**ABSTRACT:** An unprecedented CuBr–ZnI₂ combo-catalyzed mild Cu¹→Cu³⁺ switching activation of sp² C–H of highly electron-rich arenes is reported. Anilines, aldehydes, and terminal alkynes were rapidly coupled together at ambient temperature to construct a ubiquitous quinoline framework through cyclization of the C≡C bond. This smart solvent-free strategy was exploited for the direct synthesis of valuable 4-substituted, 2,4-disubstituted, and thermally labile sugar-based chiral quinolines in good yields. In contrast to the frequently used imine–alkyne cyclization reaction, this uncommonly mild Cu¹→Cu³⁺ combo-catalysis for a rapid three-component cyclization is expected to proceed through the formation of a flexible propargyl amine intermediate, which provides a Cu¹-procatalyst for rapid sp² C–H activation with cyclization involving transient Cu³⁺ species. The in situ generation of transient Cu³⁺ species was confirmed through online ultraviolet–visible spectroscopy (UV–vis), electrospray ionization mass spectrometry (ESI-MS), and X-ray photoelectron spectroscopy (XPS) analyses.
based chiral quinolines will be a valuable addition to the existing modern synthetic approaches to quinolines.

The synthesis of achiral quinolines, such as transition metal-catalyzed cyclization\(^7\) and alkyne–amine addition reactions,\(^5\) is well-documented in the literature.\(^6\) However, instead of making unstable imines through cumbersome approaches, development of an in situ coupling strategy using amines, aldehydes, and terminal alkynes and easy metallation to the ortho-sp\(^2\) C–H through coordination of the triple bond of the in situ-generated flexible propargyl amine (I, Scheme 1)

![Scheme 1. Combo-Catalysis for Mild sp\(^2\) C–H-Activated Cyclization](image)

moiety will be a valuable addition to the existing methods for the synthesis of chiral quinolines directly attached to sugars under mild conditions. In this context, the combination of two catalysts will be more useful for the direct N–C and C–C coupling of an aldehyde–carbon (3) with an amine (1) and a terminal alkyne (2). Combo-catalysis is an emerging area, and we\(^6\) have established it as a powerful tool in modern organic synthesis. For instance, the diverse cyclization reactions catalyzed by VO(acac)\(_2\)–CeCl\(_3\), Ni(0)–Cu(I), and Mo\(_{\text{V}}\)–CeCl\(_3\) developed by our group provide easy access to a wide range of heterocycles.\(^6\) CuBr–ZnI\(_2\)-mediated N–N/C–N coupling for oxidative cyclization,\(^6\) Pd\(^2\)–Ru\(^0\)-tuned Suzuki cross-coupling reactions,\(^6\) AuCl\(_3\)–AgSbF\(_6\)–tuned C–C coupled aromatization,\(^6\) Ti–Cr-catalyzed polymerization reactions,\(^7\) and [IrCuCl\(_2\)]\(_2\)–AgNTf\(_2\)-guided amination\(^7\) through sp\(^2\) C–H activation are very useful in the synthesis of combo-catalysis functionalized and sugar-based optically pure quinolines (4) under mild reaction conditions, with a significantly improved reaction rate, yield, and selectivity (without 5). Interestingly, Cu(I/II) compounds\(^7\) were reported as active catalysts for the coupling of secondary aliphatic amines with aldehydes and alkynes with the respective propargyl amines.

## RESULTS AND DISCUSSION

After several unsuccessful attempts using potential combo-catalysts\(^6\) (entries 1–8, Table 1), we used ZnI\(_2\)–CuBr (10 mol % each) for the three-component reaction among 2-bromoaniline (1a, 1 mmol), 4-ethyltoluene (2a, 1 mmol), and paraformaldehyde (3a, 1.2 mmol) in different solvents (entries 9–11, Table 1) to achieve the 4-substituted quinoline 4a at room temperature in 60–65% yield. Gratifyingly, the yield (81%) and the reaction rate (30 min) significantly improved under the solvent-free conditions (entry 12). The combo-catalysis selectively produced 4a. The possible regioisomer 5a was not detected. Catalyst loading was optimized [CuBr (7 mol %)–ZnI\(_2\) (9 mol %)] under solvent-free conditions. To understand the role of the counter anion of the combo-catalyst, several experiments were performed with different Zn\(_{\text{II}}\)–Cu\(_{\text{I}}\)-combinations (entries 13–17) under similar reaction conditions, but the reactions were not efficient. Interestingly, when using a higher and more stable oxidation state of copper in CuBr\(_2\), the reaction was unsuccessful (entry 18). We investigated the reaction with the commonly used sp\(^2\) C–H activating Pd\(^{\text{II}}\) and Ru\(^{\text{II}}\) as well as several other prospective catalysts (entries 19–25), and the results were not encouraging. Interestingly, MoO(acac)\(_2\) was found to be the alternative to ZnI\(_2\) (entry 26). However, ZnI\(_2\) was our cocatalyst of choice because of its low cost and easy availability. The reaction with the nonmetallic Lewis acid cum oxidant PhIO\(^7\) was unsuccessful because of the complexation and/or oxidation of the aromatic amine (1a, entry 27). The reaction was completely blocked in an N\(_2\) atmosphere, which confirmed the need for aerial oxygen in the construction of quinolines (4a, entry 28). However, the yield did not improve when the reaction was performed in an oxygen atmosphere (entry 29).

Tolerance of various functionalities was successfully screened for this new method (Scheme 2) through the synthesis of a large number of valuable 4-substituted quinolines\(^6\) bearing both unsubstituted and substituted aromatic residues (Table 2), a heterocycle (4b, entry 2), a biphenyl system (4j, entry 10), and a naphthalene moiety (4k, entry 11). Essentially, there was no limitation regarding the substrate choice because the reactions occurred smoothly to produce their respective quinolines on using aromatic amines bearing halogen (1a–d, entries 1–4 and 9–17), alkyl (1e–g and i, entries 5–7 and 18), and alkoxy (1h, entry 8) groups. We initially concentrated on using formaldehyde to derive less substituted quinolines, which found novel applications. Unsubstituted aniline was also effective in the robust cyclization reaction (1j, entry 19). Aryl alkynes bearing alkyl, aryl, methoxy, and thiophenyl (2a–g) groups were tolerated. An aliphatic alkyne also responded well under the developed reaction conditions (2h, entry 12). In general, these simple, mild, and solvent-free products were fully characterized using spectroscopic analyses (Supporting Information). The structure of 4a was confirmed using single crystal X-ray diffraction analyses (Scheme 2),\(^6\) and that of 4h

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**Figure 1.** 2-Substituted (A–D) and 2,3-fused (E) bioactive sugar-based quinolines.
was confirmed through a comparison with known spectroscopic data.

The widespread bioactivity and pharmaceutical application of the 2,4-disubstituted quinoline derivatives 84−89 led us to investigate their synthesis using the simple combo-catalysis strategy. To our delight, the strategy was equally applicable for aldehydes bearing aliphatic (3b, entry 1, Table 3) as well as aromatic (3c−e, entries 2−4) residues to produce 2,4-disubstituted quinolines (4t−w).90 This mild and solvent-free approach was quite fast (2−3 h) and had good yields (63−74%). Moreover, all of the synthesized products were fully characterized using relevant spectroscopic analyses (Supporting Information).

Next, we turned our attention to expanding the scope of the mild tandem cyclization process to achieve valuable sugar-based chiral quinolines. Gratifyingly, the use of glyceraldehydes produced the desired optically pure compound 7a (eq 1, Scheme 3) under the developed reaction conditions (entry 12, Table 1). To understand the versatility of the asymmetric approach, we used different pentose sugar aldehydes (6b,c,e; eqs...
Table 2. Synthesized Quinolines and Reaction Data

| Entry | Amine (1) | Alkyne (2) | Aldehyde (3) | Product (4) | Time (min) | Yield(%) |
|-------|-----------|------------|--------------|-------------|------------|----------|
| 1     | Br        | H₂C        | (HCHO)₂     | Br⁻         | 30         | 4a, 81   |
| 2     | H₃C       | S⁻         | 3a           | Br⁻         | 35         | 4b, 80   |
| 3     | Br        | H₂C        | 3a           | N⁻           | 40         | 4c, 78   |
| 4     | Cl⁻       | NH₂        | 2c           | Br⁻         | 45         | 4d, 72   |
| 5     | H₃C       | NH₂        | 2c           | N⁻           | 55         | 4c, 67   |
| 6     | H₃C       | CH₃        | 2a           | N⁻           | 50         | 4f, 67   |
| 7     | H₃C       | NH₃        | 2d           | N⁻           | 35         | 4g, 80   |
| 8     | H₃CO      | NH₃        | 2c           | OCH₃⁻       | 40         | 4h, 67   |
| 9     | 1a        | H₃C        | 2e           | Br⁻         | 25         | 4i, 77   |
| 10    | 1a        | 2f         | 3a           | Br⁻         | 35         | 4j, 73   |
| 11    | 1a        | H₃CO       | 2g           | Br⁻         | 30         | 4k, 72   |
| 12    | 1a        | CH₃O       | 2h           | H₃C⁻        | 60         | 4l, 65   |
| 13    | 1a        | 2e         | 3a           | Br⁻         | 30         | 4m, 75   |
| 14    | 1a        | 2d         | 3a           | OCH₃⁻       | 25         | 4n, 70   |
| 15    | 1b        | 2c         | 3a           | OCH₃⁻       | 25         | 4o, 71   |
Table 2. continued

| Entry | Amine (1) | Alkyne (2) | Aldehyde (3) | Product (4) | Time (min) | Yield (%) |
|-------|-----------|------------|--------------|-------------|------------|-----------|
| 16    | 1b        | 2e         | 3a           |             | 25         | 4p, 70    |
| 17    | 1d        | 2e         | 3a           |             | 45         | 4q, 62    |
| 18    | CH₃NH₂    | 2e         | 3a           |             | 55         | 4r, 67    |
| 19    | NH₂       | 2a         | 3a           |             | 20         | 4s, 78    |

Table 3. List of 2,4-Disubstituted Quinoline Derivatives

| Entry | Amine (1) | Alkyne (2) | Aldehyde (3) | Product (4) | Time (min) | Yield (%) |
|-------|-----------|------------|--------------|-------------|------------|-----------|
| 1     | 1a        | 2a         | 3b           | 3b          | 120        | 4t, 70    |
| 2     | 1e        | 2a         | 3c           |             | 120        | 4u, 66    |
| 3     | 1b        | 2c         | 3d           |             | 180        | 4v, 63    |
| 4     | 1b        | 2e         | 3e           |             | 120        | 4w, 74    |

**ZnI₂: 9 mol % and CuBr: 7 mol %.

2 and 3), which produced the desired products 7b−d in 1.5−2.0 h in good yield (63−70%). The scope of the mild combo-catalysis was successfully established for the direct synthesis of functionalized chiral quinolines bearing triose, pentose, and hexose sugar moieties (7a−f, eqs 1−4) with a rapid reaction rate (1.5−2.0 h) and good yield (63−72%). The optical purity of the quinolines was verified on a semipreparative chiral HPLC column and by measuring the optical rotation.

Ultraviolet−visible (UV−vis) spectroscopy and X-ray photoelectron spectroscopy (XPS) of the new combo-catalysis process were performed to understand the reaction. A strong absorption band of the reaction mixture (entry 1, Table 2) in dry methanol appeared at 529 nm ($\lambda_{\text{max}}$) in the UV−vis spectrum (Figure 2), which is very close to the literature value for the [aryl-CuIII−Br]Br complex reported by Ribas, Stahl, and colleagues. The XPS spectrum (Figure 3) of the reaction mixture showed the presence of two symbolic peaks at 931.9 and 952.08 eV for CuI and 933.9 and 953.8 eV for transient CuIII.

To establish the reaction mechanism, we conducted two separate control experiments (4a, entry 1, Table 2) with CuBr and ZnI₂, and the reaction did not occur. The cyclization reaction was unsuccessful upon using the imine 2-BrC₆H₄−N−CH₂ and the alkyne 2a under the reaction conditions.
(entry 12, Table 1), which indicates that the reaction progressed without the formation of an imine intermediate. On the basis of the UV−vis and XPS data, controlled experiments, and literature reports, we propose that CuI first activates the terminal C−H of the alkyne to produce R−C≡C−Cu (II, Scheme 4). This observation is also supported by the fact that the reaction was completely blocked upon using internal alkynes. The C−C and C−N bond formation between aldehyde (3), aromatic amine (1), and II with ZnI2 may give rise to propargyl amine intermediate III. The intermediate III bearing the flexible C≡C bond allows CuI to easily activate the aromatic C−H and π-bonds for oxidative C−H insertion with C−C coupling to aryI−CuIII-based intermediate (IV). The
Scheme 4. Combo-Catalysis Cycle

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generation of the transient CuIII-species was confirmed using UV–vis (Figure 2), XPS (Figure 3), and electrospray ionization mass spectrometry (ESI-MS) (for IV; $\epsilon_{\lambda}$ 441.8867 [M + H], appearance of multiple peaks due to the presence of the isotopes of the two Br atoms) analyses of the sample taken from the ongoing reaction (4a, entry 1, Table 2). The seven-membered organometallic compound IV immediately transformed into the desired product 4 through the reductive elimination of CuI and aromatization through the formation of the transient intermediate V in the presence of molecular oxygen and CuX.95 The control experiments for the amine–aldehyde–alkyne coupled cyclization (entries 20 and 21; Table 1) were unsuccessful in the absence of air or oxygen. However, the active role of oxygen during the transformation of CuI to reactive CuIII species may not be avoided.

CONCLUSIONS

In conclusion, a ZnII/CuI combo-catalyzed, solvent-free rapid general synthesis of quinolines was demonstrated through an uncommonly mild, sp2 C–H activation and functionalization with the aid of a Cu(I)-catalyzed sp2 C–H activation and functionalization with CuII (1a, 1.0 mmol), alkyne (2a, 1.0 mmol), and paraformaldehyde (3a, 1.25 mmol, 40 mg) produced 8-bromo-4-p-tolylquinoline (4a) in 81% yield (240 mg, 0.81 mmol) after purification using column chromatography on silica gel (60–120 mesh) with ethyl acetate–petroleum ether (1:25, v/v) as the eluent. The structure of the product (4a) was confirmed using single-crystal X-ray diffractometry. The synthesized quinolines (4a–w) were characterized using NMR ($^1$H and $^{13}$C), FT-IR, melting point (solid compounds only), and mass spectral (HR-MS) analyses.

Characterization Data of Substituted Quinolines (4a–w).

Bromo-6-methyl-4-(thiophen-3-yl)quinoline (4b). Yield: 81% (240 mg, 0.81 mmol). Characteristic: yellow solid. Melting point: 97–98 °C. $^1$H NMR (300 MHz, CDCl3): $\delta$ 8.89 (1H, d, $J$ = 4.5 Hz), 7.99 (1H, d, $J$ = 7.5 Hz), 7.87 (1H, d, $J$ = 8.5 Hz), 7.07–7.33 (6H, m), 2.38 (3H, s). $^{13}$C NMR (75 MHz, CDCl3): 149.9, 149.3, 144.7, 138.3, 134.0, 132.8, 128.9, 128.8, 127.8, 126.3, 125.6, 124.2, 121.6, 20.7. FT-IR (KBr, cm$^{-1}$): 1604, 1589, 1575, 1484, 1453, 1398, 1383, 783, 754, 731, 709. HR-MS (m/z) for C$_{12}$H$_{13}$BrN (M$^+$): calculated 297.0153, found 297.0155 (one of the major peaks).

Bromo-4-p-tolylquinoline (4a). Yield: 81% (240 mg, 0.81 mmol). Characteristic: yellow solid. Melting point: 97–98 °C. $^1$H NMR (300 MHz, CDCl3): $\delta$ 8.86–8.89 (1H, m), 7.84–7.85 (1H, m), 7.69–7.71 (1H, m), 7.42–7.46 (2H, m), 7.31 (1H, t, $J$ = 4.8 Hz), 7.17–7.24 (1H, m), 2.40 (3H, s). $^{13}$C NMR (75 MHz, CDCl3): $\delta$ 149.7, 144.1, 143.3, 138.1, 137.2, 135.2, 128.8, 128.0, 126.4, 125.1, 124.7, 124.6, 122.0, 21.4. FT-IR (KBr, cm$^{-1}$): 1609, 1580, 1556, 1474, 1430, 1360, 1019, 831, 686. HR-MS (m/z)
(m/z) for C14H13NO (M+): calculated 235.0997, found 235.0996.

8-Bromo-4-m-tolyquinoline (4l). Yield: 77% (230 mg, 0.77 mmol). Characteristic: yellow solid. Melting point: 97–98 °C.

8-Bromo-4-(methoxynaphthalen-2-yl)quinoline (4k). Yield: 72% (261 mg, 0.72 mmol). Characteristic: brown solid. Melting point: 148–149 °C.

8-Bromo-4-(o-tolylmethyl)quinoline (4l). Yield: 65% (212 mg, 0.65 mmol). Characteristic: brown solid. Melting point: 78–79 °C.

8-Bromo-4-phenylquinoline (4m). Yield: 75% (212 mg, 0.75 mmol). Characteristic: brown solid. Melting point: 78–80 °C.

8-Bromo-4-(4-methoxyphenyl)quinoline (4n). Yield: 70% (220 mg, 0.70 mmol). Characteristic: brown solid. Melting point: 78–80 °C.
8-Bromo-6-methyl-4-phenylquinoline (4o). Yield: 71% (212 mg, 0.70 mmol). Characteristic: yellow solid. Melting point: 80°C. 1H NMR (300 MHz, CDCl3): δ 8.85 (1H, s), 3.18 (2H, m), 2.30 (2H, m), 2.30 (2H, m), 2.10, 1.20. FT-IR (neat, cm⁻¹): 3423, 2927, 2854, 1602, 1580, 1530, 1477, 1432, 1334, 1264, 1055, 867, 839, 735, 711. HR-MS (m/z) for C24H20N2O2: calculated 432.0473, found 432.0476 (one of the major peaks).

8-Bromo-2-(2-bromophenyl)-6-methyl-4-phenylquinoline (4w). Yield: 74% (319 mg, 0.74 mmol). Characteristic: colorless solid. Melting point: 121–122°C. 1H NMR (300 MHz, CDCl3): δ 8.85 (1H, s), 8.38 (1H, dd, J = 7.8 Hz, 1H, d, J = 7.2 Hz), 7.08–8.13 (1H, m), 7.95 (1H, dd, J = 7.5, 1.8 Hz), 7.74–7.82 (2H, m), 7.60–7.66 (1H, m), 7.47 (1H, s), 7.14–7.25 (2H, m), 7.04 (1H, d, J = 8.1 Hz), 2.35 (3H, s), 2.16 (3H, s). 13C NMR (75 MHz, CDCl3): δ 159.5, 157.5, 147.6, 140.1, 137.9, 137.2, 135.3, 135.2, 133.4, 131.3, 130.0, 129.6, 128.6, 128.4, 127.7, 126.8, 125.3, 124.4, 123.9, 122.0, 21.4. FT-IR (neat, cm⁻¹): 1761, 1587, 1539, 1470, 1433, 1356, 827, 756, 702. HR-MS (m/z) for C24H20BrN2: calculated 450.9571, found 450.9574 (one of the major peaks).

Characterization Data of Chiral Sugar-Based Quinoline Line Derivatives (7a–f). Synthesis of compound 7 was performed according to the procedure for compound 4.

(R)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-6-methoxy-4-phenylquinoline (7a). Yield: 65% (218.0 mg, 0.65 mmol). Characteristic: black oil. [α]D 25 = -84.0 (c 0.18, CHCl3). 1H NMR (300 MHz, CDCl3): δ 8.27 (1H, d, J = 9.3 Hz), 7.64 (1H, s), 7.56 (4H, s), 7.46 (1H, d, J = 8.4 Hz), 7.26 (1H, d, J = 1.5 Hz), 7.22 (1H, s), 4.11 (1H, dd, J = 16.0, 7.8 Hz), 3.80 (3H, s), 3.27 (1H, dd, J = 12.0, 3.6 Hz), 3.16 (1H, dd, J = 12.0, 7.2 Hz), 1.58 (3H, s), 1.52 (3H, s). 13C NMR (75 MHz, CDCl3): δ 158.5, 156.4, 152.6, 141.7, 137.6, 129.1, 128.9, 128.8, 128.4, 127.5, 123.5, 121.3, 125.1, 118.7, 110.8, 104.1, 70.5, 67.2, 55.7, 26.8, 26.4. FT-IR (neat, cm⁻¹): 1713, 1627, 1589, 1496, 1378, 1256, 1210, 1163, 1072, 883, 836, 758, 707. HR-MS (m/z) for C24H20N2O2: calculated 432.0473, found 432.0476 (one of the major peaks).
1H, δ = 7.16 (3H, m), 6.83 (2H, d, J = 7.2 Hz), 6.19 (1H, d, J = 3.0 Hz), 5.72 (1H, d, J = 2.7 Hz), 4.75 (1H, d, J = 12.6 Hz), 4.55–4.58 (1H, m), 4.41 (1H, d, J = 11.6 Hz), 4.19 (1H, d, J = 11.7 Hz), 2.64 (3H, s), 1.61 (3H, s), 1.39 (3H, s). 13C NMR (75 MHz, CDCl3): δ 158.4, 150.0, 149.7, 145.0, 138.8, 134.4, 132.9, 128.9, 128.8, 121.1, 125.4, 124.8, 121.4, 117.9, 112.2, 105.6, 84.1, 83.4, 78.5, 72.7, 26.8, 26.4, 21.2. FT-IR (neat, cm⁻¹): 1713, 1619, 1582, 1508, 1453, 1382, 1255, 1240, 1091, 1088, 967, 73.6, 71.0, 70.7, 55.3, 26.2, 25.9, 24.9, 24.2. FT-IR (neat, cm⁻¹): 1713, 1622, 1593, 1560, 1493, 1381, 1255, 1214, 1166, 1068, 1012, 889, 833, 760. HR-MS (m/z) for C28H26BrNO6 (M⁺): calculated 643.994, found 643.992.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.6b00185.

Detailed experimental procedures, XRD, spectroscopic data, and spectra (PDF)

Crystallographic information (CIF)

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Notes
The authors declare no competing financial interest.

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