[Pd(μ-Cl)Cl(IPr*)]2 : A highly hindered pre-catalyst for the synthesis of tetra-ortho-substituted biaryls via Grignard reagent cross-coupling

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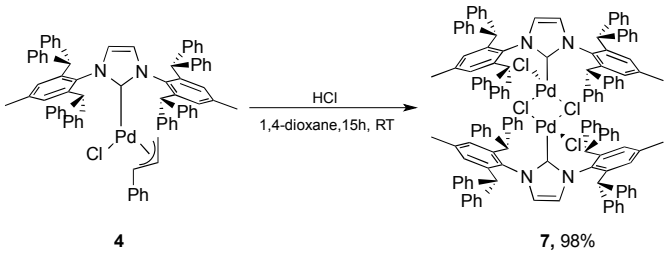
The new well-defined catalyst [Pd(μ-Cl)Cl(IPr*)]$_2$ enables the efficient Grignard reagent cross-coupling for the synthesis of tetra-*ortho*-substituted biaryls. The high reactivity of the complex is associated with the important bulkiness of the IPr* ligand. The dimer represents the most efficient catalyst reported to date for this challenging transformation.

In the course of the last 40 years, the construction of C-C bonds using transition metal catalysts[1] has emerged as an extremely powerful tool for the synthesis of pharmaceutical scaffolds and natural products.[2] The Mizoroki-Heck, Negishi, Stille and Suzuki-Miyaura cross-couplings are the most employed to form C-C bonds under mild conditions and with low catalyst loadings.[1] Recently, the coupling involving Grignard reagents with aryl and alkyl halides,[3] also known as the Kumada-Tamao-Corriu reaction, has attracted renewed attention.[4] As Grignard (or lithium) reagents are used to synthesise boronic acids and other transmetallating agents, organomagnesium compounds represent substrates that are most straightforward to employ and economically more attractive than boronic acids. Moreover, the use of an additional base in this cross-coupling reaction is not required as the organomagnesium reagent can act as the base. Unfortunately, the use of Grignard reagents as coupling partners with Pd-based catalysts has been less developed because of the often-observed formation of significant amounts of undesired homo-coupling by-products. Until now, the construction of tetra-*ortho*-substituted biaryl compounds has been the focus of a limited number of reports and therefore remains a challenge in cross-coupling catalysis.[1,5] To date, the Suzuki-Miyaura reaction remains the most often employed protocol for the synthesis of tetra-*ortho*-substituted products.[5d,e] Recently, with the development of very hindered *N*-heterocyclic carbene (NHC),[6] and bulky, electron-rich phosphines,[7] the synthesis of tetra-*ortho*-substituted biaryls *via* cross-coupling reaction has been shown feasible. Glorius, in 2004, with the synthesis of [IBiox12·HOTf] **1** reported, for the first time, the preparation of tetra-*ortho*-substituted biaryls compounds *via* Suzuki-Miyaura cross-coupling at 110°C with 3 mol% of Pd.[8] More recently, the development of very bulky NHC complexes and the use of well-defined pre-catalysts have permitted to conduct this challenging reaction under milder conditions. In 2009, Organ with the [Pd(Cl)$_2$(3-Cl-pyridine)(IPent)] **2** (IPent = *N*,*N*'-bis(2,6-bis(di-*iso*-pentylphenyl)imidazol-2-ylidene) complex performed the reaction at 65°C with 2 mol% of catalyst,[9a] while recently Fañanás-Mastral and Feringa showed that ArLi could be coupled to ArBr at room temperature using 5 mol% of **2**.[9b] Recently, two well-defined pre-catalysts bearing sterically demanding NHC ligands were reported. Dorta[10] and co-workers developed the [PdCl(cin)(*anti*-(2,7)-SICyoctNap)] **3** (SICyoctNap = *N,N'*-bis(2,7-bis(dicyclooctylnaphthalen-1-yl)-imidazolin-2-ylidene, cin = cinnamyl) system and we reported the [PdCl(cin)(IPr*)] **4** (IPr* = *N*,*N*'-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) pre-catalyst[11] in order to synthesize sterically encumbered biaryls in excellent yields under very mild conditions (Scheme 1).



4 **7**, 98%

Scheme 1. Synthesis of [Pd(μ-Cl)Cl(IPr*)]$_2$ **7**

These examples, using the Suzuki-Miyaura reaction, are illustrative of the most common procedure enabling the construction of tetra-*ortho*-substituted biaryls. These developments prompted us to investigate the potential of Grignard reagents in the synthesis of these sterically congested C-C bond linkages. The use of Grignard reagents in cross-coupling leading to tetra-*ortho*-substituted biaryls compounds using well-defined palladium/NHC complexes has been mentioned only briefly in the literature.[12] Organ and co-workers showed that using 2 mol% of [Pd(Cl)$_2$(3-Cl-pyridine)(SIPr)] **5**, 4-(2',6'-dimethylphenyl)-1,3,5-trimethyl-1*H*-pyrazole could be obtained in 70% yield.[12a] More recently, we have shown that [Pd(μ-Cl)Cl(SIPr)]$_2$ **6** can promote the synthesis of 2,2',4,6,6'-pentamethyl biphenyl and 2,2',4,4'-tetramethylbiphenyl using 0.45 mol% of **6**, in 35 and 69% yield, respectively.[12b] Considering that the dimeric species **6** has been shown highly active for the cross coupling of Grignard reagents with aryl and heterocyclic chlorides, and that

bulkier NHC ligands[5d-e,13] appear to be key for the synthesis of hindered cross-coupling products, we reasoned that a dimer bearing a bulky NHC might exhibit outstanding activity in the formation of tetra-*ortho*-substituted biaryls. Herein, we report the synthesis of such a complex and its catalytic activity in the cross-coupling of aryl bromides and chlorides with Grignard reagents, leading to the formation of tetra-*ortho*-substituted biaryls. Using the very bulky NHC ligand IPr* developed by Markó,[14] the novel pre-catalyst dimer [Pd(μ-Cl)Cl(IPr*)]$_2$ **7** was successfully synthesised from [PdCl(cin)(IPr*)] **4**[11] (Scheme 1). Numerous attempts on crystallizing **7** resulted in crystals of poor quality. However, a preliminary structure was successfully solved confirming the formation of a bridged dinuclear complex (Figure 1).[15]

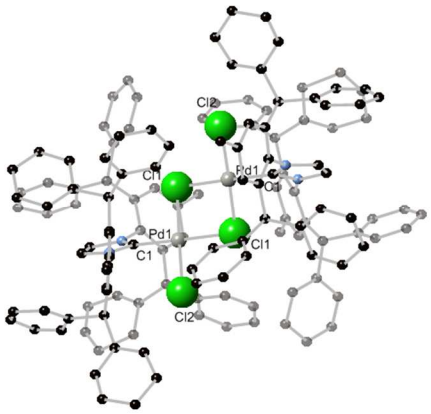


Figure 1. Molecular structure of **7**. Selected bond lengths [Å] and angles [°]: Pd1-C1 1.974(12), Pd1-Cl1 2.395(3), Pd1-Cl2 2.287(5), Pd1-Cl1^1 2.325(5); Cl2-Pd1-C1 90.0(5), Cl1^1-Pd1-C1 91.5(5), Cl1-Pd1-Cl2 92.17(14). H atoms omitted for clarity.

The metal centre adopts the expected slightly distorted square planar geometry, with the IPr* ligands almost encasing the palladium centres. In order to evaluate the steric hindrance of IPr*, the percent buried volume (%V_{Bur}) was calculated[16] and compared to those found for related dimers, [Pd(μ-Cl)Cl(IPr)]$_2$[17] and [Pd(μ-Cl)Cl(SIPr)]$_2$.[18],[19] The results show that IPr* is clearly more bulky than IPr and SIPr (39.6% *vs* 37.3% and 38.2%), however, the difference in %V_{Bur} is not as drastic as in cinnamyl analogues (44.7% *vs* 36.8% and 37.3%). The difference found for the IPr* %V_{Bur} in the two complexes can be explained by the flexibility of NHCs that can modulate their bulkiness in response to the steric requirement of the co-ligands.[20] A further analysis of the steric mapping of this ligand is depicted in Figure 2. This clearly shows the space occupied by the IPr* ligand is more homogeneously distributed in the case of the dimeric species **7** compared to that of its cinnamyl analogue **4**. Indeed, while the values calculated for the %V_{Bur} for each quadrant for IPr* in **4** range from 26.6% to 74.8%,[11] in **7** they only range from 28.6% to 53.1%. In the case of the [Pd(μ-Cl)Cl(IPr*)]$_2$ **7**, the ligand environment around the Pd centre can be seen as being divided into two sections linked through C_2 symmetry. In fact, two bulky quadrants (%V_{Bur} 53.1 and 47.9) are evidently associated to the presence of the phenyl groups and two other quadrants with smaller steric hindrance (%V_{Bur} 28.6 and 28.9) are associated with the presence of chloride atoms. In the case of the [PdCl(cin)(IPr*)] **4**, the ligand environment is divided in three parts mainly due to the presence of one twisted phenyl group on the chloride quadrant (Figure 3).[11]

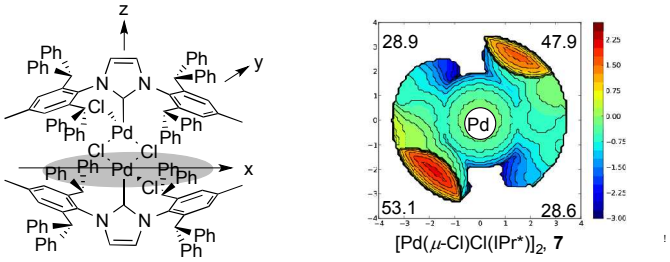


Figure 2. Mapping for complex **7** with %V_{Bur} per quadrant

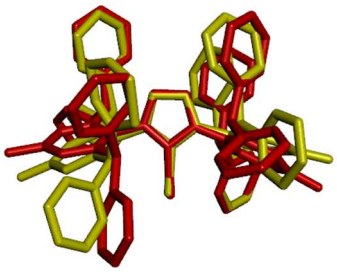
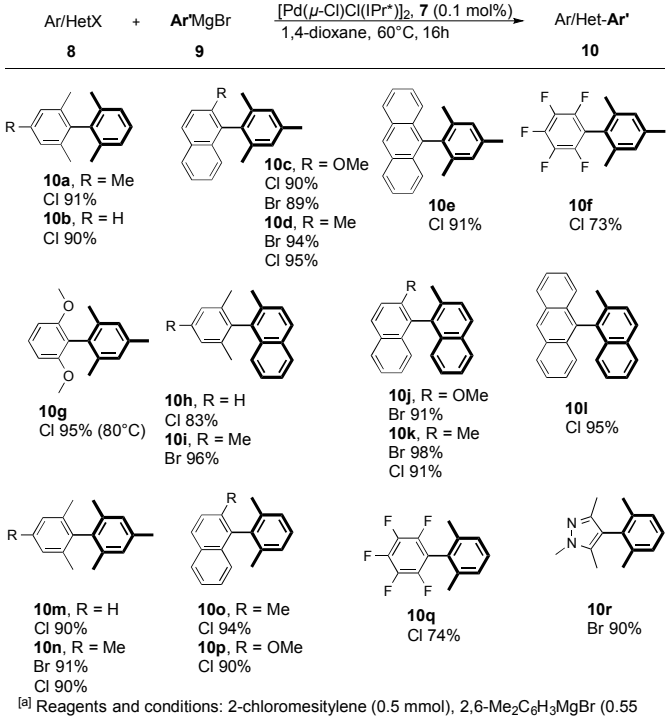


Figure 3. Overlay of the molecular structure of complexes [PdCl(cin)(IPr*)] **4** (red) and [Pd(μ-Cl)Cl(IPr*)]$_2$ **7** (yellow). Cinnamyl, Cl and H atoms omitted for clarity.

The C_2 symmetry of the IPr* ligand in **7** affects its reactivity. As an example, on a model reaction (2-ClMes (0.5 mmol), 2,6-$Me_2C_6H_3MgBr$ (0.55 mmol), 0.1 mol% Pd, 60°C, 16 h) [Pd(μ-Cl)Cl(IPr*)]$_2$ **7** leads to 72% conversion whereas [PdCl(cin)(IPr*)] **4** leads to 64% conversion. We next examined the ability of [Pd(μ-Cl)Cl(IPr*)]$_2$ **7** to promote the formation of tetra-*ortho*-substituted products. The cross-coupling of chloromesitylene with 2,6-dimethylbenzene magnesium bromide was first investigated, allowing for the direct comparison with results reported with [Pd(μ-Cl)Cl(SIPr)]$_2$. In this reaction, with a catalyst loading of 0.45 mol%, quantitative conversion is obtained with the IPr* derivative **7** compared to 35% when using [Pd(μ-Cl)Cl(SIPr)]$_2$.[12b] This confirms the theory that bulkier ligands lead to more efficient systems for the formation of sterically congested biaryls. The reaction conditions were optimised (see ESI). After 16 h at 60°C in 1,4-dioxane and 0.1 mol% of **7**, the desired cross-coupling compound **10a** was obtained in an excellent 91% isolated yield. A further decrease of the catalyst loading to 0.05 mol% is possible, but the reaction does not reach completion. Nevertheless, an acceptable 72% conversion to the desired product is obtained. The scope of the reaction was next investigated (Scheme 2). The cross-couplings of aryl or naphthyl magnesium bromides and aryl, naphthyl or heteroaryl halides proceed in very good to excellent isolated yields (73-98%, 22 examples), with no formation of homo-coupling by-products. The catalyst performs equally well with aryl chlorides or bromides, suggesting that the oxidative addition of the aryl halide is not the rate-limiting step in this reaction (**10c**, **10d**, **10k** and **10n**). The highly challenging dimethoxy derivative 1-chloro-2,6-dimethoxybenzene can also be successfully coupled, however, a slightly higher operating temperature is necessary (**10g**). Finally, tetra-*ortho*-substituted CC bonds involving heterocycles can also be formed using the reported system (**10r**).



[a] Reagents and conditions: 2-chloromesitylene (0.5 mmol), 2,6-$Me_2C_6H_3MgBr$ (0.55 mmol), **7**, solvent (2.5 mL), 60°C, 16 h. [b] Isolated yields, average of two reactions.

Scheme 2. Scope of the reaction leading to tetra-*ortho*-substituted biaryls[a][b]

In summary, a well-defined pre-catalyst $[Pd(\mu\text{-}Cl)Cl(IPr^*)]_2$ **7** bearing a very sterically demanding NHC ligand has been synthesised by a straightforward synthetic route. This complex exhibits very high catalytic activity in the Grignard reagent cross-coupling of very sterically demanding partners leading to the formation of highly hindered C-C biaryl junctions. This dimer performed the challenging formation of tetra-*ortho*-substituted biaryls from aryl or naphthyl magnesium bromides and aryl, naphthyl, heteroaryl halides exceedingly well and in very high isolated yields. Finally, the high activity/productivity of **7** is attributed to the very important bulk of the NHC ligand in the coordination sphere of the palladium. To the best of our knowledge, **7** is the most active palladium complex reported to date for the synthesis of tetra-*ortho*-substituted biaryl compounds *via* this cross-coupling reaction. Studies aimed at expanding the scope of reactions possibly benefiting from increased ligand bulk around the metal centre are on-going in our laboratories.

Notes and references

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†Electronic supplementary information (ESI) available: Optimisation details, $\%V_{Bur}$ calculations and NMR spectra of **7** and of all cross-coupling products, crystal data and structure refinement.

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