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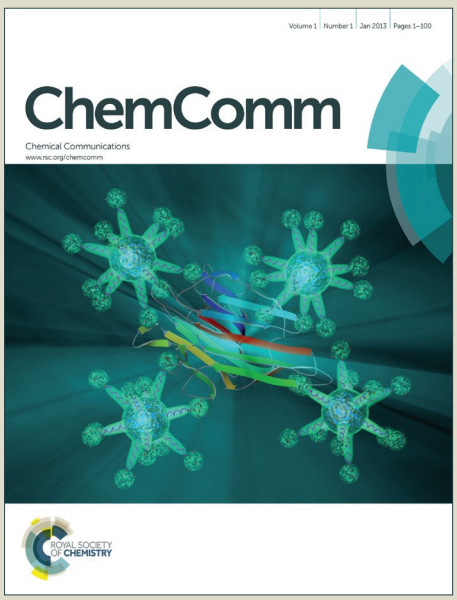

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Metal-free tandem oxidative C(sp^3)-H bond functionalization of alkanes and dearomatization of *N*−phenyl-cinnam-amides: access to alkylated 1−azaspiro[4.5]decanes

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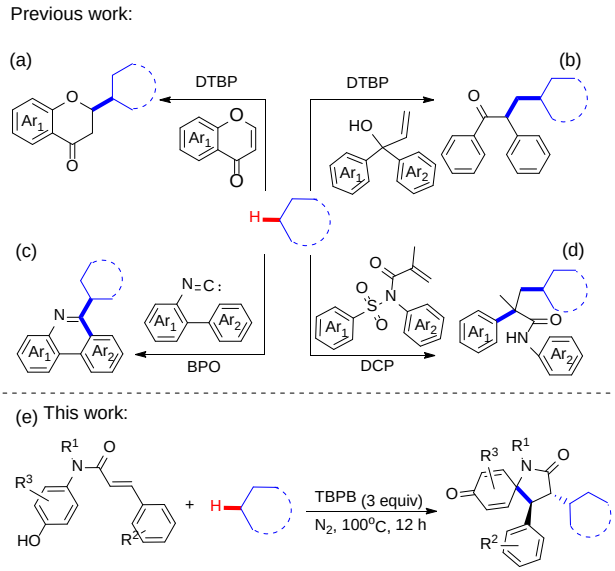
A TBPB promoted tandem oxidative C(sp^3)-H bond functionalization of simple alkanes / alkylation-initiated dearomatization of *N*-phenyl-cinnamamides is reported, providing a direct method for the synthesis of alkylated 1-azaspiro[4.5]decanes with excellent regioselectivity and diastereoselectivity. The formation of two C(sp^3)-C(sp^3) bonds and construction of spirodienone motif are involved in one step.

The direct construction of C-C bond via C-H bond functionalization has been paid considerable attention, because it can give out the desired product without multiple steps, separation of intermediates and preparation of functionalized of substrates.[1] Compared to C(sp^2)-H bond functionalization, C(sp^3)-H bond functionalization is much more challenging because of its high bond-dissociation energy (BDE) and low polarity.[2] In the past decade, C(sp^3)-H bond functionalization adjacent to unsaturated bonds, heteroatoms, electron-withdrawing-groups or phenyl groups have been well studied.[3] However, the construction of C-C bond *via* activation of inert C(sp^3)-H bond of simple alkanes is more difficult and has attracted much attention. The C-C bond formation *via* cross-dehydrogenative-coupling (CDC) reaction catalyzed by transition-metals has been well explored by Li and other groups.[4] Recently, several copper-catalyzed radical C(sp^3)-H bond functionalization of simple alkanes were established.[5, 6, 7] Compared to trasition-metal-catalyzed functionalization of C(sp^3)-H bond, it is more desirable for strategies of metal-free C(sp^3)-H bond functionalization of simple alkanes. Several examples of the C(sp^3)-H bond functionalization reactions, forming C(sp^2)-C(sp^3) bond *via* cross-dehydrogenative coupling (CDC) of heteroaromatic compounds with simple alkanes, have been reported.[8] Meanwhile, a few strategies of C(sp^3)-C(sp^3) bond formation by addition of simple alkanes and unsaturated bond were developed (Scheme 1, (a)-(c)).[9, 10] Our group reported a



Scheme 1. C-C bond faormation by metal-free C(sp^3)-H functionalization of simple alkanes

tandem oxidative C(sp^3)−H bond activation/SO_2 elimination/C(sp^3)-C(sp^3) bond formation reaction of simple cyclanes and *N*-phenyl-*p*-tosylmethacrylamides under metal-free condition(Scheme 1, (d)).

The spirodienone motif is widely found in natural products and organic molecules, which offers a base for construction of organic compounds with complex structure.[12] Especially, much effort has been spent on dearomatizing spirocyclization of phenol derivatives which provides direct access to the highly valuable spirodienone motif and can be used in complex total syntheses.[13, 14, 15] Very recently, Miranda group developed an easy access to spirodienonamides containing an acyl-functionalized all-carbon quaternary center from carbamoylxanthates under metal-free condition.[16] However, it is still challenging and highly appreciated for metal-free dearomatizing spirocyclization of phenol derivatives. Herein, we disclose a metal-free oxidative C(sp^3)-H bond functionalization of simple alkanes coupled with radical dearomatization of *N*-phenyl-cinnamamides, providing a direct towards various of alkyl group substituted 1-azaspiro[4.5] decanes

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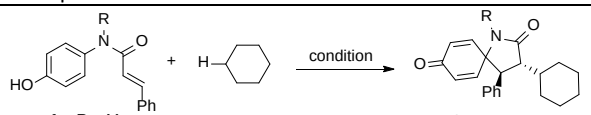
Initially, our study was carried out using *N*-(4-hydroxyphenyl)-*N*-methylcinnamamide **1a** as the model substrate. To our delight, the target molecule 3-cyclohexyl-1-methyl-4-phenyl-1-azaspiro[4.5] deca-6,9-diene-2,8-dione **2a** was obtained with 36% yield when 3.0 equiv TBPB was used as radical initiator (Table 1, entry 3), while other radical initiator gave trace or less product (Table 1, entries 1, 2, 4). Encouraged by the result, further optimization was carried out. The yield of **2a** did not increase as different amount of TBPB was loaded (Table 1, entries 5, 6). However, when the reaction was performed at 100 ^{o}C, the yield of **2a** increased to 71% (Table 1, entry 8), while different temperatures resulted in the yield decrease (Table 1, entries 7, 9). The employment of bases did not give a higher yield of **2a** (Table 1, entries 10-13). The amount of cyclohexane was also studied, and it showed that 1mL was the most suitable amount for cyclohexane (Table 1, entries 8, 14, 15). Considering that methyl group is a difficult removable *N*-protect group, it was replaced by benzyl group which is easy to remove. As *N*-benzyl-*N*-(4-hydroxyphenyl)-cinnamamide **1b** was used to further optimize the reaction condition, the yield of corresponding product 1-benzyl-3-cyclohexyl-4-phenyl-1-azaspiro[4.5]deca-6,9-diene-2,8-dione **2b** increased a little (Table 1, entry 16). The best yield was obtained when dry cyclohexane was used (Table 1, entry 17). Analysis of the NMR spectra of **2a** showed that cyclohexanyl and phenyl group were in the *trans*-configuration.

With the optimized condition in hand, we began to scope the reaction of different cinnamamides and cyclohexanes. As shown in table 2, cinnamamides with substitute groups such as Me, F, Cl, Br, CF_3 all reacted well with cyclohexane, giving the corresponding products in moderate to good yield (Table 2, **2c**-**2i**). Additionally, cinnamamides substituted by electronic-withdrawing-groups giving higher yields (Table 2, **2c** and **2d**, **2f** and **2g**). The position of substitute group on phenyl attached to the double bond has little effect on the efficiency of this transformation(Table 2, **2e** and **2**). Meanwhile, cinnamamides substituted by Cl on phenyl ring attached to N could also gave the corresponding product in 62 % yield(Table 2, **2j**). However, no product was generated by cinnamamides protedted by acetyl group (Table 2, **2k**).

Table 1. Optimization od reaction condition



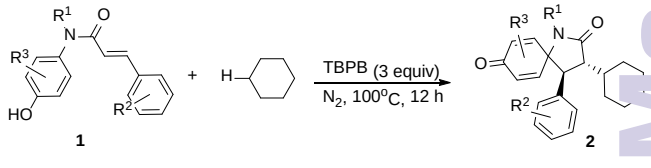
1a: R = Me
1b: R = Bn

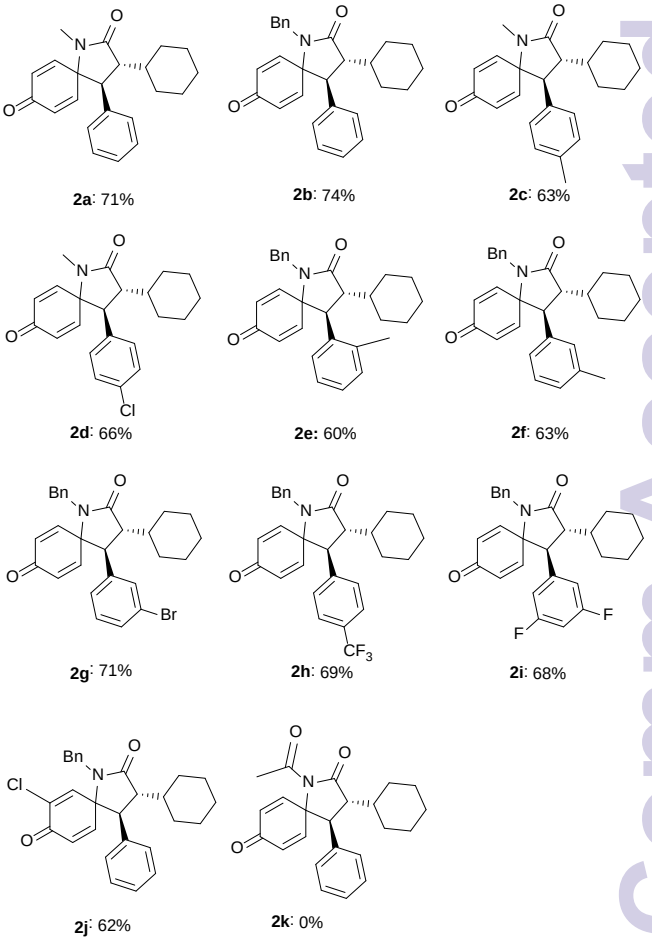
2a: R = Me
2b: R = Bn

Entry	Radical initiator (equiv)	Additive (equiv)	T (^{o}C)	Yield (%)[b]
1	DTBP (3)	—	120	trace
2	TBHP(4)	—	120	14
3	TBPB (3)	—	120	36
4	DCP (3)	—	120	10
5	TBPB (2)	—	120	26
6	TBPB (4)	—	120	30
7	TBPB (3)	—	110	42
8	TBPB (3)	—	100	71
9	TBPB (3)	—	90	60
10	TBPB (3)	*i*Pr$_2$NEt (2)	100	6
11	TBPB (3)	KOAc (2)	100	17
12	TBPB (3)	Na_2CO_3 (2)	100	56
13	TBPB (3)	Cs_2CO_3 (2)	100	17
14 [c]	TBPB (3)	—	100	37
15 [d]	TBPB (3)	—	100	32
16 [e]	TBPB (3)	—	100	76
17 [ef]	TBPB (3)	—	100	79

a. Reaction condition: **1**(0.1 mmol), cyclohexane (1 mL), 120^{o}C, 12 h under N_2 atmosphere unless other noted; b. ^{1}H NMR yield; c. Cyclohexane (2 mL); d. cyclohexane (0.5 mL); e. **1b** was used; f. dry cyclohexane (1 mL) was used.

Table 2. Metal-free cyclization and dearomatization of *N*-(4-hydroxyphenyl)-*N*-alkylcinnamamides with cyclohexane



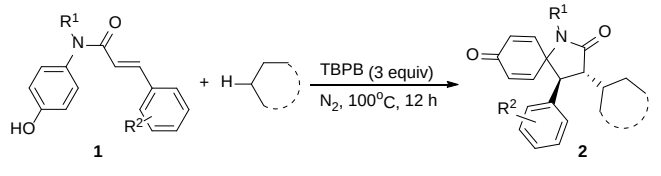


Reaction condition: **1**(0.1 mmol), dry cyclohexane (1 mL), TBPB (0.3 mmol), 100^{o}, 12 h under N_2 atmosphere. Isolated yield was provided.

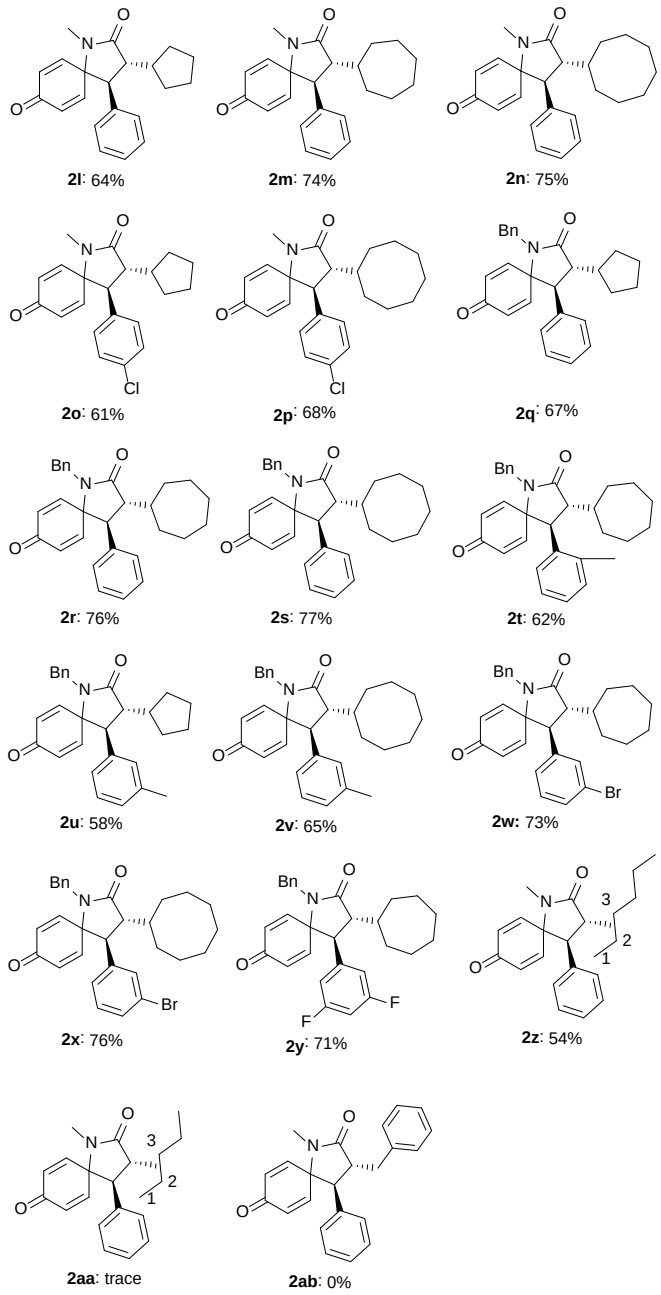
Next, different cyclanes were employed to react with *N*-(4-hydroxyphenyl)-*N*-alkylcinnamamides (Table 3). All substitute groups such as Me, F, Cl, Br were well tolerated, generating the corresponding products with moderate to good yield(Table 2, **2t**-**2**). Additionally, cinnamamides protected by benzyl group giving the corresponding products with a little higher yield than cinnamamides

protected by methyl group(Table 2, **2l** and **2q, 2m** and **2r, 2n** and **2s**). When reacted with the same cinnamamide, the bigger cyclane gives the corresponding product with a higher yield(Table 2, **2l**-**2n, 2o** and **2p, 2q**-**2s, 2u** and **2v, 2w** and **2x**). Similarly, the corresponding products were obtained with higher yields when cinnamamides were substituted by electronic-withdrawing-group. As *n*-hexane was used instead of cyclanes, a mixture of isomers was obtained with 54% yield, while trace of the corresponding product was generated when *n*-pentane was used(Table 2, **2z** and **2aa**). However, no product was observed when **1a** reacted with toluene(Table 2, **2ab**).

Table 3. Metal-free cyclization and dearomatization of *N*-(4-hydroxyphenyl)-*N*-alkylcinnamamides with cycloanes

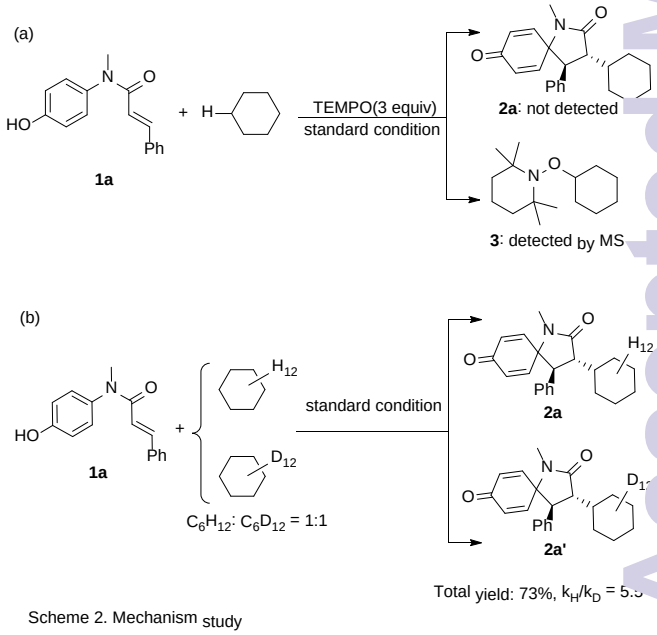


1 2



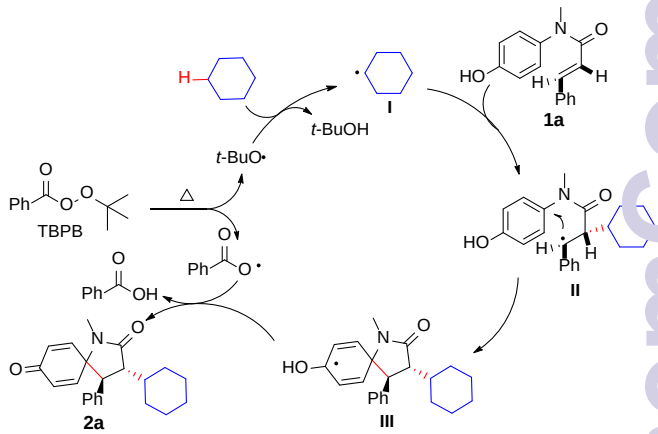
Reaction condition: **1**(0.1 mmol), dry cyclane (1 mL), TBPB (0.3 mmol), 100°C, 12 h under N_2 atmosphere. Isolated yield was provided.

To gain further investigation of this type transformation, some control experiments were carried out. Firstly, 3.0 equivalent radical inhibitor 2,2,6,6-tetramethylpiperidine oxide (TEMPO) was added to this system under standard condition. As we expected, no product 2a was detected. The cyclohexanyl radical was traped by TEMPO and the adduct was determined by MS(MS (EI) calcd. for $C_{15}H_{29}NO(M + H^+)$: 240.23, found: 240.33),[17] suggesting that this transformation may undergo a radical process(Scheme 2(a)). Furthermore, a kinetic isotope effect was observed with the value of k_H/k_D = 5.5 in intermolecular competing reaction (Scheme 2(b)). The result showed that the C(sp^3)–H bond cleavage maybe involved in the rate-limiting step of this transformation.



Scheme 2. Mechanism study

On the basis of literature reports [15, 18] and the experiment results, a possible reaction mechanism was proposed. Initially, TBPB



Scheme 3. Plausible mechanism

transformed into *tert*-butoxyl radical and the benzoate radical when it was heated. Then, the C(sp^3)–H bond of the cyclohexane is activated by the *tert*-butoxyl radical, generating the cyclohexanyl radical **I**. As the electron density of the α-position of cinnamamide **1** is slightly higher than the β-position, the cyclohexanyl radical **I** regioselectively adds to the the α-position, giving benzyl carbon-centered radical **II** which is stabilized by the phenyl group. The spirocyclic intermediate **III** was generated as the radical **II** goes thermodynamically controlled *5-exo* cyclization onto the phenol ring. Due to the steric bulk of the cyclohexanyl and phenyl groups, the *trans*-configuration is favored. Finally, the spirocyclic intermediate **III** undergoes oxidation and deprotonation to give the desired product **2a** and benzoate.

In summary, we have report a TBPB promoted oxidative C(sp^3)-H bond functionalization of simple alkanes and alkylation-initiated radical dearomatizing spirocyclization of *N*-phenyl-cinnamamides, in which two C(sp^3)-C(sp^3) bond formation were involved. A series of simple alkanes substrates were well tolerated to react with different cinnamamides, directly generating alkyl group substituted 1-azaspiro[4.5] decanes in moderate to good yields with excellent regioselectivity and diastereoselectivity. A new method for C(sp^3)-H bond functionalization of simple alkanes and increasing efficiency of C-H bond functionalization was provided, which enriched the content of dearomatizing spirocyclization as well. Further investigation of metal-free oxidative selective activation of inert C(sp^3)-H bond of simple alkanes coupled with dearomatization is underway in our laboratory.

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