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Catalytic Enantiospecific [3+2] Annulation of Aminocyclopropanes with Ketones

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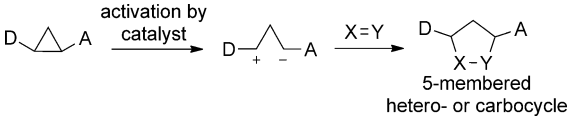
The exploitation of strain release in small rings as a driving force to trigger synthetic transformations has received increased attention over the last decade. In this context, cyclopropanes have predominantly been investigated, due to the abundance of efficient methods for their preparation, combined with their exceptional reactivity. A strategy to further enhance the inherent strain energy of cyclopropanes consists of the introduction of vicinal donor and acceptor groups (D and A, Scheme 1) able to stabilise the incipient positive and

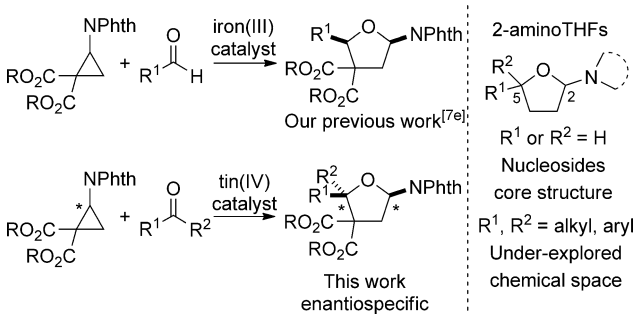


Scheme 1. Donor–Acceptor cyclopropanes as 1,3-zwitterionic synthons. D = donor. A = acceptor. X=Y = generic double bond.

negative charges derived from the cleavage of the activated σ bond. The so-called D–A cyclopropanes can therefore be considered to be synthetically equivalent to 1,3-zwitterionic synthons.[1] As such, they have been extensively used in [3+2] annulations.[2] These reactions allow the efficient assembly of a variety of 5-membered hetero- and carbocycles. In particular, the [3+2] reaction with carbonyl compounds[3,4] represents a valuable tool for the synthesis of tetrahydrofurans (THFs).[5]

The annulation of D–A cyclopropanes with aldehydes is well established, and efficient catalytic, as well as enantioselective, protocols have been reported.[3f,h–n] In contrast, only a few catalytic methods have been described for annulation reactions involving the less reactive ketones as the reaction partners.[4] Furthermore, the scarcity of highly diastereoselective protocols indicates an intrinsic difficulty in achieving face discrimination in the addition of D–A cyclopropanes to non-symmetrical ketones.[6]

In this context, and with our recent advancements involving cyclisation and annulation reactions of D–A cyclopropanes in hand,[7] we sought to develop a catalytic and stereoselective protocol for the [3+2] annulation of D–A aminocyclopropanes and ketones. There are only a few reports of the annulation and cyclisation reactions of D–A aminocyclopropanes,[8] despite their high synthetic potential for the preparation of N-containing hetero- and carbocycles. Implementing the [3+2] annulation of D–A cyclopropanes with ketones would indeed allow expedient access to a variety of 2-aminotetrahydrofurans bearing a rare quaternary carbon in position 5 (Scheme 2). Furthermore, the 2-aminotetrahydrofuran scaffold can be considered to be a privileged structure, due to its occurrence in nucleosides and in nucleoside-derived synthetic drugs.[9] It is noteworthy that current methods mainly yield analogues bearing a tertiary centre at C5 (Scheme 2), with little deviation from the natural molecules.[10] The methodology described, herein, however, allows access to the less explored chemical space populated by structures bearing a quaternary C5 atom. Herein, we report the first catalytic [3+2] annulation of D–A aminocyclopropanes with ketones, allowing the preparation of rare C5-disubstituted aminotetrahydrofurans. In contrast to our previous work with aldehydes by using an iron catalyst that induced racemisation,[7f] the tin-catalysed annulation of ketones is enantiospecific, giving access to enantioenriched aminotetrahydrofurans.



Scheme 2. The [3+2] annulation of D–A aminocyclopropanes with carbonyl compounds. Phth = phthaloyl.

We commenced our investigation by screening Lewis acids for the model reaction of phthaloyl cyclopropane **1a** with acetophenone (**2a**). At first, we tested iron(III) chloride on alumina, which successfully promoted the [3+2] annulation with aldehydes (Table 1, entry 1).[7f] Unfortunately,

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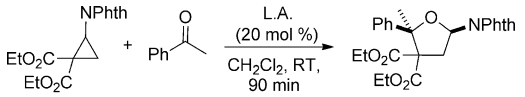
Table 1. Screening of Lewis acids in the reaction with acetophenone.[a]



1a 2a 3aa

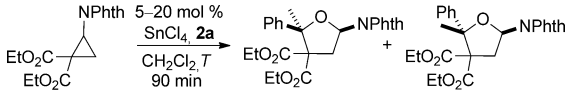
Entry	Lewis acid[b]	Yield [%][c]	Entry	Lewis acid[b]	Yield [%][c]
1	$FeCl_3$-Al_2O_3	20	5	$In(OTf)_3$	33
2	$SnCl_4$[d]	100	6	$Sc(OTf)_3$	25
3	$AuCl_3$	50	7	$Sn(OTf)_2$	13
4	$Cu(OTf)_2$	10	8	$Hf(OTf)_4$	decomp.

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), Lewis acid (20 mol%), in dichloromethane (0.1 M). Phth = phthaloyl; d.r. = diastereomeric ratio; OTf = trifluoromethanesulfonate. [b] No reaction with: Zn(OTf)$_2$, $TiCl_4$, AuCl, $EtAlCl_2$, Me_2AlCl or $CeCl_3$. [c] Yield was determined by ^{1}H NMR spectroscopy using hexamethyldisiloxane as the internal standard. [d] Performed at −78 °C; at RT, only traces of **3aa** were detected.

a poor yield was obtained, due to extensive degradation of the cyclopropane partner in the presence of the catalyst. We then examined tin(IV) chloride, which we have employed previously to promote the [3+2] annulation of phthaloyl cyclopropane with silyl enol ethers (Table 1, entry 2).[7e] At −78 °C, complete conversion was observed after 90 min, and the desired aminotetrahydrofuran **3aa** was formed quantitatively, as a single diastereoisomer. The relative configuration of **3aa** was unambiguously assigned to be 2,5-*cis* on the basis of X-ray diffraction analysis.[11] Other metal chloride salts failed to catalyse the process, with the surprising exception of gold(III) chloride, which gave **3aa** in modest yield (Table 1, entry 3). Owing to decomposition of **1a**, the screening of metal triflates (Table 1, entries 4–8) as potential catalysts did not lead to improved results.[12]

Consequently, we selected $SnCl_4$ as the catalyst to further screen for the effects of temperature (*T*) and catalyst loading on the diastereoselectivity of the [3+2] annulation between **1a** and acetophenone (**2a**; Table 2). By using 5 mol% of the catalyst, the reaction showed a classic inverse d.r. dependence with respect to temperature, with the diastereoselectivity being decreased with an increase in *T*. The 2,5-*trans* isomer *epi*-**3aa** became detectable in the crude if the reaction was run at −10 °C (Table 2, entry 4).[13] In the presence of 20 mol% of $SnCl_4$, *epi*-**3aa** was formed at even lower temperatures (−20 °C), although the increased amount of catalyst induced significant decomposition (Table 2, entry 3). At −10 °C and with 20 mol% of $SnCl_4$, it was the only diastereoisomer observed in the crude reaction mixture (Table 2, entry 4). Unfortunately, the isolated yield under these conditions was poor (19%), hampering the development of a temperature-dependent synthesis of both diastereoisomers of aminoTHFs.

Table 2. Diastereomeric ratios observed in the reaction of **1a** with **2a**, with 5 or 20 mol% $SnCl_4$, at different temperatures.[a]

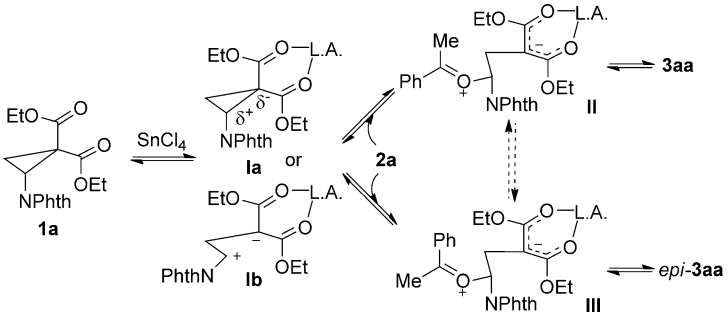


1a 3aa *epi*-3aa

Entry	*T* [°C]	d.r.[b] with $SnCl_4$	
		5 mol%	20 mol%
1	−78	>20:1	>20:1
2	−40	>20:1	>20:1
3	−20	>20:1	9:1
4	−10	5:1[c]	<1:20[d]
5	0	3:1	<1:20

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), $SnCl_4$ (5 or 20 mol%), in dichloromethane (0.1 M) at the indicated temperature. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture and expressed as *cis*/*trans* (**3aa**/*epi*-**3aa**). [c] 80% combined isolated yield. [d] 19% isolated yield.

To determine if *epi*-**3aa** could be derived from **3aa** through a tin(IV)-catalysed isomerisation, aminotetrahydrofuran **3aa** was treated with $SnCl_4$ (20 mol%) at −10 °C. In this case, its partial conversion to starting material **1a**, likely through a retro-[3+2] annulation, was mainly observed. To explain this result, we assume that **3aa** might isomerise to *epi*-**3aa** through a sequence of retro-[3+2] annulation followed by [3+2] annulation (Scheme 3).[14] As intermediates,

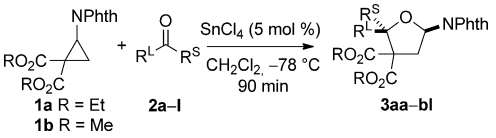


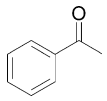
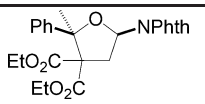
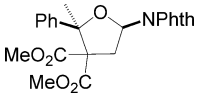
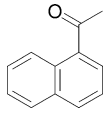
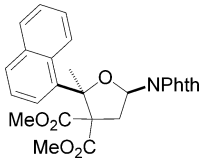
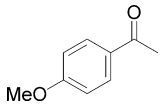
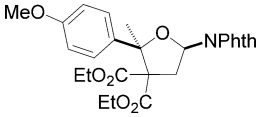
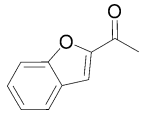
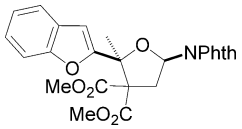
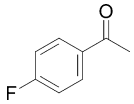
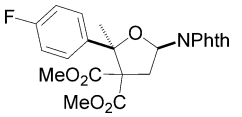
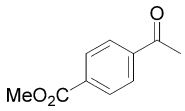
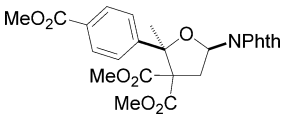
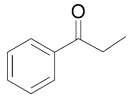
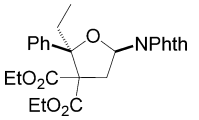
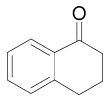
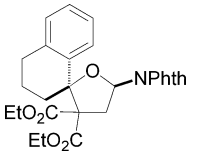
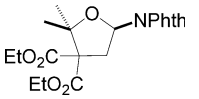
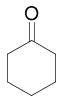
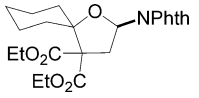
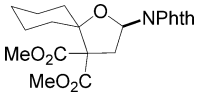
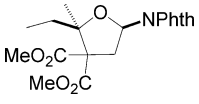
Scheme 3. The formation of tetrahydrofurans **3aa** and *epi*-**3aa** through [3+2] annulation. L.A. = Lewis acid.

both an intimate ion pair **Ia** or a completely dissociated zwitterion **Ib** could be considered. In the presence of one equivalent of **2a**, full conversion of **3aa** was achieved and *epi*-**3aa** was obtained in 45% yield. Although this result would be in good agreement with a process having either **Ia** or **Ib** as the intermediate because a higher concentration of **2a** would be particularly important for allowing efficient isomerisation in this case, the interconversion of the open zwitterions **II** and **III** or the reaction of **Ia** or **Ib** with acetophenone (**2a**) to give **3aa** directly are also possible reaction pathways.

Next, the scope of the reaction was evaluated by applying the optimised conditions to a variety of aromatic, heteroaromatic and aliphatic ketones (Table 3). D–A cyclopropanes **1a** and **1b** displayed similar reactivity towards acetophenone (**2a**), providing aminoTHFs **3aa** and **3ba** in excellent yields and diastereoselectivities (Table 3, entries 1 and 2).[15] A lower yield (79%, Table 3, entry 3) was obtained in the case of 1′-acetonaphthone (**2b**), most likely due to the unfavourable *ortho* substitution. Electron-rich aromatic ketone **2c** and heteroaromatic ketone **2d** showed lower diastereoselectivities for the [3+2] annulation (Table 3, entries 4 and 5). Nevertheless, the d.r. could be improved through a single recrystallisation.

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



Entry	Substrate	Ketone		Product		Yield [%] d.r.[b,c]
1	**1a**		**2a**		**3aa**	99 >20:1
2	**1b**		**2a**		**3ba**	96 >20:1
3	**1b**		**2b**		**3bb**	79 >20:1
4	**1a**		**2c**		**3ac**	90 16:1 >20:1[d]
5	**1b**		**2d**		**3bd**	95 4:1 14:1[d]
6	**1b**		**2e**		**3be**	93 >20:1
7	**1b**		**2f**		**3bf**	99 >20:1
8	**1a**		**2g**		**3ag**	95 >20:1
9	**1a**		**2h**		**3ah**	94 >20:1
10	**1a**		**2i**		**3ai**	94 –
11	**1a**		**2j**		**3aj**	99 –
12	**1b**		**2j**		**3bj**	99 –
13	**1b**		**2k**		**3bk**	89 10:1 16:1[d]

Electron-poor aromatic ketones **2e** and **2f** were also tested, giving the corresponding aminoTHFs **3be** and **3bf** in high yields, as single diastereoisomers (Table 3, entries 6 and 7). Excellent stereochemical discrimination between the phenyl and the ethyl substituent was also observed with propiophenone (**2g**), demonstrating the versatility of our methodology (Table 3, entry 8). 1-Tetralone (**2h**) displayed excellent reactivity and selectivity, delivering **3ah** in high yield and diastereoselectivity, but favouring the 2,5-*trans* isomer for this cyclic system (Table 3, entry 9).[16]

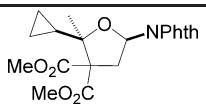
Symmetrical aliphatic ketones (**2i** and **2j**) are more established substrates in [3+2] annulations with D–A cyclopropanes. Under our conditions, they cleanly provided the corresponding aminoTHFs in nearly quantitative yields (Table 3, entries 10–12). In general, obtaining a high degree of diastereocontrol by employing nonsymmetrical aliphatic ketones remains a challenge. Gratifyingly, utilising our optimised conditions on ketones **2k** and **2l** gave yields and diastereoselectivities comparable to those obtained with aromatic substrates (Table 3, entries 13 and 14). Ketone substrate **2k** highlights the efficacy of the developed methodology, with a good d.r. (10:1, Table 3, entry 13) being obtained for a reaction in which two carbonyl substituents (methyl and ethyl) with only a small difference in size were present.

To assess the stereospecificity of the tin(IV)-catalysed [3+2] annulation, a selection of ketones was reacted with enantioenriched phthaloyl cyclopropane **1a** at −78 °C (Scheme 4).[17] Under these conditions, no loss of stereochemical purity was observed with acetophenone (**2a**) and ketones **2h–j**, although aminotetrahydrofuran **3ag** was isolated in a slightly decreased enantiomeric excess (enantiospecificity e.s. = 83 %).

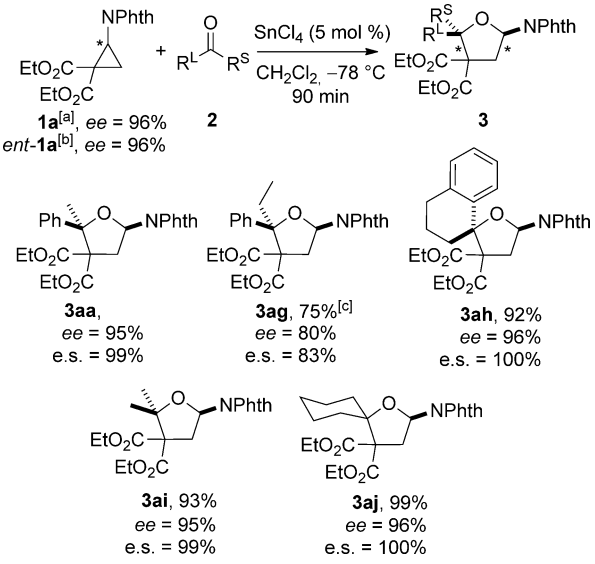
The preservation of optical purity in [3+2] annulations of D–A cyclopropanes has already been reported by Johnson et al.[3h–i,l] and by our group;[7e] nevertheless, this is the first enantiospecific reaction between aminocyclopropanes and carbonyl compounds.[18] This result is not only important for the application of the reaction in the synthesis of enantioenriched products, it also demonstrates that an open zwitterion (**Ib** in Scheme 3) is not formed during the annulation reaction.

Based on the high enantiospecificity and diastereoselectivity of the reaction, we wondered if the reaction of racemic **1a** with a chiral ketone would allow kinetic resolution to take place. For example, the reaction of cyclopropane **1a** with (−)-menthone (**2m**) should in principle favour

Table 3. (Continued)

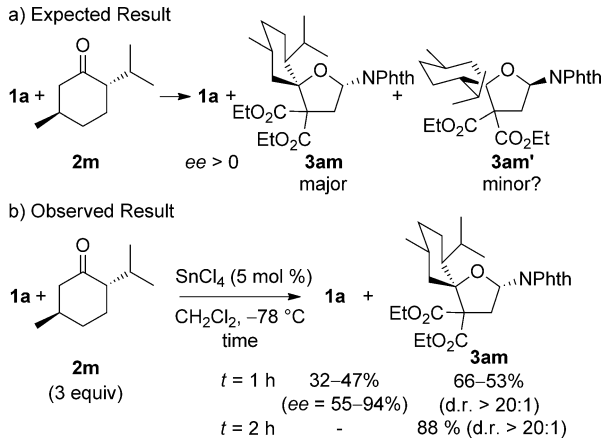
Entry	Substrate	Ketone	Product	Yield [%] d.r.[b,c]
14	**1b**		**2l**  **3bl**	96 >20:1

[a] Standard reaction conditions: **1a** or **1b** (0.2 mmol), **2a–l** (1.5 equiv), $SnCl_4$ (5 mol%), in dichloromethane (0.1 M) at −78 °C. [b] Determined by ^1H NMR spectroscopy on the crude reaction mixture. [c] Expressed as *cis*/*trans*. [d] Obtained after one recrystallisation (see the Supporting Information).



Scheme 4. Enantiospecific [3+2] annulation of D–A aminocyclopropanes **1a** with ketones. [a] Used in combination with **2a**, **2g** and **2i**. [b] Used in combination with **2h** and **2j**. [c] 99% yield based on recovered starting material. R^L = Larger substituent; R^S = Smaller substituent; *ee* = enantiomeric excess; e.s. = enantiospecificity ([*ee* of product/*ee* of starting material] × 100%).

the formation of the two diastereoisomers **3am** and **3am′** because both have the phthalimide group in a *cis* relationship to the more bulky group (Scheme 5a). Both products would be obtained as single enantiomers because enantiopure (−)-menthone (**2m**) was used as the starting material. The opposite absolute stereochemistry at the nitrogen centre would result from the enantiospecific reaction of both enantiomers of **1a**.[19] However, a severe steric interaction between the ester in **1a** and the isopropyl group in (−)-menthone (**2m**) is present only in **3am′**; consequently, the formation of this diastereoisomer is expected to be slower (mismatched case), allowing a kinetic resolution with re-isolation of enantioenriched **1a**. Unfortunately, the kinetic resolution of **1a** by using sub-stoichiometric amounts of (−)-menthone (**2m**) could not be accomplished, mainly due to the sluggish reactivity observed in this case. If the amount of **2m** was increased to three equivalents, the reaction was accelerated, allowing the isolation of enantioenriched **1a** after 1 h, although the yield and enantiomeric excess showed a strong batch dependency (Scheme 5b). Unexpectedly, after the conversion was complete (2 h), the annulation product **3am** was isolated as a single diastereoisomer in 88% yield. Consequently, the reaction was not enantiospecific, but stereoconvergent.[20]



Scheme 5. Reaction of racemic **1a** with (−)-menthone (**2m**).

Different rationales could account for this result; tin(IV) chloride is either active in the racemisation of the D–A aminocyclopropane **1a** or in the isomerisation of the product **3am**. To obtain additional clues, the loss of enantiomeric purity of enantioenriched **1a** (*ee* = 94%) in the presence of $SnCl_4$ (5 mol%) was monitored at −78 °C. After one hour, **1a** was recovered with an *ee* of 75% and after 2.5 h almost all of its stereochemical information was lost (*ee* = 20%).[3i,21] This result supports the hypothesis that the observed dynamic kinetic resolution could take place through racemisation of the aminocyclopropane **1a**, probably via an open zwitterionic intermediate **Ib** (Scheme 3). The apparently contradicting results obtained with (−)-menthone (**2m**) could be explained by a limited lifetime for a tight ion pair **Ia**; if the following annulation reaction is fast, an enantiospecific reaction takes place, but if the desired reaction is slow, as for the mismatched case with (−)-menthone (**2m**), dissociation would have time to occur, which would lead to racemisation even at −78 °C and to the stereoconvergent reaction that was observed. In contrast, the *cis*/*trans* isomerisation described in Table 2 would require a higher temperature to proceed. We note that further experiments would be required to confirm this interpretation.

In conclusion, we have reported the first enantiospecific [3+2] annulation of D–A cyclopropanes with ketones. Catalytic amounts of tin(IV) chloride were used to catalyse the reaction with a broad range of ketones, including non-symmetric ones. Yields and diastereomeric ratios were generally excellent, demonstrating the potential of this method for the stereoselective synthesis of aminoTHFs bearing a rare C5 quaternary centre. Furthermore, the developed transformation is enantiospecific, allowing access to enantioenriched aminoTHFs when starting from an enantioenriched amino-

cyclopropane. Attempts to expand the scope of N-containing cyclopropanes, as well as further functionalisation of the obtained products are currently underway in our laboratory.

Experimental Section

In a two-necked flask equipped with a nitrogen inlet, aminocyclopropanes **1a** or **1b** (0.20 mmol, 60–66 mg, 1 equiv) and one of ketones **2a**–**l** (1.5 equiv) were dissolved in anhydrous dichloromethane (2 mL) at −78 °C. After 5 min, $SnCl_4$ in dichloromethane (5 mol %, 0.01 mmol, 23 μL of a 0.43 M solution) was added. The mixture was stirred under nitrogen at −78 °C for 90 min, then the reaction was quenched by the addition of triethylamine (0.2 mL) and subsequently flushed through a short plug of silica gel, eluting with EtOAc (5 mL). The solvent was removed in vacuo to give the crude reaction mixture, which was submitted to ^{1}H NMR analysis to determine the d.r. before purification through flash column chromatography (SiO_2, 8:2 to 1:1 (*n*-hexane/AcOEt)).

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Keywords: annulation · aminotetrahydrofuran · catalysis · D–A aminocyclopropane · enantiospecificity · ketones

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[10] A 2-aminoTHF substructure search on the PubChem. Compound database gave >164000 entries for compounds with tertiary C5 atoms (3299 active in bioassays), and 3 entries for those with quaternary C5 atoms. For the PubChem. Compound database, see: E. Bolton, Y. Wang, P. A. Thiessen, S. H. Bryant, in *Annual Reports in Computational Chemistry, Vol. 4*, American Chemical Society, Washington, **2008**.

[11] CCDC-858768 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from

The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] All of the Lewis acids that gave some conversion provided **3aa** as a single diastereoisomer, except $FeCl_3$–Al_2O_3 and $Sc(OTf)_3$ (see the Supporting Information for details).

[13] CCDC-858769 (*epi*-**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] According to Johnson and co-workers (reference [3i]), intermediates **II** and **III** would provide the 2,5-*cis* tetrahydrofuran **3aa** and the 2,5-*trans* tetrahydrofuran *epi*-**3aa**, respectively. Nevertheless, pathways leading from **II** to *epi*-**3aa** and from **III** to **3aa** could also be envisaged.

[15] 2,5-Relative stereochemistry was assigned on the basis of X-ray diffraction analysis performed on compound **3aa** and extended to the other compounds in the series (**3bb**–**3am**) on the basis of the regularity of their NMR spectra.

[16] See the Supporting Information for details.

[17] Enantioenriched **1a** was obtained by preparative HPLC separation on a chiral stationary phase (see the Supporting Information for details).

[18] The [3+2] annulation of aminocyclopropanes with aldehydes was not enantiospecific (see reference [7f]).

[19] The most probable stereochemical course for the enantiospecific reaction is inversion of the stereochemistry next to nitrogen, as observed by Johnson et al. (see reference [2b]). However, this still needs to be established experimentally and will be the topic of further investigation in our laboratory.

[20] CCDC-861951 (**3am**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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