DOI: 10.1002/adsc.201000351

An Efficient and General Microwave-Assisted Copper-Catalyzed Conia-Ene Reaction of Terminal and Internal Alkynes Tethered to a Wide Variety of Carbonucleophiles

Sonia Montel,[a] Didier Bouyssi,[a,*] and Geneviève Balme[a,*]

[a] ICBMS, Institut de Chimie et Biochimie Moléculaire et Supramoléculaire – (UMR CNRS 5246) – Université Lyon I, ESCPE Lyon, Bât Curien, 43 Bd du 11 novembre 1918, 69622 Villeurbanne, France
Fax: (+33)-4-7244-8232; e-mail: bouyssi@univ-lyon1.fr or balme@univ-lyon1.fr

Received: May 5, 2010; Published online: September 2, 2010

Abstract: This paper describes a highly efficient, microwave-assisted, Conia-ene reaction of alkynes bearing a stabilizing carbon nucleophile. The reaction, catalyzed by a commercially available copper catalyst, proceeds under neutral conditions and is generally applicable even to less reactive nucleophiles such as malonate, cyanoacetate, and sulfonylacetate derivatives. This copper-mediated cycloisomerization is also applicable to internal unactivated alkynes leading exclusively to the corresponding 5-membererd products having an *E*-olefinic chemistry.

Keywords: alkynes; Conia-ene reaction; copper; cyclization; microwave irradiation

Introduction

The importance of natural products of biological interest containing the cyclopentyl moiety has stimulated in recent years the development of various synthetic methods to gain access to such structures.[1] Among them, the cyclization of terminal alkynes bearing an enolizable carbonyl group (the so-called Conia-ene type reaction) and leading to functionalized methylenecyclopentanes has been extensively explored in recent decades. Indeed, after Conia's pioneering work on the thermal cyclization of ε-acetylenic carbonyl compounds at temperatures above 300 °C,[2] the first metal-catalyzed version of this reaction was developed in 1983 by the same group by use of $HgCl_2$ in strong acidic media.[3] However the drastic reaction conditions required or the toxicity of mercury salts limited the scope of application of these two cycloisomerization reactions. Therefore, further studies have been carried out with the aim of finding milder conditions reactions or extending the scope of the reaction to a wide variety of carbonucleophilic substrates. In this context, in 1994, a cobalt-mediated ene-reaction under UV irradiation of various keto ester-tethered alkynes was developed.[4] This was followed by various transition metal- or Lewis acid-catalyzed Conia-ene reactions developed under mild and neutral conditions.[5] Although these processes are synthetically very useful, they suffer from some limitations since their applications are restricted to highly enolizable β-keto esters or β-diketones as nucleophiles.[6] Other active methylene compounds such as malonate or cyanoacetate derivatives remained unaffected due to their lower acidity and enolizable ability. In 1991, our group had overcome this restriction in successfully developing a general method allowing the cyclization of a variety of δ-acetylenic-stabilized carbanions by using catalytic quantities of both a palladium complex and potassium *tert*-butoxide.[7] More recently, we communicated a similar cyclization reaction using inexpensive copper salts such as CuI as catalyst in place of palladium.[8] However, these two last Conia-ene reactions require the presence of catalytic amounts of strong base that may limit their applicability in organic synthesis. In 2009, Li and co-workers have reported an efficient Conia-ene reaction of ε-acetylenic β-keto esters in the presence of catalytic amounts of $(CuOTf)_2{\cdot}C_6H_6$ (0.1 equiv.) and $AgBF_4$ (0.1 equiv.) in DCE at 100 °C. However, attempts to extend these results to less reactive methine compounds met with limited success.[9]

In an effort to overcome this limitation, we have revisited the copper-catalyzed Conia-ene reaction and, in this update, we report the development of a new catalytic method for this process based on the use of the inexpensive, stable to air, soluble, ready available cationic copper complex, $Cu[(phen)(PPh_3)_2]NO_3$,[10] under low catalyst loading with the assistance of microwave irradiation. This improved procedure allows the reaction to proceed in high yields, under neutral conditions, with only 1 mol% catalyst and is generally applicable even to the less reactive malonate, cyanoacetate, and sulfonylacetate derivatives. Moreover,

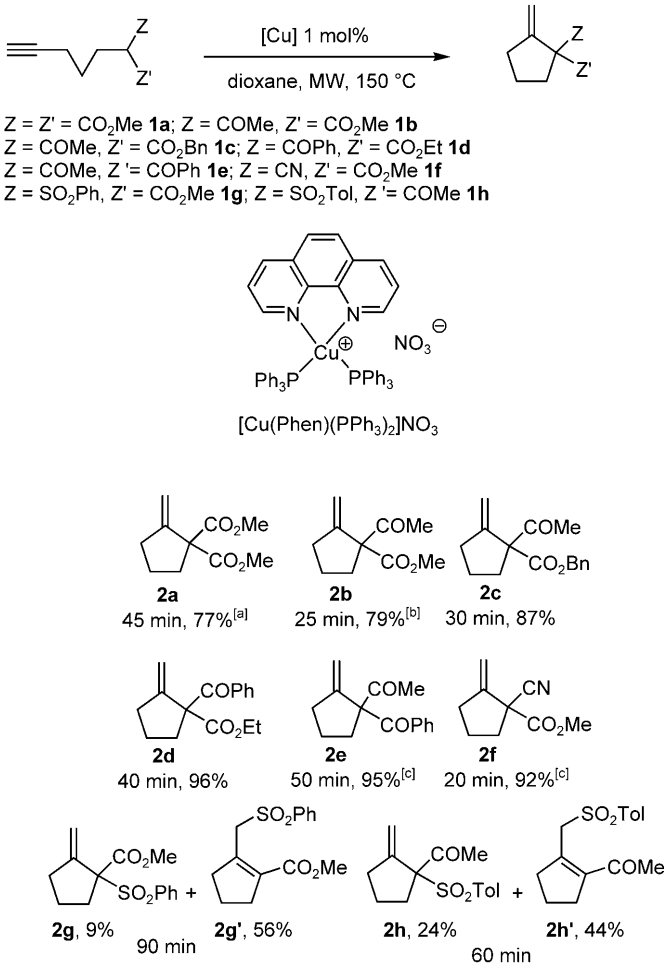
this cycloisomerization reaction was successfully extended to the more challenging non-terminal alkynes, leading exclusively to the corresponding *trans*-adducts in good to excellent yields.

Results and Discussion

Application of microwave irradiations in organic synthesis has become very popular over the past few years.[11] Indeed, this new technology is now recognized as a powerful tool to accelerate organic reactions and to improve the yields and the substrate scope. However, to the best of our knowledge, microwave irradiation to enhance the Conia-ene type reactions has never been explored. Therefore, with the idea of finding a low copper catalyst loading procedure using neutral conditions, we envisioned to perform the Conia reaction of a wide range of active methine compounds bearing a 4-alkynyl group under microwave irradiation.

Preliminary microwave experiments were performed on the diester-tethered alkyne **1a** as model substrate in order to determine the optimum conditions for the cycloisomerization reaction. The reactions were carried out at 150 °C, with 1 mol% of $Cu[(phen)(PPh_3)_2]NO_3$, in several solvents including THF, DMSO, CH_3CN, MeOH, NMP, DCE, DME, DMF, dioxane, diglyme and toluene. Only dioxane was successful in this reaction leading to the corresponding exo-cyclized product **2a** in 77% yields after 45 min reaction while the use of THF afforded only minor yields of product. In the case of the other tested solvents, no conversion was detected while a degradation of the starting material was observed. Importantly, no reaction took place under conventional heating conditions, even after a long reflux in dioxane with 5 mol% catalyst loading. Other control experiments verified that no observable reaction occurred in the absence of the copper catalyst, or in the sole presence of the phenanthroline ligand. The reaction was also conducted in the presence of CuI as catalyst but only the starting material was recovered.

To define the scope of this novel copper-catalyzed Conia-ene reaction performed under neutral conditions, several other active methine compounds bearing a 4-alkynyl group were examined using our above-mentioned optimal conditions. Representative results are shown in Scheme 1. Cyclization of the more acidic ω-acetylenic β-keto esters **1b–d** and diketone **1e** proceeded efficiently leading to the corresponding exocyclic substrates **2b–e** in excellent yields. The ω-acetylenic β-cyano ester **1f** also underwent the desired cyclization reaction to give the corresponding product in high yield after microwave irradiation at 150 °C for 20 min (2 mol% catalyst). The reactivity of the more challenging α-sulfonyl ε-acetylenic ester **1g**

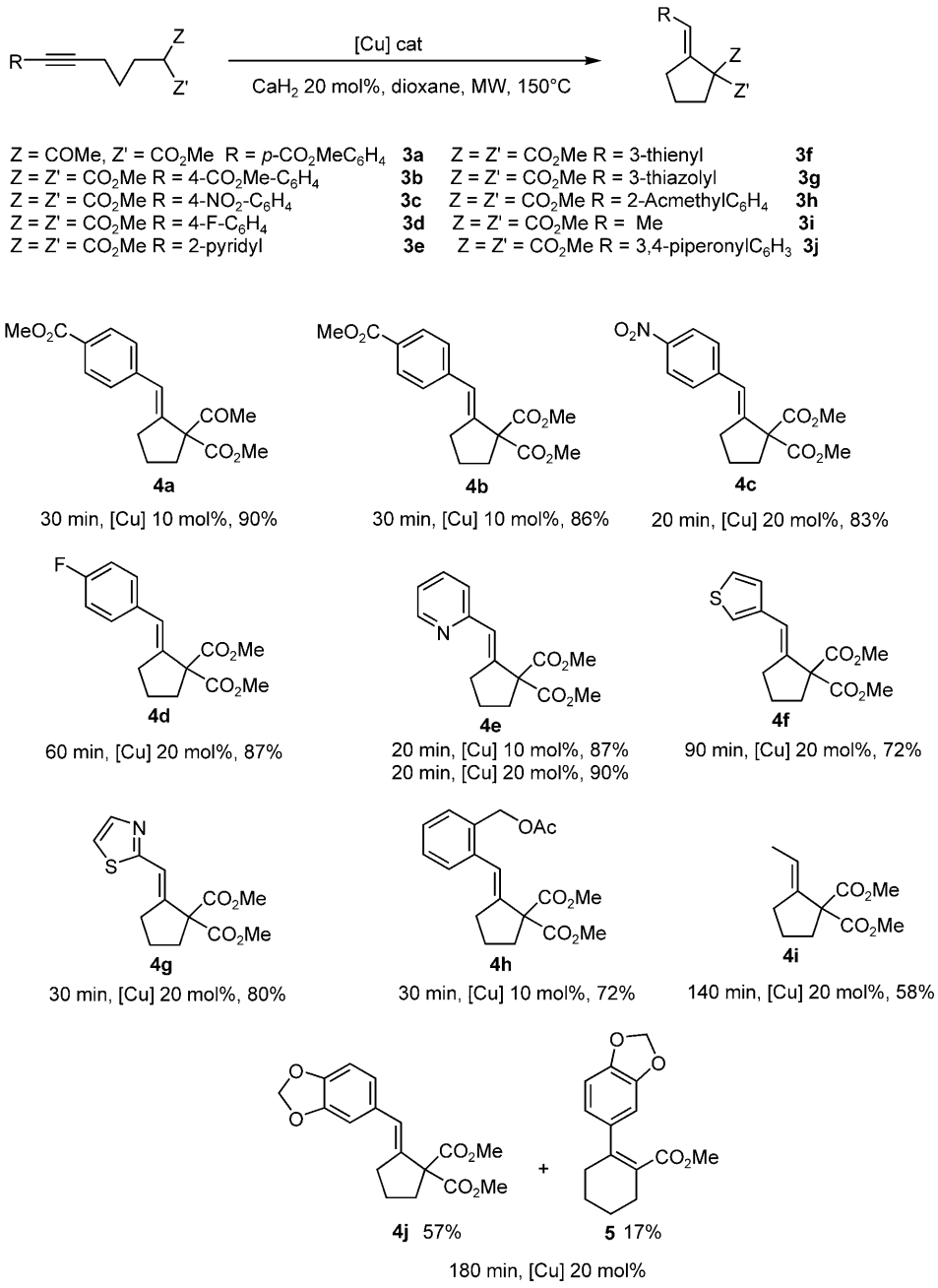


Scheme 1. Copper-catalyzed Conia-ene reaction developed on terminal alkynes. [a] All reactions were run at 150 °C under microwave irradiation in dioxane using 1 mol% of $[Cu(Phen)(PPh_3)_2]NO_3$ as catalyst.[b] THF was used instead of dioxane.[c] 2 mol% of catalyst were used.

was also investigated. Indeed, earlier work in our laboratory has shown that, in this case, due to the ability of the resulting tertiary allylic sulfonyl group to act as a leaving group, the CuI-catalyzed cycloisomerization generates a carbenoid copper complex which evolves to the formation of a dimeric compound.[12] Pleasingly, subjection of sulfonyl ester **1g** to the above microwave-mentioned conditions afforded predominantly the primary allylic sulfone **2g′** arising from the known thermal 1,3-rearrangement of the initially formed tertiary sulfone **2g** which was isolated as the minor compound.[13] Similar results were obtained with the corresponding keto sulfone **1h**.

Encouraged by these results, we further investigated the application of the above-mentioned cycloisomerization to internal alkynes.[14] To the best of our knowledge, only very few successful examples describe the Conia-ene cycloisomerization of such substrates and they are limited to those having β-keto

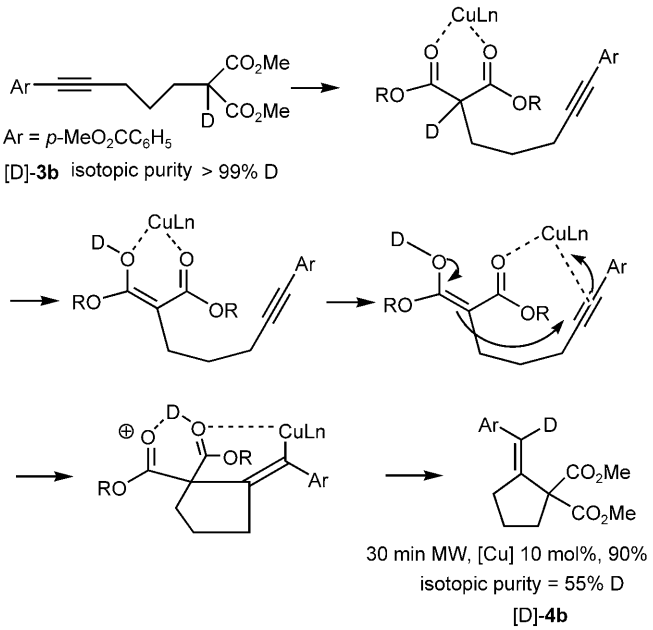
esters as nucleophiles, and a competitive 5-*exo*/6-*endo* cyclization mode is also generally observed.[15] Our first attempt to perform the cycloisomerization of the aryl-substituted alkyne **3a** under our optimized conditions failed to give a cyclized product. Increasing the quantity of copper catalyst added from 2 mol% to 10 mol% led to the formation of the 5-*exo* cyclized product **4a** along with other minor unidentified side products in a 60% global yield after microwave irradiation at 150 °C for 75 min. After several fruitless attempts to improve the formation of **4a**, we fortuitously found that catalytic addition of CaH_2 significantly enhances the yield of the cyclization reaction[16] since a 90% yield of **4a**, having exclusively *E*-olefinic chemistry,[17] was obtained when using 20 mol% of CaH_2, 10 mol% of copper catalyst, after microwave irradiation at 150 °C for 30 min in dioxane (Scheme 2). Pleasingly, these latter conditions applied to the less reactive diesters **3b** resulted in the exclusive formation of **4b** in high yield. To explore the scope of this copper-mediated cyclization, we studied the reaction of several diester-tethered alkynes substituted with various substituents including aryl, heteroaryl and alkyl groups and the results are summarized in



Scheme 2. Copper-catalyzed Conia-ene reaction developed on internal alkynes.

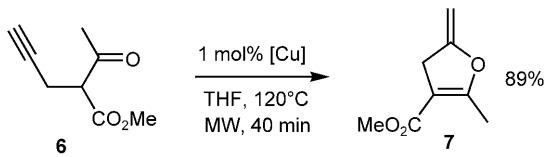
Scheme 2. The cyclization reaction proceeds with good to excellent yields with electron-deficient aryl- and heteroaryl-substituted alkynes (**4c–g**). The reaction occurred comparatively much more slowly with the substituted-alkylalkyne **3i** leading to **4i** and with the alkyne **3j** substituted with a piperonyl moiety. In this latter case, the 5-*exo* cyclized product **4j** was obtained in slightly lower yield (57%) along with 17% of the 6-*endo* cyclized monoester **5**. Interestingly, a functional group such as benzyl acetate is compatible with such conditions (**4h**). To clarify the mechanism of this copper-mediated-cyclization,[18] the reaction of the deuterated alkyne substrate [D]-**3b** was undertaken and led to the exclusive formation of [D]-**4b** with deuterium *syn* to the diester moiety.

This result suggests that this copper-mediated Conia-ene cyclization reaction proceeds *via* formation of a copper enolate intermediate which adds in a *cis* fashion across the triple bond. A subsequent intramolecular deuteration of the copper metalate gives [D]-**4b** and regenerates the copper catalyst (Scheme 3).



Scheme 3. Proposed mechanistic pathway.

The copper-catalyzed Conia-ene reaction of the 2-propynyl-1,3-dicarbonyl derivative **6** was also briefly explored (Scheme 4). It was found that the cyclization reaction took place after microwave irradiation at 120 °C for 20 min in THF, in the presence of $Cu[(phen)(PPh_3)_2]NO_3$ (1 mol%) leading exclusively to the corresponding 5-methylene-4,5-dihydrofuran **7** in 89% yield.[19]



Scheme 4. Access to 5-methylene-4,5-dihydrofuran.

Conclusions

In summary, we have developed an efficient, new, copper-catalyzed Conia-ene cyclization which proceeds under neutral conditions and microwave irradiation, using a variety of tethered stabilized nucleophiles. Moreover, the reaction was successfully extended to internal unactivated alkynes leading in good yields to the corresponding 5-*exo* cyclized products with very high stereoselectivity.

Experimental Section

General Remarks

Proton magnetic resonance (^{1}H NMR) spectra were measured at 300 MHz and carbon magnetic resonance (^{13}C NMR) spectra at 75 MHz with Bruker DRX 300 and ALS 300 spectrometers. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance of chloroform-*d* (δ = 7.26). Spectra were reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constants (reported in Hz). High-resolution mass spectra were recorded on a Thermoquest Finnigan MAT 95 Xl. Melting points (mp) were measured on a Büchi B-540 and are uncorrected. Microwave-assisted synthesis was carried out in an Initiator™ single mode microwave cavity producing controlled irradiation at 2.45 GHz (Biotage AB, Uppsala). The reactions were run in sealed vessels (0.5 to 20 mL) and magnetic stirring was used. A variable power source was employed to reach the desired temperature and then to maintain it in the vessel during the programmed period of time.

General Procedure

In a microwave vial, were successively added 0.25 mmol of active methine compound **1a–h**, 1 mol% of Cu(Phen)-$(PPh_3)_2NO_3$ and 1 mL of dioxane. For compounds **3a–j**, 10 or 20 mol% of copper complex and 20 mol% of CaH_2 were used. The vial was capped and exposed to microwave heating at 150 °C during the defined time (Initiator™ single mode microwave cavity producing controlled irradiation at 2.45 GHz, Biotage AB, Uppsala). After the completion of the reaction (monitored by TLC), the reaction mixture was filtered onto celite, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel to obtain the desired product **2a–h** or **4a–j**.

The product **4e** (yield: 90%) was isolated as a colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–1.88 (m, 1H), 2.38 (t, 2H, J = 7 Hz), 2.93 (t, 2H, J = 7 Hz), 3.75 (s, 6H), 6.8 (s, 1H), 7.09 (br s, 1H), 7.28 (br s, 1H), 7.63 (t, 1H,

$J=7$ Hz), 8.58 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 25.2, 33.3, 36.2, 53.4, 66.4, 117.8, 121.8, 124.7, 126.9, 129.1, 136.8, 147.1, 171.6; ESI-HR-MS: $m/z=276.1229$, calcd. for $[C_{15}H_{17}NO_4+H]^+$: 276.1230.

The product **4f** (yield: 72%) was isolated as a white solid; mp 60–61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.84$–1.93 (m, 2H), 2.41 (t, 2H, $J=7$ Hz), 2.71 (td, 2H, $J=7$, 2.5 Hz), 3.78 (s, 6H), 6.74 (s, 1H), 7.17 (d, 1H, $J=5$ Hz), 7.24 (br s), 7.28–7.31(m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=25.1$, 32.8, 36.5, 53.4, 65.7, 122.0, 123.7, 125.5, 128.9, 139.6, 140.3, 171.9; ESI-HR-MS: $m/z=303.0660$, calcd. for $[C_{14}H_{16}SO_4+Na]^+$: 303.0662.

References

[1] For selected references, see: a) B. M. Trost, A. B. Pinkerton, *J. Org. Chem.* **2001**, *66*, 7714; b) D. F. Taber, H. Yu, C. D. Incarvito, A. L. Rheingold, *J. Am. Chem. Soc.* **1998**, *120*, 13285; c) G. A. Molander, E. D. Dowdy, H. Schumann, *J. Org. Chem.* **1998**, *63*, 3386; d) A. Hassner, E. Ghera, T. Yechezkel, V. Kleiman, T. Balasubramanian, D. Ostercamp, *Pure Appl. Chem.* **2000**, *72*, 1671; e) M. Mikolajczyk, M. Mikina, R. Zurawinski, *Pure Appl. Chem.* **1999**, *71*, 473; f) S. Sakuda, Y. Sugiyama, Z-Y. Zhou, H. Takao, H. Ikeda, K. Kakinuma, Y. Yamada, H. Nagasawa, *J. Org. Chem.* **2001**, *66*, 3356; g) B. Heasley, *Eur. J. Org. Chem.* **2009**, *10*, 1477.

[2] a) R. Bloch, P. Le Perchec, F. Rouessac, J.-M. Conia, *Tetrahedron* **1968**, 24, 5971; b) P. Le Perchec, J.-M. Conia, *Synthesis* **1975**, 1; c) J. Drouin, F. Leyendecker, J.-M. Conia, *Tetrahedron* **1980**, *36*, 1203.

[3] J. Boaventura, J. Drouin, J.-M. Conia, *Synthesis* **1983**, 801.

[4] a) R. Stammler, M. Malacria, *Synlett* **1994**, 92; b) P. Cruciani, C. Aubert, M. Malacria, *Tetrahedron Lett.* **1994**, *35*, 6677; c) P. Cruciani, C. Aubert, M. Malacria, *J. Org. Chem.* **1995**, *60*, 2664; d) P. Cruciani, R. Stammler, C. Aubert, M. Malacria, *J. Org. Chem.* **1996**, *61*, 2699; e) J-L. Renaud, M. Petit, C. Aubert, M. Malacria, *Synlett* **1997**, 931; f) J.-L. Renaud, C. Aubert, M. Malacria, *Tetrahedron* **1999**, *55*, 5113; g) C. Aubert, O. Buisine, M. Petit, F. Slowinski, M. Malacria, *Pure Appl. Chem.* **1999**, *71*, 1463.

[5] For Mo-catalyzed Conia-ene reactions: a) F. E. McDonald, T. C. Olson, *Tetrahedron Lett.* **1997**, *38*, 7691; Re-catalyzed reactions: b) Y. Kuninobu, A. Kawata, K. Takai, *Org. Lett.* **2005**, *7*, 4823; Ni/Yb-catalyzed reactions: c) Q. Gao, B.-F. Zheng, J.-H. Li, D. Yang, *Org. Lett.* **2005**, *7*, 2185; Au-catalyzed reactions: d) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526; e) S. T. Staben, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2004**, *116*, 344; *Angew. Chem. Int. Ed.* **2004**, *43*, 340; f) A. Ochida, H. Ito, M. Sawamura, *J. Am. Chem. Soc.* **2006**, *128*, 16486; g) J.-H. Pan, M. Yang, Q. Gao, N.-Y. Zhu, D. Yang, *Synthesis* **2007**, 2539; h) H. Ito, Y. Makida, H. Ohmiya, M. Sawamura, *Org. Lett.* **2008**, *10*, 5051; i) F. Gagosz, *Org. Lett.* **2005**, *7*, 4133; Pd/Yb-catalyzed reactions: j) B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 17168; In-catalyzed reactions: k) Y. Itoh, H. Tsuji, K.-I. Yamagata, K. Endo, I. Tanaka, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 17161; Sn-catalyzed reactions: l) O. Kitagawa, H. Fujiwara, T. Suzuki, T. Tagushi, M. Shiro, *J. Org. Chem.* **2000**, *65*, 6819.

[6] A Conia-ene type cyclization of nitrogen- and oxygen-tethered acetylenic malonic esters was recently reported using catalytic amounts of $In(OTf)_3$ and DBU: K. Takahashi, M. Midori, K. Kawano, J. Ishihara, S. Hatakeyama, *Angew. Chem.* **2008**, *120*, 6340; *Angew. Chem. Int. Ed.* **2008**, *47*, 6244. For other related metal-catalyzed cyclization reactions leading to nitrogen and oxygen heterocycles, see: a) X. Marat, N. Monteiro, G. Balme, *Synlett* **1997**, 845; b) B. Clique, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1301; c) M. Cavicchioli, X. Marat, N. Monteiro, B. Hartmann, G. Balme *Tetrahedron Lett.* **2002**, *43*, 2609; d) M. Nakamura, C. Liang, E. Nakamura, *Org. Lett.* **2004**, *6*, 2015; e) S. Morikawa, S. Yamazaki, Y. Furuzaki, N. Amano, K. Zenke, K. Kakiuchi, *J. Org. Chem.* **2006**, *71*, 3540; f) A. B. Leduc, T. P. Lebold, M. A. Kerr, *J. Org. Chem.* **2009**, *74*, 8414; g) T. P. Lebold, A. B. Leduc, M. A. Kerr, *Org. Lett.* **2009**, *11*, 3770.

[7] a) N. Monteiro, G. Balme, J. Goré, *Tetrahedron Lett.* **1991**, *32*, 1645; b) N. Monteiro, J. Goré, G. Balme, *Tetrahedron* **1992**, *48*, 10103.

[8] D. Bouyssi, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1297.

[9] C.-L. Deng, T. Zou, Z.-Q. Wang, R.-J. Song, S.-M. Guo, J.-H. Li, *J. Org. Chem.* **2009**, *74*, 412. In this Cu/Ag co-catalyzed Conia-ene reaction, 2-(pent-4-ynyl)malononitrile remained unaffected while 2-(pent-4-ynyl)malonate gave moderate yields of the corresponding cyclized product having the double bond in the endocyclic position.

[10] This copper complex is commercially available or easily prepared using known procedures: a) C. G. Bates, P. Saejueng, M. Q. Doherty, D. Venkataraman, *Org. Lett.* **2004**, *6*, 5005; for the use of this copper catalyst in coupling reactions see: b) C. G. Bates, P. Saejueng, J. M. Murphy, D. Venkataraman, *Org. Lett.* **2002**, *4*, 4727; c) S. Cacchi, G. Fabrizi, L. M. Parisi, *Org. Lett.* **2003**, *5*, 3843.

[11] For recent reviews on microwave-assisted organic synthesis, see: a) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; b) A. de La Hoz, A. Diaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, *34*, 164; c) A. Loupy, (Ed.), in: *Microwaves in Organic Synthesis*, 2nd edn., Wiley-VCH, Weinheim, **2006**.

[12] Copper iodide can promote the cyclization of **1g**, but stoichiometric quantities of copper salt, base and protonating species are needed, see: a) N. Monteiro, G. Balme, J. Goré, *Synlett* **1992**, 227; b) N. Monteiro, J. Goré, B. Van Hemelryck, G. Balme, *Synlett* **1994**, 447.

[13] P. Lin, G. H. Whitman, *J. Chem. Soc. Chem. Commun.* **1983**, 1102.

[14] The required internal alkynes were easily prepared using conventional Sonogashira coupling method: K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467.

[15] For some rare examples of Conia-ene cycloisomerization of internal alkynes see: a) ref.[5h]; b) C.-L. Deng,

R.-J. Song, Y.-L. Liu, J.-H. Li, *Adv. Synth. Catal.* **2009**, *351*, 3096.

[16] A similar unexpected beneficial effect of CaH_2 was recently observed during a Pd-catalyzed coupling reaction: F. Yu, X. Lian, S. Ma, *Org. Lett.* **2007**, *9*, 1703. In our case, the role of CaH_2 is still not fully understood. It is noteworthy that when the same reaction was performed in the presence of NaH in place of CaH_2, **4a** was obtained in only 55% along with 5% of the 6-*endo* decarboxylated product.

[17] The stereochemistry of the exocyclic double bond in **4a** was found to be *E* by comparison of its spectral and analytical data with those of the compound prepared from the reaction of **1a** with methyl 4-iodobenzoate according to a procedure reported by us earlier: G. Fournet, G. Balme, J. Goré, *Tetrahedron* **1991**, *47*, 6293.

[18] Five types of mechanisms have been previously proposed for the metal-mediated Conia-ene cyclization of alkyne bearing an active methylene group see ref.[5k] and references cited therein.

[19] Examples of the cycloisomerization of 2-propynyl-1,3-dicarbonyl derivatives leading to the corresponding 5-methylene-4,5-dihydrofurans are relatively scarce. Among them, a paper describing a cyclization catalyzed by $Cu(OTf)_2$, PPh_3, in basic media was published during the preparation of this manuscript, see: Y.-F. Chen, H.-F. Wang, Y. Wang, Y.-C. Luo, H.-L. Zhu, P.-F. Xu, *Adv. Synth. Catal.* **2010**, *352*, 1163.

