

## Nickel-Catalyzed, Regio- and Stereoselective Hydroalkynylation of Methylene-cyclopropanes with Retention of the Cyclopropane Ring, Leading to the Synthesis of 1-Methyl-1-Alkynylcyclopropanes

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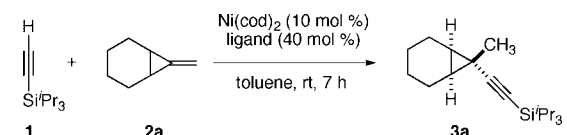
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Much interest has been focused on the reactivities of methylene-cyclopropanes (MCPs) in association with their increasing utilization as versatile reactants in organic synthesis.<sup>1</sup> Their high reactivity generally arises from the high strain of the three-membered ring, thus leading usually to ring opening of the three-membered ring in a variety of transformations.<sup>2</sup> In fact, most transition-metal-catalyzed reactions of MCPs are accompanied by cleavage of either the distal or proximal C–C bond, making it difficult to use MCPs as the starting materials for syntheses of cyclopropane derivatives. It seems to be highly desirable to develop new catalytic reactions of MCPs in which the three-membered ring is retained.

There are, however, a certain number of ring-retaining catalytic reactions of MCPs, including C–C<sup>3</sup> and C–heteroatom<sup>4</sup> bond formations. In a quite recent example, the *o*-C–H bond of pyridyl-substituted benzene adds to the C=C bond of MCPs in a highly regioselective manner.<sup>5</sup> The organic (i.e., phenyl) group adds to the methylene carbon atom of MCPs, leading to the new synthesis of substituted cyclopropane derivatives. It is highly attractive to explore new C–H additions to MCPs for the synthesis of cyclopropane derivatives that are otherwise inaccessible.<sup>6</sup> In this paper, we report our new finding on nickel-catalyzed regio- and stereoselective hydroalkynylation of MCPs, in which the alkynyl group is selectively introduced to the internal carbon atom to give alkynylcyclopropane derivatives.<sup>7</sup>

In the course of our ongoing research project on the nickel-catalyzed hydroalkynylation of the C=C bond,<sup>8</sup> we attempted reactions of triisopropylsilylacetylene (**1**) with MCPs, a class of compounds in which we also have a research interest.<sup>9</sup> In the presence of a Ni(cod)<sub>2</sub> complex with various tertiary phosphine ligands, hydroalkynylation of the cyclohexane-fused MCP **2a** proceeded at room temperature in moderate to good yields.<sup>10</sup> We found some interesting aspects of the reaction: (1) the three-membered ring was retained; (2) introduction of the alkynyl group took place at the internal carbon atom of the C=C bond, leading to the formation of a quaternary carbon center in the cyclopropane ring; and (3) the alkynyl group was introduced to the cyclopropane ring from the less sterically hindered face, giving one stereoisomer exclusively. The reaction yields were dependent on the phosphine ligand used. While PBu<sub>3</sub>, which showed the highest catalytic activity in the hydroalkynylation of 1,3-dienes,<sup>8a</sup> exhibited only moderate activity (Table 1, entry 1), PMe<sub>3</sub> afforded much better yields (entry 2). Bulkier trialkylphosphines resulted in much lower yields (entries 3 and 4). In contrast to the poor yield with PMe<sub>2</sub>Ph (entry 5), we found that PMePh<sub>2</sub> and PEtPh<sub>2</sub>, which we have established as the highest-yielding ligands in the hydroalkynylation of styrenes,<sup>8b</sup> recorded the highest catalytic activity for the MCP hydroalkynylation (entries 6 and 7). It should be noted that the hydroalkynylation was always accompanied by MCP-to-diene rearrangement to form vinylcyclohexene.<sup>3b</sup> This is the major reason that the reaction needs an excess of MCP. Because the reaction using

**Table 1.** Optimization of Phosphine Ligands in the Nickel-Catalyzed Hydroalkynylation of MCP **2a**<sup>a</sup>

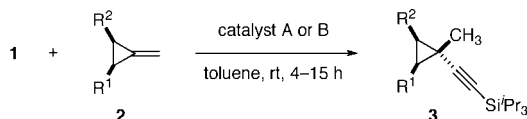


entry	ligand	% yield <sup>b</sup>
1	PBu <sub>3</sub>	41
2	PMe <sub>3</sub>	71
3	PCy <sub>3</sub>	<5
4	P <sup>t</sup> Bu <sub>3</sub>	<5
5	PMe <sub>2</sub> Ph	42
6	PMePh <sub>2</sub>	84
7	PEtPh <sub>2</sub>	86 <sup>c</sup>

<sup>a</sup> **1** (0.10 mmol), **2a** (0.20 mmol), Ni(cod)<sub>2</sub> (0.010 mmol), and triorganophosphine (0.040 mmol) were stirred in toluene (0.15 mL) at room temperature for 7 h. <sup>b</sup> GC yields (entries 1–5) or NMR yields (entries 6 and 7). <sup>c</sup> An inseparable byproduct (<5%) was also formed.

PEtPh<sub>2</sub> also gave a small amount (<5% as judged from GC integration) of a byproduct that was not separable from **3a** by silica gel column chromatography, we chose PMePh<sub>2</sub> for further reaction development. It should be noted that use of less sterically hindered alkynes such as 1-hexyne and phenylacetylene resulted in their oligomerization, as observed in the reported catalytic hydroalkynylation reactions.

Further adjustment of the reaction conditions revealed that use of less catalyst afforded the product in higher yield, as exemplified by the reaction of **2a** using 1 mol % nickel catalyst (Table 2, entry 1). Cycloheptane-fused MCP **2b** also provided the corresponding adduct **3b** in good yield (entry 2). It should be noted, however, that the corresponding cyclopentane-fused MCP did not give the product at all. Reactions of monosubstituted MCPs similarly proceeded in the presence of nickel catalysts. Although the Ni(cod)<sub>2</sub>-derived catalyst worked efficiently, cleaner reaction was realized with a different catalyst precursor, NiCl<sub>2</sub>(dme) (dme = 1,2-dimethoxyethane), with the use of Zn powder as a reductant. Although the yields were comparable for these catalyst systems, formation of the inseparable byproduct in a small quantity could be suppressed by using the COD-free catalyst precursor (entries 3 and 4). Under these reaction conditions, MCPs bearing alkyl chains with functionalities such as silyl ether, benzyl ether, pivaloyl ester, and chlorine provided the corresponding products **3d–h** in high yields with high regio- and stereoselectivity (entries 5–9). A remarkable difference in the catalytic activities of the two catalyst systems was apparent in the reaction of phenyl-substituted MCPs. Thus, **2i** underwent hydroalkynylation in high yield in the presence of the NiCl<sub>2</sub>(dme)-based catalyst, while no product was detected at all in the Ni(cod)<sub>2</sub>-catalyzed reaction (entries 10 and 11). The same catalyst system was also effective in hydroalkynylation of *p*-methoxyphenyl derivative **2j** (entry 12). The triisopropylsilyl group of the hydroalkynylation products **3** was readily removed by treatment with TBAF in THF (see the Supporting Information).

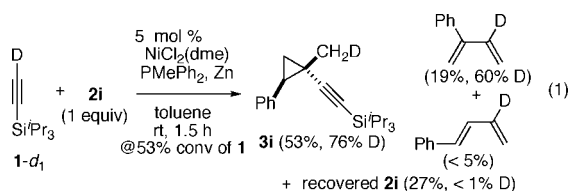
**Table 2.** Nickel-Catalyzed Hydroalkynylation of Methylene-cyclopropanes<sup>a</sup>

catalyst A: Ni(cod)<sub>2</sub> (1 mol %), PMePh<sub>2</sub> (2 mol %)  
 catalyst B: NiCl<sub>2</sub>(dme) (2 mol %), PMePh<sub>2</sub> (6 mol %), Zn (20 mol %)

entry	2 (R <sup>1</sup> , R <sup>2</sup> )	catalyst	product	% yield
1	<b>2a</b> ((CH <sub>2</sub> ) <sub>4</sub> )	A	<b>3a</b>	85
2	<b>2b</b> ((CH <sub>2</sub> ) <sub>5</sub> )	A	<b>3b</b>	84
3 <sup>b</sup>	<b>2c</b> (CH <sub>2</sub> CH <sub>2</sub> Ph, H)	A	<b>3c</b>	79
4		B	<b>3c</b>	84
5	<b>2d</b> (CH <sub>2</sub> CH <sub>2</sub> OTBS, H)	B	<b>3d</b>	92
6	<b>2e</b> ((CH <sub>2</sub> ) <sub>4</sub> OTBS, H)	B	<b>3e</b>	89
7	<b>2f</b> ((CH <sub>2</sub> ) <sub>4</sub> OBn, H)	B	<b>3f</b>	78
8	<b>2g</b> ((CH <sub>2</sub> ) <sub>4</sub> OPiv, H)	B	<b>3g</b>	94
9	<b>2h</b> ((CH <sub>2</sub> ) <sub>4</sub> Cl, H)	B	<b>3h</b>	83
10	<b>2i</b> (Ph, H)	A	<b>3i</b>	0
11		B	<b>3i</b>	89
12 <sup>c</sup>	<b>2j</b> ( <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> , H)	B	<b>3j</b>	87

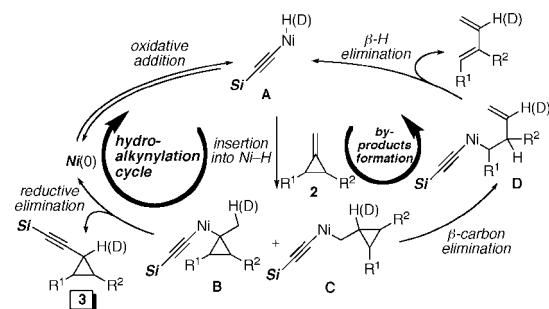
<sup>a</sup> **1** (0.30 mmol) and **2** (0.90 mmol) in toluene (0.3 mL) were reacted at room temperature in the presence of catalyst A [Ni(cod)<sub>2</sub> (3.0 μmol), PMePh<sub>2</sub> (6.0 μmol)] or catalyst B [NiCl<sub>2</sub>(dme) (6.0 μmol), PMePh<sub>2</sub> (18 μmol), Zn powder (0.060 mmol)]. <sup>b</sup> Using 0.5 mol % Ni. <sup>c</sup> Using 40 mol % Zn.

To clarify the reaction mechanism, deuterated triisopropylsilylacetylene (**1-d**<sub>1</sub>) was reacted with MCP **2i** (eq 1):<sup>8b</sup>



At 53% conversion of **1-d**<sub>1</sub>, no deuterium incorporation into the recovered **2i** was observed. In addition to product **3i**, in which the methyl group was selectively monodeuterated, careful inspection of the reaction mixture allowed us to identify as byproducts 1- and 2-phenyl-1,3-butadienes in which the 3-positions were selectively deuterated.

A plausible reaction pathway is shown in Scheme 1. The most probable route may involve the formation of alkynylnickel(II) hydride **A**, whose formation has been postulated in previous nickel catalyses.<sup>8,11</sup> Insertion of MCPs into the Ni–H bond gives regioisomeric intermediates **B** and

**Scheme 1.** Possible Reaction Pathways (Si = <sup>t</sup>Pr<sub>3</sub>Si)

**C.** Intermediate **B** undergoes reductive elimination, giving hydroalkynylation product **3**. Intermediate **C** affords **D** via β-carbon cleavage of the three-membered ring, leading to the formation of rearranged dienes in which the deuterium atoms are introduced at the 3-position in the labeling experiment. The fact that no deuterium was incorporated into the recovered **2i** indicates that the insertion of the MCP into the Ni–H bond is irreversible.

This new catalytic reaction may be attractive because the product retains stereodefined cyclopropane rings with formation of the quaternary stereogenic carbon centers. Expansion of the reaction scope and application to asymmetric synthesis are now being undertaken in this laboratory.

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

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