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Hidden Heptacyclic Chiral *N*-Acyl Iminium Ions: a New Entry to Enantioenriched Polycyclic Azepanes and Azocanes by Superacid-Promoted Intramolecular Pictet-Spengler Reaction

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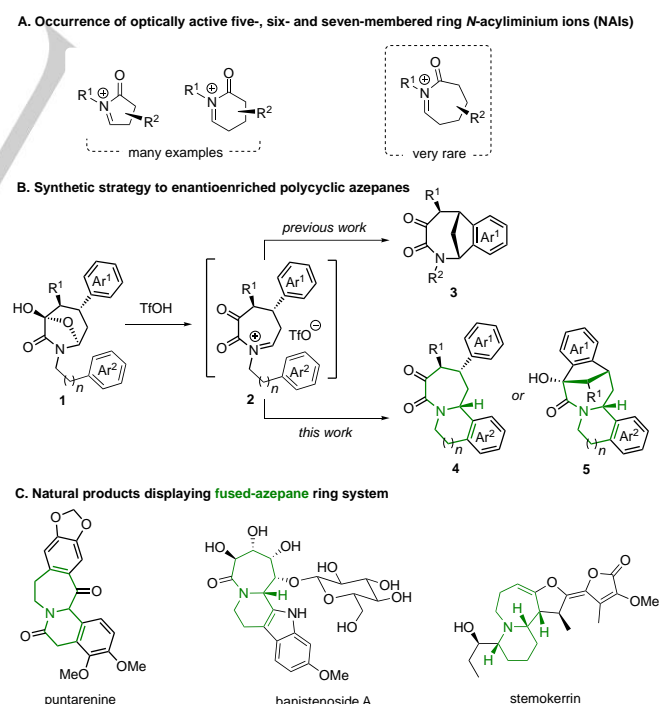
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Abstract: Enantioenriched complex fused-tricyclic azepanes or bridged-polycyclic azocanes were constructed via a two-step sequence involving an enantioselective organocascade followed by superacid activation of the domino adduct. The activated oxa-bridged azepane acts as a key hidden heptacyclic chiral *N*-acyl iminium ion triggering a chemo- and diastereoselective intramolecular mono- or di-arylation.

Introduction

New chiral non-racemic structures are essential not only from an academic point of view but also for industrial developments especially in the production of new pharmaceutical intermediates or fine chemicals.¹ This effort is particularly well-addressed by the recent development of organocatalytic enantioselective Multiple Bond-Forming Transformations (MBFTs) allowing the control of various stereogenic centers in an eco-compatible synthesis of highly functionalized polycyclic targets.² Among the numerous approaches to synthesize such scaffolds, the functionalisation of *N*-acyliminium ions (NAI) is one of the most popular,³ since it can lead to a rapid increase of the molecular complexity starting from easily available starting materials. In this field, if the stereocontrolled access to polycyclic backbones *via* functionalisation of five-⁴ and six-membered ring NAIs is well-documented,⁵ the direct catalytic access to polycyclic molecules from heptacyclic NAIs still constitutes an important synthetic challenge (Scheme 1A). This is due to the more difficult enantioselective access to their precursors combined with their challenging generation as compared to smaller penta- and hexacyclic congeners. Synthetic methodologies aimed at the functionalisation of optically-active heptacyclic NAIs are limited to only few reports, generally starting from the chiral pool, and necessitate several steps.⁶ On the basis of our recent interest in the combination of organocascades with superacid activation for the access to medium-sized ring heterocycles **3**,⁷ we devise that oxa-bridged azepane **1**, obtained in one domino reaction from easily available starting materials,⁸ could act as a hidden chiral enantioenriched heptacyclic NAI **2** under superacid activation. By

a careful design of substrates **1**, concerning the nature of the appended aromatic nucleophilic substituents (Ar^1 , Ar^2), directed chemo- and diastereoselective intramolecular arylations can be expected delivering either enantioenriched fused-tricyclic azepanes **4** or bridged-polycyclic azocanes **5** (Scheme 1B). This would allow for the fast and efficient access to the enantioenriched pyrido[1,2-*a*]azepane ring system, which is found in many biologically relevant molecules, including several natural products, such as puntarenine,⁹ banistenoside A¹⁰ or stemokerrin (Scheme 1C).¹¹



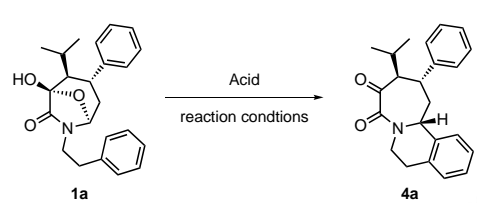
Scheme 1. A) Occurrence of optically-active cyclic *N*-acyliminium ions (NAIs) in the literature. B) Envisioned synthetic strategy to obtain polycyclic azepanes **4** and azocanes **5** in enantioenriched form. C) Selected natural products containing the pyrido[1,2-*a*]azepane scaffold.

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Results and Discussion

The feasibility of the reaction was assessed using oxa-bridged azepane **1a**,⁷ which was subjected to superacid activation¹² using triflic acid (TfOH) (Table 1). We were pleased to observe the clean formation of the tricyclic azepane **4a** via a chemoselective 6-*endo-trig* arylation in an excellent yield (98%), and modest control of the diastereoselectivity (Table 1, entry 1, dr = 3.5:1). Interestingly, the 5-*exo-trig* pathway leading to benzazocane **3a** ($R^1 = iPr$, $R^2 = \text{homobenzyl}$) was not observed. Conducting the reaction at lower temperature did not improve significantly the diastereoselectivity (Table 1, entry 2). Using toluene or polyfluoroalcohol as solvents resulted in little effect on the diastereoselectivity and the yield remained better with CH_2Cl_2 (Table 1, entries 3-6). The excess of TfOH could be reduced down to 5 equivalents with still acceptable efficiency (Table 1, entries 7, 8), but lower loading resulted in inappropriate (Table 1, entry 9). The use of other strong Brønsted acids featuring lower protonating ability (Table 1, entry 10) or Lewis acids (Table 1, entries 11-15) was shown detrimental to the reaction, highlighting the necessity to use superacid conditions.¹³

Table 1. Optimization of the superacid-promoted cyclisation of **1a**.



| Entry | Acid (50 equiv) | Solvent | T [°C] | t [h] | Yield of 4a [%] ^[a] | dr of 4a |
|-------|--|-----------------------------------|--------|-------|---------------------------------------|-----------------|
| 1 | TfOH | CH_2Cl_2 | 0 | 1 | 98 (99) | 3.5:1 |
| 2 | TfOH | CH_2Cl_2 | -40 | 16 | 57 (57) | 3.9:1 |
| 3 | TfOH | Toluene | 0 | 1 | 75 (99) | 2.6:1 |
| 4 | TfOH | $\text{CF}_3\text{CH}_2\text{OH}$ | 0 | 1 | 81 (99) | 5.6:1 |
| 5 | TfOH | $(\text{CF}_3)_2\text{CHOH}$ | 0 | 1 | 89 (99) | 4.1:1 |
| 6 | TfOH | $(\text{CF}_3)_3\text{COH}$ | 0 | 1 | 92 (99) | 3.9:1 |
| 7 | TfOH ^[b] | CH_2Cl_2 | 0 | 1 | 95 (99) | 4.6:1 |
| 8 | TfOH ^[c] | CH_2Cl_2 | 0 | 1 | 86 (99) | 4.8:1 |
| 9 | TfOH ^[d] | CH_2Cl_2 | 0 | 1 | (0) | - |
| 10 | HNTf ₂ | CH_2Cl_2 | 0 | 1 | 10 (10) | 3.5:1 |
| 11 | FeCl_3 | CH_2Cl_2 | 0 | 1 | (0) | - |
| 12 | FeCl_3 | CH_2Cl_2 | RT | 16 | -[e] | - |
| 13 | FeCl_3 ^[b] | CH_2Cl_2 | RT | 16 | -[e] | - |
| 14 | AlCl_3 ^[b] | CH_2Cl_2 | RT | 16 | -[e] | - |
| 15 | $\text{Cu}(\text{OTf})_2$ ^[b] | CH_2Cl_2 | RT | 16 | -[f] | - |

[a] Isolated yield on 0.1 mmol scale; conversion in parenthesis. [b] 10 equiv. [c] 5 equiv. [d] 1.2 equiv. [e] Complex mixture. [f] To dehydration product (25% yield, see SI), incomplete conversion.

Then, the scope of the reaction was studied with the optimum 10 equivalents loading of TfOH to evaluate the influence of the nature of both aryl groups (Ar^1 , Ar^2) in the superacid-promoted intramolecular arylation step (Figure 1). A variety of enals were used in the first organocatalyzed domino reaction, allowing the installation of various aryl groups (Ar^1 in blue) in the starting azepanes **1a-1g**. Both electron-donating and electron-withdrawing groups were well tolerated in the cyclisation step, affording the desired polycyclic azepanes **4a-g** in excellent yields. Interestingly, even in the case of **1c,d,j** possessing an electron-donating *m*-substituent (in Ar^1), which should favor the competitive 5-*exo-trig* cyclisation, the chemoselectivity was excellent, and no trace of benzazocane isomers **3c,d,j** were detected. The cyclisation of oxa-bridged azepanes with an electron-withdrawing group (**1e-g**) gave the corresponding products (**4e-g**) with slightly increased diastereoselectivity (5.6:1 to 6.4:1 dr). Next, the attention was turned toward the nature of the substituent on the nitrogen atom (Ar^2 in fuchsia) in oxa-bridged azepanes **1h-m** obtained from the corresponding ketoamide substrates (see SI).

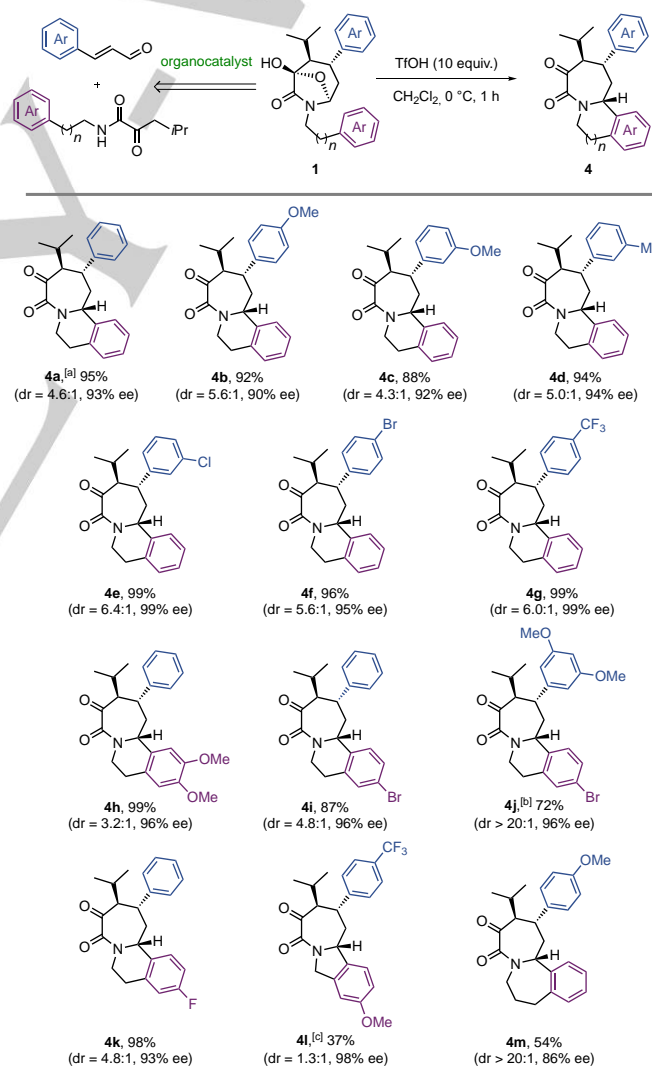


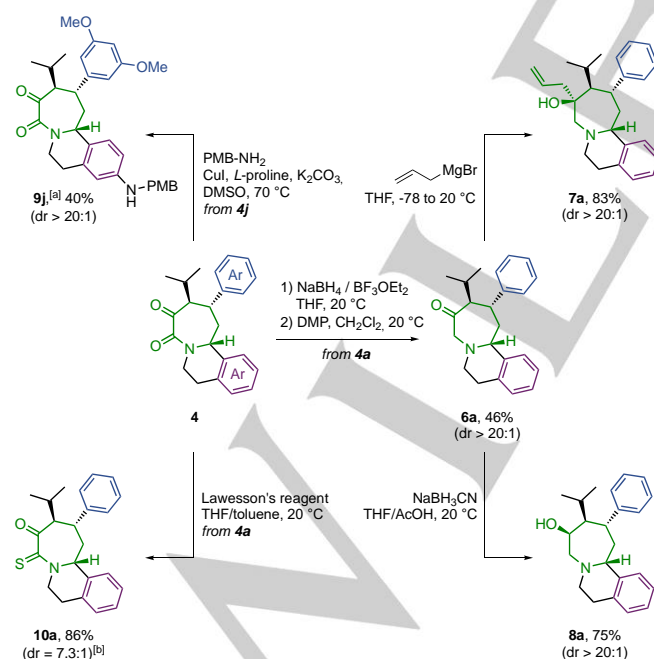
Figure 1. Reaction scope for the synthesis of tetrahydroisoquinoline-fused azepanes **4**. [a] 87% yield on gram-scale. [b] The reaction time was extended to 2 hours. [c] 50 equiv. of TfOH.

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The expected tetrahydroisoquinoline-fused azepane **4h** was obtained in nearly quantitative yield and moderate diastereoselectivity (3.2:1 dr), probably due to the increased nucleophilic character of the bis-methoxyphenyl moiety.

An electron-impoverished aryl group was also suitable (**1i-k**) and the desired product were obtained in good to excellent yields. Remarkably, product **4j** was formed with excellent diastereoselectivity (>20:1 dr) and excellent enantiocontrol (96% ee). The size of the new ring formed during the cyclisation was next evaluated by varying the length of the tether between the nitrogen and the nucleophilic aryl group ($n = 0, 2$). The robustness of the intramolecular arylation is highlighted with the isolation of the fused-pyrrolidine product **4l** from a disfavored *anti*-Baldwin 5-*endo-trig* cyclisation of the corresponding oxa-bridged azepanes **1l** ($n = 0$).¹⁴ Alternatively, the product **4m** ($n = 2$) displaying the rare azepino[1,2-*a*]azepane ring system¹⁵ was formed very efficiently (>20:1 dr, 86% ee) *via* a favorable 7-*endo-trig* cyclization.

This directed intramolecular arylation gives rise to polycyclic heterocycles with a densely-functionalized structural framework (Scheme 2). This is exemplified by the reduction of both carbonyl groups of **4a**, followed by the oxidation of the remaining secondary alcohol function, leading to fused 3-azepanone **6a** which has been isolated in 46% overall yield as a single diastereomer. From here, conversion to the corresponding tertiary alcohol **7a** *via* a diastereoselective allyl Grignard addition or a reduction to the secondary alcohol **8a** allows for the control of four stereogenic centers. From **4j**, bearing an arylbromide, an Ullmann coupling allowed the installation of a protected aniline moiety in the final structure **9j**. Finally, the amide function of **4a** could be transformed into its thioamide equivalent using the Lawesson's reagent, giving rise to **10a** in 86% yield.



Scheme 2. Post-functionalisation of polycyclic azepanes **4**. [a] PMB = *p*-methoxybenzyl. [b] After purification by flash chromatography.

We then turned our attention in the design of a superacid-promoted cascade di-arylation involving the successive C-H-functionalisation of both aryl groups. We reasoned that the ketone

function revealed in **4** could in turn be activated under the superacidic conditions, triggering a subsequent second nucleophilic addition of the remaining aryl moiety (Ar¹), which stay silent during the first step. This would give rise to a complex methylene-bridged polycyclic azocane framework **5** with four stereogenic centers and the creation of five bonds in a one-pot double intramolecular arylation sequence (Scheme 1B). Hence, by treating **1c** with TfOH (50 equiv.) in CH₂Cl₂ at 0 °C for 1 hour, we were pleased to observe the clean formation of the desired bridged-polycyclic azocane **5c** in 55% yield (Figure 2). Interestingly, **5c** was obtained as one single diastereomer. This could be explained by the absence of reaction of the minor diastereomer of **4c**. This was confirmed by the isolation of the minor diastereomer of **4c** (dr = 9:1) in 15% yield. Inspection of the double-arylation scope led us to find the requirement of an electron-rich aryl group for the second cyclisation to proceed. Interestingly, either electron-donating (**5o-p**) or electron-withdrawing (**5q-r**) substituents on the nitrogen-tethered homobenzyl group were suitable for the cascade reaction, even if higher yields were observed in the latter case. Finally, the crystallinity of **5c** enabled assignment of its absolute configuration by X-ray diffraction analysis, allowing structures **5n-r** to be assigned by analogy.¹⁶

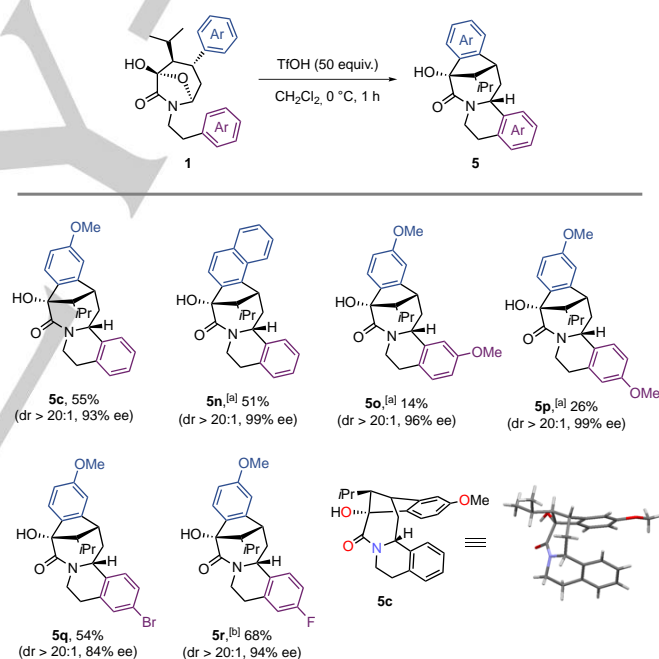


Figure 2. Reaction scope for superacid-promoted cascade di-arylation of **1**. The reaction time was extended to: [a] 4 hours, [b] 2 hours.

The preferential cyclisation of the major diastereomer obtained after the first cyclisation step motivated a computational investigation on derivative **4a** (see SI). Owing to the presence of a saturated seven-membered ring, a large conformational complexity was expected. For the sake of simplicity, the degrees of freedom relative to the free rotation of Ar¹ were put aside. In a first stage, a thorough conformer search was conducted using the recently proposed method of Grimme and co-workers (automated search based on semi-empirical tight binding-based metadynamics).¹⁷ Due to the acidity of the reaction medium, both diastereomers of **4a** were considered monoprotonated, either on the carbonyl or amide moiety. Four conformational searches were then conducted (two protomers per diastereomer), resulting

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eventually in 244 structures lying within a 6 kcal/mol relative energy window. These structures were then reoptimized at a DFT level (B3LYP/6-31G(d,p), using Grimme's dispersion model D3 with a Becke-Johnson damping), including an implicit solvation model in order to offer a closer reproduction of the reaction medium (see SI).¹⁸ In Figure 3, a representation of the lowest energy conformer for both diastereomers is provided. In both cases the amido group is the preferred protonation site (to be compared to the ketone protonation up to 10 kcal/mol more demanding in energy). An even more striking feature is the strong difference in the distance between the carbonyl group and Ar¹: in the major diastereomer (top of Figure 3), a short contact is observed, the phenyl ring directly facing the ketone (C–C distance of 2.94 Å only) as a consequence of a certain folding of the 7-membered ring. Conversely, for the minor diastereomer, the phenyl ring is not oriented towards the carbonyl group, but rather points outwards of the molecule (C–C separation of 4.42 Å), also probably related to the 7-membered ring conformation ("equatorial"-like orientation of the phenyl). Hence, from purely geometrical considerations we may already infer that the major diastereomer of **4a** is directly prone to react to form the cyclisation product **5a**, while the minor diastereomer will require a more substantial degree of reorganization (and likely energy cost) to achieve the same reaction.

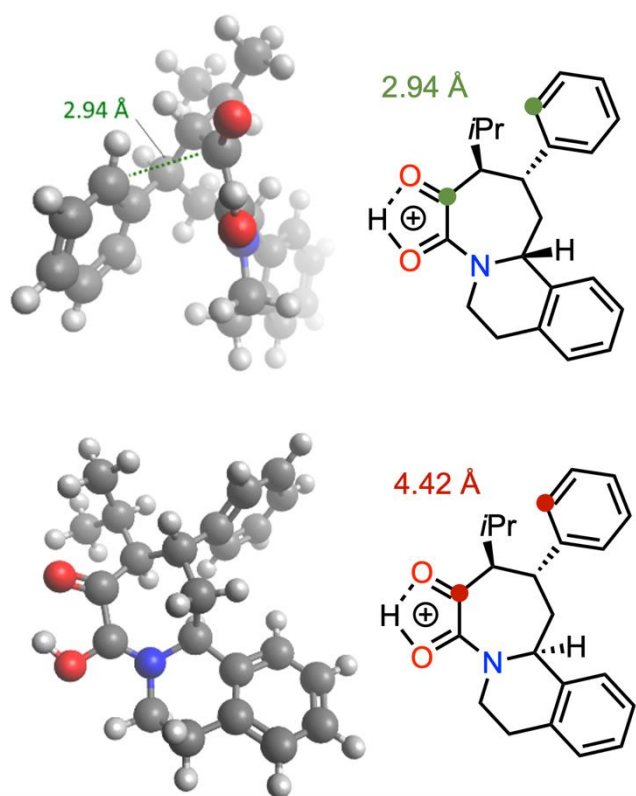


Figure 3. Ball and stick representation of the lowest energy conformer for the major (top left, side view) and minor (bottom, top view) diastereomers of **4aH**⁺. The carbonyl-phenyl short contact in the major diastereomer is depicted with a dashed green line. Colour scheme: gray, C; red, O; white, H; blue, N.

In Figure 4, plots of the carbonyl/phenyl distance against the computed relative energy of all considered conformers are provided for both diastereomers of **4aH**⁺ after protonation. The protonation of the ketone function is severely disfavored (red dots massing to the right-hand side of the plots, in the high energy

region). Nevertheless, both protomers seem to display roughly comparable geometry distributions, with phenyl/carbonyl shortest distances ranging between 2.90 and 4.75 Å. Focusing on the short contacts (below 3.5 Å), differences are evident: in the case of the major diastereomer, three conformations are found at relative energies between 0 and 2 kcal/mol, while none is observed in the same region for the minor intermediate. In fact, the first conformation displaying such short contact in this last case is found at +2.8 kcal/mol (geometry given in SI). If we assume that, starting from a conformation with a short phenyl/carbonyl contact, the activation energy of the cyclization step is a constant, then we may expect that difference in apparent activation energy (E_a) for the two diastereomers will be of 2.8 kcal/mol. Under a kinetic control of selectivity, a difference of 2.8 kcal/mol in E_a should translate in a 99.1/0.9 ratio of products, which complies rather nicely with experimental observations. The observed difference in reactivity between both diastereomers thus seems to relate to the 7-membered ring conformational preferences of the superacid-protonated intermediate: in the case of the major diastereomer, the folded ("reactive") conformation is the lowest in energy, while in the case of the minor diastereomer a more planar conformation ("unreactive", with an equatorial and thus remote phenyl) is preferred.

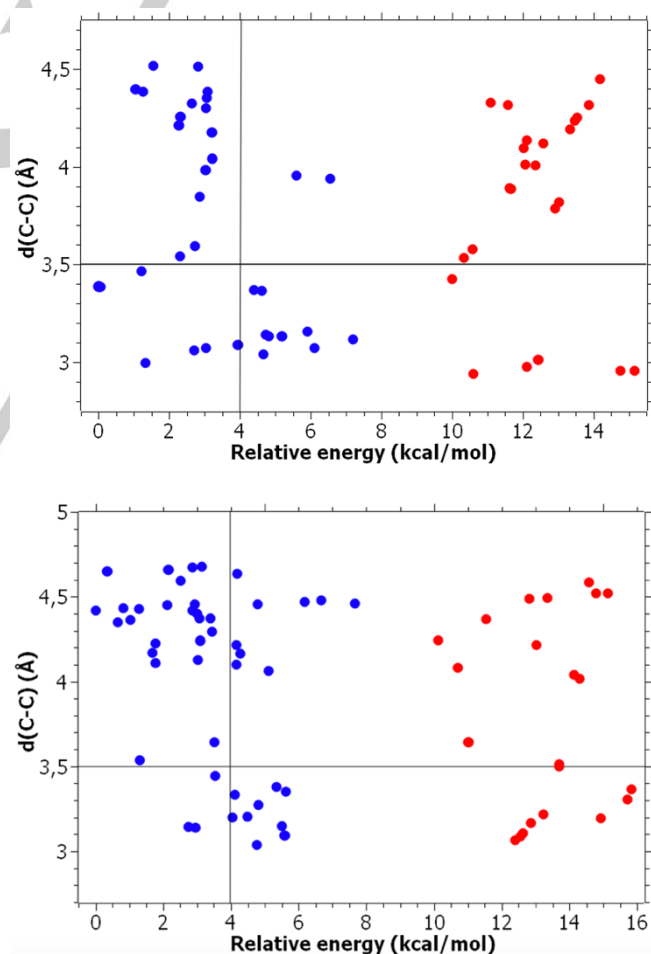


Figure 4. Plots of the carbonyl/Ar¹ distance as a function of relative energy for the various conformers of **4aH**⁺. Up: major diastereoisomer; down: minor diastereoisomer. Colour scheme: blue, protonation at amido group; red, at ketone group. The vertical solid lines correspond to an energy of 4 kcal/mol, and the horizontal lines refer to a distance between carbons of 3.5 Å.

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To further confirm these hypotheses, we then conducted transition-state (TS) calculations for the cyclisation reactions. In order to limit the computational effort, these calculations were performed on conformations displaying a phenyl/carbonyl C–C distance below or equal to 3.50 Å and a relative energy below 4 kcal/mol (solid lines in Figure 4). Three TSs were located for the major diastereomer, and two for the minor one (see SI). Interestingly, the lowest transition state is obtained for the major diastereomer, with an activation barrier of 23.6 kcal/mol (ZPE-corrected energies, relative to the lowest energy conformer). In the case of the minor diastereomer, the lowest activation barrier is of 28.2 kcal/mol, *ie* 4.6 kcal/mol higher. It may be already noted that these activation barriers are rather high, in line with the poor reactivity of **4a** (need for electron donating groups on Ar¹).

If we now focus on the difference in activation energy (which we may expect to remain rather comparable for substituted Ar¹), we observe that under a kinetic control of selectivity it would translate in a very high selectivity (0.04% percent of the minor product only), in perfect line with experiments.

Hence it can be seen that conformational degrees of freedom play a very important part in the observed selectivity: by controlling the distance between reactive substituents in space (folded versus planar 7-membered ring), one diastereomer is directly set to react, while the other one undergoes a strong energy penalty, sufficient to prevent the formation of the associated cyclisation product.

Based on this deep computational investigation, the following mechanism could then be proposed (Figure 5). The protonation of **1c** into **1cH⁺** would generate seven-membered NAI **2c** by loss of a water molecule. This would trigger a 6-*endo-trig* cyclisation affording protonated diastereomers **4cH⁺** and **4c'H⁺** in the reaction media. From here, only the folded reactive conformation of **4cH⁺** undergo a second intramolecular Pictet-Spengler reaction, which leads to the isolation of **5c** as sole diastereomer.

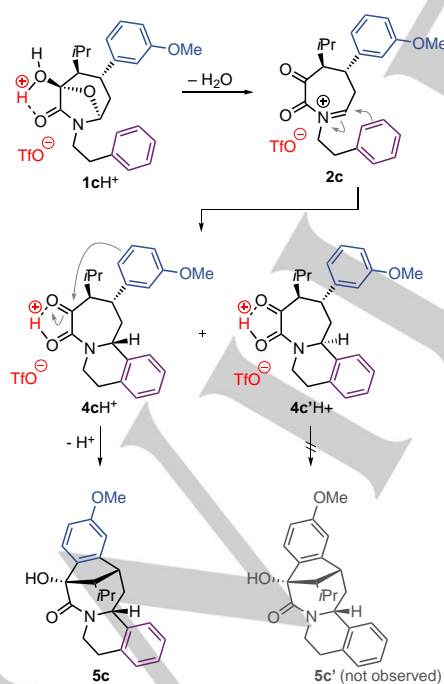


Figure 5. Mechanism for the superacid-promoted cascade di-arylation.

In conclusion, the direct generation of a functionalized chiral enantioenriched heptacyclic *N*-acyl iminium ion (NAI) allowed the rapid assembly of complex polycyclic azepanes and azocanes from simple starting materials. An organocatalyzed domino reaction allowed for the enantioselective synthesis of an oxabridged azepane, acting as a hidden key NAI under superacid activation. From here, directed chemo- and diastereoselective arylation *via* intramolecular Pictet-Spengler reaction furnished the enantioenriched polycyclic azepanes. Capitalizing on the ability to activate α -ketoamides under superacid conditions, complex methylene-bridged polycyclic azocanes exhibiting four controlled stereogenic centers were also obtained *via* a one-pot double intramolecular arylation sequence. Through a computational investigation of the conformational space of a model intermediate, rationalization of the observed selectivity for the formation of azocanes could be proposed. Depending on the azepane stereochemistry, two completely different conformations of the 7-membered ring cationic intermediate were observed, only one favoring the final cyclisation step.

Acknowledgements

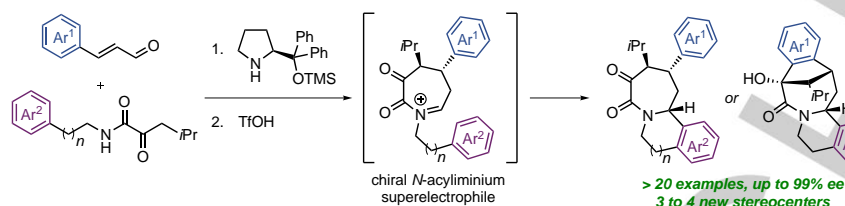
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Keywords: N-acyliminium ion • azepane • azocane • organocatalysis • superacid

Conclusion

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The combination between enantioselective organocatalysis and superacid activation allows for the construction of enantioenriched complex fused-tricyclic azepanes or bridged-polycyclic azocanes from simple acyclic substrates. The hidden heptacyclic chiral *N*-acyl iminium ion is generated by superacid activation and is the key intermediate that triggers a chemo- and diastereoselective intramolecular mono- or di-arylation.

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