ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Modular Isoquinoline Synthesis Using Catalytic Enolate Arylation and *in Situ* Functionalization

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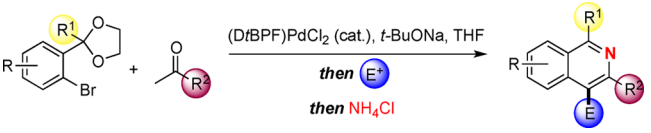
Received October 22, 2013

ABSTRACT



A methyl ketone, an aryl bromide, an electrophile, and ammonium chloride were combined in a four-component, three-step, and one-pot coupling procedure to furnish substituted isoquinolines in overall yields of up to 80%. This protocol utilizes the palladium catalyzed α-arylation reaction of an enolate, followed by *in situ* trapping with an electrophile, and aromatization with ammonium chloride. *tert*-Butyl cyanoacetate participated in a similar protocol; after functionalization and decarboxylation, 3-amino-4-alkyl isoquinolines were prepared in high yield.

The isoquinoline unit is commonly found in natural product frameworks, the cores of pharmaceutical agents, and important organic materials; however, traditional synthetic routes to these motifs suffer from a number of drawbacks. Recently, a number of groups have employed catalytic amounts of transition metals to mediate new bond forming processes en route to isoquinolines.[1]

In 2012, we published a *de novo* synthetic route to isoquinolines that utilized the palladium catalyzed α-arylation of ketone enolates.[2] In this protocol, readily available precursors were combined in a concise, convergent, and regiocontrolled manner to furnish polysubstitued isoquinolines.

The choice of ketone coupling partner determined two of the substituents (at C3 and C4) on the heteroaryl ring of the isoquinoline, arguably two of the most important to be able to manipulate. Although a reasonable scope of the method was demonstrated, the limited commercial availability of the requisite ketones, together with difficulties encountered during regioselective enolization, imparted certain limitations on the methodology.

While isoquinolines undergo nucleophilic attack at the C1 and C3 positions and can be made to react with electrophiles (albeit under forcing conditions) at the C5 and C8 positions, the C4 position is difficult to functionalize in a direct manner. However, one of the advantages of *de novo* approaches to aromatic rings is that the intermediates formed en route to the arene can be manipulated,

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10.1021/ol4030309

often giving greater flexibility in the substitution pattern of the eventual target. The carbonyl compound formed after coupling in our synthetic route appeared to be a prime candidate for elaboration at the center which would eventually become C4 on the isoquinoline (Figure 1). Consideration of the mechanism for enolate coupling reveals that the product has more acidic protons than the starting material and consequently an enolate **A** should be the species formed *in situ* by the extra base that is required for these reactions. This feature opened up the possibility of a one-pot coupling and enolate quenching procedure. Indeed the use of MeI as an electrophile to trap an enolate coupling reaction was described by Hartwig and co-workers in the palladium catalyzed α-arylation of malonates,[3] and Myers has also reported the trapping of eneamido anions en route to isoquinolines.[4]

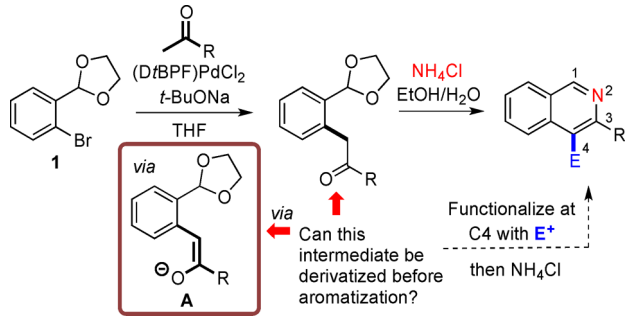
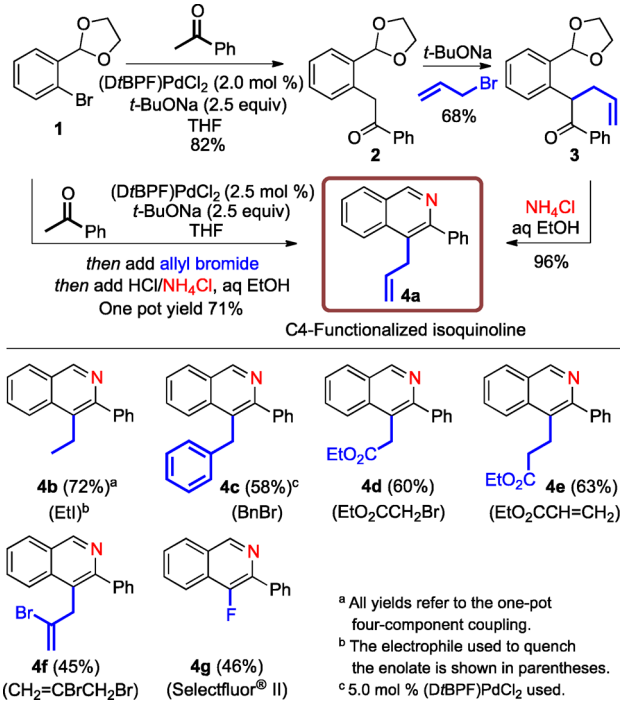


Figure 1. Design of an enolate arylation/electrophile trapping/aromatization sequence.

First, a robust set of arylation conditions were developed ((D*t*BPF)PdCl$_2$, *t*-BuONa, THF) to couple aryl bromides such as **1** with ketones such as acetophenone, furnishing intermediate **2** in high yield (Scheme 1). As a first experiment, it was found that treatment of **2** with *t*-BuONa in THF, followed by allyl bromide, formed functionalized intermediate **3** in 68% yield. Upon subjection to ammonium chloride conditions, **3** then cyclized in excellent yield to give C4-functionalized isoquinoline **4a**.

We then moved to examine one-pot arylation and enolate trapping. Gratifyingly, it was found that subjecting **1** and acetophenone to coupling and then quenching the reaction with allyl bromide delivered intermediate **3** in 78% yield. Seeking to improve the operational simplicity of this protocol further, we combined all three synthetic procedures in a one-pot operation. After quenching the enolate coupling reaction with an electrophile, the reaction mixture was neutralized with HCl, ammonium chloride was added, and the substrate was cyclized *in situ*. The sequential application of these conditions delivered isoquinoline **4a** in one pot and in an excellent yield of 71% (indeed significantly higher than the overall stepwise yield). Hence, a four-component coupling of commercially available materials (aryl bromide **1**, acetophenone, allyl bromide, and ammonium chloride) has been developed that delivers complex substitution patterns (Scheme 1). We then sought to explore the scope of this methodology and began by concentrating on the one-pot coupling of **1** and acetophenone, combined with a quench using a series of different electrophiles and followed by aromatization. The structures **4a**–**g** shown in Scheme 1 reveal that the method is broadly applicable to a range of carbon and heteroatom electrophiles, introducing different substituents at C4. All isoquinolines were produced in one pot.

Scheme 1. Examination of the Electrophile in an Enolate Arylation/Electrophile Trapping/Aromatization Sequence



The tactic of *in situ* enolate quenching gives several advantages over the preparation of a more substituted ketone before enolate coupling. Not only is the preparation of a more complex ketone now unnecessary, but problems that we had previously encountered with regioselective ketone deprotonation and enolate decomposition were obviated.

Next we extended the concept toward isoquinolines bearing substituents on the carbocyclic ring, as well as at C1 (**4h**–**o**, Scheme 2). In addition, the nature of the group adjacent to the carbonyl, ending up at C3, was examined; alternative aryl and alkyl derivatives were compatible with this methodology. In each case the isoquinoline was formed in good yield over a three-step sequence conducted in one reaction vessel.

Following the successful introduction of alkyl, allyl, benzyl, and heteroatom substituents with this methodology, we considered the incorporation of an aryl group at the C4 position by the one-pot coupling of the intermediate

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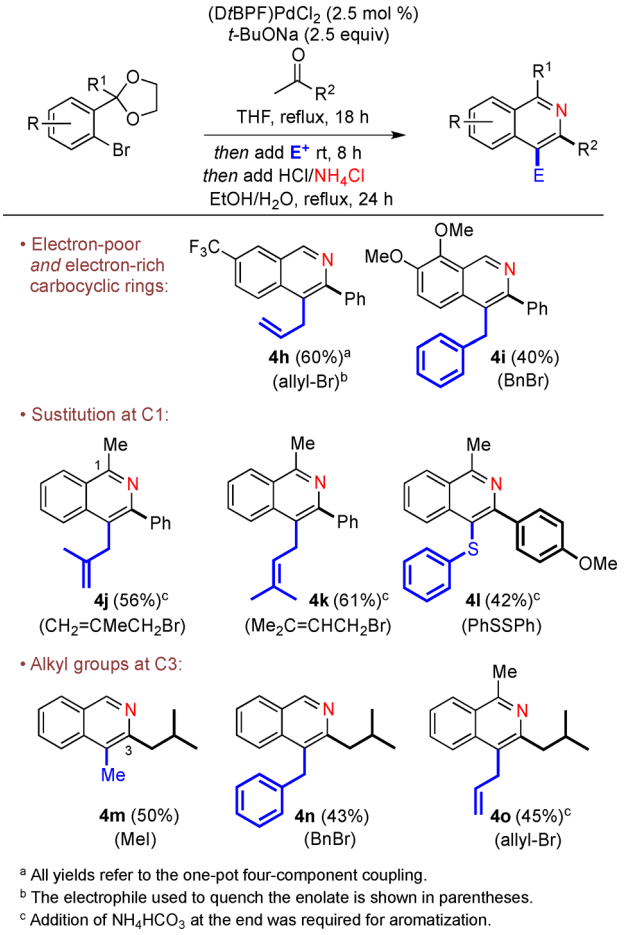
Scheme 2. C4-Substituted Isoquinolines *via* a One-Pot Process



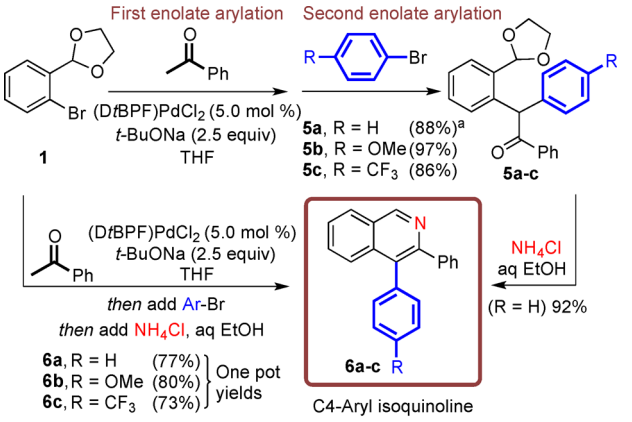
[a] All yields refer to the one-pot four-component coupling.
[b] The electrophile used to quench the enolate is shown in parentheses.
[c] Addition of NH_4HCO_3 at the end was required for aromatization.

enolate (e.g., **A**, Figure 1) with another aryl halide. The range of commercially available benzyl ketones (the requisite α-arylation coupling partner for direct access to the desired isoquinoline precursor) is limited, and C4-arylation of a preformed isoquinoline is extremely challenging. Thus, we envisaged that C4-aryl isoquinolines could be accessed through an α,α-diarylation of a methyl ketone, followed by acetal deprotection and cyclization. While the palladium catalyzed diarylation of methyl ketones has been reported, to the best of our knowledge it is limited to homodiarylation using an excess of one unhindered aryl halide,[5] or has been observed as an undesired side reaction.[6]

In our experience of making isoquinolines *via* enolate coupling, the diarylation of a ketone with an aryl bromide bearing an (*ortho*) cyclic acetal, such as **1**, was not observed, presumably due to steric hindrance slowing down the second coupling. It was therefore proposed that, in the presence of excess base, the enolate **A** (Figure 1) resulting from an initial α-arylation reaction and deprotonation could undergo another α-arylation *in situ* providing that a relatively unhindered aryl bromide was added second. This was found to be the case, and diarylated ketones **5a**–**c** were obtained in excellent yields (Scheme 3). A catalyst loading of 2.5 mol % (R = H) could be used for successful diarylation; however in order to ensure complete reaction in more complex systems, a loading of 5.0 mol % was often used. To the best of our knowledge, this is the first demonstration of a one-pot palladium catalyzed α,α-heterodiarylation of ketones.

It was desirable to attempt to simplify the reaction sequence by carrying out all three steps in a single operation. Accordingly, it was found that an ammonium chloride solution could be added directly to the diarylation product mixture to promote *in situ* deprotection and cyclization, affording isoquinolines **6a**–**c** in 73–80% yield.

Scheme 3. Development of an Enolate Heterodiarylation/Aromatization Sequence



[a] $(DtBPF)PdCl_2$ (2.5 mol %)

To explore the scope further, polysubstituted C4-aryl isoquinolines **6d**–**l** were prepared in yields ranging from 53 to 69% (Scheme 4), which is equivalent to an 81–88% yield per step. Both electron-rich and electron-poor aryl bromides were efficient in the α-arylation reactions, which could be carried out on a number of different methyl ketones. Fused biaryls could also be installed at C4 (**6e** and **6f**), and a methyl substituent in the starting acetal was also tolerated allowing access to C1-substituted, C4-aryl isoquinolines **6k** and **6l**.

Finally, we addressed the synthesis of isoquinolines at a higher oxidation level. We reasoned that these could be accessed *via* α-arylation of a nitrile rather than a ketone, since cyclization onto the pendant nitrile would result in the introduction of an amino group at C3 on the isoquinoline. Unfortunately, the α-arylation reaction of alkyl nitriles is challenging[7] and far less general than that of alkyl

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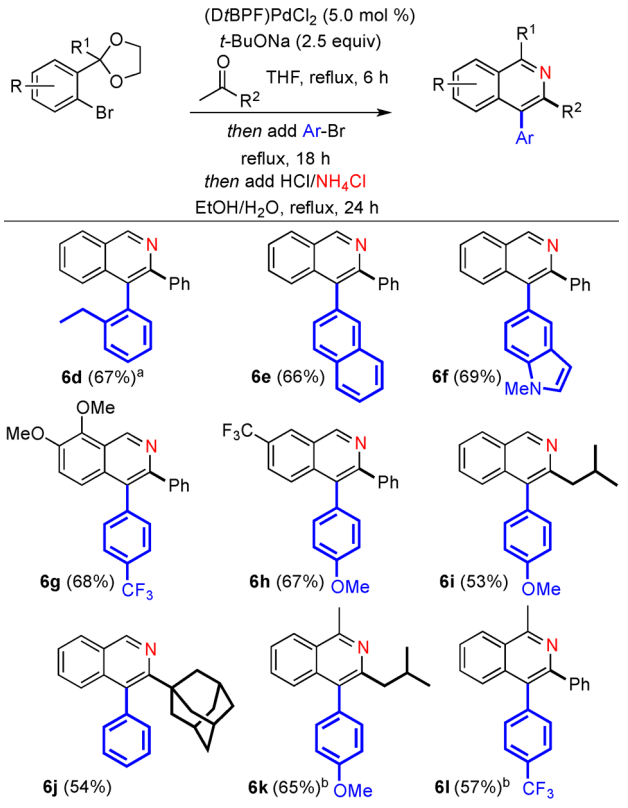
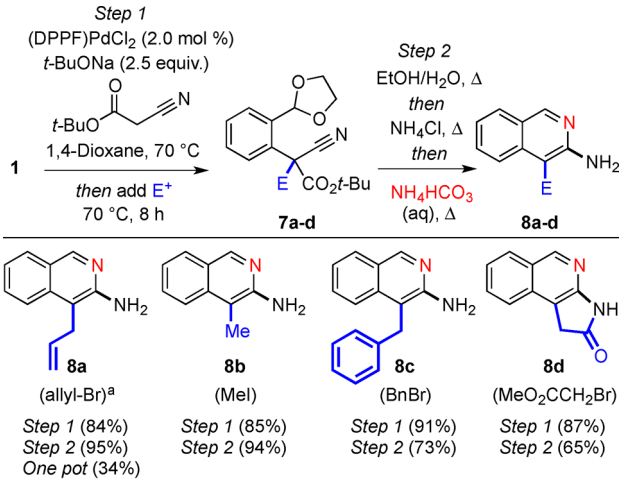
Scheme 4. C4-Aryl Isoquinolines *via* a One-Pot Process



[a] All yields refer to the one-pot four-component coupling.
[b] Addition of NH_4HCO_3 at the end was required for aromatization.

Scheme 5. C4-Substituted 3-Amino Isoquinolines



[a] The electrophile used to quench the enolate is shown in parentheses.

ketones. The α-arylation of ethyl cyanoacetate, however, has seen more application,[1q,2,8] with Wang et al. employing a $Pd(OAc)_2$/DPPF catalyst system with *t*-BuOK.[9] We anticipated that the analogous *tert*-butyl cyanoacetate arylation product might undergo hydrolysis and decarboxylation to furnish an isoquinoline precursor. It was noted that while the decarboxylative couplings developed by the groups of Shang and Feng[10,11] also allow access to these compounds, such reactions require prior alkylation of ethyl cyanoacetate followed by conversion to the potassium cyanoacetate salt. In addition, high temperatures (140−150 °C) are required for the couplings and their use with *ortho*-substituted aryl bromides has not been demonstrated.

The commercially available precatalyst $(DPPF)PdCl_2$ (2.0 mol %) in combination with *t*-BuONa effected the α-arylation of *tert*-butyl cyanoacetate with aryl bromide **1** (Scheme 5). As before, the addition of an alkyl halide to the reaction mixture, postarylation, provided alkylated intermediates **7a**−**d** in yields of 84−91%. As a second step, these underwent decarboxylation of the *tert*-butyl ester simply by heating in the presence of water, after which solid ammonium chloride was added to lower the pH and hydrolyze the acetal. Finally, in this instance, a basic source of ammonia (NH_4HCO_3) was required to drive cyclization to completion, affording 3-amino isoquinolines **8a**−**d**. Thus, the formation of C4-alkylated C3-amino isoquinolines was accomplished with a range of electrophiles and could be performed as either a one- or two-step protocol.

These studies report the development of a versatile four-component coupling protocol between readily available materials (aryl bromide, methyl ketone, electrophile, and ammonium chloride) that delivers isoquinolines with complex substitution patterns, including varied functionality at C4. The aryl bromide, ketone, and electrophile can be altered to allow the regioselective synthesis of polysubstituted isoquinolines. A novel, sequential α,α-heterodiarylation provides C4-aryl isoquinolines, while replacing the methyl ketone with *tert*-butyl cyanoacetate, results in the preparation of 3-amino-4-alkyl isoquinolines: all of the above chemistry takes place in one or two operational steps.

Acknowledgment. We thank the EPSRC, GlaxoSmithKline, and St John's College, Oxford for financial support.

Supporting Information Available. Copies of ^1H and ^{13}C NMR spectra, and experimental procedures are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.