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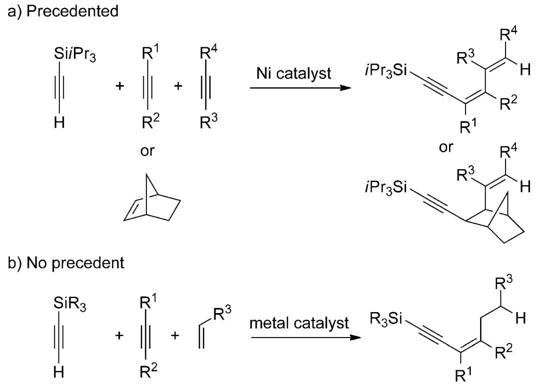
Rhodium-Catalyzed Three-Component Cross-Addition of Silylacetylenes, Alkynyl Esters, and Electron-Deficient Alkenes or Isocyanates**

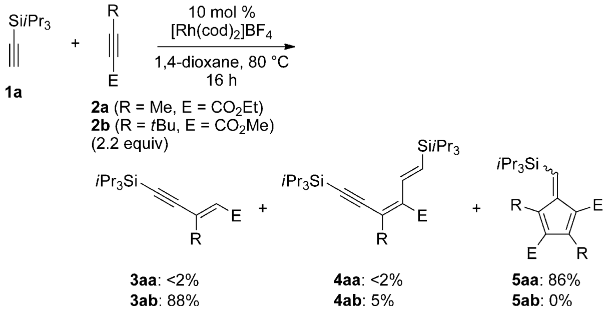
*Yuki Hoshino, Yu Shibata, and Ken Tanaka**

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 1a).[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 1a).[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 1a).[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 1b) 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-cyclotimerization 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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[*] Y. Hoshino, Y. Shibata, Prof. Dr. K. Tanaka
Department of Applied Chemistry, Graduate School of Engineering
Tokyo University of Agriculture and Technology
Koganei, Tokyo 184-8588 (Japan)
E-mail: tanaka-k@cc.tuat.ac.jp
Homepage: http://www.tuat.ac.jp/~tanaka-k/

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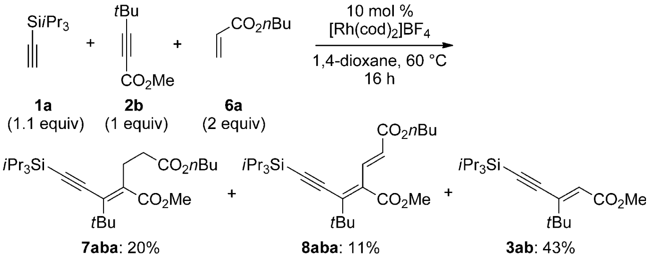


Scheme 3. Rhodium-catalyzed reactions of triisopropylsilylacetylene (**1a**), the alkynyl ester **2b**, and acrylate **6a**.

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]

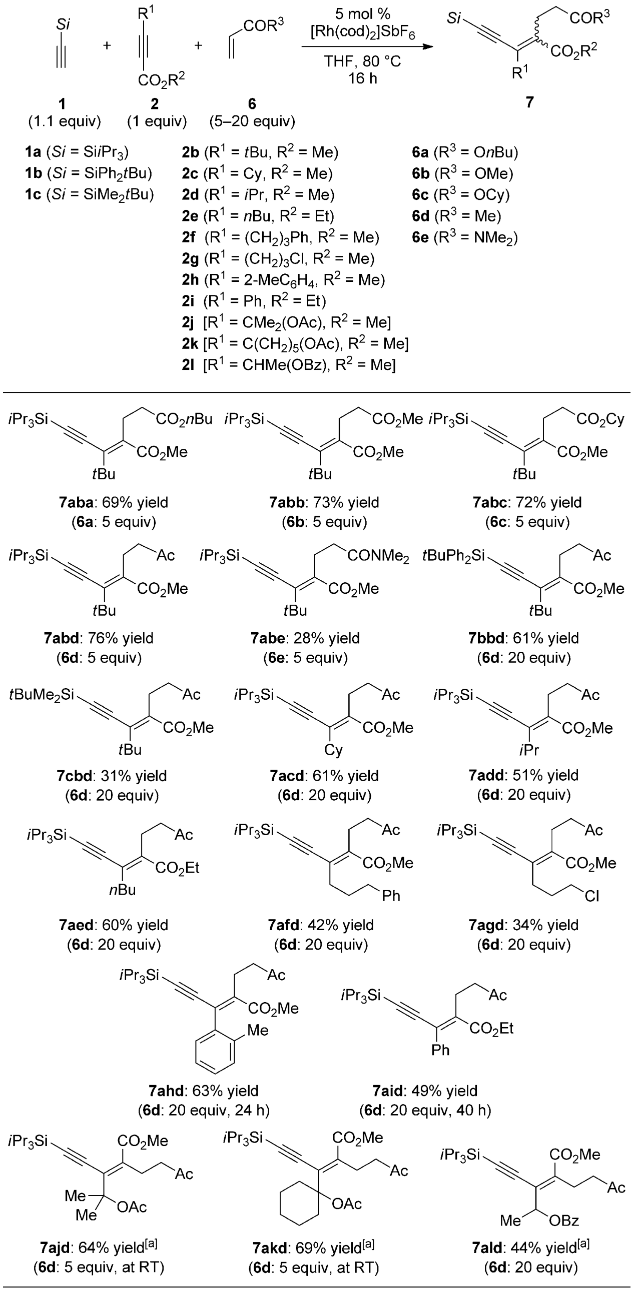
Entry	Catalyst	Solvent	Yield [%][b]		
			7aba	**8aba**	**3ab**
1	[Rh(cod)$_2$]BF$_4$	1,4-dioxane	20	11	43
2	[Rh(cod)$_2$]BF$_4$	THF	32	14	26
3	[Rh(cod)$_2$]BF$_4$	DME	16	6	49
4	[Rh(cod)$_2$]BF$_4$	(CH$_2$Cl)$_2$	0	0	48
5	[Rh(cod)$_2$]BF$_4$	toluene	0	3	39
6	[Rh(cod)$_2$]BF$_4$	CH$_3$CN	0	0	0
7	[{RhCl(cod)}$_2$]/2AgBF$_4$	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 ^{1}H 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.

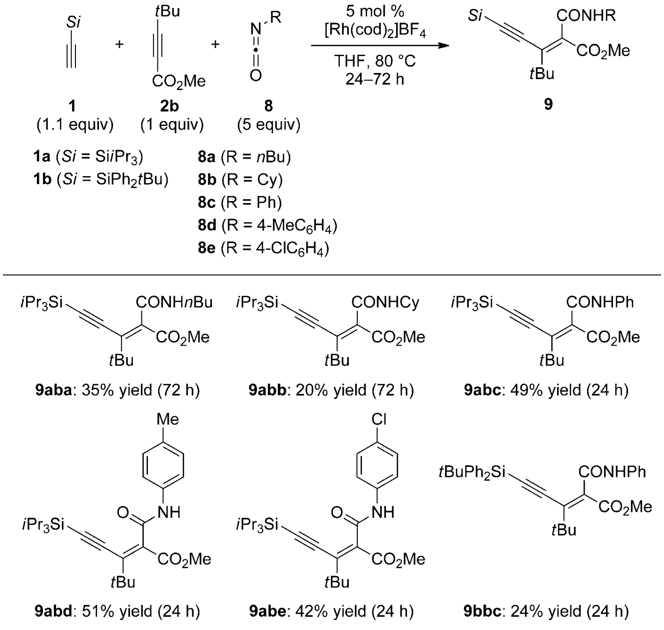
The scope of this rhodium(I)-catalyzed three-component cross-addition was examined as shown in Scheme 4.[12] With respect to electron-deficient alkenes, various acrylates (**6a–c**) and methyl vinyl ketone (**6d**) were suitable substrates for this process, while the use of *N*,*N*-dimethylacrylamide (**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.

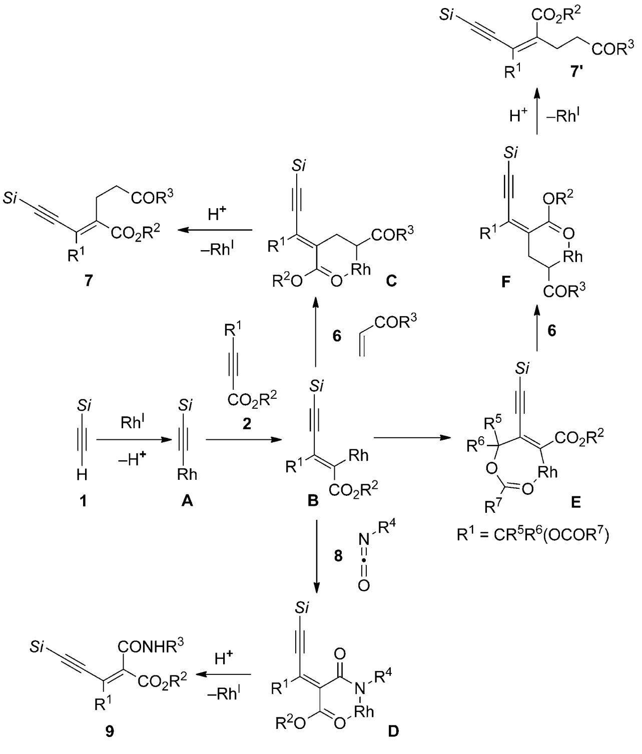
A mechanistic proposal for this rhodium(I)-catalyzed three-component cross-addition reaction is shown in Scheme 6. Carborhodation of the alkynyl ester **2** with the rhodium acetylide **A**, generated by the reaction of the silylacetylene **1**[14] and the cationic rhodium(I) complex, affords the (alkenyl)rhodium **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^{5}R^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.



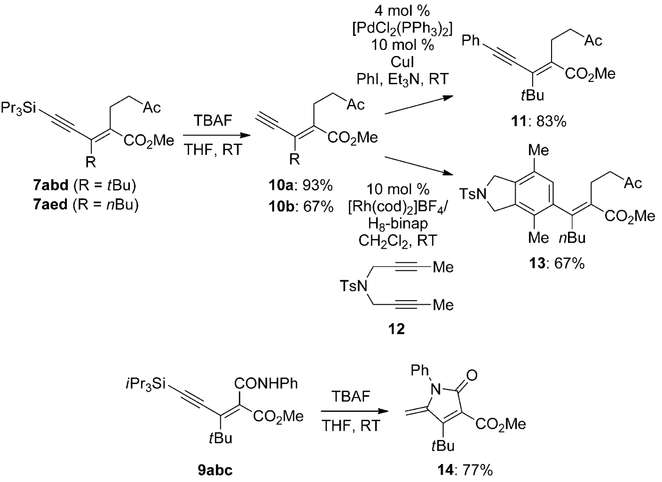
Scheme 5. Three-component cross-addition of silylacetylenes **1a,b**, alkynyl ester **2b**, and isocyanates **8a–e**. Reaction conditions: $[Rh(cod)_2]BF_4$ (0.010 mmol), **1a,b** (0.22 mmol), **2b** (0.20 mmol), **8a–e** (1.0 mmol), and THF (2.0 mL) were used. Reported yields are of those of the isolated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

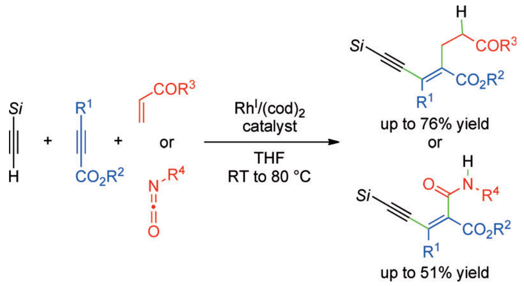
[15] We believed that this isomerization step from the intermediate **B** to intermediate **E** might be irreversible.

Communications

Multicomponent Reactions

Y. Hoshino, Y. Shibata,
K. Tanaka* ______________ ■■■■–■■■■

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



’Rh’oad crossing: A cationic Rh^{I}/(cod)$_2$ complex catalyzes the chemo-, regio-, and stereoselective title reaction with electron-deficient alkenes leading to substituted 1,3-dienes. The analogous three-component cross-addition involving isocyanates instead of alkenes has also been developed.