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

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Edited by Jack Halpern, The University of Chicago, Chicago, IL, and approved May 28, 2012 (received for review April 18, 2012)

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.

\textbf{Results}

In our disconnection approach we envisaged that key \textit{pseudo}-1,5-dicarbonyl intermediates \textit{C} could be accessed via the palladium-catalyzed α-arylation of ketones \textit{I} with aryl halides \textit{2} possessing a protected aldehyde or ketone in the \textit{ortho}-position (52). Subsequent treatment of these intermediates \textit{C} with an acidic ammonium source would lead to concomitant acetal deprotection and aromatization to the corresponding isoquinolines \textit{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 1B).

Initial optimization of the α-arylation conditions for the reaction of ketone \textit{1a} with bromide \textit{2a} (two commercially available substrates) showed that a catalyst loading of 2.0 mol\% (D\textsubscript{2}BPF\textsubscript{3})PdCl\textsubscript{2} or PdCl\textsubscript{2}(Amphos)\textsubscript{2} was sufficient to obtain high yields of the arylated product \textit{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 \textit{2b} showed comparable reactivity to bromide \textit{2a} under these conditions. Chloride \textit{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\textsubscript{2}O were screened. The solutions

\textbf{Author contributions:} T.J.D., B.S.P., and G.R.J. designed research; B.S.P. and G.R.J. performed research; B.S.P., and G.R.J. analyzed data; and B.S.P. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1206532109/-/DCSupplemental.
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 EtOH/H₂O) 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,e,f,i with alkyl, 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.

![Scheme 2](image)

**Scheme 2.** Exploring the scope of substituents R¹, R³, and R⁴.

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 3e 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 R¹ = H and 3f–j where R¹ = Me.

The subsequent deprotection and cyclization to produce isoquinolines 4a–e where R¹ = Me also proceeded in excellent yields (79–99%). For intermediates 3f–j where R¹ = 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 H₂O) 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 arylation 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 heterocoren to synthesized thieno-pyridine 4t, illustrating our ability to construct multiple heteroatom-containing ring systems, which are attractive pharmaceutical targets.
The miscibility of THF with EtOH and H₂O 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 arylation intermediate 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.

Scheme 4. A one-pot protocol.

Scheme 5. Isoquinoline N-oxides.

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 isoquino- line 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 H₂O (25 mL). The aqueous layer was extracted with Et₂O (3 × 25 mL) and the combined organics were dried over Na₂SO₄, filtered, and the solvent removed in vacuo. Purification by flash column chromatography furnished the requisite intermediate.

General Procedure for Isoquinoline Formation Where R¹ = H. A solution of NH₄Cl (1000 mol%), 1.0 M in 3 : 1 EtOH/H₂O, 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
addition of saturated aqueous NaHCO₃ (25 mL). The aqueous layer was extracted with Et₅O (3 × 25 mL) and the combined organs were dried over Na₂SO₄, filtered, and the solvent removed in vacuo. Purification by flash column chromatography furnished the requisite isoquinoline.

**General Procedure for Isoquinoline Formation** Where R₁


