$Zn(OTf)_2$-mediated C-H activation: an expeditious and solvent-free synthesis of aryl/alkyl substituted quinolines

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Graphical Abstract

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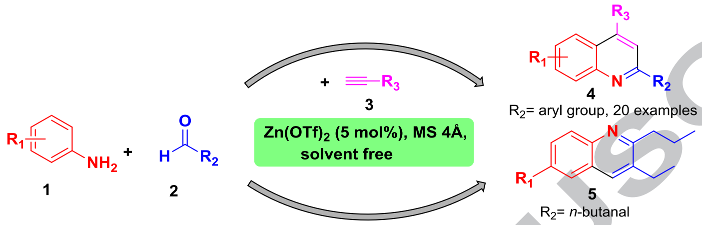

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$Zn(OTf)_2$-mediated C-H activation: an expeditious and solvent-free synthesis of aryl/alkyl substituted quinolines

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ABSTRACT

Zinc(II) triflate catalyzed three-component coupling reactions of alkynes, amines and aldehydes leading to the formation of aryl/alkyl substituted quinolines has been described. Notably, the reaction proceeded efficiently and effectively without the use of ligand, co-catalyst, solvent or inert atmosphere. This robust solvent-free process operates under an ambient atmosphere and avoids the use of precious metals, hazardous solvents and harsh reaction conditions. This atom economic process eliminates the waste generated in the multistep synthesis. Additionally, a pseudo two-component Povarov reaction of amines and butanal proceeds under the same green conditions enabling the formation of 2,3-dialkyl quinolines.

1. Introduction

Quinolines (**Figure 1**) continue to draw attention from the scientific community due to their prevalence in natural products and widespread applications in pharmaceuticals as antimalarial, anti-inflammatory, antineoplastic, antifungal, anti-infective and analgesic agents.[1-5] They also find application as luminescent materials, tunable ligands and in the formation of conjugated molecules or polymers with enhanced optoelectronic properties.[6-10]

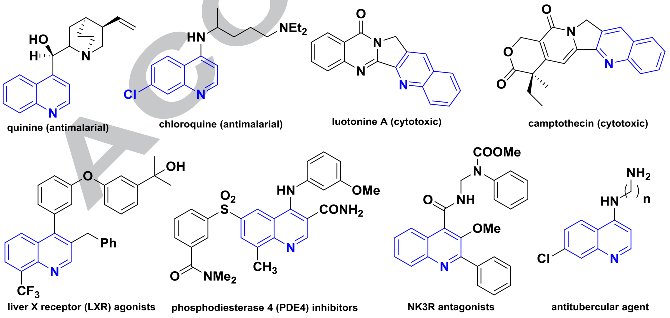
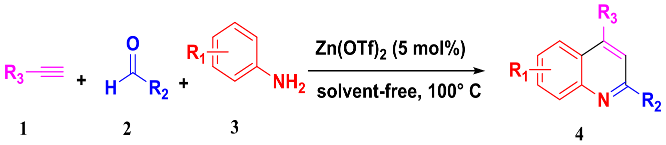


Figure 1. Substituted quinolines with bioactive indicators

The first formal synthesis by Skraup,[11] followed by its several synthetic variations like Friedlander,[12] Doebner-Von Miller,[13-15] Pfitzinger,[16] Conrad-Limpach and Combes synthesis[17-19] dominates the development taken place in the arena of quinoline synthesis. These methods however, do not provide adequate diversity and substitution for the structural decoration of the quinoline ring. Metal-catalyzed coupling cyclizations of appropriate precursors offer a better alternative in terms of both efficacy and structural diversity.[20-24] Over the past few decades, metal-catalyzed reactions of terminal alkynes have been developed as a versatile tool to construct the unique structural unit *via* activation of a terminal alkyne C-H bond and complexation of C-C multiple bonds to facilitate C-N and C-C bond-formation.[25-30] A highly efficient three-component coupling reaction of aldehydes, alkynes and amines using late transition-metal catalysts have been used for affording propargyl amines, which are key intermediates for the construction of quinolines.[31-38] In view of development of efficient synthesis of functionalized/annulated quinolines many efforts have been put forward by synthetic organic chemists. Recent efforts for the synthesis of substituted quinolines include oxidative coupling of 2-aminoaryl ketones with alkynes using $InCl_3$,[39] combination of $(PPh)_3AuCl$ with AgOTf,[40] and $PdBr_2$ with AcOH[41]. Zhang and coworker have reported oxidative coupling of acetylenic carbonyls with anilines using AgOTf.[42] Additionally, Zhu and coworkers have reported a silver based system for the synthesis of quinolines through an oxidative coupling/cyclization of *N*-arylimines and alkynes.[43] Furthermore, synthesis of quinolines in a single synthetic operation *via* a multi-component reaction (MCR) of primary aromatic amine, aldehyde and alkyne (A^3 synthesis) has also been reported using $AuCl_3/CuBr$,[21] Yb(III),[44] Fe(III),[45-47] Cu(II),[48] and Zn^{II}/Cu^{I} [49] catalytic system. Nevertheless, these synthetic approaches suffer from the need of high temperatures or harsh reaction conditions, low yields, use of hazardous and often expensive catalysts.

Zinc catalyzed reactions have emerged as a sustainable alternative to use of more precious or toxic transition metals.[50-53] Zinc triflate ($Zn(OTf)_2$) is an inexpensive catalyst having thermal stability, ease of availability, low cost and addresses problem associated with the toxicity of metals up to a great extent. $Zn(OTf)_2$ has been used for *in situ* generation of a reactive acetylide and its subsequent addition to C=O[54-56]/

nitrones[57-59]/ enones[60] to constitute propargyl derivatives. In continuation to our efforts on exploring the catalytic potential of $Zn(OTf)_2$ for C-H activation and C-C / C-N bond formation,[61] we herein present $Zn(OTf)_2$-mediated efficient and expeditious multi-component synthesis of 2,4-disubstituted quinolines (**Scheme 1**).



Scheme 1. $Zn(OTf)_2$-mediated synthesis of 2,4-disubstituted quinolines

Initially, catalytic efficacy of various Zn-salts for the synthesis of quinolines via A^3-coupling has been screened. Our study commenced with the model reaction of phenylacetylene, benzaldehyde and aniline as a substrates and toluene as a solvent. The output of the study is summarized in Table 1.

Table 1. Screening of zinc catalysts for the synthesis of quinoline **4a**[a]

Entry	Zn source (mol %)	Solvent/ Temp	Time (h)	Yield (%)[b]
1	$ZnCl_2$ (10)	toluene/reflux	20	Trace
2	$ZnBr_2$ (10)	toluene/reflux	20	Trace
3	$ZnSO_4$ (10)	toluene/reflux	20	Trace
4	Zn-dust (10)	toluene/reflux	20	Trace
5	ZnO (10)	toluene/reflux	20	45
6	$Zn(OAc)_2$ (10)	toluene/reflux	20	50
7	$Zn(CF_3COO)_2$	toluene/reflux	20	54
8	$Zn(OTf)_2$ (10)	toluene/reflux	20	70
9	$Zn(OTf)_2$ (10)	acetonitrile/reflux	20	46
10	$Zn(OTf)_2$ (10)	ethanol/reflux	20	30
11	$Zn(OTf)_2$ (10)	THF/reflux	20	35
12	$Zn(OTf)_2$ (10)	solvent free/ 100 °C	5	75
13	$Zn(OTf)_2$ (10)	solvent free/ 100 °C	5	84[c]
14	$Zn(OTf)_2$ (5)	solvent free/ 100 °C	5	84[c]
15	$Zn(OTf)_2$ (5)	solvent free / 90 °C	5	76[c]
16	$Zn(OTf)_2$ (5)	solvent free / 80 °C	5	72[c]
17	$Zn(OTf)_2$ (3)	solvent free / 100 °C	9	55[c]

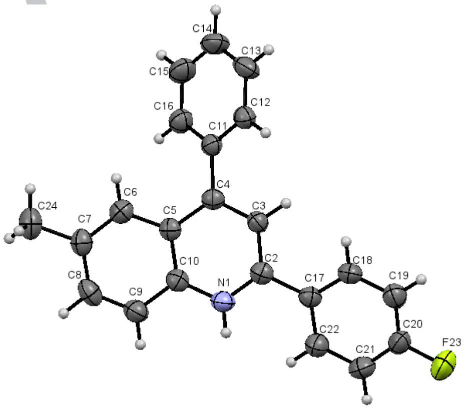
[a] 1.0 mmol benzaldehyde, 1.1 mmol aniline and 1.5 mmol phenylacetylene

[b] Isolated yields

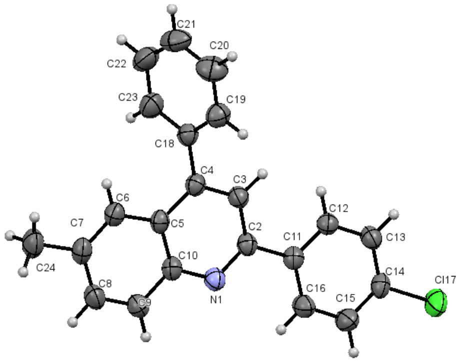
[c] MS 4 Å (30 mg) was added

To our delight, the three-component coupling reaction proceeded smoothly in the presence of 10 mol% of $Zn(OTf)_2$ and generated quinoline in 70% yield (Table 1, entry 7). The other zinc catalysts, based on metal salts containing non-nucleophilic anions and nucleophilic anions, displayed poor activity for this reaction under the same conditions (Table 1, entries 1-6). Inspired from this result, we next screened the effect of solvent on the reaction by using 10 mol% of $Zn(OTf)_2$ as a catalyst. The choice of solvent did influence the activity of the catalytic system; the solvent-free conditions (Table 1, entry 11) exhibit the best yield and reaction rate than that in solvents. Under solvent-free conditions synthesis of quinoline was achieved with 75% yield at 100 °C in 5 h. Use of solvents such as toluene, ethanol, acetonitrile and tetrahydrofuran (THF) reduced yield and lengthen the reaction time (Table 1, entries 8-10). As the reaction involves the removal of water molecule as a by-product, the addition of moleculer sieves 4 Å (MS 4Å) improved the outcome of the reaction (Table 1, entries 12). With these results in hand, we next studied the effect of catalyst loading and temperature on the outcome of the reaction. Lowering the catalyst loading up to 5 mol% did not alter the outcome; however further lowering resulted in decreased yield (Table 1, entry 16). Decreasing the reaction temperature using 5 mol% of catalyst loading decreased the yield of the product (Table 1, entries 15-16). Thus, the most optimal reaction condition for the formation of **4a** was established (Table 1, entry 13).

With this expeditious and efficient protocol in hand, its scope and generality was examined (Table 2). Aromatic aldehydes with either an electron-donating group or an electron-withdrawing group entered the reaction smoothly to give the corresponding quinolines in excellent yield. Aromatic aldehyde bearing 4-F, 4-Cl, 4-isopropyl, 3-Br, 4-methoxy and 4-methyl substituents were efficiently converted into quinolines. Subsequently, we also investigated the scope of aromatic amines such as aniline, p-toluidine, 4-nitroaniline, 4-chloroanilines, p-anisidine and 3-chloroaniline proved to be a good substrate for this transformation and the corresponding quinoline were furnished in moderate to good yield. Terminal alkynes such as phenyl acetylene and 1-octyne participated efficiently in the reaction affording corresponding 2,4-disubstituted quinolines. The structure of compound 4f and 4i were confirmed unequivocally by X-ray crystallographic analysis (Figure 2).



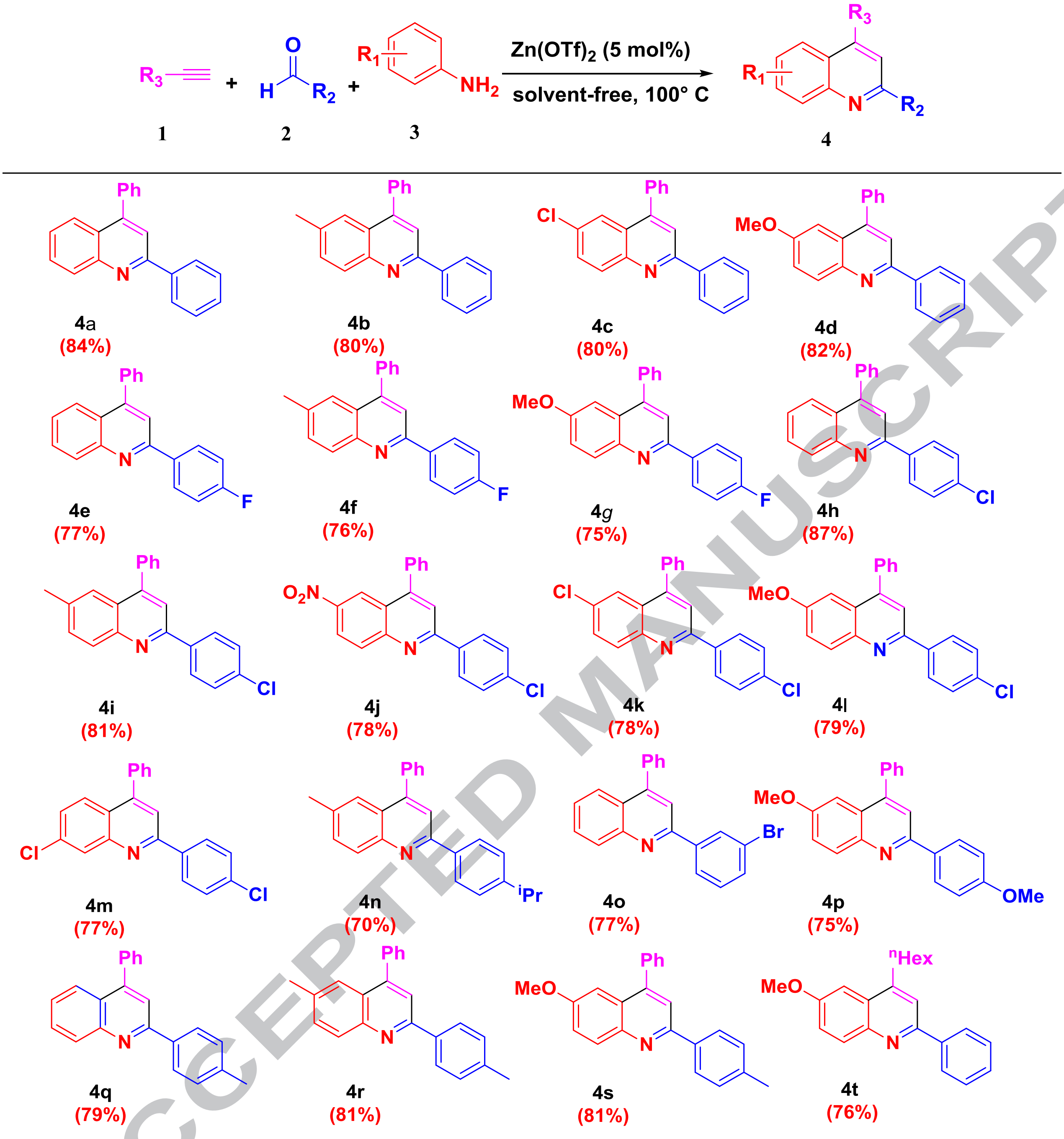
4f (CCDC 1483118)



4i (CCDC 1483117)

Figure 2. ORTEP diagram of **4f** and **4i** with displacement ellipsoids drawn at the 50% probability level

Table 2. Zn(OTf)$_2$ catalyzed synthesis of 2,4-diaryl quinolines[a,b]



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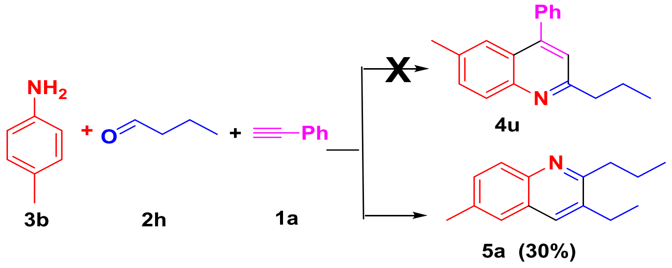
[a] 1.0 mmol aldehydes, 1.1 mmol amines and 1.5 mmol phenylacetylene

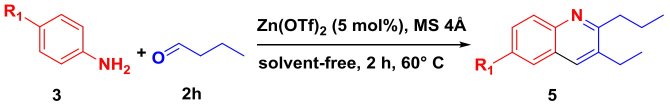
[b] Isolated yields

Considering the foresaid results we speculate that aliphatic aldehydes without α-hydrogen(s) also give similar results. Literature survey reveals that 2-alkyl-4-substituted quinolines are difficult to access. Even Friedlander annulation of 2-amino benzaldehydes with alkyl ketones can result in mixtures of 2-alkyl versus 2,3-dialkyl quinolines due to non-regioselective enolate formation.[62] Thus, access to alkyl-substituted quinolines is usually achieved by alkylation of quinoline as a starting material or by multi-step procedures involving nitroarene reduction.[3, 63] We next contemplate to test suitability of enolizable aliphatic aldehydes such as n-butanal. With a view to prepare 6-methyl-4-phenyl-2-propylquinoline (**4u**), we attempted a reaction of *p*-toluidine, phenyl acetylene and n-butanal. Unfortunately, we could not get **4u**, instead we got 3-ethyl-6-methyl-2-propylquinoline (**5a**) with only 30% yield (**Scheme 2**). This observation was in-line with the previous report by Larsen and Meyet.[48] Aliphatic aldehydes are rarely reported in A^3 coupling for syntheses of quinolines as α-hydrogens in enolizable aldehydes are more acidic than terminal hydrogen of alkynes. Thus, alkyl aldehydes enolize and produce side-products *via* Povarov reactions. α-Deprotonation is kinetically favored for less-hindered aldehydes such as n-butyraldehyde without branching at α-position to the carbonyl and thus favors Povarov reaction to obtain 2,3-dialkyl quinolines **5a**. [48, 64, 65]



Scheme 2. Reaction condition: Zn(OTf)$_2$ (5 mol%), solvent free, 100 °C

So, we attempted the reaction of aromatic amine with 2 equivalents of n-butanal. The reaction proceeded to completion within 2h at 60 °C to afford 2,3-dialkyl quinolines in good yields **(Scheme 3)**.



	R_1	Yield (%)
5a	$-CH_3$	62
5b	$-OCH_3$	64

Scheme 3. $Zn(OTf)_2$ catalyzed synthesis of 2,3-dialkyl quinolines

Multi-component synthesis of structurally diverse quinolines using aldehydes, amine and alkyne coupling (A^3 coupling) has been achieved using $Zn(OTf)_2$ as a catalyst. This method for the multi-component synthesis of quinolines maximizes diversity by the direct use of commercially available starting materials. 2-Substituted-4-alkyl quinoline was also accessed by using 1-octyne. Under similar catalytic and reaction condition substituted aniline and n-butanal produces 2,3-dialkyl quinolines *via* a pseudo two-component Povarov reaction. This robust solvent-free process operates under an ambient atmosphere and avoids the use of precious metals, hazardous solvents and harsh reaction conditions. This atom economic process eliminates the waste generated in the multi-step synthesis. Both electron -rich or -poor amines and aldehydes participates efficiently in this $Zn(OTf)_2$ catalyzed giving variedly substituted quinolines. Use of economical and readily available $Zn(OTf)_2$ offers sustainable alternative to expensive and toxic transition metals. Being three components reaction, structural decoration of quinoline ring can be achieved by choosing appropriately substituted starting aldehyde, amine and alkyne. Variation in the substituent's available on quinoline scaffolds open up the gate way to tune its properties including solubility, luminescence, and biological activity.

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Supplementary Material

Electronic Supporting Information (ESI) for this article, containing detailed procedures and spectral/analytical data for synthesized compounds is available online at

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Zn(OTf)$_2$-mediated C-H activation: an expeditious and solvent-free synthesis of aryl/alkyl substituted quinolines

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Highlights

- Zn(OTf)$_2$-mediated C-H activation
- Synthesis of aryl/alkyl substituted quinolines
- Less accessible alkyl substituted quinolone can be prepared
- Pseudo three-component Povarov reaction of anilines and butanal afforded 2,3-dialkyl quinolines.
- Robust solvent-free process avoids the use of precious metals and hazardous solvents