A Novel Route to Biaryls *via* Intramolecular Free Radical *ipso* Substitution Reactions

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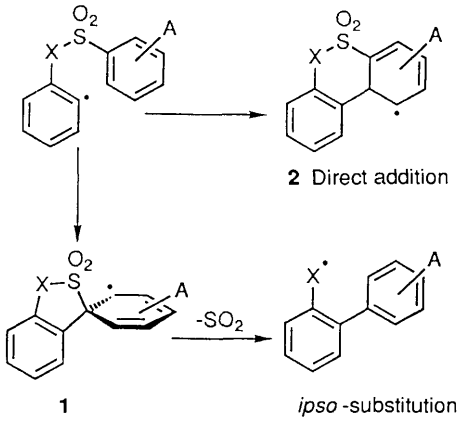
A variety of usefully functionalised biaryls may be prepared under neutral conditions by an intramolecular free radical *ipso* substitution reaction at an sp^2 sulphonyl substituted carbon atom; the overall efficiency of the process being determined both by the nature and number of atoms linking the two aromatic rings and by appropriately positioned substituents on the aromatic acceptor ring.

The biaryl unit is a fundamental feature of a very large number of natural products of differing structure, biosynthetic origin and biological activity.[1] Consequently, a variety of synthetic methods devoted to the construction of this central axis have been developed.[2–4] However, many of these require that the two aromatic rings are of substantially different electronic character whilst others are particularly sensitive to steric hindrance. We reasoned that the ability of free radical chain reactions to operate with impunity in hindered environments of widely differing polarity[5] could overcome some of these disadvantages. Accordingly, we decided to examine the possibility of developing an intramolecular free radical *ipso* substitution approach,[6] as set out in general form in Scheme 1, and featuring the selection of a sulphonyl substituted aromatic acceptor for the *ortho* substituted aryl radical, and subsequent extrusion of sulphur dioxide from the resultant spirocyclic intermediate **1**. Some support for this concept comes from studies by Speckamp[7] on the tri-n-butyl stannane reduction of 2-iodomethyl-*N*-arenesulphonyl piperidine derivatives, which revealed that [1,5] *ipso* substitution by the primary alkyl radical was a viable process, although in competition with direct [1,6] addition to the aromatic ring and straightforward reduction. We now report the results of our preliminary studies in this area, which focus on the influence of the nature and number of atoms in the bridging group X, and of substituents A, in directing *ipso* substitution *via* **1** as opposed to the alternative direct addition process to give **2** (Scheme 1).



Scheme 1

The isolated yields of products from the reduction of a variety of *ortho* halogenated derivatives are set out in the Table 1 and Scheme 2. From the practical standpoint, it should be noted that simple dehalogenation is effectively eliminated by slow addition (10–15 h, motor driven syringe) of a benzene solution of tri-n-butylstannane (1.3 mol equiv.) and azo-(isobutyronitrile) (AIBN) (0.7 mol equiv.) to a refluxing benzene solution of the substrate (0.05 mol dm^{-3}). The high proportion of AIBN used as a chain initiator, together with the quantity of starting material recovered, is, however, indicative of a relatively short chain length in these reactions.

In the first instance, we elected to examine the monoatomic series (X = O, CH_2 and NCH_3) using *para*-toluenesulphonyl derivatives **3**, **4** and **5**, which involve competition between [1,5] *ipso* substitution and direct [1,6] addition. Significantly, while all three derivatives demonstrated the occurrence of the [1,6] addition process through isolation of cyclic sulphonyl derivatives **6**, **7** and **8** respectively, only sulphonamide **5** yielded the *ipso* substitution product **9**. While detailed explanation of this fundamental preference has yet to be established, it may be pertinent to note that the decarboxyla-

tion of carbamoyloxyl radicals ($R_2NCO_2^{\bullet}$) is known to be faster than the analogous oxygen case ($ROCO_2^{\bullet}$).[8] Given the possibility of interconverting intermediates **1** and **2** (Scheme 1) and a similar rate difference for extrusion of sulphur dioxide, the above results then follow.

Our attention was then directed towards the incorporation of substituents on the aromatic acceptor ring, which might be anticipated to encourage [1,5] *ipso* substitution. Thus, the introduction of an *ortho* carbomethoxy group not only led to an improved yield of *ipso* product in the case of sulphonamide **10**, but, even more importantly, yielded lactone **15** from the phenolic derivative **13**, by a process which was totally absent in the earlier parent **3**. Lactam **12** and lactone **15** are presumably formed by base-induced cyclisation of the initially formed *ipso* products during fluoride anion treatment to remove tin residues. Lactones such as **15** have recently been shown to be important precursors for the synthesis of optically active biaryl natural products.[4] The results from incorporation of a *para* methoxy residue, as in substrates **16** and **19**, which will also stabilise an adjacent carbon centred radical, followed a similar pattern. By way of contrast however, the *para* fluoro substituent present in **22** and **25** appears to disfavour [1,5] *ipso* substitution, retard [1,6] addition, and even to allow capture of the initial σ-radical by benzene solvent, as witnessed by the isolation of **24** in low yield (9%) from reaction of **22**. Clearly, the present system provides a particularly subtle probe for electronic effects in radical reactions.

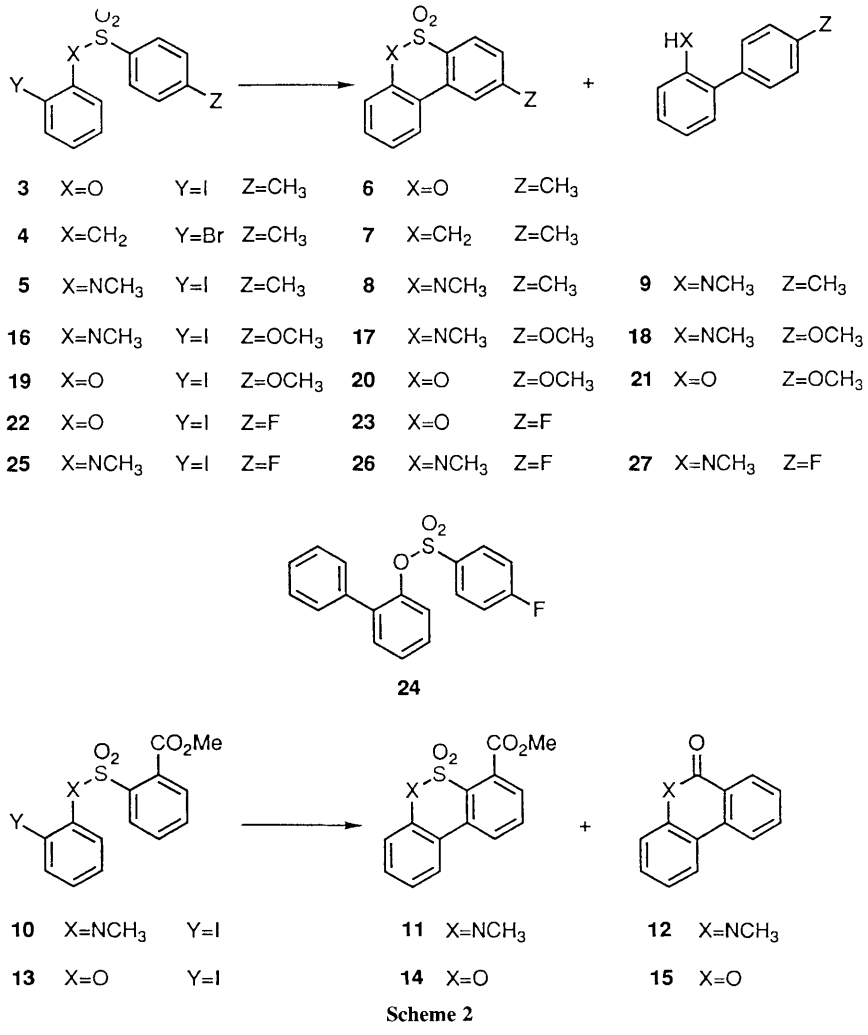
Table 1

Substrate[a]	Recovered starting material (yields %)	Products (yields %)	
		Addition product[b]	*ipso*-Substitution product
3	37	63	0
4	40	40	0
5	25	39	34
10	11	19	65
13	37	21	42
16	34	10	33
19	31	24	18
22	0	50	0
25	26	44	29
28	34	8	37
31	17	0	26

[a] Interchange of bromide and iodide in substrates **3** and **5** did not affect the relative ratio of addition and substitution products. [b] The presumed dihydroaromatic precursors of these products were not detected.

We have also studied the outcome of lengthening the linking chain X (Scheme 1) to provide opportunities for [1,6] *ipso* substitution, as in derivatives **28** and **31**. (Scheme 3 and Table 1). As anticipated, products derived from [1,7] addition are significantly diminished, with the sulphonamide **28** prepared from *ortho* iodobenzoic acid giving a 4.5 : 1 product ratio in favour of the *ipso* pathway.

In summary, the foregoing results, when taken in conjunction with the original observation of Speckamp,[7] would suggest that this strategy has considerable inherent potential for carbon–carbon bond formation to aromatic systems. The present biaryl synthesis, using readily prepared derivatives of *ortho* halo phenols, anilines, and carboxylic acids, offers a



3 X=O Y=I Z=CH_3 **6** X=O Z=CH_3

4 X=CH_2 Y=Br Z=CH_3 **7** X=CH_2 Z=CH_3

5 X=NCH_3 Y=I Z=CH_3 **8** X=NCH_3 Z=CH_3 **9** X=NCH_3 Z=CH_3

16 X=NCH_3 Y=I Z=OCH_3 **17** X=NCH_3 Z=OCH_3 **18** X=NCH_3 Z=OCH_3

19 X=O Y=I Z=OCH_3 **20** X=O Z=OCH_3 **21** X=O Z=OCH_3

22 X=O Y=I Z=F **23** X=O Z=F

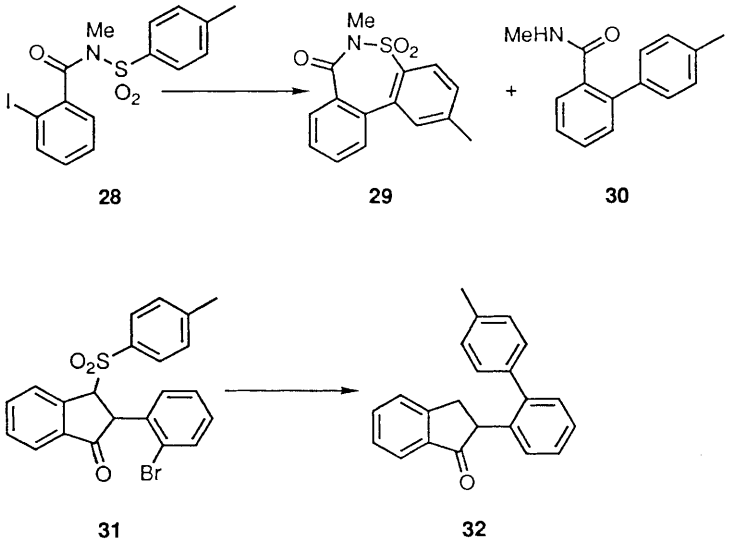
25 X=NCH_3 Y=I Z=F **26** X=NCH_3 Z=F **27** X=NCH_3 Z=F

24

10 X=NCH_3 Y=I **11** X=NCH_3 **12** X=NCH_3

13 X=O Y=I **14** X=O **15** X=O

Scheme 2



Scheme 3

flexible approach, which is not only tolerant of, but also encouraged by, appropriately sited electron donating and/or electron withdrawing groups.

We wish to thank Dr C. R. A. Godfrey and Professor A. L. J. Beckwith for helpful discussions and the SERC for the award of a studentship (to A. M. K. P.). We are also grateful to ICI Agrochemicals for invaluable financial assistance.

Received, 4th April 1991; Com. 1/01589C

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