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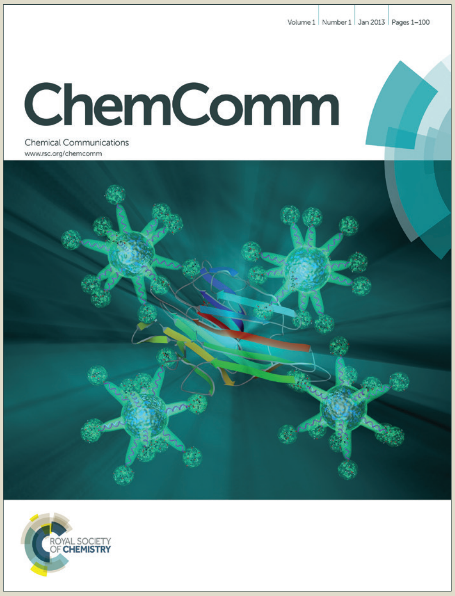

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Copper-catalysed oxidative Csp^3–H methylenation to terminal olefins using DMF

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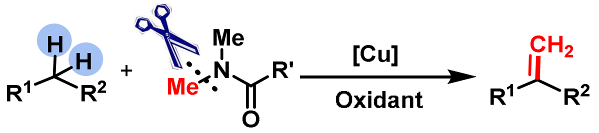
A copper-catalysed direct oxidative Csp^3–H methylenation to terminal olefins using DMF as one carbon source was developed. In this reaction, various functional groups were well tolerated, thus providing a simple way to construct arylvinylketones and arylvinylpyridines. The preliminary mechanism investigations revealed that CH_2 was from DMF (N-CH_3).

The terminal alkenes represent one of the most important synthons in organic synthesis, and they exist widespreadly in biologically active natural products and material molecules.[1] The synthesis of terminal alkenes has been extensively studied. Traditional methods to prepare terminal alkenes were usually through two pathways: the first way is the anionic reactions developed by Wittig, Johnson, and Peterson.[2] However, stoichiometric quaternary phosphorus salts are required. The other way is utilizing transition-metal-catalysed cross-coupling reactions including Suzuki reaction (aryl halides and alkenylboronic acids), Stille reaction (aryl halides and vinylstannanes) and Heck reaction (aryl halides and olefins) to synthesize terminal alkenes by palladium catalysts.[3] Considering the principle of atom-economic, sustainable and environment-friendly in organic synthesis, it is highly demanded to develop a simple and practical protocol to construct terminal alkenes.

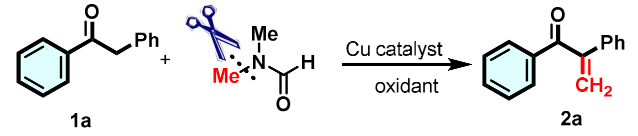
Recently, transition-metal-catalysed C–H functionalization has attracted considerable attention because it offers more efficient ways for the construction of complex chemical frameworks.[4] The construction of C=C from widely available C–H bond will undoubtedly have great significance in organic synthesis using simple C1 source as the carbon linkage. Traditionally, CH_2Br_2[5] and HCHO,[6] as the one carbon linkage, have been utilized to construct these terminal alkenes from functionalization of Csp^3–H compounds. However, the toxicity and environmental impact of these reagents have hindered its further application. Therefore, seeking a simple, available carbon source is highly desirable. As one of the most common polar solvent, *N*, *N*-dimethylformamide (DMF) is known to be employed as a cheap, readily available multipurpose building block in organic reactions for various units, such as -CO, -NMe_2 -Me, -CHO, etc.[7] Nevertheless, using DMF as one carbon source to realize the oxidative Csp^3–H methylenation to terminal alkenes is still rarely developed. Recently, the direct Csp^3–H methylenation of quinolines with DMAc pioneered by Wang and Xu, provided a rapid and straightforward access to the 2-vinylquinolines.[8] Herein, we successfully realized the copper-catalysed direct oxidative Csp^3–H methylenation of arylketones and 1-aryl-1-pyridinemethanes[9] using DMF as one carbon source which provides a simple way to construct terminal olefins.



Scheme 1. Copper-catalysed oxidative methylenation of Csp^3-H arylketones and 1-aryl-1-pyridinemethanes using DMF as one carbon source

To probe the feasibility of our proposed study, we chose the 2-phenylacetophenone (**1a**) and DMF as model substrates to evaluate the parameters (Table 1). When the reaction was performed in DMF at 100 °C under N_2 atmosphere using $FeCl_3·6H_2O$ as the catalyst, the desired product **(2a)** was not observed (Table 1, Entry 1). Then we began to apply the copper salts as catalysts, and we were pleased to get the target product albeit with low yield (Table 1, Entry 2). After screening different copper catalysts, the $Cu(TFA)_2.xH_2O$ improved the yield to 88%,

Table 1 Impact of reaction parameters on Cu-catalyzed oxidative coupling of benzophenone (**1a**) with DMF [a]

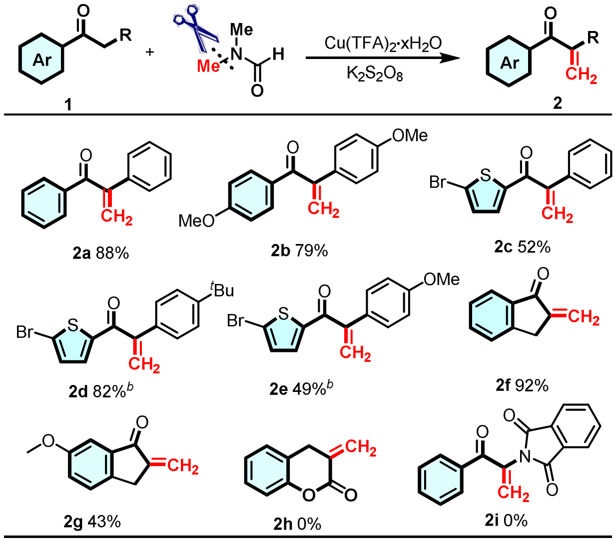


Entry	Catalyst	Oxidant	Yield[b] (%)
1[c]	$FeCl_3·6H_2O$	$K_2S_2O_8$	n.d.
2	$CuCl_2·2H_2O$	$K_2S_2O_8$	24
3	$Cu(acac)_2$	$K_2S_2O_8$	11
4	$CuBr_2$	$K_2S_2O_8$	30
5	$Cu(OTf)_2$	$K_2S_2O_8$	69
6	$CuSO_4$	$K_2S_2O_8$	57
7	$Cu(NO_3)_2$	$K_2S_2O_8$	3
8	CuI	$K_2S_2O_8$	29
9	CuBr	$K_2S_2O_8$	27
10	CuCl	$K_2S_2O_8$	28
11[d]	**$Cu(TFA)_2·xH_2O$**	**$K_2S_2O_8$**	**88**
12	--	$K_2S_2O_8$	3
13[d]	$Cu(TFA)_2·xH_2O$	$Na_2S_2O_8$	63

[a] Reaction conditions: **1a** (0.50 mmol), catalyst (20 mol%), oxidant (1.0 mmol), DMF (2.0 mL), 100 °C, N_2, 24h. [b] Yield determined by GC analysis. [c] n.d. = not detected. [d] 30 mol% catalyst, 2 equiv oxidant were used.

whereas other copper catalysts, such as $Cu(acac)_2$, $CuBr_2$, $CuSO_4$, $Cu(NO_3)_2$, CuI, CuBr and CuCl were less effective (Table 1, Entries 3–10). There was only 3% product obtained when the reaction was carried in the absence of copper catalyst (Table 1, Entry 12). However, the oxidant $Na_2S_2O_8$ showed less efficiency with the yield of 63% (Table 1, Entry 13). From these experiments, we determined the optimized condition to be: $Cu(TFA)_2·xH_2O$ (30 mol%), $K_2S_2O_8$ (2 equiv), DMF, 100 °C, 24 h.

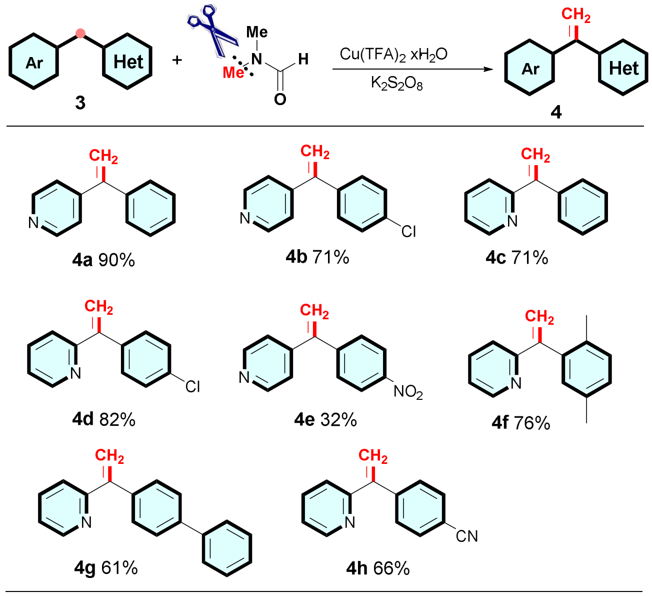
Table 2 Scope of the α-methylenation of arylketones (**1**).[a]



[a] Reaction conditions: **1** (0.50 mmol), $Cu(TFA)_2·xH_2O$ (30 mol%), $K_2S_2O_8$ (1.0 mmol), DMF (2.0 mL), 100 °C, N_2, 24 h, isolated yield. [b] $K_2S_2O_8$ (2.0 mmol) was used.

With the optimal conditions established, various arylketones were investigated and the results are summarized in Table 2. Compound **1b** with *p*-OMe group on the aryl group was transformed into the desired product in 79% yield (**2b**). In addition, the C-Br group was well tolerated in this reaction providing the possibility for further functionalization (**2c–2e**). Furthermore, 2, 3-dihydro-1H-inden-1-one and 6-methoxy-2, 3-dihydro-1H-inden-1-one were also suitable for this reaction (**2f**, **2g**). Unfortunately, direct oxidative coupling of chroman-2-one and 2-(2-oxo-2-phenylethyl)-isoindoline-1, 3-dione with DMF did not give the desired product (**2h**, **2i**).

Table 3 Scope of the α-methylenation of 1-(Hetero)aryl-1-heteroarylmethanes (**3**).[a]



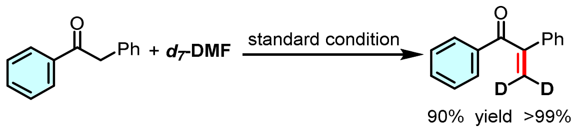
[a] Reaction conditions: **1** (0.50 mmol), $Cu(TFA)_2·xH_2O$ (30 mol%), $K_2S_2O_8$ (2.0 mmol), DMF (2.0 mL), 100 °C, N_2, 24 h, isolated yield.

Encouraged by these promising results, we further applied the substrates of copper-catalysed α-methylenation reaction to substituted benzylpyridines. To our delight, good to excellent yields were obtained with various benzylpyridines (Table 3). Both benzyl and 4-(4-chlorobenzyl)-pyridine reacted with DMF under the standard conditions to afford the coupling products in good yields (**4a**, **4b**). Similarly, benzyl and 2-(4-chlorobenzyl)-pyridine coupled well with DMF to construct the substituted pyridines (**4c**, **4d**). Substrates containing electron-donating groups provided higher yields than the substrates containing electron-withdrawing groups (**4e–4f**). The 2-(1-([1,1'-biphenyl]-4-yl)vinyl)pyridine was similarly found to be suitable substrates for this transformation and gave the desired products in good yield (**4g**). The reaction of 4-(pyridin-2-ylmethyl)benzonitrile afforded the desired product (**4h**) in 66% yield.

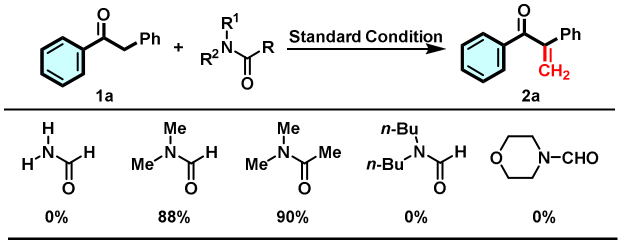
To gain some insights into the mechanism, several experiments were carried out under the optimized conditions. In order to confirm the resource of CH_2, we use d_7-DMF as the solvent to perform this reaction, the results turned out that the deuterium product was obtained in 90% (Scheme 2a) and the ration of deuterium-labelled is more than 99%. In addition, different amides were employed to test this notable transformation. Interestingly, α-methylenation of 1, 2-diphenylethanone was found to occur only in the presence of *N*, *N*-dimethylformamide and *N*, *N*-dimethylacetamide (Scheme 2b). These two results demonstrated that the carbon source was coming from the *N*-methyl of DMF. Based on the above results, a proposed mechanism is depicted in Figure S3 (SI). Furthermore, the *operando* IR was monitored to investigate this oxidative reaction presented in the Scheme 2(c). From the 3D kinetic behavior profile of this reaction, we observed that an obvious decreasing absorption of substrate (**1a**) at 716 cm^{-1}. At the same time, the peak of product (**2a**) increased at the wavenumber of 782 cm^{-1}. Therefore, this reaction happened without any inductive period from the result of *operando* IR.

Scheme 2. Investigation for mechanistic insights

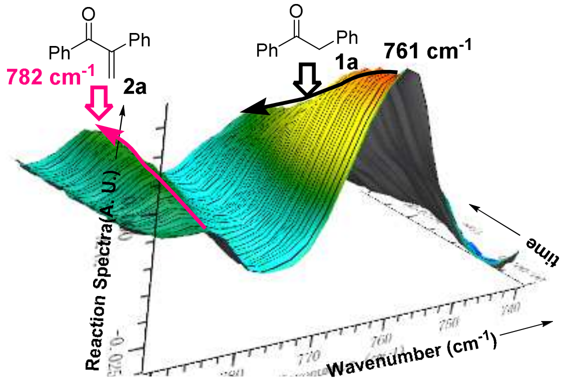
(2a) Reaction using Deuterium-Labelled DMF



(2b) Reaction using different amides



(2c) Operando IR to study this oxidative coupling.



In conclusion, we have demonstrated a copper-catalysed direct oxidative Csp^3–H methylenation of arylketones and 1-aryl-1-pyridinemethanes using DMF as one carbon source. This protocol provided a direct way to functionalization of Csp^3–H compounds. This method presented a simple way to arylvinylketones and arylvinylpyridines which shows promising potential in biological activities and pharmaceutical applications. Preliminary mechanistic investigations confirmed that the product CH_2 came from the N-CH_3 of solvent DMF. In addition, the operando IR presented that inductive period was not referred in this reaction. Further detailed mechanistic investigations are currently underway in our laboratory.

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Notes and references

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