

Highly regioselective Heck reactions of heteroaryl halides with electron-rich olefins in ionic liquid

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Received 2 February 2005; received in revised form 4 March 2005; accepted 4 March 2005

Available online 19 April 2005

Dedicated to Professor Eric Derouane on the occasion of his 60th birthday

Abstract

Palladium-catalyzed Heck reactions of the heteroaryl halides, halopyridines, bromoquinoline and bromothiophenes, with the electron-rich olefins vinyl ethers and allyl alcohol were shown to give essentially only the branched olefins in an imidazolium ionic liquid, whereas in molecular solvents a mixture of regioisomers was formed. The method obviates the need for aryl triflates and stoichiometric inorganic salt additives, providing an easy entry to functionalized heteroaromatics incorporating acetyl and 2-allyl alcohol functionalities.

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Keywords: Heck reaction; Regioselectivity; Ionic liquid; Heterocycles; Electron-rich olefins; Palladium catalysis

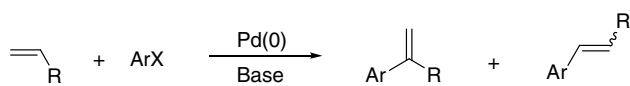
1. Introduction

Heteroaryl compounds have important biological properties and many of their derivatives can be readily accessed by metal catalyzed reactions [1,2]. Among the various reactions catalyzed by metal complexes, the palladium catalyzed Heck reactions of heteroaryl halides and alkenes have demonstrated their utility in a limited number of instances [3]. However, as with most other Heck reactions, these reactions are mainly concerned with electron-deficient olefins [4]. We have recently developed a method that allows electron-rich olefins to be arylated by aryl halides in a highly regioselective manner without recourse to any halide scavengers [5]. We now report results that extend the chemistry to heteroaromatics.

Although a great deal of progress has been made in the Heck coupling reactions in the past several years, the olefinic substrates have so far mostly been limited to electron-deficient olefins [4]. With electron-rich olefins, such as silanes, vinyl ethers, and enol amides, there exists an important issue that has not been fully resolved to date, that is the lack of regioselectivity in normal intermolecular Heck reactions [4a,4d,4e–6]. Such reactions usually give rise to a mixture of regioisomeric olefins and hence are of only limited synthetic utility (Scheme 1). The problem with the regioselectivity can be addressed by using aryl triflates instead of halides or stoichiometric amounts of halide scavengers when aryl halides are used, thallium (I) or silver (I) salts being most popular [6]. The effect of the triflates and halide scavengers on the regioselectivity stems from their effect on the reaction pathway. The Heck reaction is believed to proceed via an ionic pathway leading to the branched product and a neutral variant giving rise to the linear olefin [4–7] (Scheme 2). One can easily envision that

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R = heteroatom, alkyl, $-\text{CH}_2\text{SiR}'_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, etc.

Scheme 1.

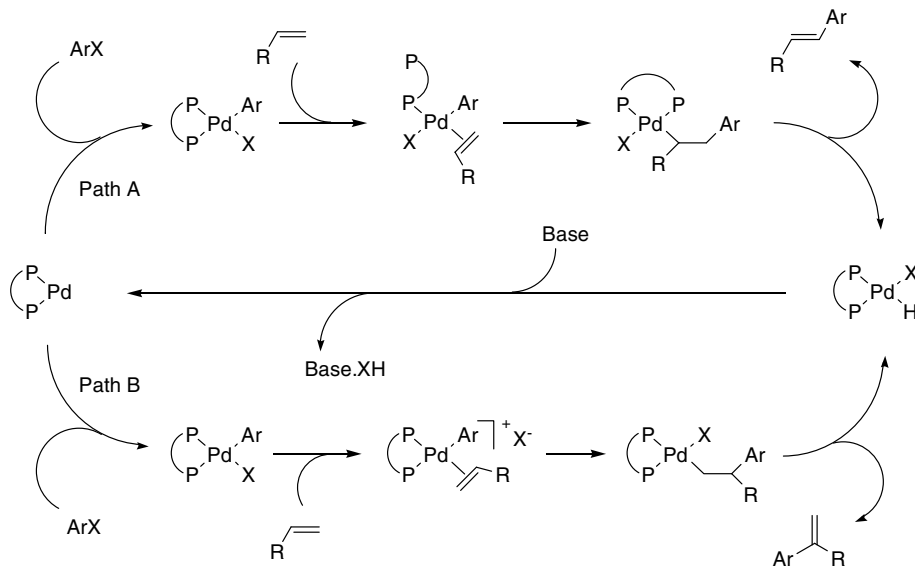
the ionic pathway would be rendered favorable when triflates or halide scavengers are chosen.

In a program aimed at developing homogeneous catalysis in ionic liquids [5,8], we disclosed that highly regioselective Heck arylation with aryl halides can be accomplished in imidazolium ionic liquids [9], obviating the need for aryl triflates or toxic and costly inorganic additives [5]. The work originated from a hypothesis that because ionic liquids are entirely composed of ions, the ionic Heck pathway (Path B, Scheme 2) would be made favorable when an arylation reaction is performed therein, thus leading to the formation of branched olefins. A similar argument was also invoked by Hallberg, Larhed and coworkers [10,11] in recent studies of the Heck reaction involving electron rich olefins. Following

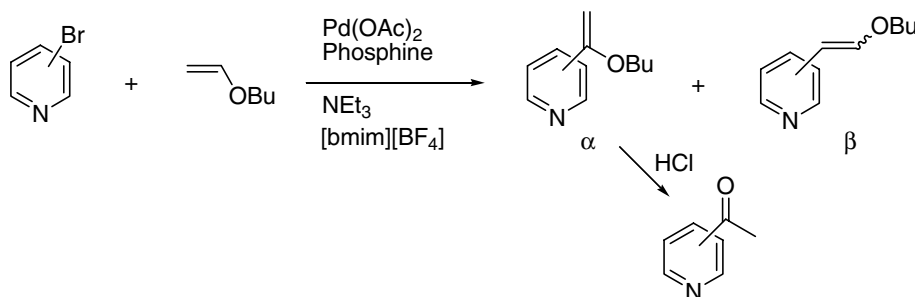
on from the work on normal aryl halides, we extended the chemistry to heteroaryl compounds. The examples presented below fall again in line with this hypothesis.

2. Results and discussion

We first targeted the Heck arylation of bromopyridines with the benchmark electron-rich olefin butyl vinyl ether. Following acidic hydrolysis, the resulting branched olefins should readily lead to acetyl pyridines, a class of compounds that are otherwise difficult to access (Scheme 3). To test out if ionic liquids would offer any advantage over a molecular solvent, the arylation of 3-bromopyridine was conducted in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) alongside five normal solvents. The reaction was carried out by heating a mixture of the bromide (1.0 mmol), butyl vinyl ether (5.0 mmol), triethylamine (1.6 mmol) in the presence of Pd(OAc)₂ (4 mol%) and 1,3-bis(diphenylphosphino)propane (DPPP, 8 mol%) in 2 mL of a chosen solvent. The results are summarized



Scheme 2.



Scheme 3.

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