Exploring coordination chemistry and reactivity of formazanate ligands
Travieso Puente, Raquel

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Chapter 4

Facile access to fluorinated [1,2,4,5]tetrazepine and indazole derivatives via nucleophilic aromatic substitution

A straightforward synthetic route to tetrazepines and indazoles via nucleophilic aromatic substitution is presented. Upon deprotonation of the NH group, a C₆F₅-substituted formazan undergoes facile cyclization as a result of intermolecular nucleophilic substitution (SNAr). The fluorinated tetrazepines and indazoles offers a handle for further functionalization and tuning of its properties as it is shown to be susceptible to subsequent selective nucleophilic displacement reactions.

\[
\begin{align*}
(4.1) & \quad (4.2) \\
(4.3) & \quad (4.4) \\
(4.1'\text{OMe}) & \quad (4.2'\text{OMe}) \\
(4.3'R) & \quad (4.3'R=\text{OMe, SC}_{8}H_{17})
\end{align*}
\]

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R. Travieso-Puente, M.-C. Chang and E. Otten*

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4.1 Introduction

Nucleophilic aromatic substitution (SNAr) is an established class of organic transformations that occur on aromatic rings with electron-withdrawing groups (EWG). Often, anionic σ-complexes (so-called Meisenheimer complexes\(^2\)) are invoked as intermediates, which are stabilized by these electron-withdrawing groups. Consequently, SNAr substitution at aromatic (sp\(^2\)-hybridized) ring-carbons is mechanistically distinct from SN1/SN2 reactions that take place at sp\(^3\)-carbon atoms, and the SNAr mechanism has been studied in detail (Scheme 4.1).\(^1\) Substitution can take place either at an aromatic C-H bond, or at the C-atom bearing the EWG (‘ipso-substitution’, Scheme 4.1 (c)). Due to the large inductive effect of NO\(_2\), Cl\(^-\) and F\(^-\) substituents, their good leaving-group ability, and the fact that compounds with these substituents are readily available, SNAr reactions using these EWG groups have found most widespread use in synthesis.\(^1,3\)

Scheme 4.1 General mechanism (a) SN1, (b) SN2 and (c) SNAr.

In this chapter, we will describe the product formation when some fluorinated (C\(_6\)F\(_5\)-substituted) formazans react with group 2 metal complexes. Often, these are thermally unstable and we show in this chapter that the decomposition products are the result of intramolecular nucleophilic aromatic substitution. Depending on the position of the C\(_6\)F\(_5\)-group on the backbone of the formazan starting material (either C- or N-C\(_6\)F\(_5\) substituted), SNAr cyclization leads to a 5-membered (indazole) or a 7-membered (tetrazepine) ring.

Before discussing the results in detail, a brief introduction to indazole and tetrazepine compounds is given below.
Nitrogen-containing heterocycles are important scaffolds that are present in a large number of biologically active molecules. A sub-class of these are indazoles (Figure 4.1), which have been shown to have significant pharmaceutical potential. In addition, indazoles have found use as electro-active materials and as building block for ligands in homogeneous catalysis.

![Figure 4.1 Tautomers of indazole.](image)

Many different synthesis routes have been developed over the years, and a large variety of substituted indazoles have been reported in the literature. Of immediate relevance to the results described in this chapter is the use of ortho-halogen substituted benzaldehydes, which may be cyclized to the corresponding indazole upon treatment with hydrazine (Scheme 4.2). However, this often requires harsh reaction conditions and is accompanied by the formation of side-products due to Wolff-Kishner reduction. Despite some previous reports of the synthesis of highly fluorinated indazoles by S_NAr reactions there is significant potential in broadening the scope of these reactions toward more complex products, in particular those with functional groups at N-1 or C-3.

![Scheme 4.2 Synthesis indazole via ortho-halogen substituted benzaldehydes.](image)

Seven-membered nitrogen-containing heterocycles are also of interest for their biological activity. In particular, (benzo)diazepines have unique therapeutic effects and are a privileged class of compounds in drug discovery. In spite of this, related seven-membered ring compounds containing three or four nitrogen atoms (tri- and tetrazepines) have received comparatively little attention. The synthesis and biological activity of (substituted) triazepines has recently been reviewed. The situation is quite different for the analogues with 4 nitrogen atoms in the ring (tetrazepines). A chapter in the monograph ‘Chemistry of Heterocyclic Compounds’ from 2008 shows a handful of compounds having this general
motif, but calls into question many of the reported structures. For example, in 1955 Jerchel and Edler reported the synthesis of the 1,3-phenyl-1H-benzo[f][1,2,4,5]tetrazepine, which was in 1973 suggested to be erroneous (a) and (b) in Figure 4.2, respectively). Reliable syntheses of compounds containing the tetrazepine framework remain scarce to date. Recently, [4+3] cycloadditions have been shown to be an efficient strategy to the construction of both triazepines as well as tetrazepines. Although the synthesis of 7-membered ring sultams via nucleophilic aromatic substitution is known, to the best of our knowledge, SNAr reactions have not been considered as a means to construct the tetrazepine scaffold.

![Figure 4.2 Structures of a proposed 1,2,4,5-tetrazepine (a), which was later identified as (2-aminophenyl)benzimidoyldiimide](image)

### 4.2 Tetrazepines derivatives

#### 4.2.1 Synthesis and characterization of tetrazepine derivatives

In the previous chapter we mentioned the formation of an unknown species when 1.5 equiv. of Ca(NTMS)$_2$(THF)$_2$ reacts with 2.0 equiv. of perfluorophenyl substituted formazan (R1NNC(p-tol)NNHC$_6$F$_5$ R1 = Mes/Ph (6-H)/(7-H), respectively) at room temperature. In both cases, $^1$H NMR spectroscopy studies show a pattern of signals corresponding to the Mes/Ph and p-tol groups similar to MgL$_2$ (6-Mg/7-Mg). However, the $^{19}$F NMR shows 4 inequivalent peaks in a ratio of 1:1:1:1. This suggests that one C-F bond of the C$_6$F$_4$ ring has been activated to give rise to a dissymmetric C$_6$F$_4$ ring in the product (Scheme 4.3).
Facile access to fluorinated [1,2,4,5]tetrazepine and indazole derivatives

Scheme 4.3 Synthesis of tetrazepine derivatives 4.1 and 4.2 via nucleophilic aromatic substitution from Ca(NTMS)$_2$(THF)$_2$.

Single crystal X-ray diffraction confirms the structure of 4.1/4.2 as 1,2,4,5-tetrazepine derivatives. It is likely that 4.1/4.2 are formed by nucleophilic aromatic substitution (with concomitant release of CaF$_2$), leading to a product with a central 7 membered ring that consists of the 5 atoms (NNCNN) of the formazan backbone and two C atoms of the fluorinated aromatic ring (Figure 4.3).

![Scheme 4.3](image)

**Figure 4.3** Single crystal X-ray diffraction of 4.1/4.2 showing 50% probability ellipsoids. All the hydrogen atoms are omitted for clarity.

In contrast to the Ca analogue, the compound MgL$_2$(THF) 6-MgTHF can be synthesized and is stable in solution at room temperature (Chapter 3). However, when a toluene solution of 6-MgTHF is heated to 130 °C, nucleophilic aromatic substitution takes place with release of MgF$_2$ also affording the tetrazepine 4.1 (vide supra).

In view of these results, we wondered if simple and cheap bases would lead to the formation of tetrazepine 4.1/4.2, without the need to synthesize and isolate any intermediate magnesium or calcium formazanate complexes. To elucidate this question, 1.5 equiv. of KH were added to a THF solution containing the formazan R1NNC(p-tol)NNHC$_6$F$_5$ (R1 = Mes/Ph (6-H))/(7-H), respectively). Upon stirring for two hours at room temperature, full conversion to the corresponding tetrazepine was obtained (4.1/4.2, respectively, Scheme 4.4).
Scheme 4.4 Synthesis of tetrazepine derivatives 4.1 and 4.2 via nucleophilic aromatic substitution using KH as base.

These findings contribute to a new synthetic route towards 1,2,4,5-tetrazepines. With this methodology, derivatives of tetrazepine similar to 4.1/4.2 can be synthesized in a straightforward manner by reacting N-C₆F₅ substituted formazans in the presence of a base. Full conversion and high isolated yields (75% and 99%, 4.1 and 4.2, respectively) are achieved following a simple workup by filtration. Thus, an easy entry to this class of compounds is established, which enables further exploration of their properties and biological activity.

4.2.2 Functionalization of tetrazepine derivatives

Further functionalization of tetrazepines 4.1 and 4.2 can be achieved in the presence of NaOH and MeOH in THF. In both cases, reaction at room temperature leads to clean formation of a new compound with full conversion. When tetrazepine 4.2 is used as starting material, ¹H NMR studies indicates the presence of Ph and p-tol groups in the product and two extra peaks at δ 3.71 and 3.33 ppm, with integration to 3 protons each. In addition, ¹⁹F NMR shows only two resonances with integration 1:1 (Figure 4.4). Thus, a double nucleophilic aromatic substitution takes place with the release of 2.0 equiv. of NaF and the addition of two methoxy groups onto the fluorinated aromatic ring.
A 2D $^1$H,$^{19}$F HOESY experiment allows elucidation of the structure of 4.2OMe (Figure 4.5). The fluorine with resonance at $\delta$ -136 ppm shows a through-space NOE interaction with the -OMe group at $\delta$ 3.3 ppm, and is also is coupled to the $\alpha$-Ph and (weakly) with the $m$-Ph protons. Thus, we suggest the fluorine at -136 ppm to be closest in space to the Ph group (C2-F), and therefore the -OMe group at $\delta$ 3.3 ppm to be the substituent at C3 (C3-OMe). The resonance of these protons shows a crosspeak with both fluorine signals, which suggests that the substituent at C4 is again F ($\delta$ -149 ppm). The observed through-space coupling pattern in
the HOESY NMR spectrum is consistent with alternating F and OMe substituents on the central aromatic ring as shown in Figure 4.5. Ultimately, the crystal structure of $4.2^{OMe}$ was obtained (Scheme 4.5) which shows a substitution pattern that is in agreement with the structure proposed on the basis of the NMR data.

**Figure 4.5** HOESY NMR tetrazepine $4.2^{OMe}$ (400/376 MHz, C$_6$D$_6$).

Direct synthesis of tetrazepine $4.2^{OMe}$ can be also achieved using the formazan PhNNC($p$-tol)NNHC$_6$F$_5$ (7-H) as a starting material instead of tetrazepine 4.2 in the presence of NaOH and MeOH in THF (pathway (b) and (a), respectively, Scheme 4.5). The direct synthesis requires stirring for only two hours at room temperature followed by simple purification by removal of solvent, addition of new portion of THF and filtration, leading to a 90% isolated yield of pure product.
4.3 Indazole derivatives

4.3.1 Synthesis and characterization of indazole derivatives

We next turned attention to the further chemistry of formazanate complexes containing a C₆F₅ group at the central C-atom of the ligand. Both ZnL₂ (8-Zn) and MgL₂ (8-Mg) show very similar NMR spectroscopic features in C₆D₆ solution, but dissolution in THF-d₈ reveals marked differences: while 8-Zn remains unchanged, the NMR spectra for 8-Mg indicate rapid disappearance of the starting material and clean formation of a new product 4.3. Before full conversion to 4.3 is achieved, a multitude of signals in both the ¹H and ¹⁹F NMR spectra indicate that the reaction pathway may involve several species, the nature of which is presently not known. Nevertheless, the final organic product 4.3 is obtained cleanly. Compound 4.3 shows 4 inequivalent ¹⁹F NMR resonances that integrate as 1F each, indicating that one of the C-F bonds of the C₆F₅ ring in 4.3 has been activated, similar to what was observed in 4.1 and 4.2.²¹ Nucleophilic attack of a terminal formazanate N-atom to the ortho-position of the C₆F₅ moiety forms the indazole derivative 4.3, the structure of which was confirmed by X-ray crystallography (Figure 4.6). A similar product has been reported for the intramolecular cyclization of the symmetrical formazan PhN NC(C₆F₅)NNH Ph.³⁴
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Treatment of formazan PhNNC(C₆F₅)NNHMes (8-H), with 1.5 equiv. of potassium hydride as a strong base in THF resulted in deprotonation of the ligand with subsequent base-induced nucleophilic aromatic substitution[^3][^35] to release KF and form the indazole heterocycle products 4.3 and 4.4 (Scheme 4.6). When the reaction is carried out at room temperature, products 4.3 and 4.4 were isolated as a mixture in 94% yield.[^34]

![Scheme 4.6 Synthesis of indazoles (4.3-4.4).](image)

Analysis of these products by [¹⁹F] NMR spectroscopy indicated that the 4.3 : 4.4 ratio is ca. 1.45 : 1.00. Both compounds are shown by NMR spectroscopy to contain a C₆F₅ moiety in addition to Ph and Mes groups. Thus, we assigned 4.3 and 4.4 to be regioisomeric indazole compounds that differ in the position of the Ph and Mes groups (Scheme 4.6). Separation of 4.3 and 4.4 was achieved based on their different solubility: pure 4.3 can be obtained in 51% yield by crystallization from toluene, in which 4.4 is significantly more soluble. Isolation of pure 4.4 from these reaction mixtures proved cumbersome. However, 4.4 is the major product when ZnMe₂ is used as the base: the bis(formazanate)zinc complex (8-Zn) that is formed by treatment of two equivalents of the ligand 8-H with Me₂Zn cleanly undergoes an SₐNAr reaction at 130 °C, giving 4.4 as the main product (4.3 : 4.4 = 0.04 : 1.00) in 54% yield. A more detailed analysis of the influence of the base on the products is discussed below (see section 4.3.3 Proposed mechanism).

Recrystallization of 4.3 and 4.4 afforded crystals that were suitable for X-ray diffraction analysis. The atom connectivity observed in the solid state structures (Figure 4.6) confirms the products are formed by nucleophilic attack of the NAr moiety onto the C₆F₅ ring in the

[^3]: Mark and Name
[^35]: Mark and Name
[^34]: Mark and Name
starting material. In these crystals, 4.3 and 4.4 have an E-configured N=N bond, but they differ in the orientation around the N(3)-C(7) bond (synperiplanar in 4.3, antiperiplanar in 4.4).

**Figure 4.6** Molecular structures of 4.3 (left) and 4.4 (right) showing 50% probability ellipsoids. Hydrogen atoms are omitted for clarity.

Further evidence of the identity of 4.3 and 4.4 was obtained from $^1$H-$^{19}$F correlation NMR spectroscopy (Figure 4.7). For compound 4.3, one cross peak is present in the $^1$H-$^{19}$F-HOESY NMR spectrum which corresponds to the coupling of the Ph o-H and the fluorine (F7) (in the vertical spectrum the proton at $\delta$ 7.74 ppm as a multiplet and integration of 2 protons and in the horizontal one the fluorine as a triplet at $\delta$ -153.9 ppm due to the proximity between both of them. For compound 4.4 a mesityl group is present as substituent in N1. Thus, the $^1$H-$^{19}$F-HOESY spectrum shows a coupling between the Mes o-CH$_3$ (singlet at 1.84 ppm, 6H) and the fluorine (F7, doublet at -163.3 ppm, $J_{FF} = 20$ Hz).
Figure 4.7 top: $^1$H,$^{19}$F-HOESY NMR spectrum of 4.3 (THF-d$_8$, 400 MHz); bottom: $^1$H,$^{19}$F-HOESY NMR spectrum of 4.4 with small impurities of 4.3 (C$_6$D$_{16}$, 400 MHz).

An NMR sample of the mixture 4.3 and 4.4 (in C$_6$D$_6$ solution), kept under ambient light for several days, shows formation of two new compounds. A mixture containing the 4 components was analyzed by GC/MS, which showed that all have the same mass (413.11 m/z), suggesting that a photochemical isomerization is responsible for the observed changes. In fact, 4.3 and 4.4 contain a diazo moiety in their structure which is responsible of the appearance of new isomers when exposed to ambient light. The azoindazoles 4.3 and 4.4 belong to the class of azoheteroarenes and are similar to the azoimidazoles$^{36-38}$ and azopyrroles/-pyrazoles$^{39}$ that were recently reported to be efficient photoswitches. Due to the importance of molecular photoswitches in a wide variety of applications, the photoswitching properties of the azoindazoles presented in this chapter are described in detail in Chapter 5.

4.3.2 Functionalization of indazoles

Aiming to take advantage of the susceptibility of the C$_6$F$_4$ ring toward further S$_N$Ar substitution, we treated compound 4.3 with MeOH in the presence of NaOH. Clean conversion to a single product was indicated by monitoring the reaction by $^{19}$F NMR spectroscopy: 3 new resonances appeared in a 1:1:1 ratio, suggesting replacement of one F
group by OMe (no further substitution takes place upon prolonged stirring under these conditions, Scheme 4.7).

\[
\begin{array}{c}
\text{Mes} \quad \text{Ph} \\
\text{N} \quad \text{N} \\
\text{F} \quad \text{F} \\
\text{F} \quad \text{F}
\end{array}
\xrightarrow{\text{Nu} \oplus \text{THF}}
\begin{array}{c}
\text{Mes} \quad \text{Ph} \\
\text{N} \quad \text{N} \\
\text{F} \quad \text{F} \\
\text{F} \quad \text{F}
\end{array}
\]

**Scheme 4.7** Synthesis of substituted indazoles \(4.3^{\text{OMe}}\) and \(4.3^{\text{SC8H17}}\).

On a preparative scale, the product was isolated in 80% yield. The \(^1\)H NMR spectrum shows a singlet at \(\delta 4.08\) ppm integrating to 3H, diagnostic for the presence of an OMe group. The \(^{19}\)F NMR resonances of the product appear as a triplet (\(\delta -136.8\) ppm) and two doublets (\(\delta -148.5\) and \(-158.3\) ppm) which show similar F-F coupling constants of ca. 20 Hz, in the range commonly found for either \(3J_{FF}\) (ortho) or \(5J_{FF}\) (para) coupling constants in fluoroaromatics.\(^{40}\) Similar to the starting material \(4.3\), compound \(4.3^{\text{OMe}}\) shows H-F coupling between the Ph \(\sigma\)-H group and a F substituent, suggesting that nucleophilic aromatic substitution does not take place at the site adjacent to the NPh group (the indazole 7-position). Homo- and heteronuclear (\(^1\)H,\(^{19}\)F) 2D NOE NMR experiments were used to unequivocally establish that \(4.3^{\text{OMe}}\) contains the OMe substituent on position C6 of the indazole (Figures 4.8 and 4.9). Similarly, the S-nucleophile \(n\)-octylthiolate reacted smoothly to give compound \(4.3^{\text{SC8H17}}\), but attempts to obtain addition of N-nucleophiles (NMR scale reactions of \(4.3\) with deprotonated pyrrolidine or benzylamine in THF-\(d_8\)) did not result in clean substitution.\(^{41}\)
Homo- and heteronuclear (1H,19F) 2D NOE NMR experiments were used to unequivocally establish that 4.3OMe contains the OMe substituent on position C6 of the indazole. HOESY NMR reveals three H-F couplings: the first cross peak derived from the coupling between the Mes o-Me at δ 2.53 ppm and the fluorine which appears at δ -134.3 ppm as a triplet (Figure 4.8). Another coupling corresponds to the proton at δ 4.11 ppm assigned to OMe and the fluorine at δ -134.3 ppm, which appears as a doublet and the remaining coupling is due to the interaction between Ph o-H (δ 7.67 ppm) and the fluorine at δ -147.7 ppm with a doublet multiplicity. Therefore, the fluorine at δ -134.3 ppm and δ -147.7 ppm were assigned to positions C4 and C7, which are the closest to the Mes and Ph, respectively. Thus, the remaining fluorine could be at C5 or C6 position. However, a 19F,19F-NOESY experiment shows coupling through space of the remaining fluorine only with the one in position C4 (triplet, δ -134.3 ppm) and not with the one in position C7 (doublet, δ -147.7 ppm, Figure 4.9). Thus, we suggest the structure in Scheme 4.7, which is also consistent with the multiplicity of each fluorine: triplet at δ -134.3 ppm due to ortho and para coupling with F-C5 and F-C7 (J_FF ≈ J_FF ≈ 20 Hz), respectively and the two remaining fluorines have only one fluorine in ortho and none in para-position, consequently each signal appears as a doublet.
4.3.3 Proposed mechanism

As we mentioned in section 4.3.1, a mixture of 8-H and KH in solution rapidly leads to the formation of 4.3 : 4.4 at room temperature in a ratio of 1.45 : 1.00, respectively (R1 = Ph, R5 = Mes, R3 = C6F5). Although 8-Zn at room temperature is stable (vide supra), at 130 °C it also undergoes S\textsubscript{N}Ar cyclization, giving the same products 4.3 : 4.4 but in a different ratio (0.05 : 1.00). In this section, we discuss a proposed mechanism to account for the differences between these two cases.

In order to conduct a kinetic study we switched from insoluble KH to the soluble base KN(SiMe\textsubscript{3})\textsubscript{2} to ensure a homogeneous solution in THF. Rapid deprotonation of the formazan 8-H occurs even at temperatures as low as -50 °C, leading to the formation of the corresponding potassium formazanate 8-K (K[PhNN(C6F5)NNMes]), which is stable overnight at -30 °C. However, upon increasing the temperature to 10 °C or above, S\textsubscript{N}Ar takes place to generate the two isomers 4.3 and 4.4.

The disappearance of the starting material 8-K was monitored by \textsuperscript{19}F NMR spectroscopy in THF (see section 4.6.4.1 for more details). Eyring analysis gave activation parameters of $\Delta H^\ddagger = 85 \pm 1$ kJ.mol\textsuperscript{-1}, $\Delta S^\ddagger = -32 \pm 3$ J.mol\textsuperscript{-1}.K\textsuperscript{-1} which result in $\Delta G^\ddagger_{298} = 95$ kJ.mol\textsuperscript{-1}.

As we described in Chapter 2, due to the high flexibility of the formazanate framework, formazanate salts show various coordination modes through N1/N5, N1/N3 or N2/N3.
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(Scheme 2.1). Unfortunately, attempts to crystallize 8-K were not successful, therefore the formazanate binding mode in 8-K is unknown. If its coordination would be through N2, N3 (similar to 1-K or 2-Na), then the two terminal nitrogens (N1, N4) would be equally accessible to act as a nucleophile. The negative activation entropy ($\Delta S^\ddagger = -32 \pm 3 \text{ J.mol}^{-1}\text{K}^{-1}$) is consistent with an ordered transition state, as anticipated for nucleophilic attack of the N-nucleophile to make a new N-C(Ar) bond. However, due to the steric hindrance, the attack of the nitrogen containing the mesityl substituent will likely require a somewhat higher barrier. Thus, the rate of nucleophilic attack from the N-Ph group is expected to be slightly higher than from the N-Mes, leading to the preferential formation of isomer 4.3 (N-Ph) as is observed experimentally (4.3 : 4.4 ratio of 1.45 : 1.00 at room temperature (Figure 4.10).

Figure 4.10 Proposed energetic profile through 8-K ionic pathway.

Previous studies have also demonstrated the backbone flexibility of formazanate through studies on bis(formazanate)zinc compounds, which can exist in equilibrium between 6- and 5-membered chelate ring complexes. Most of the previously reported bis(formazanate)zinc compounds Zn[R1NN(R3)NNR5]2 show only one set of signals, which indicates the presence of only one isomer in solution with the more enthalpically favoured 6-membered chelate ring over the 5-membered chelate ring. However, 6-Zn (R1 = Mes, R5 = C6F5, R3 = p-tol) shows in the solid state an asymmetric coordination, with one of the formazanate ligands bound by the two terminal nitrogens N1/N4 leading to 6-membered chelate ring, and the other
formazanate is bound through one terminal (N1) and one internal (N3) nitrogen, resulting in a 5-membered chelate ring. In addition to this (6-5) isomer, NMR studies in solution suggest that two additional isomers are present (the 6-6- and the 5-5-membered chelate ring).42

8-Zn complex is stable in solution at room temperature and NMR reveals only the presence of a single, 6-membered chelate ring isomer at temperatures up to 130 °C, at which S
Ar takes place leading to the formation of 4.3 and 4.4 in a ratio 0.05 : 1.00, respectively. Kinetic studies were performed temperatures between 125 and 170 °C by monitoring the appearance of the major product 4.4 by 19F NMR spectroscopy in toluene (see section 4.6.4.2 for more details). Eyring analysis gave activation parameters of ΔH‡ = 118 ± 1 kJ.mol⁻¹, ΔS‡ = -36 ± 2 J.mol⁻¹.K⁻¹ which result in ΔG²⁹⁸⁺ = 129 kJ.mol⁻¹.

Several mechanistic scenarios can be envisioned for the observed cyclization of the formazanate ligand in 8-Zn. Regardless of the precise pathway, dissociation of one of the terminal N-Ar groups of the formazanate ligand from the Zn center is involved, likely via formation of a 5-membered formazanate chelate ring as observed for 6-Zn. If conversion from a 6- to a 5-membered chelate ring would be rate-determining, a positive activation entropy is expected due to the larger conformational flexibility upon going to the latter. The experimental value for the ‘decomposition’ of 8-Zn to 4.4 is negative (ΔS‡ = -36 ± 2 J.mol⁻¹.K⁻¹), which suggests that the rate-determining step is not just dissociation of the terminal N-Ar group. Nevertheless, this dissociation needs to occur somewhere along the reaction coordinate as otherwise the cyclization reaction cannot take place. Therefore, both a concerted mechanism (simultaneous dissociation/nucleophilic attack) as well as a stepwise process in which N-Ar dissociation does not present the highest barrier, remain viable options. Due to the similarity of the activation entropy between the cyclization of 8-K and 8-Zn, and the observation that the most sterically hindered product (4.4) is obtained preferentially from 8-Zn (but not 8-K), we favor the latter pathway as discussed below.

Based on the thermodynamics for the equilibria between 6- and 5-membered chelate rings in the bis(formazanate) zinc complex 6-Zn,42 it seems likely that also in 8-Zn the 6-membered chelate ring has a favorable enthalpy, while the 5-membered ring is entropically favored. The different steric profile of both N-Ar groups (Ar = Ph, Mes) leads to a different stability of the two possible intermediates (8a-Zn and 8b-Zn, see Figure 4.11), with the N-Mes dissociation product 8a-Zn preferred due to reduced steric strain. Although we do not observe 8a/b-Zn at any temperature, i.e., both are significantly higher in energy than 8-Zn, their equilibrium
population will be different. If the barrier height to subsequent nucleophilic aromatic substitution is similar for both (as is observed for 8-K), then the product distribution $4.3 : 4.4$ will depend on the relative stability of $8a/b-Zb$, and favor formation of $4.4$ (Figure 4.11). More extensive studies are necessary to unequivocally explain the difference in cyclization chemistry of formazanate 8 when bound to K or Zn. For example, it would be interesting to evaluate the reactivity of formazanate salts with other metals, or containing non-coordinating organic cations such as NBu$. Nevertheless, the interpretation outlined above is consistent with the experimental observations made so far.

![Proposed mechanism through 8-Zn covalent pathway: reaction mechanism (top) and energetic profile (bottom).](image)

After the first SNAr in one of the formazanate ligands present in 8-Zn, one arylazoindazole is formed leaving a mono(formazanate)ZnF complex. Since both formazanate ligands ultimately form arylazoindazole products, the remaining ligand should also undergo cyclization. This could occur by two different pathways: (a) direct SNAr of the second formazanate in LZnF, leading to another equivalent of arylazoindazole and ZnF$_2$ or (b) establishing a Schlenk
equilibrium to regenerate $8\text{-Zn}$ and form ZnF$_2$. However, in the absence of any observable species other than $8\text{-Zn}$ and the final azoindazole products, it is not possible to probe this in detail.

4.4 Cyclic voltammetry studies

4.4.1 Tetrazepine derivatives

To study the redox properties of compounds 4.1 and 4.2 cyclic voltammetry studies were recorded in THF with [Bu$_4$N][PF$_6$] as electrolyte using ferrocene as internal reference.

Tetrazepine 4.1 shows two quasi-reversible redox couples at -1.42 V and -2.25 V versus Fe$^{0/+}$ (shown as I/I’ and II/II’ respectively in Figure 4.12). Scanning in a reductive direction leads to the first reduction peak I’ corresponding to a one-electron process to generate the radical anion in which the unpaired electron is assumed to be delocalized over the four nitrogens similarly to verdazyl radicals (vide supra). A more negative potential (-2.25 V versus Fe$^{0/+}$) is required to introduce a second electron in the system (II in Figure 4.12). Scanning back in an oxidative direction, the monoradical (II’) is generated in a quasi-reversible manner and consecutively the neutral tetrazepine (I’) is formed. Two small irreversible oxidation peaks (*) are present at -0.54 V and 0.00 V (vs Fe$^{0/+}$). Although their nature is unknown at the moment, their formation is related to the redox couple II/II’ due to their disappearance when only the first redox couple is swept (inset in Figure 4.12).
Similarly, cyclic voltammetry studies of tetrazepine 4.2 were performed. In this case, we can also observe two quasi-reversible redox couples, but in both cases at less negative reduction potential than for tetrazepine 4.1 (-1.34 V and -2.14 V versus Fe$^{0/+}$, shown as I/I’ and II/II’ respectively in Figure 4.13).

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**Figure 4.12** Cyclic voltammogram of compound 4.1 (1.7 mM solution of tetrazepine in THF, 0.1 M [Bu$_4$N][PF$_6$] electrolyte, scan rate 500 mV.s$^{-1}$). Inset: scanning only from -0.5 to -2.0 V under the same conditions.

**Figure 4.13** Cyclic voltammogram of compound 4.2 (0.7 mM solution of tetrazepine in THF, 0.1 M [Bu$_4$N][PF$_6$] electrolyte, scan rate 500 mV. s$^{-1}$).
4.4.2 Indazole derivatives

Similar to tetrazepine 4.1 and 4.2, indazole 4.3 can be reduced to form a relatively stable radical anion. However, only one quasi-reversible redox couple is present, which occurs at more negative potential than for both tetrazepines (-1.84 V versus Fe\(^{0+}\), shown as I/I' Figure 4.14).

For azoindazole 4.3, scanning to more negative potential leads to a complex voltammogram due to a second, irreversible reduction that is observed at a peak potential of around -2.7 V (vs. Fe\(^{0+}\)), which lead to additional oxidation peaks. All the peaks present in the voltammogram has an irreversible character.

![Cyclic voltammogram of compound 4.3](image)

Figure 4.14 Cyclic voltammogram of compound 4.3 (1.5 mM solution of tetrazepine in THF, 0.1 M [Bu₄N][PF₆] electrolyte, scan rate 10 mV.s⁻¹)

4.5 Conclusions

In this chapter, a straightforward synthesis of tetrazepines and arylazoindazoles by Nucleophilic Aromatic Substitution has been presented, leading to these products in moderate to good isolated yields. All the compounds have been characterized and the redox properties of few complexes have been explored.

In the particular case of the arylazoindazoles 4.3, 4.4, 4.3\(^{\text{OMe}}\) and 4.3\(^{\text{SC\text{H}17}}\), this synthetic route results in formation of azoheteroarene which would be difficult to synthesize by other synthetic procedures described previously in literature.\cite{12,19} The presence of the ‘azo’ group
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leads to photoactive species. The photochemistry of these compounds will be discussed in chapter 5.

4.6 Experimental

4.6.1 General considerations

The syntheses involving air-sensitive chemicals (KH, Me₂Zn) were carried out under nitrogen atmosphere using standard glovebox, Schlenk, and vacuum-line techniques. Toluene (Aldrich, anhydrous, 99.8%) was passed over columns of Al₂O₃ (Fluka), BASF R3-11-supported Cu oxygen scavenger, and molecular sieves (Aldrich, 4 Å). THF (Aldrich, anhydrous, 99.8%) was dried by percolation over columns of Al₂O₃ (Fluka). These solvents were degassed prior to use and stored under nitrogen. C₆D₆ (Aldrich) was vacuum transferred from Na/K alloy and stored under nitrogen. DMSO-d₆ (Aldrich) and THF-d₈ (Euriso-top) were used without further purification. Solvents for UV/Vis spectroscopy were used as received. Potassium hydride (Sigma-Aldrich, 30 wt% in mineral oil) was washed with hexane several times to remove the oil, and then dried in vacuo to give a powder, which was stored in the glovebox. Dimethylzinc (Acros, 1.2 M solution in toluene) was used as received. The compound PhNNC(C₆F₅)NNHMes was synthesized according to the published procedure. 43 Routine NMR spectra were recorded on Varian Gemini 400 or Varian Inova 500 spectrometers. ²⁹F,²⁹F-COSY and ²⁹F,²⁹F-NOESY NMR spectra were recorded on Agilent 400MR or Varian Inova 500 spectrometers. For the ²⁹F,²⁹F-NOESY experiments, long mixing times (2 s) were used to avoid spurious correlations due to zero-quantum artifacts. ¹H,²⁹F-HOESY NMR spectra were recorded on an Agilent 400MR spectrometer (with one NMR probe) or a Varian 400 MHz VNMR system (with an Auto Switchable (ASW) probe, with tuning optimized for both ¹H and ²⁹F). The standard ¹H,²⁹F-HOESY experiment present in the VNMRJ software was applied, using ²⁹F detection. The ¹H and ¹³C NMR spectra were referenced internally using the residual solvent resonances and reported in ppm relative to TMS (0 ppm); J is reported in Hz. Photostationary states were determined by using NMR spectroscopy (Varian Inova 500). Samples were irradiated inside the NMR spectrometer using an optical fiber cable inside of the NMR tube, which was connected to 365 nm and 420 nm LEDs for photoconversion from E→Z and Z→E, respectively. Elemental analyses were performed at the Microanalytical Department of the University of Groningen. UV/Vis absorption spectra were measured on an Analytik Jena Specord S600 diode array or a Hewlett-Packard 8453
spectrometer in a 1 cm quartz cuvette. Kinetics of thermal $Z \rightarrow E$ isomerization are measured and analyzed as described in more detail below (section ‘thermal isomerization kinetics’).

### 4.6.2 Tetrazepine derivatives

**Tetrazepine 4.1**

Treatment of 1 equiv. of formazan MesNNC($p$-tol)NNHC$_6$F$_5$ (6-H) (127.2 mg, 0.28 mmol) prepared as previously reported$^{42}$ with 1.6 equiv. of potassium hydride (18.3 mg, 0.46 mmol) as a strong base in THF at room temperature under nitrogen atmosphere resulted in deprotonation of the ligand 6-H with H$_2$ gas evolution. Subsequently, nucleophilic aromatic substitution takes place with the releasing of KF with full conversion towards the desired product 4.1. This could be separated together with the excess of KH from the organic product by removal of the solvent, and extraction into toluene to give a brown solution. Black crystals of 4.1 were obtained by slow evaporation of a pentane solution. $^1$H NMR (C$_6$D$_6$, 25 ºC, 500 MHz): δ 7.99 (d, 2H, $p$-tol o-H), 6.90 (d, 2H, $p$-tol m-H), 6.76 (s, 2H, Mes m-H), 2.46 (s, 6H, Mes o-CH$_3$), 2.10 (s, 3H, Mes p-CH$_3$), 1.97 (s, 3H, $p$-tol CH$_3$). $^{19}$F NMR (376 MHz, C$_6$D$_6$, 25 ºC): δ −145.27 (dt, 1F, $J = 23.1$, 6.8, C$_6$F$_4$), −151.48 (m, 2F, C$_6$F$_4$), −160.88 (m, 1F, C$_6$F$_4$). $^{13}$C NMR (C$_6$D$_6$, 25 ºC, 126 MHz): δ 162.87 (p-tol, ipso-C), 144.02 (d, $J = 256.3$, C$_6$F$_4$), 143.63 (d, $J = 243.9$, C$_6$F$_4$), 142.38 (p-tol p-C), 139.01 (d, $J = 268.4$, C$_6$F$_4$), 138.29 (d, $J = 259.6$, C$_6$F$_4$), 139.08 (Mes ipso-C), 137.01 (Mes p-C), 135.39 (Mes o-C), 134.04 (C$_6$F$_4$ ipso-C), 132.95 (C$_6$F$_4$ ipso-C), 130.17 (Mes m-CH), 129.81 (p-tol m-CH), 127.68 (p-tol o-CH), 21.40 (p-tol CH$_3$), 20.94 (Mes p-CH$_3$), 19.75 (Mes o-CH$_3$). Anal. calcd. for C$_{23}$H$_{18}$F$_4$N$_4$: C 64.78, H 4.25, N 13.14; found: C 60.74, H 4.84, N 10.85. DART-MS = 427.10

**Tetrazepine 4.2**

Treatment of 1 equiv. of formazan PhNNC($p$-tol)NNHC$_6$F$_5$ (7-H) (314.8 mg, 0.78 mmol) prepared as previously reported$^{42}$ with 1.5 equiv. of potassium hydride (46.8 mg, 1.17 mmol) as a strong base in THF at room temperature under nitrogen atmosphere resulted in deprotonation of the ligand 7-H with H$_2$ gas evolution followed by nucleophilic aromatic substitution and subsequent release of KF. This could be separated together with the excess of KH by removal of the solvent, addition of toluene and filtration of
the brown solution, yielding to the desired product 4.2 in 69% yield (206.1 mg, 0.54 mmol). Black crystals of 4.2 were obtained by slow evaporation of a pentane solution. $^1$H NMR (C$_6$D$_6$, 25 °C, 500 MHz): δ 8.03 (d, 2H, J = 8.2, p-tol o-H), 7.26 (d, 2H, J = 7.8, Ph o-H), 7.15 (t, 2H, J = 7.8, Ph m-H), 6.93 (t, 1H, J = 7.2, Ph p-H), 6.90 (d, 2H, J = 7.8, p-tol m-H), 1.96 (s, 3H, p-tol CH$_3$). $^{19}$F NMR (376 MHz, C$_6$D$_6$, 25 °C): δ −139.81 (dd, 1F, C 6F$_4$), −146.44 (m, 1F, C 6F$_4$), −150.92 (td, 1F, C 6F$_4$), −157.57 (m, 1F, C 6F$_4$). $^{13}$C NMR (C$_6$D$_6$, 25 °C, 126 MHz): δ 163.60 (p-tol, ipso-C), 145.01 (d, J = 2.5, Ph ipso-C), 143.38 (m, J = 257.5, C$_6$F$_4$), 143.16 (p-tol p-C), 142.89 (m, J = 257.5, C$_6$F$_4$), 140.32 (m, J = 259.3, C$_6$F$_4$), 139.60 (m, J = 255.0, C$_6$F$_4$), 134.16 (C$_6$F$_4$ ipso-C), 134.12 (C$_6$F$_4$ ipso-C), 129.96 (p-tol m-CH), 129.31 (Ph m-CH), 128.21 (p-tol o-CH), 123.47 (Ph p-CH), 115.75 (Ph o-CH), 67.84 (THF), 21.42 (p-tol CH$_3$). Anal. calcd. for C$_{20}$H$_{12}$F$_4$N$_4$: C 62.50, H 3.15, N 14.58; found: C 62.60, H 3.40, N 14.09.

**Tetrazepine 4.1OMe**

Treatment of 1 equiv. of formazan MesNNC(p-tol)NNHC$_6$F$_5$ (6-H) (100.0 mg, 0.22 mmol) prepared as previously reported$^{42}$ with an excess of NaOH pellets (36.0 mg, 0.90 mmol) in MeOH. Due to the low solubility of the ligand 6-H in MeOH, the solution was stirred at room temperature overnight. Removal of the solvent, addition of toluene and filtration through a 0.2 μm filter followed by removal of the solvent allows isolation of 4.1OMe. $^1$H NMR (C$_6$D$_6$, 25 °C, 500 MHz): δ 8.06 (d, 2H, J = 7.7, p-tol o-H), 6.91 (d, 2H, J = 8.0, p-tol m-H), 6.79 (s, 2H, Mes m-H), 3.65 (s br, 3H, OMe), 3.29 (s br, 3H, OMe), 2.57 (s, 6H, Mes o-CH$_3$), 2.12 (s, 3H, Mes p-CH$_3$), 1.98 (s, 3H, p-tol CH$_3$). $^{19}$F NMR (376 MHz, C$_6$D$_6$, 25 °C): δ −147.68 (s, 1F, C$_6$F$_2$), −151.31 (s, 1F, C$_6$F$_2$). DART-MS = 451.14

**Tetrazepine 4.2OMe**

Treatment of 1 equiv. of formazan PhNNC(p-tol)NNHC$_6$F$_5$ (7-H) (882.0 mg, 2.18 mmol) prepared as previously reported$^{42}$ with a large excess of NaOH pellets (700.0 mg, 17.50 mmol) in MeOH. Due to the low solubility of the ligand 7-H in MeOH, the solution was stirred at room temperature overnight. Removal of the solvent, addition of toluene and filtration through a 0.2 μm filter lead to the desired product 4.2OMe in 90% yield (800.1 mg, 1.96 mmol). Black crystals suitable for X-ray characterization were obtained.
by slow diffusion of pentane into a solution of 4.2 in toluene. 1H NMR (C6D6, 25 °C, 400 MHz): δ 8.07 (d, 2H, \( J = 7.9 \), p-tol o-H), 7.34 (d, 2H, \( J = 7.9 \), Ph o-H), 7.16 (t, 2H, \( J = 7.9 \), Ph m-H), 6.92 (t, 1H, Ph p-H), 6.90 (d, 2H, p-tol m-H), 3.71 (d, 3H, \( J = 1.0 \), 5-OMe), 3.33 (br, 3H, 3-OMe), 1.96 (s, 3H, p-tol CH3). 19F NMR (376 MHz, C 6D6, 25 °C): δ −135.79 (m, 1F, C2F), −148.29 (m, 1F, C4F). 13C NMR (C 6D6, 25 ºC, 126 MHz): δ 163.80 (p-tol, ipso-C), 147.82 (dd, \( J = 250.0, 4.7 \), CC2F2C2(OMe)2), 145.92 (d, \( J = 2.7 \), Ph ipso-C), 143.82 (dd, \( J = 256.3, 4.2 \), C6F2(OMe)2), 142.51 (p-tol p-C), 141.38 (dd, \( J = 11.7, 3.3, 5-\)COMe), 140.17 (t, \( J = 12.8 \), 3-\)COMe), 138.42 (C 6F4 ipso-C), 129.80 (p-tol o-CH), 129.21 (Ph m-CH), 128.54, 128.52, 128.21 (p-tol m-CH), 122.43 (Ph p-CH), 115.35 (d, \( J = 1.9 \), Ph o-CH), 62.40 (d, \( J = 3.6 \), 3-OMe), 61.52 (t, \( J = 3.9 \), 5-OMe), 21.39 (p-tol CH3). Anal. calcd. for C 22H18F2N4O2: C 64.70, H 4.44, N 13.72; found: C 64.55, H 4.49, N 13.31.

### 4.6.3 Indazole derivatives

#### Azoindazole 4.3

Treatment of formazan PhNNC(C6F5)NNHMes44 (8-H) (157.9 mg, 0.37 mmol) with 1.5 equiv. of potassium hydride (22.0 mg, 0.55 mmol) as a strong base in THF at room temperature resulted the color to fade from dark to light orange. After stirring at room temperature for 4 h, the solvent was removed \( \text{in vacuo} \) and a new portion of THF was added. The solution was filtered through a 0.2 micron syringe filter. Subsequent removal of all volatiles gave 142.1 mg of an orange solid, which was shown by NMR analysis to be a 1.45:1 mixture of compounds 4.3 and 4.4 (0.34 mmol, 94% yield). Anal. calcd. for C22H16F4N4: C 64.08, H 3.91, N 13.59; found: C 64.42, H 4.11, N 13.32. A single recrystallization of the mixture of 4.3 and 4.4 from toluene by cooling to -70 °C afforded pure compound 4.3 (51% isolated yield based on starting material 8-H). 1H NMR (C6D6, 25 °C, 500 MHz): δ 7.41 (m, 2H, Ph o-H), 7.10 (t, 2H, \( J = 7.4 \), Ph m-H), 7.03 (1H, \( J = 7.4 \), Ph p-H), 6.80 (s, 2H, Mes m-H), 2.72 (s, 6H, Mes o-CH3), 2.09 (s, 3H, Mes p-CH3). 19F NMR (C6D6, 25 °C, 470 MHz): δ −133.3 (td, 1F, \( J = 20.8 \), C6F4), −152.7 (t, 1F, \( J = 19.2 \), C6F4), −156.2 (t, 1F, \( J = 19.4 \), C6F4), -162.6 (t, 2F, \( J = 21.7, C6F4 \). 13C NMR (C6D6, 25 °C, 126 MHz): 157.10 (NNCNN), 149.16 (d, Mes ipso-C), 140.69 (Mes p-C), 139.68 (d, \( J = 253, C6F4 \), 140.69 (Mes p-C), 139.56 (Ph ipso-C), 137.09 (d, \( J = 244, C6F4 \), 134.12 (Mes o-C), 132.91 (d, \( J = 251, C6F4 \), 130.97 (Mes m-C), 129.09 (Ph m-CH), 128.66 (Ph p-CH), 126.61 (d, Cα), 125.09 (d, \( J_{CF} = 2.9 \), Ph o-CH), 104.89 (Cβ), 21.19 (Mes p-
CH₃), 20.66 (Mes o-CH₃). * long-range C-F coupling within the C₆F₄ ring (ca. 8 – 20 Hz) and smaller C-F coupling (< 5 Hz) in some of the Mes and Ph resonances is observed but not reported.

**Azoindazole 4.4**

To a solution of 208.3 mg of formazan PhNNC(C₆F₅)NNHMes⁴⁴ (8-H) (0.47 mmol) in 15 mL of toluene was added 1.2 equiv. of ZnMe₂ (232 μl of a 1.2 M solution in toluene, 0.28 mmol). The mixture was heated to 80 °C and stirred at that temperature for 40 h to form the bis(formazanate)zinc complex (8-Zn). After removal of the volatiles under vacuum, a new portion of toluene (15 mL) was added and the solution was heated to 130 °C over the course of 66 h. The solvent was evaporated and the resulting powder was analyzed by NMR, showing that it consist of a mixture of 4.3 and 4.4 in a 1.0:0.1 ratio. Further purification was attempted by silica column chromatography using toluene:hexane in a ratio 1:2 as eluent. Unfortunately, the two compounds co-eluted and no further separation of 4.3 and 4.4 could be achieved. Drying the product afforded 103 mg of orange powder (0.25 mmol, 54%). ¹H NMR (C₆D₆, 25 °C, 500 MHz): δ 8.18 (d, 2H, J = 7.8 Hz, Ph o-H), 7.15 (t, 2H, Ph m-H), 7.08 (t, 1H, J = 7.3 Hz, Ph p-H), 6.68 (s, 2H, Mes m-H), 2.06 (s, 3H, Mes p-CH₃), 1.84 (s, 6H, Mes o-CH₃). ¹⁹F NMR (C₆D₆, 25 °C, 376 MHz): δ −130.0 (m, 1F, C₆F₄), −155.7 (td, 1F, J = 20.0 Hz, 2.9 Hz, C₆F₄), −161.1 (m, 1F, C₆F₄), −163.3 (td, 1F, J = 19.5 Hz, 2.0 Hz, C₆F₄). ¹³C NMR* (C₆D₆, 25 °C, 126 MHz): 157.31 (NNCNN), 153.44 (Ph ipso-C), 140.60 (d, J = 252.3 Hz, C₆F₄), 140.12 (Mes p-C), 139.9 (d, J = 260.0 Hz, C₆F₄), 137.38 (d, J = 247.0 Hz, C₆F₄), 136.31 (Mes o-C), 135.48 (Mes ipso-C), 132.82 (d, J = 252.3 Hz, C₆F₄), 132.18 (Ph p-CH), 129.54 (Ph m-CH), 129.37 (Mes m-CH), 128.54 (d, C₆F₄), 123.60 (Ph o-CH), 103.28 (C₆F₄), 21.09 (Mes p-CH₃), 17.30 (Mes o-CH₃). * long-range C-F coupling within the C₆F₄ ring (ca. 8 – 20 Hz) and smaller C-F coupling (< 5 Hz) in some of the Mes and Ph resonances is observed but not reported.
**Azoindazole 4.3OMe**

To a solution of 25.8 mg of 4.3 (0.0626 mmol) in 0.5 mL of THF was added 12.5 mg NaOH (0.313 mmol, 5 equiv.), which was previously dissolved in 0.5 mL of MeOH. This resulted in an orange suspension, to which more THF was added until a homogeneous solution was obtained (ca. 4 mL). After stirring at room temperature overnight, the volatiles were removed on the rotavap and the resulting solid extracted into Et₂O (2 x 3 mL). Attempts to recrystallize the product were unsuccessful; a light orange powder was invariably obtained. The product was finally isolated by cooling a hot MeOH solution to -30 °C, which gave 21.3 mg (0.0502 mmol, 80%) of 4.3OMe. HRMS (ESI) calcd. for C₂₃H₂₀F₃N₄O [M+H+] 425.15837, found 425.15849. ¹H NMR (CDCl₃, 25 °C, 500 MHz): δ 7.67 (d, J = 7.3, 2H, Ph o-H), 7.54 (t, J = 7.3, 2H, Ph p-H), 7.48 (d, J = 7.3, 1H, Ph m-H), 6.98 (s, 2H, Mes m-H), 4.11 (s, 3H, OMe), 2.53 (s, 6H, Mes o-Me), 2.35 (s, 3H, Mes p-Me). ¹⁹F NMR (CDCl₃, 25 °C, 470 MHz): δ -134.3 (t, J = 20, 1F, 4-F), -147.7 (d, J = 19.3, 1F, 7-F), -156.0 (d, J = 21.2, 1F, 5-F). ¹³C NMR* (CDCl₃, 25 °C, 100 MHz): δ 156.9 (NNCNN), 148.9 (Mes ipso-C), 140.9 (d, J = 246, C₆F₃), 140.2 (Mes p-C), 139.5 (d, J = 256, C₆F₃), 139.5 (Ph ipso-C), 137.8 (C-OMe), 133.4 (Mes o-C), 130.4 (Mes CH), 129.0 (Ph m-CH), 127.3 (Ph o-CH), 103.7 (C₆), 62.6 (OMe), 21.4 (Mes p-Me), 20.1 (Mes o-Me). *long-range C-F coupling within the C₆F₄ ring (ca. 8 – 20 Hz) and smaller C-F coupling (< 5 Hz) in some of the Mes and Ph resonances is observed but not reported.

**Azoindazole 4.3SC₈H₁₇**

To a solution of 16.2 mg of 4.3 (0.0393 mmol) in 0.4 mL of THF-d₈ was added 7.2 mg C₈H₁₇SK (0.0393 mmol), which was previously suspended in 0.2 mL of THF-d₈. This resulted in an orange solution (with some white precipitate, presumably KF). The mixture was analyzed after 30 minutes by ¹H and ¹⁹F NMR, which showed > 90% conversion of the starting materials and formation of the desired compound 4.3SC₈H₁₇. After standing at room temperature overnight, the volatiles were removed on the rotavap and the resulting solid extracted into Et₂O (2 x 3 mL). Removal of the volatiles gave 21.1 mg (0.0392 mmol, 99%).
of 4.3SC8H17 as a somewhat sticky orange powder that was > 90% pure based on NMR spectroscopy. HRMS (ESI) calcd. for C30H34F3N4S [M+H+] 539.24508, found 539.24374. 1H NMR (CDCl3, 25 °C, 500 MHz): δ 7.66 (br d, J = 7.2, 2H, Ph o-H), 7.55 (t, J = 7.3, 2H, Ph m-H), 7.49 (t, J = 7.3, 1H, Ph p-H), 6.98 (s, 2H, Mes m-H), 2.95 (t, J = 7.2, 2H, SCH₂), 2.53 (s, 6H, Mes o-Me), 2.35 (s, 3H, Mes p-Me), 1.65-0.8 (C8H17S). 19F NMR (CDCl3, 25 °C, 470 MHz): δ -120.1 (d, J = 21.4, 1F, 7-F), -135.1 (t, J = 22.1, 1F, 4-F), -136.1 (d, J = 22.8, 1F, 5-F). 13C NMR (CDCl3, 25 °C, 100 MHz): δ 156.8 (NCCCN), 148.9 (Mes ipso-C), 145.6 (d, J = 241, C6F3), 143.2 (d, J = 247, C6F3), 140.3 (Mes p-C), 139.5 (Ph ipso-C), 139.1 (d, J = 255, C6F3), 133.5 (Mes o-C), 130.4 (Mes CH), 129.1 (Ph m-CH), 128.9 (Ph p-CH), 127.9 (C₂A)**, 125.7 (Ph o-CH), 113.5 (C-SOct), 108.9 (C₆), 35.1 (SCH₂), 31.9 (octyl), 30.3 (octyl), 29.2 (octyl), 29.1 (octyl), 28.6 (octyl), 22.8 (octyl), 21.4 (Mes p-Me), 20.2 (Mes o-Me), 14.2 (octyl-Me).* long-range C-F coupling within the C₆F₄ ring (ca. 8 – 20 Hz) and smaller C-F coupling (< 5 Hz) in some of the Mes and Ph resonances is observed but not reported. ** This signal is of low intensity and overlaps with an impurity, and as a consequence its assignment is somewhat ambiguous.

4.6.4 Kinetic studies

4.6.4.1 Cyclization of 8-K

The disappearance of the starting material was monitored by 19F NMR spectroscopy in THF. An acquisition array was used in which a pre-acquisition delay was programmed to obtain spectra at regular time intervals. Measurements were run at 8.1, 18.3, 28.4, 38.3, 48.4 and 58.4 °C. The regions for integration were determined by inspection of representative spectra across the time course of the experiment. The arrays of spectra were subsequently integrated automatically using a script; phase and baseline corrections were applied to each spectrum and the integrals written to a text file, which was then imported into Mathematica. For all three 19F NMR resonances of the starting material, the integration was determined relative to an internal standard (C₆H₅F) to give three separate kinetic traces. Non-linear fitting to an exponential function was performed to extract the first-order rate constants at each temperature. This analysis was performed for each of the three individual 19F NMR resonances to obtain an indication of the (random) error in the signal integration. The mean and standard deviation of these three data points were used for the subsequent Eyring
analysis. A linear fit resulted in the activation parameters as \( \Delta H^{\ddagger} = 85.2 \pm 0.8 \text{ kJ.mol}^{-1} \) and \( \Delta S^{\ddagger} = -32 \pm 3 \text{ J.mol}^{-1}.\text{K}^{-1} \).

Representative kinetic traces and the resulting Eyring plot are shown in Figure 4.15.

![Eyring plot](image)

**Figure 4.15** Left: representative kinetic traces (based on \(^{19}\text{F} \) NMR integration vs. an internal standard). Right: Eyring plot for the cyclization kinetics of 8-K in THF, with error bars shown as \( 5\sigma(\text{Ln}(k)) \). (Best fit: \( y = 19.8913 - 10242.9 \times \); \( \Delta H^{\ddagger} = 85.2 \pm 0.8 \text{ kJ.mol}^{-1} \) and \( \Delta S^{\ddagger} = -32 \pm 3 \text{ J.mol}^{-1}.\text{K}^{-1} \)).

### 4.6.4.2 Cyclization of 8-Zn

8-Zn was prepared following the procedure reported in the literature in ca. 95% purity according to \(^{19}\text{F} \) NMR spectroscopy. A 10 mg/mL stock solution was prepared in Bu2O, which was freshly distilled from Na/K. NMR samples were heated in an oil bath and reaction progress was monitored at regular intervals by \(^{19}\text{F} \) NMR spectroscopy. One of the resonances of the product was well-separated from the rest, and used for integration versus an internal standard (2-fluorobiphenyl). The kinetic experiments were performed at oil bath temperatures of 128.1, 138.8, 147.7, 157.0 and 167.8 °C. The NMR tubes were taken out of the oil bath and quickly cooled to room temperature in a water bath to halt the reaction and allow measurement of the \(^{19}\text{F} \) NMR spectrum. The \(^{19}\text{F} \) NMR integral values were imported into Mathematica, and fit to an exponential function appropriate for a first-order reaction. Fitting the rate constants thus obtained to the Eyring model afforded the activation parameters as \( \Delta H^{\ddagger} = 118.1 \pm 0.9 \text{ kJ.mol}^{-1} \) and \( \Delta S^{\ddagger} = -36 \pm 2 \text{ J.mol}^{-1}.\text{K}^{-1} \). Representative kinetic traces and the resulting Eyring plot are shown in Figure 4.16.
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Figure 4.16 Left: representative kinetic traces (based on $^{19}$F NMR integration vs. an internal standard). Right: Eyring plot for the cyclization kinetics of 8-Zn in Bu$_2$O, with error bars shown as 5σ(Ln(k)). (Best fit: $y = 19.3438 - 14156.6 \times$; $\Delta H^\ddagger = 118.1 \pm 0.9$ kJ/mol and $\Delta S^\ddagger = -36 \pm 2$ J/mol/K)

Crystallographic data

Suitable crystals of 4.2, 4.2OMe, 4.3 and 4.4 were mounted on a cryo-loop in a drybox and transferred, using inert-atmosphere handling techniques, into the cold nitrogen stream of a Bruker D8 Venture diffractometer. Intensity data were corrected for Lorentz and polarisation effects, scale variation, for decay and absorption: a multiscan absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings (SADABS)\textsuperscript{45}. The structures were solved by direct methods using the program SHELXS\textsuperscript{46}. The hydrogen atoms were generated by geometrical considerations and constrained to idealise geometries and allowed to ride on their carrier atoms with an isotropic displacement parameter related to the equivalent displacement parameter of their carrier atoms. Structure refinement was performed with the program package SHELXL\textsuperscript{46}. Crystal data and details on data collection and refinement are presented in following tables.
Facile access to fluorinated [1,2,4,5]tetrazepine and indazole derivatives

<p>| Chem. formula | Mr | Cryst syst | Color, habit | Size (mm) | Space group | a (Å) | b (Å) | c (Å) | α (°) | β (°) | γ (°) | V (Å³) | Z | ρ calc, g.cm⁻³ | Radiation [Å] | µ (Mo Kα), mm⁻¹ | F(000) | Temp (K) | θ range (°) | Data collected | min, max transm | Refs collected | Indpndt refs | Observed refs | Re f(|F|) ≥ 2.0 σ | wR(F²) (%) | Goof | Weighting a,b | Params refined | Min, max resid dens |
|---------------|----|------------|-------------|-----------|-------------|-------|-------|-------|-------|-------|-------|--------|-------|---------------|----------------|----------------|--------|-----------|-------------|---------------|--------------|---------------|-------------|-------------|----------------|-------------|------|----------------|---------------|----------------|</p>
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<thead>
<tr>
<th></th>
<th>4.3</th>
<th>4.4</th>
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<tr>
<td>chem formula</td>
<td>C\textsubscript{22}H\textsubscript{16}F\textsubscript{4}N\textsubscript{4}</td>
<td>C\textsubscript{22}H\textsubscript{16}F\textsubscript{4}N\textsubscript{4}(C\textsubscript{6}H\textsubscript{6})\textsubscript{0.5}</td>
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<tr>
<td>M\textsubscript{r}</td>
<td>412.39</td>
<td>451.44</td>
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<td>cryst syst</td>
<td>orthorhombic</td>
<td>monoclinic</td>
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<td>color, habit</td>
<td>orange, needle</td>
<td>orange, needle</td>
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<td>size (mm)</td>
<td>0.28 x 0.08 x 0.03</td>
<td>0.12 x 0.07 x 0.03</td>
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<td>P\textsubscript{2}\textsubscript{1}/c</td>
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<tr>
<td>a (Å)</td>
<td>13.194(3)</td>
<td>6.7441(4)</td>
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<tr>
<td>b (Å)</td>
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<td>c (Å)</td>
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<td>β (deg)</td>
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<td>V (Å\textsuperscript{3})</td>
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<td>ρ\textsubscript{calc}, g·cm\textsuperscript{-3}</td>
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<tr>
<td>μ(Cu K\textsubscript{α}), cm\textsuperscript{-1}</td>
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<td>100(2)</td>
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<td>-8:8, -28:28, -17:17</td>
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<td>24720</td>
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<td>4404</td>
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<td>3725</td>
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<tr>
<td>R(F) (%)</td>
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<td>wR(F^2) (%)</td>
<td>12.74</td>
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<td>-0.281, 0.281</td>
<td>-0.196, 0.246</td>
</tr>
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</table>
4.7 References

(20) Fluorine in Heterocyclic Chemistry Volume 1; Wenjenkko, V., Ed.; Springer International Publishing: Cham, 2014.
Chapter 4

(45) Bruker, APEX2 (v2012 4-3), SAINT (Version 8.18C) and SADABS (Version 2012/1), Bruker AXS Inc., Madison, Wisconsin, USA, 2012.