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Oxidative coupling of alkenes with amides using peroxides: selective amide C(sp^3)–H *versus* C(sp^2)–H functionalization†

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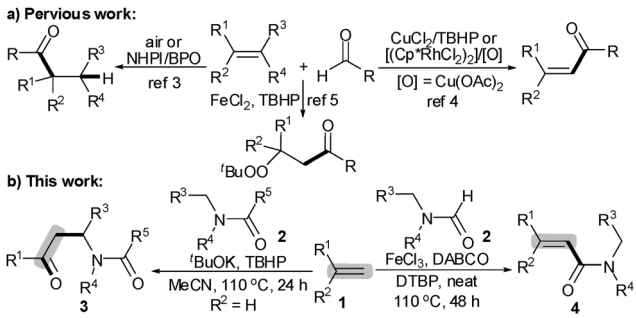
A new oxidative coupling of unactivated terminal alkenes with amides using peroxides is described, in which mono- and difunctionalization of alkenes are selectively achieved. In this reaction with amides, the chemoselectivity toward the functionalization of the C(sp^3)–H bonds adjacent to the nitrogen atom or the functionalization of the carbonyl C(sp^2)–H bonds across alkenes relies on the reaction conditions.

Alkenes are abundant organic molecules and simple chemical feedstock, and methods for their direct, selective functionalization are attractive as an important means to assemble more complex molecular entities. The transition-metal-catalyzed Heck couplings of alkenes with organic electrophiles have become some of the most efficient and common methods for the alkene functionalization due to their operational simplicity, the use of commercially available starting materials and the versatility of the resulting alkenes in synthesis.[1] Despite their widespread applications, the Heck coupling routes are typically protracted by the need to pre-functionalize the C–H bond toward the C–X bond (X = halides and pseudohalides). Therefore, an attractive alternative would involve a C–H functionalization that directly couples unactivated alkenes with broad diversification of functional groups and excellent selectivity control.

The oxidative coupling methodology involving the C–H functionalization has attracted much attention for replacing the conventional cross-coupling procedures, in part due to its step-economy by the avoidance of the pre-functionalization process.[2–5] Despite remarkable advances in the field, approaches for the coupling of alkenes, particularly unactivated alkenes, with the carbonyl C(sp^2)–H bonds are rare and limited.[2–5] Generally, these oxidative transformations focus on the coupling with the aldehyde C(sp^2)–H bonds (Scheme 1a, including 1) the coupling of electron-deficient alkenes with aldehydes (often alkyl aldehydes) initiated by air or *N*-hydroxyphthalimide (NHPI) combined with dibenzoyl peroxide (BPO) leading to saturated ketones,[3] (2) the Heck-type coupling of unactivated alkenes with aryl aldehydes by using the $[(Cp^*RhCl_2)_2]/C_5H_2Ph_4/Cu(OAc)_2$ or $CuCl_2$/*tert*-butyl hydroperoxide (TBHP) system for synthesizing α,β-unsaturated ketones,[4] and (3) the difunctionalization of arylalkenes with aldehydes and TBHP catalyzed by $FeCl_2$ accessing β-peroxy ketones.[5] However, methods for the oxidative coupling of alkenes with the formyl C(sp^2)–H bonds of formamides have not been reported.[6] Herein, we report a new oxidative coupling of terminal alkenes with amides using peroxides and a catalytic amount of bases (Scheme 1b); the chemoselectivity of this method can be controlled by changing the reaction conditions: while a catalytic amount of ^{t}BuOK combined with TBHP delivers β-amino ketones[5] from alkenes and the C(sp^3)–H bonds adjacent to the nitrogen atom of amides, the $FeCl_3$/DABCO/di-*tert*-butyl peroxide (DTBP) system assembles α,β-unsaturated amides by using alkenes to react with the carbonyl C(sp^2)–H bonds of formamides. Notably, the oxygen atoms in the new formed carbonyl groups are from hydroperoxides.



Scheme 1 Oxidative coupling of alkenes with carbonyl compounds.

We commenced our investigations by optimizing the reaction conditions for the oxidative coupling of 4-vinyltoluene (**1a**) with *N*,*N*-dimethylformamide (DMF; **2a**) (Table 1).[7] Initially, alkene **1a** was treated with DMF **2a** and TBHP at 110 °C for 24 h, but no

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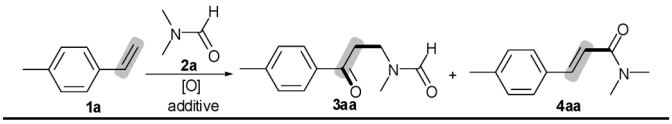
Table 1 Screening optimal conditions[a]



Entry	[O] (equiv.)	Base (mol%)	Solvent	T (°C)	Isolated yield (%) 3aa	4aa
1	TBHP (2)	—	DMF	110	0	0
2	TBHP (2)	^{t}BuOK (5)	DMF	110	26	0
3	TBHP (2)	^{t}BuOK (10)	DMF	110	70	0
4	TBHP (2)	^{t}BuOK (20)	DMF	110	69	0
5	TBHP (2)	K_2CO_3 (10)	DMF	110	65	0
6	TBHP (2)	DBU (10)	DMF	110	46	0
7	TBHP (2)	DABCO (10)	DMF	110	19	0
8[b]	TBHP (2)	^{t}BuOK (10)	DMF	110	66	0
9	TAHP (2)	^{t}BuOK (10)	DMF	110	61	0
10	CHP (2)	^{t}BuOK (10)	DMF	110	28	0
11	DTBP (2)	^{t}BuOK (10)	DMF	110	Trace	0
12	BPO (2)	^{t}BuOK (10)	DMF	110	Trace	0
13	—	^{t}BuOK (10)	DMF	110	0	0
14	TBHP (2)	^{t}BuOK (10)	DMF	80	10	0
15	TBHP (2)	^{t}BuOK (10)	DMF	120	69	0
16[c]	TBHP (2)	^{t}BuOK (10)	MeCN	110	70	0
17[d]	TBHP (2)	^{t}BuOK (10)	DMF	110	8	5
18[d]	TBHP (2)	DABCO (10)	DMF	110	Trace	9
19[d]	DTBP (2)	DABCO (10)	DMF	110	0	43
20[d]	DTBP (5)	DABCO (30)	DMF	110	0	85
21[e]	DTBP (5)	DABCO (30)	DMF	110	0	53

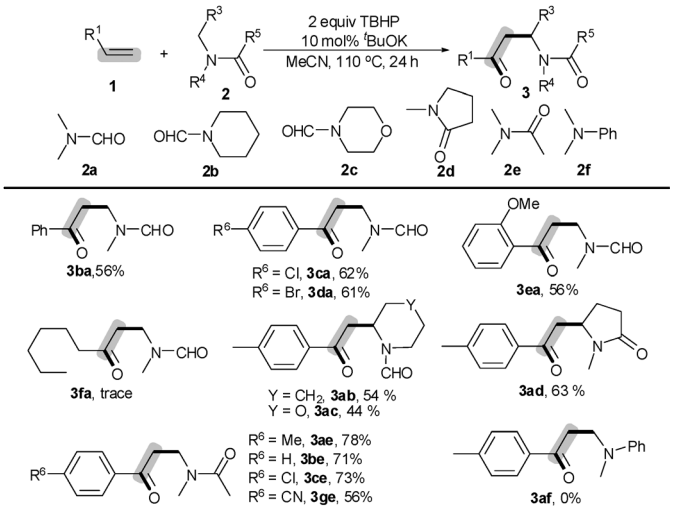
[a] Reaction conditions: **1a** (0.4 mmol), **2a**, [O] (2 equiv.), base and solvent (2 mL) for 24 h. TBHP (5 M in decane). [b] TBHP (70% in water). [c] DMF (4 mmol). [d] $FeCl_3$ (30 mol%) was added for 48 h. [e] $FeCl_2$ (30 mol%) was added for 48 h.

coupled products were observed (entry 1). Gratifyingly, we found that a catalytic amount of ^{t}BuOK could trigger the reaction, and 10 mol% ^{t}BuOK was preferred to form β-amino ketone **3aa** in 70% yield (entries 2–4). Other bases, including K_2CO_3, DBU and DABCO, could effect the reaction, but they were less efficient than ^{t}BuOK (entries 4–7). Screening of peroxides revealed that only hydroperoxides, TBHP, TAHP (*tert*-amyl hydroperoxide) and CHP (cumene hydroperoxide), could initiate the coupling (entries 2 and 8–10), and other peroxides without hydroxyl groups, DTBP and BPO, have no activities at all (entries 11 and 12). However, no product **3aa** was observed without oxidants (entry 13). After varying the temperatures, the reaction at 110 °C provided the best results (entry 3 *vs.* entries 14 and 15). Notably, the reaction was successfully performed in MeCN, delivering **3aa** in 70% yield (entry 16).

Interestingly, addition of $FeCl_3$ could shift the chemoselectivity: β-amino ketone **3aa** and (*E*)-*N*,*N*-dimethyl-3-*p*-tolylacrylamide (**4aa**)[5] were obtained in 5 and 8% yields, respectively (entry 17). Evaluation of various reaction parameters revealed that 30 mol% $FeCl_3$, 30 mol% DABCO and 5 equiv. of DTBP at 110 °C for 48 h gave the best results: product **4aa** was obtained exclusively in 85% yield (entries 17–19 and 21 *vs.* entry 20). It should be noted that $FeCl_2$ can effect the reaction, ableit lowering the yield to 53% (entry 21).

With the optimal reaction conditions in hand, we first sought to coupling of various terminal alkenes **1** with amides **2** to synthesize diverse β-amino ketones **3** (Table 2). In the presence of TBHP and ^{t}BuOK, β-amino ketone **3ba** was formed

Table 2 Coupling of alkenes (**1**) with amides (**2**), TBHP and ^{t}BuOK[a]



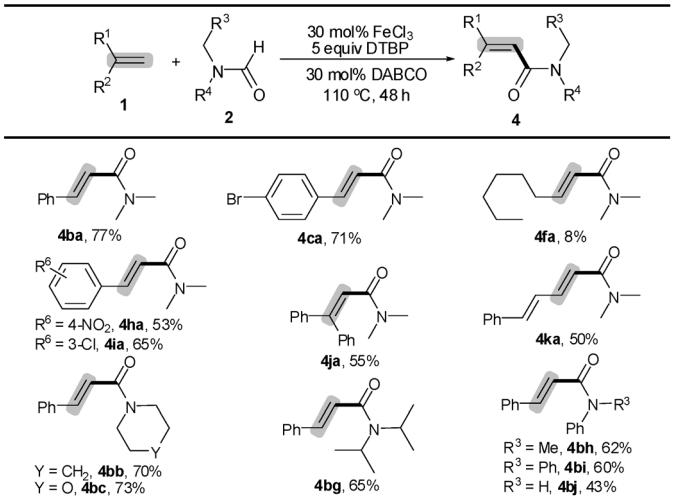
[a] Reaction conditions: **1** (0.4 mmol), **2** (4 mmol), ^{t}BuOK (10 mol%), TBHP (2 equiv.; 5 M in decane) and MeCN (2 mL) at 110 °C for 24 h.

in 56% yield from styrene (**1b**) and DMF **2a**. Interestingly, a variety of substituted arylalkenes were also compatible with the optimal conditions, and substituents, including Cl, Br, MeO and CN, on the aromatic ring were well-tolerated (**3ca–ge**). Treatment of Cl- and Br-substituted alkenes **1c** and **1d** with DMF **2a**, TBHP and ^{t}BuOK successfully afforded **3ca** and **3da** in 62 and 61% yields, respectively. *ortho*-MeO-substituted alkene **1e** also delivered **3ea** in moderate yield. Unfortunately, oct-1-ene (**1f**), an alkylalkene, was not a suitable substrate (**3fa**). The optimal conditions were applicable to various amides **2b–2e** (**3ab–ae**), but failed to an amine **2f** (**3af**). Two cycloalkylamines, piperidine-1-carbaldehyde (**2b**) and morpholine-4-carbaldehyde (**2c**), could couple with alkene **1a**, TBHP and ^{t}BuOK, providing **3ab** and **3ac** in moderate yields. 1-Methylpyrrolidin-2-one (**2d**) was also a viable substrate, generating **3ad** in 63% yield, in which alkene **1a** regiospecifically attacked the 5 position (the methylene group), and not the 1-methyl group. Moreover, the reaction of *N*,*N*-dimethylacetamide (**2e**) with various arylalkenes **1a–c** or **1g**, TBHP and ^{t}BuOK was successfully performed, furnishing **3ae**, **3ce** and **3ge** in good yields.

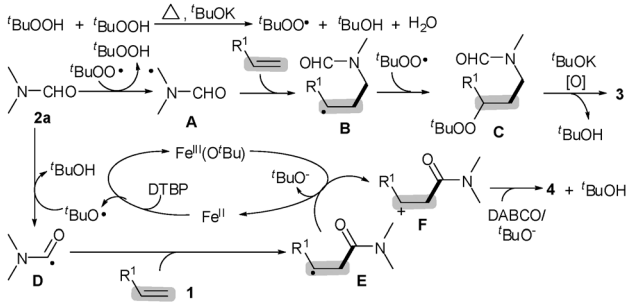
As shown in Table 3, we turned our attention to assemble α,β-unsaturated amides **4** from alkenes **1** and formamides **2** in the presence of $FeCl_3$, DTBP and DABCO. Arylalkenes **1b–c** and **1h–i** even with Br, NO_2 and Cl groups on the aryl ring successfully underwent the coupling with DMF **2a**, giving **4ba–ca** and **4ha–ia** in 53–77% yields, and the order of their reactivity is as follows: electron-rich > electron-deficient. However, alkylalkene **1f** had a relatively low reactivity (**4fa**). Gratifyingly, 1,1-diphenylethylene (**1j**) and (*E*)-phenylbuta-1,3-diene (**1k**) delivered **4ja** and **4ka** smoothly in 55% and 50% yields, respectively. It is important to note that this coupling generally proceeds in moderate to good yields with an extensive range of other formamides, including *N*,*N*-dialkylformamides **1b–c** and **1g**, *N*-methyl-*N*-phenylformamide (**1h**), *N*,*N*-diphenylformamide (**1i**) and *N*-phenylformamide (**1j**) (**4bb–bc** and **4bg–bj**).

The results of entries 3 and 9–13 in Table 1 showed that only hydroperoxides could trigger the reaction, suggesting that the

Table 3 Fe-catalyzed coupling of alkenes (**1**) with formamides (**2**)[a]



[a] Reaction conditions: **1** (0.4 mmol), **2** (2 mL), $FeCl_3$ (30 mol%), DBACO (30 mol%) and DTBP (5 equiv.) at 110 °C for 48 h.



Scheme 2 Possible mechanisms.

oxygen atoms in the new formed carbonyl group of products **3** may be from hydroperoxides. To verify this, a control experiment between alkene **1a** and DMF **2a** using 4 equiv. of $H_2{}^{18}O$ was performed: product **3aa** did not include the ^{18}O atom, ruling out the oxygen atom from H_2O. Moreover, the presence of radical inhibitors, TEMPO, hydroquinone and BHT, resulted in no detectable **3aa**, implying that the current reaction includes a radical process.

Possible mechanisms outlined in Scheme 2 were proposed for the oxidative coupling.[2–5,8] Initially, alkyl radical **A** is formed by abstracting the α-H-atom alpha to the N-atom of DMF **1a** with $^tBuOO^\bullet$, which is generated from TBHP under heating with the aid of bases.[2,8] Addition of alkyl radical **A** to alkene **1** affords the other alkyl radical **B**. The reaction of alkyl radical **B** and $^tBuOO^\bullet$ occurs to afford intermediate **C**. Finally, the O–O bond of intermediate **C** cleaved by ^{t}BuOK, followed by oxidation with TBHP produces **3** and ^{t}BuOH.

In the presence of Fe^{2+} species, DTBP is split into $Fe^{3+}(O^tBu)$ and the $^tBuO^\bullet$ radical.[2–5] Hydrogen-abstraction of DMF **2a** by the $^tBuO^\bullet$ radical delivers carbonyl radical **D**, and then addition across alkenes **1** affords alkyl radical **E**. Single-electron-transfer between alkyl radical **E** and $Fe^{3+}(O^tBu)$ gives alkyl cation **F**, Fe^{2+} species and $^tBuO^-$. Finally, β-H elimination of alkyl cation **F** with $^tBuO^-$ by using the DABCO base gives **4** and ^{t}BuOH.

The presence of $FeCl_3$ lowered the reactivity of alkenes **1** for reacting with the C(sp^3)–H bonds of amines, this is because $^\bullet$OH radical is consumed to form the Fe^{n+}(OH) species, compressing the generation of $^tBuOO^\bullet$ radical.

In summary, we have developed the first oxidative coupling of unactivated terminal alkenes with amides using peroxides for selective synthesis of β-amino ketones and α,β-unsaturated amides. This method proceeds *via* a tandem C–H/alkene functionalization step that occurs through an oxidative radical pathway with a broad substrate scope and excellent selectivity control.

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7 The detail data of screening optimal conditions are summarized in Table S1 of ESI†.

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