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Mini Review

The directed *ortho* metalation—cross coupling symbiosis. Regioselective methodologies for biaryls and heterobiaryls. Deployment in aromatic and heteroaromatic natural product synthesis

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Dedicated to Robert J.P. Corriu, Jay Kazuo Kochi, Makoto Kumada, and Akio Yamamato for taking the initial bold steps.

Abstract

In this mini-review, synthetic methods for biaryls and heterobiaryls interconnecting the directed *ortho* metalation (DoM) reaction with Corriu–Kumada, Negishi, Suzuki–Miyaura and, less, Stille cross coupling reactions are presented from perspectives of development of new reaction parameters (Suzuki–Miyaura: Schemes 4–7), new cross coupling partners (Corriu–Kumada: Schemes 9 and 11), and comprehensive evaluation (Schemes 12 and 13). Recent work on the application of these protocols to indole derivatives (Schemes 16–18), dibenzopyranones (Scheme 19), aza- and isoazacoumestans (Scheme 20), and kinamycin antibiotics (Scheme 21) is described.

Keywords: Directed *ortho* metalation; Cross coupling; Biaryls; Heteroaromatics; Natural products; Synthesis

1. Introduction

> "These reactions (Grignard reagents with organic halides) are…seldom employed in synthetic practice, due to the formation of homo coupling…and a variety of disproportionation products…" [1].

> "Selective cross coupling reactions between $C(sp^3)$ and $C(sp^2)$ centers had been one of the most difficult tasks in carbon–carbon bond synthesis until the early 1970s… Now, … (it) has become the reaction of first choice for this purpose" [2].

The 20 years separating the above comments by the mentor and the student, and then the student independently dramatically posit the changing face of synthetic methodology with respect to sp^2–sp^2 and related bond constructs. Although not yet infiltrating undergraduate first-course organic chemistry curricula, the practice of such bond formation in industry and academe have long superceded methodology based on carbonyl-Grignard condensation reactions followed by dehydration which present serious regio- and stereo-chemical deficiencies. The symposium [3] in celebration of the discovery and indication of initial promise of the transition metal catalyzed cross coupling chemistry by Robert J.P. Corriu, Jay Kazuo Kochi, Makoto Kumada, and Akio Yamamato allows homage, reflection, and prognosis of this very active area of synthetic methodology. As invariably found in scientific pursuits, humble beginnings have led to enormous utility and application.

In the area of aryl–aryl bond formation processes, Kharasch already 60 years ago [4,5] set the stage for catalytic C–C bond formation reactions. However, the original and independent work of Corriu and Kumada [6,7] clearly pointed to the synthetic promise of catalytic ArMgX plus ArHalide combinations to afford biaryls (Scheme 1). Somewhat later, Negishi reported [8] the ArZnX plus ArHalide cross coupling process

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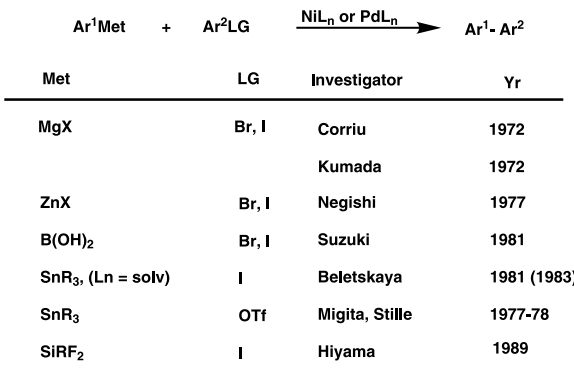
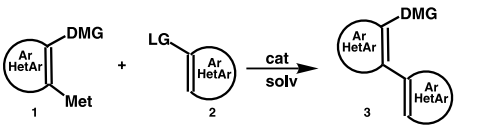
and this discovery was followed by the Suzuki and Miyaura publication [9] which demonstrated the truly novel $ArB(OH)_2$–ArHalide coupling reaction. The contributions of Beletskaya, unrecognized owing to her publications in not readily accessible literature, are of paramount significance in organomagnesium and organostannane coupling chemistry, especially the demonstration of ligandless catalysis for the Corriu–Kumada and Stille processes [10]. Following observations by Migita [11], Stille defined and systematically studied the $ArSnR_3$ plus ArHalide and subsequently, ArOTf reactions [12], thereby alerting the synthetic community to the power of the cross coupling strategy in complex molecule synthesis. The most recent addition, the Hiyama silicon-based cross coupling reaction, is clearly primed for further exploration and exploitation [13].



Met	LG	Investigator	Yr
MgX	Br, I	Corriu	1972
		Kumada	1972
ZnX	Br, I	Negishi	1977
$B(OH)_2$	Br, I	Suzuki	1981
SnR_3, (Ln = solv)	I	Beletskaya	1981 (1983)
SnR_3	OTf	Migita, Stille	1977-78
$SiRF_2$	I	Hiyama	1989

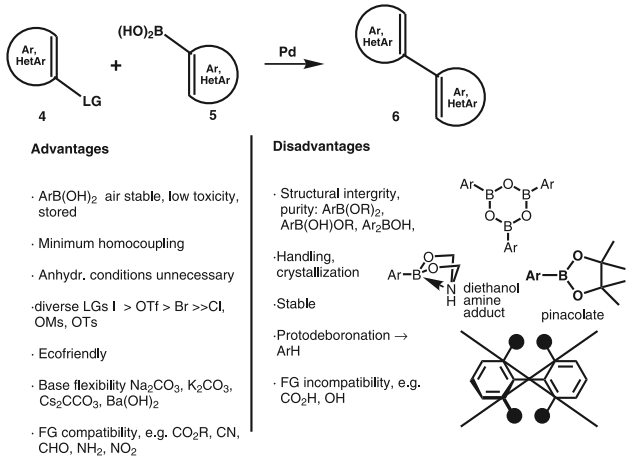
Scheme 1. Prominent transition metal caltalyzed cross coupling reactions for the aryl–aryl bond.



Met	LG	cat	Xcoupl
$B(OR)_2$	I > Br > OTf	Pd	Suzuki
MgX	OTf > $OCONEt_2$ > $SCONEt_2$	Ni	Kumada-Corriu
ZnX	hal, OTf	Ni	Negishi
SnR_3	hal, OTf	Pd	Stille

DMG = $CONEt_2$, $OCONEt_2$, OMOM, NH*t*-Boc, SO_2*t*-Bu

Scheme 2. The DoM-cross coupling nexus.



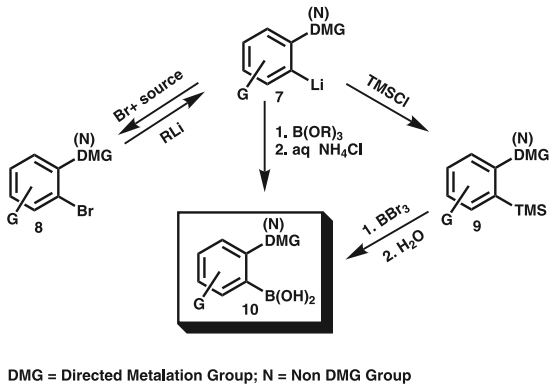
Scheme 3. The Suzuki–Miyaura Ar–Ar cross coupling reaction.

As a rational connection to the directed *ortho* metalation (DoM) [14], the sp^2–sp^2 cross coupling motif in context of aryl–aryl bond formation has been, since the mid-1980s, a continuous area of activity in our laboratories. The initial observations [15] that the Suzuki–Miyaura reaction is readily combined with DoM (**1** + **2** → **3**, Scheme 2) by simple Li → B exchange led to broad exploration of this process in methodology and total synthesis [16]. Further work in Li → Mg and Li → Zn, and Li → Sn exchange reactions allowed a range of alternate solutions for the construction not only of aryl–aryl but also heteroaryl–heteroaryl and their mixed systems. The predictability of regiochemistry dictated by the Directed Metalation Groups (DMGs), the possibility of functionality incorporation by DoM, the efficacy of some of the cross couplings, and their favorable comparison *vis-à-vis* classical methods of biaryl synthesis [17] stimulated further efforts. This mini-review summarizes research in all four named reactions from perspectives of development of useful methodology for polysubstituted aromatic and heteroaromatic synthesis and application to bioactive molecules and natural products.

2. Discussion

2.1. The lithium–boron transmetalation link

The Suzuki–Miyaura cross coupling reaction is a robust, broadly applicable, and field-tested procedure for aryl–aryl and –heteroaryl bond formation [5] about which the advantage/disadvantage differences are widely recognized (**4** + **5** → **6**, Scheme 3). While the preparation of the boronic acids via DoM–boronate ester quench and hydrolysis is a standard procedure, their use in cross coupling is fraught with uncertainties of the actual structure of the organoboron product. To confirm structural integrity, stable derivatives such as pinacolates and diethanol amine adducts [18] may be easily prepared; the latter, however, require prior hydrolysis to the cross coupling reaction [19]. Cross coupling to achieve 2,2′,6,6′-substitution patterns also continues to plague synthetic chemists. Although not widely ascertained, the two-step procedure of silylation–ipso borodesilylation followed by hydrolytic workup (**7** → **9** → **10**, Scheme 4) may lead to a cleaner boronic acid product [20]. For synthetic utility, it may be recognized that the bromo derivative **8**, derived

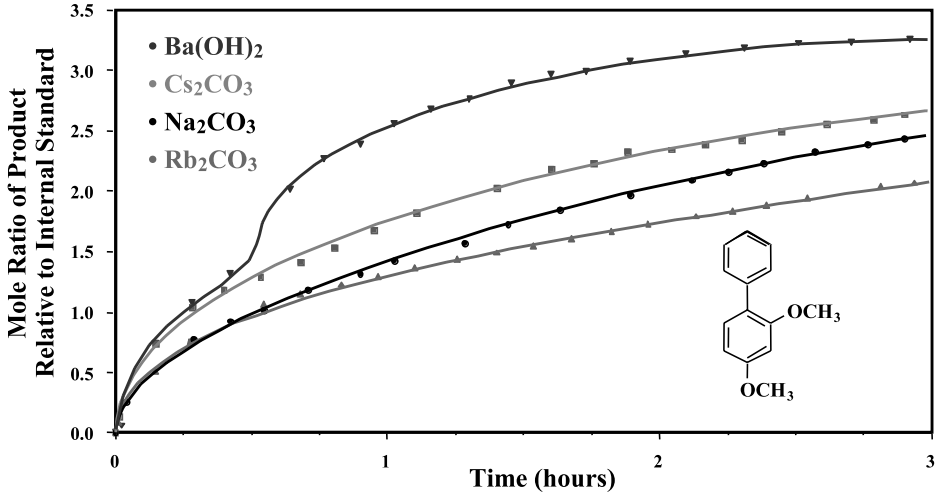


Scheme 4. Routes to *ortho*-DMG aryl boronic acids.

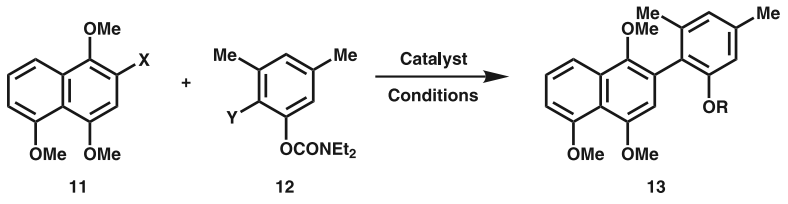
readily from **7**, is a 'holding pattern' for regeneration of *ortho*-lithiated intermediate in situations in which diffusion-controlled metal-halogen exchange may be advantageous. While choice of catalyst appears not to be a crucial factor [$Pd(PPh_3)_4$ is widely used] [21], base variation and solvent effects play significant role in yield and efficacy of the process. Studies of base variation (Scheme 5) shows that the rate of coupling increases, qualitatively, in order from Na_2CO_3 to Cs_2CO_3 and $Ba(OH)_2$ with the latter two bases used interchangeably in our laboratories particularly in sterically hindered cases [22]. However, persistent empirical observation is still the rule as indicated by a difficult cross coupling (**11** + **12** → **13**, Scheme 6) [23] encountered in a total synthesis project which eventually showed the advantage of anhydrous conditions and a different base (K_3PO_4). In an initial attempt to provide data for electron-withdrawing group (EWG) and electron-donating group (EDG) effects on a simple Suzuki reaction (**14**/**15** + **16** → **17**/**18**, Scheme 7) [22], competition experiments indicate enhancement of relative rates for EDG-containing aryl bromide **14** cross coupling partners with a surprising effect of a 4-phenyl substituent.

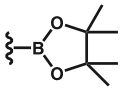
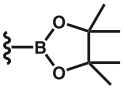
2.2. The aryl O-carbamate and S-carbamate–Grignard cross coupling reaction

Observations on vinyl *O*-carbamate–Grignard cross coupling reactions [24], in addition to factors of availability of *O*-carbamates and triflates from phenols and their interconversion, (**21** → **20**, Scheme 8) and the knowledge of the *O*-carbamates as the most powerful DMG [14] prompted aryl *O*-carbamate–Grignard cross coupling experimentation to uncover a conceptually interesting synthetic sequence **22** → **23** ≡ **24**. While the scope of this new coupling reaction has been reasonably well defined [24b], application to the preparation of unusually substituted aromatic patterns by taking advantage of conceptual elements inscribed in **31a**,**b**, Scheme 9 have been initiated only in a naphthalene case. Thus the *O*-carbamate **25**, upon metalation and treatment with $ClCONEt_2$ affords **26** which, upon a second DoM reaction and electrophile quench leads to **28**. Compound **28** may be taken in cross coupling directions with selected Grignard reagents to give the 1,2,3-trisubstituted naphthalene **27** and, by β-hydride elimination using *i*-PrMgX, the 2,3-disubstituted derivative **29** with the proviso, in both cases, that the introduced E_1 electrophile is compatible with the Grignard reagent or is appropriately protected. A different contiguous trisubstituted pattern resulting from boron introduction in the second metalation step from **28**, $X = B(OH)_2$ leads to mixed aryl–naphthyl systems **30** while a further DoM reaction–electrophile quench sequence on **28**, $E = CONEt_2$ affords 1,2,3,4-tetrasubstituted naphthalene albeit in low yield for the two derivatives **32** investigated to date [25]. Further profitable exploitation of such prototypical manipulations representing conceptual frameworks **31a**,**b** is anticipated.



Scheme 5. The Suzuki cross coupling reaction. Effect of base.



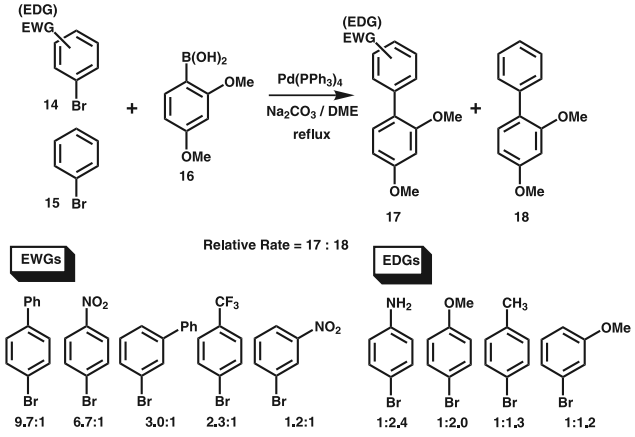
Conditions	11, X (1 equiv)	12, Y (1.5 equiv)	11		Dimer of 11 (X = H)	13
$PdCl_2(dppf) / K_3PO_4$ DMF / H_2O / rt	$B(OH)_2$	I	39 (X = H)	28 (X =OH)	13	0
$Pd(PPh_3)_4 / K_3PO_4$ PhMe / EtOH / H_2O / reflux	$B(OH)_2$	I	38 (X = H)	0	12	20 (R = $CONEt_2$) 15 (R = H)
$Pd(PPh_3)_4 / Ba(OH)_2$ DME / H_2O / reflux	Br		71 (X = Br)	0	0	24 (R = $CONEt_2$)
$Pd(PPh_3)_4 / K_3PO_4$ DMF / reflux	Br		12 (X = Br)	0	0	74 (R = $CONEt_2$)

Scheme 6. The Suzuki–Miyaura cross coupling reaction. Steric effects.

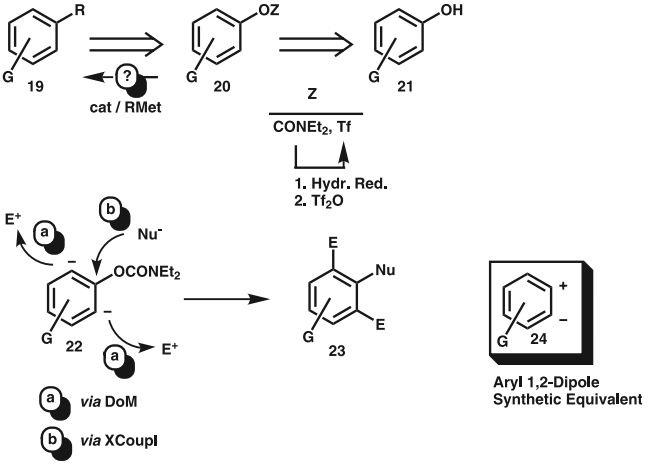
The early work of Wenkert [26] on aryl sulfur derivative–Grignard coupling reactions served as enticement for attempts to effect this reaction on aryl *S*-thiocarbamates **37** (Scheme 10), derived from the DoM (**33**–**34**)—Newman–Kwart rearrangement (**→35→36**) sequence [27], a path which leads, by hydrolysis [28], to *ortho*-substituted thiophenols **37**, thereby establishing a new **38→39** interconversion, of value in view of oxidative complications in attempts to obtain **37** by direct electrophilic substitution means. In the event, *S*-thiocarbamate–Grignard cross coupling **40→41** (Scheme 11) may be achieved although, compared with the corresponding *O*-carbamate coupling reactions (Scheme 9), the reactions require more vigorous conditions and excess Grignard reagent [25]. To answer a palpable question, cross coupling of **33** (Scheme 10) has not been successful to date.

2.3. The DoM–Negishi cross coupling connection

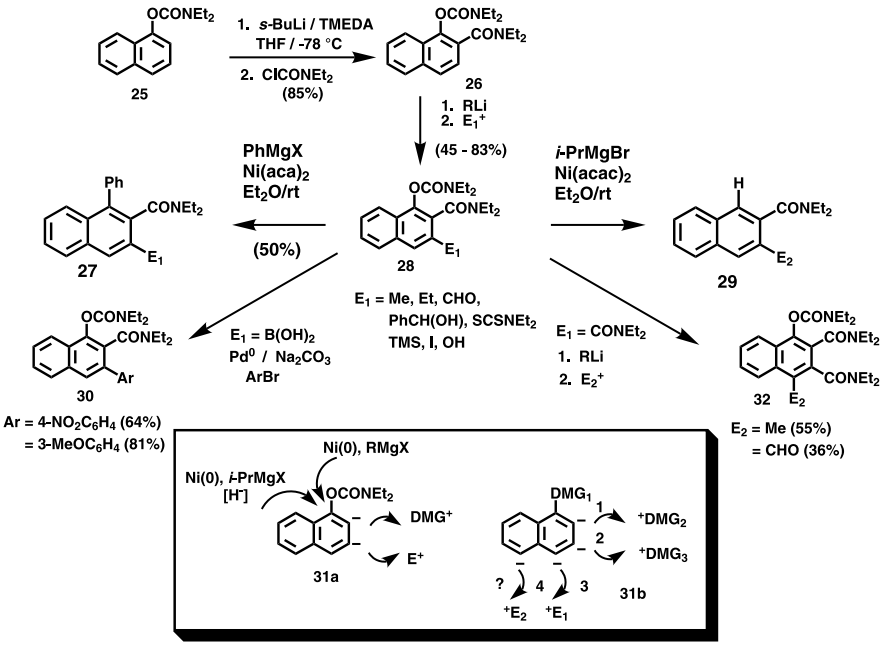
Following the groundwork rigorously provided by Negishi [8], but using aryl triflates, a systematic study led to appreciation of the scope and limitations of the combined DoM-cross coupling reaction, **42 + 43→44** (Scheme 12) [29]. From the comprehensive results [30], selected cases (Scheme 12) show aromatic triflates (with/without DMGs), heterocyclic triflates, and vinyl



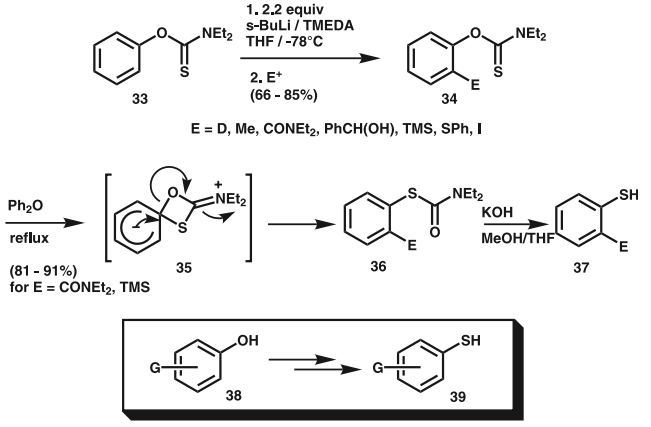
Scheme 7. EWG/EDG effects on the aryl bromide in the Suzuki cross coupling.



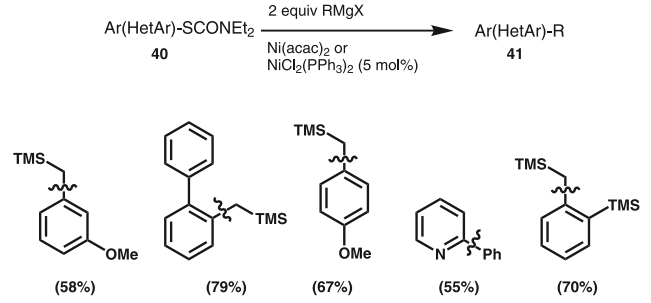
Scheme 8. Directed ortho-metalation–cross coupling connection. Regiospecific aromat 1,2-disubstitution via a conceptual 1,2-dipole synthetic equivalent.



Scheme 9. Combined DoM–cross coupling strategies for polysubstituted aromatics. Naphthalenes as a case study.



Scheme 10. DoM of *O*-aryl thiocarbamate. Link to the Newman–Kwart rearrangement.

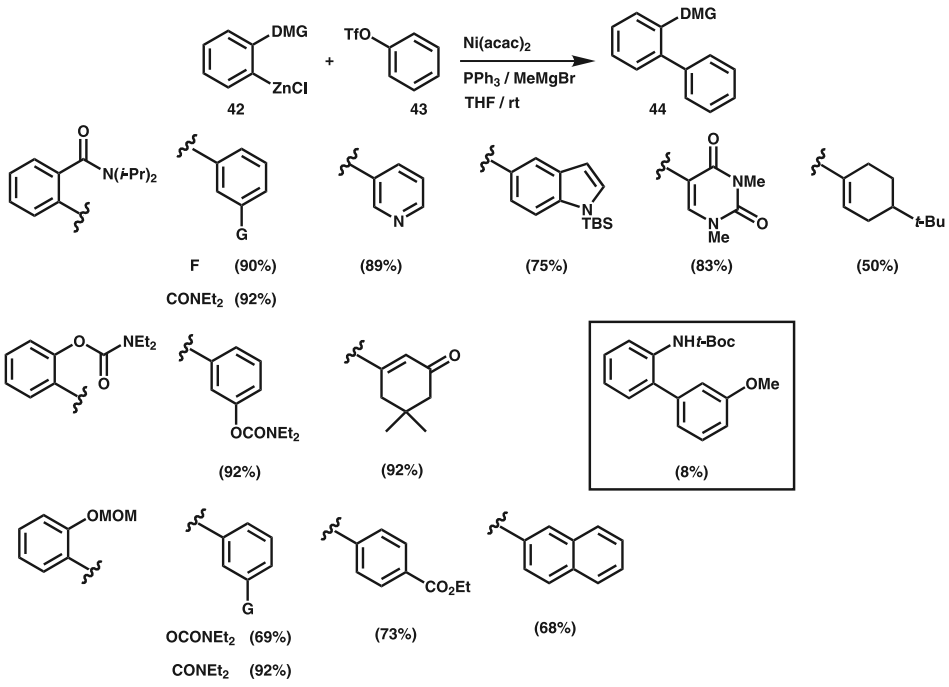


Scheme 11. The Ni(0)-catalyzed aryl *S*-thiocarbamate–Grignard cross coupling reacton. Selected examples.

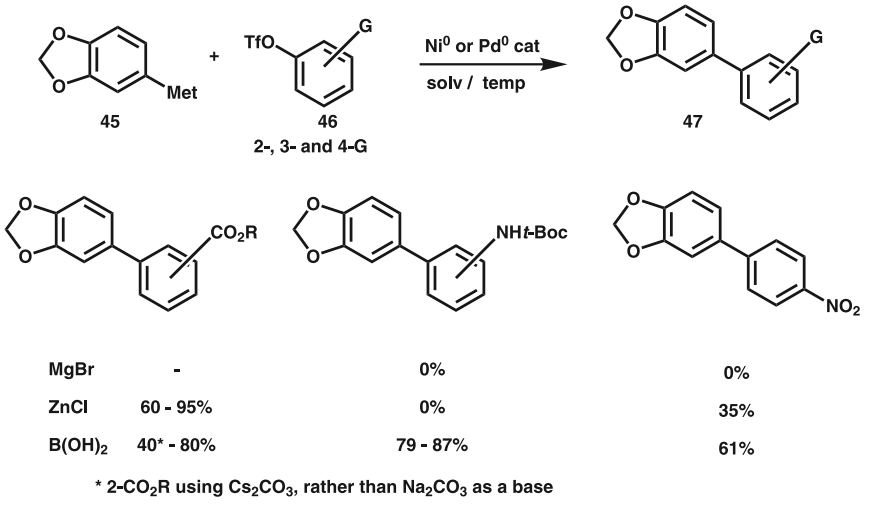
triflates participate in the process. Notably, *ortho*-NBoc arylzincs are poor metalated partners (perhaps due to stability of chelate) but a benzoate is a successful triflate partner, serving as an aide-mémoire to functional group compatibility of Negishi cross coupling reactions (Scheme 3). A similarly extensive study [30], comparing Corriu–Kumada, Negishi, and Suzuki–Miyaura methods [31] using ArOTf partners led, as depicted by **45** + **46** → **47** (Scheme 13), to the generalization, with appropriate caveats to future revision owing to the development of new conditions, that the last process is perhaps most consistent in providing reasonably efficient preparative procedures for biaryls.

2.4. DoM-cross coupling Nexus. Relevance to bioactive molecule and natural product construction

The C–C biaryl or heterobiaryl bond is readily detected in a variety of biologically active substances and numerous classes of natural products. A cursory glance through the medicinal chemistry literature amply demonstrates the increasing concentration of biaryl and heterobiaryl structures as new drug leads, advanced candidates, and commercial medicinal agents (Scheme 14). Hence, from the outset, the cross coupling methodology received baptism by fire and, as experience was gained and scope was demonstrated, quickly found wide-ranging application in drug discovery and combinatorial programs [32] as well as in pilot plants for the synthesis of key intermediates and products [33]. The robustness and operational ease of the Suzuki variation



Scheme 12. DoM –cross coupling connections. ArZnX + ArOTf partners.



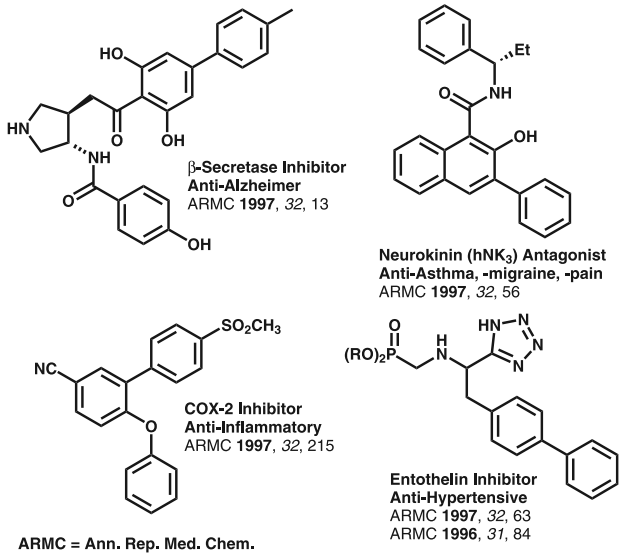
Scheme 13. Comparisons of ArMgX, ArZnX, $ArB(OH)_2$ + ArOTf cross coupling efficacies.

has been especially widely demonstrated. Logically, the combined DoM-cross coupling protocol has also been rapidly adapted to large-scale production [34].

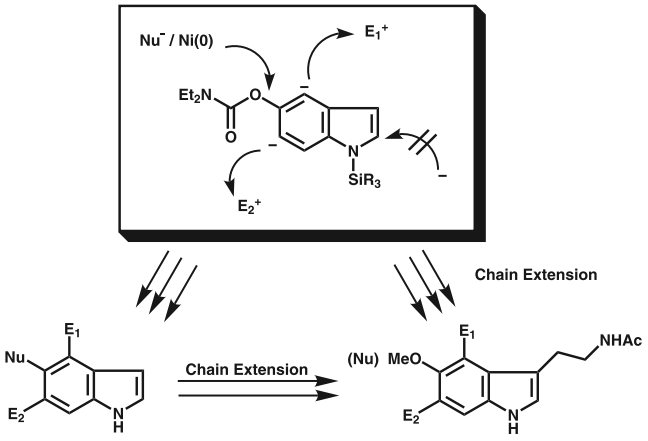
In efforts to provide practical value to the DoM-cross coupling link, as well as other modern methods, current focus in our laboratories is aimed to develop new synthetic strategies for simple and condensed heterocyclic systems which are part of well-recognized or emerging bioactive structures or constitute key fragments of natural products. The following ongoing projects are representative.

2.5. New tactics for benzenoid ring modification of indoles

Although modification of the C(2) and C(3) sites of indoles by DoM chemistry is a densely developed area, mapping the metalation reactivity in the benzenoid positions (C(4)–C(7)) of this nucleus had been, to the best of our knowledge, unexplored. To stimulate interest within the conceptual framework of Scheme 15 [35] which has the potential to provide unusual substitution patterns in both indoles and tryptamines, we estab-

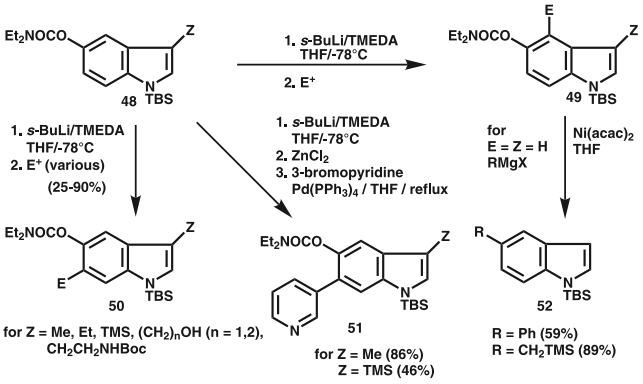


Scheme 14. Biaryl motifs in pharmaceuticals.



Scheme 15. Indole 1-silyl-5-O-diethyl carbamate. A key synthetic intermediate for substituted melatonins.

lished the 5-*O*-carbamate as a viable DMG for C(4) substituent introduction, **48** → **49** Z = H, Scheme 16). In contrast, the 3-subtituted 5-*O*-carbamate derivative **48,** Z = various, upon metalation-electrophile quench afforded C(6) substituted products **50**. Application of the zinc transmetalation tactic on the lithiated **48**, Z = Me, TMS followed by cross coupling with 3-bromopyridine led to the diheteroaryl **51** in useful yields [36]. The new *O*-carbamate–Grignard cross coupling sequence was demonstrated, **49** → **52** for selected cases [35]. In extensions which aspire towards ergot alkaloid synthesis, DoM-cross coupling successions by Suzuki and Negishi coupling modes, **53** → **54**, **55** (Scheme 17) have been successful, less so in efficacy and with TBDMS loss in the former case [36]. In very recent work [37], the availability of 3,4-dihalo indoles from gramine by a DoM-retro-Mannich route (Scheme 18), allowed the conversion **56** → **57** and hence the Stille and Suzuki



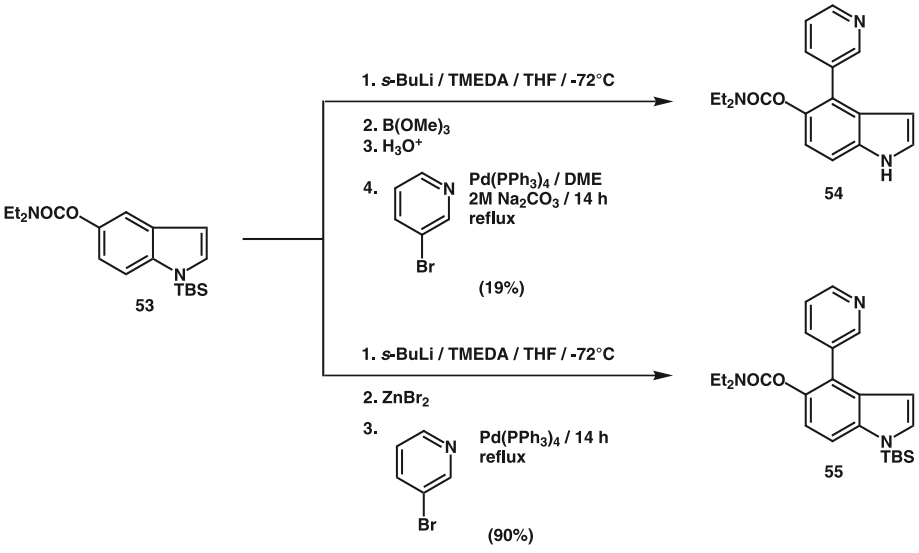
Scheme 16. DoM–cross coupling sequences on *N*-TBS indole 5-*O*-carbamate.

cross coupling reactions to **58** and **59**, molecules poised for further interesting chemistry.

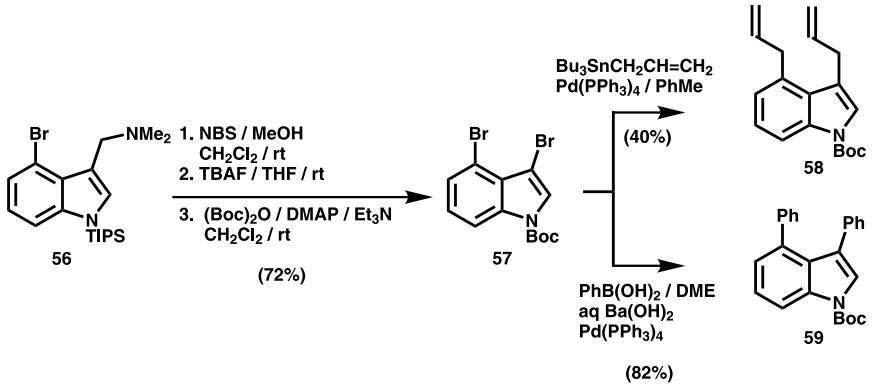
2.6. Dibenzopyran-6-ones and Coumestan analogues. DoM-cross coupling meets the remote anionic Fries rearrangement

Circumvention of sterically hindered Suzuki cross coupling reactions, which fail or proceed in low yields may be overcome, in certain cases, by application of the remote anionic Fries rearrangement (Scheme 19). Thus the biaryl carbamate **62**, PG = OMe, TMS, obtained by arylboronic acid **60** coupling with halide or triflate **61**, undergoes LDA-mediated carbamoyl migration to give, after an acid catalyzed step, the dibenzopyranone **63** [38]. The improvement in efficiency of this strategy over the direct but sterically compromised cross coupling is demonstrated by the overall yields achieved (**64a** vs. **64b**). Using this anionic rearrangement, the synthesis of a naturally occurring dibenzopyranone **65** has also been achieved; on the other hand, attempts to effect double carbamoyl transfer from a DoM–Suzuki cross coupling derived system, **66**, produced only the mono-migrated product.

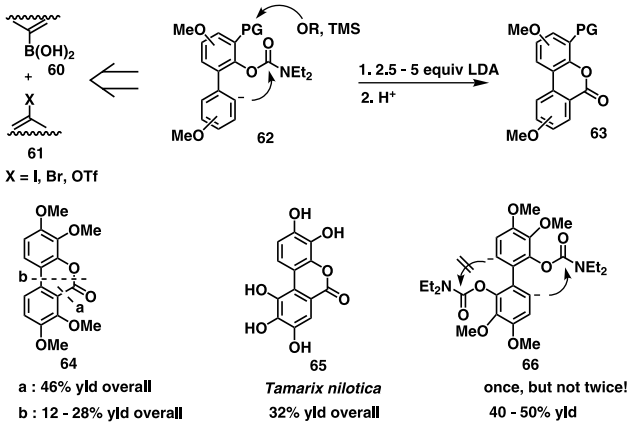
Taking an excursion into a different heterocyclic series, the combined DoM-cross coupling—remote carbamoyl migration was found to be effective in producing the isomeric azacoumestan and isoazacoumestan derivatives, **69** and **73**, respectively, (Scheme 20) [39]. Thus the indole boronic acid **67**, obtained by DoM chemistry, was coupled with the *ortho*-halo *O*-carbamate **70**, X = I, to give **68**, which, without purification was subjected to acetic acid treatment to furnish **69**. Similarly, but in an inverted partner sequence, the *ortho*-boronic acid *O*-carbamate **70**, X = $B(OH)_2$, upon coupling with the 3-bromoindole derivative **71**, obtained by electrophilic bromination, gave **72** and hence **73.** These short reaction sequences, relative to classical methods [40], have stimulated extension to also prepare a series of related *O*- and *S*-heterocycles [39a], includ-



Scheme 17. 4-Pyridyl indole 5-*O*-carbamate via DoM–cross coupling sequence.



Scheme 18. 3.4-Dihaloindoles by DoM–retro–Mannich sequences. Stille and Suzuki cross couplings.

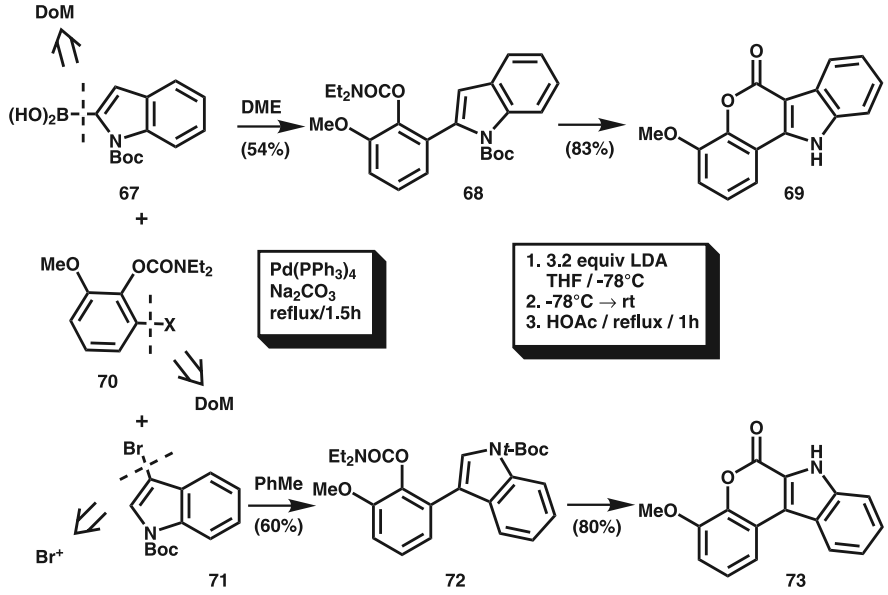


Scheme 19. Biaryl *O*-carbamate anionic remote Fries equivalent. Regiospecific route to dibenzo-[*b*,*d*]pyran-6-ones.

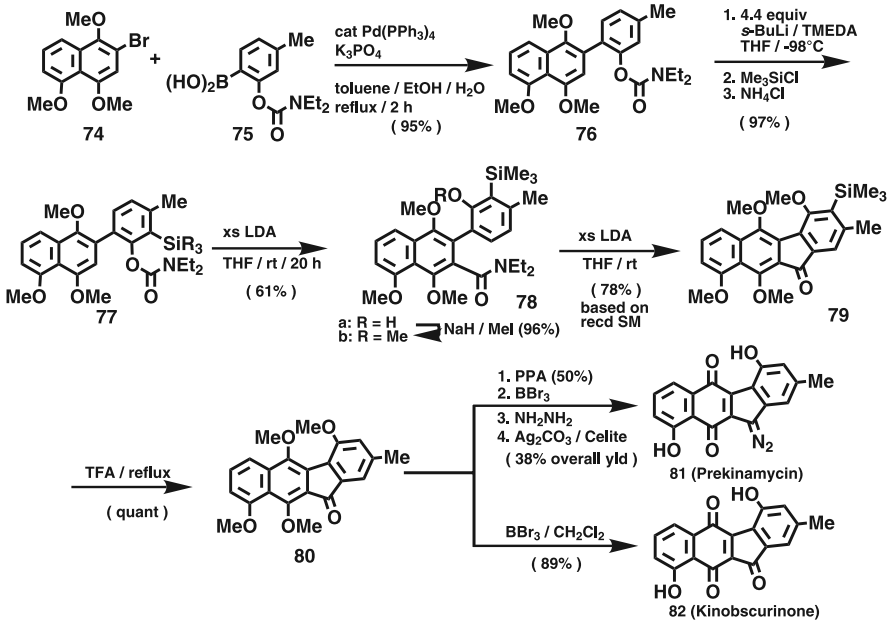
ing models of the naturally occurring coumestans themselves which are rich in diverse (phytoalexin, antifungal, estrogenic, antiestrogenic) biological activity [40].

2.7. Synthesis of Kinamycin antibiotics. The merit of cross coupling

Research in the kinamycin antibiotic substance isolated from *Streptomyces muruayamaensis* has been rewarded by intriguing structures, structural reassignment, and unusual biosynthetic pathways [41]. One series, represented by prekinamycin **81** and kinobscurinone **82**, provided a worthy challenge of the DoM-cross coupling strategy but reinforced by double remote metalation steps involving amide and *O*-carbamate functional groups (Scheme 21) [42]. Thus, cross coupling of the bromonaphthalene **74** with the *ortho*-boronic acid *O*-carbamate **75** under conditions which required considerable experimentation (see also Scheme 6), afforded **76** in excellent yield. Metalation–silylation at low temperature to avoid anionic *ortho*-Fries rearrangement gave **77** which, when subjected to excess LDA followed by protection of the incipient phenol furnished the remote amide migration product **78b** with intriguing complications of α-methylsilyl deprotonation



Scheme 20. DoM-directed remote metalation–cross coupling links. Synthesis of aza- and isoazacoumestans.



Scheme 21. DoM-directed remote metalation–cross coupling links. Formal total synthesis of prekinamycin and kinobscurinone.

[42]. The crucial second remote metalation–cyclization was accomplished also under LDA conditions to provide **79** which upon TFA-mediated desilylation gave **80**, a substance that had been previously converted into prekinamycin and kinobscurinone [43]. In this, as in related natural product synthetic work in our laboratories [39a,44], setting the stage for anionic chemistry via Suzuki cross coupling reaction is of obvious significance for the achievement of an efficient overall synthesis.

3. Concluding remarks

Aryl–aryl, heteroaryl–aryl, and heteroaryl–heteroaryl $C(sp^2)$–$C(sp^2)$ bond retrons are increasingly apparent in molecules under construction in current drug discovery and development activities [45]. Old and new natural products with this evident disconnection from plant and marine origin abound in the literature. The Corriu–Kumada, Negishi, Suzuki–Miyaura, and Stille reactions have made an immense impact on the

availability of efficient and regioselective routes to strategically functionalized aromatics and heteroaromatics which are final products or intermediates towards more complex target molecules. They have unequivocally superceded classical methods [17] and non-aromatic ring approaches, which are plagued with poor efficiency, regioselectivity, and environmental custody.

These transition metal catalyzed cross coupling reactions have played a dominant role in the work highlighted above. We have followed the path from DoM, which ensures regioselective aromatic substitution, to $ArB(OH)_2$, ArMgX, ArZnX and, less often, $ArSnR_3$ cross coupling tactics which afford substituted biaryls and heterobiaryls not readily constructed by alternative routes and furnish key building blocks which, by further DoM and directed remote metalation reactions, allow effective ascent to targeted aromatic and heteroaromatic natural products.

Avenues are open for exploration of additional links between anionic aromatic chemistry and other evolving synthetic reactions [46]. With the assurance of relentless discoveries of synthetic methods [21,47], the stellar mechanistic and synthetic guidance provided by Corriu, Kumada, Kochi, and Yamamoto will be always acknowledged and appreciated by the current and future generations of chemists.

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