Rhodium-catalyzed (*E*)-selective cross-dimerization of terminal alkynes†

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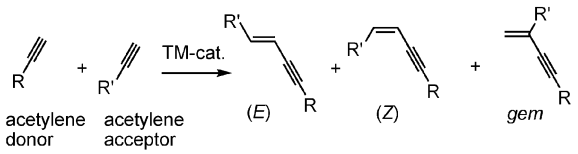
Cross-dimerization of various terminal alkynes with different bulky terminal alkynes such as triisopropylsilylacetylene and 1-trimethylsilyloxy-1,1-diphenyl-2-propyne efficiently proceeds in the presence of a rhodium catalyst system to produce the corresponding (*E*)-enynes with high regio- and stereoselectivity.

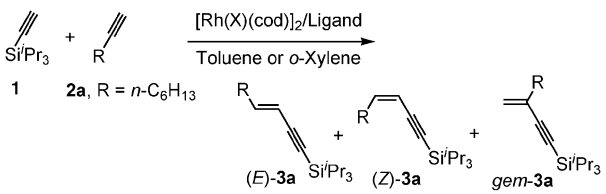
Alkyne coupling reactions by transition-metal catalysis are of genuine synthetic utility in preparing π-conjugated four carbon compounds such as enynes which are versatile building blocks in organic synthesis.[1] Thus, the dimerization of terminal alkynes as a straightforward and practical method leading to enynes has been extensively studied to selectively synthesize one of the three possible (*E*)-, (*Z*)- and *gem*-enyne isomers (*gem* = geminal). In contrast, the selective cross-dimerization of two different alkynes is, in general, difficult due to the fact that the formation of cross- and homo-dimerized regio- and stereoisomers is possible, and thus, a major challenge.[2–8] Among the early leading examples is the palladium-catalyzed reaction of internal alkynes having an electron-withdrawing group as acetylene acceptors.[2] Such reactions have also been achieved by using other transition-metal catalysts.[3] Recently, some selective cross-dimerization reactions of terminal silylacetylenes as acetylene donors with unactivated internal and even terminal alkynes have been disclosed.[4–6] However, the examples for the selective cross-dimerization of terminal alkynes are still very limited (Scheme 1). Katayama and Ozawa described that in the presence of a vinylidene–ruthenium complex, terminal arylacetylenes react with terminal silylacetylenes to selectively afford the corresponding (*Z*)-enynes.[4] In contrast, Tsukada and Inoue reported that a dinuclear palladium complex catalyzes the reaction of a number of terminal alkynes with triisopropylsilylacetylene to selectively give *gem*-enynes.[6,7] As for the selective cross-(*E*)-enyne synthesis, only a single example, that is the reaction of phenylacetylene with 1-pentyne catalyzed by a rhodium complex bearing a PNP-pincer ligand, was described by Ozerov and co-workers.[8] In the course of our study of alkyne coupling reactions,[5a,9] we have found that various terminal alkynes couple with bulky terminal alkynes such as triisopropylsilylacetylene (**1**) and 1-trimethylsilyloxy-1,1-diphenyl-2-propyne (**4**) in the presence of a selected rhodium–phosphine catalyst system to produce the corresponding (*E*)-enyne compounds with high regio- and stereoselectivity.[10]



Scheme 1 Cross-dimerization of terminal alkynes. TM-cat. = Transition-metal catalyst.

In an initial attempt, the reaction of 1-octyne (**2a**) with the silylacetylene **1** (1 equiv.) was carried out in the presence of $[RhCl(cod)]_2$ (3 mol% Rh) and PPh_3 (P/Rh = 2) in refluxing toluene (entry 1 in Table 1). After 8 h, a mixture of the corresponding (*E*)-, (*Z*)- and *gem*-enynes **3a** was formed in a ratio of 33 : >1 : 67 and a total yield of 42%. Use of P^nBu_3 as ligand in place of PPh_3 was found to accelerate the reaction to produce **3a** in 97% yield within 3 h, favorably affording the (*E*)-isomer with 83% selectivity (entry 2). It is often observed in various transition-metal catalyzed reactions that bisphosphine ligands having large bite angles enhance stereoselectivity. Thus, we next examined dppb, dCypb and Xantphos (see Table 1 for abbreviations). The ligands dppb and dCypb unexpectedly gave comparable amounts of (*E*)- and *gem*-isomers (entries 4 and 5). However, Xantphos showed a

Table 1 Cross-dimerization of 1-octyne (**2a**) with triisopropylsilylacetylene (**1**)[a]



Entry	X	Ligand	Solvent[b]	Time/h	Yield[c] (%) (*E*/*Z*/*gem*)[c]
1	Cl	PPh_3	T	8	42 (33/tr./67)
2	Cl	P^nBu_3	T	3	97 (83/7/10)
3	Cl	P^nBu_3	X	3	99 (85/4/11)
4	Cl	dppb[d]	T	6	8 (50/tr./50)
5	Cl	dCypb[e]	T	6	67 (58/4/38)
6	Cl	Xantphos[f]	T	6	21 (80/13/7)
7	Cl	Xantphos	X	3	74 (91/4/5)
8	OH	Xantphos	X	6	17 (25/50/25)
9	I	Xantphos	X	6	83 (92/3/5)
10[g]	I	Xantphos	X	8	97 (90)[h] (95/2/3)

[a] *Reaction conditions*: **1** (0.5 mmol), **2a** (0.5 mmol), $[Rh(X)(cod)]_2$ (0.0075 mmol), ligand (0.03 or 0.015 mmol, P/Rh = 2), in refluxing solvent (5 mL) under N_2. [b] T = toluene, X = *o*-xylene. [c] Total yield and ratio of *E* : *Z* : *gem* were determined by GC analysis. [d] dppb = $Ph_2P(CH_2)_4PPh_2$. [e] dCypb = $Cy_2P(CH_2)_4PCy_2$ (Cy = cyclohexyl). [f] Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [g] 0.6 mmol of **2a** was used. [h] Isolated yield.

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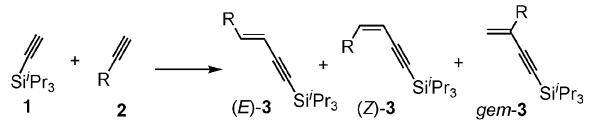
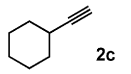
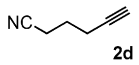
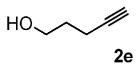
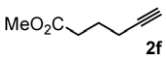
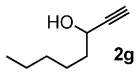
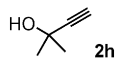
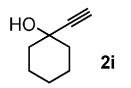
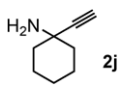
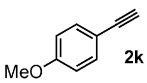
Table 2 Cross-dimerization of various terminal alkynes **2** with triisopropylsilylacetylene (**1**)[a]



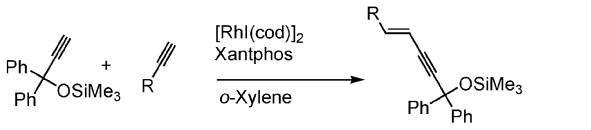
Entry	**2**	Time/h	Product, yield[b] (%) (*E*/*Z*/*gem*)[c]
1	 **2b**	6	**3b**, 76 (92/4/4)
2	 **2c**	6	**3c**, 63 (99/tr./tr.)
3[d]	 **2d**	3	**3d**, 58 (96/3/1)
4[d]	 **2e**	3	**3e**, 60 (94/3/3)
5	 **2f**	3	**3f**, 85 (96/1/3)
6	 **2g**	6	**3g**, 57 (94/tr./6)
7	 **2h**	3	**3h**, 70 (99/tr./tr.)
8[d]	 **2i**	3	**3i**, 61 (99/tr./1)
9	 **2j**	6	**3j**, 68 (89/4/7)
10	 **2k**	3	**3k**, 56 (99/tr./1)

[a] *Reaction conditions*: **1** (0.5 mmol), **2** (0.6 mmol), $[RhI(cod)]_2$ (0.0075 mmol), Xantphos (0.015 mmol), in refluxing *o*-xylene (5 mL) under N_2. [b] Isolated yield. [c] Ratio of *E*/*Z*/*gem* determined by ^{1}H NMR. [d] Reaction in refluxing toluene.

relatively high (*E*)-selectivity (entry 6), albeit the yield of **3a** was low. The reaction was enhanced in refluxing *o*-xylene (entry 7). It was also observed that use of $[RhI(cod)]_2$ in place of $[RhCl(cod)]_2$ improves the yield of **3a** (entry 9). Finally, use of a slightly excess amount of **2a** (1.2 equiv.) allowed 97% yield of **3a** and 95% (*E*)-selectivity (entry 10).

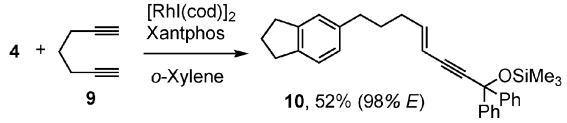
Table 2 summarizes the results for the cross-dimerization reactions of various terminal alkynes **2b–k** with the silylacetylene **1** in the presence of $[RhI(cod)]_2$/Xantphos in *o*-xylene or toluene. As is shown, good product yield and high (*E*)-selectivity were generally obtained. Various functional groups involving cyano, ester, hydroxyl and amino groups were tolerable in this reaction. However, using simple propargyl alcohol and ethyl propiolate did not give any expected products.

Possible major factors for the success of the present cross-dimerization seem to be the high reactivity and bulkiness of the silylacetylene **1**. Thus, it may act as an effective acetylene donor *via* initial C(sp)–H bond cleavage and the rate of its self-



2a, R = *n*-C_6H_{13} **5**, R = *n*-C_6H_{13}, 60% (98% *E*)
2e. R = -$(CH_2)_3$OH **6**. R = -$(CH_2)_3$OH, 77% (98% *E*)
2f, R = -$(CH_2)_3CO_2$Me **7**, R = -$(CH_2)_3CO_2$Me, 74% (98% *E*)
2l, R = Ph **8**, R = Ph, 52% (99% *E*)

Scheme 2 Cross-dimerization of terminal alkynes **2a, e, f, l** with **4**. *Reaction conditions*: **4** (0.5 mmol), **2** (0.6 mmol), $[RhI(cod)]_2$ (0.0075 mmol), Xantphos (0.015 mmol), in refluxing *o*-xylene (5 mL) under N_2 for 3–12 h.



Scheme 3 Reaction of diyne **9** with alkyne **4**. *Reaction conditions*: **4** (0.5 mmol), **9** (1.0 mmol), $[RhI(cod)]_2$ (0.0075 mmol), Xantphos (0.015 mmol), in refluxing *o*-xylene (5 mL) under N_2 for 8 h.

dimerization is slow.[11] The initially formed silylalkynyl(hydroido)rhodium intermediate is considered to undergo insertion of **2**. The subsequent reductive elimination may afford enynes **3**. The regioselective insertion of **2** is responsible for high *E*-selectivity.

Based on the above consideration, we examined the bulky alkyne **4** as a candidate of acetylene donor, whose masking group is readily removable as well as triisopropylsilyl group in **1**.[5b] The results for the reactions of **2a, e, f, l** with **4** are shown in Scheme 2. As expected, high (*E*)-selectivity more than 98% was obtained in each case. It is worth noting that 1,6-heptadiyne **9** reacted with **4** in a 2 : 1 manner to afford compound **10** (Scheme 3). The reaction is considered to proceed through initial cyclodimerization of **9** followed by co-dimerization with **4**.

In summary, the selective formation of (*E*)-enyne in the cross-dimerization of two different terminal alkynes can be achieved by employing bulky terminal alkynes as acetylene donors in the presence of a suitable rhodium-bisphosphine catalyst system.[12] This straightforward method is expected to be employed effectively for preparing various synthetically useful enyne compounds because of its high functional group tolerability as well as stereoselectivity.

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12. Rhodium-catalyzed reaction of triisopropylsilylacetylene (**1**) with 1-octyne (**2a**) (entry 10 in Table 1): A mixture of $[RhI(cod)]_2$ (0.0075 mmol, 5.1 mg), Xantphos (0.015 mmol, 8.7 mg), **1** (0.50 mmol, 91 mg), **2a** (0.60 mmol, 66 mg) and 1-methylnaphthalene (*ca*. 50 mg) as internal standard in *o*-xylene (5 mL) was refluxed for 8 h with stirring under N_2, and then the solvent was evaporated to dryness. The residue was purified by silica gel column chromatography using hexane as eluent to afford **3a** as an oil (131 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (*t*, J = 7.0 Hz, 3H), 1.08 (m, 21H), 1.19–1.44 (m, 8H), 2.10 (ddt, ^4J = 1.5 Hz, J = 7.7 Hz, J = 7.0 Hz, 2H), 5.52 (dt, ^4J = 1.5 Hz, J = 15.8 Hz, 1H), 6.20 (dt, J = 15.8 Hz, J = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.34, 14.06, 18.62, 22.57, 28.59, 28.85, 31.66, 33.09, 88.52, 106.10, 109.84, 145.85. HRMS (EI) m/z calc. for $C_{19}H_{36}Si$: 292.2586 (M^+), found: 292.2590.