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[4 + 2]-Annulations of Aminocyclobutanes

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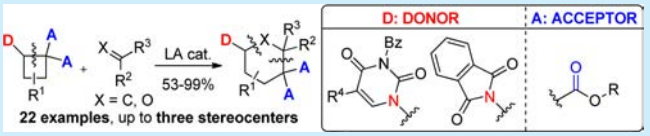
Supporting Information

ABSTRACT: The first [4 + 2]-annulation between aminocyclobutanes and aldehydes to access tetrahydropyranyl amines is reported. With phthalimido cyclobutane dicarboxylates and aromatic aldehydes, tetrahydropyrans were obtained in 53−92% yield and 3:1−17:1 dr using scandium triflate or iron trichloride as catalyst. The use of thymine- or fluorouracil-substituted cyclobutanes gave direct access to six-membered ring nucleoside analogues. Finally, the [4 + 2]-annulation between aminocyclobutanes and enol ethers led to the corresponding cyclohexylamines.



Six-membered nitrogen-substituted carbo- and heterocycles are among the most frequently encountered scaffolds in natural and synthetic bioactive compounds (Figure 1). A cyclohexylamine or a tetrahydropyranylamine ring, for example, can be found in the core of the natural alkaloids strychnine (**1**) and staurosporine (**2**), respectively. The synthetic antiviral drug Tamiflu (**3**) contains a cyclohexenyldiamine core. Synthetic methods giving access to these important scaffolds with high efficiency and broad scope are desirable to accelerate the discovery of new bioactive compounds. Whereas the Diels−Alder reaction has emerged as a powerful method to synthesize cyclohexenylamines and dihydropyranylamines,[1] there is currently a lack of transformations giving straightforward access to saturated ring systems with high convergence.

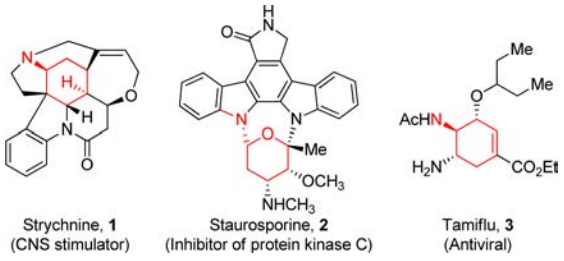
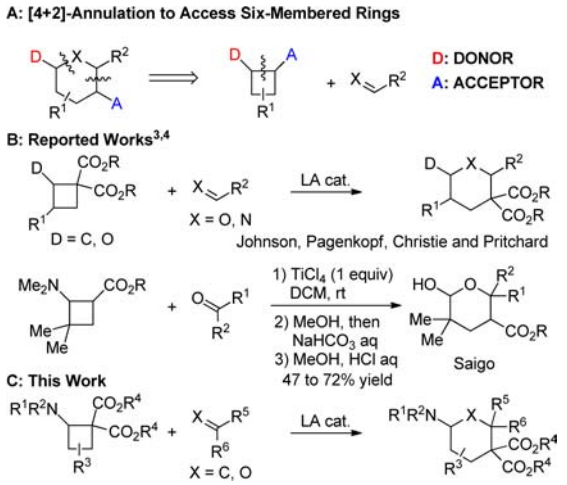


Figure 1. Bioactive compounds containing nitrogen-substituted six-membered rings.

The use of annulation reactions of donor−acceptor substituted strained rings constitutes a valuable alternative for the synthesis of saturated carbo- or heterocycles. In the case of six-membered rings, the [4 + 2]-annulation between donor−acceptor cyclobutanes and olefins or carbonyl compounds appears particularly attractive (Scheme 1, A). Nevertheless, the chemistry of donor−acceptor cyclobutanes has been much less developed than for the corresponding cyclopropanes.[2] It is only very recently that more general catalytic methods have been developed in the groups of Johnson, Christie and Pritchard, and Pagenkopf, in particular (Scheme 1, B).[3] However, these works focused on the use of oxygen and carbon as electron-donating groups, and the scope of substituents on the cyclobutanes was often limited. In the case of nitrogen as donor, an important pioneering result has been reported by Saigo and co-workers in 1991.[4] Unfortunately, the precious nitrogen functionality could not be conserved in the final product, as hydrolysis occurred upon workup.

Scheme 1. [4 + 2]-Annulations for the Synthesis of Six-Membered Rings



Recognizing the underexploited potential of nitrogen-substituted strained rings for the synthesis of bioactive compounds,[5] our group has initially focused on the discovery of new types of donor−acceptor systems which could be broadly applied in annulation reactions. In particular, we reported that imido-substituted cyclopropane dicarboxylates can be used in [3 + 2]-annulations with both enol ethers and

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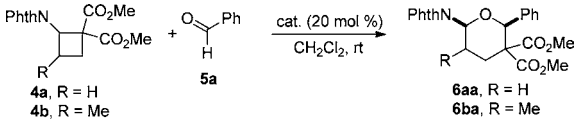
carbonyl compounds under mild catalytic conditions.[6] In 2013, we reported a new method to access the corresponding imido substituted cyclobutane dicarboxylates.[7] A single example of [4 + 2]-annulation between an aminocyclobutane and an enol ether was also described in this work. Herein, we report the first Lewis acid catalyzed [4 + 2]-annulation reaction between donor−acceptor aminocyclobutanes and carbonyl compounds and a further extended scope of the reaction with enol ethers (Scheme 1, C). In the case of aldehydes, the reaction was also successful for multisubstituted aminocyclobutanes, leading to tetrahydrofurylamines bearing up to three distinct stereocenters.

We started our investigations by examining the [4 + 2]-annulation of aminocyclobutane **4a**[7] and benzaldehyde **5a** (Table 1). The reaction proceeded with 20 mol % $FeCl_3{\cdot}Al_2O_3$ as catalyst, which had been used in the corresponding reaction with aminocyclopropanes,[6c] but the product was obtained only with low diastereoselectivity as part of a complex mixture (Table 1, entry 1). A higher diastereoselectivity (6:1) was observed with tin tetrachloride, previously used for the single example reported of [4 + 2]-annulation of enol ethers and aminocyclobutanes (Table 1, entry 2).[7] However, a complex mixture was also observed in this case. As the use of titanium tetrachloride did not lead to any improvement (Table 1, entry 3), we then turned to well-established metal triflates as catalysts. Whereas no reaction was observed with ytterbium triflate (Table 1, entry 4) and a complex mixture was obtained with hafnium triflate (Table 1, entry 5), both indium and scandium triflates led to complete conversion without the formation of side products (Table 1, entries 6 and 7). A better diastereoselectivity (13:1 vs 9:1) was observed in the case of scandium triflate.

When the methyl-substituted aminocyclobutane **4b** was examined, the reactivity dropped significantly and no conversion was observed with scandium triflate (Table 1, entry 8). However, product **6ba** could be obtained with 57% conversion and 1.5:1 dr when $FeCl_3{\cdot}Al_2O_3$ was used (Table 1, entry 9). Finally, increasing the amount of this cheap and nontoxic catalyst to 100 mol % allowed us to reach full conversion and 5:1 diastereoselectivity (Table 1, entry 10).[8]

With optimized conditions in hand, we first examined the scope of the reaction of unsubstituted donor−acceptor aminocyclobutanes (Table 2). On a preparative scale, tetrahydropyranyl amine **6aa** could be isolated in 92% yield and 16:1 dr in favor of the *cis* diastereoisomer (Table 2, entry

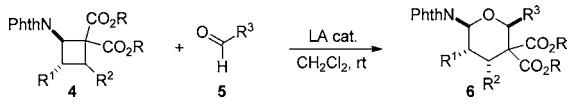
Table 1. Optimization of the [4 + 2]-Annulation

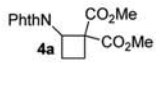
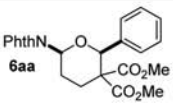
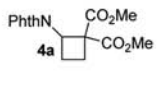
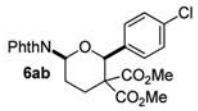
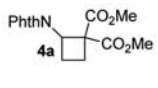
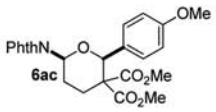
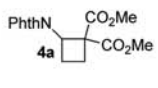
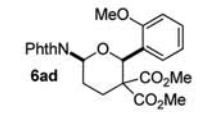
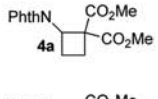
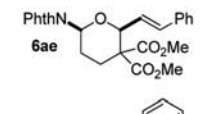
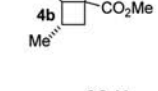
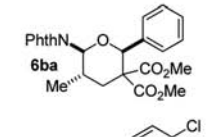
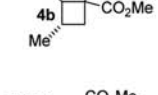
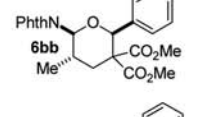
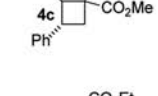
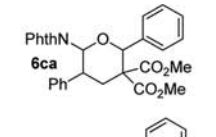
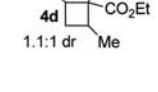
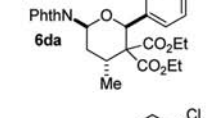
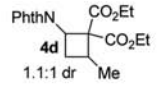
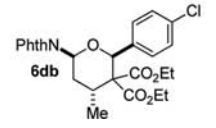


entry	4, R	catalyst	time	conversion[a] (%)	dr[b]
1	**4a**, H	$FeCl_3{\cdot}Al_2O_3$	40 min	>95[c]	2:1
2	**4a**, H	$SnCl_4$	2.5 h	>95[c]	6:1
3	**4a**, H	$TiCl_4$	2.5 h	88[c]	5:1
4	**4a**, H	$Yb(OTf)_3$	2.5 h	<5[d]	
5	**4a**, H	$Hf(OTf)_4$	2.5 h	>95[c]	9:1
6	**4a**, H	$In(OTf)_3$	2.5 h	>95	9:1
7	**4a**, H	$Sc(OTf)_3$	2.5 h	>95	13:1
8[e]	**4b**, Me	$Sc(OTf)_3$	24 h	<5[d]	
9	**4b**, Me	$FeCl_3{\cdot}Al_2O_3$	2.5 h	57	1.5:1
10	**4b**, Me	$FeCl_3{\cdot}Al_2O_3$[f]	5 h	>95	5:1

[a]Reaction conditions: 0.05 mmol of **4**, 0.075 mmol of **5a**, 20 mol % catalyst in 1.5 mL of CH_2Cl_2 at rt. Conversion estimated by the ratio of product **6** to cyclobutane **4** on the ^{1}H NMR of the crude mixture. [b]Determined on the ^{1}H NMR of the crude mixture. [c]Complex mixture of products was observed by ^{1}H NMR. [d]No product observed. [e]Temperature increased from rt to 40 °C after 7 h. [f]100 mol % catalyst loading.

Table 2. Scope of the [4 + 2]-Annulation



entry	aminocyclobutane	product	yield dr[a]
1			92% 16:1
2			75% 17:1
3			82% 6:1
4			91% 9:1
5			95% 2:1
6			64% 5:1
7			62% 5:1
8			53%[b,c] 6:1
9			63%[c,d] 3:1
10			81%[c,d] 3:1

[a]Reaction conditions: With cyclobutane **4a**: 0.20 mmol of **4a**, 0.30 mmol of **5**, 0.040 mmol of $Sc(OTf)_3$ in 6 mL of CH_2Cl_2, rt, 2 h. With cyclobutanes **4b−d**: 0.20 mmol of **4**, 0.30 mmol of **5**, 0.20 mmol of $FeCl_3{\cdot}Al_2O_3$ in 6 mL of CH_2Cl_2, rt, 5 h. Isolated yields after column chromatography are shown. [b]16 h reaction time. Structure not assigned due to peak overlap in ^{1}H NMR. [c]Product obtained in >90% purity by ^{1}H NMR. [d]Reaction mixture stirred for 2 h at 0 °C.

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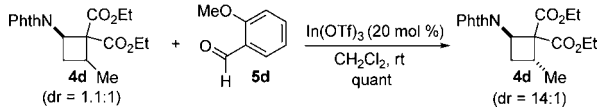
1).[9] Electron-withdrawing and donating groups in the *para* position of the aromatic ring were well tolerated (Table 2, entries 2 and 3), although a lower diastereoselectivity was observed in case of the methoxy substituent (Table 2, entry 3). Product **6ad** bearing an *o*-methoxy substituent was obtained in 91% yield and 9:1 dr (Table 2, entry 4). The [4 + 2]-annulation with cinnamaldehyde **5e** proceeded in nearly quantitative yield, but with only 2:1 dr (Table 2, entry 5). Under these reaction conditions, only low yields (<30%) and diastereoselectivities were obtained when aliphatic aldehydes or ketones were used as partners (results not shown).

We then turned to the more challenging use of substituted aminocyclobutanes. With cyclobutane **4b**, the desired tetrahydropyranyl amine **6ba** was obtained in 64% yield as a 5:1 mixture of only two diastereoisomers at the benzylic center (Table 2, entry 6). The main product obtained corresponded to the isomer with all substituents in the equatorial position, which is probably the most stable. The reaction was also successful with *p*-chlorobenzaldehyde as partner (Table 2, entry 7). When phenyl-substituted cyclobutane **4c** was used, the reaction became slower. Nevertheless, the desired product **6ca** could still be obtained in 53% yield (Table 2, entry 8). Finally, the annulation of cyclobutane **4d** bearing a substituent in the 3 position relative to the phthalimide was examined (Table 2, entries 9 and 10). This class of cyclobutanes can only be obtained as a mixture of diastereoisomers using our previously reported [2 + 2]-cycloaddition method.[7] At room temperature, a significant amount of retro [2 + 2]-cycloaddition was observed, but this side reaction could be suppressed at 0 °C. The desired products could then be obtained in 64−81% yield as a 3:1 mixture of diastereoisomers starting from a 1:1.1 mixture of cyclobutanes. The annulation reaction is therefore not stereospecific. Interestingly, we observed that the *cis* cyclobutane reacted faster than the *trans* isomer in the [4 + 2]-annulation. This difference in rate could be used to do a resolution of the difficult to separate isomers of aminocyclobutane **4d**: with the less reactive indium triflate catalyst, the *trans* isomer of aminocyclobutane **4d** could be recovered in quantitative yield and 14:1 dr (Scheme 2).

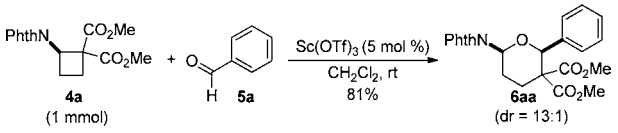
Scheme 2. Diastereospecific [4 + 2]-Annulation



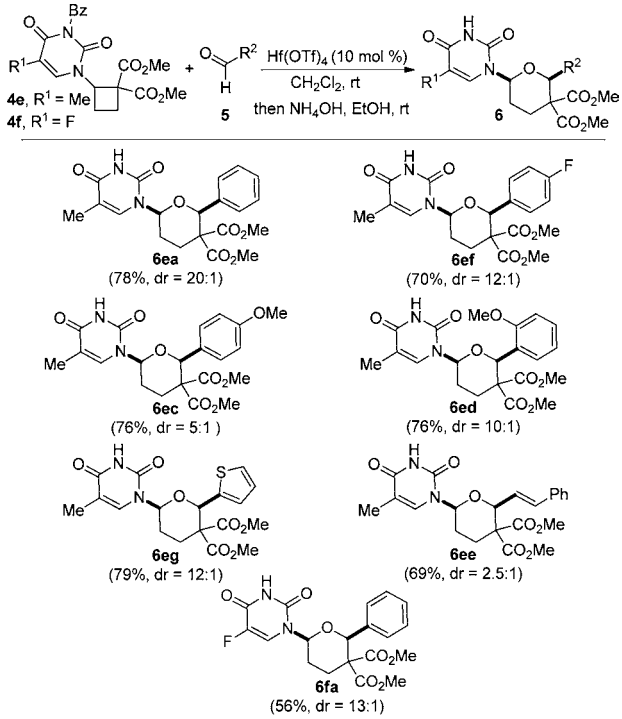
During the investigation of the scope of the [4 + 2]-annulation reaction of unsubstituted aminocyclobutanes, a relatively high catalyst loading of scandium triflate (20 mol %) has been used for practical reasons. Nevertheless, the catalyst loading could be decreased to 5 mol % when the reaction was run on a 1 mmol scale and product **6aa** was obtained in 81% yield and 13:1 dr (Scheme 3).

Recently, our group has discovered that phthalimide could be replaced by a protected thymine or uracil derivative in donor−acceptor aminocyclopropanes to access nucleoside analogues.[10] We wondered if this approach could also be applied to the [4 + 2]-annulation. In view of the synthesis of bioactive compounds containing a tetrahydropyran ring, this is particularly important, as the phthaloyl group cannot be removed on these substrates, in contrast to the corresponding carbocycles.[6a,7] Indeed, the reaction was successful with aminocyclobutane **4e** bearing a benzoyl-protected thymine substituent (Scheme 4). In this

Scheme 3. [4 + 2]-Annulation at 1 mmol Scale



Scheme 4. Nucleoside Analogues via [4 + 2]-Annulation[a]



[a]Reaction conditions: 0.30 mmol of **4**, 0.45 mmol of **5**, 0.030 mmol of $Hf(OTf)_4$ in 6 mL of CH_2Cl_2, rt, 15 min; then 1.8 mL 25% NH_4OH solution, 6 mL EtOH, rt, 16 h. Isolated yield after column chromatography and crystallization are given.

case, best results were obtained using hafnium triflate as catalyst.[8] As partial removal of the benzoyl group was observed during the reaction, the obtained crude mixture was directly treated with ammonium hydroxide in ethanol to obtain the fully deprotected product **6ea** in 78% yield and 20:1 dr.[11] The annulation with aminocyclobutane **4e** was successful with aromatic aldehydes bearing an electron-poor or electron-rich benzene ring or a thiophene heterocycle, giving the desired products **6ec,d** and **6f,g** in 70−79% and 5:1−12:1 dr. Cinnamaldehyde **5e** could also be used to give **6ee**, although the diastereoselectivity was lower, as in the case of the phthalimide substituted cyclobutane. The [4 + 2]-annulation also proceeded with benzoyl-protected fluorouracil derivative **4f** (product **6fa**).

Finally, we shortly examined the annulation reaction of enol ethers (Scheme 5). In this case, only tin tetrachloride at low temperature was successful as a catalyst. The reaction proceeded in high yield and diastereoselectivity with enol ethers substituted with a benzene derivative (products **8aa−c**). However, the diastereoselectivity was lost when a more strongly electron-withdrawing group was present on the benzene ring or when a 1,2-disubstituted enol ether was used (products **8ad** and **8ae**). The latter result demonstrated that the [4 + 2]-

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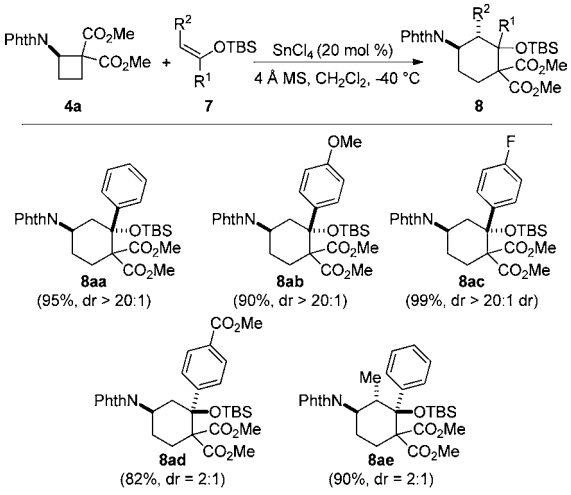
Scheme 5. [4 + 2]-Annulation with Enol Ethers[a]



[a]Reaction conditions: 0.20 mmol of **4a**, 0.30 mmol of **7**, 0.040 mmol of $SnCl_4$, 4 Å MS in 2 mL of CH_2Cl_2, −40 °C. Isolated yields after column chromatography are given.

annulation is not stereospecific in relation to the geometry of the enol ether, in contrast to the previously reported [3 + 2]-annulation reaction.[6a] The higher sensitivity of the enol ethers in comparison to the aldehydes did not allow the use of substituted cyclobutanes in the annulation process.

In conclusion, we have reported the first example of [4 + 2]-annulation between aldehydes and donor−acceptor aminocyclobutanes which proceeds without loss of the precious nitrogen functionality. The reaction proceeded in high yield and diastereoselectivity with aromatic aldehydes when using unsubstituted phthalimido cyclobutane dicarboxylates. The annulation was also successful when introducing substituents in 1,2- or 1,3-positions to the phthalimide on the cyclobutane ring. The transformation could be as well applied to the synthesis of six-membered ring carbonucleoside analogues. The [4 + 2]-annulation involving enol ethers appears more limited at this stage, as only unsubstituted cyclobutanes could be used successfully. Overall, our work demonstrated that the polarization concepts used in the case of aminocyclopropanes can be extended to their one-carbon homologues. Nevertheless, the lower reactivity of the aminocyclobutanes makes the use of sensitive reaction partners and the control of stereoselectivity more challenging than for the corresponding cyclopropanes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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