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Synthesis and investigation of 1,6-bis-di-*tert*-butylphosphinohexane and its application in Suzuki–Miyaura coupling

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Palladium catalysts have excellent compounds used in generating difficult carbon–carbon bonds. The development of these palladium catalysts has been the attention of much research. The use of alkyl-phosphines has led to many very active, bulky ligands for palladium catalysts. We report a convenient synthesis of 1,6-bis-di-*tert*-butylphosphinohexane (DTBPH) and its evaluation in palladium catalyzed Suzuki–Miyaura coupling. The combination of DTBPH and palladium has led to excellent productivity when used as catalyst for Suzuki coupling.

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Palladium catalysts have emerged as an excellent tool for organic synthesis and their use in Suzuki–Miyaura couplings has become one of the most widely used methods for creating carbon–carbon bonds in the synthesis of biaryls.[1–3] Over the course of many years it has become widely accepted that strong electron-donating, sterically-demanding ligands produce extremely active catalysts (including tri-aryl, tri-alkyl, N-heterocyclic carbenes, and chelating ligands).[4–6] To fully understand the nature of the ligand effect on the catalyst, it is necessary to follow the catalytic cycle mechanism. According to Shaughnessy, sterically bulky ligands promote ligand dissociation from a PdL_2 resting state.[7,8] This dissociation is necessary to generate a highly active PdL complex (Scheme 1).

Because of the importance of dissociation in the catalytic cycle, we were interested in designing a bidentate chelating ligand that might readily interconvert between the catalytically active PdL species and the resting state PdL_2. Previously, Bickelhaupt modeled this type of chelation using ZORA-BLYP/TZ2P calculations to show that a six carbon bridge and *tert*-butyl end groups provide an optimal bite angle when coordinated via a chelate to palladium.[9] Based on this, we wished to explore the use of 1,6-bis-di-*tert*-butylphosphinohexane (DTBPH) (**1**, Scheme 1) as a reversible bidentate ligand for palladium catalysis. This compound had been previously prepared by Shaw and co-workers, who reported that, when coupled with palladium, a dimerization of the palladium/ligand (**2**) is favored over the 9-atom macrocycle (**3**, Scheme 1).[10] We postulated that, regardless of which intermediate complex (**2** or **3**) is generated, this complex may break open to generate the catalytically active PdL species (**4**, Scheme 1).

To synthesize DTBPH, di-*tert*-butyl phosphine (**5**) in dioxane was combined with 1,6-dibromohexane (**6**, Scheme 2) and the reaction mixture was heated to reflux until a white solid precipitated. This solid was filtered and found to be a 3:1 mixture of the target **1** and di-*tert*-butylphosphepanium bromide (**7**). It was found that while **7** is insoluble in chloroform, **1** has excellent solubility in this solvent, allowing for a simple separation by filtration to provide target phosphonium salt **1** in high purity and 41% yield as an air-stable white solid.

Upon successful synthesis and purification, this ligand was tested in Suzuki–Miyaura coupling of 4-bromoanisole (**8**) and phenylboronic acid (**16**) into 4′-methyoxybiphenyl, using the conditions described in Scheme 3.[8,11] It was observed this reaction went on smoothly and in 99% yield under the employed conditions. Upon examining the reaction with electron-rich (**8**, **9**, and **12**, Table 1) and electron-deficient (**10**, **13**, and **15**, Table 1) aryl bromides, excellent conversion to product at room temperature was observed. When evaluating more sterically demanding substrates (**12** and **14**, Table 1), the same excellent conversion was obtained. When both aryl bromide and boronic acid possessed sterically demanding *ortho*-substituents (**14** and **17**, Table 1), a modest amount of coupling was observed at room temperature. When the coupling was examined at elevated temperatures, it was found that the yield improved upon heating to 45 °C, but no further yield increase was noted at 60 °C. It is postulated that the absence of

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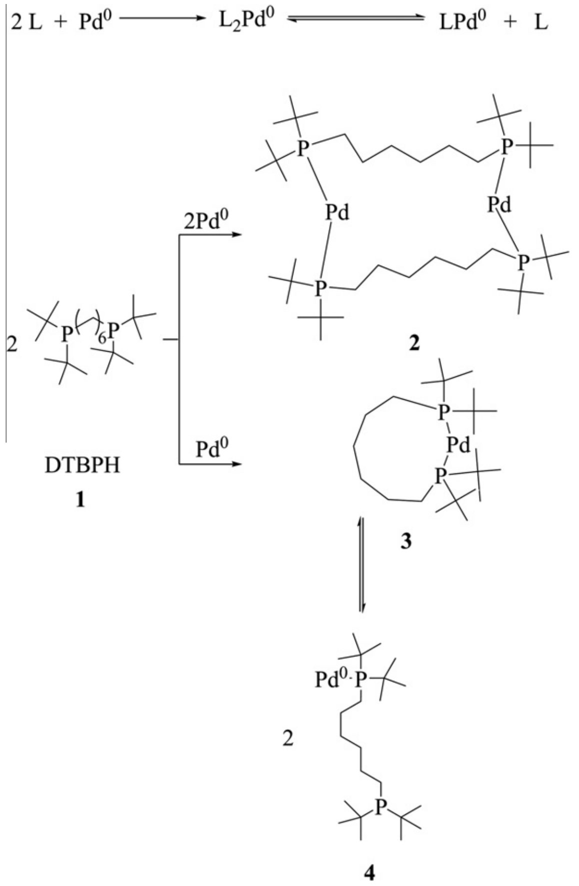
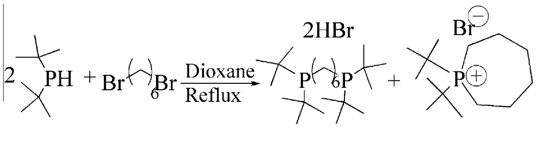


Scheme 1. L_2Pd formation/dissociation to active LPd species.



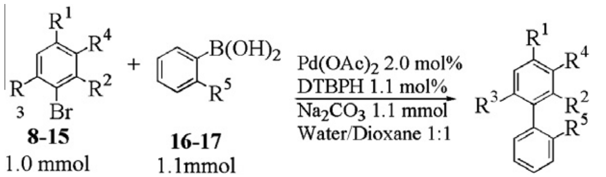
DTBPPH

5 6 1 7

Scheme 2. Synthesis and purification of 1,6-bis-di-*tert*-butylphosphoniumhexyl bromide. All reagents were used as received from the supplier (Acros, Sigma, Matrix Scientific or Strem). For ligand synthesis, dioxane solvent was purchased anhydrous and was placed directly in the glove box upon purchase. All glassware was heated in a 100°C oven prior to use. To synthesize DTBPH, reagents were charged to a 50 mL round bottomed flask with a condenser, nitrogen adaptor, and magnetic stir bar in a nitrogen filled glove box. The order of addition was di-*tert*-butylphosphine (3.75 mL, 18.9 mmol), 1,4 dioxane (20 mL), and 1,6-dibromohexane (0.75 mL, 4.9 mmol). The sealed reaction mixture was removed from the glove box and heated to reflux for 24 h under static nitrogen pressure. The white solid was filtered and washed with dioxane, then placed in 50 mL of chloroform and allowed to reflux for 1 h. The resulting solid was filtered to give an off-white solid (0.78 g, 41%).

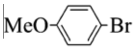
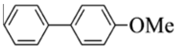
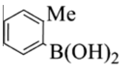
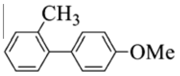
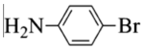
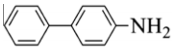
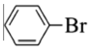
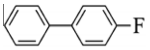
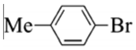
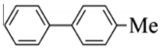
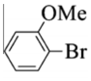
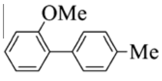
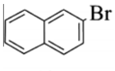
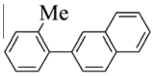
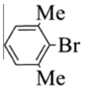
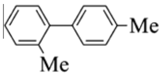
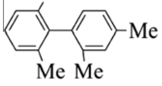
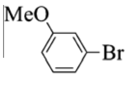
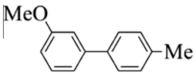
increased productivity at elevated temperature might be from catalyst decomposition.

In conclusion, we report a convenient synthesis and purification method for the chelating ligand DTBPH. The DTBPH ligand, when combined with palladium, demonstrates the ability to effectively convert aryl bromides to their corresponding biphenyl products in Suzuki couplings. While steric hindrance was well tolerated on either the aryl bromide or the arylboronic acid, a decrease in conversion efficiency was observed for cases in which both reagents were sterically hindered. This excellent activity suggests that, as postulated, the L_2Pd readily dissociates to an active LPd species.



Scheme 3. Suzuki coupling conditions and substrates used with palladium catalyst derived from DTBPH. Water and dioxane solvents were sparged with nitrogen for 15 min prior to use. The coupling reactions were staged in a 10 mL microwave vessel with a magnetic stir bar and septa top. Reactions were charged with palladium (0.2 mmol, 4.5 mg), DTBPH (4.6 mg, 0.011 mmol), phenyl boronic acid (130 mg, 1.1 mmol) aryl halide (1 mmol), and sodium carbonate (116 mg, 1.1 mmol) in a nitrogen filled glove box. Liquid aryl halides (1 mmol) were added outside the drybox through a septa. Reactions were allowed to stir for 24 h at room temperature unless otherwise noted. Aqueous extraction was carried out with 30 mL of brine and 3 × 30 mL of ethyl acetate followed by drying over magnesium sulfate and filtration. The extract was concentrated under reduced pressure and purified over silica gel via gradient elution solvent mixture of maximum polarity 85:15 heptane:ethyl acetate. All ^1H and ^{13}C NMR confirm product formation and these spectra matched when compared against the literature.[11]

Table 1
Isolated yields from Suzuki coupling with catalyst derived from Pd_2dba_3 and DTBPH

Aryl bromide	Boronic acid	Product	Yield[a] (%)
 **8**	 **16**		99
8	 **17**		87
 **9**	**16**		92
 **10**	**16**		98
 **11**	**16**		94
 **12**	**16**		95
 **13**	**17**		82
 **14**	**16**		90
14	**17**		51[b]
 **15**	**16**		99

[a] Isolated yield.

[b] Reaction was heated to 45 °C.

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