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Cobalt(II)-Catalyzed Electrophilic Alkynylation of 1,3-Dicarbonyl Compounds To Form Polysubstituted Furans *via* π–π Activation

Irwan Iskandar Roslan,[a] Jiulong Sun,[a] Gaik-Khuan Chuah,[a]
and Stephan Jaenicke[a],*

[a] Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore
Fax: (+65)-6779-1691; phone: (+65)-6516-2918; e-mail: chmsj@nus.edu.sg

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Abstract: Polysubstituted furans were obtained with excellent yields *via* the electrophilic alkynylation of 1,3-dicarbonyl compoundsws with phenyl- or ester-substituted brominated alkynes. The reaction is catalyzed by the inexpensive and readily available catalyst, cobalt(II) chloride, and has a wide substrate scope. The C(*sp*)–C(*sp*^{3}) coupling occurs under mild conditions with short reaction times and does not require an inert atmosphere or ligands. It is proposed that the reaction proceeds through a chelation complex of cobalt(II) with the deprotonated 1,3-dicarbonyl compound.

Keywords: alkynes; C–H activation; cobalt(II) catalysts; cyclization; heterocycles

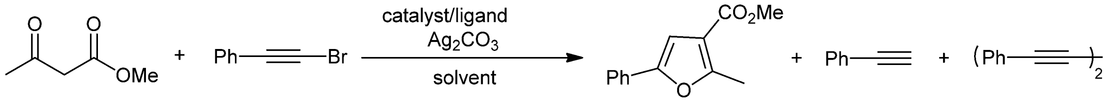
Polysubstituted furans are an important class of 5-membered heterocycles that are ubiquitous in natural products, pharmaceuticals and agrochemicals.[1] Many naturally occurring furans have medicinal properties such as antiallergic, antiasthmatic, antispasmodic, antitumor and antidiabetic activities.[2] Furans are important intermediates in the total synthesis of complex natural products,[3] and can be transformed to biofuels, polymers with electrochemical properties and macrocycles with selective binding for biomolecules.[4]

Polysubstituted furans are typically constructed from 1,4-diketones *via* the Paal–Knorr reaction,[5] but this synthesis requires high reaction temperatures and harsh acidic conditions. Thus, the quest for improved methods to obtain polysubstituted furans from a variety of starting materials continues.[6] Most of the recently developed syntheses are indeed more effective and usually require milder conditions, but they are hampered by a limited scope of reaction or difficulties with the acquisition of the starting reagents, which frequently are only accessible *via* multiple-step syntheses. However, Lei's group recently showed that polysubstituted furans can be obtained from readily available starting materials, arylacetylenes and 1,3-dicarbonyls, *via* an Ag(I)-mediated dehydrogenative cross-coupling reaction.[7]

"Umpolung" of this reaction with electrophilic alkynylating reagents such as brominated acetylenes increases the flexibility and versatility of the acetylene chemistry and extends the scope of the reaction.[8,9] The *sp*–*sp*^{2} alkynylation of aryl and heteroaromatic compounds catalyzed by group 10–13 metals such as Pd, Cu, Ni, Au or Ga has been extensively studied.[10] In contrast, there are few studies on the *sp*–*sp*^{3} electrophilic alkynylation of aliphatic compounds. One of the first reports was by Ano et al. on the alkynylation of carboxylic acid derivatives using brominated acetylenes.[11] Huang et al. utilized electrophilic alkynylation to form various aromatic *H*-pyrazolo[5,1-*a*]isoquinolines from (bromoethynyl)benzene and *N*′-(2-alkynylbenzylidene)hydrazide.[12] Wipf and Venkatraman constructed thiazoles from alkynyliodonium salts and thioamides.[13] More recently, Jiang's group showed that (bromoethynyl)benzene and ethyl 2-pyridylacetate formed 2,3,4-trisubstituted furans *via* a silver-catalyzed sequential nucleophilic addition and cyclization reaction.[14] The reaction was conducted using 20 mol% $AgNO_3$ as a Lewis acid catalyst together with 1 equivalent of DABCO (1,4-diazabicyclo[2.2.2]octane) as a strong base. These works motivated us to explore the possibility of an *sp*–*sp*^{3} electrophilic alkynylation to form polysubstituted furans from (bromoethynyl)benzene derivatives[15] and 1,3-dicarbonyls. This approach has the advantage that (bromoethynyl)benzene derivatives can be easily synthesized with a short reaction sequence while 1,3-dicarbonyls are readily available as starting materials.

We first searched for a suitable catalyst to bring about the reaction between methyl acetoacetate **1** and (bromoethynyl)benzene **2**. In addition to the desired

Table 1. Optimization of the parameters for the electrophilic alkynylation.[a]



1 **2** **3a** **4** **5**

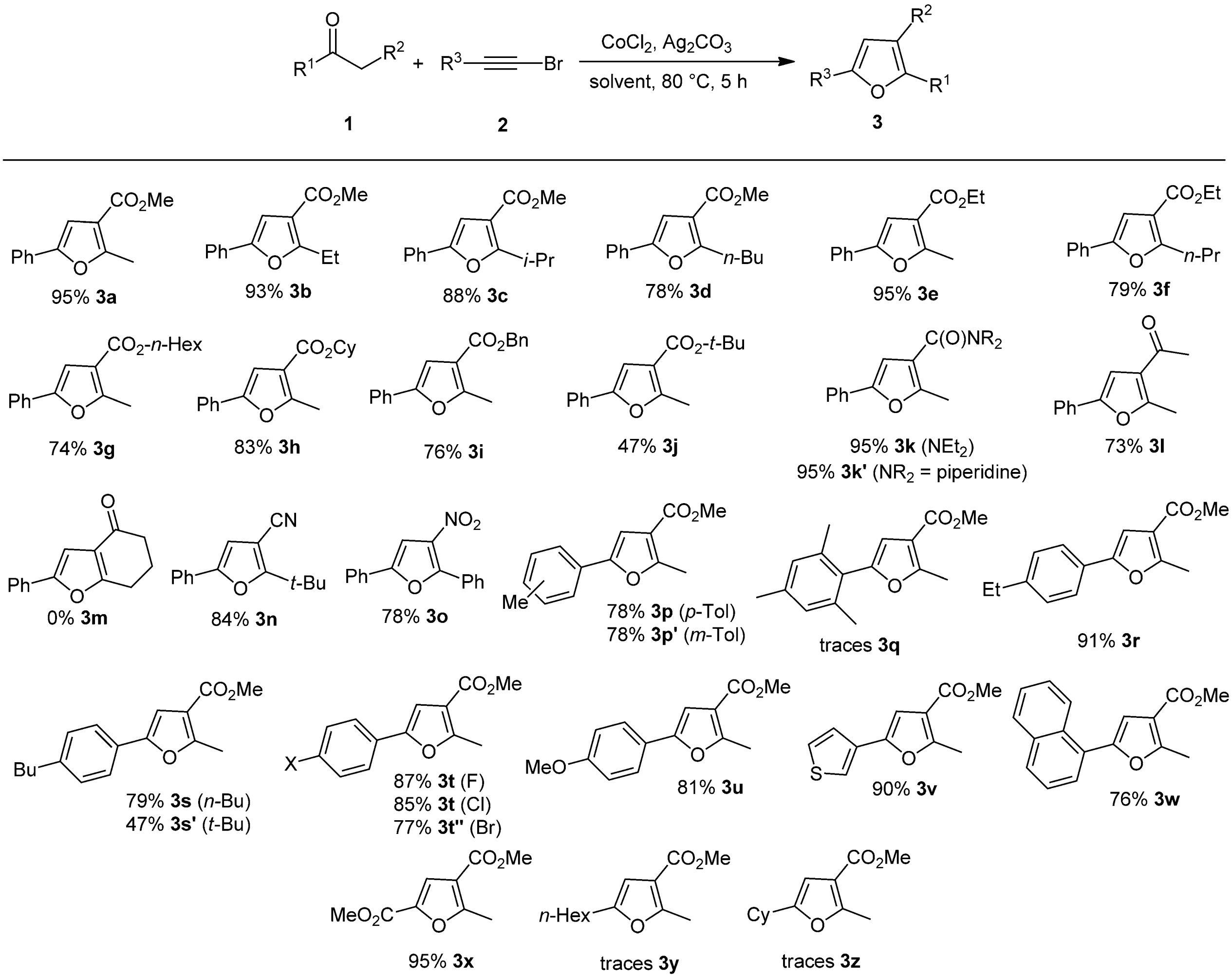
No	Catalyst	Solvent	V [mL]	Temperature [°C]	Ligand	Time [h]	**3a** Yield [%][b]
1	CuI	DMF	2	110	–	12	4
2	$PdCl_2$	DMF	2	110	–	12	12
3	$ZnCl_2$	DMF	2	110	–	12	68 (61)
4	$NiCl_2$	DMF	2	110	–	12	86 (82)
5	$CoCl_2$	DMF	2	110	–	12	93 (90)
6	$CoBr_2$	DMF	2	110	–	12	70 (65)
7	CoI_2	DMF	2	110	–	12	61 (53)
8	–	DMF	2	110	–	12	traces
9[c]	$CoCl_2$	DMF	2	110	–	12	traces
10	$CoCl_2$	DMF	2	80	–	8	47 (42)
11	$CoCl_2$	DMF	5	80	–	8	60 (53)
12	$CoCl_2$	DMF	8	80	–	8	95 (92)
13	$CoCl_2$	Toluene	8	80	–	8	4
14	$CoCl_2$	DCE	8	80	–	8	26 (10)
15	$CoCl_2$	Dioxane	8	80	–	8	51(44)
16	$CoCl_2$	DMA	8	80	–	8	86 (82)
17	$CoCl_2$	DMA/toluene	8	80	–	8	99 (94)
18	$CoCl_2$	DMA/toluene	8	80	–	5	81 (76)
19	$CoCl_2$	DMA/toluene	8	80	PCy_3	5	99 (92)
20	$CoCl_2$	DMA/toluene	8	80	PPh_2(*o*-tol)	5	91 (80)
21	$CoCl_2$	DMA/toluene	8	80	P(*o*-tol)$_3$	5	87 (78)
22	$CoCl_2$	DMA/toluene	8	80	PPh_3	5	60 (49)
23[d]	$CoCl_2$	DMA/toluene	8	80	–	5	95 (92)
24[e]	$CoCl_2$	DMA/toluene	8	80	–	5	95 (90)
25[f]	$CoCl_2$	DMA/toluene	8	80	–	5	65 (59)
26[g]	CoCl2	DMA/toluene	8	80	–	5	67

[a] *Reaction conditions:* **1** (2.0 equiv.), **2** (0.5 mmol), catalyst (10 mol%), ligand (20 mol%), Ag_2CO_3 (2 equiv.).
[b] Yield determined by GC analysis, isolated yields in parentheses.
[c] Reaction with no Ag_2CO_3.
[d] Reaction with 2.5 equiv. of **1**.
[e] Reaction with 2.5 equiv. of **1** and 1.3 equiv. of Ag_2CO_3.
[f] Reaction with 2.5 equiv. of **1** and 1.0 equiv. of Ag_2CO_3.
[g] Reaction with 1 equiv. of TEMPO and 1.3 equiv. of Ag_2CO_3.

polysubstituted furan **3a**, we observed the formation of side products such as the debrominated alkyne, phenylacetylene **4**, and the homocoupling product, 1,4-diphenyldiacetylene **5**. Various metals were screened as catalysts in the presence of Ag_2CO_3 as mediator to scavenge the liberated bromide. Cu(I) or Pd(II) salts (Table 1, entries 1 and 2) gave mainly the homocoupling product **5**. In contrast, the reaction proceeded with moderate to good yields when Zn(II), Co(II) or Ni(II) chlorides were used (Table 1, entries 3–5). The isolated yield of **3a** was 90% after 12 h at 110 °C with $CoCl_2$ as catalyst. Both $CoBr_2$ and CoI_2 gave lower yields than $CoCl_2$ (Table 1, entries 6 and 7). In the absence of any cobalt halide, the conversion was low, with only small amounts of the debrominated product **4** and traces of **3a** (Table 1, entry 8). Similarly, without Ag_2CO_3, only traces of **3a** were formed (Table 1, entry 9). These results show that both $CoCl_2$ and Ag_2CO_3 are required for the reaction to proceed with high yield. The finding that $CoCl_2$ was the most effective catalyst is fortuitous as it is inexpensive and easy to handle, allowing the reaction to proceed readily without the need for an inert atmosphere.

The reaction conditions were optimized with $CoCl_2$ as catalyst at a lower temperature of 80 °C. Diluting the reaction mixture reduced the formation of the unwanted homodimer **5**. When the volume of the dimethylformamide (DMF) solvent was increased from 2 to 8 mL, the yield of the polysubstituted furan **3a** after 8 h reaction time went up from 47 to 95% (Table 1, entries 10–12). The polarity of the solvent also affected the yield of **3a**. Non-polar solvents like

Table 2. Electrophilic alkynylation of various β-keto compounds and brominated alkynes.[a]



[a] Isolated yields. *Reaction conditions:* **1** (2.50 equiv.), **2** (0.5 mmol), $CoCl_2$ (10 mol%), Ag_2CO_3 (1.3 equiv.), DMA/toluene (v/v = 1/1) (8.0 mL), 80 °C, 5 h.

toluene and dichloroethene (DCE) gave low yields of the desired product whereas polar aprotic solvents like dimethylacetamide (DMA) and DMF resulted in excellent yields of 86 and 95%, respectively (Table 1, entries 12–16). This can be attributed to the higher solubility of $CoCl_2$ and Ag_2CO_3 in polar aprotic solvents as compared to non-polar solvents.[16] To optimize the solubility of both the organic substrates and the metal salts, mixtures containing DMA and toluene in various ratios were tested. The best yield of **3a**, 99% after 8 h, was obtained with a DMA/toluene (v/v = 1/1) mixture.

The effect of phosphine ligands was next investigated (Table 1, entries 19–22). The addition of phosphines with an electron-withdrawing phenyl substituent had a negative effect. The yield of **3a** decreased from 81% in the ligand-free system to only 60%. On the other hand, electron-rich phosphines with electron donating cyclohexyl and *ortho*-tolyl substituents yielded 91–99% of **3a** after a reaction time of only 5 h. Nevertheless, the saving in reaction time to obtain high yields of **3a** does not justify the extra costs and increased work-up with the addition of the ligand. In fact, by increasing methyl acetoacetate from 2 to 2.5 equivalents, a similarly high yield of 95% could be achieved in 5 h, suggesting that methyl acetoacetate acts as a stabilizing ligand as well (Table 1, entry 23). Reducing the amount of Ag_2CO_3 from 2 to 1.3 equivalents did not affect the reaction but a further decrease to 1 equivalent resulted in a significant drop in the yield of **3a** to 65% (Table 1, entries 23–25). Hence, the optimized conditions for high yields of **3a** are 10 mol% $CoCl_2$ as catalyst, 1.3 equiv. Ag_2CO_3 as bromide acceptor, and a mixed solvent system of 1:1 DMA/toluene at 80 °C.

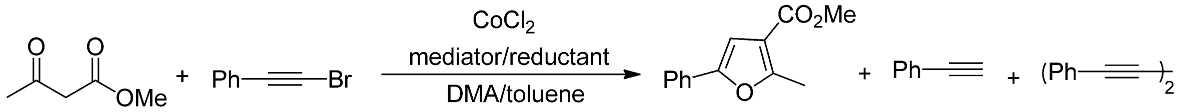
The scope of the reaction using the optimized conditions was next investigated (Table 2). Good to excellent yields of 74–95% were obtained for various β-keto esters with **2** (Table 2, **3a**–**3i**). However, the yield was significantly lower, 47%, when using the β-keto ester with a bulky *tert*-butyl substituent (Table 2, **3j**). The reaction proceeded well with secondary β-keto amides and acetylacetones (Table 2, **3k**, **3k′** and **3l**). However, no reaction occurred with 1,3-cyclohexanedione as substrate (Table 2, **3m**). Apparently, after deprotonation on C-2 the rigid diketone cannot form the chelation complex with Co^{2+}. However, benzoylnitromethane and pivaloylacetonitrile with electron-withdrawing CN and NO_2 groups are good substrates for this reaction (Table 2, **3n**, **3o**).

Various brominated phenylacetylene derivatives were tested with methyl acetoacetate to form polysubstituted furans. High yields were observed for both *para*-tolyl and *meta*-tolyl derivatives (Table 2, **3p** and **3p′**). However, only traces of product were formed with mesityl derivatives, suggesting that steric constraints at the *ortho* position are important (Table 2, **3q**). Both electron-withdrawing and electron-donating substituting groups at the *para* position including Et, *n*-Bu, OMe and F were well tolerated under the reaction conditions (Table 2, **3r**–**3t**). However, for the sterically hindered 1-*tert*-butyl-4-(bromoethynyl)benzene, the yield was only 47% (Table 2, **3s′**). Furthermore, other aromatic and heteroaromatic moieties including thiophene and naphthalene reacted to form **3v** and **3w** with good yields of 90% and 76%, respectively. It was pleasing to see that the non-aromatic methyl 3-bromopropiolate was also suitable for this reaction forming **3x** with an excellent yield of 95%. This example shows that the reaction is not limited to aromatic alkynes but also proceeds well with a propiolate moiety. However, terminal aliphatic alkynes were unsuitable for the reaction, with only traces of the desired products formed (Table 2, **3y** and **3z**).

The effect of the halogen substituent of the alkyne was examined. While (chloroethynyl)benzene gave a similar yield of **3a**, 94%, as **2**, the reaction with (iodoethynyl)benzene unexpectedly proceeded with only 63% yield. When (iodoethynyl)benzene was reacted with the more sterically hindered *tert*-butyl acetoacetate, the desired product **3j** did not form at all, compared to 47% with (bromoethynyl)benzene. Furthermore, the yield of **3s′** decreased from 47% to 30% when 1-*tert*-butyl-4-(iodoethynyl)benzene was used instead of the corresponding bromoalkyne. A similar observation had been made by Jiang and co-workers for the synthesis of 2,3,4-trisubstituted furans from haloalkynes and 2-pyridylacetic acid esters.[14] As iodoacetylenes usually perform better than their bromo equivalents due to weaker bond strengths, their lower reactivity may be due to the larger size of iodine as compared to bromine. Hence, the results suggest that the reaction is very sensitive to steric constraints.

To gain some insight into the mechanism of this electrophilic alkynylation reaction, phenylacetylene was used instead of its brominated analogue. No furans were formed, ruling out the possibility that dehalogenation at the *sp* carbon initiated the reaction (Table 3, entry 1). The introduction of silver phenylacetylide[7] together with 1 or 2 equivalents of Ag_2CO_3 produced the desired product only in low yields. Instead, more of the side products **4** and **5**

Table 3. Mechanistic studies for electrophilic alkynylation.[a]



1 **2** **3a** **4** **5**

Entry	Alkyne/	Mediator/Reductant	Yield [%][b]		
			3a	**4**	**5**
1	Ph—≡—H	2 equiv. Ag_2CO_3	–	–	–
2	Ph—≡—Ag	1 equiv. Ag_2CO_3	1	43	56
3	Ph—≡—Ag	2 equiv. Ag_2CO_3	12	55	33
4[c]	Ph—≡—Br	1 equiv. Zn, 2 equiv. Ag_2CO_3	5	–	4
5[d]	Ph—≡—H	2 equiv. Ag_2CO_3	–	–	18
6	Ph—≡—Br	2 equiv. AgOAc	87	–	7
7	Ph—≡—Br	2 equiv. Ag_2O	92	2	5
8	Ph—≡—Br	2 equiv. AgOTf	46	43	11

[a] *Reaction conditions:* **1** (2.5 equiv.), **2** (0.5 mmol), 10 mol% $CoCl_2$ in DMA/toluene (v/v = 1/1) (8.0 mL), 80 °C, 5 h.

[b] Yield determined by GC analysis.

[c] Zn and $CoCl_2$ were mixed for 10 min in solvent prior to adding the substrates and Ag_2CO_3.

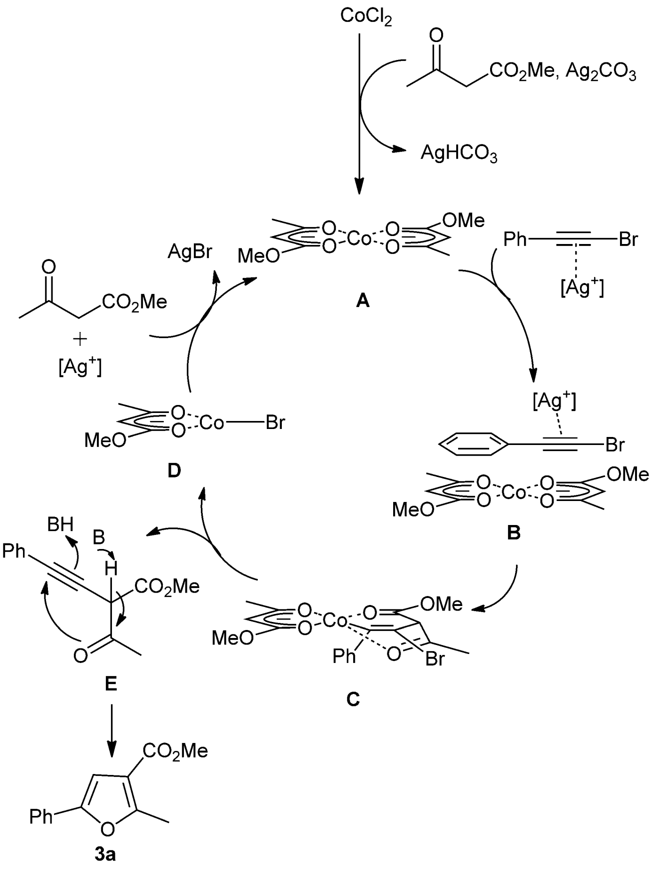
[d] 1.25 equiv. of methyl 2-bromoacetoacetate and 1.25 equiv. of methyl acetoacetate were used.

were formed (Table 3, entries 2 and 3), showing that the reaction did not proceed *via* the initial formation of the silver species. Co(II) salts as mediators for coupling reactions of bromoalkynes with organozinc halides and Grignard reagents have been described before, but the mechanism involved free radicals.[17] Similarly, a Co(II) porphyrin complex for the regioselective synthesis of polysubstituted furans initiated the metalloradical cyclization of alkynes with α-diazocarbonyl compounds.[18] The possibility that the present reaction was initiated by radicals was investigated by introducing one equivalent of 2,2,6,6-tetramethylpiperidinyl 1-oxyl (TEMPO) as radical scavenger to the reaction mixture. The yield of **3a** was 67%, which is only moderately lower than in the absence of TEMPO (Table 1, entry 26). The observation of a silver mirror on the inside walls of the round-bottomed flask shows that some Ag(I) had been reduced to Ag(0), lowering the Ag^+ concentration to below optimum. Indeed, the obtained yield of **3a** was comparable to that obtained when only 1 equivalent Ag_2CO_3 was used.

To elucidate if the catalyst operates *via* an oxidative mechanism involving Co(I)/Co(III) or a π-activation mechanism involving Co(II), zinc was used to reduce Co(II) to the Co(I) species *in-situ* prior to the reaction (Table 3, entry 4).[17b,19] An excess of zinc was used to ensure the complete reduction of Co(II) to Co(I). It was noted that the presence of zinc also led to the reduction of some Ag_2CO_3 to metallic silver. As only trace amounts of **3a** formed under these conditions, it can be inferred that the reaction does not proceed *via* a Co(I)/Co(III) mechanism but rather *via* π-activation.

To exclude the possibility that bromination of methyl acetoacetate occurs by reaction with **2**, the reaction was carried out using equal amounts of methyl 2-bromoacetoacetate and methyl acetoacetate with phenylacetylene (Table 3, entry 5). No **3a** was formed, instead the phenylacetylene reacted exclusively to the dimer **5**. It is therefore unlikely that the reaction proceeds *via* the formation of methyl 2-bromoacetoacetate as an intermediate. Different Ag salts were tested and a higher furan yield was found when AgOAc or Ag_2O were used rather than AgOTf (Table 3, entries 6–8). This suggests that in addition to increasing the electrophilicity of the brominated alkyne, Ag(I) also acts as a base that assists in the proton abstraction to form the methyl acetoacetate anion.

Based on these results, we propose that the electrophilic alkynylation reaction proceeds *via* the mechanism shown in Scheme 1. Deprotonation of the 1,3-dicarbonyl at the α-position assisted by Ag_2CO_3 forms the methyl acetoacetate anion which chelates to the cobalt ion to give a Co(II) complex **A** (Figure 1). The π electron clouds of the methyl acetoacetate anion interact with the phenyl moiety as well as with the −C≡C− moiety of (bromoethynyl)benzene. As a result of the π–π interaction, the molecules are brought close together (**B**) so that a C−C bond can form between the C-2 of the methyl acetoacetate anion and the electrophilic carbon of (bromoethynyl)benzene (**C**).



Scheme 1. Proposed mechanism for the Co-catalyzed electrophilic alkynylation reaction.

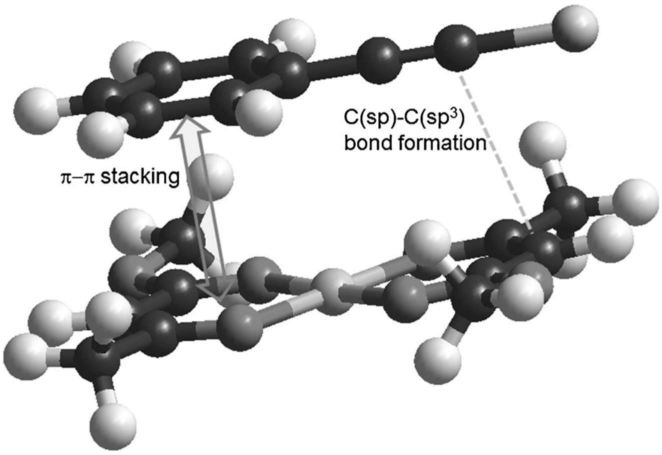
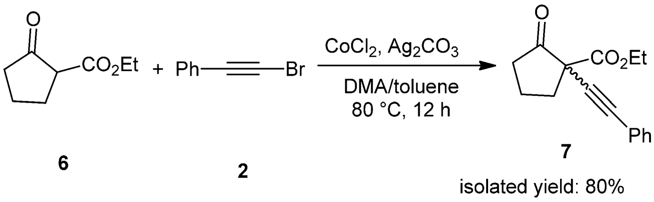


Figure 1. Proposed alignment of (bromoethynyl)benzene and the Co-methyl acetoacetate complex for π–π interaction.

This is followed by β-elimination to yield the Co–Br complex **D** and intermediate **E** which undergoes cycloisomerization to form the desired polysubstituted furan **3a**. Reaction of **D** with another molecule of 1,3-dicarbonyl under elimination of the bromide as AgBr regenerates the Co(II) complex **A**, thus completing the catalytic cycle.

The π–π interaction between the phenyl moiety and the methyl acetoacetate anion appears to be important for the reaction. The bulky *tert*-butyl group in the β-keto ester or at the *para* position of the brominated phenylacetylene interferes with the alignment, resulting in low yields of **3j** and **3s′**, respectively. Reacting these bulky substrates with the larger and therefore more sterically hindered iodide instead of bromide causes further reduction in the yields of **3a**, **3j** and **3s′**. Similarly, only trace amounts of **3q** were formed because the *ortho* methyl-substituent at the phenyl group prevents proper alignment of the phenyl group and the Co(II)-methyl acetoacetate complex. In contrast, excellent yields of **3w** were obtained with methyl propiolate which may be due to the formation of a η^3 allyl π–π interaction with the Co(II)-methyl acetoacetate complex. Brominated aliphatic alkynes are not suitable substrates as they cannot form the π–π interaction. The formation of a square planar complex between the metal and the 1,3-diketo compound facilitates the reaction by allowing favorable π–π interaction between the methyl acetoacetate anion and the phenyl component of **2** possible. Whereas Co(II) and especially Ni(II) are known to form square planar complexes,[20] and can catalyze the reaction effectively, Zn(II) is less likely to adopt such a configuration and has lower activity (Table 1, entries 3–5). To prove that the reaction proceeds *via* an intermediate **E** (Scheme 1), ethyl 2-oxocyclopentanecarboxylate **6** was used as substrate under the optimized conditions (Scheme 2). This substrate lacks a hydrogen at the α-position, and once formed, an intermediate **7** should not be able to undergo cyclization (unlike **E**). Alkyne **7** was indeed formed and could be isolated with 80% yield, lending further support to the proposed mechanism.

In summary, we have developed an efficient π–π activated electrophilic alkynylation reaction to form polysubstituted furans using Co(II) as the catalyst. The reaction proceeds *via* a C(*sp*)–C(*sp*^{3}) coupling between 1,3-dicarbonyls and bromoethynyl moieties. Ag(I) serves as a base for abstracting the α-hydrogen from the 1,3-dicarbonyl, increases the electrophilicity of the alkyne moiety, and is a sacrificial acceptor for the bromide anion. Using this novel methodology, polysubstituted furans can be synthesized under mild conditions and with short reaction times. Furthermore, the method has a wide scope of reaction and does not require an inert atmosphere. To the best of our knowledge, this is a first example of a cobalt-catalyzed electrophilic alkynylation reaction and pioneers its application in the formation of furans *via* cyclization.



Scheme 2. Reaction Scheme for the electrophilic alkynylation to form **7**.

Experimental Section

General Procedure for Electrophilic Alkynylation Reaction to form Polysubstituted Furans

A 25-mL round-bottomed flask was charged with methyl acetoacetate **1** (134.8 μL, 1.25 mmol), (bromoethynyl)benzene **2** (59.8 μL, 0.5 mmol), anhydrous $CoCl_2$ (6.5 mg, 0.05 mmol), Ag_2CO_3 (179 mg, 0.65 mmol) in a solvent mixture of DMA and toluene (v/v = 1/1) (8.0 mL). The reaction mixture was stirred at 80 °C for 5 h. The mixture was quenched with 2 M HCl (2 mL), extracted with ethyl acetate (3 × 5 mL) and the solvent was removed *via* a rotary evaporator. The crude product was subjected to column chromatography using hexane and ethyl acetate (v/v = 10/1) as eluent to afford **3a** in 95% yield.

Methyl 2-methyl-5-phenylfuran-3-carboxylate (3a): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (d, $J = 7.2$ Hz, 2H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.27 (t, $J = 7.4$ Hz, 1H), 6.88 (s, 1H), 3.85 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta =$ 164.4, 158.7, 151.7, 130.0, 128.7, 127.6, 123.6, 115.0, 105.3, 51.3, 13.8.

Acknowledgements

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Irwan Iskandar Roslan, Jiulong Sun, Gaik-Khuan Chuah, Stephan Jaenicke*

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