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Body

Carbon–carbon double and triple bonds are not only important molecular components, but are also highly amenable for further functionalization. Therefore, it is of no surprise that, over past decades, a plethora of methodology has been developed for both regio- and stereoselective functionalization of C atoms next to alkenes and alkynes. Catalytic allylic ***substitution*** reactions, invented by the Tsuji and Trost groups, fulfil this task and are now considered to be mature reactions, providing a wide range of enantiomerically enriched alkenes connected to a tetrahedral C atom ***substituted*** with C-, N- or O-centred nucleophiles. More recently, the related catalytic propargylic ***substitution*** reaction has also proved a powerful method for accessing enantioenriched alkyne-functionalized stereogenic C atoms. Both transformations can be catalysed by transition metals such as palladium, iridium, nickel and ***copper***, with the assistance of chiral ligands.

Now, writing in Nature Synthesis, the groups of Lin and He report the development of an enantioselective ***copper***-catalysed ***substitution*** reaction at a C atom that is flanked by an alkene and an alkyne (Fig.). This ***alkynylallylic substitution*** reaction is highly regio- and enantioselective and, in contrast to many other transition metal-catalysed transformations, is insensitive to water and air and operates at room temperature. Most importantly, commonly used Cu()-pyridine-bis(oxazoline) (PyBOX) complexes are the optimal catalysts, making this methodology readily available to the synthetic community.

Enantioselective ***alkynylallylic*** ***substitution***.

a, An outline of the ***alkynylallylic*** ***substitution*** reaction showing the possible starting 1,3- or 1,4-enynes, nucleophiles, catalysts, intermediate and regiomeric products. b, Selected examples of obtained enantiomerically enriched 3-***substituted*** 1,4-enynes. c, Schematic of the bis-PyBOX dicopper complex showing the origin of the stereochemical outcome of nucleophilic attack at the allenyl intermediate. Bn, benzyl; Boc, tert-butyloxycarbonyl; d.r., diastereomeric ratio; e.e, enantiomeric excess; iPr, isopropyl; L, ligand; LG, leaving group; m, meta; Nu, nucleophile; r.r., regiomeric ratio; r.t., room temperature; Tf, trifluoromethansulfonyl.

Throughout medicinal chemistry, there are numerous cases where chirality is key to obtain the required biological activity and selectivity. With this newly developed methodology, a single catalytic transformation forms tertiary stereogenic centres, adjacent to an alkene and alkyne. A broad range of functional groups are well tolerated in both the ***alkynylallylic*** and nucleophilic reaction components. Notably, the secondary amines of some natural products and pharmaceutical drugs can act as nucleophiles in the reaction (Fig.). Some of these nucleophiles contain one or more stereocentres and, in these cases, high diastereomeric ratios were found. This level of diastereocontrol indicates that the stereochemical outcome of the process is under catalytic control, with the chirality of the ligand overruling the stereochemistry of the starting chiral amine nucleophile. Impressively, even in cases where the secondary amine is adjacent to a stereocentre, for example sertraline or proline, high diastereocontrol was obtained.

X-ray crystallography and kinetic analysis reveal that a bis-PyBOX dicopper complex intermediate determines the stereochemical outcome of the reaction (Fig.). In this key intermediate, the terminal C atom of the allenyl group is bound to two Cu atoms within the two PyBOX ligands. The allenyl moiety directs the perpendicular arrangement of the planes of the Cu–C–Cu atoms and the H–C–Phe moieties. As a result, the Si face is sterically shielded by an indene unit of one of the PyBOX ligands and nucleophilic attack occurs through the Re face of the pre-transition state assembly.

A limitation of the reaction is that it is only successful for secondary amines. If primary amines are used, the resulting secondary amine product can also act as a nucleophile for subsequent ***alkynylallylic substitution***. This limitation may be overcome by adding the primary amine in excess or by using masked primary amines or imides as nucleophiles.

The utility of the reaction products, 3-amino-1,4-enynes, is demonstrated through a series of reactions on the terminal alkyne, such as a Sonogashira coupling reaction, the 2022 Nobel Prize in Chemistry-winning Cu-catalysed alkyne–azide cycloaddition, or a Larock indole synthesis. All these late-stage transformations could be carried out without erosion of the optical purity.

Along with the development of reaction conditions that can tolerate primary amines or amine surrogates, application of the reaction to the synthesis of chiral 3-hydroxy-1,4-enynes remains a synthetic challenge, either through demonstration of selective O-benzyl ether deprotection or the use of water surrogates such as carboxylates as nucleophiles. Allylic and propargylic esters have previously been shown to be capable substrates in further metal-catalysed reactions with transfer of chirality. For example, the Toste group enabled a Au()-catalysed Rautenstrauch rearrangement in which enantiomerically enriched 3-acetoxy-1,4-enynes were converted, in a stereospecific fashion, into 2-cyclopentenones — versatile chiral precursors in organic synthesis.

A challenging future opportunity could be the application of the enantioselective ***alkynylallylic substitution*** reaction to the synthesis of quaternary 3-functionalized 1,4-enynes, through the use of a quaternary ***substituted alkynylallylic*** substrate or through selective functionalization of a tertiary 3-functionalized 1,4-enyne reaction product.

Over recent decades, catalytic enantioselective allylic and propargylic nucleophilic ***substitution*** reactions have become commonplace in organic synthesis. The current contribution combines both methods into a robust protocol to make enantioenriched 1,4-enynes that are functionalized at the 3-position with a variety of N-, O- or C-centred nucleophiles. In contrast to most protocols for individual allylic or propargylic ***substitution*** reactions, the current ***alkynylallylic*** variant can be performed in the presence of air and water, at room temperature, making it robust, reproducible and scalable. Without doubt, this enantioselective ***alkynylallylic substitution*** reaction will soon find wide application in academic and industrial labs.

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