

# Iridium-catalyzed double incorporation reaction of *N*-benzylmaleimide to styrene via *ortho*-C–H bond activation, initiated by precoordination of the double bond of styrene to iridium

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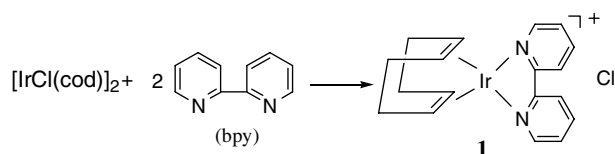
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Received 7 April 2005; revised 23 April 2005; accepted 27 April 2005

**Abstract**—Reaction of styrene with *N*-benzylmaleimide in the presence of  $[\text{IrCl}(\text{cod})]_2$  (5 mol%) and bpy (10 mol%) in an autoclave (1 MPa of Ar) at 150 °C for 18 h stereoselectively led to the formation of a new cyclic product. The structure of the product suggests that a novel iridium-catalyzed double incorporation reaction takes place via a metallacyclopentane formed after *ortho*-C–H activation.

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Styrene having an aromatic double bond with conjugated extranuclear unsaturation provides an active diene system capable of undergoing the Diels–Alder reaction. Reaction of styrene with maleic anhydride, however, gave only a copolymer.<sup>1</sup> Transition metal-mediated cycloaddition reactions,<sup>2</sup> to our knowledge, are scarcely found in which styrene directly participates. By considering the rapidly developing progress in the area of transition metal-catalyzed C–H bond activation via intramolecular coordination, especially assisted by a variety of directing groups such as imines, pyridines, and esters,<sup>3</sup> we can expect the *ortho*-C–H bond activation of styrene and the sequential C–C bond formation provided that an appropriate metal can precoordinate to the olefinic moiety of styrene. Iridium complexes have recently been reported to be effective for the reactions, involving intra- and/or intermolecular C–H activation and sequential insertion of alkenes.<sup>4</sup> Then, the reaction of styrene with *N*-benzylmaleimide was investigated as a possible [4 + 2] reaction system in the presence of cationic iridium complex **1**, produced in situ from  $[\text{IrCl}(\text{cod})]_2$  and 2,2′-bipyridine (bpy) (Scheme 1).<sup>5</sup> We disclose herein the first example of iridium-catalyzed double incorporation reaction of *N*-benzylmaleimide



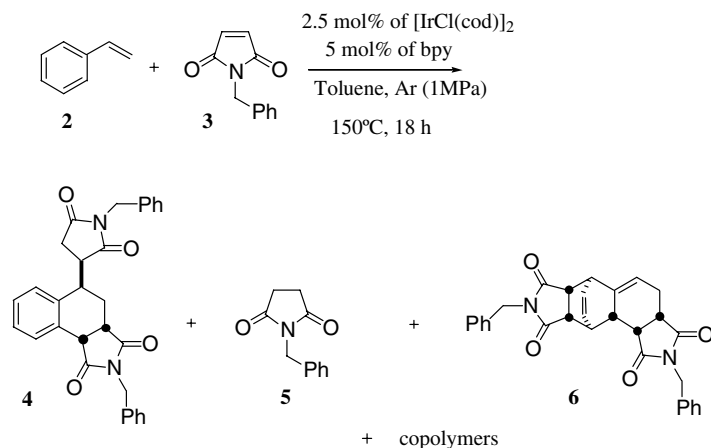
Scheme 1.

to styrene via C–H bond activation, initiated by precoordination of iridium to olefin.<sup>6</sup>

Preliminary reactions in toluene were performed with styrene **2** and *N*-benzylmaleimide **3** in a 5:1 molar ratio (2 mmol scale of styrene) in the presence of  $[\text{IrCl}(\text{cod})]_2$  (2.5 mol%) with bpy (5 mol%) as a bidentate ligand at 100 °C for 18 h under Ar atmosphere. The initial result, however, was miserable to give unknown polymeric products with recovery of a large amount of the starting materials. When the reaction was carried out in a stainless autoclave at 150 °C for 18 h under Ar atmosphere (1 MPa), a novel compound **4**<sup>7</sup> (31%) was first obtained with compounds, **5** (6%) and **6**<sup>7</sup> (3%) (Scheme 2). Product **4**, constituted of one **2** and two **3**, found to be a single stereoisomer. The entire condensation process to **4** might be to proceed in a regio- and stereoselective manner. Reduction of **3**–**5** suggests the intervention of Ir–H intermediates.<sup>8</sup> The minor product **6** is apparently formed via the Diels–Alder reaction twice. Thermal reaction of **2** and **3** (1:1 ratio) at 150 °C for 18 h under Ar (1 MPa) led to the formation of polymeric products

**Keywords:** Iridium-catalyzed double incorporation reaction; C–H bond activation; Precoordination to olefin.

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Scheme 2.

without any isolation of **4–6**. Reaction in the presence of only  $[\text{IrCl}(\text{cod})]_2$  merely gave a small amount of **5** so that the involvement of **bpy** in the catalyst precursor **1** is essential for achieving an actual catalyst,<sup>9</sup> which is presumably activated by releasing the *cod* ligand during the reaction process. Furthermore, when the reaction was conducted without **2**, the starting **3** was almost recovered with a small amount of **5** along with minute quantities of copolymer. After these experiments, ratios of **2** and **3** with ranges of reaction temperature and time were surveyed in order to optimize the reaction conditions (Table 1). When the reaction temperature was lowered from 150 °C to 100 °C, the yield of **4** was reduced and the formation of **6** was not observed (entry 2). Reaction of **2** and **3** in a 1:1 ratio led to improvement of the yield of **4** up to 63 % for 3 days and the formation of **6** was relatively limited (entries 3 and 4). The reaction path to **6** can be considered to be discrete from the major path to **4** because the ratios of products, **4** and **6**, are consequently independent of the reaction conditions. Additionally, the use of  $[\text{RhCl}(\text{cod})]_2$ , instead of  $[\text{IrCl}(\text{cod})]_2$ , did not give any **4** although the starting **3** was consumed as to lead to unknown products with copolymers.

On the basis of these results, the following catalytic cycles involving two different reaction pathways for the formation of **4** and **6**, as depicted in Scheme 3, were proposed. The major route to **4** can be explained, as follows. Coordination of cationic iridium **1** to the

relatively electron-rich double bond of styrene, compared with that of *N*-benzylmaleimide, makes the sequential reactions possible after the release of the *cod* ligand (**7**:16e). At the position  $\alpha$  to the tethered olefin, activation of the *ortho*-C–H bond takes place by oxidative addition to the coordinatively unsaturated Ir center, leading to a hydride intermediate **8** (16e). Coordination of the iridium intermediate **8** to *N*-benzylmaleimide allows to the first insertion of the double bond into the Ir–H bond via **9** to give alkylated intermediate **10**, followed by intramolecular migration of the resulting alkyl group to the iridium-coordinated double bond to afford metallacycle **11**.<sup>10</sup> The next step involves the second insertion of *N*-benzylmaleimide into the Ir–C bond of **11** to give sequential metallacycle **13** via **12** (16e) as to furnish the final product **4**. This key step results in a completely *endo*-stereoselective manner, as evidenced by the product stereochemistry. Thus, the iridium-catalyzed double incorporation reaction can be formulated. The minor route to **6** can be explained, as follows. Substrates, **2** and **3**, undergo the formal metal-catalyzed [4 + 2] cycloaddition,<sup>11</sup> as illustrated by **14**. Then, metallacycle intermediate **15**, having an isolated double bond and a conjugated diene, is formed. The intermediate undergoes the following Diels–Alder reaction with **3** to give **6** with perfect stereocontrol, accompanied by reductive elimination. The iridium cation species can be recycled in the above catalytic cycles.

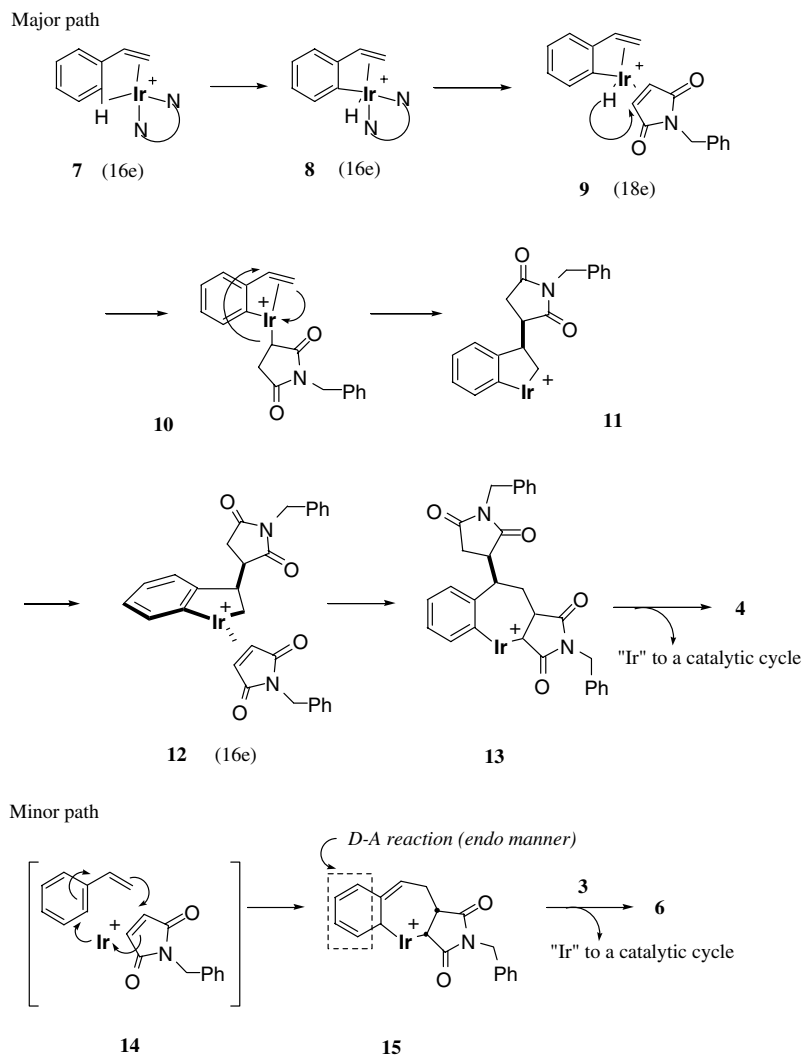
The reaction was successfully carried out as to prepare carbocycle adducts, branching a succinimide moiety at the  $\alpha$  position to the aromatic ring with a range of styrene congeners (Table 2). The yields as a whole, however, are prone to be lower owing to the formation of considerable amounts of copolymers by thermal reactions, which might be enhanced by the electron density induced by the substituents in styrene congeners. However, reaction with 4-nitrostyrene did not work as to give **4**. Stereoselective control is maintained even in reaction of  $\alpha$ -methylstyrene, in which a quaternary carbon is formed at the  $\alpha$  position (entry 1). Conversely, the  $\beta$ -substituents in styrene congeners were demonstrated to prevent the formation of the corresponding desired

**Table 1.** Iridium-catalyzed double incorporation reaction of *N*-benzylmaleimide to styrene via C–H bond activation (Scheme 2)<sup>a</sup>

Entry	2/3	Conditions with <b>1</b> in toluene	Yield <sup>b</sup> (%)		
			<b>4</b>	<b>5</b>	<b>6</b>
1	5:1	Ar/150 °C/18 h	31	6	3
2	5:1	Ar/100 °C/18 h	22	3	0
3	1:1	Ar/150 °C/18 h	47	7	2
4	1:1	Ar/150 °C/3 d	63	21	3

<sup>a</sup> Reactions were carried out in a stainless autoclave with stirring under Ar (1 MPa).

<sup>b</sup> <sup>1</sup>H NMR yields based on *N*-benzylmaleimide were determined after short-path silica gel column chromatography.



Scheme 3. Proposed reaction mechanism.

**Table 2.** Major products obtained in iridium-catalyzed double incorporation reaction of styrene congeners and *N*-benzylmaleimide<sup>a</sup>

Entry	Styrene congeners	Major products (% yield) <sup>b</sup>
1		 16 (13)
2		 17 (6)
3		 18 (35)

**Table 2 (continued)**

Entry	Styrene congeners	Major products (% yield) <sup>b</sup>
4		 19 (25)
5		No desired product
6		 20 (42)

<sup>a</sup> Reactions of styrene congeners and *N*-benzylmaleimide in a 1:1 molar ratio were run with [IrCl(cod)]<sub>2</sub> (2.5 mol%) and bpy (5 mol%) at 150 °C for 18 h in toluene under Ar (1 MPa) unless otherwise noted.

<sup>b</sup> Isolated yields.

products (entries 2 and 5). Their steric and electronic properties presumably encumber the formation of the important intermediate, for example, an analog of metallacycle **11** in Scheme 3. The desired product **20** was also obtained in reaction of the substrate involving a naphthyl moiety (entry 6).

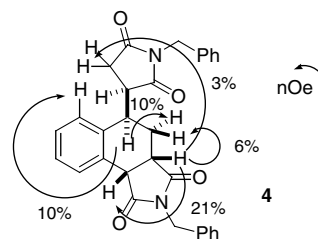
In summary, a novel iridium-catalyzed double incorporation reaction of *N*-benzylmaleimide to styrene was found. The cationic iridium complex **1** has the ability, as a catalyst precursor, to activate the *ortho*-C–H bond of styrene after the precoordination of the metal center to the olefinic moiety and to enable the subsequent reactions. Styrene congeners also gave good results in the catalytic transformation with some limitations. The almost complete stereoselection with respect to the entire transformation might provide a versatile methodology for the construction of a novel skeleton like **4**.

### Acknowledgement

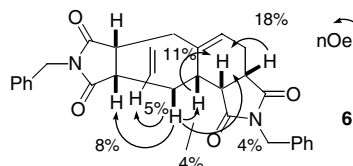
We thank a Grant-in-Aid for Scientific Research of Japan Society for the Promotion of Science.

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- The corresponding reaction using maleic anhydride was also investigated to give different products, which were not identified, compared with the case of *N*-benzylmaleimide.
- Compound **4**: mp 92 °C.



IR: 1770.3, 1699.9  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.74 (d, 1H,  $J = 7.8$ ), 7.34–7.23 (m, 11H), 6.92 (t, 1H,  $J = 7.8$ ), 6.70 (d, 1H,  $J = 7.8$ ), 4.65 (ABq, 2H,  $J = 14.3$ ,  $\nu = 18.3$ ), 4.64 (ABq, 2H,  $J = 14.3$ ,  $\nu = 20.0$ ), 3.94 (d, 1H,  $J = 9.0$ ), 3.50 (ddd, 1H,  $J = 2.2$ , 2.9, 4.2), 3.18 (ddd, 1H,  $J = 5.6$ , 9.0, 9.7), 3.12 (ddd, 1H,  $J = 2.9$ , 5.6, 9.3), 2.69 (dd, 1H,  $J = 9.3$ , 18.0), 2.24 (dd, 1H,  $J = 5.6$ , 18.0), 2.21 (ddd, 1H,  $J = 2.2$ , 5.6, 13.6), 1.94 (ddd, 1H,  $J = 4.2$ , 9.7, 13.6).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  178.2, 178.0, 175.8, 175.3, 135.5, 135.3, 134.7, 130.6, 129.5, 128.9 ( $\times 2$ ), 128.7 ( $\times 4$ ), 128.6 ( $\times 2$ ), 128.0 ( $\times 2$ ), 127.8, 127.7, 127.3, 44.1, 42.8, 42.6, 42.5, 38.0, 36.6, 31.6, 29.5. Anal. Calcd for  $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_4$ : C, 75.29; H, 5.48; N, 5.85. Found: C, 75.48; H, 5.49; N, 5.91. Compound **6**: mp 94 °C.



IR: 1771.3, 1697.0  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.29–7.21 (m, 10H), 5.68 (dd, 1H,  $J = 2.4$ , 7.1), 5.57 (dd, 1H,  $J = 5.4$ , 8.1), 5.11 (dd, 1H,  $J = 5.6$ , 7.8), 4.51 (s, 2H), 4.46 (ABq, 2H,  $J = 14.4$ ,  $\nu = 46.1$ ), 3.73 (d, 1H,  $J = 5.6$ ), 3.40 (dd, 1H,  $J = 2.4$ , 6.1), 3.22 (dd, 1H,  $J = 8.8$ , 9.0), 3.03 (ddd, 1H,  $J = 1.9$ , 5.8, 8.6), 2.88–2.80 (m, 3H), 2.33 (d, 1H,  $J = 8.8$ ), 2.03 (ddd, 1H,  $J = 2.4$ , 5.6, 15.1).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  178.5, 177.2, 177.1, 177.0, 140.5, 135.6, 131.9, 129.1 ( $\times 3$ ), 128.8, 128.5 ( $\times 2$ ), 128.4 ( $\times 2$ ), 128.3 ( $\times 2$ ), 127.8, 127.7, 117.4, 45.6, 43.8, 42.8, 42.4, 42.3, 40.5, 40.3, 35.7, 23.0. Anal. Calcd for  $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_4$ : C, 75.29; H, 5.48; N, 5.85. Found: C, 75.41; H, 5.60; N, 5.72.

- Reaction of *N*-benzylmaleimide without styrene led to the production of **5** in a low yield with a large amount of the recovered starting materials under the same conditions but we failed in our attempt to detect the dehydrogenated product, arising from the hydrogen source (*N*-benzylmaleimide).
- When 1,2-bis(diphenylphosphino)ethane (dppe) was used instead of bpy, products derived from both styrene and *N*-benzylmaleimide could not be obtained.
- (a) A similar metallacyclopentane species was isolated from the reaction of a diphenyl-iridium derivative with ethylene: Slugovc, C.; Padilla-Martínez, I.; Sirol, S.; Carmona, E. *Coord. Chem. Rev.* **2001**, 213, 129–157; (b) Gutiérrez-Puebla, E.; Monge, A.; Nicasio, M. C.; Pérez, P. J.; Poveda, M. L.; Carmona, E. *Chem. Eur. J.* **1998**, 4, 2225–2236; (c) Gutiérrez, E.; Monge, A.; Nicasio, M. C.; Poveda, M. L.; Carmona, E. *J. Am. Chem. Soc.* **1994**, 116, 791–792.
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