Stereoselective and Stereospecific Triflate Mediated Intramolecular Schmidt Reaction: Easy Access to Alkaloid Skeletons

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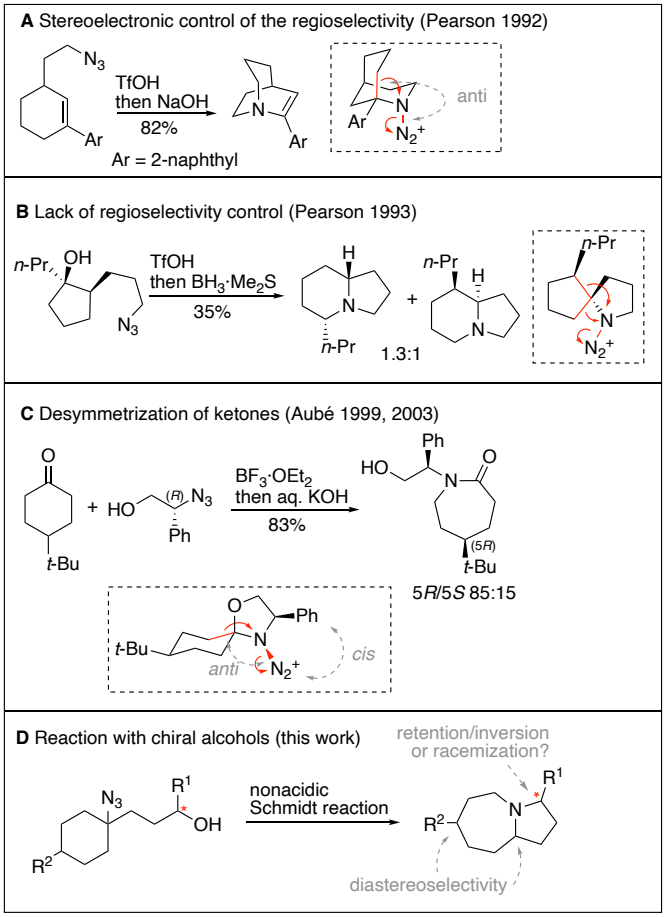
Abstract: The stereoselectivity and stereospecificity of the triflate mediated intramolecular Schmidt reaction of substituted 3-(1-azidocyclohexyl)propanol derivatives leading to octahydro-1*H*-pyrrolo[1,2-a]azepine, the structural skeleton of several important families of alkaloids such as the *Stemona* alkaloids, has been examined. The reaction involves an initial intramolecular S_N2 reaction between the azide moiety and the triflate affording an intermediate spirocyclic aminodiazonoium salt that undergoes the expected 1,2-shift/N_2-elimination followed by hydride mediated iminium salt reduction. Remarkably, chiral alcohols are converted to the azabicylic derivative with no or limited racemization. The initial asymmetric alcohol center controls the diastereoselectivity of the whole process leading to the formation of one out of the four possible diastereoisomers of disubstituted octahydro-1*H*-pyrrolo[1,2-a]azepine. The origin of the stereoselectivity is rationalized based on theoretical calculations. The concise synthesis of (–)-(*cis*)-3-propylindolizidine and (–)-(*cis*)-3-butyllehmizidine, two alkaloids found in the venom of workers of the ant *Myrmicaria melanogaster*, is reported.

Introduction

In the early 1990s, Aubé[1–5] and Pearson[6] independently reported an intramolecular Schmidt reaction involving the reaction of alkyl azides with cationic species obtained by diverse procedures including treatment of ketones, aldehydes, hemiketals, ketals, alkenes, alcohols and epoxides with Lewis or Brønstedt acids.[7,8] This reaction was applied for the synthesis of a variety of nitrogen containing heterocycles and naturally occurring alkaloids.[9,10] The regioselectivity of the carbon-to-nitrogen 1,2-shift was rationalized by assuming a concerted migration mechanism over a nitrenium formation. In the concerted process, migration of a bond that is approximately antiperiplanar[1,11] to the departing nitrogen in the aminodiazonium ion being preferred (Scheme 1, **A**).[6] No regioselectivity was observed for the reaction leading to indolizidine from tertiary alcohols (Scheme 1, **B**), this was rationalized by a non-regioselective 1,2-shift of the intermediate spirocyclic aminodiazonium salt resulting from the rearrangement of the initially formed cation followed by reaction with the azide. In such a system, the aminodiazonium salt is believed to exist as a rapidly equilibrating mixture of epimers at the nitrogen atom.[6] This assumption is in accordance with calculations by Glaser, who reported that the activation barrier on the pyramidal nitrogen is low.[7] The stereochemical outcome of the intramolecular Schmidt reaction has also been examined by Aubé, who discussed the preferential migration of the on-tether substituent and reported that the stereochemistry at the migrating carbon was preserved similarly to what is observed for other sextet rearrangement processes.[8] More interestingly, by using chiral 1,2- and 1,3-azidoalcohols, good to excellent control of the stereochemistry could be obtained for the desymmetrization of 4-substituted cyclohexanone (Scheme 1, **C**).[9,10,12] This process requires formation of an aminodiazonium cation bearing a chiral center next to the azido group followed by a stereoselective 1,2-shift. The C–C bond *anti* to the phenyl group at the chiral center of the azidoalcohol is migrating. Assuming antiperiplanar migration suggests that the migration involves a conformation where the diazonium substituent is lying *cis* to the phenyl ring.



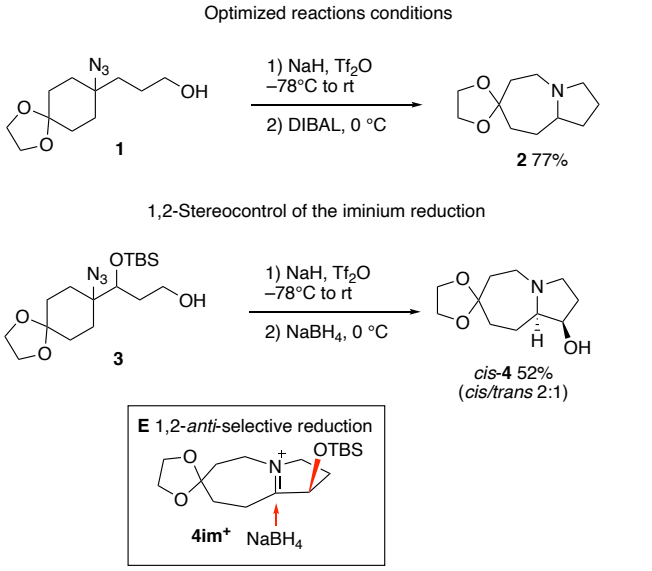
Scheme 1. Regio- and stereoselectivity of the intramolecular Schmidt reaction

In a recent paper, we reported a modified protocol in which the Schmidt reaction is run under nonacidic conditions by converting azidoalcohols into azidotriflates that rearrange spontaneously. This approach allows to avoid rearrangement of the intermediate carbocations (see Scheme 1, **B**) and was used for a concise synthesis of indolizidine 167B.[11] Interestingly, racemization caused by the formation of carbocation intermediates is expected to be suppressed opening new opportunities for asymmetric Schmidt reactions involving chiral azidoalcohols. For instance, the preparation of enantiomercially enriched substituted octahydro-1*H*-pyrrolo[1,2-a]azepine,[12] a skeleton found in many alkaloid natural products such as *Stemona* alkaloids[13] and dendrobatid frog alkaloids,[14,15] is expected to be possible starting from easily available azidoalcohols such as 1-substituted 3-(1-azidocyclohexyl)propan-1-ols (Scheme 1, **D**). We report here that such reactions involving a chiral alcohol as unique element of asymmetry are highly diastereoselective and take place with no or very limited racemization.

Results and Discussion

Reactivity of the system and 1,2-stereocontrol of the iminium reduction by an adjacent silyloxy group

The reaction conditions were optimized with the dioxolanyl acetal **1**. Under our optimized conditions,[11] the octahydropyrroloazepine **2** was obtained in good yield using DIBAL as a reducing agent (Scheme 2). Starting from the azidoalcohol **3** containing an asymmetric center adjacent to the azido group, a moderate stereocontrol for the hydride addition to iminium ion **4im**$^+$ using $NaBH_4$ leading to *cis*-**4** (after desilylation) was observed. As expected, the hydride delivery is taking place *anti* to the bulky silyloxy group (Scheme 2, **E**). Increasing the control of the diastereoselectivity using DIBAL was not attempted.

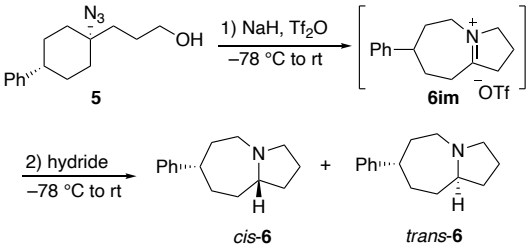


Scheme 2. Formation of pyrrolo[1,2-a]azepine **2** and **4** and stereoselectivity of the reduction of the iminium salt **4im**$^+$.

1,4-Stereocontrol of the iminium reductions and stereoselective 1,2-shift

When the acetal is replaced by a phenyl group, the starting material **5** remains achiral but the iminium ion intermediate **6im**$^+$ is chiral. Therefore, the stereochemical outcome of the reduction of the iminium ion **6im**$^+$ is controlled via a 1,4-induction process. Product **6** was formed with a moderate stereocontrol when reacted with $NaBH_4$, $NaBH_3CN$ and $LiAlH_4$. An excellent *cis* stereocontrol was obtained with DIBAL (Table 1).

Table 1. 1,4-Stereocontrol during the Schmidt reaction converting azidoalcohol **5** to pyrrolo[1,2-a]azepine **6**.



Entry	Reagent	Yield[a]	*cis*/*trans*[b]
1	$NaBH_4$	n.d.	67:33
2	$NaBH_3(CN)$	n.d	64:36
3	$LiAlH_4$	60%	84:16
4	DIBAL	98%	>95:5

[a]) Isolated yields. [b]) Determined by 1-H-NMR analysis of the crude products.

The very high *cis* diastereoselectivity observed for the reduction of the iminium ion **6im**$^+$ (1,4-induction) is puzzling. Two hypothesis were considered to explain the favoured *anti* addition (relative to the phenyl group) of the hydride: 1) strong cation-π interactions between the phenyl group and the iminium ion favour a conformation where one face of the iminium ion is shielded; 2) an extended conformation presenting a more reactive convex face. To clarify this point, a detailed analysis of the conformational space of cation **6im**$^+$ was performed (see supporting information for full details). All the QM results are reported at the PCM(CH_2Cl_2,ua0)/DLPNO-CCSD(T)/cc-pVTZ//B3LYP-D3/6-31G(d) level of theory. The best cation-π interaction-induced folded conformation is 12.5 kJ/mol and 18.3 kJ/mol higher in terms of enthalpy (ΔH_{sol}) and free energy (ΔG_{sol}) with respect to the global minimum extended conformation (Figure 1). Thus, preference for a folded conformation of iminium cation (**6im**$^+$) due to cation-π interactions as initially hypothesized is not supported by these results. Restricted conformational analysis of iminium salt **6im** indicates that triflate anion prefers to coordinate to the concave face of the iminium ion intermediate, however the energy difference between the concave/convex coordination of the triflate anion is low (1.0 kJ mol^{-1}). This conformation was also found to be prevalent in the solid-state structure of **6im** determined by single crystal X-ray analysis (Figure 1).[16] In the lowest energy conformer of iminium salt **6im**, the face *syn* to the phenyl group is blocked by triflate anion, thus favouring the formation of the *cis* product through *anti* addition of the hydride (Model **F**). Calculation of transition state energies were performed to get a better understanding of the factors governing the stereochemistry of the reduction of **6im**$^+$ with DIBAL. Reaction barriers calculated for the reduction of cation **6im**$^+$ with DIBAL predict a 9.5 kJ mol^{-1} preference for the formation of *cis*-**6** (TS-*anti*) relative to *trans*-**6** (TS-*syn*) (Figure 1). Both transition states involve hydride addition from the convex face of the iminium ion and destabilization of TS-*syn* over TS-*trans* may be attributed to steric interaction with the phenyl substituent on the convex (*exo*) face. These results imply that the experimentally observed stereoselectivity is a kinetic phenomenon, *cis*-**6**·Al(*i*-Bu)$_2^+$ being less stable than *trans*-**6**·Al(*i*-Bu)$_2^+$ by 10.9 kJ mol^{-1} in CH_2Cl_2 (see supporting information).

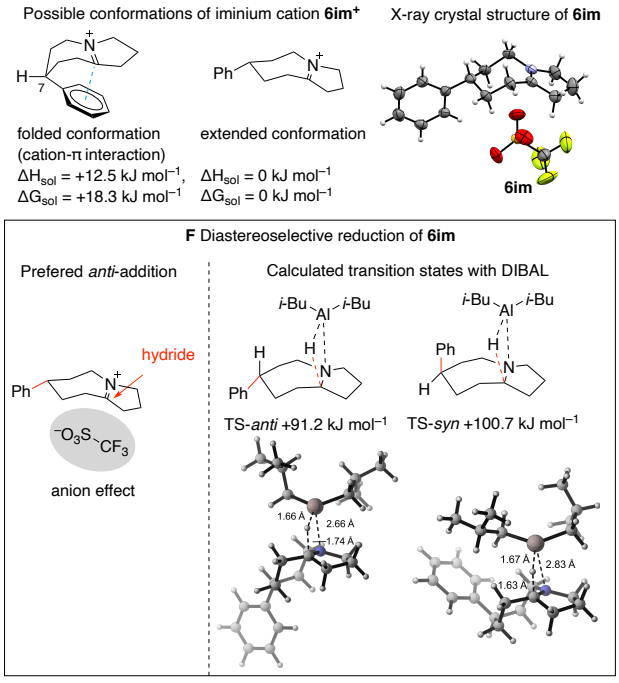
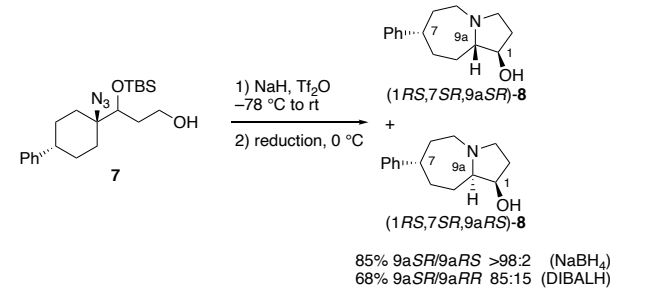
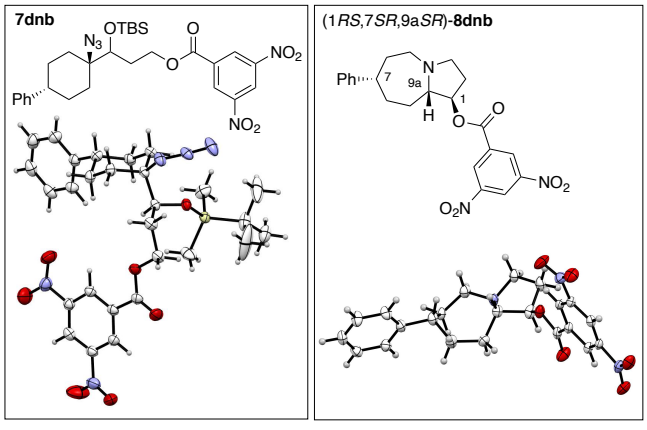


Figure 1. Conformational energetics of iminium cation **6im**$^+$. X-ray structure analysis of **6im** (ellipsoids drawn at 50% probability) and proposed model for 1,4-induction during hydride addition to **6im** as well as calculated *anti* and *syn* transition state barriers (based on best conformer) for the reaction of **6im**$^+$ with DIBAL. Calculations have been performed at the PCM(CH_2Cl_2,ua0)/DLPNO-CCSD(T)/cc-pVTZ//B3LYP-D3/6-31G(d) level of theory.

The Schmidt reaction with the OTBS substituted alcohol **7** containing a single asymmetric center at C(1) (product numbering) was investigated. The configuration of the starting material **7** was assigned by single crystal X-ray analysis of the 3,5-dinitrobenzoate ester **7dnb**.[16] During the Schmidt reaction, a second chiral center at C(7) is created during the 1,2-migration process and a third one at C(9a) is introduced during the final hydride addition step. Desilylation during workup eventually leads to aminoalcohol **8**. When the reaction was run with DIBAL, a mixture of 2 diastereomers (out of the four possible) in a 85:15 ratio was observed. By running the final iminium reduction step with $NaBH_4$, a single diastereomer was obtained (Scheme 3). The 3,5-dinitrobenzoate ester **8dnb** was prepared from the major isomer of **8** by acylation with 3,5-dinitrobenzoyl chloride. Its relative (1*RS*,7*SR*,9a*SR*) configuration could be determined unambiguously by single crystal X-ray analysis (Scheme 3).[16] Based on the relative configuration of the starting azide **7** (azido group *trans* to the phenyl substituent, see X-ray structure of **7dnb** in Scheme 3) and the relative configuration of the final product **8** (see X-ray structure of **8dnb** in Scheme 3), one can conclude that the C–C bond *anti* to the OTBS group is migrating (Figure 2, **G**) and that the final hydride addition to the iminium ion **7im**$^+$ is taking place *anti* to the phenyl group (1,4-induction) and *syn* to the adjacent OTBS group.

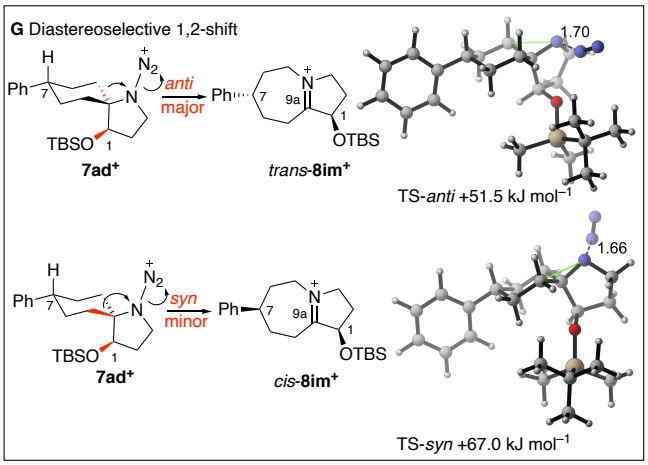




Scheme 3. Stereochemical outcome of the intramolecular Schmidt reaction with **7**. X-ray structure analysis of **7dnb** and **8dnb** (major diastereomer) (ellipsoids drawn at 50% probability).

The remarkable diastereoselectivity of the 1,2-migration process is supported by reaction path calculations. Migration of the *anti*

C–C bond in the aminodiazonium ion **7ad⁺** enjoys a barrier advantage of at least 15 kJ mol^{-1} (see Figure 2, **G**). This barrier difference is largely similar in the gas phase or in solution and may thus derive predominantly from differences in the alignment of the reacting C–C and C–N bonds with the surrounding substrate scaffold. The ring nitrogen atom is significantly more pyramidal in the TS as compared to the aminodiazonium precursor, and then becomes almost planar in the product iminium ion (see SI for more details).[17] It should be added that the energetic benefit of the *anti* over the *syn* transition state is completely lost upon formation of the respective iminium ions *cis*-**8im⁺**/*trans*-**8im⁺** (which are found to be isoenergetic). The final hydride addition to the iminium ion *trans*-**8im⁺** is taking place *anti* to the phenyl group (1,4-induction) and *syn* to the adjacent OTBS group. This process was examined through theoretical calculations in CH_2Cl_2 solution.[18] The ten energetically most favourable conformations of this cation are of the extended type, which precludes control of the reduction step through a folded transition state (see supporting information). Conformational analysis of the full ion pair *trans*-**8im**, however, indicates that the silyloxy substituent present in this system directs the triflate anion exclusively to the *anti* (relative to OTBS or bottom) face of the iminium ion. The energetically best conformer with the triflate anion in top location is located 19.5 kJ mol^{-1} higher in energy, which is in full support of the model presented in Figure 2 **H**. The use of a smaller reducing agent ($NaBH_4$) instead of DIBAL favours the top face approach by minimizing destabilizing interactions with the OTBS group.



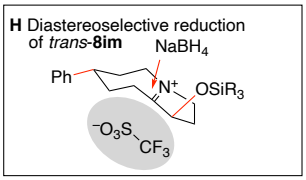
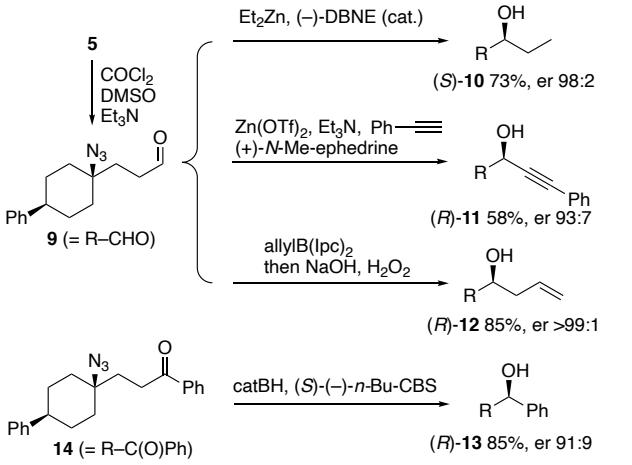
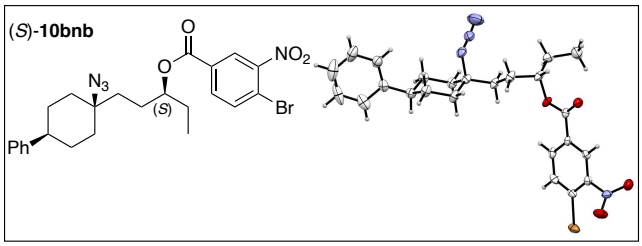


Figure 2. Rationalization of the stereochemical outcome of the conversion of **7** to **8** and transition state barriers (ΔG_{sol} , in kJ mol^{-1}) for concerted C to N bond migration (*anti* and *syn* relative to OTBS group) calculated at the PCM(CH_2Cl_2,ua0)/DLPNO-CCSD(T)/cc-pVTZ//B3LYP-D3/6-31G(d) level of theory.

Stereospecificity of the Schmidt reaction involving chiral alcohols

In Pearson's version of the intramolecular Schmidt reaction, the alcohol center is converted to a cation, therefore this center cannot be used to control the absolute configuration of the final product.[6] The triflate mediated version of the Schmidt reaction offers a possibility to use a chiral alcohol to control the absolute configuration of the products since the reaction most probably does not involve the formation of a cationic intermediate (at least for primary and secondary alcohols). To test this hypothesis, four different chiral alcohols **10**–**13** bearing a single chiral center at the alcohol position were prepared (Scheme 4). Alcohols (*S*)-**10** and **11** were prepared by a (–)-*N,N*-dibutyl-*D*-norephedrine ((–)-DBNE) and (+)-*N*-methyl ephedrine catalyzed enantioselective addition[19–22] of Et_2Zn ((*S*)-**10**) and phenylacetylene ((*R*)-**11**) to the aldehyde **9** prepared by oxidation of the primary alcohol **5**. Brown asymmetric allylboration[23] of **9** afforded the homoallylic alcohol (*R*)-**12**. Finally, the benzylic alcohol (*R*)-**13** was prepared from ketone **14** via CBS-mediated enantioselective reduction.[24] The absolute configurations of **10**–**13** were attributed based on reported stereochemical outcome of similar reactions. For compound **10**, single crystal X-ray analysis of the 4-bromo-3-nitrobenzoate ester **10bnb**[16] confirmed its (*S*)-absolute configuration in accordance with expectations.[25]

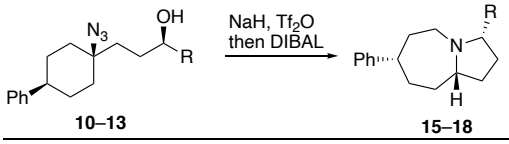




Scheme 4. Preparation of chiral alcohols **10**–**13**. X-ray structure analysis of (*S*)-**10bnb** (ellipsoids drawn at 50% probability).

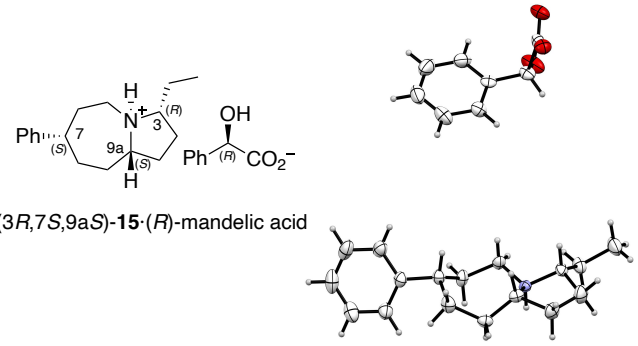
The intramolecular Schmidt reaction involving **10**–**13** was investigated next (Table 2). Under the standard reaction conditions, all four alcohols gave the desired bicyclic amides **15**–**18** in 32–85% yield as a single diastereomer. Interestingly, the enantiomeric ratio of the starting material was fully preserved for **15** and **16** and only slight loss of optical purity was observed for **17** and even more remarkably for **18** derived from the benzylic alcohol **13**. The absolute configuration of **15** could be established using single crystal X-ray analysis of its (*R*)-mandelic acid salt (Figure 3).[16]

Table 2. Intramolecular Schmidt reaction involving enantioenriched chiral alcohols **10**–**13**.



Entry	Alcohol	R	er	Product	Yield[a]	er[b]
1	(*S*)-**10**	Et	98:2	**15**	85%	93:7
2	(*R*)-**11**	PhC≡C	93:7	**16**	32%	95:5
3	(*R*)-**12**	CH_2=$CHCH_2$	>99:1	**17**	79%	92:8
4	(*R*)-**13**	Ph	91:9	**18**	71%	78:22

a) Isolated yields. b) Determined by HPLC analysis.



(3*R*,7*S*,9a*S*)-**15**·(*R*)-mandelic acid

Figure 3. Determination of the absolute configuration of (3*R*,7*S*,9a*S*)-**15** by X-ray structure analysis of its (*R*)-mandelic salt (ellipsoids drawn at 50% probability).

The absolute configurations (*S*)-**10** and (3*R*)-**15** demonstrate that the intramolecular Schmidt reaction proceeds with inversion of configuration at the alcohol stereocenter. This indicates that an S_N2-type mechanism is involved in the formation of the intermediate spirocyclic aminodiazonium salt **10ad⁺** (Figure 4, **I**). Even the benzylic alcohol **13** reacts mainly via an S_N2 pathway since only limited racemization is observed. The diastereoselectivity of 1,2-shift is then controlled by the C(3) chiral center according to Figure 4 (**J**). Selective migration of the C–C bond *anti* to the substituent at position 3 is observed. Since migration is expected to occur *anti* to the N–N_2^+ bond, it suggests that the C(3) substituent and the diazonium residue are *cis* to each other in the reactive conformation of the aminodiazonium intermediate **10ad⁺**. This result is in accordance with Aubé's results discussed in Scheme 1 (**C**),[10] and also fully supported by theoretical calculations of the reaction energy profiles (see supporting information).[18] The *anti*-migration pathway is found to be 8.5 kJ mol^{-1} more favourable than the respective *syn*-migration pathway (Figure 4, **J**). Finally, the reduction leading to the formation of the third asymmetric center at C(9a) is fully controlled by cooperative 1,4- and 1,3-induction processes from C(3) and C(7) (Figure 4, **K**).

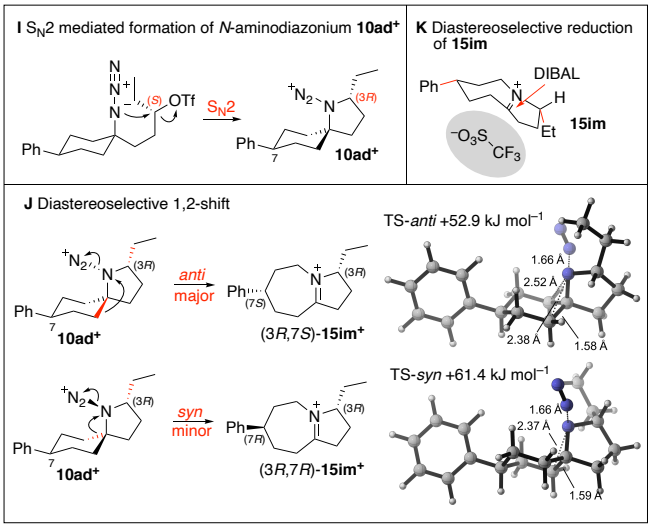
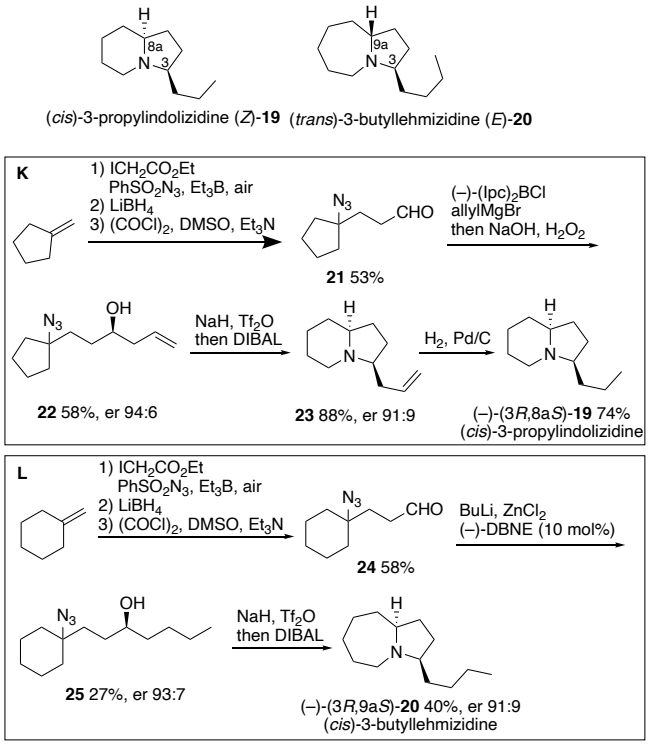


Figure 4. Stereochemical outcome of the reactions with chiral alcohol **10**. Transition state barriers (ΔG_{sol}, in kJ mol^{-1}) calculated at the PCM(CH_2Cl_2,ua0)/DLPNO-CCSD(T)/cc-pVTZ//B3LYP-D3/6-31G(d) level of theory.

Concise synthesis of indolizidine and lehmizidine alkaloids

To demonstrate the potential of our stereospecific and stereoselective intramolecular Schmidt reaction, the synthesis of two alkaloids, 3-propylindolizidine (*cis*)-**19** and *epi*-3-butyllehmizidine (*cis*)-**20** was attempted. These two alkaloids were discovered in the venom of workers of the ant *Myrmicaria melanogaster* from Brunei.[26] The relative configuration of the naturally occurring (*cis*)-**19** and (*trans*)-**20** was attributed based on a non-stereoselective synthesis of racemic (*trans/cis*)-**19** and (*trans/cis*)-**20** and their absolute configuration remains unknown to date.[26] (–)-(3*R*,8a*S*)-**19** was prepared from methylenecyclopentane (Scheme 5, **K**). The aldehyde **21** was prepared in 53% overall yield via radical mediated azidoalkylation, reduction with $LiBH_4$ and Swern oxidation. Brown asymmetric allylboration[23] with (–)-(Ipc)$_2$BCl/(allyl)MgBr afforded the key enantiorenriched azidoalcohol (*R*)-**22** in 58% yield (er 94:6). Treatment of (*R*)-**22** with NaH and Tf_2O followed by DIBAL reduction of the iminium ion intermediate gave the 3-allylindolizidine (3*R*,8a*S*)-**23** as a single diastereomer and highly preserved enantiomeric ratio (er 91:9). Finally, hydrogenation of the allyl group afforded the naturally occurring (–)-(3*R*,8a*S*)-**19** (or its enantiomer) that was fully characterized. The same strategy starting from methylenecyclohexane was used for the synthesis of (3a*R*,9a*S*)-3-butyllehmizidine (3a*R*,9a*S*)-**20**, the (C3) (or C(8a)) epimer of the naturally occurring (*trans*)-**20** (Scheme 5, **L**). In this case, the alcohol (*R*)-**25** (er 93:7) was obtained by enantioselective butylation of aldehyde **24** with a preformed dibutylzinc solution in the presence of (–)-DBNE. To the best of our knowledge, this is the first time where such an enantioselective alkylation has been run directly with a crude non-distilled dialkylzinc solution generated from the corresponding primary alkyllithium.[27,28] Conversion of (*R*)-**25** to the *epi*-3-butyllehmizidine (–)-(3*R*,9a*S*)-**20** was performed according to our standard reaction conditions (NaH/Tf_2O) using DIBAL in the final reduction step. As anticipated, the reaction is completely diastereoselective and the product enantiomeric purity (er 91:9) matches closely the one of the starting alcohol (*R*)-**25**.



Scheme 5. S*ynthesis of* enantioenriched 3-alkylated indolizidine-(*Z*)-**19** and lehmizidine (*Z*)-**20** alkaloids.

Conclusion

We have demonstrated that the triflate mediated intramolecular Schmidt reaction can be highly diastereoselective when a chiral center is present in the carbon chain linking the azide and the alcohol. Interestingly, when the chirality is at the alcohol center, the process involves an initial intramolecular S_N2 reaction between the azide moiety and the triflate. Starting from easily available enantiopure chiral secondary alcohols, azacycles are obtained with inversion of the stereocenter with no or limited racemization. With suitable substrates, highly diastereoselective 1,2-alkyl shifts are observed. Finally, the stereochemistry of the final reduction step using a hydride source is also fully diastereoselective, allowing to prepare selectively in a single step one out of the four possible diastereoisomers of disubstituted octahydro-1*H*-pyrrolo[1,2-a]azepine in a highly enantioenriched form. The stereospecific intramolecular Schmidt reaction has been applied for the first diastereo- and enantioselective syntheses of the naturally occurring alkaloid (*Z*)-3-propylindolizidine and for (*Z*)-3-butyllehmizidine, the epimer of the isolated natural compound.

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Keywords: azide • Schmidt reaction • stereochemistry • 1,2-migration • azabicyclic compounds • alkaloids

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