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Intramolecular C−H Amination Reactions: Exploitation of the Rh_2(II)-Catalyzed Decomposition of Azidoacrylates

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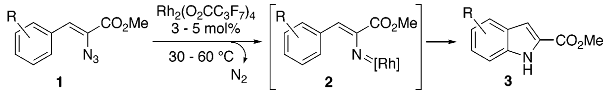
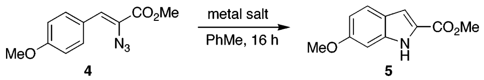
The activation of C−H bonds by dirhodium(II) carbenoids[1] and nitrenoids[2] allows access to valuable carbocycles and heterocycles efficiently and stereoselectively.[3] These reactive intermediates are most commonly accessed through the rhodium(II)-mediated decomposition of diazo compounds[4] or sulfonyliminoiodinanes.[5] While metal-mediated nitrogen atom transfer reactions from azides are well-documented,[6] the use of dirhodium(II) carboxylates has not been shown to be effective despite their proven utility in other related atom transfer reactions.[7] Although nitrenes can be formed from azides by thermolysis,[8] the high temperatures often required to promote this reaction cause safety concerns,[9] which diminish the usefulness of this method. Since azides are readily available,[10−12] the prospect of rhodium nitrenoid generation from them is highly appealing. Herein, we report a rhodium(II)-mediated C−H bond amination that transforms vinyl azides into indoles and other *N*-heterocycles (Scheme 1).[13]

Scheme 1



While a variety of metal complexes were examined to convert vinyl azide **1** to indole **3**, only dirhodium(II) carboxylates were found to be competent for indole formation (Table 1). Employing metal salts[6] (Ag,[14] Cu,[15] Co,[16] and Fe complexes[17]) or other Lewis acids known to catalyze nitrenoid chemistry from azides or other nitrene equivalents led only to recovery of **1**.[18] The activity of the rhodium catalyst is dependent upon the electronic nature of its ligands with higher yields observed with more electron-deficient carboxylates (entries 2−5). Optimal reactivity was obtained at 40 °C when rhodium(II) perfluorobutyrate was employed. The temperature of the reaction can be lowered, but higher catalyst loading is required (entry 6). Optimization of solvent revealed that toluene was superior to chlorinated or ethereal solvents.[18]

Table 1. Optimization of Catalytic Conditions



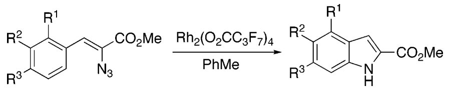
4 **5**

entry	metal salt	mol %	temp (°C)	% yield[a]
1	none	na	145	85[b]
2	$Rh_2(OAc)_4$	10	30	9
3	$Rh_2(O_2CCF_3)_4$	5	30	64
4	$Rh_2(O_2CCF_3)_4$	5	40	>95
5	$Rh_2(O_2CC_3F_7)_4$	3	40	>95
6	$Rh_2(O_2CC_3F_7)_4$	5	30	>95

[a] As determined using ^1H NMR spectroscopy. [b] After 1 h.

With the identification of the optimal reaction conditions, the scope of the reaction was investigated (Table 2).[19] The reaction tolerated substrates with both electron-donating and electron-withdrawing aryl substituents. Chemoselective formation of the indole product was observed when R^1 = Me (entry 10). For substrates containing an R^2 substituent, the major regioisomer was the 5-substituted indole, which resulted from reaction with the sterically less encumbered C−H bond (entries 13−15).

Table 2. Scope of the Rhodium-Mediated Indole Formation

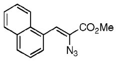
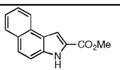
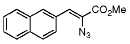
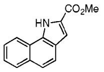
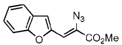
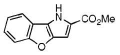
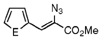
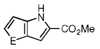
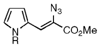
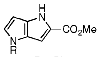


entry	R^1	R^2	R^3	mol % [Rh]	temp (°C)	% yield[a]
1	H	H	OMe	3	40	98
2	H	H	Me	5	60	88
3	H	H	*i*-Pr	5	60	91
4	H	H	*t*-Bu	5	60	71
5	H	H	H	5	60	84
6	H	H	Cl	5	60	85
7	H	H	Br	5	60	84
8	H	H	CF_3	5	60	88
9	OMe	H	H	5	60	91
10	Me	H	H	5	60	93
11	Cl	H	H	5	60	76
12	H	Cl	H	5	60	97[b]
13	H	Cl	OMe	3	40	92[c]
14	H	Br	OMe	3	40	98[d]
15	H	OMe	OMe	3	40	88[e]

[a] Isolated yield after flash chromatography over SiO_2. [b] Regioselectivity 87:13. [c] Regioselectivity 79:21. [d] Regioselectivity 92:8. [e] Regioselectivity >95:5.

In addition to indoles, a variety of aromatic *N*-heterocycles can be accessed from vinyl azides using rhodium(II) perfluorobutyrate as a catalyst (Table 3). Both 1- and 2-substituted naphthalene vinyl azides were transformed into indoles **13** and **14** (entries 1 and 2)

Table 3. Formation of *N*-Heteroaromatic Compounds

entry	substrate	mol % [Rh]	temp (°C)	product	% yield[a]
1	 **6**	3	25	 **13**	**13** 90
2	 **7**	5	60	 **14**	98[b]
3	 **8**	3	25	 **15**	91
4	 **9** E = O **10** E = S	5	60	 **16** E = O **17** E = S	**16** 79 **17** 84
5	 **11** R = Piv **12** R = Boc	5	60	 **18** R = Piv **19** R = Boc	**18** 88 **19** 94

[a] Isolated yield after flash chromatography over SiO_2. [b] Regioselectivity >95:5.

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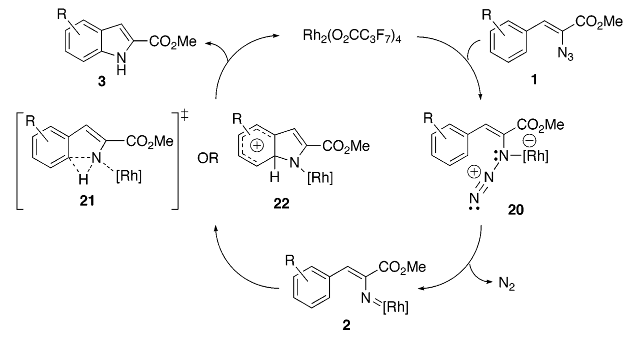
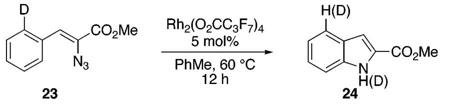
Scheme 2



though the 2-substituted naphthalene substrate required slightly harsher conditions. While 2-substituted benzofurans, furans, and thiophenes can be efficiently converted (entries 3 and 4), protection of the pyrrole nitrogen with a Piv or Boc group was necessary to access *N*-heterocycles **18** and **19** (entry 5). Presumably, the protecting group must inhibit coordination of the nitrogen to the coordinatively unsaturated rhodium catalyst.

The mechanism is believed to be similar to that proposed for the rhodium(II)-mediated C−H bond functionalization by α-diazo esters (Scheme 2).[20,21] Following this model, initial coordination of the dirhodium(II) carboxylate with the α-nitrogen of azide **1** produces **20**,[22] the presumed resting state of the catalyst.[20a] Upon rhodium nitrenoid (**2**) formation from **20**, C−N bond formation could occur by two pathways: a concerted[20] insertion of **2** into an *ortho*-C−H bond (**21**) or a stepwise[23] electrophilic aromatic substitution via arenium ion **22**. Interrogation of this step by submission of deuterium-labeled vinyl azide **23** to reaction conditions revealed a product isotope effect of 1.0 (eq 1).[24] The magnitude of the isotope effect suggests that a stepwise substitution reaction is occurring.[25] When this reaction was run to 75% completion, reisolation of the labeled vinyl azide showed no H/D exchange at the labeled *ortho*-position, indicating that C−N bond formation happened after the irreversible loss of N_2.



(1)

product isotope effect = 1.0 at 100% conversion

In conclusion, we have developed a new, mild way to access rhodium(II) nitrenoids from azides. This methodology allows rapid access to a variety of complex, functionalized *N*-heterocycles in two steps from commercially available starting materials. Currently, we are working to broaden our understanding of the unique reactivity of these azidoacrylates and to apply our mechanistic conclusions in the development of new methods that form *N*-heterocycles from azides by rhodium-mediated nitrogen atom transfer.

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Supporting Information Available: Complete ref 12, experimental procedures, spectroscopic, and analytical data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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