Article

The Palladium-Catalysed Ullmann Cross-Coupling Reaction

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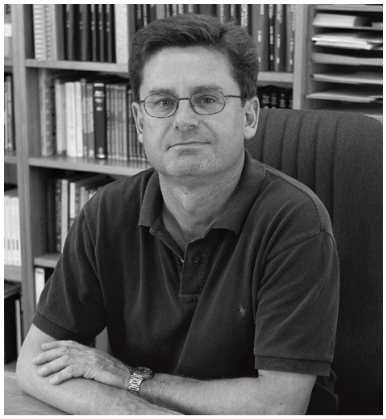
About the Senior Author



Martin Gerhardt Banwell was born in Lower Hutt on the 24th of November in 1954 of a German mother, Margot, and New Zealand father, John, who was a senior geophysicist principally involved with the exploration and development of geothermal resources in the central North Island (RSNZ Cooper medallist, 1964). The old DSIR Geophysics Division Building at Wairakei, now under GNS and refurbished, was named the Banwell Building after him on May 17 last.

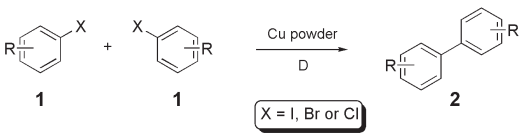
Martin attended schools in Taupo, Stokes Valley, and Wellington prior to secondary education at Scots College in Wellington, for a while in Mexico City (1967-68) and then at Wellington College (1969-72) before entering Victoria University and gaining his BSc and Honours degrees (1975 and 1976). He spent a couple of months at the Australian National University as a Vacation Scholar working under the supervision of Lew Mander.

Despite the excellent (and tempting) facilities of the ANU, Martin returned to Wellington and commenced his doctoral studies that were completed in 1979 under the supervision of Brian Halton. His postdoctoral was with Prof. Leo Paquette at Ohio State University. The sojourn at Ohio lasted about a year after which time Banwell accepted appointment as a Senior Teaching Fellow at the University of Adelaide. There he met his wife of some thirty years, Cathy Beckwith. In 1982 he took up a lectureship in organic chemistry at the University of Auckland, left for the University of Melbourne in 1986 and moved through the ranks becoming Associate Professor–Reader in 1993. He accepted appointment as a Senior Fellow at the Australian National University and settled in Canberra in 1994. He was appointed Professor in 1999.

In the year 2000, Martin was elected an Honorary Fellow of NZ's Royal Society and has continued to distinguish himself in his chosen field. He has held numerous fellowships and lectureships and continues to hold editorial board responsibilities for publications of high esteem. He has supervised in excess of 100 doctoral, masters and honours candidates and has employed 25 postdoctoral fellows; his publications number some 276 including some 15 book chapters and nine patents.

Introduction

Carbon-carbon (C–C) bond-forming processes are pivotal in synthetic organic chemistry because they allow for the assembly of more complex molecular systems from simpler ones.[1] Accordingly, an extraordinarily diverse range of methods for creating C–C bonds has been established over the last one hundred years or so and this provides the capacity to construct a remarkable array of chemical structures.[2] Amongst the most venerable of these methods is the Ullmann reaction that has a number of forms,[3] the first of which was reported in 1901[4] and involves the homo-coupling of an aryl halide **1** in the presence of an excess of copper *powder* to give the corresponding symmetrical biaryl **2** (Scheme 1).[5,6]



Scheme 1. The original Ullmann reaction.

Since its discovery, the extensive applications of the Ullmann reaction have resulted in a clear delineation of its scope and limitations.[4-6] Thus:

(i) Both halogenated aromatic and heteroaromatic compounds can participate in the reaction.

(ii) Iodinated aryls are more reactive than their brominated counterparts that are, in turn, much more reactive than the corresponding chlorinated systems. Fluorinated compounds do not react.

(iii) Intramolecular variants of the reaction have been exploited to create from 4- to 24-membered ring systems.

(iv) Substituents play an important part in determining the efficiency of the reaction with electron-withdrawing groups (especially $-NO_2$, $-CO_2R$ and –CHO) located adjacent to the halogen having particularly beneficial effects, while analogously located bulky ones have a deleterious effect. Electron-donating groups located anywhere on either ring generally diminish the yields of the coupling product.

(v) Substrates incorporating functional groups with active hydrogens, *e.g.* OH, CO_2H, NH_2, SO_2NH_2, can

participate in competing reactions including those involving C–O and C–N bond formation.[3]

(vi) While active forms of copper with freshly cleaned metal surfaces are normally used (and sonication often facilitates these reactions), various copper (I) salts (especially Cu_2O and Cu_2S) can also be employed although not normally with the same levels of efficiency.

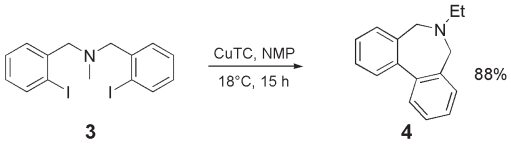
(vii) DMF is the most commonly employed solvent, although the use of pyridine, quinoline, nitrobenzene, DMSO and *p*-nitrotoluene has also been reported.

(viii) Temperatures in excess of 200 °C and long reaction times are often required.

(ix) In reactions leading to unsymmetrical biaryls, products arising from competing homo-coupling processes are often observed.

Various studies have been undertaken in attempts to understand the precise pathway by which the Ullmann coupling products are formed and both aryl radical- and aryl copper-mediated processes have been considered.[6] The latter is now the more widely accepted, not least because various aryl copper species can be isolated and have been shown to react with aryl halides so as to give biaryls.

In efforts to overcome the significant drawbacks associated with the Ullmann reaction, as recorded in entries (viii) and (ix) above, several modifications to it have been introduced. Perhaps the most notable of these involve the use of Ni[0] complexes (in place of copper metal),[6,7] preformed aryl copper species,[8] CuTC in NMP (Scheme 2)[9] (for abbreviations see above the list of references), or catalytic Pd[0].[10] While each of these modifications allows for the reaction to be carried out under much milder conditions, *i.e.* at lower temperatures, and/or the construction of highly substituted biaryls, they remain largely confined to the synthesis of symmetrical systems.[6]

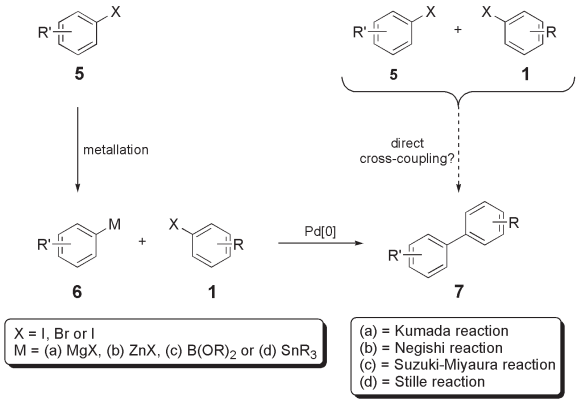


3 4

Scheme 2. A modified Ullmann reaction that proceeds at room temperature.

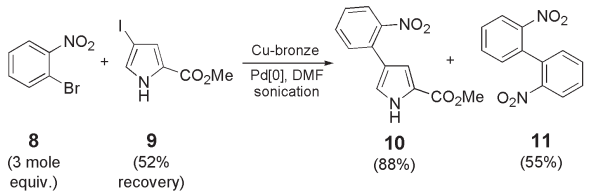
Pd[0]-Cross-Coupling Chemistries

The application of the Ullmann reaction to the synthesis of unsymmetrical biaryls and related products has received only modest attention. In part, this is because of the advent and demonstrated utility of various Pd[0]-catalysed cross-coupling processes, most notably the Kumada,[11] Negishi,[12] Suzuki–Miyaura,[13] and Stille[14] reactions (Scheme 3). However, when one considers that the metal- or metalloid-containing coupling partner **6** used in these processes is often generated from the corresponding halide **5**, the capacity to affect the direct cross-coupling of halogenated systems, *i.e.* **5** + **1**→ **7**, in an efficient manner would be advantageous. Shimizu and co-workers of the Kowa Company in Japan[15] appear to have been the first to employ the Ullmann-type version of this approach in a useful fashion (and as part of a program concerned with the development of new antiarrhythmic active agents). Remarkably, however, there have been few additional applications of this Pd[0]-catalysed Ullmann cross-coupling process since it was reported in 1993.



Scheme 3. Comparison of the Pd[0]-catalysed cross-coupling and direct cross-coupling approaches to unsymmetrical biaryls of the general form 7.

As part of a programme directed towards synthesis of the alkaloid rhazinilam,[16] we had occasion to carry out the cross-coupling of *o*-nitrobromobenzene (**8**) with the iodinated pyrrole **9** (Scheme 4) as a means of obtaining compound **10** which embodies key elements of the target natural product. In the event, and following the protocols defined by Shimizu,[15] but using ultrasonication to promote the reaction and DMF (rather than DMSO) as the solvent, we found that product **10** could be obtained in 88% yield based on recovered pyrrole **9**; 2,2'-dintrobiphenyl (**11**) (55%) represented a major by-product.



8 (3 mole equiv.) **9** (52% recovery) **10** (88%) **11** (55%)

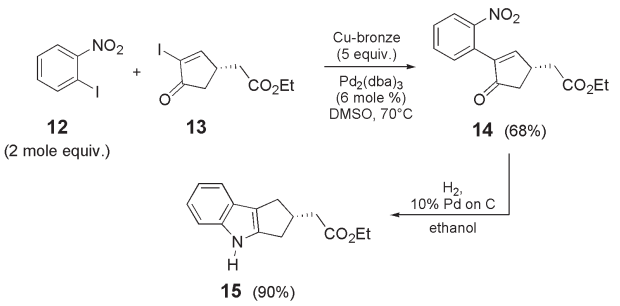
Scheme 4. The Pd[0]-catalysed Ullmann cross-coupling route to pyrrole 10.

Our view of the mechanism for the conversion **8** + **9** → **10** is based on the proposals of Shimizu.[15] Thus, we believe that substrate **8** reacts with copper metal to form a Cu(I) aryl species that engages in a substitution reaction, at palladium, with the product of oxidative addition of Pd[0] to pyrrole **9**. The ensuing arylpyrollopalladium(II) complex then undergoes 1,1-reductive elimination to give product **10** with concomitant regeneration of Pd[0].

The Pd[0]-Catalysed Ullmann Cross-Coupling Approach to Indoles

There were several aspects of the reaction shown in Scheme 4 that attracted our attention. In particular, it was operationally very simple, the coupling partners were readily available, the conversion **8** + **9** → **10** proceeded under mild conditions and the yield of the desired product was reasonably high despite the seeming electronic incompatibility of the coupling partners (pyrroles are very electron-rich aromatics). Encouraged by these features, we have since used the title reaction as a key step in the synthesis of a number of heterocyclic systems. So,

for example, we were able to show[17] (Scheme 5) that the Pd[0]-catalysed cross-coupling of the iodo-analogue **12** (of nitroarene **8**) with the α-iodocyclopentenone **13** gave the expected product **14** in 68% yield, and that upon subjecting the last compound to reaction with dihydrogen in the presence of 10% Pd on C the annulated indole **15** could be obtained in 90% yield.



Scheme 5. Example of the application of the Pd[0]-catalysed Ullmann cross-coupling reaction to the synthesis of indoles.

This type of procedure has proved sufficiently reliable that we have been able to use it in the synthesis of some relatively complex target natural products. So, for example, cross-coupling of the α-iodinated enone **16** with aryl iodide **12**[18] (Scheme 6) afforded compound **17** (75%) that was subjected to a simple sequence leading to the azide **18** (87%). Thermolysis of this last compound provided, *via* an intramolecular 1,3-dipolar cycloaddition reaction and subsequent loss of dinitrogen, the ring-fused aziridine **19** (72%) that underwent cleavage of the three-membered ring on treatment with HCl, thus giving the α-chlorocyclohexanone **20**. Reductive dechlorination and cyclization of this last compound could be accomplished using $TiCl_3$, thereby affording the tetracyclic species **21** in 46% overall yield from precursor **19**. Subjection of compound **21** to a ring-annulation protocol developed by Heathcock[19] involved its initial treatment with α-chloroacetyl chloride. The resulting amide was then engaged in a Finkelstein reaction using sodium iodide in acetone and this gave the corresponding α-iodoacetamide **22** that cyclised upon exposure to silver triflate thereby affording the lactam/indolenine **23** (35% from **21**). Finally, treatment of compound **23** with lithium aluminium hydride gave the racemic modification the target natural product aspidospermidine **24** in 77% yield.

Since compound **24** bears some resemblance to the eastern hemisphere of the clinically important binary indole-indoline alkaloid vinblastine (see Fig. 1), we are currently attempting to adapt this chemistry to its synthesis.[20]

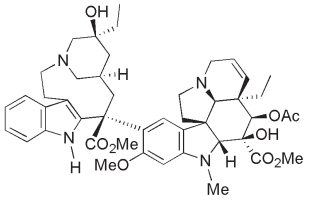
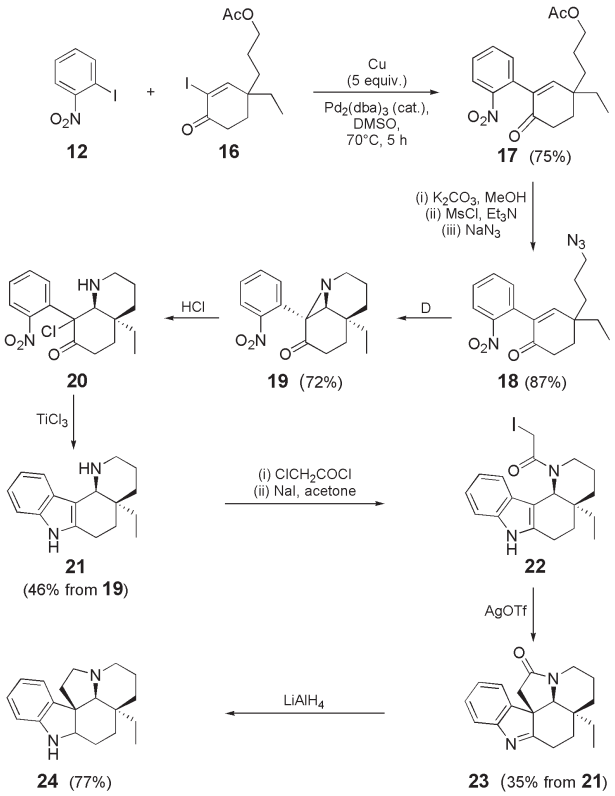


Fig. 1. The clinically significant binary indole-indoline alkaloid vinblastine.

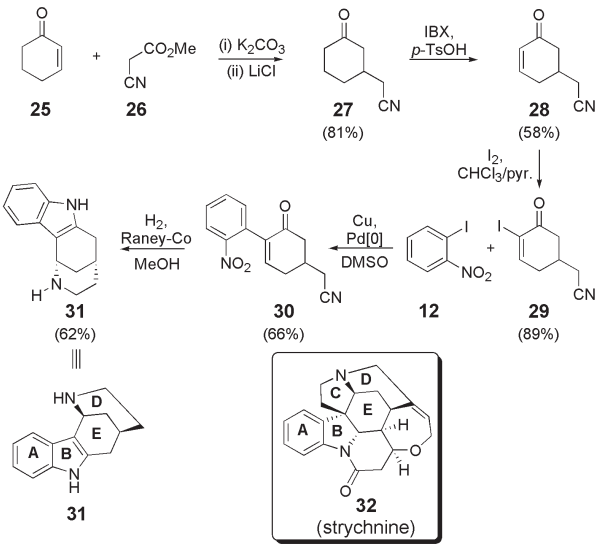
In related and ongoing studies, we are also using this indole-forming process to assemble a key substructure associated with the alkaloid strychnine (**32**) (Scheme 7), a structurally fascinating compound that was an important



Scheme 6. Application of the Pd[0]-catalysed Ullmann cross-coupling reaction route to the synthesis of the alkaloid aspidospermidine.

part of the doctor's medicine chest in Victorian times, but which is now more well known for its toxic effects.[21] The reaction sequence starts[22] with the conjugate addition of the methyl α-cyanoacetate (**26**) to cyclohex-2-en-1-one (**25**) and this leads, after ester hydrolysis and decarboxylation, to nitrile **27** in 81% yield. Regioselective dehydrogenation of this last compound could be achieved using IBX in the presence of *p*-TsOH and the enone **28** (58%) so-formed was subjected to a Johnson iodination reaction, thereby affording the corresponding α-iodoenone **29** in 89% yield. Compound **29** served as the substrate for the pivotal Pd[0]-catalysed cross-coupling reaction with aryl iodide **12** and the α-arylenone **30** was thereby obtained in 66% yield. Treatment of this last compound with dihydrogen in the presence of Raney-cobalt then afforded the tetracyclic compound **31** in 62% yield. While the sequence of events associated with the conversion **30** → **31** has not been firmly established, it is presumed that the first step involves reduction of the nitrile residue in compound **30** to the corresponding amine, which then adds in an intramolecular hetero-Michael addition reaction to the tethered enone. Reduction of the nitro group then follows and the aniline thus formed engages in an intramolecular Schiff-base condensation reaction to give an indolenine that then undergoes a prototropic shift, thus generating the observed indole **31**. A comparison of the structure of **31** with that of strychnine (**32**) reveals that the former embodies the ABDE-substructure of the latter.

The prospects for exploiting this reaction sequence so as to prepare compounds more closely related to strychnine seem reasonable. For example, the Heathcock annulation process[19] that was successfully employed in the closing stages of our synthesis of aspidospermidine (see Scheme 6) could be used to annulate the C-ring of strychnine to



Scheme 7. Application of the Pd[0]-catalysed Ullmann cross-coupling reaction route to the synthesis of ABDE-substructure associated with the alkaloid strychnine.

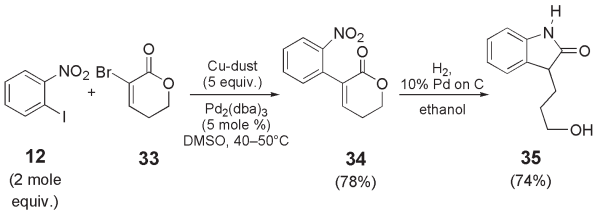
compound **31**. Furthermore, the initial conjugate addition reaction **25** + **26** → **27** likely could be carried out in an asymmetric fashion[23] and so allow for the construction of compounds such as **31** in enantiomerically enriched form. These sorts of possibilities are currently being pursued in our laboratories, although the challenges are great and all the more so because of the extraordinarily concise and elegant syntheses of natural product **32** that Reissig[24] and Vanderwal[25] have reported recently.

Improving the Cross-Coupling Reaction

As we have endeavored to exploit the Pd[0]-catalysed Ullmann cross-coupling reaction in increasingly complex situations, the deficiencies of our originally defined protocols[16,17] have become more apparent. In particular, the relatively high temperatures (≥ 70 °C) required, the continued formation of homo-coupling products, *e.g.* compound **11**, Scheme 4, and the relatively modest yields of the desired products continue to hamper our work. Accordingly, we have recently paid some attention to trying to improve the basic reaction. In that connection, we have found[26] that by using either freshly cleaned dendritic copper or freshly prepared copper nanoparticles we can run the cross-coupling reactions at close to room temperature, thereby reducing the formation of homo-coupling products to negligible levels. As a result, yields of the desired product in excess of 90% can now be realised. Interestingly, we have observed that DMSO is uniquely effective as the solvent for these reactions – DMF and NMP, solvents that have frequently been used in the more conventional Ullmann reactions, give poor yields of the desired cross-coupling products.

The Pd[0]-Catalysed Ullmann Cross-Coupling Approach to Oxindoles, Quinolines, 2-Quinolones and Phenanthridines

Given the utility of the indole-forming sequences shown above, we have sought to extend such cross-coupling/reductive cyclization protocols to the preparation of other heterocyclic systems of biological significance. The oxindole or indolone motif represents a privileged structure in medicinal chemistry and is embodied in a number of intriguing natural products. Consequently, we sought to prepare it using the title reaction. A representative example of process we have developed as a result is shown in Scheme 8.[27] Thus, cross-coupling of substrate **12** with two molar equivalents of bromolactone **33** using freshly activated copper *dust* (3 micron dendritic material, the surface of which had been cleaned with EDTA under ultrasonication) in the presence of 5 mole % $Pd_2(dba)_3$ gave the desired product **34** in 78% yield. Exposure of this to dihydrogen in the presence of 10% Pd on C then afforded the mono-alkylated oxindole **35** in 74% yield. This second step of the reaction sequence necessarily involves reduction of the double bond within the lactone ring of the substrate as well as the nitro group. Presumably, it is the resulting amino-lactone that undergoes an intramolecular *trans*-acylation reaction resulting in cleavage of the lactone ring and formation of the lactam ring associated with the observed oxindole.



Scheme 8. Example of the application of the Pd[0]-catalysed Ullmann cross-coupling reaction to the synthesis of mono-alkylated oxindoles.

Extensions of such cross-coupling/reductive cyclization protocols to the preparation of quinolines proved straightforward, as highlighted by the reaction sequence shown in Scheme 9.[28] Thus, the ring-fused β-bromo-α,β-unsaturated aldehyde **37** (readily prepared from α-tetralone **36** in good yield[29]) engages in cross-coupling with the bromoarene **38** and the cinnamaldehyde **39** so-formed (in 89% yield) readily undergoes reductive cyclization under the usual conditions, thus affording the ring-fused quinoline **40** in 91% yield. We have used this same sort of reaction sequence to establish a two-step synthesis from 6-bromopiperonal and *o*-nitrobromobenzene **8** of the phenanthridine-containing and biologically active natural product trisphaeridine (Fig. 2).[30] Given the now ready availability of the relevant substrates,[31] non-ring-fused quinolines are also accessible using the same type of chemistry. Furthermore, the synthesis of 2-quinolones is readily achieved[28] by engaging β-bromo-α,β-unsaturated esters in the same type of reaction sequence as shown in Scheme 9.

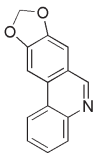
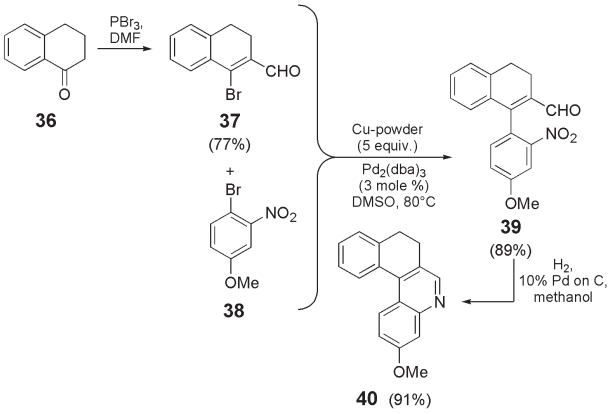


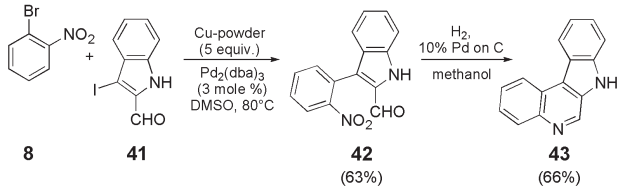
Fig. 2. The phenanthridine-containing natural product trisphaeridine.

A variation on the above mentioned reaction sequence is shown in Scheme 10. It involves cross-coupling of the readily available 3-iodoindole **41** with *o*-nitrobromobenzene (**8**) to give the 3-arylindole **42** (63%) that undergoes the usual reductive cyclization reaction on exposure



Scheme 9. Example of the application of the Pd[0]-catalysed Ullmann cross-coupling reaction to the synthesis of a fused quinoline.

to dihydrogen in the presence of Pd on C to afford 7*H*-indolo[2,3-*c*]quinoline **43** (66%), a scaffold that has been sought after for the development of new antiplasmodial drugs.[32]



Scheme 10. Application of the Pd[0]-catalysed Ullmann cross-coupling reaction to the synthesis of 7H-indolo[2,3-c]quinoline (43), a platform for the development of new antiplasmodial drugs.

Future Prospects

The Pd[0]-catalysed Ullmann cross-coupling reactions described above should continue to provide an effective means for the ready preparation of a useful range of heterocyclic compounds of medicinal and structural interest. Indeed, in an extension of the chemistry outlined in Scheme 10, we are now endeavouring to prepare members of the recently described marinoquinoline class of natural product (Fig. 3), some of which show useful levels of activity against *Palsmodium falciparum* K1 (IC_{50} values between 1.7 and 15 μM).[33]

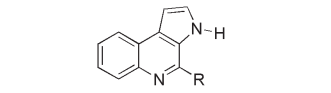
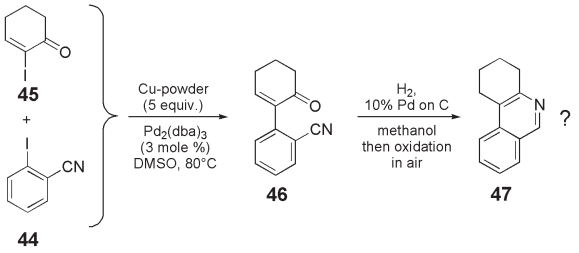


Fig. 3. The structures of some recently isolated marinoquinolines.

Another area of interest concerns the identification of cross-coupling partners that can be used in place of the *o*-nitrohaloarenes featured in all of the studies described above. In keeping with observations made regarding the original Ullmann reaction (see Introduction), it seems clear that a strongly electron-withdrawing and *ortho*-related substituent needs to be associated with one of the coupling partners participating in the Pd[0]-catalysed process. Some preliminary experiments (Scheme 11) suggest that *o*-iodobenzonitrile **44**, for example, does participate in the same types of coupling processes. Thus, this compound reacts with α-iodocyclohex-2-en-1-one **45** to give α-arylcyclohex-2-en-1-one **46**. This, in turn, undergoes reductive cyclization to give, after aerial oxidation of what is presumed to be an intermediate dihydroisoquinoline, the annulated isoquinoline **47**.[26]



Scheme 11. Application of the Pd[0]-catalysed Ullmann cross-coupling reaction to the synthesis of isoquinolines?

A third aspect of the Pd[0]-catalysed Ullmann cross-coupling reaction that continues to fascinate us concerns the α-arylcyclohex-2-en-1-ones such as **18** and **30** formed in these processes. In particular, the double bond embedded within such cross-coupling products has – by virtue of the attachment of the strongly electron-withdrawing carbonyl and *o*-nitrophenyl groups at the same end of it – some potentially very useful electrophilic properties that should be capable of exploitation in various settings.

On the basis of the foregoing, we see the title reaction as providing a very effective method for the construction of a wide-range of medicinally relevant compounds, most particularly heterocyclic ones. As such, the reaction warrants further attention and development.

Acknowledgements

We thank the Institute of Advanced Studies and the Australian Research Council for their generous support of this research. MTJ and TAR are the grateful recipients of Australian Postgraduate Awards that have supported them during their PhD studies.

Abbreviations Used

CuTC	copper(I) thiophene-2-carboxylate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
IBX	2-iodoxybenzoic acid
MsCl	methanesulfonyl chloride
NMP	*N*-methyl-2-pyrrolidinone
Raney-Co	Raney cobalt
p-TsOH	*p*-toluenesulfonic acid

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