Multicomponent Reactions

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# Rhodium-Catalyzed Three-Component Cross-Addition of Silylacetylenes, Alkynyl Esters, and Electron-Deficient Alkenes or Isocyanates**

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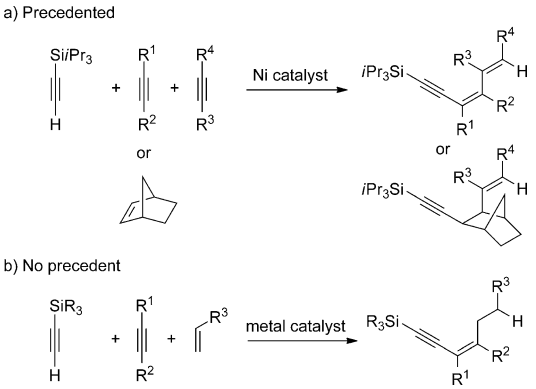
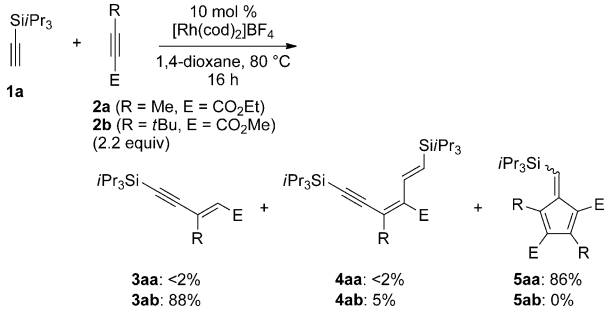
The transition-metal-catalyzed hydroalkynylation of unsaturated compounds with terminal alkynes has been extensively studied for the atom-economical synthesis of functionalized alkynes.[1] Although a number of the hydroalkynylation reactions of alkynes,[2] allenes,[3] and alkenes[4] with terminal alkynes has been reported, the cross-addition reactions of terminal alkynes and two unsaturated compounds through the formation of two C–C bonds are rare.[5] In particular, the reactions of terminal alkynes and two different unsaturated compounds are difficult as a result of the challenge in controlling the chemoselectivity.[6,7] Ogata, Fukuzawa, and co-workers realized such challenging transformations by using bulky triisopropylsilylacetylene as a terminal alkyne and nickel(0)/phosphine complexes as catalysts.[6,7] In 2009, they reported the nickel-catalyzed three-component cross-addition of triisopropylsilylacetylene and two different internal alkynes ($R^1$, $R^2$, $R^4 \neq H$, $R^3 = CH_2OR^5$) by controlling the chemoselective addition between two different internal alkynes (Scheme 1 a).[6a] In 2011, they realized the more difficult cross-addition of two different terminal alkynes [triisopropylsilylacetylene and terminal alkynes ($R^1$ = alkyl, $R^2 = H$)] and internal alkynes ($R^3$, $R^4$ = Ar) by controlling the chemoselective C–H bond activation between two different terminal alkynes as well as the chemoselective addition between the terminal and internal alkynes (Scheme 1 a).[6b] In 2010, they also reported that norbornene is able to participate in this three-component cross-addition to give the corresponding 1,5-enynes (Scheme 1 a).[7] However, the available alkenes were unfortunately strictly limited to norbornene derivatives. Herein, we report the unprecedented transition-metal-catalyzed chemo-, regio-, and stereoselective three-component cross-addition of silylacetylenes, alkynes, and alkenes, thus leading to substituted 1,3-dienes (Scheme 1 b) by using cationic rhodium(I) complexes as catalysts.[8] The analogous unprecedented three-component cross-addition involving isocyanates in place of alkenes is also disclosed.[9]




***Scheme 1.*** Transition-metal-catalyzed three-component cross-addition of silylacetylenes, alkynes, and alkenes.

Our research group previously reported that a cationic rhodium(I)/$(cod)_2$ (cod = 1,5-cyclooctadiene) complex is a highly effective catalyst for the [2+2+1] cross-cyclotrimerization of silylacetylenes and two alkynyl esters, thus leading to substituted silylfulvenes.[10,11] For example, triisopropylsilylacetylene (**1a**) reacted with two ethyl 2-butynoates (**2a**) to give the corresponding silylfulvene **5aa** in high yield (Scheme 2).[10] Interestingly, the use of the sterically demanding methyl 4,4-dimethyl-2-butynoate (**2b**) in place of **2a** did not afford the cross-cyclotrimerization product **5aa**, but instead delivered the cross-dimerization product **3ab**[2g] as a major product along with the linear cross-trimerization product **4ab**,[5k] which was generated from **2b** and two units of **1a**, as a minor product (Scheme 2).




***Scheme 2.*** Rhodium-catalyzed reactions of triisopropylsilylacetylene (**1a**) and alkynyl esters **2**.

We anticipated that when adding an excess of an electron-deficient alkene, this alkene would be incorporated into the product as a third component in place of **1a**. Pleasingly, the

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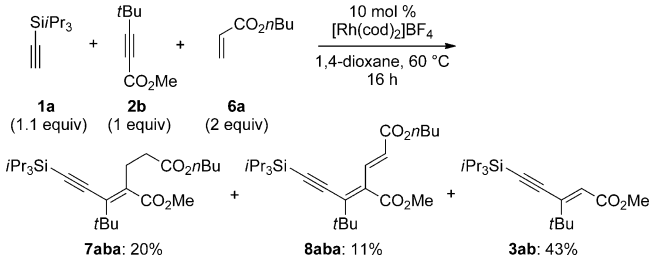



***Scheme 3.*** Rhodium-catalyzed reactions of triisopropylsilylacetylene (**1a**), the alkynyl ester **2b**, and acrylate **6a**.

reaction of **1a**, **2b**, and butyl acrylate (**6a**, 2 equiv; Scheme 3) at 60 °C afforded the expected three-component cross-addition product **7aba** along with the corresponding dehydrogenated product **8aba**, however, the major product was the cross-dimerization product **3ab**.

To improve the yield of **7aba**, the effect of the solvents was first examined (entries 1–6, Table 1). Ether solvents were effective for this transformation (entries 1–3) and the use of THF furnished **7aba** in the highest yield (entry 2). However, less-coordinating solvents (entries 4 and 5) and a highly coordinating solvent (entry 6) did not furnish **7aba** at all. Next, the effect of catalysts was examined (entries 7–14). An in situ generated cationic rhodium(I)/cod complex catalyzed the formation of **7aba** as well as a significant amount of the oligomerization products from **1a** (entry 7). The use of a cationic iridium(I)/cod complex, $[Rh(nbd)_2]BF_4$, and $[\{Rh(cod)OAc\}_2]$ predominantly furnished the cross-dimerization product **3ab** (entries 8–10). The use of a cationic rhodium(I)/*rac*-binap complex [binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] and $[\{RhCl(cod)\}_2]$ failed to catalyze the reaction (entries 11 and 12). Interestingly, changing the counter anion from $^-BF_4$ to $^-OTf$ (entry 13) or $^-SbF_6$ (entry 14) completely suppressed the formation of **8aba**, and the use of $[Rh(cod)_2]SbF_6$ furnished **7aba** in the highest yield (entry 14). However, the use of $BAr_F$ as the counter anion significantly suppressed the substrate conversion (entry 15). Increasing the amount of **6a** improved the selectivity of **7aba** over **3ab**, but the reaction rate decreased (entry 16). Elevating the reaction temperature to 80 °C increased the reaction rate and further improved the yield of **7aba** (entry 17).

***Table 1:*** Effect of catalysts and solvents on reaction of **1a**, **2b**, and **6a**.[a]

| Entry | Catalyst | Solvent | Yield [%][b] | | |
|---|---|---|---|---|---|
| | | | **7aba** | **8aba** | **3ab** |
| 1 | $[Rh(cod)_2]BF_4$ | 1,4-dioxane | 20 | 11 | 43 |
| 2 | $[Rh(cod)_2]BF_4$ | THF | 32 | 14 | 26 |
| 3 | $[Rh(cod)_2]BF_4$ | DME | 16 | 6 | 49 |
| 4 | $[Rh(cod)_2]BF_4$ | $(CH_2Cl)_2$ | 0 | 0 | 48 |
| 5 | $[Rh(cod)_2]BF_4$ | toluene | 0 | 3 | 39 |
| 6 | $[Rh(cod)_2]BF_4$ | $CH_3CN$ | 0 | 0 | 0 |
| 7 | $[\{RhCl(cod)\}_2]/2AgBF_4$ | THF | 30 | 7 | 24 |
| 8 | $[\{IrCl(cod)\}_2]/2AgBF_4$ | THF | 0 | 0 | 49 |
| 9 | $[Rh(nbd)_2]BF_4$ | THF | 0 | 6 | 58 |
| 10 | $[\{RhOAc(cod)\}_2]$ | THF | 7 | 8 | 41 |
| 11 | $[Rh(cod)_2]BF_4$/*rac*-binap | THF | 0 | 0 | 0 |
| 12 | $[\{RhCl(cod)\}_2]$ | THF | 0 | 0 | 0 |
| 13 | $[Rh(cod)_2]OTf$ | THF | 31 | 0 | 14 |
| 14 | $[Rh(cod)_2]SbF_6$ | THF | 46 | 0 | 31 |
| 15 | $[\{RhCl(cod)\}_2]/2NaBAr_F$[c] | THF | 0 | 2 | 0 |
| 16[d] | $[Rh(cod)_2]SbF_6$ | THF | 62 | 0 | 10 |
| 17[d,e] | $[Rh(cod)_2]SbF_6$ | THF | 74 | 0 | 16 |

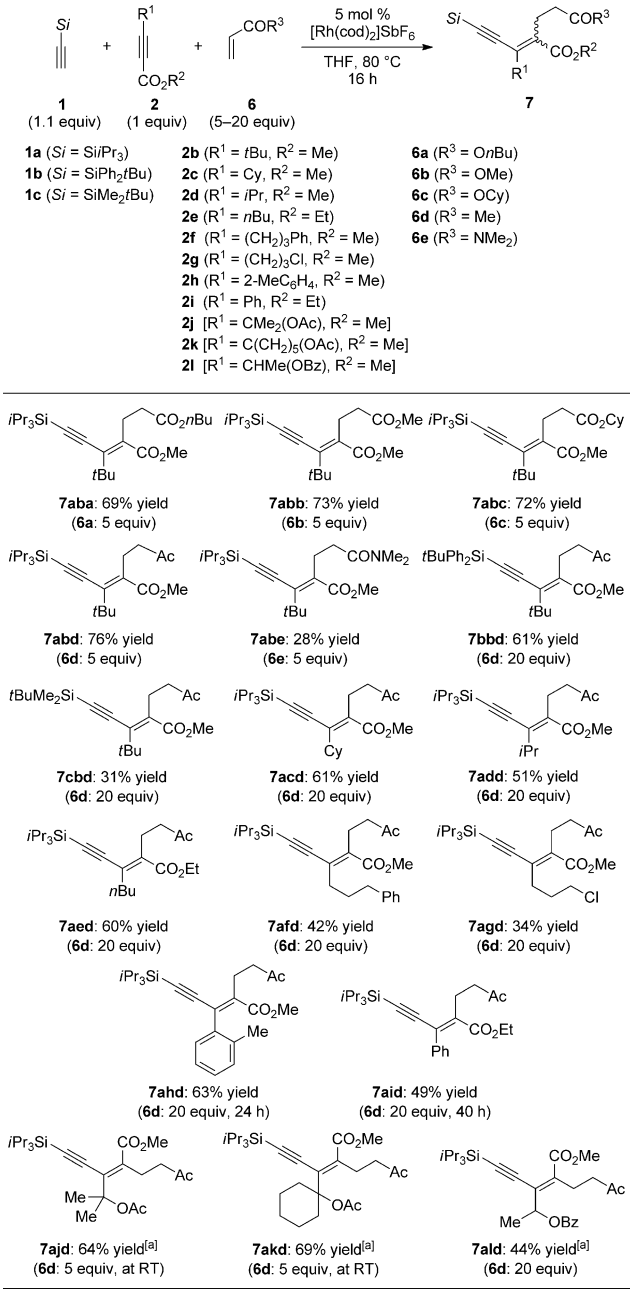
[a] Reactions were conducted using the catalyst (0.010 mmol of metal), **1a** (0.11 mmol), **2b** (0.10 mmol), **6a** (0.20 mmol), and solvent (2.0 mL) at 60 °C for 16 h. [b] Determined by $^1H$ NMR spectroscopy.
[c] $NaBAr_F$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.
[d] **6a**: 5 equiv. [e] At 80 °C. DME = 1,2-dimethoxyethane, THF = tetrahydrofuran.

The scope of this rhodium(I)-catalyzed three-component cross-addition was examined as shown in Scheme 4.[12] With respect to electron-deficient alkenes, various acrylates (**6a–c**) and methyl vinyl ketone (**6d**) were suitable substrates for this process, while the use of *N*,*N*-dimethylacrylamide (**6e**) lowered the yield of the corresponding three-component cross-addition product. With respect to the silylacetylenes, not only triisopropylsilylacetylene (**1a**) but also *tert*-butyldiphenyl- and *tert*-butyldimethylsilylacetylenes (**1b** and **1c**, respectively) could be employed, although excess **6d** (20 equiv) was required. With respect to the alkynyl esters, tertiary-alkyl- (**2b**), secondary-alkyl- (**2c**,**d**), primary-alkyl- (**2e–g**), and aryl-substituted (**2h**,**i**) alkynyl esters could react with **1a** and excess **6d** (20 equiv) to give the corresponding three-component cross-addition products in moderate to good yields. Importantly, these reactions proceeded with complete regio- and stereoselectivity. Interestingly, the reactions of propargyl acetates **2j**,**k** proceeded at room temperature to give the corresponding three-component cross-addition products in good yields, although that of benzoate **2l** required an elevated temperature. The use of the less Lewis-acidic $[Rh(cod)_2]BF_4$ in place of $[Rh(cod)_2]SbF_6$ was necessary to avoid the undesired elimination of carboxylic acids. In these reactions, stereoselectivities were opposite to those using **2b–i**.

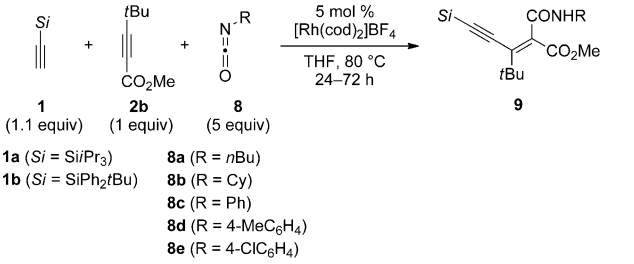
As the third addition component, isocyanates could be employed in place of electron-deficient alkenes by using the less Lewis-acidic $[Rh(cod)_2]BF_4$ as a catalyst (Scheme 5).[13] The primary and secondary alkyl isocyanates **8a**,**b** reacted with **1a** and **2b** to give the corresponding enyne amides **9**, and the use of the arylisocyanates **8c–e** improved the product yields. Although the product yield decreased, *tert*-butyldiphenylsilylacetylene (**1b**) could also be employed.

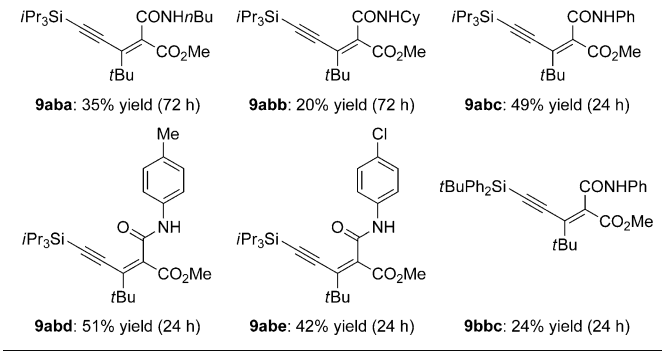
A mechanistic proposal for this rhodium(I)-catalyzed three-component cross-addition reaction is shown in Scheme 6. Carborhodation of the alkynyl ester **2** with the rhodium acetylide **A**, generated by the reaction of the silylacetylene **1**[14] and the cationic rhodium(I) complex, affords the (alkenyl)rhodium **B**, which reacts with electron-deficient alkene **6** to generate the intermediate **C**. Protonation of **C** affords the 1,3-enyne **7** and regenerates the rhodium(I) catalyst. The isocyanete **8** is also able to react with the (alkenyl)rhodium **B** to give the intermediate **D**, the protonation of which affords the enyne amide **9**. In contrast, the reaction of the rhodium acetylide **A** with the propargyl ester **2** [$R^1 = CR^5R^6(OCOR^7)$] affords the (alkenyl)rhodium **E**, in which the carbonyl oxygen atom coordinates to rhodium, through *E*/*Z* isomerization of **B**.[15] This intermedi-

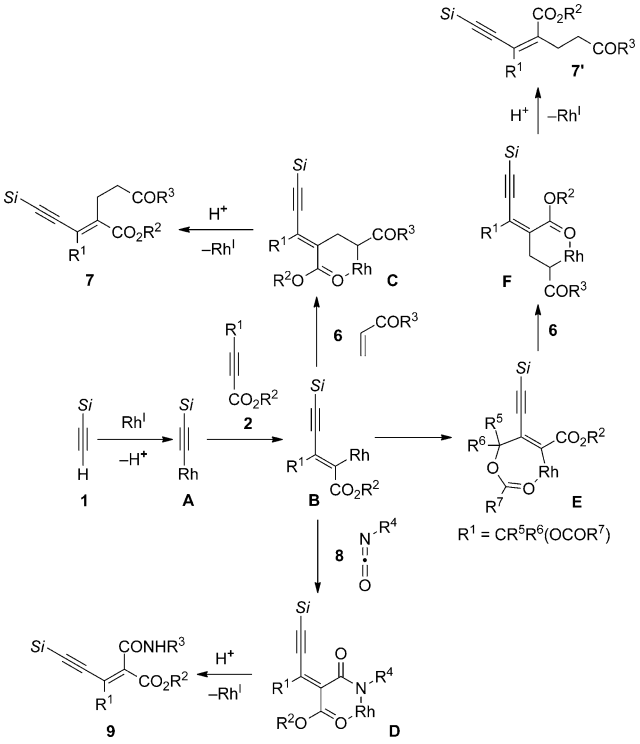



***Scheme 4.*** Three-component cross-addition of silylacetylenes **1a–c**, alkynyl esters **2b–l**, and electron-deficient alkenes **6a–e**. Reaction conditions: $[Rh(cod)_2]SbF_6$ (0.010 mmol), **1a–c** (0.22 mmol), **2b–l** (0.20 mmol), **6a–e** (1.0–4.0 mmol), and THF (2.0 mL) were used. Cited yields are of isolated products. [a] $[Rh(cod)_2]BF_4$ (0.010 mmol) was used. Bz = benzoyl.




***Scheme 5.*** Three-component cross-addition of silylacetylenes **1a,b**, alkynyl ester **2b**, and isocyanates **8a–e**. Reaction conditions: $[Rh(cod)_2]BF_4$ (0.010 mmol), **1a,b** (0.22 mmol), **2b** (0.20 mmol), **8a–e** (1.0 mmol), and THF (2.0 mL) were used. Reported yields are of those of the isolated products.

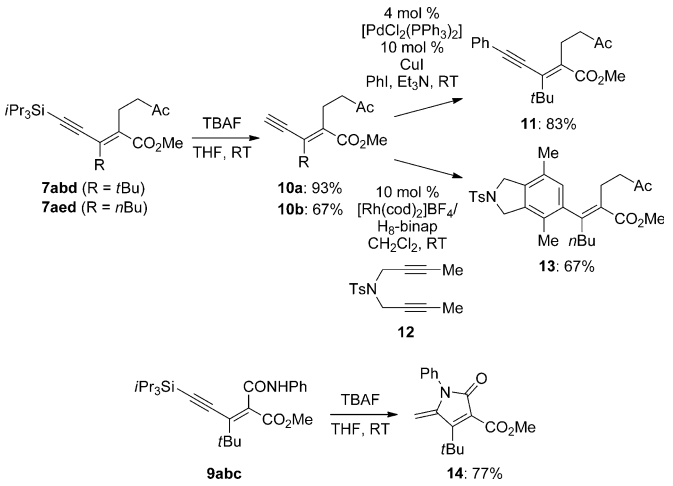



***Scheme 6.*** Proposed reaction mechanism.

ate **E** reacts with **6** to give the intermediate **F**, subsequent protonation of which affords the 1,3-enyne **7′**.

Transformations of the present three-component cross-addition products were briefly examined as shown in Scheme 7. Treatment of the 1,3-enynes **7abd** and **7aed** with TBAF (tetra-*n*-butylammonium fluoride) furnished the terminal alkynes **10a** and **10b**, respectively, in good to high yields. The palladium-catalyzed Sonogashira cross-coupling of **10a** with iodobenzene furnished the phenylacetylene derivative **11** in high yield. Alternatively, the rhodium(I)/$H_8$-binap [2,2′-bis(diphenylphospino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl] complex catalyzed [2+2+2] cycloaddition of **10b** with the 1,6-diyne **12** to furnish the densely substituted benzene **13** in good yield. In contrast, treatment of




***Scheme 7.*** Transformations of three-component cross-addition products. Ts = 4-toluenesulfonyl.

the enyne amide **9abc** with TBAF furnished the desilylated cyclization product **14** in high yield.

In conclusion, we have developed an unprecedented rhodium-catalyzed chemo-, regio-, and stereoselective three-component cross-addition of a silylacetylene, alkynyl ester, and electron-deficient alkene, thereby leading to substituted 1,3-dienes. In addition, the analogous and unprecedented three-component cross-addition involving isocyanates in place of electron-deficient alkenes has also been developed. Future work will focus on further exploitation of the catalytic three-component cross-addition reactions by using the cationic rhodium(I) complexes as catalysts.

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**Keywords:** alkenes · alkynes · multicomponent reactions · rhodium · synthetic methods

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[11] Our research group reported the rhodium(I)-catalyzed cross-trimerization of propargyl esters and two arylacetylenes leading to substituted dihydropentalenes, a reaction initiated by the hydroalkynylation of propargyl esters with arylacetylenes. See: Y. Shibata, K. Noguchi, K. Tanaka, *Org. Lett.* **2010**, *12*, 5596.
[12] When the yields of the desired products **7** were low, the following cross-dimerization products **3** or cross-timerization products **5** were generated as major by-products: **7abe** (**3ab**: 71%), **7cbd** (**3cb**: 33%), **7add** (**5ad**: 35%), **7afd** (**5af**: 31%), **7agd** (**5ag**: 46%), **7aid** (**5ai**: 14%), **7ald** (**5al**: 21%).
[13] The following cross-dimerization products **3** and cross-timerization products **4** were generated as major by-products: **9aba** (**3ab**: 14% and **4ab**: 11%), **9abb** (**3ab**: 28% and **4ab**: 40%), **9abc** (**3ab**: 35% and **4ab**: 9%), **9abd** (**3ab**: 22% and **4ab**: 12%), **9abe** (**3ab**: 44% and **4ab**: 7%), **9bbc** (**3bb**: 24% and **4bb**: 40%).
[14] For examples of the formation of rhodium acetylides from silylacetylenes, see: Ref. [2g].
[15] We believed that this isomerization step from the intermediate **B** to intermediate **E** might be irreversible.

  