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Zinc-catalyzed synthesis of 2-alkenylfurans *via* cross-coupling of enynones and diazo compounds†

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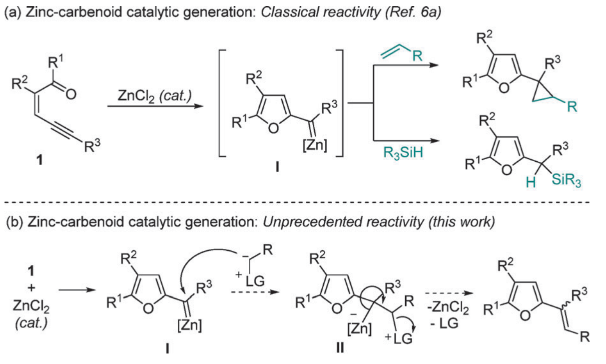
Inexpensive, less-toxic $ZnCl_2$ serves as the catalyst for selective cross-coupling of enynones and diazo compounds, an unprecedented reaction pathway for zinc carbenoids. A cascade sequence comprising formal cyclization/cross-coupling leads to a variety of 2-alkenylfurans.

The replacement of precious metals with catalysts based on more abundant and less-toxic metals is gaining relevance due to economic and environmental reasons, both in industry and academia.[1] As a result, elegant transformations based on the use of iron, copper or cobalt catalysts, among others, have appeared in recent years.[2] Whilst the utility of zinc in synthetic organic chemistry has been known for more than a century, zinc-catalyzed transformations remain less developed.[3,4] For instance, the well-known Simmons–Smith cyclopropanation is typically accomplished with over-stoichiometric amounts of zinc (moisture and oxygen sensitive Et_2Zn).[5] With the aim of overcoming this limitation, we became interested in exploring the feasibility to generate zinc carbenoids in a catalytic manner and to exploit their reactivities for the synthesis of relevant compounds. Thus, we recently reported the use of enynones **1** as carbene precursors using simple $ZnCl_2$ as the catalyst (Scheme 1a).[6,7] The cyclization of **1** generates a 2-furyl zinc carbenoid intermediate **I**,[8] which can be further trapped with alkenes or silanes to yield valuable 2-cyclopropyl- or 2-alkylsilylfurans, respectively. Computational studies provided support for the proposed 2-furyl zinc Fischer-type carbenoid intermediate.[6] This approach provides a catalytic alternative to previously established zinc-mediated cyclopropanation[5b] or Si–H insertions.[9]

In order to further explore the synthetic potential of the postulated 2-furyl zinc–carbenoid intermediate **I**, we wondered whether the reactivity could be expanded beyond its classically known reactivity patterns. According to the predicted electrophilicity of the putative zinc carbenoid, we envisioned a route to relevant 2-alkenylfuran derivatives[10] by trapping the carbenoid with a suitable carbon-nucleophilic reagent bearing a leaving group. Thus, the formation of a new C–C bond by nucleophilic attack should set the stage for an elimination process delivering the desired target and allowing catalyst turnover (Scheme 1b). Herein, we disclosed our findings regarding the unprecedented reactivity of zinc carbenoids.



Scheme 1 Reactivity of *in situ* generated 2-furyl zinc carbenoids.

The evaluation of the initial hypothesis was carried out using readily available enynone **1a** as the benchmark reagent and $ZnCl_2$ as the catalyst. As coupling reagents, we selected stabilized ylides **2–4a** (Scheme 2a) which meet the requirements to achieve the desired transformation since they are good nucleophiles and contain a leaving group. Unfortunately, only phosphorous ylide **2a** led to the formation of the desired 2-alkenylfuran, albeit in unpractical low yield (<10%). Then, we turned our attention to stabilized diazo compounds. In contrast to other transition metals, in general, stabilized diazo compounds do not decompose to carbenoids in the presence of zinc salts,[11] yet they are good carbon nucleophiles and have an excellent leaving group such as N_2.[12] Indeed, using ethyl diazoacetate (EDA, **5a**) under reaction conditions similar to those previously reported for related transformations (10.0 mol% $ZnCl_2$, 6.0 equiv. of **5a**, 25 °C, CH_2Cl_2, 1 h),[6a] we isolated 2-alkenylfuran **6a** in good yield and selectivity (89%, $Z:E = 8.5:1$) (Scheme 2b). A further optimization demonstrated that 5.0 mol% of $ZnCl_2$ and only a slight excess of **5a** (1.2 equiv., CH_2Cl_2, 25 °C, 1 h) gave rise to

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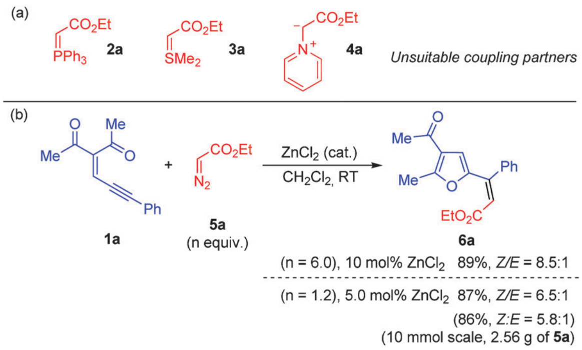


Scheme 2 Zinc-catalyzed preparation of 2-alkenylfuran **6a**: initial findings and optimized reaction conditions.

comparable results (87%, $Z:E = 6.5:1$).[13] Additionally, to check the practicality of the protocol, the test reaction was carried out on a larger scale (10 mmol) with almost the same efficiency (2.56 g of **6a**, 86%, $Z:E = 5.8:1$). The formation of compound **6a** validates our initial hypothesis as it represents an *unprecedented reaction pathway for zinc carbenoids*. Besides, the overall transformation comprises a rather unusual example of formal selective hetero-coupling of two different carbenoid precursors.[14] Notably, $ZnCl_2$ showed better efficiency and selectivity when compared to other representative metal catalysts known to be capable of generating carbenoids from enynones.[15]

With the optimized reaction conditions in hand, we next explored the scope of the transformation (Table 1). First, the reaction of EDA (**5a**) with an array of easily available enynones **1** was examined. Thus, reactions with aryl substituted enynones proceeded smoothly to afford compounds **6a–d**, and those with both electron-rich and electron-deficient aryl groups gave the expected products in good yields and variable stereoselectivity. Even an *ortho*-substituent in the aryl group is well tolerated, though a slight decrease of the yield was observed.[16] An alkenyl substituent at the alkyne terminus was also suitable giving rise to compound **6e** (63%, $Z:E = 4.6:1$). Interestingly, alkyl substituents on the alkyne, both primary and secondary, afforded efficiently the corresponding 2-alkenylfurans **6f–6j** with high *Z*-selectivity.[17] Notably, the presence of a protected alcohol in the substrate was compatible with this protocol affording the furan derivative **6h** in reasonable yield (67%) and high *Z*-selectivity. Further modifications of the substituents R^1 and R^2 in the enynone led to compounds **6k–m**. Then, we evaluated the diazo compound component. Various carboxylic esters as well as ketones as stabilizing groups of the diazo compound proved to be suitable substituents, yielding furans **6n–q** in respectable yields (77–89%). In contrast, this procedure could not be applied to phenyl-, trimethylsilyl diazomethane or ethyl 2-diazo-2-phenylacetate, which gave rise to complex reaction mixtures, under various similar reaction conditions tested, while dimethyl 2-diazomalonate proved to be unreactive.

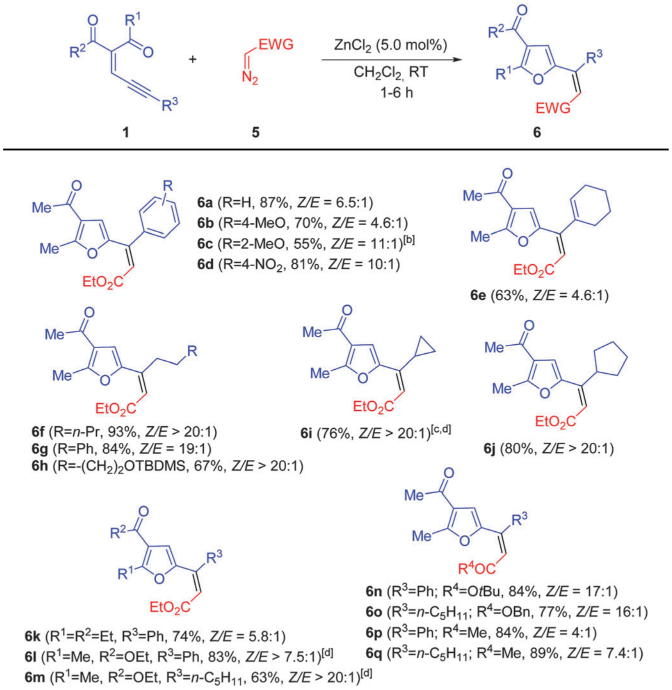
Interestingly, we found that other enynones such as compound **1n** proved to be applicable to this coupling. Indeed, treatment of **1n** with EDA (**5a**) in the presence of 10 mol% of $Zn(OTf)_2$ resulted in the formation of tetrasubstituted furan **6r** in moderate yield (49%) after stirring in 1,2-dichloroethane at 50 °C for 12 h (Scheme 3).

The preparation of chemicals bearing a trifluoromethyl group has recently attracted great interest. Since trifluoromethyl diazomethane can be conveniently generated *in situ*,[18] we checked the feasibility of accessing the corresponding alkenyl–CF_3 furyl derivatives as a complementary approach towards the relevant moiety.[19] Indeed, the reaction of various representative enynones **1** with an excess of trifluoromethyl diazomethane (**5e**, ~20 equiv.) generated from trifluoromethylamine hydrochloride and $NaNO_2$, in the presence of $ZnCl_2$ allowed us to obtain CF_3-substituted alkenes **6s–v** in synthetically useful yields (Scheme 4).[20]

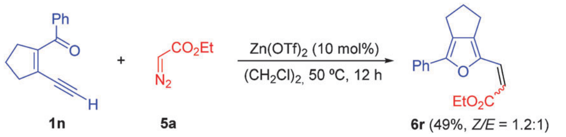
As depicted in Scheme 1(b), the formation of 2-alkenylfurans **6** can be explained through the initial 5-*exo*-dig cyclization of enynones **1** to generate the 2-furyl zinc carbenoid species **I**. Subsequent nucleophilic attack of the diazo compound **5** likely affords intermediate **II**.[12] Favoured extrusion of N_2 with a concomitant release of the zinc catalyst leads to furans **6** and allows catalyst turnover.[21,22]

In summary, we have herein reported a new zinc-catalyzed formal selective hetero-coupling of two carbenoid precursors such as enynones **1** and diazo compounds **5**. The observed reactivity constitutes an unprecedented reactivity pattern for

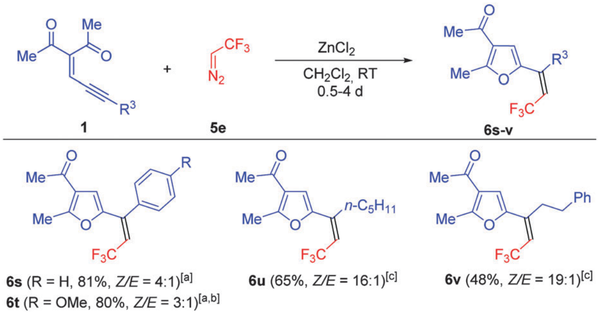
Table 1 Zinc-catalyzed synthesis of 2-alkenylfurans **6**: scope[a]



[a] Reaction conditions: **1** (0.2–0.3 mmol), **5** (1.2 equiv.), $ZnCl_2$ (5.0 mol%), CH_2Cl_2 (0.1 M), RT. Yields correspond to isolated products. *Z*/*E* selectivity was determined by NMR. [b] See ref. 16. [c] At 0 °C. [d] <5% of an unidentified isomer was detected.



Scheme 3 Zinc-catalyzed preparation of 2-alkenylfuran **6r** from enynone **1n**.



Scheme 4 Zinc-catalyzed synthesis of CF_3-substituted 2-alkenylfurans **6s–v**. Yields correspond to isolated products. *Z*/*E* selectivity was determined by NMR. [a] $ZnCl_2$ 100 mol%. [b] At 0 °C. [c] $ZnCl_2$ 20 mol%.

zinc carbenoids. This transformation has enabled the preparation of valuable 2-alkenylfuran derivatives **6** with a remarkable scope.[10] The overall process comprises cyclization of the enynone **1** followed by coupling with the diazo compound and leads to the formation of new C–O and C=C bonds. Relevant CF_3-substituted 2-vinylfuran analogues can also be accessed by this methodology using *in situ* generated trifluoromethyl diazomethane. The use of an inexpensive and less-toxic $ZnCl_2$ as the catalyst is remarkable within the context of the new avenues of chemistry regarding the development of sustainable transformations.

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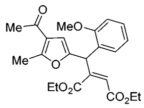
16 Enynone **1c** bearing the *o*-MeO-C_6H_4 group led to the formation of compound **6c′** (11%) as byproduct. The use of a larger excess of ethyl diazoacetate (**5a**) did not improve the yield of **6c′**.



6c′ (11%)

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20 See ESI† for specific conditions for the generation of **4e** and the reaction conditions for the formation of **6s–v**.
21 Preliminary computational studies indicate that (*E*)-**6** are the most stable isomers. Thus, without further additional evidence, we believe that *Z*/*E* selectivities likely originate from kinetic control. See the ESI† for computational details.
22 At this stage, the following pathway cannot be ruled out: (i) activation of the substrate by coordination of zinc to the carbonyl group(s); (ii) conjugate attack of the diazo compound on the triple bond; (iii) cyclization with elimination of N_2. However, other common Lewis acids tested ($BF_3 \cdot Et_2O$, $AlCl_3$, $TiCl_4$, and $MgCl_2$, under catalytic or stoichiometric conditions) did not give rise to the expected 2-alkenylfuran derivatives **6**. In contrast, other metals are known to activate alkynes to generate carbenoids as Cu or Au showed the same reactivity, see ref. 15.