Angewandte Chemie International Edition

DOI: 10.1002/anie.201308611

Heterocycles

Dirhodium(II) Carboxylate Catalyzed Formation of 1,2,3-Trisubstituted Indoles from Styryl Azides[**]

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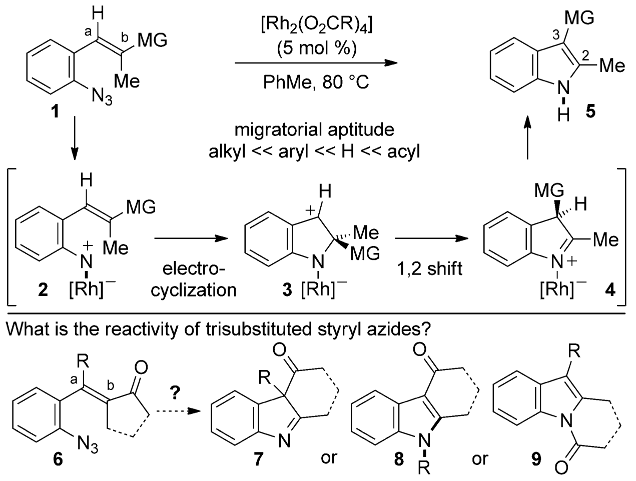
***Abstract:** Dirhodium(II)-carboxylate complexes were discovered to promote the selective migration of acyl groups in trisubstituted styryl azides to form 1,2,3-trisubstituted indoles. The styryl azides are readily available in three steps from cyclobutanone and 2-iodoaniline.*



Scheme 1. Development of a new metal-catalyzed electrocyclization/migration tandem reactions of substituted styryl azides. MG = migrating group.

The development of new processes to construct polysubstituted indoles continues to motivate the work of synthetic groups because of the fundamental importance of this structural motif across diverse disciplines.[1] Because of the poor selectivity in Fischer-Indole-type processes, the synthesis of 6- or 4-(poly)substituted indoles as single isomers remains a synthetic challenge.[2] In particular, reactions that create the indole through formation of two new C–C bonds to the nitrogen atom are exceedingly sparse.[3] Our laboratory has focused on developing transition-metal-catalyzed methods which transform vinyl or aryl azides into heterocycles by exploiting the mechanism of C–N bond formation.[4] Our investigation of β,β-disubstituted styryl azides (**1**) revealed that 2,3-disubstituted indoles could be synthesized as single isomers through a selective 1,2-shift from **3**, a shift which occurred after electrocyclization of the rhodium nitrene (Scheme 1).[5] During aromatization to give the indole **5**, we recognized that the α-hydrogen migrates to the nitrogen atom. At the conclusion of these studies we were curious to determine what the effect would be on the reaction when this α-hydrogen atom was replaced with an alkyl or aryl group. We anticipated that trisubstituted styryl azides (**6**) would be ideal substrates for this query because our migratorial aptitude studies predict that the carbonyl group should preferentially shift.[5b] Once reaction conditions are found to form a metal aryl nitrene from **6**, a cascade reaction might then be triggered to produce the N-heterocycles **7**–**9**. If the reactivity of **6** mirrors that of the β,β-disubstituted styryl azide **1** then either **7** or **8** would be produced. In contrast to our expectations, however, we report herein that rhodium(II) carboxylate complexes catalyze the formation of the 1,2,3-trisubstituted indoles **9**, as single isomers from trisubstituted styryl azides through exclusive carbonyl migration. The substitution pattern embedded in **9** is present in a variety of natural products including the *Strychnos* and *Kopsia* alkaloid families.[6,7]

To discover the optimal reaction conditions for metal aryl nitrene formation, the reactivity of the trisubstituted styryl azide **11** towards a range of transition-metal complexes was examined (Table 1). This azide is readily constructed in two steps through a palladium-catalyzed Heck cross-coupling ring-expansion reaction between 2-iodoaniline and the cyclobutanol **10**, with subsequent azidation of the resulting aniline.[8,9] The trisubstituted styryl azide **11** proved to be less reactive than the β,β-disubstituted styryl azides we previously investigated: effervescence was not observed at 80 °C (entry 1 and 2). Increasing the temperature to 100 °C, however, produced the 1,2,3-trisubstituted indole **12** as the only product when **11** was exposed to rhodium carboxylates (entries 3–6).[10] Among the rhodium complexes surveyed, we found that [Rh$_2$(OAc)$_4$] and [Rh$_2$(esp)$_2$][11] were the most efficient catalysts for indole formation (entries 2 and 6). While we attribute the success of [Rh$_2$(esp)$_2$] to the thermal robustness inherent in its tetradentate ligands,[12] the activity of [Rh$_2$(OAc)$_4$] was surprising because its insolubility rendered it impotent in our previous methods.[4,5] Its increased solubility at elevated temperatures, however, appears to transform it into a competent catalyst. On larger reaction scales, however, we found that [Rh$_2$(esp)$_2$] outperformed [Rh$_2$(OAc)$_4$] to provide the indole product with higher yields and greater reproducibility. Lowering the catalyst loading or reducing the reaction temperature led to attenuated yields of the 1,2,3-trisubstituted indole product (entries 7 and 8). Examination

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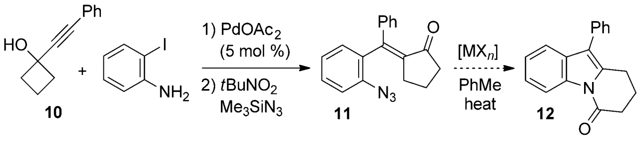
[**] We are grateful to the National Institutes of Health NIGMS (R01GM984945) and the University of Illinois at Chicago for their generous support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201308611.

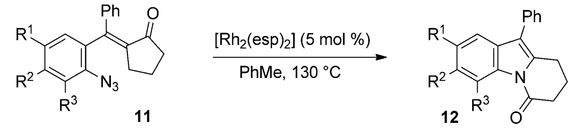
Table 1: Determination of optimal reaction conditions for indole formation.



Entry	$[MX_n]$	mol%	T [°C]	Yield [%][a]
1	none	n.a.	130	n.r.
2	$[Rh_2(O_2CCF_3)_4]$	5	100	60
3	$[Rh_2(O_2CC_3F_7)_4]$	5	100	76
4	$[Rh_2(O_2CCH_3)_4]$	5	100	90
5	$[Rh_2(O_2CC_7H_{15})_4]$	5	100	89
6	$[Rh_2(esp)_2]$	5	100	70
7	$[Rh_2(esp)_2]$	5	80	n.r.
8	$[Rh_2(esp)_2]$	5	130	90
9	$[Rh_2(esp)_2]$	1	100	75
10	CuI	10	100	n.r.
11	$FeBr_2$	10	100	42
12	$RuBr_3 \cdot nH_2O$	10	100	35
13	CoTPP	5	100	38
14	[{Ir(cod)(OMe)}$_2$]	10	100	54

[a] As determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard; only N-heterocycle obtained. esp = α,α,α′,α′-tetramethyl-1,3-benzene-dipropionate. cod = cyclo-1,5-octadiene, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, TPP = tetraphenylporphyrin.

Table 2: Scope of rhodium(II) carboxylate catalyzed carbonyl shift.



Entry	11	R^1	R^2	R^3	12 Yield [%][a]
1	**11a**	H	H	H	87
2	**11b**	OMe	H	H	93
3	**11c**	Me	H	H	96
4	**11d**	F	H	H	93
5	**11e**	Cl	H	H	95
6	**11f**	Br	H	H	95
7	**11g**	CF_3	H	H	81
8	**11h**	NO_2	H	H	90
9	**11i**	H	Me	H	97
10	**11j**	H	Cl	H	87
11	**11k**	H	H	OMe	70

[a] Yield of isolated **12** after filtration through silica gel. It was the only product obtained.

of other established nitrogen-atom-transfer catalysts, including copper,[13] iron,[14] ruthenium,[15] cobalt,[16] or iridium[17] complexes did not result in improved reaction outcomes (entries 9–13). Changing the reaction media to ethereal, chlorinated, or other aromatic solvents also did not increase the yield of the migration reaction.[18]

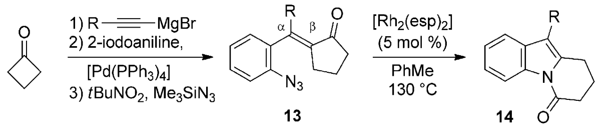
Using $[Rh_2(esp)_2]$ as the catalyst, a series of styryl azides (**11**) were examined to determine the scope and limitations of our carbonyl 1,2-shift reaction (Table 2). Our optimal reaction conditions enabled the indole product to be purified by simply filtering the reaction mixture through a pipette column of silica gel. We found that a range of electron-releasing and electron-withdrawing R^1 substituents are tolerated in our reaction to give the 1,2,3,5-substituted indoles **12a–h** (entries 1–8). Even substrates bearing strong electron-withdrawing substituents, such as the nitro group, were efficiently converted into the indole product. Pleasingly, our reaction also tolerates R^2 substituents to enable access to the 6-substituted indoles **12i** and **12j**, which cannot be made regioselectively using the Fischer–Indole reaction (entries 9 and 10).[2] Finally, the influence of increasing the steric environment around the azide was examined using **11k** (entry 11). This reaction proceeded smoothly, albeit slower, to afford **12k** in 70% yield.

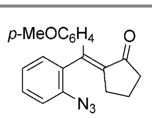
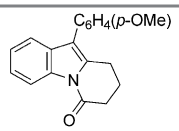
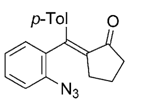
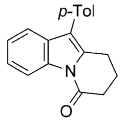
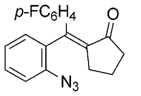
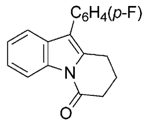
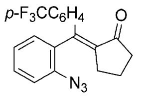
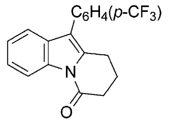
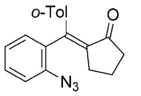
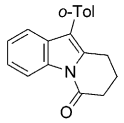
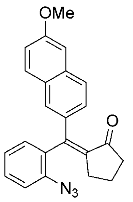
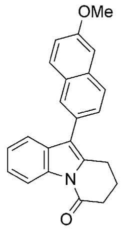
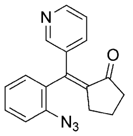
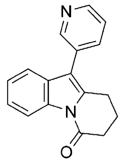
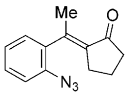
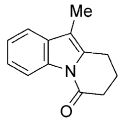
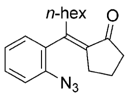
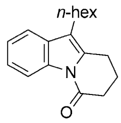
Next, the identity of the α-substituent on the styryl azide **13** was varied to determine its influence on the reaction (Table 3). These substrates were readily synthesized by simply varying the identity of the magnesium acetylide substituent.[8] We found that changing the α-aryl group, including increasing its steric nature, did not change the outcome of reaction (entries 1–6). In contrast to our earlier studies, substrates bearing Lewis-basic substituents could be converted into product (entry 7). Using our optimal reaction conditions an α-pyridyl substituent proved to be too Lewis basic: the pink color of its reaction mixture indicated that it sequestered the rhodium catalyst (entry 7). By raising the catalyst loading and the reaction temperature, however, the yield of the indole **14g** was increased from 20% to 59%. The styryl azides **13h** and **13i** illustrated that the α-aryl group could be replaced with an alkyl group without deleterious effects, thus illustrating the generality of our method (entries 8 and 9). For the substrates surveyed here, migration of the β-carbonyl group occurred exclusively to the indole nitrogen atom to afford the 1,2,3-trisubstituted indole **14** to illustrate the generality and selectivity of our process.

A catalytic cycle for our rhodium(II) carboxylate catalyzed carbonyl migration reaction can be proposed to account for the exclusive formation of the 1,2,3-trisubstituted indole product in our tandem electrocyclization/carbonyl migration reaction (Scheme 2). Coordination of the styryl azide to the rhodium carboxylate complex produces **15**.[19] Extrusion of N_2 forms the rhodium nitrene **16**,[20] which undergoes a 4π-electron-5-atom electrocyclization to form the spirocyclic cation **17**. While a 1,2 carbonyl shift from **17** could occur to form the 2*H*-indole **18**, this product was reported by Ban and co-workers to be unstable and prone to fragmentation upon exposure to Lewis or Brønsted acids.[21] Consequently, it appears likely that the Lewis-acidic rhodium(II) carboxylate triggers fragmentation of **17** or **18** to produce the acylium ion **19**. This acylium ion could be attacked by the indole at the C3-position to reform the kinetic,[22] but unstable **18**,[23] or at the anionic nitrogen atom to afford the thermodynamic indole product **12** and regenerate the rhodium(II) carboxylate catalyst.

To investigate the mechanism of the 1,2-acyl shift, a double crossover experiment was performed using the styryl azides **20** and **21** [Eq. (1)]. We anticipated that if N-acylation was slow that the acylium ion might diffuse and four indole products would be observed. If N-acylation occurred

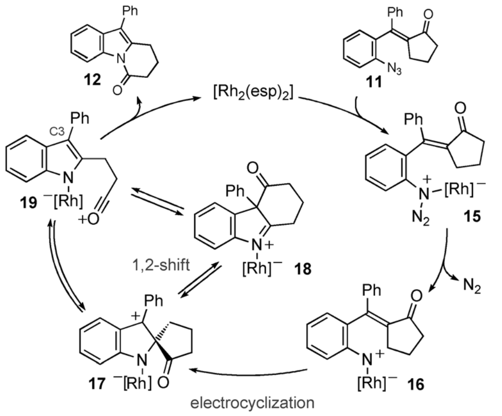
Table 3: Effect of changing the α-substituent on the reaction yield.



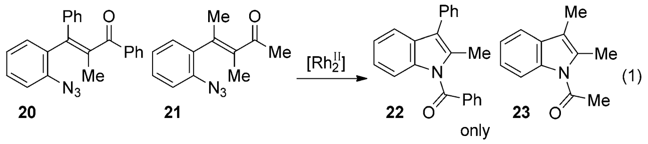
Entry	13		14		Yield [%][a]
1[c]		**13a**		**14a**	77
2		**13b**		**14b**	89
3		**13c**		**14c**	75
4		**13d**		**14d**	85
5		**13e**		**14e**	72
6		**13f**		**14f**	96
7		**13g**		**14g**	20 (59)[b]
8		**13h**		**14h**	88
9		**13i**		**14i**	55

[a] Yield of isolated **14** after chromatography on silica gel. It was the only product obtained. [b] Obtained using 10 mol% of $[Rh_2(esp)_2]$ at 140°C.

faster than diffusion, or was concerted then only two indole products would be obtained. Exposure of **20** and **21** to the reaction conditions produced only the indoles **22** and **23**, thus confirming that the 1,2-shift is either concerted or that N-acylation occurs faster than diffusion.



Scheme 2. Potential catalytic cycle.



In conclusion, we discovered that rhodium(II) carboxylate complexes catalyze the formation of 1,2,3-trisubstituted indoles from α,β,β-trisubstituted styryl azides through the exclusive migration of the β-carbonyl group. The requisite styryl azides are readily available in two steps from 2-iodoaniline, and our reaction tolerates a range of different substituents at the α-position as well as on the aryl azide. Together these attributes combine for an efficient synthesis of polysubstituted indoles, which cannot be accessed selectively using Fischer-Indole-type processes. Our future work will target exploiting this new reactivity in the design of methods which access complex, functionalized N-heterocycles from readily available trisubstituted styryl azides.

Received: October 2, 2013
Published online: November 26, 2013

Keywords: azides · electrocyclic reactions · indole · rhodium · synthetic methods

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[22] The C3-position is established as the kinetic site of reaction in indoles, see: a) F. Terrier, M.-J. Pouet, J.-C. Halle, S. Hunt, J. R. Jones, E. Buncel, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1665; b) S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, *71*, 9088.

[23] Our efforts to trap either of the catalytic intermediates **17**, **18**, or **19** through the addition of a nucleophile (e.g. allyl stannane) or by performing the reaction in 4-methoxyanisole were not successful.