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Ru(II)-Catalyzed Synthesis of Substituted Furans and Their Conversion to Butenolides

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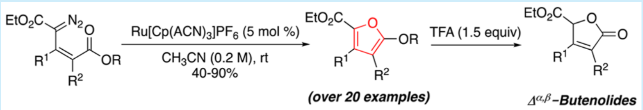
Supporting Information

ABSTRACT: The synthesis of densely functionalized trisubstituted and tetrasubstituted furans via a novel Ru(II)-catalyzed intramolecular cyclization of vinyl diazoesters is reported. The synthetic utility of these furans is further demonstrated through a simple acid-mediated reaction to access highly substituted $\Delta\alpha,\beta$-butenolides.



Furans are perhaps the most versatile of all 5-membered heterocycles. Their emergence in biologically active synthetic and naturally occurring compounds has piqued the interest of synthetic chemists for more than a century.[1] Furthermore, furans have recently found a place as potential organic semiconductors with broad implications in optoelectronic applications and related industries.[2] Furans are also considered one of the most readily available platform building blocks derived from lignocellulosic biomass, solidifying their future as renewable, nonpetroleum based feedstocks.[3] Finally, because of their relatively low resonance energy (16.2 kcal/mol), furans have unique intrinsic reactivity profiles that traverse across both classical arene chemistry and traditional electron-rich olefin and diene pathways.[4] From these combined perspectives, the versatility of furans in organic chemistry is hard to deny.

Given the multitude of methods developed to synthesize furans, one could argue that this is a mature area where only incremental advances can be made.[5,6] Yet, close inspection of both classical and modern approaches to substituted furans reveals several synthetic gaps. In particular, metal-catalyzed routes toward densely functionalized furans from simple, readily available starting materials remains an under-developed tactic toward these heterocycles. One successful approach pioneered by research groups led by Davies,[7] Padwa,[8] and others is the metal-catalyzed [3 + 2] cycloadditions between alkynes and α-diazocarbonyl compounds through the intermediacy of a metal carbenoid species.[9] Several metals beyond the prototypical Rh_2-based catalysts have demonstrated competency in these types of reactions, including Cu,[10] Co,[11] Fe,[12] and Ru.[13] However, each approach possesses inherent limitations with respect to broad substrate generality and elevated reaction temperatures that solicits additional complementary methods to synthesize substituted furans.

Several years ago, we reported our discovery and development of an approach to substituted pyrazoles via an initial Pd-catalyzed cross-coupling between (Z)-enol triflates and diazoacetates, followed by a thermal 6π electrocyclic ring closure.[14] Given the ease of accessing the intermediate vinyl diazoester intermediates, we envisioned that they could serve as richly functionalized precursors to other valuable building blocks through transition-metal-catalyzed carbenoid-type pathways (see Figure 1). In particular, we anticipated that the close proximity of the ester functional group derived from the (Z)-enol triflate would participate in a facile ring closure through insertion into the metal carbenoid, resulting in a novel approach to substituted furans. Here, we wish to report our success in this approach through a Ru(II)-catalyzed process that provides trisubstituted and tetrasubstituted furans that are rich in functional diversification.

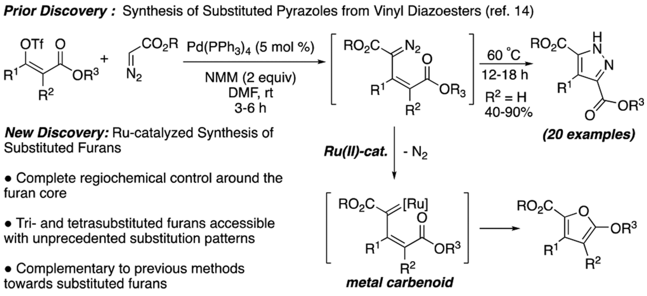


Figure 1. Divergent pathways of vinyl diazoesters toward pyrazoles or furans.

Our initial unbiased efforts began with vinyl diazoester **1** to identify a metal catalyst that could effect this transformation through a catalytic decomposition via a presumed metal carbenoid intermediate. We quickly found several Pd(II)- and Ru(II)-based catalysts that provided trisubstituted furan **2** in good yields (see Table 1). Of these, $Ru[Cp(ACN)_3]PF_6$ (Table 1, entry 12) at a loading of 5 mol % proved to be far superior than all other catalysts we had screened up to this point. In contrast, we were somewhat surprised that both Rh(I)- and Ru(I)-derived catalysts were not productive toward **2** (Table 1, entries 8 and 9) and led to a complex mixture of products.

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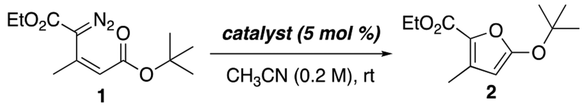
Table 1. Catalyst Screening Efforts for the Conversion of Vinyl Diazoester 1 to Furan 2[a]

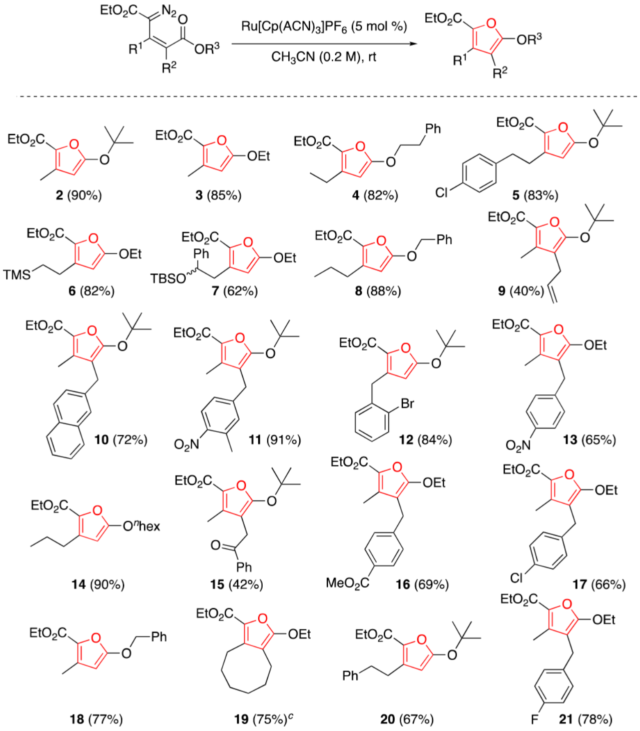


entry	catalyst	**2**, yield[b] (%)	**1**, recovery (%)
1	$Pd(OAc)_2$	10	41
2	$Pd(TFA)_2$	69	0
3	$Pd(PPh_3)_2Cl_2$	0	61
4	$Pd(ACN)_4(BF_4)_2$	0	0
5	$Zn(OTf)_2$	0	0
6	$PdCl_2$	39	29
7	$bipyPdCl_2$	0	79
8	$Rh(PPh_3)_3Cl$	0	17
9	$Ru(PPh_3)_3Cl$	0	13
10	$Ru(PPh_3)_2CpCl$	39	0
11	$Ru[Cp^*(ACN)_3]PF_6$	18	66
12	$Ru[Cp(ACN)_3PF_6$	90	0
13[c]	$Ru[Cp(ACN)_3PF_6$	78	0

[a] Reaction time = 24 h. [b] Isolated yields. [c] Reaction was performed using 2.5 mol % catalyst at 50 °C.

With the optimal catalyst identified, we embarked on exploring the scope of this method with a variety of vinyl diazoesters. Our results on 20 successful examples are summarized in Scheme 1. Given the relatively mild conditions of the reaction, a broad range of functional groups can be tolerated. This includes terminal olefins (as in **10**), ketones **16**, reactive aryl halides **13**, and silanes **7**. A key salient feature of the method lies in the ease of incorporating substituents into the starting vinyl diazoesters that translates directly to the diversity of the products. Thus, both trisubstituted and tetrasubstituted furans are readily obtained in a regiospecific manner dictated by the starting materials. Furthermore, the unique substitution pattern attained (2-carboxylate-5-alkoxy) that is predicated by the starting vinyl diazoesters is also advantageous since furans of this type have shown distinctive chemical reactivity and serve as potential topical sebum inhibitors for the treatment of acne.[15,16] Previous syntheses of these furan analogues in the past have been less than ideal.[17]

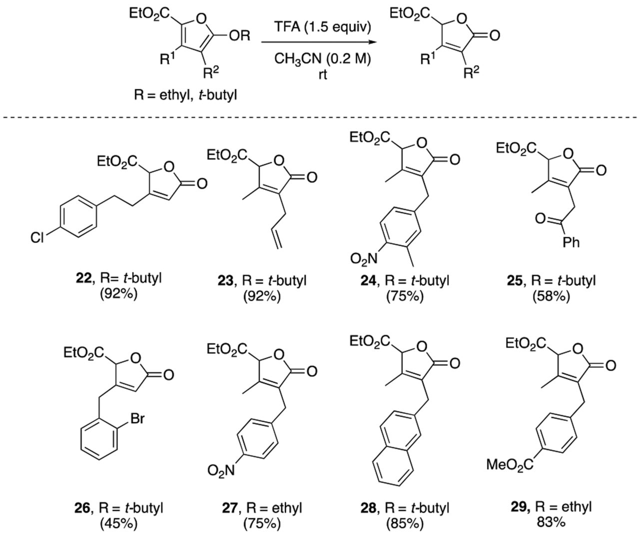
Scheme 1. Ru(II)-Catalyzed Conversion of Vinyl Diazoesters to Substituted Furans[a,b]



[a] Reactions were performed on a 1 mmol scale with reaction times of 24 h in all cases. [b] Isolated yields reported as an average of two experiments. [c] Reaction performed at 50 °C.

Furans have served as excellent precursors toward the synthesis of γ-butenolides through a multitude of transformations.[18] With this in mind, we were curious to examine the conversion of our furan products to the corresponding γ-butenolides using the 5-alkoxy substituent as a convenient handle. In the presence of TFA (1.5 equiv), we have found that 5-ethoxy and 5-*tert*-butoxy furans are cleaved into the corresponding substituted $\Delta\alpha,\beta$-butenolides exclusively (see Scheme 2). It is important to note that 5-ethoxy analogues required noticeably longer reaction times than the 5-*tert*-butoxy analogues.

Scheme 2. Acid-Mediated Conversion of Selected 5-Alkoxyfurans to $\Delta\alpha,\beta$-Butenolides[ab]

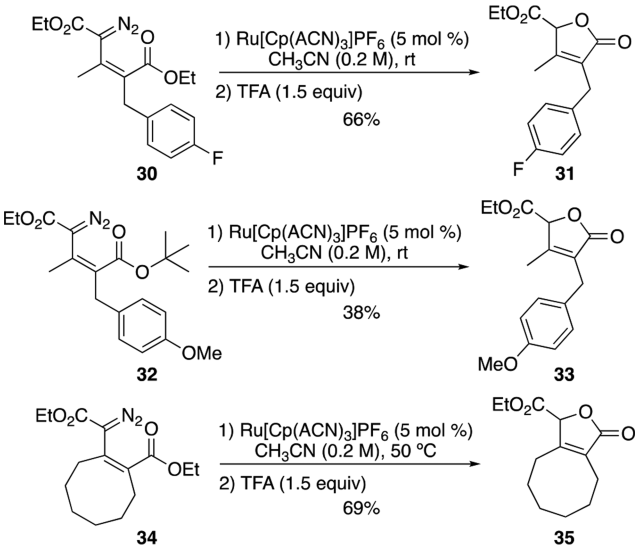


[a] Reactions were performed on a 1 mmol scale with reaction times of 24 h in all cases. [b] Isolated yields reported as an average of two experiments.

Finally, we have been able to telescope both methods into a one-pot synthesis of $\Delta\alpha,\beta$-butenolides (see Scheme 3). Following the Ru(II)-catalyzed decomposition of the vinyl diazoesters to the corresponding furans, TFA (1.5 equiv) can be added directly to the reaction flask to obtain the $\Delta\alpha,\beta$-butenolides after silica gel flash chromatography. We believe this uninterrupted approach to highly functionalized butenolides will find general synthetic utility in both academic and industrial settings.

In conclusion, we have identified a novel Ru(II)-catalyzed conversion of vinyl diazoesters to trisubstituted and tetrasubstituted furans that proceeds under mild reaction conditions with broad substrate scope. We also developed a simple acid-mediated cleavage of both 5-ethoxy and 5-*tert*-butoxy furans to the corresponding $\Delta\alpha,\beta$-butenolides. Additional studies on

Scheme 3. One-Pot Synthesis of $\Delta\alpha,\beta$-Butenolides from 5-Ethoxy and 5-*tert*-Butoxy Furans



further synthetic manipulations of the furans reported here are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02554.

> Experimental procedures and spectroscopic data for all compounds are given (^1H NMR, ^{13}C NMR, and HRMS), including images of all NMR spectra obtained (PDF)

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Notes

The authors declare no competing financial interest.

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