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Tactics for the asymmetric preparation of 2-azabicyclo[3.1.0]hexane and 2-azabicyclo[4.1.0]heptane scaffolds

Andrzej Wolan [a,†], Mohamad Soueidan [a], Angèle Chiaroni [a], Pascal Retailleau [a], Sandrine Py [b], Yvan Six [a,*]

[a] Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France
[b] Département de Chimie Moléculaire (SERCO) UMR-5250, ICMG FR-2607, CNRS Université Joseph Fourier, BP 53, 38041 Grenoble Cedex 09, France

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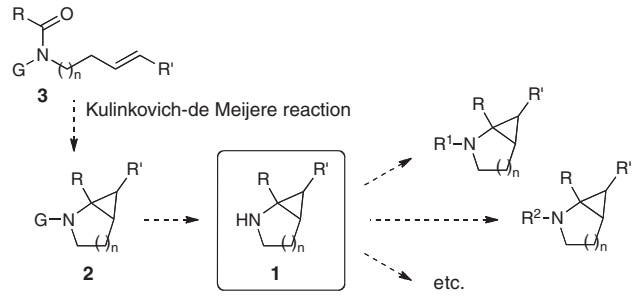
ABSTRACT

In this contribution, two methods are presented for the removal of benzyl-type protecting groups attached to the nitrogen atom of 2-azabicyclo[3.1.0]hexane and 2-azabicyclo[4.1.0]heptane systems. The first, based on the Polonovski reaction, is suitable for [3.1.0] systems. The second relies on an elimination process, starting from derivatives of *O*-methyl phenylglycinol, and is more general in terms of the substrates tolerated. Secondary bicyclic cyclopropylamines, including enantiomerically pure molecules, can thus be accessed. These compounds are then ready for further functionalisation.

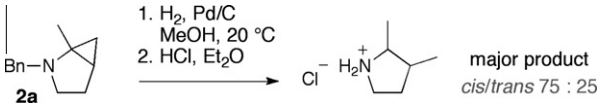
Bicyclic aminocyclopropanes are interesting molecules. Those possessing a carboxylic acid function are constrained amino acids that have found applications as organocatalysts or in the synthesis of peptidomimetics.[1] More generally, bicyclic aminocyclopropanes may undergo various ring-opening transformations and are valuable precursors of more elaborate nitrogen-containing systems of interest.[2,3] In this context, a method for the synthesis of bicyclic secondary cyclopropylamines **1** would be advantageous: functionalisation of such scaffolds at the nitrogen atom is expected to be straightforward. The preparation of various derivatives could thus be achieved quickly, without having to repeat a multi-step sequence for each target molecule (Scheme 1). Moreover, chemical functions that are not compatible with the cyclopropanation step, usually performed using an organometallic reaction, could then be introduced. The synthesis of complex aminocyclopropanes would also be more convergent.

Our strategy consisted in using bicyclic tertiary aminocyclopropylamines **2**, with a selectively removable group, G at the nitrogen atom, as precursors of **1**. In turn, compounds **2** can be synthesised from suitable *N*-alkenyl amide substrates **3** via the intramolecular Kulinkovich–de Meijere reaction, a particularly expedient and general titanium-mediated process.[4,5] An advantage of this strategy is the possibility, in principle, to use the functional group G as a chiral auxiliary to prepare enantiomerically pure aminocyclopropanes **1**.

A seemingly straightforward approach would be the introduction of a benzyl-type protecting group and its later removal by a metal-catalysed hydrogenation reaction. Indeed, such selective



Scheme 1. Synthesis of various 2-azabicyclo[3.1.0]hexanes and 2-azabicyclo[4.1.0]heptanes from common precursor **1**.



Scheme 2. Attempted selective cleavage of the Bn group of **2a**.

* Corresponding author at present address: Département de Chimie, UMR 7652, CNRS/Ecole Polytechnique, 91128 Palaiseau, France. Tel.: +33 (0)1 6933 5979; fax: +33 (0)1 6933 5972.
E-mail address: six@dcso.polytechnique.fr (Y. Six).
† Present address: Department of Chemistry, Nicolaus Copernicus University, Gagarina 7, 87-100 Toruń, Poland.

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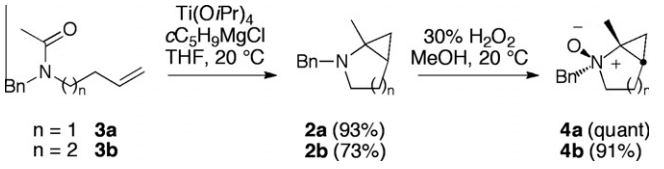
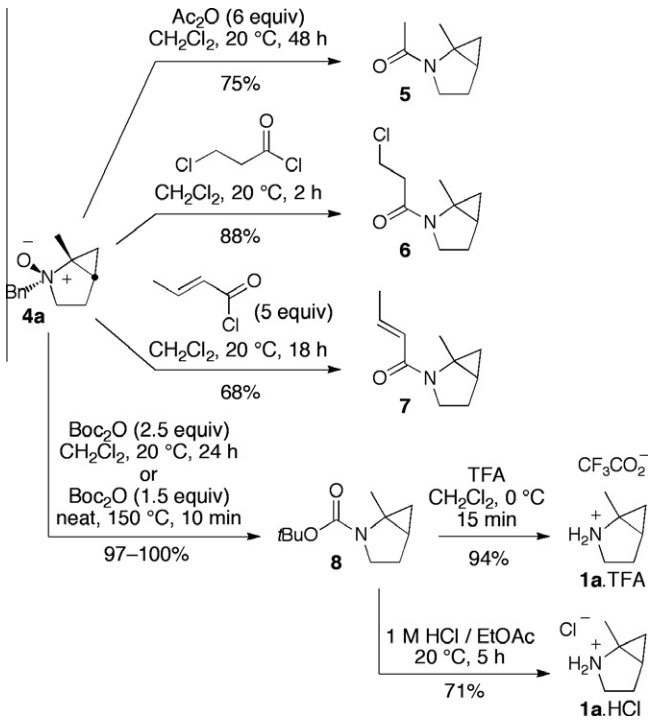
cleavage steps have been reported in the literature starting from bicyclic *N*-benzyl aminocyclopropanes.[6] However, when the bicyclic substrate **2a** was submitted to these types of conditions, opening of the cyclopropane ring was observed (Scheme 2). Similar results have been described with analogous 2-azabicyclo[3.1.0]hexanes.[7] An alternative method was thus needed.

Chemla and co-workers recently published a solution to the same problem, using the reagent 1-chloroethyl chloroformate, with low to moderate yields.[7–9] This prompts us to report our own preliminary findings. We have implemented two tactics, the first based on the Polonovski reaction, and the second on an elimination process.

The Polonovski reaction is a general transformation that can convert tertiary *N*-oxides into *N*,*N*-disubstituted amides.[10] In order to ascertain whether this reaction could be applied to the cleavage of a benzyl-type group as borne by our bicyclic aminocyclopropanes, we synthesised the *N*-oxides **4a** and **4b** from the corresponding tertiary amines **2a** and **2b**, readily obtained in good yields from the amides **3a** and **3b** (Scheme 3). Surprisingly and very interestingly, the oxidation process occurred with complete diastereoselectivity in both cases. The oxygen atom and the methyl group are *cis* to each other in **4a** as demonstrated unambiguously by X-ray diffraction performed on a single crystal of this compound.[11] It is assumed that the relative configuration of **4b** is the same as that of **4a**.[12]



Scheme 3. Synthesis of the *N*-oxides **4a** and **4b**.



Scheme 4. Conversion of the *N*-oxide **4a** into **1a** and other secondary amine derivatives.

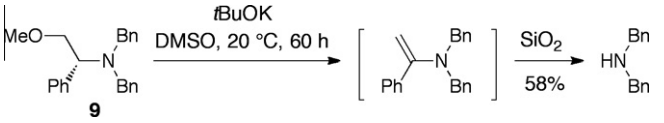
Treatment of **4a** with several acylating agents proved successful, and the amides **5**, **6** and **7** were isolated in moderate to good yields. Most interestingly, using di-*tert*-butyl dicarbonate, the Boc-protected amine **8** was obtained in excellent yield. Its conversion into the HCl or TFA salts of the secondary amine **1a** then proceeded smoothly (Scheme 4).

However, this method was not successful when applied to the homologous [4.1.0] bicyclic system **4b**: treatment of this compound with di-*tert*-butyl dicarbonate in CH_2Cl_2 at 20 °C delivered a mixture of unidentified products.[12]

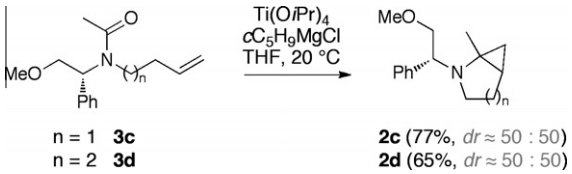
With a view to prepare enantiomerically pure **1a**, and also to circumvent the obstacle we had met with the homologous bicyclic [4.1.0] system, we investigated another tactic relying on an elimination reaction of tertiary amines with a 2-methoxy-1-phenylethyl substituent. This idea, which is reminiscent of multi-step methods developed by several groups over the past 20 years,[13–17] was first tested on the simple substrate **9**. Various reagents were scrutinised, and *t*BuOK in DMSO gave the best results (Scheme 5).[18,19]

The Kulinkovich–de Meijere intramolecular reactions of the amides **3c** and **3d** proceeded in 77% and 65% yields, respectively, with virtually no control of the relative configurations by the chiral (*R*)-2-methoxy-1-phenylethyl group (Scheme 6). The two diastereoisomers of the 2-azabicyclo[4.1.0]heptane **2d** were readily separated by silica gel flash column chromatography, and removal of the chiral auxiliary upon treatment with *t*BuOK in DMSO afforded the desired secondary amine enantiomers (*S*)- and (*R*)-**1d** in moderate yields (Scheme 7). Their absolute configurations were determined by single-crystal X-ray diffraction of (*S*)-**1d**,[11] and their opposite $[\alpha]_D$ values [−38.3 and +37.5 for the (*S*) and (*R*) compounds respectively; $c = 0.1$, $CHCl_3$] confirmed their enantiomeric relationship.

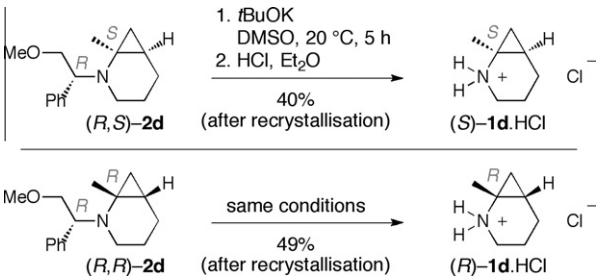
Hence, the problem of the preparation of the secondary amines, as well as the acquisition of both enantiomers, was solved in the



Scheme 5. Cleavage of the 2-methoxy-1-phenylethyl group by an elimination pathway.



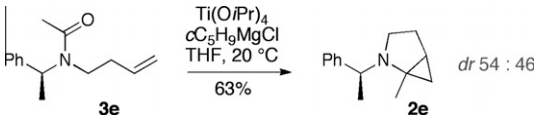
Scheme 6. Synthesis of the aminocyclopropanes **2c** and **2d**.



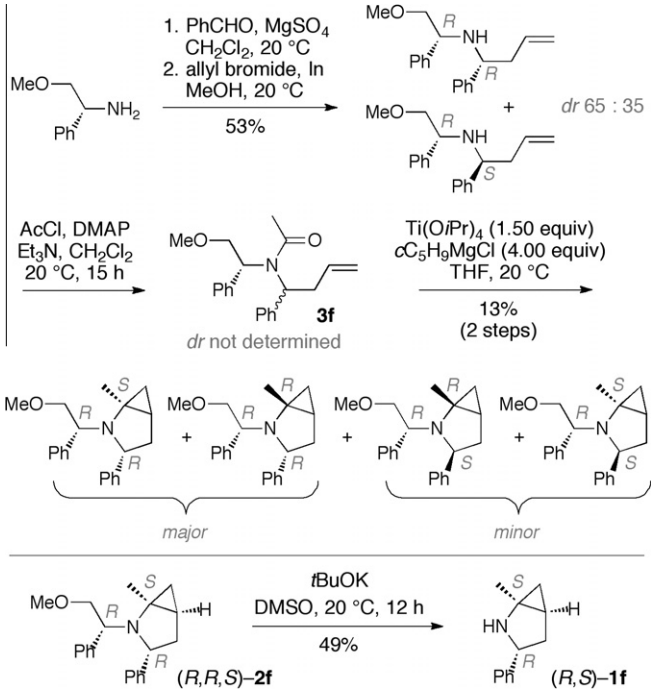
Scheme 7. Synthesis of both enantiomers of the secondary amine **1d**.

case of the 2-azabicyclo[4.1.0]heptane system. In contrast, we were not able to separate efficiently the two diastereoisomers of the 2-azabicyclo[3.1.0]hexanes **2c**, and, therefore, the elimination tactic was of no advantage in this particular case. Consequently, we investigated the use of a phenethyl chiral auxiliary that could be removed using the Polonovski reaction. The alkenyl amide **3e** was converted, with poor diastereoselectivity, into the corresponding aminocyclopropane **2e** (Scheme 8). Again, the two diastereoisomers of this compound proved extremely difficult to separate by flash column chromatography, and work is currently under progress in our laboratory to identify a more suitable chiral auxiliary.

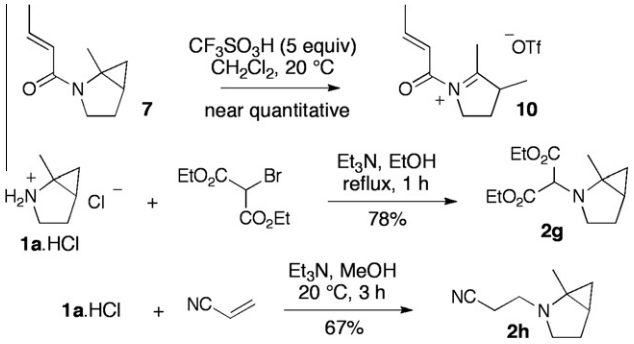
In spite of the disappointing results obtained in the simple 2-azabicyclo[3.1.0]hexane series, the example displayed in Scheme 9 shows that the elimination method may nevertheless be useful in the case of more substituted substrates. Indium-mediated allylation of the imine,[20] prepared from benzaldehyde and (*R*)-2-methoxy-1-phenylethanamine, delivered the corresponding secondary homoallylamines with moderate diastereoselectivity. Unfortunately, we were not able to separate them, and the next step, an acylation reaction, raised difficulties, presumably because of the high steric hindrance of the amine group.[21] Nonetheless, good conversion was achieved with AcCl/Et_3N with 0.1 equiv of DMAP in CH_2Cl_2 at 20 °C. However, we were not able to separate the two expected diastereoisomers **3f** by flash column chromatography, and the ^1H and ^{13}C NMR spectra proved extremely difficult to analyse because of the presence of amide rotamers and the likely restricted rotation of several bonds. We were not sure whether they were contaminated with side-products, or not. This, combined with the high steric hindrance of **3f**, accounts for



Scheme 8. Intramolecular Kulinkovich–de Meijere reaction of **3e**.



Scheme 9. Synthesis of enantiomerically pure cyclopropylamine (*R*,*S*)–**1f**.



Scheme 10. Applications of the aminocyclopropane scaffolds.

the low yield obtained in the next step, giving the mixture of aminocyclopropane diastereoisomers **2f**. The major diastereoisomer, with the shown (*R*,*R*,*S*) absolute configuration deduced from the (*R*,*R*) absolute configuration of the major diastereoisomer of the secondary amine precursor, and of previous results obtained in our laboratory,[22] could be separated and submitted to the *t*BuOK-mediated elimination reaction, delivering the expected secondary amine (*R*,*S*)–**1f** ([α] + 33.5; *c* = 0.07, $CHCl_3$). It is worth noting that not only was the cyclopropane ring preserved, but also the bond between the nitrogen atom and the intracyclic benzylic carbon atom. Equally importantly, only one diastereoisomer of the product was observed. Since epimerisation at the cyclopropane chiral centres is very unlikely, this indicates that no epimerisation occurred at the benzylic position either, and as a result (*R*,*S*)–**1f** was enantiomerically pure.

Finally, the utility of our method is illustrated by the three examples displayed in Scheme 10. The first one shows that the amide **7** can be easily converted into the acyl iminium compound **10** by protonation with triflic acid. The other two examples, an S_N2 reaction and a Michael-type reaction, are especially interesting because the aminocyclopropane products **2g** and **2h** could not have been synthesised using the Kulinkovich–de Meijere reaction from the corresponding alkenyl amides. Indeed, it is well established that ester and nitrile groups are more reactive than amides towards the titanium complexes involved in this transformation.[23]

In conclusion, we have implemented two tactics for the preparation of enantiomerically pure 2-azabicyclo[3.1.0]hexane and 2-azabicyclo[4.1.0]heptane scaffolds. These scaffolds contain a secondary amine moiety that can be functionalised to access diversely substituted bicyclic cyclopropylamines, including compounds bearing sensitive functions that could not be obtained directly via standard cyclopropanation methods. Our first tactic consists in preparing bicyclic aminocyclopropanes with a benzyl-type protecting group that is then removed by performing a Polonovski reaction from the corresponding *N*-oxide. This method is poorly applicable to the 2-azabicyclo[4.1.0]heptane systems, but gives excellent results with smaller 2-azabicyclo[3.1.0]hexane bicycles. The second tactic, being more general, relies on the selective cleavage of a chiral 2-methoxy-1-phenylethyl group using *t*BuOK in DMSO. This method does not affect other types of benzyl groups and, as such, might find applications in a wider context.

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of the *Institut de Chimie des Substances Naturelles* for their contribution to this work.

Supplementary data

Supplementary data (typical experimental procedures; X-ray crystal structures of **4a** and (*S*)-**1d**.HCl; discussion with respect to the exclusive formation of one diastereoisomer of the *N*-oxides **4a** and **4b**; proposed explanation for the differences of behaviour observed in the subsequent Polonovski reactions; NMR spectra of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.026.

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21. The mixture of diastereoisomeric amines was recovered unchanged under several standard acylating conditions: Ac_2O in pyridine at 20 °C, AcCl in CH_2Cl_2 at 20 °C in the presence of NaOH aqueous solution, and AcCl/Et_3N in $CHCl_3$ at reflux.
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