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Palladium-Catalyzed C–H Activation/ Intramolecular Amination Reaction: A New Route to 3-Aryl/Alkylindazoles

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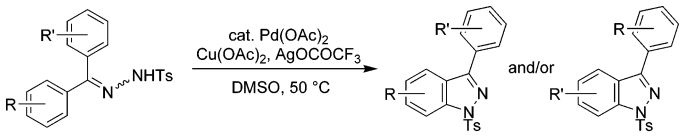
ABSTRACT



R, R' = H, OMe, NO_2, CN, CO_2Et, OH, NH_2, Br, *etc.*

A method for the catalytic C–H activation of hydrazone compounds followed by intramolecular amination is described. It requires the use of a catalytic amount of $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$ and $AgOCOCF_3$, which efficiently effects the cyclization to afford variously substituted indazoles. The reactions proceed under relatively mild conditions and thus tolerate a variety of functional groups, including alkoxycarbonyl and cyano groups and halogen atoms.

Inter- and intramolecular carbon−nitrogen bond formation is important in both academic and industrial chemistry, due to the high prevalence of nitrogen-atom-containing biologically active compounds and pharmaceuticals. In particular, Pd- or Cu-catalyzed amination reactions of aryl halides or pseudohalides have been widely used to construct such compounds, and highly active catalyst systems have been reported.[1,2] In these cases, however, aryl electrophiles must possess a halide or pseudohalide moiety, which can limit their utility. On the other hand, notable advances in which catalytic C−H bond activation is accomplished by using Ru,[3] Rh,[4] and Pd[5] followed by C−N bond formation have been described recently. Buchwald reported Pd(II)-catalyzed C−H activation/intramolecular amidation for carbazole synthesis in 2005.[5a] More recently, Che disclosed that it was possible to activate sp^3 as well as sp^2 C−H bonds in the presence of $Pd(OAc)_2$, followed by intermolecular amidation.[5b] Here we describe a new approach to the synthesis of 3-aryl/alkylindazoles,[6] which are important pharmacophores, via Pd-catalyzed C−H amination reactions of hydrazone compounds

(1) For selected recent reports on Pd-catalyzed amination of aryl halides, see: (a) Strieter, E. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 925−928. (b) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923−12931. (c) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928−3934. (d) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403−9410. (e) Olof, J. *Synthesis* **2006**, 2585−2589. (f) Shashank, S.; Hartwig, J. F. *Organometallics* **2007**, *26*, 340−351. (g) Chen, G.; Lam, W. H.; Fok, W. S.; Lee, H. W.; Kwong, F. Y. *Chem. Asian J.* **2007**, *2*, 306−313.

(2) For selected recent reports on Cu-catalyzed amination of aryl halides, see: (a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742−8743. (b) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270−3273. (c) Zhu, D.; Wang, R.; Mao, J.; Xu, L.; Wu, F.; Wan, B. *J. Mol. Catal. A* **2006**, *256*, 256−260. (d) Yeh, V. S. C.; Wiedeman, P. E. *Tetrahedron Lett.* **2006**, *47*, 6011−6016.

(3) For recent reports, see: (a) Leung, S. K.-Y.; Tui, W.-M.; Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629−16640. (b) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465−3468. (c) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. *Chem.−Eur. J.* **2002**, *8*, 1563−1572.

(4) For recent reports, see: (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379. (b) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673. (c) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600.

(5) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049.

(6) (a) Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695−2711. (b) Inamoto, K.; Katsuno, M.; Yoshino, T.; Suzuki, I.; Hiroya, K.; Sakamoto, T. *Chem. Lett.* **2004**, 1026−1027.

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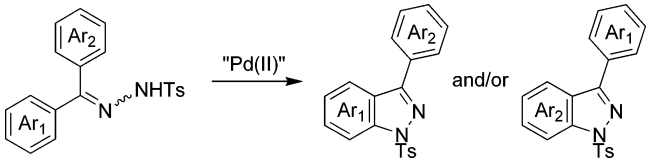
Scheme 1. C−H Amination for the Synthesis of Indazoles

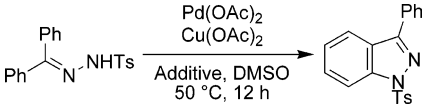


(Scheme 1). This method features the use of novel combinations such as $Pd(OAc)_2/Cu(OAc)_2/AgOCOCF_3$, which successfully effect catalytic C−H activation[7] followed by amination to give the cyclized products. Indeed, compared with the previously reported methods, this cyclization proceeds under milder reaction conditions (50 °C) and hence tolerates various functional groups such as alkoxycarbonyl and cyano groups and halogen atoms.

Our investigation began by examining the conversion of benzophenone tosylhydrazone **1** to the corresponding indazole **2** (Table 1). From systematic screenings of a range of palladium sources, oxidants, and solvents,[8] we found that the C−H amination reaction would occur in DMSO at 50 °C in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ and provide indazole **2** in high yield (85%, entry 2). In this system, however, a reduced amount of catalyst loading led to a significant drop in conversion (entry 2 vs 3). Thus, we next evaluated the effects of added compounds. We were pleased to find that some Ag salts, especially $AgOCOCF_3$, considerably enhanced the process (entries 10−12). Finally, we determined the optimal condition as 10 mol % of $Pd(OAc)_2$, 1 equiv of $Cu(OAc)_2$, and 2 equiv of $AgOCOCF_3$ in DMSO (0.05 M) (entry 12).[9]

The catalytic activity of this system was next evaluated in the cyclization of substrates with various substituents on the benzene ring (**3a**−**3f** in Table 2). Whereas the reaction of **3a**, bearing two *para*-methoxy groups, was sluggish (entry 1), **3b**, with two *para*-methyl groups, gave the desired indazole with good conversion and yield (entry 2). Notably,

Table 1. Optimization of Reaction Conditions[a]

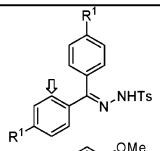
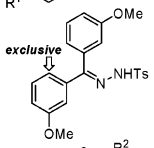
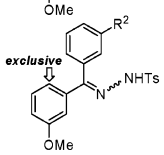


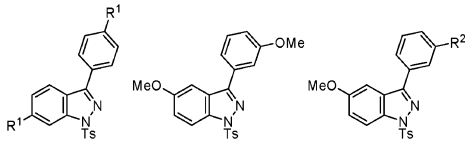
entry	$Pd(OAc)_2$ (mol %)	$Cu(OAc)_2$ (mol %)	additive (mol %)	yield[b,c] (%)	SM[d] (%)
1[e]	50	100	–	95 (95)	0
2	30	100	–	85 (85)	0
3	20	100	–	83 (58)	30
4	20	200	–	85 (58)	32
5	20	100	MS 4Å[f]	81 (65)	20
6	20	100	LiBr (30)	8 (2)	29
7	20	100	Bu_4NBr (20)	81 (43)	47
8	20	100	AgOAc (200)	94 (62)	34
9	20	100	$AgBF_4$ (200)	90 (90)	0
10	20	100	$AgOCOCF_3$ (200)	94 (94)	0
11	10	100	$AgOCOCF_3$ (100)	80 (33)	59
12	**10**	**100**	**$AgOCOCF_3$ (200)**	**90 (90)**	**0**
13	20	0	$AgOCOCF_3$ (200)	81 (26)	68

[a] Reagents: hydrazone **1** (50 mg), $Pd(OAc)_2$ (above), $Cu(OAc)_2$ (above), additive (above), and DMSO (0.05 M). [b] Based on consumed starting material. [c] Isolated yield in parenthesis. [d] SM = starting material. [e] 120 °C. [f] 100 mg.

electron-donating methoxy groups at the *meta* position greatly accelerated this process, providing the product in quantitative yield with high regioselectivity, with the cy-

Table 2. Cyclization of Hydrazones with Various Substituents on the Benzene Ring[a]

entry	substrate	R	product	yield (%)[b,c]	SM[d] (%)
1		R^1 = OMe (**3a**)	**4a**	13 (9)	31
2		R^1 = Me (**3b**)	**4b**	73 (52)	29
3		(**3c**)	**4c**	96 (96)	0
4		R^2 = NO_2 (**3d**)[e]	**4d**	99 (99)	0
5		R^2 = CN (**3e**)[e]	**4e**	98 (98)	0
6		R^2 = CO_2Et (**3f**)[e]	**4f**	84 (41)	51



4a : R^1 = OMe
4b : R^1 = Me
4c
4d : R^2 = NO_2
4e : R^2 = CN
4f : R^2 = CO_2Et

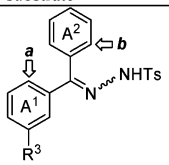
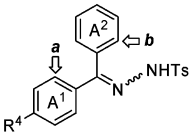
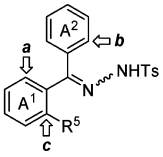
[a] Reagents: hydrazone **3** (50 mg), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (1 equiv), $AgOCOCF_3$ (2 equiv), and DMSO (0.05 M), 50 °C, 10−24 h. [b] Based on consumed starting material. [c] Isolated yield in parenthesis. [d] SM = starting material. [e] Single isomer, geometry could not been determined.

(7) For selected recent reports on Pd(II)-catalyzed C−H bond activation, see: (a) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141−1144. (b) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047−14049. (c) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134−7135. (d) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510−3511. (e) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634−12635. (f) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476−1479. (g) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627−1629. (h) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449−1451. (i) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211−5213. (j) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947−4949. (k) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485−1488. (l) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407−1409. (m) Nakano, M.; Satoh, T.; Miura, M. *J. Org. Chem.* **2006**, *71*, 8309−8311. (n) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951−5958. (o) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288−5295. (p) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328−6335.

(8) For details, see Supporting Information.

(9) (a) Use of $Pd(OCOCF_3)_2$ instead of $Pd(OAc)_2$ in the absence of $AgOCOCF_3$ gave a lower yield and conversion; see Supporting Information. (b) More concentrated conditions such as 0.1 M led to significant decreases in yields; see Supporting Information.

Table 3. Cyclization of α-Phenyl α-Substituted Phenylhydrazones[a]

entry	substrate	R	yield (%)[b,c]	SM[d] (%)	*a* : *b* (: *c*) (%)
1[e]		R^3 = OH (**3g**)[f]	75 (75)	0	75 : 0
2[e]		R^3 = NH_2 (**3h**)[f]	66 (66)	0	66 : 0
3		R^3 = OMe (**3i**)[f]	84 (81)	3	56 : 28[h]
4		R^3 = Cl (**3j**)[f]	84 (84)	0	19 : 65[h]
5		R^3 = Br (**3k**)[g]	86 (79)	9	37 : 49[h]
6		R^3 = NO_2 (**3l**)[f]	43 (32)	26	0 : 43
7[e]		R^4 = NO_2 (**3m**) (*E* : *Z* = 1 : 1.2)	37 (27)	27	0 : 37
8		R^4 = OMe (**3n**) (*E* : *Z* = 1 : 0.04)	51 (22)	57	14 : 37[h]
9		R^4 = OMe (**3n**) (*E* : *Z* = 0.31 : 1)	64 (31)	52	29 : 35[h]
10		R^5 = Br (**3o**)[g]	98 (98)	0	0 : 0 : 98

[a] Reagents: hydrazone **3** (50 mg), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (1 equiv), $AgOCOCF_3$ (2 equiv), and DMSO (0.05 M), 50 °C, 12−24 h. [b] Based on consumed starting material. [c] Isolated yield in parenthesis. [d] SM = starting material. [e] 80 °C. [f] A mixture of *E*-/*Z*-isomers (1.3:1−3:1, determined by ^{1}H NMR or HPLC), geometries could not been determined. [g] Single isomer, geometry could not been determined. [h] Regioisomeric products formed could be separated from one another except **4i**.

clization occurring at the less hindered 6-position of **3c** (entry 3). Furthermore, when the substrate had two different substituents at the *meta* position (−OMe and others, **3d**−**3f**), C−H activation occurred exclusively at the 6-position on the more electron-rich (methoxy group substituted) benzene ring (entries 4−6), suggesting that this cyclization may be controlled by both steric and electronic factors on the arene.

We next examined the scope of the $Pd(OAc)_2$/$Cu(OAc)_2$/$AgOCOCF_3$ system with a series of monosubstituted benzophenone tosylhydrazones (**3g**−**3o**, Table 3). From the reactions of hydrazones with various substituents at the *meta* position (**3g**−**3l**), the corresponding indazoles were obtained in generally good yield (entries 1−6). Interestingly, the regioselectivity of these reactions was highly dependent on the character of the substituent on the arene. For example, the reactions of substrate with electron-donating groups, such as hydroxy and amino groups, proceeded exclusively on the A^1 benzene ring (entries 1 and 2), while substrates that had an electron-withdrawing group on the arene preferentially afforded the products that resulted from the cyclization at the nonsubstituted A^2 benzene ring (entries 4−6). This means that an electron-donating group at the 3-position could accelerate the aromatic electrophilic substitution, leading to the regioselective cyclization. On the other hand, cyclization occurred preferentially on the A^2 benzene ring in the reactions of *para*-substituted hydrazones with both electron-donating and -withdrawing groups (entries 7−9). Furthermore, a comparison of the results between entries 8 and 9 provided insight into the reaction mechanism: when the reactions of **3n** of different isomer ratios (*E*:*Z* = 1:0.04 vs 0.31:1) were carried out independently, the desired indazole **4n** was obtained in similar conversions and yields from the two reactions, along with the starting material in similar *E* and *Z* ratios (*E*:*Z* = 1:1 from entry 8, 1:1.3 from entry 9). These results suggest that the isomerization of hydrazones can occur easily under the conditions used in this system. In addition, a substrate with an *ortho*-bromo group gave the dehalogenated cyclized product exclusively (entry 10).

In a further attempt to broaden the scope of the above system, we found that 3-alkylindazole **6** could also be prepared from the corresponding hydrazone **5** in good yield (Scheme 2).

This C−H amination most likely proceeds via the reaction pathway depicted in Figure 1.[10] Nitrogen-atom-directed association of Pd(II) followed by C−H bond activation may occur first, resulting in the formation of a six-membered palladacycle. Reductive elimination then affords 3-arylindazole and Pd(0). $Cu(OAc)_2$ and $AgOCOCF_3$ may be

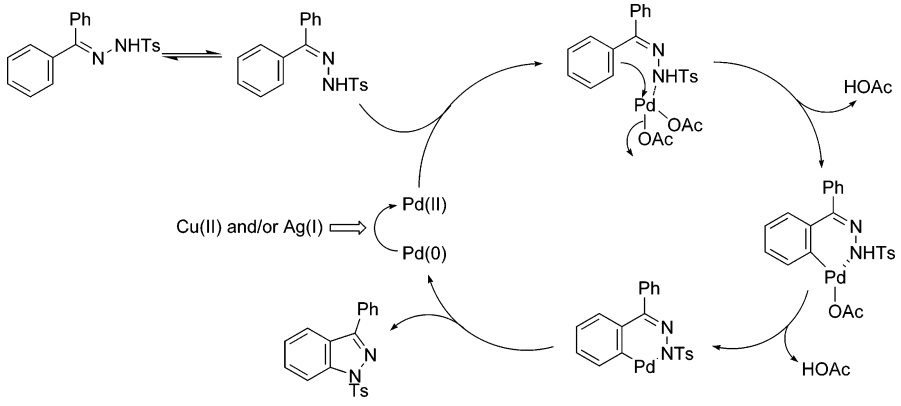


Figure 1. Postulated reaction mechanism.

Scheme 2. Synthesis of 3-Alkylindazole

5
single isomer

6

97% convn yield (SM : 32%)
66% isolated yield

involved in the reoxidation step of Pd(0), although the precise reaction mechanism for this step remains to be elucidated.[11,12]

In summary, we have developed a novel protocol for indazole synthesis via direct C−H activation followed by intramolecular amination in the presence of a Pd(II) catalyst. The reactions proceed under relatively mild reaction conditions, allowing high functional group tolerance. Efforts to understand the precise reaction mechanism as well as to expand the range of substrates are underway in our laboratory.

Supporting Information Available: Detailed experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Buchwald proposed a similar reaction mechanism for the Pd(II)-catalyzed C−H activation process; see ref 5a.

(11) Interestingly, the use of $Cu(OAc)_2$ or $AgOCOCF_3$ alone as an oxidant led to decreased conversions and yields. For details, see Supporting Information.

(12) Very recently, a similar Cu(II)/Ag(I) system was used for the reoxidation of Pd(0) to Pd(II) in C−H arylation of acetanilides; see: Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066−6067.