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Zinc Catalysis

Zinc-Catalyzed Synthesis of Functionalized Furans and Triarylmethanes from Enynones and Alcohols or Azoles: Dual X–H Bond Activation by Zinc**

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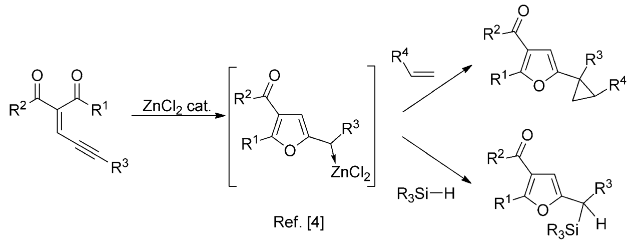
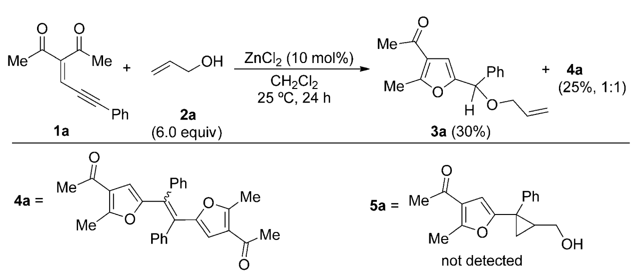
Research on transition-metal-catalyzed processes has allowed the development of highly efficient and selective synthetic procedures. Thus, transition-metal catalysis certainly constitutes one of the most-employed approaches towards the preparation of highly valuable organic compounds used in relevant research areas, ranging from medicine or biology to materials science.[1] Nevertheless, most of the transformations are based on the use of rather expensive, scarce, and toxic metals as palladium, rhodium, iridium, gold, or paltinum, among others. Considering sustainability and environmental criteria, the use of abundant, cheap, and nontoxic metal catalysts has nowadays become one of the most relevant goals in chemistry and catalysis.[2] Among these metals, the use of zinc in catalysis has been less exploited in comparison to iron, copper, or cobalt.[3] Because of our interest in the use of economical and low-toxic zinc-based catalysts, we have recently developed various zinc-catalyzed transformations.[4] In particular, we reported a catalytic version of the Simmons–Smith cyclopropanation using alkynes as a zinc carbene source (Scheme 1). In the same manner, we also described the first zinc-catalyzed carbene Si–H bond insertion reactions. Theoretical studies suggested a zinc carbene intermediate as the key species in both reactions. Additionally, the overall outcome of these transformations enabled the synthesis of highly functionalized furan derivatives. This class of heterocycles is important since furan derivatives are valuable building blocks in synthesis[5] and are present in compounds with properties of relevance in medicinal or materials chemistry, among others.[6]

As a part of our studies on the cyclopropanation reactions with in situ generated zinc carbenes through alkyne activation,[7] we found an unexpected reaction outcome when using a prototypical substrate, such as allyl alcohol (**2a**), for the Simmons–Smith reaction.[8] Thus, under the previously established reaction conditions (10 mol% $ZnCl_2$, CH_2Cl_2, 25 °C), we observed the formation of the furan derivative **3a**, a product derived from a formal zinc carbene O–H bond insertion, along with the dimeric tetrasubstituted alkene **4a** (Scheme 2). In contrast, the formation of the cyclopropane **5a** was not detected.



Scheme 1. Zinc-catalyzed furan syntheses through cyclization/cyclopropanation or Si–H bond insertion sequences.



Scheme 2. Zinc-catalyzed reaction of **1a** with allyl alcohol (**2a**): Initial finding. Yields of isolated product within parentheses.

To our knowledge, this type of transformation has not been reported to date for zinc catalysis and consequently we decided to study it in more detail. We disclose herein our findings, which describe the zinc-catalyzed synthesis of valuable compounds such as functionalized furfuryl alcohol derivatives[9] and unsymmetrically substituted triarylmethane derivatives. A mechanistic rationale based on computational studies involving a zinc-promoted dual activation of X–H bonds is also discussed.

Stimulated by the results depicted in Scheme 2, we evaluated a range of reaction conditions to achieve an efficient and selective access to benzyl ether **3a**. Optimization studies (see the Supporting Information for details) revealed

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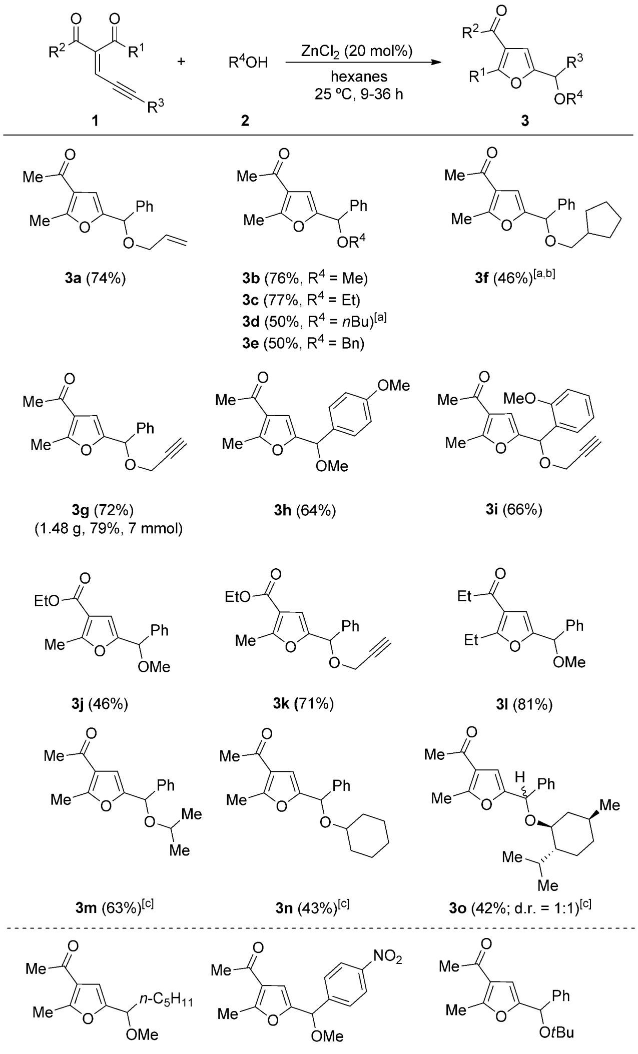
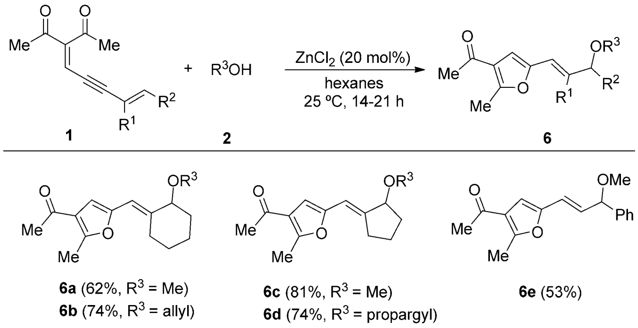
that the use of $ZnCl_2$ (20 mol %) as the catalyst at room temperature in *n*-hexane resulted in the formation of the desired furan derivative **3a** in 74 % after chromatographic purification. Interestingly, under these optimized reaction conditions, the formation of the dimer **4a** was completely suppressed. With the optimized reaction conditions in hand, we next explored the scope of this transformation (Scheme 3).

Various simple primary alcohols were first probed, thus affording the furan derivatives **3b–e** in reasonable yields. Cyclopentylmethanol was also employed to obtain the furan **3f**, although a slightly higher reaction temperature was required (Scheme 3).[10] Moreover, propargyl alcohol proved suitable for this transformation, thus giving rise to the furan **3g** in good yield, even on large scale. Electron-rich alkynes participated in this transformation as well, thus leading to the furans **3h**,**i** in useful yields. Further modifications on the substituents of the furan ring were also accomplished to furnish compounds **3j–l**. Interestingly, the use of secondary alcohols for this reaction also proved feasible, although 0.5 equivalents of $ZnCl_2$ were required. Thus, the furans **3m**,**n**, derived from isopropanol and cyclohexanol, respectively, were obtained in moderate yields. Interestingly, industrially relevant (+)-menthol was employed to prepare the furan derivative **3o** (d.r. = 1:1). As a limitation of this transformation, we found that alkynes bearing alkyl groups or electron-poor arenes either did not give rise to the expected furans or proceeded in low yield (**3p**, 12 %). Tertiary alcohols led to unsatisfactory results as well.



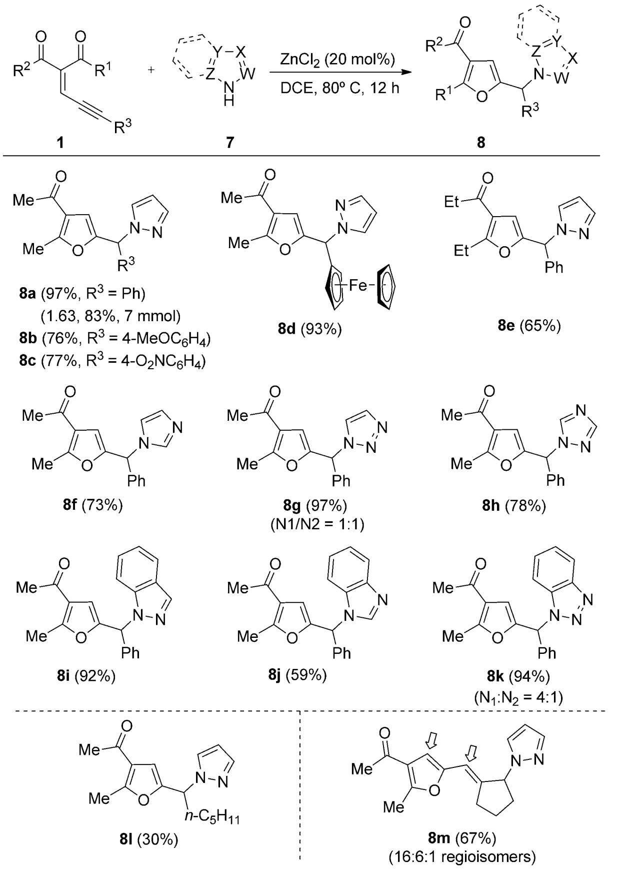
Scheme 3. Zinc-catalyzed synthesis of furfuryl ether derivatives **3**. Reaction conditions: **1** (0.2–0.3 mmol), **2** (6 equiv), $ZnCl_2$ (20 mol %), *n*-hexane (0.1 M), 25 °C. Yields of isolated product within parentheses. [a] Along with small amounts of a isomeric product (see Ref. [10]). [b] At 35 °C. [c] Used 0.5 equiv of $ZnCl_2$. n.d. = not detected.

Next, we also tried substrates bearing an additional alkenyl moiety as the alkyne substituent (Scheme 4). Remarkably, under otherwise identical reaction conditions, the alcohol partner was coupled at the vinylogous position. As a result, the allyl ether derivatives **6a–e** were obtained in moderate to good yields and with complete *E* stereoselectivity.



Scheme 4. Zinc-catalyzed synthesis of allyl ether derivatives **6**. Yields of isolated product within parentheses.

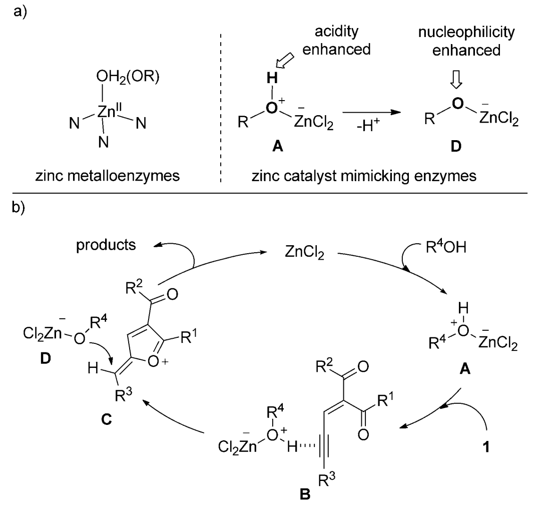
Our attention then turned towards amines or amides, which could be suitable substrates in this zinc-catalyzed process to afford products resulting from a formal N–H bond insertion. In this regard, we did not observe the formation of the desired furfuryl amines when piperidine or tosylamide were reacted with **1a** under various reaction conditions. On the contrary, when using 1*H*-pyrazole (**7a**) under mild reaction conditions (10 mol % $ZnCl_2$, CH_2Cl_2, 25–40 °C), we were pleased to observe the formation in low yields of the desired compound **8a** (ca. 30 %), which is a triarylmethane (TRAM) derivative. Since these compounds are relevant in different areas such as medicinal chemistry or materials science,[11,12] we subsequently optimized the reaction conditions and evaluated the scope. Thus, we found that the use $ZnCl_2$ (20 mol %) in 1,2-dichloroethane (DCE) at 80 °C gave rise to **8a** in almost quantitative yield (Scheme 5). A larger scale reaction was again practical, thus providing **8a** in good yield. Modifications in the enynone component were then accomplished and found to afford the corresponding TRAMs **8b–e** in good yields. This zinc-catalyzed cyclization/C–N bond formation sequence proved feasible with other azoles (Scheme 5). Thus, in addition to pyrazole, monocyclic azoles such as imidazole, 1,2,4- and 1,2,3-triazole could be successfully used in this process, thus affording the compounds **8f–h**



Scheme 5. Zinc-catalyzed synthesis of unsymmetrical triarylmethane derivatives **8a–k** and compounds **8l–m**. Reaction conditions: **1** (0.2–0.3 mmol), **7** (6 equiv), $ZnCl_2$ (20 mol%), DCE (0.1 M), 80°C. Yields of isolated product within parentheses.

in good yields. Benzofused derivatives were also suitable partners and efficiently provided the TRAMs **8i–k**. In addition, an alkyl-substituted alkyne proved applicable to this reaction, thus leading to **8l**, albeit in modest yield. Furthermore, the use of an enynone bearing an alkenyl substituent (R^3 = 1-cyclopentenyl) led to compound **8m**, which was obtained along with minor amounts of other isomers (see the Supporting Information for details).

As for our previous report,[4] a generation of the zinc carbene and subsequent O–H (or N–H) bond insertion might account for the present reaction, although there are no reports on zinc carbene O–H bond insertion to our knowledge. However, considering the ability of zinc metalloenzymes to activate nucleophiles (H_2O or alcohol residues like serine or threonine), an alternative mechanistic scenario, where the zinc catalyst plays a double role, might also be possible (Scheme 6a).[13] Thus, zinc coordination to the alcohol (**A**) might first translate into an increase of its acidity, and thus triggers the cyclization from the intermediate **B** to **C** (Scheme 6b).[14] Then, the attack of the more nucleophilic zinc alkoxide **D** would lead to compounds **3** or **6** (R^3 = alkenyl).[15] An analogous proposal could account for the formation of **8**, wherein zinc coordination to one of the N atoms activates the azole.

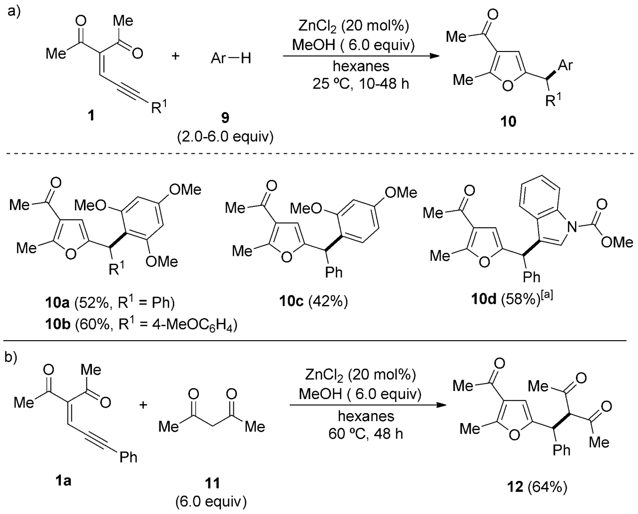


Scheme 6. Mechanistic proposal. a) Dual activation mode. b) Catalytic cycle (applicable for azoles as well).

A computational study at the B3LYP/6-31G* level of theory on the reaction of **1a** with **2a**,[16] showed that this pathway is energetically favored over a either concerted zinc carbene O–H bond insertion or an addition/elimination stepwise process. While the highest energy barrier required for the alcohol activation mechanism was $+8.7\,\text{kcal mol}^{-1}$ (found for the transition state of **B**→**C**), zinc carbene O–H bond insertions require $+38.4\,\text{kcal mol}^{-1}$ (concerted) or $+35.6\,\text{kcal mol}^{-1}$ (stepwise), thus making the latter mechanisms less likely (see the Supporting Information). An analogous reaction pathway was found for the reaction with **7a**, and it showed a higher barrier of $+17.5\,\text{kcal mol}^{-1}$, which is in agreement with the experimental observations.[17] The formation of isomers (**3d′**, **3f′**)[10] and the formation of the allyl ethers **6** (and **8m**) might arise from the intermediate **C** through nucleophilic attack on other positions.

Finally, taking into account the ability of zinc to promote Friedel–Crafts alkylations with benzylic substrates,[18] we envisioned that other unsymmetrical TRAMs could be prepared in a one-pot cascade sequence involving the in situ generation of the benzyl ether **3** and a subsequent Friedel–Crafts reaction in the presence of an appropriate arene. As shown in Scheme 7a, preliminary studies demonstrated that the activated arenes **9** were able to participate in this one-pot transformation to afford the TRAMs **10a–c** in moderate yields. Interestingly, this zinc-catalyzed reaction proved applicable to other electron-rich heteroarenes. Thus, the treatment of *N*-methoxycarbonylindole with substrate **1a** (R^1 = Ph) afforded the indole derivative **10d** in a respectful overall yield (58%). This strategy was further extended to another nucleophile, pentane-2,4-dione (**11**), which led to the compound **12** in 64% yield (Scheme 7b). Notably, in both cases the overall transformation comprised a cascade sequence involving an initial cyclization and final formation of a new C–C bond, which was performed with the single simple catalyst $ZnCl_2$.[19]

In summary, we have reported a novel zinc-catalyzed sequence, cyclization/C–O or C–N bond formation. This



Scheme 7. Zinc-catalyzed cyclization/C–C bond formation sequence. Yields of isolated product within parentheses. [a] At 60 °C.

methodology allowed the synthesis of valuable functionalized furfuryl ether derivatives when using alcohols. Analogously, the use of azoles enabled a straightforward preparation of relevant unsymmetrical triarylmethane derivatives. Besides, zinc chloride proved capable to catalyze a cascade comprising a cyclization/C–C bond formation, to afford different triarylmethanes. Computational studies point out a mechanism involving an activation of the alcohol (or the azole) by zinc, which mimics the function of zinc metalloenzymes. Considering the current demands for sustainable catalysis, our work presented herein, using ZnCl$_2$ is a remarkable example for the application of a simple, inexpensive, and low-toxic metal catalyst. We believe that this work contributes to establish zinc compounds as valuable tools for organic synthesis.

Experimental Section

Representative procedure for the synthesis of **3a**: ZnCl$_2$ (5.4 mg, 0.04 mmol, 20 mol%) was added to a solution of **1a** (42 mg, 0.2 mmol) and **2a** (70 mg, 1.2 mmol, 6.0 equiv) in *n*-hexane (2 mL). The mixture was stirred for 6 h at 25 °C (disappearance of **1a** checked by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO$_2$, *n*-hexane/EtOAc = 10:1) to yield **3a** (40 mg, 74%) as a pale-yellow oil.

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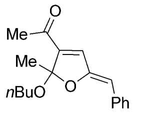
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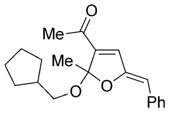
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