J|A|C|S COMMUNICATIONS

Published on Web 11/11/2008

Synthesis of Condensed Pyrroloindoles via Pd-Catalyzed Intramolecular C−H Bond Functionalization of Pyrroles

Seung Jun Hwang, Seung Hwan Cho, and Sukbok Chang*

Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701 Republic of Korea

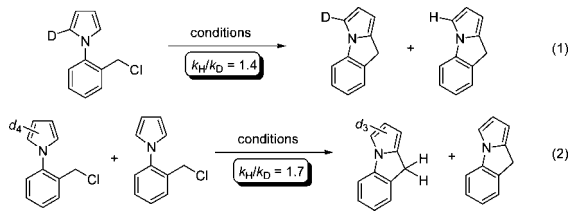
Received September 1, 2008; E-mail: sbchang@kaist.ac.kr

Condensed heterocyclic compounds are playing increasingly important roles as synthetic building blocks, pharmacophores, and electroluminescence materials.[1] Representative examples are mitomycins,[2] one of the most effective antitumor agents, and fluorazene derivatives,[3] intramolecular charge transfer species possessing dual fluorescence mechanisms. Although several efficient synthetic routes to the condensed pyrroloindole skeleton are available,[4] metal-mediated catalytic procedures have appeared only recently.[5] One important example came from Knochel and co-workers who demonstrated that the Pd-catalyzed chemoselective intramolecular sp^3 C−H activation of the methyl group in 2-bromo-*N*-(2-methylaryl)-pyrroles can afford 9*H*-pyrrolo[1,2-*a*]indoles.[6] Described herein are recent developments in establishing a practical route to pyrroloindoles relying on the Pd-catalyzed cyclization of *N*-(2-halobenzyl)pyrroles.[7]

We employed pyrrole derivatives substituted with *N*-2-benzyl (pseudo)halides as model substrates for the optimization (Table 1).[8] This substrate type is especially interesting since transformations utilizing benzylic halides are much less developed,[9] whereas Pd-catalyzed reactions with aryl, vinyl, or allylic halides have been extensively investigated.[10] While no product was obtained using *N*-(2-chlorobenzyl)pyrrole in the absence of additives (entry 1), addition of certain phosphine ligands dramatically changed the reaction progress. For example, while PPh_3 or PCy_3 exhibited limited success (entries 2−3),[11] significant improvement was achieved by employing phosphines derived from biphenyl or ferrocene in benzene. In particular, 2-(di-*tert*-butylphosphino)biphenyl (**3**) turned out to be most effective for the synthesis of fluorazene (entry 6).

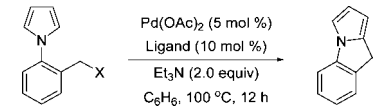
Other palladium species including $PdCl_2$, $Pd(TFA)_2$, $Pd(PPh_3)_4$, or $Pd_2(dba)_3$ displayed decreased activity.[8] The reaction efficiency was sensitive to the type of (pseudo)halides employed. For example, while substrates with mesylate-, tosylate-, or bromo groups underwent the cyclization with satisfactory yields (entries 7−9), that with an iodo group largely failed to cyclize only leading to reductive dehalogenation (entry 10).

To gain insight into the reaction mechanism, we performed kinetic isotope effect (KIE) studies (eqs 1 and 2). Experiments revealed that this cyclization exhibits kinetic isotope effects k_H/k_D (*intra*molecular) = 1.4 and k_H/k_D (*inter*molecular) = 1.7 without *d*-incorporation onto the bridge methylene group.[12]

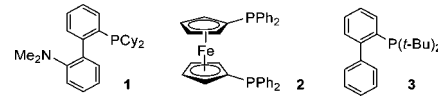


Additional mechanistic information was obtained from the comparison experiments of initial rates of substrates bearing formyl, acetyl, and methyl substituents on the pyrrole ring (Scheme 1). It was observed that electron-deficient substrates underwent the cyclization with faster rates compared to those bearing electron-donating groups.[13]

Table 1. Reaction Optimization for the Cyclization Reaction[a]

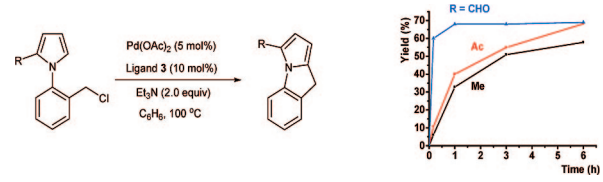


entry	X	ligand	yield (%)[b]
1	Cl	none	<2
2	Cl	PCy_3	4
3	Cl	PPh_3	18
4	Cl	**1**	45
5	Cl	**2**	64
6	Cl	**3**	97
7	OMs	**3**	81
8	OTs	**3**	82
9	Br	**3**	73
10	I	**3**	3

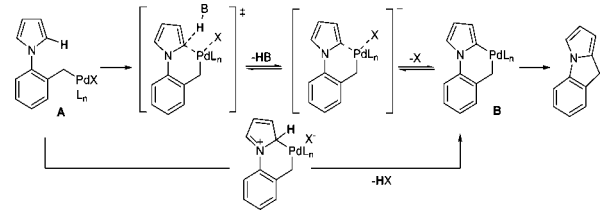


[a] Conditions: Substrate (0.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), Et_3N (2.0 equiv) in benzene (0.3 mL). [b] Isolated yield.

Scheme 1. Comparison of the Relative Initial Rates



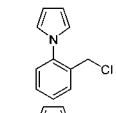
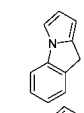
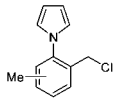
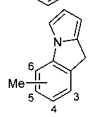
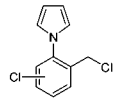
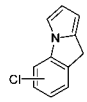
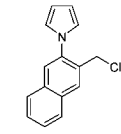
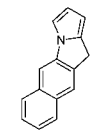
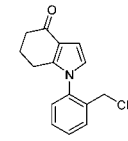
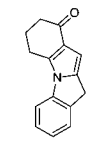
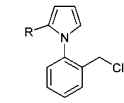
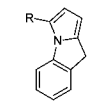
Scheme 2. Proposed Mechanistic Pathways



We tentatively propose the following mechanistic description outlines in Scheme 2. Initial oxidative addition of benzyl halide to Pd(0) takes place leading to a Pd(II) species **A**.[9,11] At this stage, the most plausible palladacycle **B** for the final reductive elimination is proposed to form via either C−H activation or electrophilic aromatic substitution.[14] However, a third possibility involving the Heck-like carbopalladation appears to be less likely judging from the lack of isotope scrambling in the KIE studies.[15]

10.1021/ja806897h CCC: $40.75

Table 2. Pd-Catalyzed Synthesis of Condensed Pyrroloindoles[a]

entry	substrate	product		time (h)	yield (%)[b]
1				0.5	97
2			R = 3-Me	12	89[c]
3			4-Me	0.5	90
4			6-Me	12	60[c]
5			R = 4-Cl	1	95
6			5-Cl	1	92
7				1	97
8				8	90
9			R = CHO	1	68
10			Ac	8	72
11			Me	12	88

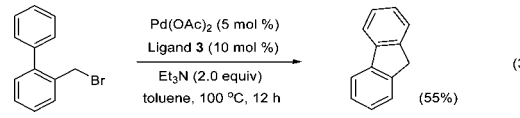
[a] Conditions: substrate (0.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand **3** (10 mol %), Et_3N (2 equiv) in benzene (0.3 mL) at 100 °C for indicated time. [b] Isolated yield. [c] $Pd(OAc)_2$ (10 mol %) and **3** (20 mol %) at 120 °C.

At present, we argue that since the reaction is facilitated by electron-withdrawing substituents, the plausible Friedel−Crafts path is not operative although the measured low KIE values do not clearly endorse a ruling out of this route.[13e] This reasoning, and in light of the recent similar observations by others,[16] led us to propose that the ring closure proceeds via a base-assisted deprotonative metalation pathway with the dependence on acidity of the C−H bond being cleaved.[17]

The Pd-catalyzed cyclization protocol was successfully applied to a broad range of *N*-(2-chlorobenzyl)pyrroles to furnish pyrroloindoles (Table 2). The substrates were readily prepared either by *N*-arylation of aryl halides with pyrroles or by the Paal−Knorr reaction of anilines with 2,5-dimethoxytetrahydrofuran.[8] In general, the Pd-catalyzed cyclization reactions proceeded with excellent efficiency irrespective of substrate types, although sterically congested substrates demanded higher temperatures with larger catalyst loadings (entries 2 and 4).

A labile chloro group on substrates was well-tolerated under the conditions giving chloropyrroloindoles in excellent yields which could be further manipulated by arylation under the subsequent Suzuki reaction conditions in one-pot (entries 5−6).[8] Cyclization of *N*-(2-chloromethyl)naphthyl pyrrole and a derivative of 4*H*-indole-4-one provided tetracyclic compounds with high efficiency (entries 7−8). Interestingly, the reaction of substrates bearing electron-deficient groups on the pyrrole was also highly efficient to give products which are difficult to obtain using the conventional Friedel−Crafts approach (entries 9−10).[4]

The cyclization protocol was briefly examined to extend for the synthesis of 9*H*-fluorene by employing 2-phenylbenzyl bromide (eq 3).[18] The desired condensed carbocycle was obtained albeit with modest yield under unoptimized conditions.



(3)

In summary, we have developed a highly efficient Pd-catalyzed cyclization of *N*-(2-halobenzyl)-substituted pyrroles or phenyl variants to afford condensed hetero- or carbocycles, respectively, via tandem activation of benzyl halide and aromatic C−H bond. Further investigations are in progress to elucidate mechanistic details.

Acknowledgment. This research was supported by the EEWS program of KAIST and KRF (Grant KRF-2006-312-C00587).

Supporting Information Available: Data and copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, U.K., 2000. (b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: New York, 2003.
(2) Galm, U.; Hager, M. H.; Van Lanen, S. G.; Ju, J.; Thorson, J. S.; Shen, B. *Chem. Rev.* **2005**, *105*, 739.
(3) Yoshihara, T.; Druzhinin, S. I.; Zachariasse, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8535.
(4) (a) Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkatramanan, M. K.; Wong, G. S. K. *J. Org. Chem.* **1989**, *54*, 644. (b) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479. (c) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **2000**, *65*, 7158. (d) Kashulin, I. A.; Nifant'ev, I. E. *J. Org. Chem.* **2004**, *69*, 5476. (e) Abbiati, G.; Casoni, A.; Canevari, V.; Nava, D.; Rossi, E. *Org. Lett.* **2006**, *8*, 4839.
(5) (a) Lee, S.; Lee, W.-M.; Sulikowski, G. A. *J. Org. Chem.* **1999**, *64*, 4224. (b) Molander, G. A.; Schmitt, M. H. *J. Org. Chem.* **2000**, *65*, 3767. (c) Siebeneicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3042. (d) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Tetrahedron* **2008**, *64*, 6876.
(6) (a) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462. (b) Ren, H.; Li, Z.; Knochel, P. *Chem. Asian J.* **2007**, *2*, 416.
(7) For related reports from this laboratory, see:(a) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750. (b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (c) Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254.
(8) See the Supporting Information for details.
(9) Liégault, B.; Renaud, J.-L.; Bruneau, C. *Chem. Soc. Rev.* **2008**, *37*, 290.
(10) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: New York, 2004.
(11) In these cases, an acetyl-substituted side product, 2-biphenylmethyl acetate, was obtained up to 10% in addition to the desired compound.
(12) (a) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140. (b) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440. (c) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (d) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (e) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636.
(13) For recent related examples of this effect, see:(a) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerner, S.; Javadi, G. J.; Cai, D.; Larden, R. D. *Org. Lett.* **2003**, *5*, 4835. (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (c) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (d) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (e) Seregin, I.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742.
(14) (a) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (b) Bowie, A. L., Jr.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207. (c) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528.
(15) (a) Toyata, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293. (b) Wang, J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923.
(16) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.
(17) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.
(18) Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 1434.

JA806897H