Catalytic Propargylation

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Transition-Metal-Catalyzed Propargylic Substitution

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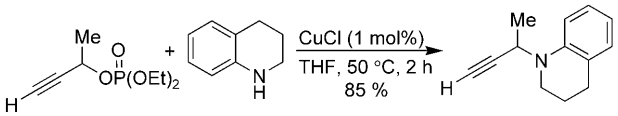
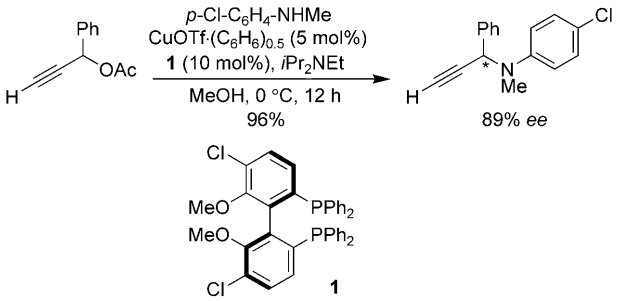
The nucleophilic substitution of allylic substrates under the catalysis of transition metals has been investigated extensively;[1] however, somewhat surprisingly, the corresponding catalytic propargylic substitution was not studied in much detail until recently. The Nicholas reaction, which involves the nucleophilic substitution of cobalt-complexed propargylic alcohols, enables the incorporation of a wide range of functionalities through the use of various nucleophiles, but has the drawback that a stoichiometric amount of the metal complex is used.[2] There is thus a need for a catalytic propargylation process. Several issues need to be considered in the development of such a reaction: 1) the type of nucleophiles that can be used; 2) restrictions in terms of the propargylic substrate (terminal/internal, aliphatic/aromatic); 3) whether or not the hydroxy functionality requires prior activation; 4) the risk of competing allene formation; 5) possibilities for development of an asymmetric version. We discuss herein the recent developments in this area, with a special focus on asymmetric processes. Organocatalytic methods are not covered, but have been reviewed recently by Kabalka and Yao.[3]

One of the earliest transition-metal-catalyzed propargylic substitution reactions described was the copper-catalyzed propargylation reaction reported in 1994 by Murahashi and co-workers,[4] who examined several copper catalysts in the reaction between propargylic phosphates and amine nucleophiles (Scheme 1). Copper(I) chloride was found to give the best results. With this catalyst, propargylic amines were formed in high yields. The reaction is limited to terminal alkynes, but allows the use of both aliphatic and aromatic amines.



Scheme 1. An early example: the copper-catalyzed propargylic amination.

Nishibayashi and co-workers studied the corresponding asymmetric copper-catalyzed propargylation reaction by using copper(I) triflate together with chiral diphosphine ligands.[5] A variety of aniline derivatives were screened as nucleophiles. The product was formed with up to 89% *ee* with chloro-substituted *N*-methylaniline (Scheme 2). Aliphatic amine nucleophiles could also be used, although the enantioselectivity was lower in this case. The reaction is limited to terminal propargylic acetates with aromatic substituents; the attempted use of an aliphatic propargylic acetate was not successful.



Scheme 2. Copper-catalyzed asymmetric propargylic amination with the biphep-type ligand **1** (biphep = (6,6′-dimethoxybiphenyl-2,2′-diyl)-bis(diphenylphosphane), Tf = trifluoromethanesulfonyl).

Simultaneously with this account, van Maarseveen and co-workers reported the use of chiral bisoxazoline (pybox) ligands and copper catalysis in propargylic amination reactions.[6] Four different copper complexes as well as eight pybox ligands were screened in the propargylic substitution of terminal propargylic acetates with aniline derivatives. Copper(I) iodide in conjunction with ligand **2** gave the best results: The substitution product was formed with up to 88% *ee* (Scheme 3). The nature of the base was found to be important not only for the reaction rate, but also for the stereoselectivity. Diisopropylamine was optimal; the yield and enantioselectivity were both lower with stronger bases. Aliphatic substrates were found to be incompatible with this methodology, as the higher reaction temperatures required for sufficient conversion in this case resulted in poor enantioselectivity. The method appears to be limited to

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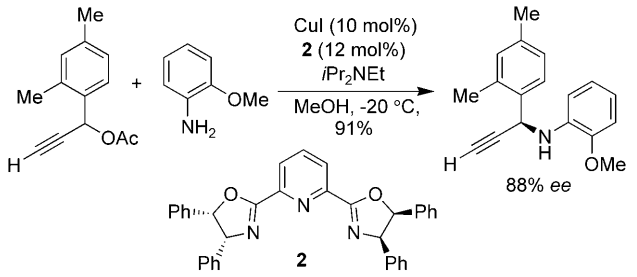
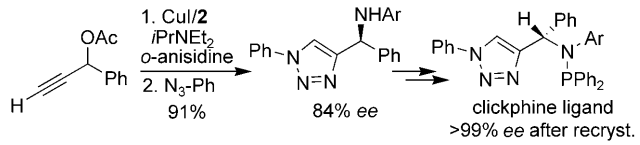


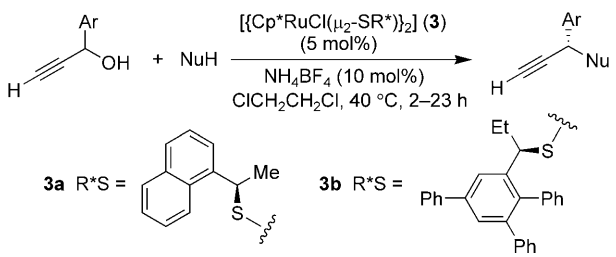
Scheme 3. Copper-catalyzed asymmetric propargylation with the pybox ligand **2** (pybox = pyridine-2,6-bisoxazoline).

terminal alkynes: The attempted use of an internal alkyne resulted in no conversion. The methodology was applied to the synthesis of a chiral P,N clickphine ligand in a convenient one-pot copper-catalyzed propargylic substitution and 1,3-dipolar cycloaddition reaction (Scheme 4).



Scheme 4. Synthesis of a chiral P,N ligand through a one-pot CuI-catalyzed asymmetric propargylic substitution/cycloaddition reaction.

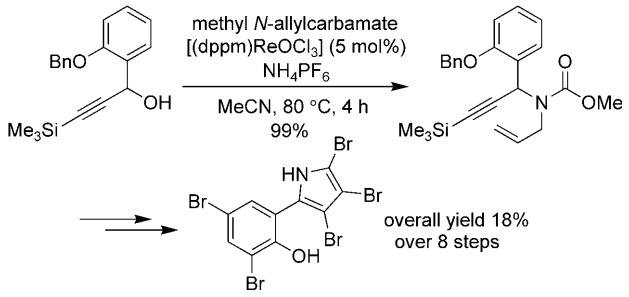
Probably the most important contribution in the field of catalytic propargylation comes from the collaborative efforts of Nishibayashi, Uemura, and co-workers, who investigated the use of thiolate-bridged diruthenium complexes in the nucleophilic substitution of terminal and internal propargylic alcohols with a large variety of nucleophiles. This methodology has been reviewed,[3,7] and herein we limit our discussion to the asymmetric version. Bridging chiral thiolate ligands were incorporated into the bimetallic ruthenium complex **3** as a catalyst for the reaction of acetone as the nucleophile with aromatic propargylic alcohols (Scheme 5). Modest enantioselectivities were observed initially with complex **3a**;[8a] however, ligand modification (see structure **3b**) led to an increase in the *ee* value of the product to 82%.[8b] When aromatic nucleophiles were used, the product was formed with up to 95% *ee* if the propargylic substrate also contained an aromatic functionality.[8c,d] The authors propose that π–π interactions between the aromatic rings on the



Scheme 5. Asymmetric propargylic substitution with chiral thiolate-bridged ruthenium complexes.

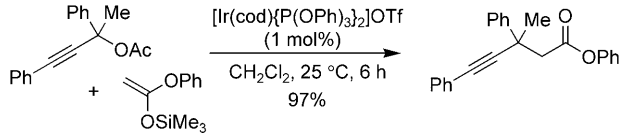
substrate and ligand are important for the stereoselectivity of the reaction.

Transition metals other than ruthenium and copper also catalyze the nucleophilic propargylic substitution. Palladium-catalyzed propargylic amination was reported at an early stage by Marshall and Wolf.[9] In a rhodium-catalyzed amination of propargylic carbonates, Evans and Lawler used a modified Wilkinson catalyst.[10] Toste and colleagues applied [(dppm)$ReOCl_3$] as a catalyst for the coupling of alcohols, allyl silanes, aromatic compounds, and electron-deficient amines with propargylic alcohols.[11] The amination reaction was applied in the synthesis of the marine antibiotic pentabromopseudilin, a potent human lipoxygenase inhibitor (Scheme 6).[11d]



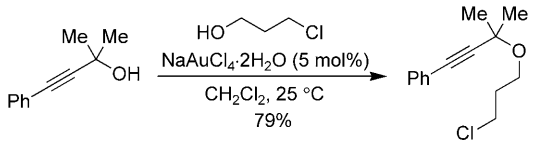
Scheme 6. Synthesis of the marine antibiotic pentabromopseudilin by employing a rhenium-catalyzed propargylic amination (dppm = $Ph_2PCH_2PPh_2$).

Iridium-catalyzed propargylation was described by Matsuda et al.: [Ir(cod){$P(OPh)_3$}$_2$]OTf, preactivated with H_2, was found to be an effective catalyst in the reaction between internal propargylic esters and various silyl enol ethers.[12] Tertiary propargylic acetates (Scheme 7) gave the best results, whereas primary and secondary substrates required diethyl phosphate as the leaving group and a higher reaction temperature.



Scheme 7. Iridium-catalyzed substitution of propargylic acetates (cod = 1,5-cyclooctadiene).

Gold species have emerged as useful catalysts for propargylic substitution. Their use was first demonstrated by Campagne and co-workers.[13a] The best results were observed with Au^{III} complexes. Internal propargylic alcohols with electron-donating substituents could be used in the reaction. A variety of carbon and heteroatom nucleophiles could be applied, and halide substituents (Scheme 8) were compatible with the reaction conditions. The gold-catalyzed propargylation has been utilized by Dyker and co-workers in the construction of heterocalixarenes, a class of ligands related to porphyrins.[13b]



Scheme 8. Gold(III) catalysis for the direct conversion of a tertiary propargylic alcohol into a chloro-substituted ether.

Although much recent progress has been made in developing the catalytic propargylic substitution reaction, we see that a number of problems still need to be solved. Many of the reported methods are restricted to terminal alkynes. Transformations with binuclear ruthenium catalysts have so far been developed the most extensively, but even the scope of these procedures is limited in terms of the substrates: Tertiary propargylic alcohols are less efficient, and the reaction is sensitive to electronic constraints in some cases. An elegant feature of the ruthenium-catalyzed method, however, is that propargylic alcohols can be used directly without converting the hydroxy moiety into a better leaving group. Propargylic amines are useful intermediates in organic synthesis and in some cases exhibit biological activity themselves. However, a number of the existing methods for the synthesis of propargylic amines are limited to the use of anilines and/or sulfonamides as nucleophiles. The recently reported catalytic asymmetric propargylic substitution is a significant advancement, and we anticipate new developments in this area. Of particular interest is the use of aromatic nucleophiles in the asymmetric reaction, as this transformation formally constitutes an asymmetric Friedel–Crafts reaction.[14] Although some problems still remain unsolved, the catalytic propargylic substitution reaction has shown itself to be highly selective and efficient. We foresee many new applications for this versatile reaction in the near future.

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