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Synthesis of 3-hydroxyoxindoles by Pd-catalysed intramolecular nucleophilic addition of aryl halides to α-ketoamides†‡

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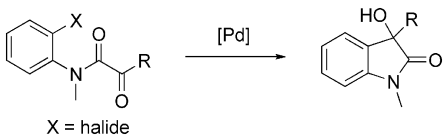
Pd/P*t*Bu$_3$-catalysed intramolecular nucleophilic addition of aryl halides to α-ketoamides in the presence of *n*BuOH and base has been realized with high yields, providing a new, direct, and efficient synthetic strategy to obtain 3-hydroxyoxindoles.

The predominantly electrophilic reactivity of aryl and vinyl organopalladium intermediates derived from the corresponding halides by an oxidative addition process with a Pd(0) catalyst is well established.[1] Conversely their use as nucleophiles has received much less attention although literature precedent exists and includes reactions with aldehydes,[2] ketones,[3] imines,[4] esters and amides,[5] anhydrides[6] and nitriles.[7] The direct catalytic addition reaction of aryl and vinyl halides to electrophilic partners is attractive since no extra organometallic reagents are needed. In the context of our interest in the synthesis of oxindoles[8] we envisioned that it might be possible to obtain 3-hydroxyoxindoles by an intramolecular addition of aryl halides to α-ketoamides using a Pd catalyst. This would provide a direct access to these compounds avoiding the use of Grignard-, organoborane-, or organolithium-reagents (Scheme 1).[9] Herein, we report the preliminary results of this new synthetic strategy to oxindoles.

The model substrate **1a** was prepared by condensation of *N*-methyl *o*-bromoaniline and 2-oxo-2-phenylacetyl chloride. Initial attempts to use Pd(PPh$_3$)$_4$ as a catalyst were not efficient for the transformation **1a** → **2a** and attempts to improve results by modifications of base, solvent, and additives were not successful. The best result was a 17% yield of **2a** with 5 mol% Pd(PPh$_3$)$_4$ in toluene at 110 °C for 24 h in the presence of 2 eq. Na$_2$CO$_3$ and 10 eq. NEt$_3$. Using *n*BuOH as solvent afforded **3a** and only trace amounts of **2a**. We then focused on the use of electron-rich ligands,[10] which should favour



Scheme 1 New route to 3-hydroxyoxindoles.

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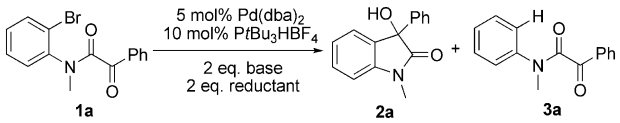
oxidative addition of the catalyst to the aryl bromide and, more importantly, facilitate the nucleophilic attack of the Pd–aryl intermediate on the ketone. Indeed, when 10 mol% P*t*Bu$_3$·HBF$_4$ was used as a ligand precursor, the reaction of **1a** proceeded smoothly in the presence of 5 mol% Pd(dba)$_2$, 2 eq. Cs$_2$CO$_3$, and 2 eq. *n*BuOH in toluene at 50 °C giving oxindole **2a** in 76% isolated yield along with 19% of the corresponding hydrodehalogenation side product **3a** (Table 1, entry 1). We note that these conditions are milder than those reported previously for this type of reaction—*e.g.* 100–150 °C for intramolecular additions to ketones.[3] Solvent examination revealed toluene to be the best choice as low yields (<15%) were observed in ether solvents such as THF, DME (1,2-dimethoxy ethane), and 1,4-dioxane. In DCE (1,2-dichloroethane) product yield was 54% after 20 h, while in DMF the reaction was completely suppressed. Although the best result was obtained when *n*BuOH was used as an additive, MeOH and EtOH afforded slightly lower yields whereas *i*PrOH gave a poor product yield (entries 4–6). In the absence of an additive, the reaction fails, as has been also reported by the Yamamoto group.[3b] Interestingly, instead of an alcohol H$_2$ (1 bar) could be used to promote this reaction with comparable yield (entry 7). Moderate yields of **2a** were observed when *n*Bu$_3$SnH and Et$_3$SiH were used and for the former no side product **3a** was detected (entries 8, 9).

Variation of the base revealed this to be an important factor. No reactions took place in the presence of Cy$_2$NMe, KF, KOAc, Li$_2$CO$_3$, and Na$_2$CO$_3$. With K$_2$CO$_3$ as base, oxindole **2a** could be isolated in 23% yield after 24 hours (entry 10). Finally, K$_3$PO$_4$·H$_2$O was found to be the best base giving the highest yield of the product albeit a longer reaction time was needed to achieve full conversion at 50 °C (entry 11). Increasing the temperature to 80 °C resulted in complete reaction in 7 hours and **2a** was isolated in 88% yield along with 7% side product **3a** (entry 12). Further investigation of the ligand showed that PCy$_3$ was also suitable (entry 13), while dppe (1,2-bis(diphenylphosphino)ethane) and 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (SIPr·HCl) as ligand or ligand precursor were inefficient in this reaction.

The optimum reaction conditions were then applied to the substrates shown in Table 2. Yields are generally good (81–92%). It is noteworthy that the reaction to oxindole **2d** with CF$_3$ as an electron-withdrawing group was complete in 3 h, while 14 h were required for the reaction of substrate **1e** with an *o*-MeO group. Not only *N*-Me substrates but also an *N*-benzyl amide (**2i**) could be used, but no reaction took place for the free *N*-H substrate (R^1 = R^2 = H, Ar = Ph).

The reaction is sensitive to the aryl halide used (eqn (1)). In comparison with **1a**, no reaction took place for the analogous

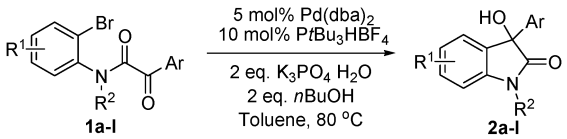
Table 1 Optimization of reaction conditions[a]

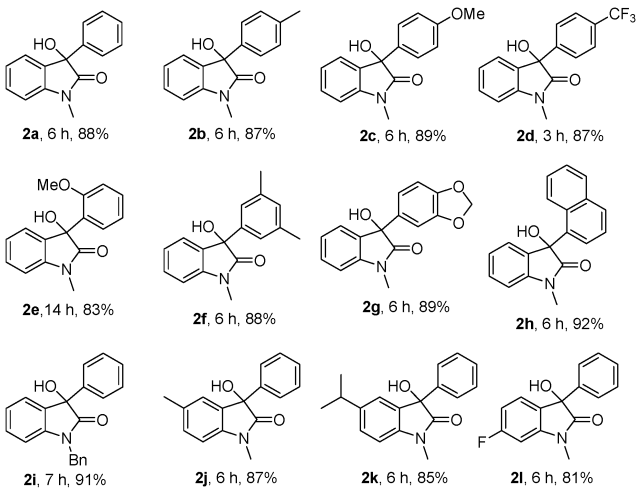


Entry	Base	Solvent	Reductant	Temp./°C	Time/h	Y[b] (%) (**2a**/**3a**)
1	Cs_2CO_3	Toluene	*n*BuOH	50	7	76/19
2	Cs_2CO_3	DCE	*n*BuOH	50	20	54/nd
3	Cs_2CO_3	*t*BuOMe	*n*BuOH	50	20	29/nd
4	Cs_2CO_3	Toluene	MeOH	50	7	69/nd
5	Cs_2CO_3	Toluene	EtOH	50	7	71/nd
6	Cs_2CO_3	Toluene	*i*PrOH	50	16	21/nd
7[c]	Cs_2CO_3	Toluene	H_2	100	12	62/28
8	Cs_2CO_3	Toluene	nBu_3SnH	100	24	43/0
9	Cs_2CO_3	Toluene	Et_3SiH	50	12	58/23
10	K_2CO_3	Toluene	*n*BuOH	80	24	23/nd
11	$K_3PO_4{\cdot}H_2O$	Toluene	*n*BuOH	50	30	85/9
12	$K_3PO_4{\cdot}H_2O$	Toluene	*n*BuOH	80	7	88/7
13[d]	$K_3PO_4{\cdot}H_2O$	Toluene	*n*BuOH	80	9	85/7

[a] 0.4 mmol scale in 8 mL solvent. [b] Isolated yield. nd = not determined. [c] With a hydrogen balloon. [d] 10 mol% PCy_3 was used instead of $PtBu_3{\cdot}HBF_4$.

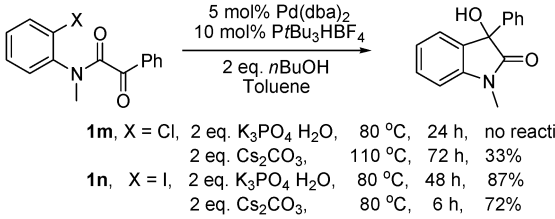
Table 2 Substrate scope[a]





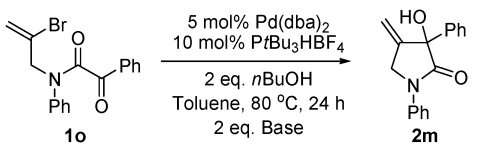
[a] 0.4 mmol scale in 8 mL toluene.

chloride substrate **1m**. Noteworthy, the reaction of the iodo substrate **1n** was slower than that of the bromo substrate **1a** and 48 h were needed to achieve full conversion. Since the reaction of **1a** with Cs_2CO_3 as base was faster than with $K_3PO_4{\cdot}H_2O$, we introduced Cs_2CO_3 to the reactions of these two substrates. Product **2a** was isolated in 72% yield from **1n** after 6 h at 80 °C and in 33% yield from **1m** after 72 h at 110 °C. Interestingly, the reaction of **1a** under standard conditions was suppressed in the presence of 3.0 eq. LiI as additive and only traces of oxindole **2a** were detected after 48 h.



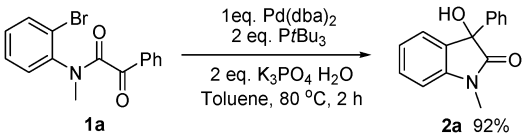
(1)

Vinyl bromide substrate **1o** was synthesized and applied in the reaction (eqn (2)). Pyrrolidinone product **2m** could be obtained; yields were low (16% for $K_3PO_4{\cdot}H_2O$ as base, 29% for Cs_2CO_3).



(2)

Next, experiments designed to shed light on mechanistic aspects of the reaction were carried out. As shown in eqn (3), oxindole **2a** could be isolated in 92% yield with stoichiometric Pd(0)/$PtBu_3$ complex in the absence of *n*BuOH, thus demonstrating that Pd(0) can perform the same role as Mg in Grignard reactions. As mentioned above, catalytic use of Pd requires an additive and primary alcohols performed best. An earlier study of an intramolecular aryl addition to ketones, catalysed by Pd with added 1-hexanol,[3b] reported that the alcohol was recovered. Our findings are different. Using piperonyl alcohol, as shown in eqn (4), piperonyl aldehyde was isolated in 95% yield. This confirms the role of the alcohol as reductant in the reaction and thus closing the catalytic cycle. Also, the deuterated dehalogenation side product was detected when MeOH-d_4 was used (eqn (5)).



(3)

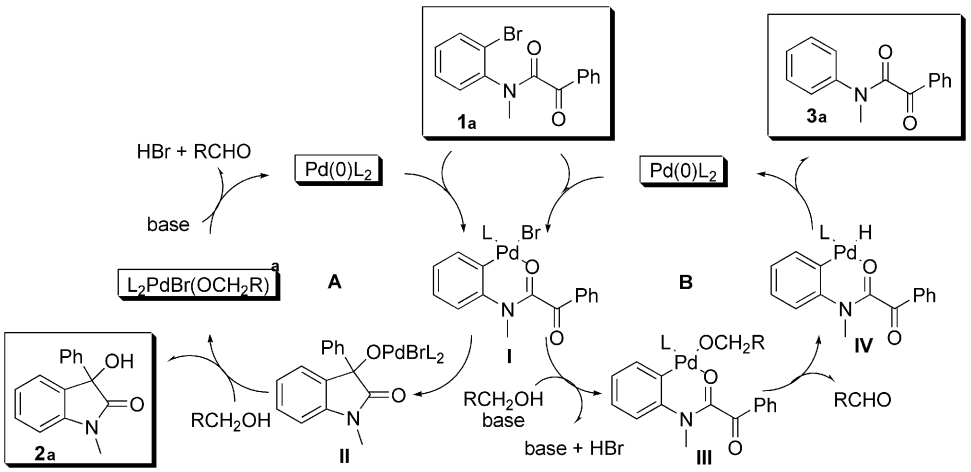
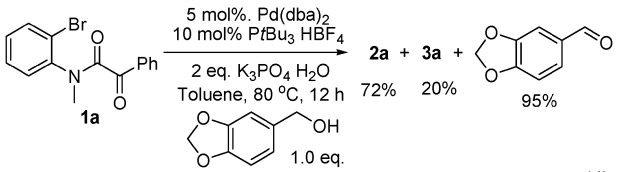
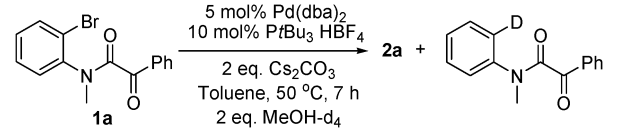


Fig. 1 Proposed mechanism.



(4)



(5)

Based on the above, we propose the mechanism shown in Fig. 1. The oxindole is formed by intramolecular addition of the oxidative addition intermediate **I** to the ketone. Alkoxy-ligand exchange **II** (cycle A) liberates product **2a** and the Pd(0) catalyst is regenerated by β-H elimination (aldehyde formation) followed by base assisted reductive elimination. For the hydrodehalogenation side product **3a** we propose halide–alcoholate ligand exchange in **I** to give **III** (cycle B). β-Elimination followed by reductive elimination affords **3a** (cycle B). The observation of the deuterated side product shown in eqn (5) supports this pathway.

In summary, we have developed a new and efficient procedure to synthesize 3-hydroxyoxindole compounds in high yields by applying palladium-catalysed direct addition of aryl halides to α-ketoamides. Both, electron-rich phosphine ligands and a reductant (alcohol, H_2) are crucial. The formation of a new stereogenic center in **2** is another important aspect that is receiving attention in ongoing research.

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10 Although PCy_3 has been used as a ligand in a similar addition reaction of simple ketone substrates (ref. 3*b*), no reaction took place from **1a** to **2a** using the reported conditions (5 mol% $Pd(OAc)_2$, 10 mol% PCy_3, 2 eq. Na_2CO_3, 5 eq. 1-hexanol in DMF).

