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ARTICLE

A ligand-free strategy for the copper-catalysed direct alkylation of trifluoromethyl ketones

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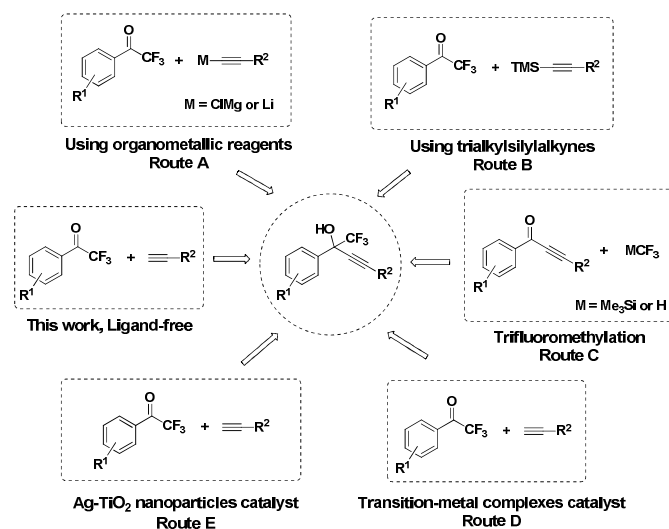
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Abstract: Most direct alkylation methods of trifluoromethyl ketones require an additional ligand. In this study, a simple, practical and efficient superbase system for the direct alkylation of trifluoromethyl ketones was developed without any additional ligand. The catalytic system can tolerate a wide range of functional groups on ketones and alkynes.

The addition of terminal alkynes to trifluoromethyl ketones has attracted considerable interest in the field of organic chemistry, because the method allows the formation of a C–C bond while simultaneously introducing a trifluoromethyl (CF₃) group.¹ The generated of functionalized alkyne products are key building blocks for the organic synthesis, especially in the determination of the important uses of Efavirenz as critical anti-HIV drug.² Organic molecules bearing CF₃ groups have received widespread attention in pharmaceutical, agrochemical and organocatalyst fields because of their unique physical and chemical properties.³ Therefore, it is not surprising that different approaches for the construction of such structural unit have been developed (Scheme 1).

The alkylation of 2,2,2-trifluoroacetophenone was firstly described using metal acetylides from terminal alkynes and strongly basic organometallic reagents such as Grignard and organolithium reagents (Route A, Scheme 1).⁴ The addition of trialkylsilylalkynes to trifluoroacetophenone has been also reported (Route B, Scheme 1).⁵ To access this important class of title compounds, the trifluoromethylation of alkynyl ketones using trifluoromethylation reagents, such as Me₃SiCF₃ and HCF₃, is an alternative strategy (Route C, Scheme 1).⁶ Recently, chemists' research focus has shifted to the direct alkylation of trifluoromethyl ketones via transition-metal-catalysed nucleophilic substitution as an economical and ecologically benign alternative (Routes D and E, Scheme 1). Shibasaki and co-workers reported the first example of direct alkylation of trifluoromethyl ketones through copper/diphosphine or diamine complexes.⁷ Li et al reported that simple alkylphosphines, such as tricyclohexylphosphine (PCy₃), used in combination with AgF can yield highly active catalysts for the direct alkylation of trifluoromethyl ketones in water.⁸ A series of efficient catalysts, such as titanium/chiral cinchona alkaloids,⁹ copper/N-heterocyclic carbene complexes¹⁰ and silver-titania nanocomposites,¹¹ have been

successfully applied in alkylation of trifluoromethyl ketones. However, most methods for the direct alkylation of trifluoromethyl ketones require an additional ligand.



Scheme 1 Different methods towards title compounds.

Although different valuable approaches to the direct alkylation of trifluoromethyl ketones have been developed, there is an urgent need to search for a simple, general and efficient synthetic protocol for their preparation because of the importance of this class of compounds. Herein, we report a simple and efficient method that requires no additional ligand for the direct alkylation of trifluoromethyl ketones using commercially available copper salts.

The direct alkylation of 2,2,2-trifluoroacetophenone with phenylacetylene was selected as a model reaction to optimise the reaction conditions, in which a range of solvent, temperature, base, copper source and atmosphere were investigated.

Firstly, the effect of different solvents on the alkylation of 2,2,2-trifluoroacetophenone with phenylacetylene was evaluated, and the results showed that solvent served a crucial

function in the alkylation. Dimethyl sulfoxide (DMSO) was most efficient for trifluoroacetophenone conversion and provided a quantitative product yield (Supporting Information, Table S1, entry 10). The reaction performed in N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), and N-methyl pyrrolidone (NMP) yielded considerably slower conversion (Supporting Information, Table S1, entries 1-3). We supposed that the strong base of KO^tBu combined with high temperature degraded the DMA, DMF, and NMP, and this effect was responsible for the poor results. Therefore, instead of KO^tBu, a weak base of K₂CO₃ was used to optimise the effect of solvents. As expected, DMF, DMA, and NMP provided good results with K₂CO₃ as base (Supporting Information, Table S1, entries 11-13). Tetrahydrofuran (THF), toluene, alcohols, and water were also examined as solvents, but only isopropanol was relatively effective for the conversion of trifluoroacetophenone and provided lower product yield (Supporting Information, Table S1, entries 4-9 and 14-19).

To simplify the operating procedures, control experiments were designed by performing the reaction in air and in nitrogen atmosphere, respectively. The results indicated that the reaction is insensitive to the atmosphere of the reaction condition, and reactions carried out in nitrogen atmosphere exhibited slightly higher catalytic activity than the reactions performed in air (Supporting Information, Table S1, entry 27). GC-MS analysis showed that oxygen promoted the homo-coupling of phenylacetylene, and an amount of phenylacetylene consumption was responsible for the decrease of efficiency.

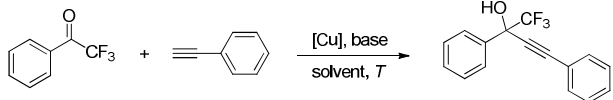
In view of the cost, the amount of phenylacetylene was optimised. The reaction rate was not affected when the amount of phenylacetylene was reduced to 1.5 mol equiv., but the rate slowed down in 1.2 mol equiv. of phenylacetylene (Supporting Information, Table S1, entries 28 and 29). Therefore, using 1.5 mol equiv. of phenylacetylene was the best compromise between cost and product yield (Supporting Information, Table S1, entry 28).

The effect of reaction temperature on alkylation was also explored. The reaction smoothly proceeded at 50 °C -70 °C (Table 1, entries 1 and 2). However, only a trace amount of product was obtained when the temperature was decreased to room temperature (Table 1, entry 3).

A range of different bases and copper sources was examined for the alkylation of 2,2,2-trifluoroacetophenone with phenylacetylene using DMSO as a solvent. Among potassium bases, potassium *tert*-butoxide, phosphate and carbonate were efficient for product formation, with hydroxide providing lower conversion (Table 1, entries 2, 5 and 6 vs. 4). Sodium bicarbonate and sodium formate were superior to other sodium bases (Table 1, entries 9 and 10 vs. 7, 8 and 11). Potassium carbonate and cesium carbonate were the most effective for conversion (Table 1, entry 5 and 12). A series of copper sources [Cu(I), Cu(II) and Cu(0)] was subsequently investigated. Among copper sources in I oxidation states, CuI and CuCl showed considerably higher catalytic activity than Cu₂O (Table 1, entries 5 and 13 vs. 14). Copper sources in II oxidation states also exhibited high catalytic activity except for CuO, and Cu(OAc)₂ was superior to the other copper sources (Table 1, entries 17-19 vs. 16). Copper powder yielded much slower conversion (Table 1, entry 15). Copper catalysed reactions of alkynes are known to be highly complex and are affected by the oxidation state of the copper source.¹² As shown in Table 1, both Cu(I) and Cu(II) works equally well, thereby indicating that copper sources may not act as an alkyne-copper catalyst, but simply as a Lewis acid or enhancer of base solubility. To

elucidate the role of copper, a series of Lewis acids instead of copper sources were examined under the same reaction conditions. All tested Lewis acids failed to trigger the reaction (Supporting Information, Table S1, entries 20-26).

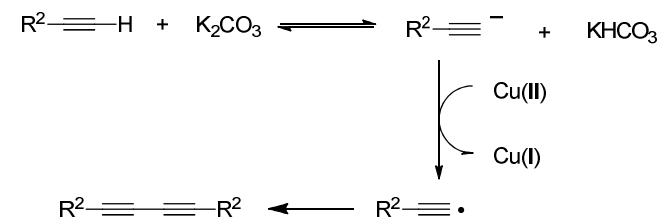
Table 1 Optimization of alkylation^[a]



Entry	Solvent	T (°C)	Base	Catalyst	Yield ^[b] (%)
1	DMSO	70	KO ^t -Bu	CuI	97
2	DMSO	50	KO ^t -Bu	CuI	91
3	DMSO	r.t.	KO ^t -Bu	CuI	trace
4	DMSO	50	KOH	CuI	25
5	DMSO	50	K ₂ CO ₃	CuI	98
6	DMSO	50	K ₃ PO ₄	CuI	89
7	DMSO	50	NaOH	CuI	49
8	DMSO	50	Na ₂ CO ₃	CuI	60
9	DMSO	50	NaHCO ₃	CuI	91
10	DMSO	50	HCOONa	CuI	90
11	DMSO	50	NaO ^t -Bu	CuI	63
12	DMSO	50	Cs ₂ CO ₃	CuI	97
13	DMSO	50	K ₂ CO ₃	CuCl	96
14	DMSO	50	K ₂ CO ₃	Cu ₂ O	46
15	DMSO	50	K ₂ CO ₃	Cu	38
16	DMSO	50	K ₂ CO ₃	CuO	23
17	DMSO	50	K ₂ CO ₃	CuSO ₄	92
18	DMSO	50	K ₂ CO ₃	Cu(NO ₃) ₂	95
19	DMSO	50	K ₂ CO ₃	Cu(OAc) ₂	99
20	DMSO	50	none	CuI	trace
21	DMSO	50	K ₂ CO ₃	none	19 (20 ^[c])

[a] Reaction conditions: 2,2,2-trifluoroacetophenone (0.5 mmol), phenylacetylene (1.0 mmol), Cu source (10 mol%), base (20 mol%) in solvent (1 mL) under N₂, 24 h. [b] Isolated yield. [c] 1.0 equiv. K₂CO₃.

To further explore the role of copper sources, control experiments were designed in the absence of either copper sources or bases. The control experiment revealed that the reaction was difficult to proceed in the presence of CuI but in the absence of bases (Table 1, entry 20). However, 19% product yield was obtained with a base in the absence of copper sources (Table 1, entry 21). A 1.0 equivalent of base in the absence of copper sources was further examined, but 20% product yield was obtained (Table 1, entry 21). These results showed that copper sources promoted reaction rates and served a catalytic function. Early investigation has demonstrated that Cu(II) served as oxidizing agent and could be reduced to Cu(I) by terminal alkynes in the reaction system (Scheme 2).^{7,13} Observation of the homo-coupling of phenylacetylene is the indirect evidence of Cu(II) reduction. The results showed that Cu(I) is the real oxidation state of copper sources in this catalytic system.



Scheme 2 Process of reducing copper from Cu(II) to Cu(I).

Despite the widespread development of copper-catalysed alkylation of trifluoromethyl ketones, the mechanism of these processes has remained unclear. Firstly, copper can chelate with carbonyl group of trifluoromethyl ketones to increase the electrophilicity of the carbon atom, while possibly coordinating with alkyne to lower the pKa of terminal hydrogen. To prove which substrate preferentially binds to copper, control experiments have been designed by conducting the reaction in the absence of trifluoroacetophenone or in the absence of phenylacetylene, respectively. Surprisingly, trifluoroacetophenone was full converted to 2,2,2-trifluoro-1-phenylethane-1,1-diol in the presence of $\text{Cu}(\text{OAc})_2$ and K_2CO_3 , but in the absence of phenylacetylene (Supporting Information, Figure S4).¹⁴ 2,2,2-Trifluoro-1-phenylethane-1,1-diol is probably an important active intermediate in the catalytic cycle, as reported by Xu.¹¹ However, the terminal hydrogen of phenylacetylene disappeared in presence of $\text{Cu}(\text{OAc})_2$ and K_2CO_3 , but in the absence of trifluoroacetophenone (Supporting Information, Figure S3). This result indicated that copper may preferentially coordinate with alkyne to form a copper-alkyne complex, which is consistent with previous reports.^{1c,7}

The combination of a strong base and dipolar aprotic solvents such as DMSO, DMF, DMA and NMP, is known to form a superbase media.¹⁵ Thus, we hypothesised that the superior performance of DMSO, DMF, DMA and NMP versus other solvents is due to the synergistic effects of the copper catalyst and the superbase media.

To obtain further evidence of the superbase function, the experiment on phenylacetylene H-D exchange was performed. As shown in Figure 1, the kinetic isotope effect is evident in this catalytic system, thereby indicating that the oxidative addition of copper to alkyne is the rate-determining step. We hypothesised that the superbase promoted the step of oxidative addition of copper to alkyne to generate an active copper-alkyne complex.

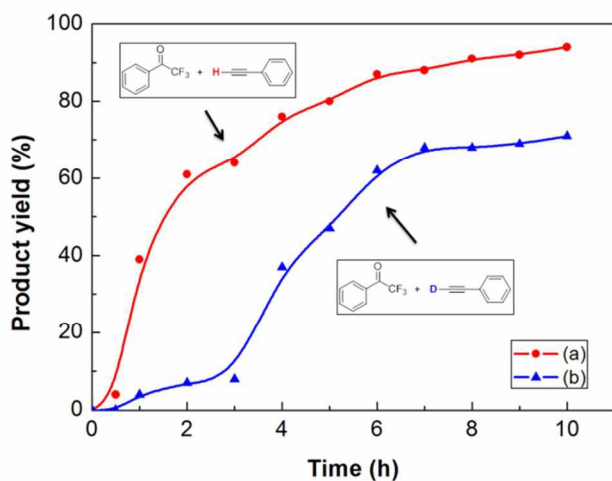


Figure 1 Time course of alkylation reaction of 2,2,2-trifluoroacetophenone with a) phenylacetylene and b) deuterium-modified phenylacetylene.

The scope and limitations of addition of the terminal alkynes to trifluoromethyl ketones was examined using $\text{Cu}(\text{OAc})_2$ as catalyst, K_2CO_3 as base and DMSO as solvent under mild reaction conditions. As shown in Table 2, the reactivity of terminal alkynes was tested under optimised reaction conditions,

and the desired products were obtained in good-to-excellent yields. The electronic effect of *para*-substituents bearing the aromatic ring of alkynes was observed. The alkynes containing electron-donating and electron-neutral groups such as 4-Me, 4-OMe, 4-Et, and 4-Ph, reacted smoothly with trifluoroacetophenone to afford the corresponding products in high yields (Table 1, entries 1-5). However, the alkynes containing electron-withdrawing group were less reactive in this system and resulted in moderate product yields (Table 1, entries 6-8). The electronic effect of *meta*-substituted compounds presented a certain influence on the reaction rate. The reaction worked well with *meta*-fluorophenyl acetylene bearing the electron-withdrawing group to afford the desired product in good yield (Table 1, entry 9). However *meta*-methylphenyl acetylene bearing the electron-donating group showed considerably slower conversion at 50 °C, and quantitative product yield was also obtained when the temperature increased to 70 °C (Table 1, entry 10).

To extend the scope of alkylation, the reaction of alicyclic and aliphatic alkynes was tested. The reactivity of alicyclic and aliphatic alkynes was lower than those of aryl alkynes, and increasing reaction temperature was required to obtain satisfactory results (Table 1, entries 11-14). Moreover, the addition of 3-ethynylthiophene to 2,2,2-trifluoroacetophenone proceeded to 90% product yield in mild reaction conditions (Table 1, entry 15).

The optimised reaction conditions were also applied in the alkylation of a series of substituted trifluoroacetophenone. The results indicated that alkylation was evidently affected by the nature of substitution on trifluoroacetophenone. Trifluoroacetophenones bearing electron-withdrawing groups were successfully converted to the desired products in good-to-excellent yields (Table 1, entries 16-17). The compounds bearing electron-donating groups resulted in moderate product yield. (Table 1, entry 18). Subsequently, with the optimised reaction conditions, the addition of ethyl 3,3,3-trifluoropyruvate with phenylacetylene smoothly proceeded and resulted in quantitative yield (Table 1, entry 19).

The reaction is practical and scalable, and could be scaled up to a gram scale without any problems (Table 1, entry 20).

In conclusion, we successfully developed a general, simple, and efficient method for the direct alkylation of trifluoromethyl ketones by utilising inexpensive copper salts as pre-catalyst. The major advantages of this process are as follows: no additional ligand is required and the reaction works well in air. A wide range of functional groups on alkynes are compatible with the reaction conditions, including aryl acetylene, alicyclic, and aliphatic alkynes. We hypothesised that the key to the success of the reaction could be the synergistic effects of the copper catalyst and the superbase media. Studies are underway in our laboratory to better elucidate the reaction mechanisms of these processes.

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Table 2 Scope of alkynylation

$\text{R}^1-\text{C}(=\text{O})-\text{CF}_3 + \text{H}-\text{C}\equiv\text{C}-\text{R}^2 \xrightarrow[\text{DMSO, 50 or 70 }^\circ\text{C}]{\text{Cu(OAc)}_2, \text{K}_2\text{CO}_3} \text{R}^1-\text{C}(\text{OH})(\text{CF}_3)-\text{C}\equiv\text{C}-\text{R}^2$			
Entry	Alkyne	Product	Yield ^a (%)
1			96
2			91
3			96
4			89
5			92
6			87
7			65
8			77
9			63
10			5(97 ^b)
11			67
12			42(61 ^b)
13			65(83 ^b)
14			28(71 ^b)
15			85
16			81
17			93
18			66
19			96
20 ^c			72

^a Reaction conditions: ketone (0.5 mmol), alkyne (0.75 mmol), Cu(OAc)₂ (10 mol%), K₂CO₃ (20 mol%) in DMSO (1 mL), 50 °C, 24 h. ^b 70 °C, isolated yield. ^c Ten times the amount of the reactants of entries 11 were used, and performed in DMSO (10 mL) at 50 °C for 24 h.

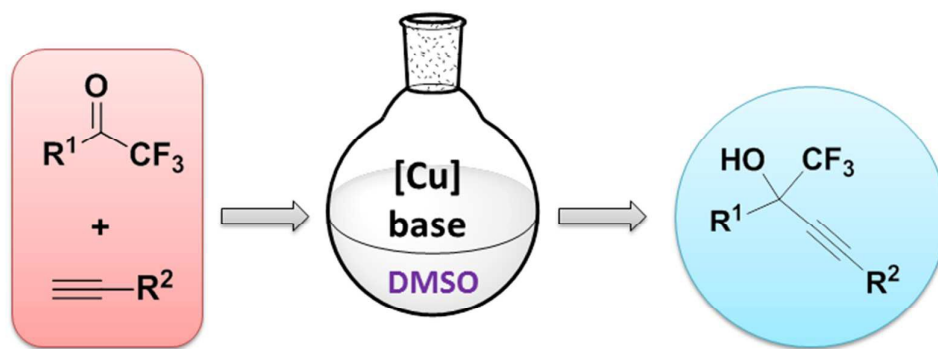
Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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R^1 = aromatic, aliphatic

R^2 = aromatic, heteroaromatic, aliphatic, alicyclic

Superbase-induced copper-catalyzed direct alkylation method of trifluoromethyl ketones was developed without any additional ligand under mild condition.