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Palladium catalyzed, heteroatom-guided C–H functionalization in the synthesis of substituted isoquinolines and dihydroisoquinolines†‡

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A new approach for the functionalization of C-4 of isoquinolines is reported. The method utilizes palladium catalyzed, hetero-atom guided (or electrophilic metalation) direct arylation *via* regioselective C–H functionalization of dihydroisoquinolines.

Direct arylation *via* C–H activation reactions is a very important substitute to arylation reactions *via* prefunctionalization.[1] Synthesis of substituted nitrogen heterocycles like pyridines, quinolines, isoquinolines, pyrazines, among others *via* C–H functionalization is not a straightforward task due to the fact that the heterocycles are electron-deficient.[2] Due to this, C–H functionalizations involving electrophilic metalation on these heteroaromatics are quite rare. Studies directed towards the functionalization of such heteroaromatics have utilized directing groups in the form of *N*-oxides, acyl groups, or tethers, amongst others, to direct the regioselectivity.[3] Other methods include employment of electrophilic metalation of non-aromatic heterocycles using the nucleophilicity of the olefinic bond to which an electron-donating heteroatom is attached.[4] In some cases, Boron–Heck reactions have also been employed for functionalization of endocyclic olefins of heterocycles.[5] In a related study, Loh and co-workers have reported regioselective functionalization of enamides.[6] We have recently reported the C-3 functionalization of quinolines in which the concept of electrophilic palladation was utilized for a regioselective direct arylation reaction.[7] We report herein, our results for a regioselective direct arylation of dihydroisoquinolines in the synthesis of 4-arylisoquinolines and 1,4-disubstituted dihydroisoquinolines.

The isoquinoline core is an important constituent in several alkaloid natural products, especially the amaryllidaceae alkaloids.[8] In particular, naturally occurring isoquinolines with a 4-aryl substituent (Fig. 1) possess very important biological properties and

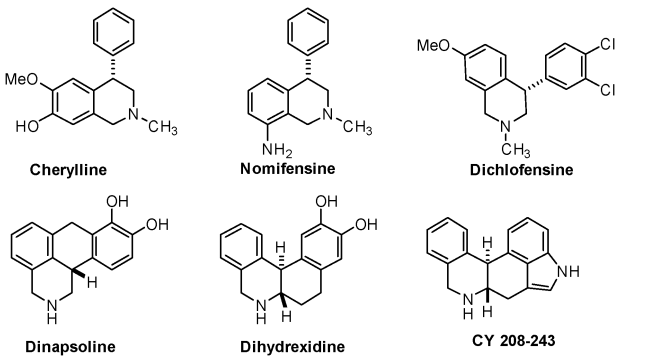

Fig. 1 4-Aryl isoquinoline containing biologically important molecules.

are important pharmaceutical agents, such as protein kinase B (PKB) inhibitors, anti-Parkinsonian drugs, anti-depressants, anti-histamines, selective serotonin reuptake inhibitors (SSRI).[9] Some are important starting materials in the synthesis of complex natural products.[10] Due to their broad array of biological significance, these building blocks have been the target of synthetic chemists since quite some time.

Synthetic methodologies for the direct functionalization of the C-4 position of isoquinoline are limited, with almost all approaches relying on pre-installation of the substituent before the cyclization to obtain the isoquinoline ring. Some approaches utilize selective halogenations of C-4 as a prelude to metal catalyzed cross-coupling reactions for C-4 functionalization of isoquinolines or dihydroisoquinolines. Recently, nucleophilic addition of β-amino carbanions to arynes has been reported by Singh and co-workers for the synthesis of 4-aryl tetrahydroisoquinolines.[11] Wang and co-workers have reported a Lewis acid mediated [3+3] annulation approach for the same class of molecules.[12] The direct arylation of isoquinoline *N*-oxide leads to the expected C-1 functionalization.[3] To the best of our knowledge, a direct arylation of the C-4 position of dihydroisoquinolines to obtain 4-arylisoquinolines is not known in the literature.

Our efforts started with screening for the best conditions for the transformation. The dihydroisoquinoline starting material was synthesized either by reduction of isoquinoline and concomitant

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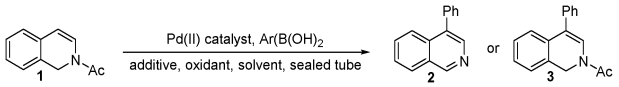
Table 1 Efforts in screening various catalyst systems



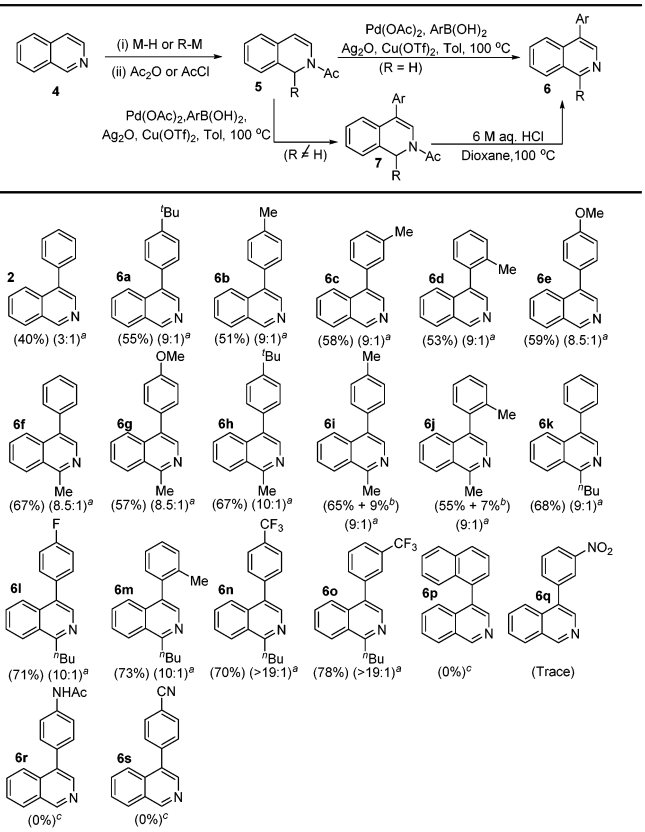
Catalyst	Additive/base/oxidant	Solvent/temp.	Result
None	CuI, AgOAc, ^{t}BuOK	Toluene, 100 °C	Only homocoupling of $ArB(OH)_2$
None	$Cu(OTf)_2$, Ag_2O	Toluene, 100 °C	Only homocoupling
$Pd(OAc)_2$	BQ, Ag_2O	Toluene, 100 °C	Only homocoupling
$Pd(OAc)_2$	K_3PO_4, AgOAc	Toluene, 60 °C	Only homocoupling
$Pd(OAc)_2$	K_2CO_3 (3 equiv.)	PivOH, 70 °C	Only homocoupling
$Pd(OAc)_2$	$Cu(OAc)_2$, AgOAc	Toluene, 100 °C	10%[b]
$PdCl_2(MeCN)_2$	$Cu(OTf)_2$, Ag_2O	Toluene, 70 °C	25%[b]
$PdCl_2(PhCN)_2$	$Cu(OTf)_2$, Ag_2O	Toluene, 70 °C	45%[b]
$PdCl_2$(dppf)	$Cu(OTf)_2$, Ag_2O	Toluene, 70 °C	Only homocoupling
$Pd(OAc)_2$	$Cu(OTf)_2$, Ag_2O	Dioxane, 100 °C	Messy reaction
$Pd(OPiv)_2$	$Cu(OTf)_2$, Ag_2O	Toluene, 60 °C	40% (unseparated 3 : 1 mix of C4 : C3 isomers)[b]
$Pd(OAc)_2$	$Cu(OTf)_2$, Ag_2O	Toluene, 100 °C	67% (unseparated 3 : 1 mix of C4 : C3 isomers)[a]
$Pd(TFA)_2$	$Cu(OTf)_2$, Ag_2O	Toluene, 100 °C	38% (unseparated 2.5 : 1 mix of C4 : C3 isomers)[a]
$Pd(TFA)_2$	$Cu(OTf)_2$, Ag_2O, 1, 10-Phen	Toluene, 110 °C	Only homocoupling
$Pd(TFA)_2$	$Cu(OTf)_2$, Ag_2O	TFA, 70 °C	52% (single C4 isomer)[a]

[a] Isolated yield. [b] GC yields.

acylation or by addition of an organolithium or a magnesium reagent followed by quenching with an acylating agent. Unlike the case of quinolines,[7] the initial attempts towards direct arylation of *N*-acyldihydroisoquinoline resulted in varying amounts of regioisomeric products (C-4 *versus* C-3 arylated). The reaction conditions were accordingly standardized and after a considerable amount of ligand and catalyst screening, the best conditions for C-1-unsubstituted dihydroisoquinolines were found to be $Pd(TFA)_2/Ag_2O$ in TFA (Table 1). However, in the case of C-1 substituted substrates, use of this highly electrophilic $Pd(TFA)_2$ in TFA resulted in regioisomers (C-4 *vs.* C-3). The direct arylation of C-1-substituted dihydroisoquinolines was best obtained using $Pd(OAc)_2/Ag_2O/Cu(OTf)_2$ in toluene. Therefore, in order to generalize, we used $Pd(OAc)_2/Ag_2O/Cu(OTf)_2$ in toluene for all the substrates.[7] Without a palladium catalyst, the reaction yielded only homocoupling products of the arylboronic acids. The use of $Cu(OTf)_2$ was essential as the oxidant. Use of other different copper sources or other oxidants did not give desirable results. Changing the catalyst to the more reactive $Pd(OPiv)_2$ also did not improve the result of transformation. Use of other Pd(II) catalysts did not yield better results than $Pd(OAc)_2$. Use of more polar solvents seemed to be detrimental to the reaction. Several bases were scanned, however best results were obtained only with Ag_2O. The substrate scope is depicted in Table 2. The reaction worked decently well under the standardized conditions with electron neutral and electron-rich arylboronic acids. In the case of the *N*-acyldihydroquinolines which are unsubstituted at C-1, the reaction did not work well with arylboronic acids with electron withdrawing substituents.

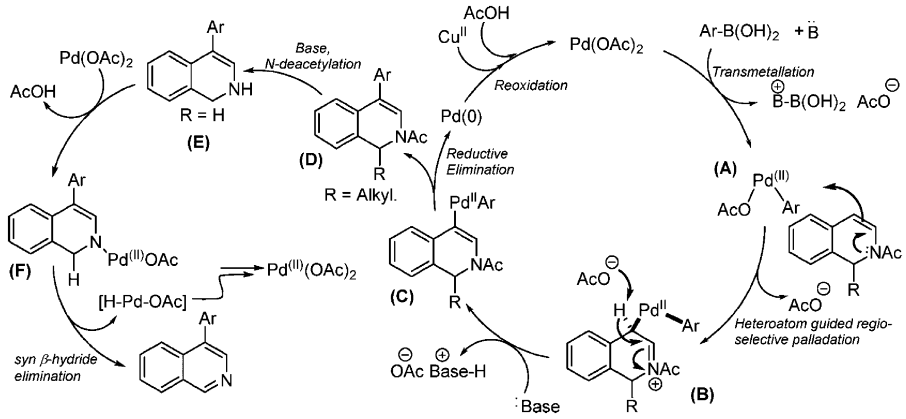
In contrast, in the case of the dihydroisoquinolines substituted at C-1, the reaction worked decently well in most cases. Even with arylboronic acids containing electron withdrawing groups, the reaction worked quite well, with the exception of 3-nitrophenyl boronic acid which gave only a trace amount of product. In this case and others that did not work out, the primary side-reaction obtained was the protodeboronation of the arylboronic acids, along with varying quantities of aromatized starting material.

Table 2 Substrate scope with arylboronic acids



All yields are isolated yields of the C-4 aryl product; general reaction conditions: $Pd(OAc)_2$ (5 mol%), $ArB(OH)_2$, $Cu(OTf)_2$, Ag_2O, toluene, 100 °C. [a] Ratio of the C-4:C-3 aryl product in a crude reaction mixture analyzed by GC-MS. [b] Isolated yield of the C-3 isomer. [c] Only the protodeboronation product was obtained.

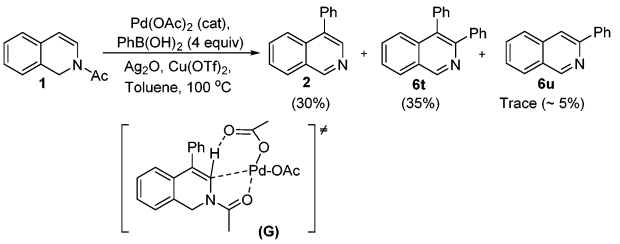
A plausible mechanism is depicted below in Scheme 1. The reaction could either proceed *via* the transmetallation of the arylboronic acid as the first step followed by the heteroatom-guided



Scheme 1 Plausible reaction mechanism.

electrophilic palladation or *vice versa*. At this moment it is difficult to conclude what would be the correct sequence for the palladation. After intermediate (C) is formed, a fast reductive elimination would lead to the C-4 C–H functionalization product. In the case of the C-1 substituted dihydroquinolines, the *N*-deacetylation is a slow process and the concomitant aromatization *via* the pathway depicted in Scheme 1 is therefore expected to be retarded. This has also been observed experimentally. Under the same reaction conditions, the C-4 arylated dihydroquinolines aromatize quickly, whereas in the case of 1,4-disubstituted dihydroisoquinolines, only trace amounts of aromatized products were observed. The aromatization reaction in the case of the 4-aryl dihydroisoquinolines could be mediated by the oxidant or could be a result of the syn β-hydride elimination from (F). We were successful in aromatizing the C-1 substituted products (7) in quantitative yields by simply deacylating them by warming in an aq. HCl–Dioxane mixture. The crude reaction mixture, containing 7, upon a preliminary work-up was directly subjected to acid-hydrolysis and aromatization to yield **6**. The regiochemistry of the major isomer was easily proved by simple spectroscopic techniques and X-ray data of some of the unaromatized substrates.[13,14]

An interesting observation was made when large excess (4 equiv.) of arylboronic acid was used in the reaction with substrate **1**. In this case, a C-3, C-4-diarylated product was observed in 35% isolated yield, along with the regular C-4 aryl product. In a way, this indicated that the arylation at C-3 was a result of a domino-type reaction pathway which could involve a transition state of the type (G) (formed after C-4 arylation) in which the *N*-acyl group is acting as a directing group for a concerted metalation deprotonation (CMD) type mechanism. A similar transition state has been proposed by Loh and co-workers in the arylation of exocyclic enamides.[6] Unfortunately for us, we were unable to isolate substantial quantities of **3** so as to use it as a starting material to try an arylation reaction at C-3 and confirm whether the C-3 arylation was indeed directed by the *N*-acyl group. This diarylation was not observed in significant quantities in the case of 1,4-disubstituted dihydroquinolines even when 4 equiv. of the arylboronic acid were used (Scheme 2). This type of transition state is also able to explain why selectivity for C-4 *versus* C-3 arylation is slightly lower with $Pd(OAc)_2$ in the case of unsubstituted dihydroisoquinolines.



Scheme 2 Plausible transition state for second arylation at C-3.

In order to prove the regioselectivity of palladation, NMR experiments were undertaken.[4d,15] In this substrate (**1**), the C-4 palladated species was not observed in NMR using DMSO-d_6 or toluene-d_8 or THF-d_8. A comparative NMR plot of the substrate upon isolation after reaction in TFA/D_2O with 1 equiv. of $Pd(TFA)_2$, taken at different intervals, is shown in Fig. 2. Upto 64% deuterium content at C-4 was observed in isolated starting material.[14] Similarly, under these highly acidic conditions, the starting material **1** deacetylated and aromatized to **4**, which was found to be with 15% deuterium content upon isolation.[14] Initially, we assumed that this was due to deuterodemetallation; however, in our case, it turned out to be a totally wrong assumption, a similar level of deuteration was obtained under the same conditions even without a palladium source. This deuteration could be due to the endocyclic enamide picking up a D^+ at electron-rich C-4 followed by elimination of H^+ to generate the C-4 deuterated starting material.

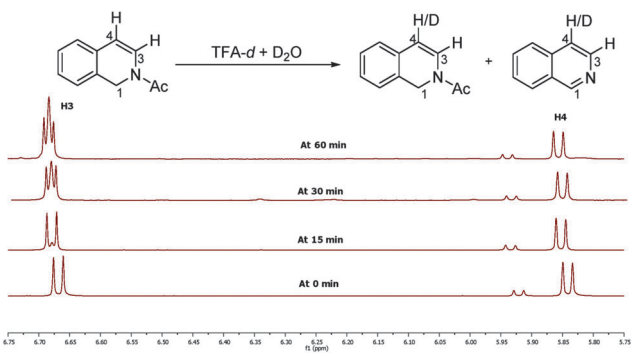


Fig. 2 Attempts to determine regioselectivity.

In conclusion, we have developed a new methodology for the regioselective direct arylation of dihydroisoquinolines for the synthesis of 4-arylisoquinolines and 1,4-disubstituted dihydroisoquinolines. This represents a regioselective two-step direct arylation of isoquinoline itself. The reaction is proposed to proceed *via* heteroatom-guided electrophilic palladation. This synthetic methodology shall be useful in the synthesis of 4-arylisoquinoline-containing pharmacologically significant heterocycles. Further utilization of this approach in natural product synthesis is currently underway.

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