

Synthesis of mixed N,N' -(Ar,Ar'-diaryl)iminoisoindolines for applications in palladacycle formations

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ABSTRACT

The synthesis of N,N' -(Ar,Ar'-diaryl)iminoisoindolines containing different aryl groups bound to the two nitrogen atoms is described. The iminoisoindolines were obtained by a three component, one-pot reaction of phthalaldehyde with 1 equivalent *p*-NO₂-aniline and 1 equivalent *p*-R-aniline, where R = H, Me, MeO or ^tPr, resulting in formation of non-symmetrically substituted (mixed) iminoisoindolines, 1-*p*-nitrophenylimino-2-*p*-R-phenylisoindoline (R = H (**1**), Me (**2**), MeO (**3**), and ^tPr (**4**)), as analytically pure precipitates requiring no further purification. Only one isomer precipitates from solution wherein the nitro group resides exclusively at the imine position while the more electron donating substituent ends up on the isoindoline ring position. Further reaction with Pd(OAc)₂ in dichloromethane at room temperature results in formation of six-membered [C,N] dinuclear cyclopalladated complexes with the general formula [(Ar,Ar'-diaryliminoisoindoline)Pd{μ-OAc}]₂.

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1. Introduction

Carbon–carbon (C–C) coupling reactions are among the most important transformations in organic synthesis. Palladium based catalysts, in particular palladacycles, have been found to be superior catalytic systems in this regard due to their ease of preparation, air and moisture stability, low loading and high activity. Palladacycles have been known since the 1960s but were not used for C–C coupling reactions until 1995 and have rapidly emerged as being among the most active catalysts known for a large variety of coupling reactions [1,2]. There is a large diversity of palladacycles reported in the literature, the most common of which are palladacycles incorporating [C,P] and [C,N] metallacyclic formations [3]. The Pd–C bonds in palladacycles are most commonly formed by intramolecular C–H activation in the *ortho* position of a proximal aryl group to form the metal–carbon bond usually resulting in five- or six-membered ring palladacycles. Several palladacycles are even commercially available; most notably the diimine-based Nájera catalyst [4], the amine-based Indolese catalyst [5] and Bedford's phosphite-based catalyst [6].

While N,N' -diaryliminoisoindolines were first synthesized in 1910, few applications have been found for this subclass of indolines, either as ligands or as organic substrates [7]. For exam-

ple, a SciFinder structure search reveals only 19 independent references in the last 100 years [8]. One possible reason for the dearth of interest in diaryliminoisoindolines is simply that they have not been found as a subunit of any natural product.

We recently reported the synthesis of a series of air and moisture stable N,N' -diaryliminoisoindoline-based palladacycles (Fig. 1) [9]. The corresponding palladacycles also required only one synthetic step and precipitate from solution as analytically pure solids. These complexes were found to be active pre-catalysts in the activation of aryl chlorides for the formation of biphenyls and cinnamates in the Suzuki and the Heck coupling reactions [9]. We further reported that with 1-*p*-nitrophenylimino-2-*p*-nitrophenylisoindoline (R = R' = NO₂; Fig. 1), there was no reaction with palladium(II) acetate and thus no formation of the corresponding palladacycle. This is likely due to the electron withdrawing/deactivating effects of the nitro substituent inhibiting both imine coordination and *ortho*-palladation. Intrigued by this result, we decided to investigate the synthesis of mixed N,N' -(Ar,Ar'-diaryl)iminoisoindolines ligands containing different aryl groups bound to the two nitrogen atoms (R ≠ R', Fig. 1) wherein the aryl groups of the mixed diaryliminoisoindoline would contain alternatively one nitro group and one neutral or electron donating group in the *para* positions. Herein we report the synthesis and characterization of a series of mixed (N,N')-Ar,Ar'-diaryliminoisoindolines and subsequent formation of the corresponding air and moisture stable iminoisoindoline-based palladacycles in a simple two-step protocol. Their applications in Mizoroki–Heck coupling reactions were also investigated.

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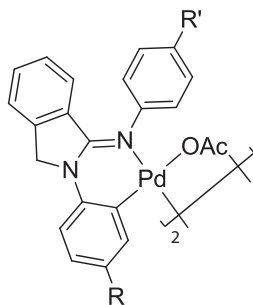


Fig. 1. Mixed iminoisoindoline-based palladacycles where $R \neq R'$.

2. Results and discussion

2.1. Ligand Synthesis

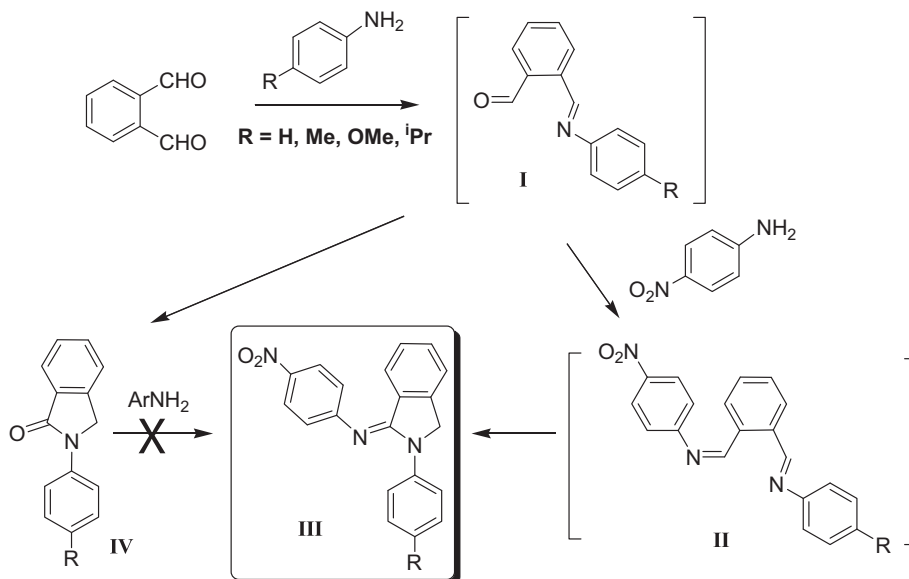
As we have previously reported, the diaryliminoisoindoline, 1-*p*-nitrophenylimino-2-*p*-nitrophenylisoindoline ($R = R' = \text{NO}_2$; Fig. 1), did not react with palladium(II) acetate to form the corresponding palladacycle which is likely due to the highly electron withdrawing nature of the nitro substituents inhibiting *ortho*-palladation [9]. We envisioned that substitution of the nitro group of the aryl ring bound directly to the isoindoline skeleton with more electron donating substituents would allow for C–H activation and subsequent palladacycle formation. As with the previously reported symmetrically substituted iminoisoindolines, the non-symmetrically substituted ligands proved remarkably easy to synthesize. The one pot reaction of phthalaldehyde with equimolar amounts of *p*-NO₂-aniline and *p*-R-aniline ($R = \text{H, Me, MeO}$ or ^{*i*}Pr) results in successful formation of non-symmetrically substituted iminoisoindoline ligands ($R = \text{H}$ (**1**), Me (**2**), MeO (**3**), and ^{*i*}Pr (**4**)) in 40–55% yield as shown in Schemes 1 and 2. In all cases, the nitro group resides exclusively at the imine position while the more electron donating substituent ends up on the isoindoline ring position. The desired compounds precipitated out of solution as analytically pure solids. The mixed iminoisoindolines are all previously unreported except for **3** [10]. Compounds **1–4** were characterized by ¹H and ¹³C NMR, mass spectrometry, elemental analysis and IR spectroscopy. ¹H NMR spectra show a characteristic singlet for the CH₂ moiety of the isoindoline ring of **1–4** at ~5 ppm

and the C=N stretching frequency in the IR spectra appears at ~1645 cm⁻¹.

The mixed Ar,Ar'-diaryliminoisoindoline synthesis likely proceeds first via reaction of phthalaldehyde with one equivalent of the more electron donating aniline resulting in formation of an imino-aldehyde **I** (Scheme 1). The resulting imino-aldehyde can then undergo a slower second condensation reaction with *p*-NO₂-aniline forming a transient γ -diimine **II**. The γ -diimine then undergoes intramolecular cyclization initiated by the more electron donating imine resulting in formation of the corresponding iminoisoindoline **III** with the NO₂ moiety residing exclusively on the imine position. We have previously shown that the γ -diimine intermediate **II** can only be isolated providing the aryl groups are sufficiently bulky to inhibit intramolecular cyclization [11]. A competing side reaction also occurs where intramolecular cyclization of the transient imino-aldehyde species results in formation of the corresponding isoindolinone **IV** which limits the overall yield of the mixed iminoisoindoline ligands. The presence of the isoindolinone was confirmed by MS analysis of the filtrate. Fortunately, under the reaction conditions employed, the isoindolinone remains in solution while the desired iminoisoindoline precipitates out as a yellow powder. The isoindolinone does not further react with ArNH₂ (Scheme 1).

Unlike the diaryliminoisoindolines, the corresponding *N*-aryl-isoindolinones have found widespread application in the pharmaceutical industry with many examples being commercially available including the isoindolinones from Scheme 1 [12]. Recent publications by the groups of Pan as well as Alajarín and Sánchez-Andrada provide mechanistic details into the formation of isoindolinones from phthalaldehyde [13,14].

When the reaction is carried out with two different anilines both bearing electron withdrawing groups in the *para* position (specifically NO₂ and COMe), the resulting iminoisoindoline precipitates as a mixture of three compounds: 1-*p*-nitrophenylimino-2-*p*-acetylphenylisoindoline (**A**), 1-*p*-acetylphenylimino-2-*p*-nitrophenylisoindoline (**B**) and 1-*p*-nitrophenylimino-2-*p*-nitrophenylisoindoline (**C**) in the ratio 17:5:1, respectively as shown in Scheme 3 in 80% overall yield. Compounds **A–C** were identified by mass spectrometry as well as ¹H and ¹³C NMR spectroscopy. Compounds **B** and **C** have been previously reported [9,10], while characterization of **A** is herein reported. Thus it appears that in order to facilitate isolation of a mixed iminoisoindoline in a one-pot



Scheme 1. Synthesis of mixed Ar,Ar'-diaryliminoisoindolines.

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