Sequential Chelation-Assisted Aromatic C–H Functionalisation via Catalytic *meta* Sulfonation

William R. Reynolds,[a,b] Po Man Liu,[b] Gabriele Kociok-Köhn,[b] Christopher G. Frost*[a,b]

[a] Centre for Sustainable Chemical Technologies, University of Bath, Claverton Down, Bath, BA2 7AY, UK

[b] Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK
Fax +44(1225)386231; E-mail: c.g.frost@bath.ac.uk

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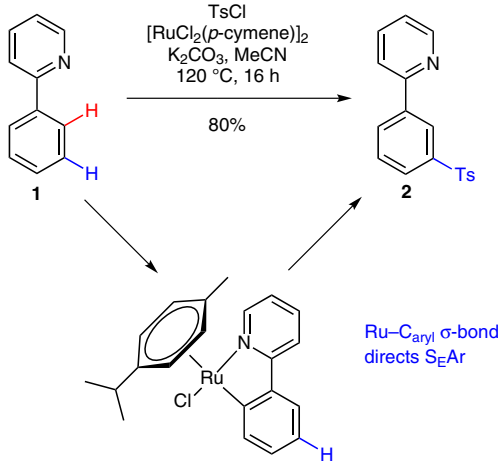
Abstract: The sequential functionalisation of 2-phenylpyridine is presented using selective *ortho*- and *meta*-directing processes. It was found that performing a reaction sequence with *meta* functionalisation first followed by *ortho* functionalisation provided novel reaction products in good yields and with complete regioselectivity.

Key words: catalysis, green chemistry, palladium, regioselectivity, ruthenium

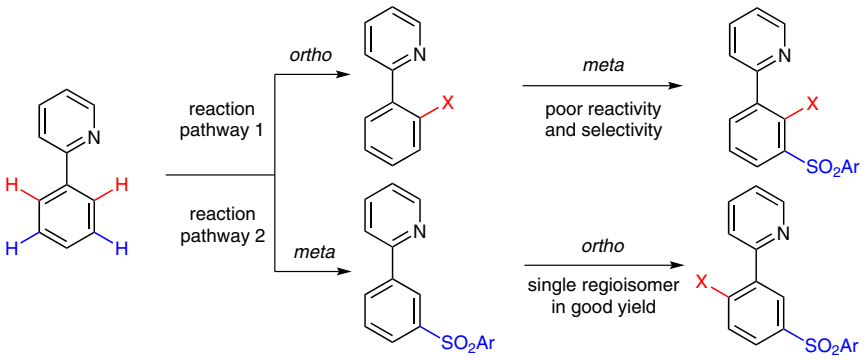
The catalytic functionalisation of C–H bonds is an important synthetic transformation and has been a topic of much interest in recent years.[1] Moreover, the ability to functionalise aromatic C–H bonds regioselectively provides a powerful tool for the efficient synthesis of complex molecular structures. Chelation-assisted *ortho* functionalisation of arenes is well established in the literature and a wide variety of substituents and catalyst systems have been developed.[2] More recently, examples of *meta*-selective catalytic C–H functionalisation have been reported offering diversity in molecular design through alternative reaction strategies. These include substrate-controlled systems,[3] chelation-assisted directing groups such as a pseudo *meta*-directing carboxylic acid moiety[4] and tethered nitrile groups.[5] We have reported a catalytic σ-activation protocol for C–H functionalisation that allows the *meta* sulfonation of 2-phenylpyridines via cyclometallated ruthenium intermediates (Scheme 1).[6] Recently, Ackermann and coworkers have reported similar reactivity with secondary alkyl halides.[7] In this communication



Scheme 1 Catalytic *meta*-directed sulfonation

the sequential functionalisation of an aromatic core is explored using selective *ortho*- and *meta*-directing processes (Scheme 2). The catalytic σ-activation protocol presented here provides a unique mechanism of operation and *meta* selectivity that complements other sequential C–H functionalisation procedures.[8] Several novel, highly substituted aromatic motifs are accessible in good yield and complete regioselectivity in two efficient, catalytic reaction steps.

First, several *ortho* substituents were installed on the phenylpyridine backbone via established C–H activation protocols including OMe, OAc, and Br.[9] The *ortho*-



Scheme 2 Comparison of two opposing reaction sequences

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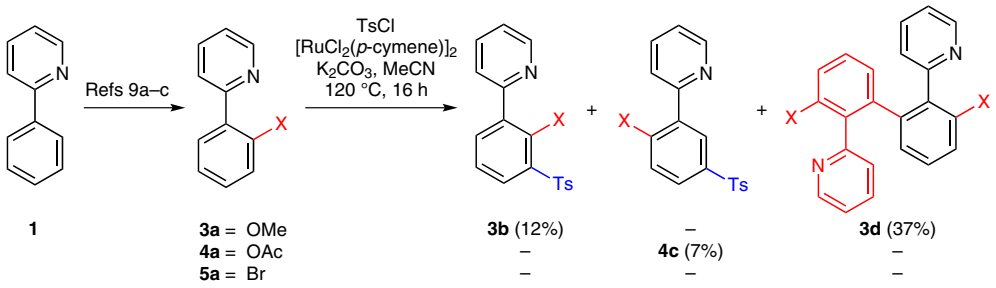

Scheme 3 Poor reactivity via *ortho* then *meta* functionalisation

substituted phenylpyridines were then subjected to the *meta*-sulfonation conditions using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst.[10] Several products were obtained from these reactions as shown in Scheme 3. For substrate **3a** the expected regioselectivity was obtained with substitution at C8–C9 (**3b**) albeit in low yield, with the major product being dimer **3d**. However, upon changing to an OAc substituent **4a** the opposite regioselectivity was obtained to give C8–C11-substituted isomer **4c**. This is likely due to a decrease in directing ability and an increase in steric bulk making this the most favourable product. Increasing the steric bulk even further and completely removing any secondary directing effects, as in **5a**, prevented any reaction from occurring, and only starting material was returned.

In contrast to reaction pathway 1, pathway 2 proved to be far more advantageous. Following an efficient catalytic *meta* sulfonation of 2-phenylpyridine **2**, a range of functional groups were installed in the *ortho* position including halogens, protected and unprotected alcohols, and a sulfonamide (Scheme 4). Catalytic homocoupling to form dimeric species **10** proceeded in good yield, including dibrominated analogue **11**. An important observation from reaction pathway 2 is the complete regioselectivity it gave for the C8–C11-substituted isomers.[11]

As the *ortho* bromination product **6** was furnished in good yield and holds the potential for further functionalisation, the scope of that reaction was then explored with a range of substituted sulfones.[12] Scheme 5 shows the scope of this two-step protocol. In general, electron-withdrawing groups afforded the highest yields, with some weakly donating groups being tolerated. Additional electron-donating functionality on the aromatic ring allowed the selective synthesis of the tetrasubstituted benzene derivative **18** in good yield. The products from sequential C–H functionalisation could be further elaborated as shown by the Suzuki coupling of **6** with boronate **20** (Scheme 6).[13]

In conclusion a reaction protocol for sequential chelation-assisted aromatic C–H functionalisation has been demonstrated, via a catalytic *meta*-directed C–S bond formation followed by an *ortho*-directed C–C or C–X bond-forming process to give complete control over the reaction products, which were obtained in good yield and high regioselectivity. Ongoing studies are focussed on expanding the catalytic σ-activation protocol to a broader range of synthetic processes for extending the sequential C–H functionalisation protocol.

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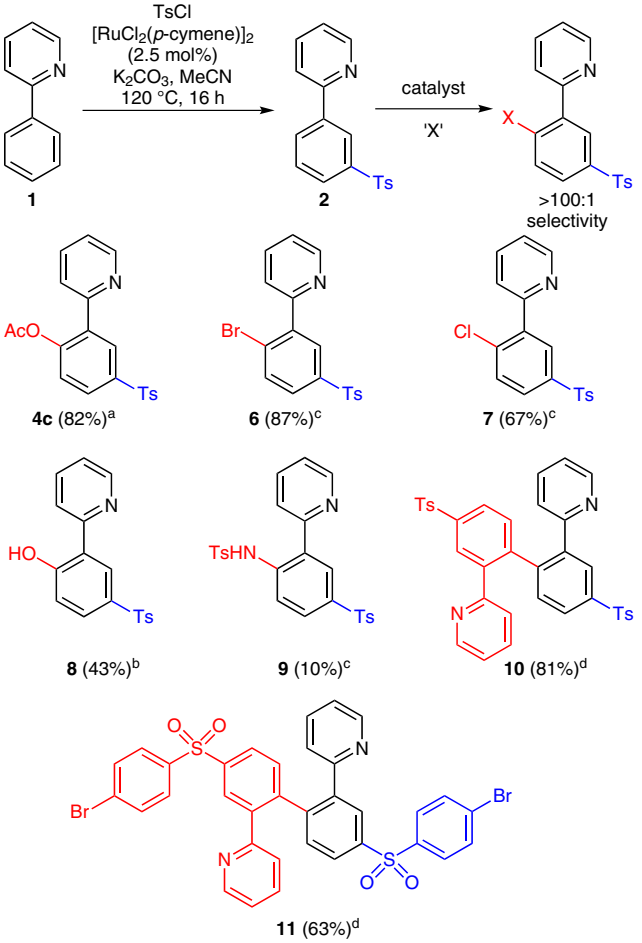

Scheme 4 Excellent selectivity via *meta* then *ortho* functionalization. *Reagents and conditions*: [a] $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$, Ac_2O, in PhMe.[9c] [b] $PdCl_2$ (5 mol%), *tert*-butylhydroperoxide in PhCl.[9b] [c] $Cu(OAc)_2$ (1 equiv), halogen source in MeCN.[9a] [d] $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), $FeCl_3$ in PhCl.[14] For full experimental details, see Supporting Information.

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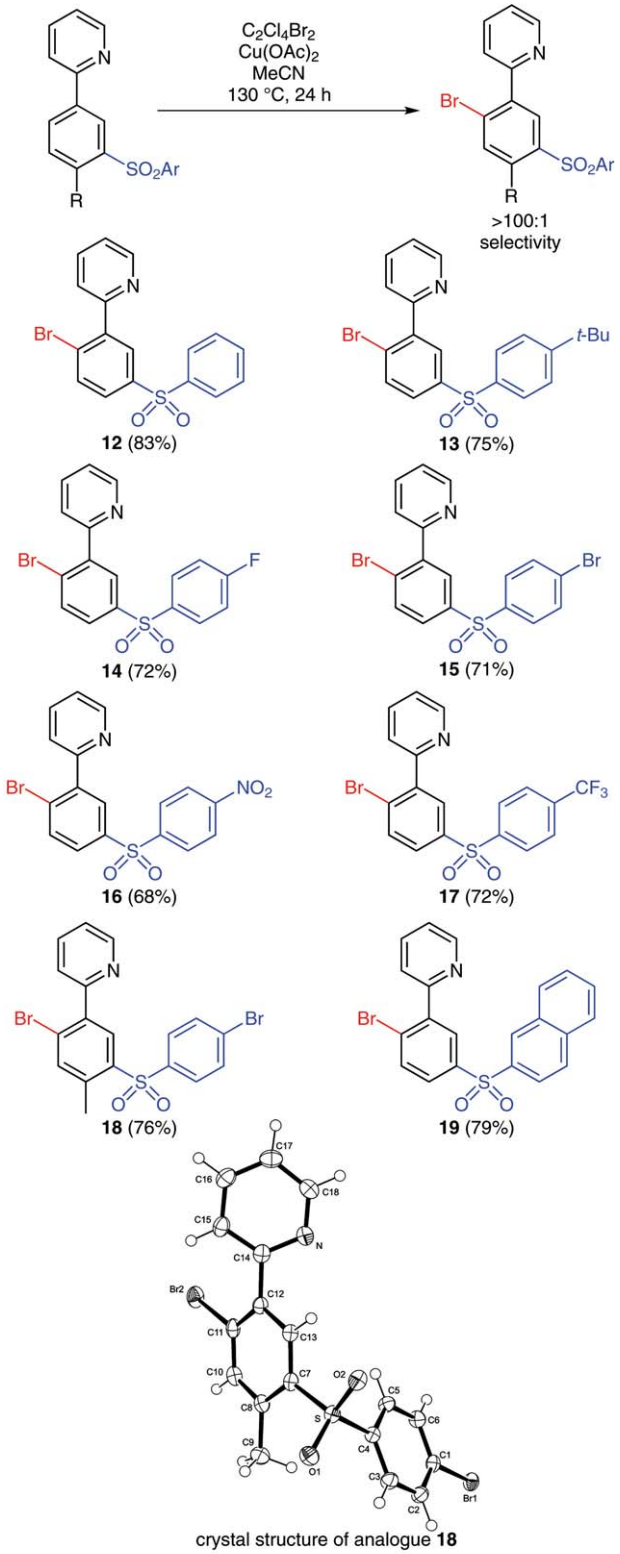
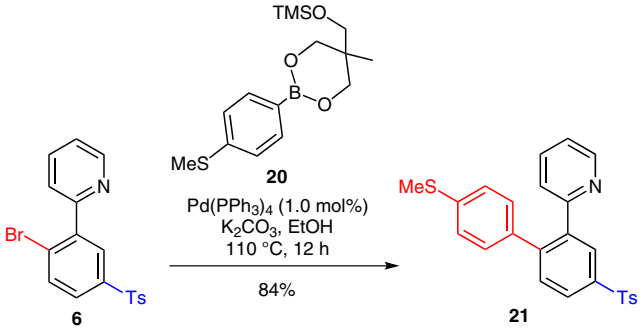


Scheme 5 Scope of sequential *meta* C–S and *ortho* C–Br bond formation. *Reaction conditions*: sulfone (1 equiv), $C_2Cl_4Br_2$ (2 equiv), $Cu(OAc)_2$ (1 equiv), MeCN, 130 °C, 24 h. Isolated yields.



Scheme 6 Product modification by Suzuki coupling

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(10) ***meta*-Sulfonation; General Procedure:** To a nitrogen-purged carousel tube was added $[RuCl_2(p\text{-cymene})]_2$ (0.12 mmol, 0.060 g), phenylpyridine derivative (2 mmol), sulfonyl chloride (6 mmol), potassium carbonate (4 mmol, 0.552 g), and acetonitrile (5 mL). The reaction was heated to 120 °C with stirring for 15 h before being cooled to r.t. The reaction mixture was washed with brine, extracted with dichloromethane, dried over $MgSO_4$, and the solvent was removed. The crude mixture was purified by flash column chromatography.

Compound 3b: According to the general procedure, from 2-(2-methoxy)phenylpyridine (2 mmol, 0.372 g) and *p*-toluenesulfonyl chloride (6 mmol, 1.144 g) in MeCN (5 mL), the title compound was obtained by flash column chromatography eluting with CH_2Cl_2–2-propanol (1:0.01) to give a white solid (12% yield); mp 160–163 °C. IR (neat): ν = 2924.21, 1590.54, 1464.65, 1140.51, 1088.93, 989.91, 776.29, 685.44, 654.76 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.7 Hz, 1 H), 8.17 (dd, *J* = 7.9, 1.8 Hz, 1 H), 7.93 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.86 (d, *J* = 8.3 Hz, 2 H), 7.68

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(d, *J* = 3.6 Hz, 2 H), 7.35 (t, *J* = 7.8 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.24 (q, *J* = 4.7 Hz, 1 H), 3.35 (s, 3 H), 2.39 (s, 3 H).^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 154.5, 150.0, 144.0, 138.9, 137.5, 136.5, 135.6, 135.0, 130.0, 129.4, 128.2, 124.4, 124.2, 122.7, 62.2, 21.7. HRMS calcd for $[M+H]^+$: 340.1008; found: 340.1090.

Compound 18a: According to the general procedure, from 2-(*p*-tolyl)pyridine (2 mmol, 0.341 ml) and 4-bromophenylsulfonyl chloride (6 mmol, 1.533 g), the title compound was obtained by flash column chromatography eluting with hexane–EtOAc (4:1), followed by recrystallisation from ethanol to give a white solid (46% yield); mp 196–198 °C. IR (neat): ν = 2974.01, 1570.40, 1431.29, 1308.22, 1148.62, 1105.96, 1067.43, 1006.20, 808.79, 771.38, 742.25, 614.92 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.80 (d, *J* = 1.9 Hz, 1 H), 8.70 (d, *J* = 4.7 Hz, 1 H), 8.18 (dd, *J* = 7.9, 1.9 Hz, 1 H), 7.84 – 7.73 (m, 2 H), 7.74 (d, *J* = 8.7 Hz, 2 H), 7.61 (d, *J* = 8.7 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.31 – 7.25 (m, 1 H), 2.45 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 149.8, 140.3, 138.8, 138.5, 138.1, 137.2, 133.5, 132.4, 132.1, 129.3, 128.4, 127.8, 122.9, 120.6, 20.2. HRMS calcd for $[M+H]^+$: 389.9941; found: 389.9960

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(12) ***ortho*-Bromination; General Procedure:** To a clean, dry carousel tube, $Cu(OAc)_2$ (1 mmol, 0.18 g) the required substrate (1 mmol), $C_2Cl_4Br_2$ (2 mmol, 0.65 g) and acetonitrile (5 mL) were added in air. The reaction was heated to 130 °C with stirring for 24 h before being cooled to r.t. The reaction mixture was washed with sat. aq $NaHSO_3$, extracted with dichloromethane, filtered through celite, dried over $MgSO_4$, and the solvent was removed. The crude mixture was purified by column chromatography.

Compound 6: According to the general procedure, from compound **2** (1 mmol, 0.31 g), the title compound was obtained after purification by flash column chromatography eluting with hexane–EtOAc–Et_3N (4:1:0.01) to give a white solid (87% yield); mp 198–200 °C. IR (neat): ν = 2925.64, 1592.48, 1478.05, 1402.41, 1311.17, 1296.68, 1151.63, 1107.45, 814.28, 692.52, 646.22 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 4.7 Hz, 1 H), 8.50 (d, *J* = 2.3 Hz, 1 H), 8.12 (d, *J* = 8.2 Hz, 1 H), 8.02 (t, *J* = 8.5 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 2 H), 7.84 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.47–7.40 (m, 1 H), 7.40–7.31 (m, 2 H), 7.15 (d, *J* = 8.7 Hz, 1 H), 2.46 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 155.9, 145.6, 143.8, 139.4, 138.7, 131.4, 130.8, 130.0, 127.4, 126.5, 122.7, 119.7, 118.6, 21.6. HRMS calcd for $[M+H]^+$: 389.9986; found: 390.0062.

Compound 18: According to the general procedure, from compound **18a** (1 mmol, 0.39 g), the title compound was obtained after purification by flash column chromatography eluting with hexane–EtOAc–Et_3N (4:1:0.01) to give a white solid (76% yield); mp 162–166 °C. IR (neat): ν = 3088.98, 2927.31, 1712.99, 1571.77, 1456.70, 1304.32, 1148.64, 1058.78, 1007.94, 892.75, 825.23, 751.21, 733.05 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.74 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H), 8.36 (s, 1 H), 7.87–7.71 (m, 3 H), 7.69–7.54 (m, 4 H), 7.35 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1 H), 2.43 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 149.6, 139.9, 139.8, 139.1, 138.0, 137.4, 136.3, 132.5, 132.3, 129.3, 128.7, 128.0, 124.8, 123.1, 19.8. HRMS calcd for $[M+H]^+$: 467.9013; found: 467.9096.

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