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Journal Name

View Article Online
DOI: 10.1039/D0CC06774A

COMMUNICATION

Iron-Catalyzed Acylation-Functionalization of Unactivated Alkenes with Aldehydes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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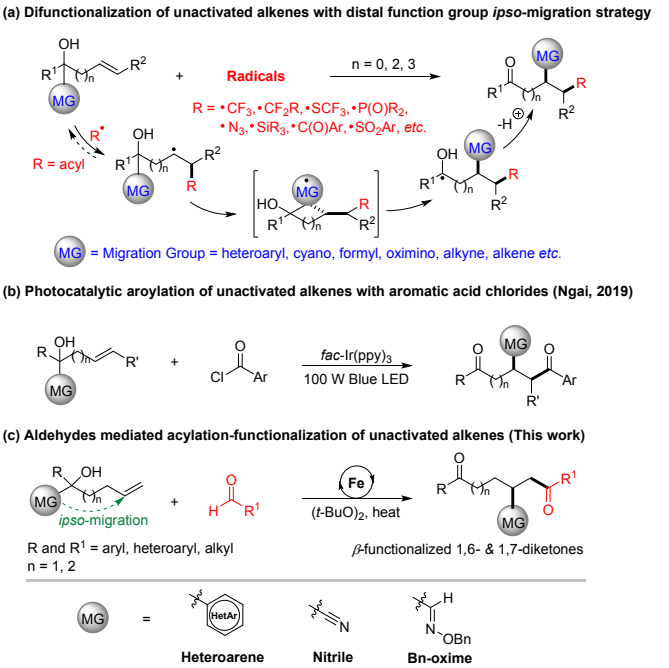
Herein, an iron-catalyzed acylation-functionalization of unactivated alkenes with aldehydes via distal group *ipso*-migration was reported. This strategy overcomed the energy barrier and reversibility in the difunctionalization of unactivated alkenes with nucleophilic acyl radicals, and a variety of β-(hetero)arylated, -cyanated and -oximated unsymmetrical 1,6- and 1,7-diketones were obtained regioselectively, chemoselectively and efficiently.

Controlled radical-mediated difunctionalization of alkenes is a state-of-the-art strategy for the utilization of alkenes.[1] In the past few decades, great progress has been made in the manipulation of activated alkenes in which an adjacent π-system (e.g., aryl, carbonyl and heteroatom) was installed.[2] The requirement of such activation group was attributed to (1) the lowered LUMO energy of C=C double bond with the aid of vicinal π-system, which facilitates its interaction with SOMO of free radical; (2) the stabilization of incipient alkyl radical intermediate via *p*-π conjugation or *p*-*p* orbital delocalization with the heteroatom. In contrast, the analogous conversion of unactivated alkenes (e.g., aliphatic alkenes) remains challenge task. To overcome this conundrum, chemists have developed the intramolecular radical functional group migration strategy as a powerful solution to realize this goal.[3] Early reports from Tu's group[4] and Wu/Li[5] group in 2013 realized the tandem trifluoromethylation/semipinacol rearrangement of allylic alcohols, in which a radical 1,2-aryl migration was indicated in the case of diarylallylic substrates used. Remarkably, Zhu and co-workers have innovatively developed the intramolecular distal functional group *ipso*-migration (FGM) strategy recently, which has well been applicable to radical difunctionalization of unactivated alkenes (Scheme 1a).[6] This protocol was proposed to proceed through extrinsic radical addition to alkene, the newly formed alkyl radical rapidly captured by intramolecular 1,n (n = 4, 5) unsaturated migratory group (e.g., heteroaryl,[7] cyano,[8] formyl,[9] oximino,[10] alkynyl[11] and alkenyl[12]), upon which cyclic C-C bond cleavage to give the functionalized products.



Scheme 1. Distal functional group *ipso*-migration strategy and its application in the acylation-functionalization of unactivated alkenes.

Carbonyls are important and versatile building blocks both in synthetic and industrial communities. Long-chain diketones, especially unsymmetrical 1,6- and 1,7-diketones, are found broad applications in the synthesis of bioactive cyclic molecules, while the efficient protocols to prepare these structures are still limited.[13] Recently, the synthesis of unsymmetric 1,8-diketones was achieved efficiently by the FGM strategy.[14] Hence, it is highly desirable to develop a general and wide-applicable strategy that enables rapid access to these diketone skeletons. Aldehydes are cheap, easily available and naturally-abundant feedstocks. Our group has long been interested in the iron-catalyzed[15] reactivity of acyl radicals[16] generated from aldehydes with alkenes. In our

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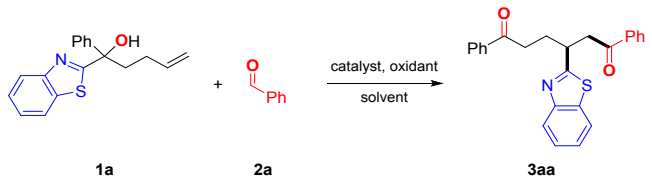
previous work,[17] activated alkenes, for example, styrenes and acrylates, could react efficiently with acyl radicals to give the difunctionalization products due to the intrinsic nucleophilic nature of acyl radicals. While its addition to unactivated (electron-rich) alkenes needs to overcome higher activation energy, and this process tends to be reversible, trapping the generated alkyl radical intermediate with another functional group except hydrogen atom is quite difficult.

We wonder if this limitation can be overcome with unactivated alkenes tethered to substituted tertiary alcohols as substrates using Zhu's intramolecular distal group *ipso*-migration strategy. Our key consideration is that intramolecular migration group capture of newly-formed alkyl radical is faster than itself decomposition (Scheme 1a, dashed line, R = acyl). Notably, during the progress of our project, Ngai and co-workers reported the use of aroyl chlorides as aroyl radical sources for such transformations under iridium/blue LED (Scheme 1b).[18] Herein, we wish to report our results that using aldehydes as acyl radical sources for the difunctionalization of unactivated alkenes under iron-catalyzed thermo conditions (Scheme 1c). Abundant aldehydes were applicable, and a variety of β-(hetero)arylated, -cyanated and -oximated unsymmetrical 1,6- and 1,7-diketones were obtained selectively and efficiently.

We started the investigation of 1-(benzo[d]thiazol-2-yl)-1-phenylpent-4-en-1-ol **1a** and benzaldehyde **2a** as the model to test our hypothesis (Table 1). Gratifyingly, after preliminary screening, the desired *ipso*-migration difunctionalization product **3aa** was obtained in 69% yield with $FeCl_2$ as the catalyst and di-*tert*-butyl peroxide (DTBP) as oxidant in the presence of chlorobenzene under 120 °C for 3 h (entry 1). Different kind of metal catalysts were then investigated and revealed that the desired **3aa** could also be obtained with CuCl, $CoCl_2$, $PdCl_2$, or $AgNO_3$, yet the yields were not as good as $FeCl_2$ (entries 2−5). The other iron catalysts, such as $FeBr_2$, FeI_2, $Fe_2(CO)_9$ and $Fe(acac)_2$, delivered **3aa** in 28-62% yields (entries 6-9). Solvent optimization revealed that toluene (PhMe), acetonitrile (MeCN) and ethyl acetate (EA) gave inferior yields of *ipso*-migration product **3aa** (entries 10-12), while no **3aa** was detected in the presence of 1,2-dichloroethane (DCE) or *N*,*N*-dimethylformamide (DMF) (entries 13 and 14). Other oxidants, such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl peroxybenzoate (TBPB) and benzoyl peroxide (BPO) were less efficient in this transformation (entries 15−17). Notably, the reaction could afford the desired product **3aa** in 86% yield when reducing the $FeCl_2$ loading to 1.5 mol% (entry 18). Control experiments revealed that **3aa** was furnished in 47% yield in the absence of metal catalyst (entry 19), while **3aa** was not detected without adding oxidant (entry 20).

Table 1 Optimization of the reaction conditions[a]

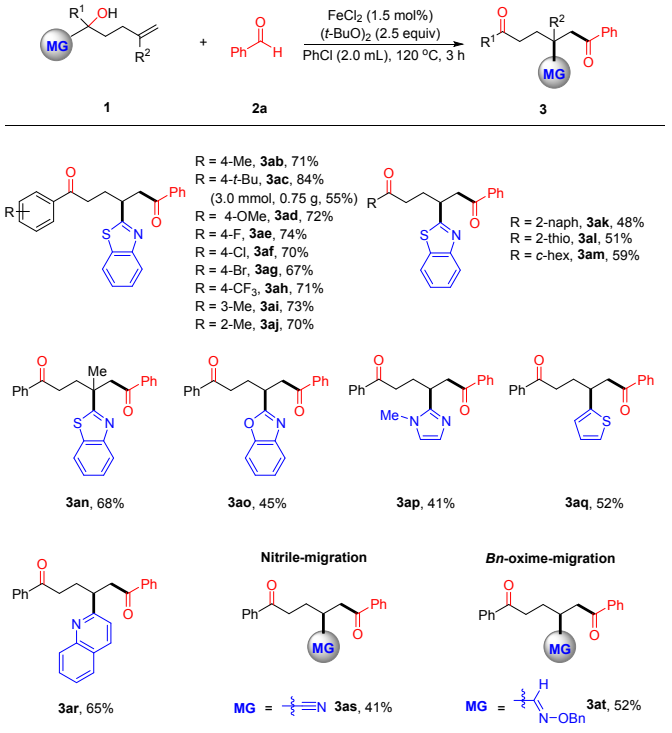


1a **2a** **3aa**

entry	catalyst	oxidant	solvent	**3aa**(%)[b]
1	$FeCl_2$	$(t\text{-BuO})_2$	PhCl	69
2	CuCl	$(t\text{-BuO})_2$	PhCl	56
3	$CoCl_2$	$(t\text{-BuO})_2$	PhCl	29
4	$PdCl_2$	$(t\text{-BuO})_2$	PhCl	18
5	$AgNO_3$	$(t\text{-BuO})_2$	PhCl	37
6	$FeBr_2$	$(t\text{-BuO})_2$	PhCl	28
7	FeI_2	$(t\text{-BuO})_2$	PhCl	45
8	$Fe_2(CO)_9$	$(t\text{-BuO})_2$	PhCl	56
9	$Fe(acac)_2$	$(t\text{-BuO})_2$	PhCl	62
10	$FeCl_2$	$(t\text{-BuO})_2$	PhMe	22
11[c]	$FeCl_2$	$(t\text{-BuO})_2$	MeCN	48
12[c]	$FeCl_2$	$(t\text{-BuO})_2$	EA	34
13[c]	$FeCl_2$	$(t\text{-BuO})_2$	DCE	N. D.
14	$FeCl_2$	$(t\text{-BuO})_2$	DMF	N. D.
15	$FeCl_2$	*t*-BuOOH	PhCl	20
16	$FeCl_2$	PhCOO*t*Bu	PhCl	12
17	$FeCl_2$	$(PhCOO)_2$	PhCl	31
18[d]	**$FeCl_2$**	**$(t\text{-BuO})_2$**	**PhCl**	**86(80)**
19	—	$(t\text{-BuO})_2$	PhCl	47
20	$FeCl_2$	—	PhCl	N. D.

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (1.5 mmol), catalyst (2.5 mol%), oxidant (0.75 mmol), solvent (2.0 mL), 120 °C, 3 h, under N_2 unless other noted. [b]NMR yields were determined by ^{1}H NMR using an internal standard (the isolated yield in parentheses). [c]Sealed tube was used. [d]1.5 mol% of $FeCl_2$ used.

With the optimal reaction conditions identified, we set out to examine the generality of this protocol. As shown in Scheme 2, chemoselective migration of benzothiazolyl group over aryl group was observed in spite of its electronic and steric characteristics. For example, aromatic rings bearing electron-donating -Me, -^{t}Bu or -OMe groups on the *para*-position gave products **3ab-3ad** in 71-84% yields. Arenes with electron-withdrawing halides, especially bromide, remained untouched, which allowed for further functionalization via cross-coupling reactions (**3ae-3ah**). The yields were not influenced when substituent attached to the *meta*- or *ortho*-position (**3ai** and **3aj**). The substrates containing naphthyl, thiophenyl, as well as alkyl substituent such as cyclohexyl, were all compatible under the optimized conditions (**3ak-3am**). This transformation can also be extended to the difunctionalization of 2,2-disubstituted alkenes, affording the product **3an** in 68% yield with a quaternary carbon center. Based on the above results, we then examined other types of migrating groups. Hetero aromatic rings such as benzoxazole, imidazole, thiophene and quinoline all migrated smoothly to give the desired products **3ao-3ar** in 41-65% yields. Gratifyingly, nitrile and Bn-oxime could also migrate and afforded functionalized unsymmetrical 1,6-diketones (**3as-3at**). Besides, gram-scale experiment of **1c** and **2a** was carried out to prove the practicability of this protocol (**3ac**, 0.75g, 55%).

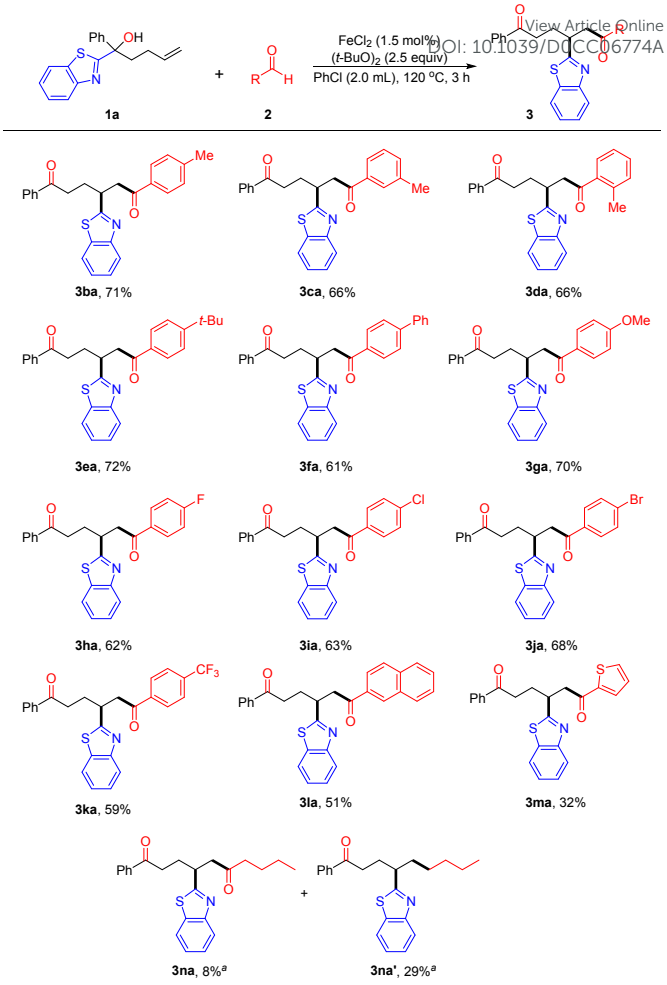


Scheme 2 Scope of unactivated alkenes. Reaction conditions: **1** (0.3 mmol), benzaldehyde **2a** (1.5 mmol), $FeCl_2$ (1.5 mol%), $(t\text{-BuO})_2$ (0.75 mmol), PhCl (2.0 mL), 120 °C, 3 h, under N_2. Reported yields were isolated yields and based on **1**.

We next examined the reaction with respect to the readily available aldehydes (Scheme 3). Electron-rich aldehydes, such as (*o*, *m* or *p*)-tolualdehyde, *p*-*tert*-butyl benzaldehyde, biphenyl formaldehyde and anisyl aldehyde, all reacted smoothly with **1a** to deliver the desired products (**3ba-3ga**) in 61-72% yields. Aldehydes with halogen functionalities attached also underwent the *ipso*-migration difunctionalization to give the corresponding 1,6-diketiones (**3ha-3ja**) in good yields. When strong electron-withdrawing CF_3 attached on the aldehyde, the yield was decreased to 59%. Other aromatic aldehydes such as 2-naphthaldehyde (**2l**) and thiophene-2-carbaldehyde (**2m**) were also applicable for this transformation (**3la** and **3ma**). Notably, valeraldehyde (**2n**) afforded the unsymmetrical 1,6-diketone **3na** in 8% yield along with the decarbonylativeproduct **3na'** in 29% yield. The results indicated that the decarbonylation of aliphatic aldehyde is predominant under the present conditions.

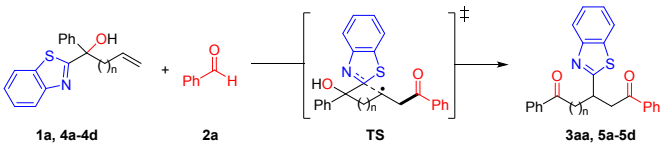
The alkyl chain length of the alkene substrates on the *ipso*-heteroaryl migration efficiency was then examined. As shown in Table 2, **5a** was obtained in 9% yield when **4a** was used as substrate. The desired products **3aa** and **5c** were obtained smoothly in 80% and 57% yield, respectively, while the corresponding **5b** and **5d** were not observed. These results indicated that the formation of three-, five- or six-membered cyclic transition state is thermodynamically favoured.

Control experiments showed that the reaction of **1a** with **2a** was completely suppressed when the radical inhibitors 2,2,6,6-tetramethylpipedinyloxy (TEMPO) or butylatedhydroxytoluene (BHT) was added. Notably, the TEMPO-aldehyde adduct was detected in GC-MS, suggesting that the existence of acyl radical in this transformation (see Supporting Information).



Scheme 3 Scope of aldehydes. Reaction conditions: **1a** (0.3 mmol), **2** (1.5 mmol), $FeCl_2$ (1.5 mol%), $(t\text{-BuO})_2$ (0.75 mmol), PhCl (2.0 mL), 120 °C, 3 h, under N_2 unless other noted. Reported yield were isolated yields and based on **1a**. [a]3.0 mmol of valeraldehyde and 1.5 mmol of $(t\text{-BuO})_2$ used, 12 h.

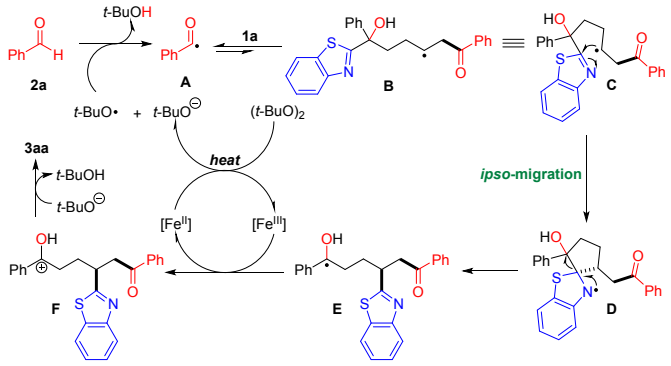
Table 2 Examination of the chain length on the reaction efficiency.



substrates	**4a**, n = 0	**4b**, n = 1	**1a**, n = 2	**4c**, n = 3	**4d**, n = 4
TS ring size	3	4	5	6	7
products (%)	**5a**, 9	**5b**, 0	**3aa**, 80	**5c**, 57	**5d**, 0

Based on the above results and previous reports,[6-11] a possible reaction mechanism for this *ipso*-migration difunctionalization of unactivated alkenes was proposed (Scheme 4). Initially, Fe^{II} mediated cleavage of DTBP under heating gives *t*-BuO- and *t*-BuO•, which abstracts the aldehyde hydrogen to deliver acyl radical **A**. Then addition of **A** to the C=C bond in **1a** produces β-carbonyl carbon radical **B**, which is trapped by C=N bond to afford more stable nitrogen radical intermediate **D**. Intramolecular radical *ipso*-migration proceeds

sequentially. Finally, oxidation by Fe^{III} and deprotonation by *t*-BuO^- gives the desired product **3aa**.



Scheme 4 Proposed mechanism

In summary, we have developed an iron-catalyzed acylation-functionalization of unactivated alkenes with both aryl and alkyl aldehydes via distal group *ipso*-migration. With this strategy, the energy barrier and reversibility in the difunctionalization of unactivated alkenes with nucleophilic acyl radicals were well solved. A wide range of β-(hetero)arylated, -cyanated and -oximated unsymmetrical 1,6- and 1,7-diketones were gained in moderate to good yields with exclusive regioselectivity and chemoselectivity.

We gratefully acknowledge the National Natural Science Foundation of China (21672259).

Conflicts of interest

There are no conflicts to declare

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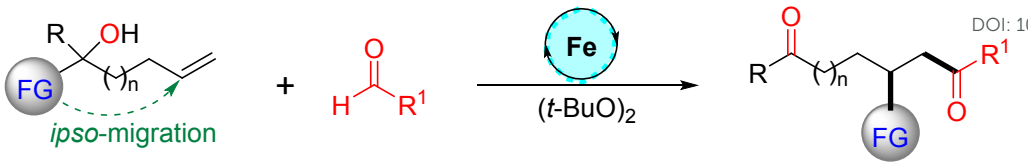
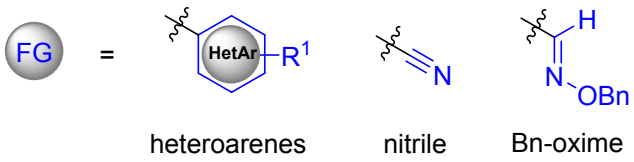


R, R^1 = Aryl, heteroaryl, alkyl; n = 1 & 2



heteroarenes nitrile Bn-oxime

Aryl and alkyl acyl radical feasible **_One-pot_ synthesis of _β_ -functionalized 1,6- & 1,7-diketones**