Abstract: The stereoselectivity and stereospecificity of the triflate-mediated intramolecular Schmidt reaction of substituted 3-(1-azidocyclohexyl)propanol derivatives leading to octahydro-1H-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_N_2 reaction between the azide moiety and the triflate affording an intermediate spirocyclic aminodiazonium 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 azabicyclic 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 four possible diastereoisomers of disubstituted octahydro-1H-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 Brønsted 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

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Scheme 1. Regio- and stereoselectivity of the intramolecular Schmidt reaction.
salt is believed to exist as a rapidly equilibrating mixture of epimers at the nitrogen atom. This assumption is in accordance with calculations by Glaser, who reported that the activation barrier on the pyramidal nitrogen is low. 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 sexet rearrangement processes. 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). This process requires formation of an aminodiazonium cation bearing a stereogenic center next to the azido group followed by a stereoselective 1,2-shift. The C–C bond anti to the phenyl group at the stereogenic center of the azidoalcohol is migrating. Assuming antiperiplanar migration suggests that the migration involves a conformation where the diazoniun substituent is lying cis to the phenyl ring.

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 carboxations (see Scheme 1, B) and was used for a concise synthesis of indolizidine 167B. 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 enantiomerically enriched substituted octahydro-1H-pyrrolo[1,2-a]azepines 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-Stereosecontrol of the Iminium Reduction by an Adjacent Silyloxy Group

The reaction conditions were optimized with the dioxolanyl acetal 1. Under our optimized conditions, the octahydroaziridinazepine 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 NaBH4 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.

Optimized reactions conditions

1,2-Stereosecontrol of the iminium reduction

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

| Entry | Reagent | Yield[6] | cis/trans[5] |
|-------|---------|----------|-------------|
| 1     | NaBH4   | n.d.     | 67:33       |
| 2     | NaBH4(CN) | n.d.     | 64:36       |
| 3     | LiAlH4  | 60%      | 84:16       |
| 4     | DIBAL   | 98%      | > 95:5      |

[a] Isolated yields. [b] Determined by '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 hypotheses 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 favor 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(CH₂Cl₂,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⁻¹ and 18.3 kJ mol⁻¹ higher in terms of enthalpy (Δ𝐻_{ vib}) and free energy (Δ𝐺_{ vib}) with respect to the global minimum extended conformation (Figure 1). Thus, conformational energetics of iminium cation 6im⁺ 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-anti 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 CH₂Cl₂ (see supporting information).

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. 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 NaBH₄, 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 (1RS,7SR,9aSR) configuration could be determined unambiguously by single crystal X-ray analysis (Scheme 3). Based on the relative configuration of the starting azide 7, 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). 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

![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 were performed at the PCM(CH₂Cl₂,ua0)/DLPNO-CCSD(T)/cc-pVTZ//B3LYP-D3/6-31G(d) level of theory.](image)

![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).](image)
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 iminium ion. The energetic benefit of the syn transition state is completely lost upon formation of the final product 7im$^-$ taking place anti to the phenyl group (1,4-induction) and syn to the adjacent OTBS group.

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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.$^{[26]}$ 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$_2$Zn ((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 the azido group trans to the phenyl substituent, see X-ray structure of 7dmb in Scheme 3) and the relative configuration of the final product 8 (see X-ray structure of 8dmb 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.

The remarkable diastereoselectivity of the 1,2-shift 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 iminium ion. The energetic benefit of the syn transition state is completely lost upon formation of the final product 7im$^-$ taking place anti to the phenyl group (1,4-induction) and syn to the adjacent OTBS group.
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 10 bnb confirmed its (S)-absolute configuration in accordance with expectations.\(^{[25]}\)

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 enantiotomic 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).\(^{[10]}\)

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| 94:6| 16      | 32%          | 95.5     |
| 3     | (R)-12  | CH$_2$=CHCH$_3$ | 98:2 | 17  | 79%          | 92:8     |
| 4     | (R)-13  | Ph   | 91:9| 18      | 71%          | 78:22    |

\(^{[a]}\) Isolated yields. \(^{[b]}\) Determined by HPLC analysis.

The absolute configurations (S)-10 and (3R)-15 demonstrate that the intramolecular Schmidt reaction proceeds with inversion of configuration at the alcohol stereocenter. This indicates that an S$_{N}$2-type mechanism is involved in the formation of the intermediate spirocyclic aminodiazonium salt 10 ad$^-$. (Figure 4, I). Even the benzylic alcohol 13 reacts mainly via an S$_{N}$2 pathway since only limited racemization is observed. The diastereoselectivity of 1,2-shift is then controlled by the C(3) chiral center according to Figure 4 (J). Selective migration of the C–C bond anti to the substituent at position 3 is observed. Since migration is expected to occur anti to the N–N$_{5}^+-$ 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 10 ad$^-$. 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).

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-butyllehmezidine cis-20 was attempted (Scheme 5, L). These two alkaloids were discovered in the venom of workers of the ant Myrmicaria melanogaster from Brunei and identified based on GC-MS analyses. Their absolute configurations and optical activities/purities were not reported.\(^{[14]}\) The relative configurations of the naturally occurring cis-19 and trans-20 were deduced by preparing racemic mixtures of trans/cis-19 and trans/cis-20 via non-stereoselective syntheses and analysis of these trans/cis mixtures by gas chromatography using a FTIR detector (GC-FTIR). The cis isomers of such alkaloids (cis-19 and cis-20) possess a broader Bohlmann band pattern than the trans isomers (see supporting information for copies of IR spectra).\(^{[15]}\) Optically active (−)-(3R,9aS)-19 ((−)-cis-3-propylindolizidine) was prepared from methylenecyclopetanone according to Scheme 5 (M). The aldehyde 21 was prepared in 53% overall yield via radical-mediated azidoalkylation, reduction with LiBH$_4$ and Swern oxidation. Brown asym-
metric allylboration\(^{23}\) with \((-\)-(Ipc)BCl(allyl)MgBr afforded the key enantioenriched azidoalcohol \((R)-22\) in 58% yield (er 94:6). Treatment of \((R)-22\) with NaH and Tf\(_2\)O followed by DIBAL reduction of the iminium ion intermediate gave the 3-allylindolizidine \((3R,8aS)-23\) as a single diastereomer and highly preserved enantiomeric ratio (er 91:9). Finally, hydrogenation of the allyl group afforded \((-\)-(3R,8aS)-19\) as the epimer of the naturally occurring \((S)-3\)-butyllehmizidine (see supporting information for copies of IR spectra). In the absence of reported NMR data for the naturally occurring \((S)-3\)-butyllehmizidine, the epimer of the isolated natural compound.

**Conclusion**

We have demonstrated that the triflate-mediated intramolecular Schmidt reaction can be highly diastereoselective when a stereogenic 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 \(S_\alpha,2\) 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 of the four possible diastereoisomers of substituted 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 structures proposed for the naturally occurring alkaloid \(cis\)-3-propylindolizidine and for \(cis\)-3-butyllehmizidine, the epimer of the isolated natural compound.

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**Conflict of interest**

The authors declare no conflict of interest.

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All geometry optimizations and calculations of thermochemical corrections to 298.15 K have been performed at the B3LYP-D3/6-31G(d) level of theory. Refined energy calculations based on these geometries were then performed with the DLPNO-CCSD(T)/cc-pVTZ method. Calculations of solvation free energies for dichloromethane (DCM, CH$_2$Cl$_2$) solution employ the gas-phase geometries and the IEFPCM continuum solvation model with UA0 radii. Combination of the solvation free energies with the gas-phase free energies calculated at DLPNO-CCSD(T)/cc-pVTZ level yields the free energies in solution (G$_{298}$) mentioned in the text (see SI file for further details).