ORGANIC LETTERS

2010
Vol. 12, No. 15
3446−3449

First C−H Activation Route to Oxindoles using Copper Catalysis

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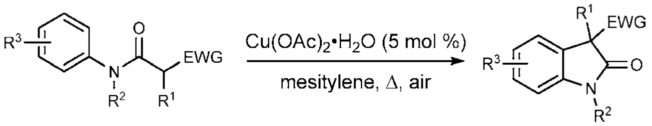
Received June 2, 2010

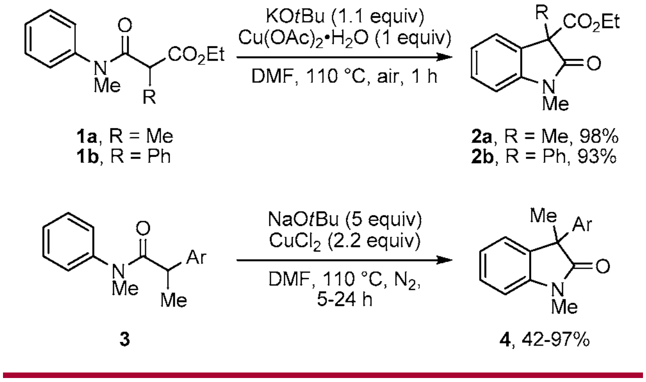
ABSTRACT



The preparation of 3,3-disubstituted oxindoles by a formal C−H, Ar−H coupling of anilides is described. Highly efficient conditions have been identified using catalytic (5 mol %) $Cu(OAc)_2·H_2O$ with atmospheric oxygen as the reoxidant; no additional base is required, and the reaction can be run in toluene or mesitylene. Optimization studies are reported together with a scope and limitation investigation based on variation of the anilide precursors. The application of this methodology to prepare a key intermediate for the total synthesis of the anticancer, analgesic oxindole alkaloid Horsfiline is also described.

Substituted oxindoles form the cornerstone of numerous natural products and bioactive lead compounds.[1,2] We recently reported an efficient new route to 3,3-disubstituted oxindoles from anilides using potassium *t*-butoxide as base and stoichiometric $Cu(OAc)_2·H_2O$ in DMF (e.g., **1** → **2**, Scheme 1).[3] This coupling process employs inexpensive reagents and does not require anhydrous conditions or the use of an inert atmosphere (other electron-withdrawing groups, such as nitrile and phosphonate, could also be employed in this sequence). This procedure is closely related to the one, also reported in 2009, by Kündig's group (e.g., **3** → **4**, Scheme 1) in which 3-aryl-3-alkyl-oxindoles **4** were prepared by a $CuCl_2$-mediated cyclization process (although in this aryl variant, Schlenk techniques, anhydrous conditions and an inert atmosphere are required).[4]

Scheme 1. Stoichiometric Approaches to Oxindoles[3,4]



The transformations shown in Scheme 1 are remarkable, and synthetically valuable, as they generate quaternary all-carbon centers via a formal double C−H activation process.[5]

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(1) For reviews on the properties of oxindoles and synthetic routes, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Cerchiaro, G.; da Costa Ferreira, A. M. *J. Braz. Chem. Soc.* **2006**, *17*, 1473. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (d) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.

(2) For recent approaches to oxindoles, see: (a) Luan, X.; Wu, L.; Drinkel, E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912. (b) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008. (c) Reddy, V. J.; Douglas, C. J. *Org. Lett.* **2010**, *12*, 952. (d) Yasui, Y.; Kamisaki, H.; Ishida, T.; Takemoto, Y. *Tetrahedron* **2010**, *66*, 1980. (e) Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820. (f) Peng, P.; Tang, B.-X.; Pi, S.-F.; Liang, Y.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 3569. (g) Song, R.-J.; Liu, Y.; Li, R.-J.; Li, J.-H. *Tetrahedron Lett.* **2009**, *50*, 3912.

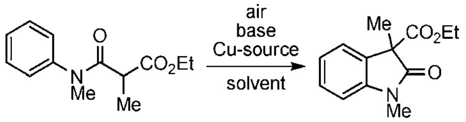
(3) (a) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. See also: (b) Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, 934.

(4) Jia, Y.-X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636.

(5) For a copper catalysed, double C-H coupling route to indoles, see: Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078.

10.1021/ol1012668

Table 1. Oxindole Preparation using Stoichiometric and Catalytic Cu(II)[a,b]



1a **2a**

entry	base	Cu-source	solvent (temp)	time	yield
i	KO*t*Bu (1.1 equiv)	$Cu(OAc)_2\cdot H_2O$ (1 equiv)	DMF (110 °C)	1 h	98%
ii	KO*t*Bu (1.1 equiv)	$Cu(OAc)_2\cdot H_2O$ (5 mol %)	DMF (110 °C)	16 h	(14%)
iii	Piperidine (10 equiv)[c]	$Cu(OAc)_2\cdot H_2O$ (5 mol %)	DMF (110 °C)	5 h	(87%)84%
iv	–	$Cu(OAc)_2\cdot H_2O$ (5 mol %)	DMF (110 °C)	16 h	(20%)
v	–	$Cu(OAc)_2\cdot H_2O$ (5 mol %)	PhMe (110 °C)	20 h	81%
vi	–	$Cu(OTf)_2$[d] (5 mol %)	PhMe (110 °C)	24 h	(75%)
vii	–	***$Cu(OAc)_2\cdot H_2O$*** (5 mol %)	***Mesitylene (165 °C)***[e]	***1.5 h***	***92%***
viii	–	$Cu(OAc)_2\cdot H_2O$ (5 mol %)	Mesitylene (165 °C)[f]	1.5 h	(<5%)

[a] Unless stated otherwise, the base (if used) was added to a mixture of the substrate and the copper salt in the solvent specified; then a reflux condenser fitted with a drying tube was inserted and the reaction heated for the time indicated. [b] Yields in parentheses determined using NMR spectroscopy against an internal standard (1,1,2,2-tetrachloroethane). [c] With piperidine (1 equiv), the reaction was still incomplete after 16 h giving **2** in 47% NMR yield. [d] The following copper salts (5 mol %) also effected the required transformation: $CuBF_4\cdot 4H_2O$, 67%; $Cu(acac)_2$, 62%; $[Me(CH_2)_3CH(Et)CO_2]_2Cu$, 63%; $Cu(TC)_2\cdot MeOH$, 70%; CuOAc, 51%; CuTC, 53%). A UK 1p coin (1980) also gave oxindole **2** (57%, 5 h). Little or no cyclization was observed using $CuCl_2$, $CuBr_2$, $CuSO_4$, $CuCl_2(phen)$, Cu_2O, CuO, and CuCl. [e] No product formation was observed in the absence of $Cu(OAc)_2\cdot H_2O$ (or when the $Cu(OAc)_2\cdot H_2O$ was replaced by KOAc). [f] Degassed and under an argon atmosphere.

Preliminary mechanistic studies[3,4] indicated that the cyclization proceeds via deprotonation, radical generation, and then homolytic aromatic substitution. Such a sequence involves two separate one-electron oxidation processes, which would require the use of 2 equiv of a Cu(II) source.

We were intrigued by the possibility that the above cyclization reactions could be carried out using catalytic quantities of Cu(II) salts by the use of a stoichiometric reoxidant, preferably atmospheric oxygen, to recycle the putative Cu(I) intermediate.[6] Such a catalytic approach, which would be of great value for larger scale processes, seemed plausible given that the original reaction shown in Scheme 1 used just 1 equiv of $Cu(OAc)_2\cdot H_2O$ and the reaction vessel was open to the air. The preliminary studies toward the development of a Cu(II)-catalyzed procedure for oxindole synthesis are shown in Table 1.

Repeating the original[3] stoichiometric $Cu(OAc)_2\cdot H_2O$/KO*t*Bu/DMF conditions gave a near quantitative yield for the conversion of anilide **1** into 3,3-disubstituted oxindole **2** after 1 h at 110 °C (entry i), whereas the use of 5 mol % $Cu(OAc)_2\cdot H_2O$ under the same conditions resulted in only 14% yield of oxindole **2** after 16 h (entry ii). However, this partial success (ca. 3 turnovers) in DMF was in contrast to the fact that little or no cyclization was observed when $Cu(OAc)_2\cdot H_2O$ was employed in other solvents such as THF or MeCN. Replacement of KO*t*Bu by organic bases was investigated next and a dramatic improvement was realized using $Cu(OAc)_2\cdot H_2O$/piperidine/DMF (entry iii); with an excess of piperidine (10 equiv) an 84% yield of oxindole **2** was isolated with a reaction time of only 5 hours.

We next carried out a control reaction in the absence of added base but were amazed to observe that oxindole **2** was still formed in approximately 20% yield (entry iv). Initially, we reasoned that the thermal decomposition of DMF at elevated temperature would release dimethylamine,[7] which could act as the base. However, changing the solvent to toluene (entry v), again using 5 mol % $Cu(OAc)_2\cdot H_2O$ with no added base, resulted in a much improved 81% isolated yield after 20 h at 110 °C.

With this remarkable result in hand, we set out to further optimize this reaction by varying the copper source whilst keeping toluene as solvent. A range of copper salts were screened and several were successful with $Cu(OTf)_2$ giving the best result (entry vi) but none were superior to $Cu(OAc)_2\cdot H_2O$. It is also noteworthy, given its use by Kündig et al.,[4] that $CuCl_2$ was completely ineffective for this transformation. In addition, replacement of toluene as solvent by mesitylene at reflux gave a dramatic improvement in yield and a reduction of reaction time (92%, 1.5 h; entry vii). Finally in this preliminary study, the importance of aerial oxidation was confirmed (entry viii); when the reaction was carried out using the mesitylene conditions but with degassing under an argon atmosphere, less than 5% of oxindole **2** was formed.

Having devised an efficient cyclization procedure using catalytic $Cu(OAc)_2\cdot H_2O$ in mesitylene, we went on to test the substrate scope using differently substituted anilides **5** (Scheme 2). As can be seen, several α-carbonyl substituents were compatible with the cyclization conditions producing oxindoles **6a**−**6c** in good yields. In addition, substitution of the aryl ring with electron donating groups (4-OMe and 2-OMe) made little difference, with oxindoles **6d** and **6e** being isolated in 88 and 75% yield, respectively. Furthermore

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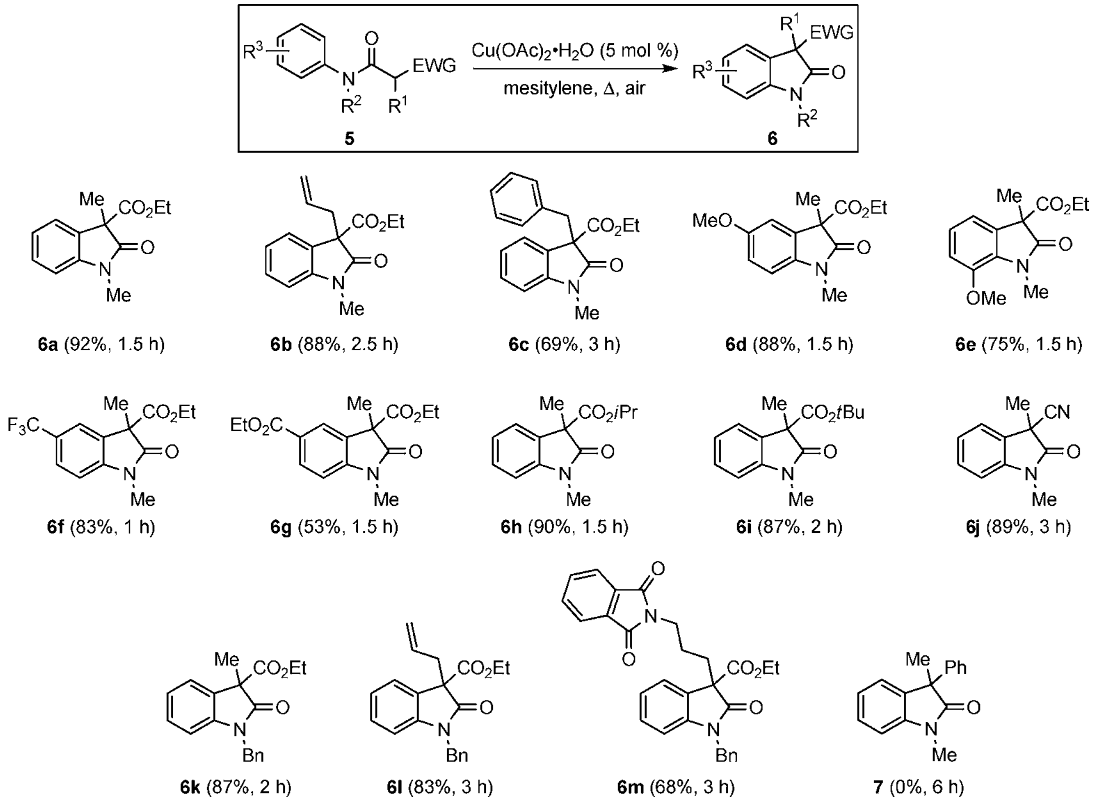
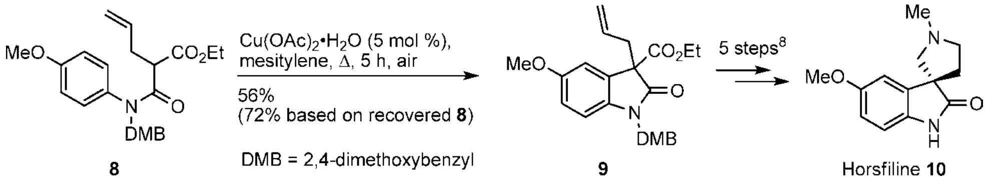
(6) For a review on aerobic copper catalysis, see: (a) Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijk, J. *Chem. Soc. Rev.* **2001**, *30*, 376. For more recent references, see: (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (c) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734.

(7) Muzart, J. *Tetrahedron* **2009**, *65*, 8313.

Scheme 2. Scope and Limitations of the Catalytic $Cu(OAc)_2{\cdot}H_2O$ Procedure



Scheme 3. Preparation of a Horsfiline Precursor **9**



electron withdrawing groups such as 4-CF_3 and 4-CO_2Et were also tolerated under the reaction conditions, giving oxindoles **6f** and **6g** in 83 and 53% yield, respectively. Changing the ester group from ethyl to *iso*-propyl or *tert*-butyl was also allowed with the expected oxindoles **6h** and **6i** being formed in excellent yield; the latter result emphasizes the compatibility of the $Cu(OAc)_2{\cdot}H_2O$/mesitylene system with acid-labile groups. In addition, this catalytic procedure was shown to be compatible with other activating groups by the preparation of nitrile **6j** in excellent yield. All of the examples mentioned to date contained *N*-Me groups but formation of the *N*-benzyl systems **6k**−**6m** was equally straightforward. Finally, we explored the cyclization of the less activated *N*-methyl-*N*-2-diphenylpropanamide but no trace of oxindole **7** was observed even after a reaction time of 6 h (and so Kundig's stoichiometric $CuCl_2$/NaO*t*Bu conditions[4] are favored in such aryl-activated cases).

The above observations seem to be consistent with the original mechanistic proposal for the stoichiometric process, that is, enolization followed by radical generation and then homolytic aromatic substitution. In the catalytic process, oxygen in air is the terminal oxidant recycling Cu(I) to Cu(II) and the enolization (possibly assisted by copper(II) chelation) is presumably effected by the substrate. It should be noted that the reactions do not appear to increase in acidity as they progress and so the hydrogens are presumably lost as water.

Trost and Brennan recently published a new synthesis of the anticancer, analgesic oxindole alkaloid Horsfiline **10**, which proceeded by way of oxindole **9** (Scheme 3).[8] To showcase the utility of the Cu(II)-mediated Ar−H/C-H coupling sequence developed herein, we prepared intermediate **9** from readily available anilide **8** in 56% unoptimised yield (72% based on recovered **8**) using the $Cu(OAc)_2{\cdot}H_2O$/mesitylene procedure. Once again, these conditions were compatible with a sensitive protecting

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(8) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027.

group (DMB) which is easily cleaved under acidic or oxidative conditions.

In summary, we have developed an operationally straightforward double C−H activation route to 3,3-disubstituted oxindoles that employs catalytic $Cu(OAc)_2 \cdot H_2O$ and atmospheric oxygen as the reoxidant; no additional base is required, and the reaction can be run in toluene or mesitylene. The mesitylene conditions have been utilized with a range of substrates, including several containing acid-labile groups, to establish the general utility of the process.

Acknowledgment. We thank the EPSRC for postgraduate (D.S.P., EP/E041302/1) and postdoctoral (A.P., EP/029841/1) support. We are also grateful to the University of York Wild fund for additional postgraduate support (J.E.M.N.K.).

Supporting Information Available: Experimental procedures and spectroscopic data for oxindoles **6a−6m** and **9** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1012668