Organic LETTERS
Letter
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Free-Radical Cascade Alkylarylation of Alkenes with Simple Alkanes: Highly Efficient Access to Oxindoles via Selective (sp^3)C−H and (sp^2)C−H Bond Functionalization

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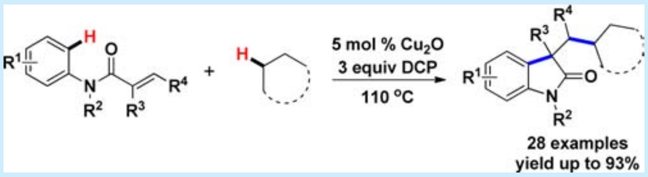
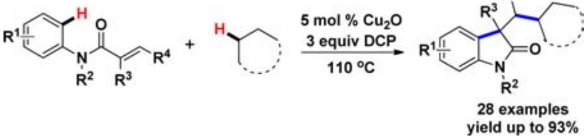
Supporting Information

ABSTRACT: A copper-catalyzed alkylarylation of alkenes with simple alkanes was achieved, which not only provided an efficient method to prepare various alkyl-substituted oxindoles, but also represented a novel strategy for selective sp^3 C−H functionalization/C−C bond formation via a free-radical cascade process. Additionally, selective activation of unactivated (sp^3)C−H and (sp^2)C−H bonds by one single step is achieved in this system, which would also provide a novel strategy for raising efficiency in C−H bond functionalization.



The construction of C−C bonds by direct C−H bond activation is of fundamental interest in modern synthetic organic chemistry.[1] Recently, various methods focused on C−C bond formation through free-radical-initiated sp^3-hybridized C−H bond activation.[2] However, most of these systems were limited by activated C−H bonds such as α-(sp^3)C−H of alcohols, ethers, amines, nitroalkanes, and 2-(sp^3)C−H of 1,3-dicarbonyl compounds. Selective activation of the inactive C−H bonds in simple alkanes to generate C−C bonds has remained a challenging target.[3] In the past several years, a series of cross-dehydrogenative-coupling (CDC) reactions forming C−C bonds by using simple alkanes were developed by Li and co-workers.[4] In addition, we[5] and others[6] have explored alternative systems producing C(sp^3)−C(sp^2) bonds with innate sp^3 C−H bonds via radical addition−elimination processes. Very recently, Antonchick and Burgmann[7] reported an efficient metal-free Minisci reaction of simple alkanes with heteroarenes. Although these studies have considerably improved this type of reactions, more efficient and selective functionalization of inert sp^{3}C−H/C−C bond formation would be highly desirable. As part of our continuous investigations[8] on C−H bond activation, we began to design a radical cascade reaction[9] of alkenes with simple alkanes, which would concisely synthesize various cyclic compounds using the strategy of (sp^3)C−H activation/C−C bond formation. Oxindoles and its derivatives represent a large class of *N*-heterocycles, which exhibit advanced pharmaceutical and bioactivities.[10] Recently, various transition metal-catalyzed cyclizations as well as radical-initiated reactions have been developed to prepare these molecules.[11] However, to the best of our knowledge, the direct 1,2-alkylarylation of alkenes with simple alkanes to generate oxindoles has never been reported. Herein, we report a free radical cascade alkylarylation of alkenes with simple alkanes, which allows for highly efficient access to alkyl-substituted oxindoles by selective functionalization of innate (sp^3)C−H and (sp^2)C−H bonds (Scheme 1).

Scheme 1. Alkylarylation of Alkenes with Simple Alkanes



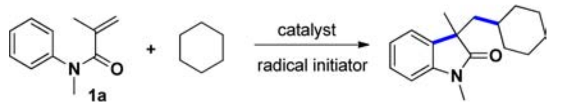
Initially, we chose *N*-methyl-*N*-phenylmethacrylamide (**1a**) and cyclohexane as the model substrates to optimize conditions for this reaction (Table 1). It was found that the catalyst and radical initiator critically affected the reaction efficiency. The desired product was obtained in only 6% yield without any catalyst (entry 1). The Cu_2O used as catalyst was more efficient than copper salts, such as CuBr and CuI, and copper powder (entries 2−5). Addition of 1 mL, 2 mL and 10 mL of cyclohexane as solvent led to the generation of the product in 32%, 44%, and 38% yields, respectively (entries 6−8). Surprisingly, the yield decreased to 44% when a decane solution of TBHP was used as the radical initiator (entry 9). Other radical initiators such as di-*tert*-butyl peroxide (DTBP), BPO, and $K_2S_2O_8$ were proved to be less efficient than dicumyl peroxide (DCP) (entries 10−13). No product was obtained when 1,2-dichloroethane (DCE) and benzene were used as solvent (entries 14 and 15). However, chlorobenzene can be used as an alternative solvent other than the alkane despite of low yield (entry 16). The reactions conducted at 80 and 130 °C resulted in much lower yields (entries 17 and 18). The desired product was isolated in 56% and 63% yields by using 2 and 10 mol % of the catalyst, respectively (entries 19 and 20).

With the modified conditions in hand, the scope of this reaction with respect to *N*-arylacrylamides and alkanes was studied (Table 2 and 3). As depicted in Table 2, the *N*-methyl,

Received: November 11, 2013
Published: December 19, 2013

dx.doi.org/10.1021/ol4032478 | *Org. Lett.* 2014, 16, 382−385

Table 1. Modification of the Typical Reaction Conditions[a]

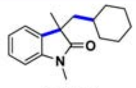
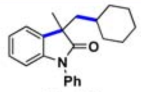
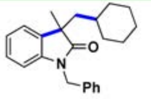
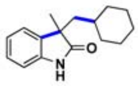
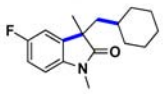
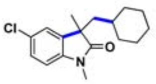
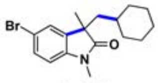
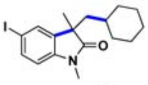
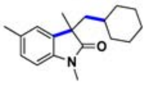
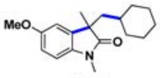
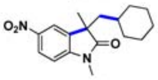
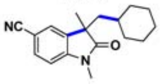
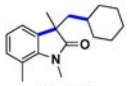
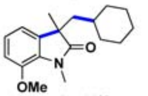
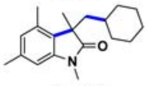
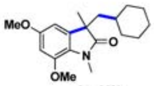
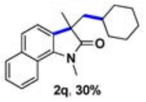
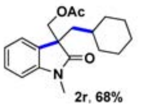


1a

entry	catalyst (mol %)	radical initiator	temp (°C)	yield[b] (%)
1		TBHP	110	6
2	CuBr (5)	TBHP	110	33
3	CuI (5)	TBHP	110	30
4	Cu (5)	TBHP	110	40
5	Cu_2O (5)	TBHP	110	72
6[c]	Cu_2O (5)	TBHP	110	32
7[d]	Cu_2O (5)	TBHP	110	44
8[e]	Cu_2O (5)	TBHP	110	38
9	Cu_2O (5)	TBHP[f]	110	44
10	Cu_2O (5)	DTBP	110	42
11	**Cu_2O (5)**	**DCP**	**110**	**93**
12	Cu_2O (5)	BPO	110	
13	Cu_2O (5)	$K_2S_2O_8$	110	
14[g]	Cu_2O (5)	DCP	110	
15[h]	Cu_2O (5)	DCP	110	
16[i]	Cu_2O (5)	DCP	110	36
17	Cu_2O (5)	DCP	80	5
18	Cu_2O (5)	DCP	130	32
19	Cu_2O (2)	DCP	110	56
20	Cu_2O (10)	DCP	110	63

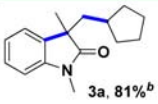
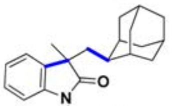
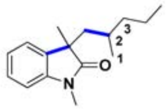
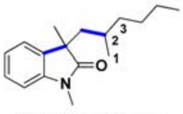
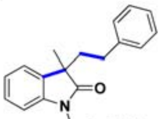
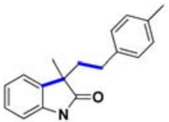
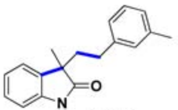
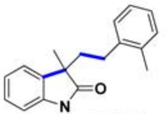
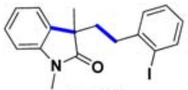
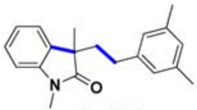
[a] Reaction conditions: *N*-arylacrylamide (0.25 mmol), radical initiator (0.75 mmol), 5 mL of cyclohexane as solvent, 22 h, unless otherwise noted. [b] Isolated yields. [c] Cyclohexane (1 mL). [d] Cyclohexane (2 mL). [e] Cyclohexane (10 mL). [f] TBHP (in decane). [g] 10 equiv of cyclohexane, DCE as solvent. [h] 10 equiv of cyclohexane, benzene as solvent. [i] 10 equiv of cyclohexane, chlorobenzene as solvent.

Table 2. Copper-Catalyzed Radical Cascade Reaction of *N*-Arylacrylamides with Cyclohexane[a]

product, yield	product, yield	product, yield
 2a, 93%[b]	 2b, 90%	 2c, 73%
 2d, 0%	 2e, 78%	 2f, 90%
 2g, 90%	 2h, 70%[c]	 2i, 60%
 2j, 58%	 2k, 0%	 2l, 0%
 2m, 40%	 2n, 60%	 2o, 76%
 2p, 60%	 2q, 30%	 2r, 68%

[a] Reaction conditions: *N*-arylacrylamide (0.25 mmol), DCP (0.75 mmol), 5 mL of cyclohexane as solvent, 110 °C, 22 h. [b] Isolated yields. [c] 46 h.

Table 3. Copper-Catalyzed Radical Cascade Reaction of *N*-Arylacrylamides with Alkanes[a]

product, yield	product, yield	product, yield
 3a, 81%[b]	 3b, 90%	 3c, 80%
 3d 3d + 3d′ = 68% (6:1)[c]	 3d′	 3e, 53% (1/2/3 = 1/6/3)
 3f, 66% (1/2/3=1/6/4)	 3g, 83%	 3h, 82%
 3i, 82%	 3j, 82%	 3k, 51%
 3l, 50%		 3m, 50%

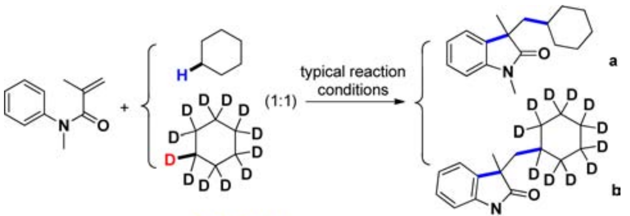
[a] Reaction conditions: *N*-arylacrylamide (0.25 mmol), DCP (0.75 mmol), 5 mL of alkane as solvent, 110 °C, 22 h, unless otherwise noted. [b] Isolated yields. [c] 10 equiv of adamantane, 5 mL of chlorobenzene as solvent.

N-phenyl, and *N*-benzyl but not *N*-H substituted *N*-phenylmethacrylamides all gave the desired products in high yields under the typical conditions (**2a**−**d**). Gratifyingly, the amides with halogen atoms such as F, Cl, Br, and I substituents on the *para*-position of the *N*-aryl moiety resulted in good to high yields of the corresponding products (**2e**−**h**). When the halogen atoms were replaced by electron-rich substituents such as methyl and methoxyl groups, the yields decreased slightly (**2i** and **2j**). However, highly electron-deficient substituents such as NO_2 and CN groups on the *N*-aryl moiety did not result in any products (**2k** and **2l**). Notably, *ortho*-substituted substrates gave moderate yields of the products (**2m** and **2n**). In addition, multisubstituted amides were also effective substrates, and the expected products **2o** and **2p** were obtained in 76% and 60% yields, respectively. Furthermore, *N*-methyl-*N*-naphthylmethacrylamide resulted in 30% yield of the desired product **2q**. It is noteworthy that CH_2OAc groups at the 2 position of the acrylamide core could be tolerated in this system (**2r**).

We next studied the reaction of *N*-methyl-*N*-phenylmethacrylamide with various simple alkanes as well as toluenes under the typical reaction conditions (Table 3). Cycloalkanes such as cyclopentane, cycloheptane, and cyclooctane all gave high yields of the desired products (**3a**−**c**). Interestingly, alkanes with high boiling points also resulted in good yields of the products in chlorobenzene. For example, when adamantane was used, **3d** and **3d′** were isolated in a yield of 68% with a ratio of 6/1. Acyclic alkanes gave moderate yields of products (**3e** and **3f**). It is noteworthy that highly selective alkylation occurred at the C2 position of the linear alkane in spite of the slightly small difference between C1 and C2 position in bond dissociation energies (BDE).[12] For pentane, the BDE of C(1)−H is 100.2 kcal mol^{-1} and 99.2 kcal mol^{-1} at the C2 position. Similarly, for hexane, the BDE of C(1)−H is 99.0 kcal mol^{-1} while the BDE of C(2)−H is 98.0 kcal mol^{-1}. Therefore, the reactivities of the sp^3-hybridized C−H bonds in alkanes should decrease in the order of tertiary > secondary > primary which might be not due to the BDE of the sp^3 C−H bond, but the stability and the steric effect of the corresponding carbon-centered radical.[5,7] Finally, a series of toluene derivatives have also been investigated. As a result, the corresponding products were obtained in moderate to high yields (**3g**−**m**).[13]

To investigate the details of the mechanism for this copper-catalyzed alkylarylation of acrylamides with alkanes, a series of experiments were carried out. No desired product was observed by addition of TEMPO as a radial inhibitor. In addition, an intermolecular competing kinetic isotope effect (KIE) experiment was carried out. As a result, a significant KIE was observed with the k_H/k_D = 9.3 at a low conversion level (Scheme 2). It indicates that the sp^3 C−H bond cleavage should be involved in the rate-determining step of this procedure.

Scheme 2. KIE Studies



At low conversion (23 %): k_H/k_D = 9.3; yields: **a** 18 %; **b** 2 %
At high conversion (80 %): k_H/k_D = 6.1; yields: **a** 66 %; **b** 10 %

Additionally, we tried to catch some radical intermediates by electron spin resonance (ESR). The ESR signal of some Cu(II) species was observed by using 2-methyl-2-nitrosopropane (MNP) as a radical spin trap, which indicates that the Cu(I) catalyst might be oxidized to Cu(II) species under this condition (Figure 1).

A plausible mechanism that is consistent with the experimental data and literature precedent is depicted in Scheme 3. The Cu(I)-assited homolysis of DCP gives cumyloxyl radical and Cu(II) species. Hydrogen abstraction reaction of cumyloxyl radical with alkanes generates alkyl radical and acetophenone,[14] which can be isolated as a byproduct. Radical intermediate **A** would be formed by addition of alkyl radical to the C═C bond. Cyclization of **A** to benzene core would give radical **B**, which then is oxidized by Cu(II) species to generate the product and regenerates the Cu(I) species. Alternatively, the radical **A** can also be oxidized by Cu(II) species to the corresponding carbocation, followed by intramolecular electrophilic aromatic substitution giving the product, which cannot be ruled out from the present system.

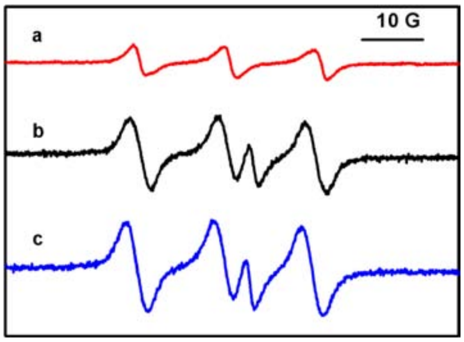
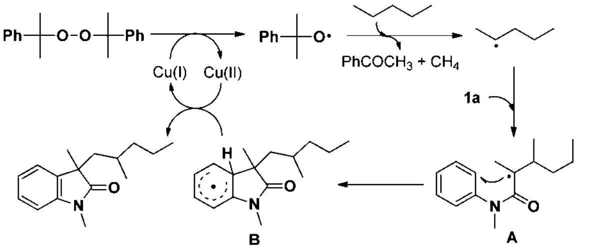


Figure 1. ESR Studies. (a) ESR spectrum of a solution of MNP (5.0×10^{-3} mol/L) in cyclohexane for 4 h. (b) ESR spectrum of a solution of MNP (5.0×10^{-3} mol/L) and $CuSO_4 \cdot 5H_2O$ (2.5×10^{-3} mol/L) in cyclohexane for 2 min. (c) ESR spectrum of a solution of **1a** (5.0×10^{-2} mol/L), DCP (0.15 mol/L), Cu_2O (2.5×10^{-3} mol/L), and MNP (5.0×10^{-3} mol/L) in cyclohexane for 5 h.

Scheme 3. Possible Mechanism



In conclusion, we developed a novel Cu-catalyzed oxidative alkylarylation of acrylamides with simple alkanes. This method not only provided a useful method for synthesis of alkyl-substituted oxindoles but also represented a new strategy for selective functionalization of simple alkanes via a free radical cascade process. In addition, selective activation of unactivated (sp^3)C−H and (sp^2)C−H bonds by one single step is achieved in this system, which would also provide a novel strategy for raising efficiency in C−H bond functionalization. Further investigation of this strategy focusing on construction of other bioactive cyclic compounds via selective sp^3 C−H bond functionalization of simple alkane is underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project is supported by the National Science Foundation of China (Nos. 21002045, 21272096).

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