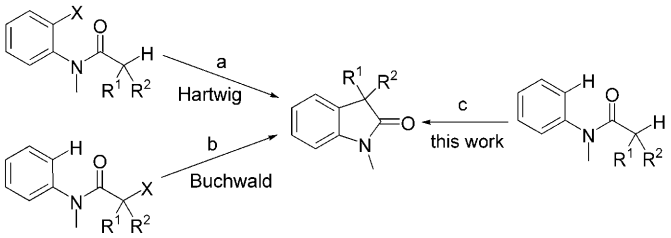
Synthetic Methods

DOI: 10.1002/anie.200805652

Oxindole Synthesis by Direct Coupling of C_{sp^2}–H and C_{sp^3}–H Centers**

*Yi-Xia Jia and E. Peter Kündig**

Oxindoles are common and important substructures in natural products and biologically active molecules.[1] Numerous methods have been reported for the syntheses of oxindoles, including the derivatization of isatin and indoles,[2] cyclization of *o*-aminophenylacetic acids and α-halo or α-hydroxy acetanilides,[2a,3] radical cyclizations,[4] palladium-catalyzed Heck reactions,[5] domino Heck/cyanation reactions,[6] and cyanoamidation reactions.[7] In particular, the methods developed by Hartwig and co-workers (Scheme 1, Method a, Pd-catalyzed arylation reaction),[8a,d] and Hennessey and Buchwald (Scheme 1, Method b, Pd-catalyzed alkylation reaction)[9] provide very useful access to oxindoles. All the aforementioned methods require a specifically functionalized precursor; for example, the presence of an *ortho* halogen, an α-halogen or α-hydroxy group, or a preexisting ring system. The development of new and more efficient methods is important. Recently, C–H activation has emerged as a highly valuable strategy for C–C coupling reactions because of its high atom economy.[10] Accordingly, processes involving direct coupling between two C–H centers have received much attention recently,[11] but examples of couplings between C_{sp^2}–H and C_{sp^3}–H centers are still scarce.[12] Herein, we describe our initial results for the synthesis of oxindoles by the direct coupling of C_{sp^2}–H and C_{sp^3}–H centers (Scheme 1, Method c).[13]



Scheme 1. Palladium-catalyzed oxindole synthesis from anilide derivatives.

Acetanilides have been recently used as substrates in *ortho* functionalizations involving C–H activation.[14] The authors propose the formation of a palladacycle intermediate **A** by electrophilic attack of Pd^{II} onto the acetanilide and subsequent deprotonation. We hypothesized that by combining this method with that of the intramolecular arylation of amides,[8] palladacycle intermediate **B** could be formed in situ. If correct, the direct coupling of two C–H bonds to give oxindoles could be realized (Figure 1).

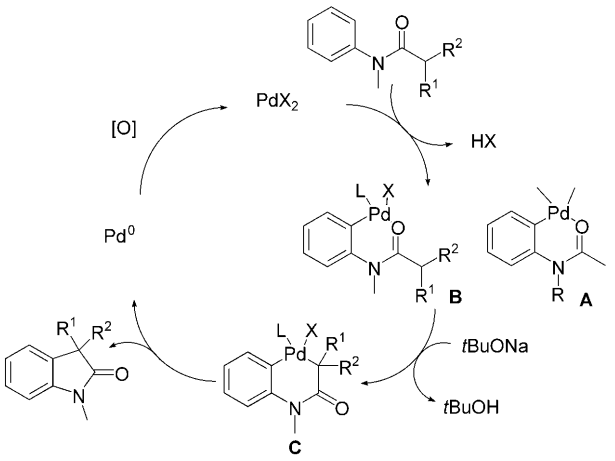


Figure 1. Initial hypothetical pathway for the catalyzed direct coupling reaction.

The initial reaction of *N*-methyl-*N*-2-diphenylpropanamide (**1a**) was carried out in the presence of 3.0 equivalents of *t*BuONa as the base and 1.2 equivalents of $CuCl_2$ as the oxidant, and by using 5 mol% $Pd(OAc)_2$ as the catalyst in toluene at 110°C. This set of conditions indeed afforded oxindole **2a** in 37% yield with 42% conversion after 20 hours (Table 1, entry 1). Other bases were tested but *t*BuONa was found to be the most efficient (Table 1, entries 1–6). The screening of different Cu^{II} compounds (Table 1, entries 7–11) revealed $Cu(OAc)_2$ to give the best result. Nearly complete conversion and a 74% yield of isolated **2a** was obtained by increasing the amount of the base and the oxidant to 5.0 equivalents and 2.2 equivalents, respectively, and by prolonging the reaction time to 36 hours (Table 1, entry 12). Solvent screening (Table 1, entries 13–17) showed that reactions were fully suppressed in dichloroethane (DCE) and that *N*,*N*-dimethylformamide (DMF) was the solvent of choice, giving **2a** upon isolation in 78% yield after a 5 hour reaction time.

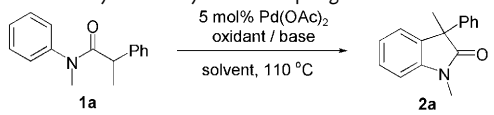
For an asymmetric version of this reaction we tested chiral *N*-heterocyclic carbene (NHC) ligands, which we had successfully used in asymmetric oxindole synthesis.[8g,h] However, all attempts, including a change in the solvent and reaction conditions, failed to give an enantiomerically enriched product. These results put into question the hypothesis of

[*] Dr. Y.-X. Jia, Prof. Dr. E. P. Kündig
Department of Organic Chemistry, University of Geneva
30 Quai Ernest Ansermet, 1211 Geneva 4 (Switzerland)
Fax: (+41) 22-379-3215
E-mail: peter.kundig@ unige.ch

[**] Support of this work by the Swiss National Foundation is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200805652.

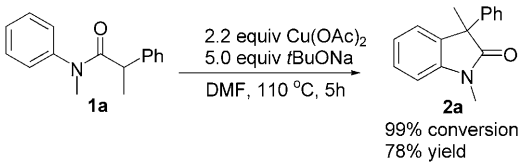
Table 1: Oxindole synthesis by direct coupling reaction.[a]



Entry	Oxidant	Base	Solvent	*t* [h]	Conv. [%][b]	Yield [%][b]
1	$CuCl_2$	*t*BuONa	toluene	20	42	37
2	$CuCl_2$	*t*BuOLi	toluene	20	20	16
3	$CuCl_2$	*t*BuOK	toluene	20	90	15
4	$CuCl_2$	NaHMDS	toluene	20	81	12
5	$CuCl_2$	NaH	toluene	20	15	13
6	$CuCl_2$	Cs_2CO_3	toluene	20	n.r.[d]	0
7	BQ	*t*BuONa	toluene	20	50	34
8[c]	$K_2S_2O_8$	*t*BuONa	toluene	20	n.r.[d]	0
9	$CuBr_2$	*t*BuONa	toluene	20	39	34
10	$Cu(OTf)_2$	*t*BuONa	toluene	20	53	41
11	$Cu(OAc)_2$	*t*BuONa	toluene	20	66	56
12	$Cu(OAc)_2$	*t*BuONa	toluene	36	97	82 (74)
13[e]	$Cu(OAc)_2$	*t*BuONa	toluene	20	97	56
14[e]	$Cu(OAc)_2$	*t*BuONa	toluene	20	98	52
15	$Cu(OAc)_2$	*t*BuONa	DCE	20	n.r.[d]	0
16	$Cu(OAc)_2$	*t*BuONa	DMSO	20	27	5
17	$Cu(OAc)_2$	*t*BuONa	DMF	5	99	85 (78)

[a] Reaction conditions: 0.4 mmol substrate in 8.0 mL solvent at 110 °C for 20 h, 1.2 equiv oxidant and 3.0 equiv base used in entries 1–11; 2.2 equiv oxidant and 5.0 equiv base used in entries 12–17. [b] Determined by GC analysis using naphthalene as an internal standard. Yield of isolated product in parentheses. [c] Potassium peroxodisulfate. [d] No reaction. [e] At 80 °C. Tf = trifluorosulfonyl, DMSO = dimethyl sulfoxide.

the palladium-catalyzed sequence shown in Figure 1. Indeed, repeating the reaction detailed in entry 17 of Table 1 in the absence of $Pd(OAc)_2$ afforded **2a** in the same yield as reported previously (Scheme 2). As palladium does not play a



Scheme 2. $Cu(OAc)_2$-mediated direct coupling reaction to give an oxindole.

significant role in the reaction of **1a**→**2a**, an alternative pathway of this direct coupling, through an intramolecular oxidative coupling reaction, is shown in Figure 2. Radical formation by amide enolate oxidation is followed by cyclization onto the aromatic ring. The resulting cyclohexadienyl radical readily aromatizes to the oxindole product.[15] The alternative pathway involving a radical coupling reaction with the second radical being formed by one-electron oxidation of the aniline amide is deemed less probable. While it has been shown that dimethylanilines can undergo intermolecular oxidative coupling,[16] we find that this reaction does not take place with acetanilides. Also, precedent for direct oxidative coupling reactions between enolates and arenes is limited to the electron-rich indoles and pyrroles.[17]

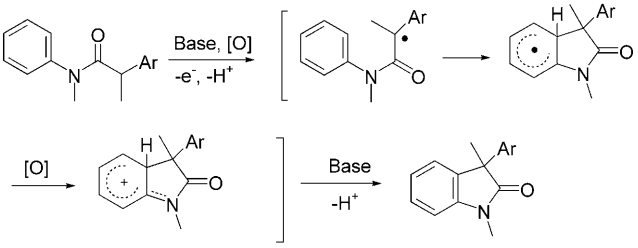
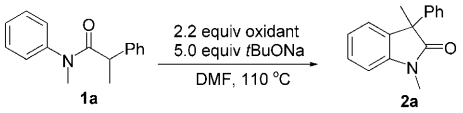


Figure 2. Revised proposed pathway for the direct C–H coupling reaction.

Different oxidants commonly used in radical chemistry were screened and the results are listed in Table 2. $CuCl_2$ was the most efficient reagent, giving oxindole **2a** in 93% yield

Table 2: Screening of oxidants in DMF.[a]



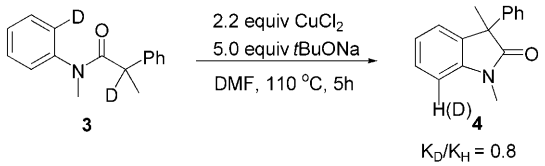
Entry	Oxidant	*t* [h]	Conv. [%][b]	Yield [%][b]
1	$CuCl_2$	5	100	98(93)
2	$CuBr_2$	3	100	87
3	$Cu(OAc)_2$	5	99	85
4	$Cu(OTf)_2$	10	81	72
5	BQ	10	88	35
6	Ag_2O	10	84	27
7	$Mn(OAc)_3$	7	61	42
8	$FeCl_3$	10	n.r.[c]	–
9	CAN	10	n.r.[c]	–
10[d]	$CuCl_2$	24	48	41
11[e]	$CuCl_2$	24	57	48

[a] Reaction conditions: 0.4 mmol substrate in 8.0 mL DMF at 110 °C. [b] Determined by GC analysis using naphthalene as an internal standard. Yield of isolated product in parentheses. [c] No reaction. [d] 2.0 equiv $CuCl_2$ and 3.0 equiv *t*BuONa were used. [e] 1.2 equiv $CuCl_2$ and 3.0 equiv *t*BuONa were used.

upon isolation after 5 hours (Table 2, entry 1). Decreasing the amount of $CuCl_2$ and *t*BuONa lowered both the conversion and yield remarkably (Table 2, entries 10 and 11). Other oxidants such as 1,4-benzoquinone (BQ), Ag_2O, and manganese triacetate ($Mn(OAc)_3$) were less efficient, and $FeCl_3$ and ceric ammonium nitrate (CAN) did not promote this reaction (Table 2, entries 5–9).

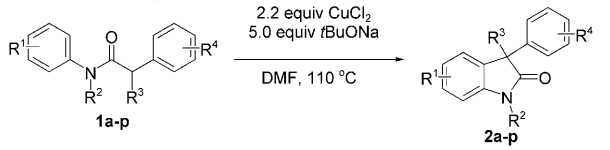
In keeping with the proposed mechanism (Figure 2), C_{sp^2}–H bond breaking is not involved in the rate-determining step as shown by the observation of a secondary isotope effect of 0.8 in the reaction of substrate **3** (Scheme 3).

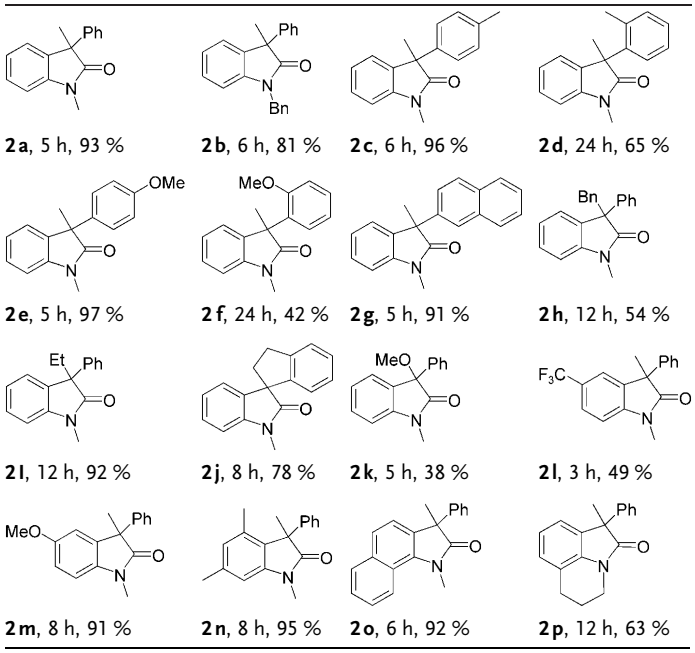
Upon exploring the scope of the reaction, a number of substrates were tested under the optimal reaction conditions found for **1a**. The data in Table 3 show yields to be usually good. Exceptions are reactions involving substrates having an *ortho*-substituted arylacetic amide fragment (e.g. **1d** and **1f**). The reactions of **1h–j** show the size of R^3 to affect the reaction. Importantly, spirooxindole **2j** was obtained in good yield, and 3-methoxy-substituted oxindole **2k** could also be obtained albeit in modest yield. Substitution within the



Scheme 3. Labeling experiment using substrate **3**.

Table 3: Substrate scope.[a]



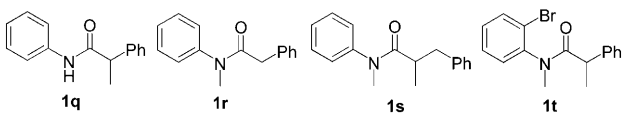


2a, 5 h, 93 %	**2b**, 6 h, 81 %	**2c**, 6 h, 96 %	**2d**, 24 h, 65 %
2e, 5 h, 97 %	**2f**, 24 h, 42 %	**2g**, 5 h, 91 %	**2h**, 12 h, 54 %
2i, 12 h, 92 %	**2j**, 8 h, 78 %	**2k**, 5 h, 38 %	**2l**, 3 h, 49 %
2m, 8 h, 91 %	**2n**, 8 h, 95 %	**2o**, 6 h, 92 %	**2p**, 12 h, 63 %

[a] Reaction conditions: 0.4 mmol substrate in 8.0 mL DMF at 110 °C (for **1a**, 1.0 mmol used); yields of isolated products are given.

aniline fragment was also probed. Although the *para*-trifluoromethyl substrate **1l** reacted rapidly, the yield of product **2l** was moderate compared to those obtained with **1m**–**o**. Finally, a tricyclic oxindole **2p** was synthesized in 63 % yield.

The method failed for substrates **1q** and **1s**, wherein starting materials were recovered (Scheme 4). In the case of **1r**, the starting material was consumed but no oxindole product was isolated. Interestingly, for the reaction of substrate **1t**, a substrate for the palladium-catalyzed intramolecular α-arylation reaction,[8] oxindole **2a** was obtained in 41 % yield rather than 7-bromo-1,3-dimethyl-3-phenyloxindole.



Scheme 4. Substrates not affording oxindole products.

In summary, we have developed a novel and efficient method for the synthesis of 3,3-disubstitued oxindoles by the direct intramolecular oxidative coupling of an aryl C_{sp^2}–H and a C_{sp^3}–H center. The reaction is mediated by inexpensive $CuCl_2$. Additional research will focus on the development of catalytic and asymmetric catalytic versions of this reaction.

Experimental Section

For full experimental and spectroscopic data, see the Supporting Information.

Synthesis of **2a**: To a dried Schlenk tube were added amide **1a** (239 mg, 1.0 mmol), $CuCl_2$ (296 mg, 2.2 mmol), and *t*BuONa (480 mg, 5.0 mmol) under N_2, and then DMF (20 mL, N_2 sat.) was introduced by syringe. The resulting mixture was stirred at 110 °C for 5 h (reaction monitored by GC analysis). After cooling to room temperature, the mixture was filtered through Celite and then brine (100 mL) and diethyl ether (40 mL) were added. Extraction with diethyl ether (2 × 30 mL), then drying of the combined organic phases over $MgSO_4$, and final evaporation of the solvent afforded a crude product that was purified by flash chromatography (pentane/diethyl ether 2:1) to give oxindole **2a** (221 mg, 93 %).

Received: November 19, 2008
Published online: January 23, 2009

Keywords: copper · oxidative coupling · oxindoles · radical reactions

[1] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; b) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209.
[2] a) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**, pp. 17, 152–154; b) R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem.* **2006**, *118*, 3431; *Angew. Chem. Int. Ed.* **2006**, *45*, 3353; c) I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921; d) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368.
[3] a) A. H. Beckett, R. W. Daisley, J. Walker, *Tetrahedron* **1968**, *24*, 6093, and references therein; b) D. Ben-Ishai, N. Peled, I. Sataty, *Tetrahedron Lett.* **1980**, *21*, 569.
[4] a) W. Cabri, I. Candiani, M. Colombo, L. Franzoi, A. Bedeschi, *Tetrahedron Lett.* **1995**, *36*, 949; b) K. Jones, C. McCarthy, *Tetrahedron Lett.* **1989**, *30*, 2657; c) W. R. Bowman, H. Heaney, B. J. Jordan, *Tetrahedron Lett.* **1988**, *29*, 6657.
[5] A. B. Dounay, K. Hatanaka, J. J. Kodanko, M. Oestreich, L. E. Overman, L. A. Pfeifer, M. M. Weiss, *J. Am. Chem. Soc.* **2003**, *125*, 6261.
[6] A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, *13*, 961.
[7] Y. Yasui, H. Kamisaki, Y. Takemoto, *Org. Lett.* **2008**, *10*, 3303.
[8] a) K. H. Shaughnessy, B. C. Hamann, J. F. Hartwig, *J. Org. Chem.* **1998**, *63*, 6546; b) S. P. Marsden, E. L. Watson, S. A. Raw, *Org. Lett.* **2008**, *10*, 2905; c) J. M. Hillgren, S. P. Marsden, *J. Org. Chem.* **2008**, *73*, 6459; Asymmetric catalysis: d) S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402; e) F. Glorius, G. Altenhoff, R. Goddard, C. Lehmann, *Chem. Commun.* **2002**, 2704; f) T. Arao, K. Kondo, T. Aoyama, *Tetrahedron Lett.* **2006**, *47*, 1417; g) E. P. Kündig, T. M. Seidel, Y.-X. Jia, G. Bernardinelli, *Angew. Chem.* **2007**, *119*, 8636; *Angew. Chem. Int. Ed.* **2007**, *46*, 8484; h) Y.-X. Jia, J. M. Hillgren, E. L. Watson, S. P. Marsden, E. P. Kündig, *Chem. Commun.* **2008**, 4040.
[9] E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084.

[10] For reviews, see: a) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; b) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; c) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; d) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; e) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077.

[11] For a review, see: a) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318, and references therein; For recent examples, see: b) E. M. Beck, R. Halley, M. J. Gaunt, *Angew. Chem.* **2008**, *120*, 3046; *Angew. Chem. Int. Ed.* **2008**, *47*, 3004; c) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; d) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904; e) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072; f) S. Würtz, S. Rakshit, J. J. Neumann, T. Droge, F. Glorius, *Angew. Chem.* **2008**, *120*, 7340; *Angew. Chem. Int. Ed.* **2008**, *47*, 7230; g) L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 7183; *Angew. Chem. Int. Ed.* **2008**, *47*, 7075; h) Z.-P. Li, L. Gao, C.-J. Li, *Angew. Chem.* **2007**, *119*, 6625; *Angew. Chem. Int. Ed.* **2007**, *46*, 6505;.

[12] a) Y. Rong, W. Lu, *Organometallics* **2007**, *26*, 4376; b) G. Deng, L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 6374; *Angew. Chem. Int. Ed.* **2008**, *47*, 6278; c) B. Liegault, K. Fagnou, *Organometallics* **2008**, *27*, 4841.

[13] During the preparation of the manuscript, a Pd-catalyzed amination of C–H bonds to form oxindoles was published: M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058.

[14] a) B. Li, S. Yang, Z. Shi, *Synlett* **2008**, 949, and references therein; b) B. Li, S. Tian, Z. Fang, Z. Shi, *Angew. Chem.* **2008**, *120*, 1131; *Angew. Chem. Int. Ed.* **2008**, *47*, 1115; c) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem.* **2007**, *119*, 5650; *Angew. Chem. Int. Ed.* **2007**, *46*, 5554.

[15] For precedent of intramolecular radical additions to arenes to form oxindoles, see: T.-M. Ly, B. Quicelet-Sire, B. Sortais, S. Z. Zard, *Tetrahedron Lett.* **1999**, *40*, 2533.

[16] C. Xi, Y. Jiang, X. Yang, *Tetrahedron Lett.* **2005**, *46*, 3909.

[17] a) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2004**, *126*, 7450; b) P. S. Baran, J. M. Richter, D. W. Lin, *Angew. Chem.* **2005**, *117*, 615; *Angew. Chem. Int. Ed.* **2005**, *44*, 609; c) J. M. Richter, B. W. Whitefield, T. J. Maimone, D. W. Lin, M. P. Castroviejo, P. S. Baran, *J. Am. Chem. Soc.* **2007**, *129*, 12857.

