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

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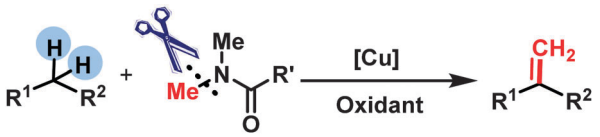
A copper-catalysed direct oxidative Csp^3–H methylenation to terminal olefins using DMF as one carbon source was developed. In this reaction, various functional groups were well tolerated, thus providing a simple way to construct arylvinylketones and arylvinylpyridines. The preliminary mechanistic investigations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

The terminal alkenes represent some of the most important synthons in organic synthesis, and they are widely present in biologically active natural products and material molecules.[1] The synthesis of terminal alkenes has been extensively studied. Traditional methods to prepare terminal alkenes usually involved 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 using palladium catalysts.[3] Considering the principle of atom-economic, sustainable and environment-friendly organic synthesis, it is highly desirable 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 the widely available C–H bond will undoubtedly have great significance in organic synthesis using a 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 by functionalization of Csp^3–H compounds. However, the toxicity and the 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 solvents, *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 not well 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).

To probe the feasibility of our proposed study, we chose 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 a 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, $Cu(TFA)_2·xH_2O$ improved the yield to 88%, 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). Only 3% product was obtained when the reaction was carried out in the absence of a copper catalyst (Table 1, entry 12). However, the oxidant $Na_2S_2O_8$ showed less



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

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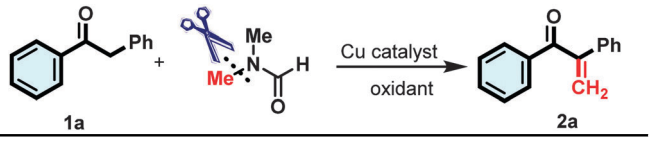
Table 1 Impact of reaction parameters on Cu-catalysed oxidative coupling of benzophenone (**1a**) with DMF[a]

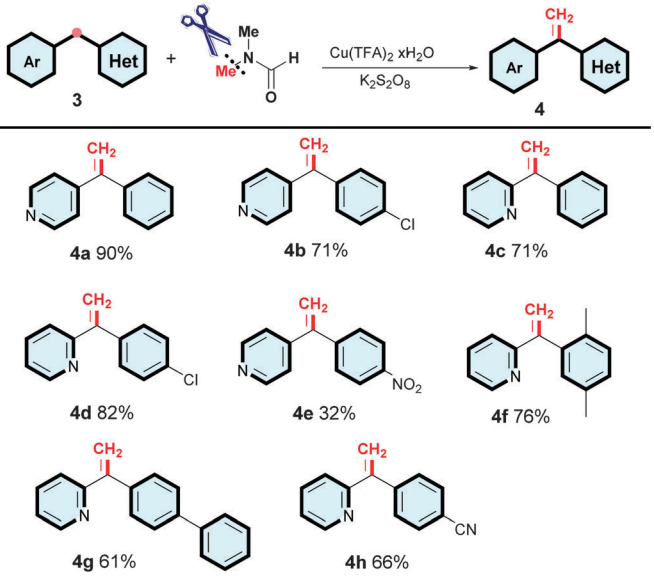


1a **2a**

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, 24 h. [b] Yield determined by GC analysis. [c] n.d. = not detected. [d] 30 mol% catalyst, 2.0 equiv. oxidant were used.

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

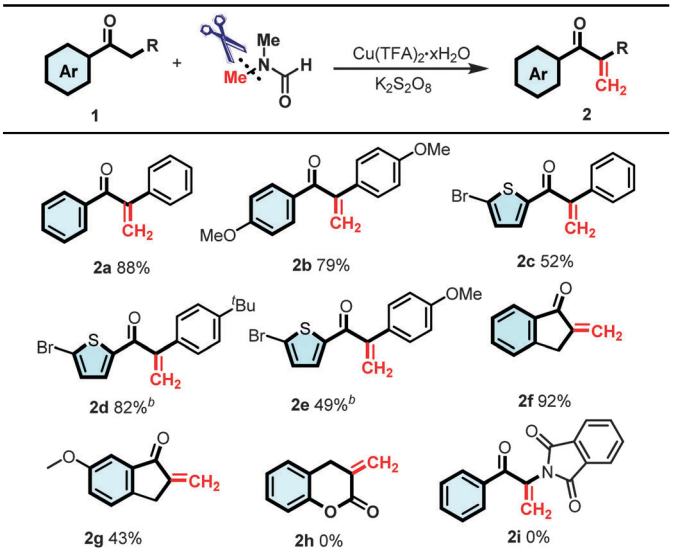


[a] Reaction conditions: **1** (0.50 mmol), $Cu(TFA)_2·xH_2O$ (30 mol%), $K_2S_2O_8$ (2.0 mmol), DMF (2.0 mL), 100 °C, N_2, 24 h, isolated yield.

efficiency with a yield of 63% (Table 1, entry 13). From these experiments, we determined the optimized conditions to be: $Cu(TFA)_2·xH_2O$ (30 mol%), $K_2S_2O_8$ (2.0 equiv.), DMF, 100 °C, 24 h.

With the optimal conditions established, various arylketones were investigated and the results are summarized in Table 2. Compound **1b** with a *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-1*H*-inden-1-one and 6-methoxy-2,3-dihydro-1*H*-inden-1-one were also suitable for this reaction

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

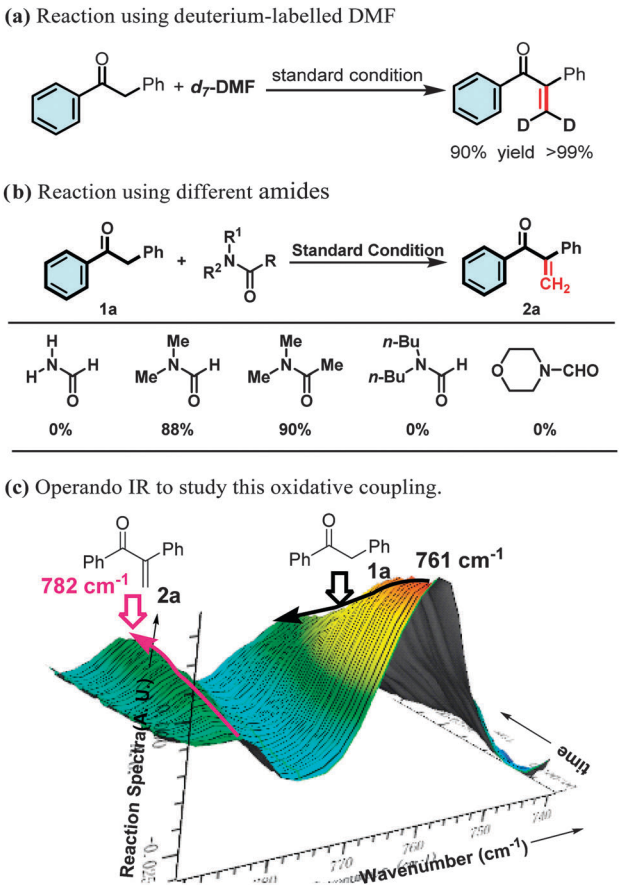


[a] Reaction conditions: **1** (0.50 mmol), $Cu(TFA)_2·xH_2O$ (30 mol%), $K_2S_2O_8$ (1.0 mmol), DMF (2.0 mL), 100 °C, N_2, 24 h, isolated yield. [b] $K_2S_2O_8$ (2.0 mmol) was used.

(**2f** and **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** and **2i**).

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** and **4b**). Similarly, benzyl and 2-(4-chlorobenzyl)-pyridine coupled well with DMF to construct the substituted pyridines (**4c** and **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 a suitable substrate 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 used 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 ratio 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 from the *N*-methyl of DMF. Based on the above results, a proposed mechanism is depicted in Fig. S3 (ESI†). Furthermore, the *operando* IR was monitored to investigate this oxidative reaction presented in Scheme 2c. From the 3D kinetic behavior profile of this reaction, we observed an



Scheme 2 Investigation for mechanistic insights.

obvious decrease in absorption of the substrate (**1a**) at 761 cm^{-1}. At the same time, the peak of the product (**2a**) increased at a wavenumber of 782 cm^{-1}. Therefore, this reaction occurred without any inductive period from the result of *operando* IR.

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 for functionalization of Csp^3–H compounds. This method presented a simple way to synthesize arylvinylketones and arylvinylpyridines which shows promising potential in biological activities and pharmaceutical applications. Preliminary mechanistic investigations confirmed that the product CH_2 is from the N–CH_3 of solvent DMF. In addition, the operando IR showed that the inductive period was not referred in this reaction. Further detailed mechanistic investigations are currently underway in our laboratory.

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