

Multicomponent Reactions

Zinc-Catalyzed Multicomponent Reactions: Easy Access to Furyl-Substituted Cyclopropane and 1,2-Dioxolane Derivatives

Sergio Mata,^[a] Jesús González,^[a] Rubén Vicente,^{*[a]} and Luis A. López^{*[a]}

Abstract: A convenient synthesis of cyclopropyl-substituted furan derivatives by a zinc-catalyzed three-component coupling of 1,3-dicarbonylic compounds, 2-alkynals and alkenes is reported. A sequence consisting of an initial Knoevenagel condensation, cyclization, and a final cyclopropanation reaction would account for the formation of the final products. In most

cases, this multicomponent process proceeds in good yield under mild reaction conditions and in the presence of a low catalyst loading. The efficient formation of 1,2-dioxolane derivatives by the zinc-promoted aerobic oxidation of some cyclopropane derivatives is also reported. The 1,2-dioxolane derivatives are also available by a four-component reaction.

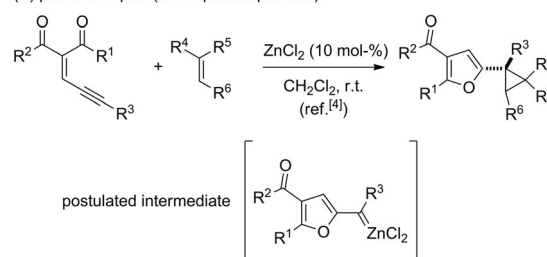
Introduction

Nowadays, there is growing agreement within the scientific community on the need for more sustainable synthetic methodologies. To reach this general goal, some approaches have been established in the last few years. One of the most popular tactics entails the use of catalysts based on affordable metals as a replacement for those still widely used catalysts based on precious metals, which exhibit several drawbacks such as limited availability, high price, and toxicity that make them clearly far from optimal, especially for large-scale applications.^[1] The use of multicomponent reactions (MCRs) has also become particularly useful, as these protocols offer clear advantages over more traditional stepwise methodologies in terms of step-economy, cost, execution time, and waste minimization.^[2]

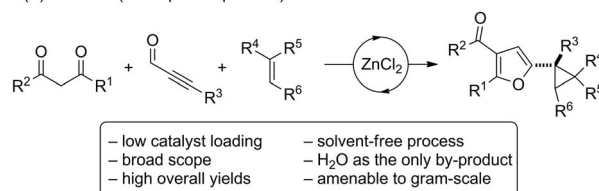
Since 2012, our laboratory has pursued the development of new synthetic methodologies based on the use of simple zinc salts as catalysts.^[3] In particular, we reported the synthesis of furyl-substituted cyclopropane derivatives from enynones and a variety of alkenes (Scheme 1A).^[4] Computational mechanistic studies on this process supported the participation of a 2-furyl-zinc(II)-carbene intermediate. According to our DFT calculations, the formation of this key intermediate would involve the initial coordination of the enynone to the metal centre and a subsequent 5-*exo-dig* cyclization.^[5]

As the enynone starting materials were prepared by conventional base-promoted Knoevenagel condensation methodolo-

(A) previous report (2-component process):



(B) this work (3-component process):



Scheme 1. Zinc-catalyzed approaches to the synthesis of furyl-substituted cyclopropane derivatives: (A) two-component approach (ref.^[4]) and (B) multicomponent approach (this work).

gies and zinc chloride catalyzes some of these condensation reactions,^[6] we realized that a sequence consisting of a zinc-catalyzed Knoevenagel condensation followed by cyclization and a final cyclopropanation reaction would represent a convenient multicomponent catalytic approach to the final cyclopropane derivatives.^[7–9]

Herein, we report the realization of this goal; specifically, we describe the Zn-catalyzed three-component reaction of 1,3-dicarbonyl compounds, 2-alkynals and alkenes as a highly efficient method for the preparation of furyl-substituted cyclopropane derivatives (Scheme 1B). In addition to the inherent advantages associated with the multicomponent reactions in this process, affordable ZnCl₂ works at very low catalyst load-

[a] Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, Julián Clavería 8, 33006 Oviedo, Spain
E-mail: vicenteruben@uniovi.es
lalg@uniovi.es

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ings under mild conditions without organic solvents or additional ligands. Preliminary studies on the reactivity of some of the prepared cyclopropane derivatives are also reported.

The present study was performed with 1,3-dicarbonyl compounds **1a–1e**, 2-alkynals **2a–2l**, alkenes **3a–3n**, dienes **3o** and **3p**, and furan derivatives **3q–3s** (Figure 1).

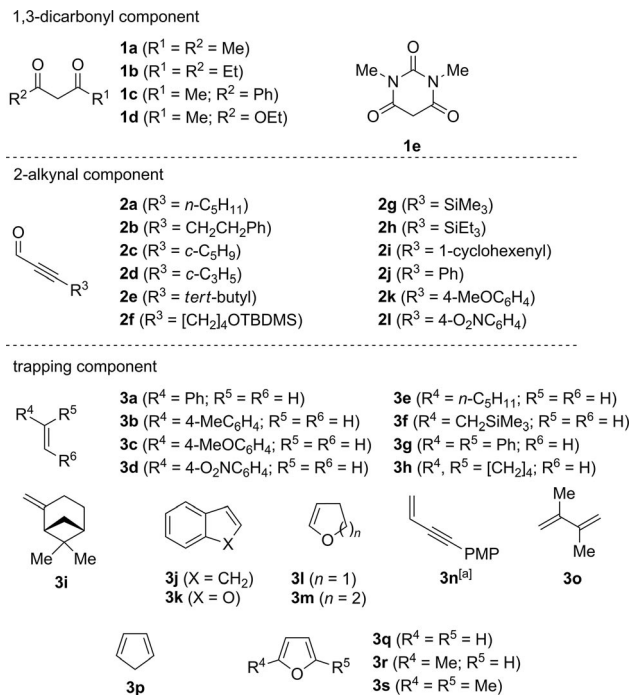


Figure 1. Starting materials used in this work. [a] PMP = *p*-MeOC₆H₄.

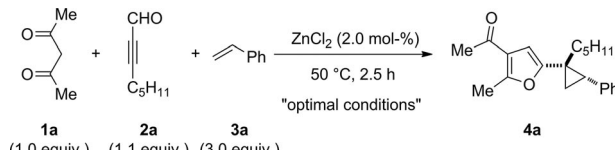
Results and Discussion

Catalyst Screening and Optimization of Reaction Conditions

We initially studied the reaction of pentane-2,4-dione (**1a**), 2-octynal (**2a**) and styrene (**3a**) as the model substrates. To our delight, we found that heating of a mixture of **1a** (1.0 equiv.), **2a** (1.1 equiv.) and **3a** (3.0 equiv.) in the presence of 2.0 mol-% of ZnCl₂ at 50 °C under solvent-free conditions afforded the desired cyclopropane derivative **4a** as a single diastereoisomer in 88 % yield after chromatographic purification (Table 1, Entry 1). A control experiment demonstrated that no reaction occurred in the absence of the Zn catalyst under otherwise identical conditions (Table 1, Entry 2). Copper and magnesium salts were less efficient catalysts in this transformation (Table 1, Entries 3–5). Furthermore, the use of a larger excess of styrene (6 equiv.) did not improve the yield of **4a** (Table 1, Entry 6). The catalyst loading had a significant effect on the yield of this multicomponent process. For instance, although the use of higher catalyst loadings (10 and 20 mol-%) resulted in reduced yields (Table 1, Entries 7 and 8), virtually the same yield was obtained with 2 and 5 mol-% (Table 1, Entry 9). Notably, this multicomponent protocol allowed for simultaneous scale-up and decreased catalyst loading with minimal loss in efficiency

(Table 1, Entries 10 and 11). For example, for a 10 mmol scale, the catalyst loading can be decreased to as low as 0.02 mol-%. In this case, the isolation of 2.45 g (79 % yield) of **4a** after chromatography demonstrated the efficiency [turnover number (TON) = 3950] and scalability of this operationally simple multicomponent process.

Table 1. Optimization of the zinc-catalyzed multicomponent coupling.



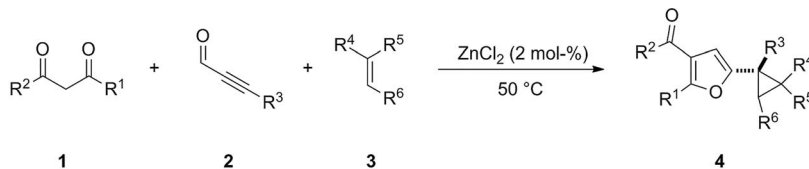
Entry	Change from "optimal conditions"	Yield [%] ^[a]
1	–	88
2	no ZnCl ₂	–
3	CuCl (10 mol-%) instead of ZnCl ₂	11
4	CuCl ₂ (10 mol-%) instead of ZnCl ₂	26
5	Mg(ClO ₄) ₂ (10 mol-%) instead of ZnCl ₂	10
6	6 equiv. of styrene	81
7	20 mol-% ZnCl ₂	50
8	10 mol-% ZnCl ₂	67
9	5.0 mol-% ZnCl ₂	86
10	0.2 mol-% ZnCl ₂ ^[b]	87
11	0.02 mol-% ZnCl ₂ ^[b]	79

[a] Yield of isolated product after chromatographic purification. [b] Performed on a 10.0 mmol scale.

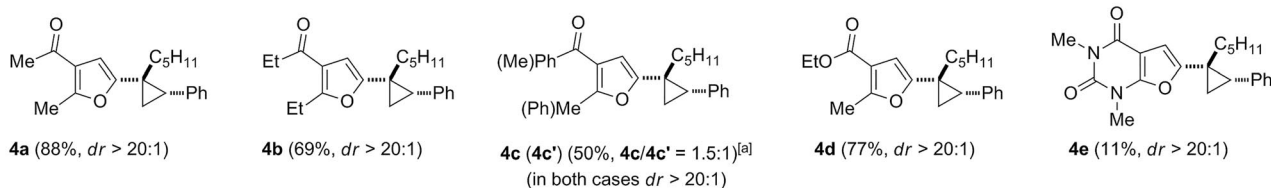
Scope of the Multicomponent Process

With the optimal conditions in hand, we next explored the scope of this multicomponent process. First, we extended the process to other common 1,3-dicarbonyl compounds (Scheme 2A). Thus, heptane-3,5-dione (**1b**) behaved well and afforded the expected furan derivative **4b** in 69 % isolated yield. The use of an asymmetric diketone, namely, 1-phenylbutane-1,3-dione (**1c**), resulted in the formation of a separable 3:2 mixture of regioisomers **4c/4c'** in moderate overall yield. A poor stereoselectivity at the Knoevenagel condensation stage might account for the formation of regioisomers **4c** and **4c'**. In contrast, ethyl 3-oxobutanoate (**1d**) afforded the corresponding product **4d** in 77 % yield.^[10] 1,3-Dimethylbarbituric acid (**1e**) was an unsuitable substrate, and a poor yield of the coupling product was obtained. Regardless of the nature of the dicarbonyl component **1**, all of the reactions involving **2a** and **3a** furnished a single stereoisomer, in accordance with the stereochemical outcome observed in the two-component version.

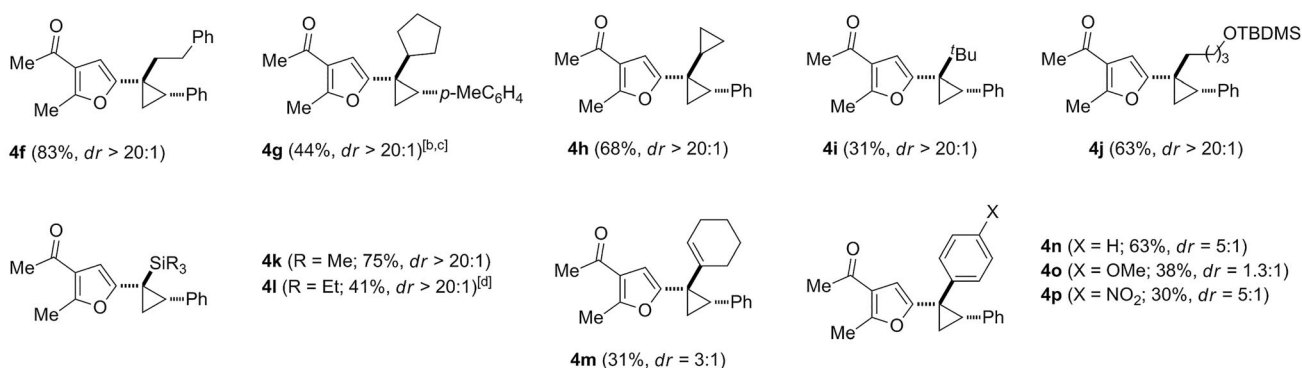
Next, we examined the scope with respect to the alkynal component (Scheme 2B). A broad set of substituents at the alkyne terminus were compatible, including alkyl, cycloalkyl, alkenyl and aryl groups. Significantly, in the reaction of enynone **2c** ($R^3 = \text{cyclopentyl}$), a 2-vinylfuran side-product (**4g'**) also formed along with the expected cyclopropane derivative **4g**.^[11] Once again, in complete agreement with the stereochemical outcome observed in the two-component process, the stereoselectivity of the process was highly dependent on the nature of the substituent on the alkynal. Although the reactions with alkynals bearing alkyl groups generally proceeded with com-



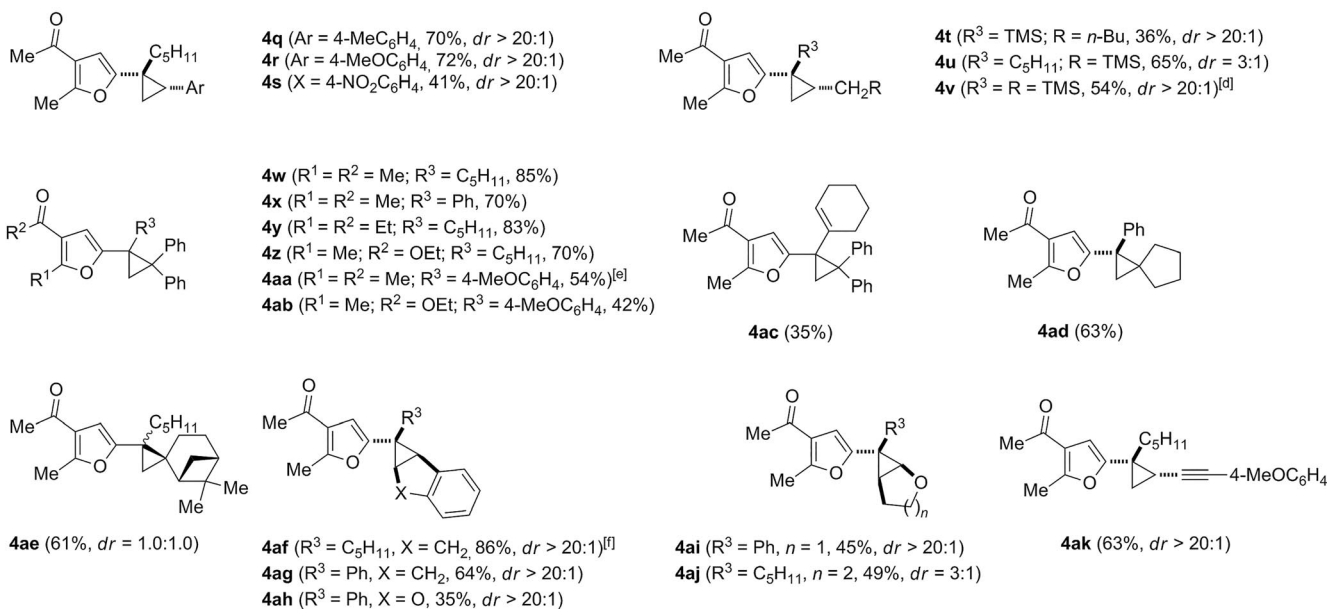
(A) evaluation of 1,3-dicarbonyl component



(B) evaluation of 2-alkynal component



(C) evaluation of alkene component



Scheme 2. Scope of the Zn-catalyzed three-component reaction of 1,3-dicarbonyl compounds **1**, 2-alkynals **2** and alkenes **3** (the isolated yields are listed; the diastereomeric ratios (*dr*) were determined by ¹H NMR spectroscopy). [a] Two separable regioisomers formed (**4c** and **4c'** in 30 and 20% yield, respectively). [b] With 10 mol-% of catalyst. [c] Along with a 2-vinylfuran side-product **4g'** (**4g/4g'**, 7.1:1). [d] Performed at 120 °C under microwave heating. [e] With 5 mol-% of catalyst. [f] The yield was 63% with 0.02 mol-% of ZnCl₂.

plete stereoselectivity, the use of those with aromatic groups led to mixtures of diastereoisomers. Even alkynals **2g** and **2h** bearing trialkylsilyl groups were tolerated without any detri-

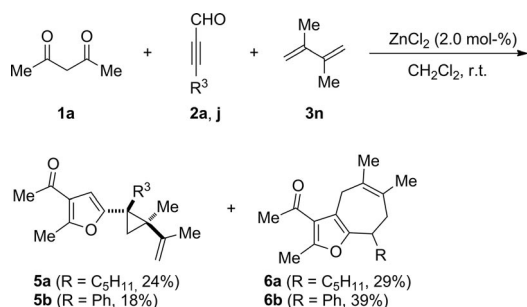
mental effect on the chemical yield of the multicomponent process. In these cases, the reactions occurred with complete stereoselectivity.

Then, several olefinic partners were also evaluated (Scheme 2C). First, we investigated the effect on the reaction outcome of the electronic nature of the substituents on the aryl ring of the styrene derivatives. Thus, we found that the electron-rich styrenes **3b** and **3c** were effective reactants and afforded the cyclopropane derivatives **4q** and **4r** in good yields (70 and 72 %, respectively) under the standard reaction conditions. In contrast, 4-nitrostyrene (**3d**) led to the corresponding cyclopropane **4s** in diminished yield (41 %). Once again, regardless of the nature of the substituted styrene used, the final adduct was isolated as a single stereoisomer for all of the reactions involving alkynal **2a**.

The reactions with monoalkyl-substituted alkenes were far more sluggish. Even so, 1-hexene (**3e**) and allyltrimethylsilane (**3f**) delivered the expected products **4t–4v** in moderate yields.

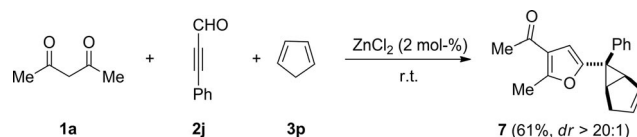
1,1-Disubstituted alkenes are also able to participate in this multicomponent process. Indeed, the reactions of 1,1-diphenylethene (**3g**) generally proceeded smoothly to deliver the cyclopropane derivatives **4x–4ac** in good yields. Likewise, methylenecyclopentane (**3h**) gave cyclopropane **4ad** in 63 % yield. Interestingly, the reaction of β -pinene (**3i**) afforded the cyclopropane **4ae** in moderate yield as a mixture of stereoisomers. Notably, no products resulting from rearrangements were observed in this reaction. Indene (**3j**) and benzofuran (**3k**) were also suitable alkenes and afforded cyclopropanes **4af–4ah** as single isomers in good yields. Enol ether derivatives **3l** and **3m** also underwent this transformation to afford cyclopropane derivatives **4ai** and **4aj** in moderate yields and selectivity. Finally, the reaction with enyne **3h** proceeded with complete chemoselectivity with the exclusive participation of the olefinic moiety.

Our attention then turned towards determining whether diene derivatives would be suitable substrates in this zinc-catalyzed multicomponent process. To this end, we first performed the reaction with pentane-2,4-dione (**1a**), 2-octynal (**2a**), 2,3-dimethyl-1,3-butadiene (**3o**) and ZnCl₂ (2 mol-%). Stirring at room temperature for 12 h resulted in the formation of an almost 1:1 mixture of vinylcyclopropane **5a**/cycloheptafuran **6a** in moderate yield (Scheme 3).^[12] Similarly, 3-phenylpropionaldehyde (**2j**) furnished a 1:2 mixture of **5b/6b**.



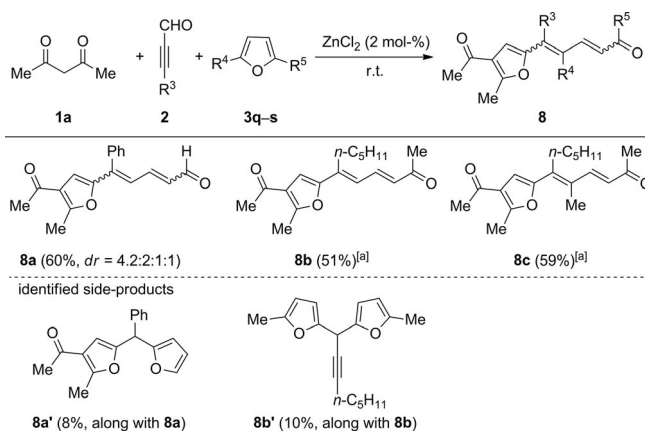
Scheme 3. Zn-catalyzed three-component reactions of pentane-2,4-dione (**1a**), alkynal **2a** or **2j** and 2,3-dimethyl-1,3-butadiene (**3n**).

The use of 1,3-cyclopentadiene (**3p**) was also explored (Scheme 4). Thus, under essentially identical reaction conditions (r.t., 2 mol-% ZnCl₂), pentane-2,4-dione (**1a**), 3-phenylpropionaldehyde (**2j**) and **3p** afforded exclusively the cyclopropane derivative **7** as a single isomer in moderate isolated yield (61 %).



Scheme 4. Zn-catalyzed three-component reaction of pentane-2,4-dione (**1a**), 3-phenylpropionaldehyde (**2j**) and cyclopentadiene (**3p**).

Finally, we examined the reactivity of furan derivatives (Scheme 5). In this process, we did not obtain cyclopropane derivatives; instead, diene derivatives resulting from a ring-opening process were isolated as mixtures of isomers in moderate yields.^[13] The reaction of pentane-2,4-dione (**1a**), 3-phenylpropionaldehyde (**2j**) and furan (**3q**) in the presence of 2 mol-% of ZnCl₂ proceeded smoothly at room temperature to give the furyl-substituted diene **8a** in moderate yield and selectivity along with side-product **8a'** resulting from the formal insertion of the zinc-carbene intermediate into the C-2-H bond of the furan. The reaction of pentane-2,4-dione (**1a**), 2-octynal (**2a**) and 2-methylfuran (**3r**) under similar conditions proceeded with complete regioselectivity to provide dieny ketone **8b** in moderate yield. Similarly, 2,5-dimethylfuran provided the diene derivative **8c** (59 % yield). It should be noted that although diene derivatives **8b** and **8c** were obtained as mixtures of stereoisomers, they can be quantitatively transformed into the most stable (*E,E*) isomer by treatment of the crude products with a catalytic amount of iodine.^[14,15]

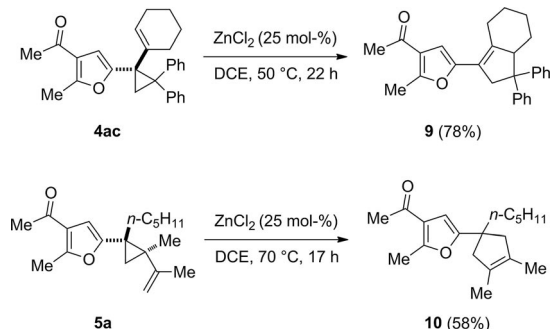


Scheme 5. Zn-catalyzed three-component reactions of pentane-2,4-dione (**1a**), alkynal **2a** or **2j** and furan derivatives **3q** (R⁴ = R⁵ = H), **3r** (R⁴ = H, R⁵ = Me) and **3s** (R⁴ = R⁵ = Me). [a] Isolated as (*E,E*) isomer after the treatment of the crude product with a catalytic amount of iodine.

Rearrangement of Vinylcyclopropanes **4ac** and **5a**

The thermally and metal-promoted rearrangements of vinylcyclopropane derivatives have become a well-established methodology for the synthesis of substituted cyclopentenes,^[16] which are important structural motifs in natural products and pharmaceuticals. Therefore, we set out to investigate the viability of a rearrangement of compounds **4ac** and **5a** featuring a vinylcyclopropane structure under zinc catalysis. Pleasingly, we found that heating of a solution of the corresponding vinylcyclopropane in 1,2-dichloroethane (DCE; 50 °C for **4ac**, 70 °C

for **5a**) in the presence of 25 mol-% of ZnCl₂ led to the rearranged products **9** and **10** in 78 and 58 % yield, respectively (Scheme 6). Remarkably, this metal-catalyzed rearrangement took place with complete regioselectivity. The carbon–carbon bond that is broken in this process is that between the more substituted carbon atoms of the cyclopropane ring.



Scheme 6. Rearrangement of vinylcyclopropanes **4ac** and **5a**.

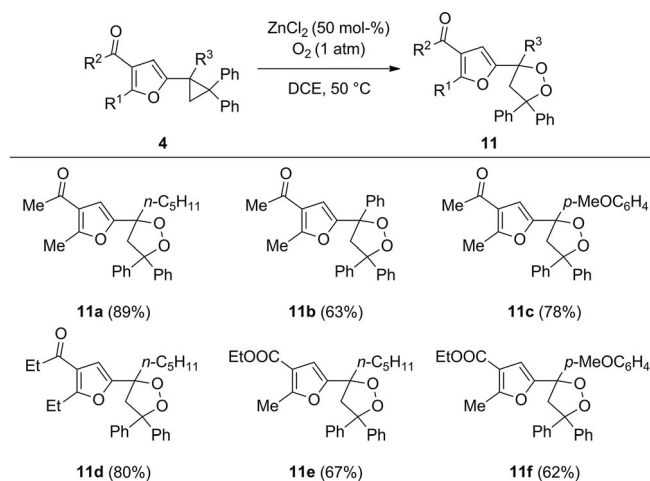
Although further experimentation is required to delineate the actual role of the zinc salt in this rearrangement process, control experiments performed in the absence of ZnCl₂ demonstrated that it has a notable influence on the reaction outcome, as low conversions were achieved in the absence of the zinc salt.^[17]

Zinc-Catalyzed Aerobic Oxidation of Cyclopropanes **4**: Synthesis of 1,2-Dioxolane Derivatives **11**

Having developed a convenient method for the preparation of furylcyclopropane derivatives, we then turned our interest to the search for some synthetic applications thereof. Owing to their interesting biological activities, mainly as antimalarial reagents, we first investigated the transformation of cyclopropane derivatives **4** into cyclic peroxide derivatives, namely, 1,2-dioxolanes.^[18] Although the oxidation of some cyclopropane derivatives by oxygen has been reported,^[19] to the best of our knowledge, the use of zinc as catalyst in this transformation is unprecedented. In this regard, we were pleased to find that 1,2-dioxolane **11a** was obtained in 41 % yield after 45 h when a mixture of cyclopropane **4w** and 0.5 equiv. of ZnCl₂ was stirred in DCE at 80 °C under air. After a brief catalyst screening and optimization of the reaction conditions, we found that the use of 1 atm of oxygen in dichloroethane at 50 °C in the presence of 50 mol-% of ZnCl₂ provided the desired product **11a** in an excellent yield after chromatographic purification (89 %).

The reaction was then extended to other cyclopropane derivatives, and the 1,2-dioxolane derivatives **11b–11f** were obtained in moderate to good isolated yields (Scheme 7). The process tolerated both alkyl and aryl groups at the C-1 position of the cyclopropane. Unfortunately, only 2,2-diphenyl-substituted cyclopropane derivatives were suitable substrates in this oxidation.^[20]

The structures of compounds **11** were ascertained by NMR spectroscopy and mass spectrometry. Moreover, a single-crystal analysis of **11b** unambiguously confirmed the proposed structure (Figure 2).^[21]



Scheme 7. Synthesis of 1,2-dioxolane derivatives **11** from diphenyl-substituted cyclopropanes **3**.

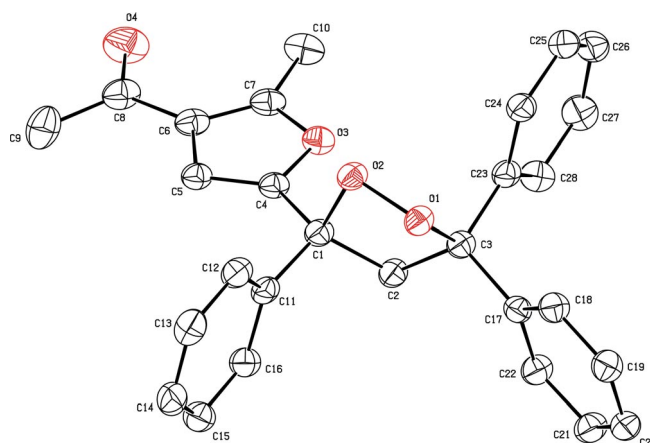
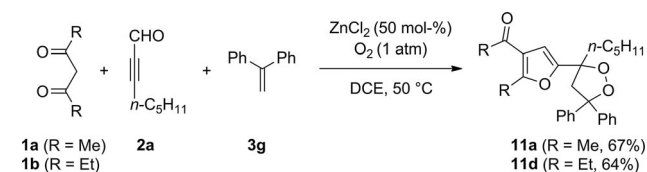


Figure 2. ORTEP view of **11b** (ellipsoids at 30 % probability level).

Finally, we wondered whether the synthesis of 1,2-dioxolane derivatives could be accomplished in a multicomponent process from 1,3-dicarbonyl compounds **1**, alkynals **2** and alkenes **3** without the isolation of the corresponding cyclopropane. Pleasingly, we found that heating of a solution of pentane-2,4-dione (**1a**), 2-octynal (**2a**) and 1,1-diphenylethene (**3g**) in DCE at 50 °C in the presence of 50 mol-% of ZnCl₂ under oxygen provided 1,2-dioxolane **11a** in 67 % yield after chromatographic purification (Scheme 8). In a similar vein, heptane-3,5-dione (**1b**) gave 1,2-dioxolane **11d** in 64 % yield.



Scheme 8. Four-component approach to 1,2-dioxolane derivatives **11**.

Conclusions

We have described an efficient synthesis of furyl-substituted cyclopropane derivatives by a zinc-catalyzed three-component

coupling of 1,3-dicarbonyl compounds, alkynals and alkenes. This coupling process, which seemingly proceeds via a 2-furyl-zinc(II)-carbene intermediate, merges Knoevenagel condensation, cyclization and cyclopropanation into a multicomponent procedure. The general features of this operationally simple multicomponent protocol are (1) the availability and low cost of the required starting materials and catalyst, (2) a wide scope for all the components, (3) its efficiency (even at catalyst loading as low as 0.02 mol-%), and (4) its suitability for multigram scale-up. Selected cyclopropane derivatives are suitable starting materials for further transformations. Specifically, the ability of ZnCl_2 to promote the vinylcyclopropane/cyclopentene rearrangement has been demonstrated for the first time. Furthermore, the synthesis of 1,2-dioxolane derivatives by a zinc-promoted aerobic oxidation of cyclopropane derivatives has also been developed. A four-component process to yield these cyclic peroxide derivatives has also been realized.

Experimental Section

Typical Procedure for the Zn-Catalyzed Three-Component Coupling. Synthesis of Cyclopropane 4a: To a mixture of 2,4-pentanedione (**1a**; 30.0 mg, 0.30 mmol), oct-2-ynal (**2a**; 41.0 mg, 0.33 mmol) and styrene (**3a**; 93.7 mg, 0.90 mmol), ZnCl_2 (0.85 mg, 2.0 mol-%) was added at ambient temperature under an inert gas. The Schlenk flask was sealed with a septum and placed in a preheated oil bath at 50 °C, and the reaction mixture was stirred at this temperature for 5 h until the starting material was consumed (checked by TLC analysis). The excess styrene was removed under vacuum. The resulting residue was purified by flash column chromatography (SiO_2 ; hexane/EtOAc, 10:1) to afford **4a** (82 mg, 88 %; *dr* > 20:1) as a pale yellow oil.

Typical Procedure for the Zn-Catalyzed Aerobic Oxidation of Cyclopropane Derivatives. Synthesis of 1,2-Dioxolane Derivative 11a: To a solution of cyclopropane **4w** (56 mg, 0.15 mmol) in 1,2-dichloroethane (0.10 M; 1.5 mL), ZnCl_2 (10 mg, 50 mol-%) was added at ambient temperature under oxygen. The Schlenk flask was sealed with a septum and placed in a preheated oil bath at 50 °C, and the reaction mixture was stirred at this temperature for 15 h until the starting material was consumed (checked by TLC analysis). After the elimination of the solvent, purification by flash column chromatography (SiO_2 ; hexane/EtOAc, 10:1) yielded **11a** (52 mg, 89 %) as a colourless oil.

Acknowledgments

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Keywords: Cyclopropanes · Dioxolanes · Oxygen heterocycles · Multicomponent reactions · Zinc

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- [10] The yield obtained in this reaction could be rationalized in terms of the isomerization of the enynone or retro-Knoevenagel condensation. The condensation of ethyl 3-oxobutanoate (**1d**) with alkynal **2a** under standard Knoevenagel conditions led to a 1.2:1 (*Z*)/(*E*) mixture of the corresponding adducts. For a similar outcome, see ref.^[9]
- [11] This side-product would arise from a competitive 1,2-hydride shift at the carbene stage. 2-Vinylfuran **4g'** was obtained in 60 % yield when **1a** and **2c** were mixed with ZnCl_2 in the absence of the alkene.
- [12] The cycloheptafuran derivatives **6a** and **6b** probably arise from the *cis*-configured cyclopropane derivatives, which can further evolve under the reaction conditions. The zinc-catalyzed [4+3] cycloaddition of enynones with electron-rich dienes to give cycloheptafuran derivatives related to compounds **6** has been reported recently: B. Song, L.-H. Li, X.-R. Song, Y.-F. Qiu, M.-J. Zhong, P.-X. Zhou, Y.-M. Liang, *Chem. Eur. J.* **2014**, *20*, 5910.
- [13] A similar ring-opening process has been reported for the reactions of furan with other metal-carbene complexes. For selected examples, see: a) K. Miki, M. Fujita, S. Uemura, K. Ohe, *Org. Lett.* **2006**, *8*, 1741; b) A. Caballero, M. M. Díaz-Requejo, S. Trofimenko, T. R. Belderrain, P. J. Pérez, *J. Org. Chem.* **2005**, *70*, 6101.
- [14] The reaction of diene **8a** with iodine afforded a complex mixture of products.
- [15] For some applications of this iodine-catalyzed isomerization reaction, see: E. Wenkert, M. Guo, R. Lavilla, B. Porter, K. Ramachandran, J.-H. Sheu, *J. Org. Chem.* **1990**, *55*, 6203.
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- [18] For a recent review on the synthesis of five- and six-membered cyclic organic peroxides, see: A. O. Terent'ev, D. A. Borisov, V. A. Vil', V. M. Dembitsky, *Beilstein J. Org. Chem.* **2014**, 10, 34.
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- [20] For example, the reaction of cyclopropane **4a** under otherwise similar reaction conditions afforded a complex mixture of products. On the other hand, no reaction was observed when cyclopropane **4ad** was subjected to the standard reaction conditions.
- [21] CCDC 1451935 (for **11b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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