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Copper(I)/N-Heterocyclic Carbene (NHC)-Catalyzed Addition of Terminal Alkynes to Trifluoromethyl Ketones for Use in Continuous Reactors

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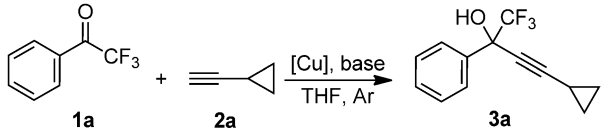
Abstract: A copper(I)/N-heterocyclic carbene complex-catalyzed addition of terminal alkynes to trifluoromethyl ketones at low loading is described. The developed process functions well using a range of terminal alkynes but functions best when an aryl trifluoromethyl ketone is used. This substrate scope is well-suited for the production of active pharmaceutical ingredients (APIs) such as efavirenz. In this vein, we demonstrate that the described method can be translated into a flow process laying the framework for a completely continuous synthesis of efavirenz in the future.

Keywords: alkynes; continuous synthesis; copper; microreactor; trifluoromethyl ketones

Earth-abundant transition metal complexes to catalyze carbon-carbon bond formation are becoming increasingly attractive as the cost of rare transition metals rise. The *in-situ* generation of metal acetylides and production of the highly functionalized propargylic alcohols or amines opens the door to a variety of subsequent transformations. Consequently, it is no surprise that the metal-catalyzed addition of terminal alkynes to aldehydes, ketones and aldimines has been extensively studied.[1] Despite the prevalence of the trifluoromethyl group in many active pharmaceutical agents and agrochemicals,[2] the alkynylation of trifluoromethyl ketones is much less developed. Shibasaki et al.[3] first demonstrated that copper-diphosphine and diamine complexes catalyzed *in-situ* activation and alkyne addition. Li[4] and co-workers used an "on-water" silver complex to catalyze the addition of phenylacetylene to 2,2,2-trifluoroacetophenone over 1–2 days. More recently, Carreira[5] described an autocatalytic improvement for the diethylzinc, alkyllithium mediated alkynylation first developed by Merck.[6] With an interest in establishing continuous routes into critical medicines for developing world applications, we sought a 1,2-addition strategy that could be incorporated into a multi-step continuous production process of the anti-HIV drug, efavirenz.[7] Efavirenz is a critical anti-HIV drug used in combination therapy in the developing world and while its price has decreased due to competition from generics companies, the cost still remains too high for millions of potential patients.[8] The published production process by Merck involves a six-step synthesis from *p*-chloroaniline.[6] Similarly, Lonza recently detailed a shorter four-step synthesis of efavirenz from 1,4-dichlorobenzene.[9] One of the C–C bond forming steps common to both synthetic procedures involves the 1,2-addition of cyclopropylacetylene to aryl trifluoromethyl ketones, *via* stoichiometric zinc. While the reported routes by Merck and Lonza have many attractive attributes, both are batch processes and as years of literature have demonstrated the commoditization of a large-scale process is almost always more efficient when made continuous.[10]

Of the existing catalytic approaches for adding alkynes to trifluoromethyl ketones, Cu(I) is attractive environmentally and has the potential for easy conversion to a continuous process. We examined catalytic systems that could perform well at low loadings and under mild conditions, and are tolerant of higher temperatures without loss of activity. The major consideration in identifying an active copper catalyst was its ability to increase the nucleophilicity of the acetylide. Typically electron-rich, bulky ligands can simultane-

Table 1. Optimization of the copper-catalyzed alkyne addition to trifluoromethyl ketones.



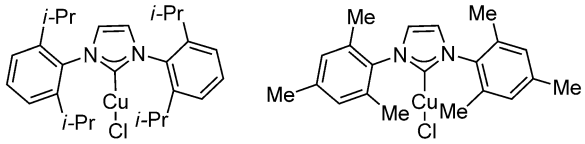
Entry[a]	[Cu]/NaO-*t*-Bu (mol%)	*T* [°C]	Yield [%]
1	–	40	ND
2	(IPr)CuCl (5)	40	86
3	(IMes)CuCl (5)	40	77
4	CuCl (5)	40	ND
5[b]	(IPr)CuCl (5)	40	ND
6	(IPr)CuCl (5)	50	99
7	(IPr)CuCl (3)	50	97
8[c]	(IPr)CuCl (3)	50	78
9[d]	(IPr)CuCl (3)	50	48

[a] *Conditions:* 0.2 mmol **1a**, 2 equiv. **2a**, copper catalyst [Cu] and base in 0.2 mL tetrahydrofuran (THF) for 16 h under argon (Ar).
[b] NaO-*t*-Bu removed.
[c] 1.5 equiv. alkynes.
[d] 8 h. ND = none detected by NMR.

ously activate the alkyne while preventing the formation of inactive polymeric copper–alkyne species. The strong electron-donating ability of N-heterocyclic carbenes (NHCs) as well as the Brønsted basic properties of copper(I) alkoxides prompted us to examine copper(I)–NHC alkoxides for the production of trifluoromethylpropargylic alcohols. We predicted that these Cu(I)–NHC alkoxides would catalyze 1,2-additions under milder conditions allowing the use of lower boiling point alkynes, for example. cyclopropylacetylene, a critical feature in the synthesis of APIs such as efavirenz.

From initial reports of their use in the conjugate ethylation of cyclic enones in 2001 by Woodward,[11] copper/N-heterocyclic carbenes have proven to be remarkably versatile catalysts.[12] Recently the Cu(I)–NHC-catalyzed carboxylations of terminal alkynes have been described.[13] These examples clearly demonstrate that Cu(I)–NHC complexes can form reactive Cu acetylides. Herein, we report that copper(I)–NHC complexes can catalyze the addition of terminal alkynes to trifluoromethyl ketones at low loadings (3 mol%). We demonstrate that this system has the necessary attributes to enable a continuous alkynylation process.

Initially, the alkynylation of trifluoromethyl ketones was optimized in batch, using 2,2,2-trifluoroacetophenone and cyclopropylacetylene as substrates (Table 1). Although both (IPr)CuCl and (IMes)CuCl (Figure 1) catalyzed the desired 1,2-addition (entries 2 and 3), the more hindered (IPr)CuCl complex provided higher yields. Control experiments confirm that



(IPr)CuCl (IMes)CuCl

Figure 1. Copper(I)/NHC catalysts.

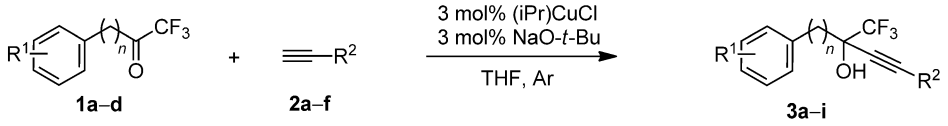
the Cu(I)–NHC complex is necessary as both removal of copper or use of simple CuCl did not yield any product (entries 1 and 4). As expected, sodium *tert*-butoxide is crucial for the reaction (entry 5), both to form the active Cu alkoxide and then, once protonated (*t*-BuOH), it facilitates proton transfer from the terminal alkyne to the product.[14] Almost quantitative conversion was achieved at increased temperatures (entry 6) and this temperature increase enabled the use of lower catalyst loadings (entry 7). Two equivalents of alkyne were necessary to achieve the highest yields, likely due to loss of material *via* evaporation as no evidence of Glaser–Hay products was identified (entry 8).

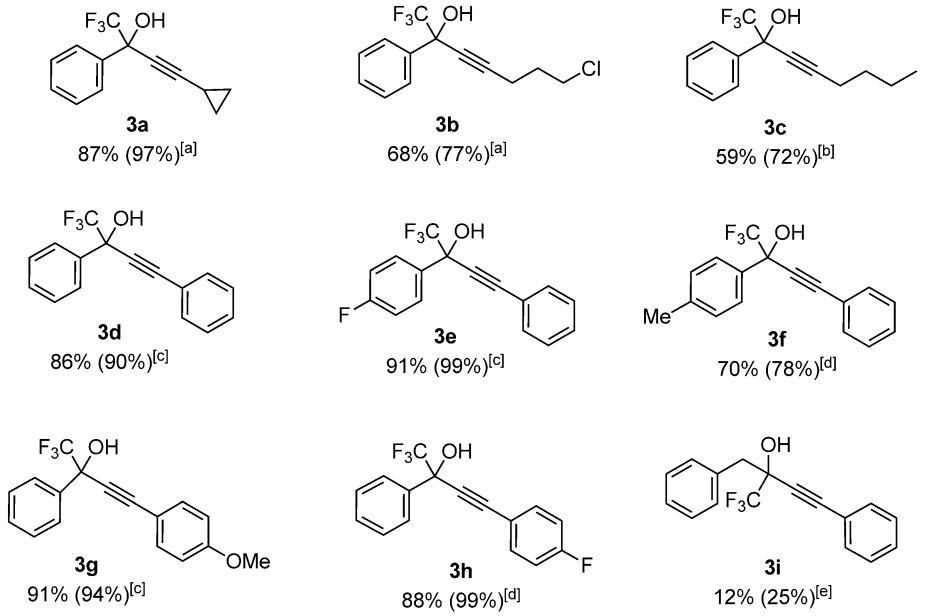
We chose the conditions as laid out in Table 1, entry 7 as our optimum system, and proceeded to examine the scope of the reaction (Table 2). Addition products were obtained in good to moderate yields for the alkynylation of aromatic trifluoromethyl ketones with various terminal alkynes. The electronics of both partners played an important role in this reaction. In some cases, higher temperatures were necessary to obtain full conversion (**3d–3i**). Even at these elevated temperatures the Cu(I)–NHC complexes remained active. It should be noted that the increased boiling point of phenylacetylene enabled us to reduce the number of alkyne equivalents used.[15]

Reactions involving the electron-rich electrophile, 4-(trifluoroacetyl)toluene, and electron-poor nucleophile, 4-fluorophenylacetylene, were sluggish and therefore needed longer reaction times to obtain full conversion to **3f** and **3h**, respectively. The alkynylation of aliphatic 3-phenyl-1,1,1-trifluoroacetone was also accomplished, albeit in lower yield. Additionally, the method supports a larger scale reaction where a 72% isolated yield of **3a** was obtained on the 1-mmol scale in batch. This lower yield may be due to less efficient heating and mixing typical of larger scale heterogeneous batch reactions.

We have a strong interest in developing low cost, high efficiency synthetic procedures for APIs to address developing world needs.[16] One potential strategy to achieve these goals is to create fully or semi-automated continuous synthetic routes by reducing labor and waste costs while at the same time providing APIs of higher quality (*via* continuous monitoring). The first step to creating a continuous process is to establish that each synthetic step can be achieved

Table 2. Scope of the copper-catalyzed alkynylation of trifluoromethyl ketones in batch.



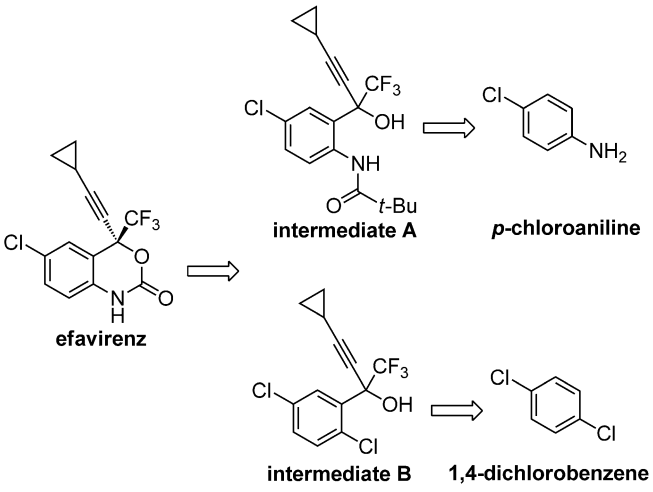


[a] 50 °C for 16 h. Isolated yields based on **1** with NMR yields reported in parenthesis.
[b] 40 °C for 24 h.
[c] 70 °C for 16 h.
[d] 70 °C for 24 h.
[e] 90 °C for 16 h.

in flow with good throughput. The fact that the Cu(I)–NHC-based alkynylation reported here can catalyze the addition of cyclopropylacetylene to aryl trifluoromethyl ketones suggests it as a key step in the synthesis of the anti-viral API efavirenz. Adaptation of this reaction to flow conditions could serve as progress towards more attractive syntheses of efavirenz intermediates A and B, the trifluoromethyl-substituted quaternary propargylic alcohols (Scheme 1). Figure 2 depicts our flow set-up where two solutions (solution 1 = substrates; solution 2 = *in situ* formed catalyst) are delivered to a T-mixer. The resulting reaction mixture would then proceed into a heated reactor loop.

Translating our method to flow required us to address solubility obstacles. The optimized solvent system defined in Table 1 resulted in reduced yields due to the lower solubility of the base, the active (IPr)CuO-*t*-Bu catalyst and sodium chloride in THF. Thus solids settling in the syringes and tubing caused inconsistent catalyst concentrations throughout the system. With cost in mind, we also needed to deliver 3 mol% of the catalyst without leaving catalyst behind or adhering to the delivery syringe.

To overcome these problems, we tested various mixed solvent systems[17] and discovered that a near neutral density slurry was formed by using a dimethylformamide (DMF), benzene and THF mixture in



Scheme 1. Merck's and Lonza's retrosynthetic analyses of efavirenz.

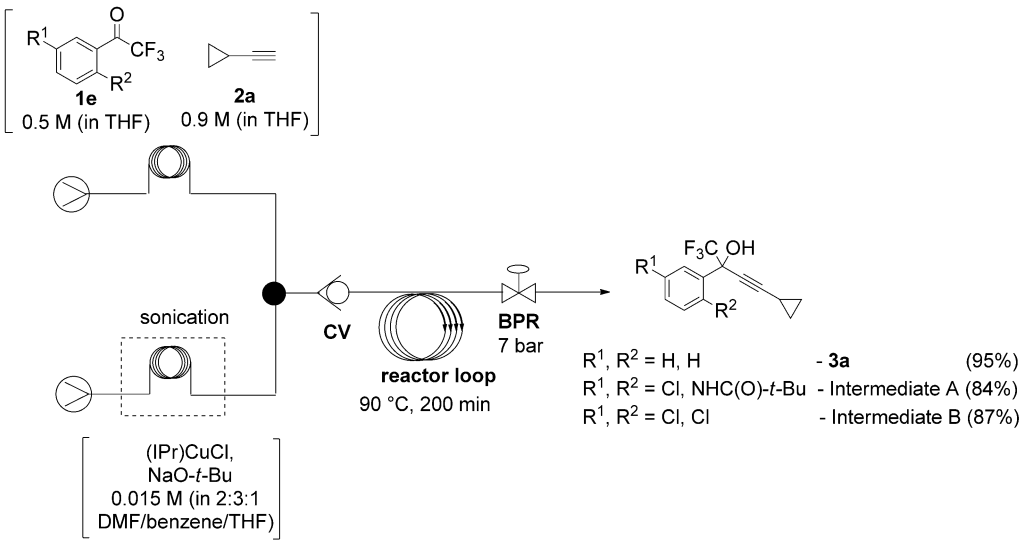


Figure 2. Flow set-up and application to biologically relevant intermediates.

a 2:3:1 ratio.[18] This slurry settled slower than when THF was used alone. To further circumvent adherence and catalyst settling, we decided to make use of an injection loop submerged horizontally in a sonication bath.[19] An in-line check valve (CV) and a 7-bar back pressure regulator (BPR) were added to allow constant flow through the 10-mL reactor loop at temperatures above the solvent's boiling point. Likewise, these conditions enabled the use of cyclopropylacetylene well above its boiling point and underscore the value of a flow chemical system. To achieve these conditions in batch would require a sealed, pressurized vessel limiting the potential scale-up and throughput.[20] Using the set-up depicted in Figure 2, the reaction was performed on a 1-mmol scale (0.5 M) of the trifluoromethyl ketone, good yields of **3a** and intermediates A and B were obtained in less than 3.5 h, almost five times faster than the batch process.

The shorter reaction time can be attributed to more efficient heating and mixing of the heterogeneous reaction in the flow reactor, as well as the increase in temperature and pressure. It should be noted that although we were able to decrease the amount of alkyne required in the flow device, it was still used in excess. It has been established that the C–C bond forming step in copper(I) alkynylation of aldehydes is a reversible process.[21]As such, it is possible that the excess alkyne is necessary for good yields due to a reversible addition to trifluoromethyl ketones in the presence of copper(I) alkoxides.

In summary, we have identified a copper(I)/N-heterocyclic carbene catalyst that can be used at low loadings for the addition of both aliphatic and aromatic alkynes to trifluoromethyl ketones in good yields in batch. The method also enabled the translation of this reaction to a flow chemistry modality, increasing throughput and providing a potential key step towards an overall continuous process. Finally, we predict that this method opens the door to realizing Cu(I)–NHC-promoted asymmetric alkynylations based on the simple manipulation of the backbone and ready availability of NHC ligands.

Experimental Section

General Procedure for the Cyclopropylacetylene Addition to 2,2,2-Trifluoromethylacetophenone (in Batch)

NaO-*t*-Bu (3 mol%, 0.006 mmol) and (IPr)CuCl (0.006 mmol) were placed in a sealable tube with magnetic stir bar. The tube was evacuated and backfilled with argon, then 0.1 mL anhydrous, degassed THF was added. 2,2,2-Trifluoroacetophenone (0.2 mmol) and cyclopropylacetylene (0.4 mmol, 34 μL) were then added, followed by 0.1 mL THF. The tube was flushed with argon, sealed and placed in an oil bath at 50 °C for 16 h. The heterogeneous mixture was cooled then flushed with ethyl acetate through a short column of silica gel. NMR yields were obtained using mesitylene as an internal standard. Compound **3a** was isolated by flash column chromatography on silica gel using a 5:1 mixture of hexanes and ethyl acetate. Full details and characterization data can be found in the Supporting Information.

General Procedure for the Cyclopropylacetylene Addition to 2,2,2-Trifluoromethylacetophenone (in Flow)

NaO-*t*-Bu (3 mol%, 0.03 mmol) and (IPr)CuCl (0.03 mmol) were mixed with 2 mL DMF/benzene/THF (2:3:1 ratio) to form a homogenous slurry and loaded into an injection loop under argon. 2,2,2-Trifluoroacetophenone (1 mmol) and cy-

clopropylacetylene (1.8 mmol) were dissolved in 2 mL THF and loaded into a second injection loop under argon. The loops were connected with a switchable IDEX T-mixer and fed into a 10-mL [1.6 mm (1/16") O.D. (outer diameter) × 0.3 mm (0.012") I.D. (inner diameter)] PTFE tubing at 90 °C and at a rate of 25 μL min^{-1} each under 7 bar back pressure. The resulting product mixture was collected and compound **3a** isolated by flash column chromatography on silica gel using a 5:1 mixture of hexanes and ethyl acetate. Full details and characterization data can be found in the Supporting Information.

Acknowledgements

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[14] Soluble bases typically used in copper-catalyzed alkynylations were also tested. Triethylamine and cesium carbonate furnished the product in only 11% and 58% yields, respectively.

[15] Please refer to the Supporting Information for full reaction conditions of each substrate.

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[18] Please see the Supporting Information for optimization of the alkynylation reaction in flow.

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[20] The comparable batch reaction of **3a** was performed on the 1-mmol scale with 1.8 equivalents of cyclopropylacetylene in THF (1 M) at 90 °C for 200 min in a tightly sealed reaction tube. An NMR yield of 84% was obtained.

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