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NHC–copper hydrides as chemoselective reducing agents: catalytic reduction of alkynes, alkyl triflates, and alkyl halides

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ABSTRACT

The NHC–copper-catalyzed *Z*-selective semi-reduction of terminal and internal alkynes, as well as the NHC–copper-catalyzed reduction of primary alkyl triflates and primary and secondary alkyl iodides and bromides are described. The high chemoselectivity demonstrated in these examples illustrates the mild nature of copper hydride complexes as reducing agents, which have applications in synthetic chemistry beyond their traditional role in the reduction of activated alkenes and carbonyl compounds.

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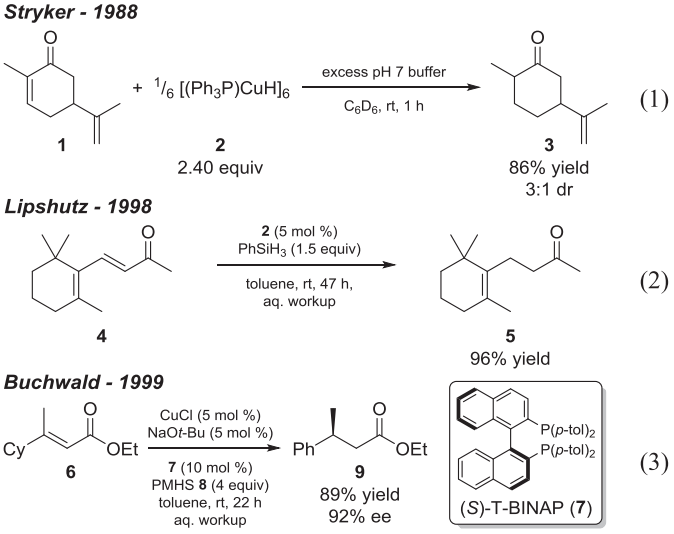
1. Introduction

Copper hydride complexes have been used extensively as mild reducing reagents in the reduction of activated alkenes and carbonyl compounds.[1–3] Although a number of copper hydride complexes had been studied as early as the 1970s,[4,5] the use of copper hydride complexes became popular following a report by Stryker in 1988.[6] He demonstrated the use of a triphenylphosphine copper hydride hexamer **2**, better known as Stryker's reagent, in the reduction of α,β-unsaturated carbonyl compounds (Scheme 1, Eq. 1). Stryker's reagent exhibited remarkable chemoselectivity, and is much less reactive toward unactivated olefins. Further developments by Stryker led to the use of catalytic amounts of **2** for the reduction of activated alkenes under high pressures of H_2.[7] In 1998, Lipshutz showed that a much more efficient catalytic reaction could be achieved with the use of silanes as the hydride source in the reduction of enones catalyzed by **2** (Scheme 1, Eq. 2).[8] Lipshutz also described the use of Stryker's reagent as a catalyst for the 1,2-hydrosilylation of ketones and aldehydes.[9]

Enantioselective reactions of phosphine-supported copper hydride complexes have also been explored. The copper-catalyzed asymmetric reduction of activated alkenes was first developed by Buchwald and used chiral bidentate phosphine ligands, such as (**7**)



Scheme 1. Phosphine copper hydrides as mild reducing agents.

(Scheme 1, Eq. 3) and polymethylhydrosiloxane (PMHS) (**8**) as the hydride source.[10] This highly enantioselective reaction was used to reduce α,β-unsaturated esters, lactams, and cyclic enones. Many other examples of enantioselective reductions[1] drew inspiration

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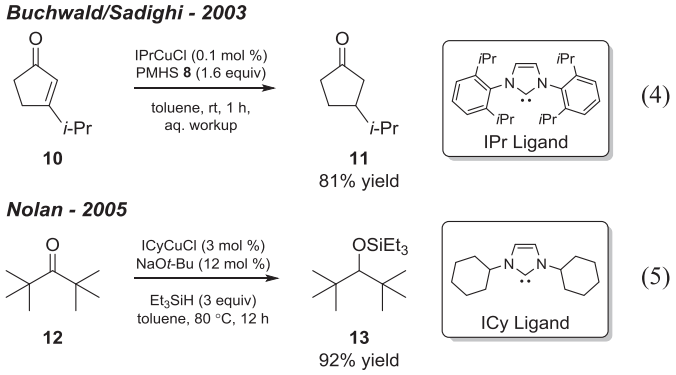
from work by Lipshutz and Carreira, who demonstrated the asymmetric conjugate reduction of acyclic enones[11] and nitroalkenes,[12] respectively.

The next stage in the development of copper hydride complexes as reducing reagents saw the introduction of electron-rich *N*-heterocyclic carbene ligands in place of phosphines, as a way of enhancing reactivity. The first use of NHC–copper complexes as catalysts in the reduction of activated alkenes was reported by Buchwald and Sadighi.[13] In this reaction, IPrCuCl used as a pre-catalyst, displayed remarkable catalytic efficiency and functional group tolerance, in the presence of PMHS (**8**) as the hydride source (Scheme 2, Eq. 4). The greater electron-donating ability of the NHC ligand resulted in increased reactivity of the copper hydride intermediate, allowing for catalyst loading as low as 0.1 mol %.



Scheme 2. Previous examples of NHC–copper hydrides as reducing agents.

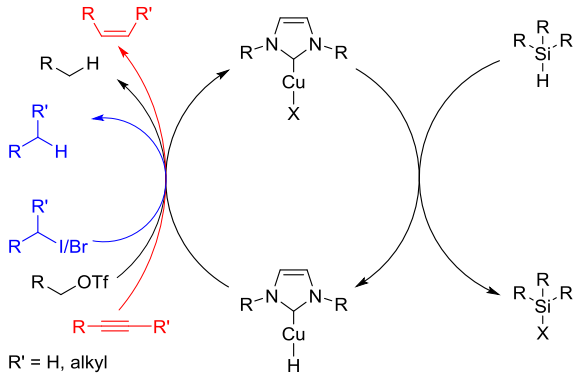
Later, Nolan showed that strong σ-donating NHC ligands allowed the efficient copper-catalyzed hydrosilylation of sterically hindered, electron-rich ketones,[14,15] illustrating the greater reactivity of NHC–copper hydride complexes as compared to those supported by phosphine ligands (Scheme 2, Eq. 5).

Despite all of these developments, copper hydride complexes are commonly recognized only for their use in the reduction of activated alkenes and carbonyl compounds, as illustrated in Schemes 1 and 2. We were interested in expanding the scope of copper hydride chemistry and exploring the use of copper hydride complexes in catalytic reduction of other classes of organic molecules. At the same time, we were hoping that the unique reactivity and the mild nature of copper hydride complexes will allow us to address two long standing problems in organic synthesis: selective semi-reduction of alkynes and mild deoxygenation of primary alcohols. In this paper, we highlight recent progress our group has made in this area. We describe the development of the copper-catalyzed semi-reduction of internal and terminal alkynes to afford *Z*-alkenes,[16] and the development of the mild reduction of primary alkyl sulfonates and primary and secondary alkyl halides[17] (Scheme 3).

2. Results and discussion

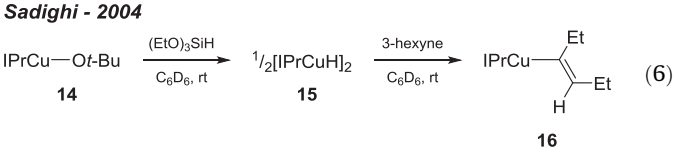
2.1. Copper-catalyzed semi-reduction of alkynes

The most common procedure for the reduction of alkynes to alkenes is the use of molecular hydrogen in the presence of the Lindlar catalyst.[18,19] Although much effort has been devoted to the development of new techniques for achieving this important transformation,[20–26] the Lindlar catalyst is still the reagent of choice despite its many drawbacks. There are two persistent problems with existing methodologies for alkyne semi-reduction:



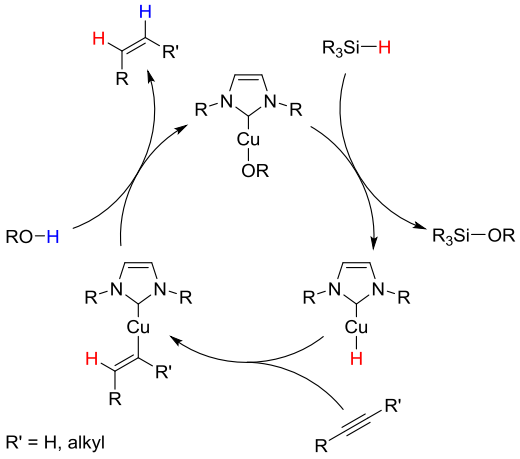
Scheme 3. NHC–copper-catalyzed reduction of alkynes, triflates, and halides.

(1) the over-reduction of the desired alkene to the alkane,[27,28] and (2) the *Z*/*E* isomerization of the desired alkene to afford a mixture of stereoisomers.[29,30] Both of these complications necessitate careful monitoring of the reaction in order to minimize the formation of undesired byproducts. These difficulties are further magnified by challenges associated with the separation of any unreacted alkyne, over-reduced alkane, and *E*-alkene isomer from the desired *Z*-alkene. Although some progress in this area has been made,[31–35] at the time we began our investigation there was no generally applicable procedure for alkyne semi-reduction that fully mitigated these problems.



Our initial investigation into the use of NHC–copper complexes as catalysts in reduction reactions drew inspiration from a report by Sadighi,[36] who showed that an unactivated alkyne in the presence of complex **15** underwent rapid *syn*-hydrocupration at room temperature to form NHC–copper alkenyl complex **16** (Eq. 6).

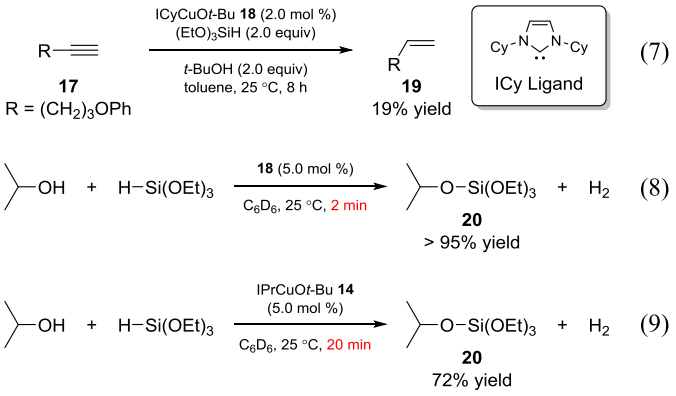
Drawing on Sadighi's work, we proposed the catalytic reaction depicted in Scheme 4, in which the hydrocupration reaction is followed by protonation of the alkenyl copper intermediate using an alcohol, releasing the desired *Z*-alkene and regenerating



Scheme 4. Proposed Cu-catalyzed semi-reduction of alkynes.

a catalytically active copper alkoxide species. This approach to the semi-reduction of alkynes by the delivery of a hydride and a proton has rarely been exploited,[37] and is distinct from traditional metal-catalyzed alkyne semi-reductions, in which hydrogen is delivered by a metal dihydride complex. Unlike metal dihydride complexes, NHC–copper hydrides are known to be unreactive toward simple alkenes.[13] As a result, we anticipated that our approach would result in minimal over-reduction and isomerization of the alkene products, and could provide a general solution to two of the most persistent problems in the semi-reduction of alkynes.

2.1.1. Terminal alkynes. Our initial efforts at the reduction of terminal alkynes using methods based on Sadighi's work were unsuccessful (Scheme 5, Eq. 7); yield of the desired alkene was only 19%, and incomplete conversion of the alkyne starting material was observed. Through the systematic study of the reactivity of the catalytic intermediates, we were able to identify three side reactions responsible for low yield. The first involved the catalytic, unproductive consumption of the silane and alcohol. The NHC–copper complex **18** rapidly catalyzed the formation of H_2 and silyl ether **20** when exposed to silane and alcohol (Scheme 5, Eq. 8). We found that by changing the NHC ligand from ICy to IPr, the rate of this reaction was suppressed significantly (Scheme 5, Eq. 9).

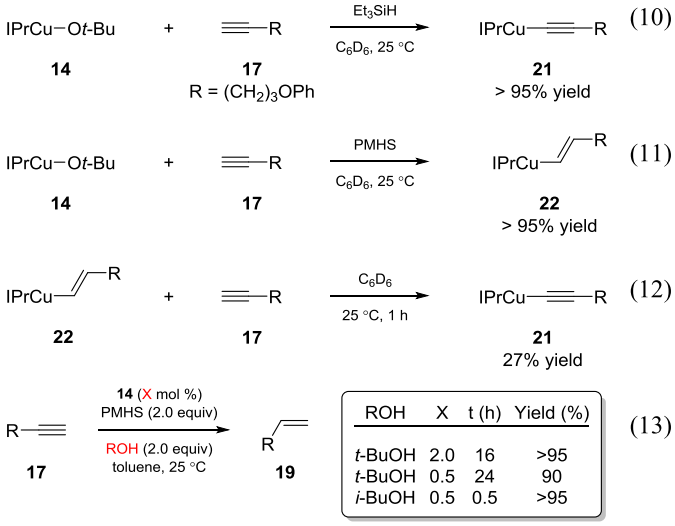


Scheme 5. Competing protonation of copper hydride by alcohol.

In addition, we found that there were two other competing reactions that contributed to deactivation of the catalyst. The first involved the deprotonation of the alkyne by copper alkoxide complex **14** to form copper acetylide complex **21**, which is catalytically inactive (Scheme 6, Eq. 10).

We were able to overcome this competing reaction by finding conditions, which increased the rate of silicon-to-copper hydride transmetallation. As shown in Scheme 6, Eq. 11, substituting triethylsilane for the more-reactive polymethylhydrosiloxane (PMHS) resulted in a dramatic increase in the yield of alkenyl copper complex **22**. The second competing reaction, which resulted in catalyst deactivation (Scheme 6, Eq. 12) again involved deprotonation of the alkyne, this time by alkenyl copper complex **22** to form the inactive copper acetylide **21**. Although this reaction is slow, we found that it is responsible for the incomplete conversion of the alkyne in reactions performed with a low catalyst loading (Scheme 6, Eq. 13). In order to find conditions, which could outcompete this reaction, we explored the use of more-acidic alcohols. We found that with the more-acidic yet sterically hindered isobutanol we can achieve complete conversion even with 0.5 mol %, and a significantly higher rate of the reaction.

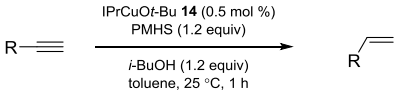
Combining these observations, we were able to find optimal conditions for the semi-reduction of terminal alkynes as illustrated

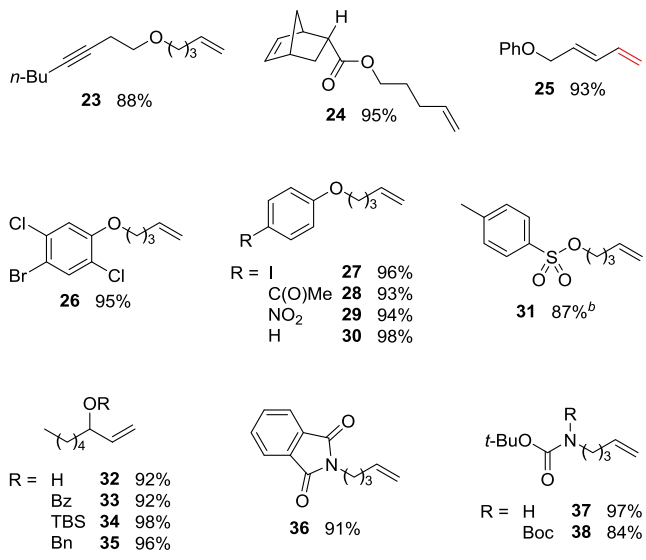


Scheme 6. Competing formation of catalytically inactive copper acetylide.

in Table 1. Using these conditions, we were able to selectively reduce terminal alkynes in the presence of a variety of functional groups that are incompatible with traditional techniques for alkyne semi-reduction. Some of the most notable examples are internal alkynes (**23**), strained alkenes (**24**), conjugated dienes (**25**), aryl halides (**26**, **27**), ketones (**28**), and nitroarenes (**29**). The reaction also performs well in the presence of polar functional groups such as sulfonates (**31**), alcohols (**32**), esters (**33**), imides (**36**), and carbamates (**37**–**38**), as well as silyl-protected alcohols (**34**). Moreover, in no case were we able to detect over-reduction of the desired alkenes to the corresponding alkanes, and allenes were not detected in the reduction of a propargylic alcohol and several of its

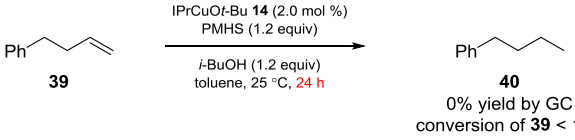
Table 1
NHC–copper-catalyzed semi-reduction of terminal alkynes[a]





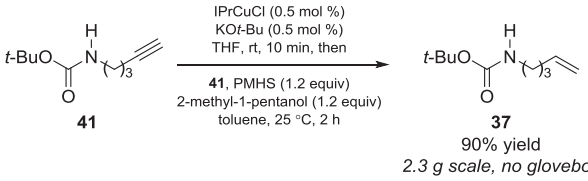
[a] Isolated yields at a 1.0 mmol scale are reported. [b] 2.0 mol % of **14** was used.

derivatives (**32**–**35**). To demonstrate that careful monitoring of the reaction is unnecessary, we showed that terminal alkene **39** is completely unreactive, and formation of alkane **40** was not observed even with prolonged exposure to these reaction conditions (Eq. 14).



(14)

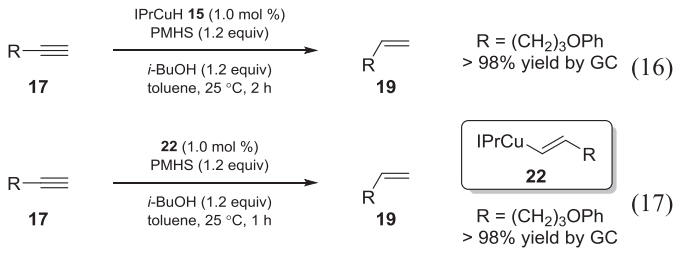
In order to make this method for semi-reduction of terminal alkynes more practical and to increase its ease of use, we developed a procedure, which can be carried out on a multi-gram scale, using commercially available IPrCuCl as a pre-catalyst, and without the need for an inert-atmosphere glovebox. As shown in Eq. 15, these modifications allowed us to prepare alkene **37** on a 14 mmol scale in 90% yield.



(15)

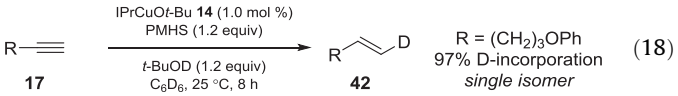
Particular emphasis was placed on developing a procedure, which allowed for convenient purification of the desired product. The major difficulty was the removal of the polymer byproducts formed from PMHS. We found that a treatment of the crude reaction mixture with acids, bases, or oxidants did not facilitate the purification of the desired product. However, we also found that these nonpolar byproducts could be easily separated by filtering the reaction mixture through a plug of alumina. The separation of the polymer byproducts was also facilitated by the use of 2-methyl-1-pentanol (Eq. 15) as the proton source, in place of isobutanol.

All of the elementary steps in the mechanism depicted in Scheme 4 are supported by experiments reported by Sadighi[36] and Tsuji.[35] To provide further rationale for the mechanism depicted in Scheme 4, we carried out the series of reactions shown in Scheme 7. As demonstrated in Eqs. 16 and 17, we were able to show that both IPrCuH complex **15**, as well as the alkenyl copper species **22** are both viable catalysts in the semi-reduction of alkyne **17**. These results support the notion that both complex **15** and an alkenyl copper intermediate lie on the catalytic cycle.



Scheme 7. Catalytic competency of proposed intermediates **9** and **16**.

We also carried out the deuterium labeling experiment depicted in Eq. 18, where deuterium-labeled *tert*-butanol was used in lieu of isobutanol, resulting in the formation of a single isomer of deuterium-labeled alkene **42**. This provides additional evidence for the alkenyl copper protonation step of the catalytic cycle, and suggests that the semi-reduction is completely selective for overall *syn*-addition, with no isomerization of the alkene products.



(18)

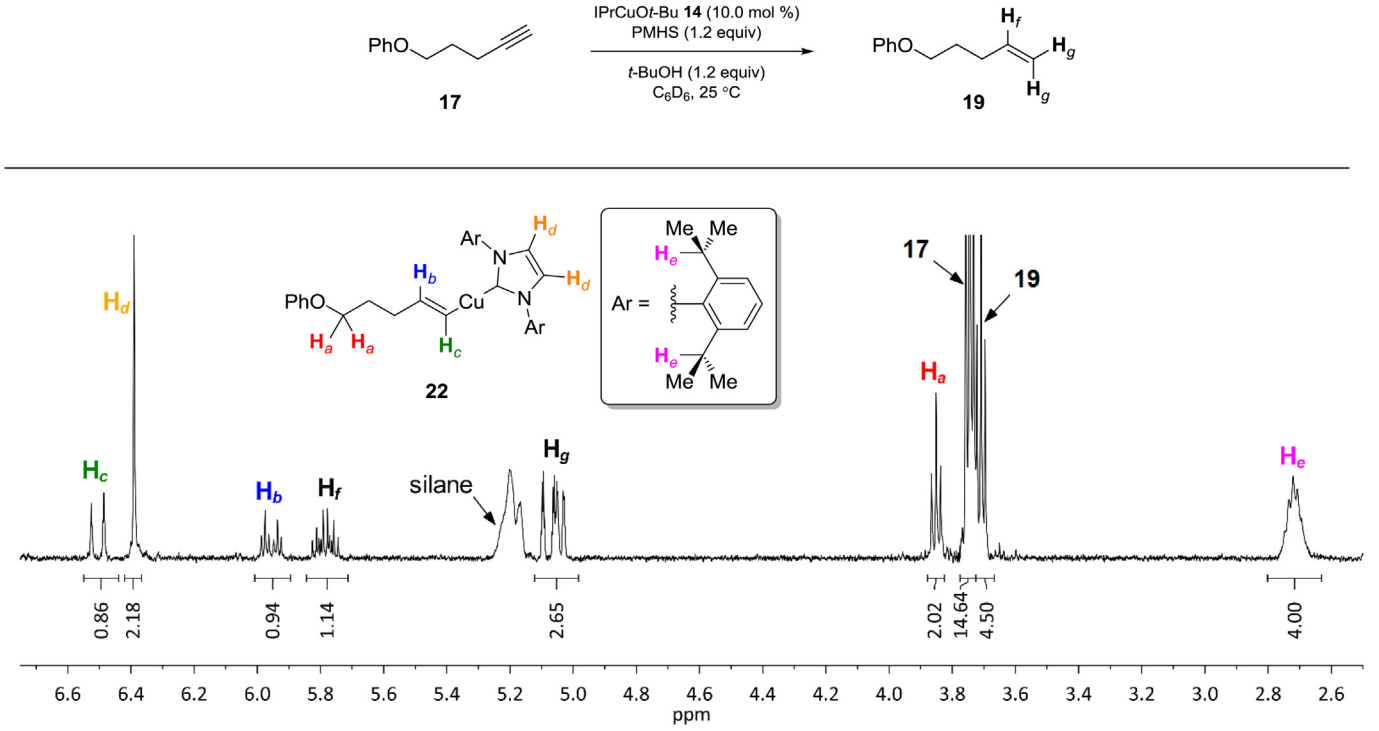
Finally, we attempted to identify the resting state of the catalyst at partial conversion by ^{1}H NMR (Scheme 8). When *tert*-butanol was used as the proton source, we found that the reaction was sufficiently slow so as to allow for convenient monitoring by ^{1}H NMR at room temperature. At roughly 25% conversion, we were able to clearly identify IPrCu-alkenyl species **22** as the sole resting state of the catalyst. Considering that the subsequent protonation step is irreversible, this strongly suggests that the turnover-limiting step of the catalytic cycle is protonation of alkenyl copper. This conclusion is also consistent with the rate enhancement observed when using more-acidic proton sources.

2.1.2. Internal alkynes. Our attempts at the semi-reduction of internal alkynes using the techniques optimized for terminal alkyne semi-reduction were unsuccessful, resulting in incomplete conversion and only 15% yield of the desired alkene (Scheme 9, Eq. 19). Furthermore, we observed complete consumption of the silane and alcohol, strongly suggesting that a reaction similar to that shown in Scheme 5, Eq. 8 was out-competing hydrocupration of the internal alkyne. To test this hypothesis, we carried out the competition experiment shown in Scheme 9, Eq. 20, in which a stoichiometric amount of IPrCuH was exposed to equal amounts of alkyne **43** and isobutanol. We observed minimal conversion of the alkyne to the alkene, along with vigorous bubbling, confirming that the unproductive formation of H_2 was out-competing the desired reaction pathway.

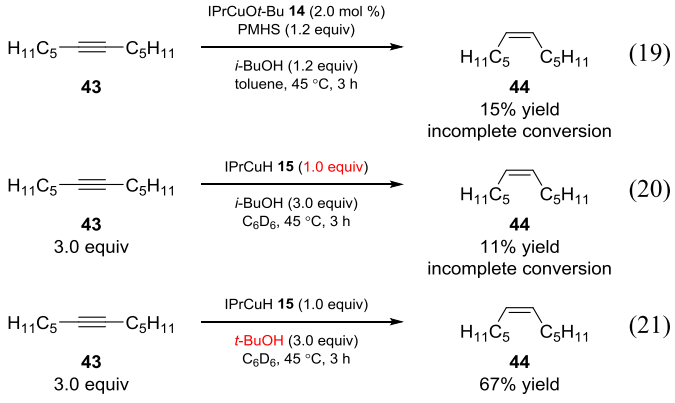
To address this competing reaction, we explored the use of *tert*-butanol as the proton source. Indeed, repeating the competition experiment with the less-acidic alcohol significantly increased yield of the desired alkene (Scheme 9, Eq. 21). This prompted further investigation of the reaction mechanism in an effort to understand the differences in reactivity between internal and terminal alkynes.

In situ monitoring of the reaction by ^{1}H NMR revealed that no alkenyl copper species could be observed. However, we were able to detect a resonance at 2.67 ppm, which is in agreement with the characteristic hydride resonance of IPrCuH dimer **15** first reported by Sadighi[36] (Scheme 10). This, together with the lack of any observed resonances characteristic of alkenyl copper, suggests that the major catalyst resting state in the reduction of internal alkynes is a copper hydride species rather than alkenyl copper. This further implies that the turnover-limiting step for internal alkyne semi-reduction is hydrocupration of the alkyne rather than protonation of alkenyl copper. Given that the alcohol is not likely involved in the hydrocupration step, the use of more-acidic alcohols, such as isobutanol, can only enhance the rate of the competing copper hydride protonation reaction. This is also consistent with our observations in the competition experiments described in Scheme 9, in which the use of less-acidic alcohols has a beneficial effect on yield of the desired alkene.

Guided by these observations of the reaction mechanism, we were able to achieve the selective semi-reduction of internal alkynes with only slight variations to the reaction conditions used for terminal alkyne semi-reduction. As shown in Table 2, we were able to selectively reduce internal alkynes in the presence of polar functional groups such as esters (**45**), carbamates (**46**), alcohols (**47**), and alkyl chlorides (**48**). Propargylic alcohol derivatives could be reduced without any observed elimination or allene formation



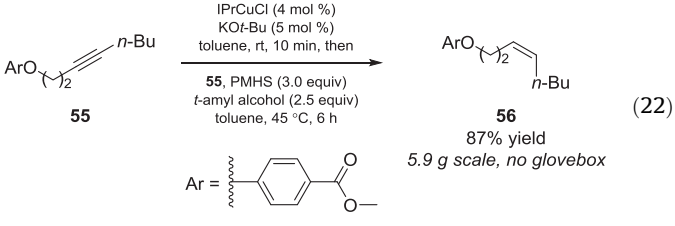
Scheme 8. Determination of catalyst resting state as alkenyl copper by ^{1}H NMR at ca. 25% conversion of the alkyne starting material.

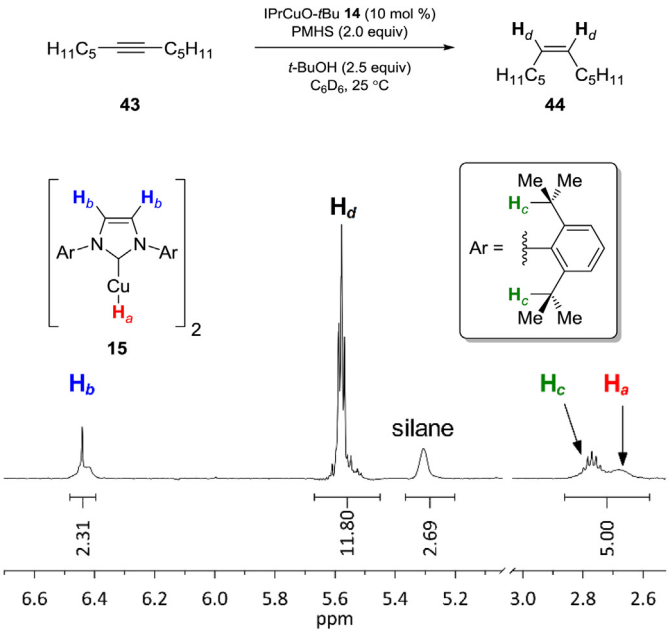


Scheme 9. Competing protonation of **15** in reduction of internal alkynes.

(**49**–**51**). Finally, functional groups that are easily reduced using traditional techniques for alkyne semi-reduction, such as benzonitriles (**52**), nitroarenes (**53**), and aryl halides (**54**) are well-tolerated under these conditions. Most importantly, the reaction was completely selective for the formation of the *Z* isomer. No isomerization of the alkene products was detected, and no over-reduction to the alkane was observed.

Similar to the adaptations we made to the reduction of terminal alkynes in order to increase its ease of use, we developed a variant to the procedure for internal alkyne semi-reduction, which allows for the multi-gram preparation of *Z* internal alkenes using a commercially available pre-catalyst and without the need for a glovebox.



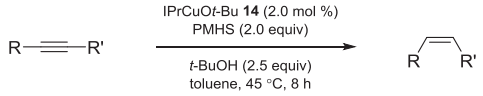


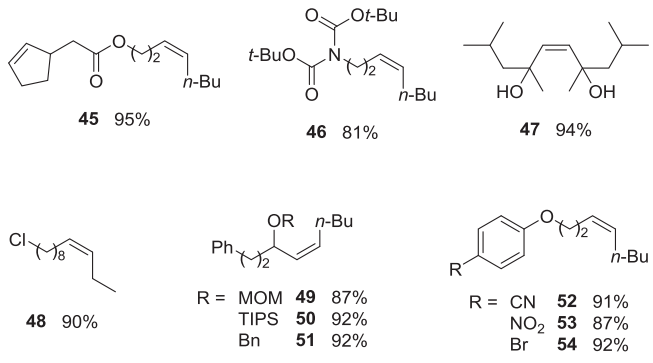
Scheme 10. Resting state experiment for internal alkyne reduction.

Eq. 22 depicts the semi-reduction of alkyne **55** on a 25 mmol scale, affording alkene **56** in 87% yield. An added convenience of this adapted procedure is the substitution of *tert*-butanol (which can solidify at room temperature, complicating addition by syringe) with *tert*-amyl alcohol (2-methyl-2-butanol), which has a melting point of −12 °C.

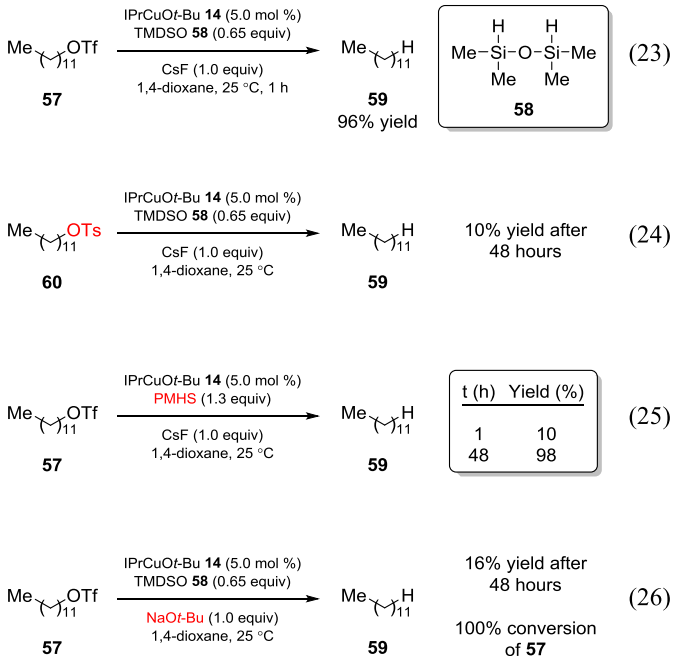
We have developed a catalytic system, which exploits the mild nature of copper hydride complexes in order to achieve the *Z*-selective semi-reduction of alkynes without any over-reduction to the alkane, providing an attractive alternative to the Lindlar catalyst. Additionally, the high chemoselectivity, scalability, and ease of use

Table 2
NHC–copper-catalyzed semi-reduction of internal alkynes[a]





[a] Isolated yields at a 1.0 mmol scale are reported.



Scheme 11. Optimization of the NHC–Cu-catalyzed reduction of triflates.

of this procedure offer a practical solution to alkyne semi-reduction.

2.2. Copper-catalyzed reduction of primary alkyl triflates

The selective reduction of alcohols and their derivatives to alkanes plays an important role in the synthesis of complex organic molecules, as it is often the case that an unwanted oxygen-containing functional group must be removed in the late stages of a multi-step synthesis.[38] While numerous methods for the deoxygenation of alcohols exist,[39–47] the most widely used approach for alcohol deoxygenation involves a two-step process in which the alcohol is converted into either a halide or Barton ester[48–50] prior to a separate reduction step using stoichiometric amounts of a tin hydride reagent.[51,52] These approaches work well for the selective deoxygenation of tertiary and secondary alcohols, and are known to be tolerant of a variety of functional groups. However, because these reactions typically involve the formation of alkyl radical intermediates, they are much less effective in the selective deoxygenation of primary alcohols.[48] Instead, the most commonly used methods for primary alcohol deoxygenation involve converting the primary alcohol to a halide or sulfonate ester prior to reduction with strong borohydride reagents.[53–57] Given the high reactivity of these reducing reagents, we considered that an alternative approach involving copper hydride could provide a more practical technique for the selective deoxygenation of primary alcohols. Although several examples of stoichiometric reduction of halides and sulfonates by copper hydrides were known,[58–60] there were no examples of catalytic reactions at the time our work in this area began.

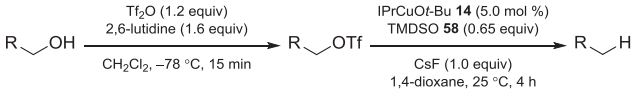
Sulfonate esters are easy to prepare from primary alcohols and commercially available sulfonyl chlorides and anhydrides,[61] and their reactivity as leaving groups can be easily modulated.[62] As shown in Scheme 11, Eq. 23, we found that primary alkyl triflate **57** could be reduced using the IPrCuO*t*-Bu catalyst **14**, tetramethyldisiloxane (TMDSO) (**58**) as the stoichiometric source of hydride, and CsF, which facilitates catalytic turnover. In the course of the reaction optimization, we determined that the highly-reactive triflate leaving group was essential for maintaining reactivity—indeed, even with prolonged reaction times, tosylate leaving groups (**60**) only achieved 10% conversion to the desired alkane (Scheme 11, Eq. 24). This further demonstrates the mild nucleophilic character of copper hydride as a reducing agent. Additionally, we were surprised to find that TMDSO (**58**) was a more reactive source of hydride as compared to PMHS in this reaction (Scheme 11, Eq. 25). Finally, while alkoxide additives are commonly used to aid in catalyst turnover in related reactions,[63,64] we found that they resulted in unproductive competing reactions, which consumed the triflate starting material (Scheme 11, Eq. 26). These competing reactions could be avoided by using the much less basic CsF additive.

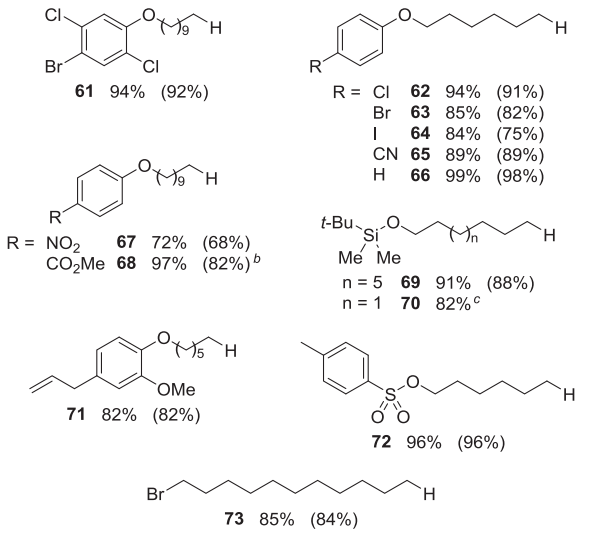
As depicted in Table 3, we were able to develop a practical, two-step triflation/reduction procedure for primary alcohol deoxygenation that proceeds with high overall yield from the starting alcohols. This technique was found to be compatible with a variety of functional groups that are commonly reduced when using traditional techniques for alcohol deoxygenation, including aryl halides (**61**–**64**), benzonitriles (**65**), and nitroarenes (**67**). Esters (**68**), silyl-protected alcohols (**69**, **70**), and alkenes (**71**) were also tolerated. Remarkably, primary triflates can be reduced selectively in the presence of both alkyl tosylates (**72**) and alkyl bromides (**73**).

We propose the catalytic cycle depicted in Scheme 12, which is based on experiments demonstrating the validity of each elementary step of the reaction. The experiment shown in Scheme 13, Eq. 27 illustrates rapid fluoride/hydride exchange between silicon and copper to form IPrCuH complex **15**. We also found that when NHC–copper hydride complex **15** is exposed to 5.0 equiv of alkyl triflate **57**, the complete and rapid disappearance of complex **15** can be observed by ^{1}H NMR. While we were unable to visualize the formation of IPrCuOTf complex **75** in the same NMR experiment, this can be rationalized based on its insolubility in 1,4-dioxane—indeed, a crystalline precipitate is observed in the NMR tube upon addition of alkyl triflate. In a separate reaction of triflate **57** and copper hydride **15**, we were able to detect formation of alkane **59** by GC (Scheme 13, Eq. 28), indicating that IPrCuH **15** is a competent reducing agent in the reduction of triflates. Finally, IPrCuF complex **74** was formed in 97% yield in the reaction of IPrCuOTf **75** and CsF (Scheme 13, Eq. 29).

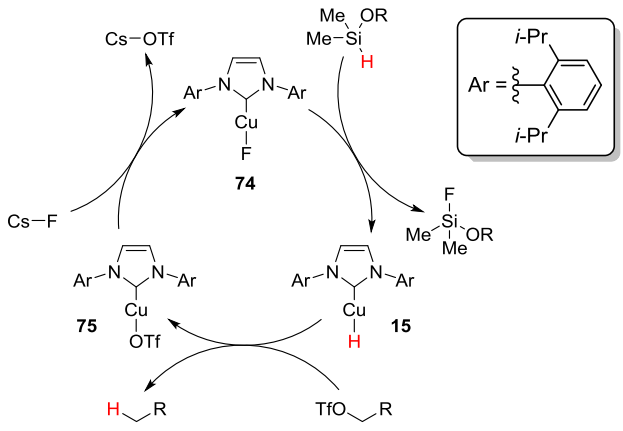
Overall, this approach to primary alcohol deoxygenation offers a practical alternative to existing techniques, owing to the high

Table 3
Two-step deoxygenation of 1° alcohols via Cu-catalyzed reduction of triflates[a]

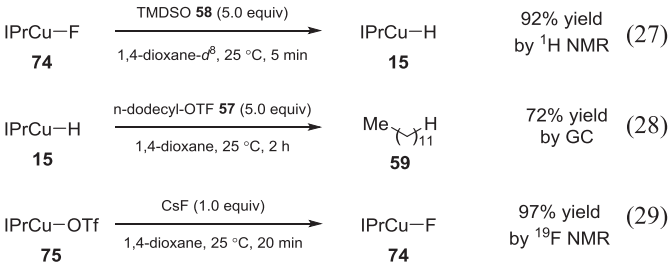




[a] Reactions were carried out on a 0.5 mmol scale. Isolated yields of the reduction step are reported. Yields over two steps are reported in parentheses. [b] 1.0 mol % of **14** was used. [c] Reaction was carried out on a 20 mmol scale.



Scheme 12. Catalytic cycle for the NHC–Cu-catalyzed reduction of triflates.



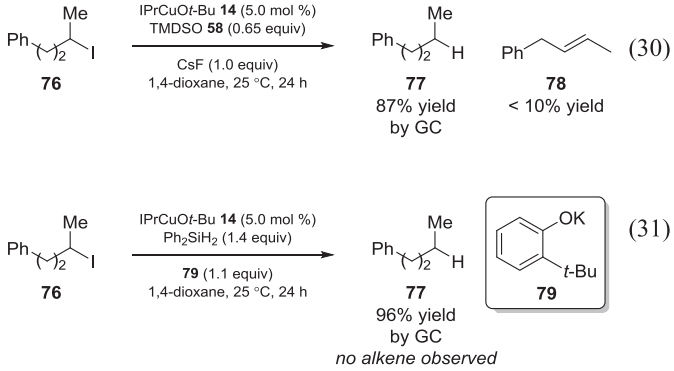
Scheme 13. Experiments demonstrating feasibility of elementary steps in the proposed mechanism for the Cu-catalyzed reduction of triflates.

functional group tolerance and mild nature of the copper hydride reducing agent.

2.3. Copper-catalyzed reduction of alkyl halides

Similar to the reduction of alkyl sulfonates, the reduction of alkyl halides is commonly used as part of a strategy for the two-step deoxygenation of alcohols, as alcohols can be easily converted into the corresponding halides. Additionally, a number of recent examples in natural product synthesis involve the reduction of alkyl halides in the late stages of a multi-step synthesis.[65–69] As discussed previously, this transformation is most often achieved using a stoichiometric quantity of tin hydride.

2.3.1. Secondary alkyl halides. In our initial attempts to reduce secondary halides using the conditions optimized for the reduction of primary triflates, we observed a competing elimination reaction, as exemplified by the reduction of iodide **76** (Scheme 14, Eq. 30). To solve this problem, we explored the use of different solvents, turnover additives, and hydride sources. Eventually, we found that by changing the hydride source to a more reactive silane (Ph_2SiH_2) and the turnover additive to potassium 2-*tert*-butylphenoxide (**79**), we were able to suppress the competing elimination reaction (Scheme 14, Eq. 31).

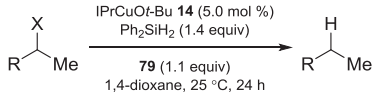


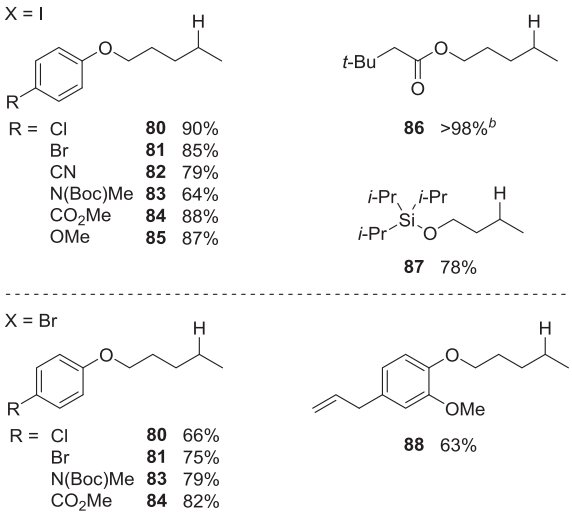
Scheme 14. Competing elimination in the reduction of 2° iodides.

Using these reaction conditions, we were able to selectively reduce a variety of secondary iodides in good to excellent yield, and in the presence of functional groups that are often reactive when using traditional methods for halide reduction (Table 4). This includes aryl chlorides (**80**), aryl bromides (**81**), and benzonitriles (**82**). Carbamates (**83**), esters (**84**, **86**), ethers (**85**), and silyl-protected alcohols (**87**) are also tolerated. In addition to secondary alkyl iodides, we found that secondary alkyl bromides containing aryl chloride (**80**), aryl bromide (**81**), carbamate (**83**), ester (**84**), and alkene (**88**) substituents can also be reduced selectively using these conditions. However, yields of the alkane products are typically lower in these cases as compared with the reduction of the corresponding secondary iodides, which can be rationalized based on the higher reactivity of alkyl iodides as compared to alkyl bromides.

2.3.2. Primary alkyl halides. We found that the same conditions used for the reduction of primary alkyl triflates was highly effective in the reduction of primary alkyl iodides, although the reaction time had to be increased to 24 h to achieve full conversion. As shown in Table 5, we were able to selectively reduce primary alkyl iodides in the presence of aryl halides (**61**, **63**, **64**), benzonitriles

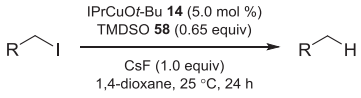
Table 4
NHC–copper-catalyzed reduction of 2° alkyl halides[a]

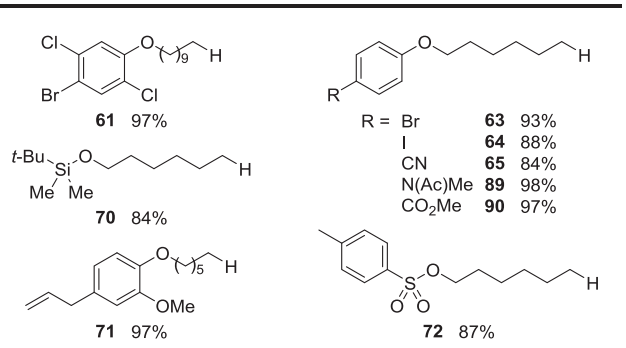




[a] Isolated yields at a 0.5 mmol scale are reported unless otherwise specified.
[b] Yield was determined by GC.

Table 5
NHC–copper-catalyzed reduction of 1° alkyl halides[a]

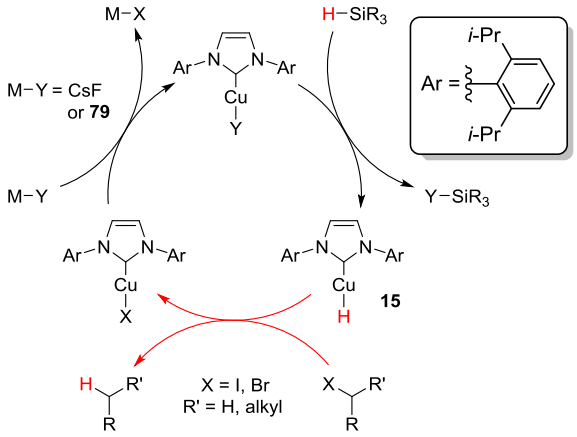




[a] Isolated yields at a 0.5 mmol scale are reported.

(**65**), amides (**89**), esters (**90**), silyl-protected alcohols (**70**), and alkenes (**71**). We were also quite surprised to find that primary iodides can be selectively reduced in the presence of alkyl tosylates (**72**).

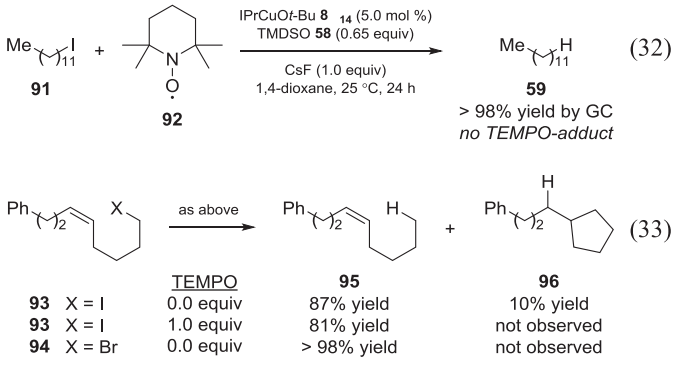
The catalytic cycle depicted in Scheme 15 describes the proposed mechanism for the NHC–copper-catalyzed reduction of alkyl halides. The silicon-to-copper transmetallation step,[16,36] as well as the additive-assisted turnover step[64] are both well-precedented, and so we focused our investigation of the reaction mechanism of the proposed step in which the halide leaving group is reduced by copper hydride complex **15**. This step is likely to occur through one of three possible pathways: (A) an oxidative-addition/reductive-elimination process, (B) nucleophilic substitution, or (C) the formation of an alkyl radical intermediate. We initially sought to



Scheme 15. Catalytic cycle for the NHC–Cu-catalyzed reduction of halides.

distinguish paths A and B, which involve two-electron process, from path C, which involves single-electron transfer.

Based on the strength of the carbon–oxygen bond,[70] and the fact that sulfonates are not known to stabilize oxygen radicals, it is highly unlikely that the reduction of triflates discussed earlier involves the formation of a free radical intermediate. Alkyl halides, however, are common radical precursors, and a recent example of an iridium-catalyzed reduction of alkyl iodides occurs through a radical mechanism.[71] Ultimately, we found evidence that the dominant mechanism of the copper-catalyzed reduction of alkyl halides is unlikely to involve the formation of free radical intermediates. This conclusion is supported by the series of experiments depicted in Scheme 16.



Scheme 16. Demonstration that a radical mechanism is not dominant.

When the reduction of primary alkyl iodide **91** was conducted in the presence of 1.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) (**92**), a reagent commonly used as a radical trap, formation of the desired alkane was not inhibited (Scheme 16, Eq. 32). Additionally, no adduct of **91** and TEMPO was detected. To provide additional support for the notion that a radical mechanism is not the dominant pathway, we carried out a competition experiment using iodide **93** (Scheme 16, Eq. 33). Iodides of type **93** have been shown to engage in a fast radical cyclization reaction after the homolytic cleavage of the carbon–iodide bond.[71] We observed that the desired linear product **95** was formed in 87% yield, while the product resulting from reductive cyclization (**96**) was minor.[72] When 1.0 equiv of TEMPO was added, the radical cyclization reaction was completely inhibited, and the desired reduction product was formed in 81% yield. Finally, when the same

experiment was repeated using bromide **94** (which is less predisposed to undergo homolytic cleavage of the carbon–halide bond), no cyclization product was formed even in the absence of TEMPO, and the desired product was formed in quantitative yield. Altogether, these results suggest that the reduction step is likely to involve a two-electron process.

In summary, these procedures provide means for the removal of halogens from primary and secondary alkyl halides with chemoselectivity that is complementary to the most common techniques for achieving this transformation, such as reduction with tin hydrides. The approach we have developed for the reduction of alkyl halides further supports the notion that NHC–copper hydrides possess greater reactivity than phosphine copper hydrides, such as Stryker's reagent, while still maintaining much of the functional group tolerance of such mild reducing agents.

3. Conclusion

Copper hydride complexes have historically been used as mild reagents for reduction of carbon–carbon multiple bonds that are activated by an electron-withdrawing group, and for reduction of carbonyls. We have shown that NHC–copper complexes can catalyze the reduction of unactivated internal and terminal alkynes with remarkable chemoselectivity. Furthermore, we have expanded the use of copper hydride complexes to the catalytic reduction of other classes of organic molecules, such as alkyl sulfonates and halides. Importantly, we have shown that the inherently mild nature of the copper hydride reagent allows these transformations to be carried out with chemoselectivity that is often complementary or superior to the selectivity of commonly used reducing reagents. As such, these new transformations offer attractive alternatives to traditional approaches to the semi-reduction of alkynes, the deoxygenation of primary alcohols, and the reduction of primary and secondary alkyl halides.

4. Experimental

4.1. General

Additional spectral data for compounds not listed here are available in:

General: All reactions were performed under a nitrogen atmosphere, using a nitrogen-filled glovebox or flame-dried glassware unless otherwise indicated. Column chromatography was performed on a Biotage Iso-1SV flash purification system using silica gel (Agela Technologies Inc., 60 Å, 40–60 μm, 230–400 mesh). Infrared (IR) spectra were recorded on a Perkin–Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s=strong, m=medium, w=weak, br=broad. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual $CHCl_3$ (7.26 ppm), C_6H_6 (7.16 ppm), CH_2Cl_2 (5.32 ppm), or CH_3CN (1.94 ppm). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent $CDCl_3$ (δ 77.2 ppm), C_6D_6 (128.1), or CD_2Cl_2 (54.0). Data are represented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br s=broad singlet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 High Resolution Mass Spectrometer, an Applied Biosystems Inc. QStar XL High Resolution Mass Spectrometer, a Bruker Esquire 1100 Liquid Chromatograph–Ion Trap Mass Spectrometer, or a Hewlett Packard 5971A Gas Chromatograph–Mass Spectrometer. GC analysis was performed on a Shimadzu GC-2010 with a flame ionization detector and an SHRXI-5MS column (15 m×0.25 mm×0.25 μm).

Materials: THF, CH_2Cl_2, toluene, and Et_2O were degassed and dried on columns of neutral alumina. 1,4-Dioxane was distilled from purple Na/benzophenone ketyl, and stored over 4 Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. All terminal alkynes, internal alkynes, primary alcohols, and secondary alcohols were prepared according to standard techniques found in literature. All other commercially available reagents were purchased from AK Scientific, Inc., GFS Chemicals, Oakwood Products, Inc., Sigma–Aldrich Co., STREM Chemicals, Inc., Tokyo Chemical Industry Co., Ltd., or VWR international, LLC. and were used as received.

4.2. General procedure for the reduction of terminal alkynes

In a nitrogen-filled glovebox, a 1-dram vial was charged with a stir bar followed by the alkyne (1.00 equiv, 1.00 mmol), PMHS **8** (1.20 equiv, 71.7 mg, 1.20 mmol), and isobutanol (1.00 equiv, 88.9 mg, 1.20 mmol). This mixture was diluted in toluene (10 mL) before adding IPrCuO*t*-Bu **14** (0.0050 equiv, 2.6 mg, 0.0050 mmol). The reaction mixture was stirred at 25 °C until complete conversion of the starting material was achieved (1 h). The mixture was then diluted with hexanes (20 mL), and filtered through a silica gel plug using a 1:1 ethyl acetate/hexane solution (100 mL). The filtrate was concentrated under vacuum, and the crude reaction products were purified either by using a 10 g silica gel column, distillation, and/or an aqueous workup. The aqueous workup was carried out by stirring the crude reaction products in a solution of NaOH (10 mL, 0.1 M in tetrahydrofuran/H_2O 5:1) for 30 min. The solution was then extracted with diethyl ether (3×20 mL), and the combined organic layers were washed with brine (20 mL), and dried over $MgSO_4$ before filtration and concentration under vacuum. See examples below for details on the purification procedure used.

4.2.1. Selected examples

*4.2.1.1. (±)-Pent-4-en-1-yl bicyclo[2.2.1]hept-5-ene-2-carboxylate (**24**).* Compound was isolated as a colorless liquid (196 mg, 95% yield) after purification by silica gel chromatography (0–10% Et_2O/hexanes with a 5% benzene additive over eight column volumes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, *J*=5.7, 3.1 Hz, 1H), 5.92 (dd, *J*=5.4, 2.8 Hz, 1H), 5.88–5.72 (m, 1H), 5.13–4.93 (m, 2H), 4.03 (td, *J*=6.6, 2.1 Hz, 2H), 3.31–3.11 (m, 1H), 3.04–2.82 (m, 2H), 2.13 (dt, *J*=6.8, 2.3 Hz, 2H), 1.97–1.84 (m, 1H), 1.80–1.63 (m, 2H), 1.43 (d, *J*=9.7 Hz, 2H), 1.38–1.16 (m, 1H). ^{13}C NMR (126 MHz, CDCl3) δ 174.9, 137.9, 137.7, 132.5, 115.4, 63.7, 49.8, 45.9, 43.5, 42.7, 30.2, 29.3, 28.0. HRMS calculated for $[M+Na]^+$ 229.1204, found 229.1215. FTIR (neat, cm^{-1}): 3063 (w), 2975 (m), 1732 (s), 1336 (s), 1186 (s).

*4.2.1.2. 1-(4-(Pent-4-en-1-yloxy)phenyl)ethanone (**28**).* Compound was isolated as a colorless oil (189 mg, 93% yield) after purification by silica gel chromatography (0–5% Et_2O/hexanes with a 5% benzene additive, over eight column volumes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J*=8.9 Hz, 2H), 6.92 (d, *J*=8.9 Hz, 2H), 5.91–5.89 (m, 1H), 5.18–4.95 (m, 2H), 4.03 (t, *J*=6.4 Hz, 2H), 2.56 (s, 3H), 2.43–2.17 (m, 2H), 2.09–1.79 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 163.1, 137.7, 130.7, 130.3, 115.6, 114.3, 67.5, 30.1, 28.4, 26.5. HRMS calculated for $[M+H]^+$ 205.1228, found 205.1233. FTIR (neat, cm^{-1}): 3076 (w), 2944 (m), 1675 (s), 1255 (s), 1019 (s).

*4.2.1.3. 2-(Pent-4-en-1-yl)isoindoline-1,3-dione (**36**).* Compound was isolated as a white solid (196 mg, 91% yield) after a THF/NaOH workup followed by silica gel chromatography (0–20% Et_2O/hexanes over eight column volumes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84

(dd, J=5.3, 3.1 Hz, 2H), 7.71 (dd, J=5.5, 3.0 Hz, 2H), 5.94–5.68 (m, 1H), 5.16–4.90 (m, 2H), 3.88–3.57 (m, 2H), 2.12 (dt, J=14.1, 7.3 Hz, 2H), 1.94–1.68 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 137.5, 134.0, 132.3, 123.3, 115.5, 37.7, 31.1, 27.7. HRMS calculated for $[M+Na]^+$ 238.0843, found 238.0852. FTIR (neat, cm^{-1}): 3061 (w), 2938 (m), 1712 (s), 1397 (m).

*4.2.1.4. N,N-Di(tert-butylcarbamate)-N-(pent-4-en-1-yl) amine (**38**).* Compound was isolated as a white solid (240 mg, 84% yield) after purification by silica gel chromatography (0–10% ethyl acetate/hexanes over eight column volumes, then 0–5% Et_2O/hexanes with a 5% chloroform additive over eight column volumes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91–5.71 (m, 1H), 5.16–4.86 (m, 2H), 3.67–3.44 (m, 2H), 2.06 (q, J=7.2 Hz, 2H), 1.68 (dd, J=14.9, 7.4 Hz, 2H), 1.52 (d, J=10.1 Hz, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 138.0, 115.1, 82.2, 46.2, 31.1, 28.2, 28.1. HRMS calculated for $[M+H]^+$ 286.2018, found 286.2010. FTIR (neat, cm^{-1}): 3077 (w), 2980 (m), 1785 (m), 1700 (s), 1128 (s).

4.3. Glovebox-free, multi-gram scale reduction of terminal alkyne

A flame-dried reaction flask was pressurized with dry nitrogen then charged with a stir bar followed by IPrCuCl (34 mg, 0.070 mmol, 0.0050 equiv), THF (7 mL), and anhydrous potassium *tert*-butoxide (1 M solution in *tert*-butanol, 70 μL, 0.070 mmol, 0.0050 equiv). This mixture was allowed to stir at ambient temperature for 15 min before adding a solution of PMHS (1.01 mL, 16.8 mmol, 1.20 equiv relative to hydride), carbamic acid, *N*-(pent-4-ynyl)-1,1-dimethylethyl ester **41** (2.69 mL, 14.0 mmol, 1.00 equiv), and 2-methyl-1-pentanol (2.08 mL, 16.8 mmol, 1.20 equiv) in toluene (70 mL). The reaction mixture was allowed to stir at ambient temperature for 2 h. At this point, the reaction mixture was filtered through a 30 g plug of silica gel with a 1:1 ethyl acetate/hexanes solution (100 mL). The filtrate was concentrated under vacuum, then loaded onto a 30 g plug of neutral alumina as a solution in hexanes (15 mL). The plug was then washed with 100 mL of hexanes, and the filtrate was discarded. This was followed by a 1:4 Et_2O/hexanes solution (200 mL), with eluents collected in 20 mL fractions. Once the desired alkene began to elute from the plug based on TLC, the plug was rinsed with 100 mL EtOAc to recover the remaining product. The product-containing fractions were collected then concentrated under vacuum to afford carbamic acid, *N*-(pent-4-enyl)-1,1-dimethylethyl ester **37** as a colorless liquid (2.3 g, 90% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 5.70–5.48 (m, 1H), 5.02–4.79 (m, 2H), 4.02 (br s, 1H), 3.06–2.78 (m, 2H), 1.91–1.65 (m, 2H), 1.46 (s, 9H), 1.32–1.11 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 156.0, 138.3, 115.0, 78.3, 40.3, 31.3, 29.6, 28.6. HRMS calculated for $C_{10}H_{19}NNaO_2$ $[M+Na]^+$: 208.1313, found: 208.1305. FTIR (neat, cm^{-1}): 3349 (s), 3078 (w), 2932 (s), 1696 (s), 1522 (s), 1252 (s), 1177 (s), 994 (m), 912 (m), 781 (w).

4.4. General procedure for the reduction of internal alkynes

In a nitrogen-filled glovebox, a 1-dram vial was charged with a stir bar followed by the alkyne (1.00 equiv, 1.00 mmol), PMHS **8** (2.00 equiv, 120 mg, 2.00 mmol), and *tert*-butanol (2.50 equiv, 185 mg, 2.50 mmol). This mixture was diluted in toluene (2 mL) before adding IPrCuO*t*-Bu **14** (0.020 equiv, 11 mg, 0.020 mmol). The reaction mixture was stirred at 40 °C until complete conversion of the starting material was achieved (8 h). The mixture was then diluted with hexanes (20 mL), and filtered through a silica gel plug using a 1:1 ethyl acetate/hexane solution (100 mL). The filtrate was concentrated under vacuum, and the crude reaction products were purified using a 10 g silica gel column (see selected examples below for mobile phase used).

4.4.1. Selected examples

*4.4.1.1. (Z)-2,4,7,9-Tetramethyldec-5-ene-4,7-diol (**47**).* Compound was isolated as a white solid (227 mg, 99% yield) after a THF/NaOH workup followed by silica gel chromatography (0–40% ethyl acetate/hexanes over eight column volumes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 2H), 4.32 (s, 2H), 1.83 (qt, J=12.9, 6.4 Hz, 2H), 1.51 (d, J=6.0 Hz, 4H), 1.34 (s, 6H), 0.96 (d, 4.7 Hz, 6H), 0.94 (d, J=6.6, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.4, 74.1, 52.8, 31.0, 24.9, 24.8, 24.7. HRMS calculated for $[M+Na]^+$ 251.1987, found 251.1991. FTIR (neat, cm^{-1}): 3219 (br), 3004 (w), 2954 (s), 1158 (s).

*4.4.1.2. (Z)-(3-(Benzyloxy)non-4-en-1-yl)benzene (**51**).* Compound was isolated as a colorless liquid (283 mg, 92% yield) after a THF/NaOH workup followed by silica gel chromatography (0–15% ethyl acetate/hexanes over eight column volumes). ^{1}H NMR (300 MHz, MeOD) δ 7.59–6.88 (m, 10H), 5.64 (dt, J=11.1, 7.5 Hz, 1H), 5.35 (dt, J=11.0, 7.1 Hz, 1H), 4.56 (d, J=11.8 Hz, 1H), 4.31 (d, J=11.8 Hz, 1H), 4.15 (dt, J=13.7, 8.3 Hz, 1H), 2.80–2.55 (m, 2H), 2.08–1.81 (m, 3H), 1.77–1.60 (m, 1H), 1.39–1.15 (m, 4H), 0.86 (t, J=6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 139.1, 133.9, 130.7, 128.6, 128.4, 128.3, 127.9, 127.5, 125.8, 73.6, 70.0, 37.5, 32.0, 31.9, 27.7, 22.5, 14.1. HRMS calculated for $[M+Na]^+$ 331.2037, found 331.2030. FTIR (neat, cm^{-1}): 3026 (w), 2955 (m), 1603 (m), 1453 (m), 1068 (s).

*4.4.1.3. (Z)-1-Nitro-4-(oct-3-en-1-yloxy)benzene (**53**).* Compound was isolated as a yellow liquid (218 mg, 87% yield) after purification by silica gel chromatography (0–10% ethyl acetate/hexanes with a 5% chloroform additive over eight column volumes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J=9.0 Hz, 2H), 6.94 (d, J=9.1 Hz, 2H), 5.57 (dt, J=17.2, 8.0 Hz, 1H), 5.43 (dt, J=17.0, 7.7 Hz, 1H), 4.05 (t, J=6.8 Hz, 2H), 2.58 (dt, J=7.5, 6.7 Hz, 2H), 2.18–2.02 (m, 2H), 1.40–1.25 (m, 4H), 0.91 (t, J=6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 141.5, 133.6, 126.1, 123.9, 114.6, 68.5, 31.9, 27.3, 27.2, 22.5, 14.1. HRMS calculated for $[M+Na]^+$ 272.1262, found 272.1274. FTIR (neat, cm^{-1}): 3011 (w), 2955 (m), 1513 (s), 1342 (s), 1021 (s).

4.5. Glovebox-free, multi-gram scale reduction of internal alkyne

A flame-dried reaction flask was pressurized with dry nitrogen then charged with a stir bar followed by IPrCuCl (507 mg, 1.04 mmol, 0.0400 equiv), toluene (6.5 mL), and anhydrous potassium *tert*-butoxide (1 M solution in *tert*-butanol, 1.30 mL, 1.30 mmol, 0.0500 equiv). This mixture was allowed to stir at ambient temperature for 15 min before adding PMHS (4.69 mL, 78.0 mmol, 3.00 equiv relative to hydride) followed immediately by anhydrous methyl 4-(oct-3-ynyloxy)benzoate **55** (6.45 mL, 26.0 mmol, 1.00 equiv) as a solution in toluene (30 mL). After stirring for 5 min, *tert*-amyl alcohol (7.03 mL, 65.0 mmol, 2.50 equiv) was added, and the reaction mixture was allowed to stir for 6 h at 45 °C. At this point, the reaction mixture was filtered through a 30 g plug of silica gel with a 1:1 ethyl acetate/hexanes solution (200 mL). The filtrate was concentrated under vacuum, then loaded onto a 300 g plug of neutral alumina as a solution in hexanes (40 mL). The plug was then washed with 500 mL of hexanes, and the filtrate was discarded. This was followed by a 1:4 Et_2O/hexanes solution (600 mL), with eluents collected in 60 mL fractions. Once the desired alkene began to elute from the plug based on TLC, the plug was rinsed with 400 mL EtOAc to recover the remaining product. The product-containing fractions were collected then concentrated under vacuum to afford (*Z*)-methyl 4-(oct-3-enyloxy)benzoate **56** as a colorless liquid (5.9 g, 87% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.15 (d, J=9.0 Hz, 2H), 6.69 (d, J=9.0 Hz, 2H), 5.58–5.42 (m, 1H), 5.42–5.26 (m, 1H), 3.54 (s, 3H), 3.49 (t, J=6.8 Hz, 2H), 2.41–2.19 (m,

2H), 1.96 (t, *J*=6.5 Hz, 2H), 1.37–1.10 (m, 4H), 0.87 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 166.5, 163.1, 132.8, 132.0, 124.9, 123.3, 114.4, 67.6, 51.4, 32.1, 27.6, 27.4, 22.7, 14.2. HRMS calculated for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1466, found: 285.1460. FTIR (neat, cm^{-1}): 3011 (w), 2955 (s), 1918 (w), 1720 (s), 1606 (s), 1511 (m), 1435 (m), 1278 (s), 1169 (s), 1105 (s), 1028 (m), 847 (m), 771 (s), 696 (w).

4.6. General triflation/reduction procedure for primary alcohol deoxygenation

A flame-dried reaction flask was pressurized with dry nitrogen then charged with a stir bar, a primary alcohol (2.0 mmol, 1.0 equiv), and CH_2Cl_2 (5.0 mL). The flask was placed in a dry ice/acetone bath at ca. −78 °C, and while stirring vigorously, 2,6-lutidine (370 μL, 3.2 mmol, 1.6 equiv) was added, followed by the drop-wise addition of triflic anhydride (460 μL, 2.4 mmol, 1.2 equiv). The reaction mixture was allowed to stir for 15 min at −78 °C before adding HCl (15 mL, 1 M solution in H_2O). The flask was then removed from the dry ice/acetone bath, and after slightly thawing, the reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (5×15 mL). The organic layers were combined then dried over Na_2SO_4 before filtration and concentration under vacuum. The resulting crude reaction products were then filtered through a 10 g plug of silica gel, which was rinsed with a 1:9 solution of ethyl acetate/hexanes until all of the desired alkyl triflate was recovered based on TLC of the eluent. The product-containing fractions were combined and concentrated under vacuum, and the alkyl triflate products were used immediately without further purification. In a nitrogen-filled glovebox, a dry 20 mL vial was charged with a stir bar, followed by cesium fluoride (76 mg, 0.50 mmol, 1.0 equiv), IPrCuO*t*-Bu **14** (13 mg, 0.025 mmol, 0.050 equiv), and 1,4-dioxane (1.67 mL). While stirring at ambient temperature, tetramethyldisiloxane (58 μL, 0.33 mmol, 0.65 equiv) was added, followed by a solution of alkyl triflate (0.50 mmol, 1.0 equiv) in 1,4-dioxane (1.67 mL). The reaction mixture was stirred at ambient temperature for 4 h, at which point it was filtered through a 10 g plug of silica gel, which was then rinsed with Et_2O (20 mL). The filtrate was concentrated under vacuum and the crude reaction products were purified by chromatography on silica gel (25 g) using a solvent gradient of 0–10% ethyl acetate/hexanes over eight column volumes.

4.6.1. Selected examples

*4.6.1.1. 1-(4-Bromophenyl)oxyhexane (**63**).* Compound was isolated as a colorless liquid (108.9 mg, 85% yield). Spectral data match reported literature values.[73]

*4.6.1.2. 1-(4-Iodophenyl)oxyhexane (**64**).* Compound was isolated as a colorless liquid (128.1 mg, 84% yield). Spectral data match reported literature values.[74]

*4.6.1.3. 1-(4-Cyanophenyl)oxyhexane (**65**).* Compound was isolated as a colorless liquid (90.2 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.6 Hz, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 3.99 (t, *J*=6.5 Hz, 2H), 1.87–1.70 (m, 2H), 1.51–1.40 (m, 2H), 1.39–1.29 (m, 4H), 0.91 (t, *J*=6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6, 134.1, 119.5, 115.3, 103.8, 68.5, 31.6, 29.1, 25.7, 22.7, 14.1. HRMS calculated for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388, found: 204.1383. FTIR (neat, cm^{-1}): 3054 (m), 2932 (s), 2225 (s), 1899 (w), 1606 (s), 1506 (s), 1264 (s), 1171 (s), 1017 (m), 835 (s).

*4.6.1.4. 1-(4-Nitrophenyl)oxydecane (**67**).* Compound was isolated as a yellow liquid (100.3 mg, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J*=9.3 Hz, 2H), 6.94 (d, *J*=9.3 Hz, 2H), 4.04 (t, *J*=6.5 Hz, 2H), 1.91–1.69 (m, 2H), 1.51–1.16 (m, 14H), 0.88 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 164.1, 141.9, 125.9, 114.4, 68.7, 32.3, 30.0, 30.0, 29.8, 29.7, 29.2, 26.2, 23.1, 14.4. HRMS calculated for $C_{16}H_{26}NO_3$ $[M+H]^+$: 280.1912, found: 280.1911. FTIR (neat, cm^{-1}): 3053 (m), 2928 (s), 1593 (s), 1521 (s), 1342 (s), 1264 (s), 1172 (m), 1111 (m), 845 (m).

*4.6.1.5. Methyl 4-(dec-1-yl)oxybenzoate (**68**).* Compound was isolated as a white solid (142 mg, 97% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.14 (d, *J*=8.9 Hz, 2H), 6.73 (d, *J*=8.9 Hz, 2H), 3.67–3.41 (m, 5H), 1.65–1.43 (m, 2H), 1.40–1.11 (m, 14H), 0.92 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 167.2, 163.6, 132.0, 123.0, 114.6, 68.9, 52.2, 32.5, 30.2, 30.2, 30.0, 29.9, 29.7, 26.6, 23.3, 14.5. HRMS calculated for $C_{18}H_{29}O_3$ $[M+H]^+$: 293.2116, found: 2293.2112. FTIR (neat, cm^{-1}): 3053 (m), 2926 (s), 1715 (s), 1605 (s), 1511 (s), 1435 (s), 1258 (s), 1010 (m), 647 (w).

*4.6.1.6. 1-Hexyloxy-2-methoxy-4-(prop-2-en-1-yl)benzene (**71**).* Compound was isolated as a colorless liquid (102.3 mg, 82% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.75 (d, *J*=2.8 Hz, 2H), 6.65 (s, 1H), 6.10–5.81 (m, 1H), 5.26–4.98 (m, 2H), 3.77 (t, *J*=6.5 Hz, 2H), 3.45 (s, 3H), 3.26 (d, *J*=6.6 Hz, 2H), 1.82–1.56 (m, 2H), 1.53–1.31 (m, 2H), 1.31–1.05 (m, 4H), 0.85 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 150.6, 148.3, 138.4, 132.7, 121.0, 115.5, 114.1, 113.4, 69.2, 55.6, 40.2, 32.0, 29.9, 26.2, 23.0, 14.3. HRMS calculated for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1854, found: 249.1849. FTIR (neat, cm^{-1}): 3059 (w), 2932 (s), 2280 (m), 1639 (m), 1590 (s), 1466 (s), 1260 (s), 1141 (s), 1040 (s), 914 (m), 812 (s).

*4.6.1.7. p-Toluenesulfonic acid, hexyl ester (**72**).* Compound was isolated as a colorless liquid (122.5 mg, 96% yield). Spectral data match reported literature values.[75]

4.7. General procedure for the reduction of secondary halides

In a nitrogen-filled glovebox, a dry 20 mL vial was charged with a stir bar, potassium 2-*tert*-butylphenoxide **79** (104 mg, 0.550 mmol, 1.10 equiv), IPrCuO*t*-Bu **14** (13 mg, 0.025 mmol, 0.050 equiv), and 1,4-dioxane (3.33 mL). While stirring, diphenylsilane (130 μL, 0.70 mmol, 1.4 equiv) was added, followed immediately by a solution of alkyl iodide or bromide (0.50 mmol, 1.0 equiv) in 1,4-dioxane (3.33 mL). The reaction mixture was stirred at ambient temperature for 24 h, at which point it was filtered through a 10 g plug of activated alumina, which was rinsed with Et_2O (20 mL). The filtrate was concentrated, and the desired alkane product was purified by chromatography on activated alumina (25 g) using a solvent gradient of 0–10% ethyl acetate/hexanes over eight column volumes.

4.7.1. Selected examples of 2° iodide reduction

*4.7.1.1. 1-(4-Bromophenyl)oxypentane (**81**).* Compound was isolated as a colorless liquid (102.8 mg, 85% yield). Spectral data match reported literature values.[76,77]

4.8. General procedure for the reduction of primary halides

In a nitrogen-filled glovebox, a dry 20 mL vial was charged with a stir bar, followed by cesium fluoride (76 mg, 0.50 mmol, 1.0 equiv), IPrCuO*t*-Bu **14** (13 mg, 0.025 mmol, 0.050 equiv), and 1,4-dioxane (1.67 mL). While stirring at ambient temperature, tetramethyldisiloxane (58 μL, 0.33 mmol, 0.65 equiv) was added, followed by a solution of alkyl iodide (0.50 mmol, 1.0 equiv) in 1,4-dioxane (1.67 mL). The reaction mixture was stirred at ambient temperature for 24 h, at which point it was filtered through a 10 g plug of silica gel, which was then rinsed with Et_2O (20 mL). The filtrate was concentrated under vacuum and the crude reaction products were

purified by chromatography on silica gel (25 g) using a solvent gradient of 0–10% ethyl acetate/hexanes over eight column volumes.

4.8.1. Selected examples

*4.8.1.1. 1-(4-Bromophenyl)oxyhexane (**63**).* Compound was isolated as a colorless liquid (119.1 mg, 93% yield). Spectral data match reported literature values.[73]

*4.8.1.2. 1-(4-Iodophenyl)oxyhexane (**64**).* Compound was isolated as a colorless liquid (133.9 mg, 88% yield). Spectral data match reported literature values.[74]

*4.8.1.3. 1-(4-Cyanophenyl)oxyhexane (**65**).* Compound was isolated as a colorless liquid (87.1 mg, 84% yield). Spectral data match values reported previously for compound **65**.

*4.8.1.4. N-Methyl-N-(4-(hex-1-yl)oxyphenyl)acetamide (**89**).* Compound was isolated as a colorless liquid (124.6 mg, 98% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.63 (d, J=9.0 Hz, 2H), 6.58 (d, J=9.0 Hz, 2H), 3.55 (t, J=6.4 Hz, 2H), 3.14 (s, 3H), 1.77 (s, 3H), 1.64–1.49 (m, 2H), 1.42–1.11 (m, 6H), 0.87 (t, J=6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 158.5, 137.4, 128.2, 115.4, 68.4, 37.4, 31.7, 29.3, 25.8, 22.7, 22.5, 14.1. HRMS calculated for $C_{15}H_{24}NO_2$ $[M+H]^+$: 250.1807, found: 250.1806. FTIR (neat, cm^{-1}): 3461 (w), 3298 (w), 3050 (m), 2931 (s), 2537 (w), 2305 (w), 2055 (w), 1885 (w), 1655 (s), 1512 (s), 1025 (m).

*4.8.1.5. 1-(tert-Butyldimethylsilyl)oxyhexane (**70**).* Compound was isolated as a colorless liquid (90.9 mg, 84% yield). Spectral data match reported literature values.[78]

*4.8.1.6. 1-Hexyloxy-2-methoxy-4-(prop-2-en-1-yl)benzene (**71**).* Compound was isolated as a colorless liquid (120.1 mg, 97% yield). Spectral data match values reported previously for compound **71**.

*4.8.1.7. p-Toluenesulfonic acid, hexyl ester (**72**).* Compound was isolated as a colorless liquid (111.6 mg, 87% yield). Spectral data match reported literature values.[75]

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Supplementary data

Additional spectral data including ^{1}H and ^{13}C NMR for products not reported in the experimental section are provided. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.04.004.

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