

Dirhodium(II)-Catalyzed Intramolecular C–H Amination of Aryl Azides**

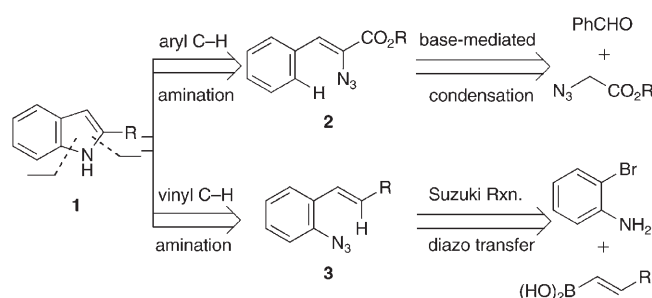
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The development of new transition-metal-catalyzed methods for selective functionalization of carbon–hydrogen bonds continues to be an active area of research.^[1] Whereas many transition-metal complexes exhibit activity,^[1] rhodium(II) dimers^[1c,2] are well established to react with α -diazo compounds^[3,4] or sulfonyliminoiodinanes^[5,6] to access metal carbenoids or nitrenoids, which can functionalize proximal aliphatic C–H bonds to form new C–C bonds or C–N bonds in a stereoselective manner. Transition-metal-mediated formation of new carbon–nitrogen bonds from vinyl or aryl C–H bonds, however, is much less common.^[7]

Azides can be employed in the amination of aromatic or vinyl C–H bonds. Thermolysis or photolysis of azides produces nitrenes,^[8,9] which react with proximal C–H bonds to form N-heterocycles.^[10] Nitrenes, however, are highly reactive and can decompose into a variety of byproducts, including amines, azobenzenes, or tars.^[8b] Whereas metal-mediated nitrogen atom transfer reactions from azides are well-known to attenuate this extreme nitrene reactivity,^[11,12] dirhodium(II) carboxylates have been rarely employed to catalyze these processes^[13–15] despite their proven utility in other related atom transfer reactions. Since azides are readily available,^[10c,16,17] their use in new transition-metal-mediated methods that create new C–N bonds is highly appealing.^[18]

We recently discovered that indoles could be generated from azidoacrylates **2** through exposure to catalytic amounts of rhodium(II) perfluorobutyrate.^[18a] Whereas this reaction exhibited a broad substrate scope, it required an α -azidomethylacetate, which restricted product formation to 2-indole-carboxylate esters.^[17c] Achievement of indole synthesis from aryl azides **3** through rhodium-catalyzed vinyl C–H bond amination would address this limitation as a broader range of aryl azides are readily available from commercial starting materials in two mild, functional group tolerant steps: palladium-catalyzed Suzuki cross-coupling of 2-bromoanilines^[19] and subsequent diazo transfer would produce **3**.^[20] The combination of this potential method with our earlier one

would enable the rhodium-catalyzed synthesis of indoles by the formation of either the aryl C–N bond (from azidoacrylates) or the creation of the vinyl C–N bond (from aryl azides; Scheme 1). As the thermal variant of this reaction, the Sundberg indole synthesis,^[8c] requires heating of the poten-



Scheme 1. Complimentary rhodium(II)-catalyzed indole syntheses.

tially explosive aryl azide and produces indole in variable yields, transition-metal-catalysis of this reaction at a reduced temperature would enhance the synthetic utility of this transformation.

Toward this goal, the potential for a transition-metal-mediated vinyl C–H bond amination reaction of **4** was investigated (Table 1). We found that the use of rhodium(II) catalysts with electron-deficient carboxylate ligands afforded promising yields and conversions (Table 1, entries 2–4). The use of 100 wt % of crushed 4 Å molecular sieves enabled the reduction of the catalyst loading to 2 mol %, and was required to produce reproducible results (Table 1, entry 3). Exposure of the aryl azide to the recovered molecular sieves did not result in any indole production. The lack of reactivity by the recovered molecular sieves indicates that rhodium is not being deposited onto the solid support to create a new heterogeneous catalyst. Whereas our earlier study identified rhodium(II) perfluorobutyrate as the only competent catalyst,^[18a] indole formation from aryl azide **4** could be mediated as well by rhodium(II) octanoate (Table 1, entry 6). With this rhodium complex, 1,2-dichloroethane was found to be the superior solvent (Table 1, entry 7). Employing other less soluble or more sterically congested rhodium(II) carboxylate or rhodium(II) lactamate complexes provided only trace indole formation (Table 1, entries 5, 8, and 9). As we observed in our previous method, no reaction was detected with other metal salts^[11] (such as Ag,^[21] Cu,^[6b] Au,^[22] Co,^[23] and Fe complexes^[24]) or Lewis (or Brønsted) acids^[25] reported to catalyze nitrenoid formation from azides or other nitrene equivalents.^[20]

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Table 1: Optimization of catalytic conditions to form 2-phenylindole.

Entry	Metal salt	mol [%]	4 Å M.S. [wt %]	Yield [%] ^[a]
1	none	n.a.	0	0
2	[Rh ₂ (O ₂ CC ₃ F ₇) ₄]	5	0	63
3	[Rh ₂ (O ₂ CC ₃ F ₇) ₄]	2	0	> 95
4	[Rh ₂ (O ₂ CCF ₃) ₄]	5	100	33
5	[Rh ₂ (OAc) ₄]	10	0	trace
6	[Rh ₂ (O ₂ CC ₇ H ₁₅) ₄]	2	100	58
7 ^[b]	[Rh ₂ (O ₂ CC ₇ H ₁₅) ₄]	2	100	> 95
8	[Rh ₂ (O ₂ CtBu) ₄]	5	0	trace
9		5	0	trace

[a] As determined by ¹H NMR spectroscopy by using CH₂Br₂ as an internal standard. [b] 1,2-Dichloroethane was employed as the solvent. M.S. = molecular sieves; n.a. = not applicable.

With the realization of an optimized procedure, the scope and limitations of this indole synthesis were investigated (Table 2). The methodology was tolerant of a variety of electronically different *para* substituents to the azide (Table 2, entries 1–6). The importance of the molecular sieve additive is illustrated in Table 2, entries 1 and 4; without molecular sieves, the yield of the process dropped precipitously. Azides with a variety of different R¹ and R² substituents were also submitted to reaction conditions to consistently provide 6- or 7-substituted indoles (Table 2, entries 7–10). If the phenyl group was moved to the α position (R⁴ group), however, the reactivity of the substrate was reduced (Table 2, entry 11). Employing rhodium perfluorobutyrate as the catalyst produced only trace indole, whereas, rhodium octanoate provided only 42 % of the indole product.

Table 2: Scope of rhodium-catalyzed indole formation.

Entry	6	R ¹	R ²	R ³	R ⁴	R ⁵	Yield [%] ^[a]
1	a	H	H	OMe	H	Ph	98 (63) ^[b]
2	b	H	H	Me	H	Ph	89
3	c	H	H	H	H	Ph	94
4	d	H	H	F	H	Ph	99 (75) ^[b]
5	e	H	H	OCF ₃	H	Ph	95 ^[c]
6	f	H	H	CF ₃	H	Ph	82
7	g	H	OMe	H	H	Ph	88
8	h	H	Me	H	H	Ph	89
9	i	H	CF ₃	H	H	Ph	89
10	j	Me	H	F	H	Ph	72 (92) ^[e]
11	k	H	H	H	Ph	H	trace ^[d] (39) ^[e]

[a] Yield of isolated product after flash chromatography on SiO₂. [b] No M.S. [c] 2 mol % [Rh₂(O₂CC₃F₇)₄]; 90 % yield. [d] 67 % recovered azide. [e] 5 mol % of [Rh₂(O₂CC₇H₁₅)₄] employed in 1,2-dichloroethane.

The importance of the identity of the R⁵ substituent on the efficiency of the C–H amination reaction prompted a more thorough study of its nature (Table 3). As long as this

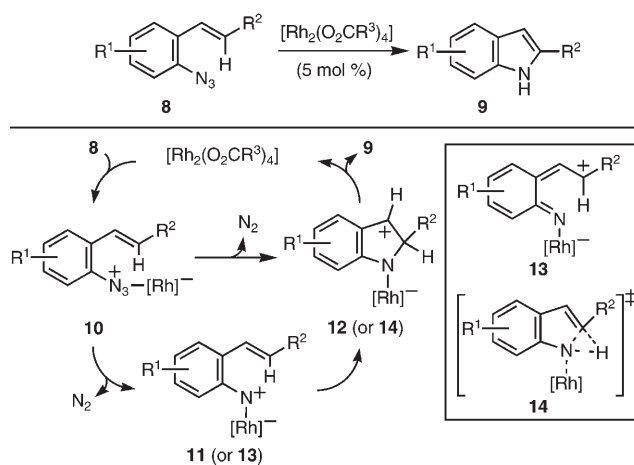
Table 3: Interrogation of the electronic influence of substituents on indole formation.

Entry	6	R ²	R ³	R ⁵	Yield [%] ^[a]
1	l	H	H	4-MeC ₆ H ₄	96
2	m	H	H	4-FC ₆ H ₄	95
3	n	H	H	3-FC ₆ H ₄	91
4	o	H	H	4-ClC ₆ H ₄	84
5	p	H	H	4-(F ₃ C)C ₆ H ₄	95
6	q	H	OMe	4-(F ₃ C)C ₆ H ₄	90
7	r	H	F	4-(F ₃ C)C ₆ H ₄	89
8	s	H	OCF ₃	4-(F ₃ C)C ₆ H ₄	91
9	t	H	CF ₃	Me	61 ^[b] (75) ^[c]
10	u	H	H	<i>n</i> -C ₆ H ₁₃	68 ^[d] (66) ^[e]

[a] Yield of product isolated after flash chromatography on SiO₂. [b] 15 % of the azide recovered. [c] 5 mol % of [Rh₂(O₂CC₇H₁₅)₄] employed in 1,2-dichloroethane; 19 % of the azide recovered. [d] Starting azide was a 98:2 mixture of *E/Z* isomers. [e] 5 mol % of [Rh₂(O₂CC₇H₁₅)₄] employed in 1,2-dichloroethane; 28 % of the azide recovered.

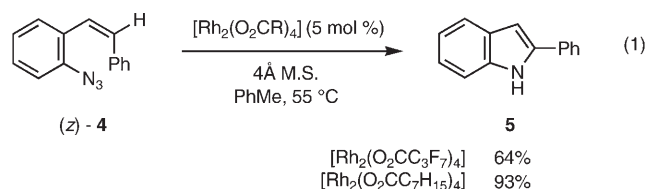
substituent was an aryl group, modulation of its electronics had little impact on the yield of the reaction (Table 3, entries 1–5). Adjusting the electronic nature of the arene, bearing the azide group, through R² or R³ substitution did not affect the yield or conversion of the reaction either (Table 3, entries 6–8). Changing the identity of the R⁵ substituent from an aryl group to an alkyl group, however, reduced both the conversion and yield (Table 3, entries 9 and 10). Rhodium octanoate proved to be a more efficient catalyst for these substrates, forming 75 % indole versus 61 % when rhodium perfluorobutyrate was employed (Table 3, entry 9).

Whereas the exact mechanism remains unclear, several different pathways could account for the indole formation (Scheme 2). Rhodium could function as a nitrogen atom transfer reagent.^[2c,6a,26] In this mechanism, coordination of the rhodium carboxylate to the α nitrogen^[27] or the terminal

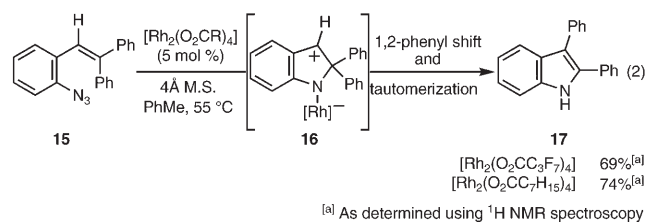

Scheme 2. Possible rhodium-catalyzed mechanisms to form 2-substituted indoles.

γ nitrogen^[28] of the azide (to form **10**) induces loss of N₂ to form nitrenoid **11** (or its resonance form **13**).^[29] Functionalization of the proximal C–H bond by **11** could occur in a stepwise fashion with C–N bond formation preceding C–H bond cleavage^[30] through **12** or through a concerted transition state (such as **14**). Alternatively, C–N bond formation could occur simultaneously with N₂ extrusion in a Schmidt-like mechanism to form **12** directly from **10**.^[31] Subsequent to the formation of **12**, a 1,5-hydride shift would produce the 1*H*-indole.^[32]

If C–N bond formation precedes C–H bond cleavage, then the *Z* isomer of **4** might be expected to form indole **5**. To test this hypothesis, (*Z*)-**4** was submitted to reaction conditions and found to afford 2-phenylindole [Eq. (1)].^[33] Higher yields (93 % versus 64 %) were obtained when [Rh₂(O₂CC₇H₁₄)₄] was employed as the catalyst. Examination of (*Z*)-**4** during the course of the reaction revealed no *E*/*Z* isomerization of the aryl azide.^[34] The comparable yields of indole formation from both (*Z*)- and (*E*)-**4** differs from the corresponding thermal reaction, which provided 2-phenylindole from (*Z*)-**4** in only 18 % yield.^[30a]



A stepwise mechanism is additionally supported by the reactivity of gem-diphenyl-substituted **15** [Eq. (2)]. Exposure of **15** to the rhodium(II) carboxylate catalyst resulted in the formation of 2,3-diphenyl indole **17**. This 2,3-phenyl shift implicates the intermediacy of cation **16**. Together with the reactivity of (*Z*)-**4**, these results suggest that indole formation occurs by a mechanism where C–N bond formation precedes N–H bond formation.^[35,36]



Dirhodium(II)-catalyzed decomposition of aryl azides was developed as a mild, functional group tolerant method for the synthesis of indoles. Future quantitative studies will probe the different reaction trends observed with rhodium(II) perfluorobutyrate and octanoate to ascertain any mechanistic differences between the two catalysts. The conclusions of these studies will be used to develop new transition-metal-mediated methods that form N-heterocycles from azides.

Experimental Section

General procedure for the synthesis of 2-arylindoles: Toluene (0.20 mL) or 1,2-dichloroethane (0.20 mL) was added to a mixture of aryl azide (0.300 mmol), [Rh₂(O₂CC₃F₇)₄] or [Rh₂(O₂CC₇F₁₅)₄] (5 mol %), and crushed 4 Å molecular sieves (100 wt %) to a final concentration of 1.5 M. The resulting mixture was heated to 60 °C. After 16 h the reaction mixture was cooled to room temperature and the heterogeneous mixture was filtered through SiO₂. The filtrate was concentrated in vacuo. Purification by using MPLC methods (EtOAc/hexanes 0:100→30:70) provided the indole as a white solid.

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