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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^tBu 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(sp²)–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 arylodonium 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 Maligrès *et al.* found PtBu₃,^{14,15} QPhos,^{16,17} and biphenylphosphine ligands¹⁸ to be most effective in palladium-catalyzed alkoxylation 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/Dalpos 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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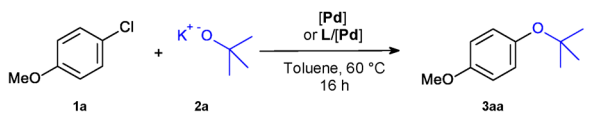
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IPent^{Cl} palladium pre-catalysts have so far only been synthesized as pyridine or cinnamyl complexes.³⁰

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*-chloroanisole 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



Reaction scheme: 1a (4-chloroanisole) + 2a (K⁺ t-BuO⁻) → 3aa (4-(tert-butoxy)anisole) using [Pd] or L/[Pd] in Toluene, 60 °C, 16 h.

Chemical structures of ligands and pre-catalysts:

- IPr^{Cl}HCl (R = Me, X = H)
- IPent^{Cl}HCl (R = Et, X = H)
- IPr^{Cl}HCl (R = Me, X = Cl)
- IPent^{Cl}HCl (R = Et, X = Cl)
- IHept^{Cl}HCl (R = *n*Pr, X = Cl)
- 3-Cl PEPPSI IPent^{Cl} (R = H, X = Cl)
- 2-Me PEPPSI IPent^{Cl} (R = Me, X = H)
- [Pd(1-MeNAP)Br]₂
- [Pd(cin)Cl]₂
- Pd G3 dimer

| 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- <i>t</i> Bu | 0 |
| 5 | [Pd(1-MeNAP)Br] ₂ | DavePhos | 2 |
| 6 | [Pd(1-MeNAP)Br] ₂ | PtBu ₃ | 0 |
| 7 | [Pd(1-MeNAP)Br] ₂ | PA-d ₃ | 11 |
| 8 | [Pd(1-MeNAP)Br] ₂ | IPr ^{Cl} HCl | 0 |
| 9 | [Pd(1-MeNAP)Br] ₂ | IPent ^{Cl} HCl | 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^tBu, GC yield using tetradecane as an internal standard. ^b 1.2 eq. KO^tBu.

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 transmetalation 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^tBu 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 ¹H-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.



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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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