The Palladium-catalysed Ullmann Cross-coupling Reaction: A Modern Variant on a Time-honored Process

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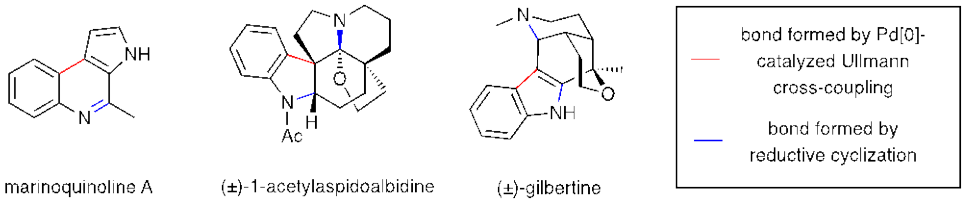
CONSPECTUS

Cross-coupling reactions, especially those that are catalysed by palladium, have revolutionized the way in which carbon-carbon bonds can be formed. The most commonly deployed variants of such processes are the Suzuki-Miyaura, Mizoroki-Heck, Stille and Negishi cross-coupling reactions and these normally involve the linking of an organohalide or pseudo-halide (such as a triflate or nonaflate) with an organo-metallic or -metalloid such as an organo-boron, -magnesium, -tin or -zinc species. Since the latter type of coupling partner is often prepared from the corresponding halide, methods that allow for the direct cross-coupling of two distinct halogen-containing compounds would provide valuable and more atom-economical capacities for the formation of carbon-carbon bonds. While the venerable Ullmann reaction can, in principle, achieve this it has a number of drawbacks, the most significant of which is that homo-coupling of the reaction partners is a competitive, if not the dominant, process. Furthermore, such reactions normally only occur under forcing conditions (viz. often at temperatures in excess of 250 °C). As such the Ullmann reaction has seen only limited application in this regard, and especially as a mid- to-late-stage feature of complex natural product synthesis. This Account details the development of the palladium-catalyzed Ullmann cross-coupling reaction as a useful method for the assembly of a range of heterocyclic systems relevant to medicinal and/or natural products chemistry. These couplings normally proceed under relatively mild conditions (<100 °C) over short periods of time and, usually, to the exclusion of (unwanted) homo-coupling events. The keys to success are the appropriate choice of coupling partners, the form of the copper metal employed and the choice of reaction solvent.

At the present time, the cross-coupling partners capable of engaging in the title reaction are confined to halogenated and otherwise electron-deficient arenes and, as complementary reactants, to α- or β-halogenated, α,β-unsaturated aldehydes, ketones, esters, lactones, lactams and cycloimides. Nitro-substituted (and halogenated) arenes, in particular, serve as effective participants in these reactions and the products of their coupling with the above-mentioned carbonyl-containing systems can be manipulated in a number of different ways. Depending on the positional relationship between the nitro and carbonyl groups in the cross-coupling product, the reduction of the former group, which can be achieved under a range of different conditions, provides, through intramolecular nucleophilic addition reactions including Schiff-base condensations, access to a diverse range of heterocyclic systems. These include indoles, quinolines, quinolones, isoquinolines, carbazoles and carbolines. Tandem variants of such cyclization processes, in which Raney cobalt is used as a catalyst for the chemoselective reduction (by hydrogen) of nitro and nitrile groups (but not olefins), allows for the assembly of a range of structurally challenging natural products including marinoquinoline A, (±)-1-acetylaspidoalbidine and (±)-gilbertine.



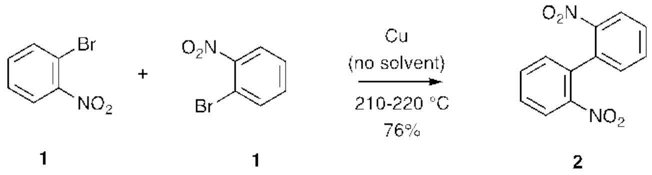
INTRODUCTION

Arguably, carbon-carbon bond formation is the most important process in organic chemistry and the development of means for doing so has been a source of conscious effort for almost two centuries.[1] In modern times cross-coupling reactions, perhaps most especially those catalyzed by palladium, nickel, copper and iron species, have revolutionized the way in which more complex organic compounds are assembled from simpler ones.[2] Named reactions such as the Suzuki-Miyaura, Mizoroki-Heck, Stille, Sonogashira, and Negishi cross-couplings immediately spring to mind in considering such matters.[2a] The coupling partners involved in these processes are normally an organohalide or pseudohalide (such as a triflate or nonaflate) and an organometallic species that is, more often than not, obtained from a halide precursor. Given this and the often unstable/sensitive nature of the organometallic species, there have been many efforts directed at effecting the reductive cross-coupling of two structurally distinct organohalides, the most conspicuous examples of which involve adaptations of the venerable Wurtz[1] and Ullmann[3] reactions. In their traditional forms, however, these processes have not found extensive application because of competition from homo-coupling reactions and/or the need to use rather aggressive reaction conditions that are incompatible with other functionalities present in the substrates. In recent times, so-called cross-electrophile couplings (XECs), especially ones carried out in reductive mode and often involving multimetallic catalysts, have come to the fore with notable contributions having been reported in the last few years by various groups.[4] The versatility of such processes is quickly becoming apparent. Herein we detail the outcomes of our own, ongoing work concerned with the development of the palladium-catalysed Ullmann cross-coupling reaction of structurally distinct, sp^2-hybridised and halogen-associated electrophiles with one another.[5,6] These reactions enable the construction products that are either useful in their our right and/or can participate in reductive cyclisation reactions and so affording various heterocyclic motifs encountered in a range of interesting natural products.

THE CLASSICAL ULLMANN REACTION

The Ullmann reaction (Scheme 1) was first reported in 1901[3a] and in the intervening period has found extensive application in chemical synthesis, most notably in the reductive coupling of an aryl halide (e.g. **1**) to form the corresponding and symmetrical bi-aryl (e.g. **2**).[3,6]

Scheme 1. The original (1901) Ullmann reaction resulting in the reductive coupling of *o*-bromonitrobenzene (**1**) and leading to *o*,*o*′-dinitrobiphenyl (**2**)

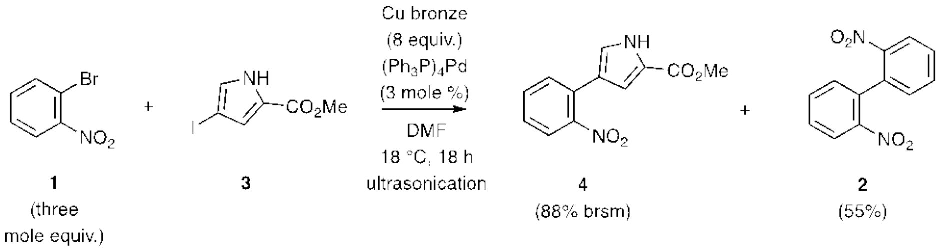


Its limitations also became evident rather quickly. These include the need to use high reaction temperatures (>200 °C), the attendant functional group incompatibilities, an inability to cleanly generate unsymmetrical bi-aryls from two structurally distinct aryl halide precursors (because of competing homo-coupling processes) and the frequently erratic yields obtained. Manifold efforts to redress such deficiencies have been undertaken over the years, including through the application of on-surface processes,[3g] the introduction of metal-chelating species,[3e] the use of varying forms of copper as well as other metal species.[3,6] These have had useful impacts as summarised in a range of recent review articles.[3]

THE DISCOVERY OF THE PALLADIUM-CATAYLZED ULLMANN CROSS-COUPLING REACTION

Some years ago, and in connection with work directed towards establishing a total synthesis of the alkaloid rhazinal,[7] a potent spindle toxin, we required access to an arylated pyrrole. We initially attempted to prepare this key intermediate through conventional Ullmann cross-coupling of the commercially available *o*-bromonitrobenzene (**1**) with the known, iodinated pyrrole **3** (see Scheme 2) but only traces of target **4** were obtained. Upon undertaking an extensive literature survey we came across the work of Thompson[8] and Shimizu,[9] both of whom reported that the synthesis of certain arylated pyridines through the Ullmann cross-coupling of the relevant arylhalide and halogenated pyridine is greatly facilitated by the addition of a palladium catalyst. Upon applying such observations to our system,[7] using DMF as solvent and a three-fold excess of compound **1**, we were able to obtain, under ultrasonication conditions, target **4** in 88% yield (based on recovered starting material – brsm) with the major by-product being 2,2’-dinitrobiphenyl (**2**) (55%) (Scheme 2).

Scheme 2. The palladium-catalyzed Ullmann cross-coupling of compounds **1** and **3** leading to the arylated pyrrole **4**



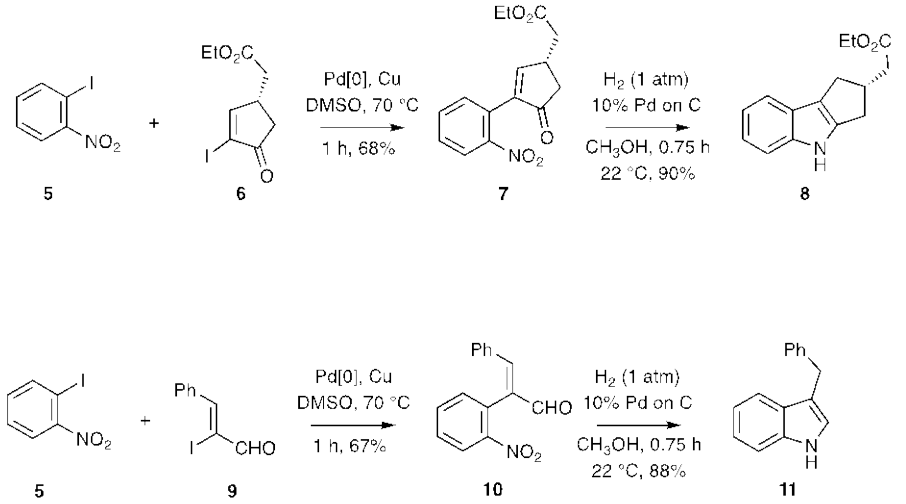
These observations triggered extensive studies of the title process that continue in our group to this day. These studies have provided, through the reductive cyclisation of the initially formed cross-coupling products, useful new means for the construction of a wide range of heterocyclic compounds, including ones embodying previously unreported frameworks. Details of these processes are presented in the following sections and categorised according to the heterocyclic frameworks that are generated.

APPLICATION TO THE SYNTHESIS OF HETEROCYCLES

(a) *Indoles*

Our first efforts to comprehensively develop the title reaction involved the cross-coupling of readily available α-halo-enones and enals with *o*-halonitroarenes and the reductive cyclisation of the ensuing α-arylated enones and enals to give indoles, including annulated variants.[10] The simple reaction sequences shown in Scheme 3 serve to highlight the possibilities for the assembly of such heterocycles and others have since exploited these processes in the total synthesis of a range of natural products.[11] Some of our own efforts in this regard are detailed in the next section.

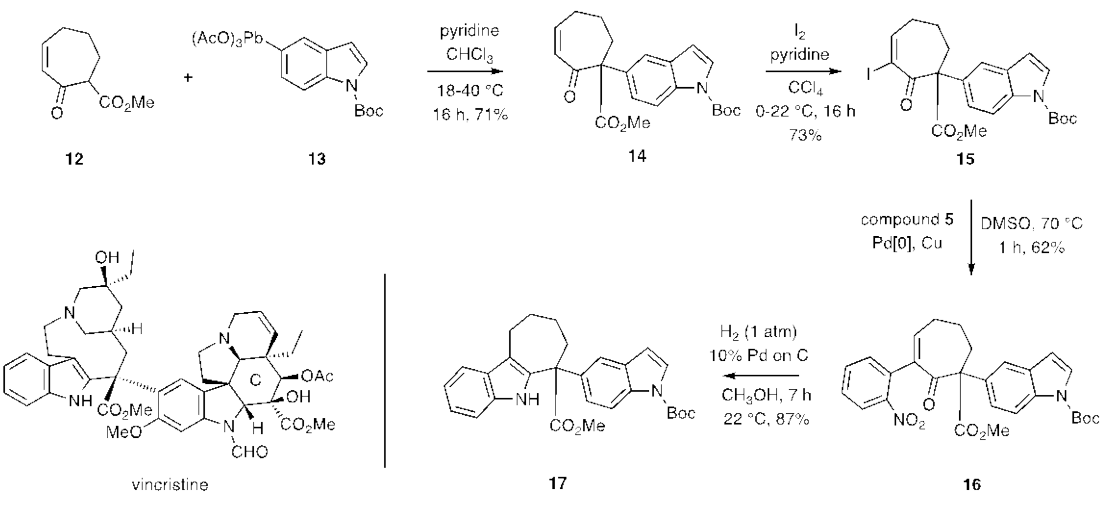
Scheme 3. Palladium-catalyzed Ullmann cross-coupling/reductive cyclization sequences leading to indoles **8** and **11**



In the course of optimizing these sorts of cross-coupling processes we established that a range of different sources of Pd[0] can be used, that DMSO appears to be the optimal solvent, that electron-deficient, halogenated arenes are required and that the lower the reaction temperature the better the ratio of cross-coupling to homo-coupling products. Indeed, in favourable circumstances the cross-coupling reactions can be conducted at near ambient temperatures and essentially to the exclusion of the homo-coupling process. As such a close to 1:1 ratio of coupling partners could often be employed, an important consideration in exploiting these processes in complex natural product synthesis and where such transformations are exploited at a late stage. Mechanistically-speaking, we believe these couplings proceed as suggested by Shimizu[9] (see the penultimate section for details) and wherein palladium[0] oxidatively adds to the α-iodo-enone or -enal and the resulting palladium[II] complex reacts with the *o*-cuprated nitroarene arising from the other coupling partner and so producing a palladated intermediate that undergoes reductive elimination to deliver the observed product {and, of course, regenerates the Pd[0] catalyst}. The nature of the copper used in these reactions has some impact on the efficiency of the process with freshly prepared, activated copper[12] being particularly effective though somewhat tedious to prepare. The simple expedient of adding some sand to the reaction mixture containing normal copper powder (copper bronze), and thus continuously generating a fresh metal surface through abrasion, is an operationally simple means of achieving often equivalent outcomes. Furthermore, adding small amounts of cuprous iodide to the starting reaction mixture can enhance the desired process[11b] although the precise origins of this benefit remain to be fully understood.

Highly functionalised indolic substructures are encountered in therapeutically significant alkaloids such as vincristine (Scheme 4) and we sought to establish methods for assembling these using our protocols.[13] In a representative process the α′-carbomethoxylated cycloheptenone **12** was subjected to a Pinhey arylation with the plumbated indole **13** and thereby affording compound **14** that was itself engaged in a Johnson-type α-iodination[14] reaction and so affording iodide **15**. The palladium-catalysed Ullmann cross-coupling of this last compound with *o*-iodonitrobenzene (**5**) gave product **16** that upon reductive cyclisation afforded the bis-indole **17** embodying key structural elements associated with the "Southern" hemisphere of vincristine.

Scheme 4. Synthetic sequence leading to bis-indole **17** resembling the Southern hemisphere of vincristine

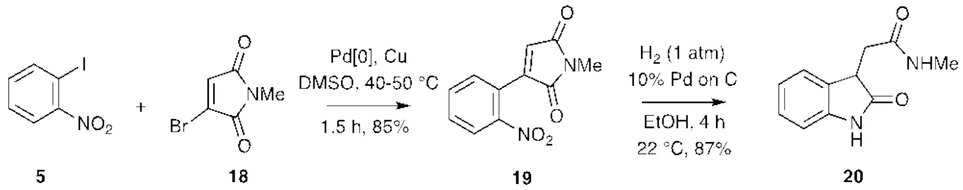


(b) Oxindoles

Oxindoles, which represent privileged structures in medicinal chemistry and motifs encountered in biologically active natural products,[15] are readily obtained using analogous processes and wherein an α-brominated α,β-unsaturated cycloimide, lactam or lactone is used as the coupling partner in a reaction with an *o*-halonitroarene and the product of this process then subject to reductive cyclisation.[15] The efficient cross-coupling of compounds **5** and **18** (Scheme 5) to produce the arylated *N*-

methylmaleimide **19** and its reductive cyclisation, under standard conditions, to give oxindole **20** is illustrative of these types of processes.

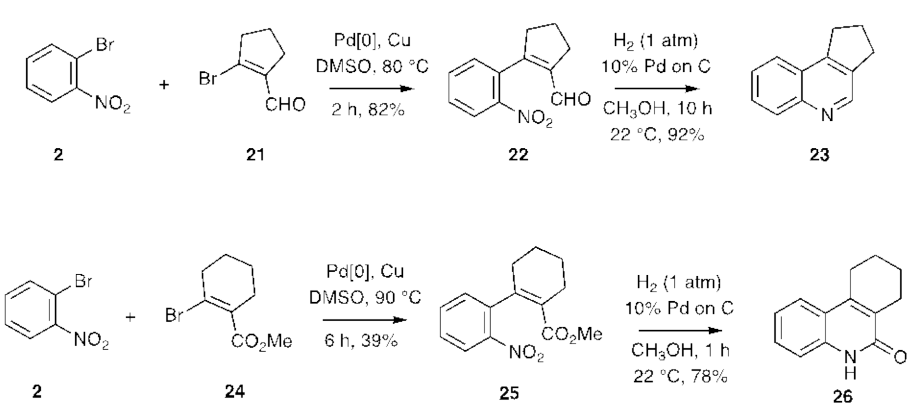
Scheme 5. Palladium-catalyzed Ullmann cross-coupling/reductive cyclization sequences leading to oxindole **20**



(c) Quinolines and Related Heterocycles

A further extension of our original processes, as shown in Scheme 3, has allowed for the formation of quinolones and related systems. In such cases (Scheme 6) the electrophiles employed are β-halo-enals, -enones or esters. So for example, the cross-coupling of arene **2** with aldehyde **21** affords the arylated enal **22** that upon reductive cyclisation produces the cyclopenta-annulated quinolone **23**. In a related but less efficient manner, cross-coupling of compounds **2** and **24** affords ester **25** that upon reductive cyclisation delivers the 2-quinolone **26**. By similar means a range of alternately substituted/annulated quinolones, phenanthridines and 6(5*H*)-phenanthridinones can be obtained. The capacity to generate electrophiles such as **21** directly from the corresponding ketone (in this case cyclopentenone) through a Vilsmeier-Haack haloformylation reaction is likely to enhance the utility of these processes.[16]

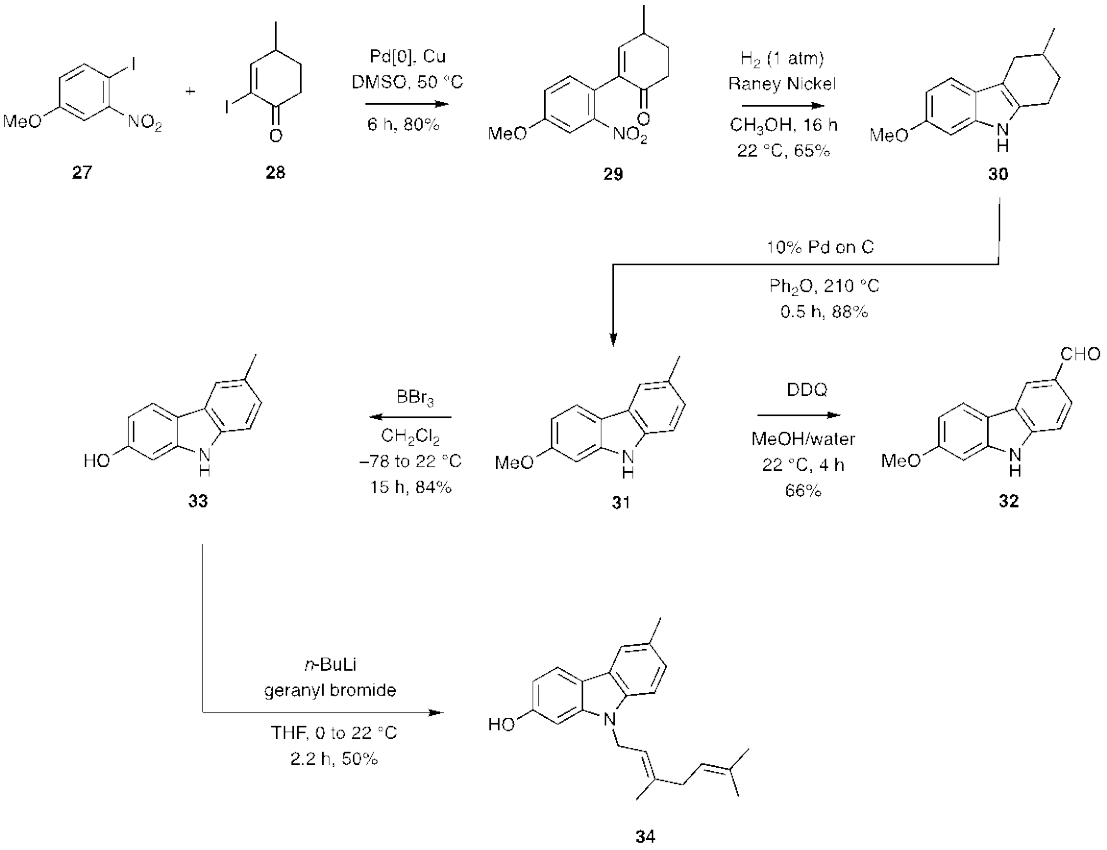
Scheme 6. Palladium-catalyzed Ullmann cross-coupling/reductive cyclization sequences leading to quinoline **23** and quinolone **26**



(d) Carbazoles

When α-iodocyclohex-2-en-1-ones are cross-coupled with halogenated nitroarenes such as **2** and **5** using the protocols detailed above and the product arylenones subjected to the reductive cyclisation then tetrahydrocarbazoles are obtained. Given that their fully aromatic counterparts (viz. carbazoles) are encountered in a wide range of biologically active natural products we sought to produce such heterocycles using variations of our earlier protocols. The routes to clauszoline K and karapinchamine A shown in Scheme 7 are illustrative of possibilities the title reaction offers in this regard.[17]

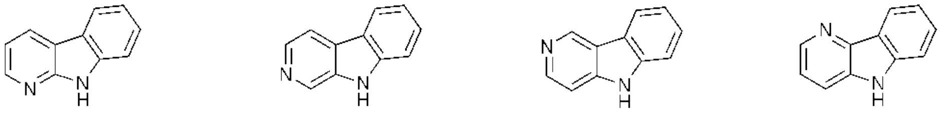
Scheme 7. Synthetic routes to carbazole natural products clauszoline K (**32**) and karapinchamine A (**34**)



Thus, reductive cross-coupling of electrophiles **27** and **28** under our now standard conditions afforded product **29** (80%) that upon reductive cyclisation using dihydrogen in the presence of Raney nickel afforded the tetrahydrocarbazole **30** (65%) and this could then be oxidized to its full aromatic counterpart, namely carbazole **31** (88%), on exposure to 10% Pd on C in diphenyl ether at 210 °C (various attempts to effect the conversion **29** → **31** in a direct manner, or at least in a one-pot-process, have been unsuccessful thus far). On exposure of compound **31** to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) it was oxidized, in 66% yield, to the natural product clauszoline K (**32**). On the other hand, treatment of compound **31** with BBr_3 effected cleavage of the associated ether residue and, thereby, formation of the anticipated phenolic product **33** (84%). Deprotonation of the latter compound with *n*-butyllithium and reaction of the ensuing anion with geranyl bromide resulted in alkylation at nitrogen and the formation of the carbazole-containing natural product karapinchamine A (**34**) that was obtained in 50% yield.

(e) *Carbolines*

There are four isomeric carbolines, namely the α-, β-, γ and δ-forms (Figure 1, **35**-**38**, respectively), and each of these frameworks is encountered in both natural products and pharmacologically active agents.[18] While various methods have been developed for their synthesis, a unified approach to them had remained elusive until our recent deployment of the title cross-coupling reaction for this purpose.[18]

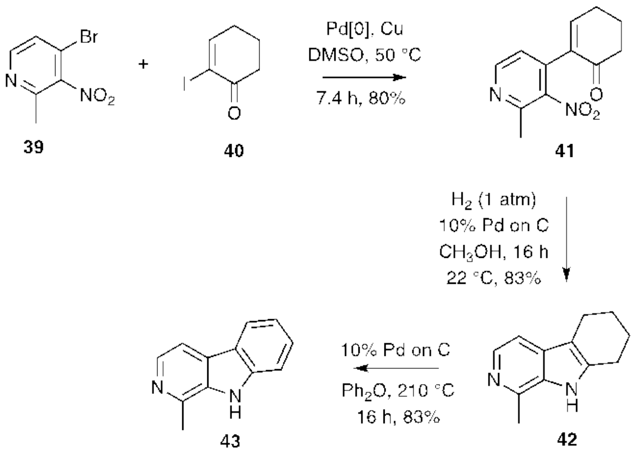


35 **36** **37** **38**

Figure 1. The four isomeric carbolines

An illustrative example of our approach is presented in Scheme 8 and starts with the palladium-catalyzed Ullmann cross-coupling of the bromonitropyridine **39** with the readily available α-iodinated cyclohexenone **40** and engaging the ensuing product in a reductive cyclisation reaction to give the tetrahydrocarboline **42** (80%) that is then dehydrogenated to give the fully aromatic compound **43** (83%) and representing the structure of the natural product harman.[18]

Scheme 8. Synthetic route to the carboline natural product harman (**43**)

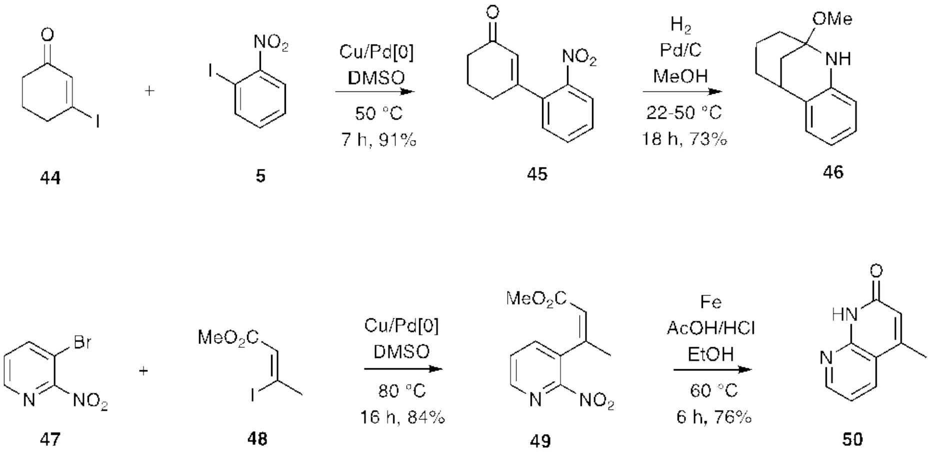


The challenge associated with deploying this type of approach to the carbolines is the need to construct the requisite, polysubstituted pyridine-based coupling partner. So, for example, the nitration reaction associated with the synthetic sequence leading to compound **39** also produced a regio-isomer and these could only be separated from one another by HPLC techniques.[18]

(f) *β-Haloenones and Related Compounds as Cross-Coupling Partners*

Recently, we have established that β-haloenones such as **44** couple particularly effectively with electrophiles including **5** and thus forming (Scheme 9) the anticipated cross-coupling product **45** (91%), a compound that on exposure to standard reductive cyclisation conditions using methanol as solvent affords the 3,4-benzomorphan **46** in 73% yield.[19] In a further illustration of the extensive utility of these types of processes, the coupling of β-iodinated crontonate **47** with the brominated pyridine **48** proceeded with retention of configuration and afforded the anticipated product **49** (84%). Reductive cyclization of this last compound using iron filings in an acidic medium then gave the 1,8-naphthyridin-2(1*H*)-one **50** (76%). Interestingly, *o*-iodobenzonitriles can be engaged in related couplings[19] although these are less efficient than those involving iodinated nitroarenes, presumably because of the weaker electron-withdrawing properties of the cyano group.

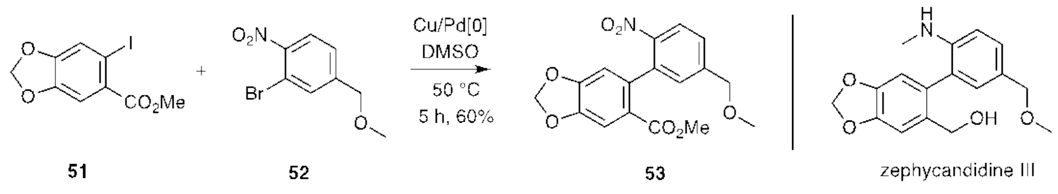
Scheme 9. Palladium-catalyzed Ullmann cross-coupling/reductive cyclization sequences leading to heterocycles **46** and **50**



(g) *Formation of Unsymmetrical Biaryls*

An obvious application of the title reaction is in the production of unsymmetrical biaryls. While we have yet to explore such processes in any comprehensive fashion, early indications have been very positive. So, as shown in Scheme 10 for example, the cross-coupling of aryl iodide **53** with bromide **54** under our by now standard conditions provided the desired biaryl **55** (60%).[20] This last compound was readily elaborated to the alkaloid zephycandidine III, a natural product reported to possess acetylcholinesterase (AChE) inhibitory properties[20] but which were not evident in the synthetically derived material despite the spectroscopic equivalence of each sample (viz. the natural and synthetic materials). More pertinent to the present discussion is that all attempts to prepare compound **55** and related systems using Suzuki-Miyaura cross-coupling reactions were unsuccessful.[20]

Scheme 10. The palladium-catalyzed Ullmann cross-coupling of halogenated arenes **51** and **52** leading to biaryl **53**, a precursor the alkaloid zephycandidine III



APPLICATION TO THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

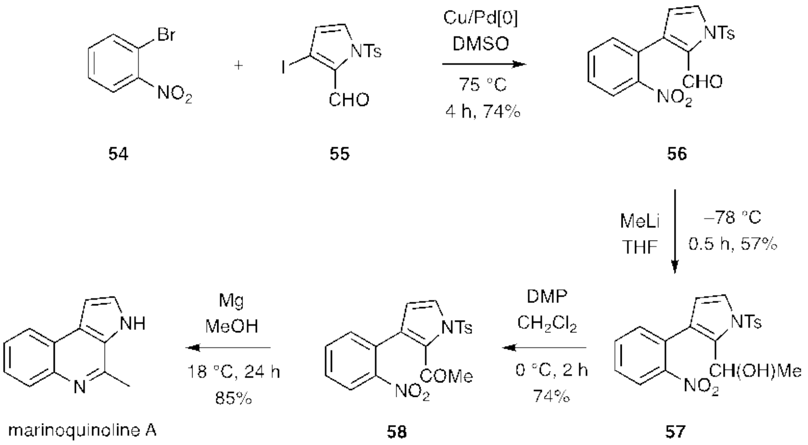
As our understanding of the palladium-catalyzed Ullmann cross-coupling reaction has developed we have been exploiting it on an increasingly frequent basis in developing syntheses of various natural products. Such is our confidence on the reliability of the process that we have often deployed it at the relatively advanced stages of a synthetic pathway and normally in conjunction reductive cyclization reactions that enable the conversion the cross-coupling products into various heterocyclic frameworks. Specific examples are given in the following sections.

(a) The Synthesis of Marinoquinoline A

As part of an ongoing interest in the cross-coupling chemistries of pyrroles[21] we were attracted to developing a synthesis of marinoquinoline A, an alkaloid isolated from a marine gliding bacterium that displays AChE inhibitory[22] as well as anti-malarial activities. The route that we ultimately established in obtaining this compound is shown in Scheme 11 and started with the palladium-catalysed Ullmann cross-coupling of *o*-bromonitrobenzene (**54**) with the iodinated pyrrole **55** and so affording the target **56** in 74% yield (significantly all our attempts to effect the Suzuki-Miyaura cross-coupling of compound **55** with *o*-nitrophenylboronic acid failed).[22] In a related vein, when *o*-iodonitrobenzene (**5**) was used as a coupling partner in this process then its homocoupling (to give 2,2′-dinitrobiphenyl) became the dominant process. Such outcomes highlight the capacity to facilitate cross-coupling processes by attenuating the reactivity of one substrate through changing the associated halogen.

The elaboration of coupling product **56** to the target alkaloid was straightforward and involved the initial addition of methyllithium to the associated aldehyde residue and oxidation of the resulting alcohol, **57**, to the corresponding methyl ketone **58** using the Dess-Martin periodinane (DMP). Reductive cyclization of this last compound to the target framework was effected using magnesium in methanol and this was accompanied by cleavage of the tosyl group and so affording marinoquinoline A in 85% yield.

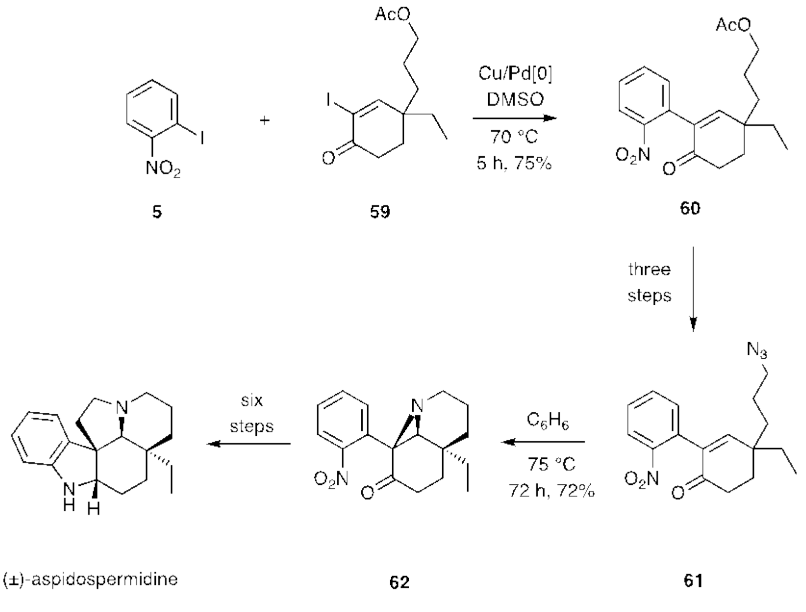
Scheme 11. A total synthesis of marinoquinoline A



(b) Total Syntheses of Aspidosperma Alkaloids Aspidospermidine, Limaspermidine and 1-Acetylaspidoalbidine and Approaches to Vindoline

In a more elaborate reaction sequence and as part of an ongoing campaign to develop a synthesis of the binary indole-indoline alkaloid vincristine (see Scheme 2), we first developed a route to the alkaloid aspidospermidine.[23] This entailed (Scheme 12), as one of two key steps, the cross-coupling of the α-iodinated cyclohexenone **59** with arene **5** and thus affording product **60** in 75% yield.

Scheme 12. A total synthesis of (±)-aspidospermidine

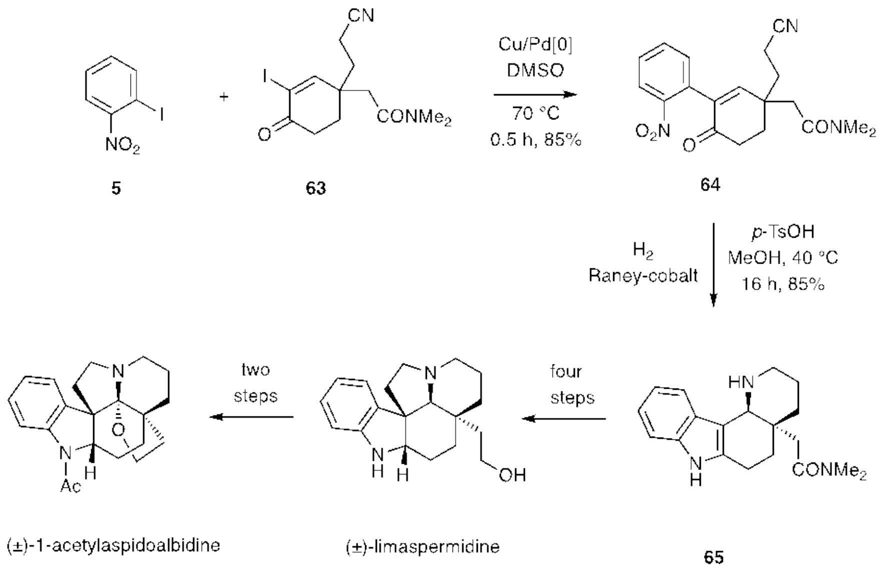


Compound **60** was readily elaborated to the azide **61** and on heating this it engaged in an intramolecular [3+2]-cycloaddition reaction then nitrogen extrusion to afford the aziridine **62** and so establishing the piperidine ring associated with the final product. Various straightforward steps, including a $TiCl_3$-mediated reductive cyclization reaction, were then deployed in elaborating compound **62** to aspidospermidine.

A related but more convergent protocol was employed in obtaining the alkaloid limaspermidine.[24] Thus, as shown in Scheme 13, compounds **5** and **63** were cross-coupled to give the α-arylated enone **64** (85%) and on subjecting this to reductive cyclization using hydrogen in the presence of Raney-cobalt then the indole-annulated and *cis*-ring fused octahydroquinoline **65** was obtained in 85% yield. This conversion involves the selective reduction of the nitro- and cyano-groups within substrate **64** while the enone moiety remains intact. As a result the associated ketone carbonyl engages in an intramolecular Schiff base condensation reaction with the aniline or *N*-hydroxyaniline arising from reduction of the nitro-group while the 1°-amine arising from the cyano-residue undergoes a hetero-Michael addition reaction and thus forming the indole and piperidine rings in a one-pot operation. The use of properly prepared Raney-cobalt[25] is critical to the success of this transformation because of the chemoselectivities it allows. If the more active Raney-nickel is used as the catalyst then reduction of the carbon-carbon double-bond of the enone residue also occurs with the result that piperidine ring formation does not take place.[24] Elaboration of compound **65** to (±)-limaspermidine was achieved over four additional steps, including several closely related to those employed in the conversion of compound **62** into (±)-apsidospermidine (Scheme 12).

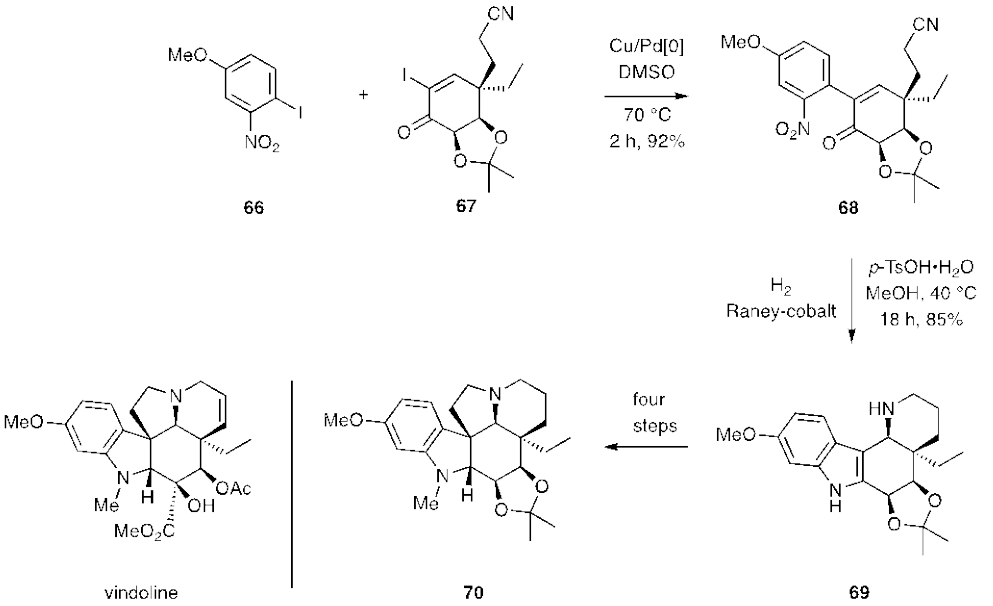
Two additional steps, including an oxidative cyclisation reaction employing mercuric acetate, were required to convert (±)-limaspermidine into (±)-1-acetylaspido-albidine.[24]

Scheme 13. Total syntheses of (±)-limaspermidine and (±)-1-acetylaspidoalbidine



The extension of the protocols defined above in an enantioselective approach to the alkaloid vindoline (and representing a crucial substructure of vincristine) is shown in Scheme 14.[26] Thus, cross-coupling of the iodinated nitroarene **66** with the homochiral α-iodinated cyclohexenone **67** (a compound obtained from an enzymatically derived *cis*-1,2-dihydrocatechol[27]) gave the anticipated product **68** in 85% yield. Reduction of this last compound using hydrogen in the presence of Raney-cobalt resulted in the formation of the tandem reductive cyclization product **69** (85%) embodying a *cis*-ring fused octahydroquinoline. Over a further four steps this could be elaborated to the hexacyclic compound **70** that embodies many of the features of vindoline and which we are seeking to convert into this alkaloid.

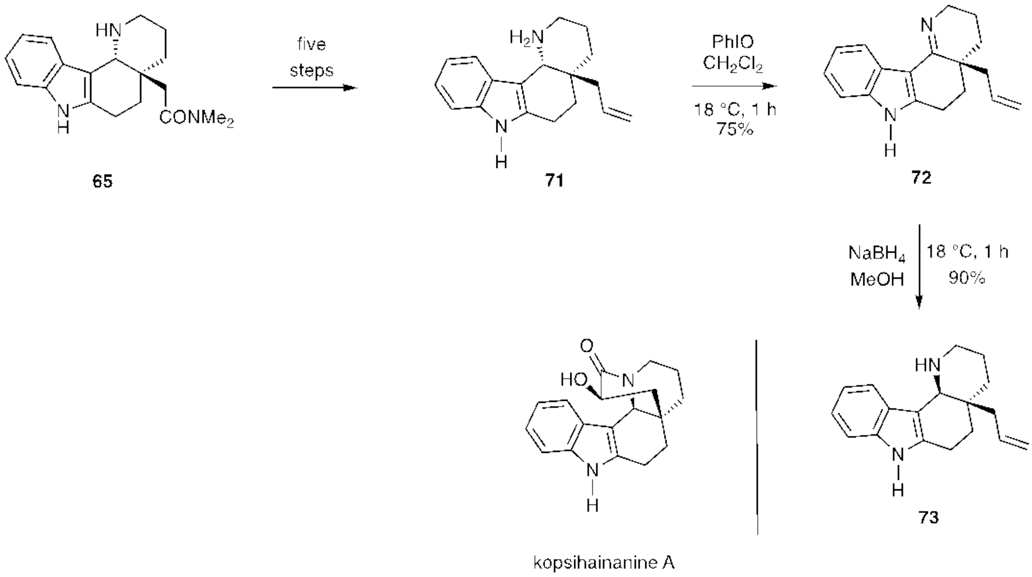
Scheme 14. The synthesis of compound **70**, an analogue of the alkaloid vindoline



(c) A Formal Total Synthesis of the Cage-like Alkaloid Kopsihainanine A

The tandem reductive cyclizations of the palladium-catalysed Ullmann cross-coupling products **64** and **68** are presumed to proceed under kinetic control and so affording *cis*-ring fused products. Given that *trans*-ring fused perhydroquinolines are encountered in a range of natural products we sought means for accessing such systems. Despite extensive investigations of the cyclization reactions, including examining a range of modifications to the conditions employed, the *cis*-ring fused products were invariably formed and on an entirely exclusive basis. As such we sought ways in which to effect epimerisation at the ring-junction carbon centre bearing the piperidine nitrogen. This turned out to be a straightforward process as illustrated in our formal total synthesis of the cage-shaped alkaloid kopsihainanine A (Scheme 15).[28] Thus, the reductive cyclization product **65** could be converted, over five steps, into the angularly allylated congener **71** and when this was exposed to iodosobenzene in dichloromethane at ambient temperatures this was oxidised to the corresponding imine **72** and upon reduction of this with sodium borohydride the epimeric octahydroquinoline **73** was obtained. Since this last compound has previously been converted into kopsihainanine A the illustrated synthetic sequence constitutes a formal total synthesis of the racemic modification of this alkaloid.

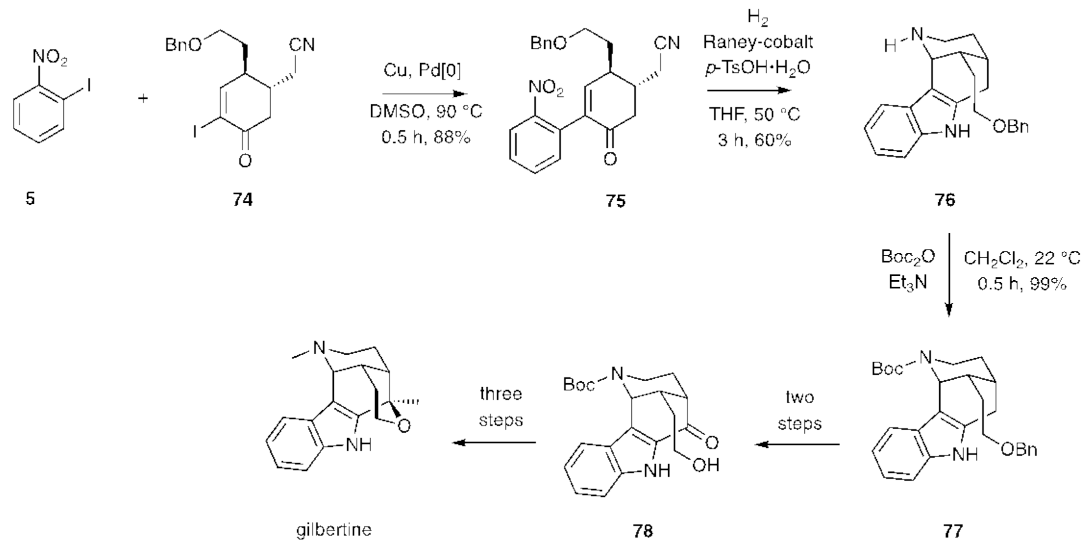
Scheme 15. The conversion of the *cis*-ring-fused octahydroquinoline **65** into its *trans*-configured congener **73**, an advanced precursor to the alkaloid kopsihainanine A



(e) Syntheses of the Uleine Alkaloids and Approaches to the Strychnos *Alkaloids*

Another cross-coupling/tandem reductive cyclization sequence is shown in Scheme 16 and has allowed for syntheses of various members of the uleine family of alkaloids.[29] Thus, the cross-coupling of compounds **5** and **74** under the usual conditions afforded the anticipated product **75** (88%) and the reductive cyclisation of this with hydrogen in the presence of Raney-cobalt afforded the tetracyclic product **76** (60%) as a result of the same type of tandem processes shown in Schemes 13 and 14. Selective Boc-protection of the piperidine nitrogen within compound **76** afforded carbamate **77** and this could be elaborated over two steps, including a pyridinium chlorochromate-mediated oxidation reaction to introduce a carbonyl moiety at the methylene adjacent to the indole ring, to the hydroxyketone **78**. Reaction of this last compound with methyllithium proceeded smoothly and the resulting tertiary alcohol engaged in a cyclo-etherification reaction on treatment with protic acid. Cleavage of the Boc-group also occurred under these conditions and the resulting 2°-amine was subject to reductive *N*-methylation and so affording (±)-gilbertine.[29a]

Scheme 16. A total synthesis of the alkaloid (±)-gilbertine



Using closely related protocols the somewhat simpler uleine alkaloids shown in Figure 2 could also be prepared in a stereoselective manner[29b] while the ABCDE-ring system of the *Strychnos* alkaloids proved accessible by similar means.[30]

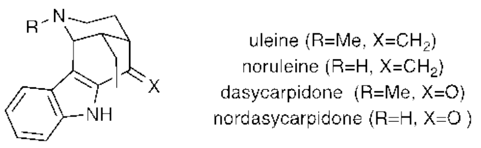
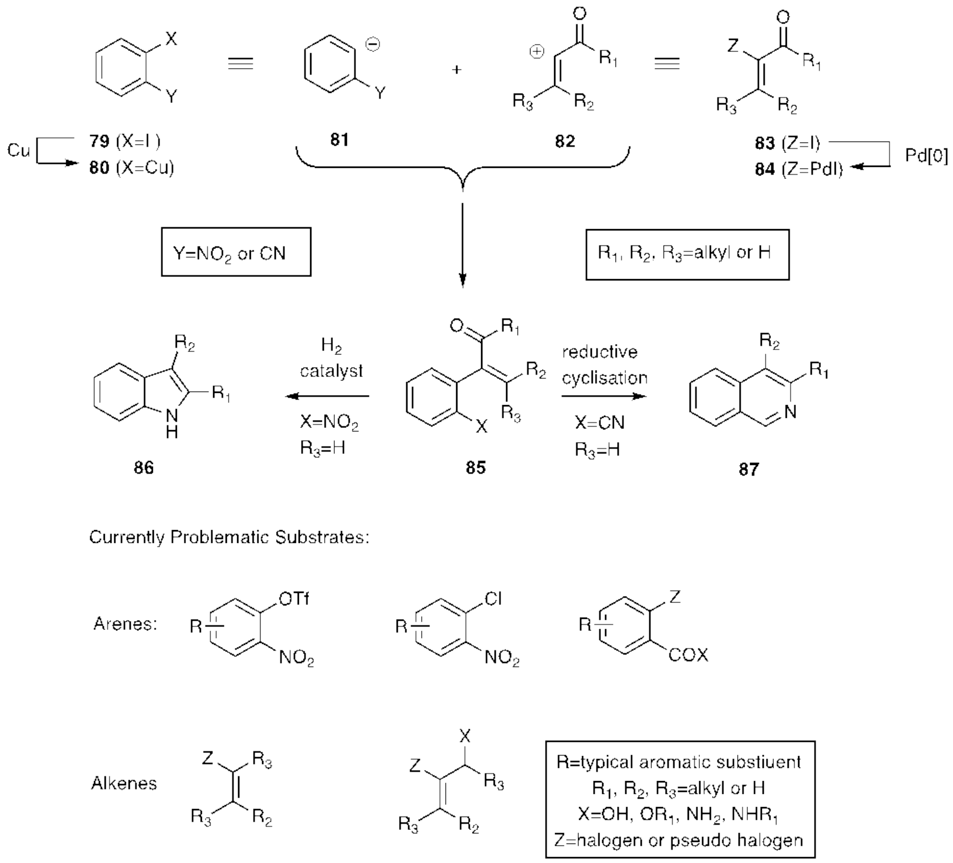


Figure 2. Structures of the simpler uleine alkaloids

A MECHANISTIC AND SYNTHETIC OVERVIEW

Our current thinking about the title process is dominated by the original mechanistic proposals of Shimizu.[9] Thus, as shown in Scheme 17, the aryl iodide **70** is presumed to react with the added cooper, through an oxidative addition/reductive deiodination process, to give the copper(I) aryl **80** and representing the aryl anion synthon **81**. This reacts with the aryl cation synthon **82** that is produced through oxidative addition of Pd[0] to the carbonyl-containing coupling partner **83** and thus affording intermediate **84**. The coupling event presumably involves nucleophilic substitution at the palladium of intermediate **84** by organometallic **80** and after reductive elimination product **85** is formed. Concurrently, of course, a Pd[0]-species is formed the re-enters the catalytic cycle. Presumably analogous pathways are involved in the potentially broadly applicable couplings shown in Schemes 9 and 10. Currently problematic substrates are also shown in Scheme 17.

Scheme 17. A mechanistic and synthetic analysis of a key example of the palladium-catalyzed Ullmann cross-coupling reaction and certain currently problematic substrates



While the majority of the title cross-coupling reactions we have studied thus far are of the general form shown immediately above, their utility is considerable because of the differing modes of reductive cyclization[12,31,32] that can be applied to the products **85**. So, as demonstrated in the multitude of settings presented above, when such products incorporate a nitro-group then cyclizations using dihydrogen in the presence various catalysts provide a range of indoles of the general form **86**. Using $TiCl_3$[13] or iron filings in acidic media[33] for the same purpose provides alternate cyclisation products while recent but as yet unpublished work has shown that certain nitrile-containing coupling products **85** (X = CN) can be converted into isoquinolines of the general form **87**.

It remains to be seen precisely how far palladium-catalyzed Ullmann cross-coupling reactions can be extended beyond those involving substrates incorporating the strongly electron-withdrawing nitro- and nitrile-groups. So, one of the challenges in this regard will be defining, if possible, how to engage more electron-rich coupling partners in analogous reactions.

FUTURE PROSPECTS

As is the case with other emergent XEC processes,[4] the title one is proving effective in a range of settings, most particularly when combined with reductive cyclization reactions that thereby afford heterocyclic compounds. Investigations of intramolecular variants of the title XECs are also likely to be profitable areas of research. Furthermore, our recent discovery[19] that *o*-halobenzonitriles are also capable of engaging in palladium-catalyzed Ulllmann cross-coupling reactions suggests that access to other types of heterocyclic systems, e.g. **87**, will become available through the reductive cyclisation of such products. Of course, the development of a more detailed mechanistic understanding of the palladium-catalyzed Ullmann cross-coupling reaction, including the role of additives such as cuprous iodide, will provide an important basis for further developments in the area.

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