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Amino-Directed Rh^{III}-Catalyzed C–H Activation Leading to One-Pot Synthesis of N–H Carbazoles

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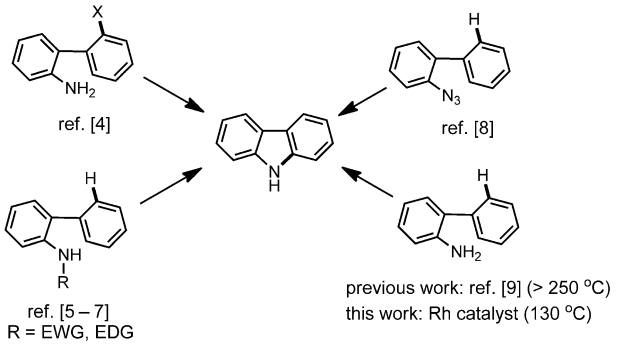
Carbazole derivatives are prominent structural motifs of many bioactive natural products, pharmaceuticals and materials,[1,2] and intense efforts have focused on the development of effective methods to synthesize these compounds.[3] Recently, intramolecular amination strategies[3g,4–7] have been reported, as shown in Scheme 1. These have included



Scheme 1. Intramolecular amination for carbazole synthesis.[4–9]

transition-metal-catalyzed C–N formation with halide-functionalized arenes;[4] metal-catalyzed or organocatalytic intramolecular C–H amination to form N-substituted carbazoles;[3g,5–7] aryl azides as substrates for N–H carbazoles via metal carbeneoid insertion,[8] thermal cyclization (550 °C),[9a] or Pt–C-catalyzed C–H activation (>250 °C) of 2-aminobiphenyl.[9b,c] To use these strategies either pre-activated substrates,[4–8] high loadings of palladium catalysts (5–20%),[3g,4–7] or very high temperatures[9] are needed. Additionally, aryl azides are not safe for a large-scale synthesis, and are usually prepared from 2-aminobiaryl compounds. Despite these successes, the direct use of non-protected 2-aminobiaryl compounds for non-protected carbazole synthesis has given only low yields (≤34%) under mild conditions with the existing catalytic system,[6] suggesting that for this type of substrates a single-component metal catalyst may not efficiently facilitate the cleavage of both C–H and N–H bonds. Thus, there is a clear need to develop a new strategy for efficient and straightforward preparation of N–H carbazoles from non-protected 2-aminobiaryl substrates without halogenation or azidation, tedious protection and deprotection processes, or the use of harsh reaction conditions.

The construction of C–N bonds from amines and organoboron reagents, assisted by Cu^{II} species, has been explored[3h,10] and, in particular, the metal-mediated C–H activation of arenes[11,12] and subsequent borylation[13,14] has been achieved. These examples offer the possibility of forming a C–N bond from a C–B bond. In the case of 2-aminobiaryl substrates, the free-amino-directed *ortho* C–H activation and subsequent C–B formation might occur. The amino group might also be sufficiently reactive to lead to intramolecular cyclization by C–N formation via a C–B bond. Herein, we report that N–H carbazoles can be directly obtained from non-protected 2-aminobiaryl starting compounds through the use of tandem $[Cp^*Rh(OTf)_2]$/$Cu(OAc)_2$ (Cp^* = pentamethylcyclopentadienyl) mediation in a one-pot reaction via a reactive C–H borylated intermediate.

Initially, the borylation of 2-aminobiaryl derivatives was studied because this type ofreaction has not been previously reported. The well-established [Ir(OMe)(cod)]/dtbpy catalytic system[13a,b] was chosen (COD = 1,5-cyclooctadiene, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine), and bis(pinacolato)diboron (B_2pin_2) was used as a boron source to form a C–B bond (Table 1). Unexpectedly, the desired compound (**2a**) was isolated in very poor yield (Table 1, entry 1). Further reaction attempts with other Ir or Rh catalysts showed little improvement (Table 1, entries 2–4, SI-Table 1 in the Supporting Information), demonstrating that the C–H activation of such a substrate is difficult under the conditions that were ideal for the reaction of other arenes.[13,14] Addition of an oxidant, such as $PhI(OAc)_2$ or $Cu(OAc)_2$, increased the yields (Table 1, entries 5 and 6, and SI-Table 2 in the Supporting Information), although the presence of dioxygen led to no product (Table 1, entry 7). However, when K_2CO_3 was added, **2a** was no longer isolated and instead, the N–H carbazole product **3a** was isolated in moderate yields (Table 1, entries 8 and 9, and SI-Table 4 in the Supporting Information). The reaction of **2a** with $Cu(OAc)_2$/K_2CO_3 was found to proceed rapidly and quantitatively to form **3a** (less than 1 hr, see SI-Table 3 in the Supporting Information), as occurred with other borylated species.[3h,10]

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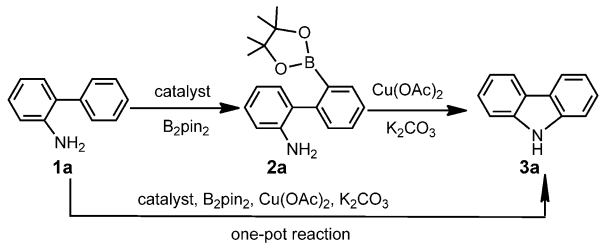
Table 1. Selected screening conditions for the synthesis of **2a** and **3a**.



	Catalyst (0.5 mol %)	Oxidant/base	T [°C]	Solvent	**2a** (**1a**) [%][d]	**3a** [%][d]
1	[Ir(OMe)(cod)]	–	80	THF	5 (>90)	–
2	[Rh(OMe)(cod)]	–	80	THF	3 (>90)	–
3	[Cp*Rh(OTf)$_2$]	–	80	THF	10 (81)	–
4	[Cp*Rh(OTf)$_2$]	–	110	toluene	15 (75)	–
5[a]	[Cp*Rh(OTf)$_2$]	$PhI(OAc)_2$	110	toluene	21 (68)	–
6[a]	[Cp*Rh(OTf)$_2$]	$Cu(OAc)_2$	110	toluene	30 (59)	–
7[a]	[Cp*Rh(OTf)$_2$]	O_2 or air	110	toluene	0 (100)	–
8[b]	[Cp*Rh(OTf)$_2$]	$Cu(OAc)_2/K_2CO_3$	110	toluene	0 (32)	55
9[b]	[Cp*Ir(OTf)$_2$]	$Cu(OAc)_2/K_2CO_3$	110	toluene	0 (45)	43
10	[Cp*Rh(OTf)$_2$][c]	$Cu(OAc)_2/K_2CO_3$	110	toluene	0 (28)	62
11[b]	[Cp*Rh(OTf)$_2$]	$Cu(OAc)_2/K_2CO_3$	130	*o*-xylene	0 (9)	80
12[b]	[Cp*Ir(OTf)$_2$]	$Cu(OAc)_2/K_2CO_3$	130	*o*-xylene	0 (38)	52
13[b]	[Ir(OMe)(cod)]	$Cu(OAc)_2/K_2CO_3$	130	*o*-xylene	0 (51)	38
14[b]	[Rh(OMe)(cod)]	$Cu(OAc)_2/K_2CO_3$	130	*o*-xylene	0 (46)	42

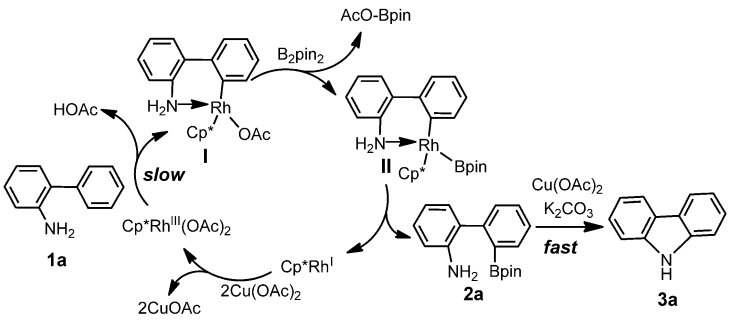
Reaction condtions: B_2pin_2 (1.0 equiv), dtbpy (1.0 mol %; appliable for Ir^I and Rh^I), 80 °C (THF), 110 °C (toluene), or 130 °C (*o*-xylene), 24 h, Ar. [a] Oxidant (2.2 equiv) or O_2 (1 atm) or air; [b] $Cu(OAc)_2$ (2.2 equiv) and K_2CO_3 (2.5 equiv); [c] catalyst (1.0 %); [d] Yield of isolated product.

These findings suggest that the C–B formation for **2a**, rather than the C–N formation for **3a**, is the rate-determining step in the one-pot reaction under the catalytic conditions used. The use of polar solvents, such as dimethylformamide (DMF) or DMSO, and other boron sources led to similar yields (SI-Table 4 in the Supporting Information). An increased loading of the Rh^{III} catalyst had no significant improvement on the yield (Table 1, entry 10). Upon elevating the temperature to 130 °C, however, the yields were remarkably increased (Table 1, entry 11 and SI-Table 4 in the Supporting Information). The use of Ir^I or Rh^I instead of Rh^{III} catalysts gave lower yields (Table 1, entries 13 and 14).

Next, the effects of electronic and steric factors of 2-aminobiaryl substrates were studied. Following a procedure for Suzuki coupling, the substituted derivatives of **1a** were prepared by using the appropriate boronic acids and 2-iodoanilines or 2-bromoanilines (see SI-5 in the Supporting Information). The resulting 2-aminobiaryl derivatives with either an electron-donating or an electron-withdrawing group (e.g., Ph, OMe, $COCH_3$, Cl, F, CF_3) on the aryl rings gave rise to the corresponding N–H carbazole products (**3a**–**3w**, Table 2) in yields of 63–93 %. In general, a substrate that contained an electron-donating group in both rings A and B (see Table 2 for labeling) led to a higher yield (e.g. **3b**, **3c** vs. **3h**, **3i**, and **3p**; **3v**, **3w** vs. **3t**, **3u**), but the yields were lower for products containing an *ortho* substituent in ring A, probably due to steric hindrance (e.g., **3b** vs. **3d**; **3e** vs. **3g**). The introduction of a fluorine unit in ring B of **1k**–**1s** did not significantly alter yields of the products **3k**–**3s**. Both electronic and steric factors may result in lower yields of **3t** and **3u**. This catalytic system is likely to be suitable for a broad range of substituted 2-aminobiaryls.

To understand the role of each compound in the formation of the N–H carbazole products, control experiments were performed (see SI-1, 2, 4, and 7 in the Supporting Information). The reaction of **1a** and B_2pin_2 mediated only by [Cp*Rh(OTf)$_2$] led to the isolation of the borylated species **2a**, demonstrating that the Rh^{III} species acts as a catalyst to drive C–H activation and C–B formation. When $Cu(OAc)_2$ was added to this reaction, the yield of **2a** was increased to 30 % from 15 % (Table 1, entries 4 and 6). The further addition of K_2CO_3 led to no formation of **2a**, but instead **3a** in a yield of 55 % (Table 1, entry 8), indicating that the addition of base assisted the conversion of **2a** to **3a**. Removal of the Rh^{III}, Cu^{II}, boron reagent, or base from the reaction mixture as shown in Table 2 led to no formation of **3a**. $Cu(OAc)_2$ played a dual role both as an oxidant to convert Rh^I back to Rh^{III}, and as the catalyst for C–N formation. Experimentally, 2 equivalents of the Cu^{II} species gave the highest yield of **3a** (SI-Table 4 int eh Supporting Information). The presence of a base was required to deprotonate N–H to promote the final C–N formation. The boron reagent B_2pin_2 was used for C–H borylation and was consumed in the reaction, as detected by ^{11}B NMR spectroscopy. Replacement of B_2pin_2 by different concentrations of $BF_3{\cdot}Et_2O$ gave no **3a**, further confirming that C–B formation played a vital role in the formation of **3a**.

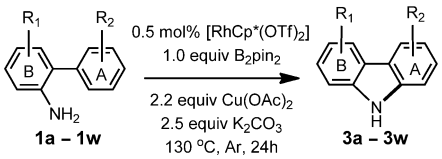
On the basis of experimental observations and previous, related mechanistic studies,[4–14] a plausible mechanism for the formation of N–H carbazoles is proposed in Scheme 2.

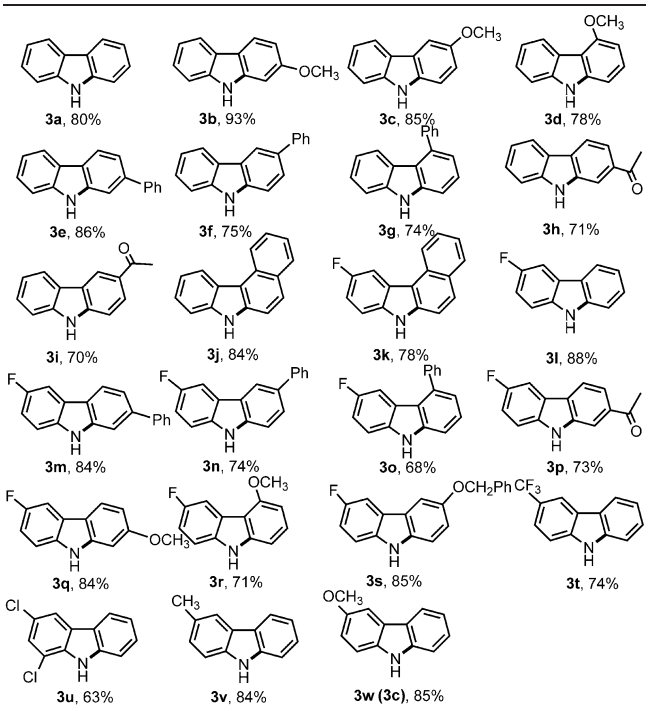


Scheme 2. Proposed mechanism for the formation of N–H carbazoles (by using **3a** as an example).

The initial amino-directed C–H activation by Rh^{III} is assumed to lead to an arylrhodium intermediate (**I**), analogous to the extensively reported, related metal-induced C–H activation of arenes.[11,12] Then, transmetalation with the diboron reagent occurs to give rise to **II** (similar examples are

Table 2. One-pot synthesis of N–H carbazoles.

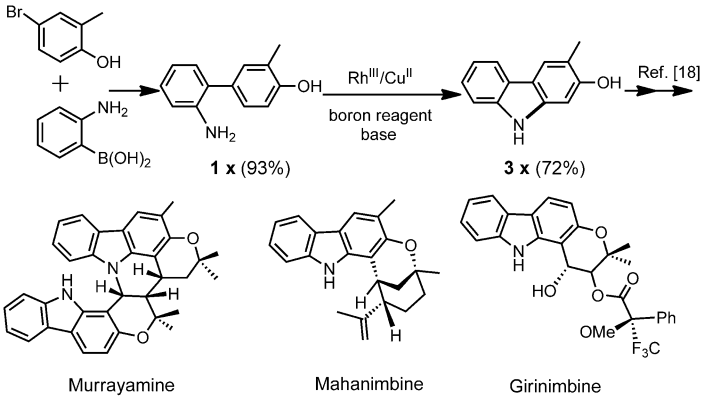




known[10a,13a,b]), followed by reductive elimination to release the borylated species **2a**, which had been isolated in the absence of either base or Cu^{II}, or of both. The resulting Rh^{I} species is re-oxidized to Rh^{III} by Cu^{II} to complete the catalytic cycle. The subsequent intramolecular cyclization of **2a** proceeds via C–B and N–H cleavage, mediated by $Cu(OAc)_2$ and K_2CO_3, to give rise to the N–H carbazole product **3a**, in a similar manner to the C–N formation from amines and organoboron reagents.[3h,10]

In this study, the low yields of the stepwise borylation to **2a** (Table 1, entries 1–6 and SI-Table 1 in the Supporting Information) might be attributed to the excess distribution of the NH_2 groups of the 2-aminobiaryl substrates around the catalyst preventing the metal from efficiently activating the C–H bond. However, in a one-pot reaction, the facile conversion of **2a** to **3a** releases the catalyst from the accumulation of **2a** and thus drives the overall reaction forwards. The boron reagent might not serve as an efficient Lewis acid in this reaction system because the interaction between B_2pin_2 and 2-aminobiphenyl is trivial, as indicated by ^1H and ^{11}B NMR data. It is worth mentioning that amine-group-directed C(sp^2)–H oxidative activation from alkylamines[15a] and arylamide[15b,c] has been reported, but free aryl-amino-directed C–H activation remains more elusive.[6,16]

This catalytic system could potentially be used for the synthesis of biologically active natural products. Girinimbines,[17] Mahanimbines[18] and Murrayamines[19] have been reported to show potent biological activity and the total syntheses of these natural carbazole alkaloids[3a,20] requires 2-hydroxy-3-methylcarbazole (**3x**) as a key precursor. With the catalytic reaction developed in this study, **3x** can be obtained in two steps with a good yield (Scheme 3, SI-5 and 6 in the Supporting Information), in contrast to existing synthetic routes that require multiple steps and give overall yields of around 35%.[20b]



Scheme 3. Synthesis of **3x**.

In summary, we have developed a synthesis of N–H carbazole products by free amino-directed, Rh^{III}-catalyzed C–H borylation and Cu^{II}-mediated ring closure of the resulting borylated anilines. This has led to the first efficient dehydrogenative cyclization of non-protected 2-aminobiaryl derivatives for the construction of non-protected carbazoles in a simple one-pot reaction with good to excellent yields. The free amine unit serves as both a directing group and a reactive group. This direct C–H amination is suitable for a broad range of substrates and has advantages over previously reported examples[3g,4–7] by using a low loading of noble metal catalyst (Rh < 0.5%) and inexpensive $Cu(OAc)_2$; thus it could prove potentially useful for the synthesis of medically important compounds.

Experimental Section

General procedure: A mixture of 2-aminobiaryl (0.5 mmol), [Cp*Rh(OTf)$_2$] (1.4 mg, 2.5 μmol), $Cu(OAc)_2$ (199.1 mg, 1.1 mmol), B_2pin_2 (127.0 mg, 0.5 mmol), and K_2CO_3 (172.4 mg, 1.25 mmol) in *ortho*-xylene (15 mL) was stirred at 130 °C under an Ar atmosphere for 24 h. After cooling, saturated, aqueous NH_4Cl (100 mL) and EtOAc (20 mL) were added. The aqueous phase was extracted with additional EtOAc (2× 10 mL). The combined organic phases were dried over Na_2SO_4 and then concentrated to give a brown oil. Further separation by column chromatography on silica gel gave the corresponding product.

Acknowledgements

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Keywords: amino-directed · boranes · C–H activation · C–N formation · homogeneous catalysis · rhodium

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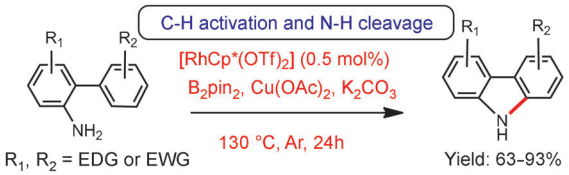
Carbazoles



One-pot synthesis: An efficient amino-directed one-pot synthesis of N–H carbazoles from unprotected 2-amino-biaryl compounds is reported. The free amino unit acts as both a directing group for ortho C–H activation and a functional group for construction of an N-heterocyclic ring (see scheme).