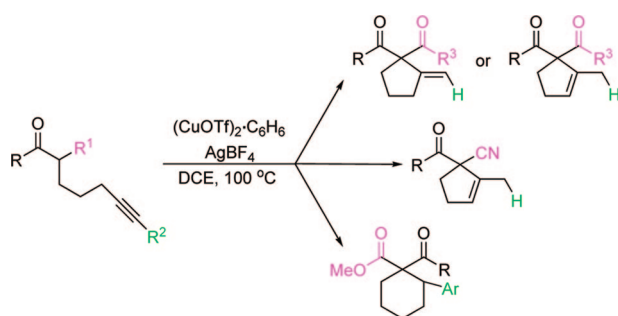# Copper/Silver-Cocatalyzed Conia−Ene Reactions of 2-Alkynic 1,3-Dicarbonyl Compounds

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A copper/silver-catalyzed Conia−ene reaction has been developed for selectively constructing five-membered and six-membered rings. In the presence of $(CuOTf)_2 \cdot C_6H_6$ and $AgBF_4$, a variety of 2-alkynic 1,3-dicarbonyl compounds underwent the Conia−ene intramolecular reaction smoothly in moderate to good yields. It is noteworthy that both 2-phenylacetylhept-6-ynenitrile and diethyl 2-(pent-4-ynyl)-malonate are also suitable substrates under the standard conditions, and the selectivity toward *endo*- or *exo*-products depends on the substitutents at the terminal of alkynes.

The intramolecular ene reaction of unsaturated ketones and aldehydes (the Conia−ene reaction) has emerged as a powerful method for carbon−carbon bond formation.[1−7] The reaction generally proceeds via two common transformations, thermal

SCHEME 1. Copper/Silver-Cocatalyzed Conia−Ene Reaction of Linear β-Alkynic β-Ketoesters
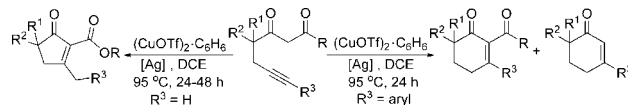
cyclization[2] and transition-metal-catalyzed cyclization.[3−7] However, the former suffers from the requirement of high temperatures, which significantly limits its application in organic synthesis. The latter transformation could be conducted smoothly at lower temperature, but additives, such as strong base,[3] strong acid,[4] and photochemical activation (often UV irradiation), are often needed.[5] Balme and co-workers, for instance, have reported the CuI-catalyzed Conia−ene reactions of α-alkynic β-ketoesters under mild conditions in the presence of a strong base, *t*-BuOK.[3] As a result, much recent attention has been attracted on the development of mild and neutral conditions for the Conia−ene reaction.[6−8] These efficiently catalytic systems include Au/Ag,[6] $Ni(acac)_2$/$Yb(OTf)_3$,[7] and $In(NTf_2)_3$.[8] Recently, we also developed a mild and effective protocol for the Conia−ene reactions of linear β-alkynic β-ketoesters using $(CuOTf)_2 \cdot C_6H_6$ and Ag(I) ($AgSbF_6$ or AgOAc) catalytic system (Scheme 1).[9] In the presence of $(CuOTf)_2 \cdot C_6H_6$ and Ag(I) ($AgSbF_6$ or AgOAc), a variety of linear β-alkynic β-ketoesters underwent the Conia−ene intramolecular reaction smoothly to selectively afforded the corresponding *exo*- or *endo*-products in moderate to good yields. Encouraged by the results, we decided to apply the Cu/Ag catalytic system in the cyclization of α-alkynic β-ketoesters. To our delight, the Cu/Ag catalytic system also displayed high efficiency for a wide range of 2-alkynic 1,3-dicabonyl compounds including α-alkynic β-ketoesters, α-alkynic β-diketo, 2-phenylacetylhept-6-ynenitrile, and diethyl 2-(pent-4-ynyl)malonate. Herein, we wish to report a general and selective protocol for the synthesis of *exo*- and *endo*-products by copper/silver-cocatalyzed Conia−ene reactions of 2-alkynic 1,3-dicarbonyl compounds (Scheme 2).

Methyl 2-acetylhept-6-ynoate (**1a**) was chosen as a model to screen the optimal reaction conditions, and the results are summarized in Table 1. Without Ag salts, treatment of substrate **1a** with $(CuOTf)_2 \cdot C_6H_6$ afforded only moderate yield of the
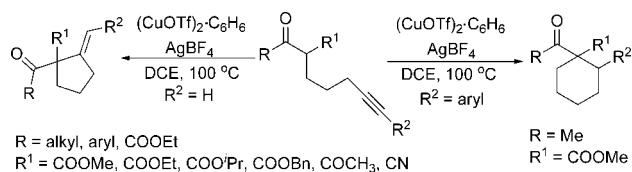
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SCHEME 2

R = alkyl, aryl, COOEt
R[1] = COOMe, COOEt, COO*i*Pr, COOBn, COCH₃, CN

R = Me
R[1] = COOMe

TABLE 1. Screening Optimal Conditions[a]

entry	cocatalyst	time (h)	yield (%)
1		24	62
2	AgOAc	24	50
3	AgSbF₆	22	40
4	Ag₂O	22	55
5	AgBF₄	23	100
6	In(OTf)₃	25	71
7	AuCl	46	50
8[b]	AgBF₄	24	75

[a] Reaction conditions: **1a** (0.2 mmol), (CuOTf)₂·C₆H₆ (10 mol %), cocatalyst (10 mol %), CH₂ClCH₂Cl (DCE; 5 mL) at 100 °C under argon atmosphere. [b] Without (CuOTf)₂·C₆H₆.
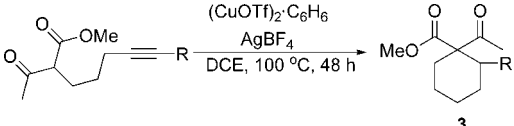
corresponding *exo*-product **2a** after 23 h (entry 1). In our previous paper, Ag(I) salts could improve the reaction.[9] Thus, a series of Ag(I) salts were then examined (entries 2−5). Surprisingly, the results indicated that both AgSbF₆ and AgOAc, the reported efficient cocatalysts, disfavored the reaction (entries 2 and 3). Identical results were observed in the presence of Ag₂O (entry 4). To our delight, AgBF₄ displayed highly active to improve the (CuOTf)₂·C₆H₆-catalyzed reaction providing quantitative yield (entry 5). The other reported effective catalysts including In(OTf)₃ and AuCl were also tested, and both are less effective than AgBF₄ (entries 6 and 7). We found that 73% yield was still achieved from the reaction of substrate **1a** using AgBF₄ catalyst alone (entry 8). Note that no decarbonylated products are observed in the present reaction.[9]

With the standard conditions in hand, we decided to explore scope of the Cu/Ag-catalyzed Conia−ene reaction. As demonstrated in Table 2, a number of α-alkynic β-ketoesters **1b−g** were first examined in the presence of (CuOTf)₂·C₆H₆ and AgBF₄ (entries 1−6). The results showed that both ester groups and β-substitutents affected the reaction to some extent. Benzyl ester **1d** was a suitable substrate providing high yields under the standard conditions (entry 3), but both ethyl ester **1b** and isopropyl ester **1c** were less active than methyl ester **1a** (entries 1 and 2). Ethyl ester **1b**, for instance, was treated with (CuOTf)₂·C₆H₆ and AgBF₄ to afford the corresponding target *exo*-product **2b** in 67% yield (entry 1). While β-phenyl β-ketoester **1f** gave the desired product in 86% yield (entry 5), only 40% yield was isolated from α-alkynic β-ketoester **1g** bearing an *i*-propyl group at the β-position (entry 6). Interestingly, β-ethyl β-ketoester **1e** could undergo the cyclization efficiently to give the corresponding cyclopentene product **2e** in 95% yield (entry 4). Next, substrate **1h**, a α-alkynic β-diketo, was investigated under the standard conditions (entry 7). It was encouraging to find that substrate **1h** underwent the Conia−ene reaction with (CuOTf)₂·C₆H₆ and AgBF₄ smoothly in good yield (entry 7). Gratifyingly, cyclization of 2-phenylacetylhept-6-ynenitrile (**1i**) could also be conducted successfully to afford

## TABLE 2. Copper/silver-cocatalyzed Conia−Ene reactions of α-alkynic β-ketoesters (1)[a]

Entry	Substrate	*t* (h)	Product	Yield (%)
1	(1b)	23	(2b)	67
2	(1c)	24	(2c)	78
3	(1d)	20	(2d)	91
4	(1e)	20	(2e)	95
5	(1f)	23	(2f)	86
6	(1g)	48	(2g)	40
7	(1h)	24	(2h)	95
8	(1i)	24	(2i)	30
9[b]	(1i)	24	(2i)	55
10[b]	(1j)	24	(2j)	trace
11	(1k)	46	(2k)	29
12[b]	(1k)	46	(2k)	50
13[b]	(1l)	24	(2l)	47

[a] Reaction conditions: **1** (0.2 mmol), (CuOTf)₂·C₆H₆ (10 mol %), AgBF₄ (10 mol %), CH₂ClCH₂Cl (5 mL) at 100 °C under argon atmosphere. All substrates were consumed completely determined by GC-MS analysis and TLC. [b] (CuOTf)₂·C₆H₆ (20 mol %) and AgBF₄ (20 mol %).

TABLE 3. Copper/Silver-Cocatalyzed Conia−Ene Reactions of α-(Substituted alkynic) β-Ketoesters (1)[a]

entry	R	yield (%)
1	C_6H_5 (**1m**)	35 (**2m**)
2	4-MeOC$_6$H$_4$ (**1n**)	30 (**2n**)
3	Me (**1o**)	messy

[a] Reaction conditions: **1** (0.2 mmol), (CuOTf)$_2$·C$_6$H$_6$ (10 mol %), AgBF$_4$ (10 mol %), CH$_2$ClCH$_2$Cl (5 mL) at 100 °C under argon atmosphere. All substrates were consumed completely determined by GC−MS analysis and TLC. The byproduct are complex including some decarbonylation and/or hydrolysis products.

SCHEME 3. A Working Mechanism
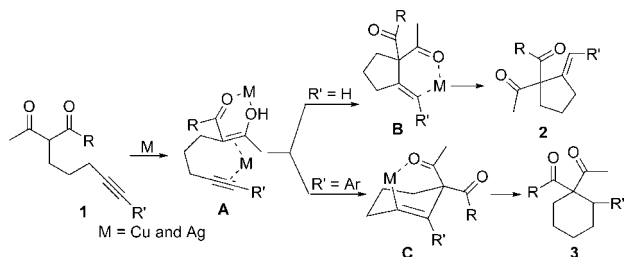
the target product **2i** in 30% yield under the standard conditions and 55% yield at 20 mol % loadings of both (CuOTf)$_2$·C$_6$H$_6$ and AgBF$_4$ (entries 8 and 9). However, cyclization of 2-(pent-4-ynyl)malononitrile (**1j**) was unsuccessful (entry 10). It is noteworthy that diethyl 2-(pent-4-ynyl)malonate (**1k**) is a suitable substrate for the reaction, which represents the first example of the cyclization of diester (entries 11 and 12). In the presence of 20 mol % of (CuOTf)$_2$·C$_6$H$_6$ and 20 mol % of AgBF$_4$, the desired product **2k** was isolated in 50% yield after 46 h from the cyclization of diester **1k** (entry 12). Interesting, 2-(pent-4-ynyl)cyclopentane-1,3-dione (**1l**) could also underwent the cyclization smoothly to afford a spiro[4,4]cyclic prdouct **2l** in moderate yield under the same conditions (entry 13).

Surprisingly, copper/silver-cocatalyzed Conia−ene reactions of α-arylalkynic β-ketoesters gave overhydrogenated *endo*-products under the standard conditions, and the results are summarized in Table 3. In the presence of (CuOTf)$_2$·C$_6$H$_6$ and AgBF$_4$, both α-phenylalkynic β-ketoester **1m** and α-(4-methoxyphenyl)alkynic β-ketoester **1n** could undergo the Conia−ene reaction to afford the corresponding over- hydrogenated *endo*-products in 35% and 30% yields, respectively (entries 1 and 2). However, aliphatic alkyne **1o**, a substrate bearing a methyl group at the terminal alkyne, gave messy results under the standard conditions.

To elucidate the above results, a working mechanism as outlined in Scheme 3 was proposed on the basis of previously reported mechanism.[1−8] Generally, two mechanisms are proposed for the Conia−ene reaction of α-alkynic β-ketoesters: (1) nucleophilic attack on a M−alkyne complex by the enol form of the ketoester and (2) a M−enolate formation by directly complex with the β-ketoester, followed by a *cis*-carbonmetalation of the alkyne.[6] The present results suggested that intermediate **A** may be generated by the complex of one metal with alkyne and another metal with β-ketoester, which is similar to the mechanism proposed by Toste.[6] The intramolecular attack of the M−enolate on the M−complex alkyne is subsequently taken place to form intermediates **B** or intermediates **C**. Intermediates **B** undergoes the protonation/isomerization sequence to give the corresponding *exo*-products **2**, and intermediates **C** undergoes the overprotonation/isomerization to give the corresponding *endo*-products. The present results showed obviously that the selectivity toward *endo*- or *exo*-products depended on the substitutes at the terminal of alkynes. Based on the previous and present results,[1−7] we deduced that the *endo*-products were obtained exclusively from α-arylacetylenic β-ketoesters due to the properties, such as steric hindrance, of the aryl group at the terminal of alkynes. The source of hydrogen in the overhydrogenation process may be from H$_2$O. Further study of the true mechanism for the selectivity is in progress.

In summary, we have developed a copper/silver-cocatalyzed Conia−ene intramolecular reaction of 2-alkynic 1,3-dicarbonyl compounds protocol for selectively synthesizing *exo*- and *endo*-products. We found that the reaction could be conducted by either (CuOTf)$_2$·C$_6$H$_6$ or AgBF$_4$, but the best results were observed using the Cu/Ag cocatalysts. In the presence of (CuOTf)$_2$·C$_6$H$_6$ and AgBF$_4$, a variety of 2-alkynic 1,3-dicarbonyl compounds, including α-alkynic β-ketoesters, α-alkynic β-diketo, 2-phenylacetylhept-6-ynenitrile, and diethyl 2-(pent-4-ynyl)malonate, selectively underwent the Conia−ene intramolecular reaction in moderate to good yields. It is worth noting that both acetylhept-6-ynenitrile and 2-(pent-4-ynyl)malonate are suitable substrates under the standard conditions, and the selectivity toward *endo*- or *exo*-products depends on the substitutents at the terminal of alkynes.

Experimental Section

Typical Experimental Procedure for the Conia−Ene Reaction. A mixture of 2-alkynic 1,3-dicarbonyl compound **1** (0.2 mmol), (CuOTf)$_2$·C$_6$H$_6$ (10 mol %), and AgBF$_4$ (10 mol %) in CH$_2$ClCH$_2$Cl (5 mL) was stirred at 100 °C under argon atmosphere until complete consumption of starting material as monitored by TLC and GC−MS analysis. Then the mixture was filtered by a crude column, washed with diethyl ether, and evaporated under vacuum. The residue was purified by flash column chromatography to afford the pure product (hexane/ethyl acetate).

Ethyl 1-acetyl-2-methylcyclopent-2-enecarboxylate (2b): colorless oil; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.70 (t, *J* = 2.5 Hz, 1H), 4.25−4.21 (m, 2H), 2.65−2.60 (m, 1H), 2.41−2.30 (m, 2H), 2.24−2.22 (m, 1H), 2.22 (s, 3H), 1.83 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 204.9, 171.7, 137.5, 132.0, 70.4, 61.2, 32.8, 30.3, 26.7, 14.8, 14.1; IR (KBr, cm^{-1}) 1726, 1669; LRMS (EI, 70 eV) *m/z* 196 (M$^+$, 10), 123 (−CO$_2$Et, 100); HRMS (EI) for C$_{11}$H$_{16}$O$_3$ (M$^+$) calcd 196.1099, found 196.1097.

Supporting Information Available: General experimental procedures, characterization data for compounds **2** and **3**, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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