Sequential *ortho*-lithiations; the sulfoxide group as a relay to enable *meta*-substitution†

Jonathan P. Flemming,[a,b] Malcolm B. Berry[b] and John M. Brown*[a]

Received 1st November 2007, Accepted 17th February 2008
First published as an Advance Article on the web 25th February 2008
DOI: 10.1039/b716954j

Sulfoxides are known to be powerful directing groups for *ortho*-lithiation, even in competition with other directors. This has been utilised to introduce substituents *meta*- to a methoxy-group by sequential lithiation, reaction with Me *tert*-butylsulfinate, and a second lithiation. Electrophilic trapping of the ensuing lithio-compound with a range of electrophiles followed by reductive removal of the sulfoxide led to *meta*-substituted anisoles. Some interesting side-reactions were uncovered, including a short synthesis of quinazolines arising from the use of PhCN in the second step.

Introduction

Directed metallation has become one of the most useful methods for the regioselective introduction of substituents into an aromatic ring.[1,2] A clear majority of examples involve organolithium reagents, and *ortho*-substitution is achieved by stabilisation of the new organolithium species. In the majority of cases this involves direct lithium ligation by the substituent, but simple inductive carbanion-stabilising effects can also lead to regiospecific metallation.[3] The magnesium[4] or zinc derivatives[5] of hindered secondary amines are also effective metallating agents towards sp^2-carbon. Similar results ensue in substituent-directed catalytic CH-activations, leading to coupling reactions that occur *ortho*- to the directing group.[6] Cases where a substituent directs metallation to more remote sites are infrequent, but lateral metallations from the *ortho*-position of a biaryl to the *ortho*-position of the remote ring are well established, however.[7] In both ferrocene,[8] and arenechromium tricarbonyl systems,[9] metallation can occur *meta*- to an existing substituent as outlined in Fig. 1. Comparable examples in simple arenes have only recently been demonstrated. Mulvey and co-workers have more recently shown that the metallation of aromatics with mixed organozinc–organoalkali reagents leads to the formation of a crystallographically characterised *meta*-metallated species.[10]

Schlosser and co-workers have demonstrated that the buttressing effect of a trialkylsilyl group can redirect the metallation of 1,3-dihalo-2-silylbenzenes to the remote CH-site, provided that potassium or mixed potassium–lithium bases were used.[11] The iridium-catalysed borylation of aromatic rings is strongly influenced by the steric consequences of existing substituents, leading to intrinsic preference for *para*-substitution of monosubstituted arenes, and for the substitution of more remote sites in polycyclic systems.[12]

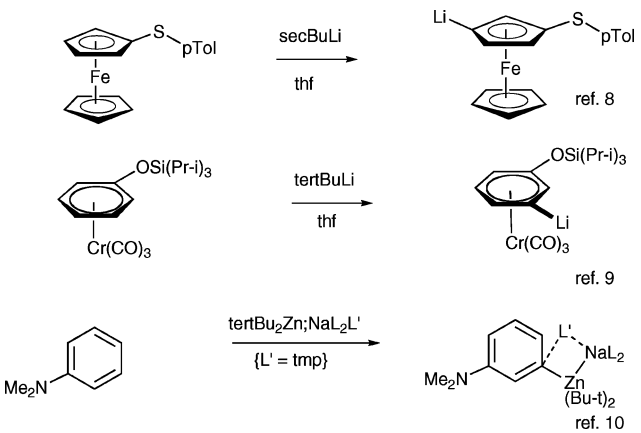


Fig. 1 Examples of *meta*-metallating procedures.

The motivation behind the present work was to develop a protocol for the introduction of a *meta*-substituent into an arene by two sequential directed *ortho*-metallations. This principle has recently been established for ferrocenes by two independent groups. Weissensteiner and co-workers demonstrated that enantiomerically pure dimethylaminoethyl-ferrocene could be lithiated and then brominated to give a single diastereomer of the monobromo derivative. In turn, this could be *ortho*-lithiated adjacent to –Br at low temperatures without LiBr elimination, and the resulting lithio-compound then trapped by electrophiles.[13] In the ferrocene series, elimination of *ortho*-halo lithium species to form an aryne is far more difficult than for 6-ring arenes, rendering this route possible. Reduction of C–Br led to the desired *meta*-disubstituted product, Similarly acetal C–O *ortho*-direction followed by sulfoxide trapping afforded a ferrocenyl sulfoxide that could be further lithiated and the desired electrophile introduced at the adjacent position. Removal of the "traceless" sulfoxide group was achieved by direct reaction with *tert*-butyllithium.[14]

[a]*Chemical Research Laboratory, Mansfield Rd, Oxford, UK OX1 3TA. E-mail: john.brown@chem.ox.ac.uk; Fax: 44 1865 285002; Tel: 44 1865 275642*
[b]*GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts, UK SG1 2NY*

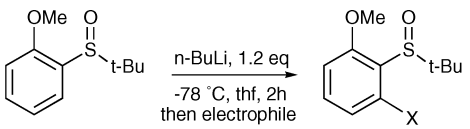
† Electronic supplementary information (ESI) available: ^{13}C Spectra for compounds in Schemes 1, 2, 3; CIF files for **4b**, **4d**, **4f**. See DOI: 10.1039/b716954j

Results and discussion

Directed sulfoxide *ortho*-lithiations and trapping of the intermediate

The dual characteristics of the sulfoxide group as a powerful *ortho*-lithiation director, coupled with its ability to be "traceless", encouraged its use in the project.[15] Methyl *tert*-butylsulfinate, **1**, prepared from dimethyl sulfite following the method of Mikolajczyk and Drabowicz in 94% yield,[16] was reacted with 2-lithioanisole, to afford 1-methoxy-2-*tert*-butylsulfinyl benzene, **2**, in 97% yield. Treatment of the substrate with 1.2 equivalents of *n*-butyllithium at −78 °C in thf for 2 h, followed by D_2O quench gave only the desired 1,2,3-trisubstituted product **3** in 96% yield. The ^2H NMR shows a single peak at 7.7 ppm.

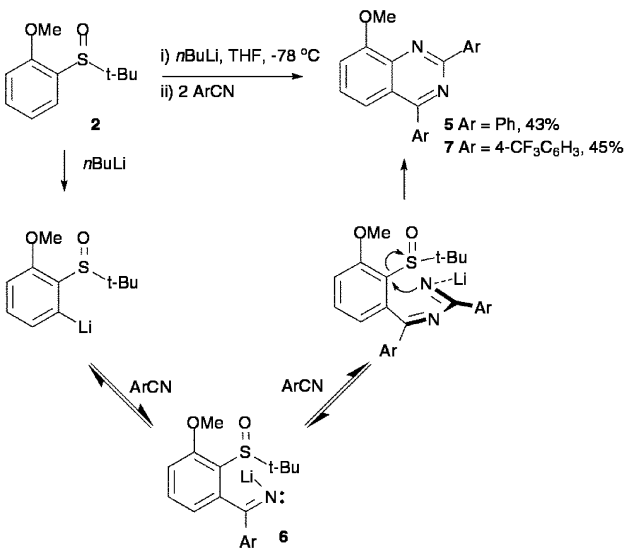
This clearly demonstrates, as expected, that the sulfinyl group is the predominant director of *ortho*-lithiation. This led us to try a range of different electrophiles in conjunction with 2-(*tert*-butylsulfinyl)-3-lithioanisole, with the outcome as reported in Scheme 1. Thus a number of electrophiles were successfully reacted with 2-*tert*-butylsulfinyl-3-lithioanisole, yielding 1,2,3-trisubstituted benzenes, **4a–f**. The dimethylamide **4a** was prepared in moderate yield from dimethylcarbamoyl chloride, whilst the aldehyde, **4b**, was prepared in 71% yield by reaction with ethyl formate. In this case the electrophile had to be added to the reaction at −100 °C to obtain this single trisubstituted product, as a complex mixture of products resulted when the reaction took place at −78 °C. Easy bromination of the aryllithium to **4c** took place in good yield using 1,1,2-tribromo-1,2,2-trifluoroethane. Generation of the primary alcohol **4d** proved successful using paraformaldehyde giving the product in 52% isolated yield. ^1H NMR spectroscopy of the product showed diasterotopic benzylic protons at 5.36 ppm and 4.24 ppm ($J = 12.2$ Hz). The X-ray crystal structure indicated an intramolecular hydrogen bond between the primary alcohol and the sulfoxide (Fig. 2). Generation of the desired boronate occurred using B-isopropyl pinacolborate as the electrophile. The use of one equivalent of the electrophile gave **4e** cleanly, which could then be used in subsequent steps without the need for any purification, whereas the use of excess reactant led to unidentified side-products. Finally, alkylation of the substrate using iodomethane worked satisfactorily giving the product **4f** in high yield. When diisopropylcarbamoyl chloride, DMF or acetyl chloride were employed however, the overall reaction was unsuccessful.



2 (ex. *t*-BuS(O)OMe, **1**) — **3**, X = D; **4a**, X = $CONMe_2$; **4b**, X = CHO; **4c**, X = Br; **4d**, X = CH_2OH; **4e**, X = $B(OCMe_2CMe_2O)$; **4f**, X = Me.

Scheme 1 Trapping of the lithio reagent; **3** D_2O −78 °C; **4a**, Me_2NCOCl, −78 °C–ambient, then 16 h, 63%; **4b**, EtOCHO, −100 °C, 1 h, 71%; **4c**, $CBrF_2CFBr_2$, as **4a**, 82%; **4d**, $(CH_2O)_n$, as **4a**, 52%; **4e**, (i-PrB(OCH_2CH_2O), as **4a**, 89%; **4f**, MeI, as **4a**, 96%.

When benzonitrile was employed as the electrophile the expected product was not formed. Instead, 8-methoxy-2,4-diphenylquinazoline **5** was produced in 85% yield. The structure of this product was elucidated from its ^1H NMR spectrum with two distinguishing multiplets at 8.73–8.70 ppm (2H) and 7.91–7.87 ppm (2H) associated with *ortho* protons on the phenyl rings at the 2- and 4-positions, respectively. High-resolution mass spectrometry gave $m/z = 313.1346$, corresponding to $[M + H]^+$. A possible pathway for the formation of compound **5** is shown in Scheme 2. Following the initial *ortho*-lithiation of the sulfoxide, nucleophilic attack on benzonitrile occurs. A further nucleophilic attack by the substrate on a second equivalent of benzonitrile takes place, followed by intramolecular SnAr displacement of the sulfoxide moiety. Previous observations on the double addition of benzonitrile to an aryllithium giving a quinazoline have been conducted with either an ^-OR or Cl^- as leaving group. In these previously reported examples, the yields for the quinazoline were low.[17] Diverse reaction conditions were employed to try and intercept the presumed intermediate **6**. Using one equivalent of benzonitrile gave **5** in 43% yield (50% maximum) suggesting that addition to the second equivalent was faster than addition to the first. Neither carrying out the reaction at −78 °C nor high dilution proved successful. Use of 4-trifluoromethylbenzonitrile as electrophile provided the quinazoline, **7**, in 45% yield. Competition between one equivalent of *ortho*-lithiated **3** and two equivalents of benzonitrile and 4-trifluoromethylbenzonitrile gave **7** as the major



Scheme 2 Route to quinazoline formation *via* double addition of PhCN.

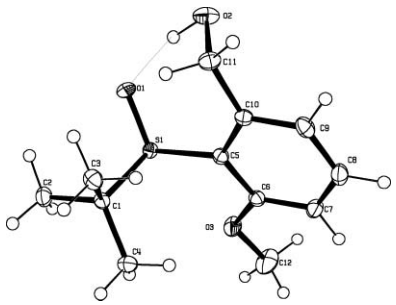
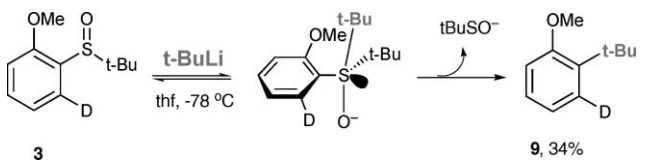


Fig. 2 X-Ray structure of **4d**; ORTEP display. X-Ray structures of **4b** and **4f** are also recorded in the ESI.†

product, but analysis of the crude ^{1}H NMR spectrum revealed *ca.* 4% of **5** (δ 8.75 ppm) along with two other unidentified products (δ 8.89 ppm [4%] and δ 8.69 ppm [6%]). There was no evidence for crossover products in the GC-MS of the crude reaction product.

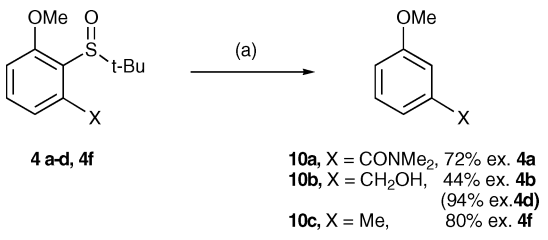
Removal of the sulfoxide group

In initial attempts, direct nucleophilic displacement was explored. Treatment of 2-*t*-butylsulfoxido-3-deuteroanisole **3** with two equivalents of *t*-butyllithium in THF at −78 °C, however, did not give the desired 1,3-disubstituted product **8** but instead yielded the ligand coupled product **9** (Scheme 3). The structure of this product was confirmed by NMR HMBC analysis, which showed long range coupling between the protons of the *tert*-butyl group and the carbon at the 2-position of the aromatic ring. The same observation has been made by Clayden *et al.* but in their case a SNAr mechanism was suggested, based on the demonstration from ^{13}C-labelling that the *t*-butyl group of the sulfoxide is completely lost in the coupled product.[18] In our hands, however, the use of *n*-BuLi leads only to *ortho*-lithiation. Our explanation of this is that ligand coupling rather than SNAr is indeed the predominant mechanism for the reaction. Attack of a nucleophile upon a tetrahedral sulfoxide furnishes a pentacoordinate intermediate, with the incoming nucleophile occupying an axial position. In the case of *t*-BuLi attacking the aromatic sulfoxide **3**, the *tert*-butyl group from *t*-BuLi takes the axial position in the pentacoordinate intermediate, which is disposed at 90° to the aromatic ring. Reductive elimination of these two groups gives rise to the ligand-coupled product **9**. If this process is faster than pseudorotation, the two *tert*-butyl groups remain distinct and only the one associated with *t*-BuLi appears in the product.



Scheme 3 A ligand coupling mechanism for the formation of product **9**.

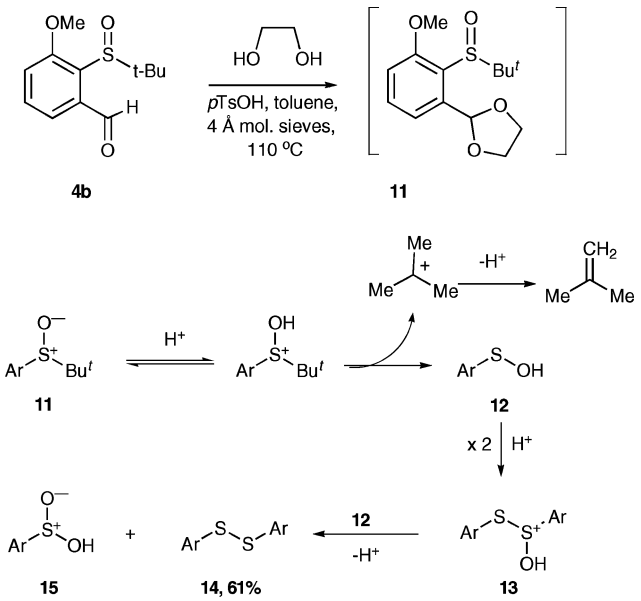
Attempted reduction of 2-*tert*-butylsulfinyl-3-methoxy-*N*,*N*-dimethylbenzamide, **4a**, with methylmagnesium bromide gave no reaction. Trying to increase the reactivity of the Grignard reagent through addition of either lithium chloride or a lithium chloride–15-crown-5 mixture also proved unsuccessful.[19] Reduction of **4a** was also attempted using lithium–naphthalene in THF at −78 °C. Once again, no reaction was obtained, and the starting material was recovered. In the light of these difficulties, reduction of products **4a–f** was attempted with Raney nickel (Scheme 4). Compounds **4a**, **4d**, **4f** were reduced cleanly to give the desired



Scheme 4 (a) Raney Ni, EtOH, reflux, 3 h, [MeOH for **4b**].

1,3-disubstituted products **10a**, **10b**, **10c** in good yield. In contrast, compound **4b** underwent reduction of both the carbon–sulfur bond and the aldehyde, giving compound **10b**.

When the aldehyde **4b** was converted into the corresponding dioxolane **11** prior to desulfurisation, an unusual reaction occurred (Scheme 5), which can be rationalised thus. Conversion of sulfanols into sulfinothioates with liberation of water is a known process.[20] Brodnitz *et al.* have also reported the thermal decomposition of the sulfinothioate garlic extract, allicin, to its corresponding disulfide.[21] Under the acidic reaction conditions, we propose that the aryl sulfoxide is protonated and then undergoes elimination of *tert*-butyl cation to give the sulfanol, **12**. This can then be protonated once again, and the resulting cation undergoes nucleophilic attack by a second molecule of **12**, eliminating water to produce the sulfanium cation, **13**. A third molecule of **12** comes into play, reducing **13** to the disulfide, **14** and forming the sulfinic acid, **15** concomitantly. As a result the disulfide, **14** can only be obtained in a maximum 67% yield.



Scheme 5 Indicated route to the disproportionation product **14**.

Attempted reduction of pinacolboronate, **4e**, was unsuccessful and hence Suzuki coupling with iodobenzene was attempted first. This gave a mixture of products, where the only one readily isolated was 3-methoxy-2-phenylsulfanylbiphenyl, **16**, in 14% yield. This curious result demonstrates that the *t*-butylsulfinyl group is labile under the conditions of Suzuki coupling, and the aryl sulfide so formed can undergo heteroatom cross-coupling with PhI.[22]

Conclusions

The paper describes a method for the relay of lithiation from the *ortho*- to the *meta*-position of an electron rich aromatic ring, utilizing the superior ability of a sulfoxide in directed lithiation. The principle is demonstrated and leads incidentally to a useful synthesis of quinazolines. Its utility is diminished by the lack of ease and generality in the final sulfoxide removal step. Future publications will address this limitation.

Experimental

Techniques, materials and instrumentation

All reactions were conducted in oven- or flame-dried glassware. Reactions involving air- and water-sensitive reagents were performed under a dry Ar atmosphere using a standard vacuum line and Schlenk techniques. Solvents used in chromatography were BDH AnalaR or GPR grade and were used without further purification. Solvents used for reactions either were distilled prior to use: CH_2Cl_2 (from CaH_2); toluene, THF and Et_2O (from benzophenone and sodium) or dried *via* an alumina Grubb's column. All other solvents or reagents were used as commercially supplied and were used without further purification except when otherwise noted. Standard chromatographic and TLC procedures were used. NMR spectra were recorded using a Bruker AV400 spectrometer, Bruker DPX400 or Bruker AMX500. FT IR spectra were recorded as thin films on a KBr disc using a Perkin-Elmer Paragon 1000 spectrometer. Mass spectra were recorded by the author or Mr R. Proctor using either Micromass GCT (CI) or V.G. Autospec spectrometers (EI and CI). Exact masses were measured on a Waters 2790-Micromass LCT spectrometer or a V.G. Autospec spectrometer using EI or CI.

1-Methoxy-2-*tert*-butylsulfinylbenzene (2). Anisole (0.55 ml, 5.0 mmol, 1 eq.) was dissolved in anhydrous THF (5 ml) under argon and treated with TMEDA (1.14 ml, 7.5 mmol, 1.5 eq.) and 1.6M *n*-BuLi in hexanes (4.69 ml, 7.5 mmol, 1.5 eq.). The reaction was stirred at ambient temperature for two hours before being cooled to −78 °C and being treated with methyl *tert*-butyl sulfinate[17] (1.02 g, 15.0 mmol, 1.5 eq.) in anhydrous THF (5 ml). The reaction was stirred at −78 °C for two hours before being quenched with sat. NH_4Cl solution (8 ml). The two layers were separated and the aqueous layer was washed ethyl acetate (2 × 20 ml). The combined organic phases were washed with 2 M HCl (3 × 20 ml) and brine (2 × 20 ml) before being dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (3 : 2 pentane–ethyl acetate) yielding the title compound (1.026 g, 97%) as a colourless oil; ν_{max} (KBr disc) 3068 (m, C–H[aromatic]), 2977 (s, C–H[aliphatic]), 2867 (m, O–CH_3), 1586 (s, aromatic ring), 1478 (s, aromatic ring), 1031 (s, S=O), 759 (s, four adjacent aromatic C–H); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.73 (1 H, dd, *J* 1.8 and 7.7, Ar*H*), 7.43–7.38 (1 H, m, Ar*H*), 7.11 (1 H, m, Ar*H*), 6.89 (1 H, dd, *J* 1.1 and 8.3, Ar*H*), 3.81 (3 H, s, OCH_3), 1.17 (9 H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 157.0, 132.2, 128.5, 127.3, 120.9, 110.6, 57.3, 55.4, 22.8; *m/z* (CI+) 213.0954 (M + H^+, $C_{11}H_{17}O_2S$ requires 213.0949). Spectroscopic data is in agreement with the literature.[17]

***ortho*-Lithiation of 1-methoxy-2-*tert*-butylsulfinylbenzene.** 1-Methoxy-2-*tert*-butylsulfinylbenzene (424 mg, 2.00 mmol, 1 eq.) was dissolved in anhydrous THF (20 ml) under argon and cooled to −78 °C. 1.6 M *n*-BuLi in hexanes (1.5 ml, 2.4 mmol, 1.2 eq.) was added to the reaction, which was stirred at −78 °C for two hours.

1-Methoxy-2-*tert*-butylsulfinyl-3-deuterobenzene (3). To this solution was added D_2O (2 ml) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic phases were washed with brine (3 × 10 ml) before being dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure yielding the title compound (409 mg, 96%) as a colourless oil; ν_{max} (KBr disc) 3064 (w, C–H[aromatic]), 2964 [m, C–H[aliphatic], 2927 (m, C–H[aliphatic]), 1581 (s, aromatic ring), 1034 (s, S=O); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.41 (1 H, dd, *J* 8.2 and 7.4, Ar*H*), 7.11 (1 H, dd, *J* 7.4 and 1.1, Ar*H*), 6.89 (1 H, dd, *J* 8.3 and 1.2, Ar*H*), 3.81 (3 H, s, OCH_3), 1.17 (9 H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 157.0, 132.2, 128.4, 127.3 (d), 120.8, 110.6, 57.3, 55.4, 22.8; δ_D (500 MHz; $CHCl_3$; $CDCl_3$) 7.78 (1 D, br s, Ar*D*); *m/z* (CI+) 213.0942 (M^+, 100%, $C_{11}H_{15}DO_2S$ requires 213.0934).

***N*,*N*-Dimethyl-2-*tert*-butylsulfinyl-3-methoxybenzamide (4a).** To a solution of 1-methoxy-2-*tert*-butylsulfinyl-3-lithiobenzene at −78 °C (2 mmol) was added dimethylcarbamyl chloride (0.55 ml, 6.0 mmol, 1.2 eq.) dropwise. The reaction was then warmed to ambient temperature and stirred for 16 hours. The reaction was quenched with sat. NH_4Cl solution (10 ml) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 ml). The combined organic phases were washed with brine (3 × 10 ml) before being dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (95 : 5 EtOAc–MeOH) yielding the title compound (898 mg, 63%): as a yellow solid; mp 110–112 °C; ν_{max} (KBr disc) 3066 (m, C–H[aromatic]), 2962 (m, C–H[aliphatic]), 1646 (s, C=O), 1570 (m, aromatic ring), 1052 (s, S=O); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.28 (1 H, m, Ar*H*), 6.77 (1 H, dd, *J* 8.3 and 1.0, Ar*H*), 6.70 (1 H, dd, *J* 7.6 and 1.1, Ar*H*), 3.67 (3 H, s, OCH_3), 2.85 (3 H, s, NCH_3), 2.47 (3 H, s, NCH_3), 1.13 (9 H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 169.7, 156.6, 138.4, 131.8, 125.3, 120.9, 110.3, 59.9, 55.1, 38.5, 34.4, 24.2; *m/z* (CI+) 284.1310 (M + H^+, $C_{14}H_{22}NO_3S$ requires 284.1320).

Related preparations with lithiated **2** (**4a–4f**, **5**, **7**; 2 mmol scale) follow:

2-*tert*-Butylsulfinyl-3-methoxybenzaldehyde (4b). With ethyl formate (0.323 ml, 4.00 mmol, 2 eq.) at −100 °C; was stirred for 50 minutes before being warmed to ambient temperature and stirred for 1 h. Workup as above and recrystallisation from 60–80 petroleum spirit–ethyl acetate to give the title compound (343 mg, 71%) as a yellow solid; mp 110–113 °C (from petroleum spirit–ethyl acetate); ν_{max} (KBr disc) 3073 (m, C–H[aromatic]), 2978 (m, C–H[aliphatic]), 1692 (s, C=O), 1570 (s, aromatic ring), 1027 (s, S=O), 807 (m, 3 adjacent aromatic C–H); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 11.26 (1 H, s, C*H*O), 7.57 (1 H, dd, *J* 7.7 and 1.3, Ar*H*), 7.51 (1 H, m, Ar*H*), 7.10 (1 H, dd, *J* 8.1 and 1.3, Ar*H*), 3.85 (3 H, s, OCH_3), 1.28 (9 H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 191.9, 157.6, 141.5, 132.3, 129.7, 121.2, 115.1, 59.3, 56.1, 23.6; *m/z* (CI+) 241.0898 (M + H^+, $C_{12}H_{17}O_3S$ requires 241.0898).‡

1-Bromo-2-*tert*-butylsulfinyl-3-methoxybenzene (4c). With 1,1,2-tribromo-1,2,2-trifluoroethane (770 mg, 2.40 mmol, 1.2 eq) in anhydrous THF (10 ml) at −78 °C, then warmed to ambient temperature and stirred for 16 h. Workup as before and purification by flash column chromatography (EtOAc) yielded the title compound (476 mg, 82%) as a white solid; mp 104–107 °C;

‡ CCDC reference numbers 665873, 672147 and 672148. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b716954j

ν_{max} (KBr disc) 3071 (w, C–H[aromatic]), 2964 (m, C–H[aliphatic]), 2926 (m, C–H[aliphatic]), 2864 (w, O–CH_3), 1575 (s, aromatic ring), 1059 (s, S=O), 776 (s, three adjacent aromatic C–H), 730 (s, C–Br); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.24–7.17 (2 H, m, 2 × Ar*H*), 6.91 (1 H, dd, *J* 7.8 and 1.3, Ar*H*), 3.84 (3 H, s, OCH_3), 1.36 (9 H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 160.7, 132.9, 129.9, 126.6, 125.3, 111.8, 60.3, 55.9, 24.9; *m/z* (CI+) Found: 291.0058 (M + H^+, $C_{11}H_{16}BrO_2S$ requires 291.0054).

2-*tert*-Butylsulfinyl-3-methoxyphenylmethanol (4d). With paraformaldehyde (120 mg, 4.00 mmol, 2 eq.), in anhydrous THF (20 ml) at −78 °C; the reaction mixture was warmed to ambient temperature and stirred for 16 h, workup as before. Recrystallisation from diethyl ether–methanol yielded the title compound (121 mg, 25%) as a white solid. The supernatant liquid was concentrated under reduced pressure and the remaining crude product was purified by flash column chromatography (ethyl acetate) yielding the title compound (130 mg, 27%) as a white solid (251 mg, 52% total); mp 123–126 °C; ν_{max} (KBr disc) 3383 (br s, OH), 2962 (s, C–H[aliphatic]), 2935 (s, C–H[aliphatic]), 1574 (s, aromatic ring), 1026 (s, S=O), 760 (m, three adjacent aromatic C–H); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.37 (1 H dd, *J* 8.4 and 7.5, Ar*H*), 7.00 (1 H, dd, *J* 7.6 and 1.3, Ar*H*), 6.87 (1 H, dd, *J* 8.4 and 1.2, Ar*H*), 5.36 (1 H, d, *J* 12.2, C*H*HOH), 4.24 (1 H, d, *J* 12.2, CH*H*OH), 3.78 (3 H, s, OC*H*), 1.31 (9 H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 158.3, 144.6, 132.5, 125.8, 125.4, 111.1, 64.5, 60.1, 55.7, 24.1; *m/z* (CI+) 243.1057 (M + H^+, $C_{12}H_{19}O_3S$ requires 243.1055).

2-[2-*tert*-Butylsulfinyl-3- methoxyphenyl]-4,4,5,5-tetramethyl-[1, 3,2]dioxaborolane (4e; 1 mmol scale). With 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxoborane (0.21 ml, 1.0 mmol, 1 eq.), stirred at −78 °C for 16 h. Standard workup yielded the title compound (302 mg, 89%) as a yellow oil; ν_{max} (KBr disc) 3071 (w, C–H[aromatic]), 2964 (m, C–H[aliphatic]), 2926 (m, C–H[aliphatic]), 2839 (w, O–CH_3), 1566 (s, aromatic ring), 1467 (s, aromatic ring), 1371 (s, B–O), 1032 (s, S=O), 942 (s, B–C), 782 (s, three adjacent aromatic C–H); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.37 (1 H, dd, *J* 7.8 and 7.4, Ar*H*), 7.23 (1 H, dd, *J* 7.2 and 0.7, Ar*H*), 6.74 (1 H, dd, *J* 8.0 and 0.6, Ar*H*), 3.73 (3 H, s, OCH_3), 1.26 (6 H, s, 2 × CH_3), 1.22 (9 H, s, 3 × CH_3), 1.20 (6 H, s, 2 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 154.9, 133.3, 124.9, 124.1, 109.7, 80.3, 60.4, 55.0, 25.7, 24.5, 23.9; *m/z* (CI+) 361.1616 (M + Na^+, $C_{17}H_{27}BNaO_4S$ requires 361.1615).

2-*tert*-Butylsulfinyl-3-methoxytoluene (4f). With iodomethane (0.17 ml, 2.7 mmol, 1.33 eq.) at −78 °C then warmed to ambient temperature and stirred for 16 h. Workup yielded the title compound (432 mg, 96%) as a white solid; mp 112–114 °C; ν_{max} (KBr disc) 3074 (w, C–H[aromatic]), 2961 (m, C–H[aliphatic]), 2952 (m, C–H[aliphatic]), 1573 (s, aromatic ring), 1048 (s, S=O), 787 (s, 3 adjacent aromatic C–H); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.25 (1 H, dd, *J* 8.3 and 8.0, Ar*H*), 6.77 (1 H, dd, *J* 7.7 and 0.5, Ar*H*), 6.74 (1 H, dd, *J* 8.3 and 0.5, Ar*H*), 3.78 (3 H, s, OCH_3), 2.64 (3 H, s, ArCH_3), 1.29 (9 H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 158.8, 142.4, 131.5, 125.6, 125.1, 109.0, 59.4, 55.5, 24.2, 19.4; *m/z* (CI+) 227.1114 (M + H^+, $C_{12}H_{19}O_2S$ requires 227.1106).‡

8-Methoxy-2,4-diphenylquinazoline (5). With benzonitrile (0.205 ml, 2.00 mmol, 1 eq.) at −78 °C then ambient for 16 h. Workup and recrystallisation from 60–80 petroleum spirit–methanol giving the title compound (266 mg, 43%–maximum 50% yield) as a white crystalline solid; mp 150–151 °C (60–80 petroleum spirit–methanol); λ_{max} (EtOH)/nm 298 (ε/dm^3 mol^{-1} cm^{-1} 8333), 237 (ε/dm^3 mol^{-1} cm^{-1} 3333), 222 (ε/dm^3 mol^{-1} cm^{-1} 5100); ν_{max} (KBr disc) 3033 (w, C–H[aromatic]), 2983 (m, C–H[aliphatic]), 2904 (m, C–H[aliphatic]), 1611 (s, conjugated cyclic imine), 1537 (s, aromatic ring), 853 (s, three adjacent aromatic C–H), 779 (s, five adjacent aromatic C–H); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.73–8.70 (2 H, m, 2 × Ar*H*), 7.91–7.87 (2 H, m, 2 × Ar*H*), 7.72–7.68 (1 H, m, Ar*H*), 7.61–7.58 (3 H, m, 3 × Ar*H*), 7.55–7.44 (4 H, m, 4 × Ar*H*), 7.25–7.22 (1 H, m, Ar*H*), 4.15 (3 H, s, OCH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 168.1, 159.6, 155.3, 144.3, 138.2, 138.0, 130.4, 130.2, 129.8, 128.8, 128.4, 122.6, 118.5, 111.5, 56.4; *m/z* (CI+) 313.1346 (M + H^+, $C_{21}H_{17}N_2O$ requires 313.1341).

8-Methoxy-2,4-bis(4-(trifluoromethyl)phenyl) quinazoline (7). With 4-trifluoromethylbenzonitrile (171 mg, 1 mmol, 2 eq.) as for the preparation of **5**. The product was purified by flash column chromatography (9 : 1 pentane–ethyl acetate) giving the title compound (100 mg, 45%) as a white solid; mp 174–178 °C; λ_{max} (EtOH)/nm 300 (ε/dm^3 mol^{-1} cm^{-1} 8500), 220 (ε/dm^3 mol^{-1} cm^{-1} 6000); ν_{max} (KBr disc) 2956 (w, C–H[aliphatic]), 1608 (m, conjugated cyclic imine), 1539 (m, aromatic ring), 1120 (s, C–F), 855 (s, two adjacent aromatic C–H), 766 (s, three adjacent aromatic C–H), 752 (m, C–F); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.80 (2 H, d, *J* 8.1, 2 × Ar*H*), 7.99 (2 H, d, *J* 8.0, 2 × Ar*H*), 7.87 (2 H, d, *J* 8.1, 2 × Ar*H*), 7.77 (2 H, d, *J* 8.3, 2 × Ar*H*), 7.62 (1 H, dd, *J* 8.4 and 1.1, Ar*H*), 7.54 (1 H, t, *J* 7.8, Ar*H*), 7.29 (1 H, dd, *J* 7.8 and 1.0, Ar*H*) 4.17 (3 H, s, OCH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 167.0, 158.2, 155.5, 144.2, 141.2, 130.5, 129.0, 128.1, 125.6–125.4 (m), 122.6, 117.8, 112.0, 56.5; *m/z* (CI+) 448.1015 (M^+, $C_{23}H_{14}F_6N_2O$ requires 448.1010).

Competition reaction between two equivalents of benzonitrile and two equivalents of 4-trifluoromethylbenzonitrile for one equivalent of 1-methoxy-2-*tert*-butylsulfinyl-3-lithiobenzene. To a solution of 1-methoxy-2-*tert*-butylsulfinyl-3-lithiobenzene at −78 °C prepared on a 0.5 mmol scale was added 4-trifluoromethylbenzonitrile (171 mg, 1 mmol, 2 eq.) and benzonitrile (103 µl, 1 mmol, 2 eq.) at the same time followed by warming to ambient temperature and stirring for 16 hours. The reaction was quenched with 2 M aqueous NaOH solution (2 ml) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic phases were washed with brine (3 × 10 ml) before being dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Analysis of the crude product by ^{1}H NMR showed that 8-methoxy-2,4-bis(4-(trifluoromethyl)phenyl) quinazoline was achieved as the major product with agreement to previously recorded spectra.

2-*tert*-Butyl-3-deuteroanisole (9). 1-Methoxy-2-*tert*-butylsulfinyl-3-deutero benzene (322 mg, 1.55 mmol, 1 eq.) was dissolved in anhydrous THF (5 ml) under argon and cooled to −78 °C. 1.5 M *t*-BuLi in pentane (2.6 ml, 3.90 mmol, 2.5 eq.) was added and the reaction stirred at −78 °C for 5 minutes. The reaction was quenched with sat. NH_4Cl solution (5 ml) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic phases were washed with brine (3 × 10 ml) before being dried over

anhydrous magnesium sulfate, filtered and concentrated under reduced pressure giving 325 mg of product. A 260 mg sample of the product was purified by flash column chromatography (4 : 1 pentane–ethyl acetate) yielding the title compound (70 mg, 34%) as a colourless oil; ν_{max} (KBr disc) 3063 (w, C–H[aromatic]), 2960 (s, C–H[aliphatic]), 2836 (m, O–CH_3), 1592 (s, aromatic ring), 1574 (s, aromatic ring); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.23 (1 H, m, Ar*H*), 6.93 (2 H, m, 2 × Ar*H*), 3.88 (3 H, s, OCH_3), 1.43 (9 H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 158.5, 138.1, 127.0, 126.3 (t), 120.1, 111.5, 60.3, 54.9, 29.7; *m/z* (CI+) 165.1238 (M^+, $C_{11}H_{15}DO$ requires 165.1264).

***N*,*N*-Dimethyl-3-methoxybenzamide (10a)[23].** *N*,*N*-Dimethyl-2-*tert*-butylsulfinyl-3-methoxy benzamide (400 mg, 1.40 mmol, 1 eq.) was dissolved in ethanol (30 ml) and treated with Raney nickel. The reaction was heated at reflux for 3 h. The reaction was cooled and filtered through celite before being concentrated under reduced pressure yielding the title compound (180 mg, 72%) as a colourless oil; δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.29–7.25 (1 H, m, Ar*H*), 6.95–6.89 (3 H, m, 3 × Ar*H*), 3.78 (3 H, s, OCH_3), 3.07 (3 H, s, NCH_3), 2.94 (3 H, s, NCH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 171.2, 159.4, 137.5, 129.3, 119.0, 115.2, 112.2, 55.2, 39.4, 35.2; *m/z* (CI+) 180.1 (M + H^+, 100%).

3-Methoxybenzyl alcohol (10b)[24]. 2-*tert*-Butylsulfinyl-3-methoxyphenylmethanol (66 mg, 0.27 mmol, 1 eq.) as **10a** gave **10b** (35 mg, 94%) as a colourless oil; δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.25 (1 H, t, *J* 8.1, Ar*H*), 6.93–6.91 (2 H, m, 2 × Ar*H*), 6.83–6.80 (1 H, m, Ar*H*), 4.63 (2 H, s, CH_2OH), 3.79 (3 H, s, OCH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 159.7, 142.5, 129.5, 119.0, 113.1, 112.1, 65.0, 55.1; *m/z* (CI+) 138.1 (M^+, 100%).

3-Methoxytoluene (10c)[25]. 2-*tert*-Butylsulfinyl-3-methoxytoluene (113 mg, 0.50 mmol, 1 eq.) as **10a** (8 h, reflux) gave **10c** (49 mg, 80%) as a colourless oil; δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.18 (1 H, t, *J* 7.6, Ar*H*), 6.80–6.70 (3 H, m, 3 × Ar*H*), 3.80 (3 H, s, OCH_3), 2.34 (3 H, s, ArCH_3); δ_C (400 MHz; $CDCl_3$; $CDCl_3$) 159.5, 139.5, 129.2, 121.5, 114.7, 110.7, 55.1, 21.5; *m/z* (CI+) 122.1 (M^+, 100%).

1,2-Bis-(2-(1,3-dioxolan-2-yl)-6-methoxyphenyl)disulfane (14). 2-*tert*-Butylsulfinyl-3-methoxybenzaldehyde (120mg, 0.5 mmol, 1 eq.) was dissolved in toluene (10 ml) and treated with ethane diol (0.11 ml, 2 mmol, 4 eq.), *para*-toluenesulfonic acid monohydrate (9.5 mg, 0.05 mmol, 10 mol%) and 4 Å molecular sieves. The mixture was heated at reflux for four hours before being cooled and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (3 : 2 pentane–ethyl acetate) yielding the title compound (64 mg, 61%) as a yellow oil; ν_{max} (KBr disc) 3071 (m, C–H[aromatic]), 2947 (s, C–H[aliphatic]), 2888 (s, C–H[aliphatic]), 2839 (s, O–CH_3), 1575 (s, aromatic ring), 779 (s, three adjacent aromatic C–H); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.34 (2 H, t, *J* 8.0, 2 × Ar*H*), 7.19 (2 H, dd, *J* 7.8 and 1.1, 2 × Ar*H*), 6.89 (2 H, dd, *J* 8.2 and 1.1, 2 × Ar*H*), 6.01 (2 H, s, 2 × ArC*H*), 4.04–4.00 (4 H, m, 2 × CH_2), 3.90–3.87 (4 H, m, 2 × CH_2), 3.68 (6 H, s, 2 × OCH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 160.1, 141.4, 130.4, 124.7, 118.0, 111.6, 101.3, 65.3, 55.9; *m/z* (CI+) 423.0932 (M + H^+, $C_{20}H_{23}O_6S_2$ requires 423.0936).

3-Methoxy-2-phenylsulfanylbiphenyl (16). 2-[2-*tert*-Butylsulfinyl-3-methoxyphenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (408 mg, 1.2 mmol, 1 eq.) was dissolved in THF (5 ml) and treated with iodobenzene (0.40 ml, 3.6 mmol, 3 eq.), tetrakis(triphenylphosphine) palladium (0) (69 mg, 0.06 mmol, 5 mol%) and 2 M aqueous potassium carbonate solution (5.7 ml, 11.4 mmol, 9.5 eq.). The reaction was heated at reflux for 22 hours before being cooled and the two layers were separated. The aqueous phase was extracted with ethyl acetate (2 × 10 ml) and the combined organic phases were washed with brine (2 × 10 ml), before being dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography yielding the title compound (40 mg, 14%) as a yellow oil; ν_{max} (KBr disc) 3064 (m, C–H[aromatic]), 2953 (s, C–H[aliphatic]), 2890 (s, O–CH_3), 1598 (s, aromatic ring), 779 (s, three adjacent aromatic C–H); δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.47 (1 H, t, *J* 7.8, Ar*H*), 7.35–7.30 (5 H, m, 5 × Ar*H*), 7.20–6.95 (7 H, m, 7 × Ar*H*), 3.75 (3 H, s, OCH_3); δ_C (100 MHz; $CDCl_3$; $CDCl_3$) 159.2, 141.3, 137.6, 136.9, 131.0, 129.1, 128.9, 127.1, 126.8, 125.2, 123.7, 121.7, 111.7, 54.9; *m/z* (CI+) 293.0990 (M + H^+, $C_{19}H_{17}OS$ requires 293.0995).

Acknowledgements

JPF thanks EPSRC and GSK for a CASE award, and University College, Oxford for a Scholarship.

References

1 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879–933; P. Beak and V. Snieckus, *Acc. Chem. Res.*, 1982, **15**, 306–312.
2 J. Clayden, *Organolithiums: Selectivity for Synthesis*, VCH, Weinheim, 2002.
3 M. Stratakis, *J. Org. Chem.*, 1997, **62**, 3024–3025, and earlier references.
4 (*a*) P. E. Eaton, C. H. Lee and Y. Xiong, *J. Am. Chem. Soc.*, 1989, **111**, 8016–8018; (*b*) W. Schlecker, A. Huth, E. Ottow and J. Mulzer, *Annalen*, 1995, 1441–1446.
5 (*a*) M. Uchiyama, Y. Matsumoto, D. Nobuto, T. Furuyama, K. Yamaguchi and K. Morokuma, *J. Am. Chem. Soc.*, 2006, **128**, 8748–8750; (*b*) M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo and T. Sakamoto, *J. Am. Chem. Soc.*, 1998, **120**, 4934–4946; (*c*) M. Uchiyama, M. Koike, M. Kameda, Y. Kondo and T. Sakamoto, *J. Am. Chem. Soc.*, 1996, **118**, 8733–8734.
6 J. Q. Yu, R. Giri and X. Chen, *Org. Biomol. Chem.*, 2006, **4**, 4041–4047, and references therein.
7 (*a*) W. Wang and V. Snieckus, *J. Org. Chem.*, 1992, **57**, 424–426; (*b*) S.-i. Mohri, M. Stefinovic and V. Snieckus, *J. Org. Chem.*, 1997, **62**, 7072–7073; (*c*) D. Tilly, S. S. Samanta, A. De, A.-S. Castanet and J. Mortier, *Org. Lett.*, 2005, **7**, 827–830.
8 C. Pichon, B. Odell and J. M. Brown, *Chem. Commun.*, 2004, 598–599.
9 (*a*) H.-G. Schmalz, T. Volk, D. Bernicke and S. Huneck, *Tetrahedron*, 1997, **53**, 9219–9232; (*b*) N. F. Masters and D. A. Widdowson, *J. Chem. Soc., Chem. Commun.*, 1983, 955–956; (*c*) M. Fukui, T. Ikeda and T. Oishi, *Tetrahedron Lett.*, 1982, **23**, 1605–1608.
10 D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman and R. E. Mulvey, *Angew. Chem., Int. Ed.*, 2006, **45**, 3775–3778. Reviewed in:; R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802–3824.
11 C. Heiss, T. Rausis and M. Schlosser, *Synthesis*, 2005, 617–621.
12 (*a*) G. A. Chotana, M. A. Rak and M. R. Smith, *J. Am. Chem. Soc.*, 2005, **127**, 10539; (*b*) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka and M. R. Smith, *Science*, 2002, **295**, 305–308.
13 M. Steurer, K. Tiedl, Y. P. Wang and W. Weissensteiner, *Chem. Commun.*, 2005, 4929.
14 B. Ferber, S. Top, R. Welter and G. Jaouen, *Chem.–Eur. J.*, 2006, **12**, 2081–2086.

15 (*a*) S. Ogawa and N. Furukawa, *J. Org. Chem.*, 1991, **56**, 5723–5726; (*b*) C. Quesnelle, T. Iihama, T. Aubert, H. Perrier and V. Snieckus, *Tetrahedron Lett.*, 1992, **33**, 2625–2628; (*c*) N. Le Fur, L. Mojovic, N. Ple, A. Turck, V. Reboul and P. Metzner, *J. Org. Chem.*, 2006, **71**, 2609–2616.
16 M. Mikolajczyk and J. Drabowicz, *Synthesis*, 1974, 124–126.
17 (*a*) W. J. Houlihan and A. J. Pieroni, *J. Heterocycl. Chem.*, 1973, **10**, 405–406; (*b*) A. C. Ranade, R. S. Mali, R. M. Gidwani and H. R. Deshpande, *Chem. Ind.*, 1977, 310; (*c*) A. C. Ranade, R. S. Mali and H. R. Deshpande, *Experientia*, 1979, **35**, 574; (*d*) B. J. Wakefield and D. J. Berry, *J. Chem. Soc. C*, **1971**, 642–645; (*e*) D. J. Berry, J. D. Cook and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2190–2192.
18 J. Clayden, C. C. Stimson and M. Keenan, *Chem. Commun.*, 2006, 1393–1394.
19 J. L. Garcia Ruano, M. T. Aranda and J. M. Aguirre, *Tetrahedron*, 2004, **60**, 5383–5392.
20 E. Block, S. Ahmad, J. L. Catalfamo, M. K. Jain and R. Apitz-Castro, *J. Am. Chem. Soc.*, 1986, **108**, 7045–7055.
21 M. H. Brodnitz, J. V. Pascale and L. J. Van der Slice, *Agric. Food Chem.*, 1971, **19**, 273–275.
22 G. Mann, D. Baranano, J. F. Hartwig, A. L. Rheingold and I. A. Guzei, *J. Am. Chem. Soc.*, 1998, **120**, 9205.
23 I. N. Somin and E. A. Germanguz, *Zh. Org. Khim.*, 1969, **5**, 1780–1783.
24 Y. Tanoue, A. Terada, I. Seto, Y. Umezu and O. Tsuge, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1221–1224.
25 W. J. Chazin and L. D. Colebrook, *Magn. Reson. Chem.*, 1985, **23**, 597–604.