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Rh_2(II)-Catalyzed Ester Migration to Afford 3*H*-Indoles from Trisubstituted Styryl Azides

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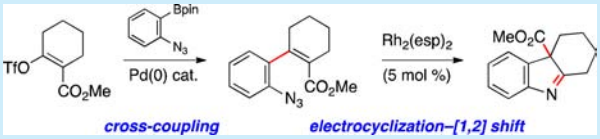
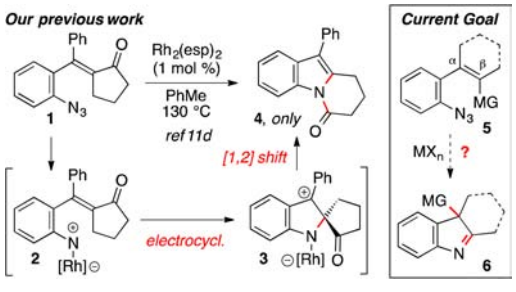
Supporting Information

ABSTRACT: Rh_2(II)-Complexes trigger the formation of 3*H*-indoles from *ortho*-alkenyl substituted aryl azides. This reaction occurs through a 4π-electron-5-atom electrocyclization of the rhodium *N*-aryl nitrene followed by a [1,2]-migration to afford only 3*H*-indoles. The selectivity of the migration is dependent on the identity of the β-styryl substituent.



The wide-ranging potency of bioactive *N*-heterocycles continues to inspire the development of new synthetic transformations that simplify access to their complex and diverse structural motifs.[1,2] In comparison to other *N*-heterocycles, the antiproliferation activity of 3*H*-indoles has only recently been recognized.[3,4] As a consequence, general methods for the construction of 3*H*-indoles—particularly nonoxygenated ones—has lagged despite their biological activity and potential value as synthetic intermediates.[5−7] This structural motif can be formed using an interrupted Fischer-indole reaction;[8] however, this reaction is neither regio- nor stereoselective.[8d] Densely functionalized carbocycles can be created using cyclization reactions to trigger structural rearrangements,[9] and the use of the Nazarov reaction, in particular, has proved to be a successful strategy to access these carbocycles.[10] Our previous investigations established that related tandem reactions can be initiated from *ortho*-substituted aryl azides:[11] the electrocyclization of **2** triggered [1,2] migration to form a 1,2,3-trisubstituted indole (**4**) (Scheme 1).[11d] We anticipated that we might be able to transform

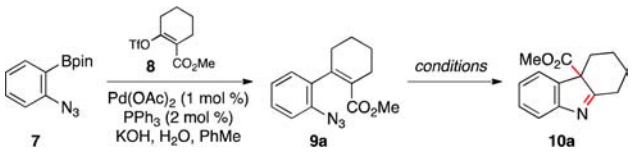
Scheme 1. Rh_2(II)-Promoted Tandem Reactions



trisubstituted styryl azides **5** into 3*H*-indoles **6** by varying the identity of the β-substituent to change the regioselectivity of the [1,2] shift. Herein, we report that readily accessible β-carboxylate- and β-methoxy-susbtituted stryryl azides are efficiently converted to 3*H*-indoles and oxindoles using a rhodium(II) carboxylate catalyst.

To determine if our tandem process could yield 3*H*-indole products, the reactivity of aryl azide **9a** toward transition metal catalysts was investigated (Table 1). Aryl azide **9a** was chosen

Table 1. Determination of Optimal Conditions for 3*H*-Indole Formation



entry	catalyst	mol %	solvent	t (°C)	%, yield[a]
1	none	–	PhMe	140	trace[b]
2	$FeBr_2$	10	PhMe	140	49
3	CoTPP	10	PhMe	140	40
4	$RuCl_3 \cdot nH_2O$	10	PhMe	140	33
5	$[(cod)Ir(OMe)]_2$	5	PhMe	140	33
6	$Rh_2(O_2CC_3F_7)_4$	5	PhMe	140	25
7	$Rh_2(O_2CC_7H_{15})_4$	5	PhMe	140	64
8	$Rh_2(esp)_2$	5	PhMe	140	78
9	$Rh_2(esp)_2$	5	DME	140	72
10	$Rh_2(esp)_2$	5	DCE	140	53
11	$Rh_2(esp)_2$	5	PhMe	100	26

[a]As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b]Decomposition of **9a** observed.

to start our investigation because of its facile construction from 2-azidophenylboronate **7a**[12,13] and β-ketoester-derived vinyl triflate **8**.[14,15] This azide proved to be remarkably robust: very little reaction occurred below 140 °C in the absence of transition metal complexes. At this temperature submission of **9a** to a series of Fe,[16] Co,[17] Ru,[18] or Ir complexes[19]—all established N-atom transfer metal catalysts—did induce decomposition but only poor yields of *N*-heterocyclic products were observed (entries 2−5). In contrast, clean conversion was

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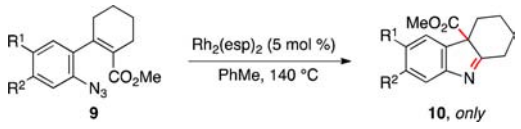
observed when **9a** was exposed to rhodium(II)-carboxylate complexes (entries 6–8). To our surprise, the 3*H*-indole product resulted from ester migration, a phenomenon not predicted by our migratorial aptitude scale.[11b] While 3*H*-indole was observed with both perflourinated and alkyl carboxylate complexes, DuBois's tetradentate $Rh_2(esp)_2$ produced **10a** in the highest, most reproducible yield (entry 8),[20] which we attribute to the thermal robustness of this catalyst.[21] A screen of different solvents revealed toluene to be the ideal reaction media: lower conversions were obtained in ethereal or chlorinated solvents (entries 8–10).[22] Lowering the temperature also led to incomplete reactions (entry 11).

Using these optimized conditions,[23] the scope of our transformation was investigated by varying the identity of the aryl azide moiety (Table 2). Aryl azides bearing a range of

Table 2. Effect of Changing the Aryl Azide Moiety on 3*H*-Indole Formation



9 **10**, *only*

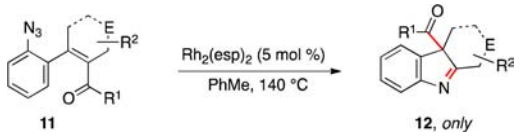
entry	#	R^1	R^2	%, yield[a]
1	a	H	H	80
2	b	Me	H	77
3	c	F	H	62
4	d	Cl	H	86
5	e	OCF_3	H	71
6	f	H	NHBoc	74
7	g	H	OMe	70
8	h	H	Me	77
9	i	H	F	68
10	j	H	CF_3	65
11	k	H	Ac	72

[a]Isolated yield of **10** after neutral alumina chromatography; only product obtained.

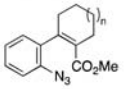
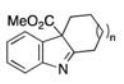
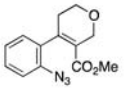
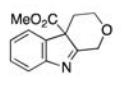
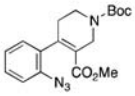
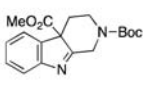
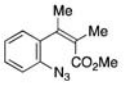
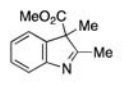
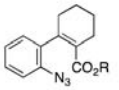
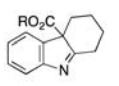
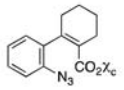
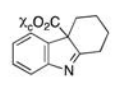
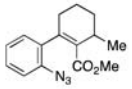
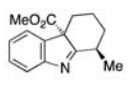
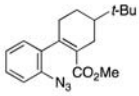
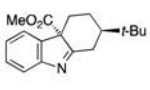
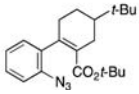
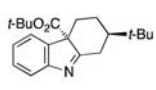
functional groups were efficiently transformed into 3*H*-indoles irrespective of the electronic nature of the R^1- or R^2-substituent. The success of 5-substituted aryl azides (entries 6–11) demonstrates that our transformation can generate 3*H*-indoles, which cannot be formed as single isomers using Fischer-indole or Fischer-indole-type reactions (entries 6–11).[24]

The scope was further investigated by systematically varying the identity of the *ortho*-substituent of the aryl azide (Table 3). First, the *o*-cyclohexenyl group could be enlarged to cycloheptene or cyclooctene without attenuating the yield of 3*H*-indole (entries 1 and 2). Further, aryl azides containing O- or N-atoms in the *o*-heterocycle were efficiently converted to product (entries 3 and 4). The latter *β*-carboline is a ubiquitous structural motif in bioactive alkaloids,[1] and our method represents a novel approach to this important substructure. A cycloalkenyl *o*-substituent is not required in our tandem reaction: aryl azide **11e** was smoothly converted into 3*H*-indole **12e** (entry 5). Next, the identity of the migrating ester was modified (entries 6–9). We found that 3*H*-indoles could be produced using isopropyl, *tert*-butyl, or allyl esters. Unfortunately, the menthol ester **11i** exhibited poor conversion and only modest diastereoselectivity (entry 9). The diastereoselectivity of our process was further probed by introducing substitution on the *o*-cyclohexenyl substituent (entries 10–14).

Table 3. Effect of Changing the *o*-Alkenyl Substituent on 3*H*-Indole Formation



11 **12**, *only*

entry	#	aryl azide	3*H*-indole	%, yield[a]
1	a			84 (n = 2)
2	b			70 (n = 3)
3	c			87
4	d			84
5	e			76
6	f			66 (R = iPr)
7	g			57 (R = *t*-Bu)
8	h			59 (R = allyl)
9	i			37 (dr 66:33)
10	j			55 (dr 75:25)
11	k			65 (dr 82:18)
12	l			30 (dr 86:14)

[a]Isolated yield of **12** after neutral alumina chromatography; only product obtained.

While only modest diastereoselectivity was observed with an allylic substituent (entry 10), an 82:18 ratio of diastereomers was observed with a homoallylic *tert*-butyl group (entry 11). This diastereoselective ratio was increased only slightly to 86:14 if the methyl ester was replaced with a *tert*-butyl ester albeit with a reduced yield (entry 12).

While several mechanisms are possible,[25] 3*H*-indole formation is attributed to the tandem electrocyclization–[1,2] migration outlined in Scheme 2. Rhodium-catalyzed decomposition of aryl azide **9a** produces rhodium nitrene **13**,[17d,26] which undergoes a 4*π*-electron-5-atom electrocyclization. The resulting *N*-heterocycle **14** contains a benzylic carbocation, which can undergo ring contraction to produce spirocycle **15** or a [1,2] ester shift to produce **16**.[10d–f] We believe that ester migration is favored because the buildup of positive charge in the transition state leading to **15** will be destabilized by the ester group.[10f] Double crossover experiments revealed that the ester does not escape the solvent sheath during the shift.[22] Release of the rhodium carboxylate affords 3*H*-indole **10a**.

If this catalytic cycle were operating, we anticipated that the 3*H*-indole product might be controlled by the identity of the *β*-

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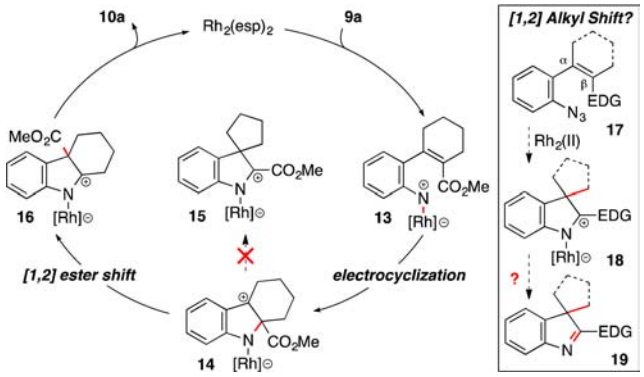
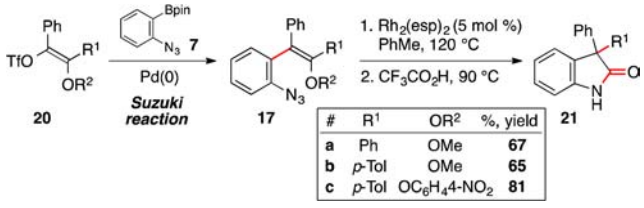
Scheme 2. Possible Mechanism for Rh_2(II)-Catalyzed 3*H*-Indole Formation



substituent (Scheme 2). Our analysis of the two possible [1,2] migration reactive intermediates (or transition states leading to them) indicated that ring contraction might be favored if the ester substituent was replaced with one that would stabilize **15** in comparison to **16**. We anticipated that incorporation of an electron-donating group (EDG) at the β-position of styryl azide **17** would trigger a [1,2] alkyl shift in **18** to enable formation of 3*H*-indoles **19**.

To test this assertion, styryl azides bearing β-alkoxy substituents were targeted to potentially access oxindoles (Scheme 3). These substrates are easily synthesized by cross-

Scheme 3. Synthesis of 3,3-Diaryl Oxindoles



#	R^1	OR^2	%, yield
a	Ph	OMe	67
b	*p*-Tol	OMe	65
c	*p*-Tol	$OC_6H_4$4-NO_2	81

coupling 2-azidophenyl boronate ester **7** with vinyl triflate **20**, which was synthesized following a report by Wood et al.[27] Exposure of the resulting styryl azide to reaction conditions produced 3*H*-indole **19**, which was converted to oxindole **21** upon acid-mediated hydrolysis in 67% yield from **21**. The identity of the migrating aryl group could be modified to *para*-tolyl to afford oxindole **21b** in 65% yield. Changing the β-alkoxy substituent to *para*-nitrophenol not only facilitated synthesis of triflate **20c** and styryl azide **17c** but also improved the yield of 3*H*-indole to 83%. These 3,3-diaryl oxindoles are common motifs present in anticancer agents, which inhibit translation initiation.[4b−e]

In conclusion, we have developed a new method to access 3*H*-indoles or oxindoles from aryl azides through an electrocyclization−[1,2] shift reaction of the rhodium *N*-aryl nitrene. The step economy of our process is enhanced by the accessibility of our substrates from cross-coupling 2-azidoarylboronates with the vinyl triflate derived from β-ketoesters. Currently, we are working toward understanding the mechanism of our reaction in order to control the selectivity of the migration step.

■ ASSOCIATED CONTENT

Supporting Information

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.

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Notes

The authors declare no competing financial interest.

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(22) Refer to the Supporting Information for more details.

(23) **General Procedure for 3*H*-Indole Formation.** To a mixture of styryl azide **9** and $Rh_2(esp)_2$ (5 mol %) was added toluene (0.1 M). The resulting mixture was heated at 140 °C. After 16 h, the mixture was cooled to rt, diluted with CH_2Cl_2, and concentrated *in vacuo*. Purification of the residue by MPLC (3:97−30:70 EtOAc/hexanes) using alumina afforded 3*H*-indole **10**.

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Org. Lett. 2015, 17, 802−805