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Nickel-Catalyzed Regioselective Hydroalkynylation of Styrenes: Improved Catalyst System, Reaction Scope, and Mechanism

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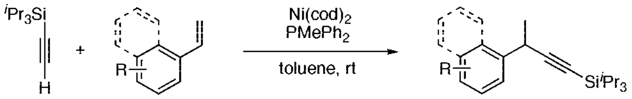
ABSTRACT



Addition of the *sp*-C−H bond of triisopropylsilylacetylene to the carbon−carbon double bonds of styrenes bearing functional groups proceeded efficiently at room temperature in the presence of 3 mol % of $Ni(cod)_2$ with a $PMePh_2$ ligand. Use of 2-deuteriotriisopropylsilylacetylene in the hydroalkynylation of styrenes resulted in regioselective incorporation of deuterium into the β-positions of recovered styrenes, along with its regioselective introduction into the product's methyl group.

Catalytic C−H functionalization has attracted much attention because of its high efficiency and the easy availability of starting materials.[1] The *sp*-C−H bond of a terminal alkyne has been the primary target for catalytic activation. Particular attention has focused on the addition of the alkyne C−H bond across carbon−carbon multiple bonds, which serves as a convenient method for the synthesis of functionalized alkynes. Much effort has been devoted to the addition to the C−C triple bond in the presence of transition-metal complexes, leading to the development of a variety of methods for homodimerization[2] of terminal alkynes and cross-dimerization,[2c,3] i.e., addition of one terminal alkyne to a different alkyne. In contrast to carbon−carbon triple bonds, C═C bonds hardly undergo the addition unless they are sufficiently activated by ring strain or cumulation. Thus, while use of cyclopropene,[4] norbornadiene,[5] and allenes[6] has been reported, hydroalkynylation to less reactive C═C bonds has not been achieved except for some limited examples in ruthenium-catalyzed codimerization of terminal alkynes with 1,3-dienes, in which the positions of the C═C bonds in the product are difficult to predict.[7] We recently reported room-

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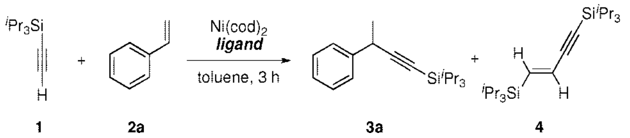
temperature hydroalkynylation of C═C bonds of 1,3-dienes and styrenes.[8] It was essential to use a Ni/PBu$_3$ catalyst with triisopropylsilylacetylene, whose bulkiness retards its homodimerization.[3k] The catalyst system was particularly effective for hydroalkynylation of 1,3-dienes, allowing highly regioselective formation of various 1,4-enynes. However, hydroalkynylation of styrene derivatives with the Ni/PBu$_3$ catalyst still encountered difficulty in reacting styrenes having no electron-withdrawing groups. For instance, in the presence of the Ni/PBu$_3$ catalyst, styrene afforded <20% yield of hydroalkynylation product under the reaction conditions, while reaction of *p*-ethoxycarbonylstyrene afforded 94% yield under the same reaction conditions. In this communication, we describe a modified catalyst system for the hydroalkynylation of styrene derivatives, including electron-rich derivatives. The mechanism of the reaction is also discussed on the basis of deuterium-labeled experiments.

Hydroalkynylation of unsubstituted styrene has been reexamined with a variety of tertiary phosphine ligands (Table 1). Use of PBu$_3$ resulted in the formation of **3a** in only 12% yield at 80 °C (entry 1). PMe$_3$ resulted in improved yield for **3a** (entry 2). It was remarkable to observe the significant increase in yields by using PMe$_2$Ph and PMePh$_2$: the latter afforded 80% yield of the product **3a** (entries 3 and 4). In sharp contrast, no product was obtained with PPh$_3$ or PCyPh$_2$, although the latter has electronic properties similar to those of PMePh$_2$ (entries 5 and 6). Using PMePh$_2$ as a ligand, the reaction proceeded at room temperature in better yield than the reaction at 80 °C (entry 7). It should be noted that no regioisomer was formed in the catalytic reaction. PEtPh$_2$ showed almost the same catalytic activity as PMePh$_2$, although a slightly longer reaction time was required (entry 8). In the presence of the bidentate ligand DPPE (1,2-bis(diphenylphosphino)ethane), only the alkyne dimerization reaction proceeded, with no formation of hydroalkynylation product (entry 9).

Table 1. Ligand Screening of Ni Catalyst[a]

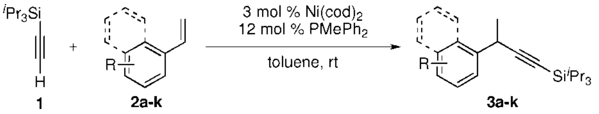


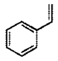
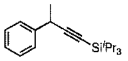
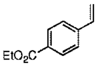
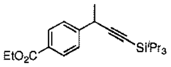
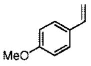
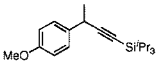
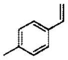
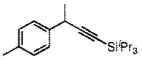
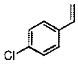
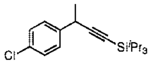
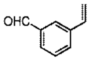
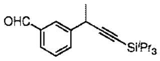
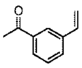
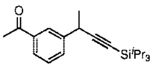
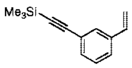
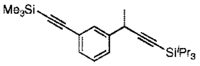
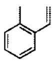
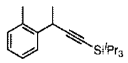
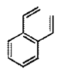
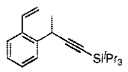
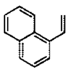
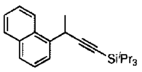
entry	ligand	*T* (°C)	% yield of **3a**[b]	% yield of **4**[b]
1	PBu$_3$	80	12	11
2	PMe$_3$	80	36	21
3	PMe$_2$Ph	80	52	28
4	PMePh$_2$	80	80	14
5	PCyPh$_2$	80	trace	42
6	PPh$_3$	80	0	38
7	PMePh$_2$	rt	87 (88)	11
8[c]	PEtPh$_2$	rt	86	15
9	DPPE	rt	0	66

[a] Acetylene **1** (1.0 mmol), styrene (3.0 mmol), Ni(cod)$_2$ (0.1 mmol), and phosphine ligand (0.40 mmol for entries 1−8, 0.20 mmol for entry 9) were reacted in toluene (1.0 M) for 3 h at the temperature indicated in the table. [b] ^{1}H NMR yield. Isolated yield in parentheses. [c] 8 h.

Taking PMePh$_2$ as the best-yielding ligand, hydroalkynylation of various styrenes (**2a**−**k**) was carried out at room temperature in the presence of 3−5 mol % of Ni(cod)$_2$/PMePh$_2$ (Ni/P = 1/4) catalyst (Table 2). Styrene afforded the hydroalkynylation product **3a** in 86% yield under these reaction conditions (entry 1). In addition to styrene **2b** having

Table 2. Scope of the Nickel-Catalyzed Hydroalkynylation of Styrenes[a]



entry	styrene	time (h)	product	yield (%)[b]
1 2[d]	 **(2a)**	6	 **(3a)**	86 78
3 4[d]	 **(2b)**	6 5	 **(3b)**	95 97
5 6[d]	 **(2c)**	24 20	 **(3c)**	86 80
7	 **(2d)**	13	 **(3d)**	84
8[c]	 **(2e)**	36	 **(3e)**	87
9	 **(2f)**	6	 **(3f)**	95
10	 **(2g)**	6	 **(3g)**	90
11	 **(2h)**	24	 **(3h)**	67
12	 **(2i)**	20	 **(3i)**	56
13	 **(2j)**	96	 **(3j)**	43
14 15[d]	 **(2k)**	6 11	 **(3k)**	93 98

[a] Reactions were performed with an excess (3.0 equiv) of styrenes on a 0.3 mmol scale in toluene (2.0 M) in the presence of Ni(cod)$_2$ (3.0−5.0 mol %) with PMePh$_2$ (P/Ni ratio = 4/1). [b] Isolated yields. [c] 5 mol % of Ni catalyst. [d] The reaction were performed with an excess (1.2−1.5 equiv) of styrenes under otherwise identical reaction conditions. See the Supporting Information for details.

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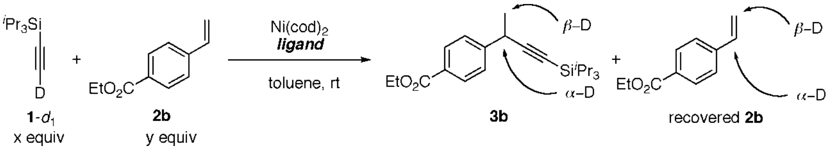
Table 3. Hydroalkynylation of *p*-Ethoxycarbonylstyrene with Deuterated Triisopropylsilylacetylene **1**-d_1[a]



							3b			**recovered 2b**		
entry	ligand	*x*	*y*	% catalyst loading	time/h	% conversion[b]	% yield[c]	% D[c]	α–D:β–D[c,d]	% yield[c]	% D[c]	α-D/β-D[c,d]
1	PMePh$_2$	1	10	10	4	>95	99	49	1:>99	92	3	3:97
2	PBu$_3$	1	10	10	24	>95	90	31	2:98	89	6	2:98
3	PMePh$_2$	1.2	1	3	3	45	44	95	1:99	55	34	3:97
4	PBu$_3$	1.2	1	3	9	38	37	103	1:99	58	70	3:97

[a] See the Supporting Information for the experimental details. [b] Conversion of **1**-d_1 (entries 1 and 2) or **2b** (entries 3 and 4). [c] Determined by ^{1}H NMR. [d] Determined by ^{2}H NMR.

electron-withdrawing substituents at the *p*-position (entry 3), those having electron-donating *p*-substituents such as methoxy and methyl groups afforded the corresponding hydroalkynylation products in high yields (entries 5 and 7). In spite of using the low-valent nickel catalyst, the *p*-chloro group of **2e** survived with these reaction conditions (entry 8). It should be noted that carbonyl groups, which could have undergone the alkynylation, were tolerable (entries 9 and 10). Moreover, *m*-ethynyl-substituted styrene underwent the hydroalkynylation at the C=C bond, with minor formation of the product in which the triple bond underwent the hydroalkynylation (entry 11). The hydroalkynylation could also be applied to *o*-substituted styrenes. *o*-Methylstyrene and *o*-divinylbenzene afforded the corresponding products in moderate yields (entries 12 and 13). In the reaction of divinylbenzene, no double addition product was detectable in the reaction mixture. The 1-naphthyl derivative, in contrast, showed high reactivity, resulting in the formation of hydroalkynylation product in high yield (entry 14). Instead of using excess styrenes, use of a small excess (1.2−1.5 equiv) of the silylacetylene also afforded good yields (entries 2, 4, 6, and 15).

In a previous report on the nickel-catalyzed hydroalkynylation of 1,3-dienes, we proposed a reaction mechanism involving the formation of (alkynyl)(hydride)nickel species, the H−Ni bond of which undergoes insertion of the C=C bond in a highly regioselective manner. To obtain insight into the reaction mechanism of the present reaction, we carried out the hydroalkynylation with 2-deuterio-labeled triisopropylsilylacetylene.

Triisopropylsilylacetylene-d_1 (**1**-d_1) was reacted with 10 equiv of styrene **2b** in the presence of Ni/PMePh$_2$ catalyst at room temperature (Table 3, entry 1). The reaction was complete after 4 h, giving hydroalkynylation product **3b** and recovered **2b** in 99% and 92% yields, respectively. In **3b**, deuterium was incorporated exclusively at the β-position (α/β = 1:>99) as judged by ^{1}H and ^{2}H NMR. It should be remarked that deuterium incorporation was also observed in the recovered styrene **2b** albeit in low deuterium content (3% D). This H−D exchange in the starting material may be responsible for the observed moderate (49% D) deuterium incorporation into the product **3b**. A similar deuterium incorporation into both product and starting material was observed in nickel-catalyzed hydrocyanation of styrenes, in which reductive elimination was proposed as the rate-determining step.[9] Our observation strongly suggests that our hydroalkynylation system also proceeds through the rate-determining reductive elimination step. This assumption is also supported by reaction of **1**-d_1 with **2b** in the presence of PBu$_3$ as a ligand, resulting in less deuterium incorporation into product **3b** with more D-incorporation into styrene **2b** (entry 2). This result also suggests that the observed higher catalytic activity of PMePh$_2$-based catalyst may be attributed to more facile reductive elimination than PBu$_3$-based one. A more pronounced difference in deuterium incorporation between PMePh$_2$ and PBu$_3$ was observed, when reactions of a small excess of **1**-d_1 with **2b** were stopped before going to completion (38−45% conversion of **2b**) (entries 3 and 4). In both reactions, we observed high deuterium incorporatin to the product because less H−D exchanges in **1**-d_1 would take place under the modified reaction conditions. The two ligands showed quite different profiles of the deuterium incorporation into the starting styrene. Much more H−D exhange in **2b** (70%) was observed for the PBu$_3$-based catalyst than the PMePh$_2$-based one (34%), suggesting again that the latter facilitated the reductive elimination step.

Deuterium incorporation into the vinyl group was also observed in the reaction of *p*-methoxystyrene (**2c**), which gave very little hydroalkynylation product **3c** (<5% conversion) (Scheme 1). 50% deuterium incorporation into the β-position of *p*-methoxystyrene (**2c**) was observed after 7 h at room temperature.

These results suggest that the present hydroalkynylation involves a reversible insertion−β-hydride elimination step (Scheme 2). Oxidative addition of the *sp*-C−H bond of silylacetylene to the Ni(0) species gives intermediate **A**, whose Ni−H bond undergoes regioselective insertion of the

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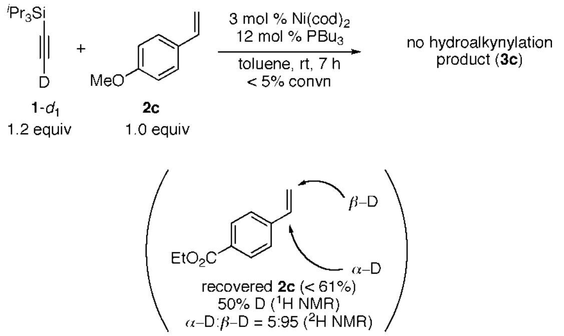
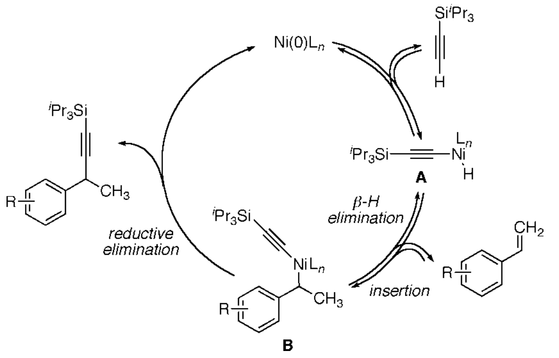
Scheme 1. Reaction of *p*-Methoxystyrene with Deuterated Triisopropylsilylacetylene **1**-d_1



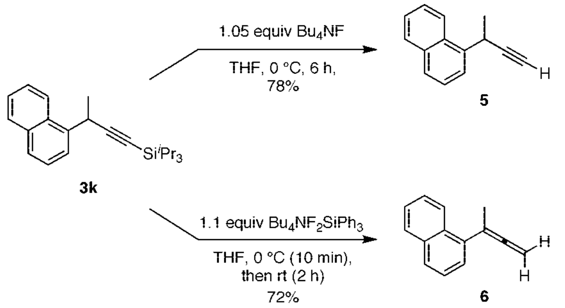
C═C bond of styrenes to give intermediate **B**. In cases where no product is formed, the intermediate **B** reverts to intermediate **A** through β-hydride elimination, leaving deuterium at the β-position of styrene. In the productive system, the kinetic barriers for the reductive elimination (forward) and β-hydride elimination (backward) from **B** are comparable, leading to the formation of the product as well as deuterated styrene. These results suggest that the reductive elimination step can be the rate-determining step in the catalytic cycle and that PMePh$_2$ may lower the barrier for this step.[3]

The products could be converted to a useful synthetic intermediate by removal of the TIPS group (Scheme 3).

Scheme 2. Plausible Reaction Mechanism of the Hydroalkynylation of Styrenes



Scheme 3. Desilylation of Hydroalkynylation Product **3k**



Treatment of **3k** with tetrabutylammonium fluoride in THF (1.0 M) afforded the desilylated terminal alkyne **5** in 78% yield. On the other hand, treatment of **3k** with tetrabutylammonium triphenylsilyldifluoride[10] selectively afforded allene **6** in 72% yield.

In summary, we have demonstrated the regioselective hydroalkynylation of styrenes with a variety of functional groups using an improved nickel catalyst system with the PMePh$_2$ ligand. The catalytic cycle may involve reductive elimination as one of the slowest steps. Further studies on improvement of the catalyst system, expansion of the reaction scope, and synthetic applications are now being undertaken in this laboratory.

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Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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