Palladium-catalysed synthesis of 2-substituted indoles

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2-Iodoaniline reacts with ketones in dioxane under reflux in the presence of a catalytic amount of $Pd(dba)_2$/1, 1′-bis(di-*iso*-propylphosphino)ferrocene along with NaO^{t}Bu to afford 2-substituted indoles regioselectively in moderate to good yield.

Keywords: α-arylation, 2-iodoaniline, indoles, ketones, palladium catalyst

The palladium-catalysed α-arylation of ketones with aryl halides and triflates is a useful synthetic tool,[1] which was developed by the following three groups almost simultaneously. It was reported by Muratake and Natsume that ketones are intramolecularly α-arylated with contiguous bromides (or triflates) in the presence of a palladium catalyst to give bridged (or spiro) compounds and phenol derivatives.[2] Buchwald *et al.*[3] and Hartwig *et al.*[4] have also reported an intermolecular palladium-catalysed α-arylation of ketones with aryl halides in the presence of a chelating ligand and a base. This α-arylation protocol has recently been used to construct naphthalenes[5] and indoles.[6] We report an α-arylative cyclisation of ketones with 2-iodoaniline with a palladium catalyst and 1,1'-bis(di-*iso*-propylphosphino)ferrocene leading to the regioselective synthesis of 2-substituted indoles.[7]

The results of several attempted α-arylative cyclisations between 2-iodoaniline (**1**) and acetophenone (**2a**) are listed in Table 1. Treatment of equimolar amounts of **1** and **2a** in the presence of a catalytic amount of $Pd(dba)_2$ (dba = dibenzylideneacetone) and 1,1'-bis(di-*iso*-propylphosphino) ferrocene (dipf) and NaO^{t}Bu under reflux for 20 h afforded 2-phenylindole (**3a**) in 30% yield (entry 1). Tuning the molar ratio of **2a** to **1** was critical for the effective formation of **3a**. The product yield increased with increase in the molar ratio of [**2a**]/[**1**] up to 1.5 (entries 2, 5 and 6). The result shown in entry 3 is the preferred choice for the effective formation of **3a**. The ligand dipf in terms of yield was the ligand of choice. With other phosphorus chelating ligands such as 1,1'-bis(diphenylphosphino)ferrocene (dppf) and 1,3-bis(diphenylphosphino)propane (dppp) combined with $Pd(dba)_2$, the yield of **3a** was lower than that when dipf was employed (entries 4 and 5). It is known that electron-rich phosphine ligands such as 2-methyl-2'-dicyclohexylphosphinobiphenyl,[1] P(^{t}Bu)$_3$, and 1,1'-bis(di-*tert*-butylphosphino) ferrocene[8] combined with $Pd(OAc)_2$ (or $Pd(dba)_2$) are highly active catalytic systems for the α-arylation of ketones with aryl halides. The catalytic system using PPh_3 combined with $Pd(dba)_2$ was as effective as that using the bidentate ligands (dppf and dppp) combined with $Pd(dba)_2$ (entry 7).

Given the controlled reaction conditions, various ketones were employed to investigate the scope of the reaction. The results are summarised in Table 2. Aryl(methyl) ketones (**2a**–**2g**) were readily α-arylatively cyclised with **1** irrespective of the functional groups on the aromatic ring to give the corresponding 2-arylindoles (**3a**–**3g**) with yields in the range of 60–75%. The indole yield was not significantly affected by the position and electronic nature of the substituent on the aromatic ring of the ketones. The reaction also took place with 2-naphthophenone (**2h**) to afford 2-(2-naphthyl)indole (**3h**) in 74% yield. The reaction proceeds likewise with heteroaryl (methyl) ketone **2i** to give the corresponding 2-heteroaryl substituted indole **3i**. With alkyl(methyl) ketones **2j** and **2k** which have both methyl and methylene reaction sites,

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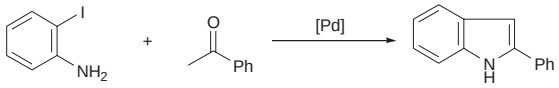
Table 1 Reactions under various conditions[a]

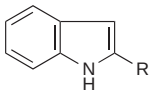
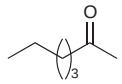
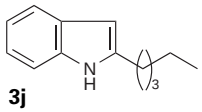
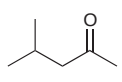
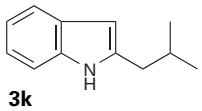
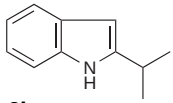


1 **2a** **3a**

Entry	[**2a**]/[**1**]	$Pd(dba)_2$ (mmol)	Ligand (mmol)	Solvent	Yield/%[b]
1	1	0.02	dipf (0.024)	Dioxane	30
2	1.5	0.02	dipf (0.024)	Dioxane	62
3	1.5	0.05	dipf (0.06)	Dioxane	71
4	1.5	0.1	dppf (0.12)	Toluene	35
5	1.5	0.1	dppp (0.12)	Dioxane	34
6	3	0.1	dppp (0.12)	Toluene	35
7	1.5	0.1	PPh_3 (0.24)	Dioxane	35

[a]Reaction conditions: **1** (1 mmol), NaO^{t}Bu (2.2 mmol), solvent (10 ml), under reflux, for 20 h. [b]Isolated yield based on **1**.

Table 2 Palladium-catalysed synthesis of indoles[a]

Ketones **2**	Indoles **3**	Isolated yield/%
		
2a R = Ph	**3a** R = Ph	71
2b R = 2-MeC_6H_5	**3b** R = 2-MeC_6H_5	66
2c R = 3-MeC_6H_5	**3c** R = 3-MeC_6H_5	68
2d R = 4-MeC_6H_5	**3d** R = 4-MeC_6H_5	69
2e R = 4-$MeOC_6H_5$	**3e** R = 4-$MeOC_6H_5$	60
2f R = 4-FC_6H_5	**3f** R = 4-FC_6H_5	68
2g R = 3-$CF_3C_6H_5$	**3g** R = 3-$CF_3C_6H_5$	75
2h R = 2-naphthyl	**3h** R = 2-naphthyl	74
2i R = 2-thienyl	**3i** R = 2-thienyl	51
		36
2j	**3j**	
		31
2k	**3k**	
		30[b]
2l	**3l**	

[a]Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), $Pd(dba)_2$ (0.05 mmol), dipf (0.06 mmol), NaO^{t}Bu (2.2 mmol), dioxane (10 ml), under reflux, for 20 h. [b]The reaction was carried out at 110°C in autoclave.

although the product yield was lower than that when aryl(methyl) and heteroaryl(methyl) ketones were used, the α-arylation took place exclusively at less hindered methyl position. This eventually led to the regioselective formation of 2-substituted indoles **3j** and **3k** by subsequent cyclodehydration. It is known that, in palladium-catalysed α-arylation of ketones with aryl halides, regioselectivity in favour of arylation occurs at the less-hindered methyl position over α-methylene and -methine occurs.[3,4] The reaction of alkyl(methyl) ketone **2l** which has methyl and methine reaction sites, with **1** also proceeds to give 2-isopropylindole (**3l**) in 30% yield.

In summary, we have demonstrated that ketones are α-arylatively cyclised with 2-iodoaniline under the reaction conditions of $Pd(dba)_2$/1,1'-bis(di-*iso*-propylphosphino) ferrocene/NaO^{t}Bu/dioxane to afford indoles in moderate to good yields. With alkyl(methyl) ketones, the α-arylation took place exclusively at the less hindered methyl position to give 2-substituted indoles regioselectively.

Experimental

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF_{254}, Merck). $Pd(dba)_2$ was prepared by the reported method.[9] Commercially available organic and inorganic compounds were used without further purification.

General experimental procedure: A solution of 2-iodoaniline (0.219 g, 1 mmol), ketone (1.5 mmol), $Pd(dba)_2$ (0.029 g, 0.05 mmol), 1,1'-bis(di-*iso*-propylphosphino)ferrocene (0.025 g, 0.06 mmol), and NaO^{t}Bu (0.211 g, 2.2 mmol) in dioxane (10 ml) was heated under reflux for 20 h. The reaction mixture was filtered through a short silica gel column using ethyl acetate–chloroform as an eluent to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give indoles. Compounds **3a**,[10] **3d**,[11] **3e**,[12] **3f**,[13] **3h**,[14] **3i**,[15] **3j**,[16] **3k**[17] and **3l**[18] are known.

2-(2-Methylphenyl)indole (**3b**): M.p. 92–93°C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 6.61 (s, 1H), 7.12–7.32 (m, 5H), 7.38 (d, J = 8.0 Hz, 1H), 7.44–7.47 (m, 1H), 7.65 (d, J = 7.5 Hz, 1H), 8.09 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6 (*C*H$_3$), 103.4 (3-*C*H), 111.2 (7-*C*H), 120.5, 121.0, 122.5, 126.5, 128.4, 129.3, 129.4, 131.5, 133.1, 136.5, 136.6, 137.9; Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76; found C, 86.67; H, 6.28; N, 6.83.

2-(3-Methylphenyl)indole (**3c**): M.p. 140–142°C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 6.79 (s, 1H), 7.11–7.19 (m, 3H), 7.27–7.35 (m, 2H), 7.40–7.44 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 8.22 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5 (*C*H$_3$), 99.8 (3-*C*H), 110.9 (7-*C*H), 120.2, 120.6, 122.2, 122.3, 125.9, 128.5, 128.9, 129.3, 132.2, 136.7, 138.0, 138.6; Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76; found C, 86.75; H, 6.30; N, 6.85.

2-(3-Trifluoromethylphenyl)indole (**3g**): M.p. 145–147°C (EtOH); ^{1}H NMR ($CDCl_3$) δ 6.89 (s, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.21–7.25 (m, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.51–7.55 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.80–7.81 (m, 1H), 7.87 (s, 1H), 8.32 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 103.6 (3-*C*H), 113.5 (7-*C*H), 123.0, 123.3, 124.1 (q, J = 3.9 Hz), 125.4, 126.4 (q, J = 270.5 Hz, *C*F$_3$), 126.5 (q, J = 3.9 Hz), 130.6, 131.4, 131.9, 133.9 (q, J = 31.9 Hz, *C*CF$_3$), 135.6, 138.6, 139.4; Anal. Calcd for $C_{15}H_{10}NF_3$: C, 68.96; H, 3.86; N, 5.36; found C, 68.77; H, 3.80; N, 5.57.

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