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Rh_2(II)-Catalyzed Nitro-Group Migration Reactions: Selective Synthesis of 3-Nitroindoles from β-Nitro Styryl Azides

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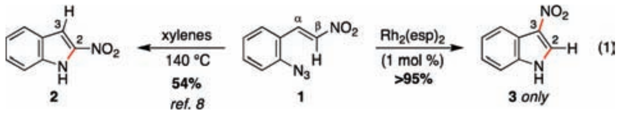
Supporting Information

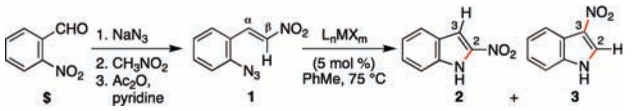
ABSTRACT: Rhodium carboxylate complexes (1 mol %) catalyze the migration of electron-withdrawing groups to selectively produce 3-substituted indoles from β-substituted styryl azides. The relative order of migratorial aptitude for this transformation is ester ≪ amide < H < sulfonyl < benzoyl ≪ nitro.

Reactions that involve a selective migration event can convert simple, readily accessible starting materials into complex functionalized products. While selective 1,2-shifts of alkyl, aryl, or other electron-releasing groups are well-established in organic synthesis,[1] the migration of strongly electron-withdrawing groups are underdeveloped[2] and have the potential to be powerful synthetic tools for constructing important biologically active small molecules.[3−5] While nitro-group migrations have been observed in isolated cases,[6] these transformations have not been harnessed for the regioselective synthesis of nitro-substituted N-heterocycles. Styryl azides have been established as useful indole precursors,[7] and our group has previously reported that Rh_2(II) octanoate catalyzes migration of a phenyl group to transform β,β-diphenylstyryl azide into 2,3-diphenylindole.[2b] When the styryl azide contains a β-hydrogen, a C−H amination reaction occurs: thermolysis of β-nitro-substituted **1** to produce 2-nitroindole (**2**) as the major product (eq 1) was reported by Pelkey and Gribble.[8] Herein, we report that Rh_2(II) carboxylates promote a fundamental change in the reactivity of **1** to form 3-nitroindole as the exclusive product, thereby providing a new synthetic method for N-heterocycle formation.



A variety of transition-metal complexes were examined for their ability to catalyze the formation of nitroindole styryl azide **1**, which was synthesized in three steps from 2-nitrobenzaldehyde (Table 1).[9] To our surprise, exposure of **1** to Rh_2(II) carboxylates (5 mol %) formed 3-nitroindole as the only product.[10] Minimal optimization was required to identify the optimal conditions for this transformation: 1 mol % $Rh_2(esp)_2$[11] in toluene cleanly converted **1** to **3** in >95% isolated yield with no observable 2-nitroindole byproduct. Other Rh_2(II) carboxylates were found to be nearly as efficient (entries 3 and 4),[12] except for Rh_2OAc_4, which was unreactive. In addition to these complexes,

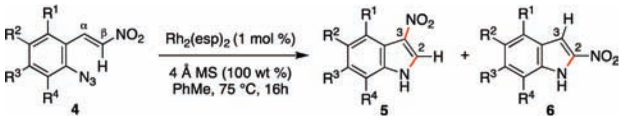
Table 1. Optimization of Reaction Conditions



entry	catalyst	conv., %[a]	yield, %[a]	2:3
1	none	0	0	n.a.
2	**$Rh_2(esp)_2$[b]**	**99**	**95**	**0:100**
3	$Rh_2(O_2CC_7H_{15})_4$	95	89	0:100
4	$Rh_2(O_2CC_3F_7)_4$	97	90	1:99
5[c]	$RuCl_3 \cdot nH_2O$	89	67	1:99
6	CoTPP	17	7	43:57
7	$[Ir(cod)OMe]_2$	29	trace	100:0

[a] As determined using ^{1}H NMR spectroscopy. [b] esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate. [c] Reaction was performed in 1,2-dimethoxyethane without the addition of molecular sieves.

Table 2. Scope of Rh(II)-Catalyzed NO_2 Migratorial Reactions



entry	4	R^1	R^2	R^3	R^4	yield, %[a]	5:6[b]
1	**a**	H	H	OMe	H	91	>95:5
2	**b**	H	H	Cl	H	79	>95:5
3[c]	**c**	H	H	CF_3	H	96	>95:5
4	**d**	H	H	CO_2Me	H	>95	>95:5
5	**e**	H	Br	H	H	87	>95:5
6	**f**	H	Cl	H	H	90	>95:5
7	**g**	H	CO_2Me	H	H	>95	>95:5
8	**h**	H	OCH_2O		H	93	>95:5
9	**i**	Cl	H	H	H	>95	>95:5
10	**j**	H	H	CH═CHCH═CH		94	49:51
11	**k**	H	H	H	OMe	>95	26:74
12	**l**	H	H	H	Me	97	30:70
13	**m**	Br	H	H	Br	71	8:92
14	**n**	H	H	H	CF_3	99	<5:95

[a] Isolated yield after SiO_2 chromatography. [b] As determined using ^{1}H NMR spectroscopy. [c] Reaction was run on a 2 mmol scale using 0.1 mol % $Rh_2(esp)_2$.

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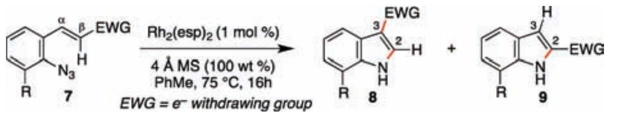
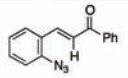
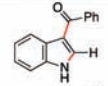
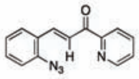
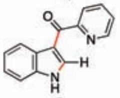
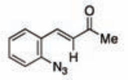
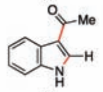
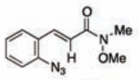
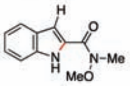
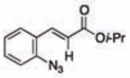
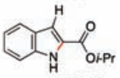
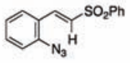
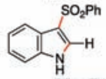
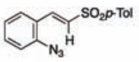
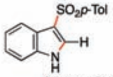
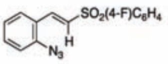
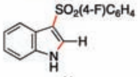
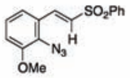
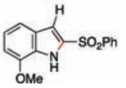
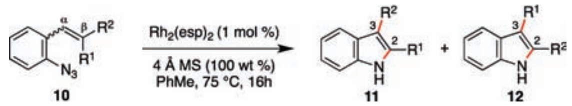
Table 3. Scope of the Migrating Group in Rh(II)-Catalyzed Migrations

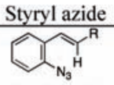
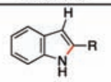
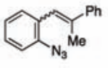
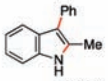
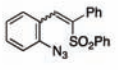
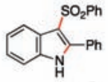
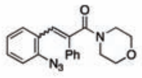
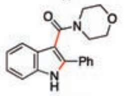
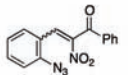
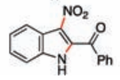


entry	7	Styryl azide	Major indole	yield, %[a]	8:9
1	a			93	>95:5
2	b			66	>95:5
3	c			65	>95:5
4	d			94	23:77
5	e			>95	<5:95
6	f			>95	89:11
7	g			78[b]	89:11
8	h			>95	90:10
9	i			>95	<5:95

[a] Isolated yield after SiO_2 chromatography. [b] 3 mol % $Rh_2(esp)_2$ was used.

Table 4. Intramolecular Competition Experiments To Compare Migration Preferences



entry	10	Styryl azide	mol %	Product	yield, %[a]
1[b]	a b	 R = n-hex or Ph	5		R = n-hex 68 R = Ph 95
2[c]	c		5		>95
3	d		5		49[d]
4	e		5		91
5	f		1		40[d]

[a] Isolated yield after SiO_2 chromatography. [b] Data from ref 7b. [c] Data from ref 12a. [d] Remaining material resulted from oligomeric decomposition.

examination of a series of known N-atom transfer catalysts identified only $RuCl_3 \cdot nH_2O$[13] to be competent, although it is less efficient than $Rh_2(esp)_2$ (entry 5). Other transition-metal complexes, including CoTPP and $[Ir(cod)OMe]_2$ (entries 6 and 7),[14] afforded <10% yield of **2** and **3**, whereas Cu or Fe salts failed to react with the styryl azide.[15,16]

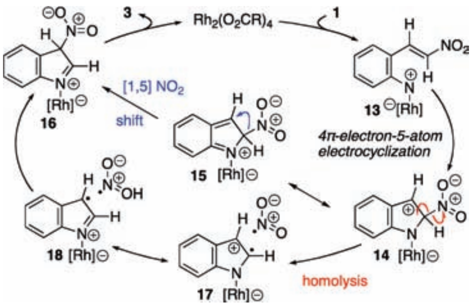
Using our optimized conditions, the scope of the rhodium(II)-catalyzed formation of nitroindoles from β-nitro-substituted styryl azides **4** was examined (Table 2). A series of 3-nitroindoles were produced selectively from substrates bearing a range of R^1, R^2, or R^3 substituents (entries 1−9). The catalyst loading could be reduced when the reaction scale was increased: conversion of 2 mmol of styryl azide **4c** to indole **5c** required only 0.1 mol % $Rh_2(esp)_2$ (entry 3). Only when an R^4 substituent on azide **4** was introduced did 2-nitroindole formation become a competitive process (entries 10−14). While mixtures of indoles **5** and **6** were obtained for aryl, methyl, and methoxy R^4 groups, azide **4n** bearing a strongly electron-withdrawing group at the ortho position ($R^4 = CF_3$) afforded only 2-nitroindole **6n** upon exposure to the reaction conditions.

Styryl azides bearing electron-withdrawing groups at the β-position were investigated to determine whether NO_2 migration is a general phenomenon (Table 3). Aryl and alkyl ketones migrated to provide only 3-substituted indoles (entries 1−3). In contrast, a mixture of indoles **8d** and **9d** was obtained from Weinreb amide **7d**, and only the 2-carboxylate indole **9e** was observed when isopropyl ester **7e** was subjected to the reaction conditions. These results show that migrations of amides and esters are less facile than those of ketones and nitro groups and suggest that more strongly electron-withdrawing groups are more prone to migrate.[17] Accordingly, sulfones were anticipated to migrate, and styryl azides **7f−h** were converted to a 9:1 ratio in favor of 3-sulfonylindole **8** irrespective of the electronic environment of the sulfonyl group. In ortho-methoxy-substituted azide **7i**, the migration of the sulfonyl group was inhibited, and only 2-sulfonylindole **9i** was formed. Together with the results for **4j−n**, these results suggest that migration can be suppressed with an additional ortho substituent.

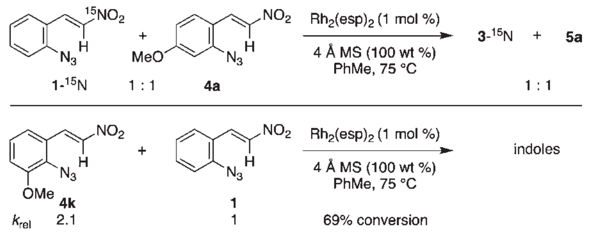
To further examine the propensity for a group to migrate, several β-substituted styryl azides were submitted to the reaction conditions, and their products were compared (Table 4). In our first report,[7b] no alkyl- or aryl-group migration was observed for styryl azides with β-hydrogen substituents (entry 1). Our subsequent study revealed that aryl groups migrate in preference to alkyl groups (entry 2).[12a] Azides **10d−f** were constructed for an intramolecular competition between migrating groups (entries 3 and 4). Exposure of **10d** and **10e** to the reaction conditions revealed that no phenyl-group migration occurred in the presence of either a β-sulfone or β-amide. The reaction of azide **10f** provided only **12f**, the product of nitro migration; no migration of the benzoyl group was observed.

Our results enabled the construction of a scale for the migration aptitudes of different β-substituents (eq 2). Styryl azide **10c** revealed that aryl-group migration is preferred over an alkyl shift.[12a] Neither group, however, migrates in the presence of a β-hydrogen.[7b] Consequently, we rank their migratorial aptitudes behind that of hydrogen. While hydrogen migration was preferred over amide migration in **7d**, azide **10e** revealed that when the β-hydrogen is replaced with a phenyl group, only amide migration is seen. Therefore, amides are placed ahead of aryl

Scheme 1. Potential Mechanism of NO_2 Migration



Scheme 2. Double-Crossover and Relative Rate Experiments



groups but behind hydrogen. The difference in reactivity between **7a**−**c** (only 3-carbonylindole) and **7f**−**h** (90:10 favoring 3-sulfonylindole) suggests that sulfones should be positioned between hydrogen and ketones. Finally, because only nitro group migration was seen for **10f**, we rank it ahead of ketones. The propensity for these electron-withdrawing groups to migrate, however, hinges on the absence of a second ortho electron-withdrawing substituent on the aryl azide.

$$\textit{migration aptitude}: \text{alkyl} < \text{aryl} < \text{amide} < \text{H} < \text{sulfonyl} < \text{ketone} < \text{nitro} \tag{2}$$

While a number of mechanisms could explain the reactivity patterns we observed, we propose that migration occurs from a common catalytic intermediate, **14** (Scheme 1). Coordination of the Rh_2(II) carboxylate to the α- or γ-nitrogen atom followed by loss of N_2 forms rhodium nitrene **13**.[18,19] A four-π-electron, five-atom electrocyclization establishes the C−N bond and generates a carbocation at C3 in **14**.[20] From this intermediate, several different pathways could produce the desired migration. Examination of **15**, a resonance structure of **14**, reveals that a [1,5] sigmatropic shift to form the C3−N bond in **16** could occur.[2a,b] Alternatively, the shift could occur stepwise: homolysis of the C−O bond in **14** could form diradical **17**, whose mesomer **18** would place the radical at C3, which could recombine to form the C−N bond in **16**. A similar diradical mechanism was proposed for the rearrangement of sulfinate ions[21] and nitro groups in electrophilic aromatic substitution.[22] Tautomerization of **16** would form the 3-substituted indole.

Several experiments were performed to test our mechanistic hypothesis (Scheme 2). A double-crossover experiment involving styryl azides **1**-^{15}N and **4a** produced only indoles **3**-^{15}N and **5a**, revealing that no solvent-separated reactive intermediates were formed in the catalytic cycle. As predicted by our previous mechanistic study,[21] styryl azide **4k** reacted 2.1 times faster than **1**. This result confirms that the reaction can be accelerated when an electron-donating group is positioned to assist in N_2 loss, supporting the hypothesis that C−N bond formation occurs via an electrocyclization.

In conclusion, we have demonstrated that rhodium(II) carboxylate complexes catalyze the migration of electron-withdrawing groups to enable the selective formation of 3-substituted indoles from β-substituted styryl azides. Our data allowed for the construction of a scale that categorizes the aptitudes of migration for a range of functional groups. Future experiments will be centered on clarifying the mechanism of this reaction as well as exploiting these reactivity trends to produce complex, functionalized N-heterocycles from simple, readily accessible styryl azides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Complete ref 4a, experimental procedures, spectroscopic and analytical data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) See: (a) Sulfur groups: Gairns, R. S.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1985**, 1818. (b) Acyl groups: Field, D. J.; Jones, D. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1909. (c) Nitro groups: Coombes, R. G.; Russell, L. W. *J. Chem. Soc. B* **1971**, 2443.

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