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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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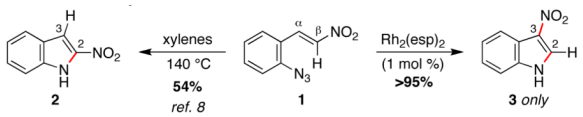
Abstract

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 strong 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 are established as useful indole precursors,[7] and our group has previously reported that Rh_2(II) octanoate catalyzes a phenyl group migration 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** was reported by Gribble and co-workers to produce 2-nitroindole **2** as the major product (eq 1).[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.



2 **1** **3** *only*

(1)

A variety of transition metal complexes were examined to catalyze the formation of nitroindole from stryryl azide **1**, which was synthesized in three steps from 2-nitrobenzaldehyde (Table 1).[9] To our surprise, exposure of azide **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 % of $Rh_2(esp)_2$ [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 (cf. entries 3 and 4),[12] except

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for Rh_2OAc_4, which was unreactive. In addition to these complexes, examination of a series of known *N*-atom transfer catalysts identified only $RuCl_3$•hydrate[13] to be competent, although 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% 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: 2 mmol of styryl azide **4c** required only 0.1 mol % of $Rh_2(esp)_2$ to be converted to indole **5c**. Only when an R^4-substituent was introduced to azide **4** did 2-nitroindole formation become a competitive process (entries 10 – 14). While a mixture of indoles **5** and **6** were obtained for aryl-, methyl- and methoxy R^4-groups, exposure of azide **4n** bearing a strong *ortho*-electron-withdrawing group ($R^4 = CF_3$) to reaction conditions afforded only 2-nitroindole **6n**.

Styryl azides bearing electron-withdrawing groups at the β-position were investigated to determine if NO_2-migration was 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 reaction conditions. These results show that migrations of amides and esters are less facile than ketones or nitro groups and suggest that stronger electron-withdrawing groups are more prone to migrate.[17] Accordingly, sulfones were anticipated to migrate, and styryl azides **7f** – **7h** 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 affording only 2-sulfonylindole **9i**. Together with **4j** – **4n**, 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 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** – **10f** were constructed for an intramolecular competition between migrating groups (entries 3 and 4). Exposure of **10d** and **10e** to 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 benzoyl group migration was observed.

Our results enable the construction of a scale for the migration of different β-substituents (eq 2). Styryl azide **10c** reveals that aryl group migration is preferred over an alkyl shift.[12a] Neither group, however, will migrate in the presence of a β-hydrogen.[7b] Consequently, we rank their migratorial aptitude behind hydrogen. While hydrogen migration is 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 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 in 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.

(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 loss of N_2 forms rhodium nitrene **13**.[18,19] A 4π-electron-5-atom electrocyclization establishes the C–N bond and generates a carbocation on 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 could occur to form the C3–N bond in **16**.[2a,b] Alternatively, the shift could occur stepwise. Homolysis of the C–O bond in **14** forms diradical **17**. The mesomer **18** places 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 between styryl azides **1**-^{15}N and **4a** produced only indoles **3**-^{15}N and **5a** to reveal 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 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, which categorizes the aptitude 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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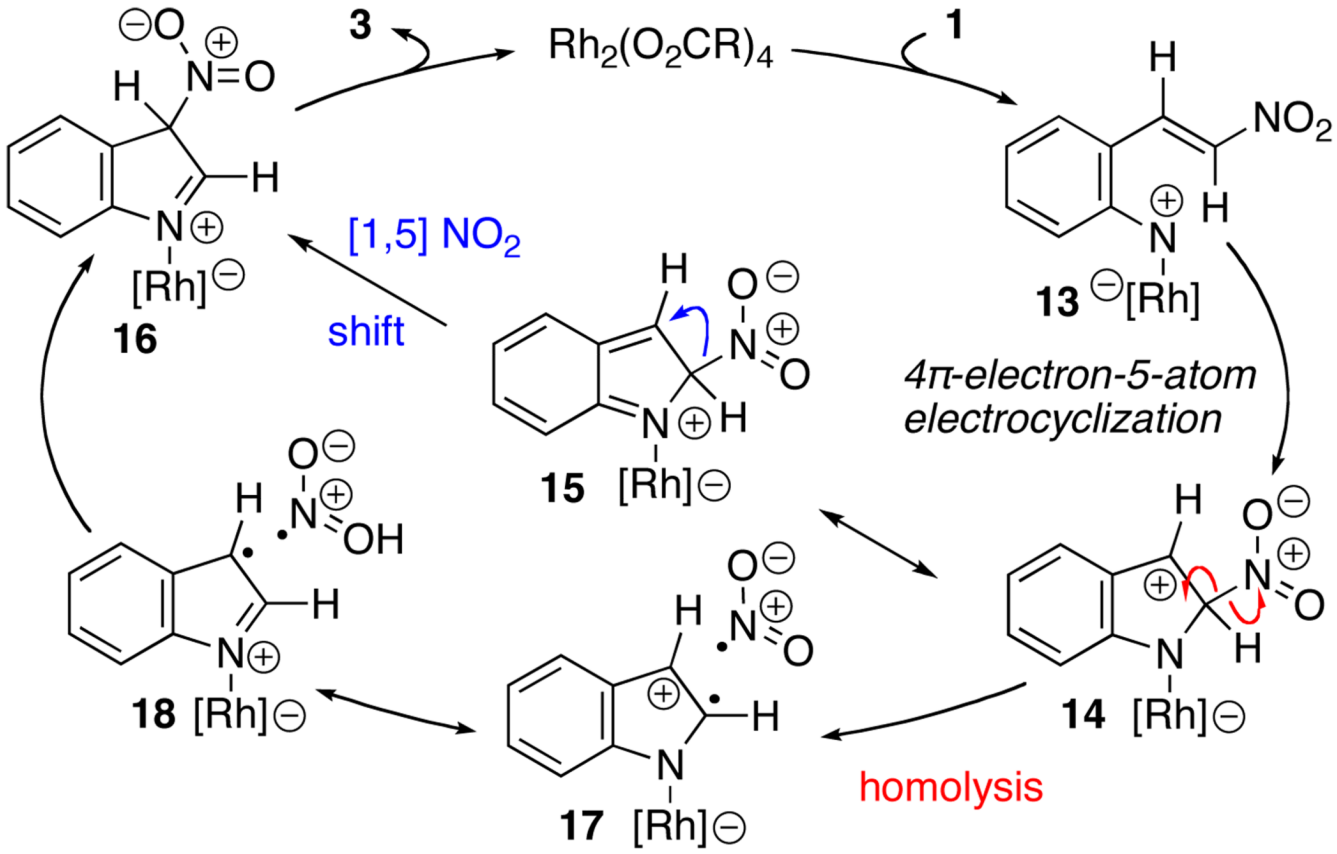
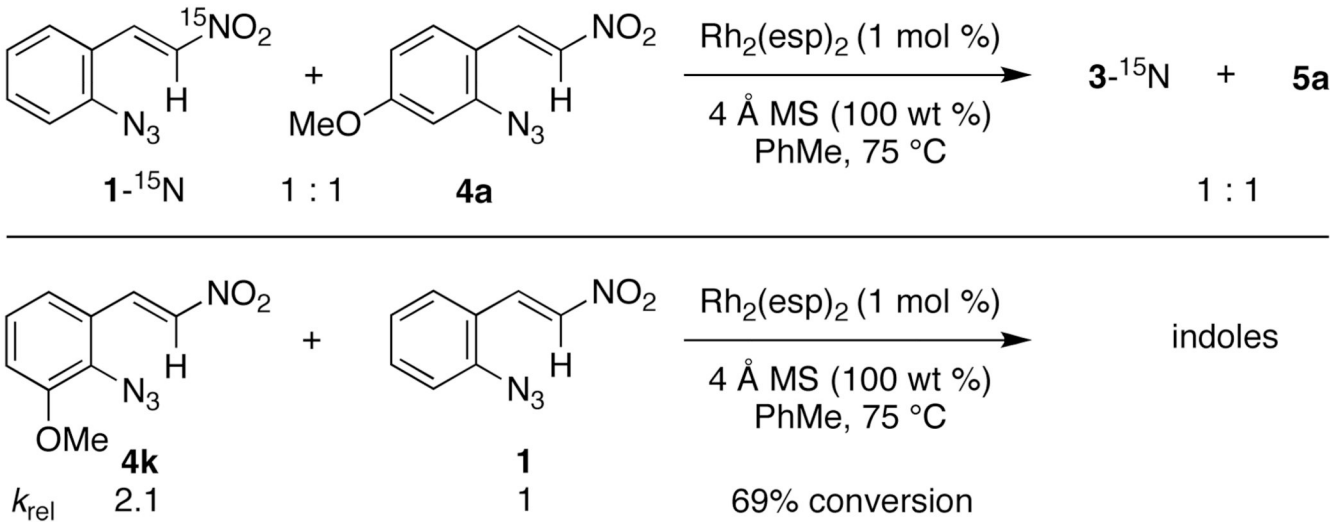


Scheme 1.
Potential Mechanism for NO_2 Migration.



Scheme 2.
Double Crossover- and Relative Rate Experiments.

Table 1

Optimization of Reaction Conditions.

entry	Catalyst	conv., %[a]	yield, %[a]	2:3
1	none	0	0	n.a.
2	**Rh_2(esp)$_2$[a]**	**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]	$RuCl_3$•*n*OH_2	89	67	1:99
6	CoTPP	17	7	43:57
7	$[Ir(cod)OMe]_2$	29	trace	100:0

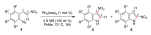
[a] As determined using ^{1}H NMR spectroscopy.

[b] esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionate.

[c] Reaction performed without the addition of MS in 1,2-dimethoxyethane.

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

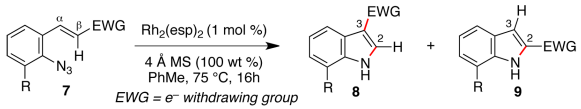
[a] Isolated yield after SiO_2 chromatography.

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

[c] 2 mmol scale using 0.1 mol% $Rh_2(esp)_2$.

Table 3

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



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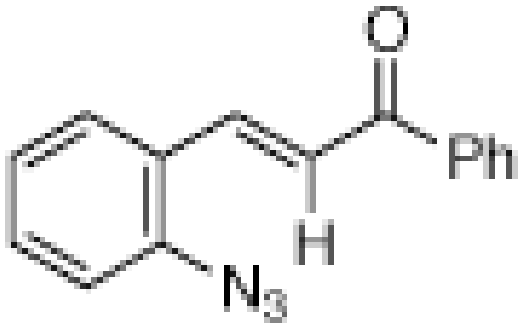
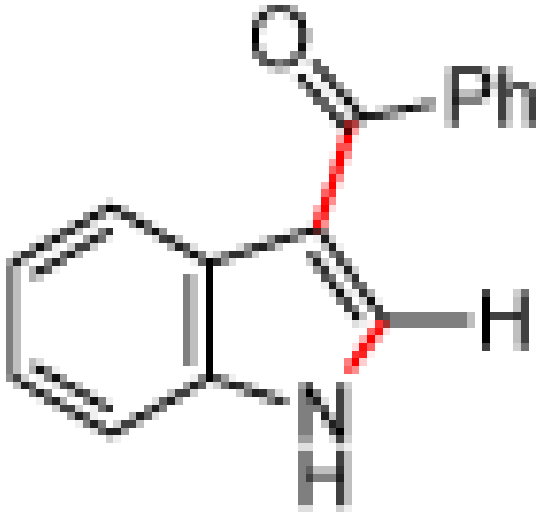
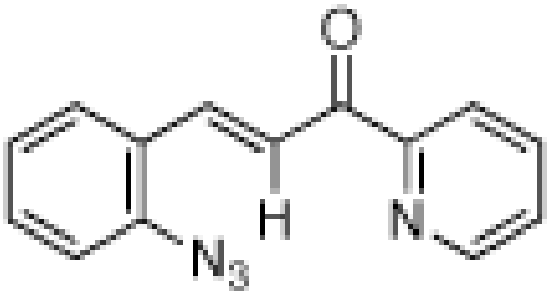
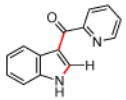
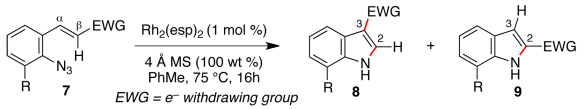
1	**a**			93	>95:5
2	**b**			66	>95:5



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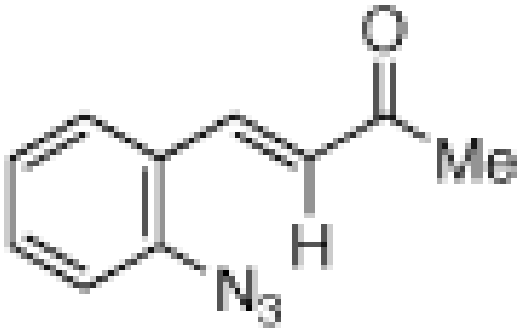
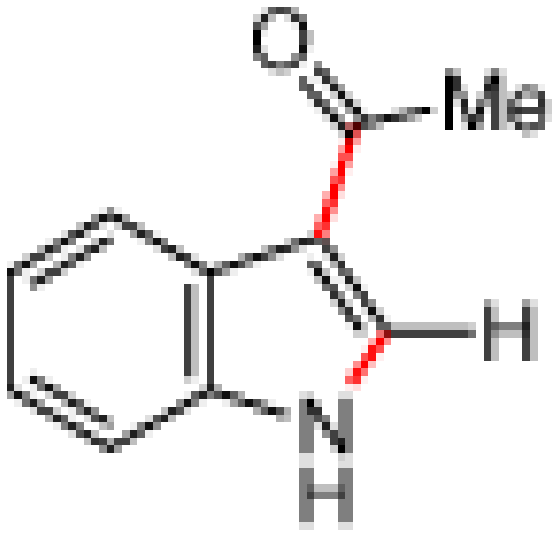
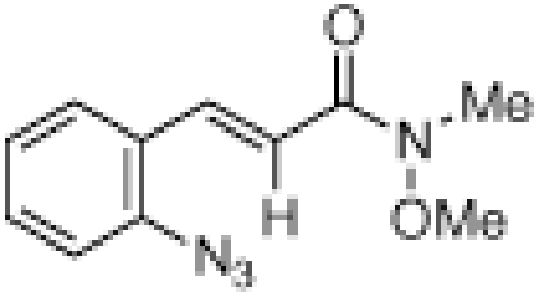
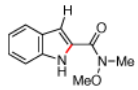
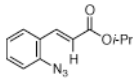
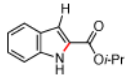
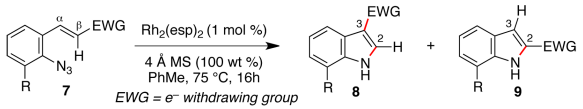
3	**c**			65	>95:5
4	**d**			94	23:77
5	**e**			>95	<5:95



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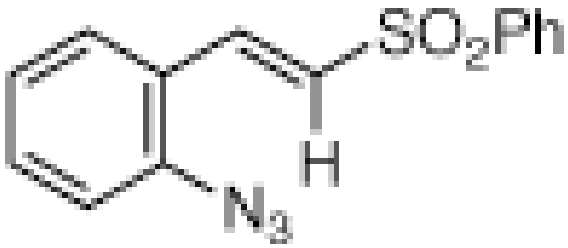
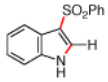
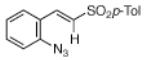
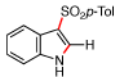
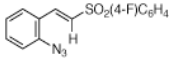
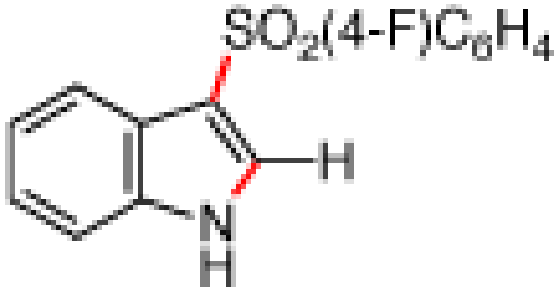
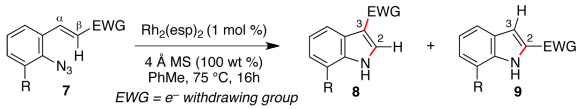
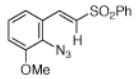
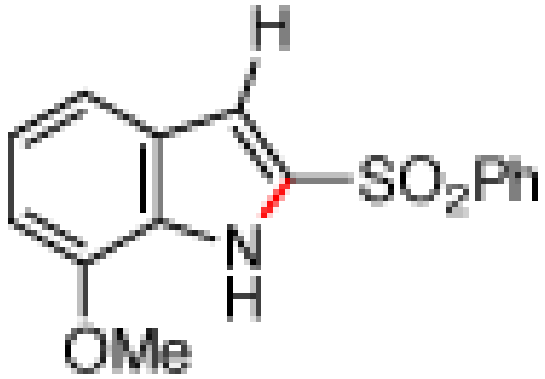
6	**f**			>95	89:11
7	**g**			78[b]	89:11
8	**h**			>95	90:10

J Am Chem Soc. Author manuscript; available in PMC 2012 April 6.



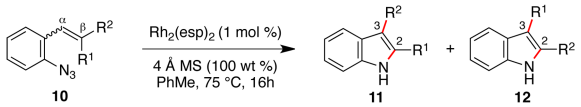
entry	7	Styryl azide	Major indole	yield, %[a]	8:9
9	**i**			>95	<5:95

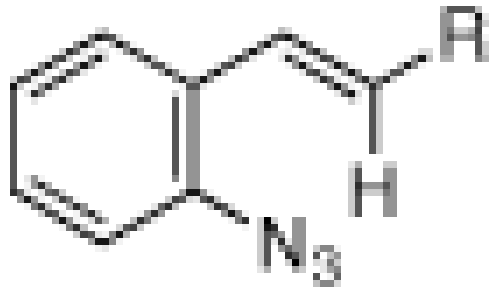
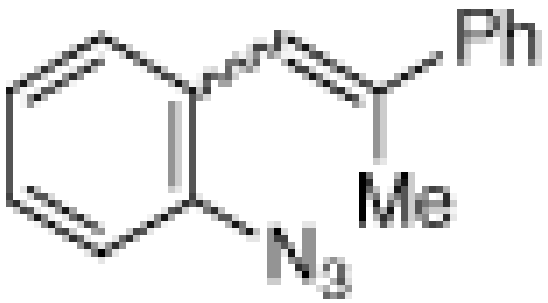
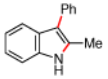
[a] Isolated yield after SiO_2 chromatography.

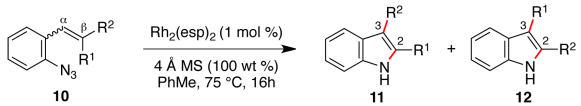
[b] 3 mol % $Rh_2(esp)_2$ used.

Table 4

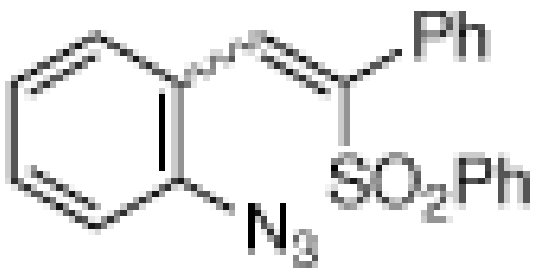
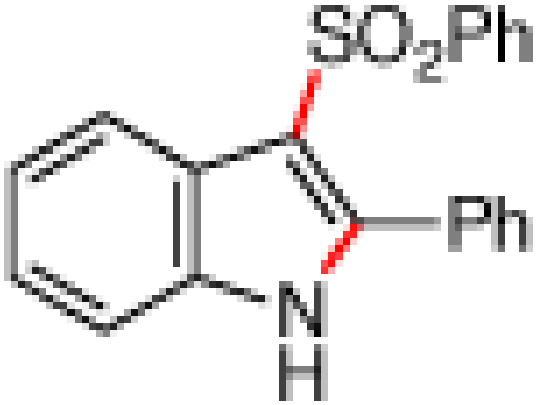
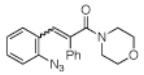
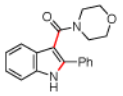
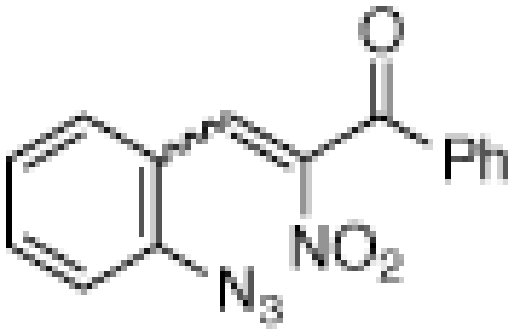
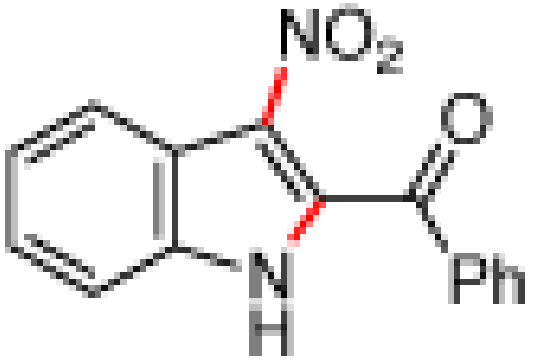
Intramolecular Competition Experiments to Compare Migration Preference.



entry	10	Styryl azide	mol %	Product	yield, %[a]
	a				R = *n*-hex 68
1[b]	**b**		5		R = Ph 95
					
2[c]	**c**		5		>95



10 11 12

entry	10	Styryl azide	mol %	Product	yield, %[a]
3	**d**		5		49[d]
4	**e**		5		91
5	**f**		1		40[d]

[a] Isolated yield after SiO_2 chromatography.

[b] ref. 7b.

J Am Chem Soc. Author manuscript; available in PMC 2012 April 6.

[c] ref. 12a.

[d] Remaining material was oligomeric decomposition.