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Rhodium(I)-Catalyzed Sequential C(sp)–C(sp^3) and C(sp^3)–C(sp^3) Bond Formation through Migratory Carbene Insertion**

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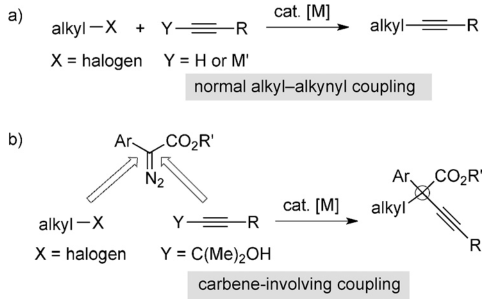
Abstract: *A Rh^I-catalyzed three-component reaction of tert-propargyl alcohol, diazoester, and alkyl halide has been developed. This reaction can be considered as a carbene-involving sequential alkyl and alkynyl coupling, in which C(sp)–C(sp^3) and C(sp^3)–C(sp^3) bonds are built successively on the carbenic carbon atom. The Rh^I-carbene migratory insertion of an alkynyl moiety and subsequent alkylation are proposed to account for the two separate C–C bond formations. This reaction provides an efficient and tunable method for the construction of all-carbon quaternary center.*

Transition-metal-catalyzed cross-coupling reactions have been established as indispensable tools for carbon–carbon bond formation in modern organic synthesis. In this context, the Sonogashira coupling, the coupling of aryl or alkenyl halides with terminal alkynes, is a straightforward methodology for the construction of C(sp)–C(sp^2) bonds, which has been widely practiced in various areas.[1] Compared to the traditional Sonogashira coupling, the construction of C(sp)–C(sp^3) bonds is much more challenging.[2–7] The direct strategy is the transition-metal-catalyzed coupling of alkyl halides with alkynyl nucleophiles.[2–5] However, the difficulty in oxidative addition of unactivated alkyl halides and the competitive β-hydride elimination of the alkyl metal intermediates are the two major challenges in those coupling reactions.[6] Nevertheless, several catalytic systems have been successfully developed during the past decade to achieve such couplings, which has largely expanded the scope of the classic Sonogashira coupling (Scheme 1 a).

On the other hand, transition-metal-catalyzed carbene-involving cross-coupling reactions have attracted considerable attention in recent years.[8] We have previously developed a Pd^0-catalyzed three-component reaction of *N*-tosylhydrazones, terminal alkynes, and aryl halides.[9] This reaction can be considered a carbene-involving traditional Sonogashira-type coupling, in which the direct coupling of terminal alkynes and aryl halides is impeded, instead, both the alkynyl and aryl moiety are connected to the carbenic carbon atom. Similarly, Yu and co-workers later reported a Rh^I-catalyzed carbene-involving Suzuki–Miyaura-type coupling, in which a large excess of coupling partners was needed to obtain the products in good yields, and the reaction was restricted to activated alkyl halides.[10] Herein, we report a Rh^I-catalyzed carbene-involving sequential alkyl and alkynyl coupling of alkynyl nucleophiles with general alkyl halides by using donor–acceptor diazo compounds as the carbene precursors.[11] This reaction represents a highly efficient and tunable method for the construction of all-carbon quaternary centers (Scheme 1 b).[12]



Scheme 1. Transition-metal-catalyzed a) normal and b) carbene-involving coupling of alkynyl nucleophiles with alkyl halides.

At the beginning of our study, terminal alkyne **3a**, donor–acceptor diazo compound **2a**, and benzyl bromide **1a** were chosen as the substrates to test the carbene-inserted sequential alkyl and alkynyl coupling. With [Rh(cod)(OH)]$_2$ (2.0 mol %) and BINAP (5.0 mol %) as the catalyst and NaOMe (1.5 equiv) as the base, the three substrates were reacted in toluene (0.2 M) at 90 °C for 1 h and the expected product **4a** was isolated in 25 % yield. However, the terminal alkyne **3a** easily underwent dimerization under the Rh^I-catalysis conditions,[13] which made improving the yield by optimizing the reaction conditions difficult. On the other hand, we have noticed that *tert*-propargyl alcohol is a good alkynyl nucleophile in Rh^I-catalyzed reactions, in which the alkynyl Rh^I species is generated in situ through selective β-carbon elimination.[13,14] It is assumed that the dimerization of terminal alkynes might be suppressed under such conditions. Gratifyingly, when *tert*-propargyl alcohol **3b** was employed in place of terminal alkyne **3a** under otherwise identical reaction conditions, the carbene-inserted sequential alkyl and alkynyl coupling product **4a** was obtained in 79 % yield [Eq. (1)].[15] A series of *tert*-propargyl alcohols were studied in this Rh^I-catalyzed coupling, and (iPr)$_3$Si-protected *tert*-propargyl

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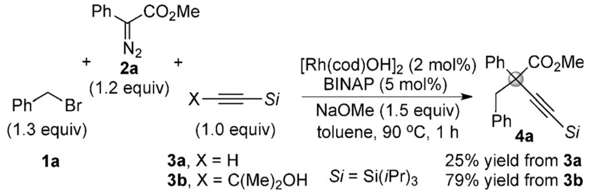
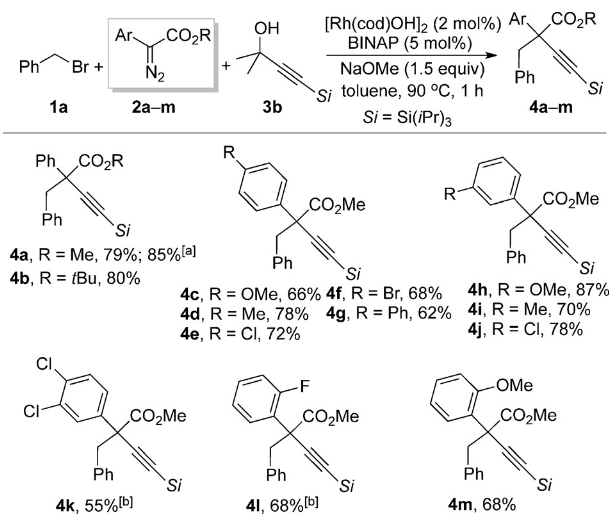


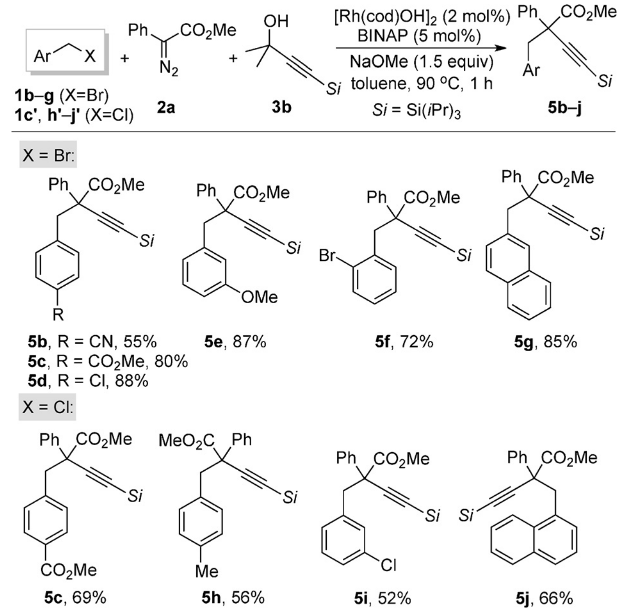
alcohol generally afforded the desired products in moderate to good yields.[15]

With the optimized reaction conditions established, we proceeded to investigate the scope of this Rh^I-catalyzed carbene-involving sequential alkyl and alkynyl coupling. A number of aryl diazoesters **2** were first examined under the optimized reaction conditions, and the corresponding products were obtained in 55–87 % yield (Scheme 2). We were delighted to find that the reaction of diazoester **2a** (bearing a methyl ester moiety) was feasible on a gram scale under the same reaction conditions, affording the product in high yield (**4a**, 85 % yield, 1.79 g). Diazo compound **2b** bearing a *tert*-butyl ester moiety gave the corresponding product **4b** in a comparable yield, thus indicating that the steric hindrance of the ester moiety had a negligible effect on this reaction. Aryl diazoesters bearing *para* (**4c–g**), *meta* (**4h–j**), and *ortho* (**4l,m**) substituents were all compatible with this transformation, thus indicating that the reaction is little influenced by the electronic properties and the steric hindrance of the substituents. Diazo compounds bearing strongly electron-withdrawing groups needed longer reaction time (2 h) for a complete conversion (**4k,l**). Notably, the halogen substituents on the aromatic ring of the diazo substrates all tolerated the reaction, thus providing the opportunity for further transformations through coupling reactions (**4e,f,j,k**).



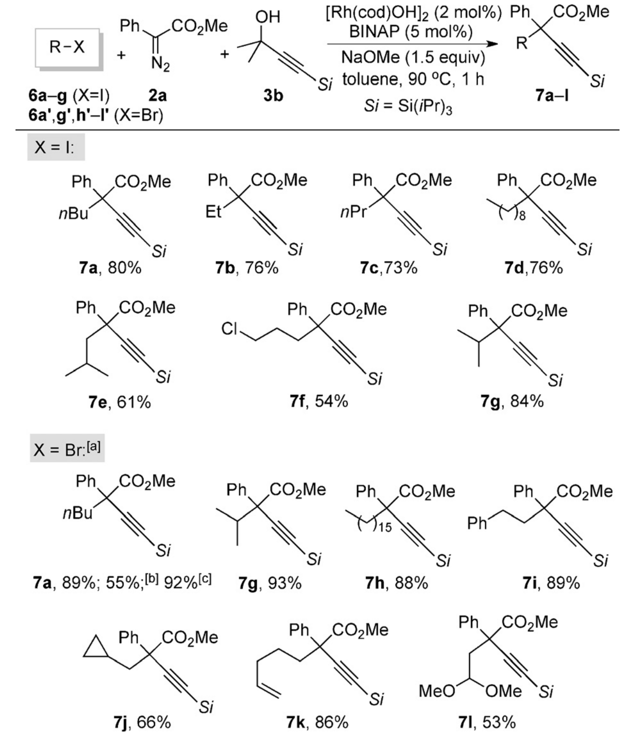
Scheme 2. Scope of diazoesters **2** in Rh^I-catalyzed coupling of *tert*-propargyl alcohol **3b** and benzyl bromide **1a**. Unless otherwise noted, the reaction was carried out on a 0.1 mmol (**3b**) scale with 1.2 equiv of **2** and 1.3 equiv of **1a**. All the yields refer to the isolated products. [a] The reaction was carried out on a 5 mmol (**3b**) scale. [b] The reaction time was 2 h.

Next, the scope of benzyl halides was investigated. A series of benzyl halides **1** were subjected to the optimized reaction conditions, affording the corresponding products in good to excellent yields (Scheme 3). The benzyl bromides bearing *p*-CN, *p*-CO_2Me, *p*-Cl, *m*-OMe, *o*-Br substituents (**1b–f**) and 2-naphthyl methyl bromide **1g** are all suitable substrates for this reaction, giving the corresponding products in good yields, except in the case of the *p*-CN-substituted benzyl bromide (**1b**). Apart from benzyl bromides, benzyl chlorides were also suitable substrates for this transformation, although the yields of the products were a little lower than the ones obtained with benzyl bromides. For example, the yield of *p*-CO_2Me-substituted product **5c** was 80 % when obtained from benzyl bromide **1c** and 69 % when obtained from benzyl chloride **1c'**. Other benzyl chlorides gave the corresponding products (**5h–j**) in moderate to good yields.

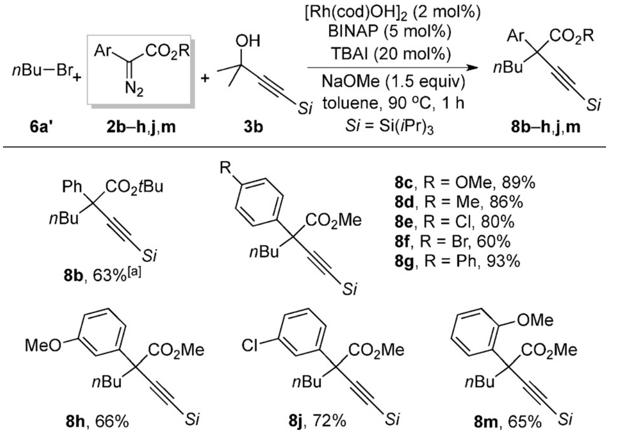


Scheme 3. Scope of benzyl halides **1** in Rh^I-catalyzed coupling of *tert*-propargyl alcohol **3b** and diazoester **2a**. The reaction conditions were the same as those described in Scheme 2. All the yields refer to the isolated products.

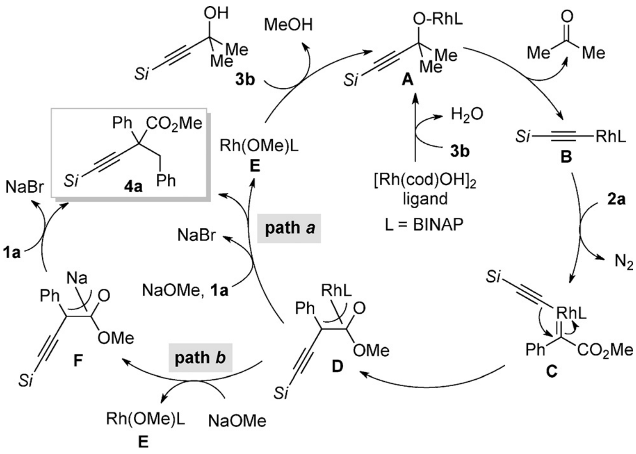
After the exploration of the reaction scope of benzyl halides, we next turned our attention to the scope of unactivated alkyl halides (Scheme 4). Gratifyingly, the reaction of *n*-butyl iodide **6a** under slightly modified conditions was successful, affording the corresponding product **7a** in 80 % yield. Other primary alkyl iodides (**6b–e**) gave similar results, but a diminished yield was observed in the reaction of ω-chlorine-substituted alkyl iodide **6f**. Furthermore, secondary alkyl iodide **6g** could also be employed as the substrate to give the corresponding product **7g** in excellent yield. Subsequently, the reaction of alkyl bromides was examined. When *n*-butyl bromide **6a'** was subjected to the same conditions as the reaction with alkyl iodides, the expected product **7a** could only be isolated in 55 % yield. The yield could be improved to 89 % when 20 mol % TBAI (tetrabutylammonium iodide) was added to the reaction mixture.



Scheme 4. Scope of alkyl halides **6** in Rh^I-catalyzed coupling of *tert*-propargyl alcohol **3b** and diazoester **2a**. Unless otherwise noted, the reactions were carried out on 0.1 mmol (**3b**) scale, with 1.3 equiv of diazoester **2a** and 2.0 equiv of alkyl halides **6**. All the yields refer to the isolated products. [a] 20 mol% TBAI was added. [b] Reaction in the absence of TBAI. [c] The reaction was carried out on a 5 mmol (**3b**) scale.



Scheme 5. Scope of diazoesters **2** in Rh^I-catalyzed coupling of *tert*-propargyl alcohol **3b** and *n*-butyl bromide **6a′**. The reactions were carried out on 0.1 mmol scale, with 1.3 equiv of diazoester **2**, 2.0 equiv of alkyl halide **6a′**, and 20 mol% TBAI. All the yields refer to the isolated products. [a] The reaction time was 2 h.



Scheme 6. Proposed reaction mechanism.

Moreover, the reaction was also successful on a gram scale, affording 1.77 g of **7a** (92% yield). Again, secondary and long-chain alkyl bromides were good substrates for the reaction (**7g**, **7h**). Alkyl bromides bearing phenyl, cyclopropyl, terminal alkene, and acetal moieties were all reacted smoothly to give the corresponding products in moderate to good yields (**7i–l**).

Finally, the scope of the reaction was further examined by reacting a series of aryl diazoesters **2** with *tert*-propargyl alcohol **3b** and *n*-butyl bromide **6a′** (Scheme 5). The diazo compound **2b** with its bulky *t*Bu moiety needed a longer reaction time for the reaction to reach completion (product **8b**). The reactions of other diazo esters **2** with *n*-butyl bromide **6a′** gave similar results to those obtained in the reactions of **2** with benzyl bromide **1a** (compare with Scheme 2), affording the corresponding products (**8c–h**,**j**,**m**) in moderate to excellent yields.

As this Rh^I-catalyzed carbene-involving sequential alkyl and alkynyl coupling is a straightforward methodology to construct all-carbon quaternary centers starting from readily available materials, we subsequently turned our attention to the asymmetric version of the transformation. However, high stereoselectivity could not be achieved with either the chiral ligand (*R*)-BINAP or by employing a diazo compound bearing a chiral auxiliary.[15]

A plausible mechanism is shown in Scheme 6. First, in the presence of the BINAP ligand, the [Rh(cod)(OH)]$_2$ dedimerizes to generate the active catalyst, which deprotonates **3b** to form alkoxy Rh^I species **A**. Then **A** undergoes a β-alkynyl elimination to generate alkynyl rhodium complex **B**,[13,14] with the extrusion of a ketone. Alkynyl rhodium complex **B** reacts with diazoester **2a** to afford Rh^I-carbene complex **C**,[10,16,17] followed by migratory insertion of the alkynyl Rh^I-carbene species to generate oxa-π-allyl Rh^I intermediate **D**.[10,12d] At this point, two pathways toward the product are possible.

Path (a) is the direct alkylation of the enolate-like Rh^I species **D** with the aid of base NaOMe. The final product is then produced with generation of a methoxy Rh^I complex **E**, which reacts with **3b** to regenerate complex **A** and completes the catalytic cycle. Path (b) depends on an exchange of the enolate-like Rh^I species **D** with NaOMe to give the corresponding Na enolate species **F**, followed by alkylation to afford the final product. The generated methoxy Rh^I complex **E** then undergoes the same process as the one described for path (a) to complete the catalytic cycle.

As mentioned above, the enantioselectivity of this reaction could not be achieved by using a chiral ligand on rhodium center, thus indicating that path (b) is more likely than path (a). This is similar to that reported by Yu and co-workers.[10] However, further investigation is needed to unambiguously distinguish these two reaction routes.

In conclusion, we have developed a highly efficient $\mathrm{Rh^I}$-catalyzed carbene-inserted sequential alkyl and alkynyl coupling. The alkynyl and alkyl moieties of the coupling partners are both linked with a carbene moiety, resulting in the formation of one $\mathrm{C(sp)-C(sp^3)}$ bond and one $\mathrm{C(sp^3)-C(sp^3)}$ bond on a carbenic center. The reaction tolerates a wide range of functional groups and can be applied in gram-scale syntheses with high efficiency. The transformation thus represents a tunable and practicable methodology for the construction of all-carbon quaternary center, starting from readily available substrates. Further investigation will be focused on the asymmetric catalysis and other types of carbene-involving coupling reactions. The results will be reported in due course.

Keywords: carbenes · cross-couplings · diazo compounds · migratory insertion · quaternary carbon center

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