CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201302139

Copper-Catalyzed Oxidative Benzylarylation of Acrylamides by Benzylic C−H Bond Functionalization for the Synthesis of Oxindoles

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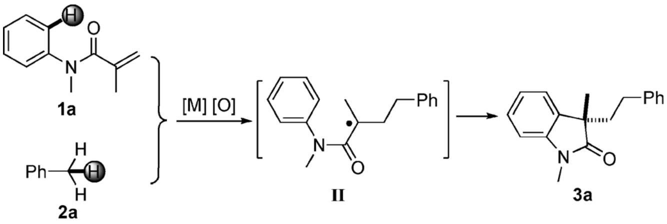
Oxindoles, important and representative nitrogen heterocycles, are of great interest to organic synthesis because of their significant biological activities and wide-ranging applications in organic synthesis.[1,2] In the past few years, a number of traditional processes for the synthesis of these motifs have been established.[3] The groups of Kündig and Taylor have reported the copper-mediated direct C_{sp^2}−H/C_{sp^3}−H functionalization of anilide to a variety of oxindoles through a radical process.[3e,f] In addition, palladium-catalyzed intramolecular difunctionalization of alkenes, including aryloxygenation,[4a] arylalkylation,[4b] and aryltrifluoromethylation[4c] provides an elegant method for the construction of the oxindole skeleton. Generally, hypervalent iodine derivatives have proven to be highly active oxidants in these transformations. Very recently, a new metal-catalyzed difunctionalization reaction of alkenes through a radical process to form functionalized oxindoles has also been reported.[5] However, there are relatively few methods available for the preparation of oxindoles through oxidative dicarbonation of alkenes by using unactivated substrates, particularly catalytic systems capable of performing direct C_{sp^3}−H functionalization.[4b,5a]

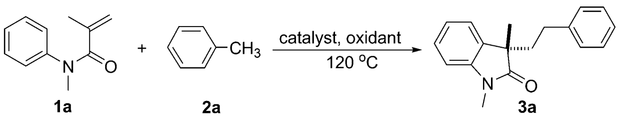
Recently, metal- or metal-free-catalyzed radical reactions have emerged as a powerful tool for C−C and C−heteroatom bond formation.[6] Among these, various benzylic hydrocarbons have been used as coupling partners due to their easily formed active benzyl radicals.[7] Inspired by recent reports on the tandem radical addition/cyclization to form functionalized oxindoles,[5,8] we envisioned that such a radical procedure might be applicable to benzylic hydrocarbons, as shown in Scheme 1. Herein, we report a copper-catalyzed oxidative benzylarylation of alkenes to form alkyl-substituted oxindoles by using readily available benzylic hydrocarbons as coupling partners.



Scheme 1. Oxidative benzylarylation of activated alkenes.

We first investigated the reaction of *N*-methyl-*N*-phenylmethacrylamide **1a** with toluene **2a** under various reaction conditions (for details, see the Supporting Information). The reaction of **1a** with **2a** in the presence of 2.0 equivalents of TBPB as the oxidant at 120 °C for 28 h, afforded the desired product **3a** in 65 % yield (Table 1, entry 1). The effect of the oxidant in the reaction was then examined, and TBPB proved to be better than the other peroxides tested for the reaction (Table 1, entries 1–4). A brief survey of different catalysts, such as $Cu(OAc)_2$, $CuBr_2$, CuCl, and Cu_2O, indicated that Cu_2O is the best (Table 1, entries 5–8). Finally, the amount of catalyst could be reduced to 2 mol % and still lead to an excellent yield (Table 1, entry 9). It should be noted that the reaction could also be scaled up to 1 mmol, and the desired product, **3a**, was isolated in 93 % yield.

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst ([mol %])	Oxidant ([equiv])	Yield [%][b]
1	–	TBPB (2.0)	65
2	–	TBHP (2.0)	24
3	–	DTBP (2.0)	46
4	–	DCP (2.0)	10
5	$Cu(OAc)_2$ (5)	TBPB (2.0)	87
6	$CuBr_2$ (5)	TBPB (2.0)	93
7	CuCl (5)	TBPB (2.0)	89
8	Cu_2O (5)	TBPB (2.0)	96
9	Cu_2O (2)	TBPB (2.0)	95 (93)[c]

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), oxidant (2.0 equiv), toluene (1.0 mL), 120 °C, 28 h. TBPB = *tert*-butylperoxy benzoate, TBHP = *tert*-butyl hydroperoxide (5–6 M in decane), DTBP = di-*tert*-butyl peroxide, DCP = dicumyl peroxide. [b] Yield of the isolated product. [c] Yield on a 1 mmol scale is given in parentheses.

With the optimized conditions in hand, the scope of the reaction towards acrylamides, **1**, was examined (Table 2). To our delight, a variety of acrylamides (**1**) reacted smoothly under the oxidative conditions, affording the desired oxin-

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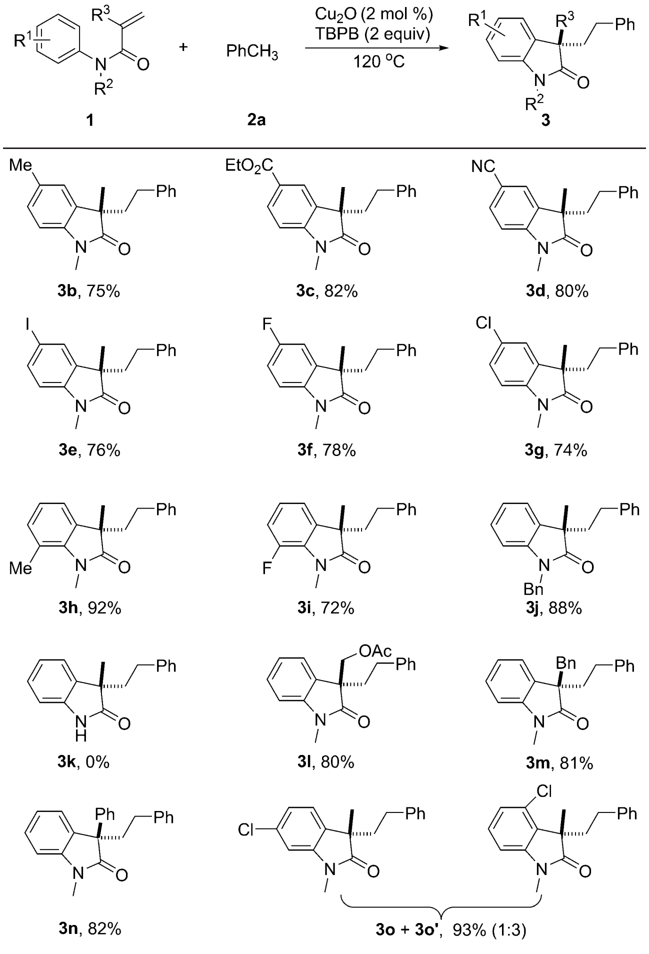
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302139.

Table 2. Scope of the reaction towards acrylamides **1**.[a]

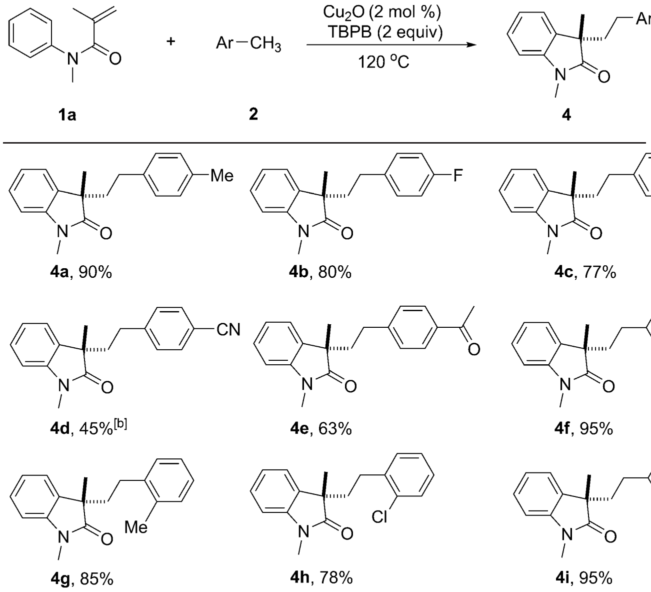


[a] Reaction conditions: Cu$_2$O (2 mol %), **1** (0.2 mmol, 1.0 equiv), TBPB (2.0 equiv), toluene (1.0 mL), 120 °C, 28 h.

doles in moderate to good yields. Sensitive functional groups on the aniline moieties such as ester and cyano groups were tolerated in this transformation (**3c** and **3d**). Halo-substituted acrylamides were also compatible and gave the corresponding products in good yields, which allows further functionalization of the oxindoles (**3e–g**). For *ortho*-substituted acrylamides, the corresponding oxindoles, **3h** and **3i**, were obtained in 92 and 72 % yields, respectively. The *N*-arylacrylamide bearing a benzyl protecting group on the nitrogen atom also reacted smoothly to give the desired product, **3j**, in 88 % yield. However, unprotected *N*-arylacrylamide did not react at all under these reaction conditions (**3k**). On the other hand, acrylamides with acetoxymethyl, benzyl, and phenyl groups at the α-position led to the corresponding products, **3l–3n**, in good yields. The use of *meta*-substituted acrylamide **1o** resulted in a mixture of the products **3o** and **3o′** with moderate regioselectivity (1:3).

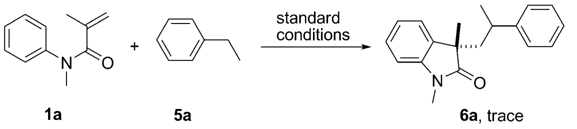
Subsequently, our protocol was extended to different benzylic hydrocarbons (Table 3). *para*-Xylene, *para*-fluorotoluene, and *para*-chlorotoluene were converted in high yields to the corresponding oxindoles (**4a–4c**). Notably,

Table 3. Scope of the reaction towards benzylic hydrocarbons **2**.[a]



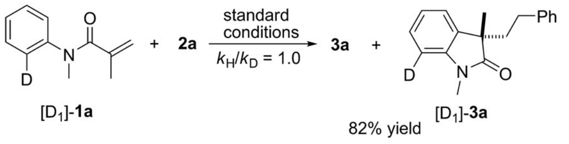
[a] Reaction conditions: Cu$_2$O (2 mol %), **1a** (0.2 mmol, 1.0 equiv), TBPB (2.0 equiv), benzylic hydrocarbons (**2**, 1.0 mL), 120 °C, 28 h. [b] **2d** (1.0 mmol, 5.0 equiv), EtOAc (1 mL).

para-tolunitrile and *para*-methylacetophenone also survived under the reaction conditions, leading to **4d** and **4e** in 45 and 63 % yields, respectively. *meta*-Xylene, *ortho*-xylene, and mesitylene, with multiple methyl groups, were transformed into the desired products in excellent yields with high selectivities (**4f**, **4g**, and **4i**). However, when ethylbenzene was used as a substrate under the optimized reaction conditions, only a trace amount of the product, **6a**, was detected [Eq. (1)].

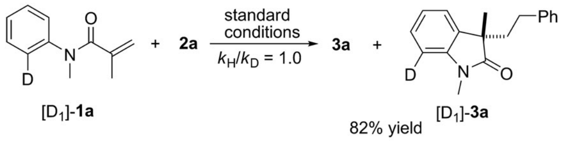


(1)

To clarify the mechanism of this process, two competition experiments were performed [Eqs. (2) and (3)]. Firstly, when [D$_1$]-**1a** and [D$_5$]-**1a** were subjected to the reaction conditions, intra- and intermolecular kinetic isotope effects (KIE) of 1.0 were observed, demonstrating that electrophilic aromatic or free-radical substitution occurred in this transformation.[5,8,9] Secondly, a clear KIE of the competitive experiment involving a 1:1 mixture of **2a**/[D$_8$]-**2a** was obtained [Eq. (4)], indicating that the cleavage of the benzyl C−H bond is the rate-limiting step. Finally, a radical-trapping reagent, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), was added and the reaction was suppressed, suggesting that free-radical intermediates were involved in the reaction.



(2)



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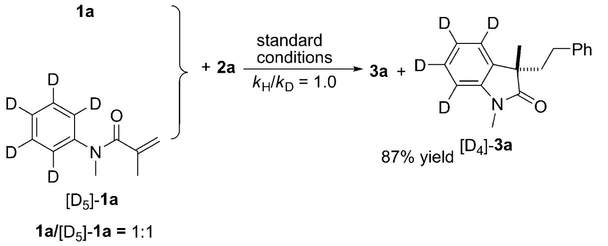
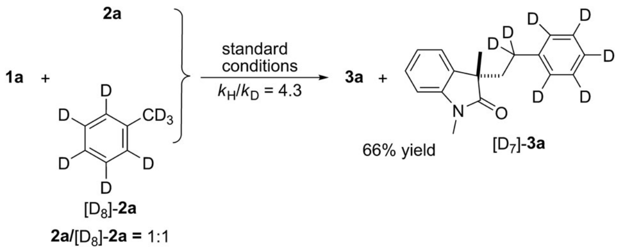
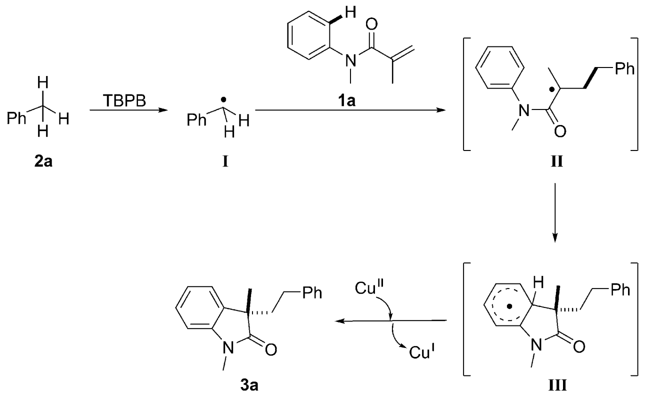


(3)



(4)

Based on these observations, a mechanism can tentatively be proposed (Scheme 2). Benzyl radical **I** is formed through homolytic cleavage of toluene in the presence of TBPB.[7] Radical **I** then adds to the double bond of acrylamide (**1a**) to generate the corresponding alkyl radical **II**.[5,8] Radical **II** then undergoes intramolecular attack to give intermediate **III**. Abstraction of hydrogen from **III** by copper(II) affords oxindole **3a**.



Scheme 2. Proposed mechanism for the benzylarylation of alkenes.

In summary, an efficient copper-catalyzed benzylarylation of activated alkenes to form alkyl-substituted oxindoles has been developed. This tandem radical addition/cyclization of acrylamides and benzyl hydrocarbons features operational simplicity and tolerance of a broad range of functional groups. This process provides an ideal and straightforward approach to functionalized oxindoles in terms of atom economy.

Experimental Section

General procedure for the benzylarylation of acrylamides with benzylic hydrocarbons: An oven-dried Schlenk tube (10 mL) was charged with Cu_2O (0.6 mg, 2 mol %) and acrylamide (**1**, 0.2 mmol, 1.0 equiv). The tube was evacuated and backfilled with nitrogen (three times). TBPB (0.4 mmol, 2.0 equiv) and the benzylic hydrocarbon (1 mL) were added by syringe. The tube was then sealed and the mixture was stirred for 28 h at 120 °C. Upon completion of the reaction, the mixture was diluted with EtOAc. The solvent was then removed under vacuum. The residue was purified with column chromatography on silica gel (eluent gradient of EtOAc/petroleum ether, 1:25 to 1:5) to give the corresponding products **3** or **4** in the yields listed in Tables 2 and 3.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 21102110 and 21102111), the Doctoral Fund of the Ministry of Education of China (No. 20110201120076), and the Fundamental Research Funds of the Central Universities is greatly appreciated.

Keywords: activated alkenes · benzylarylation · copper · oxindoles · radical addition

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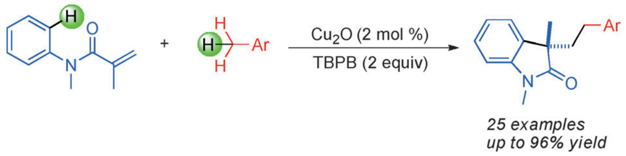
Received: June 5, 2013



Radically changing benzyls: An efficient method for the benzylarylation of activated alkenes has been developed through a copper-catalyzed tandem radical addition/cyclization strategy (see scheme). This oxidative coupling between acrylamides and benzylic hydrocarbons provides access to diverse alkyl-substituted oxindoles in good to excellent yields. A variety of functional groups were tolerated in this transformation (TBPB = *tert*-butylperoxy benzoate).

Radical Reactions

S.-L. Zhou, L.-N. Guo, H. Wang,*
*X.-H. Duan** .... ■■■■–■■■■

Copper-Catalyzed Oxidative Benzylarylation of Acrylamides by Benzylic C−H Bond Functionalization for the Synthesis of Oxindoles