Efficient Direct Alkynylation of Trifluoromethyl Ketones Catalyzed by AgF in Water and Organic Solvents

Guo-Jun Deng,[a] Chao-Jun Li*[a,b]

[a] Department of Chemistry, Tulane University, New Orleans, LA, 70118, USA

[b] Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, QC, H3A 2K6, Canada
Fax +1(514)3983797; E-mail: cj.li@mcgill.ca

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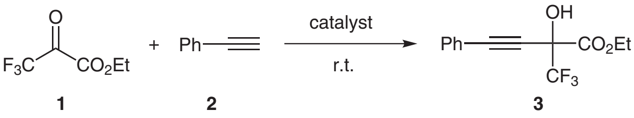
Abstract: A general and efficient method for the direct alkynylation of trifluoropyruvate and trifluoroacetophenone in water was developed by using AgF and PCy_3 as a catalyst. The ligand enhanced the catalyst activity significantly. The reaction in water is comparable to the one carried out in organic solvents.

Key words: direct alkynylation, trifluoromethyl ketones, silver fluoride

Green or sustainable chemistry has now attained the status of a major scientific discipline and has led to the search for more efficient and environmentally friendly methods for chemical synthesis.[1] One of the related research areas has been the development of Barbier–Grignard type reaction in water,[2] including allylation,[3] propargylation,[4] benzylation,[5] arylation/vinylation,[6] alkylation,[7] and the aldol-type reactions.[8] Recently, great progress has been made by our group[9] and others[10] on the Grignard-type reactions of alkynes to aldehydes and imines to generate propargyl alcohols and propargylamines via catalytic C–H activation in water (and in organic media). Compared with aldehydes and imines, however, there are very few studies on the catalytic alkynylation of ketone due to its lower reactivity.[11] Herein, we wish to report that, by using a silver–phosphine catalyst, terminal alkynes were added to trifluoromethyl ketones efficiently via the activation of alkyne C–H bonds to afford Grignard-type nucleophilic addition products in water at room temperature.

The synthesis of organofluorine compounds has attracted explosive interest in recent years due to their importance in biological studies.[12] Trifluoropyruvate is one of the most versatile building blocks for the synthesis of trifluoromethylated compounds and was chosen as a model substrate for this study.[13] In our previous studies, $AgCl/PCy_3$ (tricyclohexylphosphine) was found to be an effective catalyst for the aldehyde–alkyne coupling reaction.[9a] The reaction between ethyl 3,3,3-trifluoropyruvate (**1a**) and phenylacetylene (**2a**) was first examined with the use of $AgCl/PCy_3$ (10 mol%) prepared in situ (Scheme 1). We are pleased to see that the desired product was obtained in 12% yield (Table 1, entry 1) after 24 hours at room temperature in water. Encouraged by this preliminary result, we then tested different silver salts under the same reaction conditions. AgI and AgBr both only gave trace amounts of the desired product (Table 1, entry 2 and 3). For water-soluble silver salts, $AgPF_6$ did not catalyze the reaction at all whereas Ag_2SO_4 gave the corresponding product in only 22% yield. Silver tetrafluoroborate and Ag(OTf) showed moderate catalytic activities (gave the product in 40% and 64% yields, respectively). An excellent yield was obtained when AgF/PCy_3 was employed as a catalyst. The desired product was formed in 88% yield in 24 hours at room temperature and the reaction was completed in 48 hours (Table 1, entry 8). If the reaction temperature was increased to 40 °C, a quantitative yield was obtained in 24 hours. To understand the effect of phosphine ligand on the reaction, different phosphines were investigated under similar reaction conditions. It was found that the phosphine ligand plays an important role in this reaction. When PCy_3 was replaced by other phosphines, the yield decreased significantly. The use of AgF/PPh_3 as a catalyst gave the product in 20% yield, whereas using AgF/dppe as catalyst only produced a trace amount of the desired product. No product was observed in the absence of a phosphine ligand. It is noteworthy that the reaction can be carried out under an atmosphere of air, albeit a moderate reaction yield (45%) was obtained. If the catalyst loading was decreased from 10 mol% to 5 mol%, the yield of the desired product decreased dramatically. It was also found that the reaction in water is almost as efficient as in common organic solvents or under neat conditions. When toluene was used as solvent, 70% yield of the product was obtained which is slightly lower than the reaction carried out in water. The reaction in dichloromethane, THF, and under neat conditions gave the product with yields comparable to the one in water. Only a trace amount of the alkynylation product was observed when the reaction was carried out in either ethanol or methanol.

Subsequently, with the optimized reaction conditions, various alkynes were similarly coupled with ethyl 3,3,3-trifluoropyruvate and afforded the products in good to excellent yields. Selected results are summarized in Table 2.[14] Aromatic alkynes can couple with ethyl 3,3,3-



Scheme 1 Silver-catalyzed alkynylation

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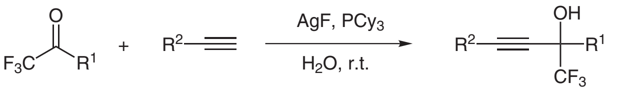
Table 1 Effect of Metal, Ligand, and Solvent on the Alkynylation of Pyruvate[a]

Entry	Metal	Ligand	Solvent	Yield (%)[b]
1	AgCl	PCy_3	H_2O	12
2	AgI	PCy_3	H_2O	<5
3	AgBr	PCy_3	H_2O	<5
4	$AgBF_4$	PCy_3	H_2O	40
5	$AgPF_6$	PCy_3	H_2O	0
6	Ag(OTf)	PCy_3	H_2O	64
7	Ag_2SO_4	PCy_3	H_2O	22
8	AgF	PCy_3	H_2O	88 (99)[c]
9[d]	AgF	PCy_3	H_2O	97
10	AgF	–	H_2O	0
11	AgF	PPh_3	H_2O	20
12	AgF	BINAP	H_2O	24
13	AgF	P*t*-Bu_3	H_2O	11
14	AgF	dppe	H_2O	1
15	AgF	PCy_3	Toluene	70
16	AgF	PCy_3	CH_2Cl_2	85
17	AgF	PCy_3	THF	89
18[e]	AgF	PCy_3	H_2O	45
19	AgF	PCy_3	–	90

[a] Conditions: A mixture of the catalyst (10 mol%), ethyl 3,3,3-trifluoropyruvate (0.5 mmol), phenylacetylene (1 mmol) in 0.5 mL solvent was stirred at r.t. for 24 h under nitrogen, unless otherwise stated.
[b] NMR yield with 1,2-dichloroethane as internal standard.
[c] Yield in parentheses was run for 48 h.
[d] Reaction was carried out at 40 °C.
[e] Under an atmosphere of air.

trifluoropyruvate effectively. The substituents on the aromatic ring did not affect the reaction yield significantly. However, when solid alkynes such as 4-ethynylbiphenyl (**2k**) and 4-bromoethynylbenzene (**2e**) were used as nucleophiles, only moderate yields were obtained possibly due to the difficulty associated with the mass transfer. A very high yield was observed when non-aromatic alkyne **2h** was reacted with trifluoropyruvate, the product was formed in 91% yield. It appears that the ester group in trifluoropyruvate plays an important role in this reaction: when methyl trifluoropyruvate was used as the ketone, the product was obtained in 64% yield, which is much lower than that of ethyl trifluoropyruvate. We also tested the alkynylation of trifluoroacetophenone under the same conditions. No desired product was obtained at room temperature. However, when the reaction was carried out at 100 °C, the desired product could be obtained in 83% yield. 1-Ethynyl-3-5-bis(trifluoromethyl)benzene, which bears electron-withdrawing groups on the phenyl ring, gave the corresponding product in only 30% yield.

Table 2 Alkynylation of Ketones Catalyzed by Silver in Water[a]



1 **2** **3**

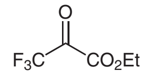
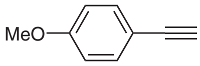
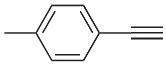
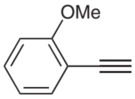
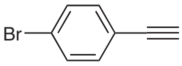
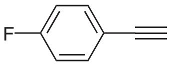
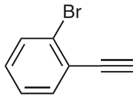
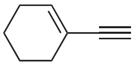
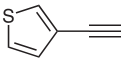
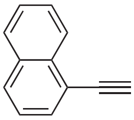
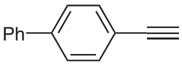
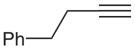
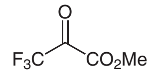
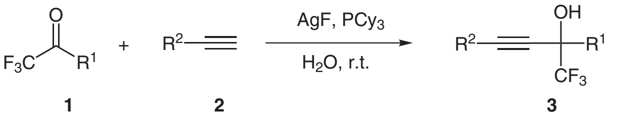
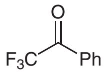
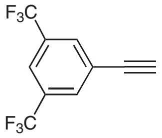
Entry	Ketone	Alkyne	Yield (%)[b]
1	 **1a**	Ph—≡ **2a**	93
2	**1a**	 **2b**	90
3[c]	**1a**	 **2c**	84
4	**1a**	 **2d**	72
5	**1a**	 **2e**	55
6	**1a**	 **2f**	73
7	**1a**	 **2g**	91
8	**1a**	 **2h**	91
9	**1a**	 **2i**	80
10	**1a**	 **2j**	84
11	**1a**	 **2k**	61
12	**1a**	 **2l**	75
13	 **1b**	**2a**	64

Table 2 Alkynylation of Ketones Catalyzed by Silver in Water[a] (continued)



Entry	Ketone	Alkyne	Yield (%)[b]
14[d]	 **1c**	**2a**	83
15	**1a**	 **2m**	30

[a] Conditions: AgF (10 mol%), PCy_3 (10 mol%), ketone (0.5 mmol), alkyne (1 mmol) in H_2O (0.5 mL) at r.t. for 1–2 d, unless otherwise stated.

[b] Isolated yields based on ketone.

[c] Reaction was carried out at 40 °C.

[d] Reaction was carried out at 100 °C.

In conclusion, we have developed a highly effective direct alkynylation of trifluormethyl ketone in water or in organic solvents with silver as the catalyst. Trifluoropyruvate was reacted with terminal alkynes efficiently in water at room temperature. By increasing the reaction temperature to 100 °C, trifluoroacetophenone can also react with phenylacetylene in water to give the alkynylation product in good yield. This process is simple and provides diverse CF_3-substituted tertiary propargyl alcohols in high yields.

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(14) **Representative Experimental Procedure**
A nitrogen-flushed 10 mL flask equipped with a magnetic stirrer and a septum was charged with AgF (6.3 mg, 0.05 mmol) and PCy_3 (14 mg, 0.05 mmol). Ethyl 3,3,3-trifluoropyruvate (85 mg, 0.5 mmol), alkyne (2 equiv), and H_2O (0.5 mL) were added by using a syringe. The reaction mixture was stirred for 1–2 d at r.t. and extracted with Et_2O. The organic solvent was evaporated and the residue was purified by column chromatography (SiO_2, hexane–EtOAc) and characterized by means of ^1H NMR, ^{13}C NMR, IR, and HRMS.