



A novel imidazol-2-ylidene as a ligand for palladium-catalyzed synthesis of oxyindoles from *o*-haloanilides

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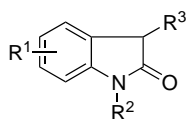
Abstract—Oxyindoles were formed in good yields from 2-bromo- or chloroanilide in the presence of a base and a novel palladium imidazol-2-ylidene complex, through a process of metal-catalyzed intramolecular arylation of amide enolates. A wide range of substrates, including electron rich aryl chlorides, were found active under the catalysis of this non-phosphinic, easily prepared ligand–metal system. © 2002 Elsevier Science Ltd. All rights reserved.

Oxyindoles (2-indolinones, **1**) are a ubiquitous class of heterocyclic compounds found in many natural products¹ and a number of marketed drugs and drug candidates.² They have served as intriguing targets as well as essential intermediates in the total synthesis of other indolic alkaloids. Methods of preparation for these compounds³ include oxidation of the parent indoles, reduction of isatins, cyclization of *o*-aminophenylacetate, construction of the phenyl ring by intramolecular cycloaddition of amides, and a number of metal-catalyzed processes.⁴ A conceptually new synthesis has recently been reported by Hartwig et al.,⁵ where a palladium-catalyzed intramolecular arylation of *o*-bromoanilide (**2**) enolate has been realized to give the heterocycle in good yields.

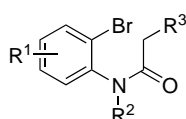
This palladium-catalyzed indole synthesis appeared as the method of choice when we encountered the need for an efficient synthesis for a drug candidate containing an oxindole moiety. Indeed, the Hartwig procedure proved reproducible when BINAP was used in combination of Pd₂(dba)₃. However, we were disappointed to find that the *o*-chloroanilides, unlike their bromo derivatives,

failed to give any appreciable level of conversion when they were subjected to the Pd₂(dba)₃/BINAP system, even at elevated temperature over a prolonged reaction time. A quick screen of catalysts using several bulky and electron rich phosphines was conducted, in light of the findings that these ligands generally favor palladium mediated reactions of inactivated aryl halides.^{5,6} However, most of these ligands were found ineffective for this particular transformation. Additionally, the use of phosphinic ligands presents certain concerns over cost and air stability.

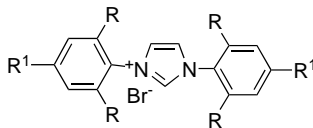
We then turned our attention to bis-aryl imidazol-2-ylidene ligand derived from (**3**) for its superior activity toward aryl chlorides in Suzuki couplings.^{7–10} Interestingly, this ligand also proved unsatisfactory for the intended oxindole formation from the corresponding anilides, when a ligand/palladium ratio of 2:1 or 1:1, and a catalyst loading of 3 mol% was employed. Suspecting that the steric bulk of **3** may have been detrimental to the intramolecular cyclization process, we prepared ligand **4** by simply alkylating mesitylimidazole



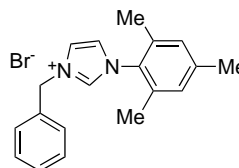
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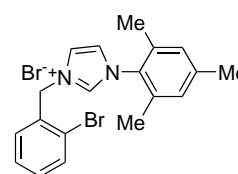
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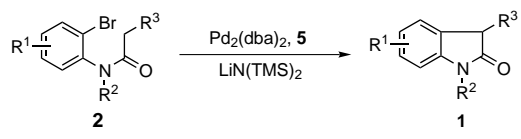
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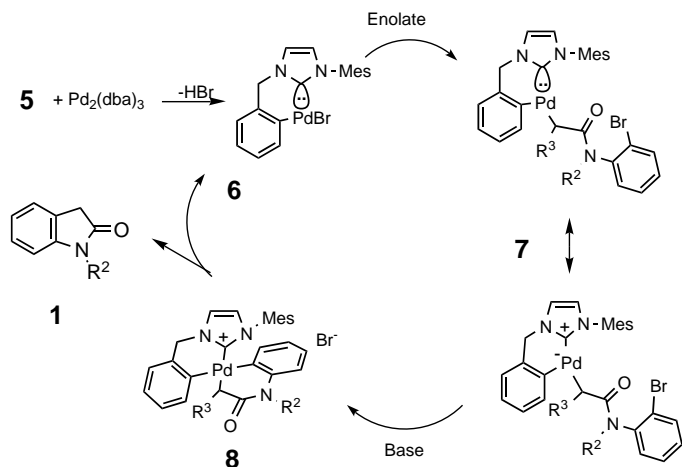
Keywords: catalysis; catalyst; oxindole; indole; palladium; imidazolylidene.

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Table 1. Synthesis of oxindoles from *o*-haloanilides


Entry	Substrate	Product	Yield ^a
1			80%
2			43%
3			83%
4			90%
5			40%
6			67%
7			47%
8			62%
9			82%

^a Isolated yields. All compounds were characterized by ¹H and ¹³C NMR. Reactions were carried out using 1.5–3 mol% of Pd₂(dba)₃, 3–6 mol% of **5**, and 1.5–2 equiv. of LiN(TMS)₂ in THF at 68°C for 1–4 h.

**Scheme 1.**

with benzyl bromide. Unfortunately, catalyst prepared from ligand **4** with palladium also failed to promote cyclization. These events, coupled with the observation by Nolan⁸ et al., respectively, seem to suggest that a palladium species with at least two tight coordinating ligands is required for the C–C bond forming reaction to proceed. However, having two imidazolylene ligands around the palladium center may impose too much steric hindrance for the cyclization to occur.

In light of these findings, we prepared 1-mesitylimidazolium salt, **5**, from 1-mesitylimidazole and *o*-bromobenzyl bromide, with the intention of providing a less bulky, intramolecular coordination site so as to limit the possibility of forming a bis-(bis-imidazolide) complex. Indeed, when compound **5** was mixed with an equal molar amount of palladium, the in situ generated catalyst proved to be effective catalyst in the oxindole forming reactions for a variety of substrates (Table 1). Catalyst derived from **5** is generally more active than the Pd/BINAP combination, as indicated by both reaction rates and product yields. Moreover, *o*-chloroanilide was found to undergo cyclization, albeit in moderate yield (entry 2).¹¹

The exact mechanism of this reaction is unclear. As a working hypotheses, we offer that the initial episode of the catalytic cycle may involve the formation of a carbene complexed palladacycle **6** through oxidative insertion of Pd(0) into the aryl bromide bond (Scheme 1). The nature of the putative palladacycle **6** should be markedly different from that of the increasingly popular palladacycle prepared from Pd(OAc)₂ and P(*o*-MeC₆H₅),⁹ and may offer some distinctive opportunities in other processes which are of current interests to the general synthetic community. Isolation and identification of the active catalytic species are in progress.

In summary, we have discovered a novel metal–ligand system and applied it to the synthesis of oxindole from *o*-haloanilides. A few features are noteworthy: first the ligand is easily prepared from readily available starting materials, and stable toward air and prolonged storage. Secondly, it represents a new class of palladacycle with its unique set of activities and selectivity with a good chance of being applied to other transition metal-catalyzed processes, a work currently in progress in these laboratories.

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