

Decoupling Deprotonation from Metalation: Thia-Fries Rearrangement**

Alan M. Dyke, Duncan M. Gill, Jeremy N. Harvey, Alison J. Hester, Guy C. Lloyd-Jones,*
M. Paz Muñoz, and Ian R. Shepperson

Aryl perfluoroalkyl sulfones ($\text{ArSO}_2\text{R}^{\text{F}}$) are of substantial utility in pharmaceutical, agrochemical, and polymer chemistry^[1] as CF_3 -transfer reagents,^[2] as precursors to aryl(alkyl) sulfones,^[3] and for binol-based (binol = 2,2'-binaphthol) catalysis.^[4,5] However, the only general method for the preparation of $\text{ArSO}_2\text{R}^{\text{F}}$ involves the oxidation of ArSR^{F} .^[6]

In 2003 we reported^[7] that a thia-Fries rearrangement^[8] ($1,3\text{-O}_{\text{Ar}}\rightarrow\text{C}_{\text{Ar}}$ migration of $\text{S}(\text{O})_n\text{R}$) can compete with aryne^[9] generation (e.g. Figure 1 **1** $\rightarrow$ **2/3**) when aryl triflates are reacted with lithium diisopropylamide (LDA) at -78°C in THF.^[10] However, rearrangement is limited in scope and in certain cases has proven to be capricious.^[11] In 2006, Butenschön and co-workers showed that $\{\text{Cr}(\text{CO})_3\}$ complexes with η^6 -aryl triflate ligands undergo a thia-Fries rearrangement very readily, and they elegantly demonstrated an enantioselective rearrangement of $[\eta^6\text{-(C}_6\text{H}_5\text{OTf)-Cr}(\text{CO})_3]$.^[12]

Herein we describe the first examples of isotopically labeled aryl triflates (^2H , ^{18}O , and ^{34}S) and their use in a mechanistic study to probe the molecularity, reversibility, and partitioning of the rearrangement^[4,7,12] and the competing aryne generation.^[10] On the basis of our findings we report that the $t\text{BuP}_4$ organosuperbase, reported by Schwesinger et al.,^[13] can induce an anionic thia-Fries rearrangement in aryl triflates that bear sufficiently electron-withdrawing substituents.

In our initial report,^[7] we found that the rearrangement is favored by a number of factors, including electron-withdrawing substituents and the presence of a group *ortho* to the triflate unit. However, many of the patterns of reactivity remain puzzling. The reaction of the regioisomers of chlorobenzene triflate **1** with LDA (Figure 1) exemplify this: *o*-**1** undergoes rearrangement ($\rightarrow$ **3**), *m*-**1** exclusively undergoes elimination ($\rightarrow$ **2**), and *p*-**1** undergoes both processes ($\rightarrow$ **2/3** in ca. a 1.8 ratio).

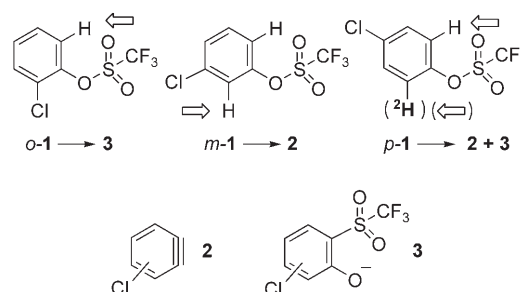
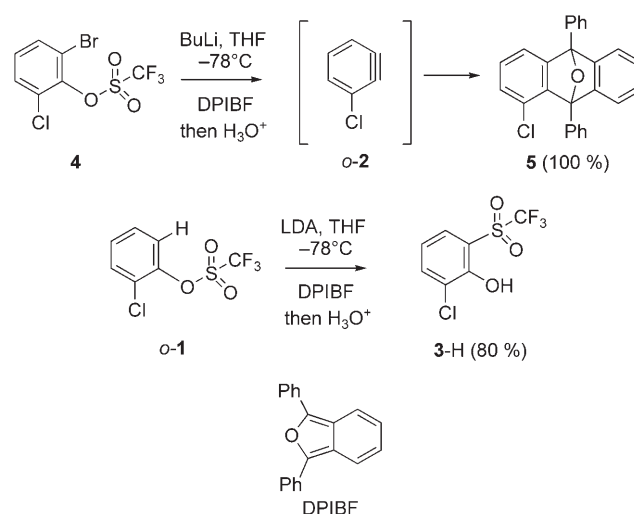


Figure 1. Sites of reaction (arrows) for *o*-, *m*-, and *p*-isomers of **1** to give **2** and **3**. Conditions: LDA (1.05 equiv) in THF at -78°C .

The net kinetic isotope effect^[14] associated with the irreversible^[15] C–H cleavage was probed intramolecularly by reaction of 2- $[\text{H}_1]$ -*p*-**1** with LDA at -40°C . The values determined for the rearrangement ($k_{\text{H}}/k_{\text{D}} = 2.5 \pm 0.2$) versus the elimination ($k_{\text{H}}/k_{\text{D}} = 2.6 \pm 0.6$) are indistinguishable, and suggest partitioning from a common intermediate generated, for example, by an LDA-mediated *ortho* lithiation reaction.^[16,17] However, the reaction of bromo-bearing aryl triflate **4** with BuLi at -78°C , Scheme 1, resulted in quantitative aryne generation (*o*-**2**)^[18] as evidenced by the in situ trapping with 1,3-diphenylisobenzofuran (DPIBF) to give **5**. Indeed, as far as we are aware, all examples of *ortho*-metalated aryltriflates (Mg, Zn)^[19,20] generate arynes,^[9d,21] rather than undergo a rearrangement. In contrast, reaction of *o*-**1** with LDA in the presence of DPIBF gave **3-H** (80% yield) together with



Scheme 1. Rearrangement of *o*-**1** ($\rightarrow$ **3**) versus aryne (*o*-**2**) generation from *ortho*-Li aryltriflate (**4** + BuLi) and capture in situ by DPIBF.

[*] Dr. A. M. Dyke, Prof. Dr. J. N. Harvey, Dr. A. J. Hester, Prof. Dr. G. C. Lloyd-Jones, Dr. M. P. Muñoz, Dr. I. R. Shepperson
School of Chemistry
University of Bristol
Cantock's Close, Bristol, BS8 1TS (UK)
Fax: (+44) 117-929-8611
E-mail: g.c.lloyd-jones@bris.ac.uk

Dr. D. M. Gill
Process R&D
AstraZeneca R&D Charnwood
Bakewell Road, Loughborough, LE11 5RH (UK)

[**] We thank AstraZeneca and the MEC (Spain) for generous funding.
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

recovered DPIBF. Taken together, these results implicate the generation of intermediates that do not involve Ar–Li bonding, for example aryl anions.

Gas phase B3LYP/6-31G(d) calculations and single point B3LYP/6-311 + G(d,p) calculations, including a continuum description of the THF solvent,^[22] were carried out for the pathways leading to the elimination and the rearrangement of $[\text{C}_6\text{H}_4\text{OTf}]^-$. Although the use of a truncated model without a counterion and a simplified continuum description of the solvent prevent us from quantitatively analyzing the partitioning of the anion, both processes are predicted to be extremely facile (Figure 2).

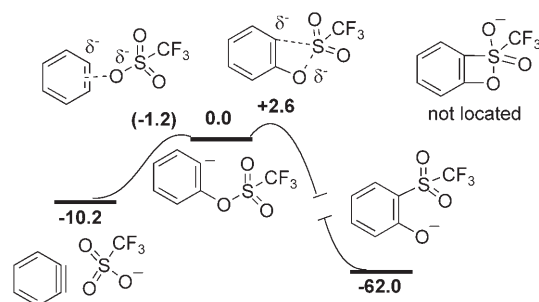
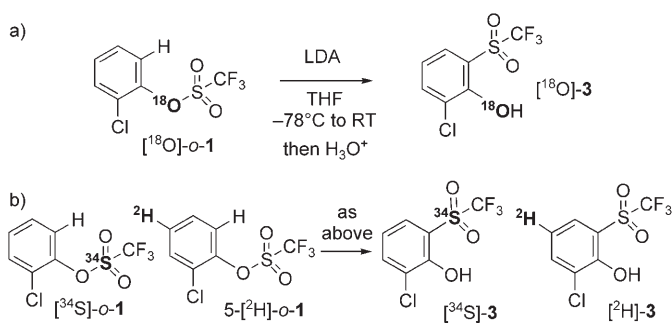


Figure 2. Computed relative energies (kcal mol^{-1}) for the elimination or the rearrangement of the cisoid isomer of $[\text{C}_6\text{H}_4(\text{OTf})]^-$ in a THF continuum.

The loss of the triflate group is predicted to be mildly exothermic ($10.2 \text{ kcal mol}^{-1}$) and the $\text{O}_{\text{Ar}} \rightarrow \text{C}_{\text{Ar}}$ sulfonyl migration is predicted to be highly exothermic ($62.0 \text{ kcal mol}^{-1}$). For the latter process, a putative 1,2-oxethietane intermediate could not be located. Instead, the $\text{O}_{\text{Ar}} \rightarrow \text{C}_{\text{Ar}}$ migration proceeded by a single and early transition state with a C–S distance of $2.68 \text{ \AA}$ ($3.07 \text{ \AA}$ in the starting species) and a breaking S–O bond length of $1.69 \text{ \AA}$ ($1.59 \text{ \AA}$ in the starting species).

Preliminary calculations show that the two barriers remain close in energy for the chlorine-substituted aromatic ring. In the gas phase calculations, a stable triflate/benzyne ion–molecule complex is found. Although this complex is $4.3 \text{ kcal mol}^{-1}$ less stable than the separated benzyne and triflate pair in the presence of a continuum solvent, it suggested that reversible formation of a benzyne/triflate ion–molecule complex might facilitate thermodynamic rather than kinetic control. However, reaction of ^{18}O -*o*-1 gave ^{18}O -phenol **3**, without $^{18}\text{O}/^{16}\text{O}$ scrambling (Scheme 2a), strongly weighing against reversible liberation of the triflate group. The possibility of an intermolecular transfer of the SO_2CF_3 group by an anionic chain reaction^[23] was tested by simultaneously reacting 5- ^{34}H -*o*-1 and ^{34}S -*o*-1 (prepared in five steps from $^{34}\text{S}_8$) with LDA in THF from -78°C →room temperature. The complete lack of crossover (Scheme 2b) demonstrates that the sulfone group transfer is intramolecular.

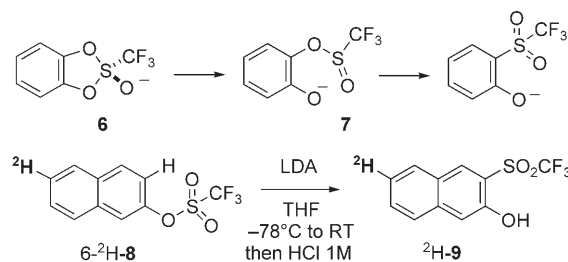
We next considered intramolecular attack of an *ortho*-anionic triflate at the sulfonyl oxygen atom to generate a trifluoromethylsulfonate (**7**) through intermediate **6**



Scheme 2. Rearrangement of ^{18}O -, ^{34}S -, and ^2H -labeled *o*-1.

a) ^{18}O -scrambling experiment. b) Crossover experiment.

(Scheme 3). Organosulfinates are known to undergo isomerization to the corresponding sulfone by a heterolytic ion-pair recombination mechanism,^[24] and thus, the combination of a trifluoromethylsulfonate and a phenolate (**7**) would be expected to isomerize readily. However, rearrangement of 6- ^{2}H -**8** gave ^{2}H -**9** as a single ^{2}H -isomer, (Scheme 3) ruling out a sulfinate-based mechanism.

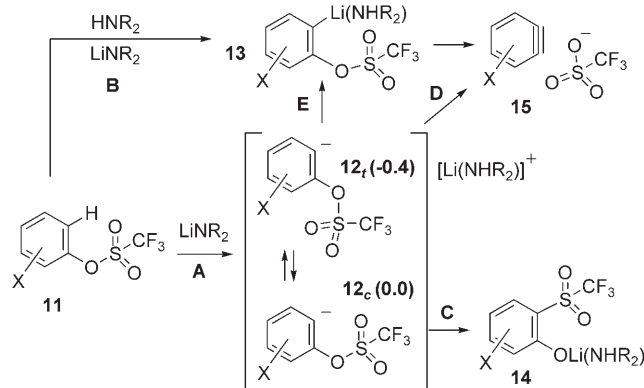


Scheme 3. Probing for symmetrical intermediate **6** by way of 6- ^{2}H -**8**.

An additional parameter affecting partitioning between the rearrangement and the elimination reactions is the concentration of the free $\text{HN}(\text{iPr})_2$ (DIPA).^[7] Whereas both processes nominally generate DIPA from the reaction of LDA with ArOTf , the DIPA remains strongly complexed to Li in the rearrangement product^[7] and is also consumed by rapid (LDA-catalyzed) reaction with the aryne to generate $\text{ArN}(\text{iPr})_2$.^[10a] Addition of DPIBF, which selectively traps the aryne (cf. **5**), bypasses DIPA consumption and leads to a rise in the DIPA concentration, which can have a profound effect on the reaction outcome. For example, reaction of **8** with DIPA-free LDA generates **9** (30%) and naphthyne-derived anilines (44%). However, in the presence of DPIBF (1 equiv) the same reaction affords no trace of **9** and a 99% yield of the naphthyne-DPIBF adduct.^[7] This sensitivity to DIPA, albeit extreme in the case of **8**, is also observed in readily rearranged substrates^[7] and suggests that DIPA catalyzes aryne generation. In Huisgen and Sauer's pioneering studies of the kinetics of aryne generation from Ar-X , the presence of HNR_2 was found to efficiently catalyze *ortho* metalation.^[25] As noted above, metalation *ortho* to a triflate group (Li, Mg, Zn) consistently results in an elimination.^[18,19] Thus, our overall model for the reaction of aryl triflates (**11**) with LDA

includes both an anionic pathway (Scheme 4, **A**; **11**→**12**) and a DIPA-catalyzed metalation pathway (**B**; **11**→**13**).

In pathway **A**, the low activation barriers for the sulfonyl group migration (**C**) and elimination (**D**) result in the

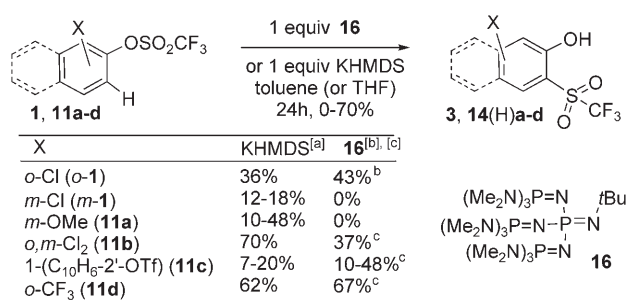


Scheme 4. Mechanisms for the elimination and the rearrangement. Values in parentheses represent the relative energies of the transoid and cisoid forms of **12**.

conformation of anion **12** playing a key role. Calculations show that when X = H, **12_t** and **12_c** (subscripts *t* = transoid and *c* = cisoid) lie close in energy, and the cisoid conformation that is required for rearrangement (**12_c**→**14**) is higher by just 0.4 kcal mol⁻¹. Substitution *ortho* to the triflate group will substantially reduce or invert this bias. The electronic demands of the substituents (X) also play a key role in terms of stabilizing (e.g. Cl and CF₃) or destabilizing (e.g. OMe) aryl anion **12** with respect to capture by the Li⁺ ion (**E**) to generate **13**. This process will be particularly facile when there is a directing group *ortho* to the anion and *meta* to the triflate group (e.g. Cl or OMe). Irrespective of the route by which it is generated (**B** or **E**), *ortho*-lithiated triflate **13** leads solely to the aryne (→**15**).^[18,19]

Although complex, the steps depicted in Scheme 4 rationalize all of our observations: *ortho* and *para*-chlorobenzene triflate (*o/p*-**1**) rearrange (the former exclusively) and the *meta* isomer (*m*-**1**) eliminates, but the more electron-deficient and conformationally-biased *o,m*-dichlorobenzene triflate undergoes rearrangement (52% yield). Analogously, the electron-withdrawing [Cr(CO)₃] unit in the [η⁶-(ArOTf)Cr(CO)₃] complexes reported by Butenschön and co-workers induces a high-yielding rearrangement irrespective of the aryl substitution pattern.^[12] On the basis of Scheme 4, aryne generation should be attenuated by inhibiting metalation (**B/E**). Accordingly, switching from Li to the less covalent K (potassium hexamethyl disilazane) induces rearrangement (10–48%) in *meta*-anisyl (**11a**) and *meta*-chlorobenzene (*m*-**1**) triflate, for which LDA (or lithium hexamethyl disilazane) affords only aryne-derived anilines (60–80%).^[7] Moreover, the phosphazene (**16**)^[13,26] reported by Schwesinger et al. (*pK_a* [**16-H**]⁺ ≈ 28, THF) is found to deprotonate suitably activated aryl triflates and induce rearrangement under metal-free conditions (Scheme 5).^[27]

In summary, the first examples of isotopically labeled (²H, ¹⁸O, and ³⁴S) aryl triflates have facilitated a mechanistic



Scheme 5. Anionic thia-Fries rearrangement by using KHMDS or **16**.

[a] –78 °C to RT in toluene. [b] –30 °C to RT in THF. [c] –78 °C to 80 °C in toluene.

investigation of the LDA-induced thia-Fries rearrangement^[7,12] and the competing elimination.^[10] Both reactions proceed after an irreversible *ortho* C–H cleavage. The rearrangement proceeds by an intramolecular^[15] anionic O_{Ar}→C_{Ar} transfer of the SO₂CF₃ group (**12_c**→**14**) through a single transition state, without the discrete formation of a 1,2-oxethietane intermediate.^[22] In contrast, direct (**B**) or indirect (**E**) arylmetalation (→**13**) results exclusively in elimination (→**15**).^[9,10,18,19]

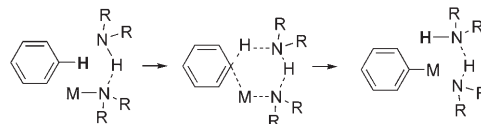
Received: February 14, 2008

Published online: May 27, 2008

Keywords: basicity · metalation · migration · rearrangements · superbases

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