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Palladium-Catalysed Cross-Coupling and Related Reactions Involving Pyrroles

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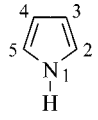
The Pd^0-catalysed cross-coupling of intact pyrroles with various reaction partners is reviewed. Coverage includes the Buchwald–Hartwig, carbonylation, Heck, Kumada, Negishi, Sonogashira, Stille, Suzuki–Miyaura, Tsuji–Trost, and (Pd^0-catalysed) Ullmann reactions. Some emphasis is given to the application of such processes in the synthesis of pyrrole-containing natural products.

1. Introduction

The electron-rich, five-membered, and aromatic heterocycle pyrrole (**1**) has been known since Runge's identification of it in coal tar in 1834,[1] but it was not until 1870 that the structure was correctly formulated by Baeyer.[2] Research on this material blossomed in 1885 when Paal and Knorr both published highly effective synthetic routes to pyrrole and its derivatives.[3,4] Indeed, their approaches are so utilitarian that they remain amongst the most effective methods available for preparing the title compounds.[5] Extensive studies on the synthesis and chemical behaviours of pyrroles continued throughout the 20th century and a particular effort was directed towards studying reactions of such systems with electrophiles.[6] Of course, a major driver behind such work was the recognition that the so-called "pigments of life", the tetrapyrroles,[7] incorporate the title ring system (**1**) as the key component. In the last few decades the emphasis in the area has shifted somewhat and in response to several factors, a major one being the emerging recognition that a very large family of structurally intriguing and biologically active mono-pyrrolic natural products exists. Many of these are produced by marine organisms.[8] A second feature of pyrroles receiving increasing attention stems from the realisation that they represent readily accessible and highly flexible building blocks for the construction of a wide-range of other compounds including natural products.[9,10] Of course, the value of pyrroles in pharmaceutical,[11] molecular recognition[12] and materials science[13] applications must also be acknowledged.



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Accompanying the activities just mentioned has been a continuing focus on the identification of new methods for the assembly of pyrrole derivatives and a number of useful reviews of this topic can be identified.[6,8c,14] Notable trends in recent years have included the exploitation of acetylenic precursors,[14] multi-component coupling reactions,[15] the development of the Barton–Zard reaction and related processes,[16] the application of carbene- and carbenoid-based processes,[14] the use of low-valent-Sm, -Sn and -Ti systems for the reductive cyclisation of a range substrates,[17] as well as the Pd^0-catalysed oxidation and cyclisation of β-hydroxyenamines.[18] Microwave-accelerated variants on some well-established methods for pyrrole synthesis represent another interesting trend.[19]

Our own interest in pyrroles has been focused on manipulating the intact system, especially through the agency of Pd^0-catalysed cross-coupling processes, so as to develop convergent routes to various biologically-active natural products incorporating the title motif. Not surprisingly,

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

such processes have proven entirely effective and, reflecting broader trends in heterocyclic chemistry, they are now used routinely for such purposes. As such, and given the seeming absence of a thorough survey of the applications of these reactions in the area, the present review seems appropriate. The following section is devoted to a brief commentary on pyrrole-containing natural products and is followed by rather more detailed descriptions of the applications (or lack thereof in some cases) of the Buchwald–Hartwig, Heck (or Mizoroki–Heck), Hiyama, Kumada, Negishsi, Songo-

Martin (Gerhardt) Banwell was born in New Zealand and educated there, receiving his PhD from The Victoria University of Wellington in 1979 and after studying with Professor Brian Halton. Following a post-doctoral year working with Professor Leo Paquette (The Ohio State University), he took up a Senior Teaching Fellowship in the (then) Department of Organic Chemistry at The University of Adelaide in South Australia. He moved to a Lectureship in Chemistry at The University of Auckland, New Zealand in 1982 and then to an equivalent position at The University of Melbourne in 1986. In 1995 he moved to the Research School of Chemistry at The Australian National University in Canberra where he is now Professor of Chemistry and Head of the Organic Chemistry Section. In 2001 he received an Alexander von Humboldt Foundation Research Award that allowed him to develop a highly enjoyable collaboration with Professor Wolfgang Steglich (Ludwigs Maximillian University of München) focused on the synthesis of 3,4-diarylpyrrole alkaloids derived from marine organisms. Professor Banwell has been the recipient of the Rennie and Birch Medals, in 1986 and 2004 respectively, of the Royal Australian Chemical Institute. In 2003 he received the Royal Society of Chemistry Award for Synthetic Organic Chemistry and was a Novartis Chemistry Lecturer in 2004/2005 as well as a Merck (UK) Lecturer in 2005. His research interests are in the areas of natural products synthesis, the development of new synthetic methodologies and catalysis (especially biocatalysis).

Thomas (Elton) Goodwin was born in Arkansas (USA) and educated there, receiving his BS from Ouachita Baptist University after research with Professor Joe Nix, and his PhD from The University of Arkansas (Fayetteville) in 1974 after studying with Professor Walter Meyer. He spent a postdoctoral year with Professor Ernest Wenkert (Rice University), after which he worked at Conoco Chemicals with Dr. Charles Starks, then spent two years at The Texas A & M University as a lecturer, and a researcher with Professor C. S. Giam. In 1978 he moved to Hendrix College as an Assistant Professor of Chemistry, where he has remained and is now the Elbert L. Fausett Professor of Chemistry. Professor Goodwin has served as Chair of the Gordon Research Conference on Heterocyclic Compounds and President of the Council on Undergraduate Research (CUR), and was the recipient of a Camille and Henry Dreyfus Foundation Scholar/Fellow Grant for Undergraduate Institutions. In 1998, he was awarded the David W. Mellor Medal for Chemical Education by the University of New South Wales, and in 2003 was selected as the U.S. Professor of the Year (for baccalaureate colleges), awarded by the Carnegie Foundation for the Advancement of Teaching, and the Council for Advancement and Support of Education (CASE). He has enjoyed and benefited greatly from his time in recent years as a Visiting Fellow in the Research School of Chemistry (Australian National University) with Professor Martin Banwell. Professor Goodwin's research interests are in the areas of pyrrole synthesis, chemical communication among African elephants, and development of green organic chemistry experiments for the introductory laboratory.

Sarah Ng was born in Hong Kong and educated in Hobart, Australia. She completed her BSc and BSc (Hons.) degrees at the University of Tasmania where she remains and is currently undertaking research for her PhD whilst working under the supervision of Dr Jason A. Smith.

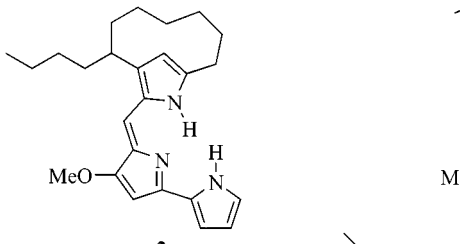
Jason (Alfred) Smith is a graduate of the Flinders University of South Australia where he obtained both his BSc (Hons.) and PhD degrees, the latter under the supervision of Professor Rolf Prager. He has carried out post-doctoral research at The Texas A&M University (with Professor Sir Derek H. R. Barton) and at The Australian National University (with Professor Martin G. Banwell). In 1999 he received an AMRAD postdoctoral award. In 2001 he joined the faculty in the School of Chemistry at The University of Tasmania where his research activities focus on, inter alia, the development of new synthetic methodologies and their application to the synthesis of biologically active and/or structurally complex molecules including the exploitation of pyrrole as a molecular template for the assembly of alkaloids. In 2004 he received The Royal Australian Chemical Institute's Division of Organic Chemistry Lectureship for Recently Appointed Staff.

David (John) Wong was born in Melbourne, Australia and educated at The University of Sydney. He obtained his BSc (Hons.) in 1997 after working with Professor Margaret A. Brimble and then pursued a PhD under the guidance of Professor Martin G. Banwell in the Research School of Chemistry at The Australian National University and during which time he established total syntheses of several biologically significant, pyrrole-containing marine natural products. In 2002 he worked, as a post-doctoral, with Professor Ian Paterson (The University of Cambridge, United Kingdom) on the development of syntheses of the phorboxazoles, laulimalide and neolaulimalide. In 2003 he returned to The University of Sydney and works in Dr Malcolm D. McLeod's group on the synthesis of pyrrolobenzodiazepine-type natural products.

gashira, Stille (or Kosugi–Migita–Stille), Stille–Kelly, Suzuki–Miyaura, Tsuji–Trost, Ullmann, and other Pd^0-catalysed cross-coupling reactions to the manipulation of pyrroles for the purposes of assembling natural products and related structures incorporating this ring system. Some emphasis is also given to the techniques that are available for the preparation of the pyrrole-containing coupling partners that participate in the title processes.[20]

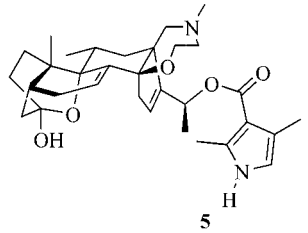
2. Pyrrole-Containing Natural Products

Natural products remain an especially important source of and/or inspiration for the development of new therapeutic agents. Indeed, despite the recent emergence of combinatorial chemistry and related techniques for facilitating drug discovery and development, natural products continue to play a prominent and, simultaneously, evolving role in the area.[21] Pyrrole-containing natural products are an integral part of this process. Beyond the well-known tetrapyrrolic "pigments of life",[7] other intriguing natural products incorporating "multiple copies" of the title ring system are also coming under scrutiny. For example, "tripyrroles" such as streptoruin B (**2**) and prodigiosin (**3**) (representing key members of the prodigiosin group of alkaloids), as well as structurally related species such as roseophilin (**4**), are attracting increasing attention because of their potential as, inter alia, immunosuppressive agents.[22]

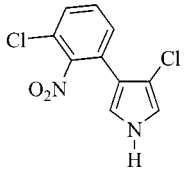


2 (streptoruin B) **3** (prodigiosin) **4** (roseophilin)

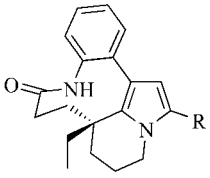
Monopyrrolic natural products are being discovered in increasing numbers and from a diverse range of sources including insects, sponges, plants, fungi and bacteria.[8a] While much rarer in vertebrates, some monopyrroles have been isolated from birds and frogs, including batrachotoxin (**5**), one of the most toxic substances known to man.[8a] Much simpler systems have also been identified, including pyrrolnitrin (**6**), a tryptophan-derived antifungal antibiotic isolated from a *Pseudomonas pyrrocinia*.[23] Plant-derived monopyrroles of some note are rhazinilam (**7**)[24] and its formyl-derivative rhazinal (**8**)[25] both of which are recognised to act as rather potent spindle-toxins and by virtue of exerting a Taxol™-like mode of action.[26] The preparation of simple analogues of these compounds that retain such properties is now an active area of research.[26] Bromopyrroles derived from sponges represent a rapidly growing class of natural product with some members of this group showing intriguing biological properties.[8a,27] For example, hymenialdisine (**9**) and its debrominated analogue **10** both exhibit antiinflammatory properties and the latter has been shown to retard joint deterioration and cartilage degradation associated with osteoarthritis in animal models.[27d] Other bromopyrrole-containing marine natural products show antifouling and antibacterial properties.[27]



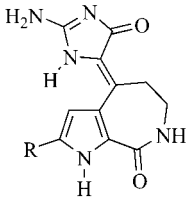
5 (batrachotoxin)



6 (pyrrolnitrin)



7 R = H (rhazinilam)
8 R = CHO (rhazinal)

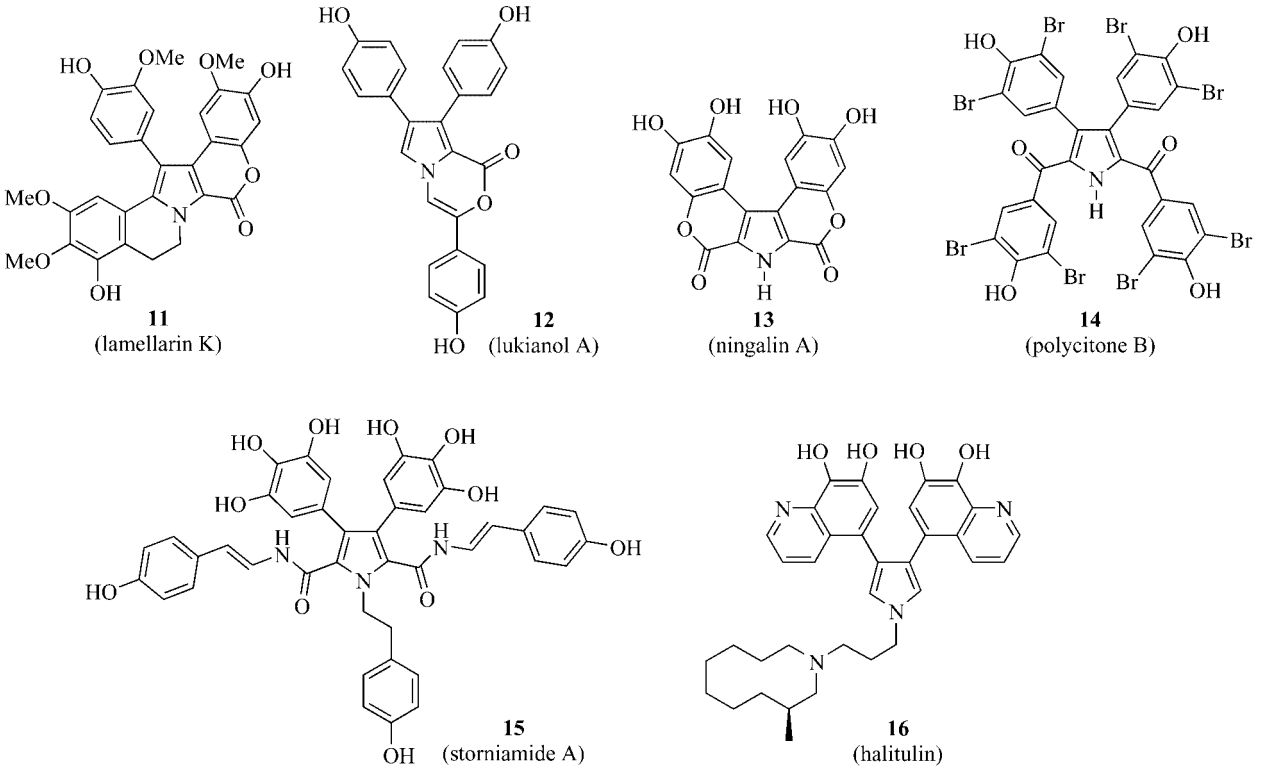


9 R = Br (hymenialdisine)
10 R = H (debromohymenialdisine)

A range of 3,4-diarylated pyrroles including the lamellarins (e.g. **11**), lukianols (e.g. **12**), ningalins (e.g. **13**), polycitones (e.g. **14**), storniamides (e.g. **15**) and halitulin (**16**) have been isolated from various marine organisms, and some of these show considerable potential for the treatment of various cancers and HIV-AIDS.[28] A comprehensive review of such natural products, with a particular focus on their synthesis, will be published elsewhere in the near future. However, it is worth noting, at this stage, that it was a consideration of possible ways to assemble the arylated pyrrole motif within such compounds that prompted one of us (MGB) to become involved in the area that is the subject of the remainder of the present article.

3. Palladium-Catalysed Cross-Coupling Reactions of Pyrroles – Opening Comments

The remarkable utility of palladium-catalysed cross-coupling processes has revolutionised the way in which synthetic chemists go about assembling organic compounds. The series of named reactions embracing these processes are now rather familiar to practitioners in the field.[29] Such reactions, as they pertain to cross-coupling processes involving pyrroles, are presented alphabetically in the following sections of this mini-review. Furthermore, each such section is divided, where appropriate, into two parts, the

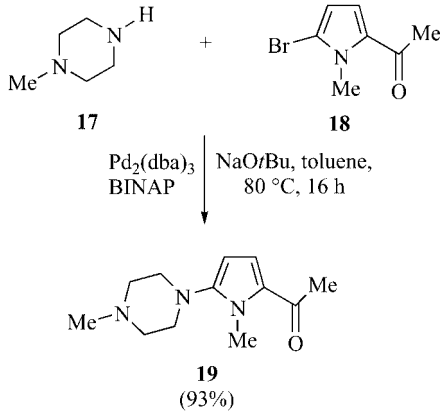


first detailing cross-coupling reactions wherein the initial palladated species is part of the pyrrole core (which we have chosen to call Type I processes) and the second describing analogous processes, but now ones where the initial palladium-containing intermediate is associated with the non-pyrrolic fragment (so-called Type II processes). In addition, we have chosen to focus on reactions involving intact pyrroles. Consequently, palladium-catalysed cross-coupling processes that involve simultaneous or subsequent assembly of this ring system are not covered. This means, for example, that even cross-coupling reactions of dihydropyrroles,[30] which are readily converted into pyrroles using a range of oxidants, are not dealt with here. Similarly, cross-coupling processes involving a reaction partner incorporating a pyrrole unit but that do not occur at this nucleus have been omitted. To assist the reader who might aspire to carry out this sort of chemistry, we have attempted to provide, at appropriate points in the following sections, some sense of the manner in which the various pyrrole-containing cross-coupling partners are obtained. We have also endeavored to provide a comprehensive coverage of the relevant literature up to April 2005.

4. Buchwald–Hartwig Cross-Coupling Reactions

4.1. Type I Processes

Type I Pd^0-catalysed C–N bond-forming reactions between *C*-halogenated pyrroles and amines, and so leading to *C*-aminated pyrroles, have only been reported recently.[31,32] The conversion **17** + **18** → **19** shown in Scheme 1 is indicative and highlights the great potential of this sort of process.



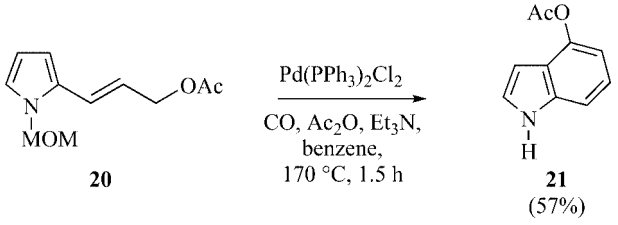
Scheme 1.

4.2. Type II Processes

At the present time, Type II Buchwald–Hartwig reactions are rather more common than their Type I counterparts. Thus, for example, Type II variants have been employed in the preparation of a rather wide range of *N*-arylated pyrroles.[33] Interestingly, analogous transformations can also be effected by treating *N*-unsubstituted pyrroles with aryl iodides in the presence of a combination of CuI and (±)-*trans*-1,2-diaminocyclohexane[34] or with arylboronic acids and stoichiometric amounts of $Cu(OAc)_2$.[35]

5. Carbonylation Reactions

The Pd^0-catalysed methoxycarbonylation of pyrroles incorporating a range of substituents including C3-trifloxy[36] and thallium-based[37] groups can be achieved as can dimethylaminomethyl-directed palladation at C3 to give a species that reacts with CO/methanol combinations, and thus also allows for incorporation of a methoxycarbonyl group at this position.[38] In perhaps the most interesting reaction within the class, a Japanese group has shown that cyclocarbonylation of the pyrrole **20** (Scheme 2) incorporating an allylic acetate side-chain attached at C2 can be achieved and thus affording the C4-oxygenated indole **21** in 57% yield.[39]

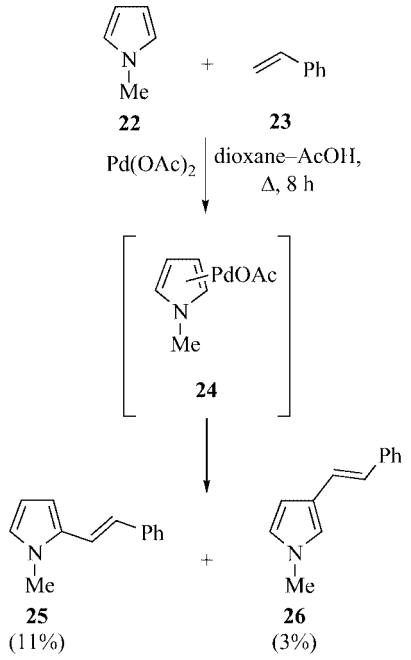


Scheme 2.

We have not uncovered any examples wherein C2-halogenated or related C2-functionalised pyrroles have been subjected to carbonylation processes. This is almost certainly a reflection of the capacity to use more conventional (and direct) S_EAr processes, such as Friedel–Crafts acylation reactions, for the introduction of carbonyl-containing groups at this position. Nevertheless, there is no evidence to suggest that such carbonylation reactions would not proceed in an effective manner.

6. Heck-Type Chemistry

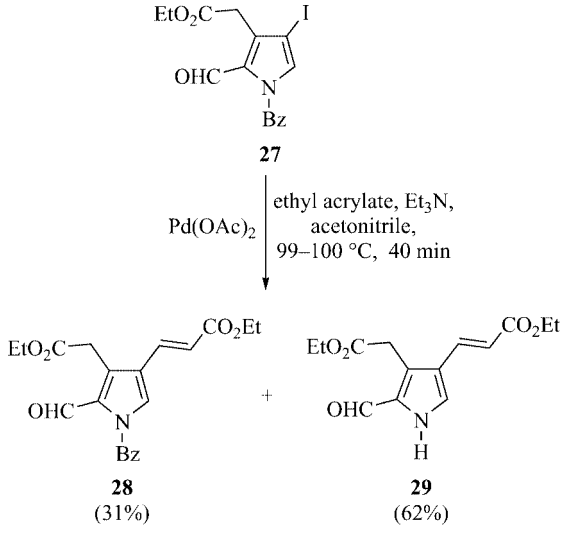
In 1973 Asano and co-workers reported that *N*-methylpyrrole (**22**) reacts with styrene (**23**) in the presence of palladium(II) acetate to give, presumably through coupling of the palladated intermediate **24** with the latter substrate, a mixture of the C2- and C3-substituted *trans*-styrylpyrroles **25** and **26** (Scheme 3).[40] Subsequent work carried out by Itahara revealed that acetic acid solutions of *N*-benzoylpyrroles react with benzene in the presence of $Pd(OAc)_2$ to give *N*-benzoyl-2-phenylpyrrole.[41] Intramolecular variants of these reactions, wherein the *N*-benzoyl substituent participates as nucleophile, are also known.[41] A very elegant application of such a process has recently been reported by Stoltz and co-workers during the course of the development of a total synthesis of (+)-dragmacidin F.[42] Of course, stoichiometric quantities of palladium are involved so such conversions are not really Heck-type processes but, rather, oxidative coupling reactions. Nevertheless, they have been included here because they are closely related to true examples of the title processes and because the prospects of developing catalytic variants of them now seem rather high.[43]



Scheme 3.

6.1. Type I Processes

The application of conventional Heck chemistry to halogenated pyrroles is known. For example, in connection with efforts to prepare porphobilinogen from pyrrole, Anderson and co-workers established that the C4-halogenated compound **27** reacts with ethyl acrylate in the presence of $Pd(OAc)_2$ and triethylamine to give the β-substituted acrylate **28** and its debenzoylated counterpart **29** (Scheme 4).[44] Related conversions involving less heavily substituted and non-halogenated pyrroles were reported by Itahara at about the same time.[45] More recently, Wong and his group demonstrated[46] that highly regioselective syntheses of 3,4-disubstituted pyrroles can be achieved through manipulation of 3,4-bis(trimethylsilyl)pyrrole. This includes processes in-

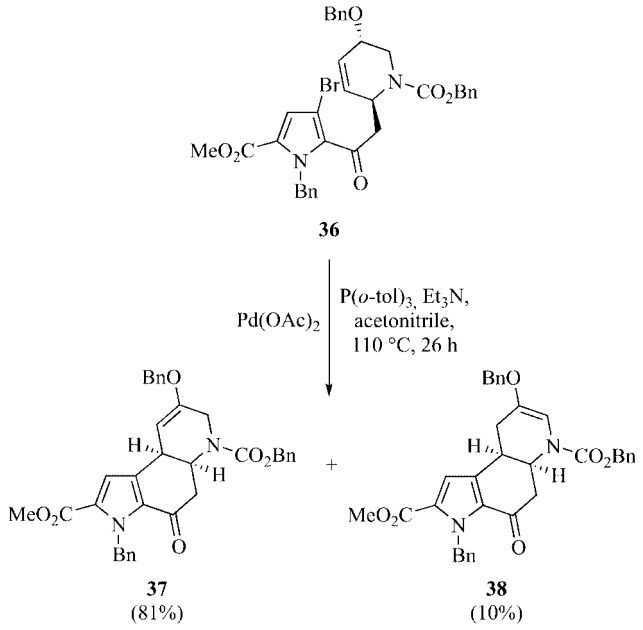


Scheme 4.

volving selective *ipso*-substitution of one of the trimethylsilyl groups with iodine then participation of the derived C3-iodinated pyrrole in Heck reactions with methyl acrylate, methyl vinyl ketone or acrylonitrile. In a similar vein, Smith's group reported that C3-unsubstituted pyrroles are readily converted into the corresponding C3-mercurated derivatives upon reaction with $Hg(OAc)_2$. Treatment of such derivatives with $LiPdCl_3$ and methyl acrylate then affords – presumably via *trans*-metallation then a Heck reaction – the expected β-substituted acrylate.[47] Monti and Sleiter have described related processes involving C3-thallated pyrroles.[48]

As part of a program directed towards the assembly of well-defined linear π-conjugated oligomers of relevance to the development of organic conductors, Tietze and his co-workers have shown[49] that compounds such as the C2-,C5-diiodinated pyrrole **30** (Scheme 5) engage in twofold Heck reactions with, for example, *p*-vinylbenzaldehyde (**31**) to give the bis-aldehyde **32**. Tandem Wittig olefination of this product then delivers the bis-styrene **33** that engages in a second twofold Heck reaction with the C5-iodinated pyrrole **34** and so affording, albeit in only 28% yield, an extended π-conjugated system, **35**, now incorporating three pyrrolic subunits.

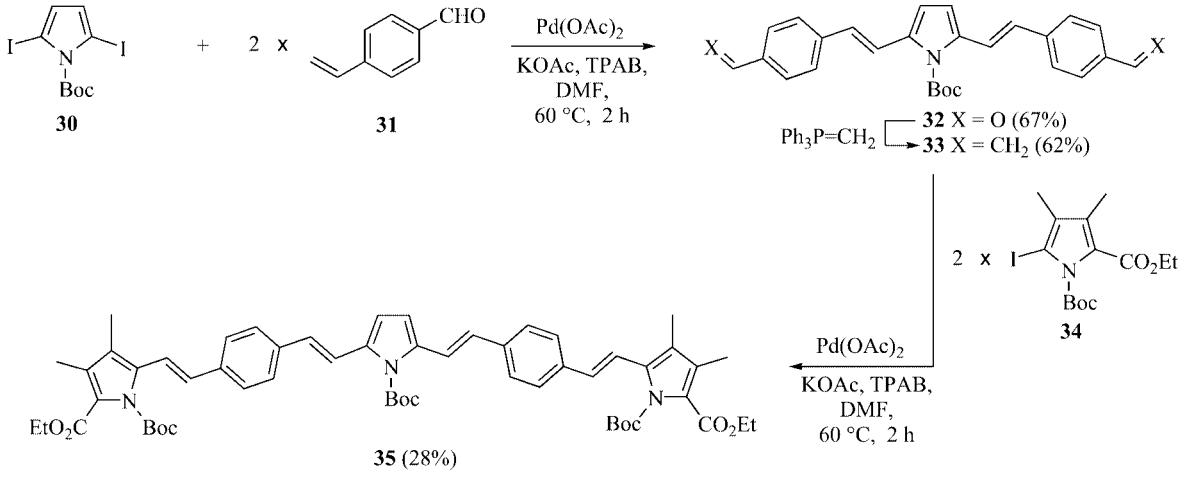
Muratake and co-workers employed an intramolecular Type I Heck reaction in their work directed towards the assembly of the potent cytotoxic antibiotic (+)-duocarmycin SA (Scheme 6).[50] Thus, treatment of the readily available C3-brominated pyrrole **36** with 10 mol% $Pd(OAc)_2$, P(*o*-tol)$_3$, and Et_3N in acetonitrile at 110 °C afforded a ca. 8:1 mixture of enol ethers **37** and **38**. Interestingly, the *cis*-isomer of compound **36** failed to engage in the equivalent cyclisation process, thus suggesting that these kinds of reactions can be sensitive to steric effects.



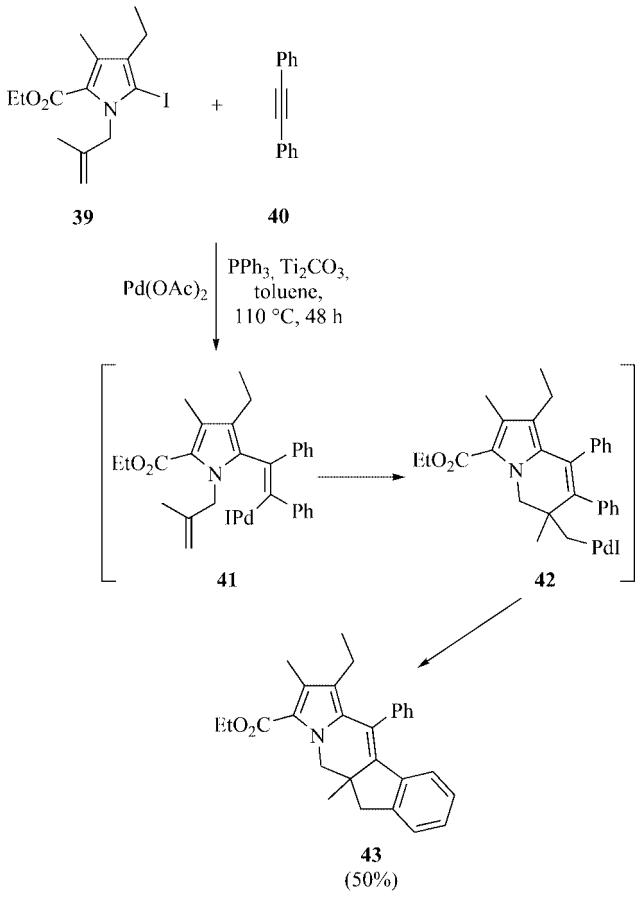
Scheme 6.

Perhaps the most intriguing application of Type I Heck reactions involving pyrroles has been reported by Grigg et al.[51] Thus, this group demonstrated (Scheme 7) that when roughly equimolar quantities of the C2-iodinated system **39** and tolan (**40**) are exposed to the appropriate Pd^0-based system, then a Type I and intermolecular Heck reaction occurs initially to afford the palladated *cis*-stilbene **41**. This last compound engages in a second and now intramolecular Heck process involving the unsaturated side-chain attached to the pyrrole nitrogen so as to deliver the bis-phenylated and palladated indolizidine **42**. The reaction cascade concludes when heterocycle **42** engages in a second intramolecular Heck process, involving a pendant phenyl ring, to give the observed product **43** which is obtained in moderate yield.

In connection with the development of an elegant synthesis of dihydrodipyrrins, Jacobi and co-workers have recently described[52] an intermolecular Type I Heck reaction between a C5-iodinated pyrrole and a γ-alkynoic acid that terminates in a lactonisation process and so delivering, with full stereochemical control, enelactones in good to excellent yield.



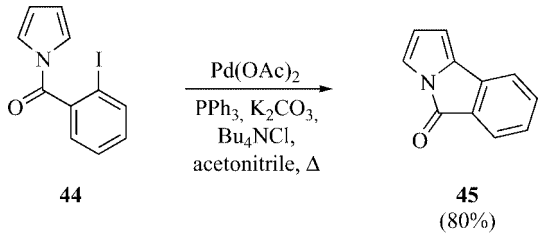
Scheme 5.



Scheme 7.

6.2. Type II Processes

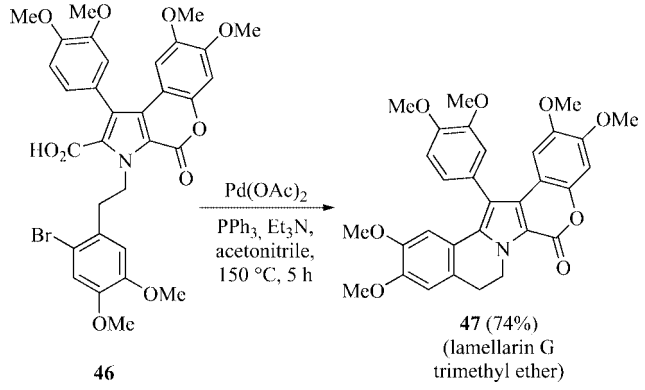
Heck-type couplings wherein the pyrrole acts as the π-system (rather than as the precursor to the initially formed palladated intermediate) are also known. For example, Grigg and co-workers have shown[53] that the palladated intermediate derived from reaction of *N*-(*o*-iodobenzoyl)pyrrole (**44**) with a mixture of $Pd(OAc)_2$ (10 mol%), PPh_3, potassium carbonate and tetrabutylammonium chloride engages in a 5-*exo*-*trig* cyclisation reaction to give, ultimately, the annulated system **45** in serviceable yield (Scheme 8).



Scheme 8.

Other Heck reactions involving the pyrrole ring as the site of termination have also been described.[54] The reported Pd^0-catalysed cross-coupling of chloropyrazines with pyrrole (**1**) and various *N*-substituted derivatives so as to afford the corresponding 2-arylated pyrrole[55] probably also proceeds by Type II processes, although no definitive evidence supporting the involvement of this sort of pathway has been presented.

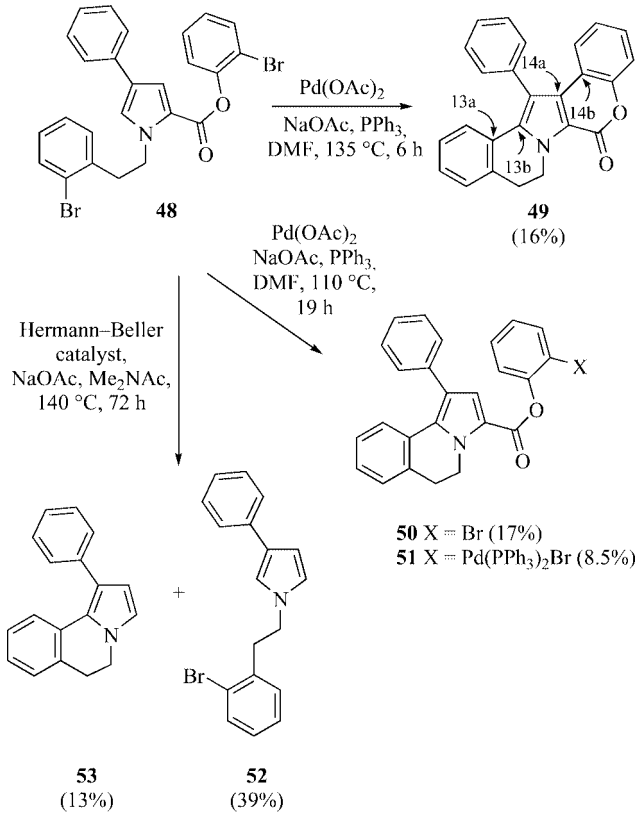
In the area of natural products synthesis, Steglich and his co-workers have reported[56a] that the fully substituted pyrrole **46** (Scheme 9) incorporating an *o*-brominated β-phenethyl side-chain at nitrogen engages in a decarbonylative Heck cyclisation reaction, on exposure to $Pd(OAc)_2/PPh_3/Et_3N$ mixtures in acetonitrile at 150 °C, to afford the trimethyl ether, **47**, of lamellarin G, a representative member of a class of biologically active alkaloid isolated from ascidians and prosobranch molluscs.[28] The authors of this work state that the conversion **46** → **47** is "the first example of a Heck reaction in which after oxidative addition, the Pd[II] intermediate fragments by elimination of CO_2." This elegant chemistry was subsequently extended to the total synthesis of the related natural product lamellarin L.[56b]



Scheme 9.

During the course of our own efforts[57] to develop a rapid route to the polycyclic framework associated with lamellarin G and various of its congeners, we sought to establish whether or not the trisubstituted pyrrole **48** (Scheme 10) would engage in tandem Heck cyclisation reactions to give product **49** embodying the target framework. In the event, when the readily accessible substrate **48** was treated with $Pd(OAc)_2/Ph_3P$ in DMF at 135 °C then compound **49** was indeed obtained, albeit in only 16% yield. In contrast, when reaction temperatures of 110 °C were employed then the monocyclised products **50** and **51** were obtained in yields of 17 and 8.5%, respectively. These results suggest that Heck-type cyclisation to form the C13a/C13b bond within the target framework (see structure **49**) is more facile than the analogous process in which the C14a/C14b bond would be produced. The rate of formation of the latter bond may be slowed by unfavourable rotamer populations about the "doubly vinylogous" carbamate-type linkage within compounds such as **48** and/or poor orbital overlap associated with the 6-*endo*-*trig*-type ring-closure that would be involved in converting this material into the target **49**. In further efforts to raise the yield of compound **49**, dihalide **48** was treated, in *N*,*N*-dimethylacetamide and the presence of sodium acetate, with the Hermann–Beller catalyst at 115–140 °C. However, under these conditions only a

1:3 mixture of the "decarbonylated" products **52** and **53** was obtained.



Scheme 10.

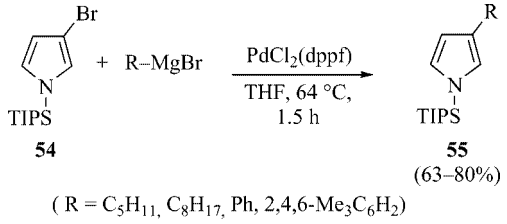
7. Hiyama and Tamao–Ito Cross-Coupling Reactions

It is quite clear that the title reactions, wherein the appropriate organosilane [$SiR_{(3-n)}F_n$ in the case of the former process and $Si(OR)_3$ in the case of the latter process] engages in Pd-catalysed cross-coupling with the relevant alkenyl or aryl halide or triflate, are enjoying increasing attention as valuable C–C bond forming protocols.[58] However, so far, they do not appear to have been applied to reactions involving pyrroles. That having been said, there can be little doubt that Type I forms of these cross-coupling reactions would be effective in generating usefully substituted pyrroles. Similarly, the *C*-silylated pyrroles required as partners for the analogous Type II processes are readily available[46,59,60] so there is no reason to believe that these could not also become powerful protocols for assembling derivatives of the title ring system (**1**).

8. Kumada Cross-Coupling Reactions

8.1. Type I Processes

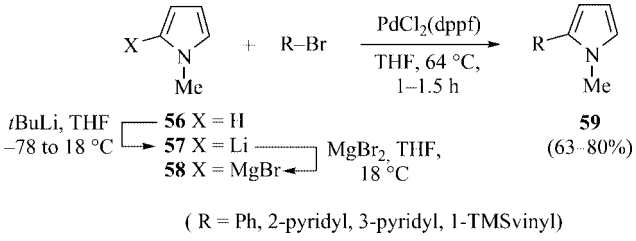
The ready availability of many halogenated pyrroles[20] has prompted a number of groups to investigate the Pd^0-catalysed cross-coupling of such species with a range of Grignard reagents. For example, the *N*-TIPS-substituted pyrrole introduced by Muchowski[60] can be mono-brominated at C3 so as to afford compound **54** (Scheme 11) and this latter species readily engages in $PdCl_2$(dppf)-catalysed couplings with various alkyl and aryl Grignard reagents so as to give the corresponding 3-substituted pyrrole **55** in useful yields.[61] Analogous couplings involving C4-iodinated pyrroles have been reported,[62] as have those involving C3,C4-dibrominated systems.[63]



Scheme 11.

8.2. Type II Processes

Since a range of methods is available for the generation of pyrrole-based Grignard reagents, Type II Kumada cross-coupling reactions involving the title ring system are reasonably well known. For example, *N*-methylpyrrole (**56**) (Scheme 12) is lithiated at C2 upon reaction with *t*BuLi in THF at –78 to 18 °C and the *N*-methyl–C2–lithiopyrrole (**57**) so-formed can be *trans*-metallated with $MgBr_2$, thus providing the corresponding Grignard reagent **58**. This last species readily engages in cross-coupling with a wide range of aryl halides so as to generate the expected C2-arylated or related products **59** in good to excellent yield.[55,64] Alkenyl halides serve equally well as coupling partners in such processes.[65] The capacity to effect C2-magnesiation of *N*-phenylsulfonylpyrrole upon treatment with isopropylmagnesium chloride and catalytic amounts of diisopropylamine has been exploited in the formation of the C2-phenylated system.[59] Related processes involving the Grignard reagent derived from compound **54** (Scheme 11) readily affords C3-arylated pyrroles.[66]



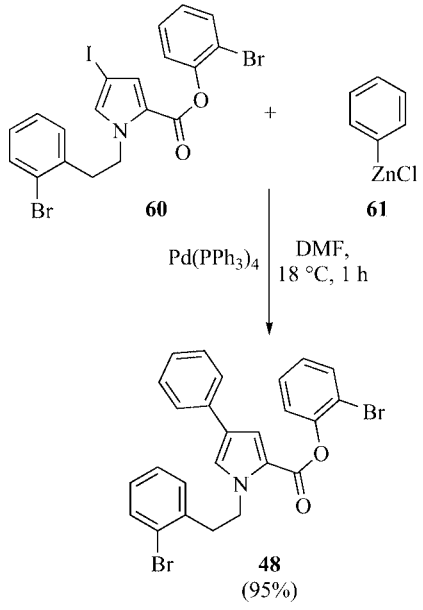
Scheme 12.

9. Negishi Cross-Coupling Reactions

9.1. Type I Processes

In light of the already noted ease of access to halogenated pyrroles,[20] it is rather surprising that only limited

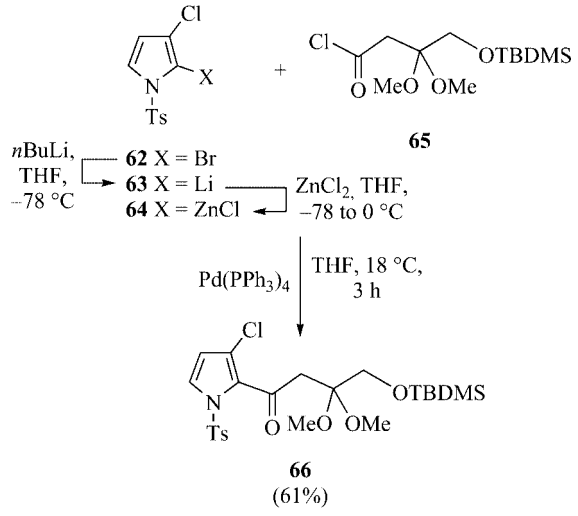
numbers of examples of Type I Negishi-type cross-coupling reactions involving this heterocyclic ring system have been described. Our experience with such processes have been especially positive in so far as this served us well during the course of preparing compound **48** (the substrate required in exploring our proposed tandem Heck approach to the framework of certain lamellarins – see Scheme 10) through cross-coupling of the C4-iodinated pyrrole **60** with phenylzinc chloride (**61**) (Scheme 13).[57] This conversion is notable for the lack of complications arising from competitive cross-coupling processes involving the *o*-bromoaryl residues incorporated within substrate **60**. Extension of this type of chemistry to the solid phase have been reported by Albericio and Álvarez during the course of the development of total syntheses of the marine natural products lamellarin O and lamellarin Q.[67]



Scheme 13.

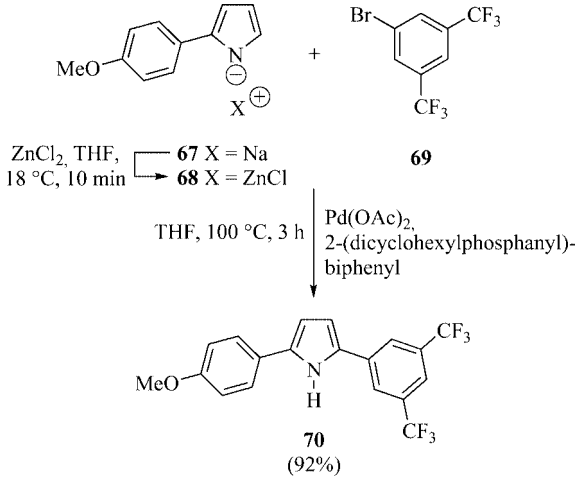
9.2. Type II Processes

C2-Zincated pyrroles, which are readily generated through transmetallation of the corresponding C2-lithiated species using $ZnCl_2$, engage in Pd^0-catalysed cross-coupling with a range of aryl and acyl halides to give the expected products.[31,64,68–70] A reaction reported by Fürstner and Weintritt during the course of their synthesis of the antitumour agent roseophilin[68] serves to highlight the utility of these sorts of processes. Thus, these researchers demonstrated the selective conversion of the C2-bromo–C3-chloro system **62**, via successive formation of intermediates **63** and **64** then cross-coupling of the latter with acid chloride **65**, into the corresponding C2-acylated product **66** (Scheme 14). In related work we have shown[71,72] that various pyrrole ring-fused analogues of the antimitotic agent combretastatin A4 (a polyoxygenated *cis*-stilbene) can be generated using similar chemistry that relies, in the early stages, on the selective mono-lithiation then zincation of either C3,C4- or C4,C5-dibromopyrroles. In the latter case the initial metal-for-halogen exchange reaction takes place preferentially at that position closer to the ring nitrogen, namely at C5.



Scheme 14.

An interesting variation on Type II Negishi cross-coupling reactions has been described by Filippini and coworkers.[73] Thus, (pyrrol-1-yl)zinc halides, readily generated from the sodium salt of pyrrole and zinc(II) halides, engage (at 140 °C) in coupling with organic halides in the presence of a palladium catalyst and phosphane affording (mainly) the corresponding 2-alkylated or -arylated pyrrole. By such means a practical route to 2-perfluoroalkylpyrroles has been developed. Recent modifications to this chemistry, particularly ones involving the use of a palladium precatalyst and Buchwald's sterically demanding 2-(dialkylphosphanyl)biphenyl ligands, have allowed various (pyrrol-1-yl)-zinc halides to be cross-coupled with a range of aryl halides at low catalyst loadings and under mild conditions.[74] The conversion of anion **67**, via cross-coupling of the derived zincated species **68** with the aryl bromide **69**, into the 2,5-



Scheme 15.

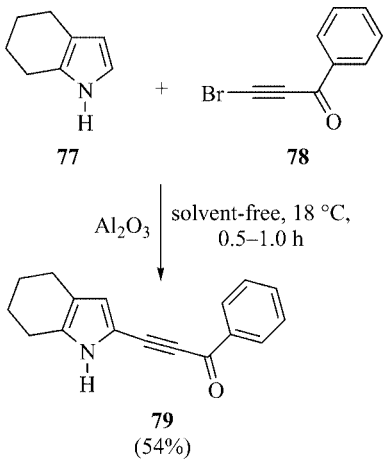
diarylated pyrrole **70** (Scheme 15) is indicative of the capacities of such protocols.

10. Sonogashira Cross-Coupling Reactions

Given the mechanistic features of the Sonogashira reaction, essentially all of these are, in terms of the present categorisations, Type 1 processes. Of course, this "restriction" has not adversely impacted on the utility of the reaction in providing a wide range of C2- and C3-alkynyl-substituted pyrroles.[46,75–84] Thus, for example, the reaction sequence shown in Scheme 16 has been employed in generating the 2,2′-diyne-linked bis-pyrrole **75**.[81] Related chemistry provided congener **76**. Compounds of this type have proven to be key building blocks for the construction of novel porphyrinoids.[82]

Twofold Sonogashira cross-couplings of 2,5-di-iodinated pyrroles with terminal alkynes have been reported,[83] but not processes leading to the corresponding 3,5-dialkynylated systems. In connection with the development of anion sensors, Sessler and co-workers have demonstrated that C3-iodinated pyrrole subunits within calix[4]pyrroles can also participate in the title cross-coupling reactions with TMS-acetylene.[84]

In light of the opening comments made in this section, it is interesting to note that a so-called "inverse Sonogashira coupling" involving ethynylation of pyrroles with 1-acyl-2-bromoacetylenes has been reported (Scheme 17).[85] Thus, typically, the relevant pyrrole (**77**) lacking a substituent at C2 or C5 is treated with, for example, 1-benzoyl-2-bromoacetylene (**78**) at room temperature in the presence of alumina to give, via a nucleophilic addition/elimination sequence, the alkynylated system **79**. Clearly, then, this process is mechanistically distinct from the true Sonogashira reaction and does not, of course, involve any catalysis by Pd-species.

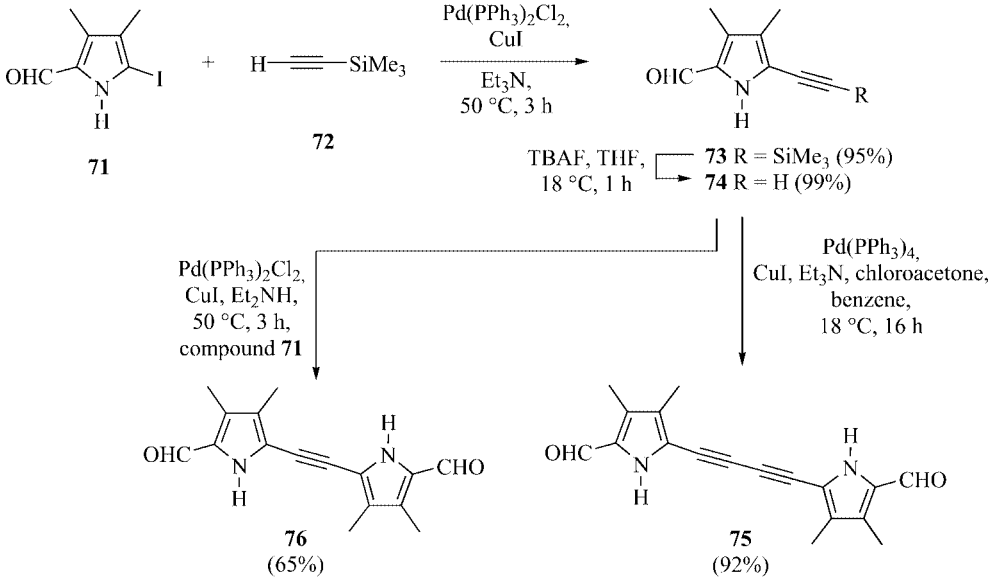


Scheme 17.

11. Stille and Stille–Kelly Cross-Coupling Reactions

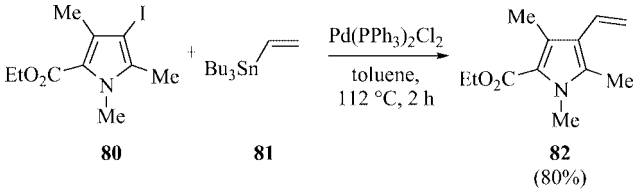
11.1. Type I Processes

Surprisingly, and in contrast to the situation with Type II processes (see below), examples of Type I Stille cross-coupling reactions are relatively rare, and this is despite the ready availability of the relevant halogenated pyrroles. Scott was the first to recognize the value of this type of process and has exploited it (Scheme 18) by cross-coupling of C4-iodopyrroles such as compound **80** with vinyltributyltin (**81**) to form C4-vinylpyrroles such as **82**.[86] Products of this sort represent important building blocks for the assembly of, inter alia, bilirubins, biliverdins and related extended π-conju-



Scheme 16.

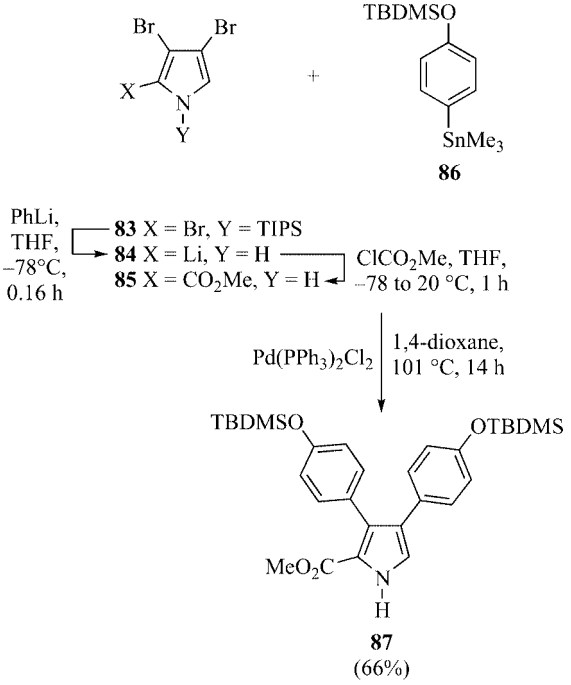
gated systems. As part of a study directed towards developing a third generation synthesis of duocarmycin SA, Natsume and co-workers demonstrated that a C3-brominated pyrrole engages in an efficient Stille cross-coupling reaction with a C3-stannylated pyridine.[87]



80 **81** **82** (80%)

Scheme 18.

As part of our program to establish syntheses of various 3,4-diarylated pyrrole-containing natural products, we have demonstrated[71] that the readily prepared tribrominated pyrrole **83** (Scheme 19) is selectively lithiated at C2 and the ensuing species **84** then reacts with methyl chloroformate to give, with concomitant loss of the *N*-TIPS group, the corresponding dibrominated ester **85**. This last compound then serves as the substrate for a twofold Stille cross-coupling with arylstannane **86** so as to afford the C3,C4-diarylated product **87** in 66% yield. Compound **87** was then readily converted into the target natural product lamellarin O using a highly efficient *N*-alkylation/*O*-desilylation sequence.

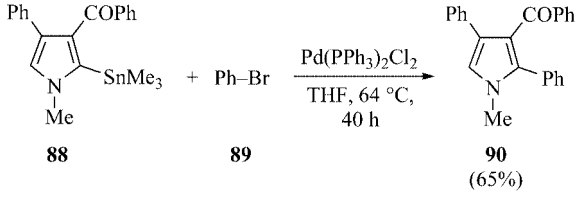


Scheme 19.

In related work concerned with the development of a synthesis of the marine natural product rigidin, a brain phosphodiesterase inhibitor, Edstrom and Wei demonstrated that a ring-fused pyrrole incorporating a C4-trifloxy group could engage in cross-coupling with a *p*-benzyloxy-substituted tri-*n*-butylarylstannane.[37]

11.2. Type II Processes

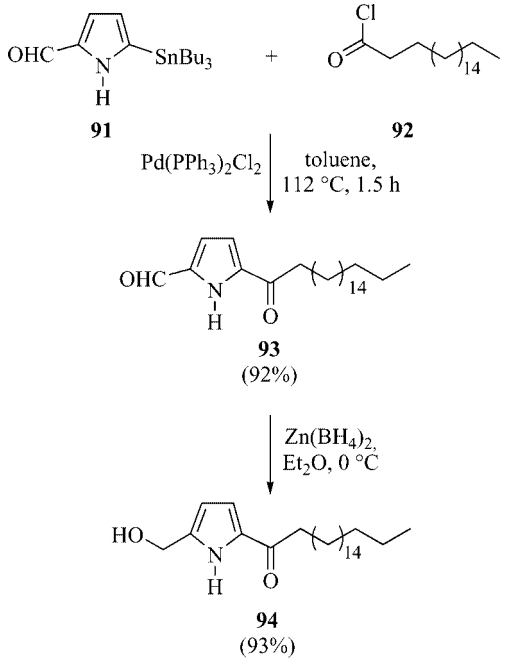
In 1973, and in a remarkably prescient study, Pommier and Lucas demonstrated that *N*-(tri-*n*-butylstannyl)pyrrole reacts with, for example, benzyl bromide upon heating in pentane at 120 °C (no palladium catalyst involved), to give 2-benzylpyrrole in 33% yield.[88] It took another thirteen years before Bailey demonstrated[89] that *N*-methyl-C2-(tri-*n*-butylstannyl)pyrrole would engage in true Type II Stille cross-coupling reactions with iodobenzene to form *N*-methyl-C2-phenylpyrrole which was obtained in 54% yield. With the advent of various effective protocols for the formation of C2-(tri-*n*-butylstannyl)pyrroles[31,90–95] and the corresponding C3-isomers,[77,95] the title couplings have enjoyed widespread use not least because of the capacity they offer to prepare heavily substituted pyrroles[96,97] and/or products where the fragment attached to the pyrrole is itself heavily substituted.[98,99] The cross-coupling of the C2-stannylated pyrrole **88** with bromobenzene (**89**), so as to provide the tetrasubstituted pyrrole **90** (Scheme 20), is illustrative.[96]



88 **89** **90** (65%)

Scheme 20.

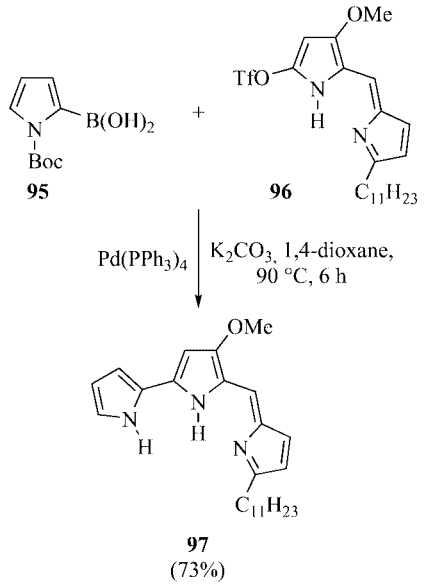
The palladium-catalysed acylation, carboalkoxylation, and carbamoylation reactions of C2-stannylated pyrroles have also been exploited in a range of applications including for the purposes of generating various natural products and certain analogues.[100–102] For example, Nabbs and



Scheme 21.

Abell[100] have prepared the marine natural product mycalazol-11 and related 5-acyl-2-hydroxymethylpyrroles using such chemistry. Thus, cross-coupling of stannane **91** with acid chloride **92** (Scheme 21) under conventional Stille-type conditions afforded the expected ketone **93** and upon reduction of the latter material with zinc borohydride the target natural product **94** was obtained. This compound and various analogues displayed significant cytotoxicity, in vitro, against the P388 murine leukemia cell line.

Despite the prospects the process offers for the assembly of, inter alia, ring-fused pyrroles, the Stille–Kelly[103] reaction has yet to be deployed for such purposes. Clearly, though, the ready availability of halogenated pyrroles and halogenated systems that can be attached to the pyrrole framework, especially by the means detailed herein, suggest that it is only a matter of time before the first applications of this protocol emerge.



Scheme 22.

12. Suzuki–Miyaura Cross-Coupling Reactions

Amongst the title processes, the Suzuki–Miyaura cross-coupling reaction[104] has, without doubt, been the most heavily exploited and this trend is likely to continue, especially given the ready capacity to convert halogenated pyrroles into the corresponding boronic acid derivatives[105] using the simple and effective protocols introduced by Masuda.[106] Related developments described by Smith and co-workers[107] may also have a significant impact on the capacity of chemists to produce borolated pyrroles that can participate in Suzuki–Miyaura cross-coupling reactions.

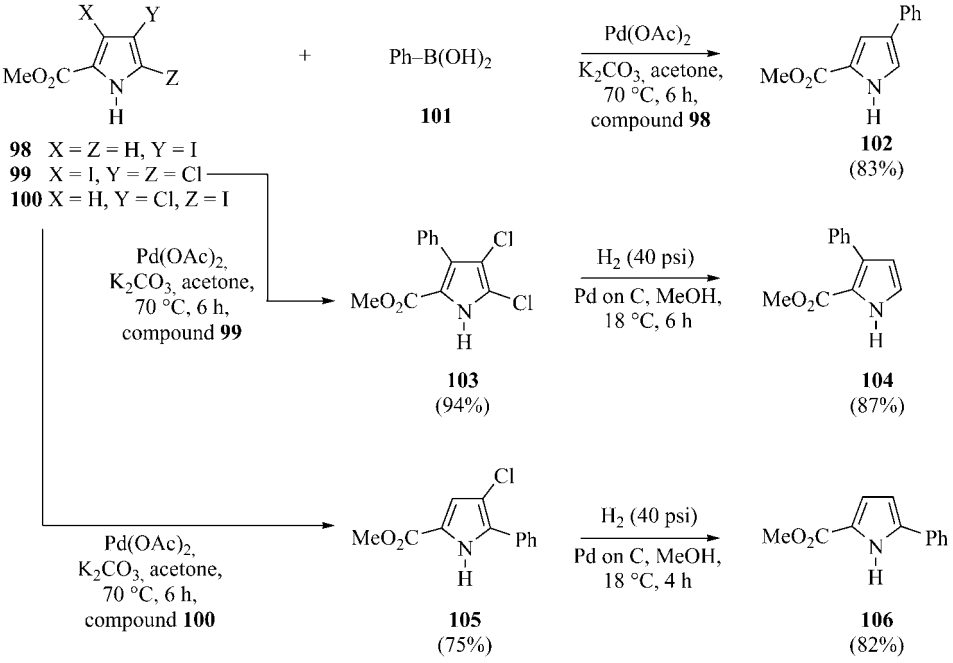
12.1. Type I Processes

Not surprisingly, these processes are as prevalent as their Type II counterparts and almost every conceivable variant (including ones conducted on the solid phase[67]) is known including its use in combination with Type II reactions. Thus, for example, as part of one of a number of programs[108] aimed at developing syntheses of the immunosuppressive agent undecylprodigiosine and related systems, the cross-coupling of boronic acid **95** with pyrrole **96**, bearing a triflate group at C2, was carried out and so delivering product **97** (Scheme 22).[108a] Related couplings involving C2-halogenated and C2-,C5-dihalogenated pyrroles have also been reported,[31,109–112] including in the assembly of tetrasubstituted pyrroles and phenyl-pyrrole mixed polymers.[109,110]

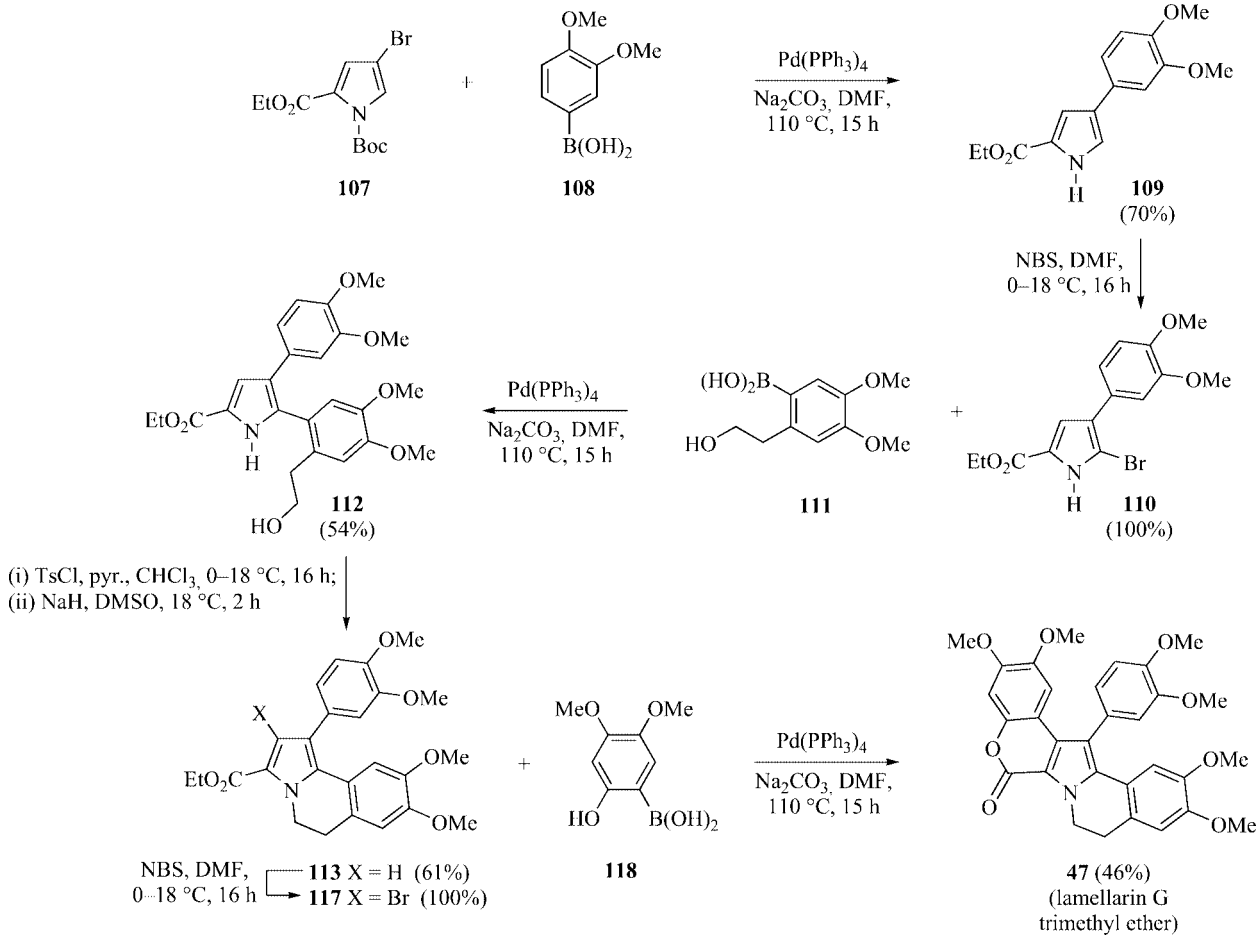
Type I processes leading to the introduction of substituents at C3, C4, and/or C5 are also known[46,71,72,113–117] and have been exploited, by us[71] and others,[28c,46] in the synthesis of lamellarin-type natural products as well as in completing the syntheses of various analogues[113] including lamellarin/combretastatin A4 hybrids.[72] In the case of the last study,[72] many of the halogenated pyrrole-containing substrates used in the relevant Suzuki–Miyaura cross-coupling reaction were prepared by Negishi cross-coupling processes as described above. In the course of developing routes to analogues of the intriguing antimitotic agent rhazinilam, Ghosez[115] and Guéritte[116] have established a general synthesis of C2-formyl-C3-arylpyrroles involving Suzuki–Miyaura cross-coupling of arylboronic acids with C3-iodopyrroles. By related means we have developed routes to (±)-B-norrhazinal as well as the alkaloids (±)-rhazinal, (–)-rhazinal, (–)-rhazinilam, (–)-leuconolam, and (+)-*epi*-leuconolam.[117]

Type I processes involving the selective manipulation of polyhalogenated and related pyrroles have been described recently.[118–121] For example, Ng and Smith have established useful new protocols for the completely regioselective introduction of aryl units onto the C3-, C4-, and C5-positions of the C2-methoxycarbonylpyrrole framework (Scheme 23).[118] These rely upon the capacity for selective coupling of aryl boronic acids with iodides rather than chlorides and the use, therefore, of the latter halogen as a blocking group during the course of the iodination reaction leading to the relevant cross-coupling partner. Hydrogenolysis of the C–Cl bonds in the Suzuki–Miyaura cross-coupling product then affords the desired dehalogenated product. These researchers favour using Novak's accelerated Suzuki–Miyaura cross-coupling protocols involving a ligandless palladium catalyst.[122] In somewhat related work, Schröter and Bach have demonstrated that various di- and tri-brominated pyrroles containing an ethoxycarbonyl or nitro group at C2 engage in selective cross-coupling at the C5-position with a range of *p*-substituted phenylboronic acids.[119]

In a very elegant sequence of reactions leading to the synthesis of lamellarin G trimethyl ether (**47**) (Scheme 24), Handy and co-workers have demonstrated[123] that three successive pairings of halogenation and Suzuki–Miyaura cross-coupling processes can be used in the synthesis of the target compound. The last of these Suzuki–Miyaura cross-coupling reactions (viz. **117** + **118** → **47**) is accompanied



Scheme 23.

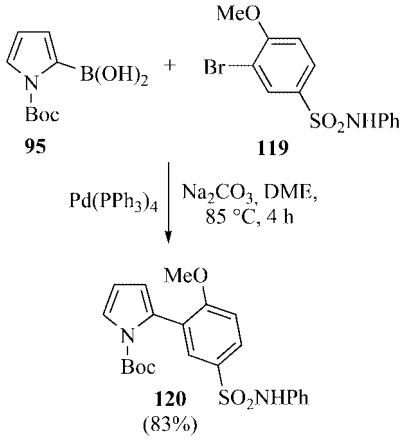


Scheme 24.

by a *trans*-esterification reaction that delivers the lactone ring associated with target **47**. Related and similarly highly effective reaction sequences have been described by Iwao and co-workers.[121] However, lest the reader now think that all Suzuki–Miyaura cross-coupling reactions involving halogenated pyrroles proceed uneventfully, it should be noted that as a prelude to the work just described, Handy et al. observed an unusual dehalogenation of C4-bromopyrrole-C2-carboxylates under the reactions conditions normally employed for these reactions.[124] Fortunately, this dehalogenation process can be suppressed by Boc-protection of the pyrrole nitrogen and under the relevant conditions the desired coupling now proceeds efficiently and is accompanied by loss of the *N*-protecting group.[124]

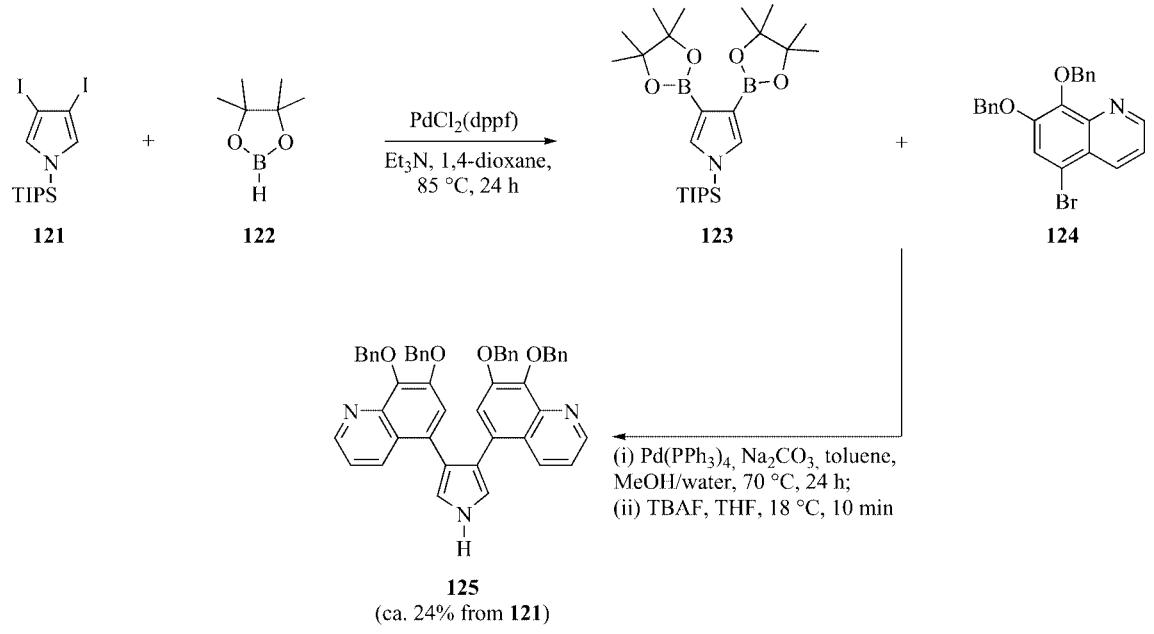
12.2. Type II Processes

As noted above, the capacity to attach boronic acid and related residues to the pyrrole core has resulted in Type II variants of the Suzuki–Miyaura cross-coupling reaction being used extensively.[42,59,77,109a,125–128] Quite a number of papers report on the ability to use various *N*-substituted pyrroles as substrates for C2-directed metallations. Trapping of the resulting organometallic (generally the lithio-species) with a boron electrophile (typically trimethoxyborane) gives, in most cases, the relevant C2-boronic acid. These acids then engage in the expected cross-coupling reactions with the relevant aryl halide. The reaction shown in Scheme 25 is indicative and was reported by Johnson et al.[125] during the course of work directed towards the preparation of novel agonists of the dopamine D3 receptor. The corresponding C3-boronic acid derivatives have been described by various groups including Muchowski and co-workers[77] who demonstrated that these systems also readily cross-couple with a range of aryl and heteroaryl bromides and iodides.



Scheme 25.

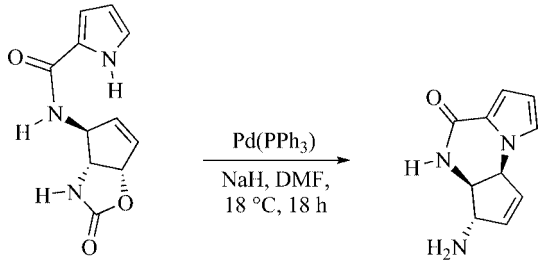
Polyborolated pyrroles are known and can also serve as perfectly viable substrates in the title cross-coupling reactions. For example, during the course of developing a total synthesis of the cytotoxic marine alkaloid halitulin (**16**),[105] Steglich and co-workers were able to convert (Scheme 26) the 3,4-diiodinated pyrrole **121** into the corresponding bis-pinacolatoboronate ester **123** using Masuda's protocols.[106] Compound **123** readily engages in a double-barreled Suzuki–Miyaura cross-coupling reaction with the C5-brominated quinoline **124** so as to deliver, after removal of the *N*-TIPS group, product **125** embodying the unusual chromophore associated with the target natural product. Indeed, this cross-coupling product could be readily elaborated to halitulin and by such means the structure, including absolute stereochemistry, of this unusual natural product was established.



Scheme 26.

13. Tsuji–Trost Cross-Coupling Reactions

In an example of a process that is likely to enjoy broader applications in the future, Weinreb and his co-workers have employed a clever intramolecular variation on the Tsuji–Trost reaction to convert the pyrrole-tethered cyclic carbamate **126** into the tricyclic product **127** (Scheme 27). This conversion, which was undertaken as part of a (successful) program directed towards the development of a total synthesis of the antitumour marine sponge alkaloid agelastatin A,[129] represents the first and, to the best of our knowledge, thus far only example of the *N*-alkylation of a pyrrole with a π-allylpalladium complex. That having been said, the transformation shown in Scheme 2 could be regarded as a carbonylative and intramolecular Tsuji–Trost reaction that leads to C3-acylation of the pyrrole ring.

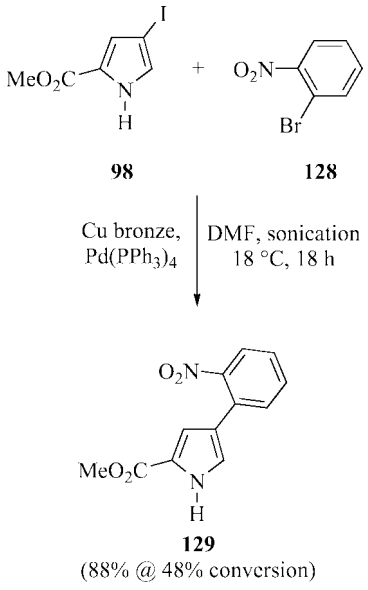


126 **127** (63%)

Scheme 27.

14. (Palladium-Catalysed) Ullmann Cross-Coupling Reactions

We have recently reported on the application of the title process[130] to the preparation of indoles[131] and quinolines,[132] but our efforts in this area originated from the observation[117b] (Scheme 28) that methyl 4-iodopyrrole-2-carboxylate (**98**) can be cross-coupled with 2-bromonitrobenzene (**128**) in the presence of copper bronze and catalytic quantities of $Pd(PPh_3)_4$ to give the 4-arylated pyrrole **129** in 88% yield at 48% conversion. It is worth noting that when this sort of reaction is performed in the absence of a palladium catalyst then the only product of reaction is 2,2′-dinitrobiphenyl arising from reductive homo-coupling of compound **128**. Our subsequent refinements of the Pd^0-catalysed Ullmann cross-coupling reactions[133] make us confident that this sort of chemistry will lend itself to the ready preparation of a range of halogenated C4-arylpyrroles such as pyrrolnitrin (**6**) and related (and biologically active) natural products.[23] Work directed towards such ends is now underway in our laboratories.



98 **128**

129
(88% @ 48% conversion)

Scheme 28.

15. Miscellaneous Processes

The Pd^0-catalysed cyanation of a C3-iodinated pyrrole has been reported by Wong,[46a] while the Pd^0-catalysed reductive de-iodination of C2-iodinated pyrroles (using sodium formate as a hydride source) has been described[134] as has the decarbonylation of a C2-formylated pyrrole.[44a] In this context it is worth noting that the decarbonylation of rhazinal (**8**) so as to give rhazinilam (**7**) can be achieved using stoichiometric amounts of Wilkinson's "catalyst".[117c]

16. Conclusions

This mini-review has attempted to demonstrate that the broad impact that Pd^0-catalysed cross-coupling reactions has had in the development of organic synthesis is reflected in the area of pyrrole chemistry.[135] Undoubtedly, many more variants, especially intramolecular ones, on the processes delineated above will surface in the coming years and be deployed in the preparation of the multitude of novel pyrrole-containing natural products and related biologically active materials that have been isolated and continue to be identified. The capacity of pyrrole and its derivatives to react, often in a fully regiocontrolled manner, with relevant electrophiles, including halogens and Pd^{II} species, suggests that the title processes will continue to play a vital role in the manipulation of this heterocyclic ring system. As such, substituted and/or annulated pyrroles are likely to continue to develop as significant scaffolds in the medicinal chemistry and materials science areas.

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