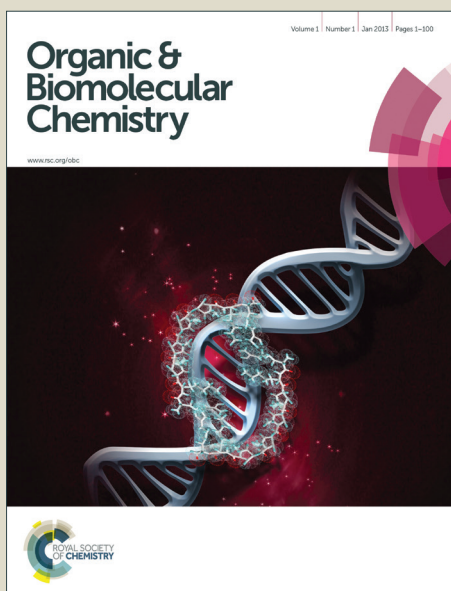


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Aryne Generation vs Truce-Smiles and Fries Rearrangements during the Kobayashi Fragmentation Reaction: A New Bi-Aryl Synthesis

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Treatment of (*ortho*-trimethylsilyl)aryl phenylsulfonates with a soluble fluoride source initiates a Truce-Smiles rearrangement leading to the formation of functionalized bi-aryls. This new carbon-carbon bond-forming reaction proceeds without recourse to transition metal catalysis, under mild reaction conditions and with good functional group compatibility.

Kobayashi's seminal observation¹ that the fluoride-induced fragmentation of *ortho*-silylaryl triflates, **1**, affords functionalised arynes **2** under relatively mild conditions (scheme 1) has led to its adoption as the method of choice for the generation of this class of reactive intermediate. This protocol has also been largely responsible for the current renaissance of "dehydrobenzene" chemistry² as it enables the generation of arynes in a controlled manner. The Kobayashi fragmentation is compatible with many common functional groups, and when coupled with the ever expanding, downstream chemistry of arynes, the reasons for renewed interest in this area become self-evident.

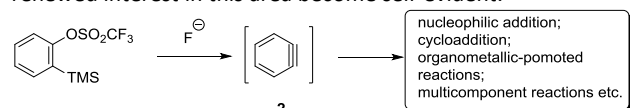
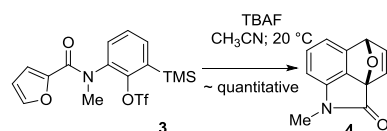


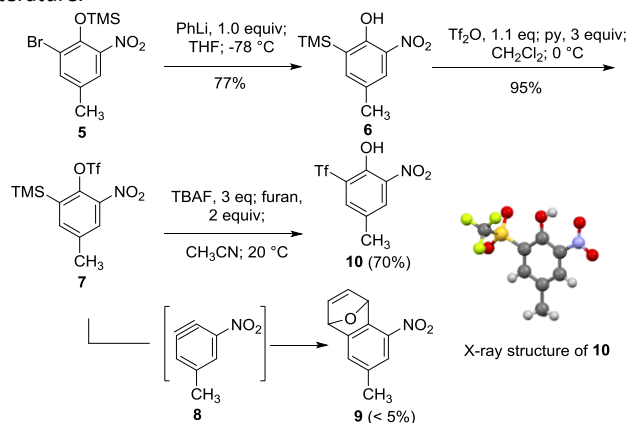
Figure 1. The Kobayashi fragmentation reaction.¹

Some time ago we reported^{3a} an approach to the synthesis of indanones based upon an intramolecular Diels-Alder reaction (IMDA reaction) of an aryne possessing a pendant furan moiety. In this study we established that an intramolecular benzyne cycloaddition reaction leading to **4** could be triggered by way of a fluoride-promoted Kobayashi fragmentation of an appropriately functionalised *ortho*-trimethylsilylaryl triflate **3**, Schme 1.



Scheme 1. An approach to indanones.^{3a}

While this cycloaddition reaction did appear to be highly effective (essentially quantitative) the relatively lengthy synthetic sequence required for the synthesis of the benzyne precursor **3** led us to question whether *intermolecular* rather than *intramolecular* Diels-Alder approaches could be utilised in the synthesis of related polycyclic indolic systems. Probing the validity of this analysis would allow us to delineate the scope and limitations of the Kobayashi fragmentation for the generation polarised arynes such as **8** and would facilitate an investigation of the regiochemical issues arising from the ensuing Diels-Alder reactions.⁴ Surprisingly the generation of nitro-substituted arynes, by other means, has received scant attention in the literature even though the presence of this particular functional group would undoubtedly be of synthetic utility.⁵ In addition, and to our knowledge, there is only one other report concerning the application of the Kobayashi fragmentation to the generation of benzyne related to **8** in the literature.⁶



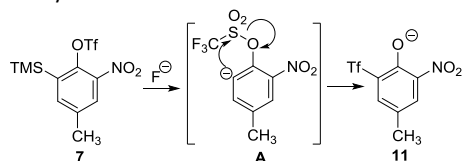
Scheme 2. Initial fragmentation reaction

Initially we wished to establish whether triflate **7** would undergo fluoride promoted fragmentation to the aryne **8** and that this intermediate could then be trapped, *in situ*, with a dienophile such as furan, leading to **9**. The key intermediate **7** was readily available from the silane **5** using the "metallo-Fries" chemistry which we had previously reported.⁷ Hence, reaction of the silyl ether **5** with phenyl lithium⁸ (PhLi, 1.0 eq; -78 °C) cleanly afforded the phenol **6** which on reaction with Tf₂O resulted in the isolation of **7** in good overall yield (73%). Surprisingly attempted generation and trapping of the aryne **8** by the reaction between **7** and TBAF (3 eq) in the presence of furan (3 equiv) at 20 °C, in acetonitrile, resulted in the

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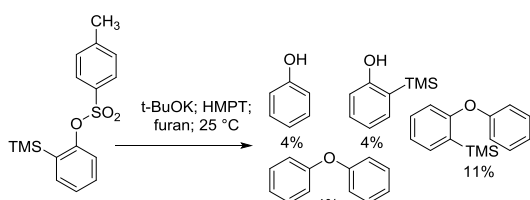
isolation of the desired Diels-Alder adduct **9** in only trace quantities (< 5%). The major product, a pale yellow-coloured crystalline solid isolated in 70% yield, was identified as triflone **10**, whose structure was unambiguously assigned on the basis of a single crystal X-ray diffraction study.⁹



Scheme 3. Anionic thia-Fries rearrangement of **7**

The formation of **10** during this reaction presumably proceeded *via* the generation of the anionic species **A** which suffered a [1,3]-oxygen to carbon rearrangement¹⁰ (an anionic thia-Fries rearrangement) leading to phenoxide anion **11** which ultimately resulted in the isolation of the observed triflone **10** upon work-up. The rearrangement of *ortho*-silylaryl triflates to aryltriflones as a minor, competing, pathway to benzyne generation has been noted sporadically^{11a} in the Kobayashi reaction but in the case of **7** the nitro-substituted triflone clearly has a major controlling influence upon the course of the reaction pathway. In particular our observations are in keeping with those recently reported by Greaney,⁶ who observed that the incorporation of electron-withdrawing functionality, for example a halogen, *ortho*- to the triflate moiety in the benzyne precursor effectively shuts down benzyne generation and promotes competing thia-Fries rearrangements. Parenthetically this outcome is more akin to that reported by Lloyd-Jones¹² on the rearrangement reactions of *ortho*-lithioaryl triflates, a reaction that has been exploited to good effect for the synthesis of functionalised triflones.

The tendency for **7** to participate *via* a fluoride-promoted Fries-rearrangement pathway, combined with the practical issues¹³ related to the preparation of aryl triflates, led us to question whether other, perhaps more readily accessible, nucleofuges could be used to promote the desired fragmentation reaction leading to aryne **8**. Encouragingly we noted that, some time ago, Cunico and Dexheimer¹⁴ attempted to prepare benzyne *via* an alkoxide-promoted fragmentation of 2-(trimethylsilyl)phenyl benzenesulphonate, Scheme 4.

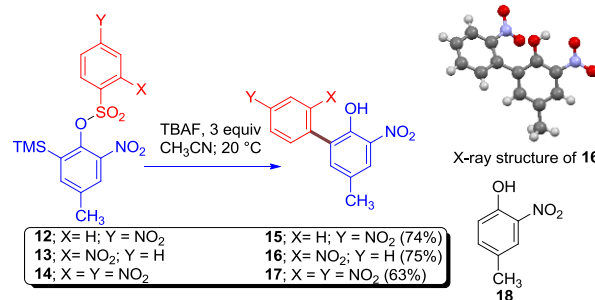


Scheme 4. An early attempt at benzyne generation.¹⁴

The Cunico and Dexheimer base-mediated fragmentation of (*o*-tosyloxyphenyl)trimethylsilane (Scheme 4) was of limited practical utility, although the observed products were indicative of benzyne generation. In this regard we mused whether a suitably activated substrate, such as arylsulfonate ester **12**, could be coaxed to generate aryne **8** using fluoride anion, rather than alkoxide as promotor. We reasoned that fragmentation of **12** to aryne **8** may be possible under such conditions in view of: *i.* the pKa of nitrobenzenesulfonic acids (*e.g.* the 4-nitro-isomer, pKa -7.2) compared to TfOH (pKa -14.2) and PhSO₃H (pKa -6.6) and *ii.* the strength of the Si-F bond in the by-product, TMS-fluoride (*ca.* 540 kJ mol⁻¹). With this idea in mind the synthesis of a series of sulfonate esters was undertaken, a task which proved to be relatively

straightforward (**6**, 1 equiv; NaH, 4.1 equiv; ArSO₂Cl, 1.1 equiv; THF), affording **12-14** as crystalline solids in good overall yields (74-83%).

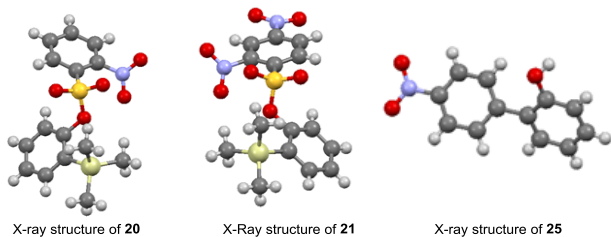
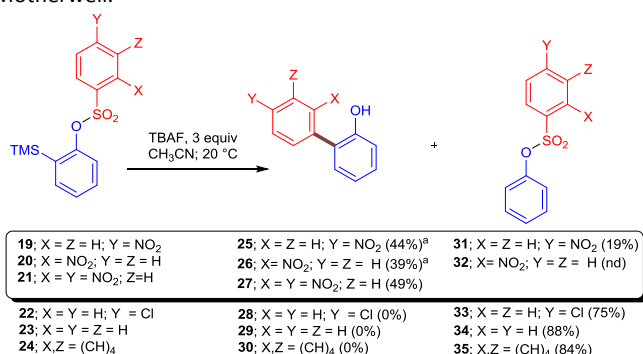
With the sulfonate ester **12** in hand the crucial Kobayashi-type fragmentation was next investigated. In the event addition of TBAF (3 equiv of a 1 M in THF) to a solution of **12** in dry acetonitrile containing furan (3 equiv) at 20 °C led to the rapid generation of a dark red-coloured reaction mixture which was quenched after 16 hours by the addition of HCl (3 M, excess). Gratifyingly, chromatography of the reaction mixture afforded a crystalline product which, unexpectedly, proved to be the bi-aryl **15**, obtained in 74% yield, rather than the Diels-Alder adduct **9**, Scheme 5. Overall this transformation, to our knowledge, represents a rare example of an anionic, Truce-Smiles, rearrangement^{15a} of aryl sulphonate esters leading to bi-aryl formation,^{15c} a process which complements a radical variant which was pioneered by Motherwell.^{16a}



Scheme 5. An unexpected Truce-Smiles rearrangement

On establishing the constitution of the bi-aryl **15** fluoride-promoted fragmentation of sulfonate esters **13** and **14** was next investigated. Pleasingly, reaction of either ester **13** or **14** with TBAF, as above, afforded the bi-aryls **16** and **17**, as crystalline solids, in 75% and 63% yield respectively. The structure of bi-aryl **16** was confirmed by way of a single crystal X-ray diffraction study. It should also be noted that, in the case of the rearrangement of the highly activated substrate **14**, that formation of **17** was also accompanied by the generation of phenol **18**, as a minor by-product, in 13% isolated yield. It is not clear, at this time, whether protodesilylation leading to **18** occurred prior to the hydrolysis of the sulfonate ester moiety. At this juncture a series of sulfonate esters were prepared, from readily available *ortho*-trimethylsilylphenol, in order to elucidate the electronic demands in the rearrangement reaction. Incorporation of a powerful electron-withdrawing nitro-substituent in either the *ortho*- or *para*-position of the arenesulfonic "acceptor" residue (as in **19** and **20**) facilitated the desired rearrangement to the bi-aryls **25** and **26** (44% and 39% yield respectively); the structure of **25** was confirmed by way of a single crystal X-ray analysis. Incorporation of two nitro-groups into the "acceptor" aromatic residue (ester **21**) also proved to be successful and resulted in the formation of bi-aryl **27**. The introduction of an inductively electron-withdrawing substituent (*e.g.* Cl; **22**; σ^- of 0.19), rather than one which exerts a mesomeric influence (*e.g.* NO₂, **19**; σ^- of 1.27), or the use of otherwise unactivated arenesulfonic acid residues (phenyl, **23** and 1-naphthyl, **24**) in the "acceptor" component proved to be ineffective in promoting the rearrangement reaction. In a number of cases protodesilylation was observed as a competing reaction (esters **19** ad **20** leading to concomitant formation of **31** and **32**), and became the exclusive product in those cases where rearrangement was apparently unfavourable (esters **22-24**). Somewhat counterintuitively the yields of bi-aryls derived from the less hindered sulfonate esters **19-21** are lower than those observed

for the more highly functionalized substrates **12-14**, an outcome which is similar to the radical processes developed by Motherwell.^{16a}



X-ray structure of 20

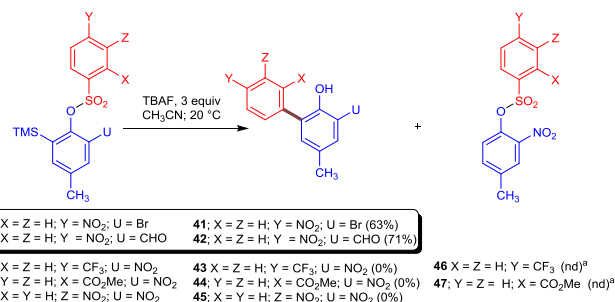
X-Ray structure of 21

X-ray structure of 25

Scheme 6. Investigation into electronic demand of the Truce-Smiles rearrangement (acceptor-aromatic ring).^a optimised (see ESI)

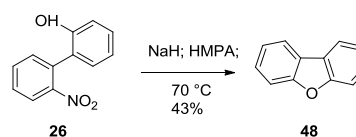
Interestingly, an examination of the X-ray structures of the sulfonate esters **20** and **21** revealed that the torsion angle between the planes containing the *ortho*-nitro-group and the aromatic ring of the sulfonic acid residue are in the range of 52-55°, suggesting that, in the solid state at least, the nitro-group is not fully conjugated with the aromatic ring. It is presumed that this ordering minimises steric interactions between the nitro-group and the neighbouring, bulky, sulfonic acid residue, while the strong polarizing effect of this nitro-residue is still sufficient to enable *ipso*-attack at the *ortho*-, nitro-bearing, carbon in these substrates.

Having investigated the effect of electronic demand with respect to the “acceptor” aromatic ring on the outcome of the rearrangement reaction we next turned our attention to substituent effects in the “donor” ring, Scheme 7. Substrates **36** and **37** were readily prepared (see ESI) from 2,6-dibromo-4-methylphenol, and esters **38-40** were prepared from the phenol **7** (*vide supra*) by reaction with the appropriate sulfonyl chloride in the presence of a suitable base. Reaction of either **36** or **37** with TBAF (3 equiv; CH₃CN; 20 °C) once again triggered a rearrangement reaction, which led to the isolation of the functionalized bi-aryls **41** and **42** in good overall yields (63% and 71% respectively). This outcome is to be compared with the reaction of **38** and **39** with TBAF under identical conditions, which merely resulted in the generation of the protodesilylated products **46** and **47**. Clearly, the introduction of either a bromo- or a formyl-substituent *ortho*- to the arenesulfonyloxy-residue, as in esters **36** and **37**, facilitated the Truce-Smiles rearrangement, while the requirement for a suitably positioned *ortho/para*-nitro-group in the “acceptor” aromatic ring was evident from the reluctance of **38** (CF₃: σ⁻ of 0.65) and **39** (CO₂Me: σ⁻ of 0.64) to participate in the rearrangement reaction. The failure of **40** to undergo the Truce-Smiles rearrangement underscores the requirement for an *ortho/para*-nitro substituent in the “acceptor” ring to provide sufficient activation for rearrangement to proceed.



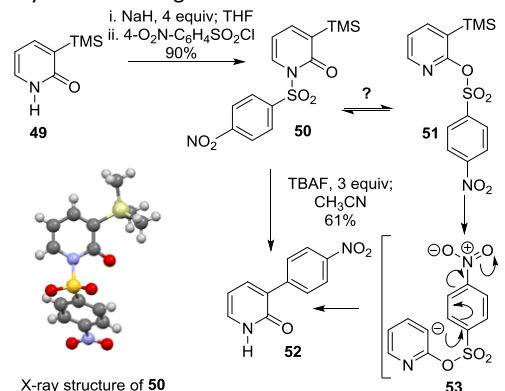
Scheme 7. Investigation into electronic demand of the Truce-Smiles rearrangement (donor-aromatic ring).

The fact that rearrangement was observed in functionalised substrates and afforded a range of biaryls such as **15-17**, **25-27** and **41-42** is noteworthy in that the use of transition metal catalysts are not required,^{17a-d} and that the crucial rearrangement reaction takes place under mild conditions and in a chemoselective fashion. From an experimental perspective the reaction does not require the use of strictly anaerobic or scrupulously anhydrous reaction conditions from simple starting materials. Downstream functionalization of the products of these rearrangement reactions has also been put to good use, as depicted in Scheme 8, where exposure of bi-aryl **26** (1 equiv) to sodium hydride (4 equiv) in HMPA at 70 °C for 24 hours afforded dibenzofuran **48** in 43% unoptimised yield.^{18a} Noteworthy is the fact that this “aromatic nucleophilic denitrocyclization reaction”^{18b,c} also proceeds without recourse to the use of transition metal reagents or catalysts



Scheme 8. Synthesis of dibenzofuran **48**.

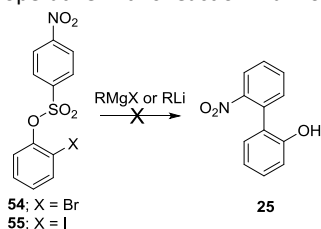
Finally, in an attempt to extend the rearrangement to heterocyclic systems the synthesis of sulfonate ester **51** and its rearrangement to **52** was attempted. Reaction of the 2-pyridone **49** with 4-nitrobenzenesulfonyl chloride in the presence of sodium hydride afforded the *N*-benzenesulfonyl amide **50**, rather than the sulfonate ester **51**. The structure assigned to **50** was wholly in accord with its spectroscopic data, and was also unambiguously confirmed on the basis of a single crystal X-ray analysis. Surprisingly exposure of **50** to TBAF, under our standard reaction conditions, resulted in the isolation of the 3-substituted pyridine **52**, the formal rearranged product of sulfonate ester **51**, which presumably proceeds *via* the anionic intermediate **53**, Scheme 9. The mechanism of this reaction is currently under investigation.



X-ray structure of 50

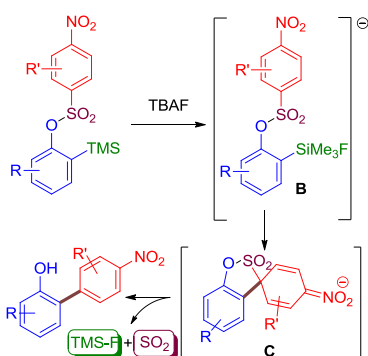
Scheme 9. Truce-Smiles-type rearrangement on a pyridine scaffold.

A number of groups have utilised the fragmentation of *ortho*-lithiated sulphonate esters for the generation of arynes. In light of these observations, halogen-metal exchange of the halo-esters **54** and **55**, using either alkyl lithium or Grignard reagents, as described by Knochel,^{5f} was investigated. All attempts to induce bi-aryl formation, to **25**, under these conditions met with failure, an observation which serves to underscore the subtle electronic effects which are operative in this reaction manifold, Scheme 10.



Scheme 10. Failed attempts at benzyne generation using organolithium and Grignard reagents.

Although similar in certain respects to the radical process reported earlier by Motherwell,^{16a} there are notable differences including the fact that this rearrangement appears to require the presence of at least one nitro-residue in the acceptor ring. As a working hypothesis, we therefore suggest that bi-aryl formation proceeds *via* the initial generation of pentavalent silicon intermediates¹⁹ **B** which on interception by the neighbouring electrophilic ("acceptor") aromatic ring affords spirocyclic Meisenheimer intermediates **C**.²⁰



Scheme 11. Truce-Smiles-type rearrangement: mechanistic proposal.

Collapse of **C**, with concomitant expulsion of SO₂ and TMSF, presumably provides sufficient entropic and enthalpic gain for the reaction to proceed, affording the observed bi-aryl products, Scheme 11.²¹ The intervention of alternate SET²² pathways for these rearrangement reactions cannot, at this stage, be ruled out. Synthetic applications of this new variant of the Truce-Smiles rearrangement are now underway, as are mechanistic studies of the key bond-forming processes.

Notes and references

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