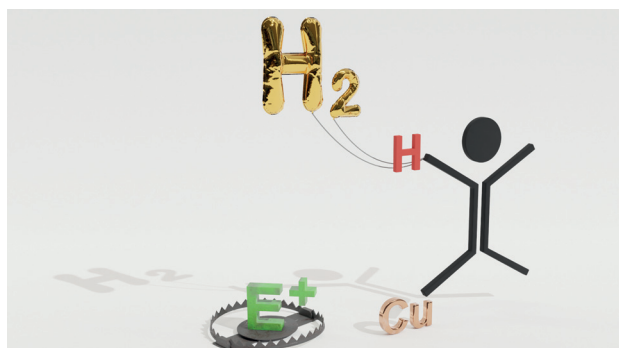# Catch It If You Can: Copper-Catalyzed (Transfer) Hydrogenation Reactions and Coupling Reactions by Intercepting Reactive Intermediates Thereof

Lea T. Brechmann
Johannes F. Teichert* [ID]

Institut für Chemie, Technische Universität Berlin,
Straße des 17. Juni 115, 10623 Berlin, Germany
johannes.teichert@chem.tu-berlin.de

Abstract The key reactive intermediate of copper(I)-catalyzed alkyne semihydrogenations is a vinylcopper(I) complex. This intermediate can be exploited as a starting point for a variety of trapping reactions. In this manner, an alkyne semihydrogenation can be turned into a dihydrogen-mediated coupling reaction. Therefore, the development of copper-catalyzed (transfer) hydrogenation reactions is closely intertwined with the corresponding reductive trapping reactions. This short review highlights and conceptualizes the results in this area so far, with H_2-mediated carbon–carbon and carbon–heteroatom bond-forming reactions emerging under both a transfer hydrogenation setting as well as with the direct use of H_2. In all cases, highly selective catalysts are required that give rise to atom-economic multicomponent coupling reactions with rapidly rising molecular complexity. The coupling reactions are put into perspective by presenting the corresponding (transfer) hydrogenation processes first.

1 Introduction: H_2-Mediated C–C Bond-Forming Reactions

The interception of reactive intermediates of catalytic transformations is a typical approach to unravel new reactivity in method development for synthetic chemistry. Especially for the construction of C–C bonds, the use of organometallic reagents has proven to be extremely effective.[1,2] However, the use of a stoichiometric organometallic
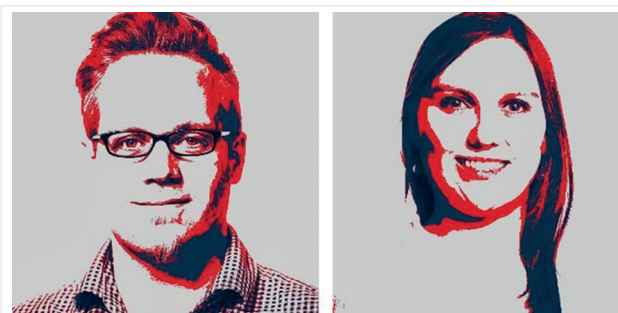
Johannes Teichert (left) is currently a junior professor at Technische Universität Berlin. He studied at Philipps-Universität Marburg (diploma thesis with Prof. Gerhard Hilt) and at Université Paul Sabatier in Toulouse, France. In 2006, he joined the group of Prof. Ben L. Feringa at Rijksuniversiteit Groningen, the Netherlands for his Ph.D. in the field of asymmetric catalysis. After a postdoctoral stay with Prof. Jeffrey Bode at ETH Zurich, he started his independent research group in Berlin. Johannes' research interests include method development in organic synthesis, transition-metal catalysis and especially reductive transformations employing H_2.

**Lea Brechmann** (right) is currently working in the group of Johannes Teichert. She studied at Philipps-Universität Marburg and at the University of Santiago de Compostela before joining the group of Gerhard Hilt for her M.Sc. degree. Since 2017 she has been studying for her Ph.D. focusing on the development of new transition-metal-catalyzed synthetic methods by activating dihydrogen as the hydride source.

reagent in, e.g., a cross-coupling reaction, inevitably leads to the formation of a stoichiometric amount of metal-based waste. The possible avoidance of such waste by means of a catalytic process based on dihydrogen (H_2) serves as a prime inspiration for developing new reactions. This approach can be driven from the vantage point of the desire for atom economy/efficiency,[3,4] and can also serve as a fruitful inspiration for method development in synthetic chemistry.

Dihydrogen can be viewed as an easily accessible and, in principle, a sustainably producible and abundant resource, and although its use in catalytic hydrogenations is by far the prime use of H_2 in synthesis,[5–7] the aforementioned features render it highly desirable as a key reagent for catalytic C–C (and C–heteroatom) bond-forming reactions. The opportunity to replace common organometallic reagents with catalytic processes based on H_2 was recognized a long time ago. Probably the most famous H_2-mediated C–C bond-forming reactions are the *Fischer–Tropsch* process (Scheme 1, a)[8,9] and alkene hydroformylation (the oxo process, Scheme 1, b).[10–12] Emanating from this, catalytic H_2-mediated C–C bond-forming reactions beyond C1 building blocks bear great potential in synthetic chemistry. In particular, rhodium-catalyzed coupling reactions of alkenes/alkynes and carbonyl derivatives have been intensively studied.[13]

Exemplary of these is a rhodium-catalyzed enantioselective reductive coupling reaction of enyne **3** with α-ketoester **4** (Scheme 1, c).[14] Key to this transformation is the activation of dihydrogen by a rhodium complex consisting of bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate and *R*-Xylyl-WALPHOS (**6**) followed by the main C–C bond-forming reaction. This and related methods[13] are impressive in themselves, as the resulting overall transformations are elegant and display high chemoselectivity (none of the alkenes formed in Scheme 1, c suffer any additional over-hydrogenation), next to the obvious atom economy. Indeed, H_2-mediated processes such as the one highlighted had been put forward in the literature as being highly sought-after.[15] The transformations highlighted in Scheme 1 revolve around the use of carbonyl and/or carboxyl acceptors. Progressing from these functional groups to other coupling partners would substantially broaden this elegant approach.

Departing from noble metal catalysts (mostly based on rhodium, iridium and ruthenium) could offer such an opportunity. In particular, base metals, which have only recently regained popularity in catalytic hydrogenations and H_2 activation processes, might lead the way to such a new approach.[5,16]
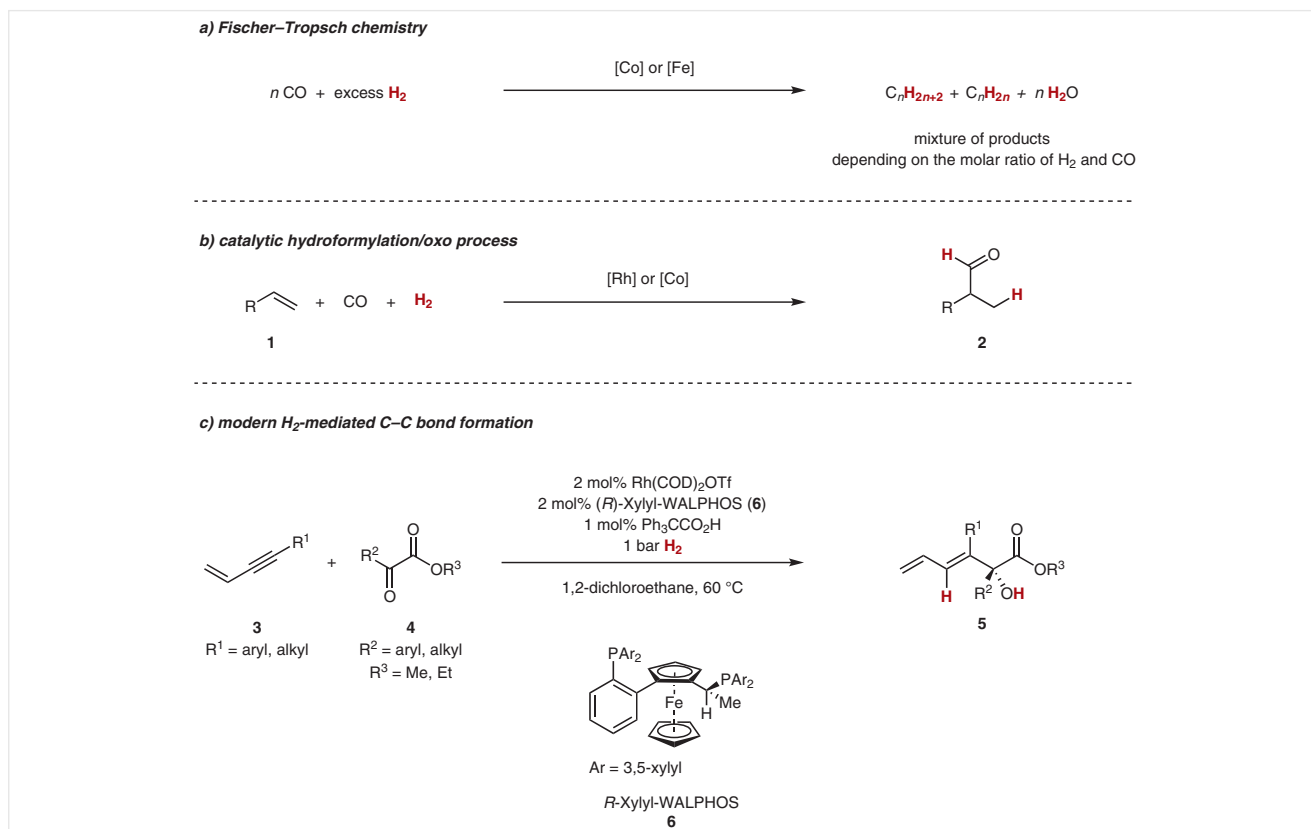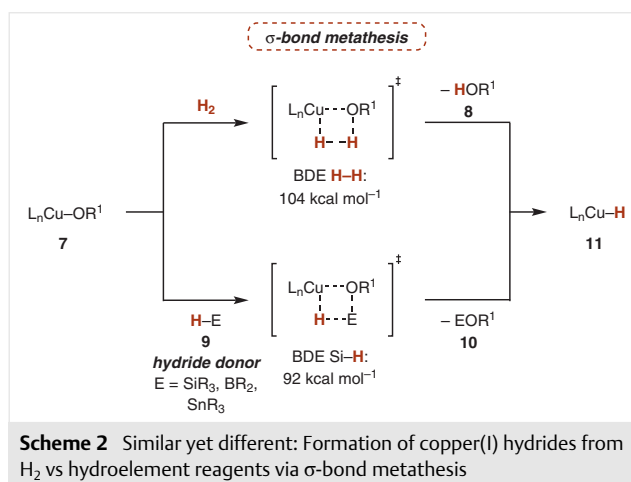

Scheme 1 Overview of catalytic, H_2-mediated C–C bond-forming processes. Only the most common metals are displayed for the processes in (a) and (b)
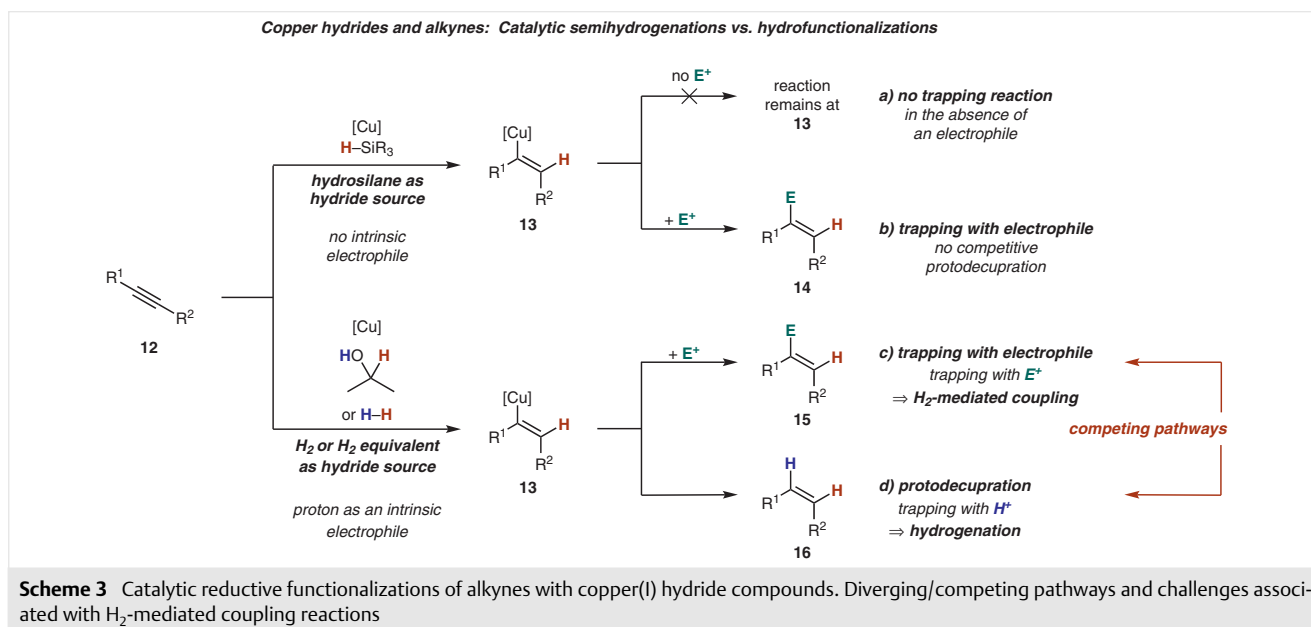
In recent years, many studies employing copper as a catalytic metal for reductive coupling reactions have been put forward (see Section 3), and first endeavors into copper-catalyzed H_2-mediated bond-forming reactions have appeared.[17–19] One of the key advantages of copper catalysis is the fact that it opens up the possibility for widening the reaction space beyond carbonyl/carboxyl derivatives as coupling partners, which have been prevalent thus far (see above). This review summarizes the developments based on copper catalysts for reductive coupling reactions of alkynes under hydrogenative or transfer hydrogenative conditions and aims at discussing the various approaches.[20]

2 Accessing Copper(I) Hydride Complexes as Key Reagents for Coupling Reactions; Requirements for Successful Trapping Reactions

Fundamental for the development of H_2-mediated bond-forming processes is the efficient in situ generation of copper(I) hydrides, which has to be compatible with all other envisaged downstream reactions. Copper(I) hydrides are widely used and well-studied reagents in organic synthesis, probably best known for their prototypical reactivity in the conjugate reduction (i.e., 1,4-reductions) of α,β-unsaturated carbonyl or carboxyl compounds, or 1,2-reductions.[21] In addition, catalytic reductive alkene or alkyne functionalization reactions have been intensively studied in the last decade.[17,18] Generally, for all the aforementioned transformations, hydrosilanes serve as salient stoichiometric hydride sources.[21–24] The mechanism of formation of the actual copper(I) hydride complex is outlined in Scheme 2. The presence of a copper–oxygen bond is the necessary

Scheme 2 Similar yet different: Formation of copper(I) hydrides from H_2 vs hydroelement reagents via σ-bond metathesis

structural motif for the formation of copper(I) hydrides: In the presence of a hydrosilane as the hydride source, copper(I) hydride **11** is known to be formed via σ-bond metathesis of the hydrosilane and copper(I) complexes **7** bearing a Cu–O bond, liberating silyl ether **10** as a by-product (E = Si) (Scheme 2, bottom).[25,26] The activation of H_2 leading to copper(I) hydrides **11** resembles that of the hydrosilane pathway (Scheme 2, top). Based on only circumstantial evidence, activation of H_2 had been suggested in the 1950s.[27] These two comparable pathways leading to the same product differ markedly by the corresponding bond strengths of the formal hydride donors (Si–H: 92 kcal mol^{-1} vs H–H: 104 kcal mol^{-1}),[28] in addition to the significant driving force that arises from the formation of the strong Si–O bond in **10** in the case of hydrosilanes. Accessing copper(I) hydride complex **11** from H_2 requires a key heterolytic H–H bond

Scheme 3 Catalytic reductive functionalizations of alkynes with copper(I) hydride compounds. Diverging/competing pathways and challenges associated with H_2-mediated coupling reactions

cleavage along the Cu–O bond. In fact, the Cu–O bond is present in the vast majority of all homogeneous catalytic hydrogenations with copper complexes.[26,29,30]

The copper(I) hydrides **11** thus generated display a high reactivity towards alkynes, which can be exploited for both catalytic hydrogenations as well as catalytic hydrofunctionalizations.[19,31] Both types of reactions share a common first step: a *syn*-hydrocupration of the copper(I) hydride with the alkyne generates a vinylcopper(I) complex **13** as a primary reactive intermediate (**12** → **13** in Scheme 3).[32] The vinylcopper(I) complex **13** is the main bifurcation point for the following reactions. Scheme 3 attempts to highlight the various pathways and the additional challenges that go along with a seemingly simple switch from hydroelement compounds as the hydride source to H$_2$. Vinylcopper(I) compound **13** can react with a suitable electrophile forming substituted alkenes **14**, resulting in an overall catalytic hydrofunctionalization of the alkyne starting material (Scheme 3, b). On the other hand, in the absence of an electrophile, the reaction remains at vinylcopper(I) complex **13**, resulting in no catalytic turnover (Scheme 3, a).[32] Therefore, when hydrosilanes are employed, the reaction rate of the trapping reaction with the externally added electrophile does not play a crucial role for the overall process **12** → **14** as the reaction is simply halted at vinylcopper(I) complex **13**. In stark contrast to this, the realm of hydrogenative copper(I) hydride based reactions with alkynes depends to a

high degree on the 'quality' of the electrophile (i.e., the reaction rate of the trapping reaction of **13**). As the copper(I) hydride formation from H$_2$ necessarily produces a proton equivalent (mostly in the form of an alcohol), a proton (or an alcohol as a protic molecule in the mixture) can always serve as an intrinsic electrophile for vinylcopper(I) complex **13**. This would lead to an overall catalytic hydrogenation and therefore to the 'simple' alkene **16** (Scheme 3, d). Any catalytic hydrofunctionalization of alkynes with H$_2$ and copper complexes must therefore overcome the challenge of this unwanted protodecupration process. In other words, the key trapping reaction with an electrophile or a coupling partner needs to exhibit a significantly higher rate than the protodecupration. Therefore, catalytic hydrofunctionalizations of alkynes based on H$_2$ are significantly more challenging to develop compared to their counterparts based on hydrosilanes (Scheme 3, c).

One general advantage of these overall reductive functionalizations is the fact that they deliver the corresponding substituted alkenes in a highly stereoselective manner. The selectivity ultimately stems from the high stereoselectivity of the *syn*-hydrocupration.[32] In addition, regioselective processes with non-symmetric alkyne starting materials **12** might be realized with a suitable catalyst or a (sterically or electronically) biased substrate. As one main advantage, the reactivity of the vinylcopper(I) complex **13** with electrophiles potentially leads away from the necessity of a
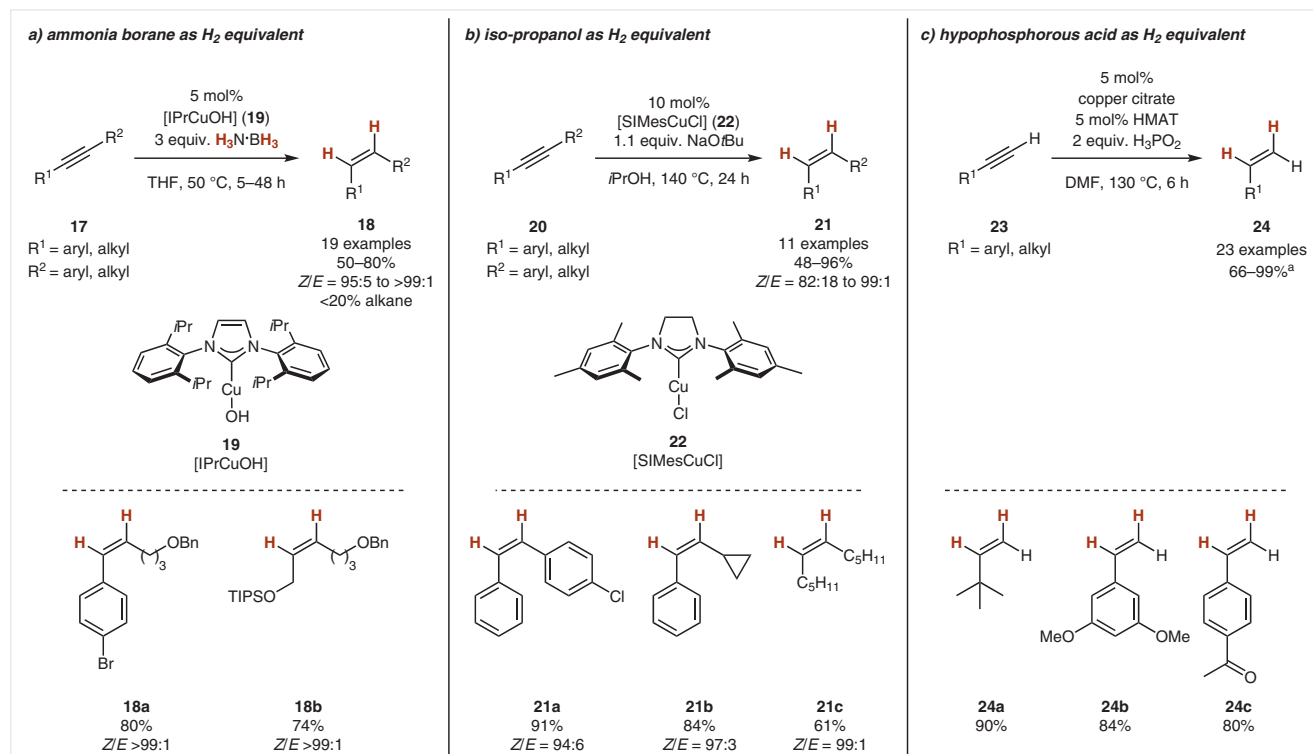
Scheme 4 Copper(I)-catalyzed transfer alkyne semihydrogenation reactions with selected substrates and various H$_2$ equivalents. [a] The isolated yield was only reported for a few substrates. (HMAT = hexamethylenetetramine)

carbonyl or carboxyl electrophile as compared to the transformations based on noble metals as discussed above (Scheme 1).

Reductive functionalization reactions could alternatively be realized in a transfer hydrogenation setting.[33] In these cases, similar challenges arise, as by default, transfer hydrogenation reagents as H_2 replacements bear a proton equivalent (again, a competitive intrinsic electrophile), which could also deter the overall reductive functionalization by directly diverging into a transfer hydrogenation of alkynes.

In the following sections, the parent copper(I)-catalyzed semihydrogenations or transfer semihydrogenations are highlighted first, followed by the corresponding trapping reactions, which often rely on the established protocols for catalytic semihydrogenations. Transfer hydrogenation processes are discussed first (Sections 3 and 4) followed by 'real' hydrogenative processes using H_2 (Sections 5 and 6).

3   Homogeneous Copper-Catalyzed Transfer Hydrogenations

Copper(I)-catalyzed hydrogenation reactions often require high pressure and therefore need specialized equipment.[29] To circumvent this requirement, transfer hydrogenation reactions with homogeneous copper catalysts have been developed. Ammonia borane ($H_3N \cdot BH_3$)[34] has been shown to be a formidable H_2 equivalent in copper(I)-catalyzed transfer hydrogenations.[35] Remarkably, N-heterocyclic carbene/copper(I) hydroxide complex **19**,[36,37] which had been successfully used in catalytic alkyne semihydrogenations earlier,[38,39] can be employed under almost identical conditions in a transfer hydrogenation setting by switching to ammonia borane. In this manner, a variety of alkynes **17** could be converted into the corresponding Z-alkenes **18** in good yields (reaching up to 80%) and with excellent stereoselectivity (Z/E > 95:5, Scheme 4, a). The exceptionally high Z-selectivity stems from the proposed stereospecific *syn*-hydrocupration as the key step forming vinylcopper(I) complex **13**,[32] as highlighted in Scheme 3. Generally, the use of NHC (NHC = N-heterocyclic carbene) ligands in copper(I)-catalyzed (transfer) hydrogenation suppresses any reactivity towards unactivated alkenes, supporting the high chemoselectivity of the overall processes.[40] Using this method, internal diaryl-, aryl/alkyl- and dialkyl-alkynes **17** with a variety of functional groups were tolerated. Though the addition of ammonia borane had to occur slowly in order to avoid catalytic dehydrocoupling (release of H_2 from ammonia borane), it has been shown that the overall protocol manifests a 'true' transfer hydrogenation and not, as one might suspect, a hydrodecoupling releasing H_2 and subsequent catalytic hydrogenation.

In a related process, terminal alkynes **23** (which are not tolerated by the abovementioned protocol based on ammonia borane) could be converted into the corresponding terminal alkenes **24** by employing hypophosphorous acid as the H_2 equivalent, while internal alkynes remained intact (Scheme 4, c).[41]

As a much more practical and ready available H_2 equivalent, it was recently shown that *iso*-propanol can also be employed in copper(I)-catalyzed transfer hydrogenations.[42] With a simple NHC/copper(I) complex **22** in catalytic amounts and NaO*t*Bu as a basic additive, internal alkynes **20** could be converted into Z-alkenes **21** in moderate to very good yield (48–96%), while maintaining a high to excellent Z/E ratio (82:18 to 99:1) (Scheme 4, b). Remarkably, even under these drastic conditions, no overreduction to the corresponding alkane was observed, again underscoring the key influence of the NHC ligand on the chemoselectivity. The reaction requires elevated temperatures, and either conventional heating (140 °C) or heating in a microwave (120 °C) could sustain the catalytic reaction. While up until now the substrate scope remains rather limited, this example marks the first use of the standard H_2 equivalent *iso*-propanol in the realm of homogeneous copper(I)-catalyzed transfer hydrogenation.[43]

4   Trapping of Reactive Intermediates of Alkyne Transfer Semihydrogenation Reactions: First Steps Towards Hydrogenative Alkyne Functionalizations

Based on the transfer hydrogenations discussed in Section 3, suitable external electrophiles tolerant of the protodecupration and the concomitant generation of copper(I) hydrides (Scheme 3, path d vs path c) have been identified. In this manner, the transfer hydrogenations can be rendered reductive functionalizations of alkynes. While in copper(I)-catalyzed transfer hydrogenations with ammonia borane the intermediate vinylcopper(I) complex **13** leads to the corresponding alkenes **16**, it could also be trapped with a halogen electrophile forming value-added substituted alkenes **15** in a stereoselective fashion, resulting in a net
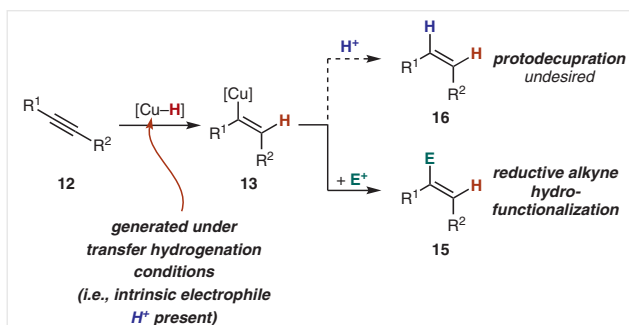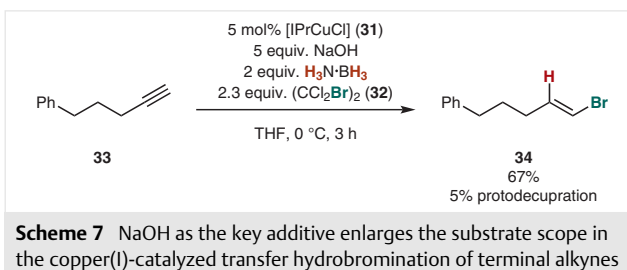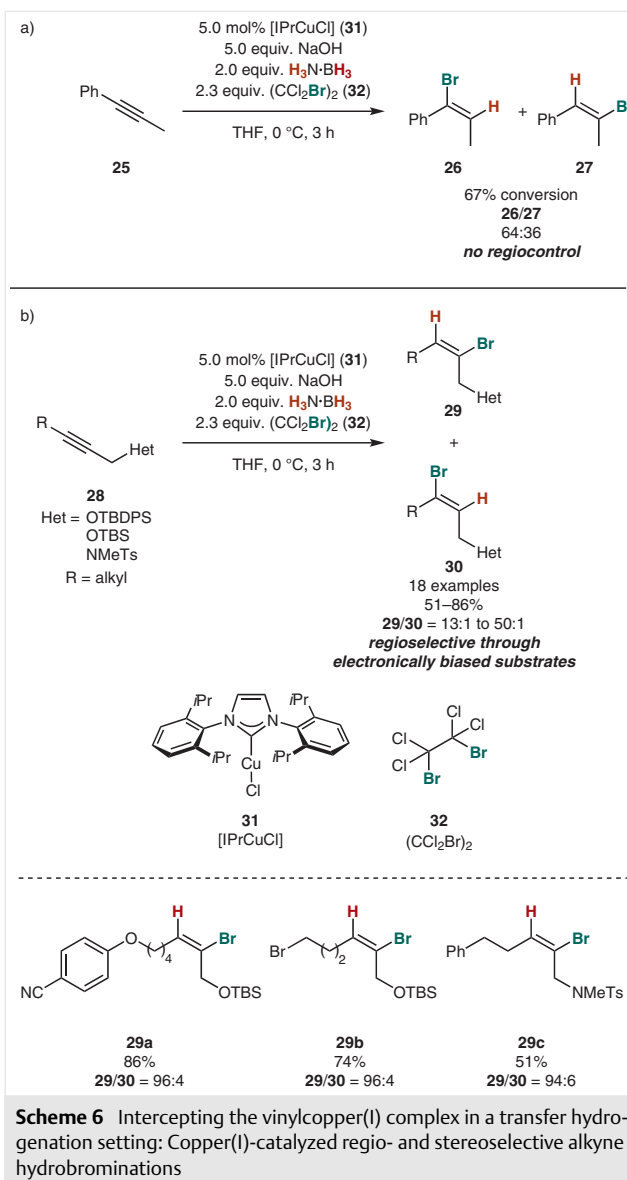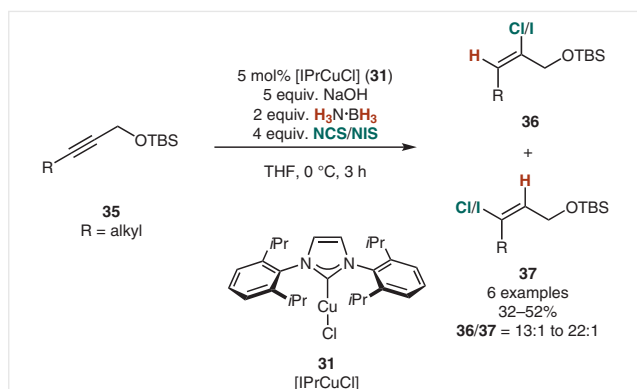

Scheme 5   Comparison of two possible reaction pathways based on a vinylcopper(I) intermediate. Transfer hydrogenation vs reductive alkyne hydrofunctionalization

hydrohalogenation of alkynes. Therefore, the trapping of the key vinylcopper(I) intermediate **13** offers an entry into substituted alkenes with controlled stereochemistry (Scheme 5).

In this vein, it has been found that electrophilic halogenation reagents react suitably fast in the trapping of the vinylcopper(I) complex **13** and lead to substituted vinyl halides in a stereoselective fashion.[44] Highly substituted vinyl bromides such as **29** are sought-after substrates for cross-coupling reactions,[1] which are hard to access in any other way.[45] In this manner, highly stereoselective hydrochlorinations, -brominations and -iodinations leading to vinyl halides were achieved using commercially available [IPrCuCl] (**31**) and NaOH as a basic additive. Again, just as in the earlier transfer hydrogenation[35] (compare Scheme 4), slow addition of both ammonia borane and the electrophile was crucial. This suppresses the competitive dehydrocoupling and undesired protodecupration (essentially leading to the transfer hydrogenation product **16**, Scheme 5). An additional bifurcation of the reaction needs to be controlled, namely the regioselectivity of the initial hydrocupration, which sets the positioning of the halide. The employment of electronically unbiased internal alkynes such as **25** led to no significant control of the regioselectivity (**26/27** = 64:36) (Scheme 6, a). This regioselectivity, however, could be controlled electronically by modifying the alkyne via the inductive effect[46] exerted by propargylic silyl ethers or protected propargylic amines **28**. With these starting materials, a highly regioselective *syn*-hydrocupration using dibromotetrachloroethane (**32**) as the source of electrophilic bromine gave rise to the selective formation of one of the hydrobromination regioisomers favoring halogenation at the β-position of the heteroatom (**29/30** = 13:1 to 50:1, Scheme 6, b). Interestingly, other leaving groups that have been shown to react with copper(I) hydrides, such as alkyl tosylates,[47] were not attacked by the catalytically generated nucleophilic copper(I) hydride. Switching to the related propargylic sulfonyl amide **28** resulted in moderate yield but still good selectivity. In addition, it is notable that terminal alkynes such as **33** could be transformed into the terminal alkene **34**, a substrate class that was barred so far due to the highly basic additives. In this case, however, NaOH allowed for the rare conversion of **33** into **34** (Scheme 7).

Using *N*-chlorosuccinimide (NCS) or *N*-iodosuccinimide (NIS), the corresponding vinyl chlorides or iodides **36/37** were obtained with similarly high selectivity (13:1 to 22:1) (Scheme 8), albeit with slightly reduced yields due to competitive transfer hydrogenation. Nevertheless, the overall catalytic stereo- and regioselective hydrohalogenation represents a both general and versatile catalytic entry to highly functionalized building blocks, namely highly substituted vinyl chlorides, bromides and iodides.[48]

Scheme 6 Intercepting the vinylcopper(I) complex in a transfer hydrogenation setting: Copper(I)-catalyzed regio- and stereoselective alkyne hydrobrominations

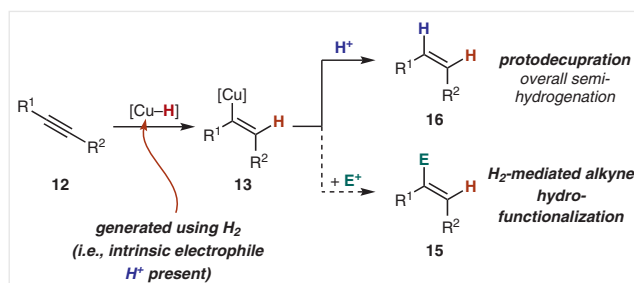**Scheme 7** NaOH as the key additive enlarges the substrate scope in the copper(I)-catalyzed transfer hydrobromination of terminal alkynes

Scheme 8 Expanding the scope: Copper(I)-catalyzed regio- and stereoselective alkyne hydrochlorinations and -iodinations

Scheme 9 Comparison of two possible reaction pathways of alkynes under hydrogenative conditions

It should be noted that the related hydrobromination of terminal alkynes to give vinyl bromides using hydrosilanes as terminal reducing agents (thus no competitive transfer hydrogenation to be feared, general pathway b in Scheme 3) had been developed earlier.[49] This protocol allows the transformation of alkyl- and aryl-alkynes in moderate to high yields. Using this approach, only hydrobrominations were feasible.

5 Copper(I)-Catalyzed Alkyne Semihydrogenations

Stereoselective semihydrogenations of alkynes are important catalytic alternatives for olefination reactions.[50] Most prominent is the Lindlar[51] catalyst delivering Z-alkenes, however, this catalyst requires careful monitoring of the reactions due to isomerization processes and frequently occurring overreduction. Therefore, selective semihydrogenation reactions not requiring close reaction control are highly desirable and represent an active field of research.[5,6,52] As depicted in Scheme 9, copper(I)-based processes again rely on stereoselective *syn*-hydrocuprations, which offer high Z-selectivity for the overall alkyne semihydrogenation.[32] In this case, the catalytically generated proton (equivalent) plays the role of electrophile for **13**, meaning that already at this stage, hydride and electrophile are decoupled in reactivity. Early alkyne semihydrogenations indeed drew upon the stoichiometric use of hydrosilanes under acidic conditions to effect a formal semihydrogenation of alkynes, in which the hydride and proton were delivered from different sources.[53] More recently, much more atom economic[3,4] variants of these catalytic conversions based on H_2 have been disclosed.

The first copper(I)-catalyzed formal semihydrogenation required $[(PPh_3)CuCl]_4$ as the catalyst, LiOtBu as the basic additive for activation and *iso*-propanol as the proton source.[54] This combination led to the transfer of a hydride and a proton from the different sources (namely H_2 and *iso*-propanol), as indicated by deuteration experiments. This protocol allowed the transformation of alkynes into alkenes with good to high yields (52–99%) and excellent stereoselectivity (Z/E = 97:3 to >99:1). Despite an elevated temperature (100 °C), almost no overreduction was observed at remarkably low H_2 pressure (5 bar).

Copper(I)-catalyzed semihydrogenations often rely on alkoxide bases as additives for the activation of H_2, meaning the requirement of a Cu–O bond for heterolytic cleavage of dihydrogen [compare Scheme 2 (σ-bond metathesis)].[27] To circumvent the need for high amounts of this additive, which can be detrimental for the tolerance of functional groups, a Z-selective copper(I)-catalyzed semihydrogenation using a tethered copper(I) alkoxide complex derived from NHC precursor **40** has been developed.[55] The catalyst features an intramolecular Cu–O bond by virtue of bidentate 'tethered' NHC/alkoxide ligand **40** (Scheme 10, a).[56] Using 100 bar H_2 pressure at 40 °C, internal alkynes **38** could be transformed into the corresponding Z-alkenes **39** by employing catalytic amounts of mesitylcopper(I) (**41**), imidazolinium salt **40** and *n*-BuLi for in situ activation. This protocol ensures the formation of the required Cu–O bond. Imidazolinium salt **40** also served as an intramolecular proton shuttle for which reason both hydrogen atoms from dihydrogen are transferred to the alkyne **38** in a 'real' semihydrogenation reaction. This was underpinned by deuteration experiments forming Z-alkene **39** with high deuterium incorporation (see also Scheme 14). This protocol is applicable for diaryl-, dialkyl- and aryl/alkyl-alkynes **38**, proceeding in moderate to high yields (60–95%) and excellent stereoselectivity (Z/E up to 99:1), while remarkably, no overreduction to the alkane was observed, even over prolonged reaction times. This catalyst tolerates other reducible functional groups such as esters, ketones and nitriles as well as heterocycles such as pyridines.

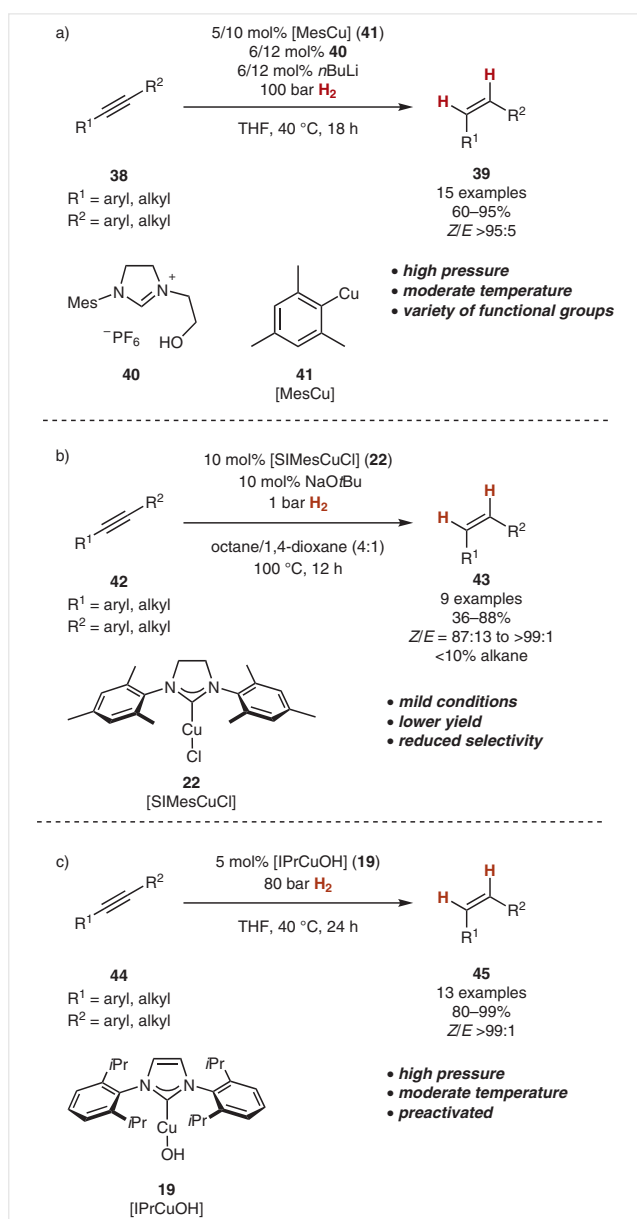Circumventing high-pressure equipment, a copper(I)-catalyzed semihydrogenation at atmospheric H_2 pressure could be achieved by employing [SIMesCuCl] (**22**) as the catalyst and NaOtBu as the activator (Scheme 10, b).[57] At elevated temperature, catalytic semihydrogenation of alkynes **42** resulted in the formation of Z-alkenes **43** in moderate to good yield (36–88%) and good to excellent

selectivity (Z/E ratios of 87:13 to >99:1), with a maximum of 10% overreduction to the corresponding alkane being observed. Despite the achievement of running the reaction at 1 bar of H_2 pressure, the yield and selectivity were generally inferior compared to the catalytic semihydrogenations mentioned above.
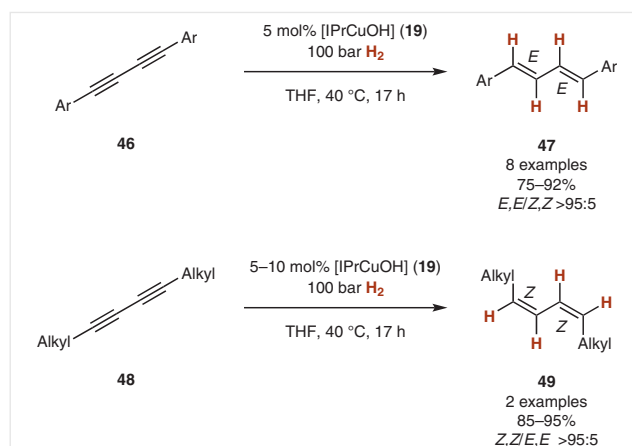
A related NHC/copper(I) complex, namely [IPrCuOH] (**19**)[36,37] displayed enhanced air and moisture stability resulting in a much more practical protocol for Z-selective semihydrogenations of internal alkynes **44**.[38] (This catalyst is also applicable to the related transfer hydrogenation, see Section 3.) Moreover, there is no need for an alkoxide addi-

tive since catalyst **19** is already preactivated towards the reaction with H_2, bearing a Cu–O bond itself. Along with the excellent chemoselectivity, almost completely suppressing the formation of alkanes, Z-alkenes **45** were obtained in high to excellent yield (80–99%) and excellent stereoselectivity of Z/E >99:1 under 80 bar of H_2 pressure at 40 °C. This protocol tolerated functional groups such as halides, esters and ethers, while a ketone was partially reduced to the corresponding alcohol. Overall, the high stability of **19** makes it the catalyst of choice for Z-selective alkyne semihydrogenations based on copper.

This protocol could also be extended to the catalytic hydrogenation of 1,3-diynes.[39] Surprisingly, in these reactions, the stereoselectivity is controlled by the diyne substituents: Whereas diaryl-substituted 1,3-diynes **46** were converted into the corresponding E,E-1,3-dienes **47** (which is counterintuitive to the observed semihydrogenations of alkynes, Scheme 10, c), complementary to this, dialkyl-substituted 1,3-diynes **48** were transformed into Z,Z-1,3-dienes **49** (Scheme 11). As a plausible explanation for this orthogonal selectivity, a facilitated rearrangement of the intermediate vinylcopper(I) complex was put forward.


Scheme 11 Copper(I)-catalyzed diyne semihydrogenation

6 Copper(I)-Catalyzed H_2-Mediated Alkyne Functionalizations; Trapping of Reactive Intermediates from Catalytic Hydrogenations

Taking inspiration from H_2-mediated C–C bond formation reactions with precious metals such as rhodium, as mentioned in the introduction (Section 1), one can wonder whether similar processes based on catalytically generated copper(I) hydride complexes would also be feasible. As previously discussed (see Scheme 3), reductive coupling reactions with copper(I) catalysts mostly relying on hydrosilanes are a mainstay in synthetic chemistry.[17–19] However, to date, the mechanistically challenging trapping reactions of catalytic hydrogenations remain rare. Reactions relying

Scheme 10 Copper(I)-catalyzed alkyne semihydrogenations: An overview of available catalysts and protocols

solely on dihydrogen (H_2) would synthetically be elegant, however, they inherently bear the problem that a rapid protodecupration **13** → **16** must be overcome (Scheme 12, compare also Scheme 3).

As already shown in the previous section (Section 5), copper(I)-catalyzed semihydrogenation reactions rely on a *syn*-hydrocupration of alkynes **12**, forming vinylcopper(I) intermediate **13**. At this stage, a new reaction pathway could be accessed: If **13** is not trapped by a proton to form the corresponding alkene **16**, but instead reacts with another electrophile, this opens up the possibility of new C–C bond (or C–heteroatom bond) formation reactions (**13** → **15**).
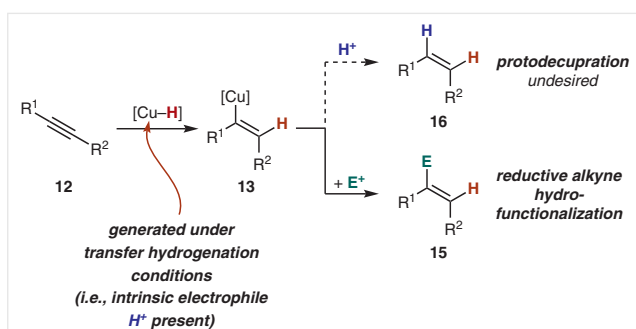

Scheme 12 Comparison of two possible reaction pathways for alkynes under hydrogenative conditions

6.1 Detour: Copper(I)-Catalyzed Allylic Reductions, Catalytic Generation of Hydride Nucleophiles from H_2

One approach to trapping reactions is the use of allylic electrophiles in combination with alkynes and copper(I) hydride complexes. However, as outlined in Section 6.2 and Scheme 15, a possible unwanted side reaction is the direct hydride transfer from the copper(I) hydride complex to the allylic electrophile. This reaction has also been developed and is therefore presented at this stage before the actual trapping reactions are discussed.

These reactions highlight a key feature of the heterolytic H_2 activation with copper(I) complexes, namely the catalytic generation of nucleophilic hydrides from H_2. Such a reactivity is rare in the realm of the catalytic activation of H_2 with transition-metal complexes and sets apart copper(I)-catalyzed reactions from transformations with noble transition metals as highlighted above (Scheme 1).[6] The catalytic hydride transfer from H_2 to allylic chlorides **50**, the so-called allylic reduction, generates terminal alkenes **51** (Scheme 13).[58] In this transformation, two main challenges have to be overcome. On the one hand, the chemoselectivity needs to be controlled, as many transition-metal catalysts for dihydrogen activation are also formidable catalysts for alkene hydrogenation.[6] This is even more pressing, as many copper(I) hydride mediated processes with alkenes are known.[17–19] In this approach, the use of NHC ligands en-

sures the suppression of any reactivity with unactivated alkenes, which is in stark contrast to the well-known reductive alkene functionalizations relying on phosphine ligands.[17–19] Therefore, the terminal alkenes generated in the allylic substitution remain untouched. On the other hand, regioselectivity could ideally be controlled to access selectively either the S_N2' or S_N2 product. The use of deuterium gas not only underpins the proposed mechanism, but also leads to selective monodeuteration, forming value-added products potentially useable in drug discovery,[59] elucidation of biosynthetic pathways[60] or mechanistic studies.[61] Employing NHC/copper(I) catalyst **53** and NaO*t*Bu as an activator with 90 bar of D_2 pressure, allylic chlorides **50** were successfully converted into the corresponding terminal alkenes **51** in yields of up to 82%, excellent γ/α-ratios (up to >95:5), and with excellent deuterium incorporation throughout (>96%) (Scheme 13).[58] Following this protocol, halides, esters and tosylates as potential leaving groups, as well as silyl- or benzyl-protected alcohols (the latter are generally cleaved under hydrogenative conditions)[62] were tolerated. Crucial for high regioselectivity of the allylic substitution was the Z-configuration of the allylic chloride: Whereas E-cinnamyl chloride resulted in a poor γ/α-ratio of 61:39, Z-cinnamyl chloride on the other hand gave high selectivity (γ/α = 89:11).[63] It should be noted that a similar process has been published earlier employing hydrosilanes as terminal reducing agents.[64]
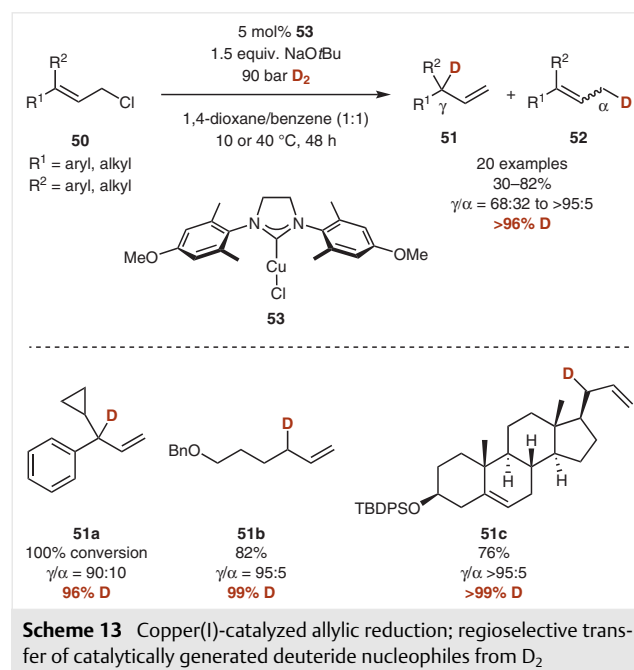
Scheme 13 Copper(I)-catalyzed allylic reduction; regioselective transfer of catalytically generated deuteride nucleophiles from D_2

As part of this study, the two fundamentally different processes involving copper(I) hydride compounds from H_2 with different functional groups (alkyne semihydrogenation and allylic reduction), as outlined above, were high-

lighted in a reaction sequence leading to the selective preparation of isotope labeling patterns. Through the combination of an alkyne semihydrogenation reaction (see Scheme 10) and an allylic reduction, with the judicious choice of H₂ or D₂ for the different processes, unique deuteration patterns were accessible. In this manner, propargylic silyl ether **54** was semihydrogenated with high deuterium incorporation (>91% D) and subsequently converted into the corresponding allylic chloride **55**-d_2. Dependent on the use of dihydrogen or deuterium gas, either terminal alkene **56**-d_3 or **56**-d_2 was formed with excellent regioselectivity (>95:5) and high deuterium incorporation (Scheme 14).
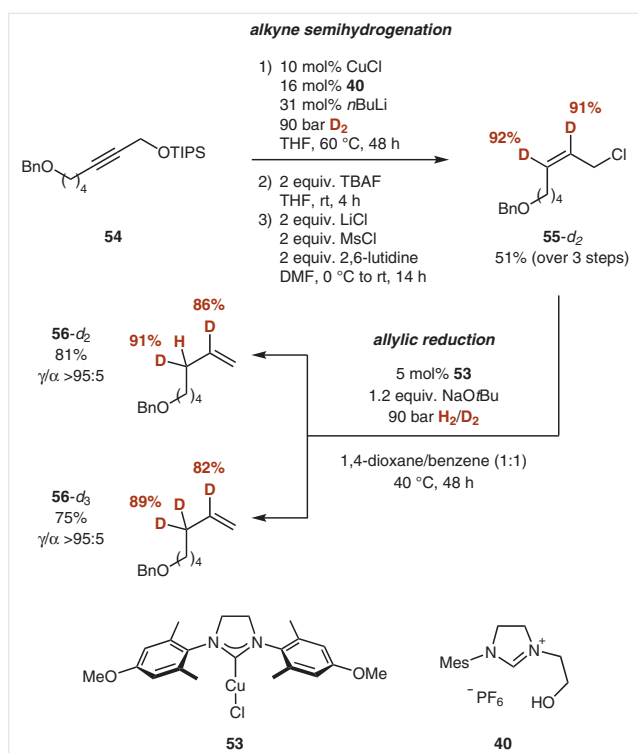
Scheme 14 Formation of isotope labeling patterns by combination of alkyne semihydrogenation and allylic reduction with H₂ or D₂

6.2 Trapping with Allylic Electrophiles: A Copper(I)-Catalyzed Hydroallylation Reaction of Alkynes

Another possibility to intercept the catalytically formed vinylcopper(I) intermediate **13** would be a subsequent allylic substitution. In this manner, the copper(I) complex serves a dual role, as it would not only mediate the hydrocupration, but also serve as a catalyst for the trapping reaction (the allylic substitution).[65] In this manner, one could depart from the imperative of C(sp²)–C(sp²) bond formation in a cross-coupling reaction, but instead one would forge a new C(sp²)–C(sp³) bond. Such processes, which offer the additional advantage of possibly generating a stereogenic center, are indeed known for reactions with hydrosilanes as

terminal reductants, in which no protodecupration can occur. In this vein, the formation of skipped dienes from internal alkynes and allylic phosphates has been reported.[46,66]

If H₂ was to be employed for a related hydrogenative coupling reaction, the overall process would be more atom economic, since common hydride sources (such as hydrosilanes, aluminum hydrides or borohydrides) and the concomitant formation of stoichiometric amounts of waste would be circumvented, whilst the molecular complexity could increase drastically in such a three-component coupling, as highlighted in the previous paragraph.
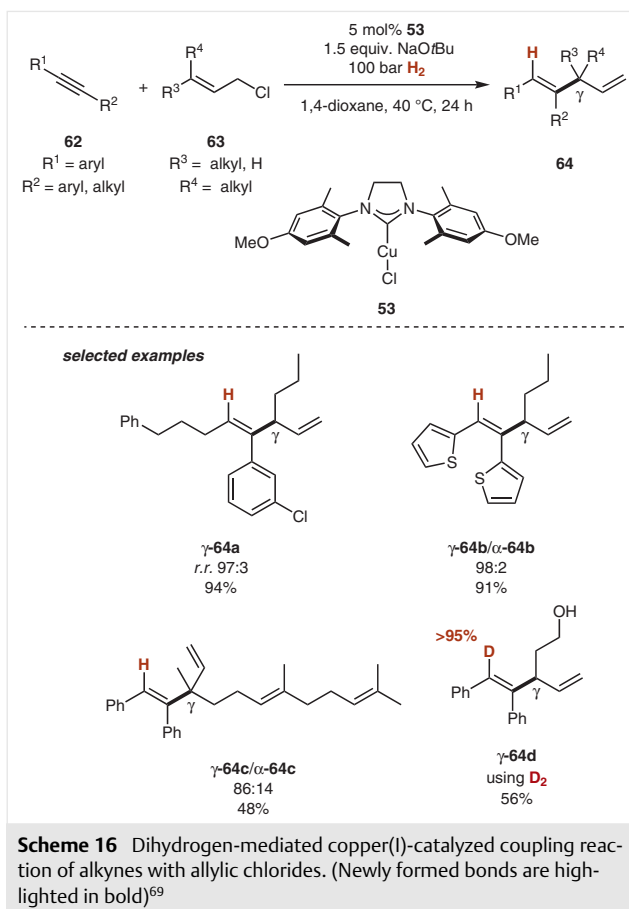
Indeed, the first hydrogen-mediated copper(I)-catalyzed reductive coupling reaction by trapping of the generated vinylcopper(I) complex **13** intermediate with an allylic chloride to form skipped dienes **60** was published recently.[58] As can be seen from Scheme 15, this process would require finely balanced rates of the single reaction steps. In principle, the copper(I) hydride complex is able to open up three different pathways: (a) Reaction with alkyne **57** leads to a semihydrogenation via protodecupration (**13** → **16**), leading to the alkene **59**, (b) allylic reduction, i.e., direct hydride transfer to the allylic chloride **58** (itself a feasible reaction,[58] see Section 6.1, Scheme 13), or (c) the desired trapping of the vinylcopper(I) intermediate **13** with allylic chloride **58** installing a new C–C bond.
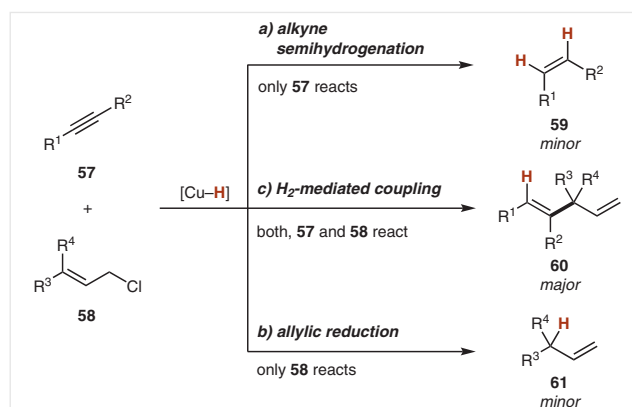
Scheme 15 Possible reaction pathways of alkynes and allylic chlorides in the presence of copper(I) hydride complexes

Hinging on the catalytic generation of nucleophilic hydrides from H₂ by employing copper(I)/NHC catalysts, a C–C bond-forming process can be realized as outlined in Scheme 15. If a prior hydrocupration of an alkyne is suitably fast, then the vinylcopper(I) intermediate **13** can itself be used as the nucleophile for an allylic substitution. This would open up a new avenue to C–C bond formation, leading to skipped dienes **64** (Scheme 16).[58,67] Therefore, conditions which suppress the two side reactions, namely the semihydrogenation of the alkyne and the allylic reduction (i.e., direct transfer of the copper(I) hydride to the allylic chloride, compare Scheme 13), but instead promoting the C–C bond formation are necessary. In this reaction, the

simultaneous control of stereo- and regioselectivity under hydrogenative conditions poses many challenges for catalyst development. Moreover, the catalyst has to be chemoselective to avoid over reduction of the newly formed alkene to the corresponding alkane, even with an elevated H_2 pressure. Furthermore, the attack of the vinylcopper(I) intermediate **13** has to proceed in a regioselective fashion to distinguish between an S_N2 or S_N2' product. Remarkably, even though a metal hydride is the key reactive intermediate in the overall reaction, no isomerization of the skipped 1,4-diene **64** to the thermodynamically favored 1,3-diene is observed. Employing NHC/copper(I) species **53**, NaO*t*Bu as the activator and allylic chloride **63** as the electrophile, alkynes **62** could be successfully coupled to give skipped dienes **64** with yields of up to 94% at 40 °C with 100 bar of H_2 pressure (Scheme 16). This protocol tolerates electron-poor as well as electron-rich alkynes and is applicable for diaryl-alkynes as well as aryl/alkyl-alkynes. Noteworthy is the formation of γ-**64a** from a non-symmetric alkyne. With such substrates, the regioselectivity of the initial alkyne hydrocupration brings up an additional complication. The catalysts employed, however, led to a highly regioselective hydrocupration (favoring the placement of copper in a quasi-benzylic position) as can be seen in the highly regioselective formation (97:3 *r.r.*) of γ-**64a**. A heteroarene-substituted alkyne was also tolerated, resulting in thiophene-substituted skipped diene γ-**64b** in high yield and selectivity (γ-**64b**/α-**64b** = 98:2). Moreover, the use of 3,3-disubstituted allylic chlorides led to a significant broadening of the substrate scope, as quaternary centers are also accessible under identical conditions. In this way, terpene-like product **64c** was obtained from commercially available farnesyl chloride. Employing D_2 indicated *syn*-hydrocupration as the first step followed by the attack on vinylcopper(I) intermediate of the allylic chloride leading to diene **64d** with excellent deuterium incorporation of >95%. This result supports the current mechanistic rationale as outlined in Scheme 12. In all cases, the competitive alkyne semihydrogenation could be suppressed reaching high chemoselectivity (up to 94:6). Furthermore, no overreduction of the formed 1,4-diene **64** was observed even under high H_2 pressure. While this copper(I)-catalyzed H_2-mediated coupling is still being investigated, it clearly shows the great potential of atom economic C–C bond formations employing dihydrogen gas and abundant and inexpensive base metals.[68] Also, while H_2-mediated C–C bond-forming reactions have served as inspiration for these developments, the highlighted transformations relying on copper catalysts offer the advantage of using different coupling partners in comparison to the reactions with noble metal catalysts. Therefore, these new transformations offer an orthogonal approach to atom-economic H_2-mediated C–C bond-forming reactions.

Scheme 16 Dihydrogen-mediated copper(I)-catalyzed coupling reaction of alkynes with allylic chlorides. (Newly formed bonds are highlighted in bold)[69]

As a noteworthy extension of this methodology, 1,3-diynes can also be employed as starting materials, leading to multiply unsaturated products with high catalytic control of the selectivities as outlined above. In this manner, diyne **65** is converted in high yield (92%) and excellent

Scheme 17 H_2-mediated copper(I)-catalyzed coupling reaction of a 1,3-diyne with an allylic chloride. (Newly formed bond is highlighted in bold)[70]
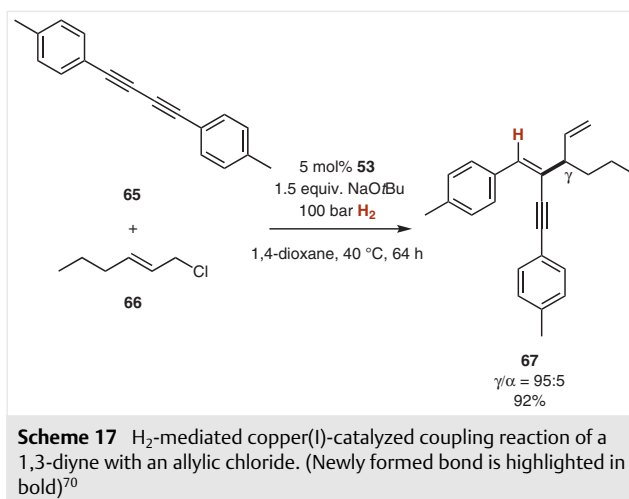
regioselectivity into dienyne **67**, while the formation of only one new C–C bond was observed (dienyne/triene = 95:5) (Scheme 17).

6.3 Trapping with Aryl Iodides

In this vein, a hydrogenative cross-coupling reaction of internal symmetric alkynes **68** with aryl iodides **69** has been disclosed.[71] Employing NHC/copper(I) complex **22**, LiOtBu as the activator, and a phosphine/palladium complex, the key vinylcopper(I) intermediate is trapped by a palladium-catalyzed cross-coupling process (Scheme 18).[72] In this co-catalytic H$_2$-mediated process, internal diaryl alkynes **68** are transformed into the corresponding trisubstituted alkenes **70** in moderate to good yield (38–73%) with high stereoselectivity, as can be expected (E/Z = 86:14 to 98:2 and Z/E = 95:5 to 98:2).[73] It is worth noting that an aryl, alkyl-alkyne results in a mixture of regioisomers for **70c** (59:41), which shows that the hydrocupration displays little regioselectivity. For high efficiency, palladium/copper cooperative catalysis is required, but in the absence of the copper(I) catalyst **22**, alkene **70** is still formed with 20% yield and high stereoselectivity. Overall, this procedure marks a remarkable cross-coupling process in which the organometallic component [namely vinylcopper(I) complex **13**] is catalytically generated, circumventing the need for a stoichiometric organometallic coupling partner.
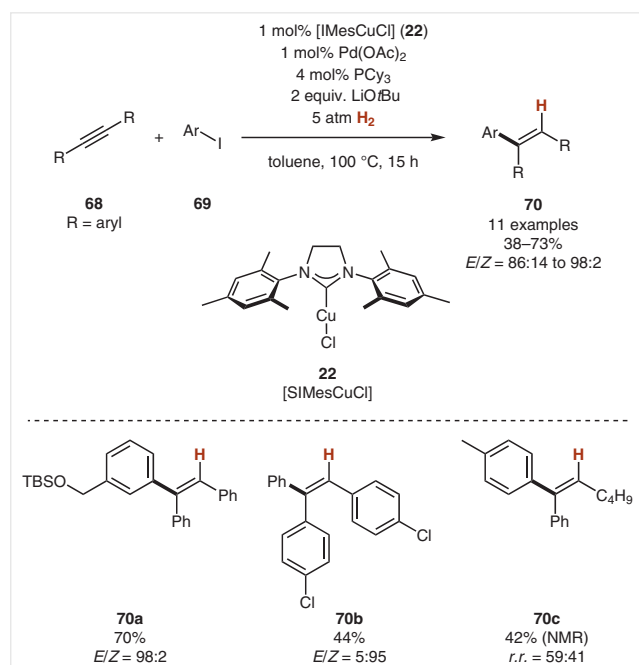
Scheme 18 Palladium/copper co-catalyzed hydrogenative cross-coupling of internal alkynes with aryl iodides. Newly formed bonds are highlighted in bold.

7 Conclusion

In this review, an emerging field of method development for synthetic chemistry has been highlighted. Emanating from H$_2$-mediated C–C bond formations revolving around the carbonyl functional group, recently, copper(I) catalysis in combination with dihydrogen as a stoichiometric reducing agent has proven to be a powerful orthogonal approach. Ultimately, H$_2$ as the key source for copper(I) hydrides builds a fertile ground for novel C–C bond and C–heteroatom bond formations. These processes could employ conditions of transfer hydrogenations with a suitable H$_2$ equivalent or H$_2$ directly. In all cases, the trapping reactions have to be fine-tuned to overcome the intrinsic challenge of protodecupration, and in this vein, well-defined NHC/copper(I) complexes have excelled so far. Employing these catalysts, several recent results have underlined that indeed such remarkable H$_2$-mediated coupling reactions based on copper(I) catalysts are feasible. This opens up a broad stage for further developments to come, of which enantioselective processes are just one open goal at this stage. It will be exciting to see whether H$_2$-driven processes will emerge as powerful synthetic transformations and how this methodology can be broadened. In comparison to the related catalytic reactions based on hydrosilanes, these H$_2$-mediated reactions are still in their infancy, but it will be great to see how new reactions based on H$_2$ –which are not hydrogenations –will be developed in the future.

References

(1) *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A.; Bräse, S.; Oestreich, M., Ed.; Wiley-VCH: Weinheim, **2014**.
(2) *Organometallics in Synthesis, Third Manual*; Schlosser, M., Ed.; John Wiley & Sins: Hoboken, **2013**.
(3) Anastas, P. T.; Warner, J. C. *Green Chemistry. Theory and Practice*; Oxford University Press: Oxford, **2000**.
(4) (a) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437. (b) Sheldon, R. A. *Chem. Commun.* **2008**, 3352. (c) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259.
(5) *Homogeneous Hydrogenation with Non-Precious Catalysts*; Teichert, J. F., Ed.; Wiley-VCH: Weinheim, **2020**.
(6) *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G.; Elsevier, C. J., Ed.; Wiley-VCH: Weinheim, **2006**.

(7) (a) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998. (b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.

(8) Fischer, F.; Tropsch, H. *Ber. Dtsch. Chem. Ges. B* **1923**, *56B*, 2428.

(9) (a) Herrmann, W. A. *Angew. Chem. Int. Ed.* **1982**, *21*, 117. (b) Rofer-DePoorter, C. K. *Chem. Rev.* **1981**, *81*, 447.

(10) Roelen, O. DE849548C, **1938**.

(11) (a) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264. (b) Breit, B.; Seiche, W. *Synthesis* **2001**, 1.

(12) (a) *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B.; Herrmann, W. A.; Beller, M.; Paciello, R., Ed.; Wiley-VCH: Weinheim, **2018**. (b) Behr, A.; Neubert, P. *Applied Homogeneous Catalysis*; Wiley-VCH: Weinheim, **2012**. (c) *Industrial Organic Chemistry*; Arpe, H.-J., Ed.; Wiley-VCH: Weinheim, **2010**.

(13) (a) Schwartz, L. A.; Krische, M. J. *Isr. J. Chem.* **2018**, *58*, 45. (b) Hassan, A.; Krische, M. J. *Org. Process Res. Dev.* **2011**, *15*, 1236. (c) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (d) Iida, H.; Krische, M. J. *Metal-Catalyzed Reductive C–C Bond Formation*, In *Topics in Current Chemistry, Vol. 279*; Krische, M. J., Ed.; Springer-Verlag: Berlin, **2007**, 77–104. (e) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653.

(14) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718.

(15) (a) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. *Green Chem.* **2007**, *9*, 411. (b) Noyori, R. *Chem. Commun.* **2005**, 1807.

(16) (a) *Non-Noble Metal Catalysis: Molecular Approaches and Reactions*; Moret, M.-E.; Gebbink, R. J. M., Ed.; Wiley-VCH: Weinheim, **2019**. (b) Alig, L.; Fritz, M.; Schneider, S. *Chem. Rev.* **2019**, *119*, 2681. (c) Liu, W.; Sahoo, B.; Junge, K.; Beller, M. *Acc. Chem. Res.* **2018**, *51*, 1858. (d) Filonenko, G. A.; van Putten, R.; Hensen, E. J. M.; Pidko, E. A. *Chem. Soc. Rev.* **2018**, *47*, 1459. (e) Chirik, P. J. *Acc. Chem. Res.* **2015**, *48*, 1687. (f) Li, Y.-Y.; Yu, S.-L.; Shen, W.-Y.; Gao, J.-X. *Acc. Chem. Res.* **2015**, *48*, 2587. (g) Zell, T.; Milstein, D. *Acc. Chem. Res.* **2015**, *48*, 1979. (h) Bullock, R. M. *Science* **2013**, *342*, 1054.

(17) For reviews, see: (a) Liu, R. Y.; Buchwald, S. L. *Acc. Chem. Res.* **2020**, *53*, 1229. (b) Mohr, J.; Oestreich, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 12148. (c) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 48. (d) Sorádová, Z.; Šebesta, R. *ChemCatChem* **2016**, *8*, 2581.

(18) For selected examples, see: (a) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830. (b) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746. (c) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1498. (d) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144. (e) Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353. (f) Bandar, J. S.; Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5821.

(19) For reductive and borylative alkyne functionalizations, see: (a) Suess, A.; Lalic, G. *Synlett* **2016**, *27*, 1165. (b) Fujihara, T.; Semba, K.; Terao, J.; Tsuji, Y. *Catal. Sci. Technol.* **2014**, *4*, 1699.

(20) Closely related to the reductive alkyne functionalizations presented here are the corresponding borylative transformations. For reviews, see: (a) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091. (b) Yoshida, H. *ACS Catal.* **2016**, *6*, 1799. (c) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Tetrahedron* **2015**, *71*, 2183. For selected examples, see: (d) Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165. (e) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314. (f) Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. *Angew. Chem. Int.*

Ed. **2014**, *53*, 3475. (g) Su, W.; Gong, T.-J.; Zhang, Q.; Zhang, Q.; Xiao, B.; Fu, Y. *ACS Catal.* **2016**, *6*, 6417. (h) Itoh, T.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2016**, *138*, 7528. (i) Rivera-Chao, E.; Fañanás-Mastral, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 9945. (j) Rivera-Chao, E.; Mitxelena, M.; Varela, J. A.; Fañanás-Mastral, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 18230.

(21) For reviews on copper(I) hydride chemistry, see: (a) Jordan, A. J.; Lalic, G.; Sadighi, J. P. *Chem. Rev.* **2016**, *116*, 8318. (b) Deutsch, C.; Krause, N. *Chem. Rev.* **2008**, *108*, 2916. (c) Rendler, S.; Oestreich, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 498.

(22) *Organosilicon Chemistry. Novel Approaches and Reactions*; Hiyama, T.; Oestreich, M., Ed.; Wiley-VCH: Weinheim, **2019**.

(23) For the seminal report on catalytic copper(I) hydride chemistry employing hydrosilanes as reducing agents, see: Brunner, H.; Miehling, W. *J. Organomet. Chem.* **1984**, *275*, c17.

(24) For the rare use of other hydride donors in copper(I) hydride chemistry, see: (a) Lipshutz, B.; Ung, C.; Sengupta, S. *Synlett* **1989**, 64. (b) Lipshutz, B. H.; Papa, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 4580. (c) Leung, L. T.; Leung, S. K.; Chiu, P. *Org. Lett.* **2005**, *7*, 5249.

(25) (a) Oestreich, M. *Synlett* **2007**, 1629. (b) Rendler, S.; Plefka, O.; Karatas, B.; Auer, G.; Fröhlich, R.; Mück-Lichtenfeld, C.; Grimme, S.; Oestreich, M. *Chem. Eur. J.* **2008**, *14*, 11512. (c) Gathy, T.; Peeters, D.; Leyssens, T. *J. Organomet. Chem.* **2009**, *694*, 3943. (d) Vergote, T.; Nahra, F.; Merschaert, A.; Riant, O.; Peeters, D.; Leyssens, T. *Organometallics* **2014**, *33*, 1953.

(26) As an alternative, copper(I) hydrides can be formed directly from copper(II) acetate and a hydrosilane, without addition of an alkoxide as activator. The mechanistic basis for this process has not been studied. For examples, see: (a) Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1638. (b) Gribble, M. W.; Pirnot, M. T.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 2192.

(27) (a) Chalk, A. J.; Halpern, J. *J. Am. Chem. Soc.* **1959**, *81*, 5852. (b) Halpern, J. *J. Phys. Chem.* **1959**, *63*, 398. (c) Goeden, G. V.; Caulton, K. G. *J. Am. Chem. Soc.* **1981**, *103*, 7354.

(28) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.

(29) Thiel, N. O.; Pape, F.; Teichert, J. F. In *Homogeneous Hydrogenation with Non-Precious Catalysts*; Teichert, J. F., Ed.; Wiley-VCH: Weinheim, **2020**, 87–109.

(30) (a) Calvin, M. *Trans. Faraday Soc.* **1938**, *34*, 1181. (b) Calvin, M. *J. Am. Chem. Soc.* **1939**, *61*, 2230.

(31) Catalytic hydrofunctionalizations of alkenes are also a mainstay of modern copper hydride chemistry, see Refs. 17 and 18. For the sake of close comparison and clarity, we herein focus on alkynes as unsaturated starting materials.

(32) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.

(33) For reviews on transfer hydrogenation, see: (a) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621. (b) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300. (c) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226.

(34) (a) Staubitz, A.; Robertson, A. P. M.; Manners, I. *Chem. Rev.* **2010**, *110*, 4079. (b) Hamilton, C. W.; Baker, R. T.; Staubitz, A.; Manners, I. *Chem. Soc. Rev.* **2009**, *38*, 279.

(35) Korytiaková, E.; Thiel, N. O.; Pape, F.; Teichert, J. F. *Chem. Commun.* **2017**, *53*, 732.

(36) Fortman, G. C.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2010**, *29*, 3966.

(37) For a review on metal hydroxide complexes, see: Nelson, D. J.; Nolan, S. P. *Coord. Chem. Rev.* **2017**, *353*, 278.

(38) Thiel, N. O.; Teichert, J. F. *Org. Biomol. Chem.* **2016**, *14*, 10660.

(39) Thiel, N. O.; Kemper, S.; Teichert, J. F. *Tetrahedron* **2017**, *73*, 5023.

(40) For reviews on copper(I)/NHC complexes, see: (a) Budagumpi, S.; Keri, R. S.; Achar, G.; Brinda, K. N. *Adv. Synth. Catal.* **2020**, *362*, 970. (b) Danopoulos, A. A.; Simler, T.; Braunstein, P. *Chem. Rev.* **2019**, *119*, 3730. (c) Yong, X.; Thurston, R.; Ho, C.-Y. *Synthesis* **2019**, *51*, 2058. (d) Nahra, F.; Gómez-Herrera, A.; Cazin, C. S. J. *Dalton Trans.* **2017**, *46*, 628. (e) Lazreg, F.; Nahra, F.; Cazin, C. S. J. *Coord. Chem. Rev.* **2015**, *293-294*, 48. (f) Egbert, J. D.; Cazin, C. S. J.; Nolan, S. P. *Catal. Sci. Technol.* **2013**, *3*, 912. (g) Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, A.; Hwang, W. S.; Lin, I. J. B. *Chem. Rev.* **2009**, *109*, 3561.

(41) Cao, H.; Chen, T.; Zhou, Y.; Han, D.; Yin, S.-F.; Han, L.-B. *Adv. Synth. Catal.* **2014**, *356*, 765.

(42) Kaicharla, T.; Zimmermann, B. M.; Oestreich, M.; Teichert, J. F. *Chem. Commun.* **2019**, *55*, 13410.

(43) For a related but conceptually different approach to copper(I)-catalyzed alkyne semireductions, see: Bao, H.; Zhou, B.; Jin, H.; Liu, Y. *J. Org. Chem.* **2019**, *84*, 3579.

(44) Das, M.; Kaicharla, T.; Teichert, J. F. *Org. Lett.* **2018**, *20*, 4926.

(45) For a good overview on synthetic approaches, see: Olpp, T.; Brückner, R. *Synthesis* **2004**, 2135.

(46) Mailig, M.; Hazra, A.; Armstrong, M. K.; Lalic, G. *J. Am. Chem. Soc.* **2017**, *139*, 6969.

(47) (a) Dang, H.; Cox, N.; Lalic, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 752. (b) Scharfbier, J.; Oestreich, M. *Synlett* **2016**, *27*, 1274. (c) Scharfbier, J.; Hazrati, H.; Irran, E.; Oestreich, M. *Org. Lett.* **2017**, *19*, 6562.

(48) Noteworthy is the fact that while NCS and NIS were employed under the optimized conditions for chlorinations and iodinations, respectively, *N*-bromosuccinimide (NBS) led to unselective reactions in the corresponding hydrobrominations.

(49) Uehling, M. R.; Rucker, R. P.; Lalic, G. *J. Am. Chem. Soc.* **2014**, *136*, 8799.

(50) Wang, J. *Stereoselective Alkene Synthesis*, In *Topics in Current Chemistry, Vol. 327*; Springer-Verlag: Berlin, **2012**.

(51) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446.

(52) For reviews on alkyne semihydrogenation, see: (a) Sharma, D. M.; Punji, B. *Chem. Asian J.* **2020**, 690. (b) Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. *Chem. Rev.* **2013**, *113*, 1313. (c) Crespo-Quesada, M.; Cárdenas-Lizana, F.; Dessimoz, A.-L.; Kiwi-Minsker, L. *ACS Catal.* **2012**, *2*, 1773. (d) Molnár, Á.; Sárkány, A.; Varga, M. *J. Mol. Catal. A* **2001**, *173*, 185.

(53) (a) Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397. (b) Semba, K.; Fujihara, T.; Xu, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2012**, *354*, 1542. (c) Whittaker, A. M.; Lalic, G. *Org. Lett.* **2013**, *15*, 1112. (d) Cox, N.; Dang, H.; Whittaker, A. M.; Lalic, G. *Tetrahedron* **2014**, *70*, 4219.

(54) Semba, K.; Kameyama, R.; Nakao, Y. *Synlett* **2015**, *26*, 318.

(55) Pape, F.; Thiel, N. O.; Teichert, J. F. *Chem. Eur. J.* **2015**, *21*, 15934.

(56) For a review on 'tethered' NHC ligands, see: Pape, F.; Teichert, J. F. *Eur. J. Org. Chem.* **2017**, 4206.

(57) Wakamatsu, T.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Organometallics* **2016**, *35*, 1354.

(58) Pape, F.; Brechmann, L. T.; Teichert, J. F. *Chem. Eur. J.* **2019**, *25*, 985.

(59) Gant, T. G. *J. Med. Chem.* **2014**, *57*, 3595.

(60) Dickschat, J. S. *Eur. J. Org. Chem.* **2017**, 4872.

(61) (a) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 7744. (b) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140.

(62) (a) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons: Hoboken, **2007**. (b) Kocieński, P. J. *Protecting Groups*; Thieme: Stuttgart, **2004**.

(63) A similar influence of the alkene geometry on the outcome of the catalytic reaction has also been observed in related reactions, see: (a) Harada, A.; Makida, Y.; Sato, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 13932. (b) Yasuda, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 10816.

(64) (a) Nguyen, T. N. T.; Thiel, N. O.; Pape, F.; Teichert, J. F. *Org. Lett.* **2016**, *18*, 2455. (b) Nguyen, T. N. T.; Thiel, N. O.; Teichert, J. F. *Chem. Commun.* **2017**, *53*, 11686.

(65) For reviews on copper(I)-catalyzed allylic substitutions, see: (a) Baslé, O.; Denicourt-Nowicki, A.; Crévisy, C.; Mauduit, M. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A.; Krause, N.; Woodward, S., Ed.; Wiley-VCH: Weinheim, **2014**, 85–126. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796.

(66) Xu, G.; Zhao, H.; Fu, B.; Cang, A.; Zhang, G.; Zhang, Q.; Xiong, T.; Zhang, Q. *Angew. Chem.* **2017**, *56*, 13130.

(67) Brechmann, L. T., Teichert, J. F. unpublished results.

(68) Enantioselective copper(I)-catalyzed hydrogen-mediated coupling could be achieved employing chiral NHC ligands.

(69) In all reactions, less than 10% of the semihydrogenation products were detected. In the case of **64c**, the amount of semihydrogenation product was 25%.

(70) Less than 5% of the triene was detected.

(71) Semba, K.; Kameyama, R.; Nakao, Y. *Chem. Lett.* **2018**, *47*, 213.

(72) For related three-component reactions employing hydrosilanes as the hydride source, see: (a) Semba, K.; Ariyama, K.; Zheng, H.; Kameyama, R.; Sakaki, S.; Nakao, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 6275. (b) Armstrong, M. K.; Goodstein, M. B.; Lalic, G. *J. Am. Chem. Soc.* **2018**, *140*, 10233.

(73) Reversion of stereoselectivity due to change of IUPAC priority rules.