Synthesis of substituted isoquinolines utilizing palladium-catalyzed α-arylation of ketones

Timothy J. Donohoe[1,2], Ben S. Pilgrim[1], Geraint R. Jones, and José A. Bassuto

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, United Kingdom

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The utilization of sequential palladium-catalyzed α-arylation and cyclization reactions provides a general approach to an array of isoquinolines and their corresponding *N*-oxides. This methodology allows the convergent combination of readily available precursors in a regioselective manner and in excellent overall yields. This powerful route to polysubstituted isoquinolines, which is not limited to electron rich moieties, also allows rapid access to analogues of biologically active compounds.

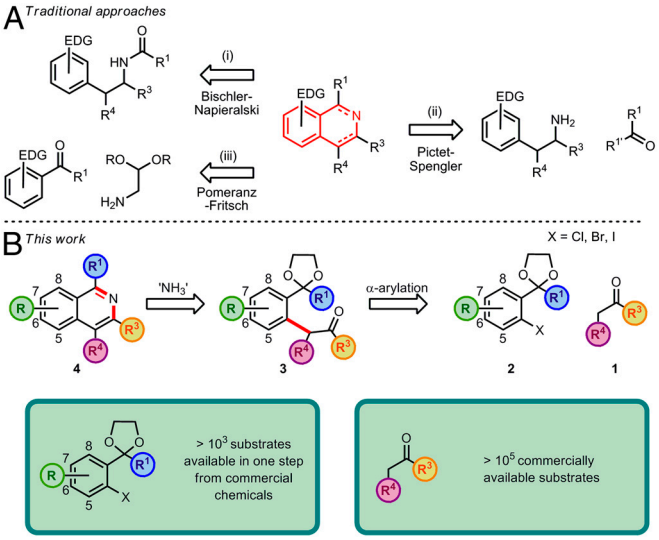
alpha arylation | heterocycle | isoquinoline-*N*-oxide | one-pot

The isoquinoline motif and its derivatives form the cores of numerous natural products (1, 2), are the central components of a number of pharmaceutical agents (3–5), and can provide the scaffold for chiral ligands (6, 7) and valuable organic materials (8). However, traditional isoquinoline syntheses such as the Bischler-Napieralski (9, 10), Pictet-Spengler (11, 12), and Pomeranz-Fritsch reactions (13–15) all centre around the lynchpin of electrophilic aromatic substitution and are thus often limited to electron-rich carbocycles (Scheme 1*A*). It is also imperative to develop routes to highly-substituted isoquinolines to fully explore this chemical space, for example, for potential pharmaceutical targets. While recent synthetic efforts have greatly expanded the diversity of isoquinoline motifs available (16–29), new routes to isoquinolines are still highly desirable, particularly ones with the ability to directly access the isoquinoline moiety in a range of oxidation levels and which do not require highly-specialized starting materials.

Originally reported by Palucki and Buchwald (30), Hamann and Hartwig (31), and Miura and coworkers (32), the palladium-catalyzed α-arylation of enolates has recently emerged as a powerful new reaction in synthetic organic chemistry (33–35). Key to its success has been the design of appropriate ligands for palladium that have precisely engineered steric and electronic properties to enable the various steps in the catalytic cycle to proceed with maximum efficiency (36–39). The reaction's utility has also been greatly enhanced by the development of robust preformed palladium catalysts. Properties such as air stability and very high reactivity in a range of systems have greatly expanded the potential uses of these catalysts (40–43). However, the α-arylation reaction has seen limited use in the de novo construction of aromatic compounds (44–51) and is still greatly underused in this regard, especially because the bond forming abilities provided by this powerful reaction can greatly simplify the design of routes to heavily-substituted aromatic compounds. Hence, we decided to explore the scope of this new catalytic method in the synthesis of important heteroaromatic ring systems, beginning our investigations with the isoquinoline nucleus.

Results

In our disconnection approach we envisaged that key *pseudo*-1,5-dicarbonyl intermediates **3** could be accessed via the palladium-catalyzed α-arylation of ketones **1** with aryl halides **2** possessing a protected aldehyde or ketone in the *ortho*-position (52). Subsequent treatment of these intermediates **3** with an acidic ammonium source would lead to concomitant acetal deprotection and aromatization to the corresponding isoquinolines **4**. The attractiveness of this route stemmed from both its potential for regioselective installation of substituents at all positions on the isoquinoline nucleus and the fact that the coupling precursors were either commercially available or could be synthesized in a short sequence (Scheme 1*B*).



Scheme 1. Retrosynthetic Strategy.

Initial optimization of the α-arylation conditions for the reaction of ketone **1a** with bromide **2a** (two commercially available substrates) showed that a catalyst loading of 2.0 mol% (D^tBPF)$PdCl_2$ or $PdCl_2(Amphos)_2$ was sufficient to obtain high yields of the arylated product **3a** (Entries 3, 10, Table 1). Yields could be further increased when 5.0 mol% of catalyst and 200 mol % of ketone were used. Furthermore, the reaction was shown to proceed well with a decreased catalyst loading of 0.5 mol% (Entries 1, 2). As expected, iodide **2b** showed comparable reactivity to bromide **2a** under these conditions. Chloride **2c** could also be employed as the aryl partner in the coupling reaction (Entry 9); this was a significant development, as the requisite aryl chlorides are both considerably cheaper than the corresponding aryl bromides and are commercially available in a greater variety of substitution patterns. As the aryl bromides presented the best compromise of reactivity and availability, these were used for further exemplification of the methodology.

For the final aromatization step, solutions of a variety of ammonium salts in $EtOH/H_2O$ were screened. The solutions

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[1]T.J.D. and B.S.P. contributed equally to this work.

[2]To whom correspondence should be addressed. E-mail: timothy.donohoe@chem.ox.ac.uk.

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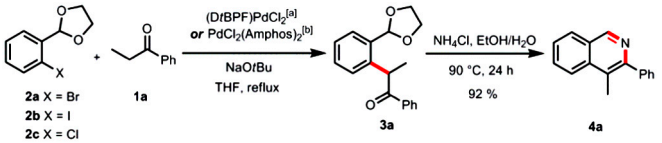
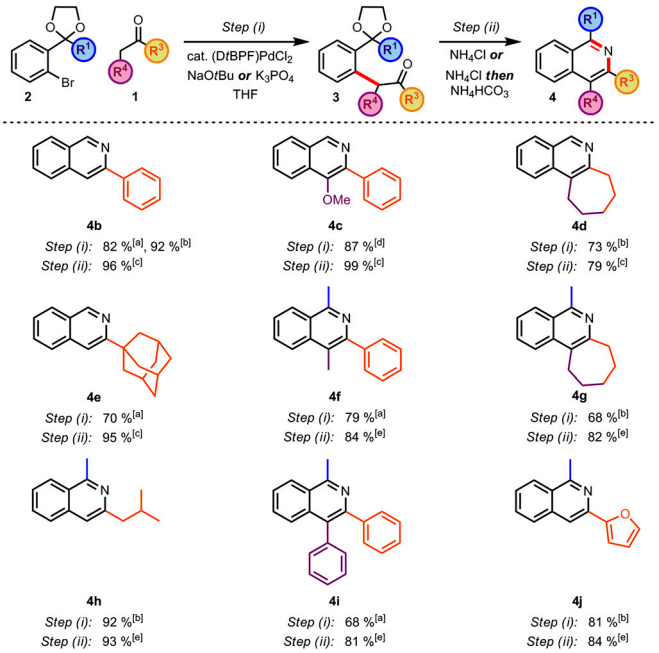
Table 1. Optimization of the arylation conditions



Entry	X	Cat. loading [mol%]	Ketone [mol%]	Time [h]	Yield [%]
1	Br	0.5[a]	120	18	71
2	Br	0.5[a]	200	18	74
3	**Br**	**2.0[a]**	**120**	**18**	**82**
4	Br	2.0[a]	200	18	83
5	Br	5.0[a]	200	18	89
6	I	2.0[a]	120	18	79
7	Cl	5.0[a]	200	18	30
8	Cl	5.0[b]	200	18	45
9	**Cl**	**5.0[b] × 2**	**200**	**96**	**74**
10	Br	2.0[b]	120	18	82

needed to be of a certain acidity (approximately pH 5) to effect acetal hydrolysis at reasonable rates. It was found that heating intermediate **3a** in a solution of ammonium chloride (1 M in 3:1 EtOH/H_2O) mediated deprotection and cyclization in excellent yield.

To examine the scope of this reaction, the substituents that could be tolerated during the arylation step and would be positioned on the heterocyclic ring of the resulting isoquinoline were investigated (Scheme 2). A range of ketones were arylated in good to excellent yields (68–92%) and a wide array of substituents was tolerated at the position to become C(3) on the isoquinoline; intermediates **3a,b,c,f,i** with aryl, **3j** with heteroaryl, and **3d,e,g,h** with alkyl substitution. The regioselectivity of the arylation reaction enabled the regio-defined construction of the intermediate **3h** where there was a choice of enolizable protons on the ketone. It was also pleasing to note that intermediate **3e**, bearing a bulky quaternary substituent, could be synthesized.



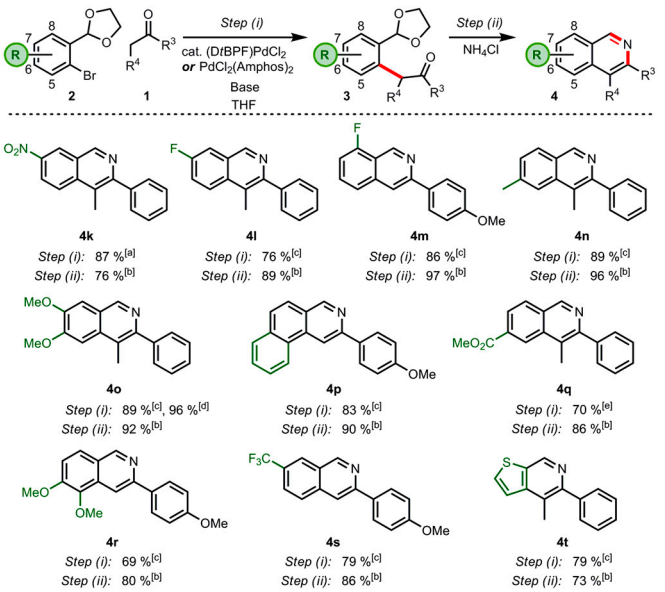
[a] (DtBPF)$PdCl_2$ (2.0 mol%), NaO*t*Bu (250 mol%), Ketone (120 mol%), THF, reflux, 18 h; [b] (DtBPF)$PdCl_2$ (5.0 mol%), NaO*t*Bu (250 mol%), Ketone (200 mol%), THF, reflux, 18 h; [c] NH_4Cl (1 M in 3:1 EtOH/H_2O), 90 °C, 24 h; [d] (DtBPF)$PdCl_2$ (5.0 mol%), K_3PO_4 (250 mol%), Ketone (120 mol%), THF, reflux, 18 h; [e] NH_4Cl (1 M in 3:1 EtOH/H_2O), 90 °C, 18 h then NH_4HCO_3 (2 M in H_2O), 90 °C, 24 h.

Scheme 2. Exploring the scope of substituents R^1, R^3, and R^4.

Even greater flexibility was achievable at the position to become C(4) on the isoquinoline and arylation reactions to produce intermediates **3a,d,f,g** with alkyl, **3i** with aryl, and **3c** with heteroatom substitution proceeded efficiently. In the bromide coupling partner, both protected aldehydes and ketones were tolerated in the arylation reaction, enabling the construction of intermediates **3a–e** where $R^1 = H$ and **3f–j** where $R^1 = Me$.

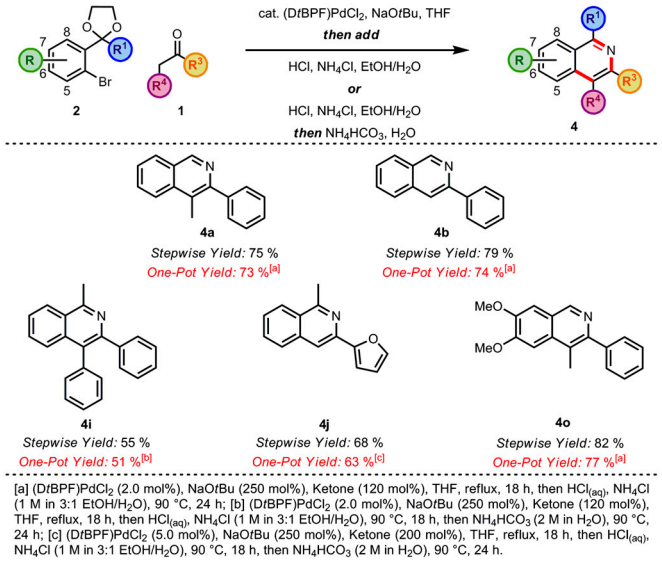
The subsequent deprotection and cyclization to produce isoquinolines **4a–e** where $R^1 = Me$ also proceeded in excellent yields (79–99%). For intermediates **3f–j** where $R^1 = Me$, we noted that while deprotection was facile under the ammonium chloride conditions, the ensuing cyclization was sluggish. It was found, however, that following complete acetal hydrolysis, subsequent basification (to approximately pH 9) with ammonium bicarbonate solution (2 M in H_2O) promoted cyclization of these substrates. Under these conditions, cyclization proceeded in good to excellent yields (81–93%) to produce isoquinolines **4f–j**.

Our investigation of the scope of substitution possible on the carbocyclic ring involved varying the substituents on the benzene ring of the aryl bromide partner (when the required aryl bromide acetal is not itself a commercially available compound, it can generally be prepared in one step and at >90% yield) (Scheme 3). The synthesis of isoquinolines with a wide variety of substitution was possible, covering all four positions, and including **4k,l,m,o,r** with heteroatom, **4n** with alkyl, **4p** with aryl, and **4q,s** with functionalized carbon substituents. The arylations proceeded in good to excellent yields (69–96%), as did the cyclizations (73–97%). Of particular note, isoquinolines **4p,r** bearing a group at the C(5) position could be synthesized from sterically-hindered bromides. The use of milder bases in the arylation step allowed sensitive functionality such as a nitro group and a methyl ester to be carried through the synthesis (isoquinolines **4k,q**). This approach could be used to synthesize isoquinolines **4k,l,m,q,s** with electron poor and isoquinolines **4n,o,p,r** with electron rich carbocyclic rings, confirming the wide applicability of this synthetic strategy—flexibility that is not offered by many conventional approaches. The benzene ring could also be replaced with a heteroarene to synthesize thieno-pyridine **4t**, illustrating our ability to construct multiple heteroatom-containing ring systems, which are attractive pharmaceutical targets.



[a] $PdCl_2(Amphos)_2$ (5.0 mol%), Cs_2CO_3 (250 mol%), Ketone (200 mol%), THF, reflux, 18 h. [b] NH_4Cl (1 M in 3:1 EtOH/H_2O), 90 °C, 24 h; [c] (DtBPF)$PdCl_2$ (2.0 mol%), NaO*t*Bu (250 mol%), Ketone (120 mol%), THF, reflux, 18 h; [d] (DtBPF)$PdCl_2$ (5.0 mol%), NaO*t*Bu (250 mol%), Ketone (200 mol%), THF, reflux, 18 h; [e] $PdCl_2(Amphos)_2$ (5.0 mol%), K_3PO_4 (250 mol%), Ketone (120 mol%), THF, reflux, 18 h.

Scheme 3. Exploring the scope of substituents R^5, R^6, R^7, and R^8.

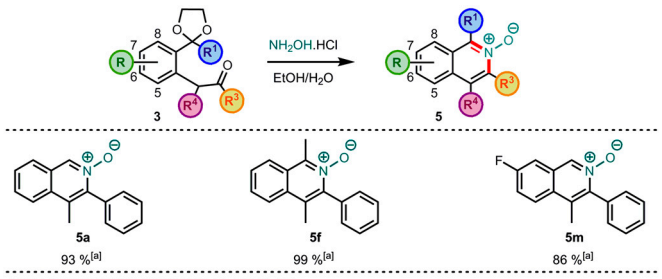


[a] (DtBPF)PdCl$_2$ (2.0 mol%), NaO*t*Bu (250 mol%), Ketone (120 mol%), THF, reflux, 18 h, then HCl$_{(aq)}$, NH$_4$Cl (1 M in 3:1 EtOH/H$_2$O), 90 °C, 24 h; [b] (DtBPF)PdCl$_2$ (2.0 mol%), NaO*t*Bu (250 mol%), Ketone (120 mol%), THF, reflux, 18 h, then HCl$_{(aq)}$, NH$_4$Cl (1 M in 3:1 EtOH/H$_2$O), 90 °C, 18 h, then NH$_4$HCO$_3$ (2 M in H$_2$O), 90 °C, 24 h; [c] (DtBPF)PdCl$_2$ (5.0 mol%), NaO*t*Bu (250 mol%), Ketone (200 mol%), THF, reflux, 18 h, then HCl$_{(aq)}$, NH$_4$Cl (1 M in 3:1 EtOH/H$_2$O), 90 °C, 18 h, then NH$_4$HCO$_3$ (2 M in H$_2$O), 90 °C, 24 h.

Scheme 4. A One-pot protocol.

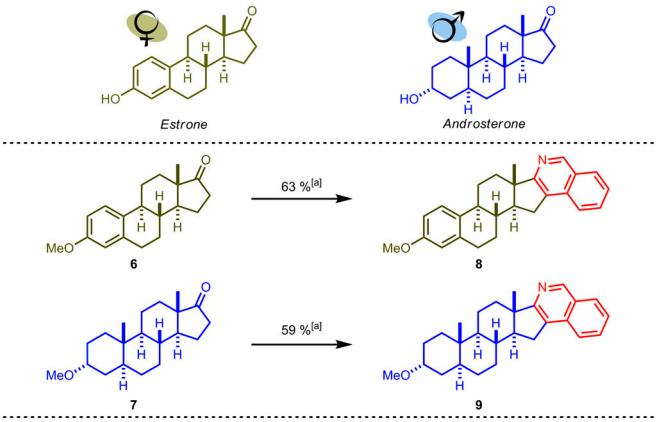
The miscibility of THF with EtOH and H_2O prompted investigation into a one-pot procedure for an arylation/cyclization sequence. After the arylation was complete, the reaction mixture was acidified to pH 5 with aqueous 1 M HCl and then the cyclization was carried out by the addition of the nitrogen source as previously described. The sequential one-pot protocol worked well for a number of substrates without significantly affecting the yield. This greatly improved the practicability of this synthetic procedure, and isoquinolines **4a** and **4b**, for example, could now be synthesized in one step from commercial materials (Scheme 4).

Whilst the majority of other isoquinoline syntheses can only give access to the isoquinoline manifold in one oxidation level, a strength of this method is that by variation of one of the reaction components, more oxidized isoquinoline scaffolds are easily accessible. The direct synthesis of isoquinoline *N*-oxides **5** was achievable by replacing the ammonium chloride in the cyclization step with the hydrochloride salt of hydroxylamine (Scheme 5). Conversion of the arylated intermediates **3** to the *N*-oxides **5** occurred more rapidly (2 h) than to the corresponding isoquinolines **4** and in excellent yields (86–99%). As a number of subsequent functionalization reactions on isoquinolines are performed via their *N*-oxides (53–56), we felt that this powerful and direct approach to their synthesis would prove extremely useful. In particular, it gives the potential to subsequently install a variety of substituents at C(1) without the need for long syntheses of complicated aryl halide precursors. Also, alternative procedures involving direct oxidations of isoquinolines to their *N*-oxides can have limited functional group tolerance and use a stoichiometric equivalent of an oxidizing agent in the process.



[a] NH$_2$OH.HCl (1 M in 9:1 EtOH/H$_2$O), 90 °C, 2 h.

Scheme 5. Isoquinoline *N*-oxides.



[a] (DtBPF)PdCl$_2$ (5.0 mol%), NaO*t*Bu (250 mol%), **2a** (150 mol%), THF, reflux, 18 h, then HCl$_{(aq)}$, NH$_4$Cl (1 M in 3:1 EtOH/H$_2$O), 90 °C, 24 h.

Scheme 6. Derivatizing estrone and androsterone.

This de novo isoquinoline synthesis has the ability to construct complex isoquinoline scaffolds in a rapid and modular fashion. The simplicity and mild conditions of the one-pot procedure make it ideal for the manipulation of existing natural product frameworks to create libraries of potentially biologically active targets for medicinal screening. The addition of a basic isoquinoline nitrogen imparts a site on a molecule for varying lipophilicity, an essential consideration in lead optimisation (57). As many potent pharmaceuticals are derivatives of naturally-occurring steroidal hormones, we chose to exemplify this concept on derivatives of the key female sex hormone estrone and the testosterone metabolite androsterone. Application of the one-pot procedure enabled the synthesis of isoquinolines **8** and **9** in 63 and 59% yields, respectively, using commercially available bromide **2a** (Scheme 6).

Conclusions

In summary, the utilization of sequential palladium-catalyzed α-arylation and cyclization reactions provides a general approach to an array of substituted isoquinolines and their corresponding *N*-oxides. The methodology presented here allows the convergent combination of readily-available precursors in a regioselective manner and in excellent overall yields (often >70% from commercially available precursors). This powerful route to polysubstituted isoquinolines, which works equally well for both electron poor and electron rich moieties, also allows rapid access to analogues of biologically active compounds.

Methods

Full experimental details and compound characterization data are included in the *SI Appendix*.

General Procedure for the Palladium-Catalyzed α-Arylation Reaction. A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon. The palladium catalyst (2.0 or 5.0 mol%) and base (250 mol%) were added to the tube. The aryl halide (100 mol%) was dissolved in dry THF (5 mL mmol^{-1} substrate) and the resulting solution was added via syringe to the tube. The ketone (120 or 200 mol%) was then added via syringe to the tube. The rubber septum was replaced with a screw cap and the tube was heated at 70 °C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Purification by flash column chromatography furnished the requisite intermediate.

General Procedure for Isoquinoline Formation Where R^1 = H. A solution of NH_4Cl (1000 mol%, 1.0 M in 3:1 EtOH/H_2O) was added to the cyclization substrate (100 mol%) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 90 °C for 24 h. The reaction was then cooled to room temperature and quenched by the

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addition of saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Purification by flash column chromatography furnished the requisite isoquinoline.

General Procedure for Isoquinoline Formation Where R^1 = Me. A solution of NH_4Cl (1000 mol%, 1.0 M in 3:1 $EtOH/H_2O$) was added to the cyclization substrate (100 mol%) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 90 °C for 18 h. A solution of NH_4HCO_3 (2.0 M in H_2O) was then added until the pH of the reaction mixture had been adjusted to approximately pH 9. The tube was resealed and heated for a further 24 h at 90 °C. The reaction was then cooled to room temperature and quenched by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Purification by flash column chromatography furnished the requisite isoquinoline.

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