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Catalyzed Propargylic Substitution

Remko J. Detz,[a] Henk Hiemstra,[a] and Jan H. van Maarseveen*[a]

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Besides being a versatile entity for further chemical transformations, the propargylic subunit is also part of various natural products, fine chemicals, and synthetic pharmaceuticals. Propargylic substitution reactions, however, are rather unexplored. An overview of this emerging field is presented. We especially focus on experimental results that deal with catalyzed substitutions of propargylic alcohols and their derivatives. Finally, some enantioselective propargylic substitution methods are discussed.

Introduction

The propargylic moiety is a popular functionality in organic synthesis. The π-nucleophilic character of the triple bond makes it a versatile entity for further chemical transformations. In terminal acetylenes the triple bond is accompanied by a fairly acidic terminal acetylenic hydrogen atom, which broadens the synthetic utility of these compounds even more. In addition, natural products, fine chemicals, and synthetic pharmaceuticals have been reported that contain the propargylic subunit as part of their structure (Figure 1).[1]

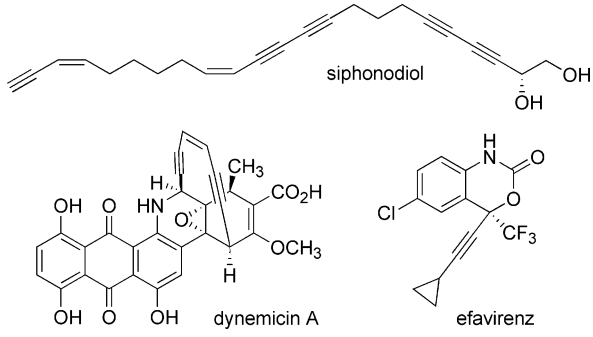
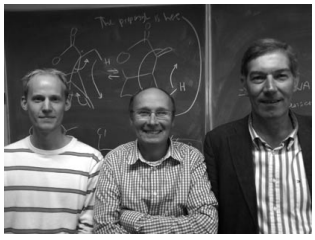


Figure 1. Some bioactive alkynes with a propargylic heteroatom.

Although allylic substitution reactions have been studied intensively,[2] the field of transition-metal-catalyzed propargylic substitutions is rather undeveloped.[3] Especially, the regioselectivity of the latter reaction is of great importance, because either alkynes or allenes can be obtained. This is in contrast to allylic substitution, which solely affords alkenes (Figure 2). To obtain the alkyne product, selective substitution at the α-position of the propargylic moiety is desired. By selecting the proper catalyst, the desired regioselective outcome of this transformation may be obtained. Herein an

[a] Van 't Hoff Institute for Molecular Sciences, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands
E-mail: J.H.vanMaarseveen@uva.nl
http://www.science.uva.nl/hims-bms



Jan van Maarseveen (center) was born in Enschede, The Netherlands, in 1963. He studied chemistry at the University of Nijmegen and received his PhD at this university with Prof. Binne Zwanenburg and Dr. Hans W. Scheeren in 1994. In the same year, he joined Solvay-Pharmaceuticals (Weesp, The Netherlands) as a group leader in the Medicinal Chemistry Department. He was appointed at the University of Amsterdam in 1999 where he is now associate professor. In 2004 he briefly joined the group of Prof. Rheza Ghadiri at the Scripps Research Institute (La Jolla, USA) to develop new methods for cyclic peptide synthesis using click chemistry. His current research interests are the development of novel synthetic methodology to enable difficult peptide cyclizations, homogeneous catalysis, and the combination of organic synthesis and biology.

Henk Hiemstra (right) was born in Dronrijp, Friesland, The Netherlands, in 1952. He studied chemistry at the University of Groningen and received his PhD at this university with Prof. Hans Wynberg in 1980. After a postdoctoral stay with Prof. Barry M. Trost at the University of Wisconsin, Madison, USA, he was appointed at the University of Amsterdam in 1982. He was promoted to full professor of organic synthesis in 1997. His favorite research areas are new synthetic methodology and the total synthesis of natural products.

Remko Detz (left) was born in Heerhugowaard, The Netherlands, in 1980. He studied chemistry at the University of Amsterdam and received his PhD at this university with Prof. Henk Hiemstra and Dr. Jan van Maarseveen in 2009. Currently, he is working for InCatT B.V., a high-tech spin-off company of the University of Amsterdam.

overview is given of the current state of the emerging field of catalyzed propargylic substitution reactions starting from propargylic alcohol derivatives.[4]

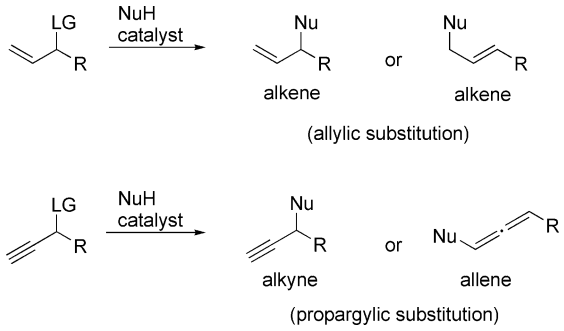
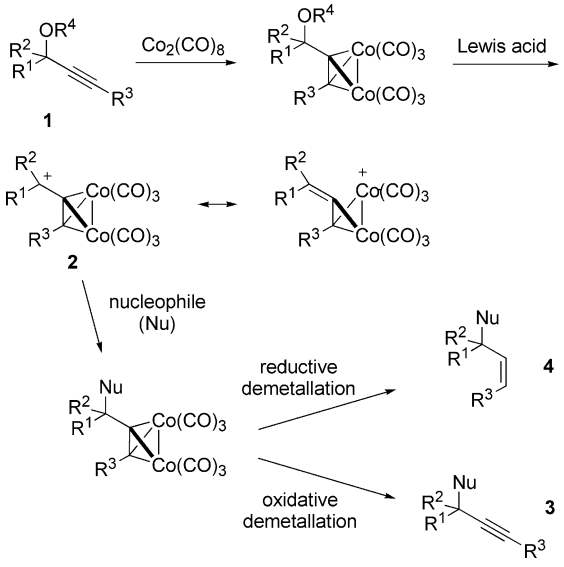


Figure 2. Allylic vs. propargylic substitution (LG = leaving group, NuH = nucleophile).

Before the various reagents that catalyze substitutions at the propargylic α-position are discussed, first the most well-known metal-mediated stoichiometric methods will be dealt with.

Stoichiometric Propargylic Substitutions

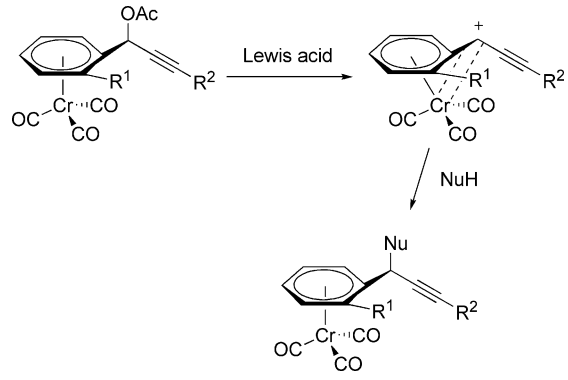
A fundamental substitution reaction of propargylic alcohol derivatives (**1**) is the Nicholas reaction, which occurs via a stoichiometric alkyne-cobalt complex (Scheme 1).[5] In this reaction the generated carbocationic charge at the carbon in α-position to the alkyne moiety (**2**) is stabilized by hexacarbonyldicobalt, $Co_2(CO)_6$, prior to treatment with a nucleophile. The reaction allows a broad range of heteroatom-centered nucleophiles, such as alcohols, amines, and thiols, but also carbon π-nucleophiles, such as ketones, silyl enol ethers, and electron-rich aromatic rings, are allowed.



Scheme 1. The Nicholas reaction.

After nucleophilic addition, the alkyne-cobalt complex can be cleaved oxidatively to afford the propargylic product **3**. Reductive demetalation gives, if desired, the alkene **4**. Although broad in scope, the required stoichiometric amounts of $Co_2(CO)_8$, and the multiple steps that are necessary to obtain the desired propargylic products are serious drawbacks of the Nicholas reaction.

Another stoichiometric method, reported by Müller and Netz,[6] makes use of an *ortho*-substituted (arene)$Cr(CO)_3$ group as substituent on the α-carbon of propargylic acetates. After acetate removal by a Lewis acid ($TiCl_4$ or TMSOTf) the cation is stabilized by this chromium complex and can be subjected to trapping reactions with C-, O-, S- and N-centered nucleophiles (Scheme 2). After reaction decoordination of the chromium is achieved by exposure to light or treatment with I_2, ceric ammonium nitrate, CO, PPh_3, or pyridine.[6d]

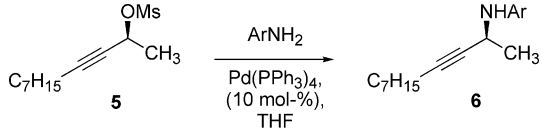


Scheme 2. Cr-mediated propargylic substitution.

Catalyzed Propargylic Substitutions

Palladium-Catalyzed Substitutions

Palladium-catalyzed reactions with propargylic compounds are known, but these usually yield the corresponding allenic systems.[7] One example in which the propargylic products were obtained was reported by Marshall and Wolf.[8] They described a Pd-catalyzed substitution of enantiopure propargylic mesylate **5** (95% *ee*) by arylamines, which occurred with retention of the configuration



6	Ar	t (h)	yield	*ee*
a	Ph	1	78%	90%
b	*p*-MeC_6H_4	0.5	71%	90%
c	*p*-$MeO_2CC_6H_4$	3	75%	84%

Scheme 3. Pd-catalyzed propargylic substitution.

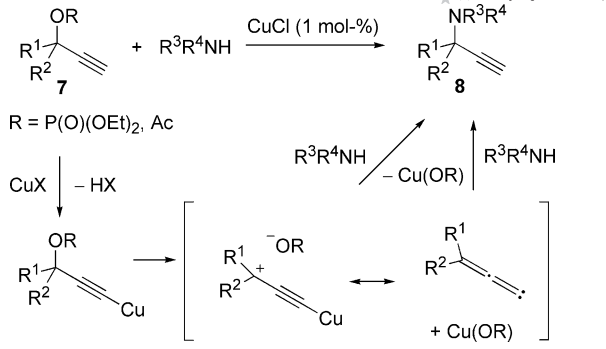
(Scheme 3). Without the Pd catalyst the mesylate was also substituted, but now with inversion of the propargylic stereocenter via an S_N2-type mechanism. More palladium-catalyzed propargylic substitutions are reported although the selectivity usually remains a problem.[9]

Copper-Catalyzed Substitutions

To avoid allene formation, Brinkmeyer and Macdonald found that in the treatment of propargylic acetates with organocuprates, blocking the terminal position of the acetylene with a bulky group afforded the desired acetylenic products in good yield.[10] In 1960, Hennion and Hanzel reported a copper-catalyzed route towards propargylic amines starting from tertiary propargylic chlorides.[11] Only with weakly nucleophilic amines (i.e. aromatic amines) the copper catalyst was necessary in order to obtain the products in good yields. It was stated that the copper catalyst may form a reactive copper acetylide species that is responsible for the improved reactivity. This protocol was also followed by Rathke et al. with more hindered amines.[12] Also aminations of propargylic oxyphosphonium salts and triflates have been reported.[13]

Murahashi et al. reported in 1994 a more practical route starting from propargylic esters **7** to prepare propargylic amines **8** under mild conditions catalyzed by copper chloride (Scheme 4).[14] Although the mechanistic aspects were not totally clear they supported the idea of Hennion and Hanzel that a zwitterion and/or carbene intermediate was the reactive species susceptible for nucleophilic attack. The observation that an internal alkyne did not undergo the amination reaction, even under forcing conditions, shows that a terminal acetylenic proton is essential, presumably for the formation of the intermediate copper-acetylide species.

The amination is highly regioselective and allenylamines could not be detected among the products. Both propargylic phosphates and acetates did react with several types of amines, such as aliphatic, benzylic, and aromatic secondary amines. With primary amines, like aniline and benzylamine, only the monopropargylated amines were obtained.

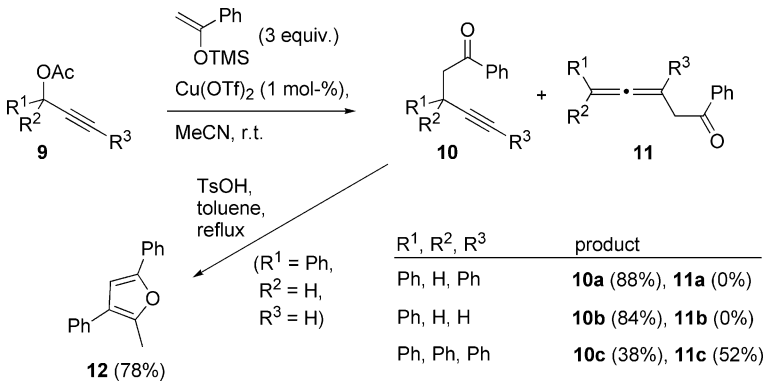


Scheme 4. Murahashi's copper-catalyzed propargylic amination.

Mann et al. reported that copper(I) iodide catalyzes the reaction between phenols and dialkylpropargyl chlorides to give aryl 1,1-dialkylpropargyl ethers.[15] Although more examples of substitutions of propargylic halides are known in literature,[16] we will only discuss here substitutions performed from propargylic alcohols and derivatives thereof.

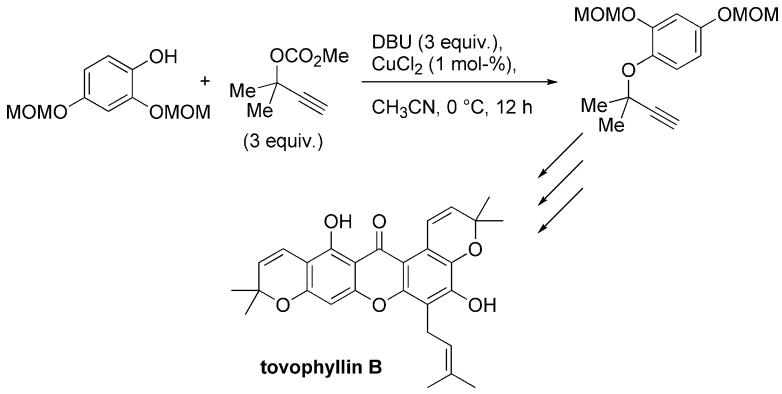
Also a copper(II)-catalyzed method was reported in which silyl enol ethers were used as nucleophiles (Scheme 5).[17] Both internal and terminal alkynes were allowed in the reaction suggesting a S_N1-type mechanism with a propargylic cation intermediate rather than a copper-acetylide species. The regioselectivity is affected by steric bulkiness at the electrophilic site which for substrate **9c** resulted in the formation of 52% of allene **11c** besides alkyne **10c** (38%). Although the regioselectivity is a problem sometimes, the low catalyst loading and short reaction time (typically 5 min) make this reaction a versatile route to γ-keto alkynes. The $Cu(OTf)_2$-catalyzed propargylic substitution allowed a sequential cyclization reaction to form tri- or tetrasubstituted furans (such as **12**) by heating with acid in toluene.

Also for the synthesis of biologically active compounds copper-catalyzed propargylations have been used.[18] This is illustrated by the total synthesis of tovophyllin B, which possesses a significant inhibitory activity against *Mycobacterium tuberculosis* (Scheme 6).



R^1, R^2, R^3	product
Ph, H, Ph	**10a** (88%), **11a** (0%)
Ph, H, H	**10b** (84%), **11b** (0%)
Ph, Ph, Ph	**10c** (38%), **11c** (52%)

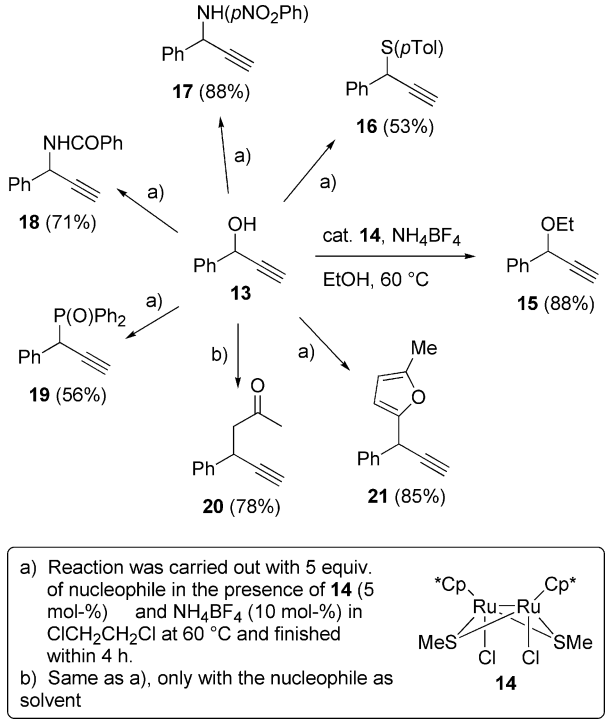
Scheme 5. Copper(II)-catalyzed propargylic substitution.



Scheme 6. Synthesis of tovophyllin B.

Ruthenium-Catalyzed Substitutions

Especially in the last decade many methods have been reported that make use of catalytic amounts of other transition metals than copper to modify the propargylic α-position by substitution of propargylic alcohols or derivatives thereof. Nishibayashi, Hidai, and Uemura and co-workers developed a ruthenium-catalyzed process in which a wide variety of nucleophiles can be used.[19] Treatment of, for example, 1-phenyl-2-propyn-1-ol (**13**) in ethanol in the presence of **14** (5 mol-%) and NH_4BF_4 (10 mol-%) at 60 °C afforded in 15 min the corresponding ethyl ether **15** in 88% yield (Scheme 7). Besides alcohols, also sulfides, amines, amides, and diphenylphosphane oxide were effective as nucleophiles, affording the corresponding products in good yields (**16**–**19**).[19,20] Even carbon π-nucleophiles, such as simple ketones (e.g. acetone, product **20**),[21] 1,3-dicarbonyl compounds,[22] and electron-rich aromatic rings (e.g. product **21**),[23] were successfully employed in the reaction. The reaction only proceeded with diruthenium(III,III) complexes, such as **14**; both diruthenium(II,III) and monoruthenium complexes were ineffective. It was also found that the dibromo- or diiododiruthenium complexes work as catalysts in the propargylic substitution reaction but the activity was lower in comparison with the dichloro analogue.[24] In all cases no allenic products were observed.

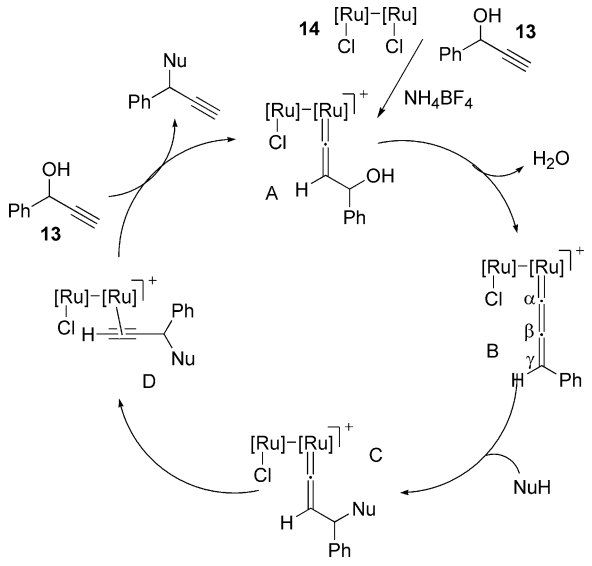


Scheme 7. Nishibayashi's Ru-catalyzed propargylic substitution (Cp* = η^5-C_5Me_5) with **14**.

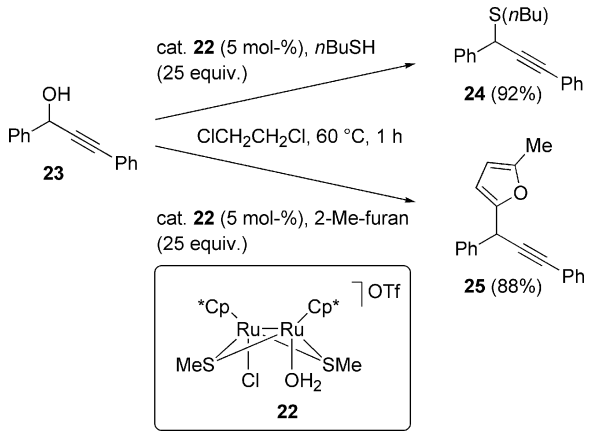
For mechanistic reasons, available substrates were limited to propargylic alcohols bearing a terminal alkyne group because the reaction proceeds via an allenylidene ruthenium complex as key intermediate (Scheme 8). This allenylidene complex (**B**) is obtained by dehydration of the initially formed vinylidene complex **A**. Nucleophilic attack on the electrophilic C_γ atom of the allenylidene first results in the formation of an alkynyl complex, which rearranges to vinylidene complex **C** (netto: addition of the NuH to the C_γ=C_β double bond). Rearrangement of complex **C** into the η^2-coordinated propargylic product gives complex **D**, which liberates the product after exchange with propargylic alcohol **13**, and regenerates complex **A**.

Nishibayashi and co-workers reported that a slight modification of the catalyst allowed in some cases the use of internal alkynes (Scheme 9).[20b] In the absence of NH_4BF_4, catalyst **22** was found to give sulfide **24** in high yield starting from internal alkyne **23**. In addition, the products derived from terminal alkynes were provided in higher yields by this catalyst system compared to the yields obtained with complex **21**. Because no allenylidene can be formed, it is suspected that this catalyst coordinates to the alkyne (as in D, Scheme 6) or only acts as a Lewis acid.

With aromatic rings as nucleophiles such as 2-methylfuran, **23** was effectively substituted using the same catalytic system. With terminal alkynes and aromatic rings as nucleophiles, cationic catalyst **22** was equally active as the neutral complex **14**. With the development of this cationic catalyst a more general approach was presented for the substitution of propargylic alcohols, with both terminal and internal alkynes. However, no propargylic substitution reactions of **23** with alcohols, amines, acetone, and silyl enol



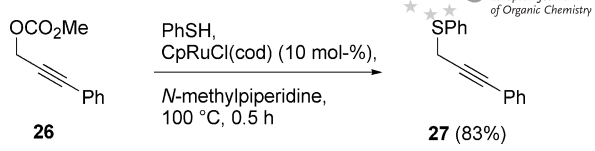
Scheme 8. Proposed catalytic cycle for the ruthenium-catalyzed propargylic substitution.



Scheme 9. Ruthenium-catalyzed propargylic substitution of internal alkynes with catalyst **22**.

ethers in the presence of **22** occurred under similar reaction conditions.

Besides the use of the successful diruthenium(III,III) complexes, some other groups succeeded to use mononuclear ruthenium complexes in propargylic substitution reactions.[25] Mitsudo et al. reported the preparation of propargylic sulfides using a catalytic amount of CpRuCl(cod) or $CpRuCl(PPh_3)_2$ (10 mol-%).[25a] Several propargylic carbonates bearing internal alkynes **26** were treated with either aryl- or alkyl sulfides in *N*-methylpiperidine giving the corresponding products **27** in reasonable to high yield (20–95%, Scheme 10). The tertiary amine solvent was crucial to prevent catalyst deactivation. The method was unsuccessful for terminal alkynes and with a α-phenyl-substituted propargylic carbonate the product was obtained in less than 10% yield besides an unexpected side product.

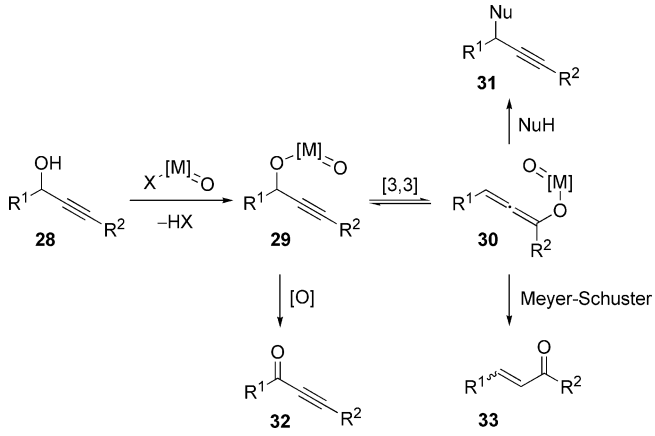


Scheme 10. Ruthenium-catalyzed propargylic substitution with mononuclear ruthenium complexes.

Also other nucleophiles were applied using mononuclear ruthenium complexes, such as alcohols,[25b] and electron-rich aromatic rings.[25c,25d] With alcohol nucleophiles good yields were obtained using 5 mol-% of a (η^3-allyl)ruthenium(II) complex: [Ru(η^3-2-C_3H_4Me)(CO)(dppf)][SbF_6] [dppf = 1,1′-bis(diphenylphosphanyl)ferrocene], although Meyer–Schuster rearrangement was a problem (see Scheme 9 for Meyer–Schuster rearrangement). The reactions in which electron-rich aromatic rings were applied as nucleophiles gave lower yields (<60%).

Rhenium-Catalyzed Substitutions

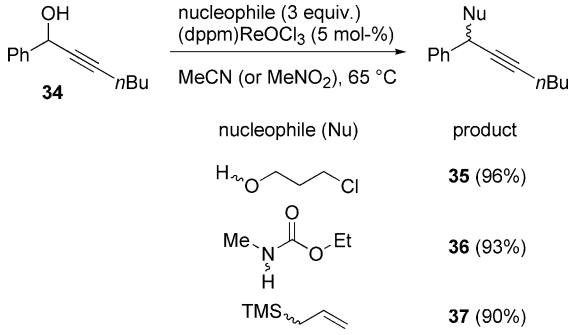
Toste and co-workers cleverly postulated that an allenolate intermediate (**30**), formed by the reaction of a propargylic alcohol (**28**) with a metal-oxo complex, could undergo S_N2' addition of a nucleophile (Scheme 11). This idea was based on the knowledge that metal-oxo complexes effect the rearrangement of propargylic alcohols to enones (**33**) (Meyer–Schuster rearrangement).[26]



Scheme 11. Proposed mechanism of propargylic substitution catalyzed by metal-oxo complexes.

They examined several metal-oxo complexes for the selective conversion of propargylic alcohol **34** to propargylic ether **35** (Scheme 12). A rhenium(V)-oxo complex bearing a bidentate phosphane ligand (dppm: diphenylphosphanylmethane) was the most effective and afforded the desired product **35** with only traces of oxidized and rearranged products (such as **32** and **33**).[27] The same conditions were applied to a variety of propargylic alcohols. It appeared that not only benzylic substrates were converted, but even disubstituted propargylic alcohols, such as 1,1-dimethylbut-2-yn-1-ol, underwent the etherification in good yield (69%). Only with two large substituents, e.g. two phenyl groups,

the enone was formed exclusively, illustrating a steric component to the reaction. Both with primary and secondary alcohols the ether products were obtained in good yields (53–88%), with tertiary alcohols moderate conversions (<30%) were observed.



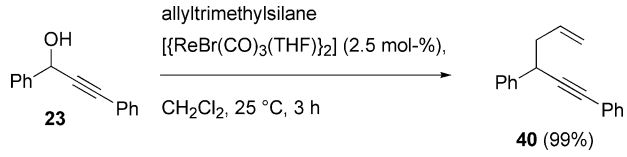
Scheme 12. Rhenium(V)-catalyzed propargylic substitution.

The mechanistic considerations led the same group to investigate the substitution of **34** by nitrogen nucleophiles as well.[28] The use of allylamine failed to yield the desired product. According to the authors, competitive binding of the Lewis basic amine to the rhenium center precluded the propargylic alcohol to coordinate. Indeed, less Lewis basic amines, such as tosylamide, *p*-nitroaniline, and ethyl methylcarbamate, gave the corresponding propargylic amines (e.g. **36**) in good yields (66–93%). Side reactions, as depicted in Scheme 8, were completely suppressed by addition of 5 mol-% of NH_4PF_6.

The formation of carbon–carbon bonds was accomplished by the same Re-catalyst taking allylsilanes as π-nucleophiles.[29a] The best results for this reaction were obtained if nitromethane was the solvent, and NH_4PF_6 was added as co-catalyst. Several benzylic propargylic alcohols were transformed into the anticipated 1,5-enynes (e.g. **37**) in good to very high yields (55–99%). Non-benzylic propargyl alcohols also participated in the substitution reaction; however, silver hexafluoroantimonate was required as the co-catalyst, instead of NH_4PF_6, to obtain reasonable yields (25–58%).

It was also shown that (hetero)aromatic compounds could be reacted with propargylic alcohols (**38**) using the rhenium(V)-oxo complex.[29b] The method was elegantly applied in the formal synthesis of the cytotoxic aryltetralin lactone podophyllotoxin (Scheme 13).

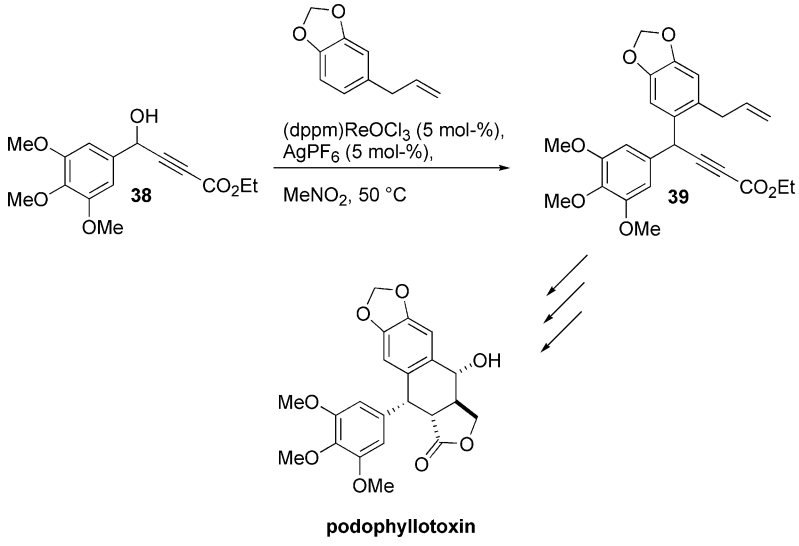
Another group reported a successful rhenium(I)-catalyzed procedure.[30] The reaction of propargylic alcohols with allyl- or alkynylsilanes in the presence of a catalytic amount of $[\{ReBr(CO)_3(THF)\}_2]$ afforded the corresponding products (**40**, Scheme 14) in good to high yield (67–99%). Also several other nucleophiles such as 1,3-dicarbonyl compounds, heteroaromatic compounds, and thiols were successfully applied.[30b]



Scheme 14. Rhenium(I)-catalyzed propargylic substitution.

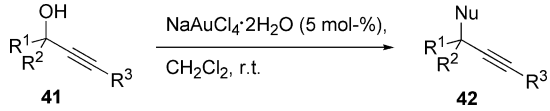
Gold-Catalyzed Substitutions

Gold(III)-catalyzed nucleophilic substitutions of propargylic alcohols were recently disclosed by the group of Campagne.[31] The best results for the allylation of 1-phenylhept-2-yn-1-ol **41a** by allyltrimethylsilane were obtained with $NaAuCl_4 \cdot 2H_2O$ (5 mol-%) as the catalyst (Scheme 15). Various propargylic alcohols were allowed in the allylation reaction, bearing electron-rich and moderately electron-poor aromatic rings (72–85%). With the strongly electron-withdrawing *p*-nitrophenyl group as substituent (R^1, R^2) no reaction was observed. Modifications on the alkynyl part



Scheme 13. Formal synthesis of (±)-podophyllotoxin.

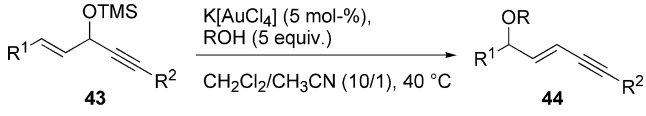
(R^3) also gave good yields (71–97%) except for an electron-poor group (CO_2Et) and a terminal alkyne (0% and 9% yield, respectively). Tertiary non-benzylic propargylic alcohols were effectively converted into the 1,5-enyne products, although in lower yields (33–59%), but secondary alkyl-substituted alcohols (e.g. **41g**) were not converted at all. Alcohols, electron-rich aromatic rings, sulfonamides, and thiols were successfully applied as nucleophiles in this gold-catalyzed method, affording the products in moderate to good yields (35–88%).



42	R^1, R^2, R^3	NuH/NuTMS	yield
a	Ph, H, *n*-pentyl	allylTMS	82%
b	Ph, Me, *n*-pentyl	allylTMS	33%
c	Ph, H, *n*-pentyl	butanol	88%
d	Ph, H, TMS	furan	46%
e	Ph, H, *n*-pentyl	$HSCH_2CO_2Et$	66%
f	Ph, H, *n*-pentyl	H_2NSO_2Ph	58%
g	Alk, H, *n*-pentyl	allylTMS	0%

Scheme 15. Gold-catalyzed propargylic substitution.

Dyker et al. demonstrated that catalytic amounts of $AuCl_3$ (0.3–1 mol-%) gave comparable results as stoichiometric amounts of $F_3B{\cdot}OEt_2$ in several Friedel–Crafts alkylations.[32] However, the more crowded dialkylated products could only be obtained using $F_3B{\cdot}OEt_2$. If 3-silyloxy-1,4-enynes (**43**) are used as starting material in the presence of excess alcohol, Kirsch et al. found out that $K[AuCl_4]$ was the catalyst of choice to obtain pent-2-en-4-ynyl ethers **44** in moderate to excellent yields (41–98%, Scheme 16).[33]



44	R^1, R^2	ROH	yield
a	Ph, Ph	*i*PrOH	70% (*E*:*Z* = 1.3:1)
b	Me, Ph	MeOH	98% (*E*:*Z* = 4:1)
c	Ph, H	*i*PrOH	43% (*E*:*Z* = 2:1)

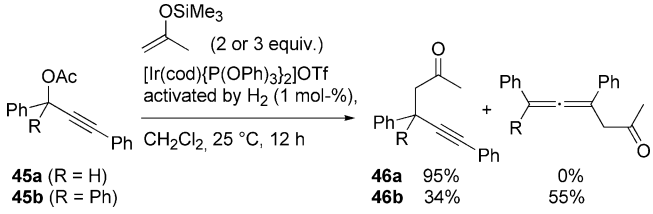
Scheme 16. Gold-catalyzed reaction with 3-silyloxy-1,4-enynes.

Tosylamide and furan reacted as well and in a complete regioselective manner although the yields were low (34% and 32%, resp.). Occasionally some 3-hydroxy-1,4-enyne was identified as by-product due to silyl ether cleavage, but the use of a hydroxy or acetate leaving group did diminish the yield and activity of the reaction. Although the allylic part of **43** may distract the attention from the propargylic group, the authors state that the triple bond was beneficial to the reaction outcome because either no conversion or complete decomposition was obtained in absence of the alkyne moiety.

Arcadi et al. reported a sequence of gold-catalyzed reactions starting from 1-phenylprop-2-yn-1-ol **13** using 1,3-dicarbonyl compounds as nucleophiles.[34] Various products were obtained after either *C*-cyclization/cyclization, *C*-alkylation/hydration, or *O*-alkylation/hydration which depended on the choice of the gold source and the reaction conditions.

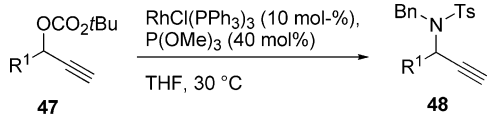
Propargylic Substitutions by Other Transition-Metal Complexes

In 2002 Matsuda and co-workers reported the transformation of propargylic acetates (e.g. **45a**) into β-alkynyl carbonyl compounds (e.g. **45a**) upon reaction with silyl enol ethers in the presence of a catalytic amount of an iridium phosphite complex, which was first activated by dihydrogen (Scheme 17).[35] Both internal and terminal alkynes were converted. In some cases the reaction was not regioselective. With two phenyl groups on the propargyl carbon, like in **45b**, reverse selectivity was observed in the regiochemistry of the substitution, and 55% of the allenic product **45b** was obtained. Steric bulkiness at the nucleophilic site was considered to be advantageous for allene formation, which was later also observed by Zhan et al. with the copper(II)-catalyzed reaction.[17]



Scheme 17. Iridium-catalyzed propargylic substitution.

Evans and Lawler examined the feasibility of the propargylic amination of propargylic carbonate **47**, catalyzed by the Wilkinson catalyst $RhCl(PPh_3)_3$.[36] The amination of the propargylic alcohol of **47** with the lithium anion of *N*-benzyltoluenesulfonamide was unsuccessful. By using as the leaving group a *tert*-butyl carbonate and as an additive trimethyl phosphite (40 mol-%) the propargylic sulfonamide **48** was obtained in 82% yield (Scheme 18).

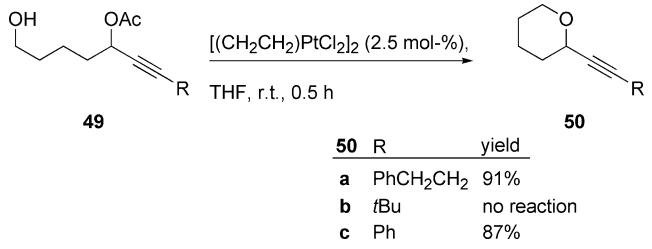


48	R^1	NuH/base	yield
a	$PhCH_2CH_2$	HN(Ts)Bn/LiHMDS	82%
b	*t*Bu	HN(Ts)Bn/LiHMDS	83%
c	Ph	HN(Ts)Bn/K_2CO_3	74%

Scheme 18. Rhodium-catalyzed propargylic substitution.

High yields were observed only with terminal alkynes for a series of alkyl-substituted propargylic carbonates (71–86%). The aryl derivatives furnished the corresponding allenyl sulfonamides, due to base-induced isomerization. Indeed, with a weaker base, K_2CO_3, the propargylic sulfonamides were obtained, in most cases as single isomers.

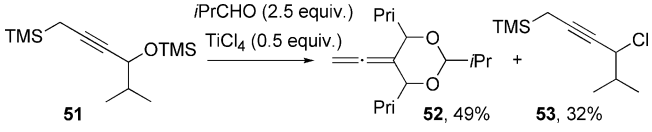
De Brabander et al. demonstrated that $[CH_2CH_2/PtCl_2]_2$ could catalyze the cycloetherification of propargylic acetates **49** bearing a hydroxy group in the side chain.[37] The propargylic ethers **50** were obtained in high yield (77–93%) under mild conditions, although the very sterically hindered *tert*-butyl alkyne **49b** gave no reaction (Scheme 19). Next to primary alcohols also secondary alcohols reacted under these conditions.



Scheme 19. Platinum-catalyzed propargylic substitution.

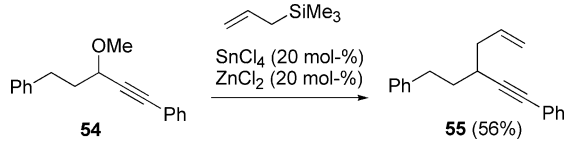
Lewis Acid Catalyzed Propargylic Substitutions

Besides transition-metal catalysis, in which the metal ion activates the alkyne, also Lewis acids have been used that predominantly activate the alcohol (derivative) to catalyze propargylic substitution reactions. Already in 1986, Pornet et al. observed an interesting side reaction during the preparation of alkyl-substituted 5-vinylidene-1,3-dioxanes (**52**) from α-silyloxypropargyltrimethylsilanes (**51**, Scheme 20). They found that the α-silyloxy group of their starting material was partially substituted by chloride in the presence of $TiCl_4$.[38]



Scheme 20. Propargylic substitution by $TiCl_4$.

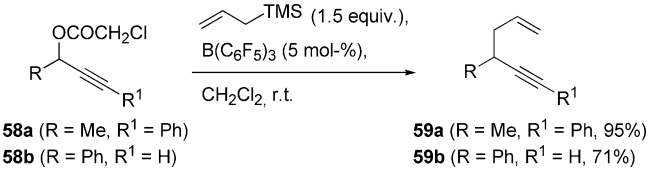
Mukaiyama et al. deliberately treated propargylic ether **54** with allyltrimethylsilane in the presence of catalytic amounts of $SnCl_4$ and $ZnCl_2$, which afforded the desired product **55** in reasonable yield (Scheme 21).[39]



Scheme 21. Lewis acid mediated substitution of propargylic ether **54**.

Recently, other Lewis acid catalyzed propargylic substitutions by allylsilanes have been reported. Saito et al. started from propargylic TMS ethers and used TMSOTf to catalyze the substitution with allyltrimethylsilane.[40] The catalyst was regenerated by the liberation of the silyl cation from the nucleophiles. The regioselectivity was determined by the substituents at the 3-position, although either the propargylic (**57a**) or the allenic product (**57b**) was formed exclusively (Scheme 22).

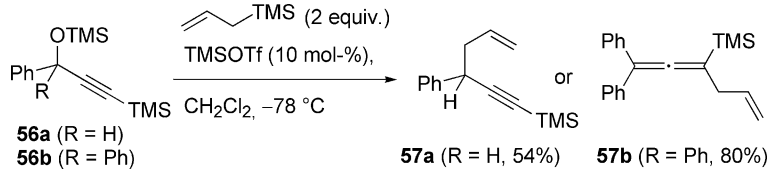
The first attempt to allylate the propargylic alcohol of **58** in the presence of $B(C_6F_5)_3$ failed, as described by Gevorgyan and co-workers.[41a] Optimization of the leaving group led to the use of **58** as the propargylic esters of choice. Both aliphatic and aromatic side chains were allowed in this transformation, and besides terminal alkynes, also internal alkynes were effectively allylated (Scheme 23). Kim et al. reported recently that the propargylic alcohol of **58**, with R = Me, R^1 = H, was successfully cyanated using one equivalent of TMSCN as nucleophile in the presence of 3 mol-% of $B(C_6F_5)_3$.[41b]



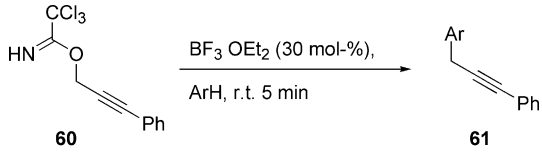
Scheme 23. $B(C_6F_5)_3$-mediated substitution of propargylic esters **58**.

Another boron-mediated substitution was reported by Li and Wang.[41c] They developed a Friedel–Crafts method to synthesize 1,3-diarylpropynes **61** starting from *O*-propargyl trichloroacetimidates **60** in good yields in the presence of a catalytic amount of $F_3B{\cdot}OEt_2$ (30 mol-%) (Scheme 24). Interestingly, this method only worked with primary propargylic substrates with internal alkynes because more steric hindrance resulted in the formation of other products, such as allenes or rearranged starting materials.

Mahrwald and co-workers described a $TiCl_4$-catalyzed nucleophilic substitution of propargylic acetates **62** by alcohols affording propargylic ethers **63a**–**c** (Scheme 25).[42] The reacting alcohol served in addition as solvent and more hindered alcohols gave lower yields. Substituents that stabilized the cationic intermediate, formed after the assumed $TiCl_4$-mediated extrusion of the leaving group, were important for good yields. Therefore, no substitution was observed when substrates with alkyl substituents at the α-position were used. Products derived from hydrolysis were sometimes obtained, but no formation of the allenic system was detected.



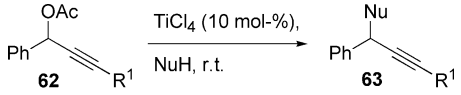
Scheme 22. TMSOTf-mediated substitution of propargylic TMS ethers **56**.



61	ArH	yield
a	benzene	85%
b	*p*-xylene	92%
c	mesitylene	60%

(for **c** ArH = 3 equiv., CH_2Cl_2 as solvent)

Scheme 24. $F_3B{\cdot}OEt_2$-mediated substitution of **60**.



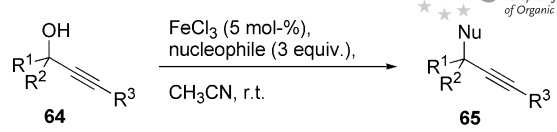
63a 95% (R^1 = Ph, NuH = MeOH)
63b 55% (R^1 = Ph, NuH = *t*BuOH)
63c 76% (R^1 = *n*Bu, NuH = MeOH)
63d 78% (R^1 = Ph, NuH = $BzNH_2$)

Scheme 25. $TiCl_4$-catalyzed propargylic substitution.

The same procedure was repeated with primary and secondary amines, instead of alcohols, but no conversion was observed. With *p*-toluenesulfonamide and acetamide the corresponding propargylic amides were obtained in low yield (19–58%); higher conversions (51–78%) were observed with benzamide as nucleophile (**63d**). Removal of the benzoyl group was accomplished by reduction with DIBAL affording the primary amine in 55% yield.

It is remarkable that Mahrwald does not report the formation of chloroallenes, because the reaction of 1-phenyl-2-octyn-1-ol with equimolar amounts of triethylamine and $TiCl_4$ gives the corresponding chloroallene in 56% yield, as reported by Periasamy and co-workers.[43] Periasamy also notes that with tertiary aromatic amines, instead of Et_3N, at –40 °C in most cases the corresponding propargylic products were obtained. For these transformations no comments were made on the possible catalytic activity of $TiCl_4$ as described by Mahrwald.

An $FeCl_3$-mediated approach to substitute propargylic alcohols has been developed by Zhan et al.,[44] allowing a broad range of nucleophiles, such as alcohols, electron-rich aromatic rings, sulfides, amides, sulfonamides, silyl enol ethers, and allyltrimethylsilane (Scheme 26). The method was working for both internal and terminal alkynes and was completely regioselective. Propargylic alcohols with aromatic side chains (Ph), but also with aliphatic side chains (Me), were effectively substituted. The primary aliphatic alcohol, 3-phenylprop-2-yn-1-ol was not substituted, which was ascribed to instability of the supposedly formed propargylic cation intermediate. Although no reaction was observed when acetamide, aniline, and piperidine were used as nucleophiles, this method is very broad in scope and allows mild reaction conditions.



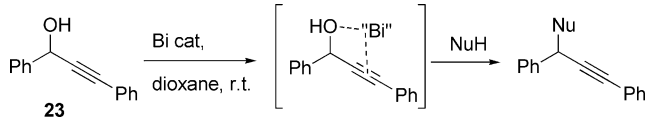
65	R^1, R^2, R^3	NuH/NuTMS	yield
a	Ph, H, *n*Bu	EtOH	90%
b	Ph, H, H	EtOH	85%
c	Me, Me, Ph	EtOH	82%
d	Ph, H, Ph	furan	82%
e	Ph, H, Ph	EtO_2CCH_2SH	92%
f	Ph, H, Ph	benzamide	73%
g	Ph, H, Ph	allylTMS	95%

Scheme 26. $FeCl_3$-catalyzed propargylic substitution.

Zhan et al. also reported an indium-catalyzed process, which was developed specifically to catalyze a one-pot three-component reaction affording highly substituted pyrroles.[45] In this propargylation/amination/cycloisomerization tandem reaction process, $InCl_3$ acts as a multifunctional catalyst. As nucleophile for the propargylic substitution 1,3-dicarbonyl compounds were used. Both terminal and internal alkynes were effectively converted using $InCl_3$.

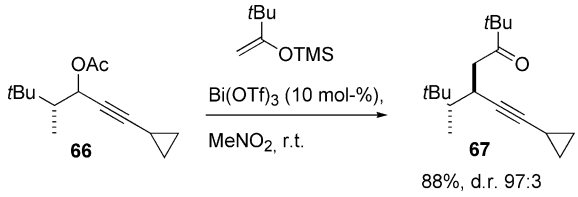
The same group reported that similar results as with the iron-catalyzed method were obtained with $BiCl_3$ as the catalyst, although slightly higher temperatures were required (35 °C, instead of room temperature).[46]

Matsunaga and Shibasaki and co-workers showed that also $Bi(OTf)_3$ was able to catalyze the substitution of propargylic (and allylic) alcohols by nitrogen nucleophiles, such as sulfonamides and carbamates.[47] The addition of KPF_6 (catalytic) and the desiccant drierite ($CaSO_4$) had a beneficial effect on the reactivity of the reaction, allowing lower catalyst loadings (1 mol-%). No terminal alkynes were tested, and with tertiary propargylic alcohols lower yields were obtained than with secondary (63–65%, and 78–82%, respectively). The working hypothesis was based on a bifunctional reactivity of the bismuth catalyst, both acting as a π-acid to activate the alkyne and as a Lewis acid to activate the hydroxy group (Scheme 27).



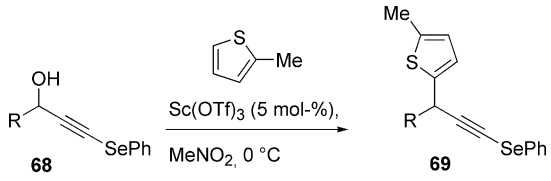
Scheme 27. Proposed mechanism of propargylic alcohol activation by a bismuth catalyst.

Bach and co-workers studied the reactivity of propargylic carbocations with weak carbon nucleophiles.[48] They found that among a wide array of potential catalysts (including $FeCl_3$, $InCl_3$, $AuCl_3$, $Cu(OTf)_2$, $[Au(PPh_3)]SbF_6$, BF_3, and TMSOTf), $Bi(OTf)_3$ was most effective for the transformation of propargylic acetate **66** into **67** (Scheme 28). Besides silyl enol ethers, trimethylallylsilane, and several aromatic nucleophiles were successful in the reaction and gave the products in high diastereoselectivity.



Scheme 28. Bismuth-catalyzed diastereoselective substitution.

Another S_N1-type process, catalyzed by $Sc(OTf)_3$, was investigated by Yoshimatsu et al.[49] A sulfanyl or selanyl group attached at the alkyne terminal C-atom (such as in **68**) was important for high activity and regioselectivity (Scheme 29). With tertiary propargylic alcohols with non-aromatic side chains the selectivity remained a problem and elimination and allene formation were observed. This selectivity was attributed to steric factors although the details of the reactions are still unclear. The selenium group of product **69a** was cleaved by treatment with nBu$_3$SnH/AIBN allowing follow-up chemistry with the terminal alkyne moiety.



69	R	yield (%)
a	4-MeOC$_6$H$_4$	87
b	nBu	66
c	tBu	62

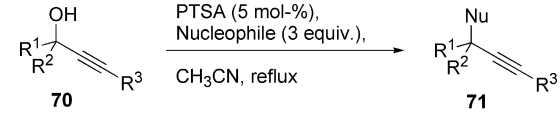
Scheme 29. Scandium-catalyzed propargylic substitution.

A similar process was developed by Zhou et al. using $Yb(OTf)_3$ to substitute propargylic alcohols (such as **23**) with 1,3-dicarbonyl compounds.[50] Substrates with aromatic as well as aliphatic side chains were converted giving the products in moderate to good yield (51–96%). In the case of tertiary propargylic alcohols a regioselective allenylation instead of propargylation took place solely affording the allene derivatives.

Also $MoCl_5$ (5 mol-%) functions as a Lewis acid in the substitution of benzylic propargylic alcohols (such as **23**) with allyltrimethylsilane.[51] The method was applicable only to benzylic substrates, because with an aliphatic side chain no reaction was observed.

Other Methods

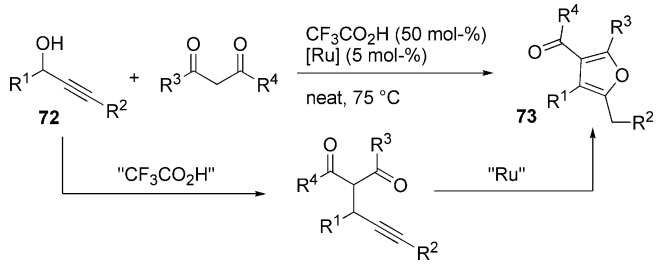
Recently, Sanz et al. found that organic acids, such as *p*-toluenesulfonic acid (PTSA), efficiently catalyze direct nucleophilic substitutions of the hydroxy groups of propargylic alcohols (**70**) with a large variety of carbon- and heteroatom-centered nucleophiles (Scheme 30).[52a] The method allows the use propargylic alcohols with both aliphatic and aromatic groups as side chain(s). Both terminal and internal alkynes gave the desired products **71**, although some side products were formed (<15%) in the former case. This metal-free strategy represents a synthetically competitive alternative to the already established use of metal complexes. Zhan et al. also applied PTSA to promote a one-pot propargylation/cycloisomerization tandem process for the synthesis of substituted oxazole derivatives from propargylic alcohols and amides.[52b]



71	R^1, R^2, R^3	NuH/NuTMS	yield
a	Ph, H, nBu	EtOH	81%
b	Ph, H, H	EtOH	58%
c	Me, Me, Ph	EtOH	86%
d	Ph, H, Ph	$PhSO_2NH_2$	67%
e	Ph, H, Ph	$CH_3(CH_2)_{11}SH$	80%
f	3-MeOPh, H, Ph	furan	76%
g	Ph, H, Ph	allylTMS	80%

Scheme 30. PTSA-catalyzed propargylic substitution.

A propargylation/cycloisomerization tandem process catalyzed by a ruthenium(II)/CF_3CO_2H system was reported in which trifluoroacetic acid is the catalyst in the propargylation step (Scheme 31).[53] Without the Ru-species the intermediate γ-diketo alkyne could be isolated in high yield proving that no ruthenium was required for substitution.

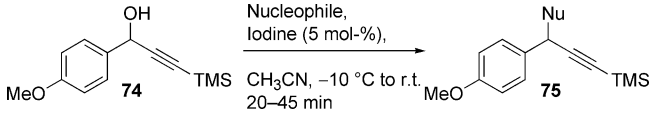


Scheme 31. PTS-catalyzed propargylic substitution.

Although the ruthenium catalyst ([Ru(η^3-2-C_3H_4Me)(CO) (dppf)][SbF_6]) was not required for the first step of the reaction, trifluoroacetic acid prevented Meyer–Schuster isomerization of the propargylic alcohol catalyzed by the ruthenium complex. This explains the large amount of acid that was used. By introduction of an additional amount of primary amine the same group managed to develop a one-pot three-component synthesis of fully substituted pyrroles using a similar process.[54]

An calix[*n*]arene sulfonic acid bearing aliphatic chains has been reported that functions as a surfactant-type Brønsted acid-catalyst in the substitution of propargylic alcohol **23** with *N*-methylindole in water.[55] The product was obtained in 69% yield after 48 h using 5 mol-% H^+ of the catalyst at 80 °C. The advantage of this catalyst was the easy recovery and reuse after extraction of the reaction mixture with organic solvent.

Besides these Brønsted acid catalyzed methods, also an iodine-catalyzed procedure is known starting from either propargylic alcohols[56a] or acetates.[56b] Different nucleophiles were allowed, such as alcohols, electron-rich aromatic rings, and allyltrimethylsilane (Scheme 32). Starting from benzenethiol, cyclopentylamine and benzylamine, only starting material could be recovered. Only benzylic propargylic alcohols were used with internal alkynes and Chen et al. stated that replacement of the aromatic by an aliphatic moiety is not allowed. Although the scope is rather small, the mild conditions, short reaction times, and high yields (85–95%) makes this reaction an attractive addition to existing procedures.



75	NuH/NuTMS	yield
a	allylOH	90%
b	propargylOH	93%
c	PhOMe	92%
d	indole	95%
e	allylTMS	90%

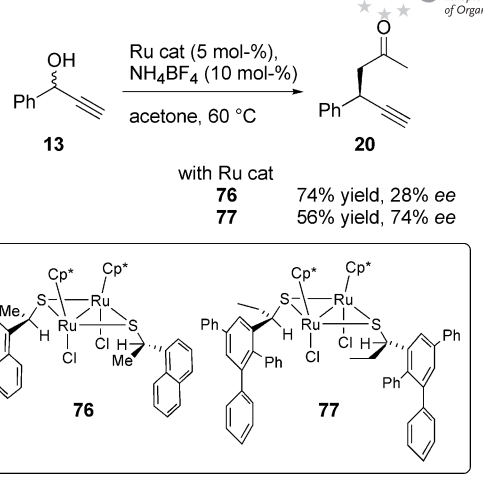
Scheme 32. Iodine-catalyzed propargylic substitution.

Enantioselective Propargylic Substitutions

A Ruthenium-Catalyzed Method

Although some diastereoselective methods have been described,[6,27,48,57] enantioselective examples of propargylic substitution reactions are limited to only two transition metals. The first example of an enantioselective propargylic substitution reaction was reported by Nishibayashi and coworkers. They showed that a chiral ruthenium complex could induce asymmetry in the C–C bond formation between acetone and 1-phenyl-2-propyn-1-ol (**13**).[58]

The reaction was carried out in the presence of catalysts generated in situ from $[Cp^*RuCl(\mu_2\text{-}Cl)]_2$ and chiral thiols. (*R*)-1-(1-Naphthyl)ethanethiol as chiral ligand led to the most selective catalyst **76** in this first study and afforded **20** in 74% yield and 28% *ee* (Scheme 33). To achieve higher enantioselectivity, a new type of chiral ligands was developed. These ligands contained a phenyl group that might interact with the phenyl ring of **13** in the ruthenium-allenylidene complex by π–π interactions (Figure 3). The concept worked and a screening of several ligands led eventually to increased enantioselectivities, with second generation catalyst **77** giving the best results.[59] A series of secondary propargylic alcohols with aromatic side chains was effectively subjected to the reaction conditions affording the anticipated products in moderate yields (14–61%) and enantioselectivities (68–82% *ee*).



Scheme 33. Enantioselective ruthenium-catalyzed propargylic substitution.

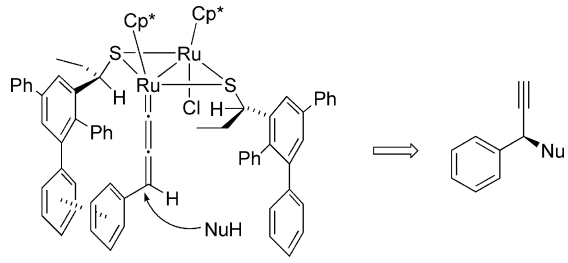
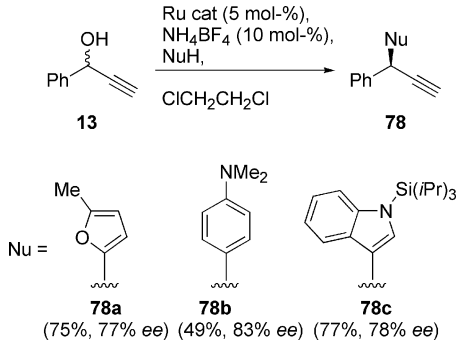


Figure 3. Proposed π-π interactions in the Ru-allenylidene intermediate.

Next to acetone, electron-rich aromatic rings were applied as nucleophiles. 2-Methylfuran and *N*,*N*-dimethylaniline were successfully propargylated by several propargylic alcohols with aromatic side chains.[60] The yields ranged between fair and good (36–83%), but generally high enantioselectivities were observed (68–94% *ee*). The low reactivity made the use of a large excess (10 equiv.) of the nucleophile necessary with a reaction temperature of 60 °C (Scheme 34).



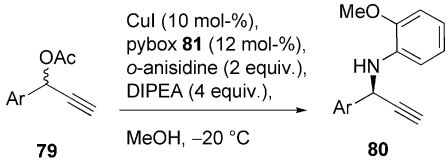
Scheme 34. Electron-rich aromatic rings as nucleophiles.

From a series of indole derivatives, *N*-(triisopropylsilyl)-indole was found to substitute propargylic alcohols like **13** with high enantioselectivities.[61a] The temperature and the amount of nucleophile could be lowered to 40 °C and 3 equiv., respectively, without affecting the yield and selec-

tivity. Similar enantioselectivities (71–95% *ee*) were observed as for 2-methylfuran, although the yields were generally higher (63–98%). In addition, an intramolecular approach was developed using a propargylic alcohol with a thiophene, or alkene moiety attached.[61b,61c] Although the enantioselective intermolecular approach was unsuccessful with thiophenes, this intramolecular cyclization gave the propargylated thiophenes in reasonable to high yields (20–96%) and high enantioselectivity (79–97% *ee*). Also the intramolecular cyclization with the alkene functionalized propargylic alcohols resulted in the elegant synthesis of a variety of optically active heterocycles such as chromane, thiochromane, and 1,2,3,4-tetrahydroquinoline derivatives. However, propargylic substitution reactions with heteroatom-centered nucleophiles, such as alcohols, amines, thiols, and diphenylphosphane oxide, did not proceed in an enantioselective fashion in the presence of a catalytic amount of the same chiral diruthenium complex. Another disadvantage of this reaction was the narrow substrate scope, because only terminal alkyne containing propargylic alcohols with aromatic side chains were tolerated.

A Copper-Catalyzed Method

Recently, we reported an enantioselective copper-catalyzed propargylic amination reaction based on the Murahashi method.[62] The combination of copper iodide and the chiral diphenyl-substituted 2,6-bis(oxazolinyl)pyridine (pybox) ligand **81** gave the best results in the transformation of propargylic acetates with aromatic side chains. Both the solvent, methanol, and the base, diisopropylethylamine (DIPEA), were essential for higher reaction rate and enantioselectivity. Several substrates with an aromatic group at the propargylic position were converted into the corresponding amine in high yield (80–97%) and with high enantioselectivity (74–88% *ee*, Scheme 35).

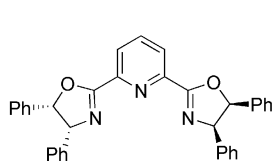


79 **80**

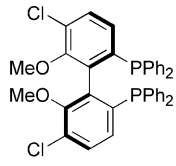
80	Ar	yield (%)	*ee* (%)
a	Ph	97	85
b	4-$MeOC_6H_4$	97	83
c	4-$CF_3C_6H_4$	84	80
d	2,4-$Me_2C_6H_3$	91	88

Scheme 35. Enantioselective copper-catalyzed propargylic amination.

o-Anisidine was chosen as the nucleophile because it can be cleaved oxidatively to liberate the primary amine.[63] The catalytic process seems to be unsatisfactory with substrates containing non-aromatic side chains and only low enantioselectivities were observed (13–57% *ee*).

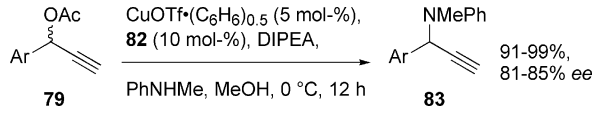


diPh-pybox **81**



(*R*)-Cl-MeO-biphep **82**

With the experience that the ruthenium catalyst system was not suitable for the preparation of optically active propargylic amines, Nishibayashi considered to use another approach, also inspired by the Murahashi method. Shortly after our paper was accepted, Nishibayashi and co-workers communicated their achievements to us, which resulted in two back-to-back publications.[64] The major difference between the two methods is the chiral ligand class chosen (Scheme 36).

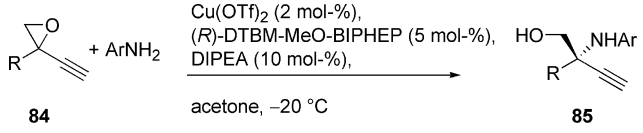


79 **83**

Scheme 36. Nishibayashi's enantioselective copper-catalyzed propargylic amination.

Instead of a pybox ligand displaying nitrogen as the donating atoms, Nishibayashi used a chiral diphosphane ligand, (*R*)-Cl-OMe-biphep (**82**) affording propargylic amines in similar yields and selectivities. Interestingly, to obtain high enantioselectivity, the use of a disubstituted amine, e.g. *N*-methylaniline, is required. As a consequence the method is less straightforward for the preparation of primary propargylic amines in high optical purity due to the *N*-Me bond, which is practically impossible to cleave. A disadvantage of both Nishibayashi's and our method is the intolerance for substrates with non-aromatic side chains. Recent observations, which will be published in due course, showed that with a different copper-pybox complex also non-aromatic side chains (e.g. Ar = *i*Pr in **79**) are allowed in the propargylic amination, as well as other type of nucleophiles.[65] Although the exact reaction mechanism still has to be elucidated, both groups report the likely formation of a copper acetylide species which explains the necessity of the terminal acetylenic hydrogen atom.

In a very recent paper Nishibayashi et al. reported the enantioselective ring-opening reaction of racemic ethynyl epoxides with amines.[66] With aniline-type nucleophiles and substrates with an aromatic group at the propargylic position the corresponding amino alcohols **85** were obtained in very high yield (85–97%) and with good to high *ee* (57–94%, Scheme 37). This copper-catalyzed reaction is also considered to proceed via a copper-allenylidene species and does indeed not occur with internal alkynes. Interestingly, substrates containing non-aromatic side chains are allowed and gave the products in good yield and reasonable enantioselectivity (**85c** and **85d**). In the presence of lower amounts of the catalyst (0.1 mol-%) the reaction proceeded as well and after 7 d the product was obtained in 84% yield and 94% *ee*.



85	R	Ar	yield (%)	*ee* (%)
a	4-MeC_6H_4	4-$MeO_2CC_6H_4$	96	94
b	2-naphthyl	4-$MeO_2CC_6H_4$	95	90
c	Me	4-$MeO_2CC_6H_4$	87	77
d	*t*Bu	4-$F_3CC_6H_4$	80	69

Scheme 37. Enantioselective copper-catalyzed ring-opening reaction.

Conclusions

As illustrated above, many catalysts have already been reported for propargylic substitution reactions. The enantioselective copper-catalyzed propargylic amination is the most recent expansion in the field and may draw growing attention to this underdeveloped area of asymmetric catalysis. We foresee that in the near future especially the scope of the enantioselective propargylic substitution reaction will be expanded due to high versatility of the substituted alkynes thus obtained.

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