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Probing the Origin of Carboxylate Migration Selectivity in Rh₂(II)-Catalyzed *N*-Heterocycle Formation from Trisubstituted Styryl Azides.

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ABSTRACT

Exposure of trisubstituted styryl azides to Rh₂(II)-carboxylate catalyst triggers a tandem 4π-electron-5-atom electrocyclization-migration reaction. Herein we illustrate that the innate preference for selectivity of the carboxylate migration to form 3*H*-indoles can be overcome by steric pressure to produce only 1,2,3-trisubstituted indoles.

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Bicyclic *N*-heterocycles appear in an array of alkaloids with significant biological activity, and have inspired significant research into easing their synthesis.¹ Throughout his career, Professor Harry Wasserman was instrumental in developing processes which eased the synthesis of these important scaffolds. By leveraging the reactivity embedded in vicinal tricarbonyls, his group was able to facilitate access to a range of heterocycles including indole-alkaloids.² Their work in elucidating the underpinning mechanistic principles of these stereoselective reactions and rearrangements continues to guide reaction development.³ Our group has pursued the regioselective synthesis of polysubstituted *N*-heterocycles from *ortho*-substituted aryl azides by exploiting the propensity of metal *N*-aryl nitrenes to participate in electrocyclization–rearrangement reactions.⁴ Recently, our investigations have focused on trisubstituted styryl azides to determine the structural elements that control the migration selectivity of the β-carbonyl substituent.⁵ We observed that β-acetyl groups migrated to N1 to afford 1,2,3-trisubstituted indoles,^{5a} whereas β-carboxylate groups shifted instead to C3 to yield 3*H*-indoles (Scheme 1).^{5b} The selectivity of the [1,2] shift appeared to be under electronic control with the major product resulting from the lower energy iminium ion transition state.^{5b} At the conclusion of these studies, we were curious if the inherent preference of the substrate could be overcome by the steric environment to turnover the regioselectivity of the carboxylate migration.

Scheme 1. Regioselectivity dependence of β-migrating group identity on indole formation.

To investigate the steric impact on our reaction, [2,2,1]-bicyclic trisubstituted styryl azides were investigated (Scheme 2). Azide **7** was readily synthesized by cross-coupling 2-azidophenylboronic acid pinacolate ester with a vinyl triflate derived from β-ketoester of norcamphor using the optimal conditions we reported/discovered that tolerated the azido-functionality.⁶ Exposure of **7** to 5 mol % of Rh₂(esp)₂ at 140 °C produced a 29:71 mixture of 3*H*-indole **8** and indole **9**.^{7,8} This result shows that increasing the steric pressure changes the reaction preference from 3*H*-indole to indole formation. To determine if the reaction could be controlled to afford only indole, the steric environment was further increased in styryl azide **10a**, which was also synthesized by a Pd-catalyzed cross-coupling reaction a vinyl triflate-derived from camphor and 2-azidoarylboronic pinacolate ester.⁶ In line with our hypothesis, submission of **10a** to Rh₂(esp)₂ at 120 °C produced only indole **12a** in 84%.

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Scheme 2. Effect of increasing the steric environment on the migration regioselectivity.

To further investigate this selectivity a series of [2.2.1]-bicyclic trisubstituted styryl azides were surveyed (Table 1). The effect of changing the electronic nature of the aryl azide was examined first. We found that adding substituents to the 4-position of aryl azide **10** did not adversely affect either the yield or the regioselectivity of the migration (entries 1 – 4). In every case, the carboxylate migrated to the nitrogen to produce indole **12**. Next, we surveyed the effect of changing the R²-group. Irrespective of whether the aryl ring was substituted with an electron-releasing- or electron-withdrawing group, indole **12** was obtained in high yield and perfect regioselectivity (entries 5 – 8). The substitution patterns present in these indoles cannot be accessed as single regioisomers from Fischer indole-type reactions.⁹ Finally, changing the identity of the migrating carboxylate was examined. While the *tert*-butylcarboxylate migrated to nitrogen to access Boc-protected indole **12i** (entry 9), to our dismay we were unable to synthesize the analogous β -allyl ester or β -benzoyl substituted aryl azide **10**. In line with our previous work,^{4b} the β -carboxylate group could be replaced with a hydrogen to afford only the C–H bond functionalization product, indole **12j** (eq 1).

Table 1. Effect of changing the electronic environment on indole selectivity.

entry	#	R ¹	R ²	CO ₂ R ³	%, yield ^a	11 : 12
1	a	H	H	CO ₂ Me	84	0 : 100
2	b	Me	H	CO ₂ Me	88	0 : 100
3	c	F	H	CO ₂ Me	93	0 : 100
4	d	Cl	H	CO ₂ Me	90	0 : 100
5	e	H	OMe	CO ₂ Me	97	0 : 100
6	f	H	Me	CO ₂ Me	89	0 : 100
7	g	H	CF ₃	CO ₂ Me	96	0 : 100
8	h	H	Ac	CO ₂ Me	85	0 : 100
9	i	H	H	CO ₂ <i>t</i> -Bu	77	0 : 100

^a Isolated yield after silica gel chromatography.

Second, we investigated the effect of changing the nature of the bicyclic *ortho*-substituent on the reaction outcome (Scheme 3). The *gem*-dimethyl carbon bridge of camphor-derived **10** was replaced in **13** with a Ts-N unit and submitted to reaction conditions. To our surprise, migration of the carboxylate group to nitrogen was accompanied with elimination of the tosyl-amine to produce indole **13** as the only isolable product in 34%. Next, the effect of moving the bridge of the bicycle one carbon further away by examining pinene-derived aryl azides **16**. As expected, reducing the steric pressure on the reaction center produced a mixture of the 3*H*-indole **17** and indole **18**. Changing the electronic nature of the aryl azide portion with a methoxy, methyl and trifluoromethoxy R-group only had a small, but measurable effect on the ratio of 3*H*-indole **17** to indole **18**. Although migration of the carboxylate group to nitrogen was the major product in all four cases, the ratio was slightly reduced as the R-substituents became more electron-withdrawing.

Scheme 3. Effect of changing the *ortho*-bicyclic substituent on the reaction outcome.

While several potential mechanisms are possible, we believe that the reaction outcome can be explained by the catalytic cycle depicted in Scheme 4. Coordination of the rhodium(II) carboxylate to aryl azide **10** followed by N₂ extrusion produces rhodium *N*-aryl nitrene **19**.¹⁰ A 4- π -electron-5-atom-electrocyclization produces **20**,¹¹ whose torqueselectivity results from minimizing the steric interactions between the *gem*-dimethyl groups and the both the rhodium catalyst and methylester. Formation of the benzyl carbocation in **20** can trigger a [1,2] carboxylate migration to produce either 3*H*-indole **21** or indole **22**. We anticipate that migration to C3 is disfavored because of the steric interactions that develop between the *gem*-dimethyl group and the aryl portion. In contrast, these destabilizing interactions do not develop if the carboxylate group migrates to the nitrogen in **22**. Release of the rhodium catalyst produces indole **12**.

Scheme 4. Potential catalytic cycle for indole formation.

Several control experiments were performed to test our proposed catalytic cycle (Scheme 5). First, a double crossover

experiment was performed to ascertain the concertedness of the carboxylate migration. Submission of a 1:1 mixture of aryl azides **10e** and **10i** to reaction conditions produced only indoles **12e** and **12i**. This result suggests that the migration is either concerted or occurs faster than diffusion of the carboxylate from the reaction. Second, the reversibility of the carboxylate migration was examined by submitting 3*H*-indole **17a** to reaction conditions. If migration was reversible, we anticipated that **17a** could be converted to indole **18a**. In contrast to our expectations, 3*H*-indole **17a** proved to be inert upon exposure to reaction conditions to suggest that the migration step is irreversible.

Scheme 5. Mechanistic experiments.

In conclusion, we have shown that the outcome of our Rh₂(II)-catalyzed tandem reaction sequence depends on both the electronic- and steric nature of the substrate. Increasing the steric environment around the *ortho*-alkenyl substituent can overwhelm the inherent electronic preference of the system. Our future studies are aimed exploiting this balance to change the mechanistic proclivity of the rhodium *N*-aryl nitrene intermediate.

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