Communication

Catalytic Suzuki couplings by an amido pincer complex of palladium

Lan-Chang Liang [a, b, *], Pin-Shu Chien [a], Liang-Hua Song [a]

[a] Department of Chemistry and Center for Nanoscience & Nanotechnology, National Sun Yat-sen University, Kaohsiung 80424, Taiwan
[b] Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 80708, Taiwan

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ABSTRACT

The catalytic feasibility of [PNP]PdCl, where [PNP]$^-$ = bis(2-diphenylphosphinophenyl)amide, on biaryl syntheses from Suzuki-type cross-coupling reactions is demonstrated. A number of electronically activated, unactivated, and deactivated (hetero)aryl bromides and iodides is viable to react with arylboronic acids. Of particular note of this catalysis is its success in the high yield production of sterically encumbered tri-*ortho*-substituted biaryls and its operative compatibility under aerobic conditions in aqueous solutions.

1. Introduction

Palladium-catalyzed cross-coupling reactions have over the last decades made a significant impact on organic syntheses [1]. Of particular note is the Nobel Prize in Chemistry 2010 awarded to three prestigious synthetic chemists in this field [2]. Among the powerful and versatile methodologies developed, Suzuki couplings [3] represent one of the most attractive approaches for C(sp^2)-C(sp^2) bond-forming biaryl syntheses and meanwhile may not necessarily require inert experimental conditions. As a widespread structural motif, biaryls are often found in natural products, liquid crystalline materials, organic semiconducting materials, and biologically and pharmacologically active species, etc. [4].

Though palladium catalysts for cross-couplings are currently popularized with derivatives of electron-rich, sterically demanding phosphines [5] and N-heterocyclic carbenes [6], phosphine palladacycles [7], e.g., 1 and 2 in Fig. 1, constitute another intriguing and prevalent class of candidates whose electronic and steric properties can be systematically tailored for catalysis purposes. We have previously reported a number of group 10 complexes [8] of amido

phosphine ligands [9] and demonstrated their catalytic activities in cross-coupling reactions [8a-f]. In particular, the dimeric palladium complex 3 and its mononuclear tricyclohexylphosphine adduct [NP]PdCl(PCy$_3$) (4) were proved to be highly active catalyst precursors for Suzuki couplings [8b]. In separate studies, compound 5a was demonstrated to exhibit efficient catalytic activities for aryl olefination [8a] and aryl alkynylation [8f] in Heck- and Sonogashira-type couplings, respectively. Constitutionally, amido complexes 3 and 5 can be regarded as an electronic modification of palladacycles 1 and 2, respectively, by analogy with the corroborated electronic variations of O versus CH$_2$ incorporated in the ligand composition of 2 for improved cross-coupling performances [7c,10].

As compared with 3, tricyclohexylphosphine incorporation in 4 is known to electronically enhance catalytic activities in Suzuki couplings [8b]. Compounds 4 and 5 are coordinatively similar in view of the ligation of their square-planar palladium center with one chloride, one amide, and two phosphorus donors. The geometric orientations of these phosphorus donors, however, are different in these complexes. Notably, the former is cis [8b] whereas the latter is trans [8a]. Given the coordinative similarity of 5 to 4, we envisioned that 5 is also an active catalyst precursor for Suzuki couplings and became interested in how important this geometric discrepancy is in terms of catalytic scopes and activities. We describe herein the competence of 5 in Suzuki-type catalysis, which is complementary to the reactivity scopes of 5a defined in the

* Corresponding author. Department of Chemistry and Center for Nanoscience & Nanotechnology, National Sun Yat-sen University, Kaohsiung 80424. Taiwan; Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 80708, Taiwan.
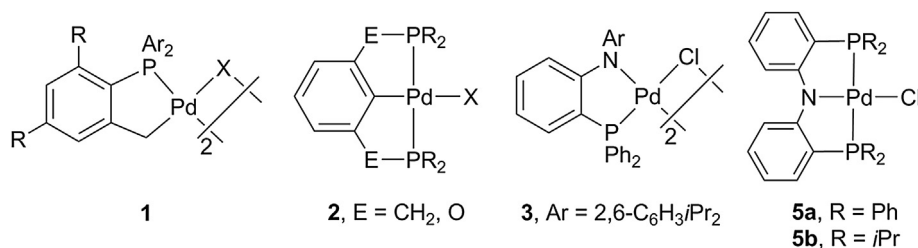E-mail address: lcliang@mail.nsysu.edu.tw (L.-C. Liang).

1   **2**, E = CH$_2$, O   **3**, Ar = 2,6-C$_6$H$_3$$iPr_2$ **5a**, R = Ph
5b, R = iPr

Fig. 1. Representative examples of phosphine palladacycles.

previously established Heck [8a] and Sonogashira reactions [8f]. This study also represents the first report of Suzuki couplings catalyzed by PNP complexes, thus effectively widening the applications of these complexes on catalysis.

2. Results and discussion

Compounds 5a and 5b were prepared following literature procedures [8a,8f]. Both complexes are not sensitive to air or moisture and remain intact upon heating in solutions at 110 °C or higher. To survey reaction parameters for Suzuki couplings, we chose to examine the reactivity of 5a toward the reaction of 4-tolyl bromide with phenylboronic acid in the presence of a variety of bases (K$_3$PO$_4$·H$_2$O, K$_3$PO$_4$, K$_2$CO$_3$, Cs$_2$CO$_3$, Na$_2$CO$_3$, NaHCO$_3$, NaOtBu) and solvents (dioxane, toluene, DME) under aerobic conditions. Due to the inherently low solubility of these bases in selected solvents at room temperature, heating the reaction mixtures to 80 °C or higher was attempted to facilitate this catalysis. In general, reactions run with K$_3$PO$_4$·H$_2$O or K$_3$PO$_4$ in dioxane or toluene solutions outperform the others, producing 4-methylbiphenyl as the desired product in satisfactory yields (Table 1, entries 1–5).

Reaction scopes of this catalysis were examined with conditions resolved from the parameter survey. As summarized in Table 1, a number of electronically activated, unactivated, and deactivated aryl bromides (entries 1–32) and iodides (entries 33–35) are competent building blocks. Compatible functional groups include keto, aldehyde, nitro, fluoro, chloro, alkyl, alkoxy, and amino, etc. Satisfactory reaction yields were realized with the employment of 0.1 mol% of 5a under aerobic conditions or even in the presence of exogenous water (entry 7). The development of water-compatible Suzuki coupling catalysis is of current interest [11]. Lowering the catalyst loading to 0.01 mol% (entries 6 and 28) gives higher turnover numbers of up to 6.2 × 10^3 based on the substrates that were surveyed. This reaction recipe also allows for successful couplings of heterocyclic (entry 16) and 2,6-disubstituted (entries 20–26) substrates. Of particular note is the high yield production of tri-*ortho*-substituted biaryls (entries 25–26). Remarkably, 5a gave the sterically encumbered 2,4,6-triisopropyl-2′-methylbiphenyl [12] in a much higher yield than 3 by 38% under similar conditions [8b], highlighting a significant improvement in the synthesis of sterically hindered biaryls with catalytic amido phosphine complexes of palladium. This apparent discrepancy in activities of 5a and 3 also underscores the significant impacts of a seemingly minor change in catalyst compositions on catalysis scopes.

The ability to achieve this catalysis at elevated temperatures in the presence of water under aerobic conditions is remarkable, considering the conformation of 5a that is composed of an intrinsically highly basic amide and a highly reactive Pd–N bond [13]. No palladium black was observed in all reactions shown in Table 1. To probe its homogeneity, entry 2 was repeated with addition of an equal volume of water to toluene and 1360 equivalents of mercury to 5a. The reaction yield of this controlled experiment was essentially unaffected, thus indicating that this catalysis is indeed homogeneous instead of a result from colloidal or bulk palladium(0) [14]. Given the increased demand on the development of green and sustainable syntheses, water-compatible homogeneous catalysts are attractive and valuable as water is the most environmentally benign, abundant, and safe solvent [11e,15].

To identify the reactivity preferences of carbon-halide bonds in this catalysis, fluorinated (entries 14–15) and iodinated (entry 34) phenyl bromides were examined, from which fluoro and bromo biaryls, respectively, were selectively produced as the cross-coupling products. The reactivity of aryl halides thus follows the order I > Br > F. In contrast to 3 and 4 [8b], 5a is rather inactive toward chloro substrates (entries 36–37), again reflective of the significance of differences in catalyst compositions.

In principle, a more electron-rich and sterically demanding palladium complex would electronically encourage oxidative addition of aryl halides and sterically facilitate reductive elimination of C–C bond forming products. In view of this, 5b that is constitutionally more electron-releasing and more sterically demanding due to P-isopropyl [8f] groups incorporated was subject to catalysis examinations (entries 38–43), but it turned out to be consistently much less reactive. The reaction yields are all significantly lower than those in the corresponding reactions employing catalytic 5a under similar conditions, thus highlighting a profound P-substituent effect of these amido phosphine complexes. Complex 5a that is less sterically demanding and less electron-releasing, on the other hand, should sterically advance oxidative addition and electronically expedite reductive elimination. It has been shown that nickel analogues of 5a have a much higher inclination to reductive elimination than those of 5b [8n]. In addition, an increase in the coordination number of these palladium catalysts after oxidative addition is highly anticipated given the fact that the phosphorus donors in analogous group 10 complexes do not tend to dissociate readily [8c,8h,8k,16]. As a result, the less sterically demanding 5a should also be advantageous in oxidative addition.

To acquire more mechanistic evidences, competitive experiments were performed employing catalytic 5a for couplings of activated, unactivated, and deactivated aryl bromides with phenylboronic acid in either dioxane at 110 °C or toluene at 100 °C, leading to Hammett plots (Fig. 2) with reaction constants ρ of 0.25 and 1.08, respectively. These small ρ values also suggest that the oxidative addition of aryl bromides is not rate-limiting in this catalysis. A similar conclusion was also deduced from Hammett plots of 3- or 4-catalyzed Suzuki couplings (ρ = 0.48 and 0.66, respectively) [8b] and 5a-catalyzed Heck olefination (ρ = 0.60) [8a] or Sonogashira alkynylation (ρ = 0.82) [8f]. In contrast to these small ρ values, larger reaction constants [17] have been consistently reported for oxidative addition of aryl halides to Pd(0), e.g., ρ = 2.3 for aryl chlorides to Pd(XPhos) [17a] and ρ = 2 for aryl iodides to Pd(PPh$_3$)$_2$ [17b]. In view of the facile reductive elimination rates found for nickel analogues of 5a [8n], we propose that reductive elimination of C–C bond forming products is not rate-limiting, either. Thus, transmetallation is more likely to be the slowest in the current study. Similar conclusions were also made in other