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Intramolecular Ir(I)-Catalyzed Benzylic C–H Bond Amination of *ortho*-Substituted Aryl Azides

Ke Sun, Rachna Sachwani, Kathleen J. Richert, and Tom G. Driver*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois, 60607-7061

Abstract

Iridium(I) catalyzes the intramolecular benzylic C–H bond amination of *ortho*-homobenzylic-substituted aryl azides to produce indolines at 25 °C.

Iridium-catalyzed functionalization of aryl C–H bonds provides regioselective access to valuable aromatic- and heteroaromatic boronic esters.¹ Analogous Ir-catalyzed C–H bond functionalizations of aliphatic substrates, however, are rare.² Since iridium complexes are known to decompose azides,³ we were interested in exploring the N-atom-transfer ability of these compounds as a means to achieve aliphatic C–H bond amination.^{4,5} Herein, we report an iridium(I)-catalyzed benzylic C–H bond amination reaction that transforms *ortho*-homobenzylic-substituted aryl azides into indolines at 25 °C (eq 1).

(1)

Aryl azide **4** (R = H) was initially selected to investigate the potential for intramolecular Ir(I)-catalyzed C–H bond amination.⁶ 2-Phenylindole and aniline **5** were produced when **4** was exposed to [(cod)Ir(Cl)]₂ (5 mol %) at 100 °C (Table 1, entry 1).⁷ Further screening showed that conversion of **4** to aniline, indole, or indoline was dependent on the identity of the iridium catalyst. No reaction was observed with either [(coe)₂Ir(Cl)]₂ or [(cod)₂Ir]BF₄ (entries 2 and 3), but 2 mol % of [(cod)Ir(OMe)]₂ catalyzed the transformation at 25 °C to form indoline **7** as the major product (entry 4).⁸ Further optimization revealed that the addition of an electron-

tgd@uic.edu.

Supporting Information Available

Complete experimental procedures, spectroscopic and analytical data for the products (PDF) is available free of charge via the Internet at <http://pubs.acs.org>.

withdrawing substituent to **4** ($R = CF_3$) provided only the indoline product in high yield (entry 5). Control experiments show that iridium is essential for this C–H bond amination process (entries 6 – 8). Metal-free thermolysis exhibited the opposite electronic trend as the iridium-catalyzed process: better indoline conversions were observed with the electron-rich aryl azide substrate (**4**, $R = H$, 70%) than the electron-deficient **4** ($R = CF_3$, 15%; entries 6 and 7).⁹ Low yields (25%) of **7** were also reported by Murata and co-workers when **4** ($R = H$) was irradiated with a high pressure mercury lamp (entry 8).^{9c} In contrast to our earlier studies,¹⁰ exposure of **4** to rhodium(II) complexes resulted in no reaction (entry 9). Rhodium(I) complexes, e.g. [(cod)Rh(OMe)]₂, were also incompetent catalysts (entry 10).⁶ These results emphasize the importance of the metal ligand combination present in [(cod)Ir(OMe)]₂ to trigger the decomposition of *ortho*-homobenzyl-substituted aryl azides at room temperature.

Investigation of the conversion of aryl azide **4** into indoline **7** provided the optimal conditions to examine the scope of the intramolecular Ir-catalyzed C–H bond amination. As suggested by the effect of the fluoride substituent in entry 5 of Table 1, the transformation was sensitive to the electronic nature of the aryl azide substituents: the yield of indoline increased as stronger electron-withdrawing R^1 - and R^2 -groups were added to aryl azide **8** (Table 2, entries 1 – 7). In contrast, the electronic identity of the homobenzylic aryl group did not influence the yield of reaction (entries 8 – 11). Presently, our Ir(I)-catalyzed reaction is limited to the amination of secondary benzylic C–H bonds as substrates with R^3 -alkyl groups or tertiary C–H bonds did not react (entries 12 and 13).^{11,12}

A variety of vinyl- and aryl azides were examined to determine if [(cod)Ir(OMe)]₂ could catalyze the amination of aryl- or vinyl C–H bonds (Scheme 1). While all azidoacrylates tested (cf. **10a**) were found to be unreactive towards [(cod)Ir(OMe)]₂, aryl azides were cleanly converted to indoles or carbazoles (**11b** – **11i**) by [(cod)Ir(OMe)]₂ in comparable yields to Rh₂(O₂CC₃F₇)₄. Enhanced regioselectivity was observed in the reaction of **10i** with [(cod)Ir(OMe)]₂ as compared to Rh₂(O₂CC₃F₇)₄. These substrates, however, required higher reaction temperatures (40 °C) and increased catalyst loading (5 mol %) of iridium than aryl azides **8**. The reactivity of aryl azides **10** was also not dependent on the electronic nature of their substituents. These differences suggest that a different mechanism (or rate-determining step) might be operating for aromatic *N*-heterocycle formation than for indoline formation.

Several intermolecular competition experiments were performed to determine if C–H bond activation accounted for indoline formation (Scheme 2).¹³ In this mechanism, activation of the benzylic C–H bond² by the iridium catalyst produces η^3 -benzyl **12**.¹⁴ Subsequent nucleophilic attack by the pendant azide then forms the C–N bond in the indoline. If this mechanism was occurring, the rate of benzylic C–H bond activation should be retarded when the electron-withdrawing R^2 -substituents are present.¹⁵ Analogously, the rate of nucleophilic addition of azide should be attenuated with electron-deficient R^1 -substituents. In contrast to these expectations, aryl azides **8b** and **8i** exhibited nearly equal reactivity towards [(cod)Ir(OMe)]₂ and the more electron-deficient **8g** reacted faster than **8b**. These results suggest that a benzylic C–H bond activation/nucleophilic addition mechanism does not account for *N*-heterocycle formation.

The faster rate of indoline formation by the electron-deficient aryl azide **8g** as well as the production of aniline, a common nitrene decomposition product, suggests that an electrophilic iridium nitrenoid (**14**) is generated in the mechanism (Scheme 3).^{3,16} This species could be produced by coordination of the aryl azide with the iridium catalyst (to form α -**13** or γ -**13**)¹⁷ followed by extrusion of N₂. Carbon–nitrogen bond formation could then occur by two different pathways: a concerted insertion of the nitrenoid via **15** or hydrogen-atom abstraction (to form **16**) followed by radical recombination.^{18,19}

To examine the mechanism of C–H bond cleavage, two competition experiments were performed (eq 2). When **8g-d₂** and **10h-d₅** were exposed to reaction conditions, intramolecular kinetic isotope effects (KIE) of 5.06 and 1.04 were observed to suggest that different mechanisms (or change in the rate-determining step) are occurring for aryl azides **8** and **10**. Our measured value for **8g-d₂** (5.06) is smaller than the intramolecular KIE of the photochemical reaction of **8g-d₁** (14.7)^{9e} and is comparable to the KIE measured for the reaction of a rhodium nitrenoid with cyclohexane (5).^{18d,20} While the photochemical KIE was interpreted as evidence for a triplet nitrene intermediate, the combination of radical clock studies, Hammett correlation studies with isotope experiments indicate that the electronic state of the rhodium nitrenoid is a singlet.^{18,20} The magnitude of our KIE (5.06) is similar to those observed for the Rh₂(II)-nitrenoid insertion mechanism,¹⁸ but further experiments are necessary to rule out alternative mechanisms,²¹ including one involving triplet **14**.^{22,23}

(2)

In conclusion, we have demonstrated that iridium(I)-complexes can catalyze the functionalization of benzylic C–H bonds to produce indolines at 25 °C. Future mechanistic experiments are aimed at determining the electronic nature of the reactive intermediates. The resulting mechanistic insight will be exploited in the development of new asymmetric methods to form *N*-heterocycles from azides by metal-mediated nitrogen atom transfer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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6. Please refer to the Supporting Information for a complete listing of the transition metal complexes examined.
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11. The pyrolysis of *ortho*-alkyl substituted aryl azides produces indolines in moderate to good yields: e.g. 3-methylindoline (44%), 2-ethylindoline (55%), hexahydrocarbazole (86%). See: ref 9b and Smolinsky G. J Org Chem 1961;26:4108.
12. Irradiation of *ortho*-alkyl-substituted aryl azides leads to varied yields of indolines: while insertion of the nitrene into a tertiary C–H bond occurs to form 50% of the indoline (see ref 9d), insertion into a secondary C–H bond produces only 11% of the indoline product (see ref 9c).
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20. An intramolecular KIE of 3.5 was measured for the Rh₂(II)-catalyzed C–H amination reaction of adamantane-1,3-d₂. See: Mueller P, Baud C, Naegeli I. J Phys Org Chem 1998;11:597.
21. A mechanism involving the oxidative addition of the C–H bond is possible, but we believe unlikely. Kinetic isotope effects of 2.0 and 4.6 were reported for iridium-catalyzed aryl C–H bond borylation. See: ref 13c.
22. A range of intramolecular kinetic isotope effects (2.8 – 8.7) were observed in the oxidation of adamantane with PhI=O–metalloporphyrin systems. See: Sorokin A, Robert A, Meunier B. J Am Chem Soc 1993;115:7293.
23. If indoline is produced by an H-atom abstraction/radical recombination mechanism, it is not apparent why azide 8m does not produce product.

Scheme 1.

Comparison of Catalytic Efficiency of Ir(I) versus Rh(II) for Aromatic *N*-Heterocycle Formation.

Scheme 2.
Intermolecular Competition Experiments.

Scheme 3.
Potential Mechanism for Benzylic C–H Amination.

Table 1

Optimization of Reaction Conditions to Form Indoline.

entry	L_nMX_n	mol %	temp (°C)	R	yield (%) ^{a,b} (5:6:7)
1	[(cod)Ir(Cl)] ₂	5	100	H	45 (15:30:0)
2	[(coe) ₂ Ir(Cl)] ₂	5	100	H	no reaction
3	[(cod) ₂ Ir]BF ₄	5	100	H	no reaction
4	[(cod)Ir(OMe)] ₂	5	25	H	90 (19:13:58)
5	[(cod)Ir(OMe)] ₂	2	25	CF ₃	93 (0:0:100)
6	none	n.a.	120	CF ₃	15 (0:0:100)
7	none	n.a.	120	H	90 (0:22:78)
8 ^c	none	n.a.	hν	H	31 (0:6:25)
9	Rh ₂ (O ₂ CC ₃ F ₇) ₄	5	100	H	no reaction
10	[(cod)Rh(OMe)] ₂	5	80	H	no reaction

^a As determined using ¹H NMR spectroscopy.^b Schlenck techniques used.^c ref 9c.

Table 2

Scope of Ir-Catalyzed Indoline Formation.

entry	8

1

entry

8

2

8b

3

8c

entry

8

4

8d

5

8e

6

8f

entry

8

7

8

entry

8

9

8i

10

8j

11

8k

entry

8

12

entry

8

13

^a As determined using ^1H NMR spectroscopy.

^b Yield of indoline and indole after chromatography over SiO_2 ; refer to the Supporting Information for more details.

^c Azide **8** recovered from reaction mixture.