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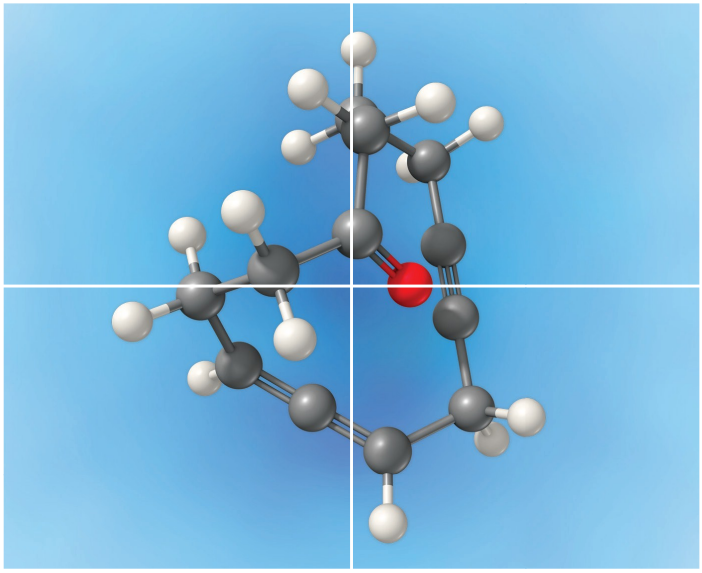

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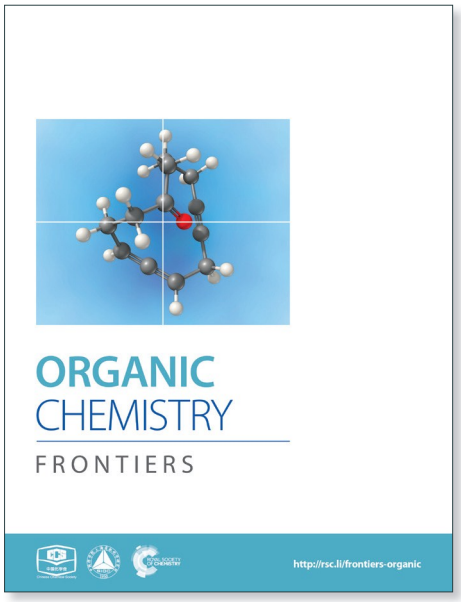

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Journal Name

ARTICLE

Synthesis and Reactivity of Alkoxy-activated Cyclobutane-1,1-dicarboxylates

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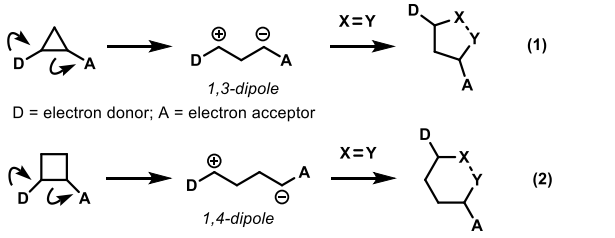
Intermolecular cycloaddition chemistry is unarguably one of the most appreciated strategies to bring complexity to products from simple starting materials. Generation of dipolar intermediates by exploitation of ring strain in carbocycles has become an efficient option. In this regard, donor-acceptor cyclopropanes have been extensively studied, but reports on extending similar synthetic transformations to the homologous cyclobutanes are comparatively limited. Recently, our group has become interested in application of alkoxy-activated cyclobutane-1,1-dicarboxylates (AACDs) in cycloaddition chemistry. This personal account discusses our contributions in this area with contextual examples from others.

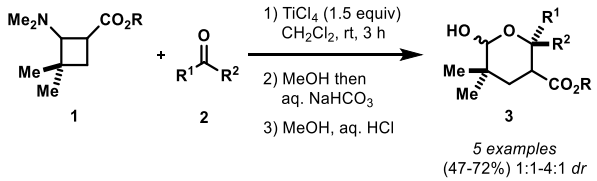
1. Introduction

Exploitation of ring strain to generate dipolar intermediates for cycloaddition reactions is a valuable strategy in modern organic synthesis. One of the most studied motifs is that of cyclopropanes, typically bearing vicinally substituted electron donating and electron accepting groups, generally termed as donor-acceptor (DA) cyclopropanes.[1] This substitution pattern polarizes the C-C bond, forming (formal) 1,3-zwitterionic intermediates which undergo facile cycloadditions with suitable dipolarophiles, typically under the influence of a Lewis acid[2] (Eq. 1, Scheme 1).[3] While this mode of reactivity has been extensively studied, reports extending similar synthetic transformations to the homologous cyclobutanes are comparatively limited (Eq. 2, Scheme 1)[4] despite having similar ring strain.[5]

It was not until 1991, when the first report of formal cycloaddition of DA cyclobutanes was disclosed by Saigo and co-workers.[6] In this work, amino-activated DA cyclobutanes **1** underwent a [4+2] cycloaddition with carbonyl compounds **2** to generate tetrahydropyrans **3** albeit with low diastereoselectivity and modest yield (Scheme 2).



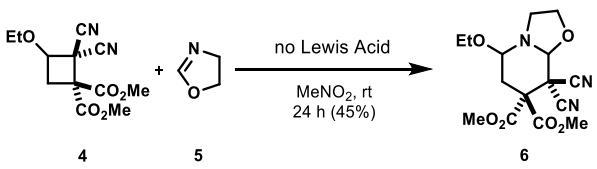
Scheme 1 Reactivity of DA cyclopropanes and cyclobutanes with generic dipolarophile **X=Y**.



Scheme 2 Cycloaddition of amino-activated DA cyclobutanes with carbonyl compounds.

A few years later, Suzuki and co-workers observed a [4+2] cycloaddition of highly activated DA cyclobutane **4** with 2-oxazoline **5** without the need for a catalyst (Scheme 3).[7]

The field remained relatively dormant for a decade, and in 2008, Matsuo and co-workers observed a conceptually similar[8] [4+2] cycloaddition with 3-alkoxycyclobutanones **7** and carbonyl compounds **2** (Scheme 4).[9]



Scheme 3 Cycloaddition of DA cyclobutane **4** with 2-oxazoline **5**.

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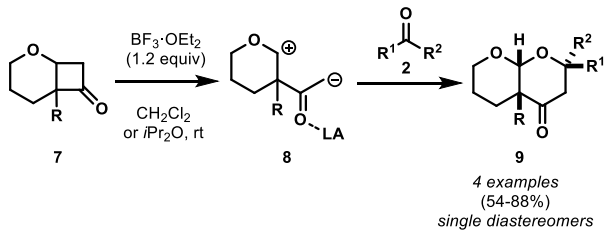
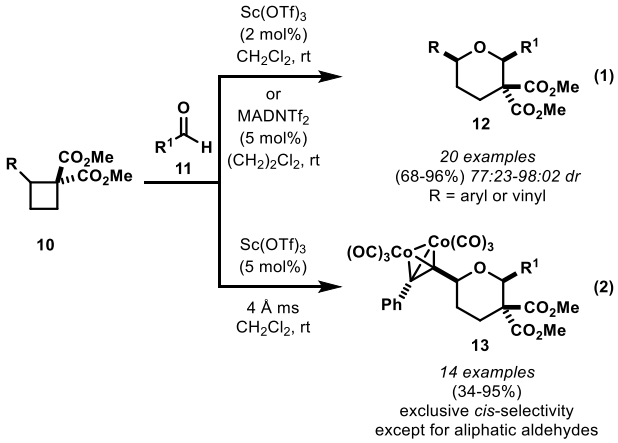


Scheme 4 The [4+2] cycloaddition 3-alkoxycyclobutanones **7** and carbonyl compounds **2**.

The first catalytic cycloaddition of DA cyclobutanes was reported by the research groups of Johnson and of Christie and Pritchard almost at the same time (Scheme 5). The [4+2] cycloaddition with aldehydes **11** were performed under mild conditions with good to excellent yields. Contrary to the work conducted by the Saigo group, these reports used carbon based electron-donor groups and 1,1-diester functionality as an electron-acceptor. Johnson found $Sc(OTf)_3$ was able to catalyse the cycloaddition with loadings as low as 2 mol% (Eq. 1, Scheme 5).[10] The cycloaddition was highly diastereoselective for 2,6-*cis*-diastereomer with most of the aryl aldehydes investigated, but when cinnamaldehyde was used the diastereoselectivity dropped to 77:23, possibly due to the slow reactivity.[11] The group was able to encompass aliphatic aldehydes with the more reactive and bulky Lewis acid, $MADNTf_2$.[12]

The work by Christie and Pritchard reported a similar reactivity of cyclobutanes with a cobalt–alkyne complex as an electron-donor and 1,1-diesters as electron-acceptors (Eq. 2, Scheme 5).[13] The group also found $Sc(OTf)_3$ as the best catalyst for this transformation. Most of the aryl aldehydes and other electron-rich aldehydes reacted in good to excellent yields as single diastereomers. When aliphatic aldehydes were used, the diastereoselectivity significantly dropped to 20-23% *de*.

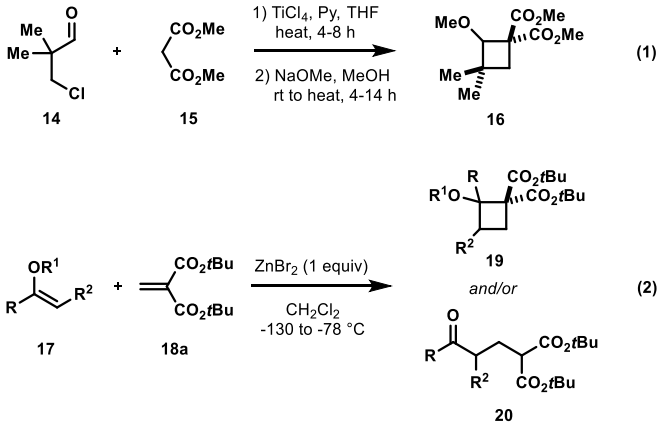


Scheme 5 The [4+2] cycloaddition of carbon-activated cyclobutane-1,1-dicarboxylates **10** with aldehydes **11**.

It became apparent from the above results that having 1,1-diesters as electron-acceptors as compared to a monoester enhances the reactivity of the DA cyclobutane as well as diastereoselectivity in cycloadditions. Inspired by these seminal reports and our ongoing interest in alkoxy-activated cyclopropane chemistry,[14] we were motivated to investigate the reactivity alkoxy-activated cyclobutane-1,1-dicarboxylates (AACDs).

2. Synthesis of Alkoxy-activated Cyclobutane Dicarboxylates

At the outset of our work, there were two literature methods available for the synthesis of AACDs.[15] The use of a Michael induced ring closure of acyclic substrates (Eq. 1, Scheme 6) was not selected as a preparative route as it offers limited control over the stereochemistry, and requires multiple steps.[16] On the other hand, the $ZnBr_2$-promoted [2+2] annulation reported by Roberts in 1986 appeared much more promising since the required alkyl enol ethers are commercially available, and the methylidene malonates can easily be made by a Knoevenagel condensation (Eq. 2, Scheme 6).[17] Disappointingly, duplication of the conditions reported by Roberts in our hands gave poor yields (insufficient for further study) with a complex mixture of polymerization and/or ring-opened by-products. More disappointingly, however, we couldn't extend this methodology to more reactive diethyl or dimethyl methylidene malonates.[17,18] Thus, a new catalyst screening was warranted, and we found $Yb(OTf)_3$ as the best catalyst for this [2+2] cycloaddition.[19] With the optimized conditions in hand, the scope of the cyclobutane synthesis was explored (Table 1).[20]



Scheme 6 Literature methods for the synthesis of AACDs.

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Table 1 The Synthesis of AACDs.

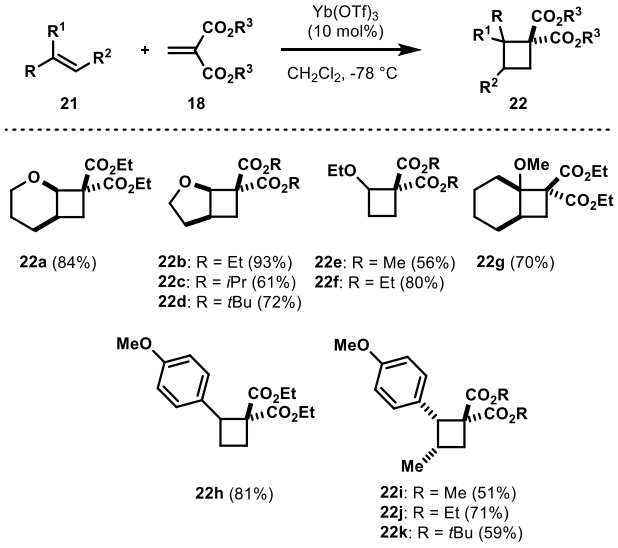
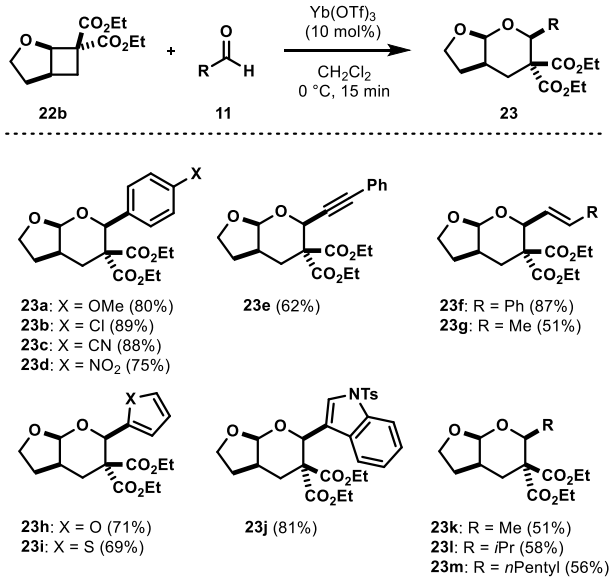


Table 2 The [4+2] cycloaddition of AACDs with aldehydes.



A range of cyclic and acyclic enol ethers were found to undergo cycloaddition with a variety of dialkyl methylidene malonates in good to excellent yields to afford AACDs as single diastereomers (**22a**-**22g**, Table 1). In addition to enol ethers, electron-rich styrenes were also found to undergo efficient cycloaddition to yield AACDs in good yields (**22h**-**22k**, Table 1).

3. Reactivity of Alkoxy-activated Cyclobutane Dicarboxylates

With the AACDs at hand, the reactivity was explored with aldehydes **11**, which were previously reported to undergo [4+2] cycloadditions with DA cyclobutanes **1** and **10** (see Schemes 2 and 5).

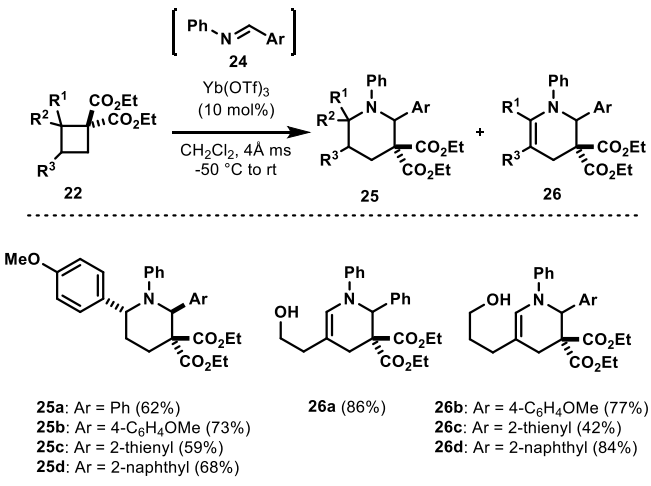
3.1. The [4+2] cycloaddition of AACDs with aldehydes.

Interestingly, initial investigations established that $Yb(OTf)_3$, which was used for the synthesis of AACDs (Table 1), can also be used for the [4+2] cycloaddition with aldehydes. A wide range of aldehydes were found to undergo cycloadditions with AACDs in good to excellent yields as single diastereomers (Table 2).[21] Aryl, heteroaryl, vinyl, and alkynyl aldehydes underwent smooth cycloadditions to afford tetrahydropyrans **23** in good to excellent yields (**23a**-**23j**, Table 2). Finally, aliphatic aldehydes were also found to engage in cycloadditions without the need for another catalyst, but only in modest yields (**23k**-**23m**).

3.2. The [4+2] cycloaddition of AACDs with imines.

With the successful cycloaddition of AACDs with aldehydes **11**, we were then interested to explore other possible dipolarophiles. Although, imines **24** were excellent dipolarophiles in cycloadditions with DA cyclopropanes,[22] their reactivity with DA cyclobutanes was unexplored. Thus, we set out to investigate the reactivity of imines **24** with AACDs.[20] Pleasingly, upon exposure of cyclobutane **22** and imine **24** (prepared *in situ*) to catalytic $Yb(OTf)_3$ at -50 °C, a mixture of bicyclic piperidine **25** and piperideine **26** were formed (Table 3). In order to converge on the piperideine product **26**, the reaction was simply warmed to room temperature after the cyclobutane was consumed.[23] Aryl ether activated cyclobutanes were also

Table 3 The [4+2] cycloaddition of AACDs with imines.



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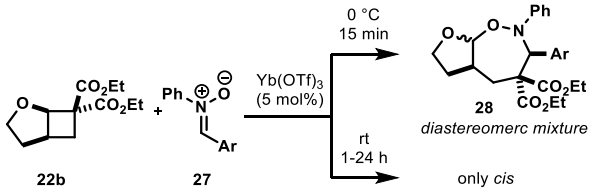
found to undergo cycloaddition to afford exclusive 2,6-trans-piperidines, but longer reaction times were necessary (**25a**-**25d**, Table 3).

3.3. The [4+3] cycloaddition of AACDs with nitrones.

Having successfully expanding the reactivity of AACDs to imines **24**, our interest turned into exploring 3-atom dipolarophiles. Nitrones **27** proved to be excellent dipolarophiles in cycloadditions with DA cyclopropanes.[24] Given this precedent, we investigated the reactivity of nitrones with AACDs under previously successful $Yb(OTf)_3$ catalysis.

A quick optimization study established 5 mol% $Yb(OTf)_3$ in dichloromethane as the best conditions for this cycloaddition.[25] Interestingly, *cis*-diastereomers were formed as thermodynamic products when the reaction was performed at room temperature, but efforts to isolate the kinetic *trans*-diastereomer at lower temperatures gave diastereomeric mixtures (Table 4).[26] Additionally, when electron-deficient nitrone **27d** was used, an inseparable third diastereomer was formed (entry 4).[27] The heterocycle 1,2-oxazepane, though not naturally occurring, displays interesting antiviral[28] and antiproliferative[29] activity.

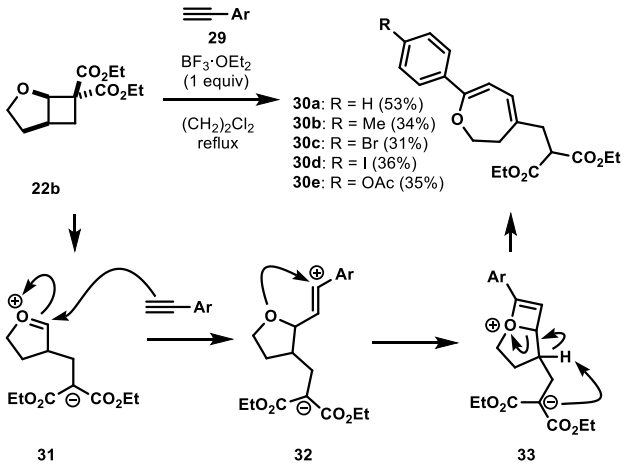
Table 4 The [4+3] cycloaddition of AACDs with nitrones.



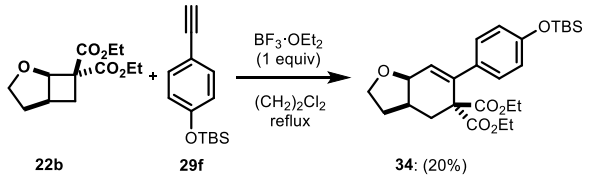
entry	1,2-oxazepane	at 0 °C yield (*cis:trans:3rd*)	at rt yield (*cis*)
1	**28a**: Ar = C_6H_5	91% (31:69)	76%
2	**28b**: Ar = 4-C_6H_4Cl	82% (29:71)	73%
3	**28c**: Ar = 4-C_6H_4OMe	88% (37:63)	74%
4	**28d**: Ar = 4-C_6H_4CN	95% (15:57:27)	76%

3.4. $BF_3{\cdot}OEt_2$ -promoted reaction of AACDs with terminal alkynes.

Intrigued with the success of above discussed cycloadditions, we were then interested to study an all carbon dipolarophile, such as a terminal alkyne. Terminal alkynes **29** were reported to undergo efficient [3+2] cycloadditions with DA cyclopropanes.[30] After numerous unsuccessful attempts under a variety of conditions, we found stoichiometric $BF_3{\cdot}OEt_2$ was able to promote this reaction. Interestingly, instead of the expected cycloadduct, the reaction resulted in 2,3-dihydrooxepine **30** through an addition/rearrangement sequence *via* a highly strained bicyclic intermediate **33** (Scheme 7).[31] Only phenylacetylenes with electron-neutral and moderately electron-rich substituents proceeded through a productive reaction manifold, albeit in low yields (**30a-30e**, Scheme 7). Substrates with strong electron-donating substituents rapidly polymerized upon exposure to $BF_3{\cdot}OEt_2$, whereas, electron-deficient alkynes failed to react.[32]



Scheme 7 $BF_3{\cdot}OEt_2$ -promoted reaction of AACDs with terminal alkynes.



Scheme 8 $BF_3{\cdot}OEt_2$-promoted [4+2] cycloaddition of alkyne **29f** with AACD **22b**.

Interestingly, when silyloxy substituted phenylacetylene **29f** was used, the reaction resulted in [4+2] cycloadduct **34** (Scheme 8). This was the only case we observed cycloaddition instead of rearrangement, which could be due to the increased bulk on the aryl ring inhibiting the polymerization and/or rearrangement.

3.5. The [4+2] cycloaddition of AACDs with nitrosoarenes.

Motivated with the successful cycloadditions of AACDs with aldehydes, imines, and nitrones, we were then interested in exploring all heteroatom dipolarophiles, such as nitroso compounds. Nitroso compounds have been utilized in various transformations: as dienophiles in nitroso Diels-Alder reactions,[33] as enophiles in nitroso-ene reactions,[34] and as either nitrogen or oxygen transfer reagents in nitroso-aldol reactions.[35] But surprisingly, at the outset of this work,

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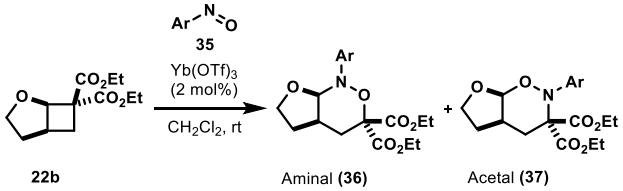
nitrosoarenes **35** have not seen application in cycloaddition chemistry with either DA cyclopropanes[36] or cyclobutanes.[37]

Gratifyingly, $Yb(OTf)_3$ was able to catalyse the reaction, with catalysts loadings as low as 0.5 mol%, but 2 mol% was chosen for experimental convenience.[38] Nitrosoarenes with electron-neutral substituents were found to be excellent reaction partners (entries 1-2, Table 5). Substrates with a moderately deactivating ester substituent resulted in good yield, but the regioselectivity dropped to 13:1 (entry 3). The nitrosoarenes with strong electron-withdrawing groups afforded moderate yields; however, the regioselectivity decreased significantly to 3:1 (entry 4). Nitrosoarene with weakly electron donating methyl substituent resulted in a poor 29% yield (entry 5). Upon incorporation of a strong electron donating group no reaction was observed, likely due to the sequestration of the ytterbium catalyst by the electron-rich nitrosoarene **35f** (entry 6).

In an attempt to extend the reaction scope to encompass electron-rich substrates, we screened several Lewis acids under a variety of conditions, and it was found that MgI_2 was the best, albeit in low yield (Table 6).[39] Interestingly the regioisomer isolated under these conditions was acetal **37** and not the aminal **36** as expected, which could be due to the enhanced nucleophilicity of the nitroso oxygen from methoxy substituent (Scheme 9). More interestingly, when the reaction was left to stir for two days at room temperature or when **37** was treated with 50 mol% MgI_2 at room temperature overnight, pyrrolidine **38** was formed (entry 2, Table 6) plausibly *via* MgI_2-promoted deoxygenation process of acetal product as shown in Scheme 9.[40] The nitroso-heteroarenes **35h** and **35i** participated in the cycloaddition, also in low yields (entries 5 and 6).

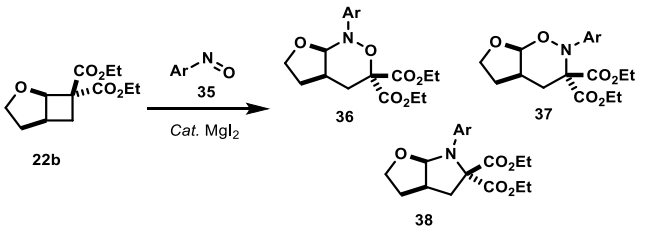
Table 5 The [4+2] cycloaddition of AACDs with nitrosoarenes.



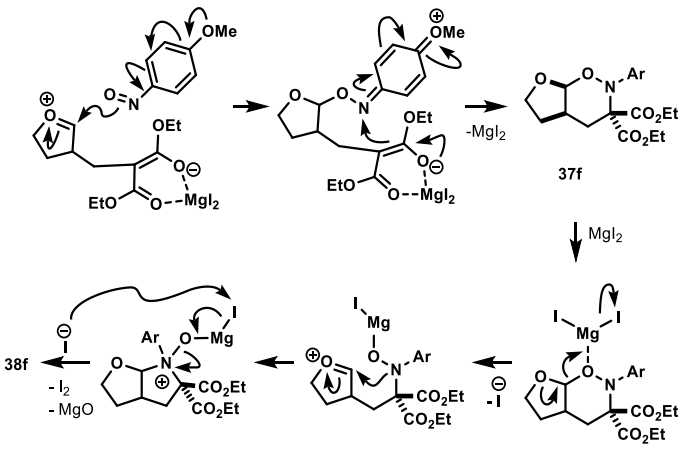
entry	nitrosoarene	**36**:**37**	yield (%)
1	**35a**: Ar = C_6H_5	>20:1[a]	92
2	**35b**: Ar = 4-C_6H_4Br	>20:1[a]	89
3	**35c**: Ar = 4-$C_6H_4CO_2Et$	13:1[b]	76
4	**35d**: Ar = 4-C_6H_4CN	3:1[b]	61
5	**35e**: Ar = 4-$C_6H_4CH_3$	>20:1[a]	29
6	**35f**: Ar = 4-$C_6H_4OCH_3$	-	-

a = based on ^1H NMR. *b* = ratio of isolated yiled.

Table 6 The MgI_2 promoted cycloaddition of AACDs with nitrosoarenes.



entry	nitrosoarene	product	MgI_2 (mol%)	yield (%)
1	**35f**: Ar = 4-C_6H_4OMe	**37f**	10	20
2	**35f**: Ar = 4-C_6H_4OMe	**38f**	50	26
2	**35g**: Ar = 4-$C_6H_4N(CH_3)_2$	**38g**	50	22
5	**35h**: Ar = 2-pyridine	**37h**	50	28
6	**35i**: Ar = *N*-BOC-5-nitrosoindole	**37i**	10	19



Scheme 9 Plausible mechanism for the formation of **37f** and **38f**.

4. Additional Cyclobutane-1,1-dicarboxylates

In recent years, several others reported interesting cycloadditions of DA cyclobutanes. Most recently, Tang and co-workers reported an enantioselective [4+3] cycloaddition of DA cyclobutanes and nitrones (Scheme 10).[41] While contributing the first enantioselective variant, the group also added several new DA cyclobutanes to the library.

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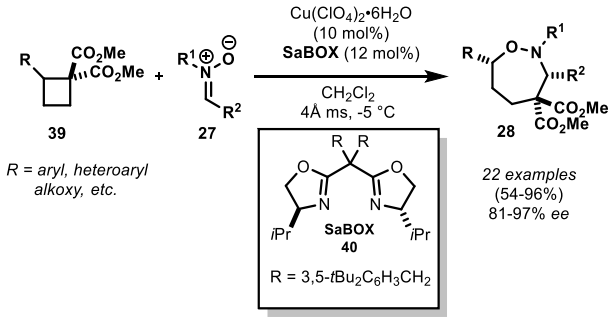
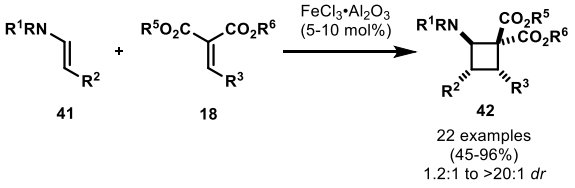


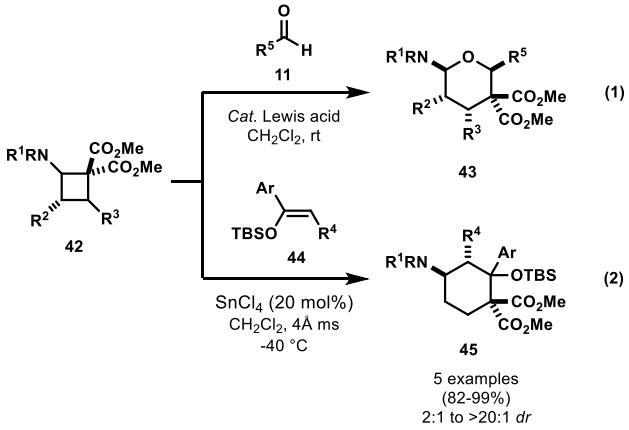
Scheme 10 Enantioselective [4+3] cycloaddition of DA cyclobutanes **39** with nitrones **27**.

Waser and co-workers enhanced the family of DA cyclobutanes by developing an Fe(III)-catalyzed [2+2] cycloaddition of enimides **41** and alkylidene malonates **21** to access amino-activated cyclobutane-1,1-dicarboxylates **42** (Scheme 11).[42]



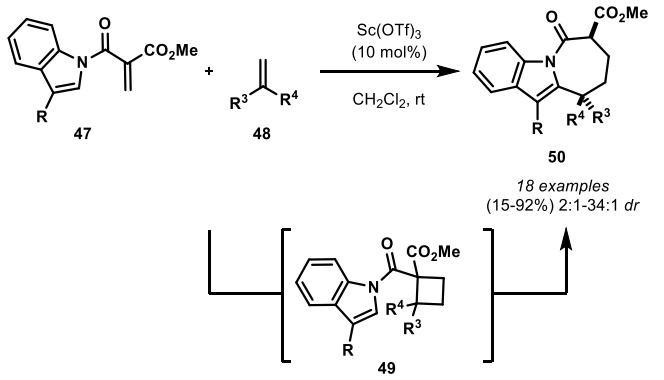
Scheme 11 Synthesis of amino-activated cyclobutane-1,1-dicarboxylates *via* a [2+2] cycloaddition.

The group also disclosed the reactivity of these DA cyclobutanes with aldehydes and silyl enolethers (Scheme 12).[43] Interestingly, in the reaction with aldehydes **11** (Eq. 1, Scheme 12), the less substituted DA cyclobutanes **42** (R_2 = R_3 = H) were able to activated with $Sc(OTf)_3$, but the more substituted **42** (R_2 = R_3 ≠ H) required $FeCl_3$·Al_2O_3. More interestingly, thymine- or fluorouracil-substituted cyclobutanes were also found to undergo cycloaddition with aldehydes under $Hf(OTf)_4$ catalysis to access six-membered ring carbonucleoside analogues. In reaction with silyl enolethers, only less substituted DA cyclobutanes **42** (R_2 = R_3 = H) were found to undergo cycloadditions (Eq. 2, Scheme 12).



Scheme 12 [4+2] cycloadditions of amino-activated cyclobutane-1,1-dicarboxylates.

The first intramolecular cycloaddition of DA cyclobutanes was recently reported by France and co-workers.[44,45] The authors described a $Sc(OTf)_3$-catalyzed [5+2] cycloaddition approach for the synthesis of azepino[1,2-a]indoles **50** *via* DA cyclobutane intermediates (Scheme 13).



Scheme 13 The [5+2] cycloaddition approach for the synthesis of azepino[1,2-a]indoles *via* DA cyclobutane intermediates.

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Conclusions

In summary, application of the long ignored DA cyclobutanes in cycloaddition chemistry has recently garnered significant attention and a number of reaction partners have been found to undergo efficient annulations to facilitate rapid access to structurally intriguing carbo- and heterocyclic frameworks. Except in few instances, the cycloadditions have a broad substrate scope and displays high level of stereo control. Recently, asymmetric and intramolecular cycloaddition variants were reported, yet the chemistry of DA cyclobutanes is only in its infancy and further studies will surely prove fruitful. Mechanistic insights into unexpected formation of 2,3-dihydrooxepines and pyrrolidines in cycloadditions with terminal alkynes and nitrosoarenes, respectively, has not yet been studied. Revelation of the mechanism will surely bring about new and exciting opportunities for this field of chemistry. In addition, elaboration of these cycloaddition adducts remains to be exploited for the synthesis of complex natural products. We hope this account serves as a guide to the reactivity of DA cyclobutanes to the interested readers.

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