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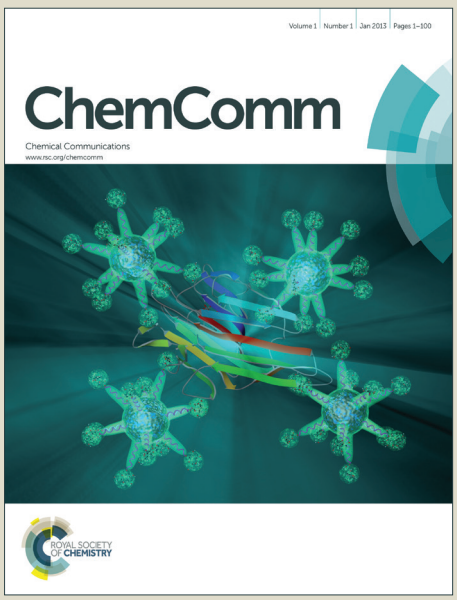

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ARTICLE TYPE

Metal-free cascade construction of C-C bond by activation of inert C(sp3)-H bond

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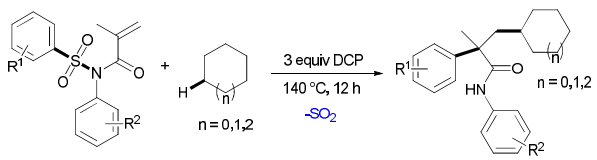
A new synthetic strategy for C-C bond formation has been developed, *via* a free radical cascade process under metal-free condition. Activation of inert C(sp^3)−H/elimination of SO_2 / C-C bond formation were achieved in sequence in this system.

Recently, a variety of strategies for C-C bond construction initiated by C(sp^3)-H activation have been developed.[1,2] However, most of these transformations were catalyzed by transition metals, and focused on activated C-H bond.[1,2] In consideration of the heavy metal residue, metal-free, organocatalytic C(sp^3)-H activation has been improved rapidly in past years.[3] Moreover, more and more attention is paid to the construction of C-C bond from C(sp^2)-H in olefin and C(sp^3)-H in simple alkane.[4]

Cascade reaction has been demonstrated as an efficent organic synthesis strategy, since it usually provides the desired product directly, without multiple processes, separation of intermediates and time-consuming.[5] In 2012, we reported a cascade reaction in which C-N, C-O and C=N bond were formed in one step, *via* metal-free radical initiate inert C(sp^3)–H bond activation.[6] To further our investigation of C-H bond activation, a metal-free catalytic radical cascade reaction using alkenes and simple alkanes was designed. In this communication, we report a metal-free cascade alkylation of alkenes with simple alkanes *via* free radical process, in which C(sp^3)–H bond activation/SO_2 elimination/C-C bond formation were achieved in sequence (Scheme 1).

N-phenyl-*N*-tosylmethacrylamide (**1a**) and cyclohexane were selected as model substrates to optimize the reaction condition. The results are sumarised in Table 1. To our delight, the desired product was separated with 51% yield when dicumyl peroxide (DCP) was used as radical initiator (Table1, entry 1). This result gave us much confidence to continue the experiment. However, no better result was obtained when radical initiators such as di-*t*-butyl peroxide (DTBP), *tert*-butyl hydroperoxide (TBHP) and *tert*-butyl peroxybenzoate (TBPB) were used (Table1, entries 2-5). In the following studies, it was found that 3 equiv DCP was the most applicable amount (Table1, entry 1) and 12 h was the most suitable reaction time (Table1, entry 10). Moreover, the effects of temperature and the concentration of the substrate were investigated (Table 1, entries 12-17). The best yield was obtained when the reaction was carried out in 1 ml cyclohexane

this work

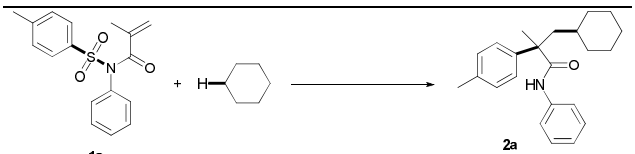


Scheme 1. Alkylation of Alkenes with Simple Alkanes

for 0.2 mmol amides at 140 °C (Table 1, entry 14).

With the optimized reaction condition in hand, we studied the scope of this reaction between a series of *N*-phenyl-*N*-(phenylsulfonyl)-methacrylamide and different cyclanes (Table 2 and Table 3). As shown in Table 2, different

Table 1 Optimization of reaction conditions [a]

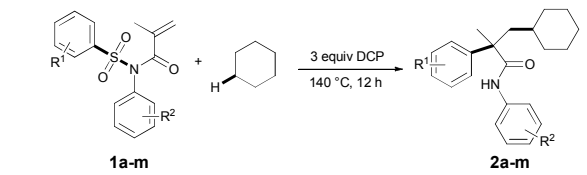


Entry	Radical initiator (equiv)	T (°C)	Yield(%)[b]
1	DCP (3)	120	51
2	TBPB (3)	120	40
3	DTBP (3)	120	43
4[c]	DTBP (3)	120	16
5	TBHP (3)	120	19
6	DCP (1)	120	30
7	DCP (2)	120	42
8	DCP (4)	120	47
9[d]	DCP (3)	120	35
10[e]	DCP(3)	120	48
11[f]	DCP (3)	120	72
12	DCP (3)	80	52
13	DCP (3)	100	67
14	**DCP (3)**	**140**	**77**
15	DCP (3)	160	72
16[g]	DCP (3)	140	47
17[h]	DCP (3)	140	67

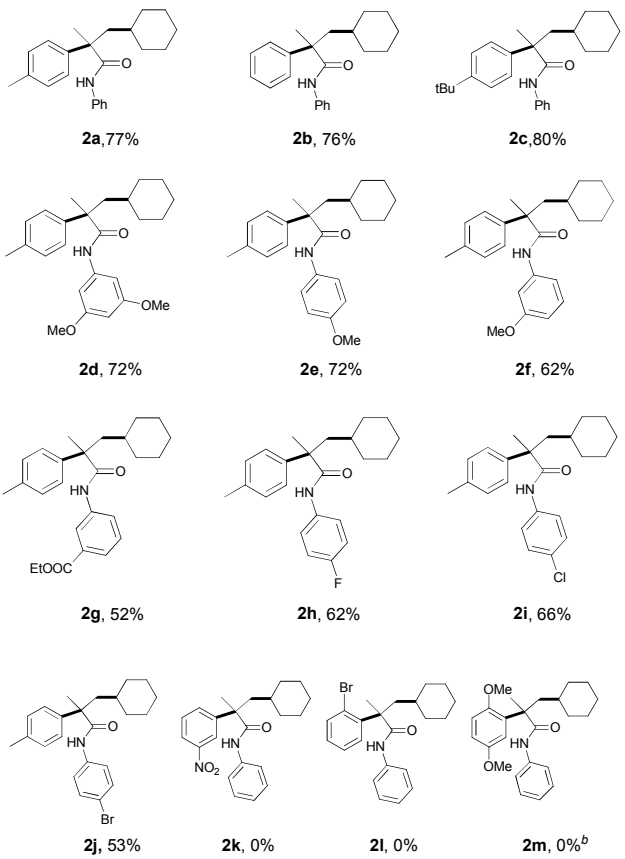
[a] Reaction condition: *N*-phenyl-*N*-(phenyl-sulfonyl)-methacryl-amides (0.2 mmol), cylcohexane (1 mL), DCP (0.6 mmol), 120 °C, 12 h under N_2 atmosphere unless other noted. [b] Isolated yield was provided. [c] 5 mol% *n*-Bu_4NI was added. [d] 4 h. [e] 8 h. [f] 16 h. [g] 0.5 ml cyclohexane was used. [h] 2.0 ml cyclohexane was used.

substituent groups in *N*-phenyl-*N*-(phenylsulfonyl)-meth-acrylamides were tolarated, providing the products in moderate to good yields. Amides with electron-donating group on phenyl such as CH_3, OCH_3, *t*-Bu, gave desired products in high yields (Table 2, **2a**, **2c-2f**). Similarly, *N*-phenyl-*N*-(phenylsulfonyl)-meth-acrylamide without substituent groups also gave a good yield (Table 2, **2b**). When phenyl was substituted by electron withdrawing group such as F, Cl, Br, COOEt, moderate yields of products were obtained (Table 2, **2g-2j**). However, amides with highly electron withdrawing groups such as NO_2, Br on the *N*-phenyl (SO_2) did not give out any products (Table 2, **2k** and **2l**). A mixture difficult to separate was got when there were two OCH_3 group on phenyl (SO_2) moiety (Table 2, **2m**).

Table 2 Metal-free cascade reaction of *N*-phenyl-*N*-(phenyl-sulfonyl)-methacrylamides with cyclohexane [a]



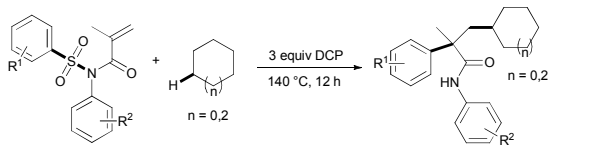
1a-m **2a-m**



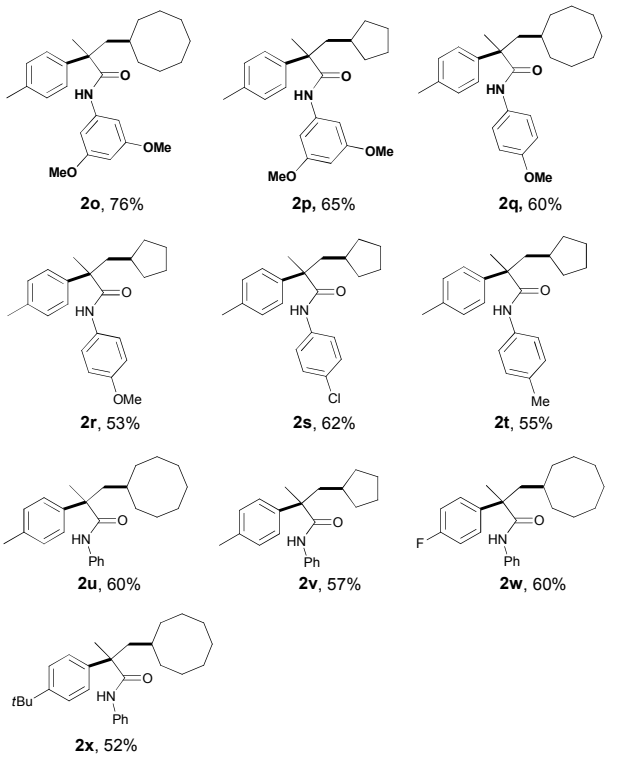
[a] Standard condition: *N*-phenyl-*N*-(phenyl-sulfonyl)-methacryl-amides (0.2 mmol), cylcohexane (1 mL), DCP (0.6 mmol), 140 °C, 12 h under N_2 atmosphere. Isolated yield was provided. [b] mixture difficult to separate.

Next, reaction of different simple alkanes with *N*-phenyl-*N*-(phenylsulfonyl)-meth-acrylamides was studied (Table 3). As expected, either cyclopentane or cyclooctane reacted with *N*-phenyl-*N*-(phenylsulfonyl)-meth-acrylamides giving corresponding products in moderate to good yield. Moreover, compared with cyclopentane, cyclooctane gave a higher yield when reacted with the same substrate (Table 3, **2o** and **2p**, **2q** and **2r**). However, a mixtrue difficult to separate was obtained when cyclanes were replaced by *n*-hexane. No desired product was detected when toluene was used.

Table 3. Metal-free cascade reaction of *N*-phenyl-*N*-(phenyl-sulfonyl)-methacrylamides with alkanes [a]



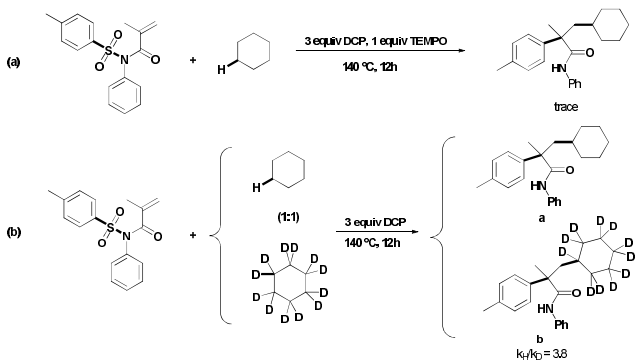
1o-x **2o-x**



[a] Standard condition: *N*-phenyl-*N*-(phenyl-sulfonyl)-methacryl-amides (0.2 mmol), alkane (1 mL), DCP (0.6 mmol), 140 °C, 12 h under N_2 atmosphere. Isolated yield was provided.

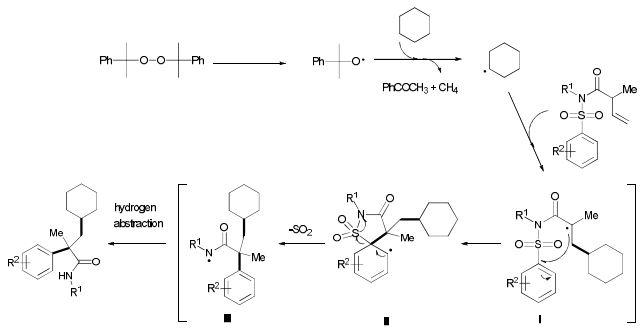
To investigate the mechanism of this type reaction, a series of control reactions were carried out. Firstly, **1a** and hexane were used to react in presence of a radical inhibitor 2,2,6,6-tetramethylpiperidine oxide (TEMPO) under standard condition. As expected, trace of product was detected (Scheme 2, (a)). Furthermore, a kinetic isotope effect was observed with the value of $k_H/k_D = 3.8$ in intermolecular competing reaction (Scheme 2, (b)). It suggested that the $C(sp^3)$–H bond cleavage step maybe involved in the rate-limiting step of this progress.

Based on the above experiments and literatures,[4,7] a plausible mechanism was proposed as shown in Scheme 3. At first, DCP



Scheme 2. Mechanism studies

genarates cumyloxyl radical when it is heated. The cumyloxyl radical abstractes a hydrogen atom from alkanes to form alkyl radical and acetophenone. Then alkyl radical adds to the C=C bond, which affording radical intermediate **I**. The 5-*ipso*-cyclization on the aromatic ring genaretes intermediate **II**, and a rapid desulfonylation gives out the key amidyl radical **III**. Finally, radical **III** transforms into the desired product after a hydrogen abstraction.



Scheme 3. Plausible mechanism

In summary, we have reported a metal-free cascade alkylation of alkenes *via* radical progress, in which activation of inert C(sp^3)-H bond, elimination of SO_2 and formation of C-C bond were achieved in sequence. This transformation provided an operationally simple method for functionalization of alkens with simple alkanes, and a new strategy to raise the efficiency in C−H bond functionalization.

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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