Mechanistic Studies

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# Decoupling Deprotonation from Metalation: Thia-Fries Rearrangement**

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Aryl perfluoroalkyl sulfones ($ArSO_2R^F$) 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 $ArSO_2R^F$ involves the oxidation of $ArSR^F$.[6]

In 2003 we reported[7] that a thia-Fries rearrangement[8] (1,3-$O_{Ar}\rightarrow C_{Ar}$ migration of $S(O)_nR$) can compete with aryne[9] generation (e.g. Figure 1 **1**→**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 {$Cr(CO)_3$} complexes with $\eta^6$-aryl triflate ligands undergo a thia-Fries rearrangement very readily, and they elegantly demonstrated an enantioselective rearrangement of [$\eta^6$-($C_6H_5OTf$)-$Cr(CO)_3$].[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*$BuP_4$ 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 (→**3**), *m*-**1** exclusively undergoes elimination (→*o*-**2**), and *p*-**1** undergoes both processes (→**2**/**3** in ca. a 1.8 ratio).

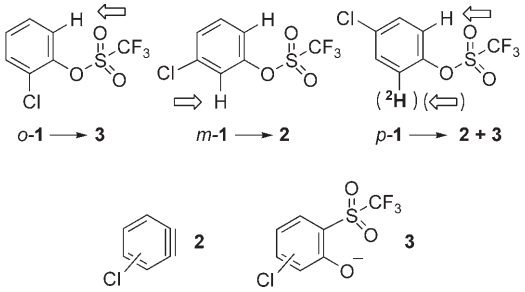
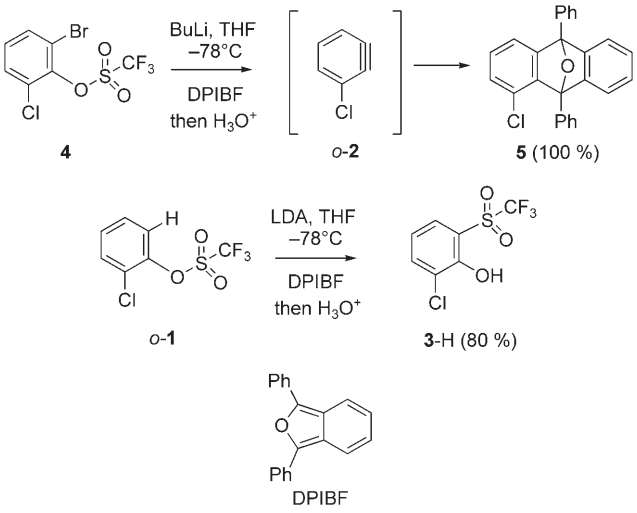



***Figure 1.*** Sites of reaction (arrows) for *o*-, *m*-, and *p*-isomers of **1** to give **2** and **3**. Conditions: LDA (1.05 equiv) in THF at −78 °C.

The net kinetic isotope effect[14] associated with the irreversible[15] C–H cleavage was probed intramolecularly by reaction of 2-[$^2H_1$]-*p*-**1** with LDA at −40 °C. The values determined for the rearrangement ($k_H/k_D = 2.5 \pm 0.2$) versus the elimination ($k_H/k_D = 2.6 \pm 0.6$) 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** (→**3**) versus aryne (*o*-**2**) generation from *ortho*-Li aryltriflate (**4** + BuLi) and capture in situ by DPIBF.

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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 $[C_6H_4OTf]^-$. 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).

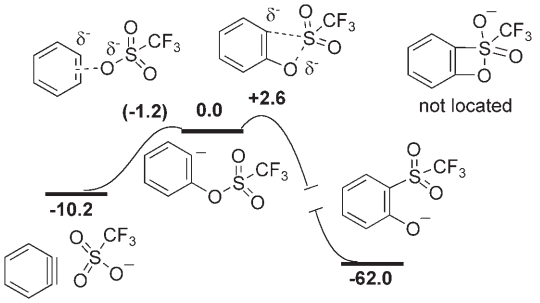
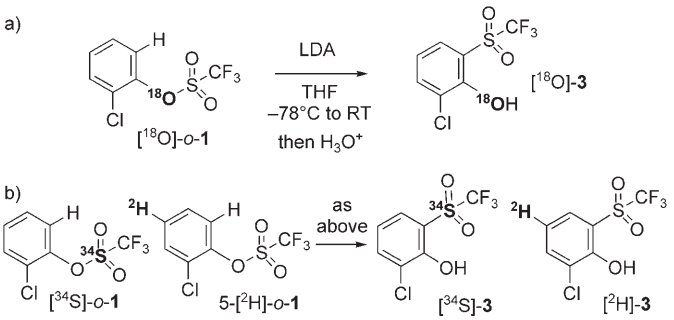



***Figure 2.*** Computed relative energies (kcal mol$^{-1}$) for the elimination or the rearrangement of the cisoid isomer of $[C_6H_4(OTf)]^-$ in a THF continuum.

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

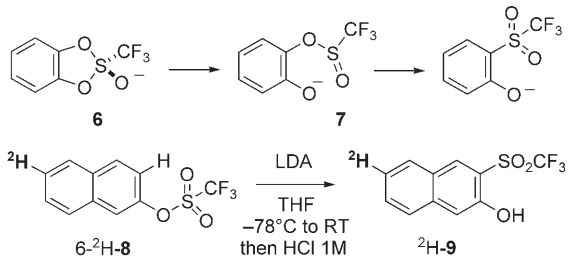
Preliminary calculations show that the two barriers remain close in energy for the chlorine-substituted aromatic ring. In the gas phase calculations, a stable triflate/benzyne ion–molecule complex is found. Although this complex is 4.3 kcal mol$^{-1}$ less stable than the separated benzyne and triflate 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 $^{18}$O/$^{16}$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-[$^2$H]-*o*-**1** and [$^{34}$S]-*o*-**1** (prepared in five steps from $^{34}S_8$) 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 trifluoromethylsulfinite (**7**) through intermediate **6**




***Scheme 2.*** Rearrangement of $^{18}$O-, $^{34}$S-, and $^2$H-labeled *o*-**1**. a) $^{18}$O-scrambling experiment. b) Crossover experiment.

(Scheme 3). Organosulfinites are known to undergo isomerization to the corresponding sulfone by a heterolytic ion-pair recombination mechanism,[24] and thus, the combination of a trifluoromethylsulfinite 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 sulfinite-based mechanism.



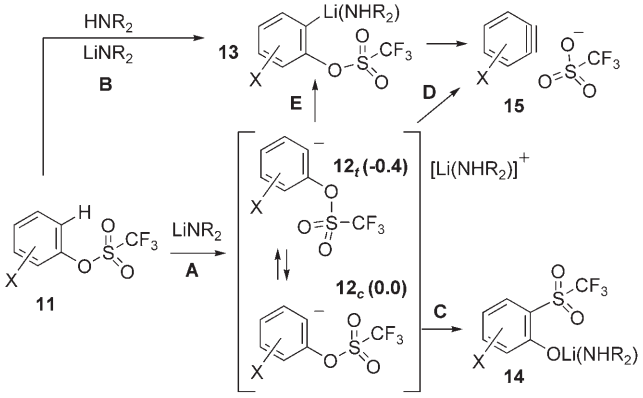

***Scheme 3.*** Probing for symmetrical intermediate **6** by way of 6-[$^2$H]-**8**.

An additional parameter affecting partitioning between the rearrangement and the elimination reactions is the concentration of the free HN(*i*Pr)$_2$ (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 ArN(*i*Pr)$_2$.[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

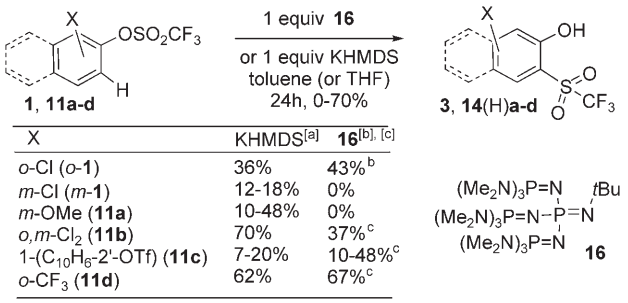



***Scheme 4.*** Mechanisms for the elimination and the rearrangement. Values in parentheses represent the relative energies of the transoid and cisoid forms of **12**.

conformation of anion **12** playing a key role. Calculations show that when X = H, $\mathbf{12}_t$ and $\mathbf{12}_c$ (subscripts $t$ = transoid and $c$ = cisoid) lie close in energy, and the cisoid conformation that is required for rearrangement ($\mathbf{12}_c$→**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 $CF_3$) 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 [$\eta^6$-(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 ($^2$H, $^{18}$O, and $^{34}$S) aryl triflates have facilitated a mechanistic




| X | KHMDS[a] | 16[b], [c] |
|---|---|---|
| *o*-Cl (*o*-**1**) | 36% | 43%[b] |
| *m*-Cl (*m*-**1**) | 12-18% | 0% |
| *m*-OMe (**11a**) | 10-48% | 0% |
| *o*,*m*-$Cl_2$ (**11b**) | 70% | 37%[c] |
| 1-($C_{10}H_6$-2'-OTf) (**11c**) | 7-20% | 10-48%[c] |
| *o*-$CF_3$ (**11d**) | 62% | 67%[c] |




***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 $SO_2CF_3$ group ($\mathbf{12}_c$→**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]

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**Keywords:** basicity · metalation · migration · rearrangements · superbases

[1] Chemical Abstracts contains >4000 unique compounds containing the moiety $C_6H_5$-$SO_2(CF_2)_nCF_3$, of which about 86% are triflones ($n$ = 0).
[2] a) M. D. Barrera, Y. Cheburkov, W. M. Lamanna, *J. Fluorine Chem.* **2002**, *117*, 13–16; b) G. K. S. Prakash, J. Hu, G. A. Olah, *Org. Lett.* **2003**, *5*, 3253–3256; c) G. K. S. Prakash, J. Hu, G. A. Olah, *J. Org. Chem.* **2003**, *68*, 4457–4463.
[3] R. W. Steensma, S. Galabi, J. R. Tagat, S. W. McCombie, *Tetrahedron Lett.* **2001**, *42*, 2281–2283.
[4] R. Kargbo, Y. Takahashi, S. Bhor, G. R. Cook, G. C. Lloyd-Jones, I. R. Shepperson, *J. Am. Chem. Soc.* **2007**, *129*, 3846–3847.
[5] O. Mouhtady, H. Gaspard-Iloughmane, A. Laporterie, C. Le Roux, *Tetrahedron Lett.* **2006**, *47*, 4125–4128.
[6] a) A. J. Beaumont, J. H. Clark, *J. Fluorine Chem.* **1991**, *52*, 295–300; b) W. Su, *Tetrahedron Lett.* **1994**, *35*, 4955–4958; c) R. Goumont, N. Faucher, G. Moutiers, M. Tordeux, C. Wakselman, *Synthesis* **1997**, 691–695; d) L. Xu, J. Cheng, M. L. Trudell, *J. Org. Chem.* **2003**, *68*, 5388–5391; e) O. Mouhtady, H. Gaspard-Iloughmane, A. Laporterie, C. Le Roux, *Tetrahedron Lett.* **2006**, *47*, 4125–4128; f) J. B. Hendrickson, K. W. Bair, *J. Org. Chem.* **1977**, *42*, 3975–3978.
[7] J. P. Charmant, A. M. Dyke, G. C. Lloyd-Jones, *Chem. Commun.* **2003**, 380–381.
[8] a) K. W. Rittler, DE 555409, **1932**; b) A. A. Aleykutty, V. Baliah, *J. Indian Chem. Soc.* **1954**, *31*, 513–518; c) H. Nozaki, R. Okada, R. Noyori, M. Kawanishi, *Tetrahedron* **1966**, *22*, 2177–2180; d) R. Martin, *Org. Prep. Proced. Int.* **1992**, *24*, 369–436; e) K. Pitchumani, M. C. D. Manickam, C. Srinivasan, *Indian J. Chem. Sect. B* **1993**, *32*, 1074–1076; f) C. Venkatachalapathy, K. Pitchumani, *Tetrahedron* **1997**, *53*, 17171–17176; g) B. Das, P.

Madhusudhan, B. Venkataiah, *J. Chem. Res. Synop.* **2000**, 200–201; h) F. M. Moghaddam, M. G. Dakamin, *Tetrahedron Lett.* **2000**, *41*, 3479–3481; i) F. M. Moghaddam, A. A. Hoor, M. G. Dekamin, *J. Sulfur Chem.* **2004**, *25*, 125–130; j) H. Sharghi, Z. Shahsavari-Fard, *Phosphorus Sulfur Silicon Relat. Elem.* **2005**, *180*, 2491–2501; k) H. Sharghi, Z. Shahsavari-Fard, *Helv. Chim. Acta* **2005**, *88*, 42–52; l) J. Kato, Y. Maekawa, M. Yoshida, *Chem. Lett.* **2005**, *34*, 266–267; m) J. Kato, H. Kakehata, Y. Maekawa, T. Yamashita, *Chem. Commun.* **2006**, 4498–4500; n) L. K. Crevatin, S. M. Bonesi, R. Erra-Balsells, *Helv. Chim. Acta* **2006**, *89*, 1147–1157; o) ArOMs: see T. Ritter, K. Stanek, I. Larrosa, E. M. Carreira, *Org. Lett.* **2004**, *6*, 1513–1514.

[9] a) R. W. Hoffman, *Dehydrobenezene and Cycloalkynes*, Verlag Chemie/Academic Press, Oxford, **1967**; Recent reviews: b) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701–730; c) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem.* **2003**, *115*, 518–546; *Angew. Chem. Int. Ed.* **2003**, *42*, 502–528; d) A. M. Dyke, A. J. Hester, G. C. Lloyd-Jones, *Synthesis* **2006**, 4093–4112.

[10] a) P. P. Wickham, K. H. Hazen, H. Guo, G. Jones, K. H. Reuter, W. J. Scott, *J. Org. Chem.* **1991**, *56*, 2045–2050; b) P. P. Wickham, K. H. Reuter, D. Senanayake, H. Guo, M. Zalesky, W. J. Scott, *Tetrahedron Lett.* **1993**, *34*, 7521–7524.

[11] Rearrangement is highly dependent on the purity of the BuLi used to prepare LDA: the presence of LiX accelerates benzyne generation.

[12] Z. Zhao, J. Messinger, U. Schön, R. Wartchow, H. Butenschön, *Chem. Commun.* **2006**, 3007–3009.

[13] a) R. Schwesinger, J. Willaredt, H. Schlemper, M. Keller, D. Schmitt, H. Fritz, *Chem. Ber.* **1994**, *127*, 2435–2454; b) R. Schwesinger, H. Schlemper, *Angew. Chem.* **1987**, *99*, 1212–1214; *Angew. Chem. Int. Ed. Eng.* **1987**, *26*, 1167–1169; c) R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter, F. G. Bordwell, A. V. Satish, G. Z. Ji, E. M. Peters, K. Peters, H. G. vonSchnering, L. Walz, *Liebigs Ann.* **1996**, 1055–1081.

[14] For KIEs for aryne generation, see: a) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., L. A. Carlsmith, *J. Am. Chem. Soc.* **1956**, *78*, 601–610; b) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, D. A. Semenow, *J. Am. Chem. Soc.* **1956**, *78*, 611–614; c) F. Scardiglia, J. D. Roberts, *J. Org. Chem.* **1958**, *23*, 629–631; d) M. Panar, J. D. Roberts, *J. Am. Chem. Soc.* **1960**, *82*, 3629–3632.

[15] Unreacted 2-[$^2$H]-*p*-**1** is recovered in high isotopic purity.

[16] For leading references, see: K. J. Singh, D. B. Collum, *J. Am. Chem. Soc.* **2006**, *128*, 13753–13760.

[17] *p*-**1** was found to be relatively inert to pure $[LDA]_2$ (P. G. Williard, G. B. Carpenter, *J. Am. Chem. Soc.* **1986**, *108*, 462–468) in THF, undergoing instead a slow triflate displacement (SNAr or SRAr).

[18] a) T. Hamura, Y. Ibusuki, H. Uekusa, T. Matsumoto, J. S. Siegel, K. K. Baldridge, K. Suzuki, *J. Am. Chem. Soc.* **2006**, *128*, 10032–10033; b) References [45–47] cited in reference [9d].

[19] a) I. Sapountzis, W. Lin, M. Fischer, P. Knochel, *Angew. Chem.* **2004**, *116*, 4464–4466; *Angew. Chem. Int. Ed.* **2004**, *43*, 4364–4366; b) W. Lin, I. Sapountzis, P. Knochel, *Angew. Chem.* **2005**, *117*, 4330–4333; *Angew. Chem. Int. Ed.* **2005**, *44*, 4258–4261; c) T. Harada, M. Chiba, A. Oku, *J. Org. Chem.* **1999**, *64*, 8210–8213; d) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514–8515.

[20] [*o*-Ar(OTf)Pd] species do not (rapidly) eliminate: a) T. Kamikawa, T. Hayashi, *Tetrahedron Lett.* **1997**, *38*, 7087–7090; b) G. Espino, A. Kurbangalieva, J. M. Brown, *Chem. Commun.* **2007**, 1742–1744.

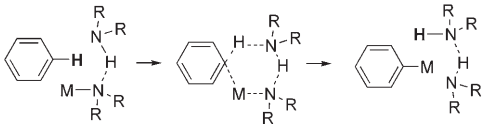
[21] *ortho*-TMS aryl triflates generate arynes, without thia-Fries rearrangement, for example: E. Yoshikawa, K. V. Radhakrishnan, Y. Yamamoto, *Tetrahedron Lett.* **2000**, *41*, 729–731.

[22] All calculations were carried out by using the Jaguar 4.0 program package (Schrodinger, Inc., Portland, Oregon, **2000**); see theSupporting Information for full computational details.

[23] This process would require generation of catalytic quantities of *o*-$(CF_3SO_2)$-$C_6H_3Cl$-$OSO_2CF_3$ as a chain propagating agent.

[24] S. Braverman, Y. Duar, *Tetrahedron* **1990**, *46*, 2975–2990.

[25] R. Huisgen, J. Sauer, *Chem. Ber. Recueil* **1959**, *92*, 192–202. The mechanism shown below was suggested for catalysis by $R_2NH$:



[26] a) For Ar–H deprotonation by using $ZnI_2$/*t*$BuP_4$ (no reaction in the absence of $ZnI_2$), see: T. Imahori, Y. Kondo, *J. Am. Chem. Soc.* **2003**, *125*, 8082–8083; b) Account: Y. Kondo, M. Ueno, Y. Tanaka, *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 453–463.

[27] Yields of rearrangement product (**3**, **14**) depend on the dryness of **16**.[13d] The hydrate [(*t*$BuP_4$H)(OH)] appears to cause hydrolysis of the triflate group and, on occasion, diaryl ether side products, presumably arising from aryne capture by the phenolate, were also detected (mass spectrometry).