Triazole-based P,N ligands : discovery of an enantioselective copper-catalyzed propargylic amination reaction

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CHAPTER 1

General Introduction

"asymmetric catalysis"

propargylic substitution

LG → Nu

R^1 + catalyst, NuH → R^1
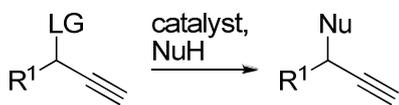
LG = leaving group, NuH = nucleophile

P,N ligands

P—M—N

chiral ligands

R⋯P—M—N⋯R
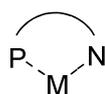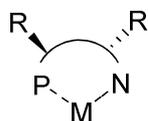
M = metal ion

azide-alkyne cycloaddition

R^2–N$_3$ + R^3

"Cu(I)"

N=N
R^2—N   R^3

1,2,3-triazole
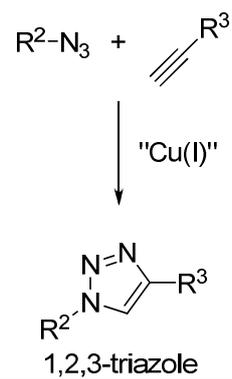
1.1 ASYMMETRIC CATALYSIS

Molecular chirality plays a key role in everyday life. In drug development it is therefore of great importance to obtain enantiopure compounds, because in the human body chiral host molecules recognize two enantiomeric guest molecules differently. Only one enantiomer usually provides the desired biological effect while the other often causes undesirable side effects. Thus, gaining access to enantiomerically pure compounds in the development of pharmaceuticals, but also agrochemicals, flavors, and fragrances is a significant endeavor.[1] Classical resolution of a racemate or the transformation of readily accessible, naturally derived "chiral pool" compounds, such as amino acids or carbohydrates are methods to arrive at enantiopure compounds. Asymmetric synthesis using chiral auxiliaries is an important approach to obtain a wide array of enantiopure substances.[1] The chiral auxiliary can be used either in stoichiometric or, preferably, in catalytic amounts. This latter category, in fact the field of asymmetric homogeneous catalysis, can be subdivided into two main areas: enzyme catalysis (biocatalysis)[2] and small molecule catalysis. In small molecule homogeneous catalysis a catalytic amount of a chiral molecule with MW below ca. 2000 is used to induce asymmetry in chemical reactions. The design and synthesis of such small chiral catalysts is often relatively simple, which allows facile catalyst optimization for a chemical transformation. The versatility of such catalyst system makes asymmetric small molecule catalysis a very efficient method to synthesize enantiomerically enriched molecules. The two major topics of interest in this field are asymmetric organocatalysis,[3] and asymmetric transition metal catalysis. Below, the latter is discussed in more detail.

1.1.1 ASYMMETRIC TRANSITION METAL CATALYSIS

In 1966, the first example of asymmetric catalysis with a transition metal complex as catalyst was reported by Nozaki *et al*. They made use of a chiral Schiff base-Cu^{II} complex to induce asymmetry in two types of carbenoid reactions.[4] Some years later, major breakthroughs in the field of asymmetric hydrogenation were enforced by Knowles, Horner and Kagan. Knowles and Horner independently replaced the triphenylphosphine groups of Wilkinson's catalyst,[5] RhCl(PPh$_3$)$_3$, by the chiral monophosphines PAMP, CAMP[6] and methylphenyl-*n*-propylphosphine **1**.[7] Hydrogenations catalyzed by rhodium complexes with these ligands already gave enantioselectivities up to 88%.[8] Kagan was the first who reported a rhodium-catalyzed hydrogenation using the diphosphine ligand DIOP. The high enantiomeric excess (*ee*) observed during catalytic hydrogenations with DIOP showed the usefulness of the bidentate diphosphine ligands.[9] These results led to the development of many chiral diphosphorus ligands, e.g. Knowles' DIPAMP[10] and Noyori's BINAP.[11] In 2001, the Nobel prize was awarded to Knowles and Noyori for their work on catalytic asymmetric hydrogenation reactions.[1,12] Kumada and Hayashi reported the BPPFA[13,14] and BPPOH[15] diphosphine ligands which contain ferrocene as a backbone.[16]
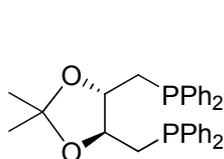
First chiral transition metal catalyst
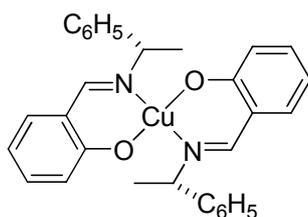
Chiral Cu catalyst
Nozaki *et al.* (1966)

Chiral monophosphine ligands
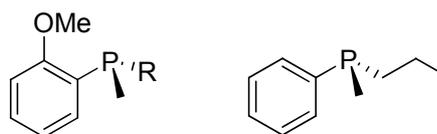
R = Ph: (*S*)-PAMP
R = Cy: (*S*)-CAMP
Knowles *et al.* (1968)

(*S*)-**1**
Horner *et al.* (1968)

Bidentate diphosphine ligands

(S,*S*)-DIOP
Kagan *et al.* (1971)
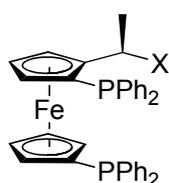
X = NMe₂: (R,*S*)-BPPFA
X = OH: (R,*S*)-BPPOH
Kumada *et al.* (1976)
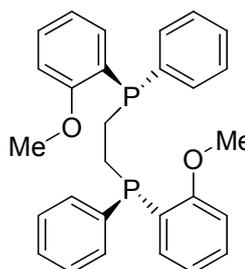
(S,*S*)-DIPAMP
Knowles *et al.* (1977)
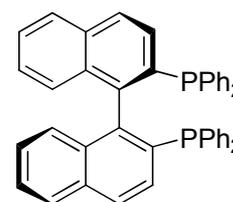
(*R*)-BINAP
Noyori *et al.* (1980)

Bidentate P,N ligands
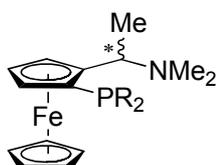
R = Ph: (*S*)-(*R*)-PPFA
R = Me: (*R*)-(*S*)-MPFA
Hayashi *et al.* (1974)
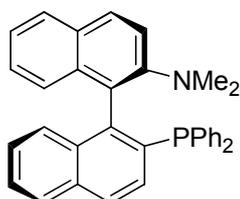
(*R*)-MAP
Kocovsky *et al.* (1998)
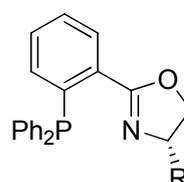
PHOX ligands
Pfaltz, Helmchen,
Williams *et al.* (1993)

R = Me   **2**
R = *i*-Pr   **3**
R = *t*-Bu   **4**
R = Ph   **5**
R = Bn   **6**

1.1.2 P,N LIGANDS

The activity, selectivity, and stability of a catalytic metal complex is highly dependent on the steric and electronic properties of the ligand.[17] Besides the diphosphine type bidentate ligand class, a widely used class of ligands are the heterodentate ligands of which the phosphorus and nitrogen containing bidentate ligands are the most important. These so-called P,N ligands combine the "soft" π-acceptor and σ-donor character of the phosphorus with the "hard" nitrogen σ-donor ability to stabilize intermediate oxidation states or geometries which form during a catalytic cycle. The ligand generates an asymmetric environment around the metal center, which may result in higher or different selectivity in the catalysis. By modifying the atoms next to the phosphorus or nitrogen atom it is possible to optimize and fine-tune the ligand properties in both an electronic and steric way.
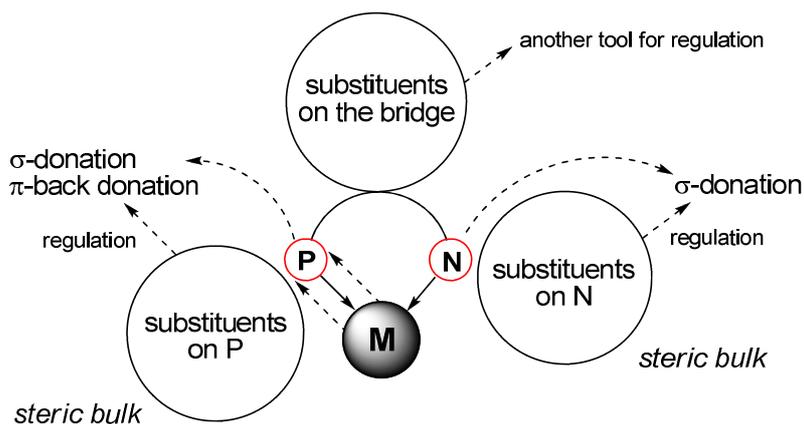
The first application of chiral P,N ligands was reported by Hayashi and Kumada in 1974.[13] They developed the (*S*)-α-[(*R*)-2-diphenylphosphinoferrocenyl]ethyldimethyl-amine (PPFA) and (*R*)-α-[(*S*)-2-dimethylphosphinoferrocenyl]ethyldimethylamine (MPFA) ligands, which just like the already mentioned BPPFA and BPPOH diphosphine ligands contain ferrocene as a backbone, and applied them in the hydrosilylation of ketones. Although the optical purity was not impressive (up to 49% *ee*), it demonstrated the ability of the ligands to induce asymmetry. As a results, many other P,N ligands have been prepared and applied in various catalytic reactions.[18] In 1998, Kočovský reported the synthesis of a novel *N*,*N*-dimethyl aminophosphine ligand (MAP),[19] which is an analogue of BINAP. This class of P,N binaphthyl ligands stands out by its high reactivity and selectivity in several transition metal-catalyzed reactions, such as Hartwig-Buchwald aminations, enantioselective Suzuki-Miyaura couplings, and formation of aryl ethers.[20] Recently, a new methodology for the construction of a variety of interesting MAP-type P,N ligands was developed within our group based on the Staudinger reaction.[21] One of the most successful ligand classes are the diphenylphosphinoaryloxazolines (**2**-**6**) which were reported independently by the groups of Pfaltz, Helmchen, and Williams.[22] The phosphinooxazoline (PHOX) ligands acquire their chirality in the oxazoline ring from amino alcohols, which are easily available from α-amino acids. Because of the modular construction, these ligands could be adapted to many metal-catalyzed reactions.[23] Different derivatives could be readily synthesized, and this made in many cases, that they outperformed P,P or N,N ligands.[24]
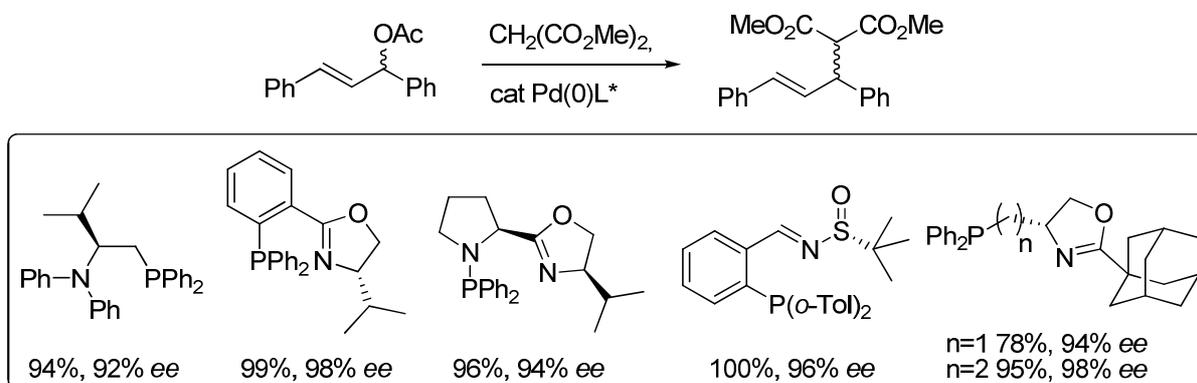
Scheme 1.1 Pd-catalyzed asymmetric allylic alkylation

A few illustrative examples of asymmetric transition metal catalyzed reactions will be given in which P,N ligands were successful. Many P,N ligands have been tested and compared in the palladium-catalyzed alllylic alkylation of (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 1.1). Small variations in the substituents of the ligands could lead to large differences in reactivity and selectivity. Therefore, a short and facile ligand synthesis, in which the substituents are easily varied is important for reaction optimization. Some effective ligands in the Pd-catalyzed allylic alkylation are collected in Scheme 1.1.[18]
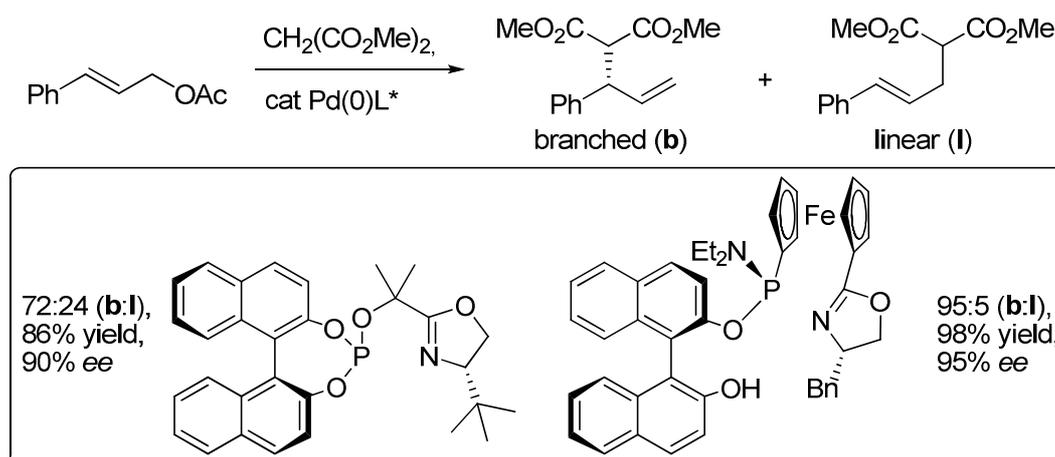
Scheme 1.2 Regioselective Pd-catalyzed asymmetric allylic alkylation

Starting with monosubstituted allylic substrates, certain P,N ligands gave a highly regioselective reaction and afforded predominantly the branched products, which were preferred for applications in asymmetric synthesis (Scheme 1.2).[25]

Also in the enantioselective copper-catalyzed addition of alkynes to imines two P,N ligands, quinap and pinap, displayed high reactivity and selectivity (Scheme 1.3). Quinap, the first successful axially chiral P,N ligand, is purified by a difficult resolution step involving fractional crystallization of diastereomeric Pd complexes and therefore rather expensive.[26] The structurally related pinap was especially developed to provide a more practical route to such compounds.[27] Besides simplifying the synthesis, the chiral auxiliary in pinap provides a tool for ligand optimization, which was illustrated by the parallel reactivity to quinap, not only in the Cu-catalyzed addition of alkynes to imines, but also in the (not shown) Ag-catalyzed azomethine cycloaddition with acrylates and the Rh-catalyzed hydroboration.
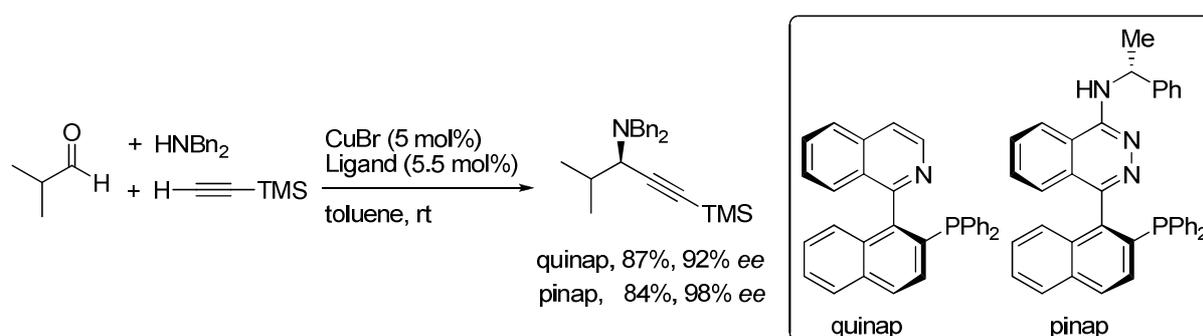
Scheme 1.3 Cu-catalyzed enantioselective addition of alkynes to imines

Since the use of heterobidentate P,N ligands in the enantioselective Rh-catalyzed hydroboration of olefins, the scope of this reaction, in terms of asymmetric induction, has been substantially expanded.[28] The use of a ligand, containing the 3,5-dimethylpyrazolyl fragment, for the hydroboration of styrene, afforded the secondary alcohol in an excellent 95% *ee* (Scheme 1.4).[29] However, the ligands were limited in terms of regiochemical control, and the ratio between the secondary and primary alcohol was 66:34 with an overall yield of 91%. The regioselectivity towards the secondary alcohol was better controlled with quinap as the ligand (for most vinylarenes >95%), while good enantioselectivity was maintained (92% *ee* for styrene).[30]

P,N ligands were also effective in the Ir-catalyzed hydrogenation of unfunctionalized olefins. More about this reaction is described in Chapter 6.
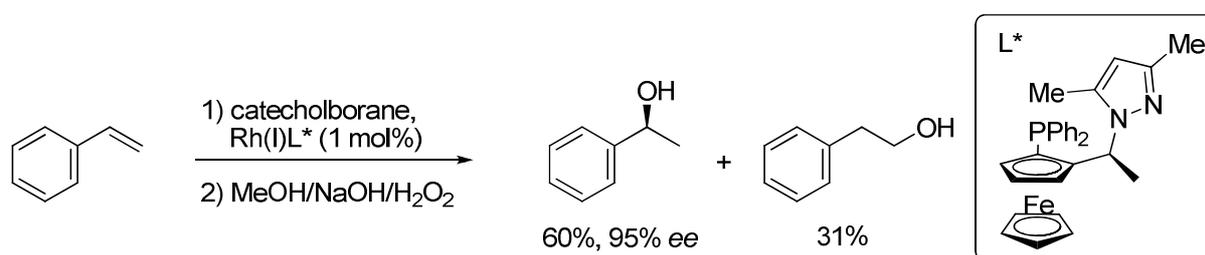
Scheme 1.4 Rh-catalyzed enantioselective hydroboration of olefins

In this small overview only the transformation of a single substrate for each asymmetric reaction has been shown. The most effective P,N ligands for these particular substrates were depicted in the schemes. Of course, the electronic and steric properties of each ligand must be fine-tuned for individual substrates, and the ease and modularity of the syntheses of these ligands are therefore of great importance. To date, a ligand which provides the maximum reactivity and selectivity across a wide range of substrates remains elusive.

The use of a 1,2,3-triazole group as part of a P,N ligand has to the best of our knowledge not been reported. We envisioned a facile and modular synthesis of a new type of P,N ligands with the triazole moiety containing the nitrogen donor atom. The recently discovered copper-catalyzed azide-alkyne cycloaddition greatly simplifies the synthesis of the triazole ring.

1.2 CLICK CHEMISTRY FOR THE SYNTHESIS OF P,N LIGANDS

The term "click chemistry" was first used by Sharpless *et al.* They envisaged the development of an expanding set of powerful, selective, and modular "blocks" that work reliably in both small- and large-scale applications.[31] These "blocks" should consist of reactions where small units join together with heteroatom links (C-X-C). The reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts, and be stereospecific (but not necessarily enantioselective). Also simple reaction conditions, readily available starting materials and reagents, and simple product isolation (by nonchromatographic methods) are important characteristics of the process. Although several

other types of reactions fall into the click chemistry category, cycloaddition reactions are probably the most prominent examples.

1.2.1 HUISGEN'S [2+3] DIPOLAR CYCLOADDITION

Hetero Diels-Alder and, especially, 1,3-dipolar cycloadditions are beautiful examples of potential click reactions. These reactions give rise to an enormous variety of five- and six-membered heterocycles by uniting two unsaturated reactants. The Huisgen's [2+3] dipolar cycloaddition[32] between azides and alkynes is potentially a near perfect reaction.[31a] Although the cycloaddition can be performed with other 1,3-dipolar components, the azide group is by far the most convenient. Besides being stable towards dimerization and/or hydrolysis, it is easy to introduce and inert to a wide variety of organic synthesis conditions. These properties make it possible to install the azide in an early stage of the synthesis and 'carry' it along until needed and the same is true for the alkyne group. This stability, being purely kinetic in origin, is responsible for the slow nature of the cycloaddition reaction. Only at elevated temperatures the reaction proceeds, usually resulting in a mixture (ca. 1:1) of the 1,4- and 1,5-disubstituted triazole regioisomers. The recently discovered copper(I)-catalyzed reaction unites azides (**7**) and terminal alkynes (**8**) in a regioselective way providing only the 1,4-disubstituted 1,2,3-triazoles (**9**, Scheme 1.5) making this reaction the "cream of the crop" in click chemistry.[33] Direct use of copper(I) species is possible, but *in situ* reduction of cheaper Cu^{II} salts ($CuSO_4 \cdot 5H_2O$ serves well) reduces the amount of undesired by-products. A catalyst loading of 0.25-2.0 mol% is sufficient to drive the reaction to completion in 6 to 36 hours at ambient temperature. As reductants metallic copper(0), ascorbic acid or sodium ascorbate serve well. The reaction proceeds in a variety of solvents, including aqueous *tert*-butyl alcohol or ethanol and water without organic co-solvent. These optimizations allowed the preparation of a broad spectrum of 1,4-triazole products in high yields and purity. The tolerance for variations in both the acetylene and the azide component was excellent. Only very sterically hindered azides, such as 2-azido-2,2-diphenylacetic acid, did not react even at elevated temperatures and prolonged reaction time.[33b]
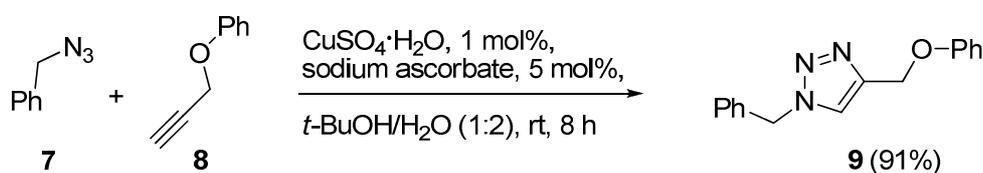
Scheme 1.5 Example of the copper-catalyzed azide-alkyne cycloaddition

The proposed catalytic cycle begins with activation of the acetylene by formation of a copper π-complex with the alkyne (Scheme 1.6, step **A**). The formation of this π-complex lowers the pK_a value of the acetylenic hydrogen atom by 10 units, as described by Fokin and co-workers,[34] which makes step **B** accessible in aqueous systems. The unexceptional formation of the copper acetylide (step **B**), which is also the case in the Sonogashira coupling,[35] is the reason why no reaction is observed with internal alkynes.
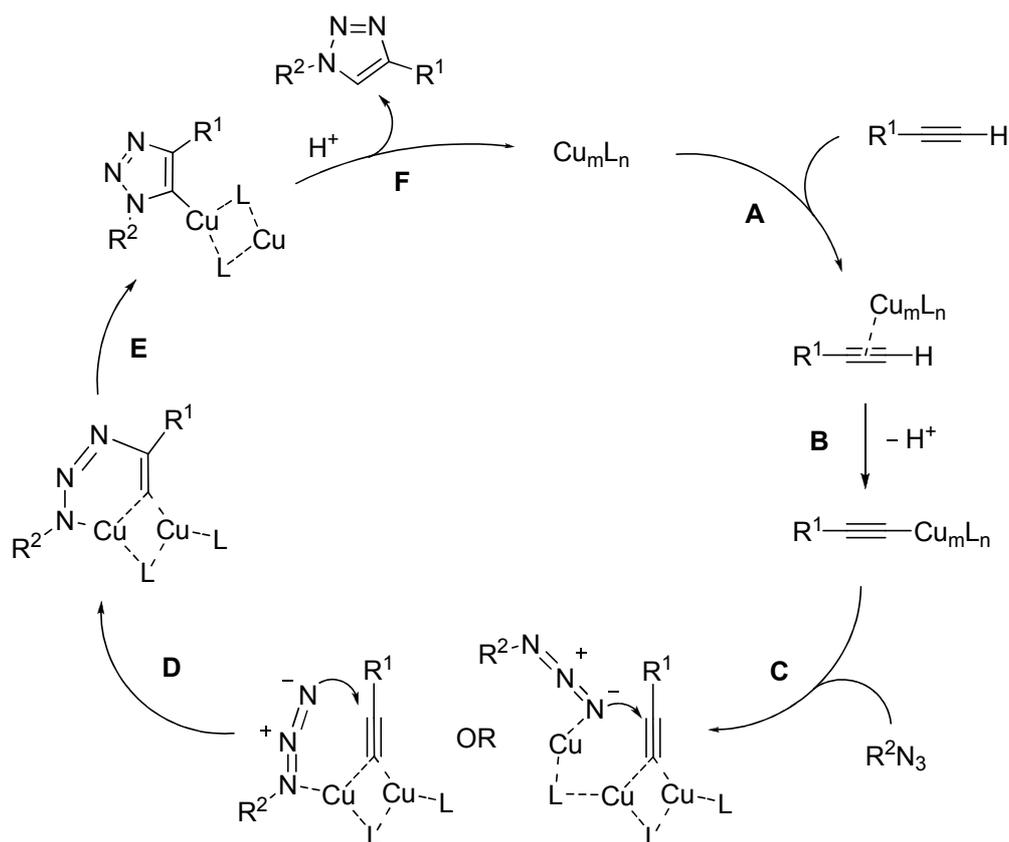
Scheme 1.6 Proposed catalytic cycle for the copper-catalyzed azide-alkyne cycloaddition

Although questions about the nature of the Cu-acetylene complexes still exist, the current evidence indicates that the active copper complex in catalysis requires at least two metal centers, one or more alkyne ligands, and other labile ligands that allow for competitive azide binding (step **C**).[34,36] In the cyclic transition state the terminal nitrogen atom of the azide attacks the electrophilic carbon of the acetylide, which can explain the absolute regioselectivity of the reaction (step **D**). Ring contraction forms the metallocene intermediate in step **E**. Upon proteolysis the product is obtained and the copper complex is ready to enter the next catalytic cycle (step **F**). The ca. 10^6 fold rate acceleration of the copper(I)-catalyzed 1,3-dipolar cycloaddition with complete conversion and high selectivity in combination with the ready availability of the starting materials reveals a pathway to highly diverse libraries. The homology of the 1,2,3-triazole ring with an amide moiety makes it a perfect target for drug discovery.[37] In contrast to amides, nature's linking devices, triazoles cannot be cleaved hydrolytically or otherwise and are stable towards reduction and oxidation. These properties boosted the use of the triazole-forming process in biomedical research, ranging from lead discovery and optimization, to tagging of biological systems.[31b] Additionally, significant progress has been made in the application of the methodology to the areas of materials science, and polymer chemistry, among others.[38,39]

1.2.2 TRIAZOLE COORDINATION

Besides being used as efficient linking device, the triazole ring has also been applied as ligand for several transition metals. In particular, the coordinating ability of the 1,2,4-triazoles

has been studied in depth and reviewed recently.[40] Also benzotriazole compounds have extensively been reported as ligands in organometallic complexes.[41] The coordinating properties of 1,2,3-triazole and its substituted analogues are less known in literature, but several examples exist.[42]
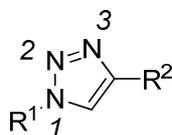
1,4-disubstituted 1,2,3-triazole

An example of spin-crossover material based on the 1,2,3-triazole as donor group was reported by Bronisz.[43] He synthesized the iron(II) 2D coordination polymer with the bidentate ligand 1,4-di(1,2,3-triazol-1-yl)butane. Reedijk *et al.* demonstrated the occurrence of an isomerization process in a cytotoxic triazole-bridged dinuclear platinum(II) complex where Pt(II) migrates from N2 to N3 in the triazole ring, upon reaction with a guanine substrate molecule.[44] Also a C-bonded triazole is known in a rhodium(I) complex, which is made from the diazoalkane complex after cycloaddition with an isocyanide.[45] Such cycloaddition process on the metal complex was also observed by Busetto *et al.*, who prepared iron and ruthenium azide complexes and reacted them with alkynes to afford the corresponding triazole complexes.[46]
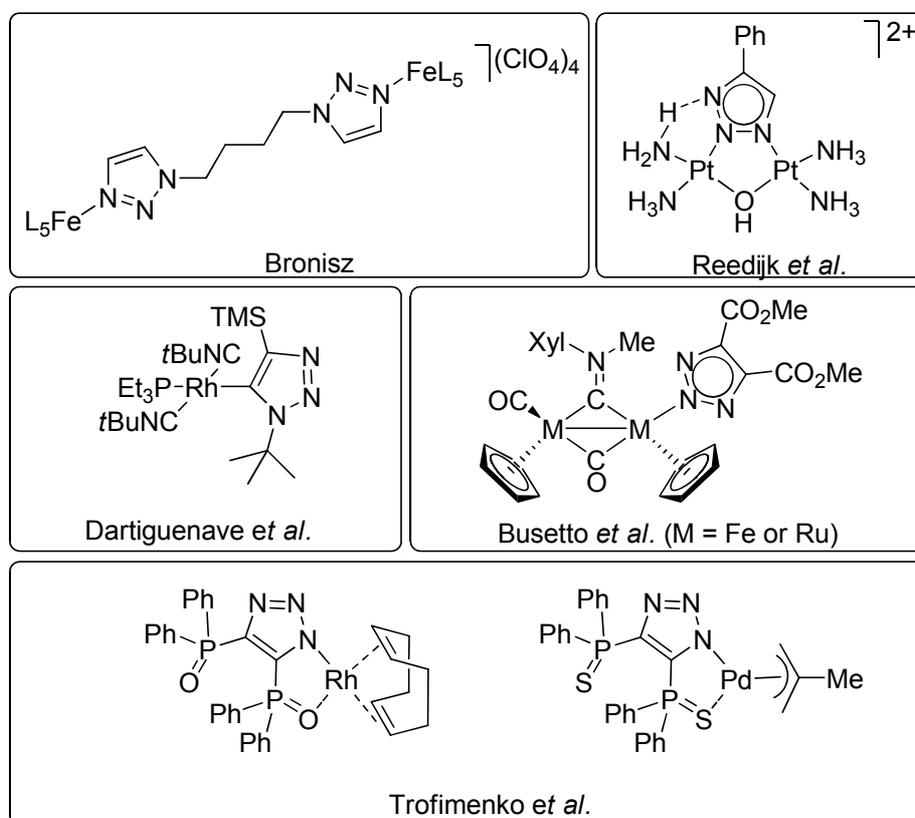
In the group of Trofimenko a triazole moiety was used as part of a bidentate ligand with as first example 4,5-bis(diphenylphosphinoyl)-1,2,3-triazole, which is thermally, oxidatively and hydrolytically very stable.[47] The developed O,N and S,N ligands can coordinate in their anionic form in a bidentate fashion with several metal ions (*e.g.* Pd, Ni, and Rh).

Since the discovery of the copper-catalyzed azide-alkyne cycloaddition 1,4-disubstituted 1,2,3-triazoles have been widely applied (see § 1.2.1). It is therefore surprising, that, prior to 2004, their role as ligands in transition metal chemistry had remained an unexplored field. Only Fokin *et al.* reported that polytriazoles (*e.g.* TBTA), obtained by the azide-alkyne cycloaddition, were competent in protecting copper(I) under aerobic aqueous conditions and promoting copper(I)-catalyzed transformations (Figure 1.1).[48] The modularity and ease of synthesis of the triazole moiety by "click" chemistry allow rapid exploration of analogues with specifically tuned properties, factors that are of vital importance for catalyst optimization.
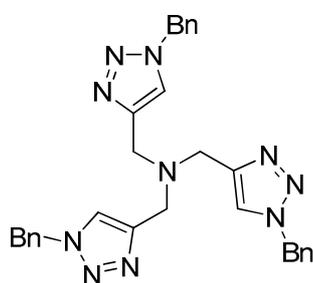
Figure 1.1 The polytriazole ligand tris-(benzyltriazolylmethyl)amine (TBTA)

As mentioned above, we envisioned that the Cu(I)-catalyzed azide-alkyne cycloaddition might lead to a new type of P,N ligands with the triazole moiety containing the nitrogen donor atom. A phosphine-functionalized propargylic moiety may function as the starting material for these ligands (Figure 1.2).
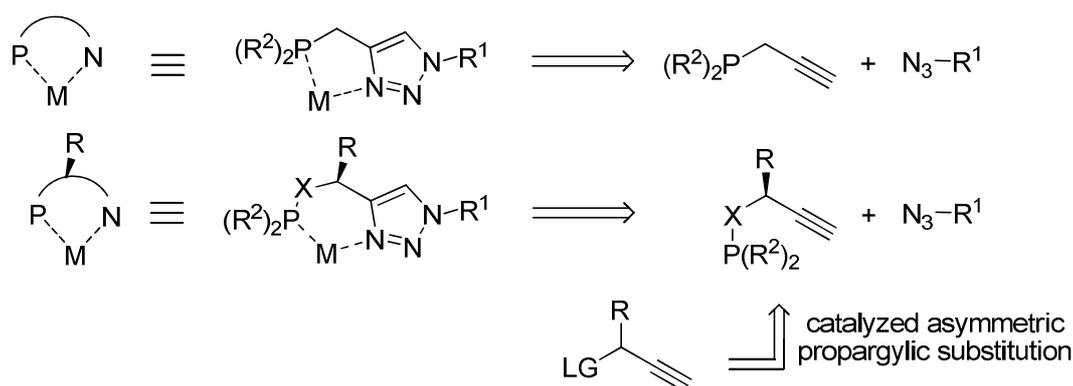
Figure 1.2 A new class of triazole functionalized P,N ligands (M = metal salt; X is *e.g.* CH$_2$, O, NH, or none; LG = leaving group)

Reaction with an azide would afford the desired P,N ligands. Introduction of a chiral propargylic moiety would allow the facile synthesis of P,N ligands for asymmetric catalysis with chirality in the bridge between the phosphorus and nitrogen. Catalytic propargylic

substitution seems to be a promising reaction to acquire these chiral propargylic building blocks. In the next section an overview of the literature about catalyzed propargylic substitutions is given.

1.3   CATALYZED PROPARGYLIC SUBSTITUTION

The propargylic moiety is a popular functionality in organic synthesis. The electron rich triple bond, in combination with the fairly acidic character of the terminal acetylenic hydrogen atom, makes it a versatile entity for further chemical transformations. Besides this, natural products, fine chemicals, and synthetic pharmaceuticals have been reported that contain the propargylic subunit as part of their structure.[49]

$$R \overset{\alpha}{\diagdown}\!\!\!\equiv\!\!\!H$$

(pK_a ~25)

Although the allylic substitution reaction has intensively been studied,[50] the transition metal catalyzed propargylic substitution is a less developed reaction type. The regioselectivity of the latter is of great importance because either alkynes or allenes can be obtained, this in contrast to allylic substitution which solely affords alkenes (Figure 1.3).

Figure 1.3 Allylic *versus* propargylic substitution (LG = leaving group)

To obtain the alkyne product, selective substitution at the α-position of the propargylic moiety is desired. The success of this transformation is depending on the selectivity of the catalyst that is used. Palladium-catalyzed reactions with propargylic compounds are known, but these usually yield the corresponding allenic systems.[51] One example in which the propargylic products were obtained was reported by Marshall and Wolf.[52] They described a Pd-catalyzed substitution of enantiopure propargylic mesylates by arylamines, which occurred with retention of the configuration. Without the Pd catalyst the mesylates were also substituted, but now with inversion of the propargylic stereocenter. 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.[53]

1.3.1 NICHOLAS REACTION

A fundamental substitution reaction of propargylic alcohol derivatives (**10**) is the Nicholas reaction, which occurs via a stoichiometric cobalt-alkyne complex (Scheme 1.7).[54] In this reaction the generated carbocationic charge at the carbon α- to the alkyne moiety (**11**) is stabilized by dicobalt hexacarbonyl, $Co_2(CO)_6$, 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 nucleophiles, such as ketones, silyl enol ethers, and electron rich aromic rings, are allowed.
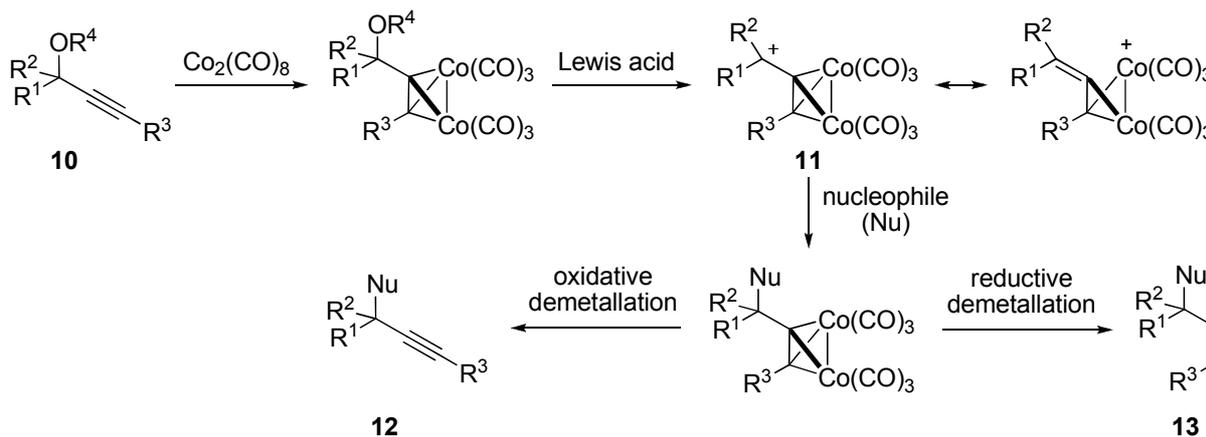
Scheme 1.7 The Nicholas reaction

After nucleophilic addition, the cobalt-alkyne complex can be cleaved oxidatively to afford the propargylic product 12. Reductive demetallation gives, if desired, the alkene, 13. 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,[55] 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 π-, S- and N-centered nucleophiles.

1.3.2 COPPER-CATALYZED SUBSTITUTIONS

In 1960, Hennion and Hanzel reported a copper-catalyzed route towards propargylic amines starting from tertiary propargylic chlorides.[56] Only with weakly basic amines (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.[57] Also aminations of propargylic oxyphosphonium salts and triflates have been reported.[58] Murahashi *et al.* reported in 1994 a more practical route starting from propargylic esters (**14**) to prepare propargylic amines **15** under mild conditions catalyzed by copper chloride (Scheme 1.8).[59] Alhough the mechanistic aspects were not totally clear they supported the idea of Hennion and Hanzel, that a zwitterion intermediate and/or carbene

intermediate was the reactive species susceptible for nucleophilic attack. The terminal acetylenic proton was essential, demonstrated by the fact that an internal alkyne did not undergo the amination even under severe conditions, which indicated the formation of the proposed copper-acetylide intermediate.
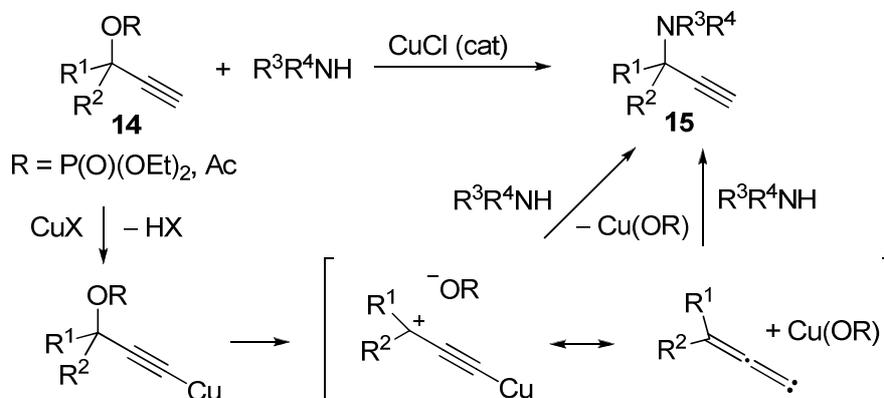

Scheme 1.8 Murahashi's copper-catalyzed propargylic amination

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.

Mann *et al.* reported that copper(I) iodide catalyzes the reaction between phenols and dialkylpropargyl chlorides to give aryl 1,1-dialkylpropargyl ethers.[60] Although more examples of substitutions of propargylic halides are known in literature, we will here only discuss the substitutions performed with propargylic alcohols and their derivatives.

1.3.3 RUTHENIUM-CATALYZED SUBSTITUTIONS

Many methods have been reported, especially in the last decade, that make use of catalytic amounts of other transition metals than copper to modify the propargylic α-position by substitution of propargylic alcohols or alcohol derivatives. Nishibayashi, Hidai, and Uemura and co-workers, developed a ruthenium-catalyzed process in which a wide variety of nucleophiles can be used.[61] Treatment of for example 1-phenyl-2-propyn-1-ol (**16**) in ethanol in the presence of **17** (5 mol%) and NH_4BF_4 (10 mol%) at 60 °C afforded in 15 minutes the corresponding ethyl ether **18** in 88% yield (Scheme 1.9). Besides alcohols, also sulfides, amines, amides, and diphenylphosphine oxide were effective as nucleophiles, affording the corresponding products in good yields (**19**-**22**).[61,62] Even carbon nucleophiles, such as simple ketones (*e.g.* acetone, product **23**),[63] 1,3-dicarbonyl compounds,[64] and electron-rich aromatic rings (*e.g.* product **24**),[65] were successfully employed in the reaction. The reaction only proceeded with diruthenium(III,III) complexes, such as **17**; both diruthenium(II,III) and monoruthenium complexes were ineffective. In all cases no allenic products were observed.
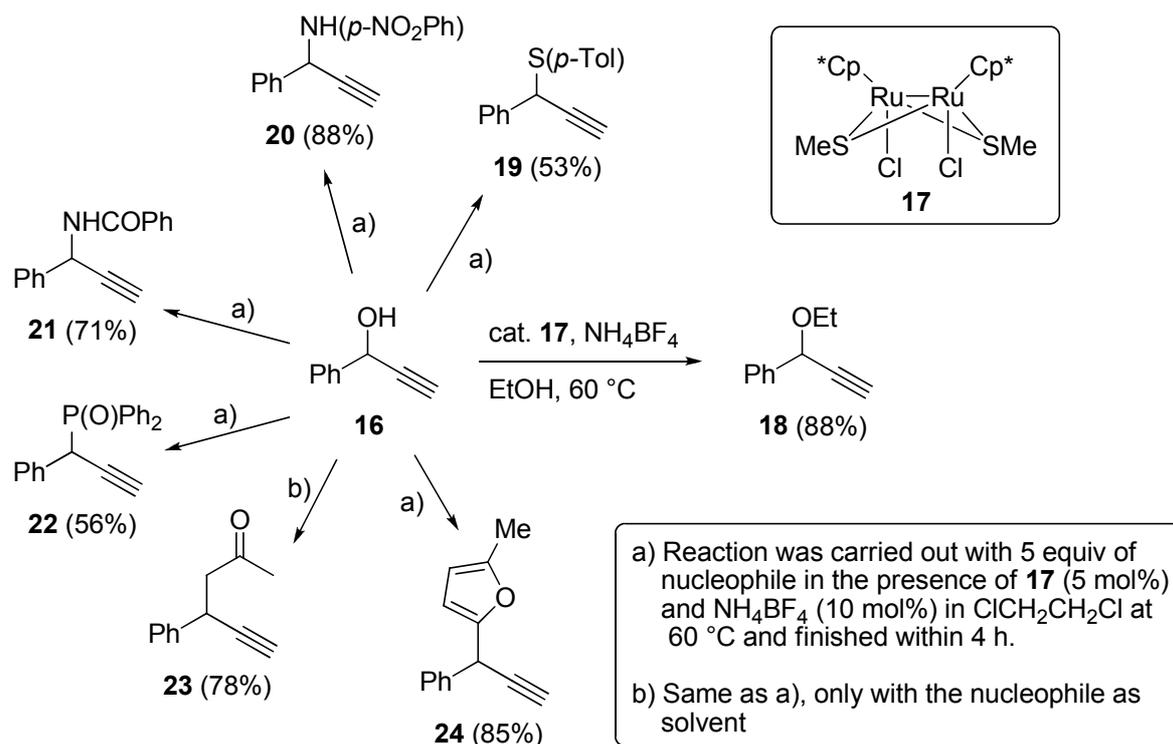
Scheme 1.9 Nishibayashi's Ru-catalyzed propargylic substitution (Cp* = η^5-C$_5$Me$_5$) with **17**

Available substrates were limited to the propargylic alcohols bearing a terminal alkyne group, because the reaction proceeds via an allenylidene ruthenium complex as key intermediate (Scheme 1.10).
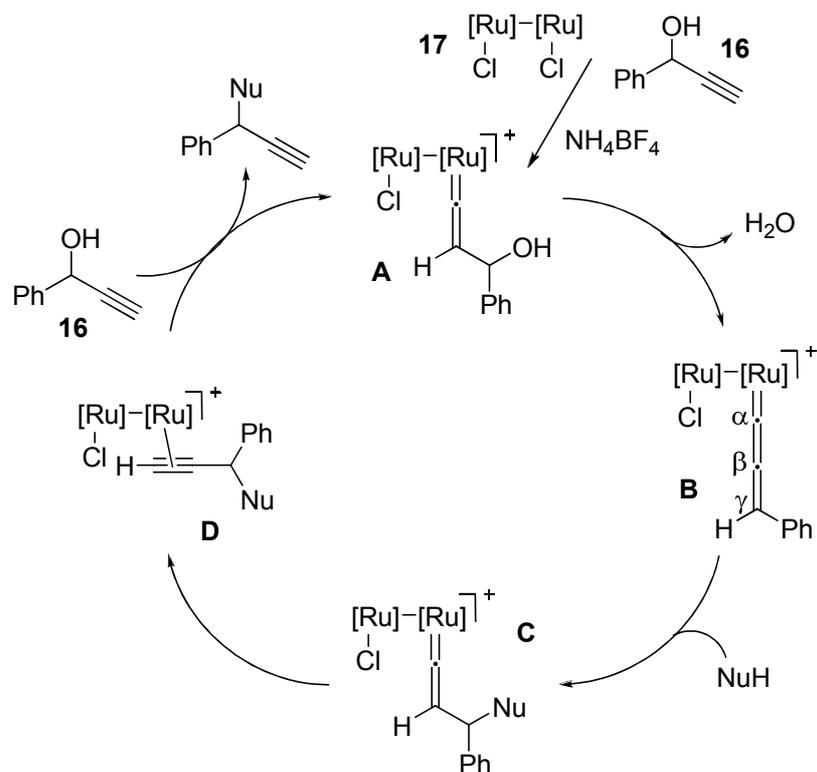
Scheme 1.10 Proposed catalytic cycle for the ruthenium-catalyzed propargylic substitution

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 $C_\gamma = C_\beta$ 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 **16**, 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 1.11).[62b] Catalyst **25** was found to give sulfide **27** in high yield starting from internal alkyne **26**, in the absence of NH_4BF_4. In addition, the products derived from terminal alkynes were provided in higher yields by this catalyst system compared to the yields obtained with complex **17**. Because no allenylidene can be formed, it is suspected that this catalyst coordinates to the alkyne (as in D, Scheme 1.10) or only acts as a Lewis acid.
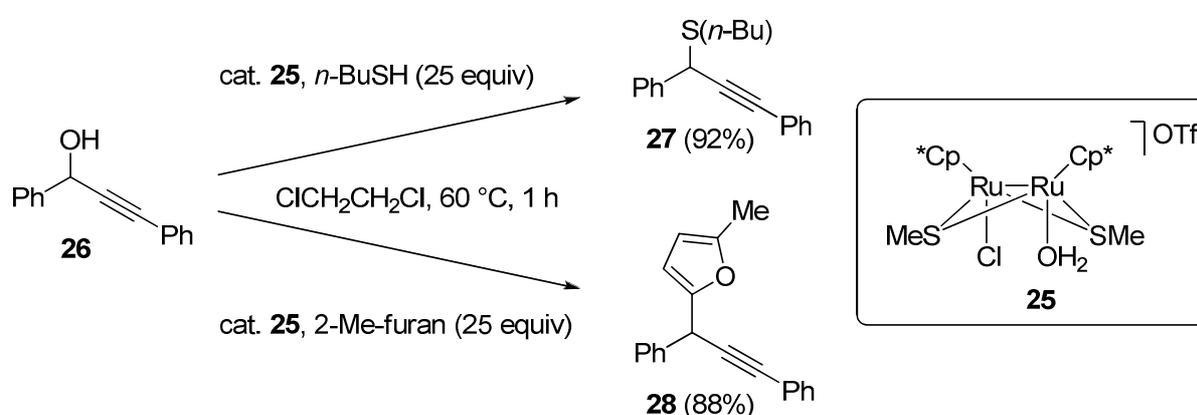
Scheme 1.11 Ruthenium-catalyzed propargylic substitution of internal alkynes with catalyst **25**

With aromatic rings as nucleophiles, such as 2-methylfuran, **26** was effectively substituted using the same catalyst system. With terminal alkynes and aromatic rings as nucleophiles, cationic catalyst **25** was equally active as the neutral **17**. 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 **26** with alcohols, amines, acetone, and silyl enol ethers in the presence of **25** occurred under similar reaction conditions.

1.3.4 RHENIUM-CATALYZED SUBSTITUTIONS

Toste and co-workers cleverly postulated that an allenolate intermediate (**31**), formed by the reaction of a propargylic alcohol (**29**) with a metal-oxo complex, could undergo S_N2' addition of a nucleophile (Scheme 1.12). This idea was based on the knowledge that metal-oxo complexes effect the rearrangement of propargylic alcohols to enones (**34**) (Meyer-Schuster rearrangement).[66]
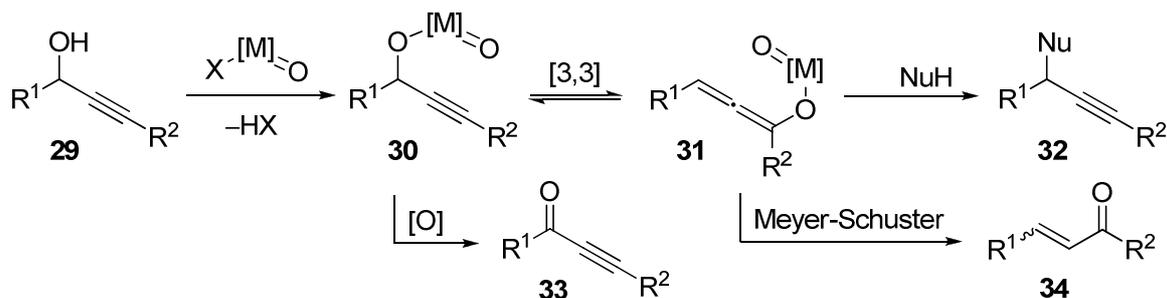
Scheme 1.12 Proposed mechanism of propargylic substitution catalyzed by metal-oxo complexes

They examined several metal-oxo complexes for the selective conversion of propargylic alcohol **35** to propargylic ether **36** (Scheme 1.13). A rhenium(V)-oxo complex bearing a bidentate phosphine ligand (dppm: diphenylphosphinomethane) was the most effective and afforded the desired product **36** with only traces of oxidized and rearranged products (such as **33** and **34**).[67] 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.

The mechanistic considerations led the same group to investigate the substitution of **35** by nitrogen nucleophiles as well.[68] 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.* **37**) in good yields (66-93%). Side reactions, as depicted in Scheme 1.12, were completely suppressed by addition of 5 mol% of NH_4PF_6.
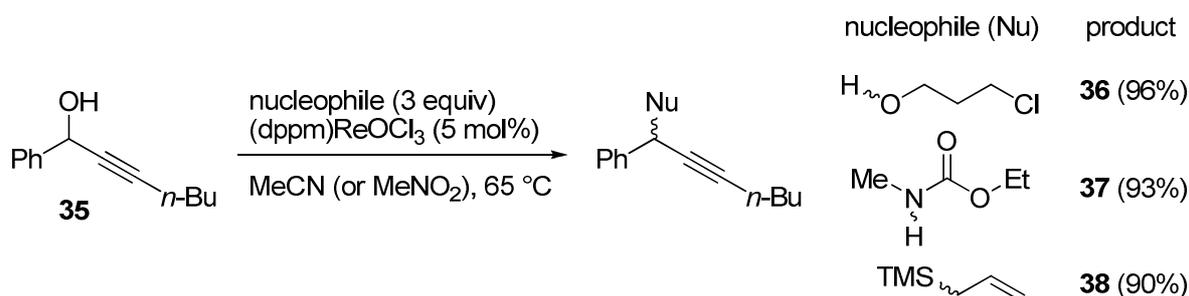
Scheme 1.13 Rhenium-catalyzed propargylic substitution

The formation of carbon-carbon bonds was accomplished by the same Re catalyst taking allylsilanes as nucleophiles.[69] The best results for this reaction were obtained if nitromethane was the solvent, and NH_4PF_6 was added as cocatalyst. Several benzylic propargylic alcohols were transformed into the anticipated 1,5-enynes (*e.g.* **38**) 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 cocatalyst, instead of NH_4PF_6, to obtain reasonable yields (25-58%).

1.3.5 PROPARGYLIC SUBSTITUTIONS BY OTHER TRANSITION METAL COMPLEXES

In 2002 Matsuda and co-workers reported the transformation of propargylic acetates into β-alkynyl carbonyl compounds 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 1.14).[70] Both internal and terminal alkynes were converted. The reaction was in some cases not regioselective. With two phenyl groups on the propargyl carbon, like in **39b**, reverse selectivity was observed in the regiochemistry of the substitution, and 55% of the allenic product (**40b**) was obtained. Steric bulkiness at the nucleophilic site was considered as well to be advantageous for allene formation.
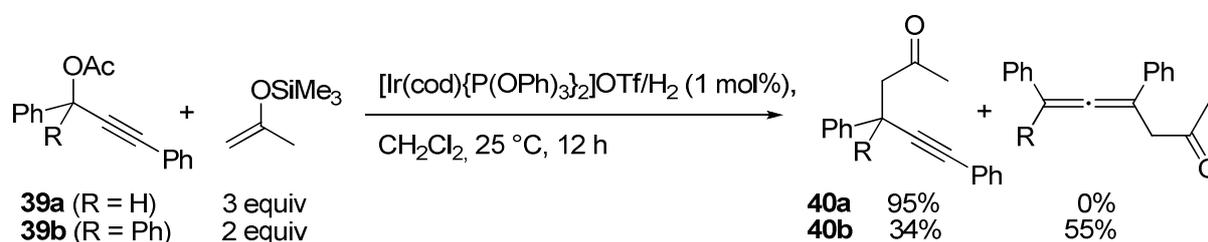
Scheme 1.14 Iridium-catalyzed propargylic substitution

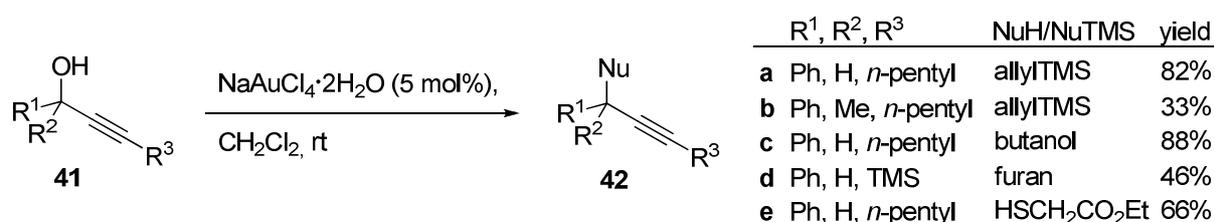Gold(III)-catalyzed nucleophilic substitutions of propargylic alcohols were recently disclosed by the group of Campagne.[71] Best results in the allylation of 1-phenylhept-2-yn-1-ol **41a** by allyltrimethylsilane were obtained with $NaAuCl_4 \cdot 2H_2O$ (5 mol%) as the catalyst (Scheme 1.15). Various 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 as substituent no reaction was observed. Modifications on the alkynyl part led to good yields (71-97%) except for an electron-poor group (CO_2Et), which resulted in no reaction. Tertiary and non-benzylic propargylic alcohols were effectively converted into the 1,5-enyne products, although in lower yields (33-59%). Alcohols, electron-rich aromatic rings, and thiols were successfully applied as nucleophiles in this gold-catalyzed method, affording the products in moderate to good yields (35-88%). Surprisingly, the use of nitrogen nucleophiles and terminal alkynes is not mentioned.

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$_2$CO$_2$Et	66%

Scheme 1.15 Gold-catalyzed propargylic substitution

Evans and Lawler examined the feasibility of the propargylic amination of **43** catalyzed by the Wilkinson catalyst, RhCl(PPh$_3$)$_3$.[72] The amination of the propargylic alcohol of **43** 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 **44** was obtained in 82% yield (Scheme 1.16).


R^1	NuH/base	yield
a PhCH$_2$CH$_2$	HN(Ts)Bn/LiHMDS	82%
b *t*-Bu	HN(Ts)Bn/LiHMDS	83%
c Ph	HN(Ts)Bn/K$_2$CO$_3$	74%
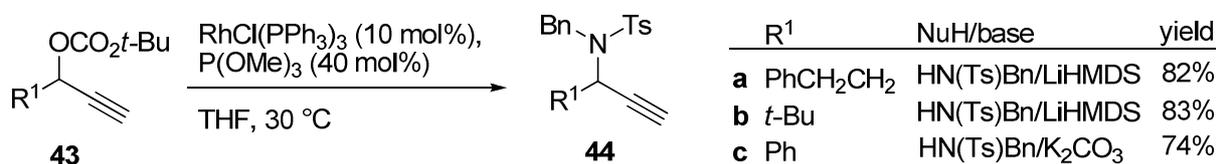
Scheme 1.16 Rhodium-catalyzed propargylic substitution

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$_2$CO$_3$, the propargylic sulfonamides were obtained, in most cases as single isomers.

1.3.6 LEWIS ACID-CATALYZED 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 from α-silyloxypropargyltrimethylsilanes (Scheme 1.17). They found that the α-silyloxy group of their starting material was partially substituted by chloride in the presence of TiCl$_4$.[73]
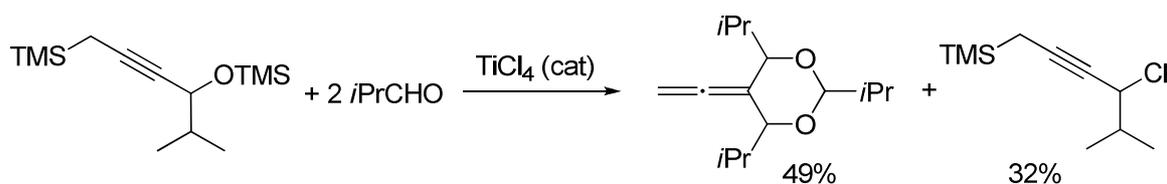
Scheme 1.17 Propargylic substitution by TiCl$_4$

Mukaiyama *et al.* deliberately treated propargylic ether **45** with allyltrimethylsilane in the presence of catalytic amounts of SnCl$_4$ and ZnCl$_2$, which afforded the desired product **46** in reasonable yield (Scheme 1.18).[74]
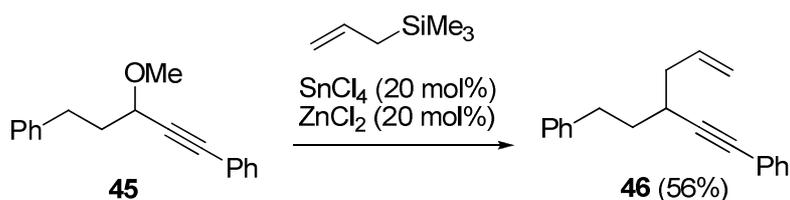
Scheme 1.18 Lewis acid mediated substitution of propargylic ether **45**

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.[75] 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 (**48a**) or the allenic product (**48b**) was formed exclusively (Scheme 1.19).

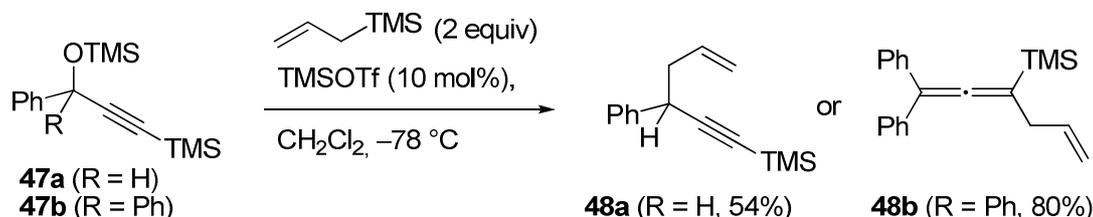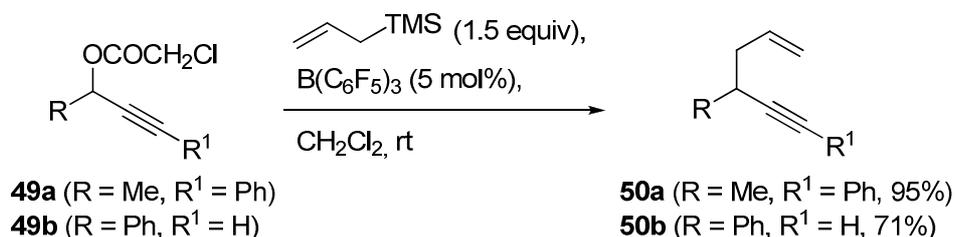**Scheme 1.19** TMSOTf mediated substitution of propargylic TMS ethers **47**

The first attempt to allylate the propargylic alcohol of **49** in the presence of $B(C_6F_5)_3$ failed, as described by Gevorgyan and co-workers.[76] Optimization of the leaving group led to the use of **49** 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 1.20).

Scheme 1.20 $B(C_6F_5)_3$ mediated substitution of propargylic esters **49**

Mahrwald and co-workers described a $TiCl_4$-catalyzed nucleophilic substitution of propargylic acetates **51** by alcohols affording propargylic ethers **52a-c** (Scheme 1.21).[77] 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.

52a 95% (R^1 = Ph, NuH = MeOH)
52b 55% (R^1 = Ph, NuH = *t*-BuOH)
52c 76% (R^1 = *n*-Bu, NuH = MeOH)
52d 78% (R^1 = Ph, NuH = BzNH$_2$)
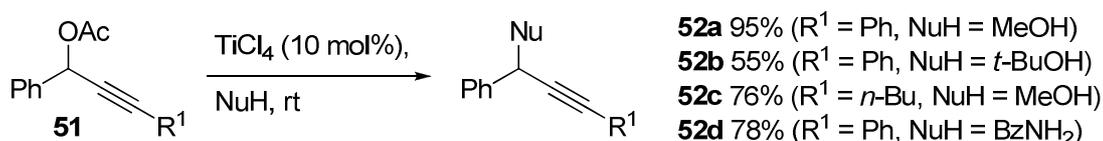
Scheme 1.21 $TiCl_4$-catalyzed propargylic substitution

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 (**52d**). Removal of the benzoyl group was accomplished by reduction with DIBAL affording the primary amine in 55% yield.
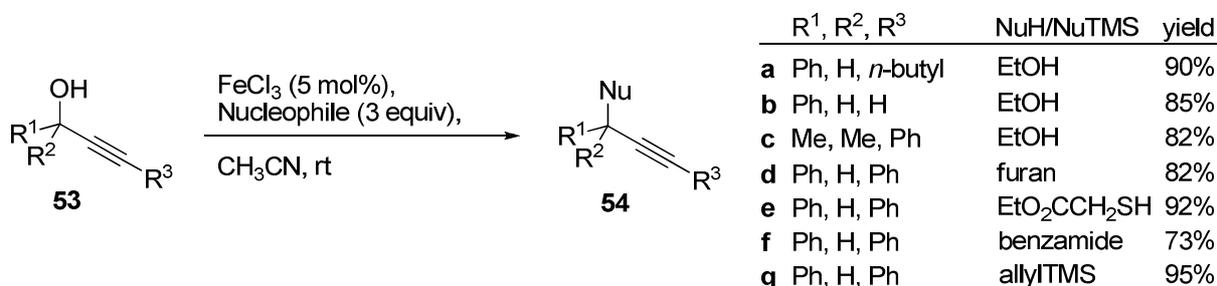
It is remarkable that Mahrwald does not report the formation of chloroallenes, because the reaction of 1-phenyl-2-octyn-1-ol with equimolar amounts of triethylamine and $TiCl_4$ gives the corresponding chloroallene in 56% yield, as reported by Periasamy and co-workers.[78] Periasamy also notes that with 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.*,[79] allowing a broad range of nucleophiles, such as alcohols, electron-rich aromatic rings, sulfides, amides, sulfonamides, and allyltrimethylsilane (Scheme 1.22). 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 unstability 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.

R^1, R^2, R^3	NuH/NuTMS	yield
a Ph, H, *n*-butyl	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%

Reaction: **53** (R^{1}R^{2}C(OH)-C≡C-R^3) → FeCl$_3$ (5 mol%), Nucleophile (3 equiv), CH$_3$CN, rt → **54** (R^{1}R^{2}C(Nu)-C≡C-R^3)

Scheme 1.22 $FeCl_3$-catalyzed propargylic substitution

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).[80]

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 sulphonamides and carbamates.[81] 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%, resp.). 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 hydroxyl group (Scheme 1.23).
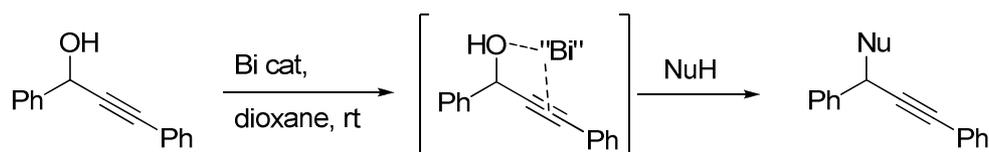
Scheme 1.23 Proposed mechanism of propargylic alcohol activation by a bismuth catalyst

1.3.7 A BRØNSTED ACID-CATALYZED METHOD

Recently, Sanz *et al.* found that organic acids, such as *p*-toluenesulfonic acid (PTS), efficiently catalyze direct nucleophilic substitutions of the hydroxy groups of propargylic alcohols with a large variety of carbon- and heteroatom-centered nucleophiles (Scheme 1.24).[82] The method allows the use propargylic alcohols with both aliphatic and aromatic groups as side chain(s). Although side products were formed (<15%), terminal alkynes, besides internal, were also converted into the desired products. This metal-free strategy represents a synthetically competitive alternative to the already established use of metal complexes.

	R^1, R^2, R^3	NuH/NuTMS	yield
a	Ph, H, *n*-butyl	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%
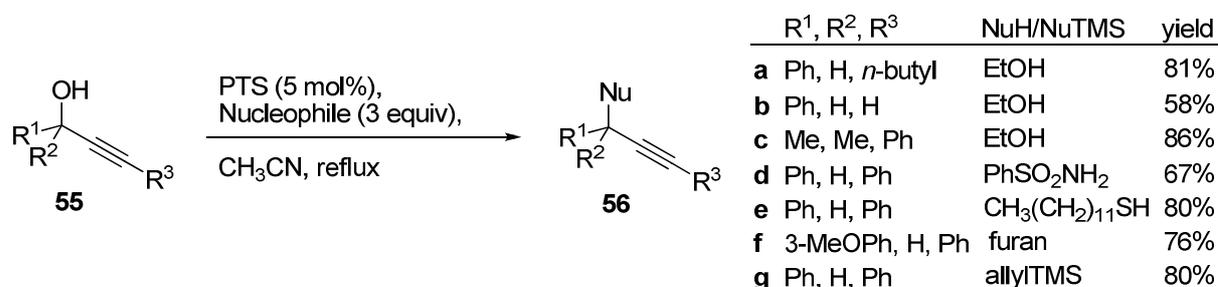
Scheme 1.24 PTS-catalyzed propargylic substitution

1.4 ENANTIOSELECTIVE PROPARGYLIC SUBSTITUTIONS

Although some diastereoselective methods have been described,[55,69,83] enantioselective examples of propargylic substitution reactions are limited to only one transition metal. Nishibayashi and co-workers showed that a chiral ruthenium complex could induce asymmetry in the C-C bond formation between acetone and 1-phenyl-2-propyn-1-ol.[84]
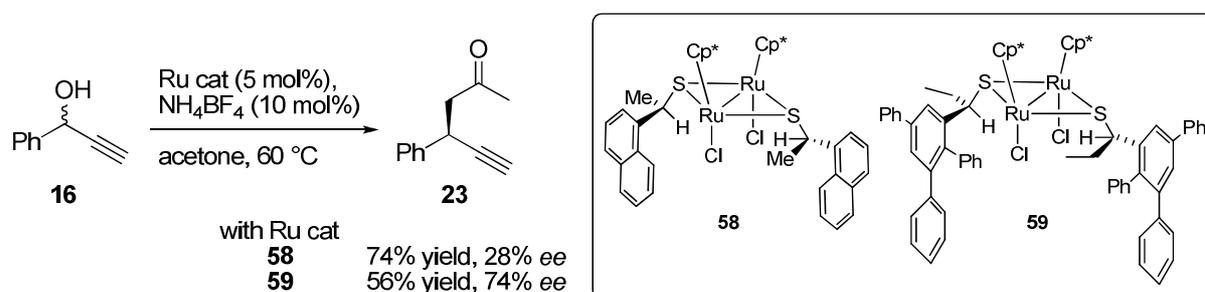
Scheme 1.25 Enantioselective ruthenium-catalyzed propargylic substitution

The reaction was carried out in the presence of catalysts generated *in situ* from [Cp*RuCl(μ_2-Cl)]$_2$ and chiral thiols. (*R*)-1-(1-Naphthyl)ethanethiol as chiral ligand led to the most selective catalyst (**58**) in this first study and afforded **23** in 74% yield and 28% *ee* (Scheme 1.25). 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 **16** in the ruthenium-allenylidene complex by π-π interactions (Figure 1.4). The concept worked and a screening of several ligands led eventually to increased enantioselectivities, with second generation catalyst **59** giving the best results.[85] 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*).
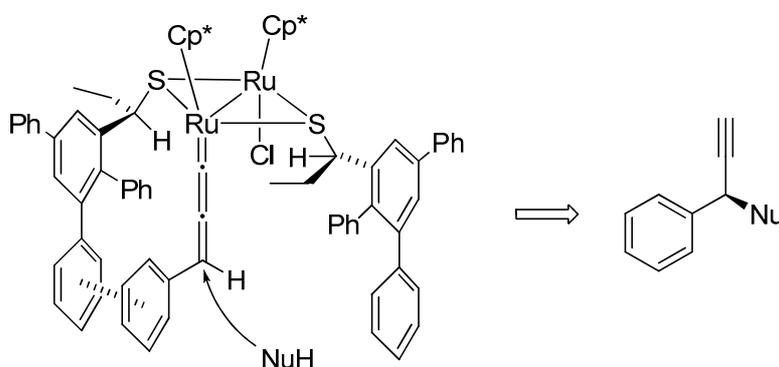

Figure 1.4 Proposed π-π interactions in the Ru-allenylidene intermediate

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.[86] 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. From a series of indole derivatives, *N*-(triisopropylsilyl)indole was found to substitute propargylic alcohols like **16** with high enantioselectivities.[87] The temperature and the amount of nucleophile could be lowered to 40 °C and 3 equiv, respectively, without affecting the yield and selectivity. Similar enantioselectivities (71-95% *ee*) were observed as for 2-methylfuran, although the yields were generally higher (63-98%). However, propargylic substitution reactions with heteroatom-centered nucleophiles, such as alcohols, amines, thiols, and diphenylphosphine oxide, did not proceed enantioselectively 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.

1.5 OUTLINE OF THE THESIS

The main theme in this thesis is the facile preparation of triazole-based P,N ligands for transition metal catalysis. In **Chapter 2**, the synthesis of this new type of P,N ligands (called ClickPhine) using the copper-catalyzed azide-alkyne "click" cycloaddition is described. Preliminary experiments show the efficacy of these ligands in the palladium-catalyzed allylic alkylation reaction. In **Chapter 3**, a route to prepare chiral, enantiopure building blocks for the synthesis of chiral P,N ligands is presented. To this end a novel enantioselective copper-catalyzed propargylic amination is developed, which emerges as a promising research topic. After an optimization study, the scope of the reaction is examined. In **Chapter 4**, a series of nitrogen and carbon nucleophiles is tested in the copper-catalyzed propargylic amination. Furthermore, the acquired propargylic amines are applied in formal syntheses of anisomycin and cytoxazone. In **Chapter 5**, initial rate kinetics and ESI-MS experiments, among other experiments, shed some light on the mechanism of the copper-catalyzed propargylic amination. A proposed catalytic cycle and a model to explain the observed asymmetric induction are presented. In **Chapter 6**, two routes for the synthesis of chiral, enantiopure, ClickPhine P,N ligands are described. The iridium complexes of these ligands are tested in the iridium-catalyzed asymmetric hydrogenation of challenging olefins.

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