EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402474

Di-*tert*-butylneopentylphosphine (DTBNpP): An Efficient Ligand in the Palladium-Catalyzed α-Arylation of Ketones

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Keywords: Synthetic methods / C–C coupling / Palladium / Phosphane ligands / Heterocycles / Ketones

Di-*tert*-butylneopentylphosphine (DTBNpP) and palladium(II) acetate provide an efficient catalytic system for the α-arylation of ketones. Aryl bromides were coupled with ketones using 0.25–0.5 mol-% $Pd(OAc)_2$/DTBNpP in toluene at 50 °C, whereas aryl chlorides required a higher catalyst loading (0.5–2.0 mol-%) and a higher temperature (80 °C). Coupling of 2-bromophenol with ketones using the Pd/DTBNpP system provides an efficient route for the synthesis of benzofurans.

Introduction

The palladium-catalyzed α-arylation of carbonyl derivatives originally reported by Buchwald,[1] Hartwig,[2] and Miura[3] has become a powerful method for synthesis of 2-aryl carbonyl derivatives.[4] The utility of this methodology has been demonstrated in the synthesis of complex natural products and in process-level production of active pharmaceutical intermediates.[5] There have been great advances over the past decade towards the α-arylation of various carbonyl groups. Sterically demanding, electron rich mono-[6] and bidentate[7] phosphines and N-heterocyclic carbenes[8] provide highly active catalysts for the coupling of aryl halides and pseudohalides with a range of carbonyl derivatives.

Coupling of aryl halides with silyl enol ethers is an alternate approach to palladium-catalyzed synthesis of α-aryl carbonyl derivatives. Verkade and Hartwig reported that $Pd(OAc)_2$/TTBP gave high yields in the presence of a mixture of CsF and Bu_3SnF.[9] In 2010, Shreeve, et al. reported that silicon reagents with bulky substituents increase the yield of desired α-arylated products.[10] In this methodology, it was discovered that a fluorine in the α position of the silyl enol ether improved reaction rates. A drawback of this method is that it requires an extra synthetic step to generate the silyl enol ether from a ketone precursor.

Enolate α-arylation is highly sensitive to the steric and electronic environment at the catalyst center. The ligand properties affect whether the enolate prefers to be *O*- or *C*-bound as well as the rate of reductive elimination.[11] Our group has reported the use of di-*tert*-butylneopentylphosphine (DTBNpP)[12] in palladium-catalyzed C–N and C–C bond-forming reactions (Figure 1).[13] The neopentyl group provides a unique set of steric effects compared to that of *tert*-butyl groups. Whereas the *tert*-butyl group provides a relatively constant steric influence as a function of conformational changes, the neopentyl substituent affords a conformationally flexible steric influence. Calculated structures for $Pd(PR_3)$ complexes predict small Pd–P–C–C dihedral angles for the neopentyl group, leading to a larger steric influence than is exerted by *tert*-butyl [solid cone angles: TTBP (194°) < DTBNpP (198°) < TBDNpP (210°) < TNpP (227°)].[13a] Similar conformations are seen in X-ray structures of $Pd(PR_3)_2$ complexes of these ligands.[14] Structurally characterized four-coordinate Pd^{II} complexes have larger Pd–P–C–C dihedral angles for the neopentyl substituent than are seen for two-coordinate Pd^0 complexes, resulting in a lower steric demand. This diminished steric demand allows Pd-TNpP complexes to be effective catalysts in the coupling of sterically demanding substrates.[15] We envisioned that α-arylation of ketones would be an interesting platform in which to explore the steric effects of neopentyl ligands.

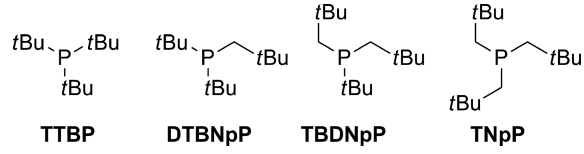

Figure 1. Neopentylphosphine ligands.

Our group, in collaboration with Colacot, reported initial results on the α-arylation of ketones using Pd-DTBNpP catalysts generated in situ [$Pd_2(dba)_3$/DTBNpP] or from Pd(0, I, or II) precatalysts.[14] The application of Pd(η^3-allyl)(DTBNpP)Cl and $Pd(DTBNpP)_2$ resulted in good

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402474.

yields for the coupling of aryl bromides and chlorides with propiophenone, whereas catalysts formed in situ from $Pd_2(dba)_3$ and DTBNpP were less effective. We sought to identify conditions where the in situ-generated catalyst could be used effectively. Herein, we report that the catalyst formed from $Pd(OAc)_2$/DTBNpP is highly effective in the synthesis of α-arylated compounds from aryl bromides and chlorides and also in condensations of 2-bromophenol with ketones to afford benzofurans.

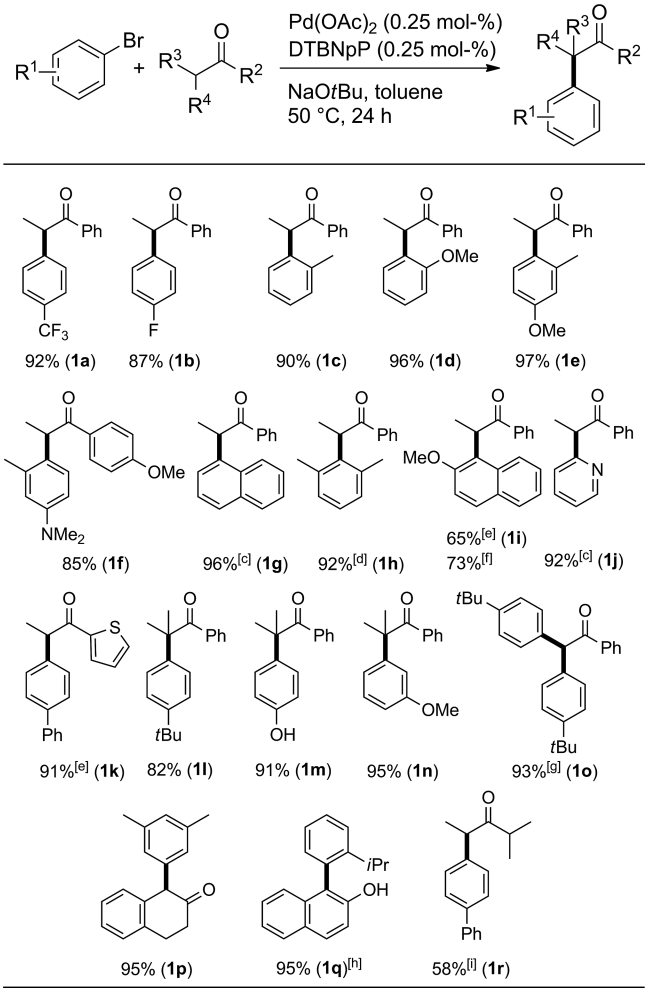
Results and Discussion

Initial optimization of the coupling of 2-bromotoluene and propiophenone with a variety of inorganic bases (i.e. NaO*t*Bu, Na_2CO_3, K_3PO_4 etc.) and amine bases (Et_3N, iPr_2NEt, Cy_2NMe, etc.) showed NaO*t*Bu to be the optimal base. Different polar and non-polar solvents, along with varying temperatures, were applied to our substrates; toluene was found to be a suitable solvent producing high product yields at 50 °C. Under these conditions, high yields were obtained using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP.

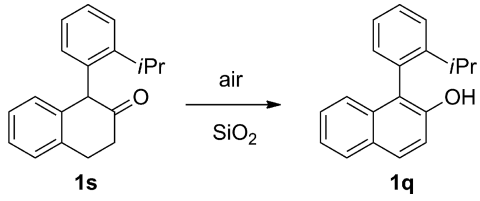
With these optimized conditions in hand, a variety of aryl bromides were coupled with ketones (Table 1). Propiophenones were efficiently coupled to a range of aryl bromides with high selectivity for the monoarylation product. Excellent yields were obtained for aryl bromides with either no, or one, *ortho*-substituent (**1a**–**1g**). Both electron-deficient and electron-rich aryl bromides gave good yields. The more hindered 2-bromo-*m*-xylene gave low conversions to **1h** using DTBNpP. However, the use of the more sterically flexible TNpP ligand provided a 92% yield of **1h**. We have seen similarly improved performance for Pd/TNpP catalysts in the coupling of hindered aryl halides with arylamines.[15] In the case of 1-bromo-2-methoxynaphthalene, high yields of **1i** were achieved using the DTBNpP ligand, although 1 mol-% of $Pd(OAc)_2$ was necessary. A slightly improved yield was achieved using $Pd_2(dba)_3$ (0.5 mol-%) instead of $Pd(OAc)_2$. The heterocyclic substrate 2-bromopyridine was tolerated by the catalyst, although a slightly increased catalyst loading [0.5 mol-% $Pd(OAc)_2$] was required to achieve high yields. The use of 1-(2-thienyl)propanone also led to high yields of mono-α-arylated product using 1 mol-% catalyst.

The more sterically hindered isobutyrophenone substrate could be arylated with *para*- and *meta*-substituted aryl halides to afford **1l**, **1m**, and **1n** in 82, 91, and 95% yield, respectively. However, no conversion was obtained with *ortho*-substituted aryl bromides, even with TNpP as the ligand. Notably, monoarylation of methyl ketones is often a challenge due to competing overarylation.[6e,6f,16] The DTBNpP/Pd system provides poor monoarylation selectivity with methyl ketones. Arylation of acetophenone with 1-bromo-4-*tert*-butylbenzene gave a mixture of mono- and diarylated products. The application of 2 equivalents of the aryl bromide gave the diarylated product (**1o**) in 93% yield. 2-Tetralone was coupled to 5-bromo-*m*-xylene with complete regioselectivity for the more acidic α-position to give **1p** in 95% yield. Coupling of 1-bromo-2-isopropylbenzene and tetralone gave 1-(2-isopropylphenyl)-2-naphthol (**1q**) in 95% isolated yield. This product was proposed to have formed upon air oxidation of tetralone **1s** during column chromatography [Equation (1)]. Aromatization was not observed with **1p** under similar isolation conditions.

Table 1. Coupling of aryl bromides and ketones.[a,b]

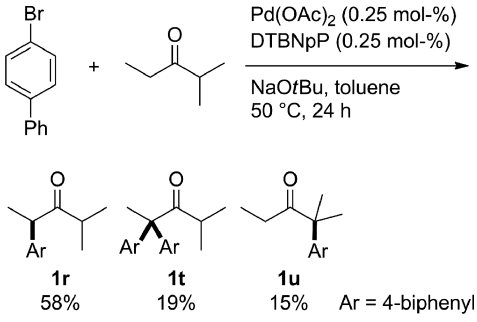


[a] Reaction conditions: 2 mmol aryl bromide, 2.4 mmol ketone, 0.25 mol-% $Pd(OAc)_2$, 0.25 mol-% DTBNpP, 3.0 mmol NaO*t*Bu, 50 °C, 24 h (time unoptimized). [b] Isolated yields (average of three runs). [c] 0.5 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP. [d] 0.25 mol-% TNpP. [e] 1 mol-% $Pd(OAc)_2$. [f] 0.5 mol-% $Pd_2(dba)_3$ and 1 mol-% DTBNpP. [g] 2 equivalents aryl bromide. [h] The tetralone product underwent air oxidation to naphthol **1q** during isolation. [i] Product obtained as a mixture with 2,2-di(4-biphenyl)-4-methyl-3-pentanone (**1t**, 19%) and 2-(4-biphenyl)-2-methyl-3-pentanone (**1u**, 15%). Total yield of arylated product was 92%.



(1)

Arylation of 2-methyl-3-pentanone was achieved with high yields but only moderate regioselectivity for the less hindered α-position. Using two equivalents of the ketone, a mixture of monoarylated product **1r** (58%), diarylated product **1t** (19%), and **1u** (15%) resulting from arylation of the more hindered α-position was obtained [Equation (2)]. The regioselectivity for initial arylation of the less-hindered side of the ketone compared to the more hindered side was 84:16. This selectivity was slightly higher than that achieved with tri-*tert*-butylphosphine (76:24).[6a]

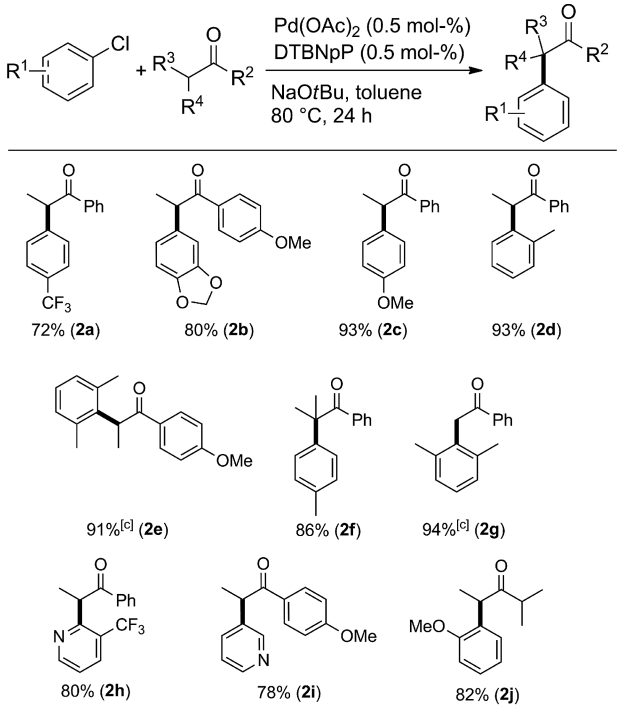


(2)

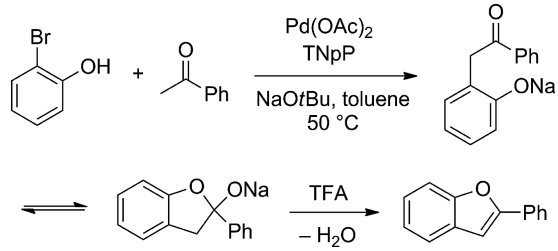
Aryl chlorides could also be efficiently coupled using this methodology by raising the reaction temperature to 80 °C and the catalyst loading to 0.5 mol-% (Table 2). Sterically unhindered, electron-deficient or -rich aryl chlorides were coupled with propiophenone in good to excellent yields (**2a**, **2b**). Additionally, an *ortho*-substituted aryl chloride afforded a good yield of coupled product (**2d**). As was seen in the aryl bromide case, low yields were obtained with 2-chloro-*m*-xylene using DTBNpP/$Pd(OAc)_2$, but good yields could be achieved by switching to TNpP as the ligand (**2e**). Coupling of isobutyrophenone to 4-chlorotoluene afforded an 86% yield of **2f**. Selective monoarylation of acetophenone was achieved using 2-chloro-*m*-xylene and the catalyst derived from TNpP and $Pd(OAc)_2$. With the more hindered aryl substrate, no overarylation was observed. Heteroaryl chlorides 2-chloro-3-trifluoromethylpyridine and 3-chloropyridine provided good yields of α-arylated products **2h** and **2i** under the standard conditions. 2-Chloroanisole was regioselectively coupled with 2-methyl-3-pentanone to give **2j** in 82% yield with no diarylation product noted. The more hindered aryl halide provided selective arylation of the less hindered α-position in contrast to the mixture of regioisomers obtained with the unhindered 4-bromobiphenyl (Table 1).

The 2-arylbenzofurans have wide ranging biological activity making them attractive synthetic targets. Recent efforts have focused on modular approaches to these structures capable of displaying a high degree of structural diversity. Burch reported the condensation of 2-bromophenols with ketones using a $Pd(OAc)_2$/2-(di-*tert*-butylphosphanyl)-1,1′-binaphthyl catalyst system (5 mol-% Pd) at 80 °C to give benzofurans in 40–84% yield.[17] The reaction involves α-arylation of the ketone, followed by acid-catalyzed hemiacetal formation and dehydration to give the benzofuran ring (Scheme 1). Cossío has reported an alternative approach involving the alumina-promoted condensation of α-bromo ketones with phenols.[18] The reaction is proposed to proceed through alumina-promoted hemiacetal formation followed by electrophilic aromatic substitution to form the C–C bond. This methodology generally provided low yields (10–85%) and was limited to the synthesis of electron-rich benzofurans.

Table 2. Coupling of aryl chlorides and ketones.[a,b]



[a] Reaction conditions: 2 mmol aryl chloride, 2.4 mmol ketone, 0.5 mol-% $Pd(OAc)_2$, 0.5 mol-% DTBNpP, 3.0 mmol NaO*t*Bu, 80 °C, 24 h (time unoptimized). [b] Isolated yields (average of three runs). [c] TNpP (0.5 mol-%) used as ligand.

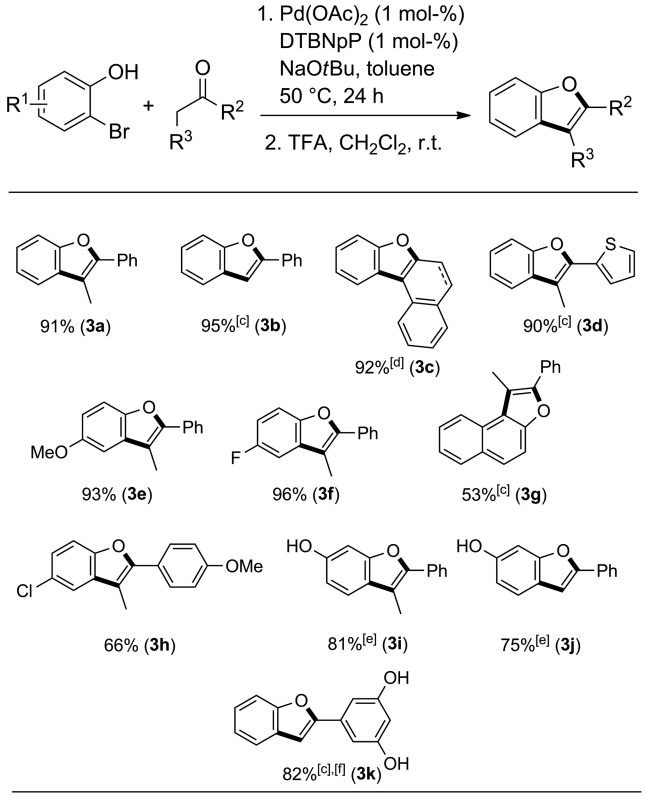


Scheme 1. Condensation of 2-bromophenol and acetophenone to give 2-phenylbenzofuran.

We were gratified to find that the $Pd(OAc)_2$/DTBNpP (1–2 mol-%) catalyst system effectively promoted the coupling of 2-bromophenols with ketones to give 2-arylbenzofurans in generally high yields at 50 °C after acidic workup. Notably, these conditions use significantly lower palladium loadings and lower temperature, while providing higher yields, than the method reported by Burch. This method is more general than that reported by Cossío. 2-Bromophenol was coupled with propiophenone (**3a**), acetophenone (**3b**), 2-tetralone (**3c**), and 1-(2-thienyl)propanone (**3d**) in high

yields (Table 3). Product **3c** was partially oxidized to aromatic analog, naphtho[2,1-*b*]benzofuran, during workup. Additionally, 4-methoxy- and 4-fluoro-functionalized bromophenols were coupled with propiophenone in greater than 90% yield (**3e** and **3f**); no apparent substituent effects were noted for this condensation. The ability to include electron-withdrawing substituents on the phenol ring suggests that a wide range of structures will be accessible. These substrates gave low yields (34–58%) in Burch's method.[17] When 1-bromo-2-naphthol was used as the substrate, only 53% of the desired naphthofuran was obtained in the presence of 2 mol-% $Pd(OAc)_2$ and 2 mol-% DTBNpP (**3g**). Lower yields were also obtained in the coupling of 1-bromo-2-methoxynaphthalene to propiophenone (Table 1). Consequently, the lower yield of **3g** likely reflects the increased difficulty of the initial coupling reaction. Compound **3k**, which can be converted in one step to eupomatenoid,[17,19] was obtained in a 66% yield by condensation of 2-bromo-4-chlorophenol and 4′-methoxypropiophenone. Palladium-catalyzed condensation of ketones with 2-haloanilines to give indoles[20] has also been reported. Importantly, attempts to couple propiophenone with 2-bromoaniline or protected variants were unsuccessful under our conditions.

Table 3. Synthesis of benzofurans.[a,b]



[a] Reaction conditions: 1 mmol 2-bromophenol, 1.2 mmol ketone, 1.0 mol-% $Pd(OAc)_2$, 1.0 mol-% DTBNpP, 1.5 mmol NaO*t*Bu, 50 °C, 24 h (time unoptimized). [b] Isolated yields (average of three runs). [c] 2.0 mol-% $Pd(OAc)_2$ and 2.0 mol-% DTBNpP used. [d] 9:1 ratio of 5,6-dihydronaphtho[2,1-*b*]benzofuran (**3c**)/naphtho[2,1-*b*]benzofuran obtained. [e] 2.0 mol-% $Pd(OAc)_2$, 2.0 mol-% DTBNpP and 4.5 mmol NaO*t*Bu used. [f] 3′,5′-Di(*tert*-butyldimethylsiloxy)acetophenone used as ketone substrate followed by deprotection with TBAF.

Polyhydroxylated 2-arylbenzofurans are common natural products and possessing a range of biological activities. 4-Bromoresorcinol was coupled with aryl ketones to give **3i** and **3j** in 81 and 75% yield, respectively, using 2 mol-% catalyst. The additional phenol group was tolerated without the need for protection. Single crystals of **3i** were obtained from slow evaporation of a diethyl ether solution. The solid-state structure is shown in Figure 2, and confirms formation of the benzofuran structure.[21] Benzofuran **3i** crystallizes in space group $P\bar{1}$ with four molecules in the asymmetric unit. The molecules pack with hydrogen bonding between the hydroxy groups forming a unidirectional chain along the *a* axis (see Supporting Information for crystal packing diagrams). The phenyl rings of adjacent benzofuran molecules are arranged in a roughly perpendicular way leading to a favorable herringbone motif.

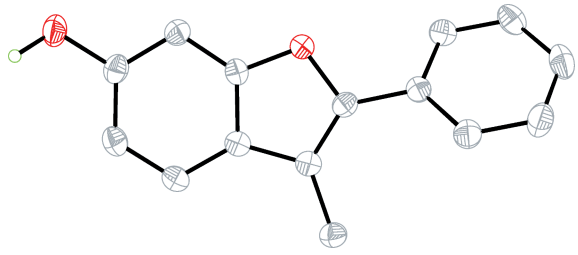
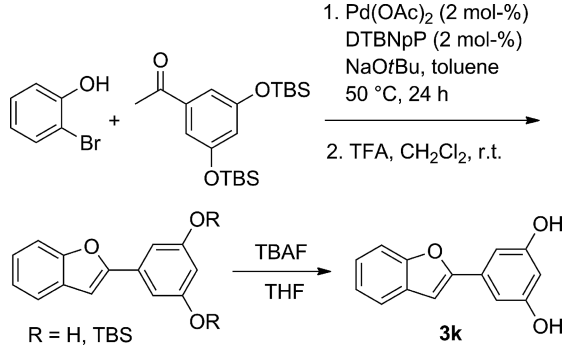


Figure 2. Thermal ellipsoid plot (50% probability) of one of the independent molecular structures in the asymmetric unit of **3i**.

Attempts to directly couple 3′,5′-dihydroxyacetophenone with 2-bromophenol failed to produce **3k**. Efficient conversion to the benzofuran was achieved using a di-TBS-protected 3′,5′-dihydroxyacetophenone derivative. After treatment with TFA to effect the ring closure, a mixture of mono- and di-TBS-protected benzofuran products was obtained. The mixture was fully deprotected with TBAF in THF to give **3k** in 82% isolated yield (Scheme 2).

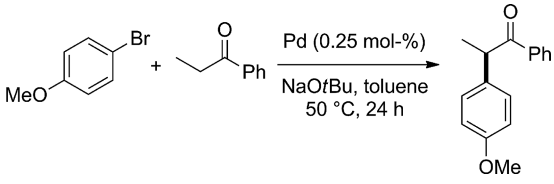


Scheme 2. Synthesis of 2-(3,5-dihydroxyphenyl)benzofuran (**3k**).

Using the conditions optimized for the DTBNpP/$Pd(OAc)_2$ catalyst system, the capabilities of DTBNpP-derived precatalysts were explored. The coupling of 4-bromoanisole with propiophenone was performed using in situ catalyst [DTBNpP/$Pd(OAc)_2$], $Pd(DTBNpP)_2$,

$Pd(DTBNpP)_2Cl_2$, and $[Pd(DTBNpP)Cl(\mu\text{-}Cl)]_2$ (Table 4). The application of the catalyst derived from $Pd(OAc)_2$ and DTBNpP enabled almost complete conversion to be reached (97%) after 4 h. By comparison, the use of $Pd(DTBNpP)_2$ resulted in a slightly slower rate of conversion (89% after 4 h). The slower rate observed with $Pd(DTBNpP)_2$ may be due to the higher ligand/Pd ratio. Interestingly, higher conversion rates were achieved with the Pd^{II} chloride precatalysts. The catalyst derived from $Pd(DTBNpP)_2Cl_2$ nearly reached completion after 2 h (93%) and was fully converted after 3 h. Dimeric $[Pd(DTBNpP)Cl(\mu\text{-}Cl)]_2$ precatalyst with a 1:1 DTBNpP/Pd ratio gave the highest rate of conversion with 94% conversion achieved after 1 h. The reason for the higher rate with chloride-derived catalysts is unclear yet clearly warrants further examination. The application of these air-stable Pd^{II} precatalysts will be further explored.

Table 4. Comparison of DTBNpP/$Pd(OAc)_2$ and preformed Pd-DTBNpP complexes.[a]



	% Yield[b]				
	1 h	2 h	3 h	4 h	24 h
$Pd(OAc)_2$/DTBNpP (1:1)	5	27	83	97	100
$Pd(DTBNpP)_2$	20	33	52	89	100
$Pd(DTBNpP)_2Cl_2$	57	93	100		
$[Pd(DTBNpP)Cl(\mu\text{-}Cl)]_2$	94	100			

[a] Reaction conditions: 1 mmol 4-bromoanisole, 1.2 mmol propiophenone, 1.5 mmol NaO*t*Bu, 0.25 mol-% Pd/DTBNpP precatalyst, 2 mL toluene, 50 °C. [b] Yield determined by GC.

Conclusions

In conclusion, we have successfully shown that DTBNpP is an effective catalyst for the α-arylation of ketones with aryl bromides and chlorides. The system provides high yields for a range of substrates with low catalyst loadings and moderate temperatures for both aryl bromide and chloride substrates. Sterically hindered starting materials are effectively coupled using TNpP as the ligand with no other change in reaction conditions. The Pd/DTBNpP catalyst system provides higher yields and displays a broader substrate scope in the condensation of 2-bromophenols with ketones to give benzofuran, while using lower catalyst loading and temperature, than do previously reported methods.[17,18] This methodology provides a modular approach to the synthesis of benzofurans from readily available bromophenol and ketone precursors.

Experimental Section

General Experimental Details: All chemicals were obtained from commercial sources and used as received, except where noted. DTBNpP[12] and TNpP were obtained from FMC, Lithium Division and were stored under nitrogen in a glove box. $Pd(OAc)_2$ and $Pd_2(dba)_3$ were provided by Johnson-Matthey. $Pd(DTBNpP)_2$,[22] $Pd(DTBNpP)_2Cl_2$,[23] and $[Pd(DTBNpP)Cl(\mu\text{-}Cl)]_2$[23] were prepared according to literature procedures. Toluene was distilled from sodium under nitrogen prior to use in coupling reactions. THF was distilled from sodium/benzophenone under nitrogen. All cross-coupling reactions were assembled in a nitrogen-filled glovebox. Reaction temperatures refer to previously equilibrated oil bath temperatures. ^1H and ^{13}C NMR spectra are referenced to the NMR solvent peaks or internal TMS. HRMS were obtained on a magnetic sector mass spectrometer using EI ionization and operating in the positive ion mode.

General Procedure for α-Arylation of Ketones: A screw-capped vial was placed in a glove box where $Pd(OAc)_2$ (0.25–2.0 mol-%), DTBNpP or TNpP (0.25–2.0 mol-%), and NaO*t*Bu (1.5 equiv.) were added. The vial was sealed with a septum and taken out of the glove box. Aryl halide (2 mmol), ketone (4.8 mmol) and toluene (2 mL) were added and the reaction was placed in an oil bath preheated to 50 or 80 °C. After the reaction had reached completion as judged by GC, the reaction mixture was dissolved in ethyl acetate and filtered through a plug of silica gel. After drying under vacuum, the crude reaction mixture was purified by flash chromatography (2.5–20% EtOAc/hexane) to afford pure product.

α-(4-Trifluoromethylphenyl)propiophenone (1a, 2a):[8b] Using the general procedure, 4-bromobenzotrifluoride (280 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a white solid (528 mg, 92%). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04–7.99 (m, 2 H), 7.59 (d, J = 8.1 Hz, 2 H), 7.53–7.45 (m, 3 H), 7.45–7.39 (m, 2 H), 4.84 (q, J = 6.9 Hz, 1 H), 1.60 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.5, 145.4 (q, J = 0.9 Hz), 136.0, 133.0, 129.0 (q, J = 32.5 Hz), 128.6, 128.5, 128.1, 125.7 (q, J = 3.8 Hz), 124.1 (q, J = 272.0 Hz), 47.3, 19.2 ppm.

Alternatively, 4-chlorobenzotrifluoride (267 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 80 °C to generate α-(4-trifluoromethylphenyl)propiophenone (400 mg, 72%).

α-(4-Fluorophenyl)propiophenone (1b):[24] Using the general procedure, 1-bromo-4-fluorobenzene (220 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a yellow oil (397 mg, 87%). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, J = 7.0 Hz, 1 H), 7.47 (tt, J = 7.3, 1.2 Hz,1 H), 7.37 (t, J = 7.6 Hz, 1 H), 7.28 (dd, J = 8.7, 5.3 Hz, 1 H), 6.96 (dd, J = 8.7, 8.7 Hz, 1 H), 4.71 (q, J = 6.9 Hz, 1 H), 1.54 (d, J = 6.9 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.0, 161.6 (d, J = 245.4 Hz), 137.0 (d, J = 3.2 Hz), 136.2, 132.7, 129.2 (d, J = 8.0 Hz), 128.5, 128.4, 115.6 (d, J = 21.4 Hz), 46.7, 19.4 ppm.

α-(2-Methylphenyl)propiophenone (1c, 2d):[6a] Using the general procedure, 2-bromotoluene (240 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a clear, colorless crystal (403 mg, 90%). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.0 Hz, 2 H), 7.47 (t, J = 7.3 Hz, 1 H), 7.38 (t, J = 7.7 Hz, 2 H), 7.24 (d, J = 7.1 Hz, 1 H), 7.17–7.06 (m, 3 H), 4.81 (q, J = 6.8 Hz, 1 H), 2.54 (s, 3 H), 1.53 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.8, 140.1, 136.5, 134.4, 132.5, 130.9, 128.4, 126.9, 127.0, 126.9, 44.5, 19.5, 17.9 ppm.

Alternatively, 2-chlorotoluene (234 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$

and 0.5 mol-% DTBNpP at 80 °C to generate α-(2-methylphenyl)-propiophenone (417 mg, 93%).

α-(2-Methyoxyphenyl)propiophenone (1d):[25] Using the general procedure, 2-bromoanisole (249 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a clear, colorless crystal (451 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.2 Hz, 2 H), 7.48 (tt, J = 7.3, 1.1 Hz, 1 H), 7.38 (t, J = 7.5 Hz, 2 H), 7.23–7.17 (m, 2 H), 6.93–6.87 (m, 2 H), 5.16 (q, J = 6.8 Hz, 1 H), 3.88 (s, 3 H), 1.54 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.1, 155.6, 136.4, 132.3, 130.0, 128.2, 128.2, 128.0, 120.8, 110.7, 55.2, 40.2, 17.4 ppm.

α-(2-Methyl-4-methoxyphenyl)propiophenone (1e):[7a] Using the general procedure, 4-bromo-3-methylanisole (282 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a clear, colorless crystal (492 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.3 Hz, 2 H), 7.43 (t, J = 7.3 Hz, 1 H), 7.34 (t, J = 7.6 Hz, 2 H), 7.01 (d, J = 8.5 Hz, 1 H), 6.80 (d, J = 2.8 Hz, 1 H), 6.64 (dd, J = 8.5, 2.8 Hz, 1 H), 4.75 (q, J = 6.8 Hz, 1 H), 3.68 (s, 3 H), 2.49 (s, 3 H), 1.51 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.7, 158.0, 136.4, 135.7, 132.2, 132.0, 128.1, 127.7, 116.4, 111.4, 54.6, 43.5, 19.5, 17.9 ppm.

α-[3-Methyl-(4-dimethylamino)phenyl]-4′-methoxypropiophenone (1f): Using the general procedure, 4-bromo-3,*N*,*N*-trimethylaniline (428 mg, 2 mmol) and 4′-methoxypropiophenone (421 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 50 °C to give the product as a yellow oil (505 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.8 Hz, 2 H), 6.94 (d, J = 8.6 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 2 H), 6.62 (d, J = 2.8 Hz, 1 H), 6.50 (dd, J = 8.6, 2.8 Hz, 1 H), 4.66 (q, J = 6.7 Hz, 1 H), 3.78 (s, 3 H), 2.90 (s, 6 H), 2.50 (s, 3 H), 1.47 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.8, 162.6, 149.1, 134.8, 130.4, 129.6, 128.4, 127.4, 114.7, 113.3, 110.8, 54.0, 43.2, 40.2, 19.9, 18.0 ppm. HRMS *m*/*z* calcd. for $C_{19}H_{23}NO_2$ $[M]^+$ 297.1733, found 297.1729.

α-(1-Naphthyl)propiophenone (1g):[8b] Using the general procedure, 1-bromonaphthalene (280 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 50 °C to give the product as a white solid (499 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, J = 8.5 Hz, 1 H), 7.96 (d, J = 7.0 Hz, 2 H), 7.93 (d, J = 8.2 Hz, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 7.68 (ddd, J = 8.4, 6.8, 1.4 Hz, 1 H), 7.58 (t, J = 7.5 Hz, 1 H), 7.43–7.34 (m, 2 H), 7.33–7.25 (m, 3 H), 5.46 (q, J = 6.8 Hz, 1 H), 1.73 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.5, 137.9, 136.2, 134.2, 132.5, 130.5, 129.2, 128.3, 128.3, 127.4, 126.6, 125.7, 125.7, 124.9, 122.4, 43.5, 18.4 ppm.

α-(2,6-Dimethylphenyl)propiophenone (1h):[7a] Using the general procedure, 2-bromo-*m*-xylene (266 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% TNpP at 50 °C to give the product as a clear, colorless crystal (438 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.0 Hz, 2 H), 7.40 (t, J = 7.4 Hz, 1 H), 7.27 (t, J = 7.8 Hz, 2 H), 7.05–6.96 (A_2B m, 3 H), 4.56 (q, J = 6.8 Hz, 1 H), 2.32 (br. s, 6 H), 1.55 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.8, 139.7, 136.6, 135.3, 132.3, 129.3, 128.02, 128.00, 126.5, 46.0, 20.3, 14.7 ppm.

α-(2-Methoxy-1-naphthyl)propiophenone (1i): Using the general procedure, 1-bromo-2-methoxynaphthalene (474 mg, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd_2(dba)_3$ and 1.0 mol-% DTBNpP at 50 °C to give the product as a yellow oil (423 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.6 Hz, 1 H), 7.82 (d, J = 8.1 Hz, 1 H), 7.78–7.71 (m, 3 H), 7.59 (t, J = 7.1 Hz, 1 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.30 (t, J = 7.4 Hz, 1 H), 7.17 (t, J = 7.8 Hz, 2 H), 7.12 (d, J = 9.0 Hz, 1 H), 5.09 (q, J = 6.8 Hz, 1 H), 3.73 (s, 3 H), 1.68 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 202.0, 153.4, 137.0, 131.8, 131.7, 129.6, 129.0, 128.9, 127.8, 127.7, 127.1, 124.3, 123.4, 122.3, 113.5, 55.9, 41.4, 15.5 ppm. HRMS *m*/*z* calcd. for $C_{20}H_{18}O_2$ $[M]^+$ 290.1307, found 290.1304.

α-(2-Pyridyl)propiophenone (1j):[7b] Using the general procedure, 2-bromopyridine (191 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 50 °C to give the product as a yellow oil (388 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (ddd, J = 5.0, 1.9, 1.0 Hz, 1 H), 8.03–7.97 (m, 2 H), 7.55 (td, J = 7.7, 1.9 Hz, 1 H), 7.46–7.40 (m, 1 H), 7.34 (t, J = 7.7 Hz, 2 H), 7.22 (dt, J = 7.9, 1.1 Hz, 1 H), 7.06 (ddd, J = 7.6, 4.9, 1.2 Hz, 1 H), 4.93 (q, J = 6.9 Hz, 1 H), 1.57 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.4, 160.9, 149.5, 136.8, 136.3, 132.7, 128.8, 128.3, 121.8, 121.7, 50.5, 17.8 ppm.

2-(4-Biphenyl)-1-(2-thienyl)-1-propanone (1k): Using the general procedure, 4-bromobiphenyl (466 mg, 2 mmol) and 1-(2-thienyl)-1-propanone (299 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 50 °C to give the product as a white solid (531 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (dd, J = 3.8, 1.2 Hz, 1 H), 7.63–7.59 (m, 4 H), 7.57 (dd, J = 5.0, 1.1 Hz, 1 H), 7.50–7.44 (m, 4 H), 7.38 (t, J = 7.4 Hz, 1 H), 7.07 (dd, J = 5.0, 3.8 Hz, 1 H), 4.63 (q, J = 6.9 Hz, 1 H), 1.66 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 193.1, 143.6, 140.4, 140.2, 139.8, 133.5, 132.4, 128.6, 128.04, 127.96, 127.5, 127.2, 126.8, 48.8, 19.0 ppm. HRMS *m*/*z* calcd. for $C_{19}H_{16}SO$ $[M]^+$ 292.0922, found 292.0919.

α-(4-*tert*-Butylphenyl)-isobutyrophenone (1l):[11] Using the general procedure, 1-bromo-4-*tert*-butylbenzene (346 μL, 2 mmol) and isobutyrophenone (360 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a white solid (549 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (dd, J = 8.3, 1.5 Hz, 2 H), 7.43–7.39 (m, 2 H), 7.35 (td, J = 7.3, 1.3 Hz, 1 H), 7.33–7.29 (m, 2 H), 7.22 (t, J = 7.8 Hz, 2 H), 1.64 (s, 6 H), 1.36 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 203.6, 149.4, 141.9, 136.3, 131.4, 129.6, 127.8, 125.7, 125.2, 50.8, 34.2, 31.3, 27.7 ppm.

α-(4-Hydroxyphenyl)isobutyrophenone (1m): Using the general procedure, 4-bromophenol (346 mg, 2 mmol) and isobutyrophenone (360 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a white solid (437 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (dd, J = 7.3, 1.2 Hz, 2 H), 7.37 (tt, J = 7.4, 1.1 Hz, 1 H), 7.23 (t, J = 7.7 Hz, 2 H), 7.21–7.18 (m, 2 H), 6.94–6.89 (m, 2 H), 6.70 (s, 1 H), 1.59 (s, 6 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 205.5, 154.8, 136.7, 136.3, 131.7, 129.6, 127.9, 126.9, 116.0, 50.8, 27.8 ppm. HRMS *m*/*z* calcd. for $C_{16}H_{16}O_2$ $[M]^+$ 240.1150, found 240.1159.

α-(3-Methoxyphenyl)isobutyrophenone (1n):[6a] Using the general procedure, 3-bromoanisole (253 μL, 2 mmol) and isobutyrophenone (360 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a light, yellow oil (483 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (dd, J = 7.2, 1.5 Hz, 2 H), 7.31–7.26 (m, 1 H), 7.23 (t, J = 8.0 Hz, 1 H), 7.16 (t, J = 7.8 Hz, 2 H), 6.91 (dd, J = 7.1, 1.3 Hz, 2 H), 6.80–6.76 (m, 1 H), 3.69 (s, 3 H), 1.59 (s, 6 H) ppm. ^{13}C

NMR (126 MHz, $CDCl_3$): δ = 202.8, 159.8, 146.6, 135.9, 131.3, 129.7, 129.3, 127.6, 117.8, 111.7, 111.3, 54.7, 51.0, 27.5 ppm.

2,2-Bis(4-*tert*-butylphenyl)-1-phenylethanone (1o): Using the general procedure, 1-bromo-4-*tert*-butylbenzene (728 μL, 4.2 mmol) and acetophenone (233 μL, 2.0 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a white solid (714 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, 7.5 Hz, 2 H), 7.52 (t, J = 7.3 Hz, 1 H), 7.43 (t, J = 7.7 Hz, 2 H), 7.36 (d, J = 8.3 Hz, 4 H), 7.26 (d, J = 8.4 Hz, 4 H), 6.03 (s, 1 H), 1.32 (s, 18 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.5, 149.7, 137.0, 136.1, 132.9, 129.0, 128.7, 128.5, 125.6, 58.5, 34.4, 31.3 ppm. HRMS *m*/*z* calcd. for $C_{28}H_{32}O$ $[M]^+$ 384.2453, found 384.2454.

3,4-Dihydro-1-(3,5-dimethylphenyl)-2(1*H*)-naphthalenone (1p): Using the general procedure, 5-bromo-*m*-xylene (272 μL, 2 mmol) and 2-tetralone (317 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give the product as a light, yellow oil (455 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 2 H), 7.31–7.26 (m, 1 H), 7.08 (d, J = 7.4 Hz, 1 H), 6.96 (s, 1 H), 6.79 (s, 2 H), 4.75 (s, 1 H), 3.21 (ddd, J = 15.5, 8.0, 6.2 Hz, 1 H), 3.07 (dt, J = 15.7, 6.5 Hz, 1 H), 2.80 (ddd, J = 16.7, 6.6, 6.3 Hz, 1 H), 2.67–2.59 (m, 1 H), 2.32 (s, 6 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 209.6, 138.0, 137.5, 136.7, 136.6, 129.5, 128.8, 127.7, 127.0, 126.9, 126.3, 59.6, 36.9, 28.2, 21.2 ppm. HRMS *m*/*z* calcd. for $C_{18}H_{18}O$ $[M]^+$ 250.1358, found 250.1352.

1-(2-Isopropylphenyl)-2-naphthol (1q):[26] Using the general procedure, 1-bromo-2-isopropylbenzene (306 μL, 2 mmol) and tetralone (317 μL, 2.4 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C. The crude product was dissolved in a minimum of dichloromethane and evaporated onto silica gel. Flash chromatography under standard conditions gave the oxidized naphthol product **1t** as a clear, colorless crystal (498 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93–7.87 (m, 2 H), 7.65 (dd, J = 7.9, 1.3 Hz, 1 H), 7.57 (td, J = 7.6, 1.5 Hz, 1 H), 7.46–7.36 (m, 4 H), 7.34–7.29 (m, 2 H), 5.10 (s, 1 H), 2.74 (sept, J = 6.9 Hz, 1 H), 1.22 (d, J = 6.9 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.4, 149.8, 133.6, 131.8, 131.6, 129.32, 129.30, 128.8, 128.0, 126.7, 126.5, 126.4, 124.6, 123.2, 120.1, 117.2, 30.2, 24.3, 23.8 ppm.

2-(4-Biphenyl)-4-methyl-3-pentanone (1r): Using the general procedure, 4-bromobiphenyl (466 mg, 2 mmol) and 2-methyl-3-pentanone (494 μL, 4.0 mmol) were coupled using 0.25 mol-% $Pd(OAc)_2$ and 0.25 mol-% DTBNpP at 50 °C to give a white solid (443 mg) that was shown by ^{1}H NMR spectroscopy to be a 76:15:9 mixture of **1r** (292 mg, 58%), 2,2-di(4-biphenyl)-4-methyl-3-pentanone (**1t**, 75 mg, 19%), and 2-(4-biphenyl)-2-methyl-3-pentanone (**1u**, 75 mg, 15%). Masses were determined based on NMR ratios of the components. Characterization data for **1r**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.62 (m, 6 H), 7.53–7.46 (m, 3 H), 7.44–7.36 (m, 5 H), 4.05 (q, J = 6.9 Hz, 1 H), 2.81 (sept, J = 6.9 Hz, 1 H), 1.61 (s, 1 H), 1.52 (d, J = 6.9 Hz, 3 H), 1.19 (d, J = 7.0 Hz, 3 H), 1.05 (d, J = 6.8 Hz, 4 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 214.0, 140.2, 139.63, 139.59, 128.6, 128.1, 127.2, 127.1, 126.7, 50.4, 39.0, 18.9, 18.1, 18.0 ppm. HRMS: *m*/*z* calcd. for $C_{18}H_{20}O$ (**1r**, **1u**, M^+) 252.1514, found 252.1520; calcd. for $C_{30}H_{28}O$ (**1t**, M^+) 404.2140, found 404.2145.

α-(1,3-Benzodioxol-5-yl)-4′-methoxypropiophenone (2b): Using the general procedure, 5-chloro-1,3-benzodioxole (233 μL, 2 mmol) and 4′-methoxypropiophenone (421 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 80 °C to give the product as a yellow oil (454 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, J = 9.0 Hz, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 6.78 (d, J = 1.7 Hz, 1 H), 6.76–6.69 (m, 2 H), 5.88 (d, J = 1.4 Hz, 1 H), 5.86 (d, J = 1.4 Hz, 1 H), 4.56 (q, J = 6.8 Hz, 1 H), 3.78 (s, 3 H), 1.48 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.7, 163.1, 147.9, 146.3, 135.6, 130.9, 129.3, 120.8, 113.6, 108.5, 107.9, 100.9, 55.3, 46.9, 19.5 ppm. HRMS *m*/*z* calcd. for $C_{17}H_{16}O_4$ $[M]^+$ 284.1049, found 284.1055.

α-(4-Methyoxyphenyl)propiophenone (2c):[6a] Using the general procedure, 4-chloroanisole (245 μL, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 80 °C to give the product as a white solid (447 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.3 Hz, 2 H), 7.44 (t, J = 7.88 Hz, 1 H), 7.37 (t, J = 7.7 Hz, 2 H), 7.26 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.9 Hz, 2 H), 4.70 (q, J = 6.7 Hz, 1 H), 3.69 (s, 3 H), 1.57 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.1, 158.2, 136.2, 133.2, 132.4, 128.5, 128.4, 128.2, 114.1, 54.7, 46.6, 19.2 ppm.

α-(2,6-Dimethylphenyl)-4′-methoxypropiophenone (2e): Using the general procedure, 2-chloro-*m*-xylene (265 μL, 2 mmol) and 4′-methoxypropiophenone (421 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% TNpP at 80 °C to give the product as a white solid (488 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.9 Hz, 2 H), 7.06–6.96 (m, 3 H), 6.76 (d, J = 8.9 Hz, 2 H), 4.50 (q, J = 6.8 Hz, 1 H), 3.75 (s, 3 H), 2.31 (br. s, 6 H), 1.52 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.4, 162.8, 140.2, 135.4, 130.3, 129.7, 129.4, 126.5, 113.3, 55.1, 45.8, 20.4, 14.8 ppm. HRMS *m*/*z* calcd. for $C_{18}H_{20}O_2$ $[M]^+$ 268.1463, found 268.1453.

α-(4-Tolyl)isobutyrophenone (2f):[27] Using the general procedure, 4-chlorotoluene (237 μL, 2 mmol) and isobutyrophenone (360 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 80 °C to give the product as a white solid (410 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.56 (m, 2 H), 7.40–7.34 (m, 1 H), 7.30–7.24 (m, 4 H), 7.21 (t, J = 8.0 Hz, 2 H), 2.38 (s, 3 H), 1.65 (s, 6 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 203.6, 142.1, 136.2, 136.1, 131.4, 129.54, 129.52, 127.7, 125.4, 50.9, 27.7, 20.8 ppm.

α-(2,6-Dimethylphenyl)acetophenone (2g):[7a] Using the general procedure, 2-chloro-*m*-xylene (265 μL, 2 mmol) and acetophenone (280 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% TNpP at 80 °C to give the product as a white solid (412 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (dd, J = 7.2, 1.1 Hz, 2 H), 7.66 (tt, J = 7.3, 1.5 Hz, 1 H), 7.56 (td, J = 7.6, 1.5 Hz, 2 H), 7.20–7.16 (m, 1 H), 7.13 (br. d, J = 7.5 Hz, 2 H), 4.43 (s, 2 H), 2.28 (s, 6 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.8, 137.1, 136.9, 133.1, 132.4, 128.6, 128.0, 127.9, 126.8, 39.6, 20.3 ppm.

α-(3-Trifluoromethyl-2-pyridyl)propiophenone (2h): Using the general procedure, 2-chloro-3-(trifluoromethyl)pyridine (363 mg, 2 mmol) and propiophenone (319 μL, 2.4 mmol) were coupled using 2.0 mol-% $Pd(OAc)_2$ and 2.0 mol-% DTBNpP at 80 °C to give the product as a white solid (447 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (d, J = 4.4 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 8.7 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 1 H), 7.33 (t, J = 7.7 Hz, 2 H), 7.22 (dd, J = 7.9, 4.9 Hz, 1 H), 5.06 (q, J = 6.8 Hz, 1 H), 1.62 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.9, 159.5, 152.4, 136.5, 134.5 (q, J = 5.5 Hz), 132.4, 128.4, 128.2, 123.8 (q, J = 31.5 Hz), 123.9 (q, J = 273.1 Hz), 121.2, 47.1, 17.4 ppm. HRMS *m*/*z* calcd. for $C_{15}H_{12}NOF_3$ $[M]^+$ 279.0871, found 279.0860.

α-(3-Pyridyl)-4′-methoxypropiophenone (2i): Using the general procedure, 3-chloropyridine (189 μL, 2 mmol) and 4′-methoxypropio-

phenone (421 μL, 2.4 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 80 °C to give the product as a yellow oil (376 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.55 (d, J = 2.3 Hz, 1 H), 8.39 (dd, J = 4.8, 1.6 Hz, 1 H), 7.88 (d, J = 8.9 Hz, 2 H), 7.55 (dt, J = 8.0, 2.0 Hz, 1 H), 7.13 (ddd, J = 8.1, 4.8, 0.9 Hz, 1 H), 6.81 (d, J = 9.0 Hz, 2 H), 4.65 (q, J = 6.9 Hz, 1 H), 3.74 (s, 3 H), 1.47 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.7, 163.2, 149.1, 147.9, 137.0, 134.7, 130.7, 128.5, 123.4, 113.5, 55.1, 44.1, 19.0 ppm. HRMS m/z calcd. for $C_{15}H_{15}NO_2$ $[M]^+$ 241.1103, found 241.1109.

2-(2-Methoxyphenyl)-4-methyl-3-pentanone (2j): Using the general procedure, 2-chloroanisole (253 μL, 2 mmol) and 2-methyl-3-pentanone (494 μL, 4.0 mmol) were coupled using 0.5 mol-% $Pd(OAc)_2$ and 0.5 mol-% DTBNpP at 80 °C to give the product as a light, yellow oil (338 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (ddd, J = 8.1, 7.5, 1.6 Hz, 1 H), 7.11 (dd, J = 7.6, 1.7 Hz, 1 H), 6.92 (td, J = 7.5, 1.1 Hz, 1 H), 6.89 (d, J = 8.2 Hz, 1 H), 4.31 (q, J = 7.0 Hz, 1 H), 3.83 (s, 3 H), 2.66 (sept, J = 6.8 Hz, 1 H), 1.34 (d, J = 7.0 Hz, 3 H), 1.07 (d, J = 7.1 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.2, 156.5, 129.4, 128.4, 127.9, 120.8, 110.5, 55.2, 43.7, 38.5, 19.3, 18.1, 16.4 ppm. HRMS m/z calcd. for $C_{13}H_{18}O_2$ $[M]^+$ 206.1307, found 206.1304.

General Procedure for Synthesis of Benzofurans: A screw-capped vial was placed in a glove box where $Pd(OAc)_2$ (1.0–5.0 mol-%), DTBNpP (1.0–5.0 mol-%), and NaOtBu (3.0 equiv.) were added. The vial was sealed with a septum and taken out of the glove box. Aryl halide (1 mmol), ketone (1.2 mmol) and toluene (2 mL) were added and the reaction was placed in an oil bath preheated to 50 °C for 24 h. After the 24 h, TFA/CH_2Cl_2 (1:1, 2 mL) was added to reaction mixture and stirred at room temperature for 2 h. The reaction mixture was added to a saturated NH_4Cl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were dried with $MgSO_4$, filtered, and dried by rotary evaporation. The crude reaction mixture was purified by flash chromatography (0–50% EtOAc/hexane) to afford pure product.

3-Methyl-2-phenylbenzofuran (3a):[17] Using the general procedure for benzofuran synthesis, 2-bromophenol (116 μL, 1 mmol) and propiophenone (160 μL, 1.2 mmol) were coupled using 1.0 mol-% $Pd(OAc)_2$ and 1.0 mol-% DTBNpP at 50 °C to give the product as a clear, colorless oil (189 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97–7.93 (m, 2 H), 7.67–7.57 (m, 4 H), 7.48 (tt, J = 7.4, 1.0 Hz, 1 H), 7.43 (td, J = 7.3, 1.2 Hz, 1 H), 7.38 (td, J = 7.6, 1.0 Hz, 1 H), 2.58 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.8, 150.6, 131.4, 131.1, 128.5, 127.8, 126.6, 124.3, 122.3, 119.2, 111.2, 110.9, 9.4 ppm.

2-Phenylbenzofuran (3b):[17] Using the general procedure for benzofuran synthesis, 2-bromophenol (116 μL, 1 mmol) and acetophenone (140 μL, 1.2 mmol) were coupled using 2.0 mol-% $Pd(OAc)_2$ and 2.0 mol-% DTBNpP at 50 °C to give the product as a white solid (184 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (dd, J = 8.4, 1.3 Hz, 2 H), 7.63 (d, J = 7.3 Hz, 1 H), 7.58 (d, J = 8.1 Hz, 1 H), 7.50 (t, J = 7.8 Hz, 2 H), 7.40 (t, J = 7.4 Hz, 1 H), 7.34 (td, J = 7.8, 1.2 Hz, 1 H), 7.30 (td, J = 7.4, 1.1 Hz, 1 H), 7.07 (s, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.9, 154.9, 130.5, 129.2, 128.8, 128.5, 124.9, 124.2, 122.9, 120.9, 111.2, 101.3 ppm.

5,6-Dihydronaphtho[2,1-*b*]benzofuran (3c): Using the general procedure for benzofuran synthesis, 2-bromophenol (116 μL, 1 mmol) and 2-tetralone (159 μL, 1.2 mmol) were coupled using 1.0 mol-% $Pd(OAc)_2$ and 1.0 mol-% DTBNpP at 50 °C to give the product as a clear, colorless oil (202 mg, 92%) that was an inseparable mixture of **3c** (91%) and naphtho[2,1-*b*]benzofuran (9%) resulting from air oxidation of **3c**. **3c:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (dd, J = 7.3, J = 1.6 Hz, 1 H), 8.00 (d, J = 8.9 Hz, 0.12 H), 7.90 (dd, J = 7.6, 1.3 Hz, 1 H), 7.67–7.62 (m, 1 H), 7.49–7.39 (m, 3 H), 7.38–7.34 (m, 1 H), 7.29 (td, J = 7.6, 1.3 Hz, 1 H), 3.24 (t, J = 8.0 Hz, 2 H), 3.14 (t, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.5, 155.1, 133.4, 131.5, 128.0, 126.8, 125.8, 125.5, 123.3, 123.1, 122.6, 119.8, 113.4, 111.3, 29.2, 22.2 ppm. HRMS m/z calcd. for $C_{16}H_{12}O$ $[M]^+$ 220.0888, found 220.0889. Naphtho[2,1-*b*]benzofuran: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.72 (dd, J = 8.2, 1.2 Hz, 1 H), 8.49 (dd, J = 7.8, 1.4 Hz, 1 H), 8.11 (dd, J = 8.2, 1.2 Hz, 1 H), 7.82 (m, 2 H), 7.61–7.55 (m, 2 H), 7.49–7.39 (m, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.8, 154.2, 130.4, 129.1, 129.0, 128.5, 127.0, 125.8, 124.9, 124.3, 123.4, 123.1, 121.9, 117.5, 112.6, 111.8 ppm.

3-Methyl-2-(thiophen-2-yl)benzofuran (3d):[17] Using the general procedure for benzofuran synthesis, 2-bromophenol (116 μL, 1 mmol) and 1-(2-thienyl)-1-propanone (149 μL, 1.2 mmol) were coupled using 2.0 mol-% $Pd(OAc)_2$ and 2.0 mol-% DTBNpP at 50 °C to give the product as a clear, colorless oil (192 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, J = 7.0 Hz, 1 H), 7.54–7.50 (m, 2 H), 7.42 (dd, J = 5.1, 1.2 Hz, 1 H), 7.36–7.28 (m, 2 H), 7.19 (dd, J = 5.0, 3.6 Hz, 1 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.7, 146.8, 133.4, 130.8, 1275, 125.4, 124.7, 124.4, 122.5, 119.1, 110.8, 110.7, 9.1 ppm.

5-Methoxy-3-methyl-2-phenylbenzofuran (3e):[17] Using the general procedure for benzofuran synthesis, 2-bromo-4-methoxyphenol (203 mg, 1 mmol) and propiophenone (160 μL, 1.2 mmol) were coupled using 1.0 mol-% $Pd(OAc)_2$ and 1.0 mol-% DTBNpP at 50 °C to give the product as a clear, colorless crystal (221 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.0 Hz, 2 H), 7.51 (t, J = 7.8 Hz, 2 H), 7.44–7.37 (m, 2 H), 7.02 (d, J = 2.5 Hz, 1 H), 6.95 (dd, J = 8.8, 2.6 Hz, 1 H), 3.92 (s, 3 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.8, 151.5, 148.8, 131.7, 131.5, 128.6, 127.8, 126.6, 112.9, 111.3, 101.9, 56.1, 9.7 ppm. Two aromatic carbons were coincident.

5-Fluoro-3-methyl-2-phenylbenzofuran (3f):[17] Using the general procedure for benzofuran synthesis, 2-bromo-4-fluorophenol (191 mg, 1 mmol) and propiophenone (160 μL, 1.2 mmol) were coupled using 1.0 mol-% $Pd(OAc)_2$ and 1.0 mol-% DTBNpP at 50 °C to give the product as a clear, colorless crystal (217 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.1 Hz, 2 H), 7.52 (t, J = 7.7 Hz, 2 H), 7.45–7.38 (m, 2 H), 7.20 (dd, J = 8.5, 2.6 Hz, 1 H), 7.03 (td, J = 9.0, 2.7 Hz, 1 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.1 (d, J = 238.0 Hz), 152.5, 150.0, 132.0 (d, J = 10.1 Hz), 131.1, 128.6, 128.2, 126.7, 111.8 (d, J = 26.3 Hz), 111.5 (d, J = 9.5 Hz), 111.4 (d, J = 3.9 Hz), 104.8 (d, J = 24.7 Hz), 9.4 ppm. ^{19}F NMR (339 MHz, $CDCl_3$): δ = –121.2 (td, J = 8.8, 4.0 Hz) ppm.

1-Methyl-2-phenylnaphtho[2,1-*b*]furan (3g):[17] Using the general procedure for benzofuran synthesis, 1-bromo-2-naphthol (223 mg, 1 mmol) and propiophenone (160 μL, 1.2 mmol) were coupled using 2.0 mol-% $Pd(OAc)_2$ and 2.0 mol-% DTBNpP at 50 °C to give the product as a white solid (137 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.55 (d, J = 8.4 Hz, 1 H), 8.04 (d, J = 8.1 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 2 H), 7.81–7.72 (m, 2 H), 7.67 (ddd, J = 8.3, 6.9, 1.4 Hz, 1 H), 7.62–7.55 (m, 3 H), 7.48 (t, J = 7.3 Hz, 1 H), 2.90 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.7, 150.8, 131.2, 130.8, 129.0, 128.5, 127.7, 127.4, 126.0, 125.4, 123.9, 123.7, 123.0, 113.4, 112.2, 12.3 ppm. Two aromatic carbons were coincident.

5-Chloro-2-(4-methoxyphenyl)-3-methylbenzofuran (3h):[17] Using the general procedure for benzofuran synthesis, 2-bromo-4-chloro-

phenol (207 mg, 1 mmol) and 4′-methoxypropiophenone (210 μL, 1.2 mmol) were coupled using 1.0 mol-% $Pd(OAc)_2$ and 1.0 mol-% DTBNpP at 50 °C to give the product as a clear, colorless oil (179 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.8 Hz, 2 H), 7.46 (d, J = 2.2 Hz, 1 H), 7.37 (d, J = 8.6 Hz, 1 H), 7.22 (dd, J = 8.6, 2.2 Hz, 1 H), 7.02 (d, J = 8.8 Hz, 2 H), 3.88 (s, 3 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.6, 152.3, 151.9, 132.7, 128.1, 127.8, 123.8, 123.6, 118.6, 114.1, 111.6, 109.2, 55.3, 9.2 ppm.

2-Phenyl-3-methyl-6-benzofuranol (3i): Using the general procedure for benzofuran synthesis, 4-bromoresorcinol (189 mg, 1 mmol) and propiophenone (160 μL, 1.2 mmol) were coupled using 2.0 mol-% $Pd(OAc)_2$ and 2.0 mol-% DTBNpP at 50 °C to give the product as a white solid (182 mg, 81%). X-ray quality crystals were obtained by slow evaporation of a solution of **3h** in diethyl ether. ^{1}H NMR (500 MHz, CD_3CN): δ = 7.75 (dd, J = 8.5, 1.3 Hz, 2 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.38 (d, J = 8.4 Hz, 1 H), 7.34 (t, J = 7.4 Hz, 1 H), 7.10 (br. s, 1 H), 6.95 (d, J = 2.1 Hz, 1 H), 6.81 (dd, J = 8.4, 2.1 Hz, 1 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (126 MHz, CD_3CN): δ = 156.5, 155.8, 150.3, 132.5, 129.8, 128.6, 127.1, 125.1, 120.9, 112.8, 112.6, 98.5, 9.8 ppm. HRMS m/z calcd. for $C_{15}H_{12}O_2$ $[M]^+$ 224.0837, found 224.0830.

2-Phenyl-6-benzofuranol (3j):[28] Using the general procedure for benzofuran synthesis, 4-bromoresorcinol (189 mg, 1 mmol) and acetophenone (233 μL, 2.0 mmol) were coupled using 2.0 mol-% $Pd(OAc)_2$ and 2.0 mol-% DTBNpP at 50 °C to give the product as a white solid (157 mg, 75%). ^{1}H NMR (500 MHz, CD_3CN): δ = 7.81 (dd, J = 8.4, 1.0 Hz, 2 H), 7.45–7.41 (m, 3 H), 7.33 (td, J = 7.4, 0.9 Hz, 1 H), 7.16 (br. s, 1 H), 7.04 (s, 1 H), 7.01 (dd, J = 1.6, 0.3 Hz, 1 H), 6.81 (dd, J = 8.4, 1.1 Hz) ppm. ^{13}C NMR (126 MHz, CD_3CN): δ = 156.9, 156.4, 155.7, 131.6, 130.0, 129.2, 125.3 123.1, 122.4, 113.4, 102.6, 98.8 ppm.

2-(3,5-Dihydroxyphenyl)benzofuran (3k): Using the general procedure for benzofuran synthesis, 2-bromophenol (116 μL, 1 mmol) and 3′,5′-bis(*tert*-butyldimethylsiloxy)acetophenone (183 μL, 1.2 mmol) were coupled using 2.0 mol-% $Pd(OAc)_2$ and 2.0 mol-% DTBNpP at 50 °C. The crude product was treated with TBAF·xH$_2$O (784.5 mg, 3 mmol) in THF (10 mL) for several hours until TLC analysis showed complete deprotection. The resulting mixture was treated with saturated aqueous NH_4Cl and extracted with diethyl ether. The crude product was flash chromatographed to give the product as a white solid (185 mg, 82%). ^{1}H NMR (500 MHz, CD_3CN): δ = 7.60 (d, J = 7.3 Hz, 1 H), 7.52 (dd, J = 8.2, 0.9 Hz, 1 H), 7.31 (td, J = 7.8, 1.3 Hz, 1 H), 7.24 (td, J = 7.5, 1.0 Hz, 1 H), 7.17 (s, 2 H), 7.10 (d, J = 1.0 Hz, 1 H), 6.87 (d, J = 2.2 Hz, 2 H), 6.33 (t, J = 2.2 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, CD_3CN): δ = 159.6, 156.7, 155.7, 133.3, 130.2, 125.6, 124.2, 122.2, 112.0, 104.7, 104.2, 102.9 ppm.

Structure Analysis of 3i: X-ray crystallographic data collection was performed at 173.0(1) K using a Bruker diffractometer with a Platform 3-circle goniometer and an Apex 2 CCD area detector. Crystals were cooled under a cold nitrogen stream using an N-Helix cryostat. A hemisphere of data was collected for each crystal using a strategy of omega scans with 0.5° frame widths. Unit cell determination, data integration, absorption correction, and scaling were performed using the Apex2 software suite from Bruker.[29] Space group determination, structure solution, refinement, and generation of ORTEP diagrams were done using the SHELXTL software package.[30]

3-Methyl-2-phenyl-6-benzofuranol (**3i**) crystallizes in a lattice with cell parameters a = 9.7881(5) Å, b = 10.1304(5) Å, c = 22.583(1) Å, α = 83.697°, β = 89.699(3)°, γ = 89.944(3)° and Z = 8. The cell parameters are very close to that of a monoclinic cell with a as the unique axis. However, the R_{int} value for equivalent reflections corresponding to a monoclinic cell was very high and all attempts to solve the structure in a monoclinic space group met with considerable difficulty. Ultimately the crystal was solved in the triclinic space group $P\bar{1}$ with Z' = 4.

Supporting Information (see footnote on the first page of this article): Discussion of the structure refinement and the crystal packing of compound **3i** and copies of ^{1}H and ^{13}C NMR spectra of compounds from Tables 1, 2, and 3.

Acknowledgments

Financial support of this work by the National Science Foundation (NSF) (CHE-1058984) is acknowledged. FMC, Lithium Division is thanked for donation of TNpP, and Johnson-Matthey for donation of palladium compounds.

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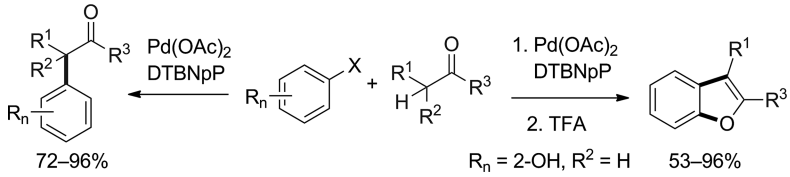
Received: April 23, 2014
Published Online: ■



Ketone α-arylation with aryl bromides and chlorides using di-(*tert*-butyl)neopentylphosphine (DTBNpP) in combination with palladium is described. This catalyst system provides an efficient route to benzofurans through the condensation of 2-bromo phenols with ketones.

Keywords: Synthetic methods / C–C coupling / Palladium / Phosphane ligands / Heterocycles / Ketones

