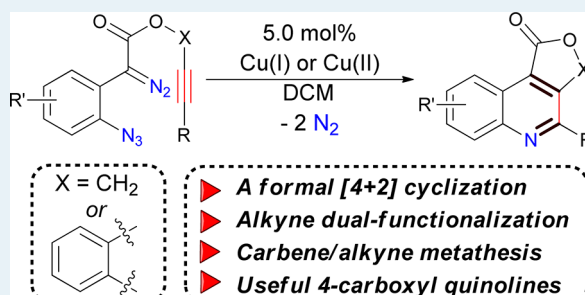


Dual-Functionalization of Alkynes via Copper-Catalyzed Carbene/Alkyne Metathesis: A Direct Access to the 4-Carboxyl Quinolines

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Supporting Information

ABSTRACT: A copper-catalyzed novel carbene/alkyne metathesis cascade reaction with alkyne-tethered diazo compounds is described. The whole transformation features a dual-functionalization of alkyne to install one C=N and one C=C bond on each carbon with azide and diazo groups, respectively, in one reaction, which represents a practical synthetic alternative to the multisubstituted 4-carboxyl quinoline derivatives and with most of them in high to excellent yields.



KEYWORDS: diazo compound, azide, alkyne functionalization, carbene/alkyne metathesis, cascade reaction, quinoline

Quinolines are an important class of heterocyclic motifs and are found in many natural products, pharmaceuticals, and agrochemicals.¹ During the last few decades, efforts have been made to develop the synthetic methods that access quinoline derivatives with structural diversity,² either by aromatic ring formation³ or ring decoration.^{2a,b} Among these approaches, straightforward approaches to the multisubstituted 4-carboxyl quinoline derivatives are rare.⁴ In contrast, many of these compounds show broad bioactivities (Figure 1), including compounds A, which are reported as potential antimalarial and cytotoxic agents;⁵ Brequinar (B) is an inhibitor of human dihydroorotate dehydrogenase (hDHODH);⁵ compound C shows potent antiviral activity;⁷ and D is a leading compound for treatment of arthritis.⁸ Herein, we disclose a generally efficient and practical approach to the multisubstituted 4-carboxyl quinoline derivatives with alkyne-tethered diazoacetates.

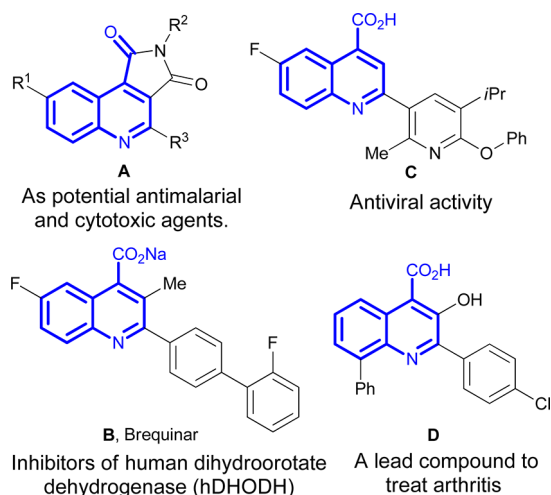
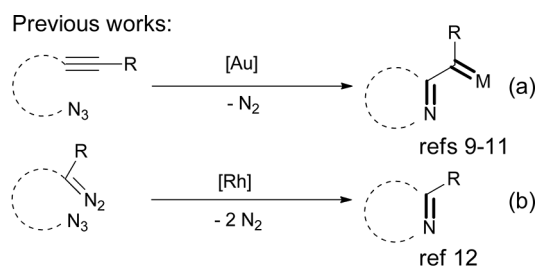


Figure 1. Examples of bioactive 4-carboxyl quinoline derivatives.

shows potent antiviral activity;⁷ and D is a leading compound for treatment of arthritis.⁸ Herein, we disclose a generally efficient and practical approach to the multisubstituted 4-carboxyl quinoline derivatives with alkyne-tethered diazoacetates.

Azide was used as a nucleophilic reagent in the gold-catalyzed alkyne transformations, and a α -imino gold carbene could be generated via gold-assisted N₂ exclusion (Scheme 1a).

Scheme 1. Catalytic C=N Bond Formation Reaction with Azides



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Pioneering work in this context was reported by Toste in the acetylenic Schmidt reaction to give the pyrrole rings with high regioselectivity,⁹ and recent progress in this transformation was demonstrated by Zhang,¹⁰ Gagosz,¹¹ and others^{9b–d} for the efficient construction of *N*-heterocycles. On the other hand, C=N bond formation reactions with azide was reported by Doyle and others¹² in their dirhodium-catalyzed metal carbene transformations,¹³ which formed the corresponding imines by releasing two molecules of N₂ (Scheme 1b). Inspired by these reports and our continuing interests in this field,¹⁴ a quinoline synthesis could be envisioned by introducing an azido group on the aryl ring of the alkyne-tethered diazoacetates (Scheme 1c). Moreover, this process featured a dual-functionalization process of alkynes to install one C=N and one C=C bond with azide and diazo groups respectively in one reaction.

At the very onset, dirhodium catalysts were tested for the carbene cascade reaction using **1a** as the model reactant at room temperature in dichloromethane, and although all the starting material was consumed in 30 min, the yields for the desired quinoline derivative **2a** were low to moderate (Table 1,

Table 1. Optimization of Reaction Conditions^a



entry	catalyst (X mol %)	yield ^b (%)
1	Rh ₂ (OAc) ₄ (1.0 mol %)	30
2	Rh ₂ (pfb) ₄ (1.0 mol %)	15
3	AuCl ₃ (5.0 mol %)	12
4	PdCl ₂ (PPh ₃) ₂ (5.0 mol %)	NR
5	RuCl ₂ (PPh ₃) ₃ (5.0 mol %)	NR
6	[Ir(cod)Cl] ₂ (5.0 mol %)	NR
7	Cu(OTf) ₂ (5.0 mol %)	50
8	Cu(CH ₃ CN) ₄ PF ₆ (5.0 mol %)	73
9	Cu(hfacac) ₂ (5.0 mol %)	86
10 ^c	Cu(hfacac) ₂ (5.0 mol %)	97
11 ^{c,d}	Cu(hfacac) ₂ (5.0 mol %)	93

^aReaction was carried out in 0.2 mmol scale in DCM (3.0 mL) at room temperature, and **1a** was added via syringe pump in 0.5 h.

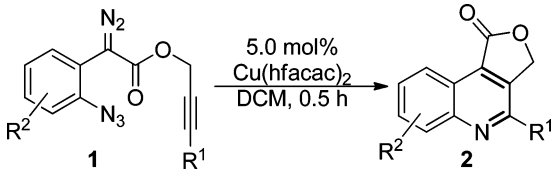
^bIsolated yield. ^cUnder Ar atmosphere. ^dReaction was carried out in 5.0 mmol scale. NR = no reaction.

entries 1 and 2). These results encouraged us in further investigation, and an extensive screening of various metal catalysts was performed, which were reported to be decomposition of diazo compounds to form the corresponding metal carbenes, including Au, Pd, Ru, Ir, and Cu (entries 3–11). Except for the Cu(I)- or Cu(II)-catalysts which improved the yield significantly (entries 7–11), all the other catalysts turned out to give inferior results, and most of them showed no activity at all (entries 4–6); Cu(hfacac)₂ proved to be the most effective catalyst for this cascade transformation (entry 10, 86% yield). In these copper-catalyzed reactions (entries 8–10), one minor byproduct was identified, which was a ketone generated via the oxidation of the initially formed metal carbene with oxygen. In this context, the best reaction conditions were established when the reaction was carried out under Ar atmosphere to give **2a** in 97% yield (entry 11). In addition, the diazo compound is relative stable and could be kept in the

refrigerator for a week without obvious decomposition, and the reaction could be performed in gram scale with the high yield maintained (entry 11).

With the optimized reaction conditions in hand, we turned our attention to the exploration of the reaction scope, and the results were listed in Table 2. All the substrates derived from

Table 2. Substrate Scope^a



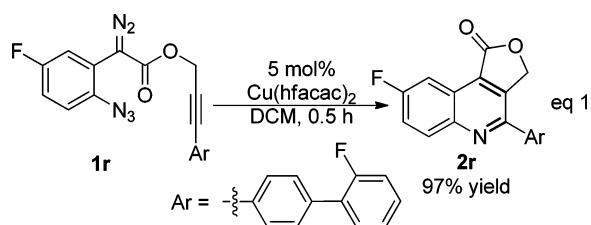
entry	R ¹ /R ² (1)	products 2	yield ^b (%)
1	C ₆ H ₅ /H (1a)	2a	97
2	4-FC ₆ H ₄ /H (1b)	2b	92
3	4-ClC ₆ H ₄ /H (1c)	2c	94
4	4-BrC ₆ H ₄ /H (1d)	2d	95
5	4-CF ₃ C ₆ H ₄ /H (1e)	2e	92
6	4-MeOOC ₆ H ₄ /H (1f)	2f	95
7	4-MeOC ₆ H ₄ /H (1g)	2g	96
8	3-MeC ₆ H ₄ /H (1h)	2h	87
9	2-MeC ₆ H ₄ /H (1i)	2i	90
10	2-BrC ₆ H ₄ /H (1j)	2j	86
11	2-ClC ₆ H ₄ /H (1k)	2k	90
12	1-naphthyl/H (1l)	2l	92
13	H/H (1m)	2m	49
14	Et/H (1n)	2n	32
15	Ph/5-Me (1o)	2o	96
16	Ph/5-F (1p)	2p	86
17	Ph/4-Cl (1q)	2q	77

^aReaction was carried out in 0.2 mmol scale with Cu(hfacac)₂ (5.0 mol %) in DCM (3.0 mL) at room temperature under Ar Atmosphere and **1** was added via syringe pump in 0.5 h. ^bIsolated yield.

arylacetylenes (R¹ = Ar) gave high to excellent yields, regardless of the position pattern or electronic property of the substitutions on the aryl ring (entries 1–12). Meanwhile, the alkyl-substituted ones were also tolerated in the reaction with moderate yields (entries 13 and 14), and about 30% of byproduct diene was detected (**2n'**, with both *Z* and *E* isomers, see SI for details), which was generated from carbene/alkyne metathesis followed by β -hydrogen shift. The influence of substitutions on the azidobenzenes had little effect on the outcome of the reaction, and the corresponding products **2o**–**2q** were all obtained in good to excellent yield (entries 15–17). Furthermore, the structure of these products was confirmed by single-crystal X-ray diffraction analysis of **2e**.¹⁵

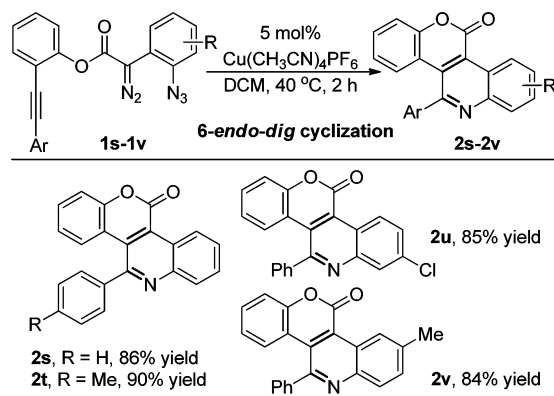
To extend the scope of the reaction, substrate **1r** was employed under the standard conditions to give the cyclized product **2r** in 97% yield, which is a potential intermediate for the Brequinar synthesis (Figure 1), which had all the substitutes on the aryl ring installed (eq 1).⁶

Further exploration of the substrates by switching the linker with a *ortho*-substituted phenol instead of methene did not make much difference on the reaction outcomes; however, simple modification in reaction conditions was necessary to ensure the high yields the reaction temperature was elevated to 40 °C and with Cu(I) as the catalyst. In this context, 6-*endo-dig* cyclization instead of 5-*endo-dig* cyclization occurred to form the six-membered ring in the carbene/alkyne metathesis



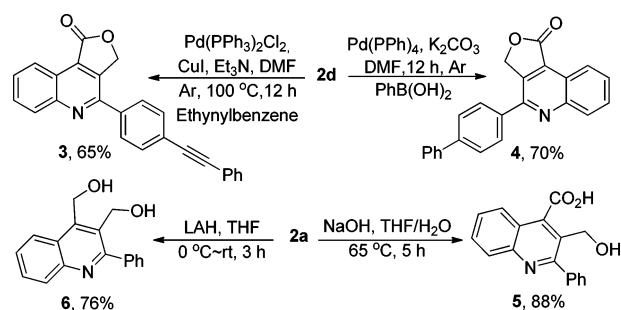
reaction, and the reactions afforded the tetracyclic products **2s–2v** in 84–90% yield (Scheme 2). The structure of these products was also confirmed by single-crystal X-ray diffraction analysis of **2s**.¹⁵

Scheme 2. Carbene Cascade Reaction for 6-endo-dig Cyclization



To demonstrate the synthetic utility of the current method, the cyclized products **2** were subjected to further transformations. The bromo-substituted product **2d** could be easily led to **3** or **4** via Sonogashira coupling reaction or Suzuki coupling reaction in 65% and 70% yields, respectively (Scheme 3). The hydrolysis product of **2a** was obtained as a white solid

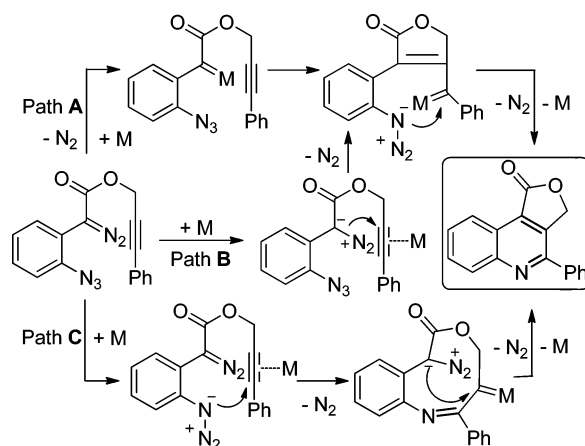
Scheme 3. Further Transformations



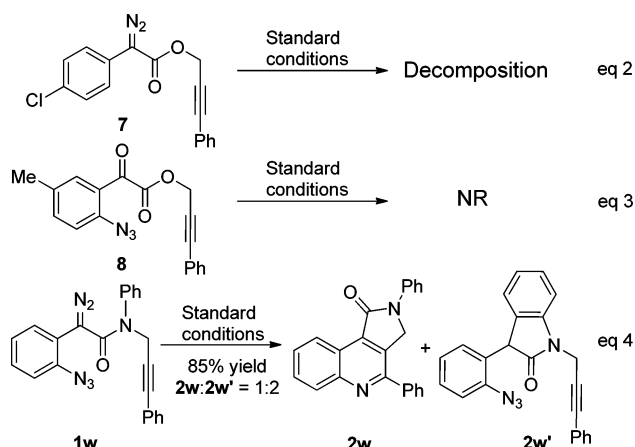
in 88% yield via simple filtration after acidification of the reaction mixture. Additionally, treatment of **2a** with lithium aluminum hydride in THF gives the reduced diol **6** in 76% yields.

We proposed that the reaction pathway went through a carbene/alkyne metathesis and terminated with carbene reaction with the azide group to form the quinoline framework (Scheme 4, Path A). A few control reactions were carried out to verify the proposed process, and some of the other possibilities could be ruled out. First, the reaction with diazo compound **7** under standard conditions resulted in decomposition of this substrate, which indicated that the metal-catalyzed diazo

Scheme 4. Proposed Reaction Pathways



decomposition might initially occur under these conditions (eq 2). Another control reaction with azide **8** under standard condition gave no reaction at all (eq 3), which might rule out the copper-catalyzed alkyne activation process (Scheme 4, Path C).^{9–11} In addition, the reaction with diazo compound **1w** under standard conditions gave both carbene/alkyne metathesis product **2w** and metal carbene aromatic substitution product **2w'** in 85% total yield with 1:2 ratio (eq 4).¹⁶ This result also supports the metal-carbene-initiated reaction pathway, and any other possibility to generate the vinyl carbene intermediate to give the final product couldn't be totally ruled out (Scheme 4, Path B).



In conclusion, we have disclosed a copper-catalyzed novel carbene/alkyne metathesis cascade reaction of alkyne-tethered diazo compounds that provides a practical and effective access to multisubstituted 4-carboxyl quinoline derivatives, which are found as the core unit in many bioactive compounds. The transformation features a dual-functionalization of alkyne to install one $\text{C}=\text{N}$ and one $\text{C}=\text{C}$ bond on each carbon with azide and diazo groups, respectively, in one reaction. Potential applications using this strategy for the polycyclic compounds synthesis are under exploration in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02648.

Experimental details and characterization data for all materials and products (PDF)

X-ray analysis data for **2e** (CIF)

X-ray analysis data for **2s** (CIF)

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Notes

The authors declare no competing financial interest.

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