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Rh_2(II)-Catalyzed Synthesis of Carbazoles from Biaryl Azides

Benjamin J. Stokes, Brankica Jovanović, Huijun Dong, Kathleen J. Richert, Ryan D. Riell, and Tom G. Driver*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607

tgd@uic.edu

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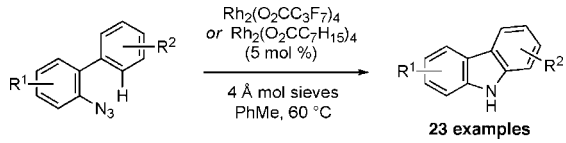

An array of carbazoles (23 examples) can be synthesized from substituted biaryl azides at 60 °C using substoichiometric quantities of $Rh_2(O_2CC_3F_7)_4$ or $Rh_2(O_2CC_7H_{15})_4$.

A long-standing goal of organic synthesis is the development of new methods that access aromatic nitrogen heterocycles,[1] such as carbazoles, because they are prevalent in important medicinal compounds and materials.[1,2] Historically, methods to access these *N*-heterocycles have relied on transformations of pre-existing functional groups, such as halides or carbonyls.[3] Such prerequisites can lead to an increased number of synthetic steps necessary to generate the starting materials. Recent efforts to circumvent this functional group manipulation have produced carbazoles through transition metal-mediated oxidative C−H bond functionalization.[4−8]

Dirhodium(II) complexes are well-known atom-transfer catalysts.[9] They are particularly effective in aliphatic C−N bond formation,[10] enabling access to nitrogen heterocycles efficiently and stereoselectively by the decomposition of sulfonyliminoiodinanes[11,12] and *N*-tosyloxycarbamates.[10c,f] Employing azides as substrates would complement these existing technologies as well as related deoxygenation methods,[13,14] as azides are easily obtained,[15] intrinsically prone to decomposition,[16,17] and produce N_2 as the only byproduct. Despite the proclivity of rhodium(II) dimers to mediate atom transfer reactions,[10] their use in the decomposition of azides is uncommon.[18,19]

We reported recently that rhodium(II) carboxylates can catalyze the intramolecular formation of C−N bonds from vinyl or aryl azides to provide indoles and pyrroles.[20] We envisioned that our method might be extended to biaryl azides for the synthesis of carbazoles. The requisite biaryl azides (**3**) were synthesized from 2-bromoaniline **1** by a Suzuki cross-coupling

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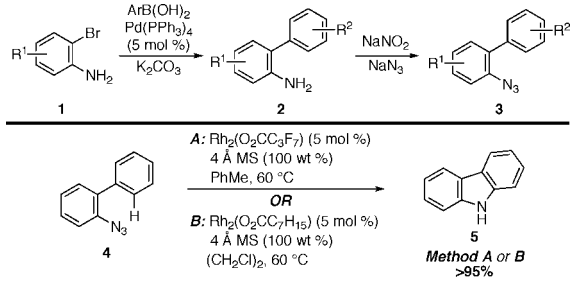
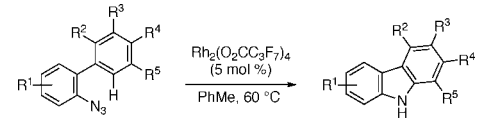
SCHEME 1. Synthesis of Biaryl Azides for Carbazole Study

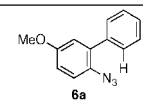
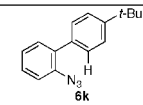
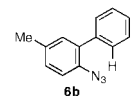
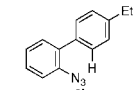
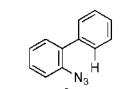
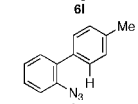
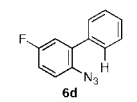
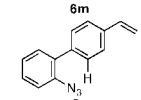
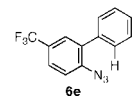
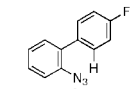
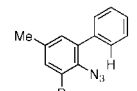
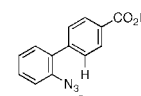
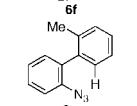
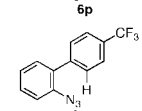
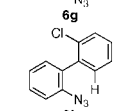
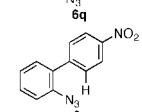
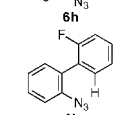
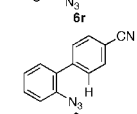
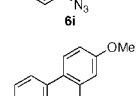
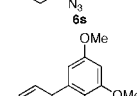


reaction[21] followed by a diazotization/azidation sequence[15,22] (Scheme 1). We found that substoichiometric quantities of rhodium(II) perfluorobutyrate or rhodium(II) octanoate efficiently generated the desired carbazole **5** from 2-azidobiphenyl (method A or B).[23] As before, crushed 4 Å molecular sieves (100 wt %) were required to achieve reproducible yields.

To examine the scope and limitations of the reaction, we tested our method on substrates, which varied the electronic and steric environments on each ring of the azidobiaryl. As shown in Table 1, electron-donating groups and electron-withdrawing groups were well tolerated for R^1 (entries 1−6). The reaction could be performed on a gram scale: 3.17 mmol of bromo-substituted biaryl azide **6f** was converted smoothly to the corresponding carbazole in 85% yield. In contrast to the nearly uniform reactivity of substrates **6a**−**f**, we found that carbazole formation depended more strongly on the electronic and steric identity of the R^2, R^3, or R^4 substituent. Electron-deficient R^2 groups (e.g., F and Cl, entries 8 and 9) were high yielding, whereas reduced conversion and yield were observed for R^2 = Me (entry 7). Both electron-donating and electron-withdrawing R^4 groups were allowed (entries 10−18). Low reaction conversion, however, was observed for biaryl azide **6m** bearing an R^4-methyl (entry 13) for reasons not apparent at this time.[24] No reaction was observed for R^4 = CN (entry 19), presumably due to nitrile coordination to the rhodium(II) catalyst.[25] Diminished reactivity was also observed for dimethoxy-substituted biaryl azide **6t** (entry 20): modest amounts of carbazole **7t** were obtained only when rhodium octanoate was employed. In general, the reaction was more efficient when a

TABLE 1. Scope and Limitations of Rhodium-Catalyzed Carbazole Formation from Biaryl Azides



entry	biaryl azide	yield (%)[a]	entry	biaryl azide	yield (%)[a]
1	 **6a**	71	11	 **6k**	72
2	 **6b**	86	12	 **6l**	87
3	 **6c**	98	13	 **6m**	44[c]
4	 **6d**	86	14	 **6n**	71
5	 **6e**	83	15	 **6o**	88[d]
6	 **6f**	85[b]	16	 **6p**	91
7	 **6g**	60[c]	17	 **6q**	91
8	 **6h**	93	18	 **6r**	91[d]
9	 **6i**	92	19	 **6s**	n.r.
10	 **6j**	82	20	 **6t**	n.r. (65)[e]

[a] Yield after flash chromatography over SiO_2. [b] Reaction performed on gram scale. [c] Remainder of material was aryl azide **6**. [d] 2 mol % of $Rh_2(O_2CC_3F_7)_4$. [e] 5 mol % of $Rh_2(O_2CC_7H_{15})_4$.

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(20) (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (b) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191. (c) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056.

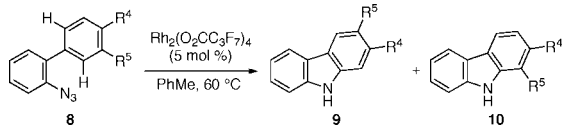
(21) For recent examples of anilines employed as substrates in the Suzuki reaction, see: (a) Miura, Y.; Nishi, T.; Teki, Y. *J. Org. Chem.* **2003**, *68*, 10158. (b) Camacho, D. H.; Salo, E. V.; Guan, Z. *Org. Lett.* **2004**, *6*, 865. (c) Wu, Y.; Li, J.; Fu, Y.; Bo, Z. *Org. Lett.* **2004**, *6*, 3485. (d) Miura, Y.; Muranaka, Y.; Teki, Y. *J. Org. Chem.* **2006**, *71*, 4786. (e) Arnold, L. A.; Kiplin Guy, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5360.

(22) (a) Smith, P. A. S.; Clegg, J. M.; Hall, J. H. *J. Org. Chem.* **1958**, *23*, 524. (b) Smith, P. A. S.; Hall, J. H. *J. Am. Chem. Soc.* **1962**, *84*, 480.

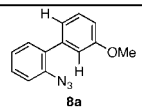
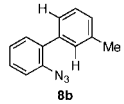
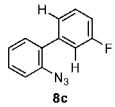
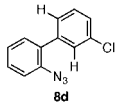
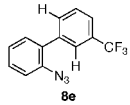
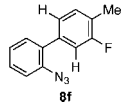
(23) See the Supporting Information for a complete description of the reaction conditions screened.

(24) Multiple attempts by several researchers with different batches of **6m** yielded the same low conversion to carbazole **7m**.

TABLE 2. Regioselectivity of Rhodium-Catalyzed Carbazole Formation from Biaryl Azides



8 9 10

entry	biaryl azide	regioselectivity (**9** : **10**)[a]	yield (%)[b]
1	 **8a**	52:48	33[a,c]
2	 **8b**	66:34	25[a,c]
3	 **8c**	89:11	65[a,c]
4	 **8d**	>95:5	82
5	 **8e**	>95:5	84
6	 **8f**	39:61	59[a,c]

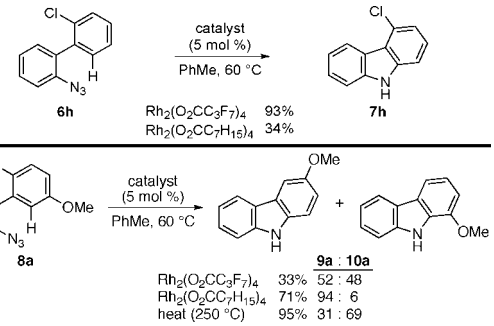
[a] As determined using ^{1}H NMR spectroscopy. [b] Yield after flash chromatography over SiO_2. [c] Remainder of reaction mixture was aryl azide **8**.

new C−N bond to an electron-deficient arene was formed (compare entry 18 to entry 20).

The lack of reactivity observed for dimethoxy-substituted **6t** motivated us to study additional substrates substituted at the 3′-position of the biaryl azide (Table 2). We discovered that both the regioselectivity and reaction conversion depended upon the electronic identity of the R^5-substituent. While reduced selectivity and conversion were observed with electron-rich aryl groups (entries 1 and 2), substrates bearing electron-withdrawing groups led to increased yields and substantially improved regioselectivities (entries 3−5). The positive effect of an electron-withdrawing R^5-substituent, however, was attenuated when an R^4-methyl group was added: exposure of biaryl azide **8f** to reaction conditions produced carbazoles **9f** and **10f** in diminished yield and with reduced regioselectivity (compare entry 6 with entry 3).

The conversion and selectivity of carbazole formation was also affected by the identity of the carboxylate ligand (Scheme 2). Switching from electron-poor $Rh_2(O_2CC_3F_7)_4$ to electron-rich $Rh_2(O_2CC_7H_{15})_4$ reduced the formation of **6h** from 93% to just 34% conversion. This decreased reactivity observed for rhodium octanoate was not general: improved conversion and regioselectivity was seen in the decomposition of the electron-

SCHEME 2. Influence of the Carboxylate Ligand on Reaction Conversion and Selectivity



rich biaryl azide **8a**. Exposure of **8a** to $Rh_2(O_2CC_3F_7)_4$ resulted in only a 33% conversion to afford a 52:48 mixture of carbazoles **9a** and **10a**. Employing $Rh_2(O_2CC_7H_{15})_4$, however, afforded a 94:6 mixture of **9a** and **10a** in 71% yield. In contrast, metal-free thermolysis of aryl azide **8a** favored the formation of the opposite carbazole, **10a** (31:69). We interpret the ability of the rhodium carboxylate catalyst to reverse the thermal regioselectivity of carbazole formation as evidence against the intermediacy of free nitrene.[17,21] The enhanced regioselectivity exhibited by $Rh_2(O_2CC_7H_{15})_4$ could be explained by the increased steric interactions between the larger octanoate ligand and the substrate to favor functionalization of the less sterically congested C−H bond.

In conclusion, we have shown that substituted carbazoles can be accessed from readily available biaryl azides using a Rh$_2$(II)-carboxylate catalyst. Quantitative mechanistic experiments that probe the relationship between the carboxylate ligand and reaction rate are underway. Future experiments are also aimed at determining the origin of regioselectivity observed for aryl azides **8**. The results of these studies will guide further method development.

Experimental Section

4-Methoxy-2-phenylaniline. In a dry 100 mL round-bottom flask, phenylboronic acid (0.400 g, 3.29 mmol, 1.3 equiv), K_2CO_3 (1.65 g, 12.0 mmol, 4.0 equiv), and $Pd(PPh_3)_4$ (0.345 g, 0.299 mmol, 0.1 equiv) were dissolved in 20 mL of toluene, 10 mL of H_2O, and 5 mL of EtOH. 2-Bromo-4-methoxyaniline (0.604 g, 2.99 mmol, 1.0 equiv) was added, and the resulting mixture was heated to 95 °C for 16 h. After cooling, the biphasic solution was diluted with 100 mL of saturated aqueous NH_4Cl and 100 mL of CH_2Cl_2 and separated. The aqueous phase was extracted with an additional 2 × 100 mL of CH_2Cl_2, and the combined organic phases were washed 1 × 100 mL of water and 1 × 100 mL of saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford a brown oil. Purification by MPLC (0:100−30:70 EtOAc/hexanes) afforded 4-methoxy-2-phenylaniline as a brown oil (0.490 g, 82%): R_f = 0.27 (20:80 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49−7.43 (m, 4H), 7.38−7.34 (m, 1H), 6.80−6.72 (m, 3H), 3.78 (s, 3H), 3.51 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.8 (C), 139.5 (C), 137.2 (C), 129.1 (CH), 128.8 (2CH), 127.3 (CH), 116.9 (CH), 115.7 (CH), 114.5 (CH), 55.8 (CH_3); IR (thin film) 3356, 2830, 1602, 1505, 1416, 1273, 1215, 1175, 1041 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{15}H_{13}ON$ (M^+) 199.0997, found 199.0998.

4-Azido-3-phenylanisole (6a). In a 20 mL scintillation vial, 4-methoxy-2-phenylaniline (0.353 g, 1.77 mmol, 1.0 equiv) was dissolved in 10 mL of HOAc and 5 mL of H_2O and chilled in an ice bath. $NaNO_2$ (0.171 g, 2.48 mmol, 1.4 equiv) was added slowly, and the resulting mixture was stirred at 0 °C for 1 h. NaN_3 (0.172

(25) The reaction mixture turned pink (from dark green) upon exposure to the azide bearing the nitrile group. Coordination of nitriles to rhodium(II) complexes induces a color change and is used to aid the purification of these complexes. See: Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Kazala, A. P.; Westrum, L. J. *Org. Synth.* **1998**, *9*, 322.

g, 2.65 mmol, 1.5 equiv) was then added slowly, and the resulting mixture was warmed to ambient temperature and stirred for 30 min. The solution was diluted with 20 mL of water and 20 mL of CH_2Cl_2 and basified by the slow addition of K_2CO_3 until bubbling ceased. The phases were separated, and the aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phases were washed 1 × 20 mL of water and 1 × 20 mL of brine. The resulting organic phase and dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford an oil. Purification by MPLC (0:100−30:70 EtOAc/hexanes) afforded azide **6a** as a yellow oil (0.313 g, 70%): R_f = 0.63 (20:80 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55−7.48 (m, 4H), 7.46−7.42 (m, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.00 (dd, J_1 = 8.5 Hz, J_2 = 3.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.9 (C), 138.2 (C), 134.9 (C), 129.7 (C), 129.5 (CH), 128.3 (CH), 127.8 (CH), 120.0 (CH), 116.6 (CH), 114.4 (CH), 55.7 (CH_3); IR (thin film) 2119, 1483 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{13}H_{11}ON_3$ (M^+) 225.0902, found 225.0900.

4-Methoxycarbazole (7a). To a mixture of 0.049 g of 4-azido-3-phenylanisole **6a** (0.217 mmol), 0.013 g of $Rh_2(O_2CC_3F_4)_4$ (0.012 mmol, 5 mol %), and 0.049 g of crushed 4 Å molecular sieves was added 0.47 mL of toluene (0.5 M). The resulting mixture was stirred at 60 °C for 16 h. The heterogeneous mixture was filtered through SiO_2, and the filtrate was concentrated in vacuo. Purification by MPLC (0:100−30:70 EtOAc/hexanes) afforded 4-methoxycarbazole **7a** as a white powder (0.031 g, 71%): mp 147−148 °C; R_f = 0.32 (20:80 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (d, J = 7.5 Hz, 1H), 7.87 (br s, 1H), 7.58 (d, J = 2.5 Hz, 1H), 7.44−7.36 (m, 2H), 7.30 (d, J = 9.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.08 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.9 (C), 140.3 (C), 134.4 (C), 125.8 (CH), 123.8 (C), 123.4 (C), 120.3 (CH), 119.1 (CH), 115.1 (CH), 111.4 (CH), 110.8 (CH), 103.2 (CH), 56.13 (CH_3); IR (thin film) 3403, 2361, 1459 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{13}H_{11}ON$ (M^+) 197.0841, found 197.0840.

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Supporting Information Available: Complete experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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