Synthetic Methods

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Catalytic [3+2] Annulation of Aminocyclopropanes for the Enantiospecific Synthesis of Cyclopentylamines**

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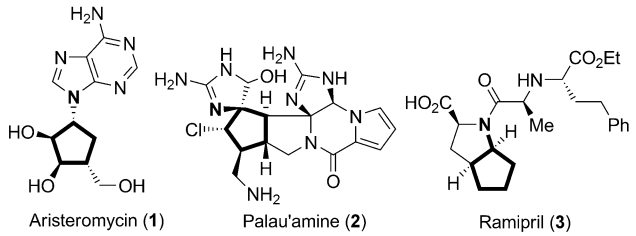
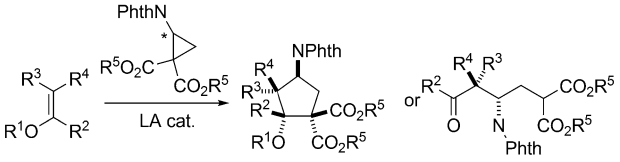
Cyclic structures are encountered in the core of most bioactive synthetic and natural products. Carbo- and heterocyclic rings give rigidity to molecules, thus fixing the spatial arrangement of the functional groups. As a result, specific interactions with biomolecules without important entropy costs become possible. Nitrogen-based functional groups are especially important in synthetic and medicinal chemistry. In this respect, cyclopentylamines constitute an important subclass of cyclic structures, and are present in both relatively simple natural products, such as the antibiotic and antiviral aristeromycin (**1**),[1] and in dauntingly complex polycyclic structures, such as palau'amine (**2**), one of the most sought for targets in modern organic chemistry (Scheme 1).[2] These



Scheme 1. Cyclopentylamines in natural and synthetic products.

cyclic structures are also found in synthetic drugs. For example, ramipril (**3**), an angiotensin converting enzyme (ACE) inhibitor, was one of the top 100 generic drugs in 2008 for the treatment of high blood pressure and heart failure.[3] Consequently, the development of new synthetic procedures to access polysubstituted cyclopentylamines is an important task for organic chemists.[4]

One of the most efficient ways to access five-membered rings is by concerted cycloaddition reactions or related stepwise annulation processes. In particular, the formal [3+2] cycloaddition, more correctly called the [3+2] annulation, of donor-acceptor activated cyclopropanes[5] with alkenes or alkynes,[6] carbonyls,[7] and imines[8] has been highly successful in the last decades for the synthesis of cyclopentanes, cyclopentenes, tetrahydrofurans and pyrrolidines respectively. Cyclopropanes bearing electron-donating oxygen-containing or aromatic substituents have been especially useful in Lewis or Brønsted acid catalyzed reactions. In contrast, annulation reactions of aminocyclopropanes have been limited to radical-initiated ring opening involving electron-rich amines.[9] To the best of our knowledge, no catalytic [3+2] annulation of aminocyclopropanes has ever been reported. Donor–acceptor aminocyclopropanes have been mostly used as 1,4-imino carbonyl precursors,[10] as well as in a few rare ring-opening reactions.[11] In 2010, we applied them in an efficient formal homo-Nazarov cyclization for the synthesis of natural alkaloids.[12] However, a formal cycloaddition approach would be inherently more convergent and efficient to access molecular complexity. Herein, we report phthalimide-substituted acceptor cyclopropanes as unique partners in [3+2] annulation reactions with silyl and alkyl enol ethers (Scheme 2). High yields and diastereoselectivities were



Scheme 2. Lewis acid (LA) catalyzed reactions of aminocyclopropanes with enol ethers. Phth = phthaloyl.

obtained using $SnCl_4$ as the catalyst with a broad range of enol ethers as substrates. The reaction was stereospecific in relation to the configuration of the enol ether and enantiospecific, thus giving asymmetric access to chiral cyclopentylamines. Finally, the use of $In(OTf)_3$ as the catalyst gave access to important acyclic β-amino ketones, and removal of the phthalimide group, as well as further functionalization, was possible under mild reaction conditions.

As a model system to study the annulation reaction with several aminocyclopropanes **4a–f**, stable enol silyl **5a** was chosen as an electron-rich alkene, as it was expected to have a higher reactivity than nonactivated alkenes and should also allow a good control over the regioselectivity (Table 1). We started with $SnCl_4$ as the Lewis acid in dichloromethane, because these reaction conditions have been successful in the case of oxygen-substituted cyclopropanes.[6f] However, no reaction was observed with cyclopropanes **4a**, **4b**, and **4c** bearing a Cbz-protected amine, a lactam, and an oxazolidinone substituent, respectively (Table 1, entries 1–3). At this

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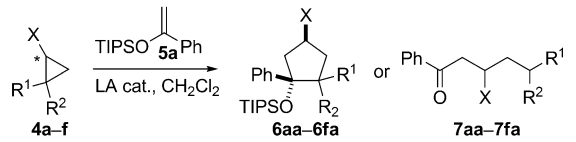
Table 1: Optimization of the [3+2] annulation.



Entry	R^1, R^2	X	Catalyst[a]	T [°C]	Conv. [%][b]	Ratio 6/7[c]
1	CO_2Et, H	 (**4a**)	$SnCl_4$	−78	0	–
2	CO_2Et, H	 (**4b**)	$SnCl_4$	−78	0	–
3	CO_2Et, H	 (**4c**)	$SnCl_4$	−78	0	–
4	CO_2Et, CO_2Et	NPhth (**4d**)	$SnCl_4$	−78	100 (98)[d]	>20:1
5	CO_2Et, H	NPhth (**4e**)	$SnCl_4$	−78	0	–
6	CO_2Et, CO_2Et	NPhth (**4d**)	$SnCl_4$	RT	100	1:1
7	CO_2Et, CO_2Et	NPhth (**4d**)	$Cu(OTf)_2$	RT	100	5:1
8	CO_2Et, CO_2Et	NPhth (**4d**)	$Yb(OTf)_2$	RT	100	5:1
9	CO_2Et, CO_2Et	NPhth (**4d**)	$Sn(OTf)_2$	RT	100	2:1
10	CO_2Et, CO_2Et	NPhth (**4d**)	$Sc(OTf)_3$	RT	100	1:3
11	CO_2Et, CO_2Et	NPhth (**4d**)	$In(OTf)_3$	RT	100	<1:20
12	CO_2Et, CO_2Et	NPhth (**4d**)	$HNTf_2$	RT	100	<1:20
13	CO_2Me, CO_2Me	NPhth (**4f**)	$SnCl_4$	−78	100 (95)[d]	>20:1

[a] Reaction conditions: **4** (0.040 mmol), **5a** (0.060 mmol), catalyst (0.008 mmol), CH_2Cl_2 (0.5 mL), 1 h. [b] Conversion of **4** determined by ^1H NMR spectroscopy. [c] Determined by ^1H NMR spectroscopy of the crude mixture. [d] Yield of the isolated product after column chromatography on a 0.30 mmol scale. Cbz = benzyloxycarbonyl, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl.

point, we attempted to enhance the reactivity of lactam- and oxazolidinone-substituted cyclopropanes by the introduction of a second ester group.[6d,h,7c–e] However, the obtained cyclopropanes were unstable and readily decomposed during purification. These results further emphasized how difficult it is to modulate the reactivity of aminocyclopropanes in comparison with other donor-acceptor cyclopropanes. To decrease the electron-donating ability of the nitrogen group, phthalimidecyclopropane **4d** was investigated next (Table 1, entry 4). For the first time, a clean annulation was observed, giving exclusively the *trans* diastereoisomer **6da** of the desired cyclopentylamine.[13] Importantly, phthalimide-substituted cyclopropanes can be obtained in a single step on a multigram scale from commercially available *N*-vinylphthalimide and diazomalonates by Rh-catalyzed cyclopropanation.[14] On the other hand, removal of one of the ester groups led again to an unreactive cyclopropane (**4e**; Table 1, entry 5). The use of $SnCl_4$ at room temperature led to partial ring opening (Table 1, entry 6). At this point, several other Lewis acids, which have been successfully used in related [3+2] annulations,[6–8] were examined (Table 1, entries 7–12). Immediately, the exceptional reactivity of cyclopropane **4d** became apparent, as full conversion could be obtained with a broad range of Lewis acids.[15] Nevertheless, a mixture of cyclization and homoaldol products was obtained in most cases, with the exception of $In(OTf)_3$ (Table 1, entry 11) and $HNTf_2$ (Table 1, entry 12), both of which led to complete ring opening. Finally, full conversion to a single diastereoisomer was also obtained with dimethyl ester **4f** (Table 1, entry 13) and the cyclopentylamine could be obtained in 95% yield upon isolation after column chromatography.

In view of the importance of cyclopentylamines, and the lack of general methods for their synthesis, we decided to investigate first the scope of the annulation reaction using $SnCl_4$ as the catalyst with cyclopropane **4f** (Table 2).[16] The size of the silyl group on the enol ether had no influence on the yield or selectivity and the desired product was obtained in quantitative yield with very high diastereoselectivity

Table 2: Scope of the [3+2] annulation.[a]

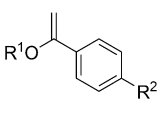
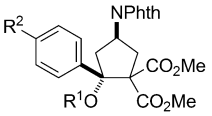
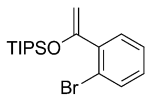
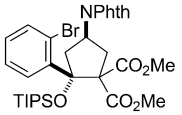
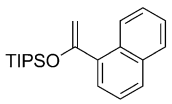
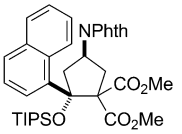
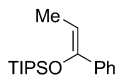
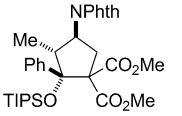
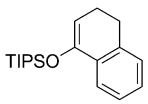
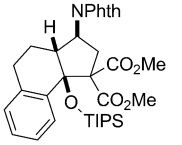
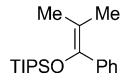
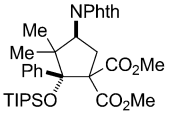
Entry	Olefin		Product		Yield [%]	d.r.
						
1	R^1 = TIPS, R^2 = H	**5a**	R^1 = TIPS, R^2 = H	**6fa**	95	>20:1
2	R^1 = TBS, R^2 = H	**5b**	R^1 = TBS, R^2 = H	**6fb**	98	>20:1
3	R^1 = TMS, R^2 = H	**5c**	R^1 = TMS, R^2 = H	**6fc**	95	>20:1
4	R^1 = TIPS, R^2 = F	**5d**	R^1 = TIPS, R^2 = F	**6fd**	91	>20:1
5	R^1 = TIPS, R^2 = CO_2Me	**5e**	R^1 = TIPS, R^2 = CO_2Me	**6fe**	95	>20:1
6	R^1 = TIPS, R^2 = CN	**5f**	R^1 = TIPS, R^2 = CN	**6ff**	70	>20:1
7	R^1 = TIPS, R^2 = OMe	**5g**	R^1 = TIPS, R^2 = OMe	**6fg**	99	>20:1
8		**5h**		**6fh**	92	>20:1
9		**5i**		**6fi**	91	>20:1
10		**5j**		**6fj**	92	20:1
11		**5k**		**6fk**	91	10:1
12		**5l**		**6fl**	81	4:1

Table 2: (Continued)

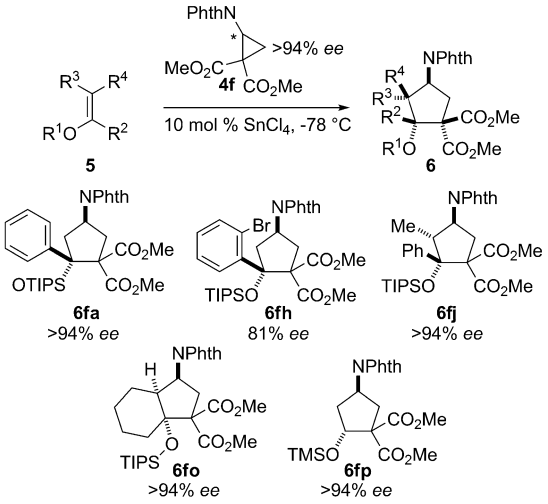
Entry	Olefin		Product		Yield [%]	d.r.
13	TIPSO, Bu (86% pure)	**5m**	NPhth, Bu, CO_2Me, TIPSO, CO_2Me	**6fm**	96 (60)[b]	17:1
14	Me, TIPSO, Et, *E*/*Z* = 1:8	**5n**	NPhth, Me, Et, CO_2Me, TIPSO, CO_2Me	**6fn**	96	11:4:1
15	TIPSO	**5o**	NPhth, H, CO_2Me, O, CO_2Me, TIPS	**6fo**	90	4:1
16	TMSO	**5p**	NPhth, CO_2Me, TMSO, CO_2Me	**6fp**	77	20:1
17	BuO	**5q**	NPhth, CO_2Me, BuO, CO_2Me	**6fq**	99	20:1
18	O	**5r**	NPhth, CO_2Me, O, CO_2Me	**6fr**	99	1.7:1

[a] Reaction conditions: **5** (0.45 mmol), **4f** (0.30 mmol), $SnCl_4$ (0.015 mmol), CH_2Cl_2 (2 mL), 1 h, −78 °C. [b] Yield of the major product determined by ^1H NMR spectroscopy. Contaminated by other regioisomers. TBS = tert-butyldimethylsilyl, TMS = trimethylsilyl.

(Table 2, entries 1–3).[17] Both electron-donating and electron-withdrawing groups in the *para* or *ortho* positions were well tolerated on enol ethers derived from acetophenone (Table 2, entries 4–9).

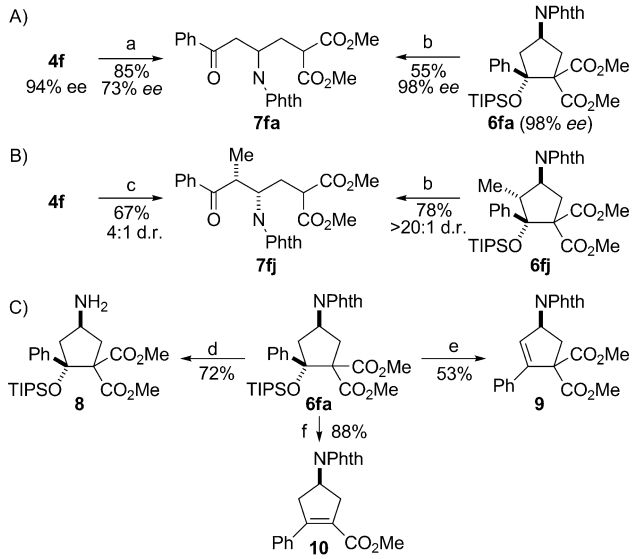
The yields were quantitative, except in the case of a cyanophenyl-substituted enol ether **5f**, which led to a slow reaction with incomplete conversion (Table 2, entry 6). The reaction was stereospecific with *Z*-enol ether **5j** giving a highly substituted cyclopentylamine **6fj** with perfect diastereoselectivity (Table 2, entry 10). Interestingly, the opposite diastereoisomer, in which the nitrogen and the oxygen are in a *syn* relationship, was obtained using the enol ether **5k** derived from tetralone (Table 2, entry 11). Trisubstituted enol ether **5l** could also be used, giving a sterically congested product with two all-carbon N-substituted quaternary centers and one tertiary silyloxy group next to each other (Table 2, entry 12). We then turned to silyl enol ethers derived from aliphatic ketones (Table 2, entries 13–15). Gratifyingly, these substrates also worked very well in the annulation reaction, but difficulties in obtaining distereomerically pure regioisomers of the enol ethers led to product mixtures in the case of acyclic substrates (Table 2, entries 13 and 14). The diastereoselectivity was moderate only in the case of cyclic enol ether **5o** (Table 2, entry 15). The commercially available silyl enol ether **5p** derived from acetaldehyde gave the secondary alcohol product also with high diastereoselectivity, thus demonstrating that the reaction was not limited to enol ethers derived from ketones (Table 2, entry 16). Finally, alkyl enol ethers could also be used (Table 2, entries 17 and 18). Good diastereoselectivity was obtained in the case of acyclic substrate **5q** (Table 2, entry 17), but cyclic substrate **5r** gave no selectivity in the annulation reaction (Table 2, entry 18). Taken together, these results emphasize the exceptional properties of cyclopropane **4f** in [3+2] annulation reactions with enol ethers. Most reported methods with other classes of donor-acceptor cyclopropanes for annulation with alkenes led to lower yields and diastereoselectivities or had a limited substrate scope.[6]

When considering previous work on annulation reactions of donor-acceptor cyclopropanes,[7c] two mechanisms can be envisaged for the first step of the annulation: either a stepwise process involving ring opening of the cyclopropane to form a zwitterionic intermediate with a subsequent attack of the enol ether, or a process via an "intimate ion pair"[7d] involving a concerted attack of the enol ether *anti* to the malonates.[18] When using an enantiopure aminocyclopropane, racemization would be expected with the former mechanism, whereas the latter would lead to an enantiospecific reaction. In the event, when enantiopure aminocyclopropane **4f** was used,[19] an enantiospecific reaction was observed with all substrates except in the formation of **6fh** (Scheme 3), thus giving access to enantiopure cyclopentylamines.



Scheme 3. Enantiospecific reaction of cyclopropane **4f**.

To further establish the synthetic potential of the method, a few transformations of the cyclopentylamine products were examined (Scheme 4). Ring-opened product **7fa** can be obtained in a single step from aminocyclopropane **4f** using $In(OTf)_3$ as the catalyst, but a partial racemization was observed (Scheme 4A). In contrast, the reaction of **6fa** in the presence of $In(OTf)_3$ led to a smooth transformation to the acyclic β-amino ketone **7fa** without loss of the enantiopurity. Also α-substituted β-amino ketone **7fj** can be obtained directly from **4f**, but with only 4:1 d.r. (Scheme 4B). If cyclopentylamine **6fj** is formed prior to ring opening, perfect



Scheme 4. Transformations of the cyclopentylamines. Reaction conditions: a) **5a**, 20 mol% $In(OTf)_3$, CH_2Cl_2, RT; b) 20 mol% $In(OTf)_3$, CH_2Cl_2, RT; c) **5j**, 20 mol% $In(OTf)_3$, CH_2Cl_2, RT; d) 1,2-diaminoethane, *i*PrOH, 80 °C; e) TMSOTf, CH_2Cl_2, 0 °C; f) NaCl, DMSO, H_2O, 170 °C. DMSO = dimethylsulfoxide.

syn diastereoselectivity is observed. This is an important result as stereocontrol in the case of acyclic products is especially challenging. Finally, it is also possible to retain the cyclopentane ring in further transformations (Scheme 4C). Deprotection of the phthalimide was possible under mild reaction conditions.[20] Two isomeric cyclopentenylamines **9** and **10** could be obtained using trimethylsilyl triflate and the Krapcho decarboxylation conditions,[21] respectively. The obtained cyclopentenylamines form part of important bioactive compounds, such as the drug Abacavir, used in the treatment of HIV infection,[22] or can be used as platforms for further functionalization.

In summary, we have reported the first catalytic [3+2] annulation of aminocyclopropanes with enol ethers. The introduction of a phthalimide group on a cyclopropane diester was key to enable high yield and selectivity in the reaction. Quantitative yields and a very broad substrate scope make the reaction highly useful for the synthesis of substituted cyclopentylamines, for which truly general synthetic methods are scarce. Enantiopure cyclopentylamines can be easily obtained because the reaction is enantiospecific. Finally, substituted β-amino ketones and useful cyclopentenylamines can be accessed, either directly from the cyclopropane or from the cyclopentylamine products.

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Keywords: cycloaddition · cyclopentylamines · diastereoselectivity · enantioselectivity · organocatalysis

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