCl (5 mol%)/ AgSbF_6 (5 mol%) afforded the desired product in poor to moderate yield except for $[\text{Ph}_3\text{PAuNTf}_2]_2\text{PhMe}$ (1 mol%) which afforded piperidine in 81% yield.

The mechanistic pathway for gold-catalyzed synthesis of the two types of piperidines is illustrated in Scheme 181. In both



Scheme 180 Facile synthesis of two types of 2-substituted piperidines from propargylic alcohols using hard and soft gold catalysts.





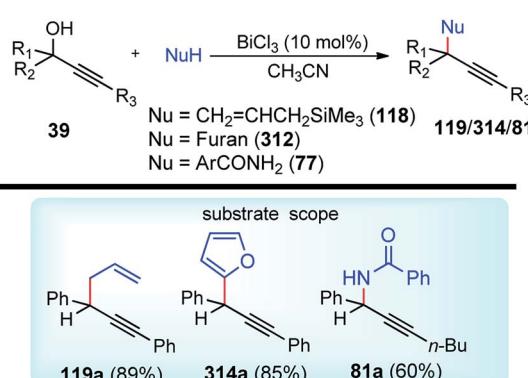
Scheme 181 Mechanism for the synthesis of two types of 2-substituted piperidines from propargylic alcohols using hard and soft gold catalysts.

cases, complex **357a** would be formed as a common reaction intermediate, whose character would play a pivotal role in determining the reaction pathway. Hard gold(III) in complex **357a** strongly activated the hydroxyl group to induce cyclization by intramolecular nucleophilic substitution, to afford piperidine having an acetylenic moiety (pathway a). On the other hand, soft gold(I) in complex **357a** promoted the addition of methanol to generate an allenyl ether, which hydrolyzed to furnish α,β -unsaturated ketone (**357e**) which smoothly cyclized to afford the desired product.

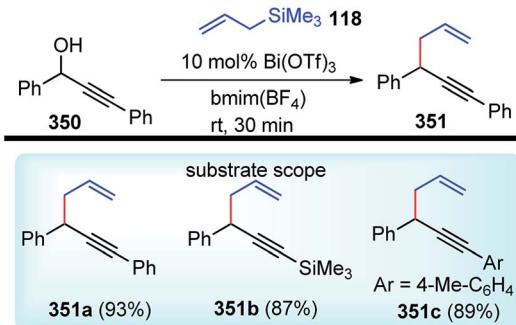
5.23. Bismuth derived catalysts

Bismuth(III) compounds have gained extensive interest in organic synthesis due to their low toxicity, low cost and relative insensitivity to air and traces of moisture. Due to the pronounced lanthanide contraction, bismuth(III) compounds exhibits Lewis acidity and they have been used in many chemical transformations.^{217–220} Bismuth trichloride is particularly attractive because it not only is commercially available and inexpensive but also highly stable.

Zhan and co-workers in the year 2006, demonstrated a BiCl_3 -catalyzed propargylic substitution reaction of propargylic alcohols **39** with C-, O-, S- and N-centered nucleophiles **77/118/312**, Scheme 182.²²¹



Scheme 182 BiCl_3 catalyzed nucleophilic substitution of propargylic alcohols.



Scheme 183 $\text{Bi}(\text{OTf})_3$ in $[\text{BMIM}][\text{BF}_4]$ as an efficient catalytic system for allylation, alkynylation, and deoxygenation of propargylic alcohols.

The reaction proceeded smoothly with various aryl- and alkyl-substituted propargylic alcohols. Electron-rich or moderately electron-poor aromatic substrates reacted smoothly with allyl trimethylsilane affording the corresponding allylated products in high yields.

Because of the strong co-ordinating properties of sulfur-containing compounds, transition metal-catalyzed coupling of propargylic alcohols with thiols was rarely reported. Gratifyingly, this methodology offered the construction of sp^3 C-S bonds by the nucleophilic substitution of propargylic alcohols with a series of thiols employing 10 mol% BiCl_3 as the catalyst.

Several studies on coupling of allylic and benzylic alcohols with allylsilanes have appeared, using various Lewis and Brønsted acids, namely BiCl_3 , ZrCl_4 , ion-exchanged montmorillonite, phosphomolybdic acid, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, and $\text{HN}(\text{SO}_2\text{F})_2$.^{222,223} Despite the availability of these earlier methods, development of environmentally benign efficient processes that employ readily available catalysts in combination with non-volatile solvents that can be recycled and reused is highly desirable.

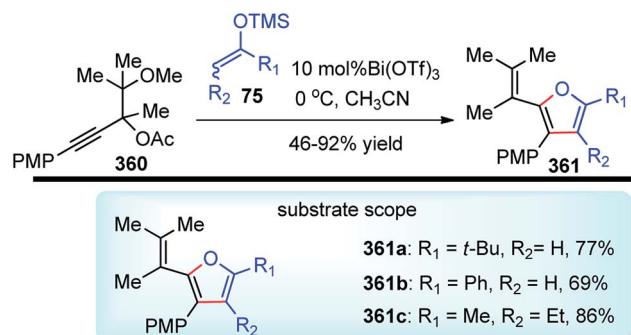
In search of a greener protocol for the propargylic substitution reaction, Laali and co-workers in the year 2012 described the use of ionic liquid as the reaction medium for the efficient allylation, alkynylation, and deoxygenation of propargylic alcohols **350** using $\text{Bi}(\text{OTf})_3$, Scheme 183.²²⁴

Reactions were performed at room temperature and furnished products in good yield within a brief period. These attributes coupled with the recycling and reusability of the ionic liquids made this a superior method for the synthesis of various propargylic substituted products over several other reported methods.

Bach in the year 2014 developed a bismuth(III) triflate-catalyzed synthesis of substituted 2-alkenylfurans **361** via a successive 2-fold $\text{S}_{\text{N}}^{\prime}$ -type substitution reaction at methoxy-substituted propargylic acetates **360** with enolsilylethers **75**, Scheme 184.²²⁵

The reaction progressed in a similar fashion like the FeCl_3 -catalyzed substitution reaction of secondary propargylic acetates with silyl enol ethers affording the corresponding γ -alkynyl ketones. The mechanistic pathway is highlighted in Scheme 185. The tertiary group adjacent to the α -position prevents the usual $\text{S}_{\text{N}}^{\prime}$ -type attack and directs the nucleophile





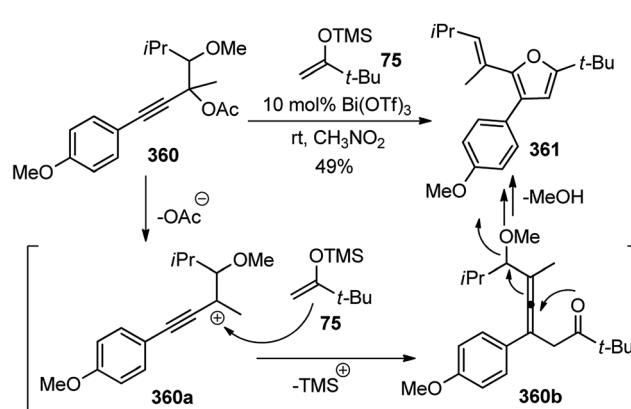
Scheme 184 Bi-catalyzed synthesis of 2-alkenyl furans from propargylic alcohols.

to form allene intermediate **360b**. Deprotonation at the resulting cationic intermediate generates the observed product **361**.

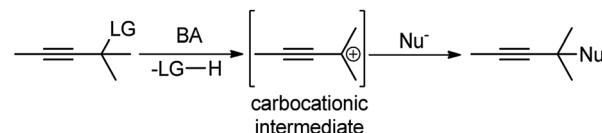
The reaction appeared in general for several substitution patterns at both the substrates and allow for the construction of a diverse array of 2-alkenylfurans.

6. Brønsted acid catalyzed reactions

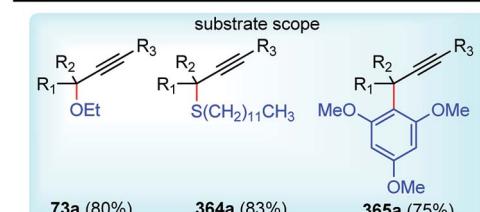
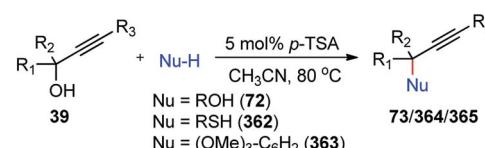
Several catalytic methodologies for the substitution of propargylic alcohols have been reported in the presence of metal catalysts like copper, ruthenium, rhenium, platinum, palladium, gold, as well as other metal salts like BiCl_3 , FeCl_3 , AlCl_3 etc. However, all these strategies were limited by the syntheses and costs of the catalysts, the need for anhydrous conditions, elevated temperatures, use of costly, corrosive and toxic catalysts. In general, harsh reaction conditions, costly catalysts and the chromatographic purification of products are not the desirable parameters due to the high operational cost associated with them. Thus, the development of efficient substitution reactions of propargylic alcohols using inexpensive air and moisture tolerant catalyst under mild reaction conditions was inevitable. Use of Brønsted acid in the propargylic substitution reaction could have been a solution to the problem. Since the reaction implies the use of very simple starting materials and catalysts under mild conditions which could be easily scalable,



Scheme 185 Mechanism for the Bi-catalyzed synthesis of 2-alkenyl furans from propargylic alcohols.



Scheme 186 General mechanism for the Brønsted acid catalyzed propargylic substitution reaction.



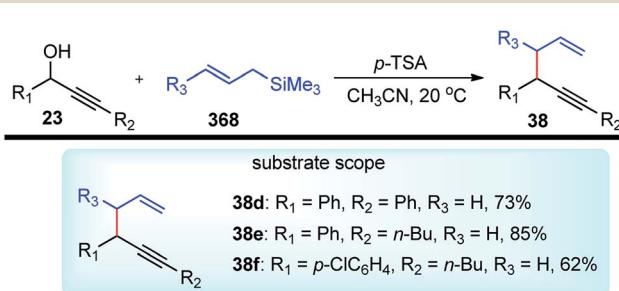
Scheme 187 *p*-TSA catalyzed propargylic substitution by a heteroatom and carbon-centered nucleophiles.

this methodology represents a clean, an environmentally friendly alternative to the existing protocols. Based on this concept several Brønsted acids catalyzed propargylic substitution reactions has evolved in the last couple of decades.

Most of the Brønsted acid-mediated propargylic substitution mechanistically proceeded *via* a propargylic cation intermediate followed by the nucleophilic substitution reaction, Scheme 186.

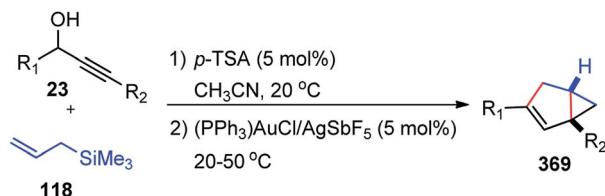
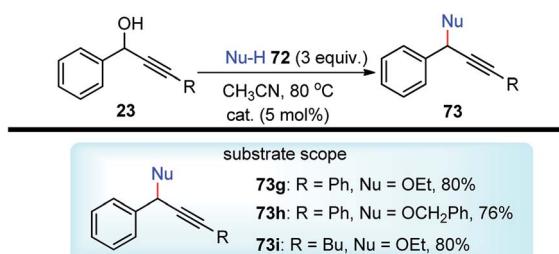
In 2006 Sanz and co-workers demonstrated the use of simple organic acids as catalysts for the direct propargylic substitution of hydroxy groups by different heteroatom and carbon-centered nucleophiles, Scheme 187.²²⁶

Various other Lewis acid catalysts like as InCl_3 , AlCl_3 , and CeCl_3 also afforded the desired product but propargylic substituted products are obtained in short times and in essentially quantitative yields with organic acids like *p*-TSA or (\pm) -CSA. The reaction progressed efficiently with various electron-rich arenes like 1,3,5-trimethoxybenzene, phenols and heteroaromatic compounds like furan and *N*-methylindole with complete regioselectivity.



Scheme 188 *p*-TSA catalyzed preparation of 1,5-enynes from propargylic alcohols.



Scheme 189 *p*-TSA catalyzed synthesis of bicyclo[3.1.0]hexanes.Scheme 190 Nucleophilic substitution of propargylic alcohols catalyzed by *p*-TSA.

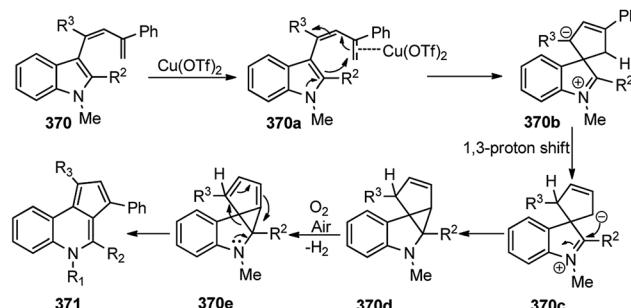
Sanz and co-workers in 2007 also demonstrated the use of *p*-toluenesulfonic acid as a catalyst in the preparation of 1,5-enynes **38** from propargylic alcohols **23** and allylsilanes **368**, Scheme 188.²²⁷

To explore the synthetic potential of this methodology, the authors developed a practical sequential dual catalytic protocol for the synthesis of bicyclo[3.1.0]hexenes **369** from the same starting materials, Scheme 189. The one-pot tandem sequential reaction reported by Sanz *et al.* involved both *p*-TSA and gold-catalyzed reaction, Scheme 189.²²⁷

This metal-free, air and moisture tolerant methodology represented a greener protocol compared to the existing protocols employing metal catalysts.

A similar type of *p*-TSA catalyzed propargylic substitution reaction by a series of heteroatom- and carbon-centered nucleophiles for the synthesis of propargylic ethers, thioethers, amines, and amides were reported by Rodríguez and co-workers in the year 2007, Scheme 190.²²⁷

The reaction was found to be air and moisture tolerant and released water as the only by-product. The reaction also

Scheme 192 Mechanistic pathway for the *p*-TSA/Cu(OTf)₂ catalyzed synthesis of highly conjugated cyclopenta[c]quinolines from propargylic alcohol.

proceeded effectively with terminal alkynols albeit in longer durations. Enantiomerically enriched propargylic alcohol (94% ee) furnished racemic ether after the reaction indicating that the reaction followed an S_N1 pathway.

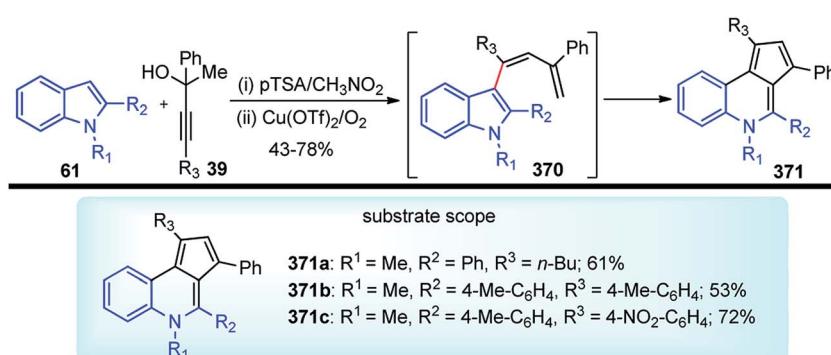
KumaraSwamy and co-workers in 2014 developed a novel one-pot methodology for the synthesis of highly conjugated cyclopenta[c]quinolines **371** by the reaction of indoles **61** with propargyl alcohols **39**, Scheme 191.²²⁸ The key step being the propargylic substitution of propargyl alcohols **39** with indoles **61**.

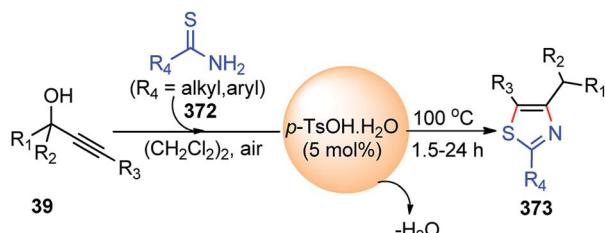
The mechanism for this reaction is illustrated in Scheme 192. The Brønsted acid catalyzed Friedel-Crafts alkenylation and isomerization, followed by copper-catalyzed dehydrogenation/oxidative ring expansion leads to the desired product.

Electron-withdrawing groups on propargyl alcohols furnished better yields than those containing an electron donating substituents. Alkyl chain containing propargyl alcohol also led to good yields of the products. Even alkyl substituent on indole furnished the desired products in moderate yields.

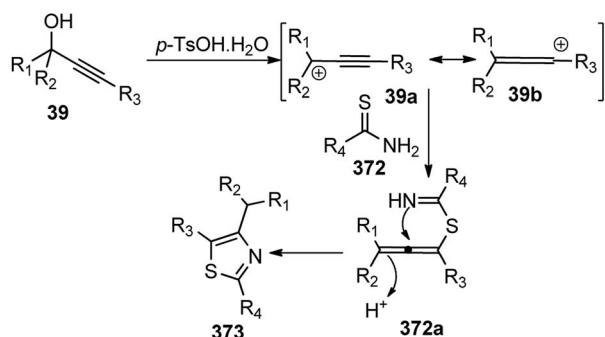
Chan and co-workers in the year 2010 described an efficient *p*-TsOH·H₂O-catalyzed protocol to prepare 2,4-di- and trisubstituted thiazoles **373** from trisubstituted propargylic alcohols **39** and thioamides **372**, Scheme 193.²²⁹

The reaction was found to be temperature dependent and poor yield was obtained when the reaction was carried out at room temperature with 10 mol% of *p*-TSOH. Solvent screening

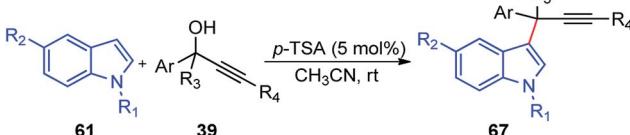
Scheme 191 Synthesis of highly conjugated cyclopenta[c]quinolines from propargylic alcohols catalyzed by *p*-TSA.



Scheme 193 Efficient synthesis of 2,4-di- and trisubstituted thiazoles via *p*-TsOH·H₂O-catalyzed cyclization of trisubstituted propargylic alcohols.



Scheme 194 Mechanism for the synthesis of trisubstituted thiazoles.



Scheme 195 Propargylation of indoles catalyzed by *p*-TSA.

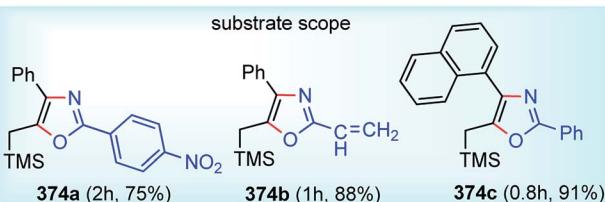
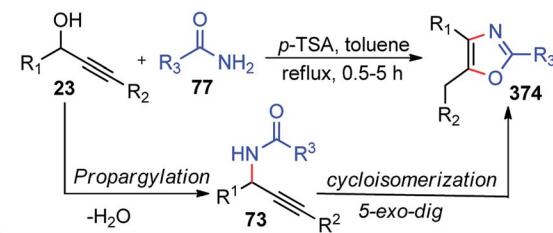
revealed that 1,2-dichloroethane, MeNO₂, MeCN, 1,4-dioxane, or toluene were inefficient. Poor yield was observed when stronger Brønsted acid catalysts like TfOH, TFA, and H₃PO₄ were examined.

The proposed mechanistic pathway is illustrated in Scheme 194 which involved Brønsted acid-mediated dehydration of the propargyl alcohol to generate allenic carbocation 39b. Subsequent nucleophilic attack by the thioamide 372 at the sterically less hindered allenic carbocation center followed by 5-exo-trig cyclization resulted in the thiazole product 373.

Sanz and co-workers in the year 2010 developed direct alkylation of indoles 61 with a wide variety of tertiary propargylic alcohols 39 using *p*-TSA as a catalyst, Scheme 195.²³⁰

Several Lewis acids were also found to catalyze the process, however; the substitution reactions were significantly slower and/or less efficient. Propargylic substitution reaction did not take place in the absence of a catalyst.

Earlier reports for the synthesis of substituted oxazoles by sequential propargylation/cycloisomerization of propargylic alcohols with amides were reported using [Cp^{*}RuCl(μ²-SMe)₂]-RuCp^{*}Cl]/AuCl₃/NH₄BF₄ or Zn(OTf)₂/TpRuPPh₃(CH₃CN)₂PF₆,



Scheme 196 *p*-TSA catalyzed synthesis of oxazoles from propargylic alcohols.

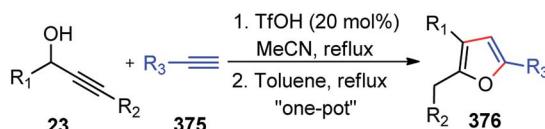
catalysts.^{140,204} These methodologies were only compatible with terminal propargylic alcohols and two different catalysts were involved in the process making it economically less feasible.

Therefore, in the process to design a more economical and environmentally acceptable methodology, Zhan and co-workers in the year 2009 described the synthesis of substituted oxazole 374 by an efficient one-pot tandem propargylation/cycloisomerization process from propargylic alcohols 23 and amides 77 using *p*-toluenesulfonic acid as a bifunctional catalyst, Scheme 196.²⁰⁵

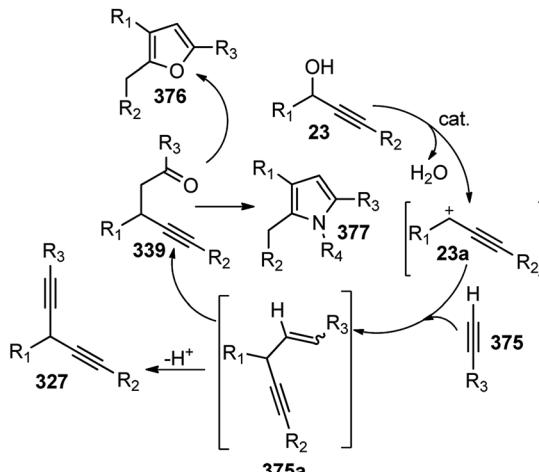
Several other Lewis acids like Cu(OTf)₂, FeCl₃, and InCl₃, although furnished the propargylated product but did not catalyze the intramolecular cycloisomerization step to afford the cyclized product. A very slow reaction rate was observed when the amount of *p*-TSA decreased from 1 equiv. to 50 mol%. With 50 mol% of *p*-TSA, the propargylation proceeded rapidly but subsequent intramolecular cycloisomerization was sluggish. The results showed that stoichiometric amount of *p*-TSA was essential for cycloisomerization probably by counteracting the basicity of the oxazole and making the reaction medium acidic. Other Brønsted acids like oxalic acid and hydrochloric acid failed to catalyze the reaction. Reaction in solvents like acetonitrile and 1,2-dichloroethane were also sluggish. However, toluene had a positive impact on the reaction rate and obviously reduced the reaction time from 24 to 0.8 h. The reaction pathway proceeded *via* a nucleophilic attack by the amide 77 followed by a 5-exo-dig cyclization in a one-pot manner to furnish the desired product. The reaction has a wide substrate scope and many functional groups like bromo, chloro, vinyl, TMS, methoxy are well tolerated under this reaction condition.

Although the stoichiometric amount of *p*-TSA was necessary, the methodology provided an easy access to the substituted oxazoles from simple starting materials and reagents using an inexpensive catalyst.

Cycloisomerizations of alkynyl- and allenyl functionalized compounds is particularly an attractive strategy to synthesize polysubstituted furans and pyrroles. However, these strategies



Scheme 197 TfOH catalyzed synthesis of polysubstituted furans/pyrroles from propargyl alcohols and terminal alkynes.



Scheme 198 Mechanism for the synthesis of polysubstituted furans/pyrroles from propargyl alcohols and terminal alkynes.

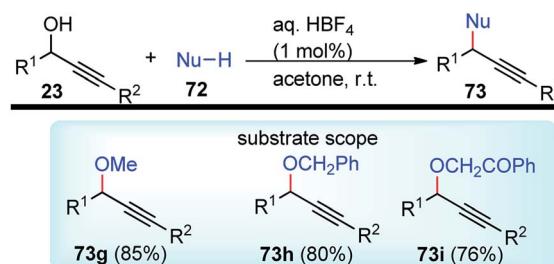
mostly utilize noble metal catalysis, multiple synthetic steps, or highly functionalized substrates. As a result, the development of efficient synthetic routes allowing the facile assembly of polysubstituted furans and pyrroles from readily available precursors will be a challenging process.

Zhan and co-workers in the year 2011, reported a novel efficient synthetic method for the synthesis of polysubstituted furans 376 as well as pyrroles from propargyl alcohols 23 and terminal alkynes 375 using TfOH as the catalyst, Scheme 197.²³¹

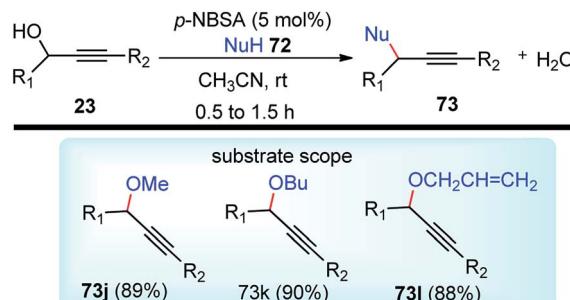
With 10 mol% of TfOH in refluxing CH₃CN, the reaction of propargyl alcohols and terminal alkynes leads to the selective formation of 1,4-dynes which eventually cyclized to polysubstituted furans/pyrroles. The reaction is highly solvent dependent and maximum yield of the 1,4-dynes was reported in CH₃CN. Notably, removal of H₂O using 4 Å molecular sieves improved the product yield.

The mechanism for the reaction is highlighted in Scheme 198. The activation of propargyl alcohol 23 by the Brønsted acid affords the propargylic carbocation followed by a nucleophilic attack of the alkyne 375 leading to the formation of alkenyl cation 375a. Subsequent hydrolysis results in the formation of γ -alkynyl ketones 339 which then transforms to furan 377 under the reaction condition.

Silvia Díez-González and co-workers in the year 2015 demonstrated the use of HBF₄ as a catalyst for the substitution of propargyl alcohols 23 with several nucleophiles in excellent yields, towards the formation of C–O, C–N and C–C bonds, Scheme 199.²³²



Scheme 199 HBF₄ as a practical catalyst for propargylation reactions.



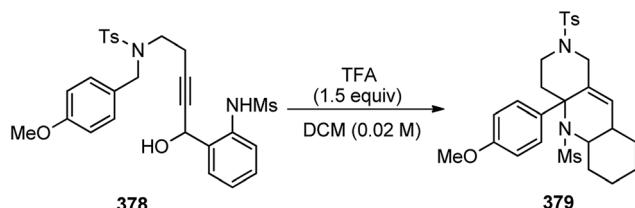
Scheme 200 NBSA catalyzed nucleophilic substitution of propargyl alcohols.

The high regioselectivity without any formation of allene intermediate and simple aqueous workup without any chromatographic purification are the advantages of this process. Electron-poor propargylic alcohols or acid-sensitive indoles furnished the products, although with little forcing conditions. A thorough solvent screening revealed that reactions were sluggish in THF and water whereas high conversions were obtained in solvents like DCM, acetonitrile, and acetone.

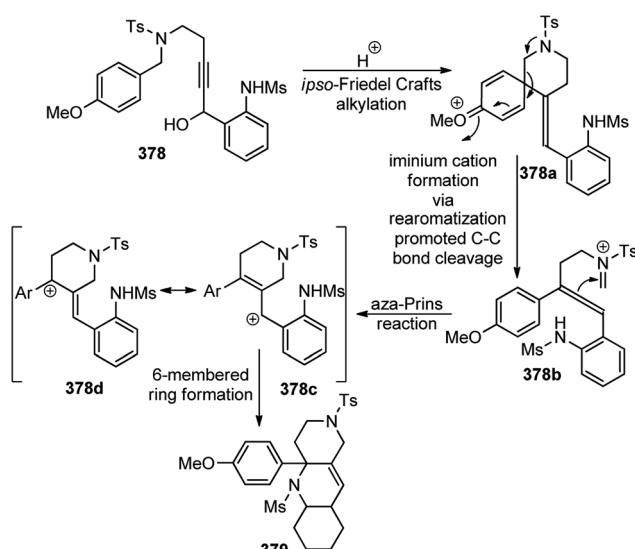
Savarimuthu and co-workers in 2014 employed NBSA as a cost-effective catalyst for the nucleophilic substitution of propargyl alcohols 23 with several nucleophiles like alcohols, amines, and heterocycles, Scheme 200.²³³

The reaction was devoid of any corrosive and costly metal catalysts, toxic solvents and does not involve any column chromatographic purification. The authors screened several protic acids like *p*-toluenesulfonic acid (*p*-TSA), benzene sulfonic acid (BSA), *p*-nitrobenzene sulfonic acid (NBSA) in acetonitrile, tetrahydrofuran and dichloromethane solvents. But the use of 5 mol% of 4-nitrobenzenesulfonic acid in CH₃CN provided very good yields of the desired products with several O, N and C centered nucleophiles. The reaction proceeds *via* the protonation of the hydroxyl group of 1,3-diphenyl-prop-2-yn-1-ol by *p*-NBSA followed by the removal of water to form a secondary carbocation, which is in equilibrium with allene carbocation. Afterward, nucleophilic substitution *via* S_N1 reaction by several nucleophiles furnishes the product in good to excellent yields.

Hamada and co-workers in 2014 reported the efficient synthesis of fused heterocycles 379 by an acid-promoted intramolecular *ipso*-Friedel-Crafts alkylation of phenol derivatives 378, Scheme 201.²³⁴



Scheme 201 Acid-promoted intramolecular *ipso*-Friedel-Crafts alkylation of phenol derivatives involving propargylic substitution reaction.

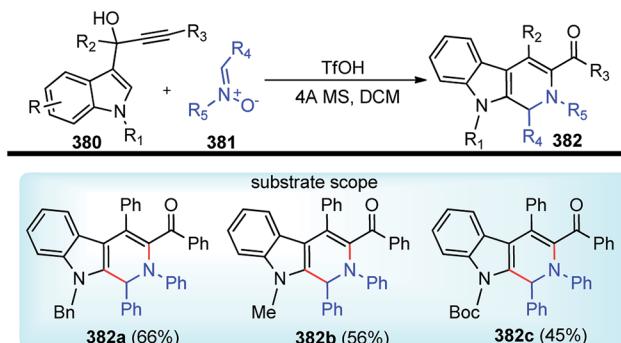


Scheme 202 Mechanism for the acid-promoted fused heterocycles from propargylic alcohols.

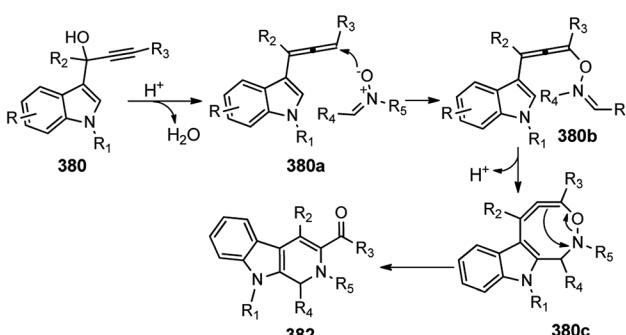
The use of other catalysts like $\text{TsOH} \cdot \text{H}_2\text{O}$, $\text{Sc}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$ and $\text{B}(\text{C}_6\text{F}_5)_3$ did not furnish any desired product in considerable yield. A plausible reaction pathway of this cascade cyclization process is shown in Scheme 202 where the Brønsted acid promotes the intramolecular *ipso*-Friedel-Crafts alkylation of phenol derivatives, followed by the formation of an iminium cation **378a** *via* a rearomatization promoted C-C bond cleavage. Then an aza-Prins reaction and subsequent 6-membered ring formation in the presence of TFA affords the fused-tricyclic dihydroquinoline derivatives **379**.

Liu and co-workers in the year 2012 described a facile synthesis of substituted dihydro- β -carbolines *via* Brønsted acid promoted cascade reactions of α -indolyl propargylic alcohols **380** with nitrones **381**, Scheme 203.²³⁵

A plausible reaction pathway of this cascade cyclization process is illustrated in Scheme 204. Initially, allenyl cation is generated *via* a Meyer-Schuster rearrangement, which is attacked by nitrone **381** to generate the intermediate **380b** which undergoes intramolecular cyclization leading to eight-membered N-O heterocycle **380c**. Subsequent 1,3-rearrangement with cleavage of the N-O bond delivers highly substituted β -carboline **382**.



Scheme 203 Synthesis of substituted dihydro- β -carbolines promoted by Brønsted acid.



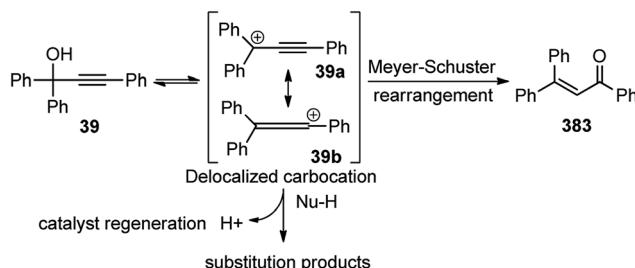
Scheme 204 Mechanism for the synthesis of substituted dihydro- β -carbolines promoted by *p*-TSA.

The authors observed that elevating the reaction temperature to 150 °C did not improve the reaction, and the product was isolated in 24% yield. Advantageously, the use of 30 mol% of $\text{Sc}(\text{OTf})_3$ enabled the reaction to proceed at 0 °C and improved the yield of the product to 62%. Notable variation in the reaction yield was not observed on changing the amounts of the catalyst. Other Brønsted acids, such as $\text{TsOH} \cdot \text{H}_2\text{O}$, MsOH , or CF_3COOH , were found less effective.

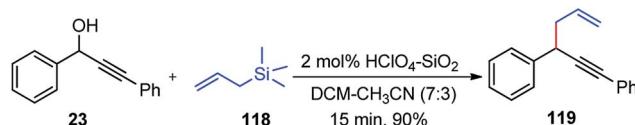
Heterogeneous catalysis has played a significant role in various organic transformations.²³⁶ Among several heterogeneous catalysts, ion-exchange resins are widely used owing to their low cost, reusability, wide range of acid/base strength, ease of handling, environmental compatibility, and low toxicity.²³⁶ Moreover, they can be easily recovered from reaction mixtures by filtration and can be reused after activation or even without activation, making the process economically viable. Aluminosilicates are solid acids with industrial applications for ion-exchange, gas separation, and catalysis.²³⁷ Between them, zeolites are by volume the most used catalysts worldwide, with an important impact in both petrochemical and fine chemical industries. Since zeolite with larger external surface area can efficiently generate carbocation and stabilize them, they become subject of synthetic interest as several catalytic transformations using zeolite would increase significantly, Scheme 205.

The activity of heterogeneous catalysts occurs at the surface atoms. Therefore, significant effort is made to maximize the





Scheme 205 Zeolite catalyzed propargylic substitution reaction.

Scheme 206 Silica supported HClO_4 catalyzed allylation of propargylic alcohols.

surface area of a catalyst by distributing it over the support. Typical supports include various kinds of carbon, alumina, and silica *etc.* Several propargylic substitution reactions were also reported with the solid supported catalyst. These clean and operationally simple methods with an easy work-up procedure, involving simple filtration of the catalyst, made those protocols attractive.

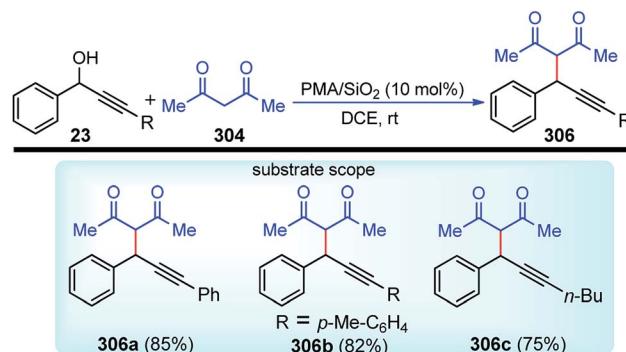
Perchloric acid supported on silica gel has already been shown to be a promising catalyst for numerous synthetically relevant organic transformations.²³⁸ Chen and co-workers in 2011 demonstrated HClO_4 -supported on silica gel as a very mild and efficient catalyst for the allylation of propargyl alcohol 23, Scheme 206.²³⁹

Allylated products were obtained in excellent yields, and allyltrimethylsilane was only used in a 1.5 equivalent. The reusability of the catalyst also enhances the synthetic applicability of this process.

Recently, heteropoly acids, HPAs, has gained much attention as an environmentally friendly alternative to harsh inorganic acids due to their ease of handling and high catalytic activities and reactivities.²⁴² These compounds possess unique properties, such as well-defined structure, Brønsted acidity, redox modulating property, ability to accept and release electrons, and high proton mobility. In view of green chemistry principles, the replacement of harmful liquid acids by reusable solid HPAs as catalysts is a promising application of these acids.²⁴⁰ Among them, phosphomolybdic acid (PMA, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$) is one of the less expensive and commercially available catalysts.

Yadav and co-workers in the year 2008, described a mild environmentally friendly protocol involving of phosphomolybdic acid supported on silica gel (PMA/SiO₂) catalyst for the synthesis of 2-propargylic-1,3-dicarbonyl compounds 306 in excellent yields and with high selectivity, Scheme 207.²⁴¹

Several silica-supported acid catalysts such as $\text{HClO}_4/\text{SiO}_2$, $\text{H}_2\text{SO}_4/\text{SiO}_2$ and $\text{NaHSO}_4/\text{SiO}_2$ were screened for this reaction. PMA/SiO₂ was found to give the best results in terms of

Scheme 207 Phosphomolybdic acid supported on silica gel (PMA/SiO₂) for propargylic substitution.

Scheme 208 Silica supported PMA in the nucleophilic propargylic substitution reaction.

conversion and reaction time. The advantages of this method are the ready availability of alcohols, high atom efficiency, no salt formation and water as the only by-product.

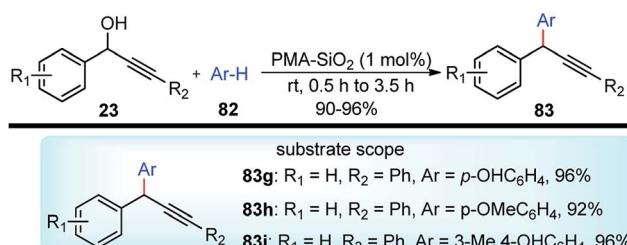
Yadav and co-workers have also demonstrated the use of PMA-SiO₂ as a heterogeneous catalyst for O-, S-, and N-nucleophilic substitution reactions of aryl propargyl alcohols 23, Scheme 208.²⁴²

The authors demonstrated the use of phosphomolybdic acid supported on silica gel (PMA/SiO₂) as an excellent heterogeneous solid supported catalytic system, for the nucleophilic propargylic substitution reaction.

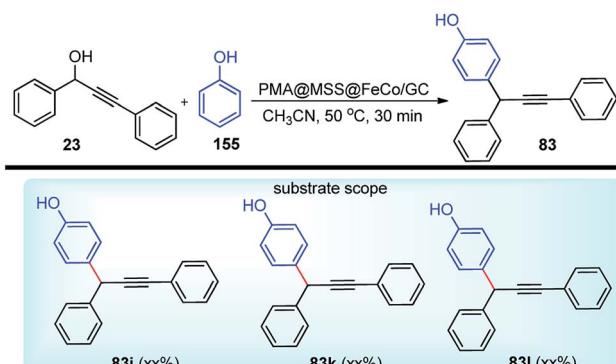
Srihari and co-workers in the year 2008, utilized PMA-silica to catalyze efficiently the propargylation of aromatic compounds with arylpropargyl alcohols 23 in the absence of solvent under environmentally benign conditions, Scheme 209.²⁴³

Different acids such as 4-toluenesulfonic acid, phosphomolybdic acid, silica gel, silica gel supported sodium bisulfate, and silica gel supported perchloric acid and heterogeneous catalysts such as Amberlyst and montmorillonite K-10 were also tested for propargylation. It was found that PMA-silica gel and perchloric acid were the best in terms of yields and reaction time, while others including phosphomolybdic acid without silica gel took longer for complete conversion. The solvent study revealed that reaction proceeded faster in absence of solvent

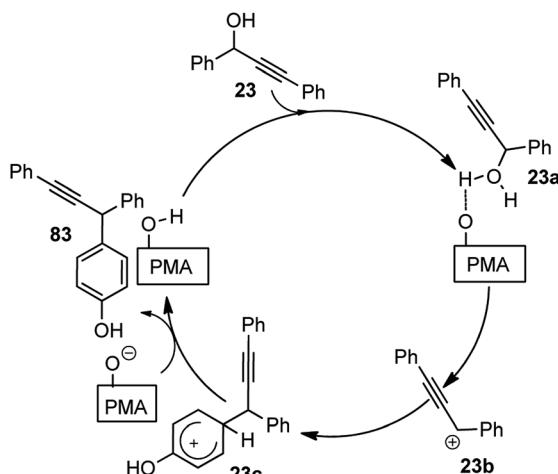




Scheme 209 Silica supported PMA for the propargylation of electron rich arenes.



Scheme 211 Propargylic substitution using recyclable mesoporous silica spheres embedded with Fe–Co/graphitic shell nanocrystals.



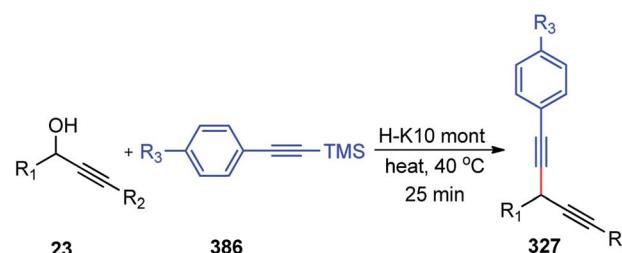
Scheme 210 Mechanism for the PMA catalyzed propargylic substitution reaction.

than in solvents like nitromethane, dichloromethane, 1,2-dichloroethane, polyethylene glycol (PEG), and water. The mechanism for the propargylation is shown in Scheme 210.

First, the hydroxyl group of the propargylic alcohol is protonated by the H^+ active site to generate propargylic carbenium ion through dehydration followed by the nucleophilic attack by the electron-rich arene to the carbenium compound. Finally, the removal of a proton from the intermediate regenerates the H^+ -active site of PMA and furnished the product.

Park and co-workers in 2015 used mesoporous silica spheres embedded with Fe–Co/graphitic shell nanocrystals as recyclable catalysts for the propargylic substitution reactions with various electron rich arenes 155, Scheme 211.²⁴⁴

The authors studied the solvent scope for this propargylic substitution reaction and observed that hydrophilic solvents such as water and PEG-400 showed low conversion, whereas hydrophobic solvents such as acetonitrile, dichloromethane, and dichloroethane showed high conversion. The highest yield was observed in acetonitrile. The reaction yield has a positive effect on the variation of catalyst loading, reaction temperature and reaction time. The authors also demonstrated the recyclability of the PMA@FeCo/GC@MSS catalyst by a magnetic separation which could be recycled for atleast five times without any change in the catalyst morphology. The propargylic substitution reactions for PMA@FeCo/GC@MSS followed the $\text{S}_{\text{N}}1$ mechanism.



Scheme 212 K-10 catalyzed propargylic substitution reaction.

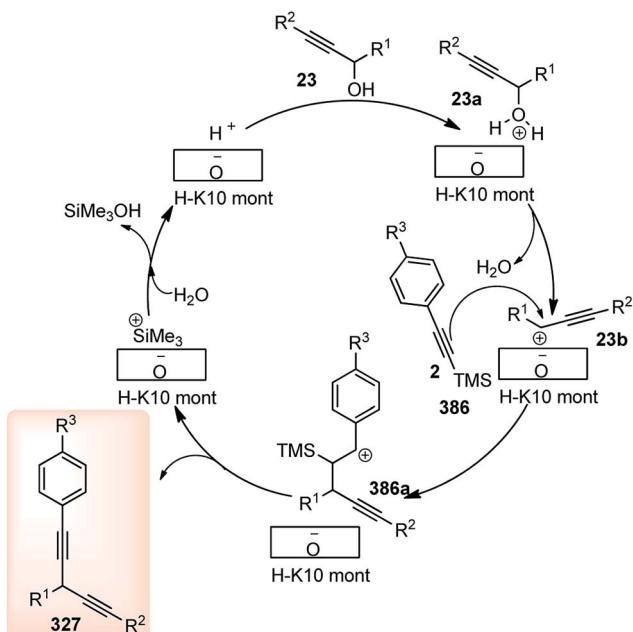
Zhan and coworkers reported HCl treated K10 montmorillonite for the nucleophilic substitution of propargylic alcohols by terminal TMS-alkynes to form 1,4-dynes under solvent-free condition. In the beginning, the reaction was studied by commercial virgin K10 under a neat condition which led to the formation of the desired product with only 48% yield, Scheme 212.²⁴⁵

It was anticipated that due to lack of adequate exchangeable protons in the catalyst the reaction did not work well. Thus, K10 mont was treated with different concentrations of hydrochloric acids in different temperature. Finally, K10 mont obtained after the treatment of the catalyst in 1 M HCl at 80 °C proved to be the most efficient one. Acid-treated K10 mont catalyzed the substitution of propargylic alcohols by trimethyl(phenylethynyl) silane to form 1,4-dynes with 89% yields in 25 min.

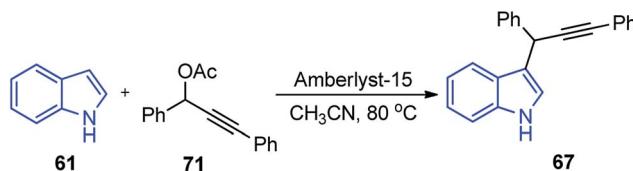
Treatment of the substrates with other Brønsted acids like HCl or *p*-TsOH resulted in trace amount of product after 24 h of stirring. On the other hand, TfOH resulted in only 37% product after 24 h. However, the reaction did not proceed at all in the absence of a catalyst. Several 1,4-dynes were synthesized using this methodology by varying the substituents in the propargylic alcohols as well as in the nucleophile. A positive Sheldon test confirmed that the reaction was occurring on the surface of the catalyst which led to the conclusion that K-10 mont catalyzed reactions were heterogeneous in nature.²⁴⁶ The proposed mechanism for the catalytic pathway is shown in Scheme 213.

Corma and co-workers in the year 2015 showed the application of zeolites under mild reaction conditions for propargylic substitution reaction towards the synthesis of a variety of

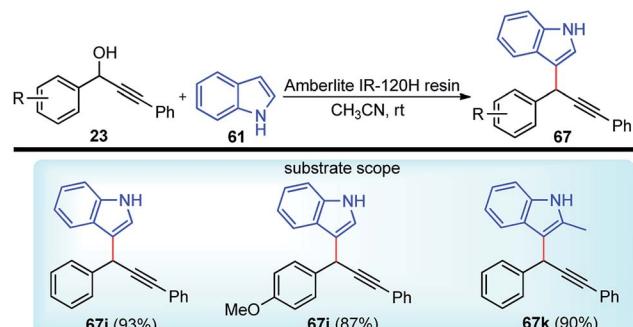




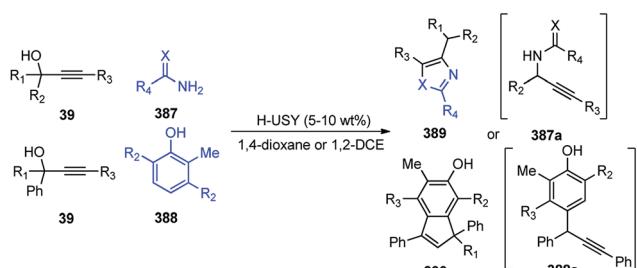
Scheme 213 Mechanism for the K-10 catalyzed propargylic substitution reaction.



Scheme 215 Efficient alkylation of indoles with propargylic acetates using Amberlyst-151.



Scheme 216 Propargylation of indoles by amberlite resin catalyst.



Scheme 214 Zeolite as a catalyst for propargylic substitution reaction.

heterocycles like oxazoles 389, thiazoles 389, and indenols 390 with high yield, and good selectivity, Scheme 214.²⁴⁷

Zeolites generate and stabilize delocalized carbocations after dehydration of propargyl alcohols 39, under mild reaction conditions, and then catalyze the synthesis. Following previously proposed mechanisms for homogeneous acid catalysts, the first step is the formation of the carbocation on the acid sites, followed by nucleophilic attack and cyclization.

Yadav and co-workers in the year 2007 described an efficient alkylation of indoles 61 with propargylic acetates 71 using Amberlyst-151 as a novel promoter, Scheme 215.²⁴⁸

The reaction proceeds *via* an S_N2 pathway and the operationally simple and efficient methodology with mild reaction conditions makes it a useful and attractive process for the alkylation of indoles. Interestingly, a highly acid sensitive pyrrole and furan gave the desired propargylated derivatives without the formation of any side products arising from the polymerization.

Another direct nucleophilic substitution of propargylic alcohols 23 with various nucleophiles using Amberlite IR-120H-

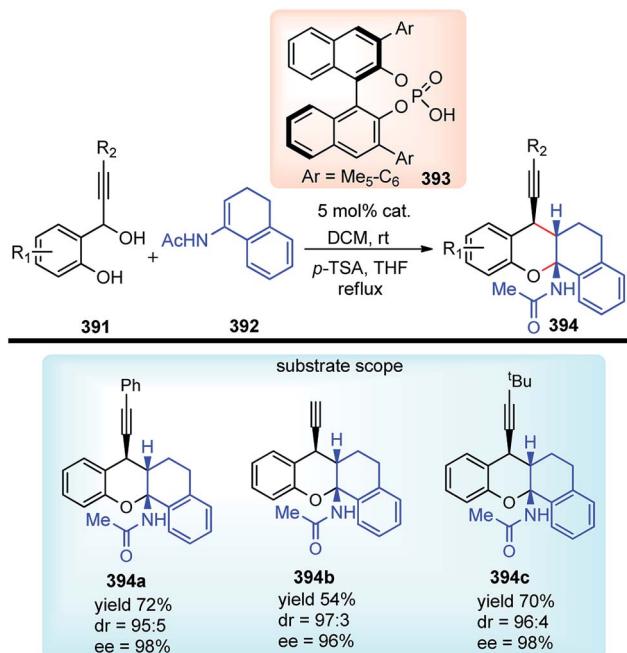
resin as a catalyst was reported by Zheng and co-workers in the year 2013, Scheme 216.²⁴⁹

The rate of the reaction was found to be dependent on the amount of resin used. With 300 mg mmol⁻¹ of resin, the reaction completed within 30 min at room temperature to give 3-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-1*H*-indole 67j in 93% yield. The method features short reaction times, mild reaction conditions, simplicity in operation, zero aqueous waste generation, complete regioselectivity.

Recently quinone methides (QMs), featuring a unique assembly of carbonyl and olefinic moieties, have gained considerable interest as a highly reactive intermediate. A wide range of catalytic, enantioselective transformations has been successfully developed for *o*-QM chemistry using Brønsted acid catalyst.^{250–252} Schneider and co-workers in 2015 reported a highly enantioselective conjugate addition of enamides and ene-carbamates to *in situ* generated *ortho*-quinone methides, towards the synthesis of acetamido-substituted tetrahydroxanthenes.²⁵³

In continuation of their research on *ortho*-quinone methide chemistry, the same group in 2015 demonstrated a highly enantioselective BINOL-based, chiral phosphoric acids catalyzed propargylic substitution of 1-(*o*-hydroxyphenyl)propargylic alcohols 391 with enamides 392 towards the synthesis of substituted benzoc[x]anthenes 394 and related heterocycles in a one-pot operation, Scheme 217.²⁵³

Various chiral BINOL based catalysts were screened for this reaction and the results revealed that *ortho*-substitution within the 3,3'-aryl substituents in the BINOL backbone of the phosphoric acid catalyst gave superior enantioselectivities and the products were obtained in good yields irrespective of the substitution pattern within the alkynyl or the aryl group. A



Scheme 217 Chiral phosphoric acid catalyzed highly enantioselective synthesis of 7-alkynyl-12a-acetamido-substituted benzo[c]xanthenes in very good yields from propargylic alcohols.

has been an incredible progress in the design and development of catalysts for propargylic substitution reaction. In this account, we have attempted to document comprehensively the developments and evolution of catalysts in the last few years that has witnessed an exponential growth. Some reactions involved newer methods, safer catalysts, environmentally friendly conditions, significantly contributing to simplifying the methodology, towards the synthesis of novel molecules. Despite these advancements, further efforts toward the development of better and safer catalysts are necessary. The appearance of new catalysts and chemical transformations is expected to provide avenues for the propargylic substitution reaction, leading to the discovery of molecules with new properties and biological activities. We conclude this review by hoping that it will stimulate researchers to develop new and creative methods for the propargylic substitution reaction which will be instrumental in the advancement of many branches of chemistry. Despite the impressive progress that has been made in this area, it is still highly desirable to explore more efficient and practical, as well as sustainable, catalytic systems for the propargylic substitution reactions. Thus, we hope this review will promote continued interests in developing new catalytic methodologies and encourage chemists to employ these valuable methodologies in heterocyclic, medicinal chemistry as well as in other branches of chemistry.

Conflicts of interest

The authors declare no conflict of interest.

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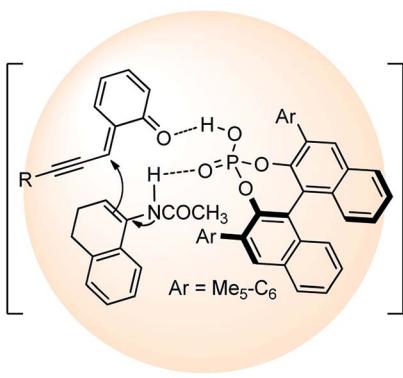


Fig. 23 Transition state structure for the formation of 7-alkynyl-12a-acetamido-substituted benzo[c]xanthenes in high enantioselectivity.

probable mechanism along with the proposed transition state is shown below, Fig. 23.

The phosphoric acid catalyzes the generation of the intermediate *ortho*-quinone methide from the *ortho*-hydroxy propargylic alcohol derivatives which is then subsequently attacked by the enamide 392 with high facial selectivity guided by the chiral BINOL based phosphoric acid catalyst.

7. Conclusions

Catalytic propargylic substitution continues to be a very active field of research due to the alkyne handle which provides ample opportunity for the synthesis of various heterocyclic structures which are important building blocks in organic synthesis. There



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