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Diversified Construction of Chromeno[3,4-*c*]pyridin-5-one and Benzo[*c*]chromen-6-one Derivatives by Domino Reaction of 4-Alkynyl-2-oxo-2*H*-chromene-3-carbaldehydes

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Abstract: Silver-catalyzed three-component, tandem reactions of 4-alkynyl-2-oxo-2H-chromene-3-carbaldehydes, amines and various nucleophiles result in the formation of highly functionalized chromeno[3,4-c]pyridin-5-ones in high yields. Gold-catalyzed [4+2] cycloadditions of 4-alkynyl-2-oxo-2H-chromene-3-carbaldehydes with alkynes or alkenes have also been achieved to afford benzo[c]chromen-6-ones efficiently.

Keywords: benzo[*c*]chromen-6-ones; chromeno[3,4-*c*]pyridin-5-ones; coumarins; cycloaddition; Lewis acids

Introduction

Propargylic compounds are important building blocks in synthetic chemistry due to their easy coordination with alkynophilic Lewis acids, leading to their susceptibility to nucleophilic addition and cycloaddition etc.[1] A large number of alkynophilic Lewis acid-catalyzed reactions of propargylic compounds with diverse nucleophiles have been developed in recent years for the construction of diverse heterocycles.[2] Among these, *ortho*-alkynylaldehydes has been identified by Wu and Larock as powerful building blocks to synthesize a wide variety of heterocyclic and carbocyclic compounds through rationally designed domino reactions or cycloadditions.[3]

Coumarin (2*H*-chromen-2-one) is a core moiety of many biologically important compounds and members of coumarin families are widely utilized as anticancer,[6] antimicrobial,[7] antioxidation,[8] anti-HIV[9] agents, fluorescent probes,[10] and triplet sensitizers,[11] etc. Among these derivatives, chromeno[3,4-*c*]pyridin-5-one[12] and benzo[*c*]-chromen-6-ones[13] are two classes of special families which are present in a variety of natural products and bioactive molecules with important applications in medicinal chemistry (Figure 1). For example, chromeno[3,4-*c*]pyridin-5-one **A** can act not only as a selective human dopamine D4 receptor antagonist, but also as a potential antipsychotic agent,[12a] **B** shows a wide range of pharmacological properties such as antimicrobial and antitumor activities,[12b] schumanniophytine **C** shows central and autonomic nervous system depressant properties and may have potential antiviral activity,[12g] alternariol **D** exhibits antifungal and phytotoxic activity, and is reported to inhibit cholinesterase enzymes,[13j] gilvocarcin **E** is a kind of bactericidal and antitumor natural product,[13k] and cannabinol **F** can be employed clinically as an immunosuppressant. Due to the great importance of the compounds of these families, we wanted to develop new methodologies for the efficient construction of them.

With great interest in manipulation of coumarin blocks, recently we have successfully achieved a facile catalyst-free sp^3 C–H activation of 2-alkylazaarenes with (thio)coumarin-3-carboxylic acids for the efficient construction of azaarenes-substituted 3,4-dihydro(thio)coumarins.[14a] As a continuation of this work and our efforts for developing new methodologies to construct biologically important heterocyclic compounds,[14] we planned to design a new type of β-alkynyl aldehyde compounds as the key intermediate to synthesize various chromeno[3,4-c]pyridin-5-one and benzo[c]chromen-6-one derivatives, thus 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehyde **1** came to mind and eventually was identified as the key intermediate for diversified electrophilic cyclization and cycloaddition reactions, with which a series of domino reactions and cycloaddition reactions were developed

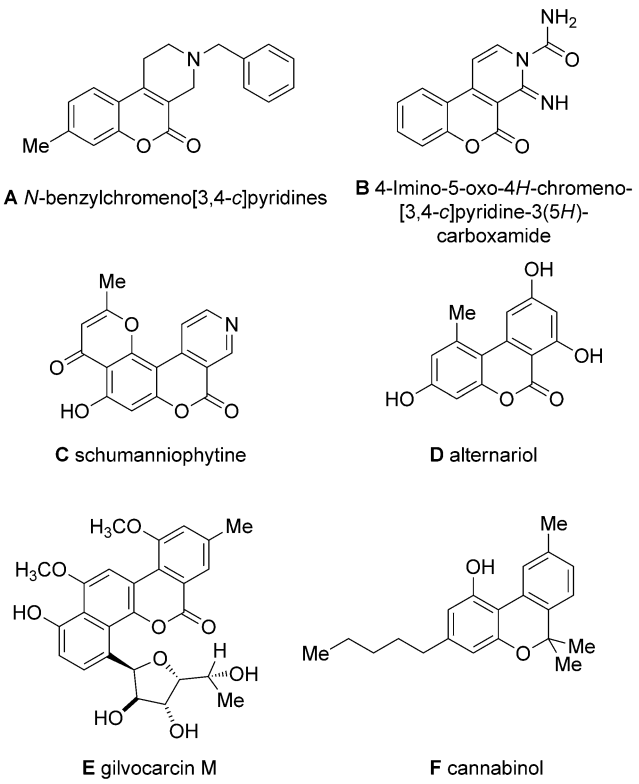
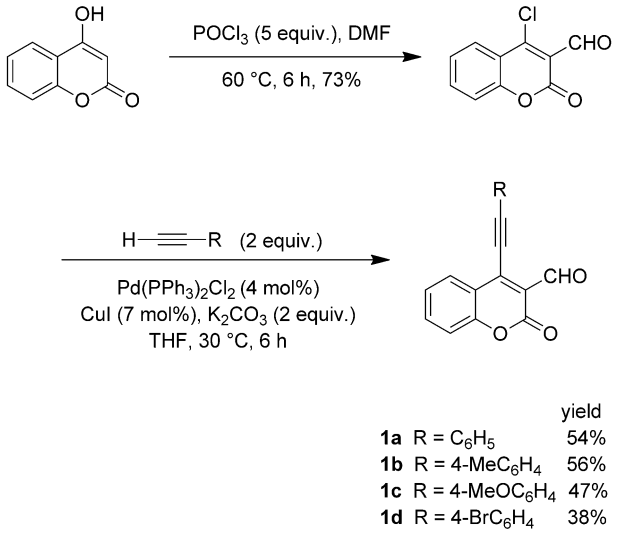


Figure 1. Natural products and bioactive molecules possessing chromenone core structures.

to construct various chromeno[3,4-*c*]pyridin-5-one and benzo[*c*]chromen-6-one derivatives efficiently (Figure 2).

Results and Discussion

4-Alkynyl-2-oxo-2*H*-chromene-3-carbaldehyde could be prepared from 4-hydroxycoumarin in two steps in-



Scheme 1. Preparation of **1a**.

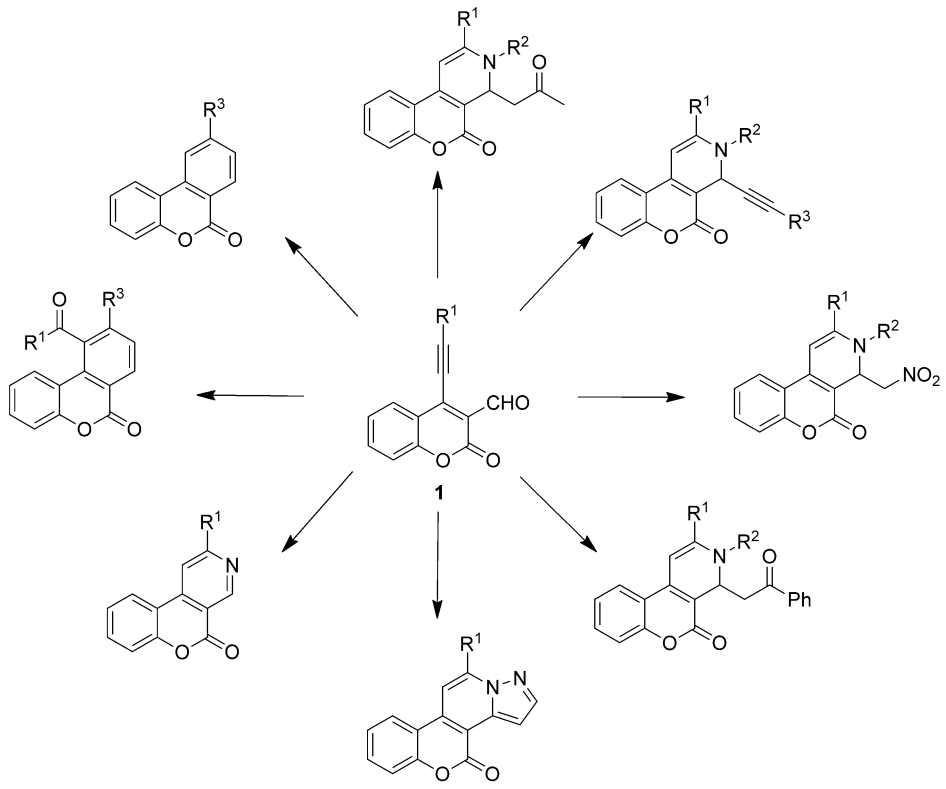
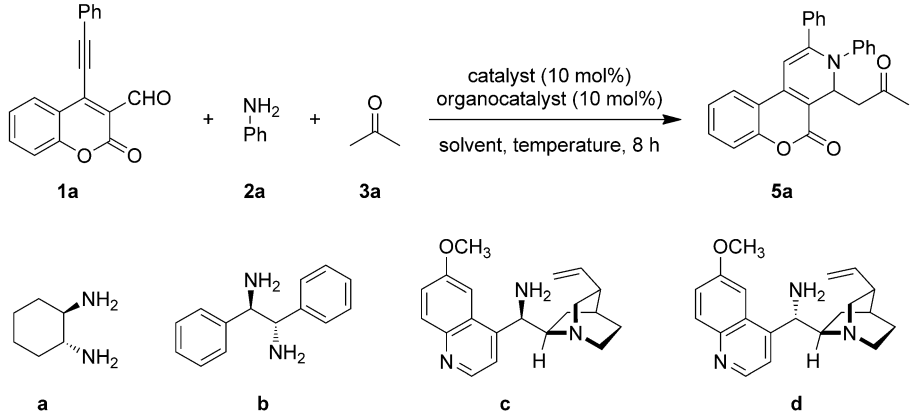


Figure 2. Diversified synthesis of chromeno[3,4-*c*]pyridin-5-one[15] and benzo[*c*]chromen-6-one derivatives.

volving formylation, chlorination and Sonogashira coupling (Scheme 1).[15] Treatment of 4-hydroxycoumarin with $POCl_3$ in DMF to furnish 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde in 73% isolated yield[16] was followed by a Sonogashira coupling with phenylacetylene catalyzed by $Pd(PPh_3)_2Cl_2$ and CuI (7 mol%) which afforded the desired 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehyde **1a** as a yellow solid which can be stored at 4 °C for several months without noticeable decomposition.

With this key intermediate in hand, the reaction of **1a**, amine **2a** and ketone **3a** was conducted in ethanol at 60 °C using 10 mol% AgOTf and 10 mol% L-proline as catalysts with the hope of achieving enantioselectivity (Table 1, entry 1). To our delight, the desired product was obtained in 86% yield, although as a racemic compound. The employment of other solvents did not lead to any improvement in yield (Table 1, entries 2–9). When $AgNO_3$ was exploited as a catalyst at 60 °C, the yield rose to 93% (Table 1, entry 10). Both increasing the temperature and lowering the temperature only led to lower isolated yields due to side reactions (Table 1, entries 11 and 12). When primary amines **a**–**d** were used as organocatalysts, only a trace

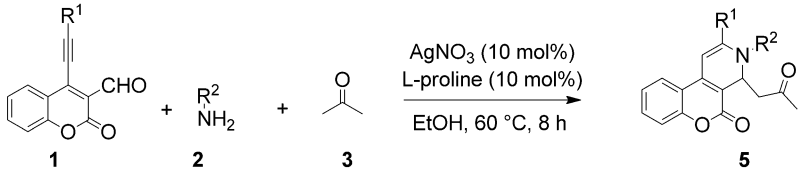
Table 1. Screening of the reaction conditions.[a]



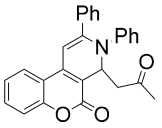
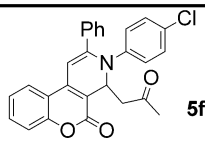
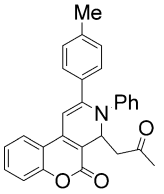
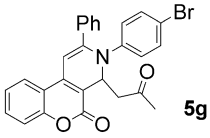
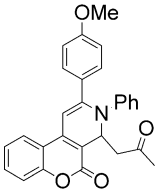
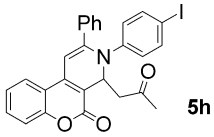
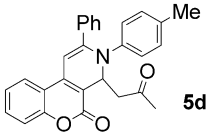
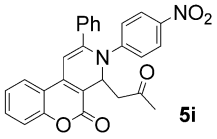
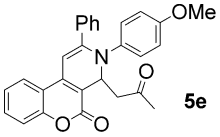
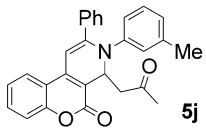
Entry	Catalyst	Organocatalyst	Solvent	Temperature [°C]	Yield [%][b]
1	AgOTf	L-proline	EtOH	60	86
2	AgOTf	L-proline	MeOH	60	77
3	AgOTf	L-proline	MeCN	60	78
4	AgOTf	L-proline	toluene	60	61
5	AgOTf	L-proline	THF	60	54
6	AgOTf	L-proline	DCM	60	73
7	AgOTf	L-proline	DMF	60	52
8	AgOTf	L-proline	1,4-dioxane	60	66
9	AgOTf	L-proline	acetone	60	81
10	**$AgNO_3$**	**L-proline**	**EtOH**	**60**	**93**
11	$AgNO_3$	L-proline	EtOH	80	82
12	$AgNO_3$	L-proline	EtOH	30	8
13	$AgNO_3$	primary amine **a**	EtOH	60	trace
14	$AgNO_3$	primary amine **b**	EtOH	60	trace
15	$AgNO_3$	primary amine **c**	EtOH	60	trace
16	$AgNO_3$	primary amine **d**	EtOH	60	trace
17[c]	$AuCl_3$	L-proline	EtOH	60	10
18	$PdCl_2$	L-proline	EtOH	60	16
19	$Pd(OAc)_2$	L-proline	EtOH	60	23
20	$Cu(OTf)_2$	L-proline	EtOH	60	12
21	$InBr_3$	L-proline	EtOH	60	18
22[d]	TfOH	L-proline	EtOH	60	7
23	$AgNO_3$	–	EtOH	60	12
24	–	L-proline	EtOH	60	NR

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.3 mmol), **3a** (1.8 mmol), Lewis acid (10 mol%), organocatalyst (10 mol%), 2 mL solvent, 30–60 °C, 8 h.
[b] Isolated yield after column chromatography.
[c] 5 mmol% catalyst.
[d] 20 mmol% catalyst.

Table 2. Reactions of **1**, amines **2** and acetone **3**.[a]



1 **2** **3** **5**

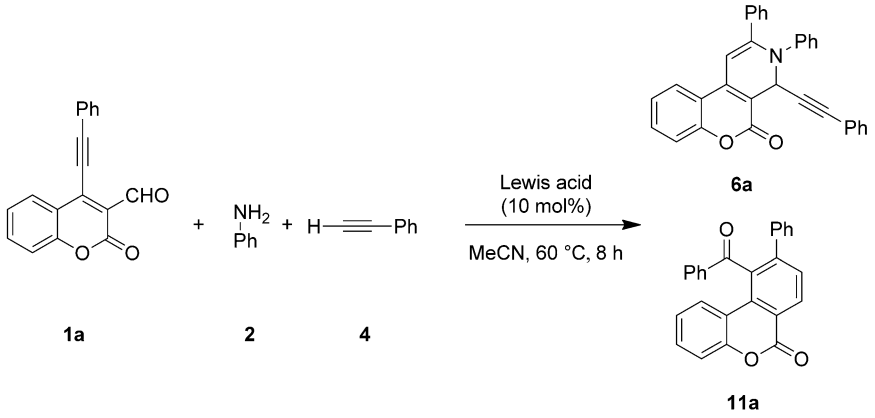
Entry	R^1	R^2	Product	Yield [b]	Entry	R^1	R^2	Product	Yield [b]
1	C_6H_5	C_6H_5	 **5a**	93%	6	C_6H_5	4-ClC_6H_4	 **5f**	95%
2	4-MeC_6H_4	C_6H_5	 **5b**	84%	7	C_6H_5	4-BrC_6H_4	 **5g**	97%
3	4-$MeOC_6H_4$	C_6H_5	 **5c**	78%	8	C_6H_5	4-IC_6H_4	 **5h**	76%
4	C_6H_5	4-MeC_6H_4	 **5d**	92%	9	C_6H_5	4-$NO_2C_6H_4$	 **5i**	37%
5	C_6H_5	4-$MeOC_6H_4$	 **5e**	85%	10	C_6H_5	3-MeC_6H_4	 **5j**	84%

[a] *Reaction conditions:* 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehyde **1** (0.3 mmol), aniline **2** (0.3 mmol), acetone **3** (1.8 mmol), $AgNO_3$ (10 mol%), L-proline (10 mol%), ethanol 2 mL, 60 °C, 8 h.
[b] Isolated yield after column chromatography.

of the desired product **5a** could be achieved (Table 1, entries 13–16). The employment of other Lewis acids such as $AuCl_3$, $Sc(OTf)_3$ and $InBr_3$ as well as the Brønsted acid catalyst TfOH only resulted in inferior results (Table 1, entries 17–22). Remarkably, **5a** was obtained merely in 12% yield only with $AgNO_3$, and no reaction occurred at all only with L-proline, indicating the importance of cooperative dual catalysis by $AgNO_3$ and L-proline in this reaction.

With the optimized conditions in hand, the generality of this reaction was investigated (Table 2). Electron-donating groups on the arylalkyne moiety were well tolerated (Table 2, entries 2 and 3); both electron-poor and electron-rich anilines were good substrates and gave similar yields; *para*-toluidine and *para*-anisidine gave the desired products **5d** and **5e** in 92% and 85% yields (Table 2, entries 4 and 5). Similarly, **1a** reacted with 4-chloroaniline, 4-bromoaniline and 4-iodoaniline smoothly, giving rise to the desired products in 95%, 97% and 76% yields (Table 2, entries 6–8). This would be more desirable as the C–X (X = Br or I) bonds are versatile synthetic handles for further elaborations. Furthermore, 4-nitroaniline was

Table 3. Optimization of the reaction conditions.[a]



Entry	Catalyst (10 mol%)	Yield [%][b] of **6a**	Yield [%][b] of **11a**
1	$AgNO_3$	82	0
2	AgOTf	96	0
3	$PdCl_2$	15	0
4	$Pd(OAc)_2$	21	0
5[c]	$AuCl_3$	14	39
6[c]	$AuBr_3$	19	24

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.3 mmol), **4a** (1.8 mmol), catalysts (10 mol%), acetonitrile 2 mL, 60 °C, 8 h.
[b] Isolated yield after column chromatography.
[c] 5 mmol% catalyst.

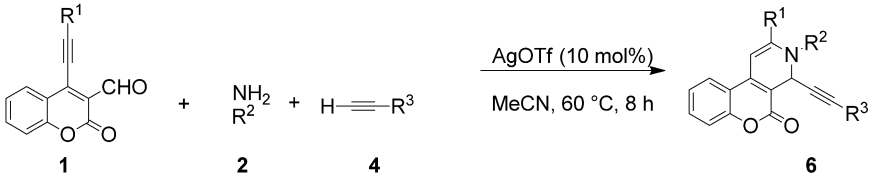
also tolerated under the standard reaction condition, albeit with somewhat lower yield (Table 2, entry 9).

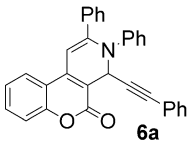
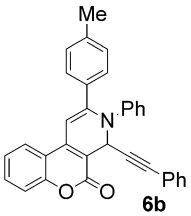
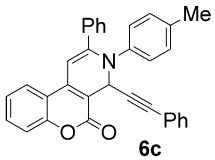
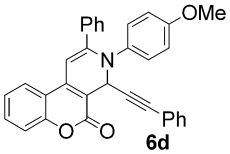
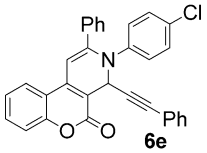
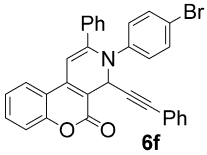
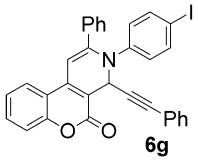
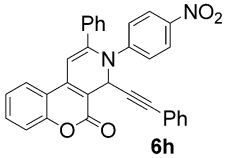
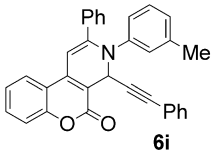
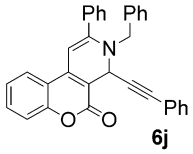
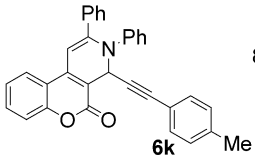
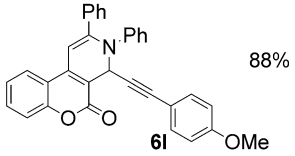
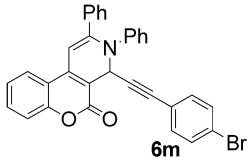
We reasoned that terminal alkynes and acetone would be of comparable reactivity as pronucleophiles in the present protocol. Indeed, a clean reaction between 1-phenylethyne **4a**, 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehydes **1a** and aniline **2a** was achieved at 60 °C in the presence of 10 mol% AgOTf, and the adduct **6a** could be isolated in 96% yield (Table 3). When other Lewis acid catalysts such as $AgNO_3$, $AuCl_3$ and $AuBr_3$ were used in this reaction, a [4+2] cycloaddition also occurred, giving rise to 10-benzoyl-8-phenyl-6*H*-benzo[*c*]chromen-6-one **11a** in 39% and 24% yields. The scope of the conversion of **1** to **6** is reported in Table 4. Various alkynes and anilines afforded the target products in high yield (Table 4). Notably, benzylamine also worked very well and the desired product **6j** was isolated in 88% yield (Table 4, entry 10). Different aryl-substituted terminal alkynes also reacted with **1a** and **2a** with comparable efficiency (**6k**–**6m**), affording the desired products in good yields (Table 4, entries 11–13).

Moreover, other nucleophiles, for example, nitromethane and silyl enol ether, could also be employed in this reaction and the corresponding products **7** and **8** were obtained in 83% and 95% yields (Scheme 2). A plausible reaction mechanistic pathway was proposed according to the experimental results (Scheme 3). Firstly, condensation of **1** with amine affords the intermediate **A**. Because of high alkynophilicity of Ag(I), the π-complex **B** undergoes a *6-endo-dig* cyclization to furnish intermediate **C**. Ultimately, the nucleophile attacks the electrophilic moiety of intermediate **C**, furnishing the final products **D** with simultaneous regeneration of the catalyst.

Inspired by the recent development of the dioxygen/copper system[17a,b] and the Ag/Cu co-catalyzed reaction reported by Wu,[17c] we found that reaction of **1a** with $TsNHNH_2$ could proceed in the presence of 5 mol% AgOTf and 5 mol% $CuCl_2$ in DCE to furnish **9** in 58% yield at 60 °C with a 16% yield of **10** (Scheme 4). In addition, when ammonia reacted with **1a**, a clean reaction was achieved to afford product **10** in 91% yield.[18] Following the identification of benzo[*c*]chromen-6-one **11a** as by-product (Table 3, entries 5 and 6), as this structure is the core moiety of many natural products,[19] we decided to seek the optimal reaction conditions for its synthesis. Ultimately we found that in the presence of 10 mol% of $AuCl_3$ at 60 °C the target product **11a** was formed in 87% yield (Scheme 5). Other alkynes were also tolerated and the corresponding benzannulation products **11b**–**11d** could be produced in good yields. Besides gold catalysis, iodonium activation could also be utilized to construct the identical compound skeletons.[20] These alkyne-based halocyclization reactions are versatile and can be viewed as metal-free alternatives of gold catalyzed alkyne cyclizations. Unfortunately, when the

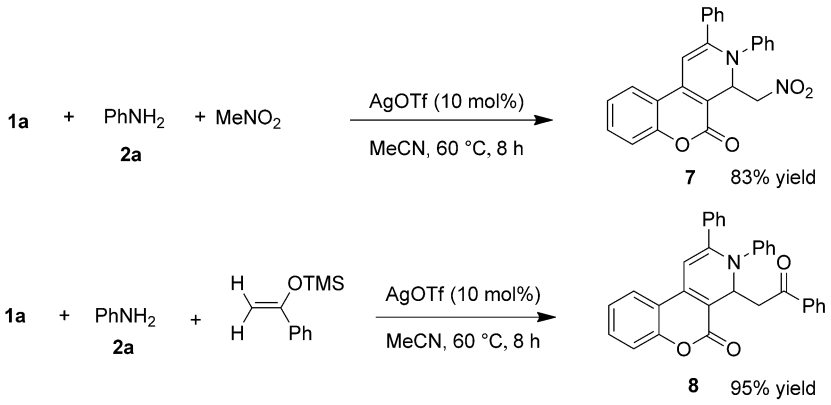
Table 4. Reactions of **1**, amines **2** and alkynes **4**.[a]



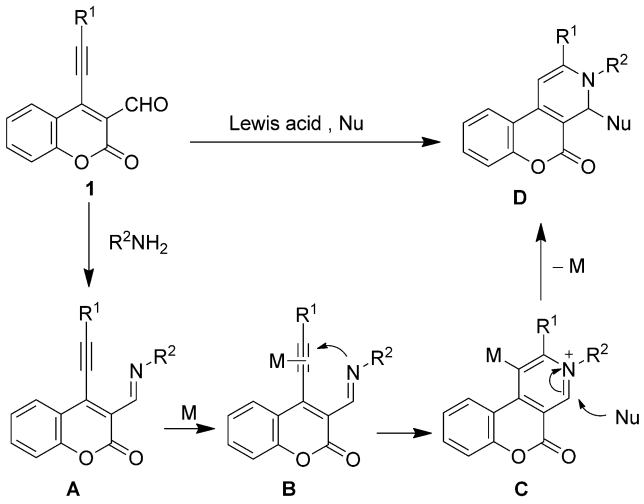
Entry	R^1	R^2	R^3	Product	Yield [b]
1	C_6H_5	C_6H_5	C_6H_5	 **6a**	96%
2	4-MeC_6H_4	C_6H_5	C_6H_5	 **6b**	83%
3	C_6H_5	4-MeC_6H_4	C_6H_5	 **6c**	93%
4	C_6H_5	4-MeOC_6H_4	C_6H_5	 **6d**	91%
5	C_6H_5	4-ClC_6H_4	C_6H_5	 **6e**	95%
6	C_6H_5	4-BrC_6H_4	C_6H_5	 **6f**	87%
7	C_6H_5	4-BrC_6H_4	C_6H_5	 **6g**	76%
8	C_6H_5	4-$NO_2C_6H_4$	C_6H_5	 **6h**	74%
9	C_6H_5	3-MeC_6H_4	C_6H_5	 **6i**	87%
10	C_6H_5	Bn	C_6H_5	 **6j**	88%
11	C_6H_5	C_6H_5	4-MeC_6H_4	 **6k**	86%
12	C_6H_5	C_6H_5	4-MOeC_6H_4	 **6l**	88%
13	C_6H_5	C_6H_5	4-BrC_6H_4	 **6m**	85%

[a] *Reaction conditions:* 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehyde **1** (0.3 mmol), aniline **2** (0.3 mmol), terminal alkyne **4** (0.6 mmol), AgOTf (10 mol%), acetonitrile 2 mL, 60 °C, 8 h.

[b] Isolated yield after column chromatography.

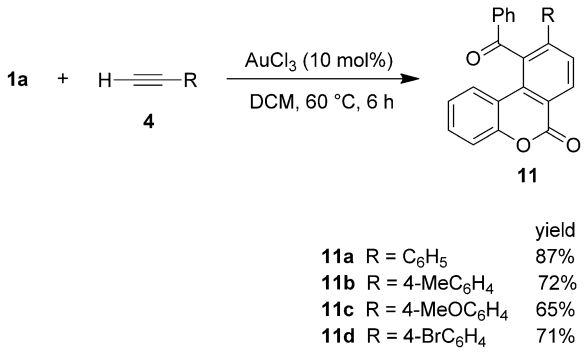


Scheme 2. Reactions of **1a**, **2a** and other nucleophiles.

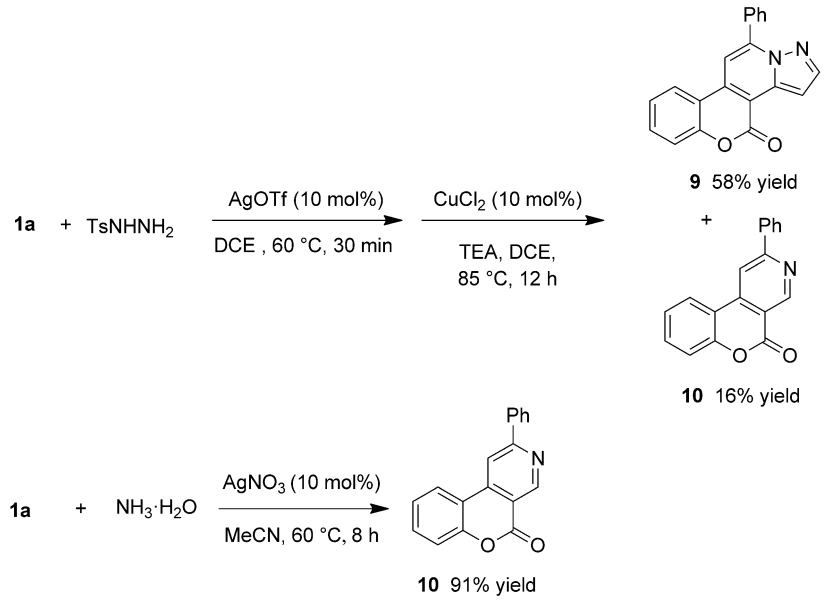


Scheme 3. Proposed mechanistic pathway.

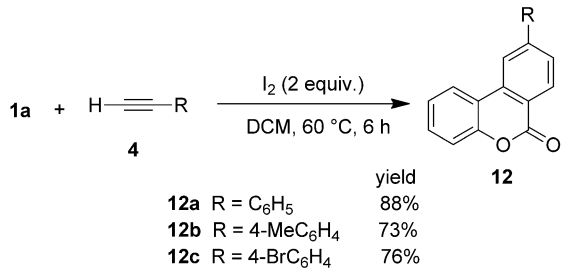
reaction was carried out using 2 equiv. of I_2 instead of $AuCl_3$ catalyst, the desired product **11a** was not obtained, whereas another clean reaction was observed and the unexpected adduct **12a** was isolated in 88%



Scheme 5. Synthesis of products **11**.



Scheme 4. Synthesis of products **9** and **10**.

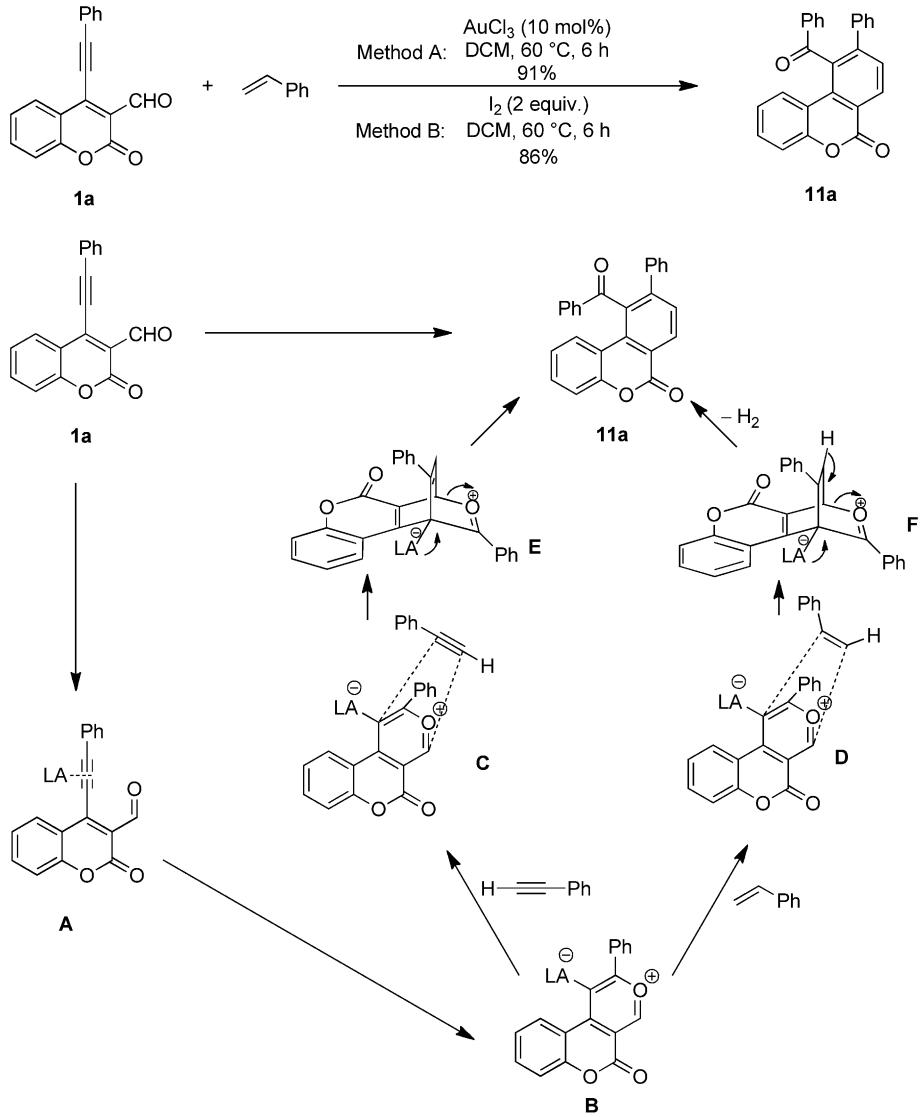


Scheme 6. Synthesis of products **12**.

yield (Scheme 6).[21] Notably, unlike other iodide-catalyzed cycloaddition reactions, no iodine atom was incorporated into the final product, which might be ascribed to the high reaction temperature and long reaction time. To further investigate the substrate scope of this reaction, some other alkynes were examined and it was found that **12b** and **12c** could also be obtained in moderate to good yields (Scheme 6).

Moreover, when styrene was exploited instead of phenylacetylene, the reaction with 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehydes **1a** afforded the same product **11a** in 91% yield.[22] Intriguingly, when 2 equiv. of I_2 were employed instead of $AuCl_3$, the identical product **11a** was isolated in 86% yield (Scheme 7).

According to these experimental results, a plausible mechanism was proposed: Firstly, the activation of alkyne **1a** by Lewis acid, followed by *6-endo-dig* cyclization can give rise to zwitterionic intermediate **B** which works as the precursor of a Diels–Alder reaction to trap dienophilic phenylacetylene or styrene, producing the cycloaddition intermediate **E** or **F**. A subsequent elimination of metal or iodine results in



Scheme 7. Synthesis of products **11** and a plausible mechanistic pathway.

rearomatization and formation of the desired product **11a**.

Conclusions

In conclusion, we have identified 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehydes as the key intermediates to participate in a series of domino reactions and cycloadditions for efficient syntheses of biologically important chromeno[3,4-*c*]pyridin-5-one and benzo[*c*]-chromen-6-one derivatives. Silver-catalyzed three-component, tandem reactions of 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehydes with amines and various nucleophiles provided a facile synthesis of highly functionalized chromeno[3,4-*c*]pyridin-5-ones in good yields. Gold-catalyzed [4+2] cycloadditions of 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehydes with alkynes or alkenes have also been achieved to afford benzo[*c*]chromen-6-ones efficiently. These methods should find applications in the synthesis of biologically important structures and future work will be focused on the enantioselective synthesis of these products using chiral catalysts.

Experimental Section

Procedure for the Synthesis of Compound 5a

To a 25-mL flask equipped with a magnetic bar were added **1a** (0.3 mmol), $AgNO_3$ (0.03 mmol), L-proline (0.03 mmol), ethanol (2 mL), aniline **2a** (0.3 mmol) and acetone (1.8 mmol). The mixture was then stirred at 60 °C in air for 8 h. Subsequently the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite. Afterwards the solvent was removed under vacuum. Purification was performed with flash column chromatography on silica gel using EtOAc and petroleum ether as eluent.

Procedure for the Synthesis of Compound 6a

To a 25-mL flask equipped with a magnetic bar were added **1a** (0.3 mmol), AgOTf (0.03 mmol), acetonitrile (2 mL), aniline **2a** (0.3 mmol) and phenylethyne (0.6 mmol). The mixture was then stirred at 60 °C in air for 8 h. Subsequently the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite. All the volatiles were evaporated under vacuum. Purification was performed by flash column chromatography on silica gel using EtOAc and petroleum ether as eluent.

Procedure for the Synthesis of Compounds 9 and 10

1a (0.30 mmol) was added to a solution of 4-methylbenzenesulfonohydrazide (0.30 mmol) in DCE (1.0 mL). The mixture was stirred at room temperature in air for 10 min. Then AgOTf (5 mol%) was added and the solution was stirred at 60 °C in air for 30 min. After the reaction mixture had been cooled to 30 °C, $CuCl_2$ (10 mol%), and tertiary amine (3.0 mmol) in DCE (1.0 mL) were added. The mixture was then stirred at 85 °C for 12 h. Subsequently the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite. All the volatiles were removed under vacuum. Purification was performed by flash column chromatography on silica gel using EtOAc and petroleum ether.

Procedure for the Synthesis of Compound 10

To a 25-mL pressure tube equipped with a magnetic stirrer bar were added **1a** (0.3 mmol), $AgNO_3$ (0.03 mmol), acetonitrile (2 mL) and NH_3 (6 mmol, 28% NH_3 in H_2O). The mixture was then stirred at 60 °C in air for 8 h. Subsequently the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite, followed by removal of all volatiles under reduced pressure. Purification was performed by flash column chromatography on silica gel using EtOAc and petroleum ether.

Procedure for the Synthesis of Compound 11a

To a 25-mL flask equipped with a magnetic bar were added **1a** (0.3 mmol), $AuCl_3$ (0.03 mmol), dichloromethane (2 mL) and phenylethyne (0.6 mmol), respectively. The mixture was then stirred at 60 °C in air for 6 h. Subsequently the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite, afterwards solvent was removed under vacuum. Purification was performed by flash column chromatography on silica gel using EtOAc and petroleum ether.

Procedure for the Synthesis of Compound 12a

To a 25-mL flask equipped with a magnetic bar were added **1a** (0.3 mmol), iodine (0.6 mmol), dichloromethane (2 mL) and phenylethyne (0.6 mmol), respectively. The mixture was then stirred at 60 °C in air for 6 h. Subsequently the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite and all the volatiles was evaporated under vacuum. Purification was performed by flash column chromatography on silica gel using EtOAc and petroleum ether.

Procedure for the Synthesis of Compound 11a under Conditions A

To a 25-mL flask equipped with a magnetic stirrer bar were added **1a** (0.3 mmol), $AuCl_3$ (0.03 mmol), dichloromethane (2 mL) and styrene (0.6 mmol), respectively. The mixture was then stirred at 60 °C in air for 6 h. Subsequently the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite, followed by removal of all volatiles under vacuum. Purification was performed by flash column chromatography on silica gel using EtOAc and petroleum ether.

Procedure for the Synthesis of Compound 11a under Conditions B

To a 25-mL flask equipped with a magnetic bar were added **1a** (0.3 mmol), iodine (0.6 mmol), dichloromethane (2 mL) and styrene (0.6 mmol), respectively. The mixture was then stirred at 60 °C in air for 6 h. Subsequently the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite, followed by removal of all volatiles under vacuum. Purification

was performed by flash column chromatography on silica gel using EtOAc and petroleum ether.

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