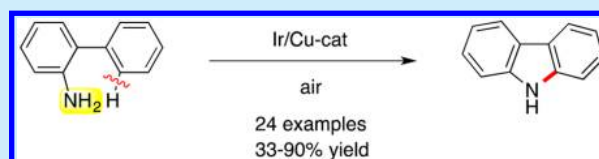


Direct Synthesis of *N*-H Carbazoles via Iridium(III)-Catalyzed Intramolecular C–H AminationChiharu Suzuki,<sup>†</sup> Koji Hirano,<sup>†</sup> Tetsuya Satoh,<sup>\*,†,‡</sup> and Masahiro Miura<sup>\*,†</sup><sup>†</sup>Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan<sup>‡</sup>JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

## S Supporting Information

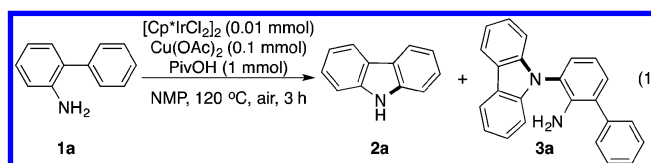
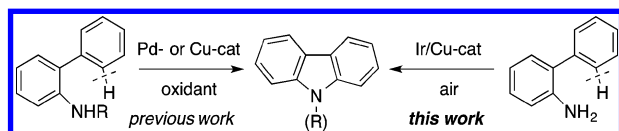
**ABSTRACT:** The iridium-catalyzed dehydrogenative cyclization of 2-aminobiphenyls proceeds smoothly in the presence of a copper cocatalyst under air as a terminal oxidant through intramolecular direct C–H amination to produce *N*-H carbazoles. A similar iridium/copper system can also catalyze the unprecedented dimerization reaction of 2-aminobiphenyl involving 2-fold C–H/*N*–H couplings.



*N*-H carbazole derivatives have been recognized as important building blocks for constructing organic materials.<sup>1</sup> Moreover, such motifs can be seen in naturally occurring as well as synthesized bioactive compounds.<sup>2</sup> Among general methods for constructing carbazole frameworks is the intramolecular C–N coupling of 2-amino-2'-halo-1,1'-biphenyls.<sup>3</sup> However, such substrates need to be prepared via complicated multistep routes. One of the simplest, most straightforward approaches to the structure is the dehydrogenative C–H/*N*–H coupling of 2'-unsubstituted 2-amino-1,1'-biphenyls.<sup>4–6</sup> Carbonyl-, sulfonyl-, alkyl-, and heteroaryl-substituted amino groups have been shown to act as good directing groups for C–H bond cleavage at the 2'-position under palladium or copper catalysis to form *N*-substituted carbazoles as dehydrogenative cyclization products (Scheme 1, previous work).<sup>4</sup> Compared to these protected

dimerization of 2-aminobiphenyl took place predominantly. These new findings are described herein.

The reaction of 2-amino-1,1'-biphenyl (**1a**) was explored to optimize the reaction conditions, as shown in the Supporting Information (Table S1). The dehydrogenative cyclization product, *N*-H carbazole (**2a**), was formed in 74% isolated yield upon treatment of **1a** (0.5 mmol) in the presence of catalytic amounts of [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (0.01 mmol, 2 mol %) and Cu(OAc)<sub>2</sub> (0.1 mmol, 20 mol %) as well as PivOH (pivalic acid, 1 mmol) under air in NMP at 120 °C for 3 h,<sup>11</sup> along with a small amount (4%) of dehydrogenative dimerization product **3a** (eq 1 and Table 1, entry 1).

Scheme 1. Carbazole Synthesis via C–H/*N*–H Coupling

amino functions, a free amino group has been less frequently utilized as a directing group because of its tight coordination to transition metals to suppress catalytic processes.<sup>7</sup> Actually, the dehydrogenative cyclization of *N*-free 2-aminobiphenyls forming *N*-H carbazoles could be conducted only under harsh conditions (>250 °C) using a Pt/C catalyst.<sup>8</sup> In the context of our studies of free amino group directed C–H functionalization,<sup>9</sup> we succeeded in finding that the step- and atom-economical synthesis of *N*-H carbazoles can be achieved by the iridium-catalyzed dehydrogenative C–H/*N*–H coupling<sup>10</sup> of 2-aminobiphenyls through free amino-directed C–H bond cleavage (Scheme 1, this work). In the presence of a copper cocatalyst, the reaction can be carried out smoothly even using air as a terminal oxidant. Under modified conditions, a unique dehydrogenative

The cyclization of 4'-substituted 2-amino-1,1'-biphenyls **1b–j** was next examined (Table 1, entries 2–10). While 2-methylcarbazole (**2b**) was obtained in 67% yield upon treatment of 4'-methyl substrate **1b** under standard conditions (conditions A), the reactions of other substrates **1c–j** needed a higher loading of [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (4 mol %, conditions B) to produce **2c–j** in reasonable yields. Only in the case with **1f** did the product yield remain moderate even under conditions B due to unidentified side reactions (entry 6). The cyclization of 3'-substituted substrates **1k–m** took place regioselectively, involving C–H cleavage at the sterically less hindered 6'-position to afford 3-substituted carbazoles **2k–m** (entries 11–13). Expectedly, the reactions of 2'-substituted **1n–p** gave exclusively 4-substituted carbazoles **2n–p** in good yields (entries 14–16). It should be noted that *N*-H 4-alkoxycarbazoles, including carvedilol and

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Table 1. Reaction of 2', 3', and 4'-Substituted 2-Aminobiphenyls 1<sup>a</sup>

| entry | 1                          | conditions | time (h) | product(s), % yield <sup>b</sup> |
|-------|----------------------------|------------|----------|----------------------------------|
|       |                            |            |          |                                  |
| 1     | 1a: R = H                  | A          | 3        | 2a: R = H, 74 <sup>c</sup>       |
| 2     | 1b: R = Me                 | A          | 6        | 2b: R = Me, 67                   |
| 3     | 1c: R = OMe                | B          | 3        | 2c: R = OMe, 76                  |
| 4     | 1d: R = F                  | B          | 3        | 2d: R = F, 72                    |
| 5     | 1e: R = Cl                 | B          | 3        | 2e: R = Cl, 76                   |
| 6     | 1f: R = Br                 | B          | 12       | 2f: R = Br, 33                   |
| 7     | 1g: R = CF <sub>3</sub>    | B          | 3        | 2g: R = CF <sub>3</sub> , 70     |
| 8     | 1h: R = CO <sub>2</sub> Me | B          | 3        | 2h: R = CO <sub>2</sub> Me, 79   |
| 9     | 1i: R = C(=O)Ph            | B          | 6        | 2i: R = C(=O)Ph, 76              |
| 10    | 1j: R = Ph                 | B          | 3        | 2j: R = Ph, 80                   |
|       |                            |            |          |                                  |
| 11    | 1k: R = Me                 | A          | 3        | 2k: R = Me, 76                   |
| 12    | 1l: R = OMe                | B          | 3        | 2l: R = OMe, 67                  |
| 13    | 1m: R = CF <sub>3</sub>    | B          | 3        | 2m: R = CF <sub>3</sub> , 82     |
|       |                            |            |          |                                  |
| 14    | 1n: R = Me                 | B          | 6        | 2n: R = Me, 81                   |
| 15    | 1o: R = OMe                | B          | 3        | 2o: R = OMe, 89                  |
| 16    | 1p: R = F                  | A          | 6        | 2p: R = F, 77                    |
|       |                            |            |          |                                  |
| 17    | 1q                         | B          | 3        | 2q, 90                           |
|       |                            |            |          |                                  |
| 18    | 1r                         | A          | 3        | 2r, 79                           |
|       |                            |            |          |                                  |
|       |                            |            |          | 2r', 10                          |

<sup>a</sup>Reaction conditions: (A) **1** (0.5 mmol), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (0.01 mmol), Cu(OAc)<sub>2</sub> (0.1 mmol), PivOH (1 mmol) in NMP (3 mL) under air at 120 °C; (B) **1** (0.25 mmol), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (0.01 mmol), Cu(OAc)<sub>2</sub> (0.05 mmol), PivOH (0.5 mmol) in NMP (3 mL) under air at 120 °C. <sup>b</sup>Isolated yield. <sup>c</sup>A small amount (4%) of **3a** was also formed.

carazolol, are of interest because of their biological activities.<sup>12</sup> Similarly, 2-(naphthalen-1-yl)aniline (**1q**) underwent cyclization to form benzo[*c*]carbazole **2q** in 90% yield (entry 17). Treatment of 2-(naphthalen-2-yl)aniline (**1r**) gave a separable mixture of benzo[*b*]carbazole **2r** and benzo[*a*]carbazole **2r'** in 79 and 10% yields, respectively (entry 18).

Under conditions B, the cyclization of 5-substituted 2-aminobiphenyls **1s–u** proceeded efficiently to give the corresponding 3-substituted carbazoles **2k**, **2s**, and **2m** in 81–90% yields (Table 2, entries 1–3). The syntheses of 1,3- and 2,6-disubstituted carbazoles **2t–v** were also achieved by the reactions of 3,5- (**1v,w**) and 4',5- (**1x**) disubstituted 2-amino-1,1'-biphenyls (entries 4–6).

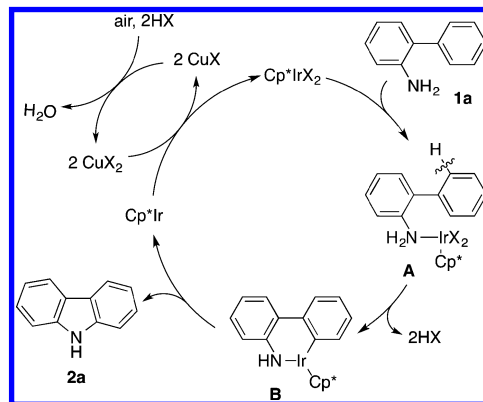
A plausible pathway for the transformation of **1a** to **2a** is illustrated in Scheme 2. Coordination of the nitrogen atom of **1a** to a Cp\*Ir(III) species gives an intermediate **A**. Then,

Table 2. Reaction of 3-, 4', and 5-Substituted 2-Aminobiphenyls 1<sup>a</sup>

| entry | 1                       | time (h) | product, % yield <sup>b</sup> |
|-------|-------------------------|----------|-------------------------------|
|       |                         |          |                               |
| 1     | 1s: R = Me              | 3        | 2k: R = Me, 82                |
| 2     | 1t: R = Cl              | 3        | 2s: R = Cl, 81                |
| 3     | 1u: R = CF <sub>3</sub> | 2        | 2m: R = CF <sub>3</sub> , 90  |
|       |                         |          |                               |
| 4     | 1v: R = Me              | 2        | 2t: R = Me, 75                |
| 5     | 1w: R = Cl              | 6        | 2u: R = Cl, 54                |
|       |                         |          |                               |
| 6     | 1x                      | 2        | 2v, 79                        |

<sup>a</sup>Reaction conditions: **1** (0.25 mmol), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (0.01 mmol), Cu(OAc)<sub>2</sub> (0.05 mmol), PivOH (0.5 mmol) in NMP (3 mL) under air at 120 °C. <sup>b</sup>Isolated yield.

Scheme 2. Plausible Mechanism for the Reaction of 1a



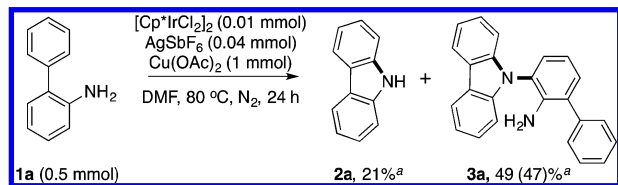
amino-directed C–H bond cleavage takes place at the 2' position to form an iridacycle intermediate **B**,<sup>13</sup> which undergoes C–N reductive elimination to afford **2a**. The Cp\*Ir(I) species generated in the last step may be reoxidized by a copper(II) cocatalyst to regenerate the iridium(III) species along with copper(I).<sup>14</sup> The latter may be reoxidized under air in the reaction system.

To obtain further mechanistic insight, the reaction of deuterated 2-aminobiphenyl [2-(NH<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>–C<sub>6</sub>D<sub>5</sub>, **1a-d<sub>5</sub>**] was examined. In the early stage (15 min), no significant D/H exchange at the 2'-position of recovered **1a-d<sub>5</sub>** as well as the 4-position of produced **2a-d<sub>4</sub>** was observed (Scheme S1, Supporting Information). Comparison of the reaction rates of **1a-d<sub>5</sub>** and nondeuterated **1a-d<sub>0</sub>** (~20 min) gave a very small KIE value (Scheme S2 and Figure S1, Supporting Information, *k<sub>H</sub>*/*k<sub>D</sub>* = 1.1). These results suggest that the amino-directed C–H bond cleavage step may be irreversible and may not be involved in the rate-determining step.

Next, we examined the dehydrogenative dimerization of **1a** to form **3a**, which was formed as a minor product in eq 1 along with **2a**. During preliminary trials, we obtained **3a** predominantly in 47% isolated yield by treatment of **1a** (0.5 mmol) in the presence

of  $[\text{Cp}^*\text{IrCl}_2]_2$  (0.01 mmol),  $\text{AgSbF}_6$  (0.04 mmol), and  $\text{Cu}(\text{OAc})_2$  (1 mmol) in DMF at 80 °C under  $\text{N}_2$  (Scheme 3).

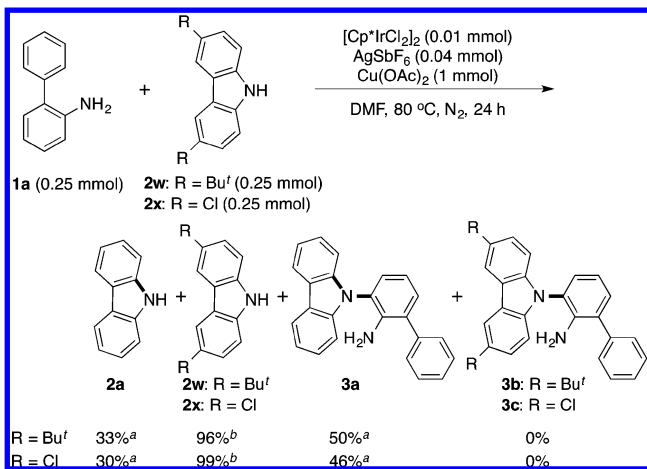
### Scheme 3. Dehydrogenative Dimerization of **1a**<sup>a</sup>



<sup>a</sup>GC yield based on the amount of **1a** used. Value in parentheses indicates isolated yield.

At the present stage, the reaction mechanism for the formation of **3a** is obscure. Recently, Patureau and co-workers reported an interesting dehydrogenative coupling of *N*-H carbazoles with secondary anilines under ruthenium catalysis to produce *N*-(2-aminophenyl)carbazoles.<sup>15</sup> In the present reaction, it would be possible for **3a** to form via a similar dehydrogenative coupling of **1a** with once formed **2a**. However, this pathway could be excluded by crossover experiments with the addition of substituted carbazoles. Thus, treatment of **1a** (0.25 mmol) with 3,6-di-*tert*-butyl- (**2w**) and 3,6-dichlorocarbazoles (**2x**) (0.25 mmol) in the presence of  $[\text{Cp}^*\text{IrCl}_2]_2$  (0.01 mmol),  $\text{AgSbF}_6$  (0.04 mmol), and  $\text{Cu}(\text{OAc})_2$  (1 mmol) in DMF at 80 °C under  $\text{N}_2$  for 24 h gave only **3a** and **2a** with almost complete recovery of **2w** and **2x**, with no crossover products **3b** and **3c** being detected (Scheme 4).

### Scheme 4. Crossover Experiments with **1a** and **2**<sup>a,b</sup>

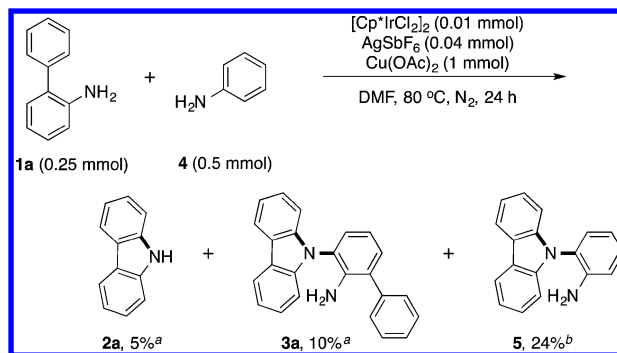


<sup>a</sup>GC yield based on the amount of **1a** used. <sup>b</sup>Recovery of **2** determined by GC.

While **1a** did not react with carbazoles **2**, **1a** was found to undergo cross-dehydrogenative coupling with another aniline molecule. Thus, **1a** coupled with aniline itself (**4**) under standard conditions to give **5** along with **3a** and **2a**, albeit with low yield (Scheme 5).

In summary, we have demonstrated that the iridium-catalyzed dehydrogenative cyclization of 2-aminobiphenyls can be conducted efficiently even under aerobic conditions. This provides a straightforward route to *N*-H carbazoles. A relevant dimerizative coupling under similar iridium catalysis has also been discovered. Work is underway toward the better understanding and applications of the unique catalysis.

### Scheme 5. Cross-Dehydrogenative Coupling of **1a** with **4**<sup>a,b</sup>



<sup>a</sup>GC yield based on the amount of **1a** used. <sup>b</sup>Value in parentheses indicates isolated yield.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, additional results, and characterization data of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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