Enantioselective [1,2]-Stevens rearrangement of quaternary ammonium salts. A mechanistic evaluation†

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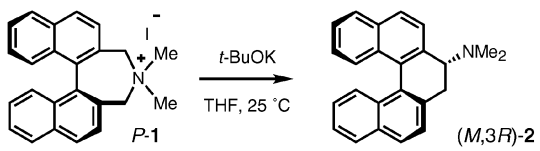
Using a supramolecular asymmetric ion pairing strategy, an enantioselective [1,2]-Stevens is feasible on substrates devoid of stereogenic quaternary nitrogen atoms.

The [1,2]-Stevens rearrangement, which is the spontaneous transformation of ammonium ylides into tertiary amines, has been strongly studied for its interesting mechanism and for its synthetic utility.[1] Despite the many studies, asymmetric versions of this reaction still remain a challenge probably reflecting the radical character of the process.[2] In fact, strict enantioselective [1,2]-Stevens rearrangement of quaternary ammonium ions has not been reported,[3] and enantiospecific transformations occur usually with some loss of enantiomeric purity.[4] These latter reactions that use substrates containing stereogenic quaternary nitrogen atoms involve intramolecular transfer of chirality (ToC) from the N-atom to the adjacent C-position. The enantioselectivity of the ToC depends upon the ionization conditions as shown recently by West and Tayama (ee 54 to 99%).[5] In view of these precedents, it was debatable whether an enantioselective [1,2]-Stevens could ever be developed for compounds devoid of stereogenic quaternary nitrogen atoms. Herein, on designed substrates and using a novel supramolecular asymmetric ion pairing strategy,[6,7] we report a ''proof of concept'' mechanistic study that sees an enantioselective [1,2]-Stevens rearrangement occurring despite its diradical mechanism [eqn (1)].



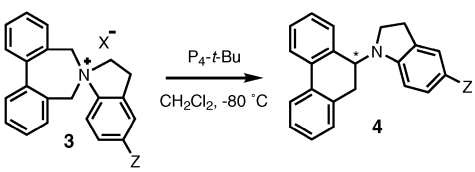
(1)

If enantioselective [1,2]-Stevens rearrangements of quaternary ammonium ions have been elusive, many useful diastereoselective reactions have been developed.[8] Previously, Mislow and Závada have shown that [1,2]-Stevens rearrangements of *configurationally stable* biarylazepinium cations occur readily upon ylide formation.[9,10] The reactions proceed with high selectivity as, for instance, cations of type **1** [eqn (1)] react with strong bases to produce dihydrohelicenes of type **2** as single diastereomers (99% yield).[9a] The ToC from the biaryl axis of the diarylazepinium precursor to the new sp^3 stereogenic center is complete. With this established precedent, it occurred to us that any other twisted biaryl azepinium entity of analogous structure and geometry could react similarly and selectively in [1,2]-Stevens rearrangements—and ''simple'', readily available from indole derivatives, diphenylazepinium cations of type **3** (Table 1) in particular.

The caveat with compounds **3** was however their configurational lability at ambient and low temperatures. In fact, studies performed on analogous diphenylazepines or diphenylazepinium salts have revealed that the 7-membered dibenzo[*c*,*e*]azepinium ring presents an axial chirality with a low kinetic barrier of enantiomerization ($\Delta G^{\ddagger} \approx 12$–14 kcal mol^{-1}).[11,12] Diphenylazepinium cations of type **3** thus exist as 1 : 1 mixtures of freely interconverting *P* and *M* atropisomers in solution. As such, these *tropos* derivatives were not used in stereoselective [1,2]-Stevens rearrangements.[13]

Previously, hexacoordinated phosphorus anion BINPHAT **5** (Δ and Λ enantiomers, Fig. 1)[14] has been shown to be a general NMR chiral solvating, resolving and asymmetry-inducing reagent for chiral organic cationic species. When associated with configurationally labile cations, supramolecular diastereoselective interactions can occur and one diastereomeric ion pair can become predominant over the other.[6] The occurrence of such behavior, called the Pfeiffer effect,[15] is the

Table 1 Enantioselective [1,2]-Stevens rearrangement of the BINPHAT salts of cations **3a** to **3e**[a]



Z	Salt	Yield (%)	ee[b] (%)	$[\alpha]_D$[c]	de[d] (%)	ToC[e] (%)
H	[**3a**][Δ-**5**]	90	33	(+)	33	100
H	[**3a**][Λ-**5**]	88	33	(−)	33	100
OMe	[**3b**][Δ-**5**]	52	27	(+)	30	90
OBn	[**3c**][Δ-**5**]	50	20	(+)	20	100
F	[**3d**][Δ-**5**]	50	49	(+)	50	98
Cl	[**3e**][Δ-**5**]	48	55	(+)	60	92

[a] Treatment with **6** (1.5 equiv., CH_2Cl_2, −80 °C, 4 h); average of at least two runs. [b] Enantiomeric purity of **4a–4e** determined by CSP-HPLC. [c] Sign of the optical rotation of **4a–4e**. [d] Diastereoselectivity of the ion pairing determined by ^1H and ^{19}F NMR at 193 K, precision ±2–3%. [e] Transfer of Chirality defined as the ratio of the enantioselectivity [ee] over the ionic stereoinduction [de], precision ±2–3%.

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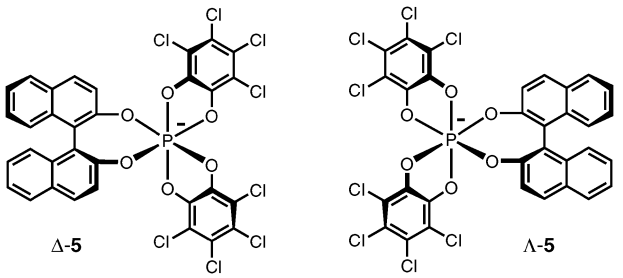


Fig. 1 BINPHAT anion **5** (*Δ* and *Λ* enantiomers shown).

result of the formation of one thermodynamically more stable ion pair in solution.[16] The association of this enantiopure anion **5** with cations **3** was then interesting for the development an asymmetric [1,2]-Stevens rearrangement, any imbalance in the population of the diastereomeric salts, *e.g.* [*P*-**3**][*Δ*-**5**] over [*M*-**3**][*Δ*-**5**], resulting possibly in the preferential formation of one enantiomer of rearranged product **4** over the other (Table 1).

This hypothesis was assessed by preparing a series of compounds **3** with various substituents at the 5-position on the indolinium ring. Salts [**3a**][Br] to [**3e**][Br] (Table 1, Z = H, OMe, OBn, F, Cl), were prepared in one step by condensation of 2,2′-bis(bromomethyl)biphenyl and the respective commercially available or simply prepared indolines (K_2CO_3, CH_3CN, 80 °C, 71–90%). The ion pairing with anion **5** was realized by mixing solutions of the bromides salts with that of [Me_2NH_2]-[*Δ*-**5**] (or its enantiomer, 1.2 equiv.) in CH_2Cl_2–acetone. Chromatography of the mixtures on basic alumina (eluent CH_2Cl_2) afforded the desired pairs [**3a**][*Δ*-**5**] to [**3e**][*Δ*-**5**] as the only eluted salts (70–98%).[17] Salt [**3a**][*Λ*-**5**] was prepared similarly (87%).

For the Stevens rearrangement, care was taken to select a neutral base so as not to upset the possible asymmetric ion pairing situation by addition of another salt, and Schwesinger base P_4-*t*-Bu **6** in particular.[18,19] Treatment of the bromide salts of ammonium cations **3a** to **3e** with **6** (1.5 equiv., CH_2Cl_2, −80 °C, 4 h) resulted, as desired, in the formation of the racemic rearrangement products **4a** to **4e**. The yield was excellent for **4a** (92%) and moderate with the substituted derivatives **4b** to **4e** (46–53%, see ESI†).[20] With these results and conditions in hand, salt [**3a**][*Δ*-**5**] and its enantiomer [**3a**][*Λ*-**5**] were treated with **6** to yield non-racemic amines (+)-**4a** and (−)-**4a**, respectively. Chiral Stationary Phase (CSP)-HPLC revealed an enantiomeric purity of 33% for both (Table 1). The occurrence of an enantioselective reaction was confirmed by the reactions of salts [**3b**][*Δ*-**5**] to [**3e**][*Δ*-**5**] which afforded amines (+)-**4b** to (+)-**4e**. The yields were in complete accordance (±2%) with that of the bromide salts. Whereas electron-donating ether substituents led to poor ee values (20% and 27% for OBn and OMe), the presence of electron-withdrawing halogen atoms (F and Cl) improved the enantioselectivity to 49% and 55%, respectively; values high enough to be clearly considered as "proof of concept".[21] The substituent effect, somewhat surprising at first glance, could be rationalized in the course of the following study.

To establish that the enantioselectivity of the reactions was, as imagined, the result of the predominance of one diastereomeric ion pair, a series of variable temperature NMR experiments were performed on the bromide and BINPHAT salts under essentially the reaction conditions. First, in the ^{1}H NMR, clear AB patterns appeared at −40 °C in CD_2Cl_2 for the benzylic protons of the bromide salts demonstrating, without ambiguity, that the exchange between the *P* and *M* conformers of **3** was slow on the NMR-timescale at that (and lower) temperature. Then, salts [**3a**][*Δ*-**5**] to [**3e**][*Δ*-**5**] were studied at −40 and −80 °C and, in all cases, anion *Δ*-**5** acted as an NMR chiral solvating agent. NMR signals were clearly split into two sets, one for each of the atropisomers of **3**. In ^{1}H NMR, the differentiation was better followed in the *δ* 5.8–6.5 ppm region corresponding to some of the aromatic protons. The singlet signals of the MeO substituent of **3b** or of the fluorine atom of **3d** in ^{19}F NMR (Fig. 2) were also effective probes to follow. More importantly, these experiments revealed an asymmetric induction from **5** onto the cations as one of the diastereoisomeric ion pairs, [*P*-**3**][*Δ*-**5**] or [*M*-**3**][*Δ*-**5**], is clearly favored in solution. Integration of the split signals gave ratios from 1.5 : 1 to 4.0 : 1 (±2–3%) corresponding to diastereomeric excesses of 20% to 60% (±2–3%), respectively.[22] The results are reported in Table 1. Better selectivities were obtained for the cations bearing electron-withdrawing halogen atoms.

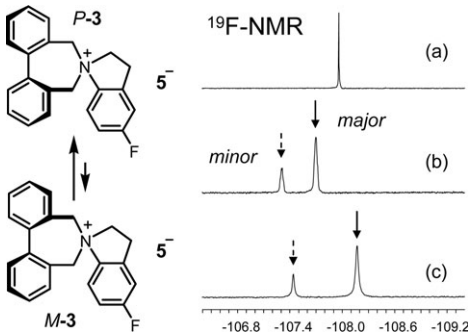
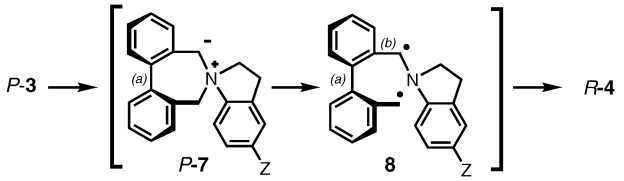


Fig. 2 Ion pairing of anion **5** and cation **3d**. Asymmetric induction as evidenced by ^{19}F NMR (CD_2Cl_2, 352 MHz): (a) [**3d**][Br], 233 K; (b) [**3d**][*Δ*-**5**], 233 K, de 50% and (c) [**3d**][*Δ*-**5**], 193 K, de 52%.

Significantly, the values for the diastereoselectivity within the asymmetric ion pairs are essentially identical to that of the enantiomeric purity of the corresponding tertiary amines **4**. Direct comparison between the two sets of data points to the existence of an essentially linear correlation.[23] This indicates that the ToC from the preferred atropisomers of **3** to the non-racemic amines **4** occurs with excellent stereoselectivity (from 90 to 100%, Table 1).

Interestingly, as we have mentioned earlier, achieving such a high selectivity was not obvious considering the probable mechanism (Scheme 1). The [1,2]-Stevens rearrangement of **3** should involve principally two successive intermediates. The first is zwitterionic ylide **7** generated by deprotonation and the second is radical pair **8** produced by homolytic fragmentation (Scheme 1). Both compounds **7** and **8** are neutral and hence afford the possibility for **5** to diffuse out of the reaction pocket. Loss of enantiomeric purity can then simply occur by (a) rotation around the biaryl axis of **7** or **8**, or (b) by rotation (180°) of the C_{aryl}–CHN bond of **8**. Although it is premature at this stage to speculate, the high selectivity for the ToC



Scheme 1 Possible intermediates **7** and **8** in the rearrangement of **3** to **4**. Loss of chirality may occur by rotation of (a) the biaryl C–C bond or (b) of the C_{aryl}–CHN bond; configurations are assumed.[24]

probably indicates that all the steps leading to **4** are extremely fast on the reaction time-scale.[2]

In conclusion, this paper reports that a strict enantioselective [1,2]-Stevens rearrangement of quaternary ammonium ions is feasible, using enantiopure anionic counterions as asymmetric auxiliaries in particular. The methodology constitutes an interesting example of double transmission of chirality: (i) a supramolecular transfer of the helical chirality of anion **5** to the axial chirality of cation **3** and then (ii) its very effective translation (90 to 100%) during the [1,2]-Stevens rearrangement to the centered chirality of amines **4**.

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21 The global ee values may appear to be low but they are in line with that of the enantiospecific studies (ref. 5) if one takes into account that recrystallizations are necessary at the stage of the formation of the stereogenic quaternary ammonium ions to remove minor diastereomeric salts. Without the purification prior to the Stevens rearrangement, lower levels of enantioselectivity are achieved.

22 At 193 K, the precision of the measurement is slightly limited by some line-broadening. At 233 K (−40 °C), the NMR resolution was sharper and the diastereomeric excesses measured are in complete agreement with that observed at −80 °C.

23 Linear regression of de = f(ee) affords the following trendline ($y = 0.9109x + 1.6395$, $R^2 = 0.9879$).

24 By analogy with the study of Závada and coworkers, the (*P*)-**3** and (*M*)-**3** conformations ought to lead to the formation of (*R*)-**4** and (*S*)-**4**, respectively.