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Journal:	*ChemComm*
Manuscript ID	CC-COM-07-2018-005623.R1
Article Type:	Communication

Journal Name

COMMUNICATION

Rhodium(II)-catalysed generation of cycloprop-1-en-1-yl ketones and their rearrangement to 5-aryl-2-siloxyfurans†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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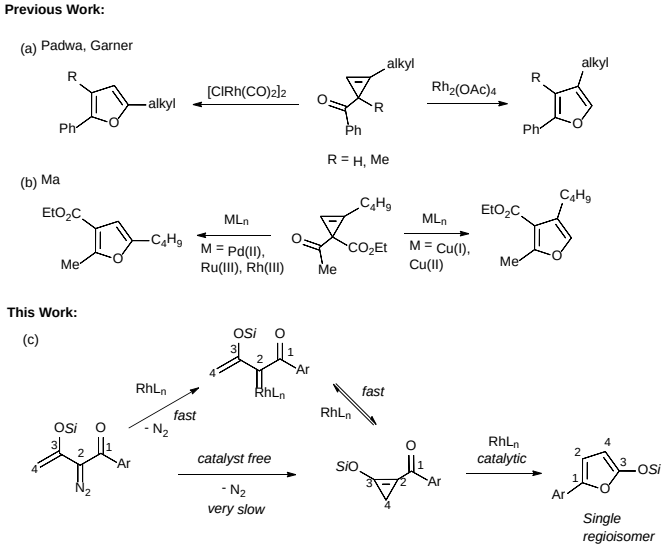
Donor–acceptor cyclopropenes formed from enoldiazoketones undergo catalytic rearrangement to 5-aryl-2-siloxyfurans *via* a novel mechanism that involves a nucleophilic addition of the carbonyl oxygen to the rhodium-activated cyclopropene.

Furan derivatives are among the most common and readily available heterocycles,[1] and they have broad applications in organic synthesis[2,3] and drug discovery.[4] The use of diazo compounds and metal carbene chemistry has become a powerful tool for the construction of furan ring.[5] First reported by Garner[6a] and developed by Padwa,[6b] diazoketone compounds have been used to provide access to furans through initial catalytic cyclopropenation of alkynes with subsequent catalytic rearrangement of the cycloprop-2-en-1-yl ketones to furans. The metal catalyst Rh(I) vs. Rh(II) defined the selectivity of the reaction (Scheme 1a);[6b,c] use of the Rh(I)-catalyst led to 2,3,5-trisubstituted furans, while the Rh(II)-catalyst afforded 2,3,4-trisubstituted furans predominantly. Ma and co-workers subsequently reported a catalyst-controlled divergent ring-opening cycloisomerisation of cycloprop-2-en-1-yl carboxylates (Scheme 1b).[7a] The same regioselectivity (2,3,5- vs. 2,3,4-) as from the Rh(I)-catalyst (Scheme 1a) was observed with Pd(II)-, Ru(III)-, or Rh(III)-catalysts, and the same regioselectivity as Rh(II) was observed with Cu(I) or Cu(II). The reaction scope was also expanded to cycloprop-2-en-1-yl dicarboxylates, which afforded methoxyfurans.[7b] The Lewis acid $BF_3{\cdot}Et_2O$ was also used for the ring-opening cycloisomerisation of spiro-cyclopropenes and the construction of fused furans (2,3,5-selectivity).[7c] 2,3,4-Selectivity in this case was achieved with the use of copper(II) triflate.



Scheme 1 Divergent outcomes of metal-catalysed rearrangement of cycloprop-2-en-1-yl vs. cycloprop-1-en-1-yl ketones.

We previously reported that enoldiazoacetates and enoldiazoacetamides undergo dinitrogen extrusion thermally and with selected catalysts, to form donor–acceptor cyclopropenes quantitatively under mild conditions.[8] These cyclopropene products are stable at room temperature, but they have proven to be effective metal carbene precursors with appropriate catalysts,[9] and they are reactive dipolarophiles for [3+2] cycloaddition reactions.[10] In our efforts to broaden the scope of enoldiazocarbonyl compounds and their reactions, we have prepared enoldiazoketones and found that they expectedly extrude dinitrogen to form the corresponding cycloprop-1-en-1-yl ketones, but these products then undergo a surprising catalytic skeleton rearrangement to furans under mild conditions and in high yields (Scheme 1c).

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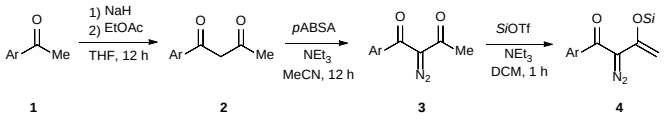
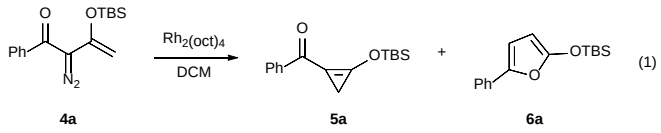
† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra of compounds and computational details. See DOI: 10.1039/x0xx00000x



Scheme 2 Synthesis of enoldiazoketones **4**.

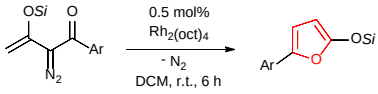
Enoldiazoketones **4** were prepared in a 3-step procedure from commercially available acetophenones **1** (Scheme 2). As in the previously reported conversions to donor–acceptor cyclopropenes, 3-(*tert*-butyldimethylsilyloxy)-2-diazo-3-butenoylbenzene (**4a**, Ar = Ph, *Si* = TBS) was treated with a catalytic amount of dirhodium(II) tetrakis(octanoate) [$Rh_2(oct)_4$] in dichloromethane at room temperature. Dinitrogen evolution was rapid, and 2-(*tert*-butyldimethylsilyloxy)-1-benzoylcyclopropene (**5a**) was formed along with 2-(*tert*-butyldimethylsilyloxy)-5-phenylfuran (**6a**) (eqn (1)) whose yield increased at the expense of **5a** in the presence of the dirhodium catalyst. In the absence of the catalyst, cyclopropene **5a** did not rearrange to furan **6a**, but **5a** was slowly formed from **4a** even at room temperature.

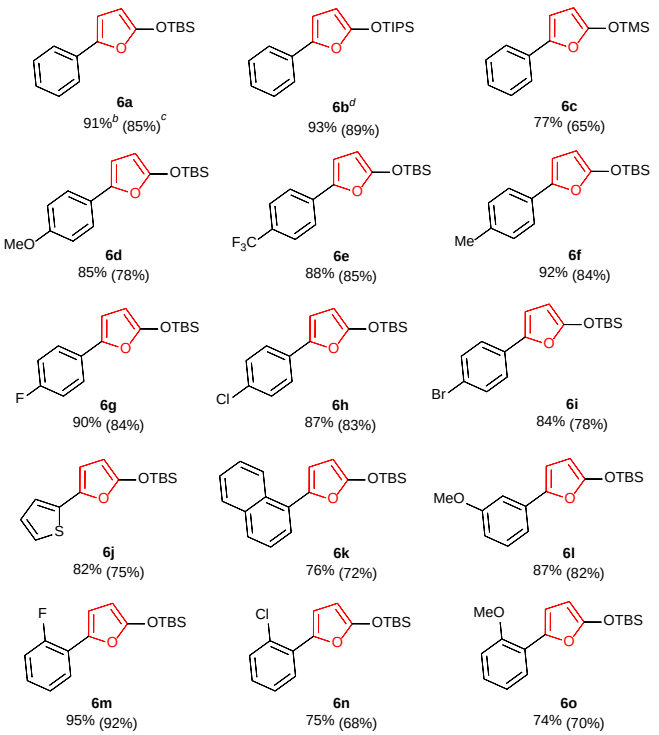


Furthermore, since both donor–acceptor cyclopropene and furan formation occur in sequence, the overall transformation can be initiated from the enoldiazo compound. In view of the novelty of this transformation, which takes place through skeleton rearrangement and hydrogen migration, as well as the potential utility of the products, we further investigated this transformation.

As with $Rh_2(oct)_4$, a catalytic amount of $Cu(MeCN)_4BF_4$ generates the donor–acceptor cyclopropene **5a** rapidly, but use of this catalyst does not lead to the furan ring. Alternative catalysts, $[Ru(p\text{-cymene})Cl_2]_2$, $Pd(PhCN)_2Cl_2$ and dirhodium(II) caprolactamate [$Rh_2(cap)_4$], had limited reactivity for the dinitrogen extrusion step and formed the furan ring in yields lower than 30% under identical conditions as those used for $Rh_2(oct)_4$ and $Cu(MeCN)_4BF_4$ catalysis.[11] Among rhodium(II) carboxylates, $Rh_2(oct)_4$ was found to be the most efficient catalyst for furan formation, and 0.5 mol% was the optimal catalyst loading. Although dirhodium(II) tetraacetate [$Rh_2(OAc)_4$] and bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] [$Rh_2(esp)_2$] afforded furan in high yields, the rates of their reactions were slower. The presence of electron-deficient or sterically encumbered substituents in Rh(II) carboxylates {dirhodium(II) tetrakis(perfluorobutyrate) [$Rh_2(pfb)_4$] and dirhodium(II) tetrakis(triphenylacetate) [$Rh_2(tpa)_4$]} does not facilitate furan formation, although they generated cyclopropene **5a** very rapidly. Treatment of **5a** with Lewis acids like $AgBF_4$ and $Sc(OTf)_3$ facilitated the formation of furan, but also led to TBS removal to form 5-phenylfuran-2(3*H*)-one (**7a**).

Table 1 Substrate scope for the synthesis of 5-aryl-2-siloxyfurans **6**





[a]Synthesis of furans **6** was carried out on a 1.0 mmol scale of enoldiazoketones **4**. [b]Yield was determined by the ^1H NMR spectral analysis of the reaction mixture with 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield after flash chromatography. [d]Reaction time was 12 h.

Having the optimal catalyst in hand we explored the substrate scope of this one-pot transformation of enoldiazoketones **4** to 5-aryl-2-siloxyfurans **6** (Table 1). Use of the TBS protecting group was preferred because of its relative stability. Although the TIPS-protected furan **6b** was also formed in very high yield (93%), its reaction time was double of that for TBS-protected substrate. The introduction of electron-donating or -withdrawing substituents at the *para* position of the aromatic ring did not affect reactivity (**6d–i**). Substrates with 2-thiophenyl and 3-methoxyphenyl substituents were also tolerant and afforded the target furans **6j** and **6l** in yields higher than 80%. 1-Naphtyl-, 2-chlorophenyl- and 2-methoxyphenylfurans **6k**, **6n**, **6o** were obtained in lower yields (75% in average). The highest yield (95%) was achieved on 2-fluorophenyl substrate **4m**, even higher than with **4a**. Diazoacetyl analogues of **4** formed the corresponding cyclopropenes rapidly and in high yields, but produced only minor amounts of the corresponding furans in complex product mixtures with the same catalyst at or above room temperature.

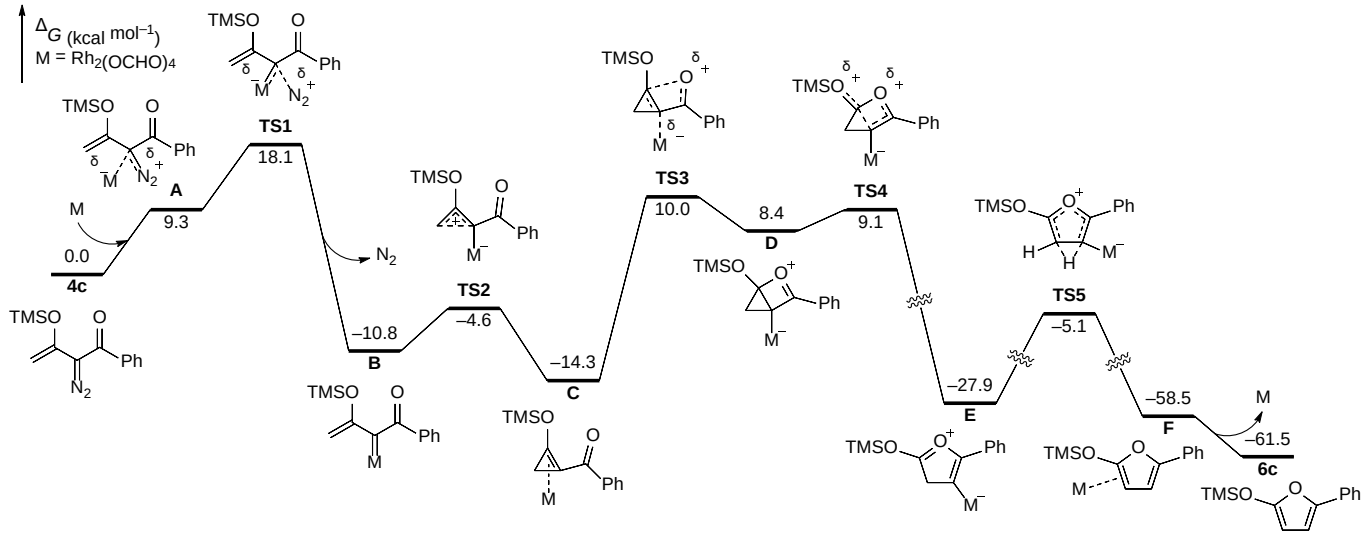
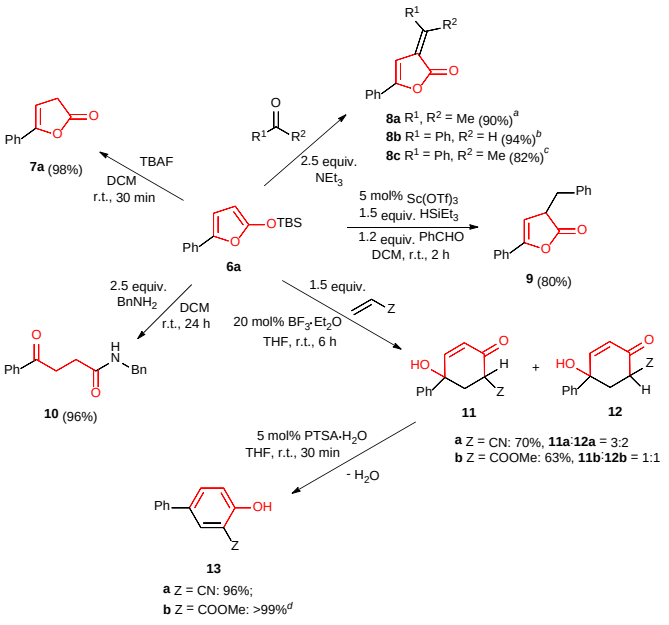


Fig. 1 Gibbs energy profile for the reaction of substrate **4c** under the catalysis of rhodium(II) formate. Computed at the B3LYP/def2-SVP level.[13]

Furan formation from donor–acceptor cyclopropenes (Scheme 1c) is quite different from that previously developed (Scheme 1a,b). To shed some light on the reaction mechansim, we performed DFT calculations on the reaction of substrate **4c** under the catalysis of a model catalyst, rhodium(II) formate (Fig. 1).[12] The reaction begins with dinitrogen extrusion of the rhodium–substrate complex **A** *via* transition state **TS1**, generating a rhodium carbene intermediate **B**. Then, a C–C bond formation takes place *via* a 2π-disrotatory electrocyclisation transition state **TS2**, leading to a rhodium–cyclopropene complex **C**. The small energy barrier (<10 kcal mol^{-1}) between **B** and **C** indicates the reversibility of such an interconversion. Subsequently, **C** dissociates to give cyclopropene **5c** or undergoes an intramolecular nucleophilic addition of the carbonyl oxygen to the rhodium-activated cyclopropene *via* transition state **TS3**. The Gibbs energy of activation for such a C–O bond formation step is 24.3 kcal mol^{-1}. The resulting zwitterionic intermediate **D** then undergoes a rapid ring expansion *via* transition state **TS4**, leading to the formation of a vinylrhodium intermediate **E**. Such a process should better be regarded as a ring opening of cyclopropyl silyl ether followed by electronic reorganisation, rather than a 4π electrocyclic ring opening, which requires a geometrically unrealisable conrotatory transition state. After that, a suprafacial [1,5] sigmatropic hydrogen shift occurs,[14] furnishing a rhodium–furan complex **F**. Finally, the dissociation of **F** gives the catalyst and the furan product **6c**. Removing the siloxy group or replacing the benzoyl group by an acetyl group leads to a significant increase in the overall Gibbs energy of activation,[12] demonstrating the important role of electron-donating siloxy and aryl groups on the stabilisation of the intermediates and transition states along the reaction path, which facilitates the reaction to occur.

We have also considered an alternative mechanism in which the initially formed donor–acceptor cyclopropene **4c** undergoes a [1,3] sigmatropic hydrogen shift to generate a 3-acylcyclopropene and then completes the furan synthesis (Scheme 1a). However, it is unlikely to take place, not only because of the extremely high Gibbs energy of activation for the symmetry-forbidden suprafacial [1,3] sigmatropic hydrogen shift,[15] but also because the exclusive 2,5-selectivity observed in our experiments is different from the preference for the 2,4-selectivity in the rearrangement of 3-acylcyclopropene under Rh(II) catalysis (Scheme 1a, right).[6]

This methodology provides convenient access to 5-aryl-2-siloxyfurans, which are of considerable value in nucleophilic and electrophilic reactions. Upon loss of the silyl group, **6a** readily forms 5-phenylfuran-2(3*H*)-one (**7a**) (Scheme 3). Furan-2(3*H*)-ones **7** are analogues of butenolides – a class of compounds[16] the structural unit of which is found in numerous natural products.[17] Interestingly, 2-siloxyfurans, which do not have a substituent at position 5, normally react with



[a]Reaction was carried out in acetone at 22 °C, reaction time 12 h. [b]1.2 Equiv. of benzaldehyde used, DCM, 22 °C, 4 h. [c]1.5 Equiv. of acetophenone used, DCE, 80 °C, 16 h. [d]Complete aromatisation occurred at r.t. in 24 h without the use of acid.

Scheme 3 Chemical transformations of 5-phenyl-2-siloxyfuran **6a**.

electrophiles to form furan-2(5*H*)-ones.[18] However, 5-aryl-substituted 2-siloxyfurans form 3-substituted 5-arylfuran-2(3*H*)-ones exclusively as the thermodynamic product. Compound **6a** reacts with acetone and benzaldehyde at room temperature in the presence of triethylamine to form 5-phenyl-(3-ylidene)furan-2(3*H*)-ones **8a**,**b** in very high yields (Scheme 3). The reaction of **6a** with acetophenone required a higher temperature to achieve a good yield of 5-phenyl-(3-ylidene)furan-2(3*H*)-one **8c** (82%) that was formed with exclusive *E*-selectivity. Highly regioselective one-pot coupling-hydrogenation of **6a** was carried out using benzaldehyde and triethylsilane. Upon reaction with benzylamine, furan **6a** forms ring opened product **10** in 96% yield. Reaction of **6a** with acrylonitrile or methyl acrylate formed Diels–Alder cycloadducts and subsequent hydrolytic ring opening gave **11** and **12** as a mixture of diastereomers in moderate yields. Nitriles **11a** and **12a** were stable at room temperature, whereas esters **11b** and **12b** underwent loss of water and quantitative aromatisation to form 2-substituted 4-phenylphenol **13b**, a compound that was previously accessible only by cross-coupling reactions.[19] Analogous 2-cyano-4-phenylphenol **13a** was obtained in 96% yield from a mixture of **11a** and **12a** by treatment with a catalytic amount of *p*-toluenesulfonic acid (PTSA) at room temperature (Scheme 3).

In summary, we have discovered a new mechanistic pathway for the formation of 2,5-disubstituted furans from cycloprop-1-en-1-yl ketones generated from silyl-protected enoldiazoketones. The regioselectivity of the process is totally different from those formed from cycloprop-2-en-1-yl ketones. The rearrangement is catalyst-dependent with rhodium(II) carboxylates being the most efficient. DFT calculations have been performed to understand the reaction mechanism, showing that the electron-donating siloxy and aryl groups are both essential to facilitate the reaction. Synthesized furans are good sources of valuable furan-2(3*H*)-ones. Unlike the reported unsubstituted 2-siloxyfurans or 5-alkyl-2-siloxyfurans, our 5-aryl-2-siloxyfurans underwent coupling reactions with electrophiles at position 3 selectively.

We acknowledge U.S. National Science Foundation (CHE-1212446) and the National Natural Science Foundation of China (21232001) for supporting this research. The NMR spectrometer used in this research was supported by a grant from the U.S. National Science Foundation (1625963).

Conflicts of interest

There are no conflicts to declare.

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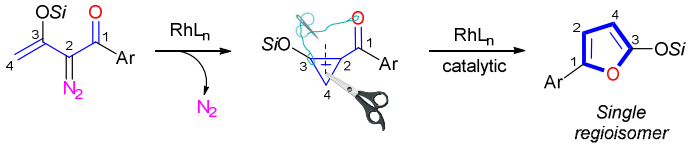

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