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Rh₂(II)-Catalyzed Intramolecular Aliphatic C–H Bond Amination Reactions Using Aryl Azides as the *N*-Atom Source

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Abstract

Rhodium(II) dicarboxylate complexes were discovered to catalyze the intramolecular amination of unactivated primary-, secondary-, or tertiary aliphatic C–H bonds using aryl azides as the *N*-atom precursor. While a strong electron-withdrawing group on the nitrogen atom is typically required to achieve this reaction, we found that both electron-rich- and electron-poor aryl azides are efficient sources for the metal nitrene reactive intermediate.

The development of transition metal-catalyzed aliphatic C–H bond amination reactions that is stereoselective, uses readily accessible starting materials and catalysts, and is environmentally benign continues to inspire the efforts of research groups around the world.^{1,2} While considerable progress has been made, the current methods are still limited by the oxidative conditions to form the nitrene and the requirement for strong electron-withdrawing groups on the nitrene (Scheme 1). The use of azides as the source of the *N*-atom source would address these limitations because no oxidant would be required and the only by-product of the reaction would be the environmentally benign N₂-gas.³ While azides have been used for a variety of *N*-atom transfer reactions,^{2b,4} these transformations also require electron-withdrawing groups on the azide. We anticipated that a more general, complementary solution for aliphatic C–H bond amination might emerge if conditions were found to use electron-neutral aryl azides as the nitrogen-atom source. While we have reported a number of sp²-C–H bond amination reactions using aryl azides,⁵ our mechanism studies suggest that C–N bond formation occurs via a 4π-electron-5-atom electrocycloization.^{5b} In contrast, aliphatic C–H bond amination requires metal-catalyzed C–H insertion or H-atom abstraction mechanisms—processes that have remained elusive to control using aryl azides as the *N*-atom source.⁶

In search of the optimal conditions to achieve intramolecular aliphatic C–H bond amination using aryl azides, the reactivity of *ortho-tert*-butyl aryl azide **1a** towards transition metal complexes was examined (Table 1).⁷ This aryl azide is relatively thermally robust with no reaction observed at 120 °C (entry 1).⁸ Exposure of **1a** to commercially available transition metal complexes known to catalyze *N*-atom transfer reactions was met with limited success. Indoline **3a** was not observed in the presence of iron,⁹ copper,¹⁰ cobalt,^{2b,4a-c} ruthenium,^{2a,6,11} or iridium¹² complexes (entries 2 – 7). Partial conversion to indoline **2** was observed when rhodium octanoate was used (entry 8). We anticipated that the partial conversions resulted from catalyst decomposition, and we found that using more thermally

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robust $\text{Rh}_2(\text{esp})^{13}_2$ improved both the conversion and yield of the process (entry 9). Examination of alternative solvents, concentration, and temperatures, however, did not increase the yield, and control experiments revealed that oxidative decomposition of the indoline occurred during purification.

To improve the isolated yield of the amination reaction, in situ protection of the nitrogen atom was attempted. In line with our assumption, we found that the reaction yield was improved when the indoline was protected with either a Boc or Ac-group (entries 10 and 11). The reaction outcome appeared to correlate with the pKa of the acid by-product of the protection reaction: aniline was produced when the stronger benzoic- and triflic acids were produced (entries 12 and 13).¹⁴

Using these optimal conditions, the electronic- and steric constraints of the aliphatic C–H bond amination reaction was investigated (Table 2). In contrast to existing amination processes,^{2,4} our method does not require an electron-withdrawing group on the nitrogen: aryl azides bearing either *para*-electron-releasing, neutral or withdrawing groups were converted to indolines (entries 1 – 7). Illustrating the chemoselectivity of our process, olefins were tolerated as substituents (entry 5).

To further examine the scope of the transformation the identity of the *ortho*-alkyl substituent was varied (Table 3). While replacing one of the methyl groups with an ester group did not diminish the yield (entry 1), substitution with hydrogen reduced the reaction efficiency (entry 2). Amination can be achieved at tertiary- and secondary C–H bonds, although dehydrogenation of **5d** occurred to afford indole. Dehydrogenation could be circumvented if an additional substituent was introduced at the benzylic position in of the aryl azide. Submission of **4e** – **4k** to reaction conditions produced indolines as single diastereomers (entries 5 – 11). In contrast, pyrolysis of aryl azide **4g** was reported by Smolinsky to produce a 1:1 mixture of diastereomers.¹⁵ Although reaction with the methyl C–H bond in azide **4l** could produce a six-membered ring, only amination of the methyl C–H bond was observed to afford indoline **5l** as the sole product. While single diastereomers were obtained from substrates bearing *orthocyclopentyl*- or *cyclohexyl*-groups, diminished stereoselectivity was observed with *ortho*-cycloheptyl substituted aryl azide **4m** (entry 13).

While indoline formation could occur through several different mechanisms,^{12a,16} our reactivity trends suggest that C–N bond formation occurs through *N*-atom transfer (Scheme 2). Coordination of the rhodium(II) carboxylate to either the α - or γ -nitrogen of the aryl azide produces **7**.¹⁷ Extrusion of N_2 then forms the rhodium nitrene **8**.¹⁸ While rhodium could mediate a reversible one-electron oxidation to generate free nitrene,¹⁹ our current mechanistic hypothesis is that the nitrene remains metal bound for the C–H bond amination step since pyrolysis involving free nitrene is not diastereoselective.¹⁵ The mechanism of the amination step could be stepwise or concerted: hydride-²⁰ or *H*-atom abstraction^{16a,21} (to form **9** or **10**) followed by recombination produces the C–N bond; alternatively this bond could be formed through the concerted insertion^{16c,22} of the metal nitrene into the proximal C–H bond via transition state **11**. Finally, the indoline is produced upon dissociation of the rhodium complex from **12**.

Insight into the initial steps of the catalytic cycle was provided by the reactivity of 4-substituted aryl azides towards reaction conditions (eq 1). Underscoring the difference between our method for aliphatic C–H bond amination and others, we found that more electron-rich aryl azides (e.g. **1b**) were more reactive toward reaction conditions. The increased reactivity of **1b** relative to **1a** could be due to either preferred coordination of **1b** to $\text{Rh}_2(\text{esp})_2$ or an accelerated N_2 extrusion from the resulting azide-metal complex **7**.

To examine the nature of the C–H bond cleavage step, two-labeled aryl azides were examined (Scheme 3). We anticipated that the number of indoline diastereomers from **14-*d*₂** would reveal if the mechanism of C–H bond amination was stepwise or concerted. If the reaction was concerted, insertion into either the β-C–H or β-C–D bond would produce only two products. In contrast, if a radical (or cation) was formed at the β-carbon then scrambling of the C2-stereocenter could occur before recombination to form both **15-*d*₂** and **16-*d*₂**. In support of a stepwise C–H bond amination, two diastereomers of 2-phenyl indoline (d.r. 50:50) and an intramolecular kinetic isotope effect of 6.7 were observed.²³ The magnitude of this isotope effect is significantly smaller than reactions involving an H-atom abstraction by an aryl nitrene²¹ or an aryl metal nitrene^{6c} ($k_{\text{H}}/k_{\text{D}}$ 12 – 14), but larger than hydride shift reactions ($k_{\text{H}}/k_{\text{D}}$ ~ 2 for Cannizzaro reaction and Meerwein–Ponndorf–Verley reduction).^{24–26} Smaller kinetic isotope effects were observed at lower reaction temperatures revealing that our amination reaction occurs above the isokinetic temperature and as a consequence is under entropic control.^{27,28} We found, however, that the spatial constraints of this reaction override these isotope effects: cyclopentanone-derived aryl azide **17-*d*₁** reacted preferentially with the *syn*-C–D bond to form **18** exclusively.²⁹

In conclusion, we have developed an efficient and diastereoselective rhodium(II)-catalyzed aliphatic C–H bond amination reaction that uses an aryl azide as the nitrogen-atom source. Our method distinguishes itself from previously reported aliphatic C–H bond amination reactions by not requiring a strong electron-withdrawing group on the nitrogen atom. The reactivity of stereospecific labeled aryl azides revealed that the amination reaction occurred stepwise with the *syn*-C–H bond. Our current aims are to more deeply examine the nature of the catalytic intermediates in this C–H bond amination reaction and to extend this newfound reactivity of aryl azides to the stereoselective synthesis of complex, functionalized *N*-heterocycles

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Nitrogen Substituent Requirements for Aliphatic C–H Bond Amination.

Scheme 2.
Possible Mechanisms for Intramolecular Aliphatic C–H Bond Amination from Aryl Azides.

Scheme 3.
Isotope Labeling Studies.

Table 1

Development of Optimal Conditions.

entry	catalyst	additive	conv., % ^a	yield, % ^b
1	none	n.a.	0	0
2	FeBr ₂	n.a.	0	dec ^c
3	CuBr	n.a.	0	0
4	CoTPP	n.a.	0	0
5	RuCl ₃ • <i>n</i> OH ₂	n.a.	0	0
6	[Ir(cod)OMe] ₂	n.a.	0	0
7	[Rh(cod)OMe] ₂	n.a.	10	0 ^c
8	Rh ₂ (O ₂ CC ₇ H ₁₅) ₄	n.a.	35	35
9	Rh ₂ (esp) ₂	n.a.	99	75
10	Rh ₂ (esp) ₂	Boc ₂ O	99	90
11	Rh ₂ (esp) ₂	Ac ₂ O	99	83
12	Rh ₂ (esp) ₂	Bz ₂ O	99	aniline
13	Rh ₂ (esp) ₂	Tf ₂ O	99	aniline

^a As determined using ¹H NMR spectroscopy.

^b Isolated after silica gel chromatography.

^c Aniline formed.

Table 2

Scope and Limitations of Indoline Formation.

entry	1	R	yield, % ^a
1	a	H	84
2	b	OMe	63
3	c	Me	54
4	d	CH ₂ CH ₂ Ph	64
5	e	CHCHPh	70
6	f	Ph	54
7	g	3,5-OMe ₂ C ₆ H ₃	58
8	h	Br	73

^aIsolated after silica gel chromatography.

Table 3

Scope and Limitations of Indoline Formation.

entry	4	aryl azide	indoline	yield, % ^a
1	a			70
2	b			20
3	c			55 ^b
4	d			30 ^c
5	e			80
6	f			73
7	g			70
8	h			63

entry	4	aryl azide	indoline	yield, % ^a
9	i			85
10	j			73
11	k			82
12	l			86
13	m			63 d.r. 82:18

^a Isolated after silica gel chromatography.

^b 20% aniline observed.

^c 30% aniline observed.