DOI: 10.1002/adsc.200900588

General Zinc-Catalyzed Conia-Ene Reactions of 1,3-Dicarbonyl Compounds with Alkynes Including the Classically Challenging Substrates under Neat Conditions

Chen-Liang Deng,[a] Ren-Jie Song,[b] Yi-Lin Liu,[b] and Jin-Heng Li[a,b,*]

[a] College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, People's Republic of China
Fax: (+86)-577-8836-8607; phone: (+86)-577-8836-8607; e-mail: jhli@hunnu.edu.cn

[b] Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research (Ministry of Education), Hunan Normal University, Changsha 410081, People's Republic of China

Received: August 26, 2009; Revised: October 20, 2009; Published online: November 24, 2009

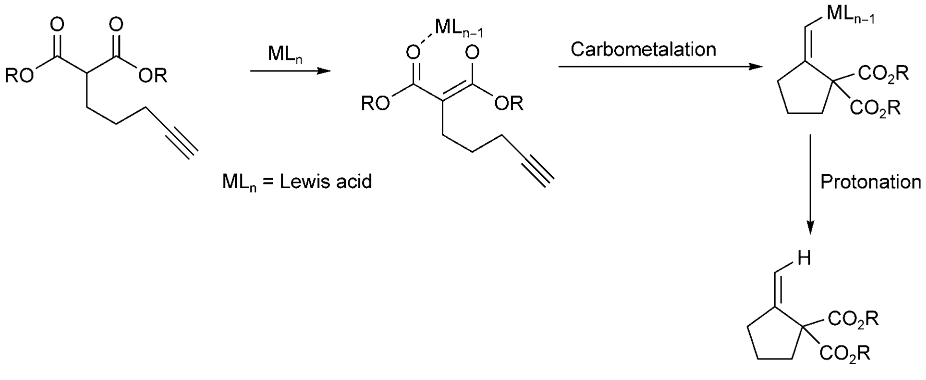
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900588.

Abstract: A simple, versatile new approach to four-membered ring to six-membered ring products has been developed by zinc-catalyzed intramolecular Conia-ene reactions of 1,3-dicarbonyl compounds with alkynes. This new route allows a wide range of dicarbonyl compounds, including the classically challenging 1,3-diesters and *N,N′*-disubstituted 1,3-keto amides, to be used for the Conia-ene reaction with inexpensive zinc chloride ($ZnCl_2$) under neat conditions.

Keywords: alkynes; 1,3-dicarbonyl compounds; intramolecular conia-ene reaction; solvent-free reactions; zinc

The Conia-ene cyclization of an alkyne with an enolizable carbonyl group is a fundamental method in organic synthesis for carbon-carbon bond formation.[1–7] However, major limitations in its application to organic synthesis are the reaction conditions, such as high temperature (>260 °C),[1] strong base, strong acid or photochemical activation (often UV irradiation).[2,3] Recently, a few new catalytic systems, including Au/Ag,[4] $Ni(acac)_2/Yb(OTf)_3$,[5] $In(NTf_2)_3$,[6] and $(CuOTf)_2{\cdot}C_6H_6/Ag$,[7] were developed for the Conia-ene reaction under mild and neutral conditions. Despite the great advantages of these methods, certain limitations are still presented: (i) less reactive nucleophiles, such as 1,3-diesters[3,7b] and *N,N′*-disubstituted 3-ketoamides,[4a,5] are unsatisfactory substrates under these conditions; (ii) construction of a four-membered ring remains an unexplored area; (iii) These new catalytic systems are highly expensive,[8] and the used solvents are harmful in view of the environment. To overcome these drawbacks, herein we report a general and inexpensive Zn-catalyzed Conia-ene protocol capable of converting acetylenic 1,3-dicarbonyl compounds, including the classically challenging substrates, to four-membered ring to six-membered ring products under neat conditions.[9,10]

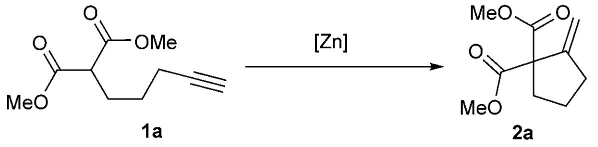
The key step for the Conia-ene reaction is the enolized α-position of the carbonyl group (Scheme 1). The current Conia-ene reactions of alkynylated malonates



Scheme 1. The reported Lewis acid-mediated mechanism.

approach uses an excess stoichiometric amount of strong Ti,[3a] Zn (an example)[3a] and Sn[3b] Lewis acids with the aid of bases. Although this method is compatible with alkynylated malonates in good yields, the high metal loadings, resulting in toxic by-products, hardly make this an attractive procedure. By comparison with these results and Ley's results,[3,9] we envisioned that a new catalytic access to cyclization of 1,3-diesters using Zn may be feasible. To verify this, our initial investigation began with the reaction of dimethyl 2-(pent-4-ynyl)malonate (**1a**) using various Zn salts (Table 1, entries 1–5). As expected, treatment of substrate **1a** with Zn salts at 100 °C afforded the target product **2a** in moderate to good yields, and the active order is $ZnCl_2$, $Zn(OTf)_2 > ZnBr_2 > ZnI_2$ in terms of yields. Other Lewis acids, including $FeCl_3$, $AlCl_3$ and $SnCl_4$, are less effective (entries 6–8). A good yield is still achieved at a loading of 5 mol% of $ZnCl_2$ (entry 9). The reaction at room temperature gave 36% yield in 24 h (entry 10). It is noteworthy that under neat conditions the pure product **2a** can be obtained directly in 96% yield after 9 h by washing with water, extracting with diethyl ether and evaporating under vacuum without column chromatography (the purity is over 98% determined by GC-MS analysis using nitrobenzene as the internal standard; entry 11).

Table 1. Screening reaction conditions.[a]



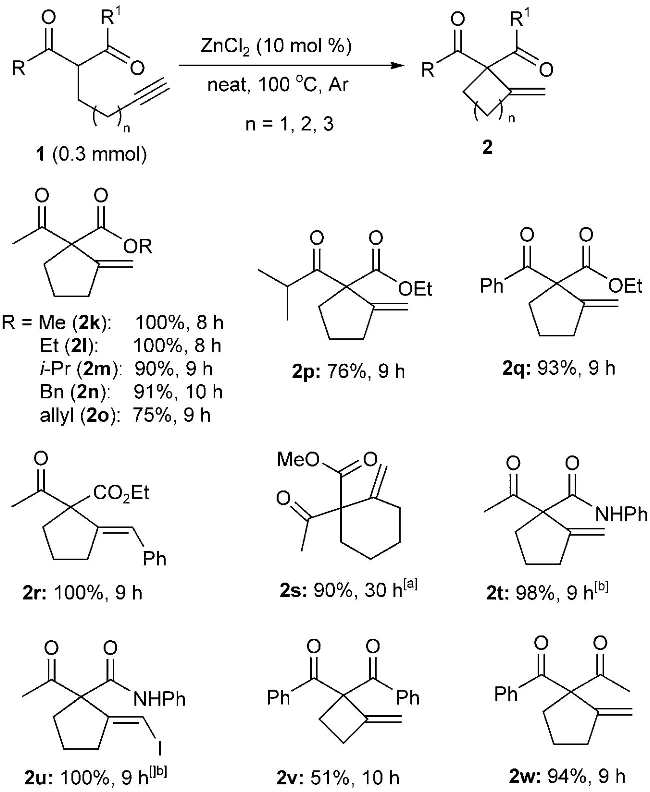
Entry	Lewis acid	Solvent	T [°C]	Time [h]	Yield [%]
1	ZnI_2	toluene	100	24	70
2	ZnI_2	$ClCH_2CH_2Cl$	100	24	75
3	$ZnBr_2$	$ClCH_2CH_2Cl$	100	24	80
4	$ZnCl_2$	$ClCH_2CH_2Cl$	100	24	86
5	$Zn(OTf)_2$	$ClCH_2CH_2Cl$	100	24	85
6	$FeCl_3$	$ClCH_2CH_2Cl$	100	24	trace
7	$AlCl_3$	$ClCH_2CH_2Cl$	100	24	trace
8	$SnCl_4$	$ClCH_2CH_2Cl$	100	24	25
9[b]	$ZnCl_2$	$ClCH_2CH_2Cl$	100	24	70
10	$ZnCl_2$	$ClCH_2CH_2Cl$	25	24	36
11	$ZnCl_2$	–	100	9	96

[a] *Reaction conditions:* **1a** (0.3 mmol), Lewis acid (10 mol%) and solvent (2 mL).

[b] $ZnCl_2$ (5 mol%) was added.

A variety of challenging substrates, including alkynylated malonates **1b–1h** and amides **1i–1j**, were subsequently examined under the optimized neat conditions (Table 2). We found that a number of ester groups, such as methyl, allyl, isopropyl, ethyl, or benzyl groups, were tolerated well but the *tert*-butyl group was inconsistent (entries 1–9). While good yields were obtained from methyl, allyl, isopropyl or ethyl esters, both benzyl and *tert*-butyl esters provided moderate yields (entries 1–6). Moreover, decarboxylation of *tert*-butyl ester **1e** took place to afford methyl 2-methylcyclopent-1-enecarboxylate (**2e**) in 60% yield (entry 4). Iodo-substituted internal alkyne **1g**, for instance, was converted to the target product (*E*)-**2g** in 91% yield (entry 6).[11] Interestingly, 2-(but-3-ynyl)-malonate **1h** could be cyclized to the corresponding four-membered ring product **2h** in moderate yield (entry 7). It was pleasing to observe that *N,N′*-disubstituted amides **1i** and **1j** were suitable substrates under the optimized neat conditions, although substrate **1i** required higher loadings of $ZnCl_2$, resulting in satisfactory yield (entries 8 and 9). Keto amide **1j**, an inert substrate in the earlier reports,[4a,5] was highly active with $ZnCl_2$ in 98% yield (entry 9).

As shown in Scheme 2, the Zn-catalyzed reaction also accommodates a wide range of acetylenic 1,3-keto esters, keto amides and diketones to construct the corresponding four-membered ring to six-membered ring products. Significantly, both internal and

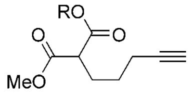
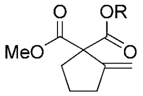
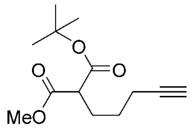
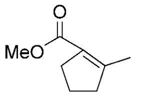
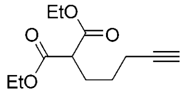
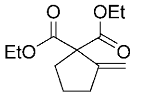
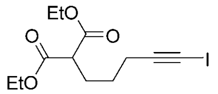
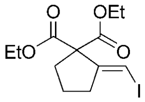
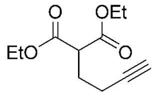
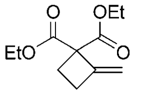
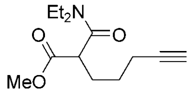
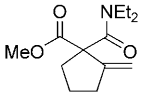
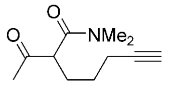
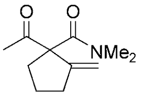


[a] $ZnCl_2$ (40 mol%).

[b] Reaction conducted in $ClCH_2CH_2Cl$ (2 mL).

Scheme 2. $ZnCl_2$-catalyzed Conia-ene reactions of keto esters, keto amides and diketones.

Table 2. $ZnCl_2$-catalyzed reactions of challenging substrates.[a]

Entry	Substrate **1**		Product **2**		Time [h]	Yield [%]
1		R = Bn (**1b**)		R = Bn (**2b**)	15	55
2		R = allyl (**1c**)		R = allyl (**2c**)	9	91
3		R = *i*-Pr (**1d**)		R = *i*-Pr (**2d**)	8	92
4		(**1e**)		(**2e**)	10	60
5		(**1f**)		(**2f**)	9	86
6		(**1g**)		(**2g**)	9	91
7		(**1h**)		(**2h**)	18	46
8[b]		(**1i**)		(**2i**)	30	62
9		(**1j**)		(**2j**)	9	98

[a] *Reaction conditions:* **1** (0.3 mmol) and $ZnCl_2$ (10 mol%) at 100 °C.

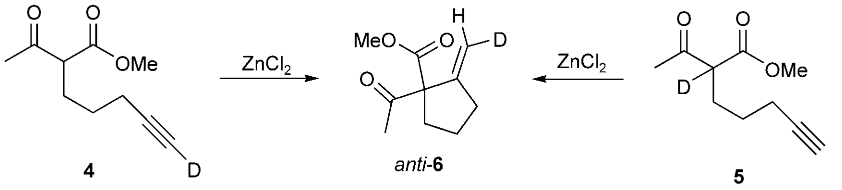
[b] $ZnCl_2$ (40 mol%).

terminal alkynes are perfectly tolerated. Both ethyl 2-acetylhept-6-ynoate and ethyl 2-acetyl-7-phenylhept-6-ynoate, for instance, were treated with $ZnCl_2$ smoothly to afford the corresponding products **2l** and **2r** in quantitative yields. Excellent yields were obtained from the reaction of 1,3-keto amides, two solid substrates, using $ZnCl_2$ catalyst and CH_2ClCH_2Cl solvent. To our delight, the same conditions also were compatible with both ethyl 2-acetyloct-7-ynoate and 2-(but-3-ynyl)-1,3-diphenylpropane-1,3-dione, providing a six-membered ring product **2s** and a four-membered ring product **2v**, respectively.

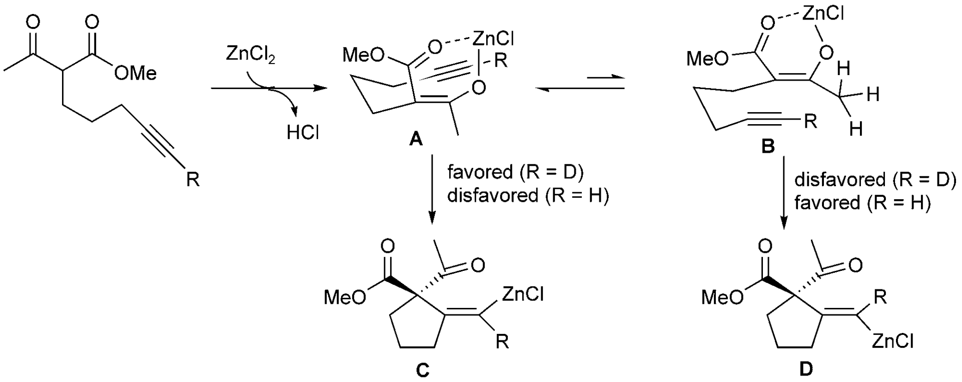
To elucidate the mechanism, two deuterated keto esters **4** and **5** were reacted under the neat conditions (Scheme 3). Cyclization of both **4** and **5** gave the *anti*-deuterated product **6** (the deuterium contents in product **6** are about 40%; **4** to **6**: *anti/syn* = 12:1; **5** to **6**: *anti/syn* = 8:1) as the major product.

Consequently, a possible mechanism was proposed as outlined in Scheme 4 on the basis of the present results and the reported mechanism.[1–7,10] Complexation of substrate with $ZnCl_2$ readily occurs to give intermediates **A** and **B**, followed by cyclization to afford the corresponding intermediates **C** and **D**, respectively.[3] Finally, the target products are obtained from protonation of intermediates **C** and **D**, respectively. The selectivity toward intermediate **C** or intermediate **D** may depend on the properties, including the steric effect, of the R group. Studies on the detailed mechanism are in progress.

In summary, a simple, versatile new approach to the synthesis of four-membered ring to six-membered ring products has been developed. This new route allows a wide range of alkynylated dicarbonyl compounds, including the classically challenging 1,3-diesters and *N,N'*-disubstituted amides, for the Conia-



Scheme 3. The deuterated keto ester experiments.



Scheme 4. Possible mechanism.

ene reaction with a catalytic amount of inexpensive $ZnCl_2$ catalyst under neat conditions. Importantly, we provide the first example of the construction of four-membered rings by the Conia-ene reaction. Work to understand the mechanism and extend the scope of both the reaction and products in the preparation of biologically active compounds is currently underway.

Experimental Section

Typical Experimental Procedure for Zn-Catalyzed Conia-ene Reaction:

A mixture of substrate **1** (0.3 mmol) and $ZnCl_2$ (10 mol%) under neat or DCE (2 mL) conditions was added in turn into a 25-mL glass sealed tube, the mixture was stirred under an argon atmosphere at 100 °C for the desired time until complete consumption of the starting material as monitored by TLC and GC-MS analysis. Then the mixture was diluted with diethyl ether, washed with saturated NaCl, and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the pure product **2**.

Dimethyl 2-methylenecyclopentane-1,1-dicarboxylate (2a):[3a] Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.30$ (t, $J = 2.5$ Hz, 1H), 5.27 (t, $J = 2.0$ Hz, 1H), 3.75 (s, 3H), 2.48–2.44 (m, 2H), 2.35 (d, $J = 7.0$ Hz, 2H), 1.78–1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.2$, 148.2, 112.0, 63.5, 52.7, 36.3, 33.7, 24.1; IR (KBr): $\nu = 1730$ cm^{-1}; LR-MS (EI, 70 eV): m/z (%) = 198 (M^+, 4), 138 ($M^+ - COOMe$, 100).

Acknowledgements

We thank the National Natural Science Foundation of China (No. 20872112), Zhejiang Provincial Natural Science Foundation of China (No. Y407116), and Program for New Century Excellent Talents in University (No. NCET-06–0711) for financial support.

References

[1] a) J. M. Conia, P. Le Perchec, *Synthesis* **1975**, 1; b) D. Caine, in: *Comprehensive Organic Synthesis*, (Eds.: B. M.Trost, I. Fleming), Pergamon Press, New York, **1991**, Vol. 3, pp 1–63.

[2] Pd: a) T. Lomberget, D. Bouyssi, G. Balme, *Synthesis* **2005**, 311, and references cited therein; b) B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 17168; Mo: c) F. E. McDonald, T. C. Olson, *Tetrahedron Lett.* **1997**, *38*, 7691; Cu: d) D. Bouyssi, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1297; Hg: e) M. A. Boaventura, J. Drouin, J. M. Conia, *Synthesis* **1983**, 801; Co: f) P. Cruciani, C. Aubert, M. Malacria, *Tetrahedron Lett.* **1994**, *35*, 6677; g) R. Stammler, M. Malacria, *Synlett* **1994**, 92; h) J.-L. Renaud, M. Petit, C. Aubert, M. Malacria, *Synlett* **1997**, 931; i) J.-L. Renaud, C. Aubert, M. Malacria, *Tetrahedron* **1999**, *55*, 5113.

[3] For papers on Lewis acid-mediated reactions, see for Ti or Zn (an example): a) O. Kitagawa, T. Suzuki, T. Inoue, Y. Watanabe, T. Taguchi, *J. Org. Chem.* **1998**, *63*, 9470; Sn: b) O. Kitagawa, H. Fujiwara, T. Suzuki, T. Taguchi, M. Shiro, *J. Org. Chem.* **2000**, *65*, 6819.

[4] Au: a) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526; b) S. T. Staben, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2004**, *116*, 5464; *Angew. Chem. Int. Ed.* **2004**, *43*, 5350; c) N. Mezailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133; d) A. Ochida, H. Ito, M. Sawamura, *J. Am. Chem. Soc.* **2006**, *128*, 16486; e) J.-H. Pan, M. Yang, Q. Gao, N.-Y. Zhu, D. Yang, *Synthesis* **2007**, 2539; f) H. Ito, Y. Makida, A. Ochida, H. Ohmiya, M, Sawamura, *Org. Lett.* **2008**, *10*, 5051; g) Y. Kuninobu, A. Kawata, K. Takai, *Org. Lett.* **2005**, *7*, 4823.

[5] Ni: Q. Gao, B.-F. Zheng, J.-H. Li, D. Yang, *Org. Lett.* **2005**, *7*, 2185.

[6] In: a) H. Tsuji, K.-i. Yamagata, Y. Itoh, K. Endo, M. Nakamura, E. Nakamura, *Angew. Chem.* **2007**, *119*, 8206; *Angew. Chem. Int. Ed.* **2007**, *46*, 8060; b) Y. Itoh, H. Tsuji, K.-i. Yamagata, K. Endo, I. Tanaka, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 17161; c) K. Takahashi, M. Midori, K. Kawano, J. Ishi-

hara, S. Hatakeyama, *Angew. Chem.* **2008**, *120*, 6340; *Angew. Chem. Int. Ed.* **2008**, *47*, 6244.

[7] Cu/Ag: a) C.-L. Deng, R.-J. Song, S.-M. Guo, Z.-Q. Wang, J.-H. Li, *Org. Lett.* **2007**, *9*, 5111; b) C.-L. Deng, T. Zou, Z.-Q. Wang, R.-J. Song, J.-H. Li, *J. Org. Chem.* **2009**, *74*, 412; c) T. Yang, A. Ferrali, F. Sladojevich, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 9140.

[8] Zinc chloride, anhydrous, 98+%: 35.3 USD/500 g (Alfa Aesar Cop.).

[9] The Conia-ene reaction of methyl 3,3-dimethyl-6-oxo-2-(pent-4-ynyl)cyclohexanecarboxylate by ZnI_2 has been reported, but the scope of this cyclization has not yet been examined, see: W. P. Jackson, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1* **1981**, 1156.

[10] For selected papers on Zn-catalyzed intramolecular reactions, see: a) P. J. Lennon, D. P. Mack, Q. E. Thompson, *Organometallics* **1989**, *8*, 1121; b) M. Nakamura, T. Fujimoto, K. Endo, E. Nakamura, *Org. Lett.* **2004**, *6*, 4837; c) M. Nakamura, C. Liang, E. Nakamura, *Org. Lett.* **2004**, *6*, 2015; d) M. Nakamura, C. Liang, E. Nakamura, *Org. Lett.* **2004**, *6*, 3017; e) S. Morikawa, S. Yamazaki, Y. Furusaki, N. Amano, K. Zenke, K. Kakiuchi, *J. Org. Chem.* **2006**, *71*, 3540; f) S. Morikawa, S. Yamazaki, M. Tsukada, S. Izuhara, T. Morimoto, K. Kakiuchi, *J. Org. Chem.* **2007**, *72*, 6459; g) Y. Yin, W. Ma, Z. Chai, G. Zhao, *J. Org. Chem.* **2007**, *72*, 5731; h) A. Sniady, A. Durham, M. S. Morreale, K. A. Wheeler, R. Dembinski, *Org. Lett.* **2007**, *9*, 1175; i) S. Yamazaki, S. Morikawa, K. Miyazaki, M. Takebayashi, Y. Yamamoto, T. Morimoto, K. Kakiuchi, Y. Mikata, *Org. Lett.* **2009**, *11*, 2796.

[11] The stereochemistry of the products **2g** and **2w** was assigned on the basis of the authoritatively reported chemical shift of the olefinic proton of the corresponding products (In the ^{1}H NMR spectra: $\delta = 6.59$ for **2g**; 6.75 for **2w**; 6.59 for (*E*)-l-,l-dicarbomethoxy-2-(iodomethy1ene)cyclopentane and 6.46 for (*Z*)-l-,l-dicarbomethoxy-2-(iodomethy1ene)cyclopentane, see: O. Kitagawa, T. Inoue, K. Hirano, T. Taguchi, *J. Org. Chem.* **1993**, *58*, 3106, also see ref.[6b]