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Intramolecular C–H Amination Reactions: Exploitation of the Rh₂(II)-Catalyzed Decomposition of Azidoacrylates

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The activation of C-H bonds by dirhodium(II) carbenoids¹ and nitrenoids² 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 compounds⁴ 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 salts⁶ (Ag, ¹⁴ Cu, ¹⁵ Co, ¹⁶ and Fe complexes¹⁷) 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
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	MeO 4	PhMe, 16 h	MeO NH	CO₂Me
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 ₂ CCF ₃) ₄	5	30	64
4	Rh ₂ (O ₂ CCF 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 o	f the	Rhodium-Mediated	Indole	Formation
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B1		Ŗ1
R ² CO ₂ Me	Rh ₂ (O ₂ CC ₃ F ₇) ₄	R ²
R ³ N ₃	PhMe	

				mol %		
entry	R1	R ²	R ³	[Rh]	temp (°C)	% yield ^a
1	Н	Н	OMe	3	40	98
2	Н	Н	Me	5	60	88
3	Н	Н	<i>i</i> -Pr	5	60	91
4	Н	Н	t-Bu	5	60	71
5	Н	Н	Н	5	60	84
6	Н	Н	Cl	5	60	85
7	Н	Н	Br	5	60	84
8	Н	Н	CF ₃	5	60	88
9	OMe	Н	Н	5	60	91
10	Me	Н	Н	5	60	93
11	Cl	Н	Н	5	60	76
12	Н	Cl	Н	5	60	97^{b}
13	Н	Cl	OMe	3	40	92^c
14	Н	Br	OMe	3	40	98^d
15	Н	OMe	OMe	3	40	88^{e}

^{*a*} Isolated yield after flash chromatography over SiO₂. ^{*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	% yieldª
1	CO ₂ Me	3	25	H CO₂Me	13 90
2	T CO ₂ Me	5	60		98 ^b
3	N ₃ 8 CO ₂ Me	3	25	15 H CO ₂ Me	91
4	P E = 0 10 E = S	5	60	$H = O_2 Me$ 16 E = O 17 E = S	16 79 17 84
5	$N_{\rm H} = Piv$ 11 R = Piv 12 R = Boc	5	60	H H H H H H H H H H H H H H H H H H H	18 88 19 94

^{*a*} Isolated yield after flash chromatography over SiO₂. ^{*b*} Regioselectivity >95:5.

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 concerted²⁰ insertion of **2** into an ortho-C-H bond (21) or a stepwise²³ 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 N₂.



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 Nheterocycles 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.

References

- (a) Taber, D. F.; Joshi, P. V. J. Org. Chem. 2004, 69, 4276. (b) Davies, H. M. L.; Manning, J. R. J. Am. Chem. Soc. 2006, 128, 1060. (c) Bykowski, D.; Wu, K.-H.; Doyle, M. P. J. Am. Chem. Soc. 2006, 128, 16038
- (2) (a) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* 2004, *15*, 1019. (b) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. J. Am. Chem. Soc. 2004, *126*, 15378. (c) Lebel, H.; Huard, K.; Lectard, S. J. Am. Chem. Soc. 2005, 127, 14198. (d) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. Angew. Chem., Int. Ed. 2006, 45, 4641. (e) Reddy, R. P.; Davies, H. M. L. Org. Lett. 2006, 8, 5013. (f) Fiori, K. W.; Du Bois, J. J. Am. Chem. Soc. 2007, 129, 562. (3) For demonstrations of Rh(II)-mediated atom transfer reactions in total
- 2002, 67, 2954. (b) Hinman, A.; Du Bois, J. J. Am. Chem. Soc. 2003, 125, 11510. (c) Davies, H. M. L.; Dai, X.; Long, M. S. J. Am. Chem. Soc. 2006, 128, 2485. (d) Mejía-Oneto, J. M.; Padwa, A. Org. Lett. 2006, 8. 3275
- (4) Ye, T.; McKervey, M. A. Chem. Rev. 1994, 94, 1091.
 (5) (a) Breslow, R.; Gellman, S. H. J. Am. Chem. Soc. 1983, 105, 6728. (b) Mansuy, D.; Mahy, J.-P.; Duréault, A.; Bedi, G.; Battioni, P. Chem. Commun. 1984, 1161.
- (6) For recent reviews on the formation and reactivity of metal nitrenoids formed from the reaction of metal complexes and azides, see: (a) Katsuki, T. Chem. Lett. 2005, 34, 1304. (b) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. Coord, Chem. Rev. 2006, 250. 1234
- (7) Photolysis of NsN3 produces nitrene, which was reported to react with styrene in the presence of a Rh(II) bis(naphthol)phosphate catalyst to produce an aziridine in 9% yield. In the absence of hv, no aziridine was produced. See: Mueller, P.; Baud, C.; Naegeli, I. J. Phys. Org. Chem. 1998. 11. 597
- (8) For leading reviews, see: (a) Moody, C. J. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Ley, S., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 21. (b) Söderberg, B. C. G. Curr. Org. Chem. 2000, 4, 727
- (9) For a discussion of the safety issues of processes involving azides, see: Wiss, J.; Fleury, C.; Onken, U. Org. Process Res. Dev. 2006, 10, 349. (10) The vinyl azides employed herein were synthesized by the condensation
- of an aromatic or heteroaromatic aldehyde with methyl azidoacetate. Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. Angew. Chem., Int. Ed. (11)
- 2005, 44, 5188. An alkyl azide is a key intermediate in the Roche Tamiflu synthesis. See: (12)
- Federspiel, M; et al. *Org. Process Res. Dev.* **1999**, *3*, 266. (13) For leading reports on the thermal version of the reaction, see: (a) Hemetsberger, H.; Knittel, D.; Weidmann, H. Monatsh. Chem. 1970, 101, 161. (b) Moody, C. J. Stud. Nat. Prod. Chem. 1988, 1, 163. (c) Moody, C. J.; Warrellow, G. J. J. Chem. Soc., Perkin Trans. 1 1990, 2929. (14) Cui, Y.; He, C. Angew. Chem., Int. Ed. 2004, 43, 4210.
- Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. J. Am. Chem. Soc. 2001, 123, 7707. (15)
- Ragaini, F.; Penoni, A.; Gallo, E.; Tollari, S.; Gotti, C. L.; Lapadula, M.; (16)Mangioni, E.; Cenini, S. Chem.-Eur. J. 2003, 9, 249.
- Bach, T.; Schlummer, B.; Harms, K. Chem.-Eur. J. 2001, 7, 2581. (17)
- See Supporting Information for a complete listing of the reaction conditions (18)employed. (19) In the absence of catalyst, no indole product was formed at this
- temperature.
- (20) For mechanistic and computational studies of related Rh(II)-mediated carbene transfer reactions, see, respectively: (a) Pirrung, M. C.; Liu, H.; Morehead, A. T., Jr. J. Am. Chem. Soc. **2002**, 124, 1014. (b) Nakamura, E.; Yoshikai, N.; Yamanaka, M. J. Am. Chem. Soc. **2002**, 124, 7181.
- (21) For a study of the mechanism of the intramolecular C-H bond insertion of aryl nitrenes, see: Murata, S.; Tsubone, Y.; Kawai, R.; Eguchi, D.; Tomioka, H. J. Phys. Org. Chem. 2005, 18, 9.
- (22) For reports of Lewis acid coordination to the α -nitrogen of an azide, see: (a) Takeuchi, H.; Maeda, M.; Mitani, M.; Koyama, K. Chem. Commun.
 1985, 287. (b) Olah, G. A.; Ramaiah, P.; Wang, Q.; Prakash, G. K. S. J. Org. Chem. 1993, 58, 6900. (c) Wrobleski, A.; Aubé, J. J. Org. Chem. 2001, 66, 886.
- (23) For a related Rh(II)-mediated C-H functionalization reaction postulated to occur in a stepwise fashion, see: Clark, J. S.; Dossetter, A. G.; Wong, Y.-S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. J. Org. Chem. 2004, 69, 3886.
- (24) For related isotope studies of C-H bond functionalization by rhodium carbenoids, see: (a) Wang, P.; Adams, J. J. Am. Chem. Soc. 1994, 116, 3296. (b) Clark, J. S.; Wong, Y.-S.; Townsend, R. J. Tetrahedron Lett. 2001, 42, 6187.
- (25)For a discussion on the isotope effects observed in electrophilic aromatic substitution, see: Perrin, C. L. J. Org. Chem. 1971, 36, 420.

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