The Directed ortho Metallation–Cross-Coupling Fusion: Development and Application in Synthesis

Platinum group metals catalytic synthetic strategy for pharmaceutical, agrochemical and other industrial products

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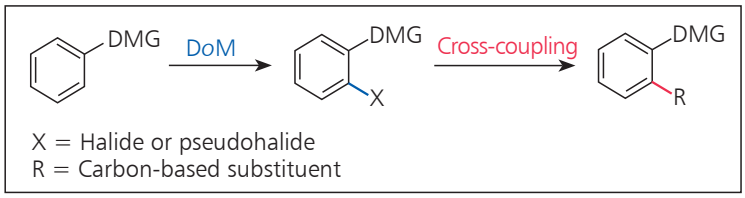
This review constitutes a detailed but non-exhaustive examination of the directed ortho metallation (DoM)–cross-coupling fusion in its many flavours. Special attention is paid to the application of the concept of the linked reactions and the synthetic utility that it endows, particularly in the case of one-pot reactions that can greatly increase the ease and efficiency of the process. Personal experience of particular issues that can arise from these reactions and examples of their solutions are given, as well as illustrations of the rapid access to complex molecules that the technique encourages.

Introduction

Since its disclosure, the combination of DoM and transition metal-catalysed cross-coupling has evolved into a common strategy in synthesis (1, 2) and, in particular, has found widespread use in the preparation of biologically interesting aromatic and heteroaromatic compounds. A variety of functional groups such as I, Br, Cl, SiR_3, SnR_3, $B(OR)_2$ have been introduced using DoM, followed by different cross-coupling reactions to form carbon–carbon, carbon–oxygen, carbon–nitrogen and carbon–sulfur bonds in order to prepare synthetically and biologically interesting molecules. Herein we present selected examples of the use of the DoM–cross-coupling strategy from the period of 2000 to 2012 in order to demonstrate its advantages and outline the potential issues that may be faced in its application. The main focus will be on cross-couplings involving the platinum group metals (pgms); however several examples using other metals such as copper are included for comparison. In order to make this review more accessible, it is divided into sections according to the type of bond being formed and the type of metallation reaction. For further clarification, a scheme describing the reaction discussed appears at the beginning of each section.

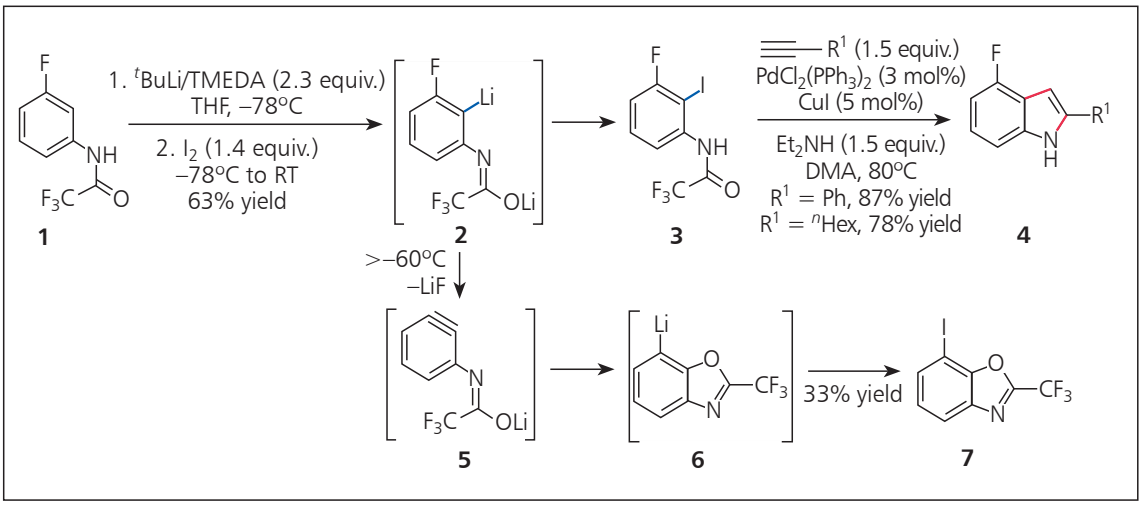
1. *Do*M–C–C Cross-Coupling Reactions



1.1 Sequential (Multi-Pot) DoM–Cross-Coupling Methods

The formation of C–C bonds through the sequence of DoM–halogenation to insert an *ortho* halide or pseudohalide, followed by cross-coupling has been carried out using Ullmann, Heck, Sonogashira, Negishi, Stille and Suzuki-Miyaura reactions, among others. As an example, Sanz *et al.* (3) have synthesised valuable 4-fluoro-2-substituted-1*H*-indoles **4** through a sequence involving DoM mediated iodination of 3-fluorotrifluoroacetanilide **1**, followed by reaction with terminal aromatic or aliphatic alkynes by a Sonogashira coupling–cyclisation process (**Scheme I**). When the DoM reaction was carried out at temperatures higher than –60°C, competitive lithium fluoride elimination took place forming a benzyne intermediate **5** which underwent subsequent intramolecular cyclisation to provide iodinated benzoxazole **7**. This phenomenon occurring during the directed metallation of 3-fluoroaniline bearing *N*-pivaloyl, *N*-Boc directing metallation groups (DMGs) or an *N*-benzoyl group had been previously observed (4).

The Suzuki-Miyaura cross-coupling is one of the most popular and widely used reactions in the C–C DoM–cross couple fusion strategy (for examples, see (5,6)). When partnered with DoM, the major advantage of the Suzuki-Miyaura reaction is that boronation reagents such as $B(OR)_3$ are often compatible with lithium bases (usually lithium dialkylamides, but some boronates are even compatible with *s*-BuLi) (7). This allows the boronating agent to be present in the same reaction vessel as the base in order to quench the metallated species as it is formed. These conditions are known in our laboratories as either Barbier or Martin (8, 9) type conditions according to the order of addition. (Descriptions of these *in situ* quench conditions are as follows: under Barbier type conditions the base is added to a mixture of substrate and electrophile; under inverse Barbier conditions a solution of substrate and electrophile are added to a solution of the base; under Martin conditions the substrate is added to a solution of base and electrophile; under inverse Martin conditions a solution of base and electrophile are added to a solution of the substrate. Compatible electrophiles include, but are not limited to, trimethylsilyl chloride (TMSCl), Me_2SiCl_2, $B(OMe)_3$ and $B(O^iPr)_3$.) Halide sources are not usually compatible with strong bases; for instance, premixing I_2 and lithium

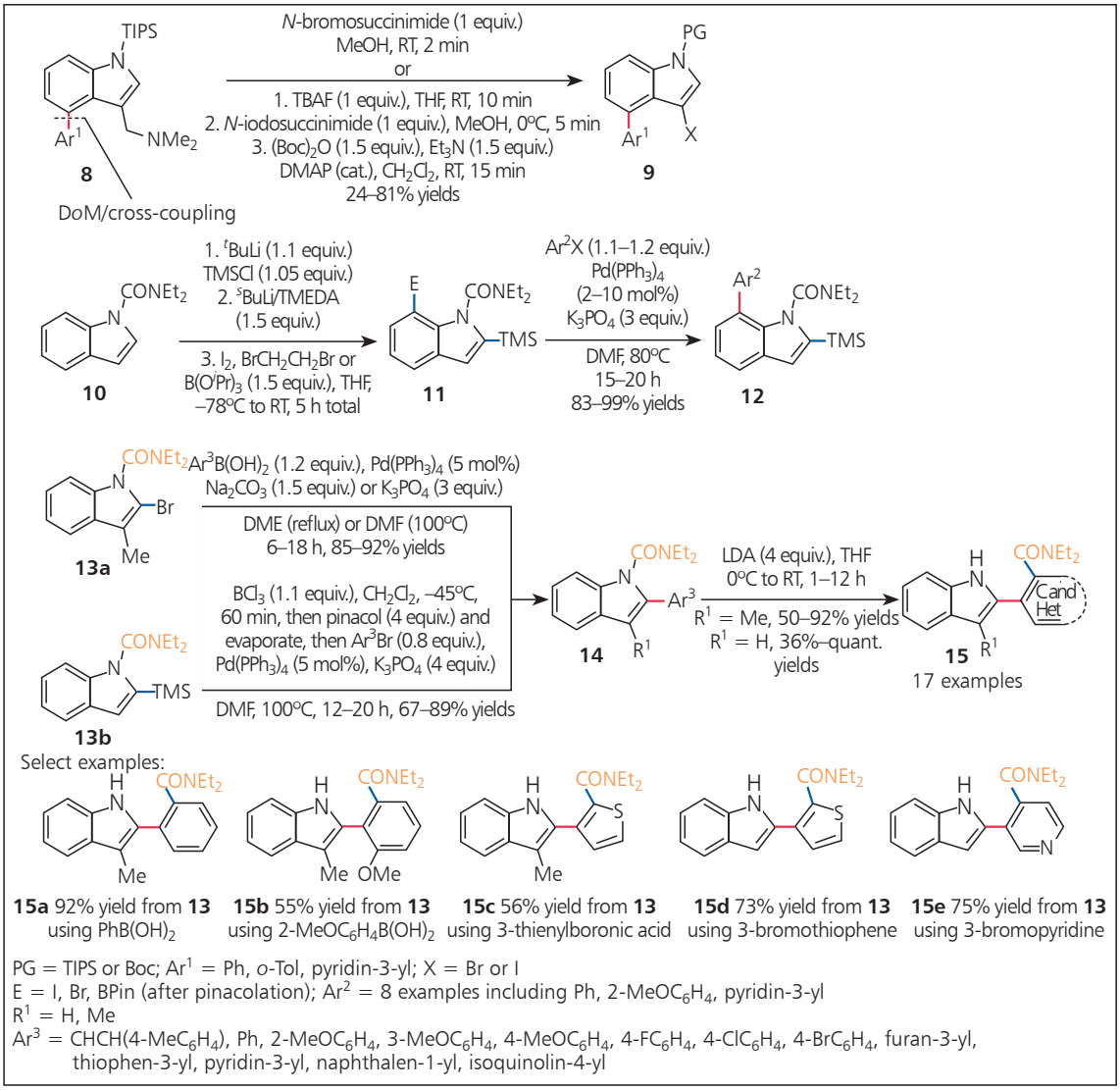


Scheme I. Sequential DoM and Sonogashira cross-coupling for the synthesis of indoles

2,2,6,6-tetramethylpiperidide (LiTMP) before addition of the metallation substrate has resulted in low yields of iodinated material in our laboratories. Vedsø *et al.* have shown that ester, cyano and halogen substituents are tolerated when LiTMP/B(O^{i}Pr)$_3$ is used for *in situ* boronation of unstable *ortho* metallated species (10).

In our group we have found that the DoM–cross-coupling strategy finds particular utility in the functionalisation of indoles. Stimulated by work performed by Iwao *et al.* (11), we have developed routes to 3,4-substituted indoles by utilising DoM–Negishi cross-coupling sequences to afford gramines **8** which undergo useful retro-Mannich fragmentation to give indoles **9** (12). Similarly, C-7-substituted indoles **12** have also been synthesised by either sequential or one-pot C-2 metallation, C-2 silylation, C-7 metallation and C-7 electrophile treatment of indoles **10** to provide the boronates or halides **11**, followed by Suzuki-Miyaura cross-coupling to give **12** (13). In addition, 2-aryl/heteroarylindoles **15** have also been synthesised from *N*-carbamoyl-2-bromoindoles using either Suzuki-Miyaura (**13a**) or one-pot *ipso* borodesilylation–Suzuki-Miyaura (**13b**) reactions to provide indoles **14**, followed by a lithium diisopropylamide (LDA)-induced anionic N–C carbamoyl migration (**Scheme II**) (14).

Due to the higher C–H acidity of heteroaromatic systems, the DoM component of the DoM–cross-coupling fusion of these systems is dominated by the use of bases other than butyllithium, such as the lower



Scheme II. Indole functionalisation utilising the DoM and cross-coupling protocol

pK_a lithio dialkylamides or Grignard bases; the cross-coupling component has been dominated by Suzuki-Miyaura and Negishi reactions. The consideration of which base to choose is heavily influenced by the DMG and by the other functionalities within the system. For instance, if the DMG is a halogen then benzyne formation may need to be avoided through the use of lower temperatures or milder bases less prone to induce MX elimination. On the other hand, if the DMG is weak and the system is electron rich then stronger bases will be required which may result in nucleophilic attack of the base upon the heteroaromatic ring, especially in the case of π-deficient systems. Usually the accepted wisdom is to use as mild a base as possible, at a temperature as close to room temperature as is possible in order to achieve the greatest degree of functional group compatibility and experimental simplicity. Certain DMGs are less tolerant of higher temperatures than others, such as *N*,*N*-diethyl-*O*-carbamate which may undergo the anionic *ortho* Fries rearrangement (1, 15, 16). We have found also that the variation of solvents can have a profound effect on the selectivity of the metallation; in particular the switch between tetrahydrofuran (THF) and diethyl ether can make the difference between the success or failure of a reaction.

Although in many cases this type of DoM–cross-coupling strategy can be performed with relative ease simply by using conditions precedented for a similar system, both the DoM and cross-coupling may have non-trivial problems which should be solved through methodical application of standard optimisation techniques, such as variation of solvent, base and catalyst system. An instructive example concerns work which eventually led to the discovery of soraprazan (**16**, **Figure 1**), a clinically studied H^+/K^+-ATPase inhibitor (17).

Thus, as shown by deuterium quench experiments, the *ortho* deprotonation of an *N*-pivaloyl imidazo[1,2-*a*]pyridine **17** gave the highest ratio of C-5:C-7 (**18**:**19**) deprotonation when *t*-butyllithium was used in diethyl ether (**Scheme III**). When this reaction was performed in THF, products **18** and **19** were obtained in almost equal conversion. These results were rationalised by the observed poor solubility of the kinetically preferred C-7-anion in diethyl ether which presumably prevented it from undergoing equilibration with the more thermodynamically preferred C-5-anion. On the other hand, in THF the greater solubility of the C-7 anion allowed it to equilibrate with the C-5 anion thereby eradicating

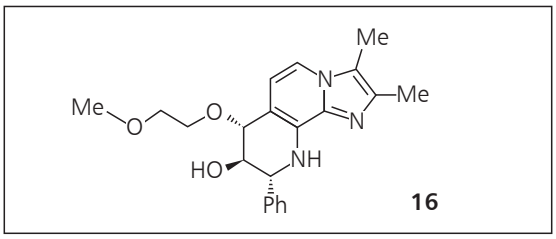
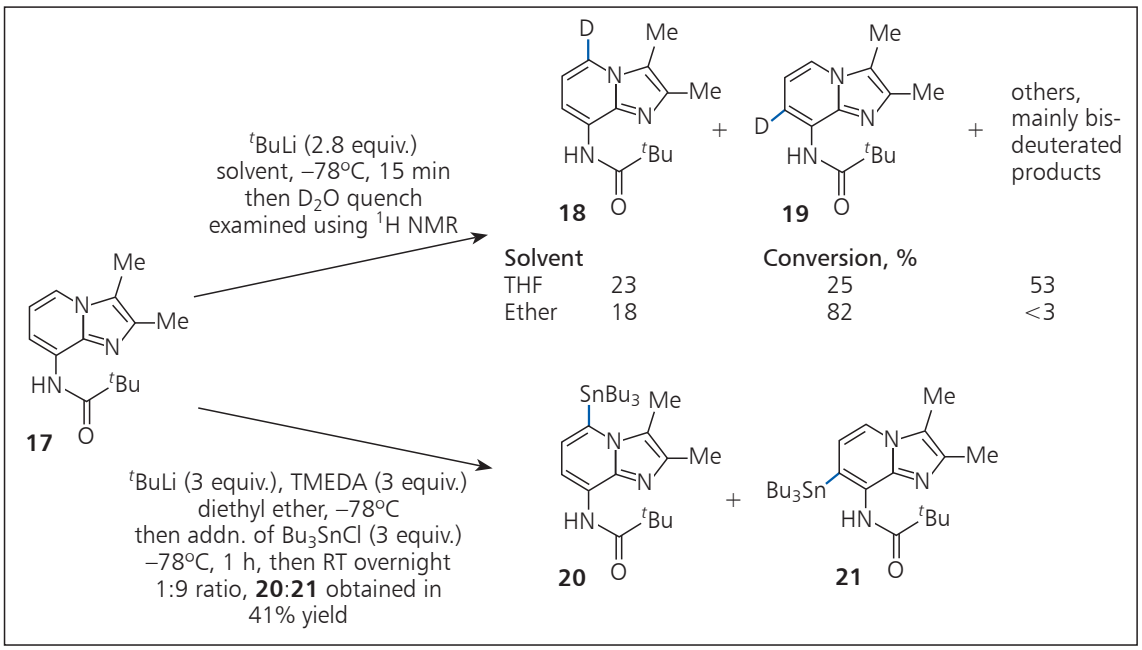


Fig. 1. Soraprazan, a H^+/K^+-ATPase inhibitor (17)

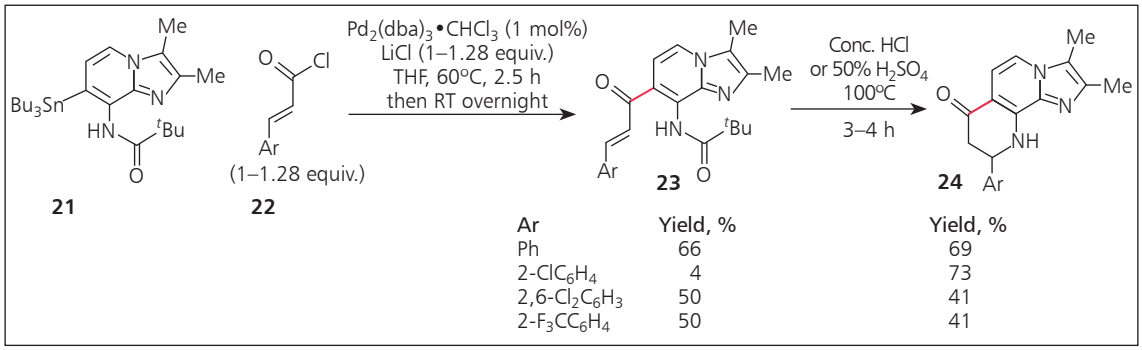


*Scheme III. DoM studies of the N-pivaloyl-imidazo[1,2-a]pyridine **17** (17)*

the selectivity. When the reaction was performed using the weaker *n*-butyllithium, no selectivity between C-5 and C-7 metallation was achieved, and a large amount of starting material was recovered even when the reaction was conducted over longer periods of time or at higher temperatures. This is presumably due to the moderate *ortho*-directing ability of the *N*-pivaloyl group. Use of the optimised deprotonation conditions followed by stannylation afforded the desired C-7 product **21** in acceptable yield in a 1:9 ratio together with the undesired C-5 regioisomer **20**.

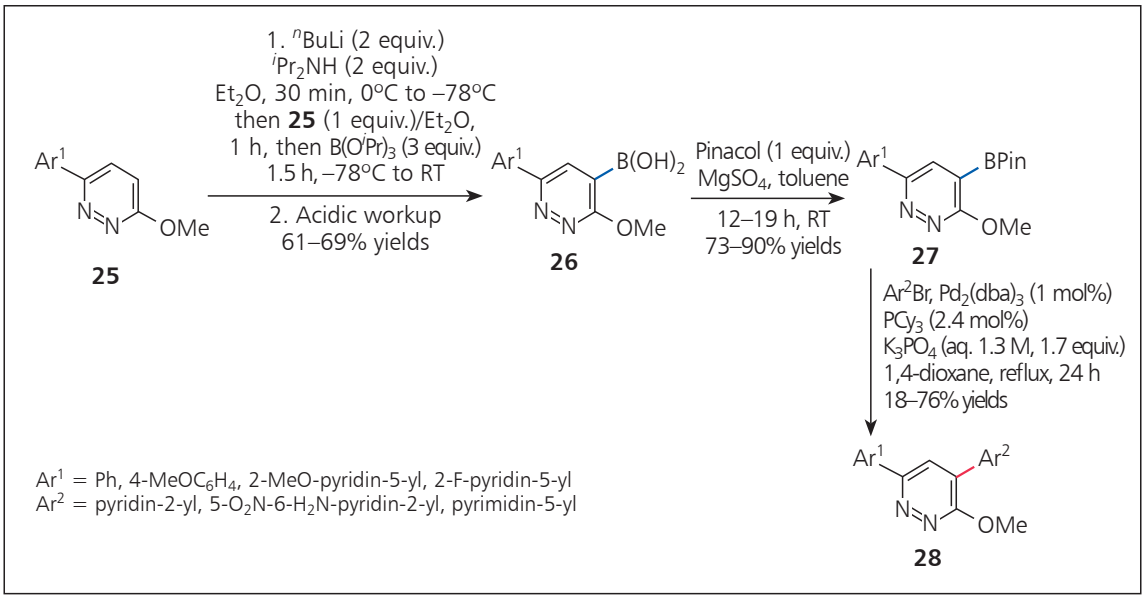
The derived compound **21** was used in acylative Stille cross-couplings with cinnamoyl chlorides to give compounds **23**, which by straightforward acid-mediated Michael cyclisation-depivaloylation afforded compounds **24**, which are intermediates for sorapazan (**16**) and its analogues (**Scheme IV**). The execution of the Stille cross-coupling was far from trivial and therefore deserves comment. Experiments with a variety of palladium sources were unsuccessful and only the combination of $PdCl_2(MeCN)_2$ and a three-fold excess of the cinnamoyl chloride led to cross-coupled products **23**, in poor yields, which precipitated from the reaction mixture as the hydrochloride salts. The known advantages of using halide salts in Stille cross-couplings of aryl triflates (18–20) led to speculation about the role of halide salts in the reaction. Thus, on addition of one equivalent of lithium chloride to the reaction mixture, conversion to products **23** was achieved in moderate yield.

Despite the demonstration in our laboratories of the advantages of performing a DoM–Suzuki Miyaura cross-coupling in a one-pot fashion (such as fewer chemicals used, eradication of at least one workup step, higher efficiency and convenience), most reported reactions are performed with isolation of the DoM products. **Schemes V** and **VI** (21, 22)

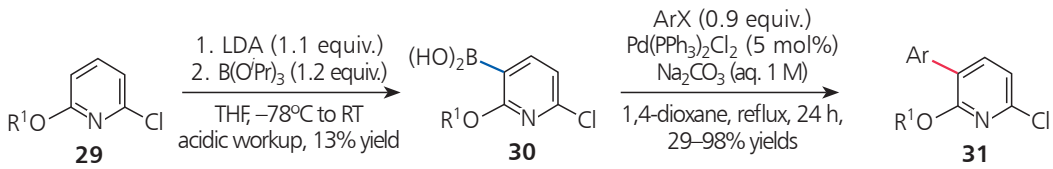


Ar	Yield, %	Yield, %
Ph	66	69
2-ClC_6H_4	4	73
2,6-$Cl_2C_6H_3$	50	41
2-$F_3CC_6H_4$	50	41

*Scheme IV. Acylative Stille cross-coupling of **21** to provide products **23** and thence sorapazan precursors **24***



*Scheme V. Sequential DoM–Suzuki Miyaura synthesis of arylpyridazines **28** (21)*



*Scheme VI. Sequential DoM–Suzuki Miyaura synthesis of aryl-2-chloropyridines **31** (22)*

depict cases in which the boronic acids **26** and **30,** generated from DoM reactions, are isolated prior to cross-coupling. Of particular note is the low yield of boronic acid **30**, which is likely attributable in part to the instability of this heterocyclic boronic acid.

1.2 One-Pot DoM–Cross-Coupling Methods

A more efficient process than shown so far is a DoM–cross-coupling protocol carried out without isolation of the intermediate species (boronic acid, zincate for instance) which is most often accomplished using Suzuki-Miyaura or Negishi cross-coupling reactions. For instance, as part of a campaign towards the synthesis of the antimicrobial agent GSK966587 (**32**, **Figure 2**), a 'one-pot' DoM–cross-coupling method was developed (23).

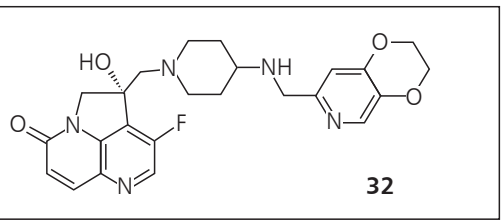
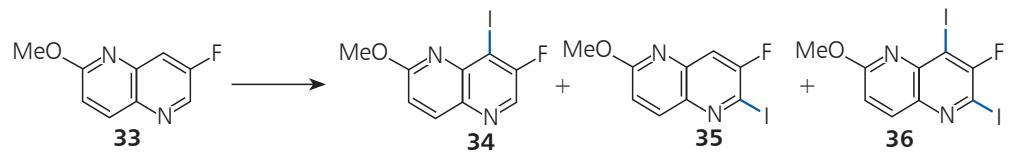


Fig. 2. Antimicrobial agent GSK966587

Thus, the DoM–iodination reaction of **33** was investigated (**Scheme VII**) in preparation for Heck coupling chemistry (**Scheme VIII**). The use of the more traditional alkyllithium and lithium amide bases was complicated by the formation of dianions and by competitive fluoride displacement. The use of LDA at low temperatures under short reaction times was promising but gave mixtures of both mono-iodides **34** and **35** and bis-iodide **36**. Although the Uchiyama zincate mixed metal base TMPZn(^{t}Bu)$_2$Li gave predominantly the undesired mono-iodide **35**, the analogous (^{i}Pr)$_2$NZn(^{t}Bu)$_2$Li gave an encouraging result. A further shift to (^{i}Pr)$_2$NZnEt$_2$Li (prepared by mixing Et$_2$Zn and LDA) gave excellent selectivity for the desired iodide **34** which was eventually isolated in 85% yield (74% from starting material **39, Scheme VIII**).

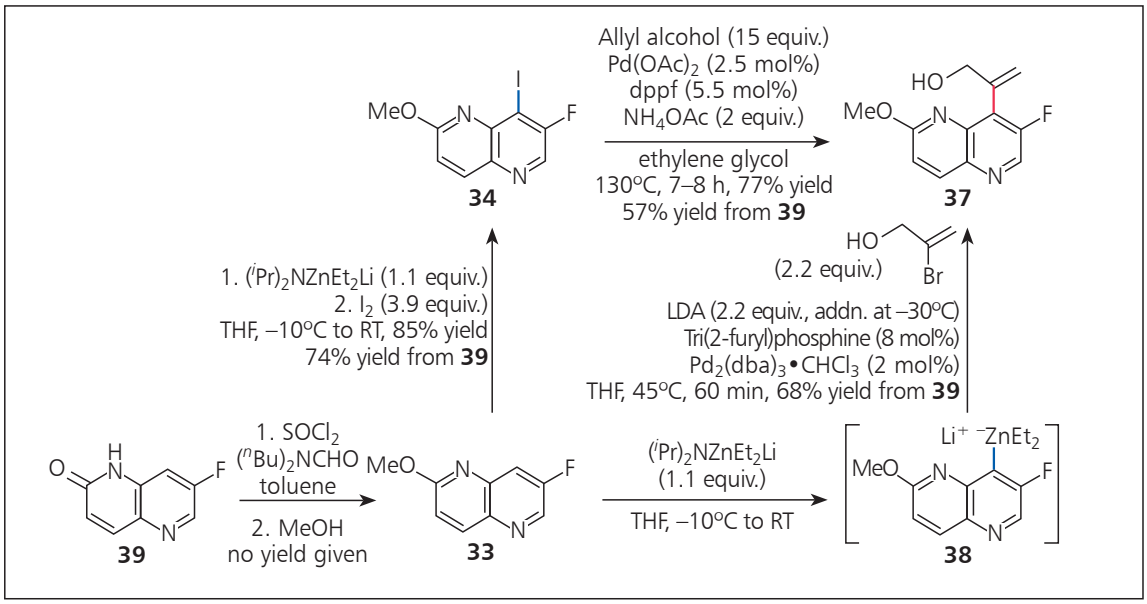
After extensive screening, Heck coupling of iodide **34** with allyl alcohol was achieved to give the α-coupled product **37** in 77% yield (57% yield from **39**, **Scheme VIII**). As a more efficient alternative to this sequential procedure, the Negishi cross-coupling of the zincate intermediate **38** (the presumed metallated species from the DoM reaction of **33**) was realised and gave a comparable yield of **37** (68% yield from **39**) but required no iodine and fewer purification steps.



Base	Equiv.	Time, min	Temp., °C	Area, %, by HPLC analysis	
LDA	1.5	15	–70	42	8	40
LDA	1.1	5	–60	83	8	1.5
TMPZn(^{t}Bu)$_2$Li	1.1	30	23	26	34	23
(^{i}Pr)$_2$NZn(^{t}Bu)$_2$Li	1.0	120	23	45	5	0
(^{i}Pr)$_2$NZnEt$_2$Li	1.2	30	–10	96[a]	4	0

[a]*85% isolated yield*

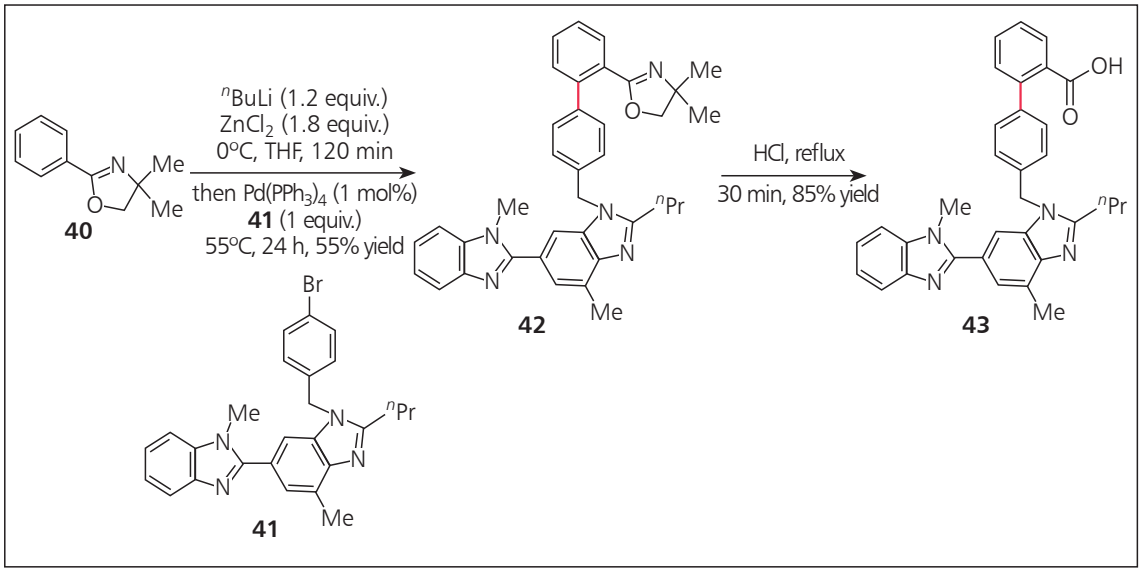
*Scheme VII. DoM route to 7-fluoro-8-iodo-2-methoxynaphthyridine **34** (23)*



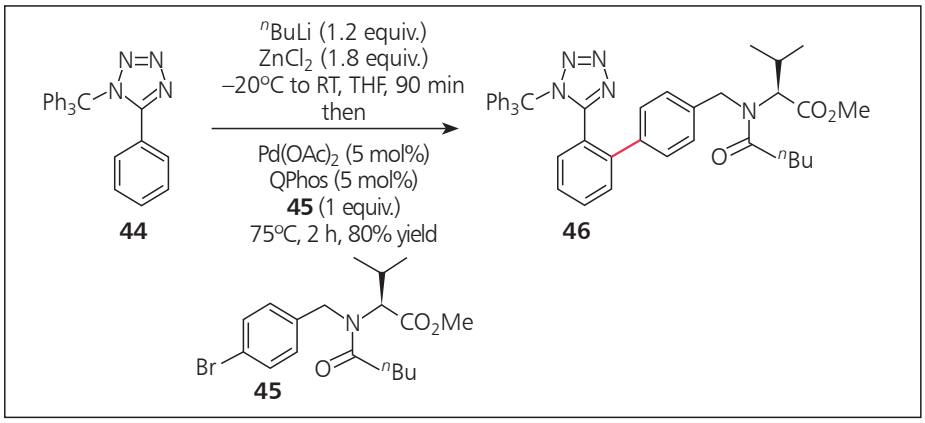
*Scheme VIII. Sequential and 'one-pot' DoM–Heck coupling synthesis of naphthyridine **37** (Note: The authors provide the yields for the optimisation, but also for a process whereby all of the batch is taken through the whole process with only minimal purification. Hence overall yields comparing the two processes are given even though no yield is given for the conversion of **39** to **33**)*

By its nature, the DoM–Negishi cross-coupling protocol lends itself to a one-pot procedure whereby the deprotonation, transmetallation (if necessary) to a zincate and transition metal-catalysed cross-coupling occur sequentially in the same reaction vessel. Among the cases illustrated in **Schemes IX–XI** (24–26), of note is the use of the oxazole DMG which by hydrolysis provides the desired carboxylic acid in the target molecule **43** (**Scheme IX**). This is a further demonstration of the use of tetrazole as a DMG in the synthesis of the 'sartan' pharmaceutical **46** (**Scheme X**) and the use of catalytic zinc chloride and of the pyridine *N*-oxide as a DMG in the preparation of azabiaryl **49** (**Scheme XI**).

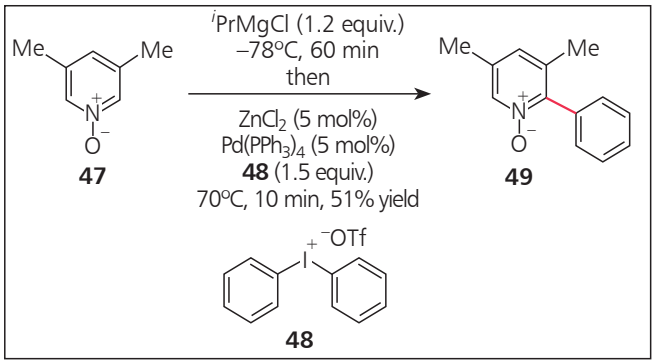
Recently, a one-pot DoM–Negishi cross-coupling strategy that can utilise esters as DMGs



*Scheme IX. One-pot DoM–Negishi cross-coupling strategy for the synthesis of telmisartan **43** angiotensin II receptor antagonist (24)*

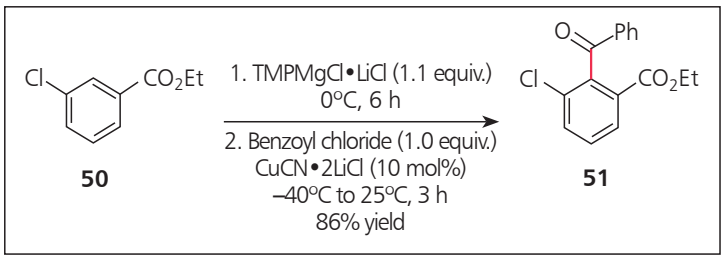


*Scheme X. One-pot DoM–Negishi cross-coupling strategy to synthesise valsartan **46** angiotensin II receptor agonist (25)*

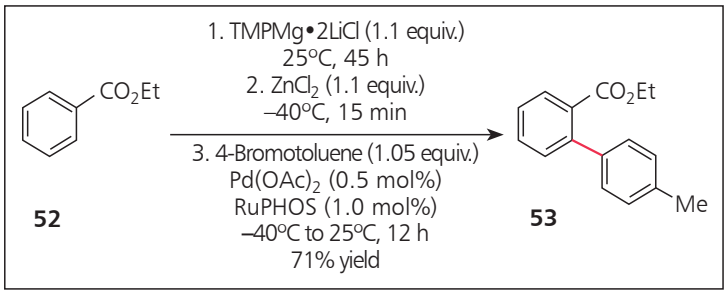


*Scheme XI. One-pot DoM–Negishi cross-coupling strategy using catalytic zinc chloride for the synthesis of azabiaryl N-oxide **49** (26)*

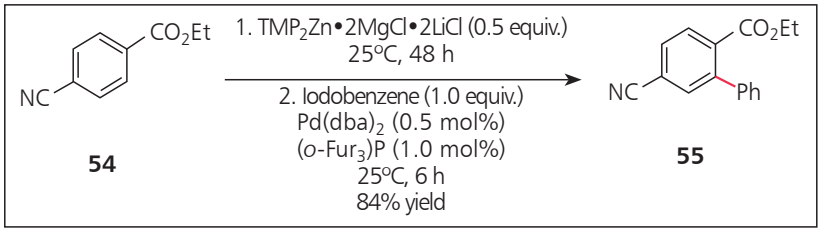
has been developed by Knochel and coworkers involving the amide bases tmpMgCl·LiCl (tmp = 2,2,6,6-tetramethylpiperidyl), tmp_2Mg·2LiCl and tmp_2Zn·$2MgCl_2$·2LiCl (27). These bases are used in stoichiometric amounts (no extreme excess is required), facilitated by LiCl which complexes and solubilises the bases and leads to monomeric metallic amides. Due to its stability (at least 6 months at 25°C under inert atmosphere) (28, 29) tmpMgCl·LiCl is commercially available and is capable of metallating moderately C–H acidic aromatic compounds. For more demanding aromatic cases tmp_2Mg·2LiCl (30) may be used and for systems that contain sensitive functional groups tmp_2Zn·$2MgCl_2$·2LiCl (31) has proven to be effective. Unfortunately the latter two bases are not as stable as tmpMgCl·LiCl; for instance tmp_2Mg·2LiCl is stable only for 24 h at 25°C (27). These reagents are usually prepared fresh for each reaction, or set of reactions, from tmpMgCl·LiCl by the addition of LiTMP or $ZnCl_2$, respectively. The use of these bases for combined metallation–cross-coupling reactions greatly increases the potential substrate scope of this strategy, as illustrated by the synthesis of aromatic esters **51**, **53** and **55** (**Schemes XII–XIV**). Noteworthy is the last case since nitrile groups are not normally compatible with the use of Grignard reagents. In addition, only 0.5 equivalents of tmp_2Zn·$2MgCl_2$·2LiCl are required (i.e. both potential TMP anions are available) and transmetallation is unnecessary as this reagent



Scheme XII. One-pot DoM–Negishi cross-coupling protocol using commercially available tmpMgCl·LiCl



Scheme XIII. One-pot DoM–Negishi cross-coupling protocol using $tmp_2Mg·2LiCl$



Scheme XIV. One-pot DoM–Negishi cross-coupling protocol using 0.5 equivalents $tmp_2Zn·2MgCl·2LiCl$

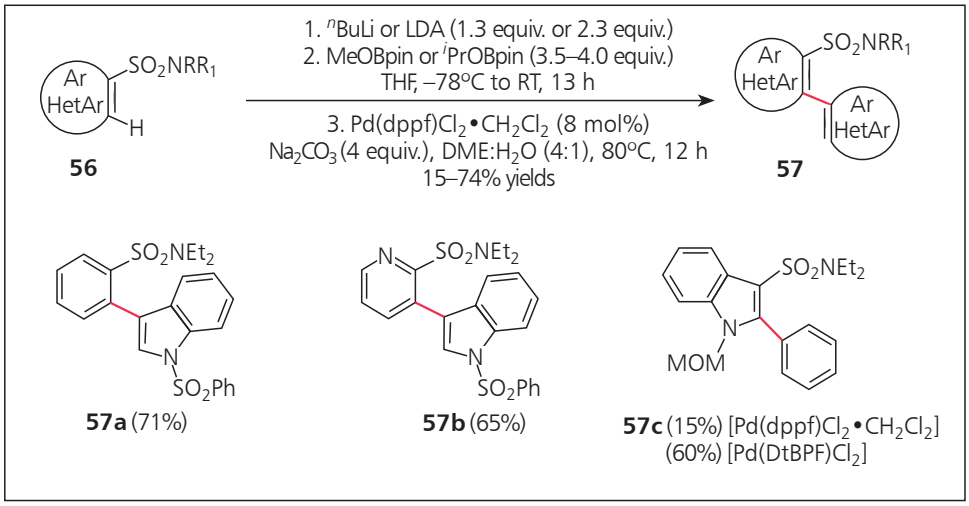
directly provides a zincate suitable for Negishi cross-coupling under relatively standard conditions. Although these reactions were developed and optimised on 1–2 mmol scale, all of these examples were performed on 80–100 mmol scale in order to demonstrate good scale up potential.

The combined DoM–Suzuki-Miyaura cross-coupling also lends itself to a one-pot procedure. An illustration of this is our recent extension of previous work on one-pot DoM–Suzuki-Miyaura reactions (32), in which the synthesis of heterobiaryl sulfonamides was developed with the aim of increasing the available methodology for the construction of bioactive molecules bearing the popular sulfonamide pharmacophore (**Scheme XV**) (7).

This one-pot metallation-boronation–cross-coupling procedure was generalised for tertiary and secondary sulfonamides **56** in couplings with electron-rich and -poor aryl and heteroaryl bromides and chlorides to furnish biaryl sulfonamides **57**. A change to a bulkier catalyst was needed when *meta* or *ortho* substituted sulfonamides were used as shown by example **57c**.

1.3. Iridium-Catalysed Boronation–Suzuki-Miyaura Cross-Coupling: A Complementary Method

The knowledge that iridium-catalysed boronation of aromatics is qualitatively determined by steric effects (33–37) led us to explore this reaction in DMG-bearing substrates in order to establish complementarity with



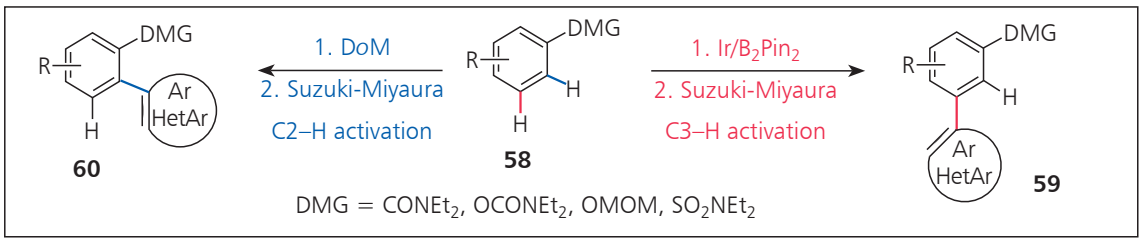
*Scheme XV. One-pot DoM–Suzuki-Miyaura cross-coupling route to heterobiaryl sulfonamides **57** (7)*

the DoM–Suzuki-Miyaura cross-coupling process (**Scheme XVI**) (38). Thus, complementary methods of considerable scope for the synthesis of biaryls and heterobiaryls were demonstrated by C–H activation at C-2 (DoM) and at C-3 (Ir-catalysed boronation) of **58** which offer new routes for the regioselective construction of substituted biaryls **60** and **59** respectively.

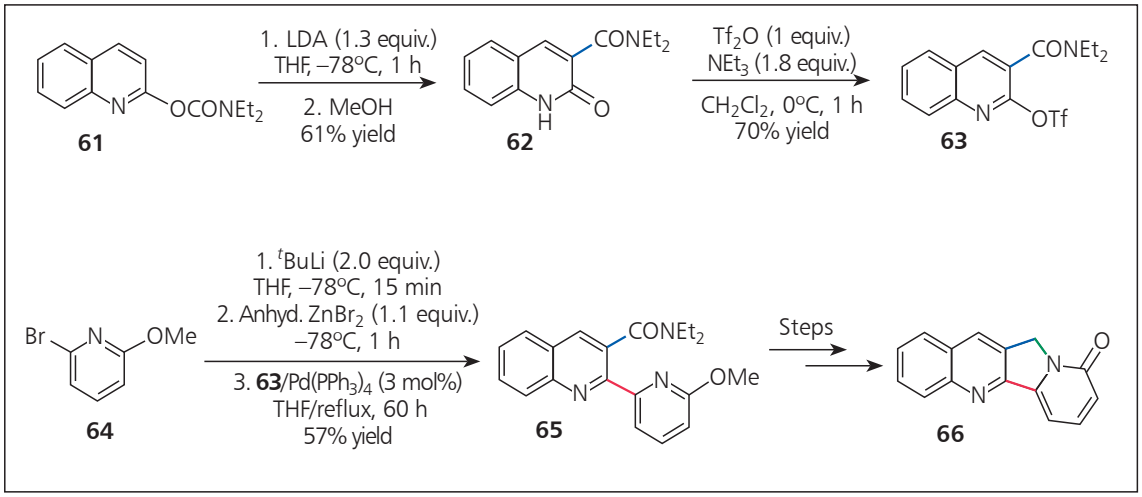
1.4 The Use Of DoM–Cross-Coupling Strategies in Total Synthesis

We have also employed the DoM–cross-coupling strategy as part of syntheses of targeted drugs and natural product intermediates. In 2004, we reported a synthesis of the tetracyclic A/B/C/D ring core **66** of the antitumour agent camptothecin (**Scheme XVII**) (39). This route is highlighted by an anionic *ortho*-Fries rearrangement of *O*-carbamate **61** to give the quinolone **62**, a Negishi cross-coupling of triflate **63** to give biaryl **65**, and a modified Rosenmund–von Braun reaction to provide the tetracyclic core **66** of the antitumour alkaloid camptothecin in seven steps with an overall 11% yield.

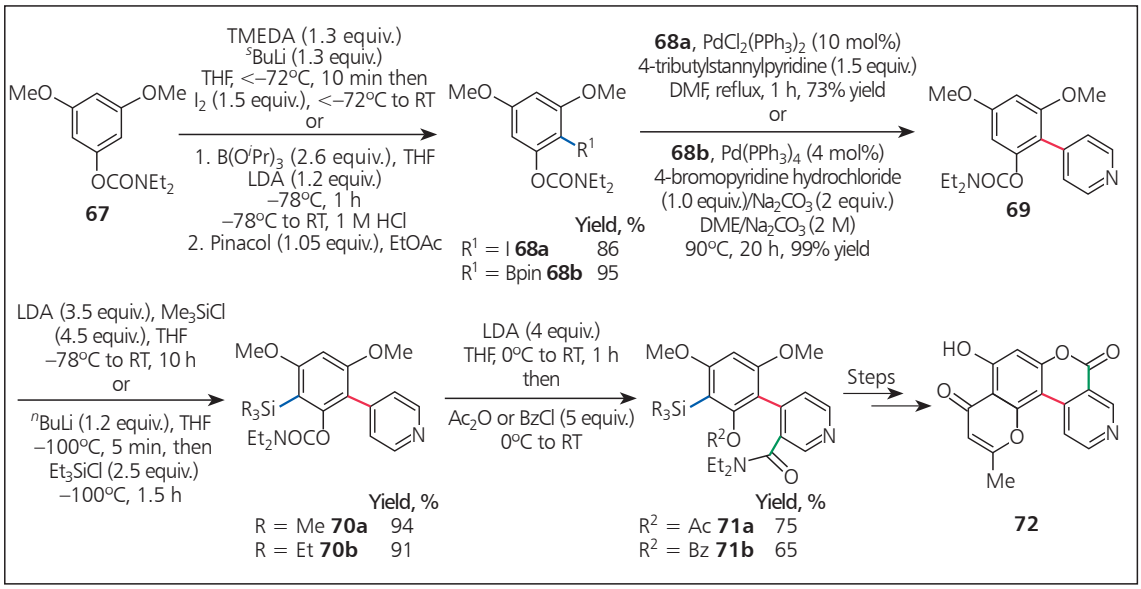
Most recently, we have completed a total synthesis of schumanniophytine **72** (**Scheme XVIII**) (40), a natural product which had been prepared only once previously (41). Starting with DoM chemistry to obtain the cross-coupling partners **68** from **67**, our route takes advantage of a combined DoM–cross-coupling strategy using Stille or Suzuki-Miyaura reactions to synthesise biaryl **69**, and also incorporates a key *ortho*-silicon-induced *O*-carbamate remote anionic Fries rearrangement of carbamates **70** to provide amides **71**.



Scheme XVI. Complementary ortho and meta boronation/Suzuki–Miyaura cross-coupling reactions of DMG bearing aromatics (38)

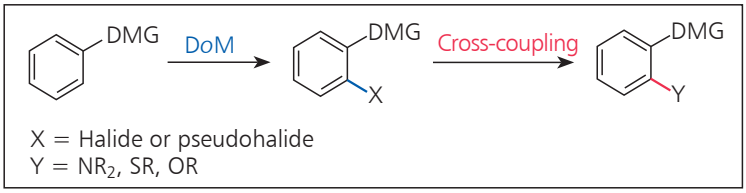


*Scheme XVII. Key reactions in the synthesis of the tetracyclic core **66** of camptothecin: anionic ortho-Fries rearrangement **61–62** and Negishi cross-coupling **64–65** (39)*



Scheme XVIII. Key reactions in the total synthesis of schumanniophytine ***72*** *(40)*

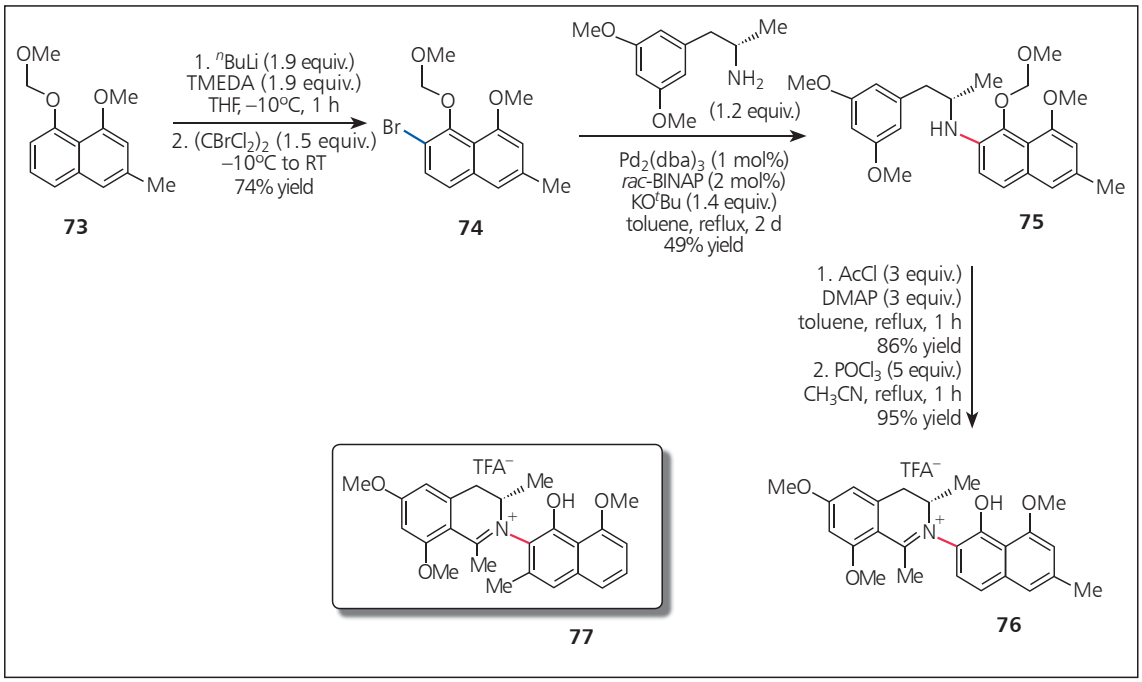
2. DoM–C–Heteroatom (N, S, O) Cross-Coupling Reactions



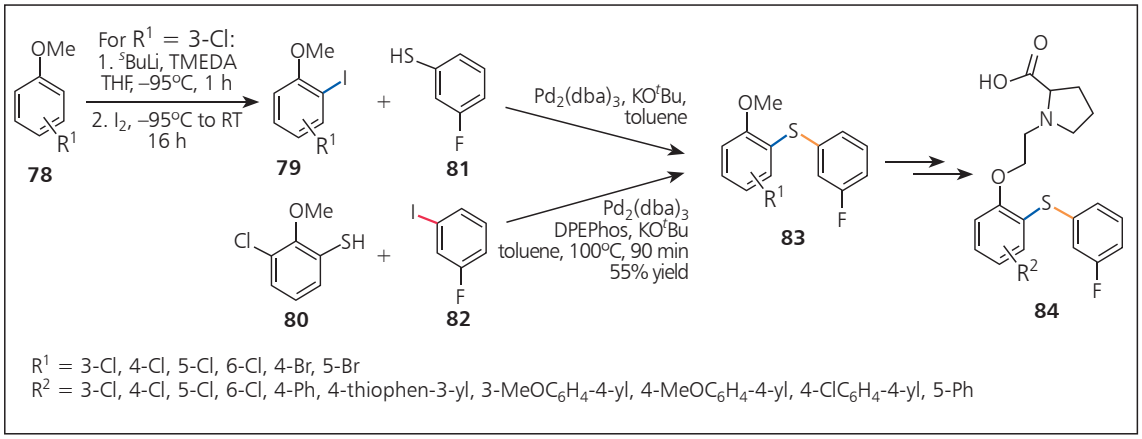
With the advent of transition metal-catalysed C–N, C–O and C–S cross-coupling technologies, these reactions have also been fused with DoM and the combined DoM–heteroatom cross-coupling methodology has become viable for the construction of biologically interesting molecules and natural products. Thus the naphthyldihydroisoquinoline alkaloid ancistrocladinium B **76** (**Scheme XIX**), which shows high *in vitro* antileishmanial activities, has been synthesised from **73** *via* methoxymethyl (MOM) directed metallation-bromination to provide bromide **74**, followed by Buchwald-Hartwig amination to furnish the key intermediate **75**. The synthesis of ancistrocladinium C (**77**) was also achieved using a similar strategy (42).

Similarly, the construction of a C–O bond has been accomplished using DoM–cross-coupling strategies. Although copper catalysis is the preferred choice for C–O bond formation (43–45), it is also possible to use pgm catalysis as an alternative (46–48).

Among the DoM–C–heteroatom cross-coupling strategies, the DoM–C–S regimen is far less evident in the literature. In an instructive study which shows the utility of inverting the coupling partners, substituted 2-iodo-anisoles **79** (**Scheme XX**) were synthesised using DoM chemistry and subjected to Buchwald-Hartwig coupling with 3-fluorobenzenethiol **81**, to afford biaryl sulfide derivatives **83** which were further modified to give the desired compounds **84**. Alternatively, 3-chloro-2-methoxyphenyl thiol **80** was coupled with 3-fluoroiodobenzene **82** to furnish similar analogues **83**. These were demonstrated to possess *in vitro* potency for blocking glycine transporter-1 (GlyT-1), which has been recognised as a potential strategy for the treatment of schizophrenia (49).

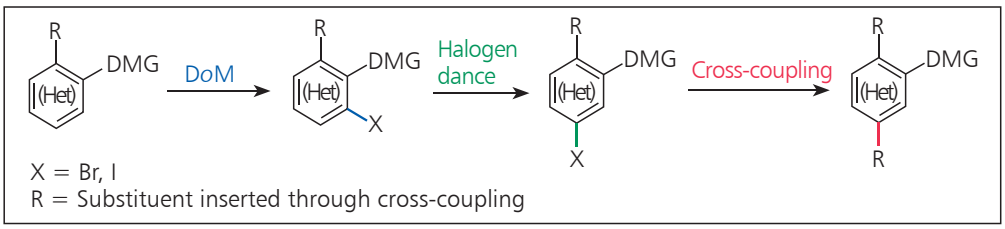


*Scheme XIX. Synthesis of ancistrocladinium B **76** as atropo-diasteromers (P/M) 46/54 and ancistrocladinium C **77** as atropo-diasteromers (P/M) 3/2 using a DoM–C–N cross-coupling strategy (42)*



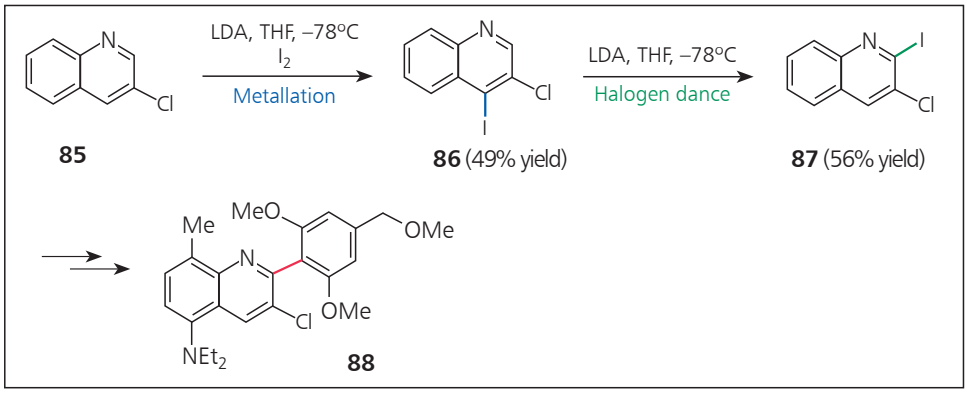
*Scheme XX. DoM–C–S cross-coupling route to diaryl sulfides **84***

3. DoM–Halogen Dance–Cross-Coupling Reactions



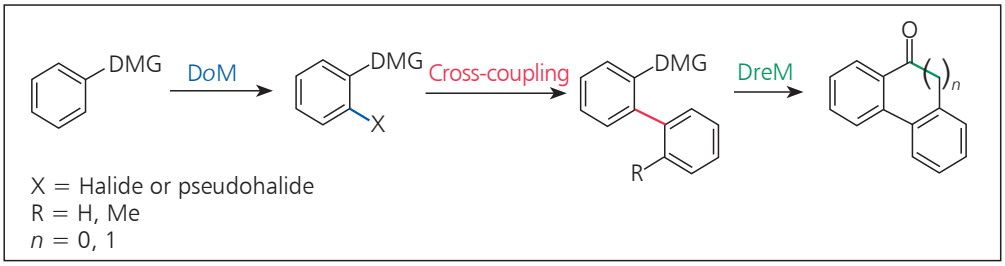
The DoM reaction on halogenated aromatic and heteroaromatic compounds may be accompanied by halogen dance reactions in which halogens, most notably iodine, undergo migration to the incipient

anion and provide, generally but not invariably, the most thermodynamically stable anion (50). This not only provides an option to halogenate positions which are otherwise difficult to access, but also enables the introduction of an external electrophile at the site bearing the newly formed anion. In this context, we have developed routes to polyfunctionalised pyridines (51) and others have utilised halogen dance in the formation of heterobiaryls (**Scheme XXI**) to provide substituted 2-arylquinolines as novel CRF_1 receptor antagonists (52). Thus, metallation-iodination of quinoline **85** afforded iodoquinoline **86** which, when subjected to a second metallation-protonation, gave the halogen dance product **87**. Suzuki-Miyaura cross-coupling and subsequent steps led to the substituted arylquinolines **88**. We have found that it is important to be vigilant for potential undesired halogen dance reactions which may arise in many metallation reactions of halogenated heterocycles.



*Scheme XXI. Metallation–halogen dance–Suzuki-Miyaura route to 2-arylquinoline **88** CRF_1 receptor antagonist*

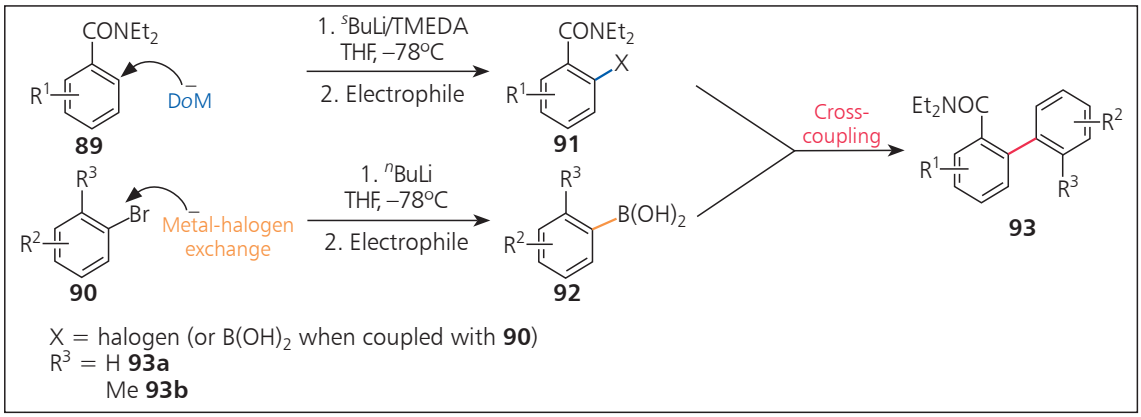
4. DoM–Cross-Coupling–DreM Reactions



The synthesis of interesting polycyclic aromatic and heteroaromatic molecules has a long history in the Snieckus laboratories (a recent example uses the Suzuki-Miyaura cross-coupling (53)). To construct these systems, the directed remote metallation (DreM) reaction (54, 55) on specifically designed 2-DMG biaryls is the key reaction to forge the central aromatic bridging ring. Generally this method complements already established methods for their synthesis and allows easy access to previously unreported compounds. The standard conditions for a DreM reaction are formation of the anion by treatment with LDA at –20°C or 0°C, followed by warming to room temperature to ensure completion of the anionic cyclisation. Depending on the type of substituents in the biaryl starting material, often a minimum of 2 equivalents of LDA is required, proposed to be due to 'losing' one or more equivalents to coordination with these substituents.

4.1 Synthesis of Biaryls Using DoM–Cross-Coupling Reactions

For the construction of requisite biaryls, the DoM–Suzuki-Miyaura protocol is frequently practiced, although other cross-coupling strategies such as DoM–Negishi are also used. Thus, in general (**Scheme XXII**), cross-coupling partners 2-halodiethylbenzamides **91** and boronic acids **92** are synthesised using standard DoM conditions from diethylbenzamides **89** and by metal halogen exchange on bromobenzenes **90** respectively, although currently many of the boronic acids may be



Scheme XXII. DoM–Suzuki-Miyaura cross-coupling synthesis of biaryls ***93***

purchased. Alternatively, the cross-coupling partners may be inverted so that DoM derived boronic acids **91** (X = $B(OH)_2$) may be directly coupled with aromatic triflates or with bromobenzenes **90** without the need for metal halogen exchange. We have found that the Suzuki-Miyaura reaction usually requires only minimal development using standard palladium sources and ligands, although the reactions are still substrate dependent. On the other hand, certain boronic acids, especially heteroaromatic cases, can be difficult to handle and unstable due to their propensity for protodeboronation. As a notable example, we have learned from experience that 3-methoxy-*N*,*N*-diethylbenzamide-2-boronic acid is difficult to isolate, and is reliably synthesised only if the aqueous quench of the reaction mixture is performed at –40°C slowly by the addition of a CH_2Cl_2/H_2O mixture. Others have reported similar problems regarding this boronic acid (56).

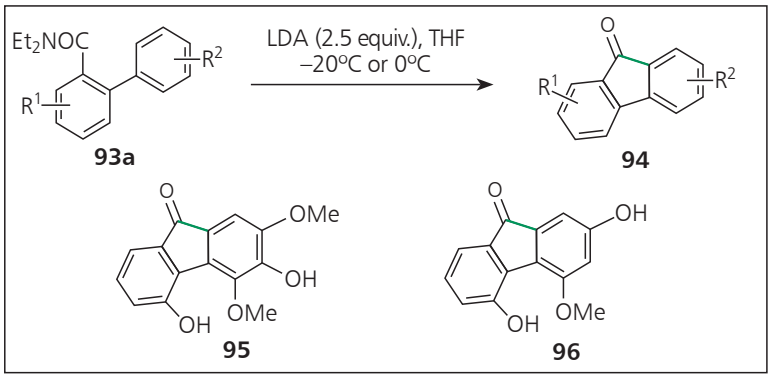
The absence of reports concerning aryl sulfonamide *ortho*-boronic acids prompted a study in which the problems associated with the synthesis of this class of unstable boronic acids was solved, at least in this particular case (7). Although it was determined that metallation of aryl sulfonamides proceeds uneventfully, as evidenced by deuterium quench experiments, quenching the metallated species with $B(OR)_3$ reagents followed by aqueous workup provided boronic acids in low yields, accompanied by recovery of starting material, which suggested instability of the *ortho*-boronic acids. This problem was circumvented by utilising an *in situ* quench with MeOBpin or ^{i}PrOBpin as electrophiles, leading directly to the boropinacolate derivatives which are known to be more stable than the corresponding boronic acids. Similarly in the even more unstable pyridine boronic acid series, *in situ* formation of boropinacolates was advantageous in isolation of compounds useful for Suzuki-Miyaura cross-coupling reactions (32).

Another solution for the synthesis of problematic arylboronic acids stemming from our laboratories is the *ipso*-borodesilylation reaction of trimethylsilyl arenes (57). The silylated starting materials are readily obtained in high yields using DoM chemistry, and are quite stable with the exception of certain heteroaromatic silanes. Treatment with BCl_3 or BBr_3 affords the Ar-BX_2 species which, without isolation, may be converted into the corresponding boropinacolates by stirring with pinacol, or otherwise may be used directly in a one-pot cross-coupling process.

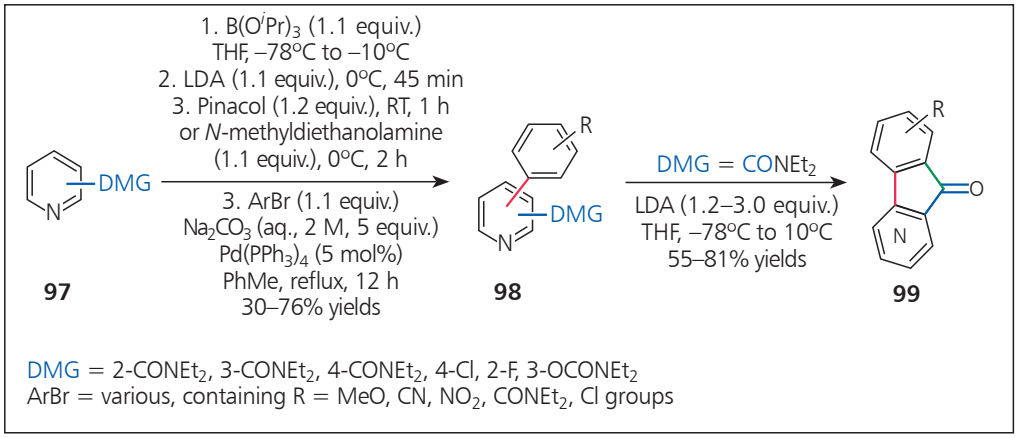
4.2 Combined DoM–Suzuki-Miyaura–DreM Synthesis of Fluorenones

Treatment of biaryl-2-amides **93a**, derived from DoM–cross-coupling reactions, under standard DreM conditions results in alternate ring deprotonation followed by cyclisation to provide fluorenones **94** in good yields (**Scheme XXIII**). As ourselves and others (58,59) have demonstrated, various substituted fluorenones, azafluorenones and two natural products dengibsinin **95** and dengibsin **96** may be synthesised using this strategy (60,61).

Generally the highest yields are obtained for biaryl cases bearing an additional 3′-DMG which promotes synergistic metallation, thereby leading to regioselective cyclisation. In the synthesis of azafluorenones **99** using this strategy (**Scheme XXIV**), the use of a one-pot DoM–Suzuki-Miyaura protocol was



*Scheme XXIII. Synthesis of fluorenones using the combined DoM–cross-coupling–DreM strategy for dengibsinin **95** and dengibsin **96***



*Scheme XXIV. One-pot DoM–Suzuki-Miyaura–DreM synthesis of azafluorenones **99** (32)*

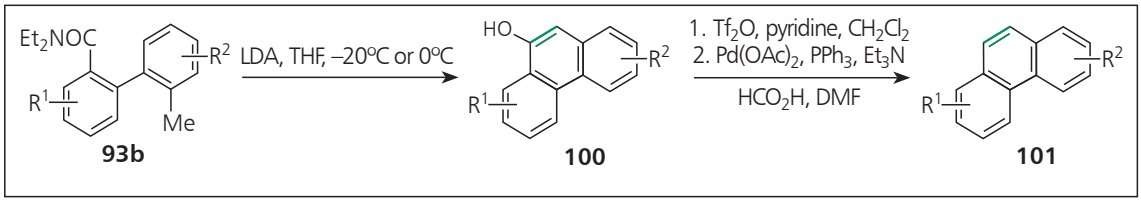
essential due to the instability of the pyridyl boronates towards protodeboronation (32).

This method proved useful for the construction of diverse azafluorenones with electron-donating and electron-withdrawing substituents. This sequential DoM–cross-coupling–DreM strategy allows the construction of azafluorenones which are inaccessible or afford isomeric mixtures by the traditional Friedel-Crafts reactions.

4.3 Combined DoM–Suzuki-Miyaura–DreM Synthesis of Phenanthrols and Phenanthrenes

Treatment of biaryls exhibiting 2′-methyl substituents **93b** under standard DreM conditions affords 9-phenanthrol derivatives **100** (**Scheme XXV**). The deprotonation is often – but not always – indicated by a deep red colour attributed to the generated tolyl anion. Conversion of the resulting phenanthrols **100** to phenanthrenes **101** is readily achieved using triflation followed by palladium-catalysed hydrogenolysis. Often no purification is required for the intermediate steps, and the final phenanthrenes may be obtained in good yield and high purity after a simple recrystallisation.

This route is scalable and reliably provides substituted phenanthrenes in high purity which have been used successfully in our collaborative projects to conduct toxicity studies concerning the effects of substituted polyaromatic hydrocarbons on fish (62).



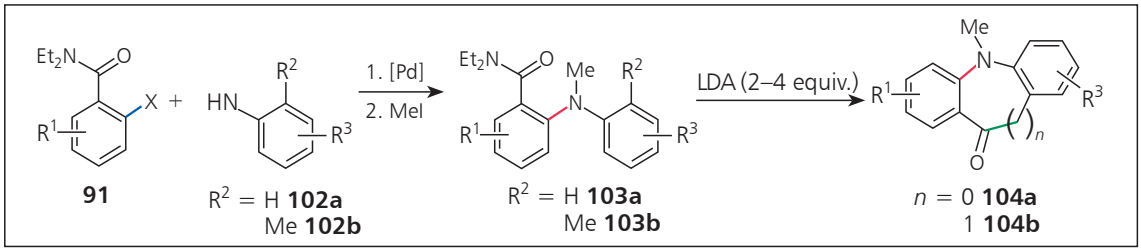
*Scheme XXV. Synthesis of phenanthrenes **101** by the combined DoM–Suzuki-Miyaura–DreM strategy*

4.4 Combined DoM–Suzuki-Miyaura–DreM Synthesis of Acridones and Benzazepinones

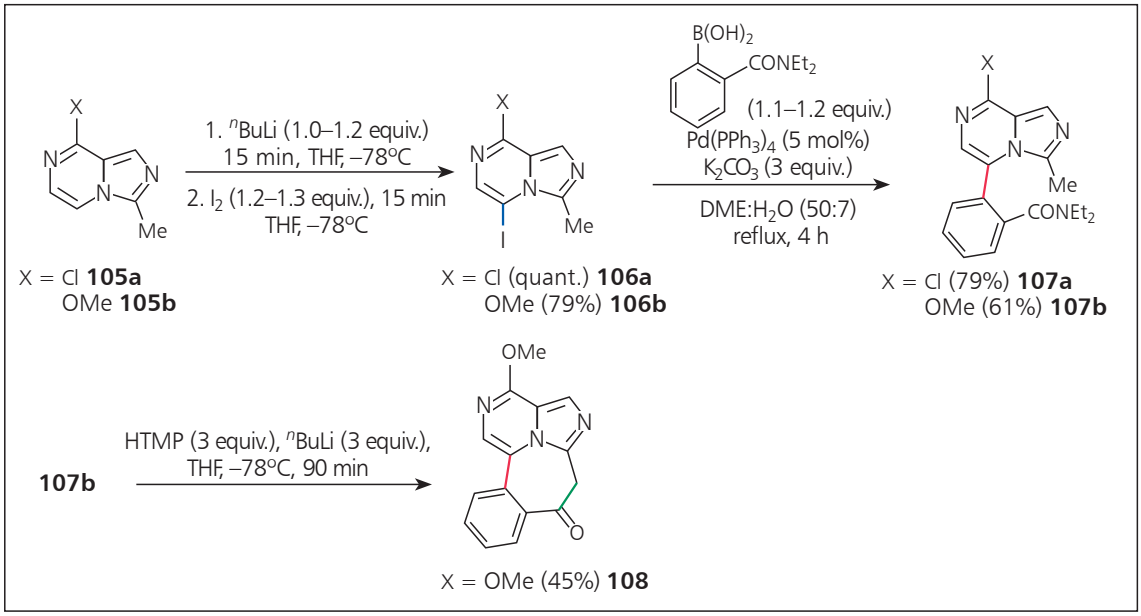
A DreM process analogous to that shown in **Scheme XXV** may also be achieved on diarylamines **103**, which are prepared using palladium-catalysed Buchwald-Hartwig cross-coupling of anilines **102** with DoM derived halo or pseudohalo diethylbenzamides **91**, followed by *N*-alkylation. Thus treatment of diarylamine **103a** (R^2 = H), under standard DreM conditions provides acridones **104a** (n = 0) in good to excellent yields. In an analogous fashion to the formation of phenanthrenes (**Scheme XXV**), subjection of the diarylamine **103b** (R^2 = Me) to standard DreM conditions affords dibenzazepinones **104b** (n = 1), also in good to excellent yields (**Scheme XXVI**) (63).

These protocols constitute anionic equivalents of Friedel-Crafts type cyclisations affording acridones, and complement existing syntheses of dibenzoazepinones, compound classes which both exhibit significant bioactivities. For instance, acridone derivatives possess antimalarial properties (64), and dibenzoazepinone derivative trileptal is an antiepileptic drug (65).

In a collaborative study, we investigated the multi-nitrogen-containing imidazo[1,5-*a*]pyrazine **105** for use as a scaffold for the preparation of potentially bioactive molecules. Without prediction based on available precedent, the metallation of **105a** and **105b** followed by iodination afforded C-5 iodinated compounds **106a** and **106b** in high yields. Subsequent Suzuki-Miyaura cross-coupling with 2-(diethylcarbamoyl)phenylboronic acid (synthesised from *N,N*-diethylbenzamide using a DoM protocol) provided biaryls **107a** and **107b**. Treatment of **107b** with LiTMP at cryogenic temperatures furnished the previously unknown triazadibenzo[*cd,f*]azulen-7(6*H*)-one **108b** (**Scheme XXVII**) (66). To the best of our knowledge, DreM processes of complex heterocycles such as **107** had not been previously reported.



Scheme XXVI. Synthesis of acridones and dibenzazepinones using DoM–C–N cross-coupling–DreM strategy

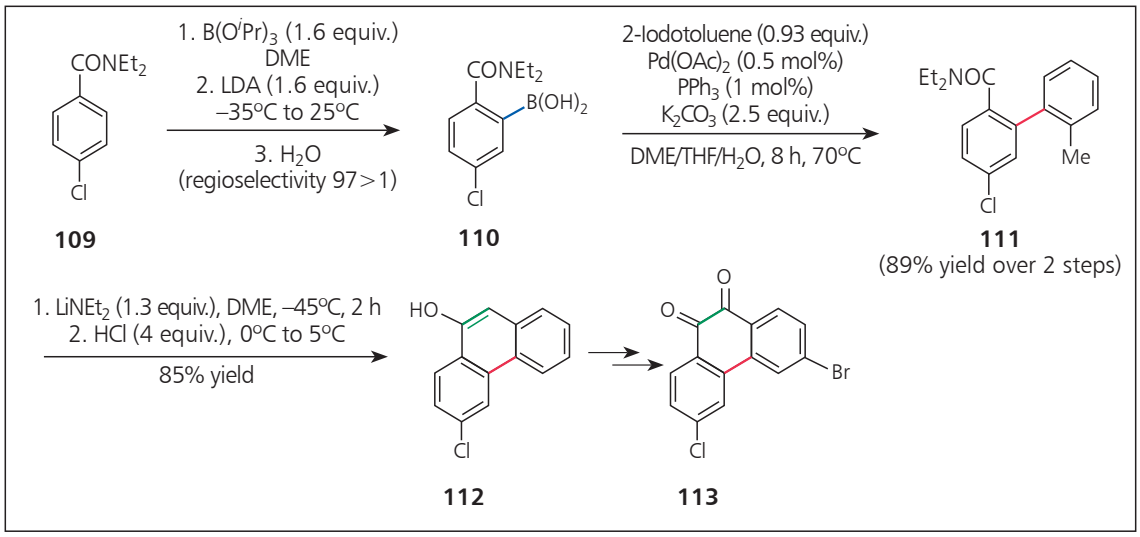


*Scheme XXVII. DoM–Suzuki–DreM–cyclisation route to triazadibenzo[cd,f]azulen-7(6H)-one **108b** (64)*

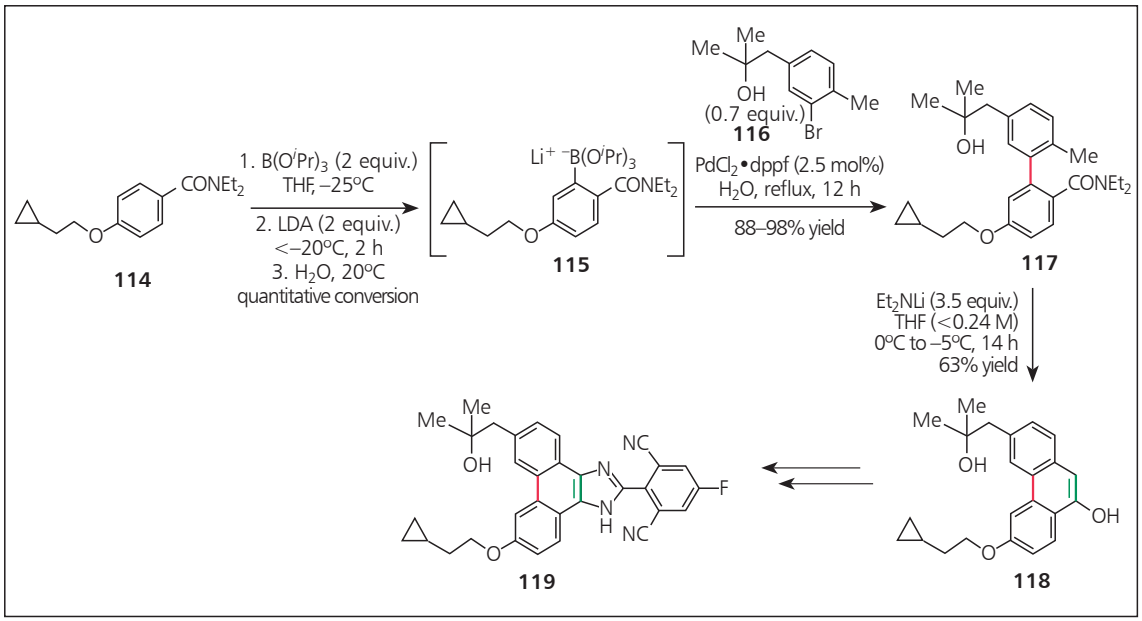
5. Scale-Up and Industrial use of DoM–Cross-Coupling–DreM Reactions

If proper safety protocols are followed and temperature and stirring of the reaction mixture are controlled and maintained, metallation chemistry may be effectively used for large scale synthesis. In fact, there is often no viable alternative to the use of a DoM–cross-coupling sequence at multi-kilogram scale in the pharmaceutical and fine chemical industry (67–69). For instance, Merck has recently demonstrated a practical, efficient and multi-hundred gram synthesis of 3-bromo-6-chloro-phenanthrene-9,10-dione **113** using a DoM–cross-coupling–DreM sequence (**Scheme XXVIII**) (70). Compound **113** is a useful building block for the preparation of pharmaceutically important phenanthrenequinones and phenanthreneimidazoles.

Similarly, as further evidence of utility, Merck has achieved a kilogram-scale chromatography-free synthesis of mPGE synthase I inhibitor MK-7285 **119** (**Scheme XXIX**) (71). Thus DoM–boronation of **114** provided the lithioborate **115**



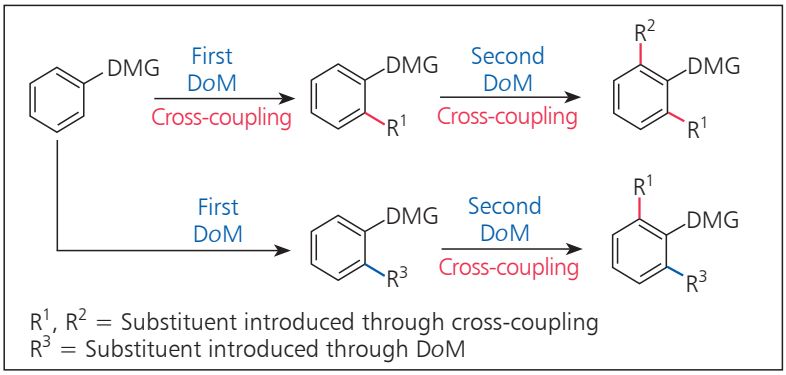
*Scheme XXVIII. Large scale synthesis of phenanthrene-9,10-diones **113** using a combined DoM–cross-coupling–DreM strategy. **109** was used at a scale of 245.7 g, **111** was produced at a scale of 311.5 g and **112** at 200 g (68)*



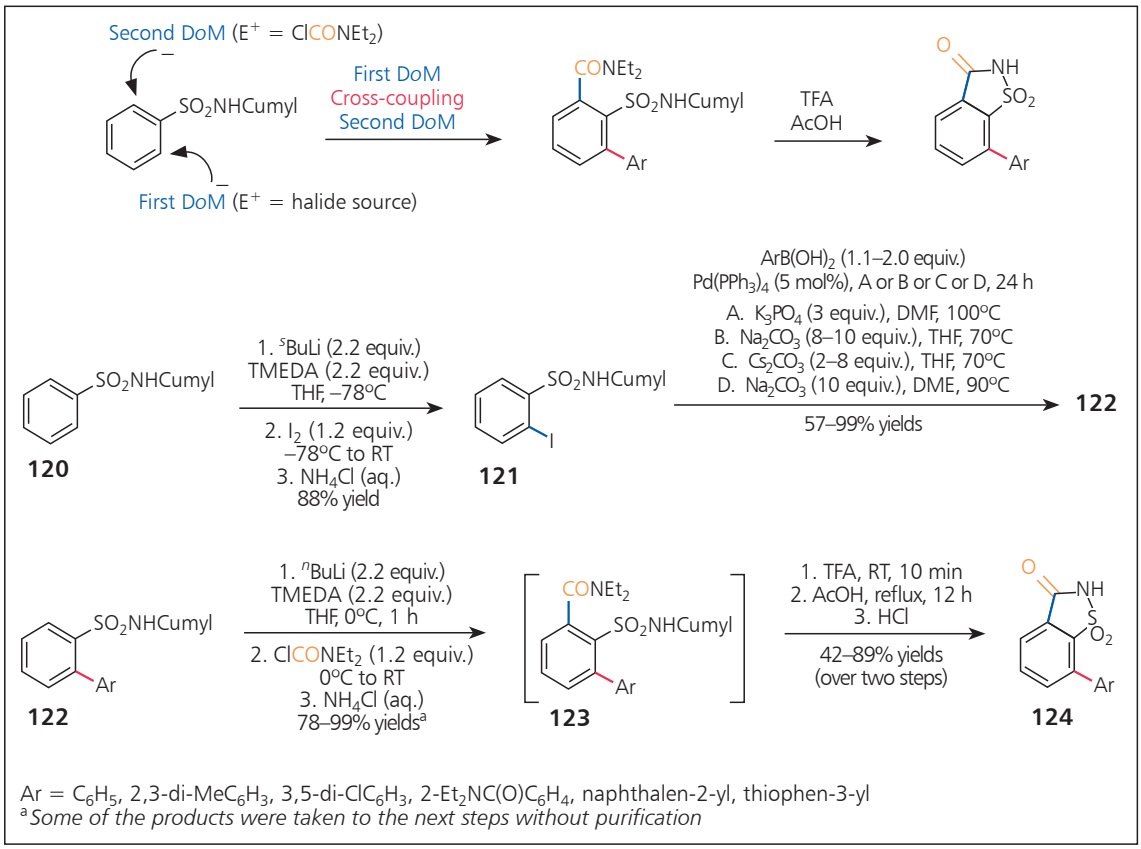
*Scheme XXIX. Large scale synthesis of mPGE synthase I inhibitor **119** using the combined DoM–cross-coupling–DreM strategy. **114** was used at a scale of 3.75 kg, **117** was produced at a scale of 7.69 kg (69)*

which, without isolation, was subjected to Suzuki-Miyaura cross-coupling with bromobenzene **116** to afford biaryl **117**. In the key step, treatment of biaryl **117** with lithium diethylamide resulted in a DreM cyclisation to provide the phenanthrol **118** in acceptable yield. A significant observation was that in the DreM reaction, at concentrations greater than 0.24 M, competitive intermolecular condensation provided 5–10% of an undesired product.

6. Diversification of the DoM–Cross-Coupling Strategy



The unique power and considerable synthetic advantage of DoM chemistry is the regioselective *ortho* introduction of only one functional group per DMG. Furthermore, synthetic strategies may be devised to use the same DMG to achieve 2,6-disubstitution and thus to construct 1,2,3-trisubstituted aromatic systems (72). Using the *N*-cumylsulfonamide DMG, this strategy has been adapted for the synthesis of 7-substituted saccharins (**Scheme XXX**) (73). Thus, as conceptually illustrated below, the straightforward



Scheme XXX. Double use of the N-cumylsulfonamide DMG in the synthesis of substituted saccharins ***124***

DoM–halogenation–Suzuki-Miyaura coupling of *N*-cumylbenzenesulfonamides **120** provided, *via* iodide **121**, the biaryls **122**. Then the same *N*-cumyl sulfonamide DMG served for a second DoM–carbamoylation to furnish the biaryl amide sulfonamide **123**. Decumylation of **123** using TFA, followed by acid-mediated cyclisation gave rapid access to saccharins **124** in good overall yield.

Aside from interesting pharmaceutical properties and use in the fields of flavour, polymer and coordination chemistry, the saccharin core has played a role in the discovery of a human leukocyte elastase inhibitor, KAN400473 (**125**, **Figure 3**), used for the treatment of emphysema (74). It also features in the Merck carbapenem antibacterial agents (**126**, **Figure 3**) (75).

Double DoM–double cross-coupling reactions involving multiple DMGs are also useful synthetic tactics. Thus the first total syntheses of natural, unsymmetrical 2′,3′-diacyloxy-*p*-terphenyls, thelephantin O **131a** (**Scheme XXXI**) and terrestrins C and D (**131b** and **131c**, respectively), were achieved using double DoM and bromination of **127** to give the hexasubstituted benzene **128** which, after Suzuki-Miyaura cross-coupling with **129**, afforded the key intermediate teraryl **130**. Synthesis of the symmetrical diesters vialinin A/terrestrin A **131d** and terrestrin B **131e** was also achieved using the same sequence (76).

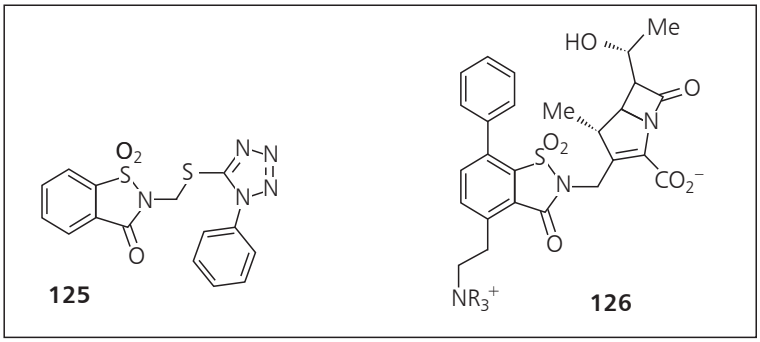
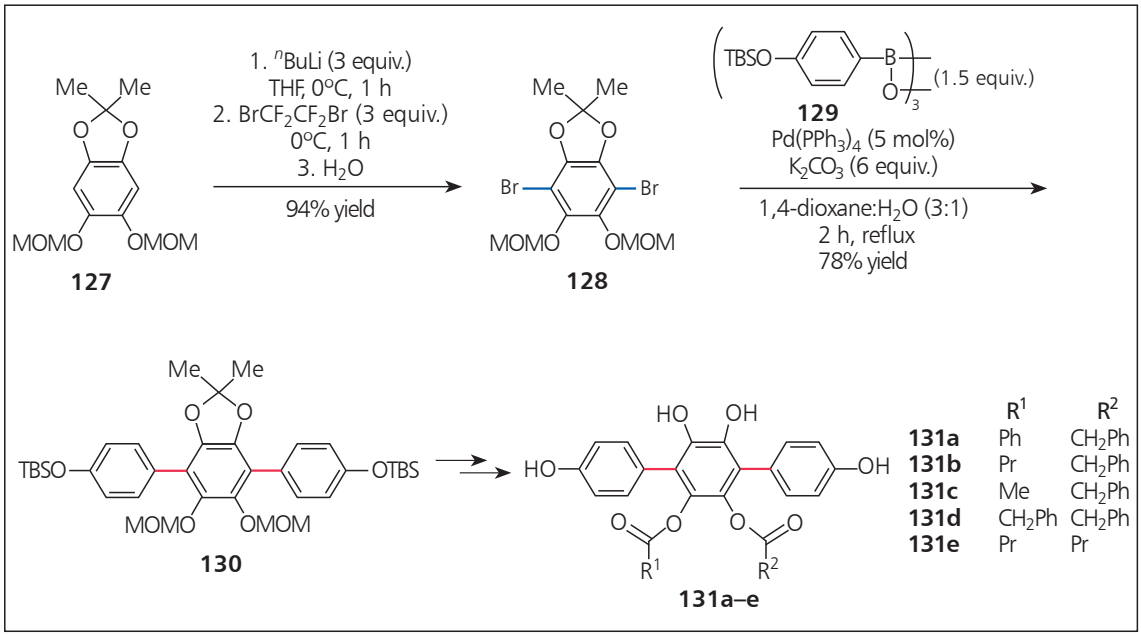
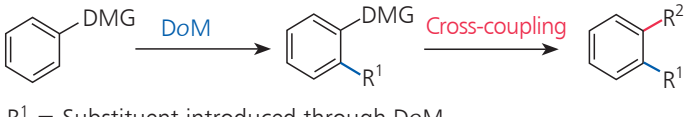


Fig. 3. Biologically active saccharins KAN400473 ***125*** *and Merck antibacterial agents* ***126***



Scheme XXXI. Synthesis of teraryl natural products using double DoM–Suzuki-Miyaura cross-coupling sequence

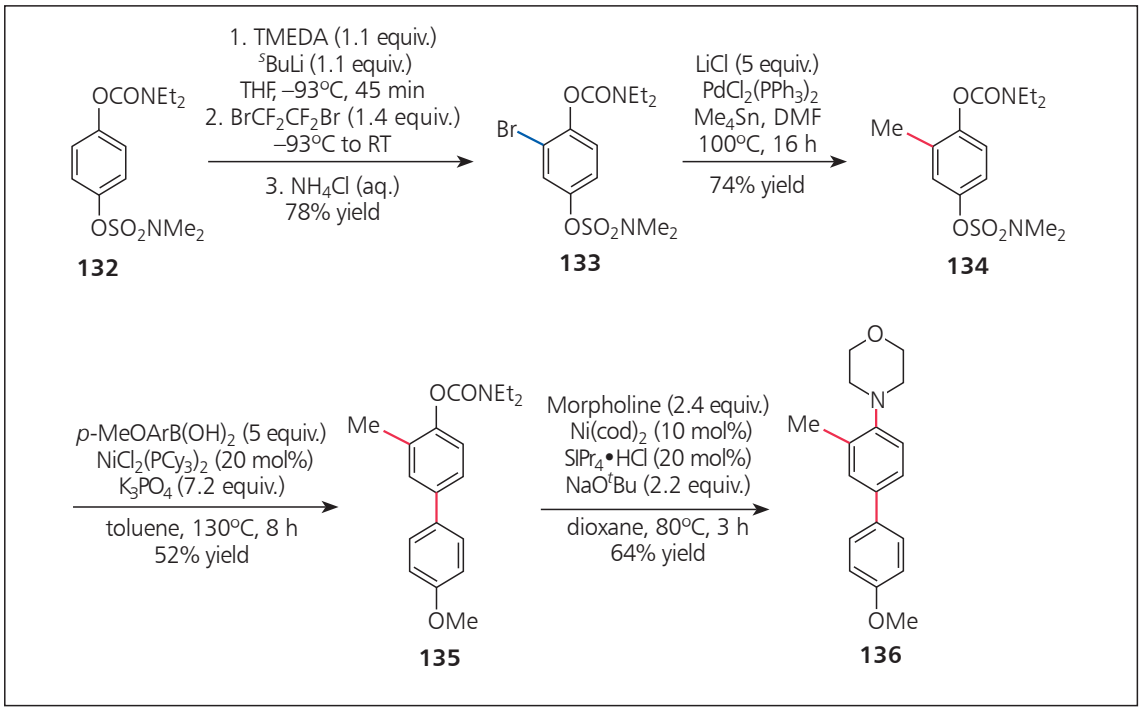
7. The DMG as a Pseudohalide in Cross-Coupling Reactions



R^1 = Substituent introduced through DoM
R^2 = Substituent introduced through cross-coupling

As documented in this review, cross-coupling of DoM derived species such as B, Zn, Sn and Mg has become a highly useful synthetic strategy. The development of DMGs that themselves act as cross-coupling partners was first achieved in our group with *O*-carbamates (77) and subsequently with sulfonamides (78) under $Ni(acac)_2$ conditions. Furthermore, these DMGs may be excised from the aromatic framework using the β-hydride donor properties of $^{i}PrMgCl$ and $^{i}Pr_2Mg$ respectively, thus establishing the latency concept of DMGs (77, 78). Recently additional DMGs such as ethers, esters, *O*-carbamates under Suzuki-Miyaura conditions (79, 80) and *O*-sulfamates (79) have been established as cross-coupling partners (81). The non-reactive nature of some of these groups in palladium-catalysed coupling reactions allows the establishment of orthogonal processes (82, 83). For example, subsequent to work in our laboratories (80), Garg *et al.* (84) recently explored regioselective construction of biaryls based on differential reactivity of bromide, *O*-carbamate and *O*-sulfamate groups toward Pd and Ni catalysts (**Scheme XXXII**). Thus, DoM–bromination of **132** furnishes aromatic bromide **133**, which undergoes sequential and selective palladium-catalysed Stille, nickel-catalysed Suzuki-Miyaura and nickel-catalysed C–N cross-coupling to rapidly provide biaryl **136** in good yield. Recent efforts on transition metal-catalysed cross-coupling reactions of new *O*-based electrophiles *via* C–O bond activation have focused on nickel and iron based catalysis (85–87).

Authors' note added in proof: after the submission of this review, Feringa and co-workers established the palladium-catalysed cross-coupling of alkyl, alkenyl and aromatic lithiates (some derived using DoM) with aromatic bromides (88).



Scheme XXXII. Use of O-carbamate and O-sulfamate DMGs as cross-coupling partners

Conclusions

This brief review has demonstrated that the combined D*o*M–cross-coupling strategy, first developed in our laboratories in the mid-1980s, has considerable value in organic synthesis. In this aim, we have attempted firstly to provide supportive evidence using selected recent examples derived from industrial and academic laboratories, including many from our own work. Emphasis has been placed on heterocycles, which constitute 80% of current marketed drugs, with synthetic case studies on a variety of bioactive molecules in early, clinical or process stages of development, including soraprazan (**Figure 1**), GSK966587 (**Figure 2**), ancistrocladinium B and C (**Scheme XIX**) and CRF_1 receptor antagonist (**Scheme XXI**). As will be recognised, the heterocycles range from recognisable to more unusual and complex frameworks (for example **Scheme XXVII**). The pgms, particularly palladium, catalyse many of the processes, contributing to the enormous versatility of this strategy.

The second aim of the review has been to offer, in various described processes, practical from-the-bench tips based on our experience, at least in small-scale reactions. These include the advantage of deuterium-quench experiments to establish the extent of the D*o*M step before taking the road to scale-up (for example **Scheme III**), and the caveat regarding purity of starting materials and their instability.

Prognosis for the DoM–Cross Coupling Strategy

Emerging from the content of this review are the following features:

1. **DoM–C–C Cross-Coupling Reactions**
   - This section suggests that among the cross-coupling reactions used in combination with D*o*M: Ullmann, Heck, Sonogashira, Negishi, Stille and Suzuki-Miyaura, the latter dominates the synthetic landscape with increasing presence of the Negishi protocol.
   - The advent of new nontraditional lithium bases such as the commercial Knochel type tmpMgCl·LiCl combined with zinc transmetallation and Negishi coupling (**Scheme XII**) are beginning to provide more convenient conditions for the D*o*M–cross-coupling strategy.
   - Iridium-catalysed boronation offers a complementary method for *meta* boronation compared to the D*o*M–Suzuki-Miyaura coupling process (**Scheme XVI**).
   - Only an inkling has been given of the potential for D*o*M–cross-coupling in natural product synthesis (**Schemes XVII** and **XVIII**) and this can only be expected to grow in importance.
2. **DoM–C–Heteroatom (N, S, O) Cross-Coupling Reactions**
   - Based on our literature review, this motif has considerable use in combined D*o*M–Hartwig-Buchwald C–N and C–O cross-coupling processes and is as yet underdeveloped for C–S fusion reactions.
3. **DoM–Halogen Dance–Cross-Coupling Reactions**
   - Although the agreeably named halogen dance is of some vintage, its application in the construction of substituted aromatics and heteroaromatics has considerable, as yet unfulfilled, promise.
   - Among the practical tips is the caveat that, to eventual regret, it may be easy to overlook the occurrence of the halogen dance in the dash to publication.
4. **DoM–Cross-Coupling–DreM Reactions**
   - The D*o*M–cross-coupling sequence finds additional advantage in synthesis when combined with the DreM process.
   - Thus, the regioselective synthesis of substituted fluorenones (**Schemes XXIII** and **XXIV**), phenanthrenes (**Scheme XXV**) and acridones and dibenzazepinones (**Scheme XXVI**) become feasible in practical, efficient and environmentally friendly ways compared with, for example, traditional electrophilic substitution methods. Specifically, the DreM approach to fluorenones and azafluorenones (**Scheme XXIV**) demonstrates the complementarity between Friedel-Crafts and DreM tactics.
5. **Scale-Up and Industrial use of DoM–Cross-Coupling–DreM Reactions**
   - As in the case of D*o*M chemistry which was dormant for about a decade after developments in our laboratories in the late 1970s, the DreM concept has been nurtured in industry and is now appearing in the open literature. It is encouraging to see the application of the combined D*o*M–cross-coupling technology (**Scheme XXVIII**),

including DreM (**Scheme XXIX**) methods, on a multi-kilogram scale.

6. Diversification of the DoM–Cross-Coupling Strategy

- While DoM reactions constitute one functional group per DMG for synthetic considerations, significant advantage is gained in diversification, with or without protection requirements, to the creation of 2,6-disubstituted DMG-bearing aromatics. Perhaps insufficiently appreciated and adapted as yet, such a sequence is shown in **Scheme XXX**.
- Another conceptual element, a double DoM process (**Scheme XXXI**), may also be the tip of the iceberg in synthesis.

7. The DMG as a Pseudohalide in Cross-Coupling Reactions

- Adaption of methodology which uses the DMG aromatic as a pseudohalide coupling partner, already demonstrated in our Corriu-Kumada reaction of aryl *O*-carbamates in the early 1990s, has taken on new possibilities in *O*-carbamate, *O*-sulfamate and sulfonamide Corriu-Kumada and Suzuki-Miyaura reactions (**Scheme XXXII**) in our laboratories as well as others. The potential of this chemistry, including the excision of the DMG by transition metal-catalysed β-hydride elimination processes, is only now surfacing in the literature.

We hope the aims of this review have been met and will be valuable to synthetic chemists. The prognostic views expressed throughout this final section are, as many times experienced by all, dangerous to place, as we do, into the literature.

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Glossary

Term	Definition
DoM	directed *ortho* metallation
DreM	directed remote metallation
DMG	directed metallation group
Het	heterocycle

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