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Copper Promoted Synthesis of Substituted Quinolines from Benzylic Azides and Alkynes

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A novel copper promoted synthesis of substituted quinolines from various benzylic azides and internal alkynes has been demonstrated. The reaction features a broad substrate scope, high product yields and excellent regioselectivity. In contrast to the known two-step process of acid promoted [4+2] cycloaddition reaction and oxidation, the present methodology allows the synthesis of quinolines in a single step under neutral reaction conditions and can be applied to the synthesis of biologically active 6-chloro-2,3-dimethyl-4-phenylquinoline (antiparasitic agent) and 3,4-diphenylquinolin-2(1*H*)-one (p38αMAP kinase inhibitor). A plausible reaction mechanism involves rearrangement of benzylic azide to *N*-arylimine (Schmidt reaction) followed by intermolecular [4+2] cyclo addition with internal alkynes.

Introduction

Quinoline and its derivatives are potential heterocyclic scaffold found in many natural products[1-3], and bio-active molecules.[4-10] They are also key structures in materials, agrochemicals, dyestuffs, and pharmaceuticals.[11-15] In particular, the use of quinoline derivatives as ligands for transition metal complexes for organic synthesis and organic light-emitting materials has attracted great attention for their synthesis (Fig. 1).[16-21]

Regardless of many classical methods, such as Pfitzinger, Skraup, Friedlander, Doebner von Miller, Conrad–Limbach, and Combes reactions known for the synthesis of quinolines, most are limited by harsh reaction conditions, limited substrate scope and low yields.[22] Among the various synthetic strategies,[23-24] Lewis acid promoted tandem cyclization reaction of *N*-aryl imines with terminal alkynes under oxidative condition allows the access to a variety of 2,4-disubstituted quinolines.[25-28] The proposed reaction mechanism involves the nucleophilic addition of a terminal alkyne to imine to form propargylamine intermediate, which undergoes intramolecular cyclization, followed by oxidation to afford quinoline products. Similar cyclization reactions using internal alkynes are difficult and hardly achieved.[29] These reactions are not suitable for the synthesis of quinolines without substitution at C-2 position (Scheme 1a).

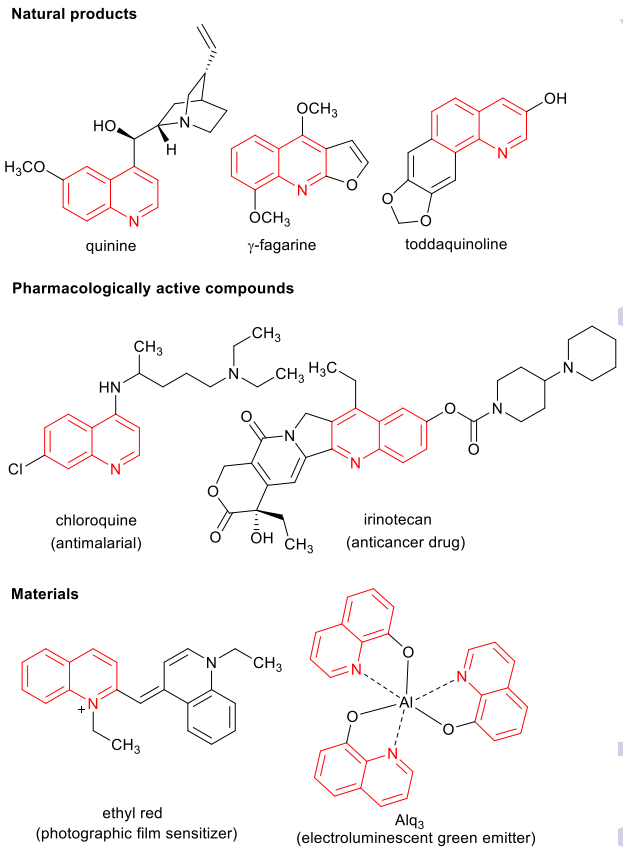

Fig. 1 Examples of useful quinoline cored compounds.

Recently, the in situ generation of *N*-aryliminium ions from benzylic azides by means of strong acids has been utilized for the synthesis of tetrahydroquinoline scaffolds, which can be oxidized to quinolines by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[30-31] The drawbacks of these reactions are

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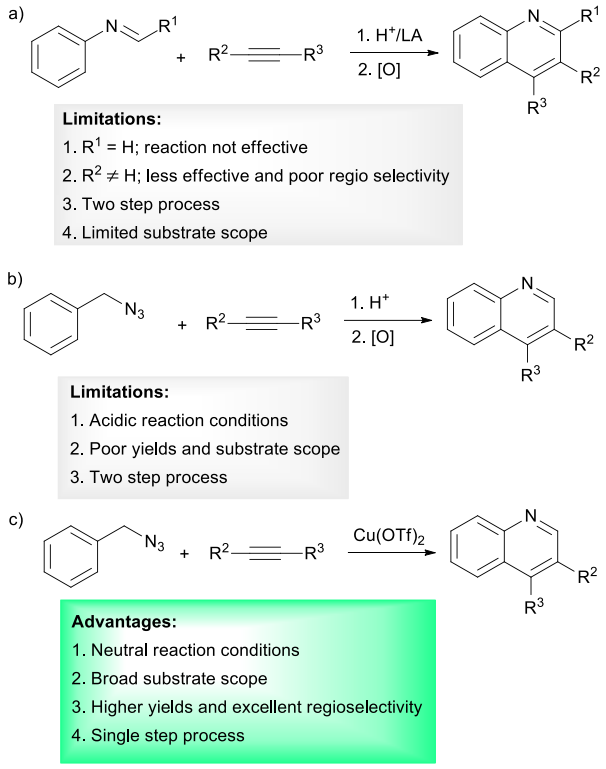
(i) lower product yields, (ii) use of strong acid, (iii) poor regioselectivity and (iv) a two-step process (cyclization and oxidation) (Scheme 1b). Because of the useful applications of quinolines and the lack of simple and high yielding method for their synthesis, the search for new synthetic methodologies are still highly sought after. Our continuing interests in the quinoline synthesis[32-33] lead us to envision that the *in situ* generation of *N*-aryliminium ion from benzylic azide using a Lewis acid catalyst which is also an oxidant under acid free condition provides a good opportunity to avoid the above mentioned problems at least in part. In this report, we disclose a simple and a novel method for the synthesis of various substituted quinolines from benzylic azides and internal alkynes under neutral reaction conditions using $Cu(OTf)_2$ as both a Lewis acid and oxidant (Scheme 1c).

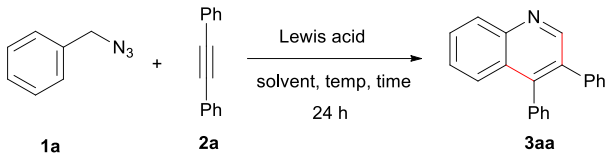


Scheme 1 Synthetic strategies for substituted quinolines.

Results and discussion

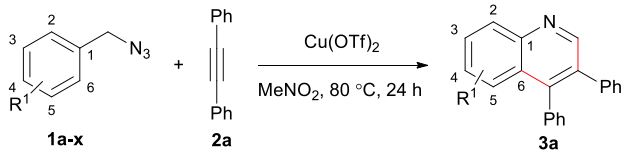
Initially, several Cu^{II}-salts were screened for the reaction of benzyl azide (**1a**) and diphenylacetylene (**2a**) to form 3,4-diphenylquinoline (**3aa**) (Table 1). Treatment of **1a** (0.34 mmol), and **2a** (0.28 mmol) in the presence of $Cu(OTf)_2$ (0.56 mmol) in $MeNO_2$ at 100 °C for 24 h gave **3aa** in 36% yield (Table 1, entry 2). The product was unambiguously confirmed by its ^1H and ^{13}C NMR, HRMS, and X-ray structure analysis.[34] Among the Cu(II)-salts and other Lewis acids tested, only $Cu(BF_4)_2{\cdot}6H_2O$ showed considerable potency to give **3aa** in 33% yield (See, Table SI for the detailed optimization studies). By reversing the ratio of **1a** and **2a** from 1.2:1 to 1:1.2, **3aa** was obtained in 63% yield (entry 7). The yield of **3aa** further increased to 77%, as the amount of **2a** was raised to 2 equiv. (entry 8). We then optimized the amount of $Cu(OTf)_2$, reaction time and temperature. The optimized reaction conditions with **1a** (0.28 mmol), **2a** (0.56 mmol), and $Cu(OTf)_2$ (0.70 mmol) in $MeNO_2$ (2 mL) at 80 °C for 24 h provided 3,4-diphenylquinoline (**3aa**) in 93% isolated yield. The choice of solvent is crucial to obtain a high product yield. Among the several solvents tested, $MeNO_2$ afforded the highest product yield, while $PhNO_2$ and CF_3CH_2OH also gave **3aa** in 60 and 75% yields, respectively (Table 1). The attempt to use $Cu(OTf)_2$ as catalyst by employing 0.5 equivalent of $Cu(OTf)_2$ with a stoichiometric amount of $K_2S_2O_8$ or $(NH_4)_2S_2O_8$ as oxidants gave the quinoline product in about 50% yield (See Table 1).

Table 1 Optimization studies for the synthesis of 3,4-diphenylquinoline from benzyl az and diphenylacetylene

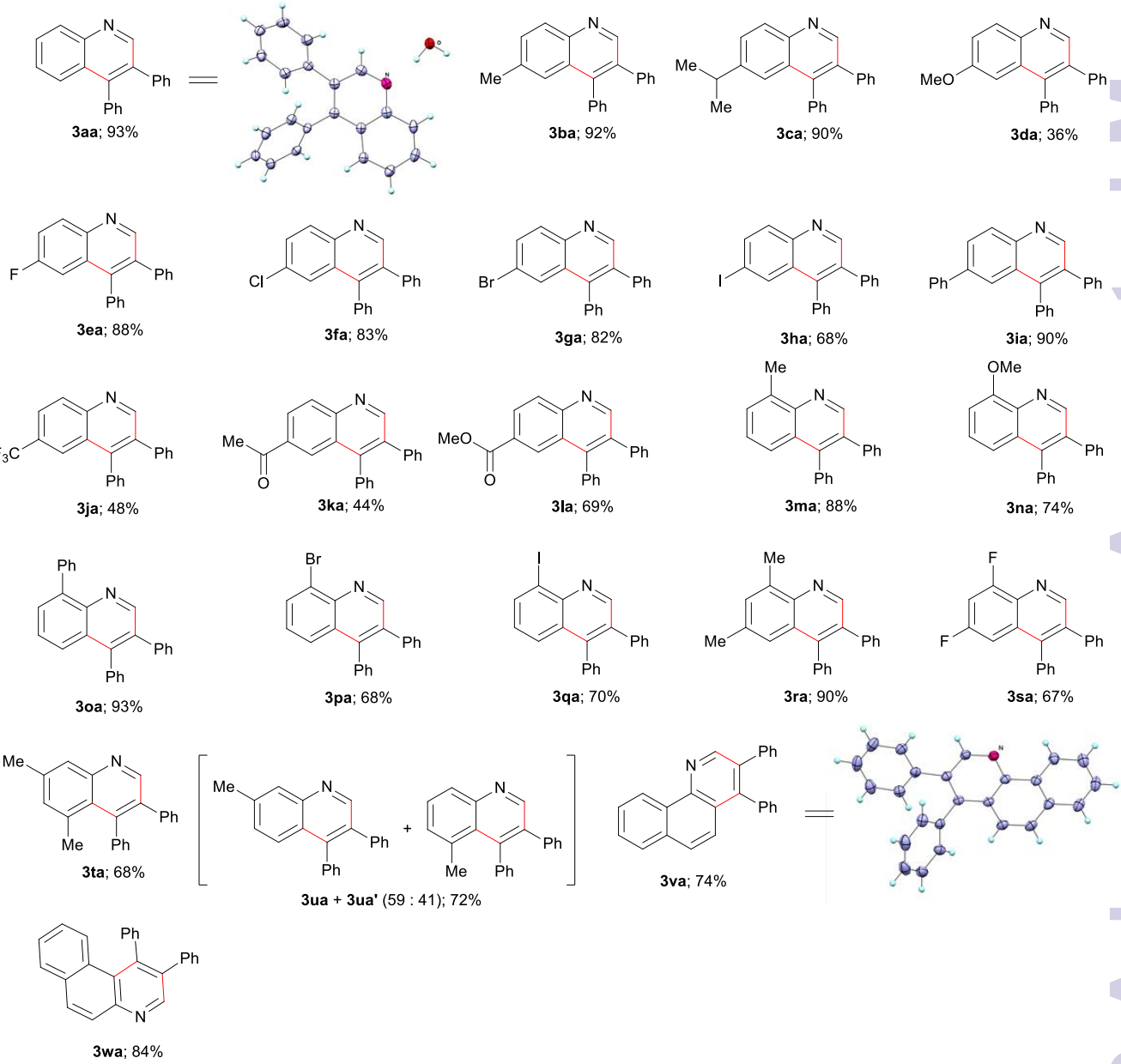


Entry	Lewis acid (equiv)	Solvent	Temp.(°C)/ Time (h)	Yield (%)[a]
1	$Cu(OAc)_2$ (2)	$MeNO_2$	100/24	--
2	$Cu(OTf)_2$ (2)	$MeNO_2$	100/24	36
3	$Cu(OCOCF_3)_2$ H_2O (2)	$MeNO_2$	100/24	trace
4	$Cu(BF_4)_2{\cdot}6H_2O$ (2)	$MeNO_2$	100/24	33
5	$CuCl_2$ (2)	$MeNO_2$	100/24	--
6	CuF_2 (2)	$MeNO_2$	100/24	--
7	$Cu(OTf)_2$ (2)	$MeNO_2$	100/24	63[b]
8	$Cu(OTf)_2$ (2)	$MeNO_2$	100/24	77[c]
9	$Cu(OTf)_2$ (3)	$MeNO_2$	100/24	92[c]
10	$Cu(OTf)_2$ (4)	$MeNO_2$	100/24	87[c]
11	$Cu(OTf)_2$ (3)	$MeNO_2$	80/24	89[c]
12	$Cu(OTf)_2$ (3)	$MeNO_2$	60/24	80[c]
13	**$Cu(OTf)_2$ (2.5)**	**$MeNO_2$**	**80/24**	**93**[c]
14	$Cu(OTf)_2$ (2.5)	$MeNO_2$	80/15	72[c]
15	$Cu(OTf)_2$ (1), 1 atm O_2	$MeNO_2$	80/24	45[c]
15	$Cu(OTf)_2$ (3)	EtOAc	80/24	36[c]
16	$Cu(OTf)_2$ (3)	DCE	80/24	22[c]
17	$Cu(OTf)_2$ (3)	$PhNO_2$	80/24	60[c]
18	$Cu(OTf)_2$ (3)	TFE	80/24	75[c]
19	$Cu(OTf)_2$ (0.5), $K_2S_2O_8$	$MeNO_2$	100/24	49[c,d]
20	$Cu(OTf)_2$ (0.5), $(NH_4)_2S_2O_8$	$MeNO_2$	100/24	52[c,d]

[a]Unless otherwise mentioned, all reactions were performed with **1a** (0.34 mmol), **2a** (0.28 mmol, limiting reagent), and Lewis acid (as given in the table) in $MeNO_2$ (2 mL) at 100 °C for 24 h. Isolated yields based on the limiting reagents were given. Yield given in the parenthesis was isolated yield. DCE: 1,2-dichloroethane; TFE: 2,2,2-Trifluoroethanol.. [b]**1a** (0.28 mmol, limiting reagent), and **2a** (0.34 mmol) were used. [c]Reactions were performed using **1a** (0.28 mmol, limiting reagent), **2a** (0.56 mmol), and Lewis acid (as given in the table) in $MeNO_2$ (2 mL) at the given temperature and time. [d]$Cu(OTf)_2$ (0.14 mmol) was used along with $K_2S_2O_8$ or $(NH_4)_2S_2O_8$ (0.32 mmol).



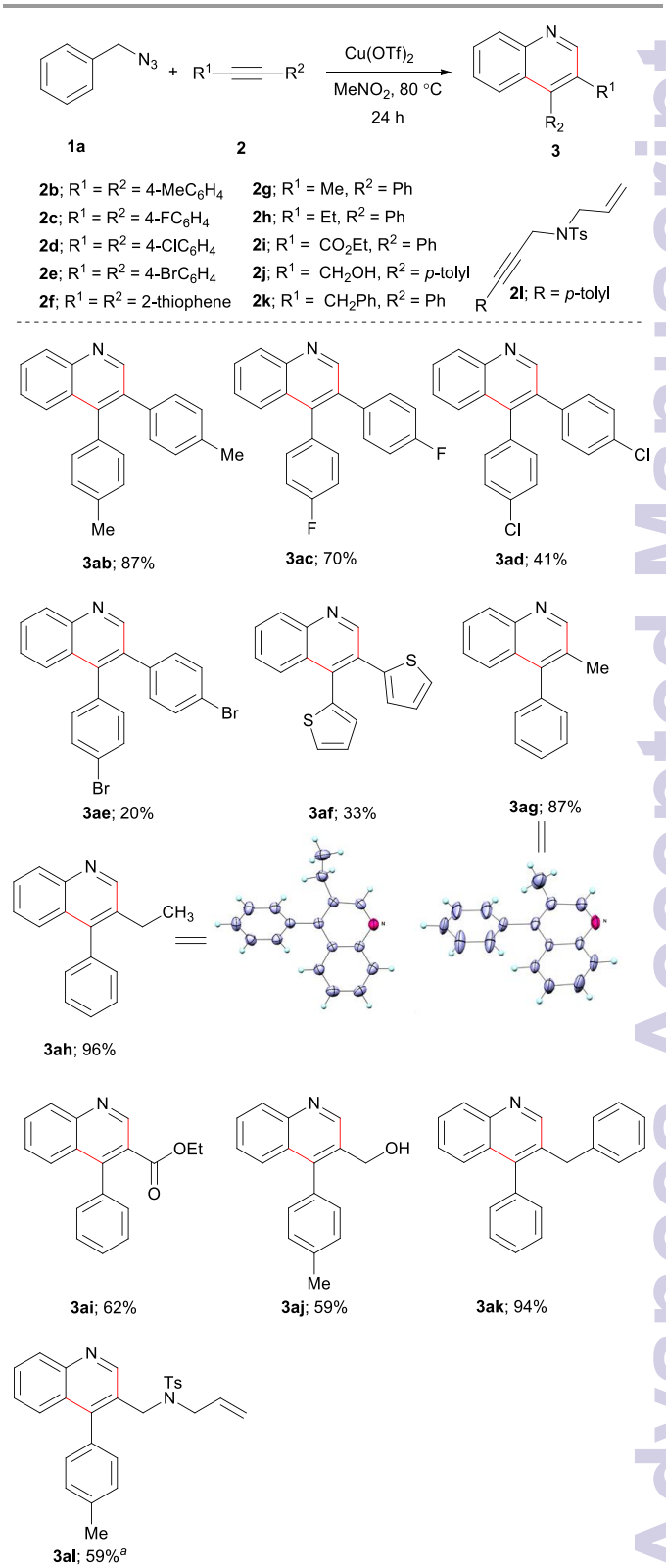
1a; R^1 = H
1b; R^1 = 4-Me
1c; R^1 = 4-*i*Pr
1d; R^1 = 4-OMe
1e; R^1 = 4-F
1f; R^1 = 4-Cl
1g; R^1 = 4-Br
1h; R^1 = 4-I
1i; R^1 = 4-Ph
1j; R^1 = 4-CF_3
1k; R^1 = 4-Ac
1l; R^1 = 4-CO_2Me
1m; R^1 = 2-Me
1n; R^1 = 2-OMe
1o; R^1 = 2-Ph
1p; R^1 = 2-Br
1q; R^1 = 2-I
1r; R^1 = 2,4-di-Me
1s; R^1 = 2,4-di-F
1t; R^1 = 3,5-di-Me
1u; R^1 = 3-Me
1v; 1-(azidomethyl) naphthalene
1w; 2-(azidomethyl) naphthalene



Scheme 2 Scope of benzylic azides in the synthesis of substituted quinolines. Conditions: **1** (0.28 mmol), **2a** (0.56 mmol), and $Cu(OTf)_2$ (0.70 mmol) in $MeNO_2$ (2 mL) at 80 °C for 24 h. Isolated yields were determined based on **1**.

Next, we applied the optimized reaction conditions to a variety of benzylic azides to probe the generality of the reaction (Scheme 2). First, we tested the *para* substituted benzylic azides **1b-l**. Both electron-donating-group (EDG) and electron-withdrawing-group (EWG) substituted substrates were effectively transformed into the respective quinoline products. Thus, the EDG, 4-Me and 4-*i*Pr substituted substrates offered products **3ba** and **3ca** in 92% and 90% yields, respectively, but the very electron-donation 4-methoxy substituted benzyl azide (**1d**) yielded only 36% of product **3da**. Halo-substituted benzylazides **1e-h** are compatible under the reaction conditions to give the expected products **3ea-ha** in good yields. EWGs containing benzylic azides **1i-1** provided the respective substituted quinolines **3ia-la** in 44-90% yields. The steric hindrance of *ortho* substitution at benzylic azides does not show consistent influence on the yield of this cyclization reaction. We studied the reactions of benzylic azides possessing different ortho substituents such as Me, OMe, Ph, Br, and I with alkyne **2a**. The results reveal that most of the reactions afforded the respective quinolines in high yields (Scheme 2, products **3ma-qa**). Tetra substituted quinolines **3ra-ta** were obtained in good yields by employing disubstituted benzylic azides **1r-t**. The reaction of 3-methylbenzylic azide gave an inseparable mixture of regioisomeric quinoline products **3ua + 3ua'** (6:4) in 72% yield. Synthesis of substituted benzo[*h*]quinoline (**3va**) and benzo[*f*]quinoline (**3wa**) were achieved from **1v** and **1w** in 74 and 84% yields, respectively. The structure of **3va** was further confirmed by X-ray analysis.[34] It is worth to mention that the halo substituted quinoline products **3ea-ha**, **3pa-qa** are useful for further functionalization via cross couplings.

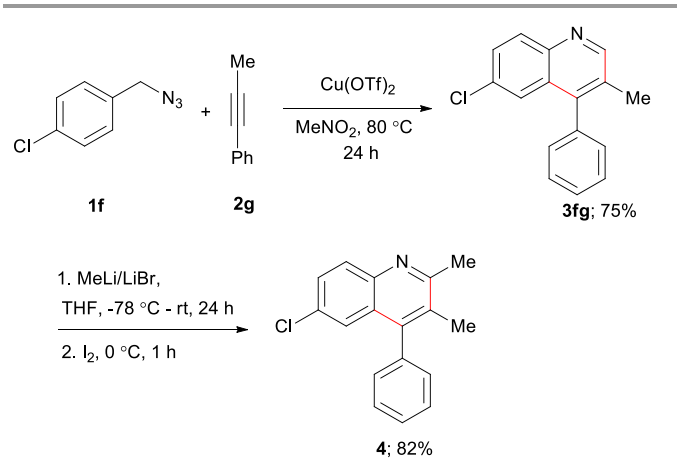
This copper(II) promoted quinoline synthesis was further expanded to a range of symmetrical and unsymmetrical internal alkynes (Scheme 3). Thus, the reaction of *p*-ditolylacetylene (**2b**) with **1a** gave the expected product **3ab** in 87% yield. Similarly, *p*-F, *p*-Cl, *p*-Br substituted diarylacetylenes **2c-e** reacted with **1a** to provide the corresponding quinolines **3ac-ae** in moderate yields. Di(2-thienyl)acetylene also underwent the cyclization reaction to provide **3af** in 33% yield. Next, we tested a number of unsymmetrical alkynes **2g-l** with **1a** and found that the reactions are highly regioselective giving exclusively a single regioisomeric product for each of these reactions. Under the reaction conditions, 1-phenylpropyne (**2g**) and 1-butynylbenzene (**2h**) provided the respective quinolines **3ag** and **3ah** in 87 and 96% yields, respectively. The regioselectivity of the products were confirmed by X-ray structure analysis.[34] Electron-deficient alkyne such as ethyl phenylpropiolate (**2i**) is also active affording the expected quinoline product **3ai** in 62% yield. Moreover, 3-tolylpropargyl alcohol (**2j**), benzyl phenyl acetylene (**2k**) and 3-tolylpropargyl amine derivative (**2l**) also operative to produce quinoline derivatives **3aj - 3al** in good to excellent yields.



Scheme 3 Scope of alkynes in the synthesis of substituted quinolines. Conditions: **1a** (0.28 mmol), **2** (0.56 mmol), and $Cu(OTf)_2$ (0.70 mmol) in $MeNO_2$ (2 mL) at 80 °C for 24 h. [a]$Cu(BF_4)_2{\cdot}6H_2O$ (0.70 mmol) was used instead of $Cu(OTf)_2$.

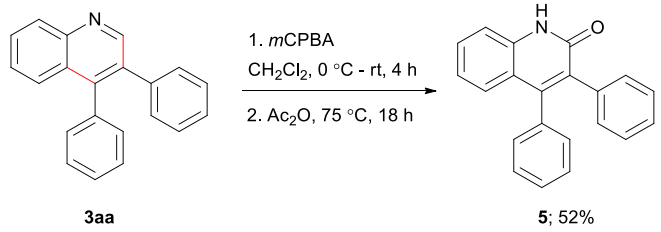
To demonstrate the synthetic utility of the present copper promoted cyclization reaction, we synthesize biologically active compound 6-chloro-2,3-dimethyl-4-phenylquinoline (**4**) by the

present method. The quinoline compound is known to show effectiveness against *Leishmania donovani*, *Trypanosoma cruzi*, *T. b. rhodesiense*.[35] As shown in Scheme 4, compound **4** was conveniently synthesized from **1f** and **2g** in two steps with 62% overall yield.



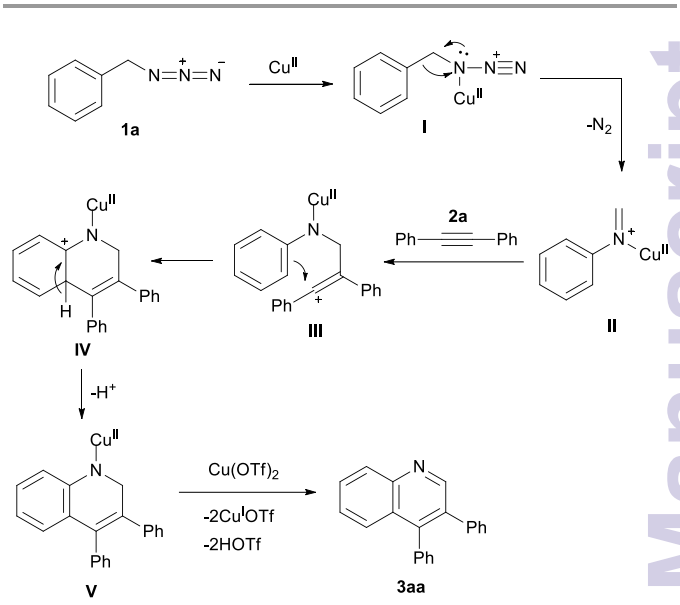
Scheme 4 Synthesis of biologically active 6-chloro-2,3-dimethyl-4-phenylquinoline **4**.

We also demonstrated the synthesis of 3,4-diphenylquinolin-2(1*H*)-one (**5**) from 3,4-diphenylquinoline (**3aa**) (Scheme 5). Compound **5** is known to be a potential p38αMAP kinase inhibitor.[36,37]



Scheme 5 Synthesis of 3,4-diphenylquinolin-2(1*H*)-one **5**.

A plausible reaction mechanism for the copper promoted intermolecular cyclization of benzylic azides and internal alkynes is shown in Scheme 6. The reaction is initiated by Cu^{II} assisted rearrangement of benzylic azide into *N*-aryliminium ion **II** by the loss of N_2 and the migration of the phenyl group.[38,39] Next, the intermolecular nucleophilic attack of alkyne to **II** forms a vinyl cation intermediate **III**. An intramolecular electrophilic aromatic substitution of intermediate **III** followed by oxidation afford the final quinoline product. It is worth to mention that the reaction offer high regioselectivity for unsymmetrical alkynes **2h-i** (Scheme 2) and good yields for electron withdrawing group substituted benzylic azides (Scheme 1). Presumably, the high regioselectivity is due to the better stabilization of the vinyl cation intermediate **III** by the phenyl ring than the alkyl or ester group on the alkyne substrate. During this copper promoted cyclization, substituted benzylic azides are turned into an electron-rich substituted aryl amine (see intermediate **III**). As a result, an electron withdrawing substituent on the phenylamide ring will not completely stop the electrophilic cyclization of **III**.



Scheme 6 Plausible reaction mechanism.

Conclusions

The copper(II)-promoted synthesis of 3,4-disubstituted quinolines by the intermolecular cyclization reaction of benzylic azides and internal alkynes have been demonstrated. It has been shown that the effectiveness of Cu^{II}-salt in the rearrangement of benzylic azide into *N*-arylimine (Schmidt reaction) which has previously only been achieved by strong acids. The catalytic reaction is highly efficient with a wide range of substituted benzylic azides. Excellent regioselectivity was observed for the reaction with unsymmetrical alkyne giving a single regioisomeric product in high yield. The present reaction system is further applied to the synthesis of two biologically active compounds.

Experimental section

General procedure for the synthesis of benzyl azides[40]

Substituted benzylic bromide (1.0 equiv) and sodium azide (1.5 equiv) were dissolved in DMF (2.0 mL/mmol) and stirred at 30 °C for 12 h. At the end of the reaction, the mixture was diluted with water and extracted with diethyl ether. The combined solution was concentrated in vacuo and the mixture was purified by a silica gel column (hexane/EtOAc, 90:10) to afford benzylic azide.

Typical procedure for the synthesis of substituted quinoline 3aa

A sealed tube containing $Cu(OTf)_2$ (254 mg, 0.70 mmol) and diphenylacetylene **2a** (100 mg, 0.56 mmol) was evacuated and purged with nitrogen gas three times. Then, a solution of benzyl azide **1a** (38 mg, 0.28 mmol) in $MeNO_2$ (2.0 mL) was added to the system by syringe under a nitrogen atmosphere and the reaction was stirred at 80 °C for 24 h. At the end of the reaction, the mixture was diluted with CH_2Cl_2 (10 mL), filtered through a Celite pad, which was then washed three times with CH_2Cl_2 (2

X 20 mL). The combined filtrate was concentrated in vacuo and the mixture was purified by a silica gel column using hexane/EtOAc (95:5) as eluent to afford the desired pure product **3aa** in 91% (71 mg) yield.

Yellow solid: m.p. 135-137 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.99 (s, 1 H), 8.18 (d, *J* = 8.4 Hz, 1 H), 7.74-7.64 (m, 2 H), 7.49-7.43 (m, 1 H), 7.37-7.30 (m, 3 H), 7.23-7.14 (m, 7 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.8 (*C*H), 147.5 (C), 145.5 (C), 138.1 (C), 136.3 (C), 133.1 (C), 130.5 (2 *C*H), 130.1 (2 *C*H), 129.5 (*C*H), 129.1 (*C*H), 128.1 (2 *C*H), 128.0 (2 *C*H), 127.7 (*C*H), 127.2 (C), 127.0 (*C*H), 126.8 (*C*H), 126.6 (*C*H); **HRMS** (FAB) cal for $C_{21}H_{15}N$ [M^+] 281.1204, found 281.1204; **IR** (KBr): 2923, 2854, 1727, 1565, 1488, 1442, 1380, 1272, 1072, 1025, 763 and 701 cm^{-1}.

Procedure for the synthesis of biologically active compound 4[41]

Compound **3fg** was synthesized in 75% yield from 1-(azidomethyl)-4-chlorobenzene (**1f**) and phenylpropyne (**2g**) using a procedure similar to that for the synthesis of quinoline **3aa**.

Compound **3fg** (110 mg, 0.43 mmol) was dissolved in THF (4.0 mL) and MeLi/LiBr (0.40 mL (2.2 M in Et_2O, 0.87 mmol) was added to the solution at -78 °C. The mixture was allowed to warm to room temperature for 24 h. At the end of the reaction, iodine (328 mg, 1.29 mmol) was added to the mixture at 0 °C and stirred for 1 h at the same temperature. The mixture was then quenched with a saturated sodium thiosulfate solution (10 mL). The resulted biphasic solution was extracted with EtOAc (3 X 30 mL). The combined organic solution was concentrated in vacuo and the mixture was purified by a silica gel column using hexane/EtOAc (95:5) as eluent to afford the desired pure product **4** in 82% (94 mg) yield.

Yellow solid: m.p. 125-127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.8 Hz, 1 H), 7.54-7.44 (m, 4 H), 7.25 (d, *J* = 2.4 Hz, 1 H), 7.21-7.18 (m, 2 H), 2.72 (s, 3 H), 2.15 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.3 (C), 145.5 (C), 144.4 (C), 136.9 (C), 131.2 (C), 130.1 (*C*H), 129.3 (2 *C*H), 128.9 (*C*H), 128.7 (2 *C*H), 128.5 (C), 128.0 (*C*H), 127.6 (C), 124.8 (*C*H), 24.5 (CH_3), 17.0 (CH_3); **HRMS** (ESI) $[M+H]^+$ cal for $C_{17}H_{15}ClN$ 268.0893, found 268.0885; **IR** (KBr): 3062, 2923, 2854, 1727, 1666, 1589, 1481, 1373, 1172, 1072, 948, 825 and 701 cm^{-1}

Procedure for the synthesis of 3,4-diphenylquinolin-2(1*H*)-one 5.[36]

Compound **3aa** (100 mg, 0.36 mmol) was dissolved in CH_2Cl_2 (4.0 mL) and *meta*-chloroperoxybenzoic acid (134 mg, 0.54 mmol) was added to the solution at 0 °C and stirred for 4 h at the same temperature. After that the reaction was quenched with saturated sodium bicarbonate solution (5 mL). The resulted biphasic solution was extracted with CH_2Cl_2 (3 X 10 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation. The crude product was dissolved in Ac_2O (3.0 mL) and heated at 75 °C for 18 h. At the end of the reaction, the mixture was quenched with saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (3 X 10 mL). The combined solution was dried over $MgSO_4$ and concentrated in vacuo and the resulted residue was purified by a silica gel column using hexane/EtOAc (95:5) as eluent to afford the desired pure product **5** in 52% (55 mg) yield.

Yellow solid: m.p. 173-175 °C; **^{1}H NMR** (400 MHz, d_6-DMSO): δ 12.0 (bs, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.32-7.22 (m, 3 H), 7.18-7.04 (m, 8 H), 6.99 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, d_6-DMSO): δ 161.2 (C), 148.1 (C), 138.2 (C), 136.1 (C), 135.7 (C), 131.9 (C), 130.6 (2 *C*H), 130.1 (*C*H), 129.5 (2 *C*H), 127.9 (2 *C*H), 127.5 (*C*H), 127.1 (2 *C*H), 126.8 (*C*H), 126.5 (*C*H), 121.7 (*C*H), 119.9 (C), 115.1 (*C*H); **HRMS** (ESI) $[M+H]^+$ cal for $C_{21}H_{16}ON$ 298.1232, found 298.1225; **IR** (KBr): 3162, 1727, 1643, 1596, 1481, 1442, 1288, 705 and 701 cm^{-1}.

Acknowledgements

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Graphical Abstract:

Copper Promoted Synthesis of Substituted Quinolines from Benzylic Azides and Alkynes

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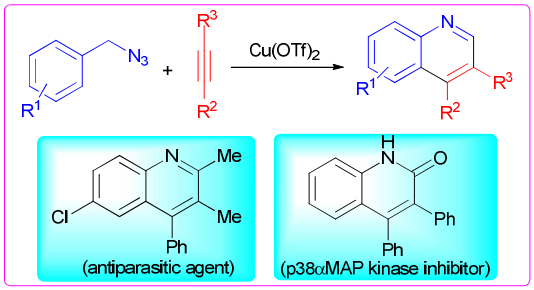

A novel method for the synthesis of substituted quinolines from benzylic azides and internal alkynes using $Cu(OTf)_2$ is described. The reaction features a broad substrate scope, high product yields and excellent regioselectivity.