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Silver catalyzed synthesis of 4-trifluoromethyl substituted quinolines in water†

Bing-Chuan Zhao,[a] Qing-Zhou Zhang,[a] Wen-Yu Zhou,[b] Hu-Chun Tao*[a] and Zi-Gang Li*[a]

Herein we report the first silver catalyzed fluorinated quinoline synthesis *via* a cascade alkyne–ketone–amino coupling/addition/condensation process in water.

One of the most important conceptual revolutions of chemistry research and the chemical industry in the late 20th century is the increasing attention from the public regarding designing and developing environmentally-benign chemical processes from the very beginning.[1–10] Collecting and disposal of organic solvents consume a major section of the chemical industry spending.[11] One recent important advance is using less polluting solvents, such as water,[12–18] ionic liquid[19–22] and super critical CO_2,[23–26] as substitutes for halogen-containing and/or aromatic organic solvents. Water has superior commercial accessibility over any other solvents and also shows some special accelerating characteristic in catalysis.[27,28] Thus, the need of developing synthesis methodologies in water becomes increasingly demanding. "Atom Economy" has also drawn the community's attention. It plots an ideal chemical process which converts maximum atoms from the substrate(s) into the target molecule(s), avoiding by-products (wastes) by not making them.[29,30]

Quinolines are important heterocycle cores of various natural products and commercial drugs, such as quinine,[31,32] buchapine,[33] 2-acetylevolitrine,[34] skimmianine,[35] aurachin RE[36] (Fig. 1). They are also important building components for organic light-emitting diodes (OLEDs) and photovoltaic devices.[37,38]

Traditional approaches towards quinolines such as Skraup, Doebner–von Miller, and Combes reactions can be applied in synthesizing simple quinoline derivatives with relatively poor regioselectivity.[39–43] Recent developments of quinoline synthesis *via* Friedlander conditions involve condensation of 2-aminoaryl-ketones with specially prepared β-keto-ester type substrates. This process could provide substituted quinolines in good yield, however, it may still have regio-selectivity issues[44] (Fig. 2).

Due to fluorinated compounds' special chemical, physical and physiological effects,[45–48] the chemical community cast significant interests over them.[49–53] The reports of synthesis of 4-trifluoromethyl substituted quinolines are rare, stoichiometric amount of metal salts and organic solvents are necessary with limited substrate scope.[54] Herein, we want to report a facile synthesis of 4-trifluoromethyl substituted quinolines *via* an aqueous silver-catalyzed environmentally-friendly tandem process with high atom economy. The only by-product is one molecule of H_2O per molecule of quinoline product.

This facile tandem process is composed by a propargyl alcohol synthesis *via* a *sp* C–H activation followed by an amine–alkyne addition and a final condensation to give final quinoline products.[54] The substrate scope can be extended to simple aliphatic alkynes and avoid using of stoichiometric amount of metal salts/organic solvents comparing with previous report, which makes this methodology more applicable in synthesis in addition to its environmental merits.[1–3]

We employed *o*-aminophenyltrifluoroethanones and alkynes as substrates. After screening different catalysts, we found silver showed superior catalytic ability when applied together with phosphine ligands and organic bases. Electron rich phosphine ligands, such as tricyclohexyl phosphine, show similar accelerating effect as triphenyl phosphine, while electron deficient phosphines are significantly less effective. Due to the economical reasons, triphenyl phosphine is chosen as the ligand for the standard
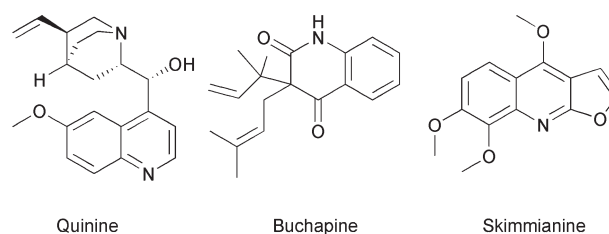
[a] Peking University Shenzhen Graduate School, Shenzhen University Town Peking University Campus, Shenzhen, Guangdong, 518055, P.R.C..
E-mail: taohc@pkusz.edu.cn; lizg@pkusz.edu.cn; Fax: +86 755-2603-3174
[b] Shenzhen Second People's Hospital, 3002, ShunGang West Road, Shenzhen, Guangdong, 518055, P.R.C.

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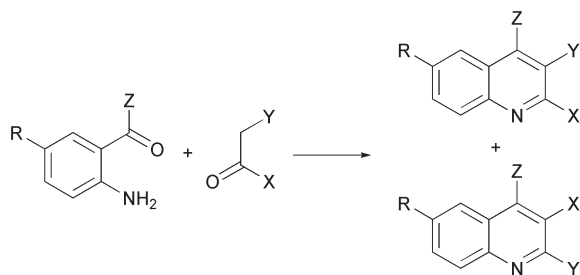

Fig. 1 Representative compounds containing quinoline core.

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Fig. 2 Friedlander reaction.

condition. AgF gives higher yields over other silver salts screened and triethylamine is chosen as the base, solid inorganic bases are not suitable for this reaction (Table 1).

O-Aminophenyltrifluoroethanones bearing both electron donating or electron withdrawing groups can undergo this reaction to give corresponding products (Table 2), however, ketones with electron withdrawing groups like **1a** or **1c** give higher yields (Entry 1–4, 9–12), which could be explained by the higher ketone carbonyl reactivity towards alkynes. In general, aromatic alkynes **2a** and **2d** give better yields than aliphatic ones **2b** and **2c**. Notably, ethynylcyclopropane **2c** shows better reactivity than 1-hexyne **2b**, gives moderate to good yields with all ketones (Entry 3, 7, 11, 15). This retention of cyclopropyl group suggests this reaction may go through a homogenous metal catalyzed C–H activation pathway in the step of propargyl alcohol formation, instead of a radical initiated reaction.

Transition metal catalyzed alkyne addition to normal ketones is a formidable task to be yet fully conquered, it is also true in our case.[55] Ketones bearing a CF_3 group give good to excellent yields with both aromatic and aliphatic alkynes, normal ketones could not undergo this reaction, which is still a unsolved task based on our knowledge. If the amine is protected, we can isolate corresponding propargyl alcohol **3ea** in good yield (Scheme 1). Thus, we propose the reaction mechanism as: silver catalyst first

Table 1 Optimization of reaction conditions[a]

Entry	Catalyst	Base	Yield (%)
1	AgF	NEt$_3$	73
2	AgNO$_3$	NEt$_3$	43
3	Ag$_2$O	NEt$_3$	43
4	AgOAc	NEt$_3$	58
5	AgF	DIPEA	48
6	AgF	Pyridine	38
7	AgF	Pyrrolidine	46

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (0.6 mmol), AgX (0.01 mmol), PPh$_3$ (0.01 mmol) and base (0.4 mmol) in 4 ml water, isolated yields of **3aa** were reported.

Table 2 Scope of substrates[a]

| Entry	R$_1$		R$_2$			Yield (%)
1	**1a**	Cl	**2a**	Ph	**3aa**	73[b]
2	**1a**	Cl	**2b**	*n*-Bu	**3ab**	83
3	**1a**	Cl	**2c**	cyclopropyl	**3ac**	85
4	**1a**	Cl	**2d**	4-methylphenyl	**3ad**	80
5	**1b**	OMe	**2a**	Ph	**3ba**	90
6	**1b**	OMe	**2b**	*n*-Bu	**3bb**	24
7	**1b**	OMe	**2c**	cyclopropyl	**3bc**	48
8	**1b**	OMe	**2d**	4-methylphenyl	**3bd**	57
9	**1c**	CF$_3$	**2a**	Ph	**3ca**	69
10	**1c**	CF$_3$	**2b**	*n*-Bu	**3cb**	60
11	**1c**	CF$_3$	**2c**	cyclopropyl	**3cc**	81
12	**1c**	CF$_3$	**2d**	4-methylphenyl	**3cd**	70
13	**1d**	H	**2a**	Ph	**3da**	38
14	**1d**	H	**2b**	*n*-Bu	**3db**	21
15	**1d**	H	**2c**	cyclopropyl	**3dc**	56
16	**1d**	H	**2d**	4-methylphenyl	**3dd**	37

[a] All reactions were carried out with **1** (0.2 mmol), **2** (0.6 mmol), AgF (0.01 mmol), PPh$_3$ (0.01 mmol) and NEt$_3$ (0.4 mmol) in 4 ml water, isolated yields of **3** were reported. [b] If the reaction was carried out at 2 mmol scale in 5 ml water, 66% **3aa** was isolated after 24 h reaction.

activates the *sp* C–H bond and its addition to ketones to form propargyl alcohols **7**, then the *o*-amino group adds to alkyne which followed by a condensation step to give the products and one molecule H_2O as by product (Scheme 2).

During this research, we also find an intriguing transformation: we propose to use an aldehyde carbonyl group instead of amine in the nucleophilic addition step, thus we employ 1,2-dibenzaldehyde **8** as the substrate, two products are identified as shown in Scheme 3. Interestingly, together with the easily understandable hemi acetal product, an indenone product is also identified, which could only form though an unusual addition of carbonyl C–H bond to alkynes.
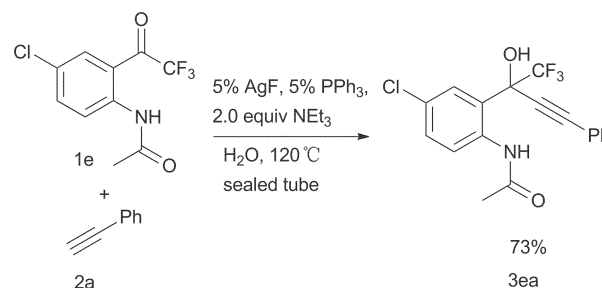

Scheme 1 Propargyl alcohol formation. All reactions were carried out with 1e (0.2 mmol), 2a (0.6 mmol), AgF (0.01 mmol), PPh$_3$ (0.01 mmol) and NEt$_3$ (0.4 mmol), isolated yield.
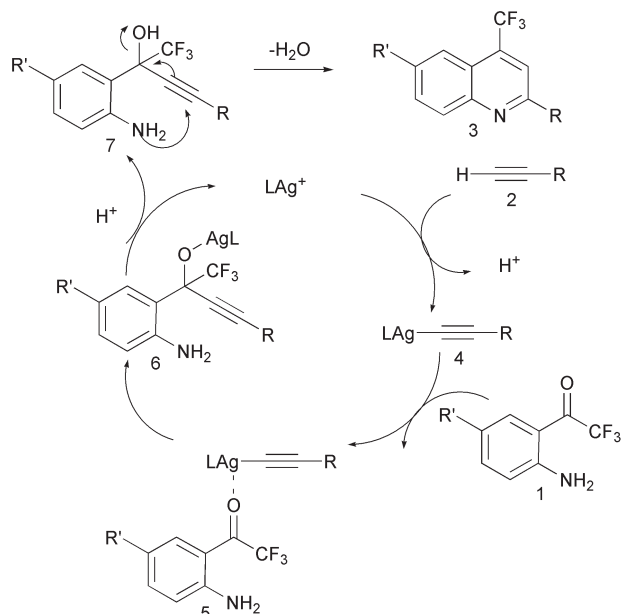
Scheme 2 Proposed mechanism of the quinolines synthesis catalyzed by silver in water.

Due to the intrinsic competition of the facile hemi acetal formation, the indenone transformation could only give moderate yield. The hemi acetal product will decompose if we increase the reaction time to over 12 h, which facilitate the isolation of desired indenone product. Although at this moment, this transformation is still limited by scope and efficiency, it implicates a broader scope of further application of the silver catalyzed alkyne addition reactions[56,57] (Scheme 3).
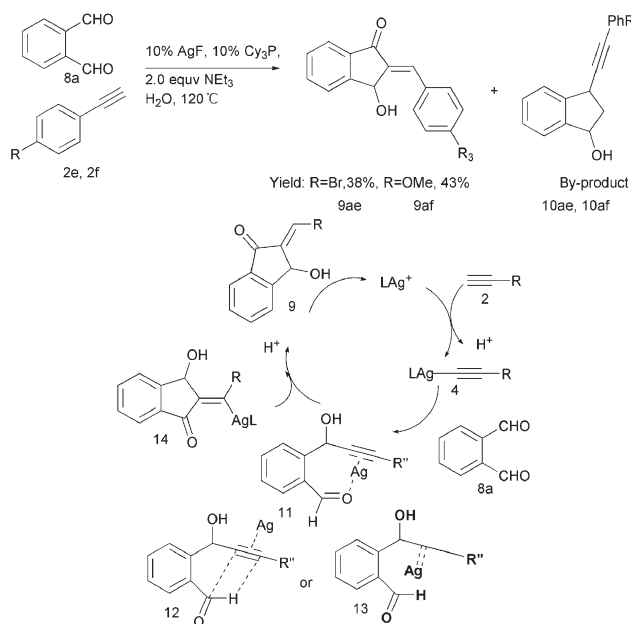
Scheme 3 Indenone formation.

We propose a tentative mechanism for the intriguing indenone formation as shown in Scheme 3. The first step also goes through a silver catalyzed *sp* C–H activation, which results in corresponding propargyl alcohol **11**; the hydroxyl group of the newly formed propargyl alcohol may attack the neighboring carbonyl carbon center to form hemi acetal **10** or the alkynyl group may react with the carbonyl C–H bond to afford indenone **9**. The role of silver catalyst in the indenone formation is still illusive, it may go through either a silver catalyzed alkyne-ketone metathesis intermediate **12** or a silver catalyzed carbonyl C–H activation *via* carbene insertion intermediate **13**.

Conclusions

Herein we report a facile silver catalyzed 4-trifluoromethyl substituted quinoline synthesis in water with high atom economy. It provides new approaches for important quinoline intermediates bearing CF$_3$ group, this protocol is applicable with both aromatic and aliphatic alkynes. Further research of this transformations with normal ketones and the silver catalyzed carbonyl C–H addition is under current investigations.

Experimental

General procedure for production of quinoline derivatives

To a sealed tube equipped with magnetic stir bar and Teflon-seal screw cap was added 0.2 mmol aniline, 4 ml water, then 0.01 mmol AgF, 0.01 mmol PPh$_3$, 0.6 mmol alkynes and 0.4 mmol NEt$_3$ (66 μl) was added to the mixture in the sealed tube under the atmosphere of air. The mixture was stirred at the temperature of 120 °C (bath temperature) for 0.5–3 h. After the reaction was complete, the reaction mixture was extracted with ethyl acetate. The mixture was concentrated under a reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent = hexane–EtOAc 50–100 : 1).

Acknowledgements

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