Communication
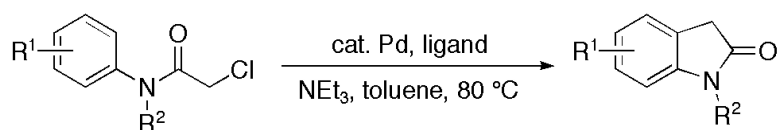
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Synthesis of Substituted Oxindoles from α-Chloroacetanilides via Palladium-Catalyzed C−H Functionalization

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The oxindole ring is a prominent structural motif found in numerous natural products and pharmaceutically active compounds.[1] The importance of this heterocyclic system notwithstanding, existing methods for oxindole synthesis are limited in their scope and generality. Among the techniques commonly used in synthesis are derivatization of other heterocycles (e.g. Wolf−Kishner reduction of the corresponding isatin, oxidation of the corresponding indole[2]), cyclization of o-aminophenylacetic acid derivatives,[2] and radical cyclization reactions.[3] The intramolecular Heck reaction can be used to generate oxindoles,[4] and asymmetric cyclizations have found widespread use in synthesis. Alternatively, the intramolecular arylation of amides[5] or amide enolates[1,6] has been employed to access oxindoles. Unfortunately, all of the aforementioned methods inherently require a specifically functionalized precursor (e.g., the presence of an ortho-halogen, an amino group, a preexisting ring system). Thus, a nontrivial synthetic sequence may be required to prepare the appropriate precursors. A classical approach to the oxindole system that circumvents the need for such functionalization is the Friedel−Crafts cyclization onto α-halo[7] or α-hydroxy[8] acetanilides. While it is a modular technique in that the reactive functional group is transferred away from the aromatic nucleus, the strongly acidic conditions and high temperatures required for such reactions limit the range of functional groups that are tolerated.[9]

In this communication, we report on the development of a novel variant of the Friedel−Crafts procedure using palladium-catalyzed C−H functionalization,[10] obviating the need for harsh reaction conditions. Specifically, the combination of catalytic amounts of palladium acetate, 2-(di-tert-butylphosphino)biphenyl (1) as a ligand, and triethylamine as base, α-chloroacetanilides can be smoothly converted to oxindoles in high yields with high levels of regioselectivity. The requisite substrates are easily prepared by the condensation of the corresponding aniline with the inexpensive chloroacetyl chloride.[11] Among the phosphine ligands examined, only 1 is highly effective for this transformation. Even structurally similar phosphines commonly used in cross-coupling reactions provided considerably lower amounts of oxindole in the time reactions employing 1 proceeded to nearly complete conversion.

As shown in Table 1, a variety of substituted oxindoles can be obtained in high yields. Substrates that can result in two distinct products cyclize with high regioselectivity. Apparently, steric interactions direct the ring substituents to the 6-position, rather than the 4-position, of the oxindole. Even electron-deficient aromatic nuclei are reactive, allowing for the synthesis of oxindoles that may be difficult to obtain using classical Friedel−Crafts methodology. Importantly, functional groups incompatible with strong Lewis acids (−OMe, −CF₃, −TMS) are well tolerated, as is typical of reactions catalyzed by late transition metals. This method is also compatible with electron-rich aryl chlorides, allowing for palladium-catalyzed coupling reactions to occur after the oxindole cyclization reaction.[12] In addition, aryl-TBS ethers, which are prone to cleavage

**Table 1.** Palladium-Catalyzed Synthesis of Oxindoles

[a] Isolated yield (average of two runs; estimated to be >95% pure by ¹H NMR and combustion analysis). PMB = p-methoxybenzyl, TBS = tert-butyldimethylsilyl, TMS = trimethylsilyl, DPM = diphenylmethyl. [b] 15:1 regioselectivity. [c] 14:1 regioselectivity. [d] >20:1 regioselectivity. [e] Reaction conducted at 100 °C for 19 h.

in the presence of palladium salts,[13] are stable under the reaction conditions.

Despite the efficiency of the cyclization reaction, the substrate scope is limited to N-alkyl or N-aryl chloroacetanilides. As of yet, we have been unable to cyclize N-H or N-acyl (amide, carbamate) substrates. In addition, 2,5-disubstituted chloroacetanilides are essentially unreactive under these and more forcing conditions,

Scheme 1. Observed Kinetic Isotope Effects
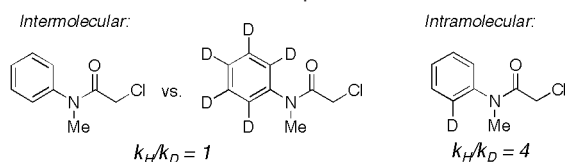
possibly due to combined steric interactions in the cyclization transition state.

To probe the mechanism of this transformation, we have conducted experiments with isotopically labeled substrates (Scheme 1). No kinetic isotope effect was observed in the competitive reaction of *N*-methyl chloroacetanilide and the corresponding pentadeuterated substrate. However, an intramolecular primary isotope effect of 4 is seen in the cyclization of the ortho-monodeuterated substrate.[14]

Scheme 2. Possible Mechanistic Pathways for Cyclization
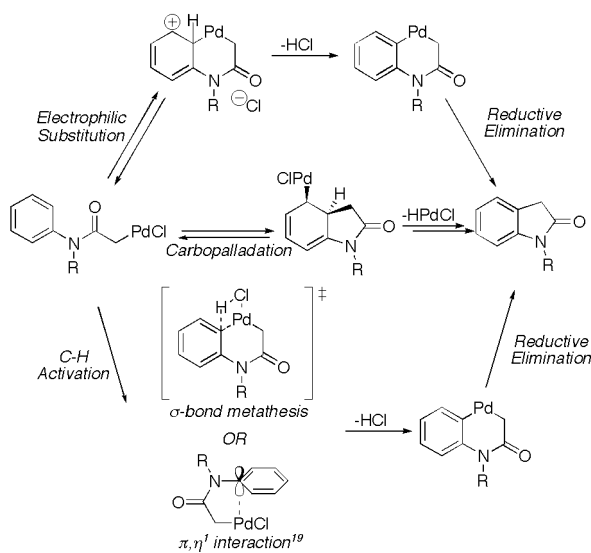
On the basis of these findings, we suggest several plausible reaction mechanisms (Scheme 2). The process is most likely initiated by oxidative addition of the α-chloro amide to Pd(0), resulting in a Pd(II) enolate.[15] The observed isotope effects suggest, somewhat surprisingly, that this bimolecular step is slow relative to subsequent intramolecular processes and is rate determining overall.[16] The formation of the carbon−carbon bond may proceed by an electrophilic aromatic substitution to give a six-membered palladacycle,[17] which undergoes reductive elimination to afford the product oxindole and regenerate the active Pd(0) species. Alternatively, carbopalladation of the aromatic ring followed by *anti*-elimination of HPdCl (or isomerization and *syn*-β-hydride elimination) would afford the same product,[18] and it is possible that both mechanisms are operative under the reaction conditions. The observed intramolecular isotope effect implies that either palladation process would be reversible and rapid relative to C−H bond cleavage. A third mechanistic possibility consistent with this observation is a true "C−H activation," which may proceed via σ-bond metathesis or through the intermediacy of a π,η^1 interaction[19] (whereby the palladium enolate acts as a π-acid to the nearby arene, sufficiently weakening the C−H bond that is eventually broken).

In conclusion, we have developed a reliable and operationally simple protocol to regioselectively synthesize substituted oxindoles. The high levels of functional group tolerance without the need for ortho-halogenation should make this an attractive synthetic alternative to currently used methods. Future work will concentrate on expanding the substrate scope to include α-substituted halo-acetanilides (forming 3-substituted oxindoles) as well as gaining a firmer mechanistic understanding of the process.

Supporting Information Available: Experimental procedures, characterization data for all unknown compounds, and spectral data for isotope effect determination (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435 and references therein.
(2) Sundberg, R. J. *Indoles*; Academic Press: London, 1996; pp 17, 152−154.
(3) (a) Cabri, W.; Candiani, I.; Colombo, M.; Franzoi, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949. (b) Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673. (c) Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, *30*, 2657. (d) Bowman, W. R.; Heaney, H.; Jordan, B. J. *Tetrahedron Lett.* **1988**, *29*, 6657.
(4) (a) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 8G and references therein. (b) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, *20*, 1133. (c) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, *17*, 1807.
(5) Kametani, T.; Ohsawa, T.; Ihara, M. *Heterocycles* **1980**, *14*, 277.
(6) (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (b) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.
(7) Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093 and references therein.
(8) Ben-Ishai, D.; Peled, N.; Sataty, I. *Tetrahedron Lett.* **1980**, *21*, 569.
(9) This reaction has been conducted photochemically as well, although yields are generally moderate. See: Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1981**, *29*, 128.
(10) For recent reviews on C−H activation, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698.
(11) See Supporting Information.
(12) Higher catalyst loadings are required to achieve complete conversion for these substrates, likely due to nonproductive, competitive oxidative addition at the aryl chloride. Thus, bromide or iodide substituents on the aromatic ring are presumably not compatible with our current protocol.
(13) (a) Wilson, N. S.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2918. (b) Wilson, N. S.; Keay, B. A. *Tetrahedron Lett.* **1996**, *37*, 153.
(14) This is similar to isotope effects previously observed in aromatic palladation reactions; for example, see: (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586 (k_H/k_D = 3). (b) Shue, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 7116 (k_H/k_D = 5).
(15) (a) Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. *Organometallics* **1999**, *18*, 5571. (b) Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1993**, *12*, 4899.
(16) Another possibility is that rotation about the carbonyl C−N bond of the palladium enolate into a reactive conformation is slow relative to the palladation event. For an analogous situation, see: Cohen, T.; McMullen, C. H.; Smith, K. *J. Am. Chem. Soc.* **1968**, *90*, 6866. We are grateful to a reviewer for making this suggestion.
(17) Echavarren, A. M.; Gómez-Lor, B.; González, J. J.; de Frutos, Ó. *Synlett* **2003**, 58 and references therein.
(18) This mechanistic dichotomy has been discussed previously. See (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (b) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301. (c) Toyota, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293. (d) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569.
(19) (a) Cámpora, J.; Gutiérrez-Puebla, E.; López, J. A.; Monge, A.; Palma, P.; del Río, D.; Carmona, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3641. (b) Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147.

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