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Direct Synthesis of *N*-H Carbazoles via Iridium(III)-Catalyzed Intramolecular C−H Amination

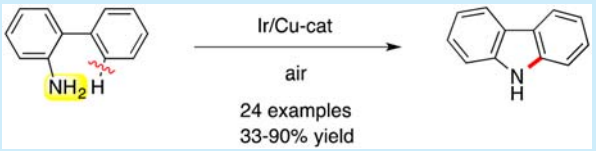
Chiharu Suzuki,[†] Koji Hirano,[†] Tetsuya Satoh,*[,†,‡] and Masahiro Miura*[,†]

[†]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[‡]JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

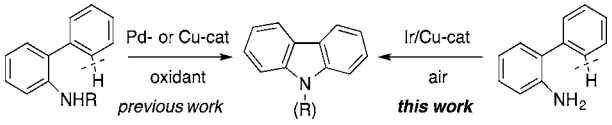
Supporting Information

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.



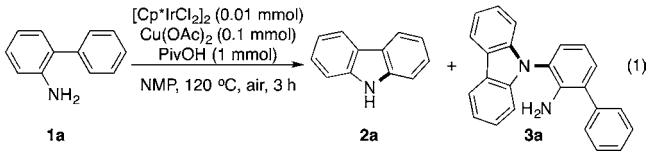
N-H carbazole derivatives have been recognized as important building blocks for constructing organic materials.[1] Moreover, such motifs can be seen in naturally occurring as well as synthesized bioactive compounds.[2] Among general methods for constructing carbazole frameworks is the intramolecular C−N coupling of 2-amino-2′-halo-1,1′-biphenyls.[3] 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.[4−6] 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).[4] Compared to these protected

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.[7] 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.[8] In the context of our studies of free amino group directed C−H functionalization,[9] 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[10] of 2-amino-biphenyls 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 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 $[Cp^*IrCl_2]_2$ (0.01 mmol, 2 mol %) and $Cu(OAc)_2$ (0.1 mmol, 20 mol %) as well as PivOH (pivalic acid, 1 mmol) under air in NMP at 120 °C for 3 h,[11] along with a small amount (4%) of dehydrogenative dimerization product **3a** (eq 1 and Table 1, entry 1).



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 $[Cp^*IrCl_2]_2$ (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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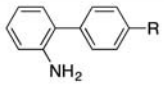
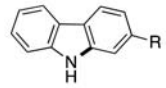
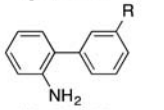
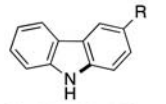
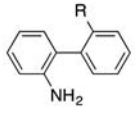
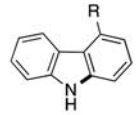
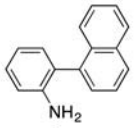
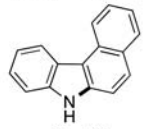
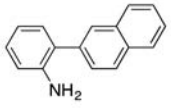
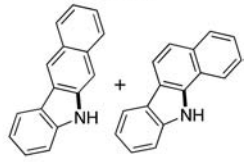
Table 1. Reaction of 2′-, 3′-, and 4′-Substituted 2-Aminobiphenyls 1[a]

entry	1	conditions	time (h)	product(s), % yield[b]
				
1	**1a**: R = H	A	3	**2a**: R = H, 74[c]
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_3	B	3	**2g**: R = CF_3, 70
8	**1h**: R = CO_2Me	B	3	**2h**: R = CO_2Me, 79
9	**1i**: R = COPh	B	6	**2i**: R = COPh, 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_3	B	3	**2m**: R = CF_3, 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

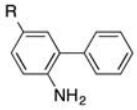
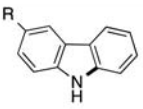
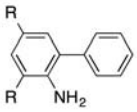
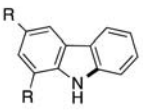
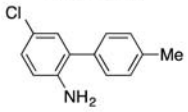
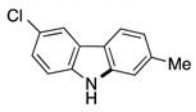
[a]Reaction conditions: (A) **1** (0.5 mmol), $[Cp^*IrCl_2]_2$ (0.01 mmol), $Cu(OAc)_2$ (0.1 mmol), PivOH (1 mmol) in NMP (3 mL) under air at 120 °C; (B) **1** (0.25 mmol), $[Cp^*IrCl_2]_2$ (0.01 mmol), $Cu(OAc)_2$ (0.05 mmol), PivOH (0.5 mmol) in NMP (3 mL) under air at 120 °C. [b]Isolated yield. [c]A small amount (4%) of **3a** was also formed.

carazolol, are of interest because of their biological activities.[12] 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).

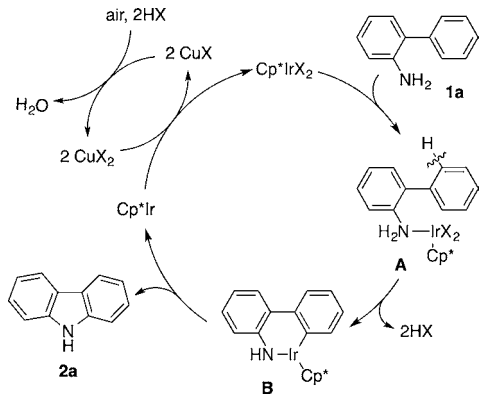
A plausible pathway for the transformation of **1a** to **2a** is illustrated in Scheme 2. Coordination of the nitrogen atom of **1a** to a Cp*-iridium(III) species gives an intermediate **A**. Then,

Table 2. Reaction of 3-, 4′-, and 5-Substituted 2-Aminobiphenyls 1[a]

entry	1	time (h)	product, % yield[b]
			
1	**1s**: R = Me	3	**2k**: R = Me, 82
2	**1t**: R = Cl	3	**2s**: R = Cl, 81
3	**1u**: R = CF_3	2	**2m**: R = CF_3, 90
			
4	**1v**: R = Me	2	**2t**: R = Me, 75
5	**1w**: R = Cl	6	**2u**: R = Cl, 54
			
6	**1x**	2	**2v**, 79

[a]Reaction conditions: **1** (0.25 mmol), $[Cp^*IrCl_2]_2$ (0.01 mmol), $Cu(OAc)_2$ (0.05 mmol), PivOH (0.5 mmol) in NMP (3 mL) under air at 120 °C. [b]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**,[13] 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).[14] The latter may be reoxidized under air in the reaction system.

To obtain further mechanistic insight, the reaction of deuterated 2-aminobiphenyl [2-(NH_2)C_6H_4–C_6D_5, **1a**-d_5] was examined. In the early stage (15 min), no significant D/H exchange at the 2′-position of recovered **1a**-d_5 as well as the 4-position of produced **2a**-d_4 was observed (Scheme S1, Supporting Information). Comparison of the reaction rates of **1a**-d_5 and nondeuterated **1a**-d_0 (~20 min) gave a very small KIE value (Scheme S2 and Figure S1, Supporting Information, k_H/k_D = 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

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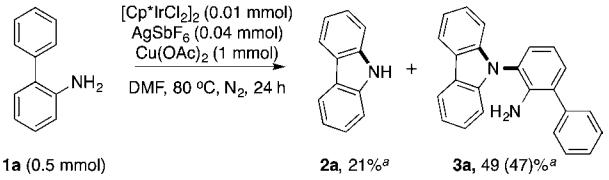
of $[Cp^*IrCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mmol), and $Cu(OAc)_2$ (1 mmol) in DMF at 80 °C under N_2 (Scheme 3).

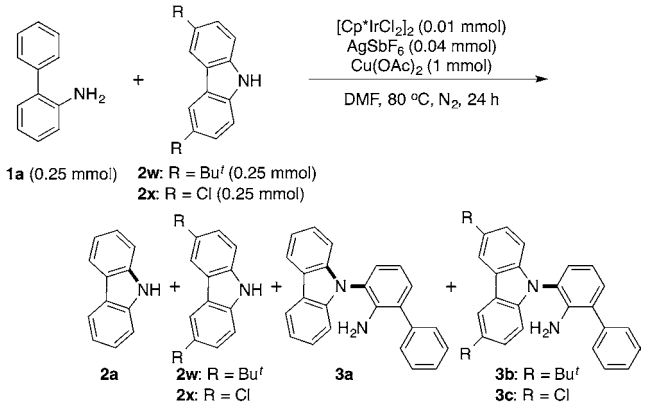
Scheme 3. Dehydrogenative Dimerization of 1a[a]



[a]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.[15] 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 $[Cp^*IrCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mool), and $Cu(OAc)_2$ (1 mmol) in DMF at 80 °C under 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[a,b]



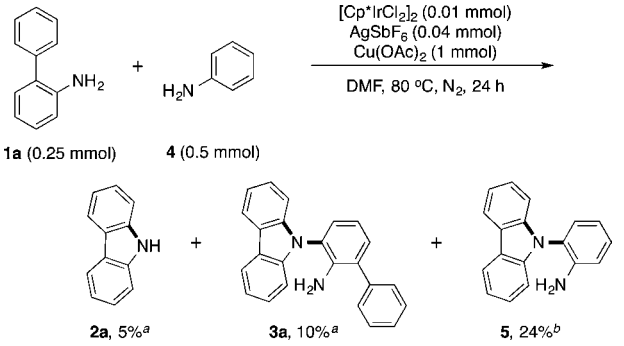
R = Bu^t	33%[a]	96%[b]	50%[a]	0%
R = Cl	30%[a]	99%[b]	46%[a]	0%

[a]GC yield based on the amount of **1a** used. [b]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[a,b]



[a]GC yield based on the amount of **1a** used. [b]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.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: satoh@chem.eng.osaka-u.ac.jp.
*E-mail: miura@chem.eng.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

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