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Rh_2(II)-Catalyzed Selective Aminomethylene Migration from Styryl Azides

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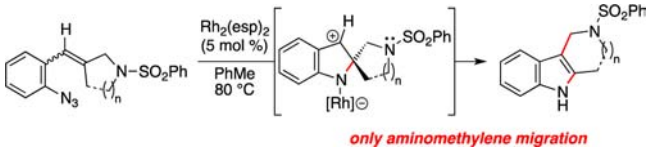
ABSTRACT



Rh_2(II)-Carboxylate complexes were discovered to promote the selective migration of aminomethylenes in β,β-disubstituted styryl azides to form 2,3-disubstituted indoles. Mechanistic data are also presented that suggest that the migration occurs stepwise before diffusion of the iminium ion.

The formation of new carbon−carbon bonds through transition metal-catalyzed migration reactions continues to be pursued by researchers because it rapidly transforms simple starting materials into complex, functionalized products.[1] While metal-catalyzed carbene reactions are well established to induce 1,2-shifts from the resulting oxonium[2−4] or ammonium ylide,[5] triggering these migratorial processes with the analogous N-atom transfer remains significantly underdeveloped.[6] We have pursued using aryl azides in Rh_2(II)-catalyzed C−H bond amination reactions,[7,8] and our mechanistic experiments suggested that C−N bond formation occurred through a 4π-electron-5-atom electrocyclization.[9] We exploited this mechanism to induce selective 1,2-shifts of β-substituents[10] and discovered that aryl group migration could be triggered from β,β-disubstituted styryl azides such as **1** to afford 2-alkyl-3-aryl indoles as the only product (Scheme 1).[10a,11] The identities of the two β-substituents in these substrates, however, differed considerably, and we were curious if our migratorial process could distinguish between two β-methylene units if one was substituted with an amine. Despite the well-established use of heteroatoms as

(1) For recent reviews, see: (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (b) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341. (c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (d) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676.

(2) For leading reviews, see: (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (c) *Nitrogen, Oxygen and Sulfur Ylide Chemistry: Practical Approach in Chemistry*; Clark, J. S., Ed.; Oxford University Press: Oxford, 2002; Chapter 1, pp 1−98.

(3) For seminal reports, see: (a) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655. (b) Kirmse, W.; Chiem, P. V.; Schurig, V. *Tetrahedron Lett.* **1985**, *26*, 197. (c) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (d) West, F. G.; Naidu, B. N; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892. (e) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420. (f) Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97. (g) Doyle, M. P.; Ene, D. G.; Forbes, D. C.; Tedrow, J. S. *Tetrahedron Lett.* **1997**, *38*, 4367.

(4) For leading reports, see: (a) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561. (b) Marmsäter, F. P.; Murphy, G. K.; West, F. G. *J. Am. Chem. Soc.* **2003**, *125*, 14724. (c) Marmsäter, F.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657. (d) Murphy, G. K.; West, F. G. *Org. Lett.* **2005**, *7*, 1801. (e) Jaber, D. M.; Burgin, R. N.; Hepler, M.; Zavalij, P.; Doyle, M. P. *Chem. Commun.* **2011**, *47*, 7623.

(5) (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420. (b) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31. (c) Vanecko, J. A.; West, F. G. *Org. Lett.* **2002**, *4*, 2813.

(6) For notable exceptions, see: (a) Thornton, A. R.; Blakey, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 5020. (b) Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434.

(7) Cf.: (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (b) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056. (c) Nguyen, Q.; Sun, K.; Driver, T. G. *J. Am. Chem. Soc.* **2012**, *134*, 7262.

(8) For recent reviews of the use of azides in metal-catalyzed *N*-atom transfer reactions, 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. (c) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831. (d) Jenkins, D. M. *Synlett* **2012**, *23*, 1267.

(9) Stokes, B. J.; Richert, K. J.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 6442.

(10) (a) Sun, K.; Liu, S.; Bec, P. M.; Driver, T. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 1702. (b) Stokes, B. J.; Liu, S.; Driver, T. G. *J. Am. Chem. Soc.* **2011**, *133*, 4702.

(11) For leading reports of related aryl 1,2-shifts triggered by Nazarov electrocyclizations, see: (a) Huang, J.; Lebuf, D.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 6307. (b) Lebuf, D.; Gandon, V.; Ciesielski, J.; Frontier, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 6296.

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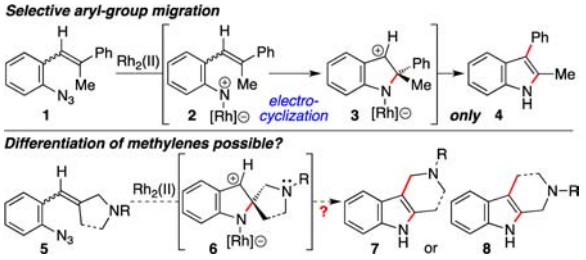
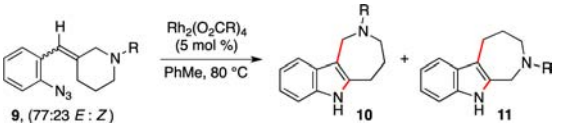
stereochemical controlling elements in many transformations,[12] their use to control the selectivity of 1,2-shifts is surprisingly rare.[4b,d,5b] We anticipated that demonstrating the ability of an amine[13] to control the selectivity of these reactions would facilitate the synthesis of *N*-heterocycles, and herein, we describe the development of a selective Rh_2(II)-catalyzed aminomethylene shift reaction that transforms β,β-disubstituted styryl azides into tetrahydrocarbolines or indoloazepines.[14]

Scheme 1. Can β-Methylene Units Be Distinguished in Our Reaction?



To examine the effect of distal substitution on the selectivity of methylene migration, β,β-dialkyl-substituted styryl azide **9** was examined (Table 1). We anticipated that the β-aminomethylene substituent would enable investigation of the influence of the N-atom on the alkyl 1,2-shift, and the effect of modifying its electronic nature by changing the identity of the *N*-substituent. At the outset, the amine was arbitrarily substituted with a sulfonyl group. While no reaction was observed in the absence of a transition metal catalyst, exposure of styryl azide **9a** to rhodium carboxylate complexes did trigger the desired aminomethylene migration (entries 1−6).[15] Both the yield and migration selectivity, however, depended on the identity of the catalyst with the best results obtained with $Rh_2(oct)_4$ or $Rh_2(esp)_2$ to afford **10a** as the major product.[16] Importantly, the stereochemistry of the starting material did not impact the selectivity of the reaction: both the *E*- and *Z*-isomer formed **10a** smoothly. Our screen identified $Rh_2(esp)_2$ as the optimal catalyst, and the reaction outcome did not improve when the solvent was changed from toluene to chlorinated or ethereal solvents.

Table 1. Examination of the Migratorial Aptitudes of Substituted Methylenes



entry	MX_n	R	**9**	% yield[a]	**10:11**
1	none	SO_2Ph	a	n.r.	n.a.
2	$Rh_2(O_2CCH_3)_4$	SO_2Ph	a	n.r.	n.a.
3	$Rh_2(O_2CCF_3)_4$	SO_2Ph	a	36	86:14
4	$Rh_2(O_2CC_3F_7)_4$	SO_2Ph	a	32	80:20
5	$Rh_2(O_2CC_7H_{15})_4$	SO_2Ph	a	85	100:0
6	$Rh_2(esp)_2$	SO_2Ph	a	87	100:0
7	$Rh_2(esp)_2$	Boc	b	46	60:40
8	$Rh_2(esp)_2$	Bz	c	42	66:34
9	$Rh_2(esp)_2$	Bn	d	18	100:0

[a] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Using these optimal conditions, the effect of changing the nature of the N-substituent was investigated (Table 1). We found that substitution of the sulfonyl group with other common protecting groups led to lower reaction conversions (entries 7−9). Substitution of the nitrogen with a Boc or Bz group (**9b** or **9c**) significantly attenuated the selectivity of the methylene migration to provide a mixture of indoles **10** and **11**. While the selectivity of the migration was restored using the alkyl tertiary amine **9d**, the reaction conversion was significantly diminished (entry 9). We attribute this low conversion to complexation of the benzyl nitrogen atom with the Lewis acidic catalyst. Based on these results, we decided to further examine the scope of aminomethylene migration using substrates bearing a phenylsulfonyl *N*-substituent.

A series of styryl azides **12** were examined to determine the scope and limitations of our Rh_2(II)-catalyzed aminomethylene 1,2-shift reaction (Table 2). Our migration reaction proved remarkably tolerant to substrate modifications. First, the reaction was not dependent on the size of the ring expansion: both azetidine **12a** and pyrrolidine **12b** were smoothly converted to the indole product (entries 1 and 2). The effect of modifying the electronic nature of the aryl azide on the migration reaction was investigated with azides **12c**−**12i** (entries 3−9). While indoloazepines **13** were obtained in all cases, slightly higher yields were obtained with more electron-deficient substrates (compare entries 6−9). The *ortho*-R^3-substituent exerted a larger effect on the yield of the migration reaction with a methoxy group having a more deleterious effect than a methyl group (entries 10 and 11). Our reaction enables access to

(12) For recent reviews of anchimeric assistance, see: (a) Bowden, K. *Chem. Soc. Rev.* **1995**, *24*, 431. (b) Cai, F.; Wu, B.; Crich, D. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 251. (c) Kimatrai, M.; Cruz-Lopez, O.; Garcia-Rubino, M. E.; Morales, F.; Gomez-Perez, V.; Campos, J. M. *Curr. Org. Chem.* **2010**, *14*, 1461.

(13) To the best of our knowledge, there are no examples of using amines to control the selectivity of 1,2-shifts.

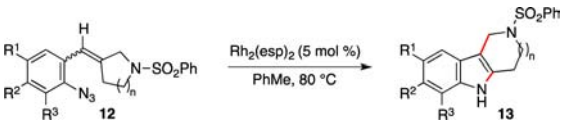
(14) The tetrahydrocarboline and indoloazepine scaffold are present in a broad range of pharmaceuticals and bioactive molecules. For reviews, see: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (b) Gribble, G. W.; Saulnier, M. G.; Pelkey, E. T.; Kishbaugh, T. L. S.; Liu, Y.; Jiang, J.; Trujillo, H. A.; Keavy, D. J.; Davis, D. A.; Conway, S. C.; Switzer, F. L.; Roy, S.; Silva, R. A.; Obaza-Nutaitis, J. A.; Sibi, M. P.; Moskalev, N. V.; Barden, T. C.; Chang, L.; Habeski nee Simon, W. M.; Pelcman, B.; Sponholtz, W. R., III; Chau, R. W.; Allison, B. D.; Garaas, S. D.; Sinha, M. S.; McGowan, M. A.; Reese, M. R.; Harpp, K. S. *Curr. Org. Chem.* **2005**, *9*, 1493. (c) Edwankar, C. R.; Edwankar, R. V.; Namjoshi, O. A.; Rallapappi, S. K.; Yang, J.; Cook, J. M. *Curr. Opin. Drug Discuss. Dev.* **2009**, *12*, 752.

(15) For a complete listing of the reaction conditions surveyed, refer to the Supporting Information.

(16) The structure of the major product was established by X-ray crystallography.

8-substituted indoloazepines **13f**–**13i**, which cannot be made regioselectively using the Fischer indole reaction.[17]

Table 2. Scope of Rh_2(II)-Catalyzed Aminomethylene 1,2-Shift



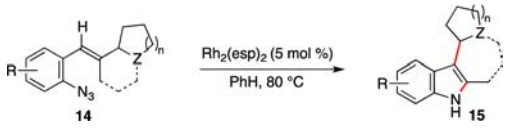
entry	**12**	R^1	R^2	R^3	n	**13** yield, %[a]
1	a	H	H	H	0	82
2	b	H	H	H	1	78
3	c	MeO	H	H	2	70
4	d	Me	H	H	2	81
5	e	Cl	H	H	2	77
6	f	H	MeO	H	2	58
7	g	H	Me	H	2	67
8	h	H	Cl	H	2	84
9	i	H	F_3C	H	2	82
10	j	H	H	Me	2	61
11	k	H	H	MeO	2	35[b]

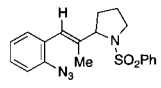
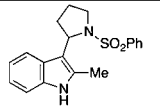
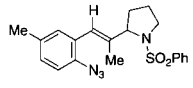
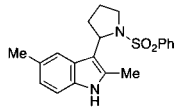
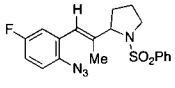
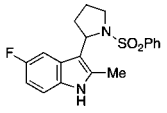
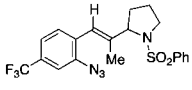
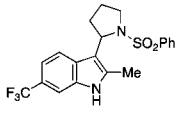
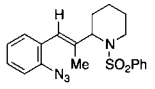
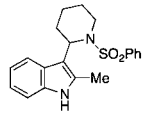
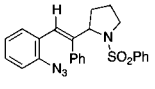
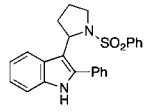
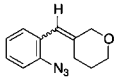
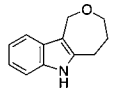
[a] Isolated yield of **13** after silica gel chromatography; only product obtained. [b] The percent conversion of the reaction was 100%; oligomeric decomposition obtained.

The effect of changing the identities of the β-substituents was investigated next (Table 3). While our Rh_2(II)-catalyzed aminomethylene 1,2-shift reaction did not require a tether between the β-substituents, we discovered that only the *E*-isomer of the proline-derived styryl azides **14** was smoothly transformed to 2,3-disubstituted indoles **15**.[18] We attribute the lack of reactivity of the *Z*-isomer to destabilizing steric interactions with the rhodium catalyst. The reaction, however, was not sensitive to the electronic nature of the aryl azide (entries 1–4). Changing the ring size of the migrating group also did not prevent the migration; piperidine **14e** was efficiently converted to **15e** albeit with a slightly reduced yield (entry 5). Next, we tested styryl azide **14f** to test the migratorial preference of the aminomethylene versus a phenyl group, which we previously established to migrate in preference of an alkyl group (entry 6).[10a] Exposure of **14f** to reaction conditions resulted in only aminomethylene migration. To determine if this phenomenon could be extended to selective ethereal methylene migration, styryl azide **14g** was examined and found to produce indole **15g** as the major product with $< 5\%$ of the other regioisomer observed (entry 7). Both the *E*- and *Z*-isomer of **14g** were converted to the indole product.

The reactivity trends of our substrates have suggested a potential catalytic cycle for our Rh_2(II)-catalyzed aminomethylene migration reaction (Scheme 2). Coordination of

Table 3. Scope of Rh_2(II)-Catalyzed Selective Methylene Shift



entry	#	styryl azide **14**	indole **15**	yield, %[a]
1	a			83
2	b			69
3	c			81
4	d			75
5	e			58
6	f			56[b]
7	g			75[c,d]

[a] Isolated yield of **15** after silica gel chromatography; only product obtained. [b] 2-Phenylindole (15%) also isolated. [c] Indole formed as a 95:5 mixture of regioisomers. [d] Reaction performed in toluene using a 78:22 *E*/*Z* mixture of isomers of **14g**.

the styryl azide to the rhodium carboxylate complex produces **16**.[19] Extrusion of N_2 forms rhodium nitrene **17**,[20] which undergoes a 4π-electron-5-atom electrocyclization to form benzyl cation **18**. We have interpreted the nearly equal reactivity of the *E*- and *Z*-isomer of the styryl azide **9a** as evidence that N_2 extrusion occurs before cyclization. Formation of **18** triggers the concerted[21] or stepwise migration of the aminomethylene via iminium ion

(17) For a discussion on the limits of regioselectivity in the Fischer indole reaction, see: (a) Phillips, R. R. *Org. React.* **1959**, *10*, 1143. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227 and references therein.

(18) Submission of *Z*-**14e** to reaction conditions resulted in no reaction.

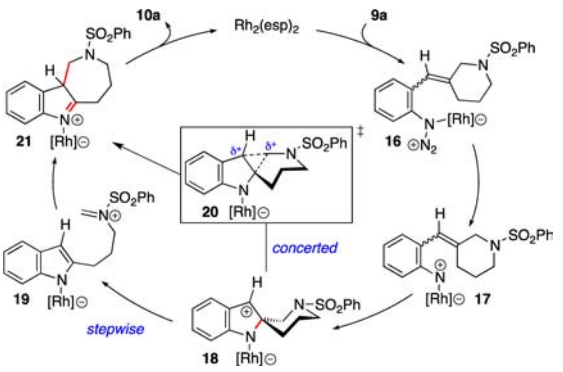
(19) For leading crystal structures of metal azide complexes, see: (a) Waterman, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2008**, *130*, 12628. (b) Fickes, M. G.; Davis, W. M.; Cummins, C. C. *J. Am. Chem. Soc.* **1995**, *117*, 6384.

(20) For computational studies on the mechanism of related copper and cobalt nitrenoid formation from azides, see: (a) Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011**, *133*, 12264. (b) Badiei, Y. M.; Dinescu, A.; Dai, X.; Palomino, R. M.; Heinemann, F. W.; Cundari, T. R.; Warren, T. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9961.

(21) For seminal descriptions of a bridging transition state in 1,2-shifts, see: (a) Winstein, S.; Morse, B. K.; Grunwald, E.; Schreiber, K. C.; Corse, J. *J. Am. Chem. Soc.* **1952**, *74*, 1113. (b) Traylor, T. G.; Hanstein, W.; Berwin, H. J.; Clinton, N. A.; Brown, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 5715.

19 to form **21**.[22,23] Tautomerization of **21** produces indole **10a** and $Rh_2(esp)_2$.

Scheme 2. Potential Catalytic Cycle

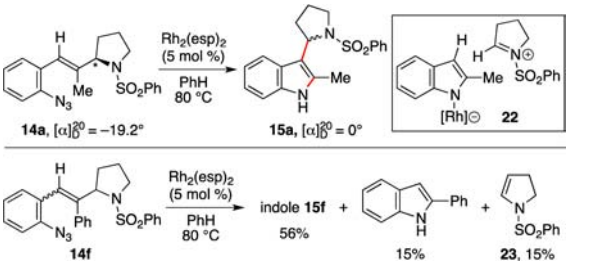


To gain insight into the mechanism of the aminomethylene 1,2-shift, we examined the reactivity of enantiomerically enriched styryl azide **14a** toward our reaction conditions (Scheme 3). We anticipated that if the migration was concerted that the indole product would remain enantiomerically enriched, whereas if the shift occurred stepwise, then **15a** would be formed as the racemate. In contrast to the stereoretention observed in the related Stevens 1,2-shift of oxonium ylides,[4b,5b,5c] exposure of enantiomerically enriched **14a** to reaction conditions produced racemic **15a** to support a stepwise mechanism via ion pair **22**. In further support of this stepwise mechanism, exposure of styryl azide **14f** to reaction conditions produced 2-phenylindole and dihydropyrrole **23** as byproducts to 2,3-disubstituted indole **15f**. This result suggests that in the presence of a β-phenyl substituent (**14f**) deprotonation of the iminium ion intermediate starts to become competitive with the 1,2-phenyl shift. These byproducts, however, were unique to **14f**; in the absence of the β-phenyl substituent, only the 2,3-disubstituted indole was obtained.

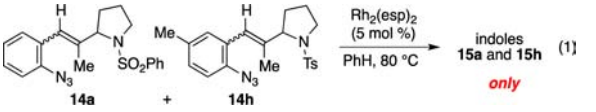
(22) The stepwise migration could be viewed as a retro-Mannich reaction. For leading reports of the retro-Mannich reaction, see: (a) Winkler, J. D.; Siegel, M. G.; Stelmach, J. E. *Tetrahedron Lett.* **1993**, *34*, 6509. (b) Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229. (c) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815. (d) White, J. D.; Ihle, D. C. *Org. Lett.* **2006**, *8*, 1081. (e) Chen, P.; Carroll, P. J.; Sieburth, S. M. *Org. Lett.* **2009**, *11*, 4540.

(23) Alternatively, the stepwise 1,2-shift could occur via a diradical pair. Products attributed to radical intermediates have been observed in the related Stevens [1,2]-rearrangement of ammonium ylides. See: (a) Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479. (b) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009.

Scheme 3. Mechanistic Experiments



To determine if the iminium ion escaped the solvent shell, a double crossover experiment was performed (eq 1). Submission of a 1:1 mixture of styryl azides **14a** and **14h** to reaction conditions produced only indoles **15a** and **15h**. Together with the experiments described in Scheme 3, these results reveal that the 1,2-aminomethylene shift occurs stepwise without diffusion of the iminium ion intermediate.



In conclusion, we discovered that exposure of β,β-dimethylene-substituted styryl azides to a dirhodium(II) carboxylate complex triggers a preferential aminomethylene 1,2-shift after initial electrocyclization of the rhodium nitrene. Our mechanistic experiments suggest that this migration occurs stepwise before diffusion of the iminium ion. Together with our previous studies, our migratorial aptitude scale can be updated to ester $\ll$ alkyl $\ll$ aryl $\ll$ aminomethylene $<$ amide $<$ H $<$ sulfone $<$ ketone $\ll$ nitro. Our future experiments are aimed at further understanding and exploiting our mechanistic studies in the design of new Rh_2(II)-catalyzed transformations to access complex, functionalized *N*-heterocycles.

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

The authors declare no competing financial interest.