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C(sp)−C(sp^3) Bond Formation through Cu-Catalyzed Cross-Coupling of *N*-Tosylhydrazones and Trialkylsilylethynes

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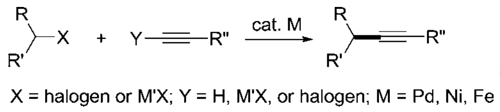
Supporting Information

ABSTRACT: Copper-catalyzed cross-coupling of *N*-tosylhydrazones with trialkylsilylethynes leads to the formation of C(sp)−C(sp^3) bonds. Cu carbene migratory insertion is proposed to play the key role in this transformation.

The Sonogashira reaction has been established as a powerful tool for incorporating an alkynyl moiety into organic molecules since its discovery in 1975.[1] Because alkynes are an important structural unit of various bioactive molecules and are frequently used as synthetic intermediates and precursors for natural products as well as for organic electronic materials,[2] enormous efforts have been devoted to the enhancement of this method over the past decades. Despite the great success of the Sonogashira reaction in the construction of C(sp)−C(sp^2) bonds, the corresponding coupling with nonactivated alkyl halides, namely, the construction of C(sp)−C(sp^3) bonds, has remained a considerable challenge. This is mainly due to the reluctance of alkyl halides to undergo oxidative addition and the propensity to have unproductive *β*-hydride elimination of the alkylmetal intermediates.

In spite of the challenges, significant progress has been made in this area recently (eq 1). Eckhardt and Fu first reported the Sonogashira coupling of primary alkyl halides by employing a Pd/*N*-heterocyclic carbene catalyst system.[3] Following this pioneering work, Glorius and co-workers further expanded the scope of the coupling reaction to secondary alkyl bromides, also with a Pd/*N*-heterocyclic carbene catalyst system.[4] More recently, Hu and co-workers introduced a Ni(II) pincer complex as the catalyst, expanding the Sonogashira coupling to primary alkyl chlorides.[5] Other coupling reactions for C(sp)−C(sp^3) bond formation, such as those using organometallic reagents, have also been extensively explored recently.[6] Besides, inter- or intramolecular decarboxylative cross-coupling has also been applied to C(sp)−C(sp^3) bond formation.[7]



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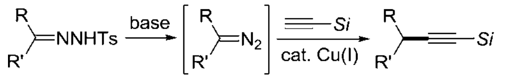

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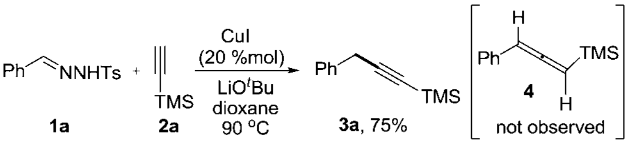
Although remarkable progress has been made, we have considered that it is still highly desirable to develop novel approaches for C(sp)−C(sp^3) bond formation, preferably by using simple and cheap catalysts and easily available starting materials.

Recently, *N*-tosylhydrazones, which are easily prepared from aldehydes or ketones, have emerged as a new type of cross-coupling partner in transition-metal-catalyzed reactions.[8−14] In this area, we reported the Cu(I)-catalyzed direct C−H bond benzylation or allylation of 1,3-azoles with *N*-tosylhydrazones.[11] We also developed the Cu(I)-catalyzed cross-coupling of terminal alkynes and *N*-tosylhydrazones, which leads to the formation of allenes.[12−14] These reactions are proposed to follow a similar pathway that involves Cu carbene formation and subsequent migratory insertion. Herein we further report the Cu(I)-catalyzed cross-coupling of *N*-tosylhydrazones and trialkylsilylethynes (eq 2), which leads to the formation of ethynylation products. This reaction represents a highly efficient and practical approach for C(sp)−C(sp^3) bond formation.

In the course of the investigation of the Cu(I)-catalyzed synthesis of allenes through cross-coupling of *N*-tosylhydrazones and terminal alkynes,[12] we observed that using trimethylsilylethyne (**2a**) as the cross-coupling partner allowed the ethynylation product **3a** to be isolated, while the corresponding allene **4** was not detected (eq 3). This result is similar to the previous report by Suarez and Fu on Cu(I)-catalyzed reaction of terminal alkynes with *α*-diazo carbonyl compounds, which gives 3-alkynoates as the major products.[15] In view of the importance of C(sp)−C(sp^3) bond formation, we decided to optimize this ethynylation reaction.[16] With *N*-tosylhydrazone **1a** and trimethylsilylethyne **2a** as the substrates, it was found that the alkyne product **3a** could be isolated in 75% after optimization of the reaction conditions (eq 3).



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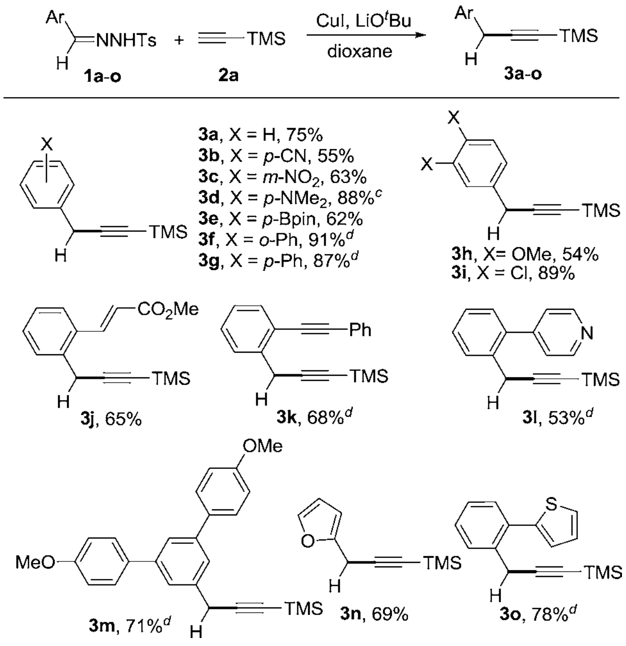
Next, we proceeded to explore the scope of the *N*-tosylhydrazones for the reaction with **2a**. As shown in Scheme 1, the reaction was efficient with a series of *N*-tosylhydrazones derived from aromatic aldehydes. Both electron-withdrawing groups such as chloro, cyano, ester, and nitro groups (Scheme 1, **3b**, **3c**, **3i**, **3j**) and electron-donating groups such as *N*,*N*-dimethylamino and alkoxyl groups (Scheme 1, **3d**, **3m**) were all tolerated under the reaction conditions, and moderate to good yields of the corresponding ethynylation products were obtained. It is noteworthy that *N*-tosylhydrazones bearing heterocyclic substituents were also suitable substrates for this reaction (Scheme 1, **3l**, **3n**, **3o**).

Scheme 1. Cross-Coupling of *N*-Tosylhydrazones Derived from Aromatic Aldehydes and Trimethylsilylethyne[a,b]

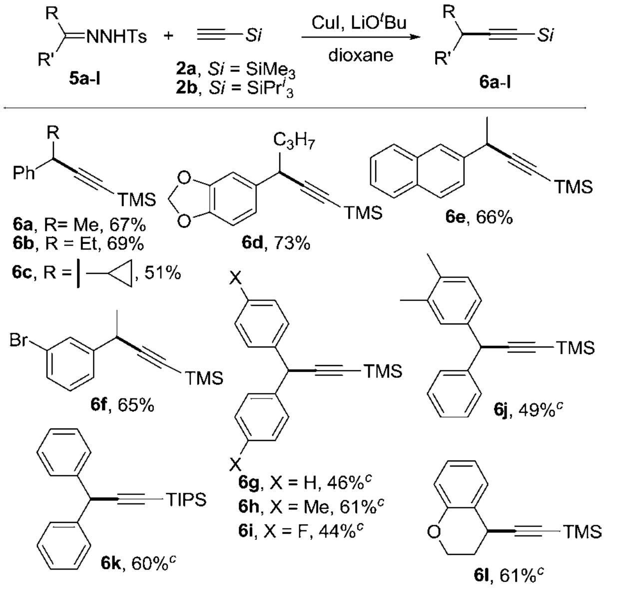


[a]Unless otherwise noted, the reaction conditions were the following: *N*-tosylhydrazone **1a–o** (0.88 mmol), alkyne **2a** (0.4 mmol), CuI (20 mol %), LiO^{t}Bu (1.4 mmol), dioxane (5 mL), 90 °C, 1 h. [b]Isolated yields are shown. [c]The reaction was run at 110 °C. [d]The reaction was run with *N*-tosylhydrazone (0.48 mmol) and LiO^{t}Bu (1.0 mmol).

The scope of the coupling reaction can be extended to *N*-tosylhydrazones derived from aromatic ketones (Scheme 2). The reaction was found to be only slightly affected by the substituents on the aromatic ring. To our delight, the cyclopropyl moiety could also survive the reaction conditions (Scheme 2, **6c**). It was also noted that a slightly improved yield could be obtained when triisopropylsilylethyne (**2b**) was used instead of **2a** (Scheme 2, compare **6g** and **6k**).

Encouraged by these results, we further proceeded to explore the cross-coupling reactions with *N*-tosylhydrazones derived from aliphatic aldehydes and ketones. As shown by the results summarized in Scheme 3, both straight-chain and *β*-branched substrates can be reacted smoothly under the same reaction conditions (Scheme 3, **6m–p**, **6s–t**, **6v–w**); however, the relatively lower boiling point contributes to the diminished yield in the case of **6s.** The reaction with *α*-alkenyl-substituted *N*-tosylhydrazone **5q** afforded the expected 1,4-enyne product **6q**. The low yield in this case is presumably due to the unstability of the in situ-generated diazo intermediate at elevated temperature. It is noteworthy that the reactions with substrates bearing a bulky group such as a *tert*-butyl group also proceeded smoothly (Scheme 3, **6r**, **6u**). To our delight, the cross-coupling reactions of *N*-tosylhydrazones derived from cyclic ketones such as cyclopentanone and cyclohexanone also gave moderate to good yields (Scheme 3, **6x–z**).

Scheme 2. Cross-Coupling of *N*-Tosylhydrazones Derived from Ketones[a,b]



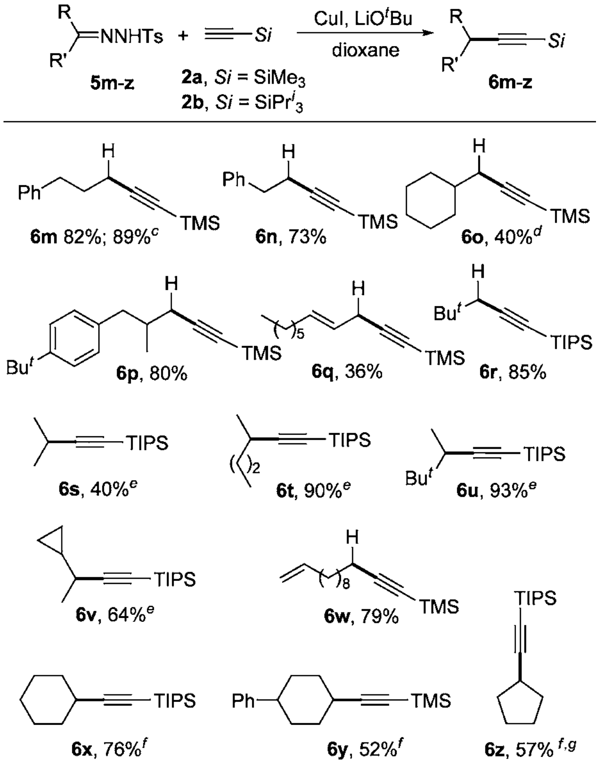
[a]Unless otherwise noted, the reaction conditions were the following: *N*-tosylhydrazone **5a–l** (0.6 mmol), alkyne **2a** or **2b** (0.4 mmol), CuI (20 mol %), LiO^{t}Bu (1.12 mmol), dioxane (5 mL), 110 °C, 1 h; TIPS = triisopropylsilyl. [b]Isolated yields are shown. [c]The reaction was carried out with *N*-tosylhydrazone (0.72 mmol) and LiO^{t}Bu (1.2 mmol).

Finally, since the transformation of a ketone or aldehyde to the corresponding *N*-tosylhydrazone is highly efficient, a one-pot cross-coupling reaction was then performed starting from aldehyde or ketone without separation of the *N*-tosylhydrazone. As shown in Scheme 4, the one-pot reactions afforded the desired coupling products in good yields. It is noteworthy that these two-step transformations can be viewed as reductive cross-couplings of ketones or aldehydes with terminal alkynes.

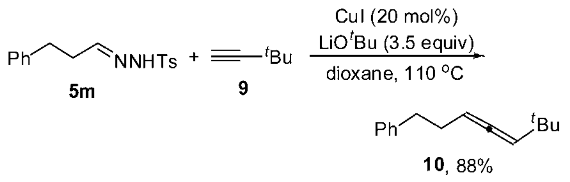
A plausible mechanism to account for the Cu(I)-catalyzed coupling (Scheme 5) is proposed on the basis of our understanding of the Cu-catalyzed cross-coupling reaction of *N*-tosylhydrazones.[12] In the presence of base and Cu(I) salt, copper acetylide **A** is formed from the trialkylsilylethyne. Reaction of copper acetylide **A** with diazo substrate **B**, which is generated in situ from the *N*-tosylhydrazone in the presence of base, leads to the formation of copper carbene species **C**. Migratory insertion of the alkynyl group at the carbenic carbon gives intermediate **D**. Subsequently, protonation affords the ethynylation product.

It is noted that in our previous study, in which the alkynes used in the cross-coupling bear substituents other than a silyl group, the protonation occurred preferentially at the sp carbon to afford the trisubstituted allene product.[12] Thus, the trialkylsilyl substituent plays a vital role in the alkyne formation. To gain some insights into the effect of substituents, *tert*-butyl-substituted alkyne **9** was subjected to the identical reaction conditions with *N*-tosylhydrazone **5m** (eq 4). The reaction

Scheme 3. Cross-Coupling with *N*-Tosylhydrazones Derived from Aliphatic Aldehydes and Ketones[a,b]



[a]Unless otherwise noted, the reaction conditions were the following: *N*-tosylhydrazone **5m−z** (0.88 mmol), alkyne **2a** or **2b** (0.4 mmol), CuI (20 mol %), LiO^{t}Bu (1.4 mmol), dioxane (5 mL), 110 °C, 1 h. [b]Isolated yields are shown. [c]The yield refers to the 10 times scaled-up reaction (0.77 g of **6m** was obtained). [d]CuI (40 mol %). [e]The reaction was run with *N*-tosylhydrazone (0.6 mmol) and LiO^{t}Bu (1.12 mmol). [f]The solution of *N*-tosylhydrazone in 4 mL of dioxane was added with a syringe pump. [g]A 25% yield of alkyne was recovered.



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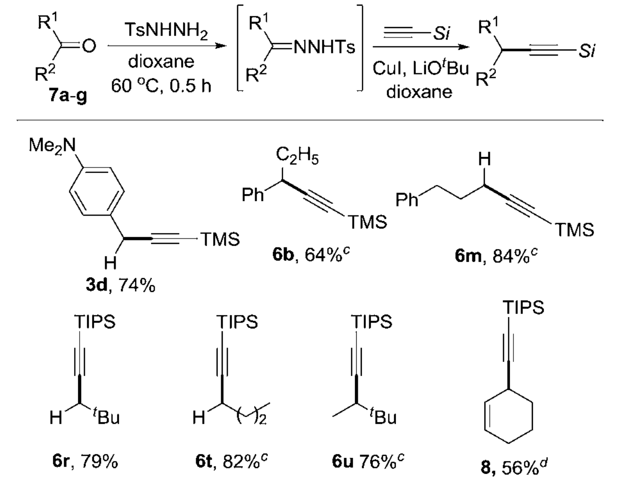
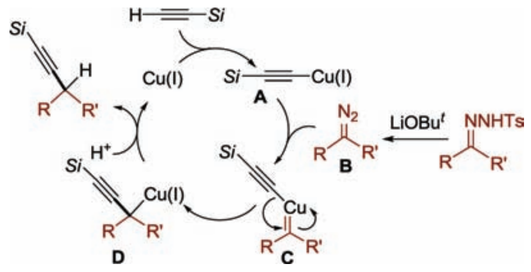
afforded allene **10** in good yield. By comparison with the result obtained using the trimethylsilyl-substituted ethyne (Scheme 3, **6m**), it can be concluded that steric effects do not account for the alkyne/allene selection because Me_3Si and Me_3C have similar steric bulkiness. However, the details of the mechanism are ambiguous at present and will be the subject of future study.

Scheme 4. One-Pot Cross-Coupling Starting from Ketones or Aldehydes[a,b]



[a]Unless otherwise noted, the reaction conditions were the following: **7a−f** (2.2 mmol) and *N*-tosylhydrazine (1 equiv) were reacted in 5 mL of dioxane for 0.5 h at 60 °C; next, to the reaction mixture were added trialkylsilylethyne (4 mmol), CuI (20 mol %), LiO^{t}Bu (22 mmol), and dioxane (35 mL), and the mixture was heated under N_2 for 1 h at 110 °C. [b]Isolated yields are shown. [c]The reaction was run with **7b**, **7e**, or **7f** (6.0 mmol) and LiO^{t}Bu (16 mmol). [d]The reaction was run with cyclohexenone **7g** (0.72 mmol), **2b** (0.4 mmol), and LiO^{t}Bu (2.0 mmol).

Scheme 5. Proposed Reaction Mechanism



In conclusion, we have developed a novel strategy for the formation of C(sp)−C(sp^3) bonds starting from *N*-tosylhydrazones and trialkylsilylethynes, with CuI as the catalyst. This C(sp)−C(sp^3) bond-forming reaction is mechanistically different from other transition-metal-catalyzed cross-coupling reactions with terminal alkynes. *β*-Hydride elimination, which is a common challenge for the cross-coupling with alkyl halides, is not a problem in the cross-coupling with *N*-tosylhydrazones. The salient feature of this coupling reaction is that a complicated ligand is not required and simple CuI can be used as the catalyst. In view of the fact that *N*-tosylhydrazones are easily prepared from the corresponding aldehydes or ketones and the silyl substituent of the coupling products can be readily removed,[17] we consider this transformation to be a practically useful method for converting carbonyl functionality into an ethynyl group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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