One-pot synthesis of benzolactones and lactams *via* a cobalt-catalyzed regioselective [2 + 2 + 2] cocyclotrimerization of alkynyl alcohols and amines with propiolates†

Hong-Tai Chang, Masilamani Jeganmohan and Chien-Hong Cheng*

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An efficient method for the synthesis of benzolactones and benzolactams *via* a cobalt-catalyzed [2 + 2 + 2] cocyclotrimerization of alkynyl alcohols and alkynyl amines with propiolates is described.

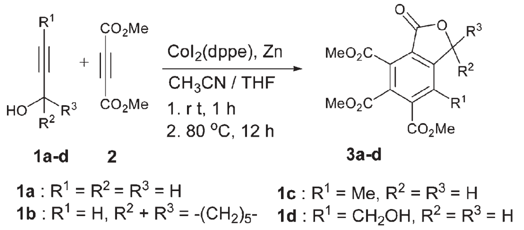
The transition metal catalyzed [2 + 2 + 2] cycloaddition reaction of unsaturated molecules is an efficient method to construct six-membered cyclic compounds with the formation of three new carbon–carbon bonds.[1] This cycloaddition reaction has been known for the past few decades. Of these cycloadditions, the intramolecular and partially intermolecular modes of cyclotrimerization have been established as powerful synthetic methods.[2] However, completely intermolecular versions of [2 + 2 + 2] cycloaddition generally have encountered difficulties in the control of chemo- and regioselectivity. When two or three different alkynes are used for the cycloaddition, in most cases, a mixture of several benzene derivatives was obtained.[3] Therefore, the search for a highly chemo- and regioselective intermolecular [2 + 2 + 2] cycloaddition reaction of two or three different monoynes is greatly challenging. Recently, several groups have devoted substantial effort in this area.[4] We demonstrated a nickel-catalyzed regio- and chemoselective [2 + 2 + 2] cocyclotrimerization of propiolates with allenes.[5] Takeuchi and Nakaya reported a iridium-catalyzed [2 + 2 + 2] cycloaddition reaction of DMAD with substituted propargyl alcohols to afford substituted benzolactones,[4d] but only few examples were studied. Our continuous interest in this type of cycloaddition reactions[6] prompted us to explore the possibility of alkynyl alcohols with propiolates. Herein, we wish to report that cobalt catalyzed the [2 + 2 + 2] cycloaddition reactions of alkynyl alcohols and amines with propiolates to give various substituted benzolactones and lactams in a highly chemo- and regioselective fashion.

Benzolactones and lactams are found in plants and they show several pharmacological effects, such as fungicidal, bactericidal, herbicidal and analgesic activities.[7] The present catalytic reaction provides a convenient method for the synthesis of various substituted benzolactones and lactams in one pot with good to excellent yields.

Substituted benzolactone **3a** was successfully prepared in 91% of isolated yield from the reaction of propargyl alcohol (**1a**) (1.00 mmol) with DMAD (**2**) (2.2 mmol) in the co-solvent CH_3CN and THF (2.0 + 2.0 mL) in the presence of CoI_2(dppe) (5.0 mol%) and zinc metal powder (2.75 mmol) (Scheme 1). It is necessary that the solution was initially stirred at room temperature for 1 h to reduce the Co(II) complex (pale green) to the active species (dark green) and then at 80 °C for 12 h to obtain high yield of product **3a**. Presumably, the formation of **3a** is *via* a [2 + 2 + 2] cocyclotrimerization of two molecules of **2** and a molecule of **1a** followed by transesterification. Product **3a** was thoroughly characterized by its ^1H, ^{13}C NMR and mass spectral data. Control experiments revealed that in the absence of the cobalt catalyst or Zn powder, no **3a** was obtained.

To understand the nature of the catalytic reaction and to determine optimal reaction conditions, the activities of various cobalt phosphine complexes and the effect of solvents on the [2 + 2 + 2] cocyclotrimerization of **1a** with **2** were examined. Monodentate phosphine complexes $CoCl_2(PPh_3)_2$ and $CoI_2(PPh_3)_2$ exhibited low catalytic activity, affording **3a** in 47 and 41% yields, respectively. Cobalt complexes with bidentate phosphine ligands dppm and dppp, gave **3a** in 53 and 58% yields. The highest yield of **3a** in 95% was obtained using CoI_2(dppe) as the catalyst. The solvent used is critical to the catalytic reaction. Of the solvents tested, the co-solvent acetonitrile and THF (2 + 2 mL) was most effective. Acetonitrile alone was also efficient, affording product **3a** in 78% yield. The other solvents, THF, toluene, ethyl acetate and NMP, were not active for present catalytic reaction.

Under similar reaction conditions, substituted alkynyl alcohols **1b–d** also underwent the [2 + 2 + 2] cocyclotrimerization reaction with **2** to afford the corresponding benzolactone derivatives in excellent yields (Table 1). Thus, the reaction of **2** with 1-ethynylcyclohexanol (**1b**) afforded product **3b** in 77% yield (entry 2), whereas but-2-yn-1-ol (**1c**) gave **3c** in 85% yield (entry 3). Similarly, but-2-yne-1,4-diol (**1d**) undergoing reaction with **2** affording bislactone **3d** in 50% yield (entry 4).

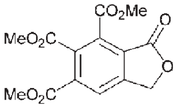
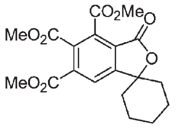
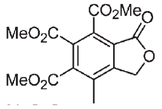
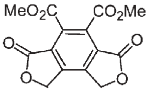
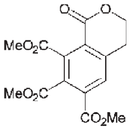
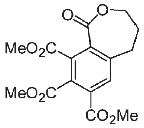
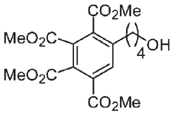


Scheme 1

Department of Chemistry, National Tsing Hua University, Hsinchu, 30013, Taiwan. E-mail: chcheng@mx.nthu.edu.tw; Fax: 886-3-5724698; Tel: 886-3-5721454

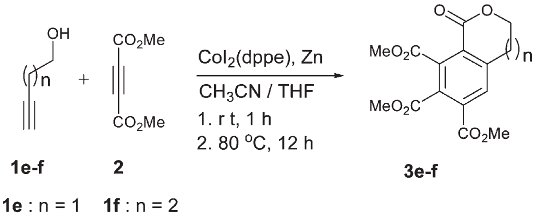
† Electronic supplementary information (ESI) available: General experimental procedure, melting point, spectral data (IR, ^1H, ^{13}C NMR and HRMS) and copy of ^1H and ^{13}C NMR spectra of all compounds. See http://dx.doi.org/10.1039/b509731b

Table 1 Results of cobalt-catalyzed cocyclotrimerization of alkynyl alcohols **1** and DMAD **2**[a]

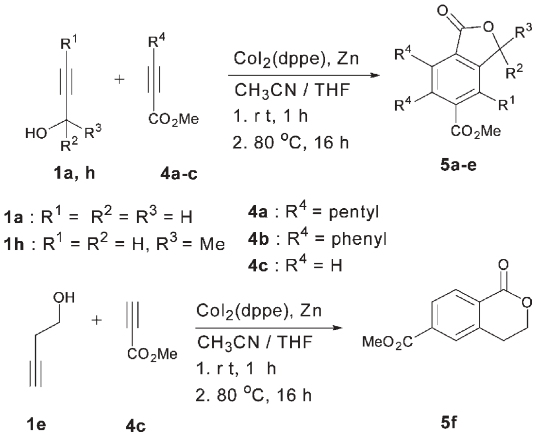
Entry	1	2	Product	3	Yield[b] (%)
1	**1a**	2		**3a**	91 (95)
2	**1b**	2		**3b**	77
3	**1c**	2		**3c**	85
4	**1d**	2		**3d**	50
5	**1e**	2		**3e**	91
6	**1f**	2		**3f**	82
7	**1g**	2		**3g**	80

[a] All reactions were carried out using alkynyl alcohols **1** (1.00 mmol), DMAD (**2**) (2.2 mmol), CoI_2(dppe) (5.0 mol%), Zn (2.75 mol%) and CH_3CN and THF (2.0 + 2.0 mL) at room temperature for 1 h and then at 80 °C for 12 h. [b] Isolated yields: the yields in parenthesis was determined by ^1H NMR integration method.

The cobalt-catalyzed [2 + 2 + 2] cocyclotrimerization reaction can also be used for the preparation of six- and seven-membered benzolactones (Scheme 2). Thus, treating but-3-yn-1-ol (**1e**) and pent-4-yn-1-ol (**1f**) with **2** under the standard conditions afforded lactones **3e–f** in 91 and 82% yields, respectively (Table 1, entries 5–6). However, an attempt to make an eight-membered lactone ring from the reaction of hex-5-yn-1-ol **1g** and **2** afforded only the noncyclized product **3g** in 80% yield (entry 7).



Scheme 2

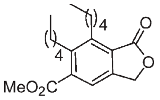
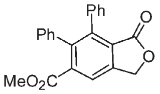
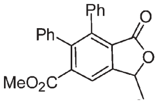
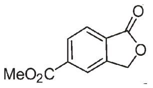
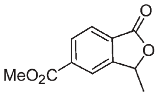
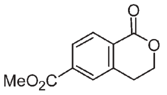


Scheme 3

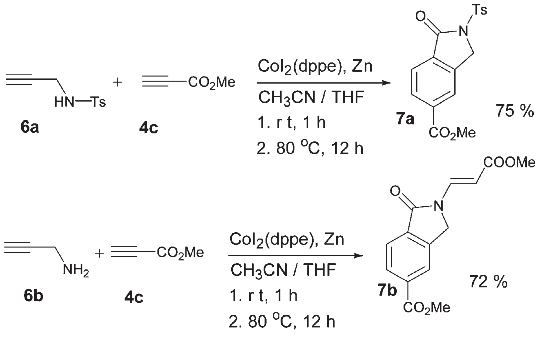
The present protocol can be further applied to propiolates **4a–c** with alkynyl alcohols **1a**, **1e** and **1h** under the similar reaction conditions to give highly regio- and chemoselective [2 + 2 + 2] cycloaddition and transesterification products **5a–f** in good yields (Scheme 3). The reaction of **1a** with pentylpropiolate **4a** afforded highly substituted benzolactone **5a** in 45% yield (Table 2, entry 1). The NOE data of product **5a** support the proposed structure in entry 1 and exclude the other possible regioisomers. Similarly, phenylpropiolate **4b** underwent cycloaddition reaction with **1a** and **1h** to afford products **5b,c** in 40 and 35% yields, respectively. Again, NOE studies of these products were consistent with the proposed structures with the two phenyl groups *ortho* to each other.

In a similar manner, methyl propiolate (**4c**) reacts smoothly with **1a**, **1h** and **1e** catalyzed by the CoI_2(dppe)/Zn system to yield products that contain a five- and six-membered lactone ring **5d–f** in 70–80% yields (Table 2, entries 4–6). The reaction is completely regioselective; in each case only one regioisomer of the

Table 2 Results of cobalt-catalyzed cocyclotrimerization of alkynyl alcohols **1a**, **1e** and **1h** and propiolates **4a–c**[a]

Entry	1	4	5		Yield[b] (%)
1	**1a**	**4a**		**5a**	45
2	**1a**	**4b**		**5b**	50
3	**1h**	**4b**		**5c**	35
4	**1a**	**4c**		**5d**	80
5	**1h**	**4c**		**5e**	74
6	**1e**	**4c**		**5f**	70

[a] All reactions were carried out using alkynyl alcohols **1** (1.00 mmol), propiolate **4** (2.2 mmol), CoI_2(dppe) (5.0 mol%), Zn (2.75 mol%) and CH_3CN and THF (2.0 + 2.0 mL) at room temperature for 1 h and then at 80 °C for 16 h. [b] Isolated yields.



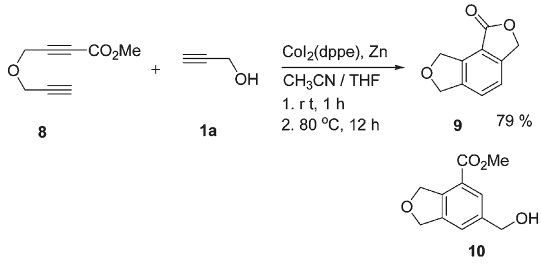
Scheme 4

cycloaddition product was observed and the structure was confirmed by NOE studies. In all of these reactions, the homo cyclotrimerization products of propiolates were observed in 5–20% yields.

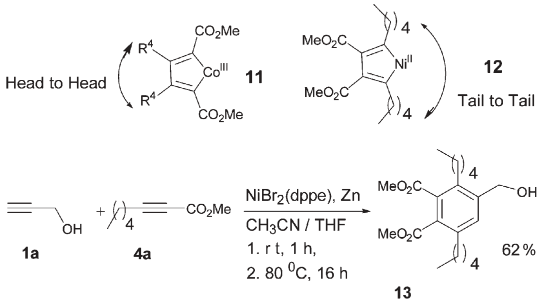
In addition to propargyl alcohols, the reaction was further extended into propargyl amines (Scheme 4). The reaction of propiolate **4c** with *N*-propargyl *p*-toluenesulfoneamide **6a** in the presence of CoI$_2$(dppe)/Zn afforded benzolactam derivative **7a** in 75% yield. Under similar reaction conditions, propargyl amine **6b** also underwent [2 + 2 + 2] cocyclotrimerization with **4c**, but the expected product appears to react further with a propiolate molecule to give **7b** in 72% yield.

The regioselectivity of propargyl alcohol **1a** in the present cobalt-catalyzed [2 + 2 + 2] cycloaddition was demonstrated with unsymmetrical diyne **8** under the standard reaction conditions affording phthalide derivative **9** in 79% yield as the exclusive product. The other possible product **10** was not detected in the ^{1}H NMR spectrum of the crude reaction mixture indicating excellent regioselectivity of **1a** in the reaction (Scheme 5).

The origin of formation of benzolactones **3**, **5** and lactams **7** from the present cobalt-catalyzed cycloaddition of alkynyl alcohols or amines **1** or **6** with propiolates **2** or **4** is likely from the regioselective head to head (R^4) oxidative cyclometalation of propiolates to give cobaltacyclopentadiene intermediate **11**.[1] Insertion of a molecule of alkynyl alcohol (or amine) into a Co–carbon bond of **11** in which the two ester groups are next to the metal center, followed by reductive elimination and transesterification afforded the final product **3**, **5** or **7**.



Scheme 5



Scheme 6

It is known that nickel complexes also catalyze the [2 + 2 + 2] cycloaddition of alkynes. To compare the regioselectivity in the nickel- and cobalt-catalyzed reaction, the cycloaddition of **1a** with **4a** catalyzed by the NiBr$_2$(dppe)/Zn system was studied. As shown in Scheme 6, an entirely different product **13** in 62% yield was observed. In this product, the two ester groups are *meta* and *para* to the hydroxymethyl group and thus, no transesterification could occur. The difference of regioselectivity in the oxidative cyclometalation of propiolates to nickel and cobalt complexes should account for these results. A tail–tail (pentyl group R^4) oxidative cyclometalation of pentyl propiolate **4a** with the nickel complexes to give intermediate **12** is known.[1,2,5,6] We have observed the same type of regioselective products in our pervious nickel-catalyzed [2 + 2 + 2] cycloaddition of propiolates and allenes.[5]

In conclusion, we have developed a cobalt-catalyzed [2 + 2 + 2] cyclotrimerization of alkynyl alcohols with propiolates. The reaction is highly regio- and chemoselective affording benzolactone derivatives in good to excellent yields. Further extension of this work into partially intermolecular version and a detailed mechanistic study is underway.

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Notes and references

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