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Regiodivergent formal [4+2] cycloaddition of nitrosoarenes with furanyl cyclopropane derivatives as 4π components†

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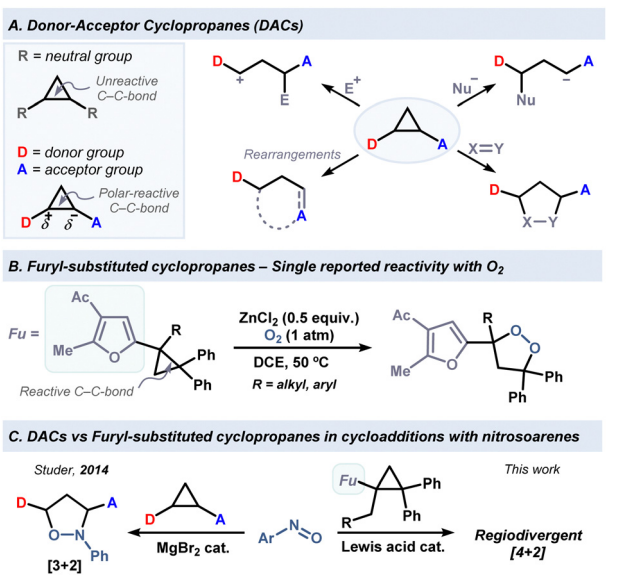
Cyclopropanes are commonly used as valuable 3-carbon building blocks. Herein, we disclose a different reactivity pattern of furanyl cyclopropanes, which serve as a 4-carbon component in Lewis acid-promoted [4+2] cycloadditions with nitrosoarenes to afford 1,2-oxazine derivatives. Importantly, the regioselectivity of the cycloaddition reaction can be controlled by the appropriate choice of the Lewis acid.

Cyclopropanes constitute a unique and valuable class of compounds in organic chemistry.[1] In spite of their inherent strain energy, unbiased cyclopropane derivatives are generally stable and reluctant to undergo ring-opening reactions.[2] In contrast, the polarization of a C–C-bond of the cyclopropane by the presence of suitable vicinal groups facilitates selective heterolytic ring-opening processes.[3] This fact was already reported in 1977 by Prof. Wenkert and coworkers.[4] In the 1980s, Prof. Reissig, who introduced the term donor–acceptor cyclopropane (DAC), demonstrated their synthetic value as versatile 3-carbon synthons by developing their fundamental reactivity.[5,6] However, in the last 15 years, the chemistry of DACs has been successfully exploited enabling access to an impressive structural diversity.[7] The characteristic reactivity of polarized cyclopropanes comprises the ring-opening reaction in the presence of nucleophiles or electrophiles, rearrangements and [3+*n*] cycloadditions (Scheme 1A). In particular, a plethora of cycloaddition reactions have been described with diverse (hetero)-2- or 4π-components to access highly functionalized carbo- and heterocycles of different ring sizes.[7a,d] Besides, in the last few years, our group[8] as well as others[9] have reported the synthesis of furanyl-substituted cyclopropanes through the cyclopropanation of alkenes with furanyl carbenes generated *in situ* from conjugated enynones.[10] In contrast to DACs, the reactivity of these cyclopropanes has not been explored. Thus, reactions with isolated furanyl cyclopropanes are restricted to our study describing a zinc-promoted [3+2] cycloaddition with O_2 to afford 1,2-dioxolane derivatives (Scheme 1B).[8c,11] Taking into account the versatility of DACs in cycloaddition reactions, we wondered if furanyl cyclopropanes could be employed in other types of cycloaddition reactions. In particular, we focused on nitroso compounds, which are well-known as 2π-components in [4+2] cycloaddition reactions.[12]

In the case of DACs, Studer and co-workers described the magnesium-catalysed [3+2] cycloadditions of DACs with nitrosoarenes to afford isoxazolidine derivatives (Scheme 1C).[13] Herein, we present our study with furanyl-substituted cyclopropanes, which showed a distinctive reactivity since they participate as 4-carbon synthons in regiodivergent formal [4+2] cycloadditions.



Scheme 1 (A) Donor–acceptor cyclopropanes (DACs): structure and typical reactivity. (B) Furanyl-substituted cyclopropanes – reaction with O_2. (C) Reactivity of DACs *vs.* furanyl-substituted cyclopropanes with nitrosoarenes.

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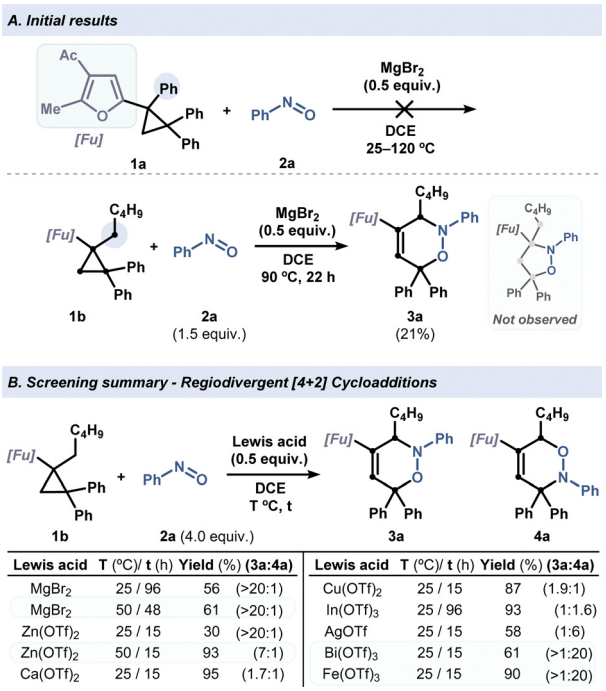
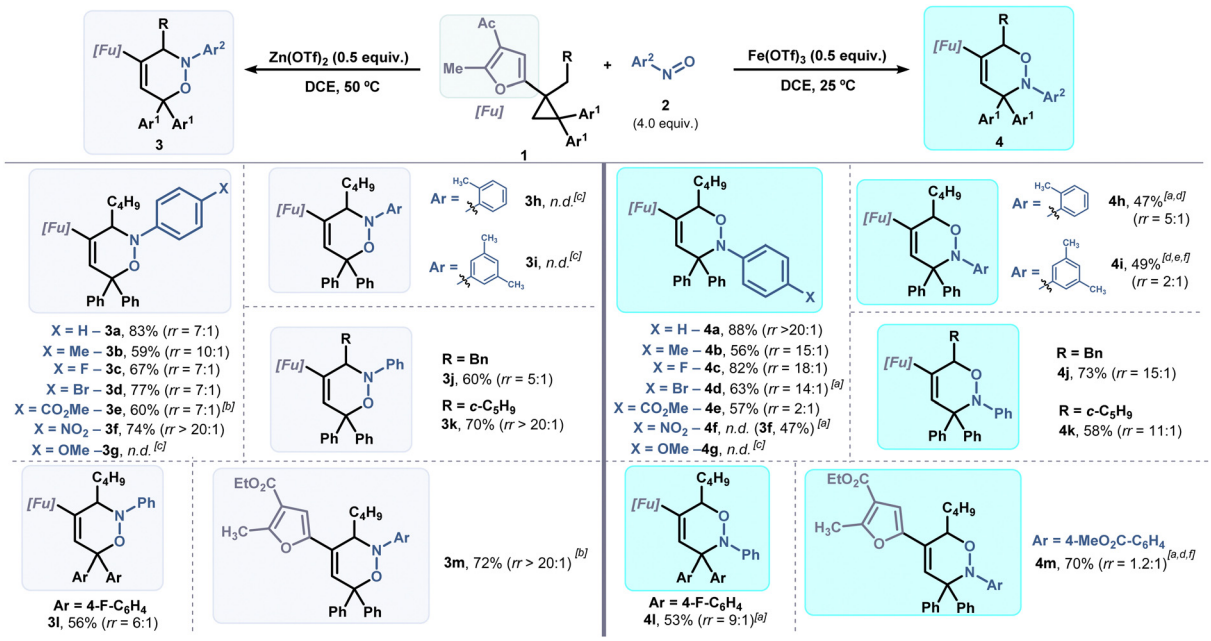


Lewis acid	T (°C)/ t (h)	Yield (%) (3a:4a)		Lewis acid	T (°C)/ t (h)	Yield (%) (3a:4a)	
$MgBr_2$	25 / 96	56	(>20:1)	$Cu(OTf)_2$	25 / 15	87	(1.9:1)
$MgBr_2$	50 / 48	61	(>20:1)	$In(OTf)_3$	25 / 96	93	(1:1.6)
$Zn(OTf)_2$	25 / 15	30	(>20:1)	AgOTf	25 / 15	58	(1:6)
$Zn(OTf)_2$	50 / 15	93	(7:1)	$Bi(OTf)_3$	25 / 15	61	(>1:20)
$Ca(OTf)_2$	25 / 15	95	(1.7:1)	$Fe(OTf)_3$	25 / 15	90	(>1:20)

Scheme 2 Lewis acid-promoted reaction of furanyl cyclopropanes **1a,b** and nitrosobenzene (**2a**). (A) Initial findings. (B) Lewis acid-controlled regiodivergent formation of 1,2-oxazines. Combined yields and regioisomeric ratio were determined by ^{1}H NMR using CH_2Br_2 as a standard.

At the outset, we employed similar conditions as previously reported by Studer,[13] to evaluate the reaction of furanyl-substituted cyclopropane **1a**[8c] with nitrosobenzene (**2a**) (Scheme 2A). Regrettably, we did not detect products arising from a cycloaddition reaction and only degradation was observed when forcing reaction conditions. In contrast, the use of furanyl cyclopropane **1b**, bearing an alkyl group, was more promising. Thus, along with unreacted starting materials (**1b**, 61% NMR yield), we observed the regioselective formation of 1,2-oxazine **3a** in an appreciable yield (21%), instead of the expected isoxazolidine derived from a [3+2] cycloaddition. In sharp contrast, compound **3a** arises from a formal [4+2] cycloaddition involving the methylene unit directly attached to the cyclopropane along with the net loss of two hydrogen atoms. This reaction outcome is unusual. Indeed, a single related example reported by Nishida and co-workers described a reaction of cyclopropanes as a 4-carbon synthon in a [4+2] cycloaddition.[14] Consequently, we performed an extensive screening of the reaction conditions to improve the results (Scheme 2B, see ESI,† for additional details). First, we observed that the amount of nitrosobenzene (**2a**) had a strong impact on the reaction.

Thus, the use of $MgBr_2$ as a Lewis acid and 4 equivalents of **2a**, led to **3a** in better yields under milder reaction conditions (56% at 25 °C; 61% at 50 °C), yet long reaction times were required. Notably, by employing different Lewis acids, we observed the formation of regioisomeric 1,2-oxazine **4a**. For instance, with $Zn(OTf)_2$ (50 mol%, 50 °C, 15 h), a mixture of **3a** and **4a** was obtained in excellent overall yield (93%) and good product selectivity in favour of 1,2-oxazine **3a** (**3a**:**4a** = 7:1). Other Lewis acids such as $Ca(OTf)_2$, $Cu(OTf)_2$ or $In(OTf)_3$ were also effective and had strong impact on the regioselectivity, which was poor in those cases. In order to evaluate the feasibility to direct the reaction towards compound **4a**, we tested other Lewis acids. Gratifyingly, we found that the use of AgOTf and, particularly, $Bi(OTf)_3$ and $Fe(OTf)_3$ led to a remarkable switch on the regioselectivity, leading to 1,2-oxazine **4a** in good yields ($Bi(OTf)_3$,



Scheme 3 Scope: metal-controlled regiodivergent formation of 1,2-oxazines **3–4** from furanyl cyclopropanes **1** and nitrosoarenes **2**. Yields correspond to the isolated major regioisomer (n.d. = not detected; rr = regioisomeric ratio). [a] Using $Bi(OTf)_3$. [b] Using $MgBr_2$. [c] Degradation of the starting materials was observed. [d] Combined yield. [e] Using $In(OTf)_3$. [f] Separable regioisomers.

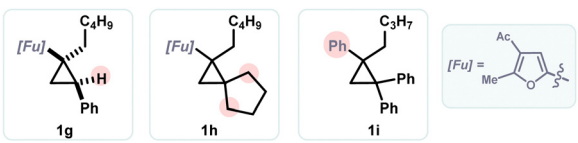
61%, **3a**:**4a** > 1:20; $Fe(OTf)_3$, 90%, **3a**:**4a** > 1:20). Thus, we could control the regioselectivity of this transformation of furanyl cyclopropanes by the choice of the Lewis acid.

With the optimized conditions in hand, we explored the scope of the reaction as described in Scheme 3. First, different 4-substituted nitrosoarene derivatives could be employed in the synthesis of the corresponding 1,2-oxazines **3a–f** and **4a–e**. The isolated yields for the major regioisomers ranged from moderate to good. Interestingly, the regioselectivities were similar, except for the case of nitrosoarenes bearing strong electron-withdrawing groups, which showed preference for the formation of the corresponding 1,2-oxazines **3**. Thus, poor selectivity was observed when attempting the formation of 1,2-oxazine **4e** (Ar^2 = 4-MeO_2C-C_6H_4, **4e**:**3e** = 2:1), while the formation of 1,2-oxazine **4f** (Ar^2 = 4-O_2N-C_6H_4, **4f**:**3f** = 0:1) was not detected under the standard conditions typically leading to this isomer. Electron-rich nitrosoarenes were not tolerated and only degradation of the starting materials was observed under the standard conditions. Unpredictably, unbiased substitutions at *ortho*- or *meta*-positions in the nitrosoarene (Ar^2 = 2-Me-C_6H_4; 3,5-Me_2-C_6H_4) also impacted the reactivity. Thus, the expected oxazines **3h–i** were not observed when using $Zn(OTf)_2$. In contrast, the corresponding oxazines **4h–i** were prepared in moderate yields and regioselectivity using $Fe(OTf)_3$ and $In(OTf)_3$, respectively. Using nitrosobenzene (**2a**), modifications on the furanyl cyclopropane were also studied. Other primary alkyl[15] groups were used as demonstrated by the efficient preparation of regioisomeric oxazines **3j–k** and **4j–k**. Similarly, phenyl and furanyl groups on the furanyl cyclopropanes were modified, enabling the synthesis of oxazines **3l–m** and **4l–m**.

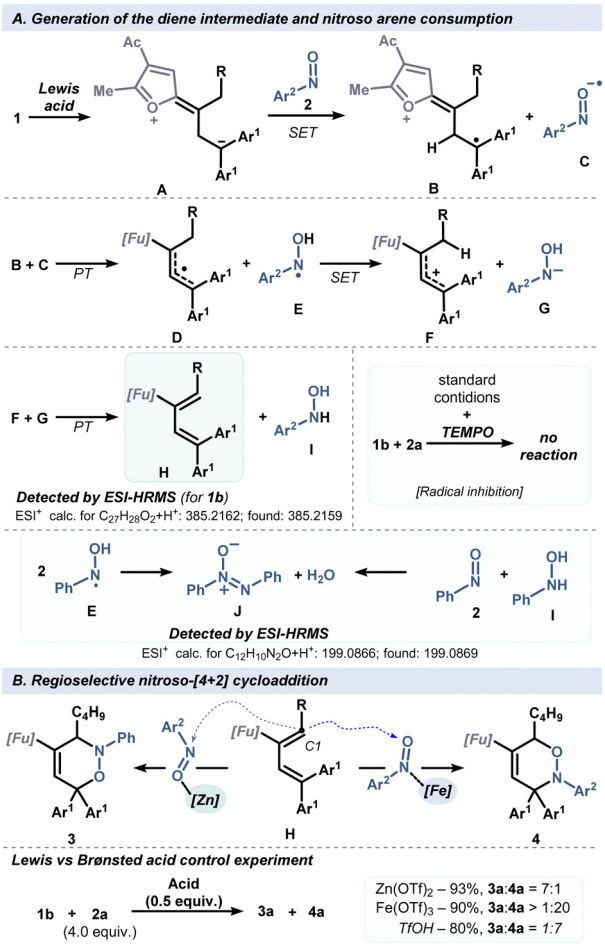
This reactivity pattern is very exclusive regarding the substitution (Scheme 4). Indeed, the two aryl groups in the furanyl cyclopropane are required, since analogue compounds **1g–h** were unreactive under otherwise identical reaction conditions. Moreover, cyclopropane **1i** showing a phenyl instead of the furanyl group proved also unreactive, highlighting the crucial role of the furanyl group.

The mechanism proposed for this transformation is depicted in Scheme 5. First, the formation of the 1,3-diene intermediate is required for the [4+2] cycloaddition (Scheme 5A).

An initial single electron transfer (SET), as proposed by Nishida,[14] seems unlikely according to the oxidation potentials of cyclopropanes **1b** (E(**1b**–**1b**$^{\bullet+}$) = +1.34 V *vs.* Ag/AgCl) and **1i** (E(**1i**–**1i**$^{\bullet+}$) = +1.92 V *vs.* Ag/AgCl), which should be able to reduce nitrosobenzene (E(**2a**–**2a**$^{\bullet-}$) = −1.10 V *vs.* Ag/AgCl).[16] In contrast, these furanyl cyclopropanes might react as a push–pull cyclopropane in the presence of Lewis acids to generate species **A**,[17] which would not be feasible from cyclopropane **1i**.



Scheme 4 Unreactive substrates.



Scheme 5 Proposed mechanism.

Then, a SET process with nitrosoarene **2** might lead to radical cation **B** and radical anion **C**. A subsequent proton transfer (PT) from species **B** to **C** could generate allyl radical **D** and protonated nitrosoarene radical **E**.[16] According to the literature, species **E** can undergo a SET process to form hydroxyamide anion **G**,[17] which is associated in this case with the oxidation of **D** to allyl cation **F**. A new PT should lead to the required 1,3-diene **H** and hydroxylamine **I**. It should be noticed that species **E** is known to undergo a self-dimerization/dehydration process to generate azoxybenzene (**J**) and the reaction of **G** with nitrosoarene **2** also led to the formation of **J**.[16c] The formation of diene **H** and azoxybenzene (**J**) was detected by ESI-HRMS analysis. Indeed, the formation of **J** by consumption of nitrosoarene **2** in these processes justifies its use in excess. Moreover, inhibition observed using TEMPO as an additive is consistent with the participation of radical species.

Besides, the generation of diene **H** sets the stage for the [4+2] cycloaddition with nitrosoarene **2** (Scheme 5B). The presence of the furan ring should make C1 the most nucleophilic position of the diene and, therefore, the regioselectivity might be dictated by the effect of the Lewis acid employed.[18] On the one hand, zinc complexes are known to coordinate nitroso compounds at the O-atom,[19] a fact that might explain the formation of

1,2-oxazines **3**. In contrast, iron complexes preferentially coordinate to the N-atom of **2**,[18d] favouring the formation of regioisomeric 1,2-oxazines **4**.[20] Control experiments indicated that the reaction does not occur in the absence of a Lewis acid. Notably, TfOH is also promoting the reaction (80% NMR yield, **3a** : **4a** = 1 : 7), but the different regioselectivity compared to Lewis acids indicates that the Lewis acid plays a crucial role in the reaction outcome.[21]

In summary, we have reported the unusual behaviour of cyclopropanes as a 4-carbon component. In particular, furanyl-substituted cyclopropanes served as 1,3-diene precursors for [4+2] cycloaddition reactions with nitrosoarenes to afford 1,2-oxazine derivatives. Importantly, a remarkable degree of control over the regioselectivity of the cycloaddition can be achieved by selecting the Lewis acids in order to prepare regioisomeric 1,2-oxazine derivatives. The study of other cycloaddition reactions of furanyl cyclopropanes and the extension of this novel reactivity to other cyclopropanes are currently underway in our laboratories.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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