

## Iridium complex-catalyzed method for the construction of a quaternary carbon center $\alpha$ to allene

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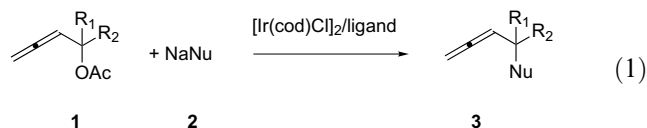
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**Abstract**—[Ir(cod)Cl]<sub>2</sub>/dppe-catalyzed allylic alkylation of 1,1-disubstituted-2,3-butadienyl acetates gives a product bearing a quaternary carbon center  $\alpha$  to allene in high yield.

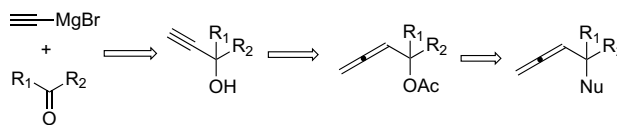
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The development of methods for the construction of all-carbon-substituted quaternary carbon centers is an important challenge in modern organic synthesis,<sup>1</sup> since such quaternary carbon centers are found in a diverse range of natural products. Transition metal complex-catalyzed reactions such as the Michael reaction,<sup>2</sup> Diels–Alder reaction,<sup>3</sup> and allylic alkylation<sup>4</sup> have been reported to be efficient for the construction of quaternary carbon center. However, new catalytic methods are still needed to expand the reaction scope and selectivity. We previously reported that a  $\pi$ -allyl iridium intermediate was useful for the construction of a quaternary carbon center, that is, iridium complex-catalyzed allylic alkylation of 1,1-disubstituted-2-propenyl acetates gave products bearing a quaternary carbon center in high yields.<sup>5</sup> We extended this chemistry to the reaction of 1,1-disubstituted-2,3-butadienyl acetates (Eq. 1). In this communication, we report an efficient method for constructing a quaternary carbon center  $\alpha$  to allene. Since a wide variety of 1,1-disubstituted-2,3-butadienyl acetates are easily obtained from 1,1-disubstituted-2-propyn-1-ols by Crabbé's method,<sup>6</sup> our method is useful for the synthesis of various allenes bearing a quaternary carbon center (Scheme 1). Synthetic transformation of allenes<sup>7</sup>

should lead to such compounds as useful building blocks bearing a quaternary carbon center.



The reaction of 1-(1,2-propadienyl)cyclohexyl acetate (**1a**; R<sub>1</sub>=R<sub>2</sub>=(CH<sub>2</sub>)<sub>5</sub>-) with diethyl sodiomalonate (**2a**) in the presence of a catalytic amount of [Ir(cod)Cl]<sub>2</sub> and ligand gave **3aa**. Product **3aa** arose from alkylation at the carbon substituted with an acetoxy group. A quaternary carbon center  $\alpha$  to allene could be constructed. No product was obtained from alkylation at the central or terminal carbon of allene. The ligand that was added had a substantial effect on the yield of the product. The effects of the ligand and iridium complexes were examined. The results are summarized in Table 1. Among the ligands surveyed, dppe gave the best result. The reaction was completed in 1 h under refluxing THF and gave **3aa** in 85% yield (entry 2).<sup>8</sup> The reaction at room temperature decreased the yield of **3aa** (entry 3).



Scheme 1.

**Keywords:** Quaternary carbon center; Iridium; Allylic alkylation; Allene; Nucleophilic substitution.

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**Table 1.** Effect of catalyst<sup>a</sup>

Entry	Ir complex	Time/h	Yield of <b>3aa</b> / <sup>b</sup>
1	[Ir(cod)Cl] <sub>2</sub> /dppm	1	67
2	[Ir(cod)Cl] <sub>2</sub> /dppe	1	85
3 <sup>c</sup>	[Ir(cod)Cl] <sub>2</sub> /dppp	20	57
4	[Ir(cod)Cl] <sub>2</sub> /dppp	1	74
5	[Ir(cod)Cl] <sub>2</sub> /dppb	1	73
6	[Ir(cod)Cl] <sub>2</sub> /dpph	4	60
7	[Ir(cod)Cl] <sub>2</sub> /1,2-bis(diphenylphosphino)ethylene	4	63
8	[Ir(cod)Cl] <sub>2</sub> /1,2-bis(diphenylphosphino)benzene	2	62
9	[Ir(cod)Cl] <sub>2</sub> /dppf	2	70
10	[Ir(cod)Cl] <sub>2</sub> /PPh <sub>3</sub>	2	60
11	[Ir(cod)Cl] <sub>2</sub> /PPh <sub>2</sub> Me	3	77
12	[Ir(cod)Cl] <sub>2</sub> /P(OPh) <sub>3</sub>	17	62
13	[Ir(cod)Cl] <sub>2</sub> /P(OEt) <sub>3</sub>	3	66
14	[Ir(cod)OMe] <sub>2</sub> /dppe	1	83
15	[Ir(cot) <sub>2</sub> Cl] <sub>2</sub> /dppe	1	83
16 <sup>d</sup>	[Ir(cod) <sub>2</sub> ]BF <sub>4</sub> /dppe	1	87

<sup>a</sup> A mixture of **1a** (2 mmol), NaCH(CO<sub>2</sub>Et)<sub>2</sub> (4 mmol), Ir complex (0.04 mmol), ligand (P/Ir = 2), and THF (10 mL) was stirred under refluxing THF.

<sup>b</sup> Yields were isolated yields based on **1a**.

<sup>c</sup> At room temperature.

<sup>d</sup> [Ir(cod)<sub>2</sub>]BF<sub>4</sub> (0.08 mmol).

**Table 2.** Effect of nucleophile

Entry	Nucleophile	Time/h	Product	Yield/ <sup>b</sup>
1	<b>2a</b> ; Nu=CH(CO <sub>2</sub> Et) <sub>2</sub>	1	<b>3aa</b>	85
2	<b>2b</b> ; Nu=CHAc(CO <sub>2</sub> Et)	2	<b>3ab</b>	78
3	<b>2c</b> ; Nu=CH(CO <sub>2</sub> <i>tert</i> -Bu) <sub>2</sub>	3	<b>3ac</b>	61
4	<b>2d</b> ; Nu=CMe(CO <sub>2</sub> Et) <sub>2</sub>	1	<b>3ad</b>	70

<sup>a</sup> A mixture of **1a** (2 mmol), NaNu (4 mmol), [Ir(cod)Cl]<sub>2</sub> (0.04 mmol), dppe (0.08 mmol), and THF (10 mL) was stirred under refluxing THF.

<sup>b</sup> Yields were isolated yields based on **1a**.

Increasing the methylene length between two phosphorous atoms in the ligand decreased the yield of **3aa** (entries 2, 4–6). With PPh<sub>3</sub>, the same yield was obtained as with dpph (entry 10). Although P(OPh)<sub>3</sub> was the most efficient ligand in iridium complex-catalyzed allylic substitution,<sup>5</sup> P(OPh)<sub>3</sub> was less efficient than dppe in this reaction (entry 12). Based on these results, we examined the catalytic activity of several iridium complexes with dppe (entries 14–16). The product was obtained in nearly identical yields.

The reaction of **1a** with various stabilized carbon nucleophiles was examined. The results are summarized in

**Table 2.** With all nucleophiles, alkylation at the carbon substituted with an acetoxy group took place exclusively. Ethyl sodioacetoacetate could be used for the reaction (entry 2). The yield of the product was 78%. Nucleophiles **2c** and **2d**, which are sterically more crowding nucleophiles than **2a**, slightly decreased the yield of the product (entries 3 and 4). Bis(1,1-disubstituted-2,3-butadienyl)malonate or acetoacetate was not obtained at all.

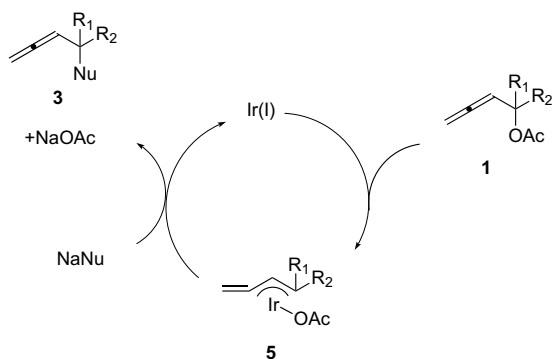
We examined the reaction of a series of 1,1-disubstituted-2,3-butadienyl acetates with diethyl sodiomalonate (**2a**) in the presence of a catalytic amount of [Ir(cod)Cl]<sub>2</sub>/dppe. The results are summarized in **Table 3**. Substrate **1b** in which a phenyl group is  $\alpha$  to allene, smoothly reacted with **2a** to give **3b** in 74% yield (entry 1). Similarly, **1c** in which a phenyl group is apart from allene reacted with **2a** to give **3c** in 73% yield (entry 2). When **1d**, bearing a 2-furyl group, was used as a substrate, the yield was slightly decreased (entry 3). Nucleophilic substitution of alkyl chloride with **2a** can compete the reaction, but the catalyzed reaction proceeded preferentially, that is, alkylation at the carbon substituted with an acetoxy group took place exclusively (entry 4). An alkene functionality was tolerated in the reaction.

**Table 3.** Allylic alkylation of **1b–j** with **2a**<sup>a</sup>

Entry	Substrate	Time/h	Product	Yield/ <sup>b</sup>
1	<b>1b</b> ; R <sub>1</sub> = Me, R <sub>2</sub> = Ph	3	<b>3b</b>	74
2	<b>1c</b> ; R <sub>1</sub> = Me, R <sub>2</sub> = PhCH <sub>2</sub> CH <sub>2</sub>	2	<b>3c</b>	73
3	<b>1d</b> ; R <sub>1</sub> = Me, R <sub>2</sub> = (2-Furyl)CH <sub>2</sub> CH <sub>2</sub>	1	<b>3d</b>	60
4	<b>1e</b> ; R <sub>1</sub> = Me, R <sub>2</sub> = ClCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	2	<b>3e</b>	65
5	<b>1f</b> ; R <sub>1</sub> = Me, R <sub>2</sub> = Me <sub>2</sub> C=CHCH <sub>2</sub> CH <sub>2</sub>	2	<b>3f</b>	76
6	<b>1g</b> ; R <sub>1</sub> = Me, R <sub>2</sub> = Me <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub>	1	<b>3g</b>	74
7	<b>1h</b> ; R <sub>1</sub> = Me, R <sub>2</sub> = <i>n</i> -Pentyl	2	<b>3h</b>	77
8	<b>1i</b> ; R <sub>1</sub> = Et, R <sub>2</sub> = <i>n</i> -Pentyl	2	<b>3i</b>	67
9	<b>1j</b> ; R <sub>1</sub> = R <sub>2</sub> = -(CH <sub>2</sub> ) <sub>6</sub> -	2	<b>3j</b>	61
10	<b>1k</b> ; R <sub>1</sub> = R <sub>2</sub> = -(CH <sub>2</sub> ) <sub>7</sub> -	4	<b>3k</b>	42

<sup>a</sup> A mixture of **1** (2 mmol), NaCH(CO<sub>2</sub>Et)<sub>2</sub> (4 mmol), [Ir(cod)Cl]<sub>2</sub> (0.04 mmol), dppe (0.08 mmol), and THF (10 mL) was stirred under refluxing THF.

<sup>b</sup> Yields were isolated yields based on **1**.



Scheme 2.

Product **3f** was obtained in 76% yield (entry 5). The reaction of an ethyl group-substituted substrate **1i** with **2a** gave the product in a slightly decreased yield compared to that of a methyl group-substituted substrate **1h** (entries 7 and 8). This may be due to a steric effect. The reaction of 1-(1,2-propadienyl)cycloheptyl acetate (**1j**) with **2a** gave **3j** in 61% yield (entry 9). The size of the ring affected the yield of the product. The reaction of **1k**, an eight-membered ring, gave the alkylation product in 42% yield together with 1-(1,2-propadienyl)cyclooctene (**4**) in 42% yield (entry 10). 1,2-Elimination of **1k** gave a conjugated allene during alkylation.

A possible mechanism is outlined in Scheme 2. Oxidative addition of **1** gives 1-methylene-3,3-disubstituted  $\pi$ -allyl iridium intermediate **5**.<sup>9</sup> Nucleophilic attack at the disubstituted allylic terminus gives the product **3**. When the substrate was **1j**, conjugated allene **4** was obtained along with the alkylation product **3j**. Conjugated allene **4** is formed by  $\beta$ -hydride elimination from intermediate **5**.<sup>10</sup> Diethyl sodiomalonate (**2a**) acted as a base to induce  $\beta$ -hydride elimination.

In conclusion, we have developed a new and general method for the construction of a carbon quaternary carbon center  $\alpha$  to allene. The reaction using a heteroatom nucleophile will give a product bearing a heteroatom-substituted quaternary carbon center. Studies on this reaction are underway in our laboratory.

**Experimental procedure.** A flask was charged with [Ir(cod)Cl]<sub>2</sub> (26.9 mg, 0.04 mmol) and dppe (31.9 mg, 0.08 mmol). The flask was then evacuated and filled with argon. 5.0 mL of THF was added to the flask, 1-(1,2-propadienyl)cyclohexyl acetate (**1a**; 360 mg, 2.0 mmol) were added with stirring. In a separate flask, diethyl malonate (640 mg, 4.0 mmol) was added to a slurry of sodium hydride (96 mg, 4 mmol) in 5.0 mL of THF. The resulting clear solution was added dropwise to the former flask by a syringe, and the combined mixture was stirred for 1 h under refluxing THF. The progress of the reaction was monitored by GLC. After **1a** was consumed, the reaction mixture was partitioned between ether and water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were concentrated in vacuo. The

residue was purified by column chromatography (*n*-hexane/AcOEt = 98/2) to give **3aa** (477 mg, yield 85%).

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- Diethyl 1-(1,2-propadienyl)cyclohexylpropanedioate (**3aa**). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.26 (t, *J* = 7.1 Hz, 6H), 1.43–1.60 (m, 8H), 1.80–1.83 (m, 2H), 3.42 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 4H), 4.74 (d, *J* = 6.8 Hz, 2H), 5.36 (t, *J* = 6.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz)  $\delta$  14.0 (2C), 22.1 (2C), 25.8, 34.1 (2C), 40.1, 60.8 (2C), 61.5, 76.6, 95.0, 167.7 (2C), 208.3. Anal. Calcd for C<sub>16</sub>H<sub>24</sub>O<sub>4</sub>: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.33; H, 8.65.
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