ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2025, **61**, 19433

Received 6th October 2025,
Accepted 3rd November 2025

DOI: 10.1039/d5cc05726d

rsc.li/chemcomm

Mild cross-coupling of tertiary alkoxides with aryl chlorides enabled by a shelf-stable methylnaphthyl palladium NHC complex

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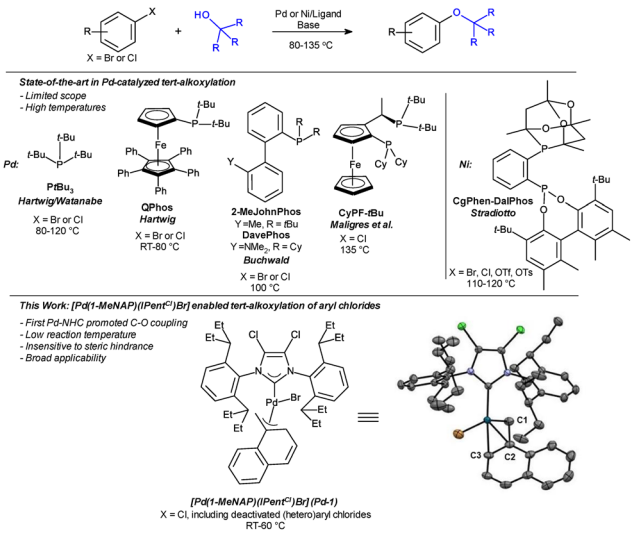
The catalytic coupling of tertiary alkoxides with aryl halides has a high energetic barrier, which makes KO*t*Bu an advantageous base in cross-couplings. A palladium methylnaphthyl (MeNAP) catalyst bearing the IPent^{Cl} ligand was found to promote this C–O coupling with high efficiency, enabling the synthesis of aryl *t*-alkyl ethers from abundant aryl chlorides.

The frequent occurrence of C(sp^2)–O bonds in natural products, agrochemicals and pharmaceuticals has inspired intense efforts towards the development of efficient C–O bond-forming methodologies.[1] The incorporation of tertiary alkyl ether groups is of specific interest in drug discovery as these groups increase lipophilicity and provide a defined steric bulk.[2,3] *t*-Butoxy groups can also serve as masked hydroxy functionalities. It can be synthetically advantageous to introduce phenolic hydroxyl groups in a protected form and liberate these sensitive functionalities at a late stage of the overall synthesis.[4]

The introduction of tertiary alkoxy substituents is traditionally achieved by metal-free methods *via* S_NAr or aryne mechanisms starting from aryl fluorides or bromides,[5–7] and multistep syntheses from arylammonium or aryliodonium salts.[8,9] Cross-couplings of aryl halides with tertiary alcohols are promoted by Pd, Ni, and Cu catalysis, but in contrast to other C–O bond forming reactions,[10] these couplings are still somewhat underdeveloped.[11–13] Hartwig, Buchwald, Watanabe, and Maligres *et al.* found P*t*Bu$_3$,[14,15] QPhos,[16,17] and biphenylphosphine ligands[18] to be most effective in palladium-catalyzed alkoxylations of aryl halides, whereas the JosiPhos-type ligand CyPF-*t*Bu is particularly suited for heteroaryl chlorides (Scheme 1).[19] Stradiotto and co-workers demonstrated that nickel/Dalphos systems promote alkoxylation of various (hetero)aryl electrophiles.[20] However, all of these processes call for relatively high catalyst loadings and temperatures above 85 °C.



Scheme 1 Catalytic couplings of aryl halides with tertiary alcohols. In the depicted X-ray of the [Pd(1-MeNAP)(IPent^{Cl})Br] catalyst, displacement ellipsoids are shown at the 50% probability level, and hydrogens are omitted for clarity (CCDC = 2492026). Selected bond lengths (Å): C_{NHC}–Pd = 2.049(3), Pd–C1 = 2.092(3), Pd–C2 = 2.242(3), Pd–C3 = 2.267(3).

The use of N-heterocyclic carbenes (NHCs) has led to major advances in Pd-catalyzed cross-coupling with numerous efficient catalytic reactions being disclosed in the last decade.[21] Backbone-modifications of NHCs have been shown to enhance their catalytic reactivity by adjusting steric and electronic properties.[22–25] In this context, Organ *et al.* reported that the dichlorinated NHC ligand IPent^{Cl} promotes C–N,[26] C–S,[27] and C–C cross-coupling reactions more efficiently than its non-halogenated counterpart.[28] The chloro-substituents are believed to induce a high but flexible steric bulk and increase the π-electron-accepting abilities of NHC ligands while maintaining their strong σ-donating character. This allows IPent^{Cl} systems to master both challenging oxidative addition and reductive elimination processes.[29] IPent^{Cl} catalysts can be generated *in situ* from various palladium precursors, but stable, one-component

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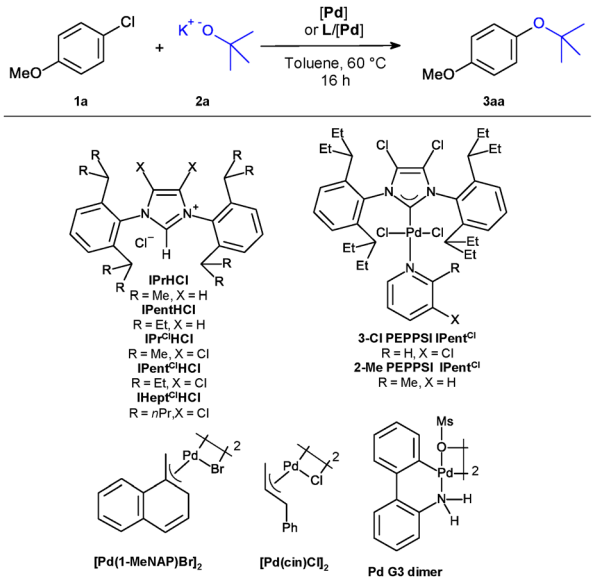
IPent^{Cl} palladium pre-catalysts have so far only been synthesized as pyridine or cinnamyl complexes.[30]

During our studies on Pd-methylnaphthyl (MeNAP) complexes as bench-stable, rapidly activating palladium sources,[31] we discovered that complexes generated from [Pd(MeNAP)X]$_2$ and halogenated carbene ligands showed catalytic activity in challenging couplings of aryl chlorides with *t*-alkoxides. This raised our attention, since to the best of our knowledge, there is no literature precedence of an aryl ether synthesis promoted by a Pd-NHC system.

We systematically investigated the catalytic activity of various complexes generated from [Pd(1-MeNAP)Br]$_2$ and phosphine or NHC ligands using the reaction of *p*-chloroanisol and potassium *t*-butoxide as a model system (Table 1). Comparative experiments revealed that state-of-the-art systems, which have been shown to promote this coupling at elevated temperatures, give only marginal conversion at 60 °C (entries 1 and 2).

Table 1 Screening of the ligands and pre-catalysts[a]



Entry	Pd pre-catalyst	Ligand	**3aa** (%)
1	Pd(dba)$_2$	QPhos	2
2	Pd(OAc)$_2$	2-MeJohnPhos	0
3	[Pd(1-MeNAP)Br]$_2$	QPhos	2
4	[Pd(1-MeNAP)Br]$_2$	CyPF-*t*Bu	0
5	[Pd(1-MeNAP)Br]$_2$	DavePhos	2
6	[Pd(1-MeNAP)Br]$_2$	P*t*Bu$_3$	0
7	[Pd(1-MeNAP)Br]$_2$	PAd$_3$	11
8	[Pd(1-MeNAP)Br]$_2$	IPrHCl	0
9	[Pd(1-MeNAP)Br]$_2$	IPentHCl	2
10	[Pd(1-MeNAP)Br]$_2$	IPr^{Cl}HCl	0
11	[Pd(1-MeNAP)Br]$_2$	IPent^{Cl}HCl	98
12	[Pd(1-MeNAP)Br]$_2$	IHept^{Cl}HCl	25
13	[Pd(cin)Cl]$_2$	IPent^{Cl}HCl	76
14	Pd G3 dimer	IPent^{Cl}HCl	20
15	3-Cl PEPPSI IPent^{Cl}	—	23
16	2-Me PEPPSI IPent^{Cl}	—	85
17	[Pd(1-MeNAP)(IPent^{Cl})Br]	—	>99[b]

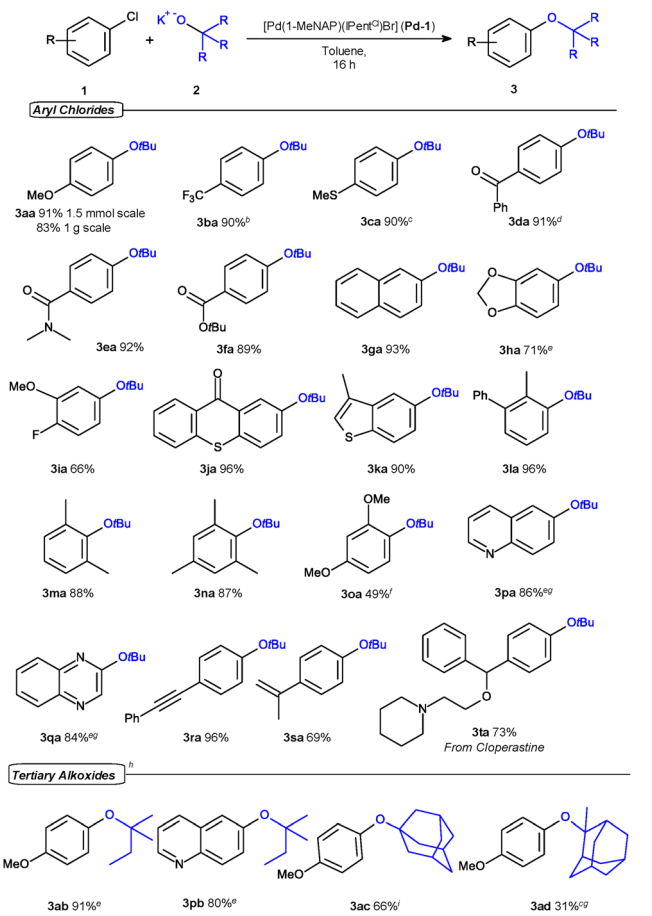
[a] 0.5 mmol scale, 60 °C, 2 mL toluene, 16 hours, 2.5 mol% [Pd] and ligand (2.7 mol% of phosphine ligands), 2 eq. KO*t*Bu, GC yield using tetradecane as an internal standard. [b] 1.2 eq. KO*t*Bu.

Even when switching to [Pd(1-MeNAP)Br]$_2$ as the palladium source, none of the tested phosphine ligands promoted the target reaction, although many of them induced high catalytic activity in other Pd-mediated cross-couplings (entries 3–7). Non-halogenated NHC ligands were also ineffective (entries 8 and 9). In sharp contrast, the 4,5-dichlorinated NHC ligand IPent^{Cl}HCl gave quantitative conversion and near quantitative yield of the desired aryl-*t*-butyl ether **3aa** (Entry 11). The catalyst is very sensitive to variations of the chain length of the N-substituents (entries 10–12): For the smaller isopropyl substituted derivative IPr^{Cl}HCl, a derivative of the widely used IPr NHC ligand, no conversion was observed, and IHept^{Cl}HCl bearing larger isoheptyl substituents gave a rather low yield. These results highlight the significant influence of the ligand's steric bulk, which primarily affects transmetallation and reductive elimination. We next probed the influence of the palladium source on the reaction outcome and found that the MeNAP complexes are clearly superior to established systems (entries 13–17). Neither the cinnamyl complex [Pd(cin)Cl]$_2$ – the gold standard among Pd-allyl precursors,[32] nor PEPPSI-type complexes or palladacycles of the Buchwald generation 3 type performed similarly well. This aligns with recent reports that MeNAP Pd-halide precursors decisively enhance the performance of cross-coupling catalysts both for phosphine and NHC systems.[31,32b]

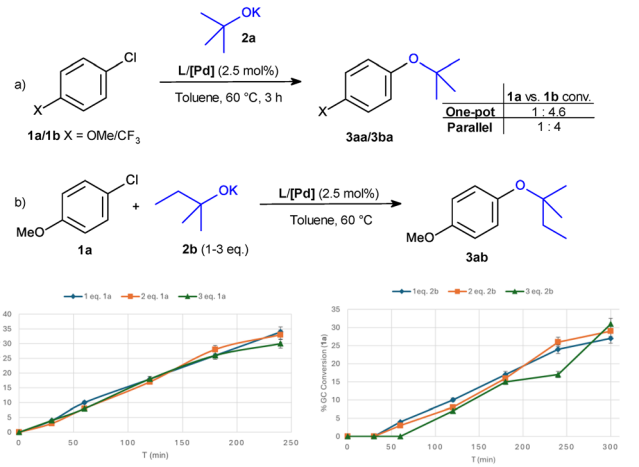
Comprehensive screening tables can be found in the SI. They show that the reaction is more effective with potassium than with sodium or lithium *t*-butoxide and that toluene and dioxane are the most effective solvents. NMR-studies revealed that the reaction of commercially available [Pd(1-MeNAP)Br]$_2$, IPent^{Cl}HCl and excess KO*t*Bu proceeds quantitatively within minutes with the formation of the corresponding NHC complex. Under these conditions, activation takes place within 10 minutes, as judged by the disappearance of the characteristic MeNAP signals of **Pd-1** in ^{1}H-NMR. To obtain [Pd(1-MeNAP)(IPent^{Cl})Br] (**Pd-1**) in a microanalytically pure form, we treated [Pd(1-MeNAP)Br]$_2$ with the preformed carbene IPent^{Cl}. This way, **Pd-1** was obtained in near quantitative yield as an air-stable, easy to administer complex. Its molecular structure was confirmed by single crystal X-ray diffraction analysis (see Scheme 1). The use of **Pd-1** as a catalyst gives full conversion and near quantitative yields of **3aa**, even when the base is used only in 1.2-fold excess (entry 17).

We proceeded to investigate the scope of aryl-*t*-alkyl ether synthesis, varying both the aryl halide and the alkoxide component. As illustrated by the examples in Table 2, both electron-rich and electron-deficient aryl chlorides bearing substituents in the *ortho*-, *meta*- or *para*-position were successfully converted. **3aa** was synthesized on a gram scale demonstrating the scalability of the process. Various functional groups were tolerated, *e.g.* thioethers, non-enolizable ketones, amides, and esters (**3ca**–**3fa**). Sulphur- and nitrogen-based heterocyclic scaffolds are also compatible (**3ja**, **3ka**, **3pa**, **3qa**). Notably, electron-deficient aryl chlorides were found to be more reactive than electron-rich ones. For example, **1b** was converted even with only 1% catalyst, and **1d** gave high yields already at room temperature.

Table 2 Reaction scope with regard to aryl chlorides and tertiary alkoxides[a]



[a] Conditions: 0.50 mmol **1**, 0.60 mmol **2**, 2 mL toluene, 2.5 mol% **Pd-1**, 60 °C, 16 h. [b] 1.0 mol% **Pd-1**. [c] 4.0 mol% **Pd-1**. [d] At RT. [e] 3.0 mol% **Pd-1**. [f] 75 °C. [g] 70 °C. [h] 2.0 eq. alkoxide. [i] 3.0 eq. alkoxide.



Scheme 2 (a) Competition experiments: 0.50 mmol aryl chloride, 1.00 mmol **2a**. (b) Experiments conducted at 0.50 mmol scale, 60 °C, in 2 mL toluene, with 1.25 mol% $[Pd(1\text{-}MeNAP)Br]_2$ and 2.5 mol% $IPent^{Cl}HCl$: yield of **3aa** vs time using increasing eq. of **1a** (left) and conversion of **1a** *vs.* time using increasing eq. of **2b** (right). GC yield/conversion using tetradecane as an internal standard. Each datapoint represents the average of two runs.

Still, even the extremely electron-rich aryl chloride **1o**, bearing alkoxy substituents in the *ortho* and *para* positions, was successfully converted, albeit at slightly higher temperature. The catalyst is also remarkably tolerant of steric hindrance. Even aryl chlorides with two *ortho* methyl groups were cleanly converted. Compounds **3ma–3oa** have never been accessed by catalytic alkoxylation reactions, which underlines the high efficiency of this protocol. The synthesis of a *t*-butoxylated derivative of the commercial drug cloperastine illustrates the synthetic utility of the transformation (**3ta**). Alkyne and alkene functionalities were left intact, without even traces of Heck-type products being observed (**3ra**, **3sa**), whereas primary or secondary amino groups are incompatible, as they couple preferentially over the tertiary alkoxides. Acidic functionalities such as phenols, carboxylic acids, or enolizable carbonyl groups are not tolerated. The reaction scope with regard to the tertiary alcohols includes *t*-amyl and adamantyl derivatives (**3ab**, **3pb**).[33] The reaction protocol extends to tertiary alcohols, exclusively. Primary and secondary alcohols undergo redox reaction to form arenes and aldehydes, which is expected as the $IPent^{Cl}$ ligand has an unsuitable steric profile to facilitate reductive elimination over β-hydride elimination.

A series of mechanistic experiments were conducted to shed some light on the reaction mechanism (Scheme 2a). Electron-rich aryl chloride **1a** reacts more slowly than electron-poor **1b**, both in parallel and one-pot competition reactions. This seems to point towards oxidative addition as the rate-limiting step. However, neither the starting concentration of the aryl chloride nor that of the alkoxide has any effect on the reaction rate (Scheme 2b), ruling out both the oxidative addition and transmetallation as rate-determining. Varying the catalyst loading revealed a first-order rate dependence on the catalyst (Fig. S1 in SI). Further experiments revealed that the reactivity increases with decreasing steric bulk in the series adamantanol, *t*-amyl alcohol and *t*-butanol (Scheme S2 in the SI). In contrast, Stradiotto *et al.* found that for Ni-based systems, bulkier alcohols react at higher rates.[20]

The above findings align with mechanistic studies by Hartwig,[11,34a] as well as Wiedenhoefer and Buchwald.[34b] They found that reductive eliminations of aryl ethers from palladium complexes are accelerated by electron-withdrawing substituents. We can, thus, conclude that the reductive elimination of the aryl ether product is rate-determining for **Pd-1**. This explains why the electron-withdrawing chloro substituents on the bulky $IPent^{Cl}$ enable mild, catalytic C–O bond formation.

Overall, $[Pd(1\text{-}MeNAP)(IPent^{Cl})Br]$ is an easy-to-use, one-component catalyst precursor with unparalleled catalytic activity in the coupling of aryl halides with tertiary alkoxides. Our findings show how strongly the palladium precursor can impact a catalytic reaction. The unexpected discovery of a C–O coupling mediated by a Pd-NHC catalyst shows that there is still much left to explore in metal carbene catalysis.

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy – EXC 2033–390677874 – RESOLV and the A. v. Humboldt Foundation (Fellowship to NVT). We thank Dr. Bert Mallick for help with the X-ray crystallography and M. Wüstefeld for HRMS measurements.

Conflicts of interest

UMICORE AG & Co. KG is commercializing many Pd complexes described in this work including [Pd(1-MeNAP)(IPent^{Cl})Br].

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental details and copies of spectra. See DOI: **https://doi.org/10.1039/d5cc05726d**.

CCDC 2492026 contains the supplementary crystallographic data for this paper.[35]

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