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A new activating mode of donor–acceptor cyclopropane: the tug-of-war between strain and aromaticity, transient generation of quinone methides and their reactions with *C*-nucleophiles

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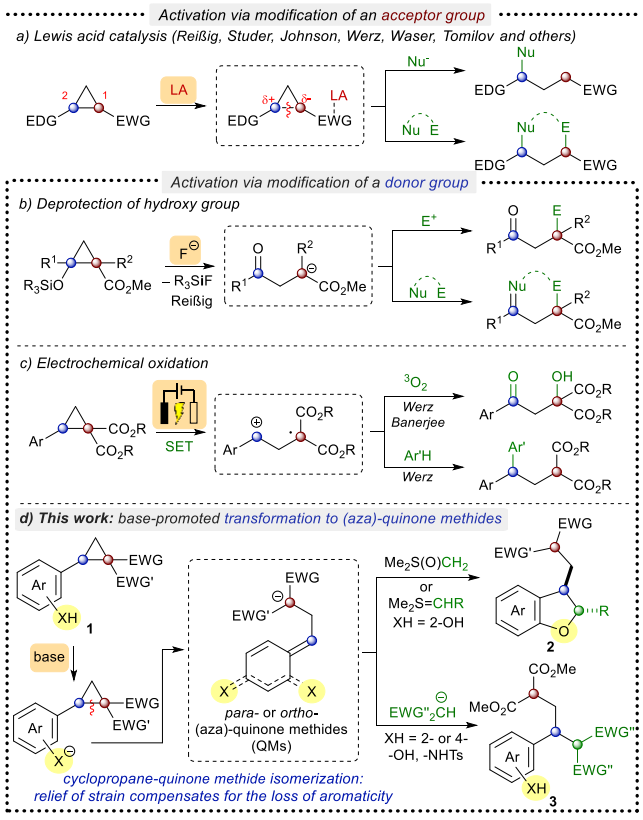
Dedicated to Professor Hans-Ulrich Reißig, on the occasion of his 75th birthday

Here, we present a new approach for activation of donor-acceptor cyclopropane systems in ring-opening reactions, which does not require the use of Lewis or Brønsted acid as a catalyst. Under treatment with a base, donor-acceptor cyclopropanes containing a phenolic group as the donor undergo deprotonation and fast isomerisation to the corresponding quinone methides. This innovative strategy was applied to achieve [4+1] annulation of 2-(2-hydroxyaryl)-substituted DA cyclopropanes with sulfur ylides, affording functionalised dihydrobenzofurans. A plausible mechanism for this process has been proposed based on theoretical calculations. Additionally, the generated *ortho*- and *para*-quinone methides as well as their aza-analogues can be trapped by nucleophiles formed from deprotonated CH-acids. This provides a simple path toward polyfunctional compounds, which serve as promising building blocks for the synthesis of more complex and biologically interesting cyclic structures.

Introduction

Cyclopropane is an archetypical small carbocycle which is kinetically stable despite its high strain energy (*ca*. 27.6 kcal/mol).[1] The introduction of a donor and an acceptor to the vicinal positions of the cyclopropane ring selectively polarises the C–C bond between atoms bearing these groups. Such donor-acceptor (DA) cyclopropanes[2-24] are significantly more reactive than cyclopropane itself in diverse ring-opening reactions. However, even these compounds still require an additional activation in most processes.

Thermal activation of DA cyclopropane ring-opening has limited applications due to low reaction selectivity under harsh conditions.[25-28] Other strategies, which do not alter the overall structure of the donor/acceptor framework, such as radical,[29] organocatalytic and nucleophilic[30,31] activation are relatively uncommon, and only a limited number of such ring-openings have been reported.



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Scheme 1 Examples of activating modes of donor-acceptor cyclopropanes.

Over the past two decades, the explosive growth in cyclopropane research has been associated with the active application of Lewis acids (LA, Scheme 1a): the coordination of which to acceptor substituent(s) enhances their electron-withdrawing ability that increases the polarisation of the C(1)–C(2) facilitating its heterolysis.[2-24] Lewis acids have been widely used as effective ring cleavage initiators in various synthetic transformations of DA cyclopropanes, including nucleophilic ring-openings, cycloadditions, annulations, rearrangements, ring expansions, dimerization, and 1,3-difunctionalisations.[2-22] Brønsted acids also catalyse DA cyclopropane reactions *via* similar activation mechanism, but they are less commonly used now.[13,32-38] Our group contributed to this area of research by developing the protic ionic liquids as triplex reagents serving as: a) a regenerable solvent, b) a source of Brønsted acid for DA cyclopropane activation, and c) a source of a nucleophile.[37,38]

For activation of DA cyclopropanes *via* acceptor group modification, diverse modes of organocatalysis are applied, depending on the nature of acceptor group(s).[39-44] For example, DA cyclopropanes with the aldehyde group as acceptor were activated by the treatment with secondary amines, generating iminium ions with a higher electron-withdrawing ability than the starting aldehyde group.[40-42] For the activation of nitrocyclopropanecarboxylates, ureas capable of forming H-bonds between their NH groups and both oxygens of nitro group were applied.[43,44] Some other methods for activating DA cyclopropanes *via* the acceptor group modification have also been reported.[45-47]

In contrast to the activation of DA cyclopropanes through modifications to the acceptor, the activation of small ring-opening by altering the electron-donating group has been less studied.[48-59] The pioneering work of Reißig,[48] who introduced the concept of DA substituted cyclopropanes, serves as an example of such modification of the donor part. It shows that the ease of DA cyclopropanes opening with R_3SiO-substituents depends on the *in situ* release of the corresponding alkoxy anion (Scheme 1, b). In recent years, other strategies involving photocatalytic,[50-52] electrochemical[53-56] (Scheme 1, c) and organocatalytic[57-61] conversions of DA cyclopropanes have attracted an increased attention from mechanistic, theoretical, and synthetic viewpoints. Despite this, the activation modes utilized in the modifications of the donor group are relatively constrained, leaving considerable space for further investigations.

Intrigued by this scarcity, we focused on synthetically available 2-(2-hydroxyaryl)substituted cyclopropanes **1**, which have previously been successfully used in Lewis-acid initiated [4+2] annulation with alkenes[62] and in intramolecular nucleophilic ring-opening.[63] We hypothesised that the deprotonation of the phenol group in cyclopropanes **1** could lead to the spontaneous three-membered ring-opening to deliver an *ortho*-quinone methide (*o*-QM) based intermediate that can be trapped by suitable nucleophiles (Scheme 1, d). In this study, we have investigated the ring-opening of cyclopropanes **1** with various *C*-nucleophiles, namely, sulfur ylides and anions of selected CH-acids. We have shown that [4+1] annulation of *o*-QMs, generated from DA cyclopropanes **1**, with sulfur ylides could lead to 2,3-dihydrobenzofurans, an important structural unit of some modern FDA-approved drugs (Fig. 1). Furthermore, this transformation is conceptually interesting from an additional perspective. Generally, transformation of phenols to quinone methides requires oxidative conditions. This is so well-established that even found applications in the design of "chameleonic" pharmaceuticals, i.e., the phenols which are converted from antioxidants to cytotoxic agents *in situ* under the oxidative stress conditions typical for tumours.[64] In the present system, the phenol/quinone methide transformation only needs a base.

Moreover, we found that not only *ortho*-, but *para*-quinone methides, as well as their aza-analogues intermediates, also could be obtained by this method from corresponding precursors. Alternatively, they could be trapped with CH-acids to give an access to polyfunctional derivatives of γ-disubstituted butanoic acids. Herein, we report the results of our investigation.

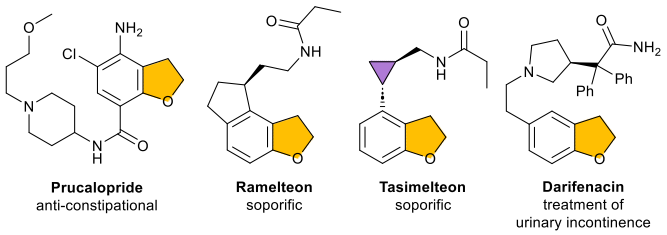


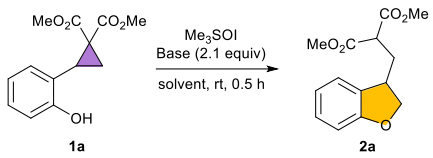
Fig. 1 FDA-approved dihydrobenzofuran-based drugs.

Results and discussion

We initiated our study with [4+1] annulation of cyclopropanes using **1a** as a model four-atom component and dimethylsulfoxonium methylide (DMSOM, Corey ylide) as a methylene group source. The main results of the screening of reaction conditions (solvent, type of base and ratio of reagents) are summarised in Table 1. Since the process under study needs a base for the cyclopropane **1a** activation, we found it convenient to use DMSOM as both the annulation agent and a homogeneous base. We started the process optimisation by adding substrate **1a** to DMSOM (2.1 equiv), generated *in situ* from equimolar quantities of trimethylsulfoxonium iodide (as 0.2 M solution in DMF) and NaH at room temperature. To our delight, dihydrobenzofuran **2a** was obtained after stirring for 0.5 h in 77% yield (Table 1, entry 1). Concentration screening revealed that the use of 0.4 M DMF solution of **1a** led to the decrease of the yield to 72% while decreasing **1a** concentration to 0.1 M raised the yield to 84% (Table 1, entries 2, 3). Reversed dropwise addition of DMSOM to a solution of **1a** in DMF resulted in a dramatic drop of the yield to 37% (Table 1, entry 4), indicating high activity of deprotonated **1a** under presented conditions. Further, the solvent effect was investigated. We were pleased to find that

2a was produced in 96% yield in 0.1 M DMSO, demonstrating the crucial influence of solvent on the efficiency of this process (Table 1, entry 5). Despite the reaction proceeding in nearly quantitative yield, we tried to optimise its synthetic efficiency and environmental impact by using other commercially available bases and reducing the amounts of DMSO and ylide.

Table 1 Optimisation of reaction conditions for the model cyclopropane **1a**[a]



Entry	Me_3SOI, equiv	Base	Solvent	C, M	Yield, %[b]
1	2.1	NaH	DMF	0.2	77
2	2.1	NaH	DMF	0.4	72
3	2.1	NaH	DMF	0.1	84
4[c]	2.1	NaH	DMF	0.1	37
5	**2.1**	**NaH**	**DMSO**	**0.1**	**96**
6	2.1	NaH	DMSO	0.2	95
7	1.1	NaH	DMSO	0.1	73
8	1.1	*t*-BuOK	DMSO	0.1	71

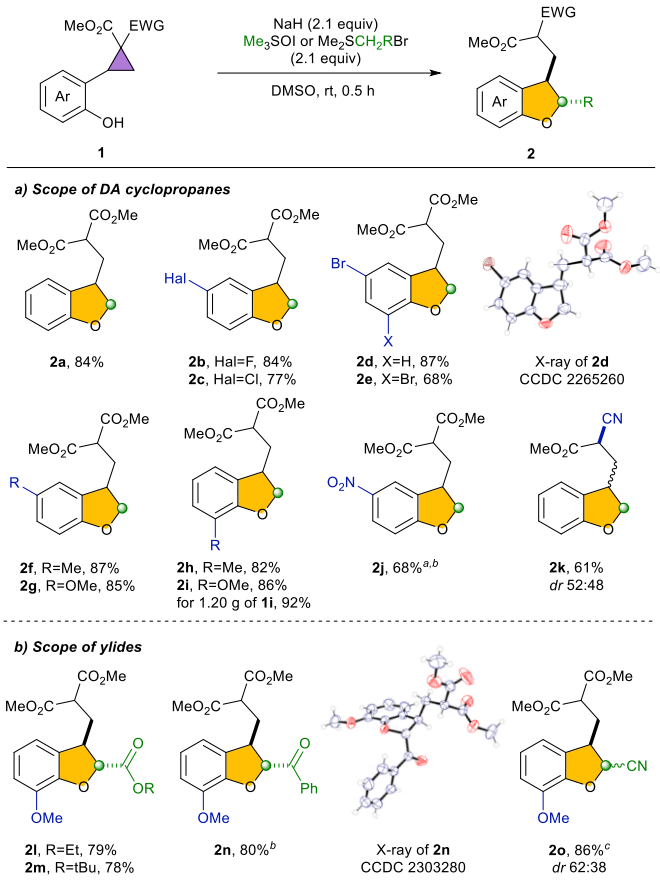
[a] Reaction conditions: base (0.84 mmol) and Me_3SOI were stirred in DMF or DMSO under argon atmosphere for 40 min at room temperature followed by addition of **1a** (0.4 mmol). [b] ^1H NMR yield using 1,1,1,3,3,3-hexamethyldisiloxane as an internal standard. [c] Reversed addition of ylide was used.

Unfortunately, deviation in both cyclopropane concentration and type of base (*t*-BuOK instead of NaH) did not lead to an increase in yield (Table 1, entries 6-8). To summarise, the optimal conditions for carrying out the process under study are the reaction of 0.1 M DMSO solution of cyclopropane **1a** with 2.1 equiv of Corey ylide at room temperature for 0.5 h.

With the optimised conditions in hand, the substrate scope of the disclosed [4+1] annulation was evaluated, and the results were summarised in Scheme 2. Reaction of **1** with DMSOM was well-tolerated to halogen, methyl and methoxy substituents in *ortho*- and *para*-position relative to OH-moiety, affording desired products **2b-d,f-i** in 77-87% yield (Scheme 2, a). On the contrary, the presence of electron-withdrawing groups at the same positions decelerated three-membered ring-opening stage (see the reaction mechanism below). For this reason, yield of substrate **2e**, bearing two bromine atoms, decreased to 68% compared to 87% for **2d**. For cyclopropane **1j** with 5-NO_2 group in the benzene ring, this effect was revealed to a greater extent. To accelerate the annulation process, this reaction was performed with a three-fold excess of Corey ylide. As a result, dihydrobenzofuran **2j** was obtained in 68% yield after stirring for 3 h. Next, compound **1k** with nitrile group as an acceptor in cyclopropane ring was tested, and compound **2k** was isolated as the mixture of two diastereoisomers in a nearly equal ratio in 61% yield. The lower efficiency of [4+1] annulation for this substrate presumably results from the realisation of some side reactions with participation of cyano-group. Additionally, structure of **2d** was unambiguously proved by single crystal X-ray diffraction.

The scalability was illustrated by converting 1.20 g of **1i** into 1.16 g of **2i** in 92% yield.

For a better understanding of the scope and limitations of this protocol, we studied the reactivity of cyclopropane **1i** toward diverse stabilised sulfonium ylides (Scheme 2, b). Reaction of substrate **1i** with bulky ylides, bearing CO_2Et, CO_2tBu or COPh moieties, led to 2-substituted dihydrobenzofurans **2l-n** in 78–80% yield as a single diastereomer. The *trans*-arrangement of substituents was

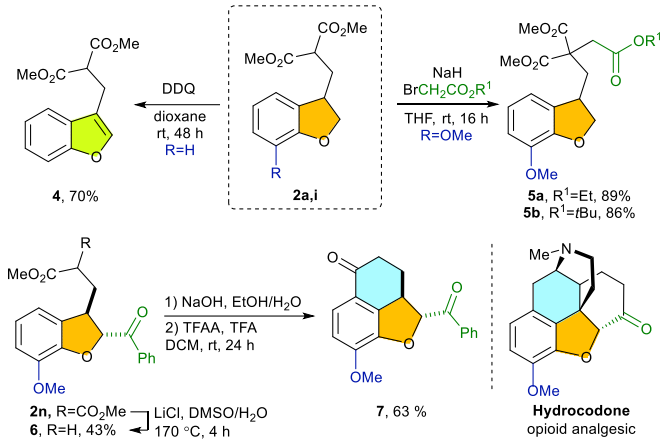


Scheme 2 Substrate scope for synthesis of dihydrobenzofurans 2. [a] 3.0 equiv of Me_3SOI and 3.0 equiv of NaH were used. [b] Reaction time was 3 h; [c] 2 h.

confirmed by NOESY spectra and single crystal X-ray diffraction of compound **2n**. In contrast, the reaction of the less hindered ylide Me_2S=CHCN afforded dihydrobenzofuran **2o** in 86% yield as a mixture of diastereomers in a 62:38 ratio with a predominance of *trans*-isomer. It should be noted that, while using ylides with COPh and CN moieties, the reaction time was extended to 2-3 hours. This is because the corresponding sulfonium ylides are not as basic as DMSOM and deprotonate phenol group (i.e., activate the cyclopropane) less efficiently.

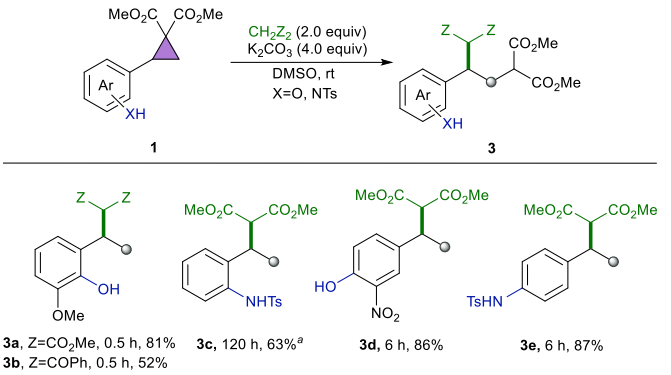
The synthetic utility of obtained 2,3-dihydrobenzofurans was further studied (Scheme 3). Compound **2a** was successfully aromatised with DDQ to benzofuran **4** in 70% yield. In contrast to unsubstituted dihydrobenzofurans, synthetic potential of substrates **2** is primarily conditioned by carbon chain, implemented in their structures. This fragment can be used as a linker to bind dihydrobenzofuran core with

other moieties, that was demonstrated by alkylation of **2i** with ethyl and *tert*-butyl bromoacetates to afford products **5a**,**b** in 89% and 86% yield, respectively. Moreover, compounds **2** are pre-organised for intramolecular annulation: Friedel-Crafts acylation of dealkoxycarbonylated product **6** (43% yield from **2n**) furnished tricyclic compound **7** in 63% yield. The latter is a structural analogue of hydrocodone – the main component of Vicodin analgesic.



Scheme 3 Synthetic applications of dihydrobenzofurans **2**.

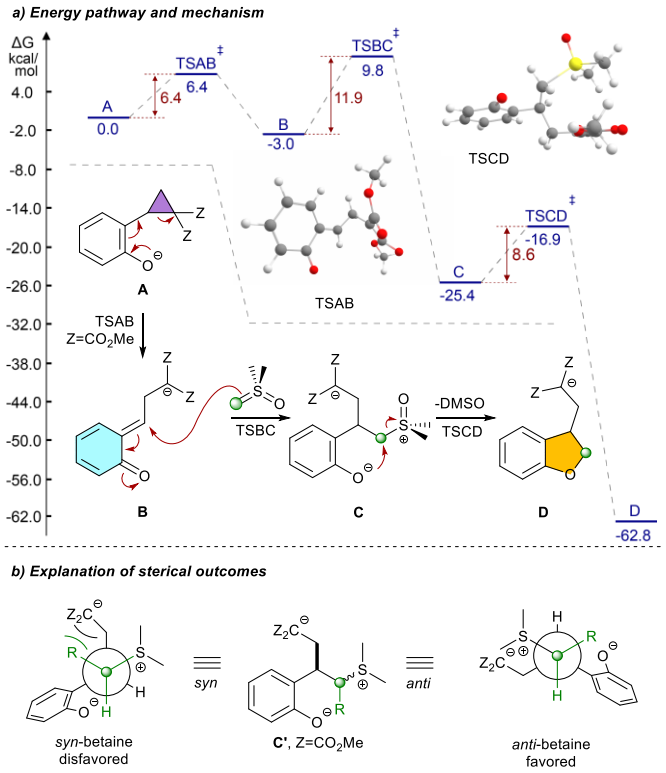
To demonstrate the versatility of the new DA cyclopropane activating mode, compound **1i** was subjected to a ring-opening by a series of typical CH-acids, such as dimethyl malonate and dibenzoylmethane. Under treatment with 2.0 equiv of carbonyl compound and 4.0 equiv of potassium carbonate, polyfunctional products **3a** and **3b** were obtained in 0.5 h in 81% and 52% yields, respectively (Scheme 4). Next, we applied the same strategy to DA cyclopropanes, whose anions are capable of undergoing isomerisation to *ortho*-aza-quinone methide. For this purpose, we tested cyclopropane **1l**, bearing the NHTs moiety in the *ortho*-position of the donor aromatic substituent, in reaction with excess of dimethyl malonate in the presence of potassium carbonate. To our delight, after stirring at room temperature for 3 hours, the product of small ring-opening **3c** was observed, however, although a significant portion of starting material remained unreacted. We associate the reaction deceleration with the high stability of the anion of **1l** that results in the low concentration of the quinoid form in the reaction mixture. To achieve the full conversion, cyclopropane **1l** was stirred in the presence of a large excess of reagents for 5 days affording compound **3c** in 63% yield. Moreover, the strategy under investigation was applied to substrates **1m** and **1n**, bearing -OH and -NHTs groups in *para*-position relative to cyclopropane ring. Under mild conditions, products of ring-opening with dimethyl malonate **3d** and **3e** were obtained after 6 hours in 86% and 87% yields, respectively.



Scheme 4 Other application of new DA cyclopropane activating mode. [a] $CH_2(CO_2Me)_2$ (5.0 equiv) and K_2CO_3 (6.0 equiv) were used.

In order to deeper understand the mechanism of these transformations, we have analysed the reaction between anion of **1a** and DMSOM with DFT calculations using ORCA 5.0 software package (Scheme 5, a and ESI).[65] Unlike the parent phenol/dienone tautomerisation which is ~20 kcal/mol uphill (ESI), the anionic cyclopropane/quinone methide rearrangement is exergonic. Despite the loss of aromaticity, the isomerisation of phenoxide **A** into *ortho*-quinone methide **B**, is favourable both kinetically ($\Delta G^{\ddagger}_{AB}$ = 6.4 kcal/mol) and thermodynamically (ΔG_{AB} = -3.0 kcal/mol) and proceeds effectively at room temperature. Considering similar stability of phenoxide and malonate anions, which can be evaluated from their basicity (pK_as of both conjugate acids are ~18-19 in DMSO),[66,67] the ~22-23 kcal/mol increase in exergonicity should largely stem from the strain stored in the cyclopropane moiety (~28 kcal/mol).

Upon attack by a DMSOM molecule, the quinoid intermediate **B** restores aromaticity to form much more stable sulfoxonium salt **C**. Subsequent intramolecular 5-*exo*-*tet* nucleophilic substitution of DMSO by the phenolate anion results in five-membered ring closure, leading to compound **D**. Finally, the intermediate **D** is protonated to yield dihydrobenzofuran **2**. Annulation with the stabilised sulfonium ylides follows a similar path. However, in this case, intermediate **C'** is formed as a mixture of *syn*- and *anti*-isomers (Scheme 5, b). As shown in the Newman projections, in the conformation favoured for the 5-membered ring closure, the bulky substituents are pushed apart in *anti*-betaine, while in *syn*-betaine their proximity causes significant steric repulsion. This leads to a faster consumption of *anti*-betaine and formation of predominantly *trans*-2,3-dihydrobenzofurans **2l-o**. Moreover, stabilised sulfonium ylides are known to add reversibly,[68] which shifts the equilibrium completely towards the formation of *trans*-2,3-dihydrobenzofurans **2l-o** when annulated with bulky sulfonium ylides.



Scheme 5 a) Energy path of the [4+1] annulation of **1a** with DMSOM. Calculations were performed at B3LYP/D4/6-311++G(d,p)/CPCM=DMSO level of theory. b) Diastereoselectivity explanation via Newman projections.

Conclusions

In conclusion, we have developed a conceptually new method for activation of DA cyclopropanes which is based on conversion of structural strain (a small ring) into electronic strain (loss of aromaticity). Deprotonation of donor aromatic substituents in the cyclopropanes leads to the rapid ring opening with conversion into quinone methide intermediates. Computational analysis of the reaction path confirmed that *in situ* isomerisation of deprotonated substrate to *ortho*-quinone methide is thermodynamically favorable. When applied to DA cyclopropanes with appropriate phenolic or aniline substituents, this method generates *ortho*- or *para*-quinone methides and their aza-analogues. These intermediates can be trapped with CH-acidic compounds as nucleophiles, providing an effective route toward acyclic polyfunctional derivatives of γ-disubstituted butanoic acid, which serve as promising building blocks. The cyclopropanes bearing 2-hydroxyphenyl moiety can be annulated with sulfur ylides, resulting in the formation of substituted dihydrobenzofurans in good yields. Having demonstrated this concept, we are currently conducting studies to exploit such dual activation in the design of other transformations.

Data availability

Crystallographic data: deposition numbers 2265260 (**2d**) and 2303280 (**2n**) contain the ESI† crystallographic data for this paper. Experimental procedures and analytical data (NMR, MS, IR, EA and melting points) can be found in the ESI.† Copies of NMR spectra are also provided.

Author Contributions

All authors took part in the conceptualisation of this study. S. V. V., T. T. P. and F. A. V. carried out the experimental work. Z. S. S. and T. V. A. carried out NMR and X-ray studies. V. V. S., A. I. A. and R. N. K. wrote the ESI. C. B. K. and A. I. V. performed the DFT calculations. I. O. A., U. M. G., A. I. A., V. V. S. and T. I. V. wrote the original draft of the manuscript. All authors contributed to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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