



A robust, efficient catalyst system for enolate arylation leading to quaternary 3-aminoxindoles

Emma L. Watson^a, Stephen P. Marsden^{a,*}, Steven A. Raw^b

^aSchool of Chemistry and Institute of Process Research and Development, University of Leeds, Leeds LS2 9JT, UK

^bAstraZeneca Process R&D, Charter Way, Silk Road Business Park, Macclesfield SK10 2NA, UK

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ABSTRACT

A catalyst screening programme has revealed that a combination of Pd(0) and the *N*-heterocyclic carbene ligand SIPr forms a particularly robust and efficient catalyst for the formation of important quaternary 3-aminoxindoles via intramolecular enolate arylation. Catalyst loadings of 0.1 mol % give complete conversion in under 4 h.

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The 3,3-disubstituted oxindole skeleton occurs commonly in medicinally active compounds of both natural and synthetic origin. Amongst these structures, compounds bearing heteroatom substituents occur frequently, as in the 3-hydroxyoxindole growth hormone secretagogue SM-130686 (**1**),¹ the 3-aminoxindole vasopressin V1b receptor antagonist SSR-149415 (**2**)² and in the 3-fluorooxindole Maxi-K channel opener BMS-204352 (**3**, Fig. 1).³

We have recently reported convenient syntheses of quaternary 3-alkoxy⁴ and 3-aminoxindoles⁵ by intramolecular palladium-catalysed arylation⁶ of *ortho*-bromoanilides of readily prepared α -alkoxy and α -amino acid derivatives. In collaboration with the group of Kündig, highly enantioselective variants of these reactions were also reported,⁷ which constitute the first *de novo* asymmetric approach to aminooxindole derivatives.

In our initial reports^{4,5}, we found that the conventional reactions were extremely sluggish and that efficient conversions could most conveniently be achieved under microwave irradiation using 10 mol % of a catalyst derived from palladium(II) acetate and tricyclohexylphosphine. Such high catalyst loadings are common in oxindole-forming arylation reactions, with 5–10 mol % of the palladium source being used in nearly all reported examples.^{8,9} This requirement undoubtedly reflects the highly hindered nature of the substrates as well as the relatively high pK_a of the anilides, since efficient catalyst systems (1 mol % of palladium or less) have been reported for the intermolecular arylation of ketones,¹⁰ esters¹¹ and

zinc enolates of amides.¹² With respect to the 3-aminoxindoles, the high catalyst loadings and the necessity for microwave irradiation present economic and practical barriers to the potential scale-up of these reactions, even within a laboratory setting. We therefore sought to establish more efficient conditions for the arylation under standard convection heating conditions, and report herein a robust catalyst system based upon a palladium(0)/NHC complex capable of operating at loadings of 0.1 mol %.

In our previous microwave study, we had employed the Pd(OAc)₂/PCy₃ catalyst system reported by Hartwig as optimal for oxindole formation.⁵ Repeating the reactions using conventional convection heating gave very poor conversion after 24 h (at best 14% oxindole). Previous poor results with Pd(PPh₃)₄ had led us to avoid palladium(0) complexes, but we were encouraged to rethink this approach by the reported excellent performance of the pre-formed complex Pd(P^tBu₃)₂ in amide and ester enolate

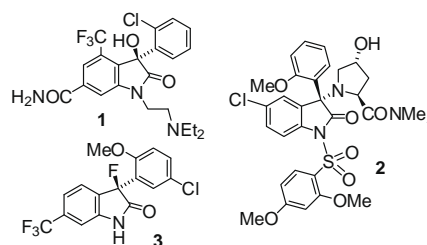
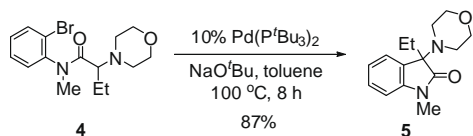


Figure 1. Representative 3-hetero-substituted oxindoles.

* Corresponding author. Tel.: +44 113 343 6425; fax: +44 113 343 6565.
E-mail address: s.p.marsden@leeds.ac.uk (S.P. Marsden).



Scheme 1. Aminooxindole formation using Pd(P^tBu_3)₂.

arylations.^{11,12} In the event, we were pleased to find that on treating substrate **4** with 10% Pd(P^tBu_3)₂ under conventional heating at 100 °C for 8 h, an 87% yield of oxindole **5** was obtained (Scheme 1). By contrast, a reaction employing the same ligand but with Pd(OAc)₂ as the palladium source gave only a 5% yield after heating at reflux for 24 h (67% recovered starting material).

These results suggested that Pd(0)-based systems may prove to be superior catalysts for the transformation, and a ligand and solvent screen was therefore carried out using 5 mol % of Pd₂(dba)₃ (10 mol % palladium) and 10 mol % of a ligand. The ligands chosen were PCy₃, P^tBu_3 (both added as their air-stable tetrafluoroborate salts), BINAP, DavePhos and the *N*-heterocyclic carbene derived from *N,N'*-bis(2,6-diisopropylphenyl)-4,5-dihydro-imidazolium chloride (SIPr), while the solvents selected were toluene, anisole, dimethoxyethane (DME) and cyclopentyl methyl ether (CPME). The latter is increasingly popular amongst process chemists owing to its high boiling point and low propensity for peroxide formation.

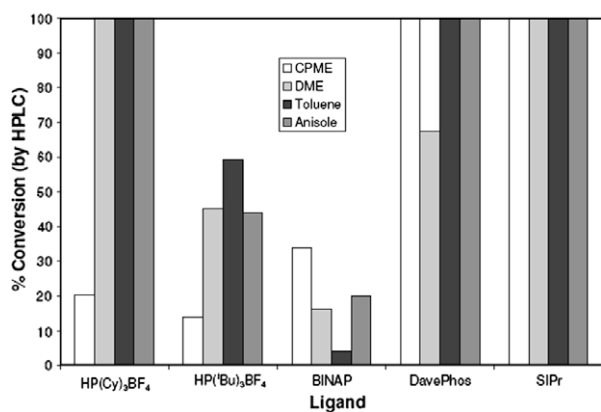


Figure 2. Conversion of compound **4** after 8 h, using 10 mol % catalyst loading and 3 equiv NaOtBu. Reactions in CPME and DME were run at 80 °C, those in toluene and anisole were run at 100 °C.

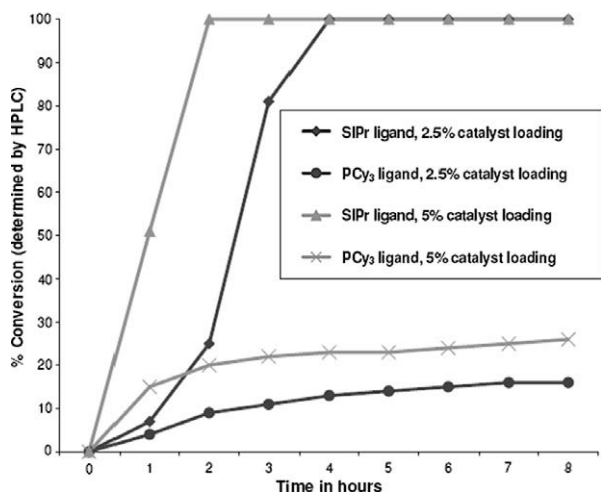


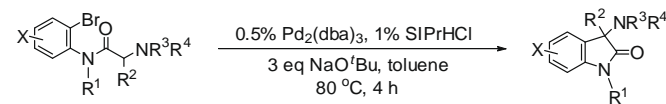
Figure 3. Conversion of compound **4** using 2.5 and 5 mol % of Pd(0)/ligand.

Conversions after 8 h were measured by HPLC and the results are shown in Figure 2.

From this, we established that tricyclohexylphosphine, DavePhos and SIPr offered good conversions across a range of solvents. The use of other NHC ligands with Pd₂(dba)₃ gave poorer results

Table 1

Substrate scope of low-loading Pd₂(dba)₃/SIPr-catalysed aminooxindole formation



Entry	Product	Yield ^a (%)
1		88 (83 ^b)
2		73
3		81
4		65
5		88
6		89
7		81
8		71
9		68
10		69

^a Isolated yield.

^b Yield using 0.05 mol % Pd₂(dba)₃/0.1 mol % SIPrCl.

than SIPr,¹³ while interestingly the preformed Pd(II)-SIPr complex PEPPSi¹⁴ returned the product in a reduced 45% yield. The reaction tolerates the range of solvents but formation of the oxindole product was accompanied by hydrodebrominated starting material (between 1% and 8%) when using ethereal solvents, and so we elected to continue our studies with toluene.

We next sought to examine the behaviour of the two most effective ligands (PCy₃ and SIPr) at lower catalyst loadings. The reaction of **4** was therefore repeated with both ligands at 5% and 2.5% loadings, analysing for conversion by HPLC at hourly intervals. As can be seen from Figure 3, at these lower loadings the SIPr-derived catalyst demonstrates markedly superior performance, with full conversion being obtained inside 2 h at 5 mol % and 4 h at 2.5 mol %.

This catalyst system was therefore adopted as optimal, and we next sought to demonstrate the substrate scope of the process. Thus, the catalyst was screened at 1 mol % loading against ten substrates and the results are shown in Table 1.^{15,16} Pleasingly, the Pd(O)/SIPr system performed well across a broad range of substrates at this lower catalyst loading and temperature. The yields of the 3-alkyl-substituted oxindoles are comparable to those previously reported, giving an average yield for compounds **5–7** of 81%, cf. 83% under the high loading, microwave-mediated conditions.⁵ Moreover, we were pleased to note that the 3-aryl-substituted oxindoles performed consistently better under the new conditions, with the average yield for compounds **10–12** being 10% higher than the previous values at 80%. This may reflect reduced substrate and/or enolate decomposition at the lower reaction temperatures. The novel fluorinated oxindoles **8** and **13** were formed in slightly lower yields than their non-fluorinated counterparts, suggesting a negative impact of the electronegative atom upon the reaction. Finally, we were pleased to note that *N*-benzyl protecting groups and 3-indolyl substituents were both tolerated (entries 5 and 10). In particular, no trace of the product of direct C2-arylation of the indole was seen in the crude NMR of **14**, in contrast with the previously reported conditions.⁵

Finally, we elected to study the reaction at still lower loading, to gauge the robustness of the system. Using a 0.1 mol % palladium/ligand loading, we were delighted to find that formation of oxindole **5** was still complete within 4 h (entry 1), giving an isolated yield of 83%. This represents the lowest catalyst loading used to form oxindoles to date.

In summary, we have developed an effective and robust new methodology for the formation of oxindoles using standard convection heating rather than microwave irradiation. Examples representing the lowest catalyst loadings used in enolate arylation reactions to date are found. Given the challenging nature of the cyclisation substrates under study here, it is expected that this catalyst system will offer improved performance in a range of other arylation reactions.

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- Standard experimental protocol for arylations*: To a mixture of Pd₂(dba)₃ (0.0014 mmol), 1,3-bis-(2,6-diisopropylphenyl)-imidazolium chloride (0.0028 mmol) and Na^tBu (0.84 mmol) was added toluene (1.2 mL). A solution of the substrate (0.28 mmol) in toluene (minimum to dissolve the substrate) was added and the mixture was stirred and heated to 80 °C for 4 h. The reaction mixture was cooled and concentrated under reduced pressure to leave a dark brown powdery residue. This was dry loaded onto a silica gel column and purified by chromatography.
- All oxindoles have been previously reported in Ref. 5, apart from the following. **Compound 8**: $\nu_{\max}/\text{cm}^{-1}$ (film) 2967, 2855, 1713, 1619; δ_{H} (300 MHz, CDCl₃) 7.07–6.96 (2H, m, ArH), 6.74 (1H, dd, *J* 8.4, 4.1, ArH), 3.70–3.59 (4H, m, O(CH₂)₂), 3.17 (3H, s, CH₃), 2.68–2.58 (4H, m, N(CH₂)₂), 2.00–1.92 (2H, m, CH₂), 0.67 (3H, t, *J* 7.4, CH₃); δ_{C} (75 MHz, CDCl₃) 177.5, 159.8 (d, ¹*J*_{CF} 239.3), 140.4, 131.8 (d, ³*J*_{CF} 7.5), 115.3 (d, ²*J*_{CF} 23.3), 112.7 (d, ²*J*_{CF} 24.8), 108.7 (d, ³*J*_{CF} 7.5), 71.3, 67.9, 47.6, 27.6, 26.2, 8.0; HRMS: *m/z* calculated for C₁₅H₂₀FN₂O₂ [MH⁺]: 279.1503; found 279.1496. **Compound 13**: $\nu_{\max}/\text{cm}^{-1}$ (film) 2960, 2855, 1712, 1618; δ_{H} (300 MHz, CDCl₃) 7.53 (2H, m, ArH), 7.37–7.27 (3H, m, ArH), 7.10–7.00 (2H, m, ArH), 6.78 (1H, dd, *J* 8.5, 4.1, ArH), 3.80–3.57 (4H, m, O(CH₂)₂), 3.23 (3H, s, CH₃), 2.69–2.45 (4H, m, N(CH₂)₂); δ_{C} (75 MHz, CDCl₃) 175.7, 159.6 (d, ¹*J*_{CF} 242.2), 139.9, 138.3, 131.1 (d, ³*J*_{CF} 7.5), 129.1, 128.7, 127.9, 115.6 (d, ²*J*_{CF} 23.3), 114.2 (d, ²*J*_{CF} 24.8), 109.2 (d, ³*J*_{CF} 8.3), 74.8, 67.9, 48.0, 26.6; HRMS: *m/z* calculated for C₁₉H₂₀FN₂O₂ [MH⁺]: 327.1503; found 327.1499.