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

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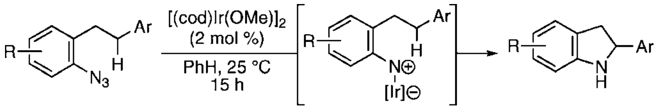
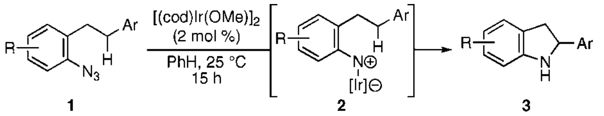
ABSTRACT



Ir-Catalyzed Benzylic C–H Bond Amination

Iridium(I) catalyzes the intramolecular benzylic C−H bond amination of *ortho*-homobenzyl-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*-homobenzyl-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)$_2$Ir(Cl)]$_2$ or [(cod)$_2$Ir]BF$_4$ (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-

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[1] (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (c) Lu, B.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 7508.

[2] Ir-catalysts were found to be significantly less reactive than the corresponding Rh-complexes, see: (a) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (b) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168.

[3] (a) Collman, J. P.; Kubota, M.; Vastine, F. D.; Sun, J. Y.; Kang, J. W. *J. Am. Chem. Soc.* **1968**, *90*, 5430. (b) Basolo, F.; Lane, B. C.; McDonald John, W.; Myers, V. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 4934. (c) Johnson, E. D.; Basolo, F. *Inorg. Chem.* **1977**, *16*, 554.

[4] Reviews of aliphatic C−H bond functionalization: (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Du Bois, J. *Chemtracts* **2005**, *18*, 1. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (e) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.

[5] For recent, leading reports of related Pd-catalyzed C−H aminations, see :(a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (c) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184.

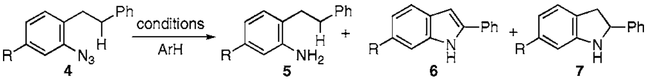
[6] Please refer to the Supporting Information for a complete listing of the transition metal complexes examined.

[7] When air and water were not rigorously excluded from the reaction mixture, only 10−15% of aniline **5** was produced.

[8] The formation of aniline appears to inhibit the reaction. When 10 mol % of aniline was added to the reaction mixture, no consumption of azide **4** was observed.

10.1021/ol901317j CCC: $40.75

Table 1. Optimization of Reaction Conditions to Form Indoline



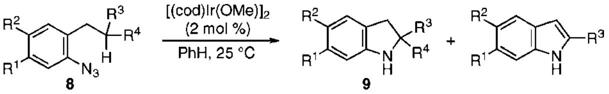
entry	L_nMX_n	mol %	temp (°C)	R	yield (%)[a,b] (**5**:**6**:**7**)
1	$[(cod)Ir(Cl)]_2$	5	100	H	45 (15:30:0)
2	$[(coe)_2Ir(Cl)]_2$	5	100	H	no reaction
3	$[(cod)_2Ir]BF_4$	5	100	H	no reaction
4	$[(cod)Ir(OMe)]_2$	5	25	H	90 (19:13:58)
5	$[(cod)Ir(OMe)]_2$	2	25	CF_3	93 (0:0:100)
6	none	n.a.	120	CF_3	15 (0:0:100)
7	none	n.a.	120	H	90 (0:22:78)
8[c]	none	n.a.	hν	H	31 (0:6:25)
9	$Rh_2(O_2CC_3F_7)_4$	5	100	H	no reaction
10	$[(cod)Rh(OMe)]_2$	5	80	H	no reaction

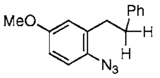
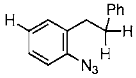
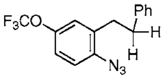
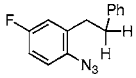
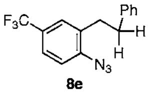
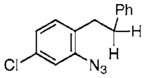
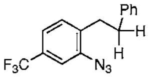
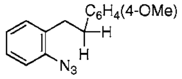
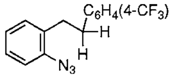
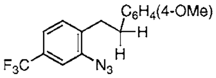
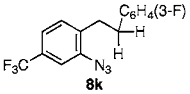
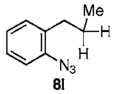
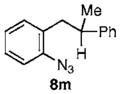
[a] As determined using ^{1}H NMR spectroscopy. [b] Schlenk techniques used. [c] Reference 9d.

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).[9d] In contrast to our earlier studies,[10] exposure of **4** to rhodium(II) complexes resulted in no reaction (entry 9). Rhodium(I) complexes, for example, $[(cod)Rh(OMe)]_2$, 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]

Table 2. Scope of Ir-Catalyzed Indoline Formation



entry	8	9 yield, %[a]	indole yield, %[a]	isolated[b]
1	 **8a**	no reaction[c]		...
2	 **8b**	58	11	52
3	 **8c**	75	13	72
4	 **8d**	72	21	66
5	 **8e**	91	2	81
6	 **8f**	81	13	71
7	 **8g**	93	4	82
8	 **8h**	53	15	59
9	 **8i**	29	39	60
10	 **8j**	81	4	75
11	 **8k**	85	8	80
12	 **8l**	no reaction[c]		...
13	 **8m**	no reaction[c]		...

[a] As determined using ^{1}H 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.

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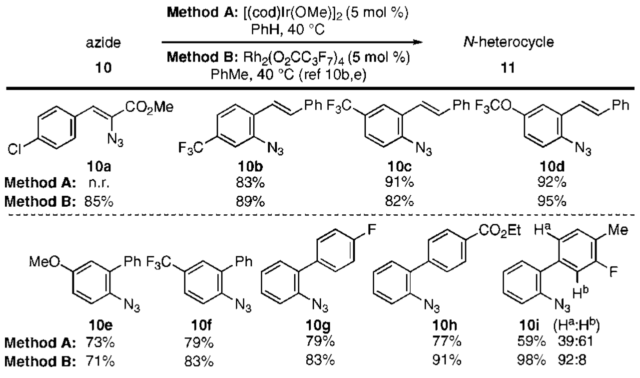
(9) For related reports on the thermolysis or photolysis of aryl azides with alkyl-*ortho*-substituents, see: (a) Rapoport, H.; Smolinsky, G. *J. Am. Chem. Soc.* **1960**, *82*, 934. (b) Smolinsky, G. *J. Am. Chem. Soc.* **1961**, *83*, 2489. (c) Smolinsky, G.; Feuer, B. I. *J. Am. Chem. Soc.* **1964**, *86*, 3085. (d) Murata, S.; Yoshidome, R.; Satoh, Y.; Kato, N.; Tomioka, H. *J. Org. Chem.* **1995**, *60*, 1428. (e) Murata, S.; Tsubone, Y.; Kawai, R.; Eguchi, D.; Tomioka, H. *J. Phys. Org. Chem.* **2005**, *18*, 9.

(10) (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (b) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056. (c) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191. (d) Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367. (e) Stokes, B. J.; Jovanoviæ, B.; Dong, H.; Riell, R. D.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 3225.

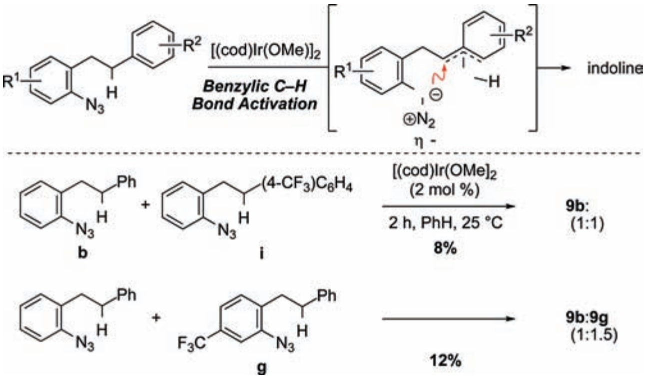
A variety of vinyl and aryl azides were examined to determine if $[(cod)Ir(OMe)]_2$ could catalyze the amination of aryl or vinyl C−H bonds (Scheme 1). While all azidoacrylates tested (cf. **10a**) were found to be unreactive toward $[(cod)Ir(OMe)]_2$, aryl azides were cleanly converted to indoles or carbazoles (**11b**−**11i**) by $[(cod)Ir(OMe)]_2$ in comparable yields to $Rh_2(O_2CC_3F_7)_4$. Enhanced regioselectivity was observed in the reaction of **10i** with $[(cod)Ir(OMe)]_2$ as compared to $Rh_2(O_2CC_3F_7)_4$. 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.

Scheme 1. Comparison of Catalytic Efficiency of Ir(I) versus Rh(II) for Aromatic *N*-Heterocycle Formation



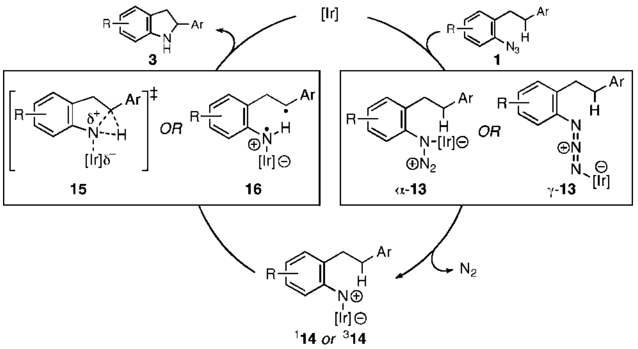
Several intermolecular competition experiments were performed to determine if C−H bond activation accounted for indoline formation (Scheme 2).[13] In this mechanism, activation of the benzylic C−H bond[2] by the iridium catalyst produces η^3-benzyl **12**.[14] Subsequent nucleophilic attack by the pendant 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 toward $[(cod)Ir(OMe)]_2$ 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.

Scheme 2. Intermolecular Competition Experiments



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 N_2. 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]

Scheme 3. Potential Mechanism for Benzylic C−H Amination



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[11] The pyrolysis of *ortho*-alkyl substituted aryl azides produces indolines in moderate to good yields: for example, 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 9d).

[13] For recent, leading mechanistic studies of related iridium-mediated C–H bond activations, see: (a) ref 1a and 1b. (b) Yung, C. M.; Skaddan, M. B.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 13033. (c) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263. (d) Tenn, W. J.; Young, K. J. H.; Oxgaard, J.; Nielsen, R. J.; Goddard, W. A.; Periana, R. A. *Organometallics* **2006**, *25*, 5173. (e) Zhu, Y.; Fan, L.; Chen, C.-H.; Finnell, S. R.; Foxman, B. M.; Ozerov, O. V. *Organometallics* **2007**, *26*, 6701.

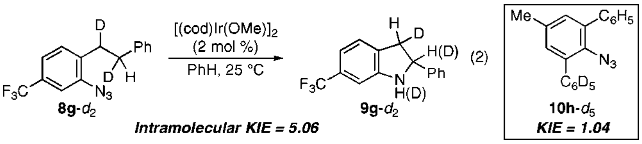
[14] For iridium η^3-benzyl complexes, see: Fryzuk, M. D.; McConville, D. H.; Rettig, S. J. *J. Organomet. Chem.* **1993**, *445*, 245.

[15] For a discussion of the effect of aryl-substitution on benzylic C−H bond activation, see: (a) Driver, T. G.; Day, M. W.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **2005**, *24*, 3644. (b) Heyduk, A. F.; Driver, T. G.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2004**, *126*, 15034.

[16] For recent reports of Ir-catalyzed C-atom-transfer reactions, see: (a) Lebel, H.; Ladjel, C. *Organometallics* **2008**, *27*, 2676. (b) Whited, M. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **2008**, *130*, 5874. (c) Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 10327.

[17] For the crystal structure of benzyl azide coordinated to an Ir(III)-complex through the α-*N*-atom, see: Albertin, G.; Antoniutti, S.; Baldan, D.; Castro, J.; Garcia-Fontan, S. *Inorg. Chem.* **2008**, *47*, 742.

To examine the mechanism of C−H bond cleavage, two competition experiments were performed (eq 2). When **8g**-d_2 and **10h**-d_5 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**-d_2 (5.06) is smaller than the intramolecular KIE of the photochemical reaction of **8g**-d_1 (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 Rh_2(II)-nitrenoid insertion mechanism,[18] but further experiments are necessary to rule out alternative mechanisms,[21] including one involving triplet **14**.[22,23]



Intramolecular KIE = 5.06

KIE = 1.04

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.

Acknowledgment. We are grateful to the National Institutes of Health NIGMS (R01GM084945), Petroleum Research Fund administered by the American Chemical Society (46850-G1), and the University of Illinois at Chicago for their generous support. We also thank Profs. L. Anderson (UIC) and M. Newcomb (UIC) for insightful discussions, Mr. B. J. Stokes (UIC) for repeating entry 7, Table 2, and Mr. Furong Sun (UIUC) for mass spectrometry data.

Supporting Information Available: 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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(18) Rh_2(II): (a) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562. (b) Lin, X.; Zhao, C.; Che, C.-M.; Ke, Z.; Phillips, D. L. *Chem.—Asian J.* **2007**, *2*, 1101. (c) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343. (d) Huard, K.; Lebel, H. *Chem.—Eur. J.* **2008**, *14*, 6222. (e) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558.

(19) For a review of the H-atom abstraction-recombination mechanism of the related C−H bond hydroxylation, see: Newcomb, M.; Toy, P. H. *Acc. Chem. Res.* **2000**, *33*, 449.

(20) An intramolecular KIE of 3.5 was measured for the Rh_2(II)-catalyzed C-H amination reaction of adamantane-1,3-d_2. 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.