The Importance of Ligand Steric Effects on Transmetalation

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Summary: A very striking phosphine steric effect on the rate of transmetalation of phenyl zinc bromide to platinum complexes has been observed: most Pt(II) complexes of type [Pt(diphosphine)(Ph)Br] react with PhZnBr rapidly, the slowest reacting complexes being those derived from bis(dicyclohexylphosphino)ethane and bis-(di-tert-butylphosphino)xylene.

In the last twenty years, group 10 metal-catalyzed cross-coupling reactions have emerged as some of the most important reactions used in organic synthesis today.[1] Mechanistic studies have guided catalyst design and provided knowledge on the basic mechanism of these reactions. There are generally thought to be three key steps in cross-coupling: Oxidative addition, transmetalation, and reductive elimination. Mechanistic studies on the oxidative addition step of the reaction have shown that certain types of (generally bulky, electron-donating) phosphines generally favor this step,[2−7] and in the last 10 years the application of electron-donating mono-,[8−11] di-,[2,12] and hemilabile[13,14] bulky phosphines has made the cross-coupling of aryl chlorides, which oxidatively add to Pd(0) complexes reluctantly, a possibility. It has been shown that the reductive elimination step is promoted by ligands that are either electron-poor, bulky, or possessing a wide bite angle.[15−18] There is therefore a subtle balancing act required to match up a ligand/catalyst for a given reaction or substrate. This explains why such a large array of phosphines have been tested in these reactions and why so many of these have found a niche for a specific substrate or reaction. There are still many substrates/reactions in cross-coupling chemistry that remain difficult.

It is often noted that transmetalation is the least understood of the fundamental steps in cross-coupling chemistry, and the reactions of group 10 metal halide complexes with organoboronic acids or organozinc reagents are only recently beginning to receive attention.[19−23] The specific case of transmetalation of tin nucleophiles to Pd(II) and Pt(II) complexes has been the subject of a fascinating debate over the last 15 years,[24−33] and the reaction of organotins with $[Pd(AsPh_3)_2(Ar)X]$ is now beginning to be understood: changing the nature of incoming nucleophile, solvent, temperature, ligand, leaving group, and aryl ligand can alter both the rate and actual reactive species taking place in the transmetalation reaction. The more difficult transmetalation of silicon nucleophiles to platinum and palladium

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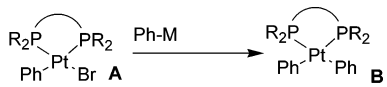
complexes has also begun to attract attention and can be promoted by AgO, fluoride, or hydroxide salts.[34−36]

In the course of our catalytic experiments on the cross-coupling of organosilicon reagents with aryl chlorides (Hiyama coupling),[37] we observed the failure of palladium complexes of the bulky, electron-rich diphosphine 1,2-bis(di-*tert*-butylphosphino)xylene (dtbpx) to catalyze Hiyama cross-coupling. Palladium complexes of dtbpx have all the structural features to ensure rapid oxidative addition and reductive elimination, which suggested a pronounced ligand effect on the (rate-determining) transmetalation step of the catalytic reaction, and highlighted to us the importance of understanding more about phosphine ligand effects on transmetalation to group 10 metal complexes in general.

The existing knowledge in this area mainly stems from a study by Farina and co-workers that demonstrated the beneficial effect of less electron donating ligands such as tris-furylphosphine and triphenylarsine on Stille coupling of aryl iodides under catalytic conditions.[25] However, subsequent work by the Espinet, Amatore, and Jutand groups seems to suggest that this is an indirect electronic effect: although two contrasting mechanisms have been put forward, they both involve loss of a weakly donating triphenylarsine or trifurylphosphine ligand either before[27] or during[31] the transmetalation process. Farinas study did not reveal a predictable steric effect in Stille cross-coupling. The apparent absence of data on direct ligand effects on any transmetalation reaction prompted us to undertake the work described here. In this paper, we report striking ligand steric effects on the rate of transmetalation of organozincs to platinum-diphosphine phenyl bromide complexes. Platinum complexes were chosen because palladium diaryl species rapidly reductively eliminate to give unstable Pd(0) species. The rate of decomposition of both the palladium-diaryl and the Pd(0) species will be highly dependent on the ligand, presenting considerable difficulties for studying ligand effects on the transmetalation step in isolation. We have restricted our preliminary study of this reaction to *cis*-diphosphine complexes of platinum of type [Pt(diphosphine)(Ph)Br]. Diphosphine complexes were chosen to distinguish direct stereoelectronic effects from the formation of complexes with different geometry or coordination number that could occur with monophosphines.

The reactions of [Pt(dppe)(Ph)Br] with $PhSi(OMe)_3$/TBAF, $PhB(OH)_2$/TBAF, or PhZnBr were studied initially. This revealed very sluggish reactions between silicon and boron reagents that only yielded small amounts of [Pt(dppe)Ph_2] under harsh conditions. In the case of $PhB(OH)_2$, the low yield of [Pt(dppe)Ph_2] was accompanied by an unknown side product. In contrast, the reaction of PhZnBr was quantitative at room temperature. Thus, the direct transmetalation of the more polar zinc reagent is actually many, many times more facile than either organoboronic acids or organosilanes, even when they are activated by fluoride.

Scheme 1. Comparison of Nucleophiles in Transmetalation



M= ZnBr; 20 °C, 15 min.: 0% A, 100%B
M= $B(OH)_2$/F-: 20 °C, 15min. 100 % A, 0% B
M= $B(OH)_2$/F-: 75 °C, 15min. 45%A, 33% B,
(22 % unknown)

The rates of the reactions between [Pt(diphosphine)(Ph)Br] and PhZnBr were therefore studied in more detail. A series of six related complexes with different diphosphine ligands were prepared. The diphosphines were chosen according to differences in steric or electronic parameters.

The six complexes were reacted with 13 equiv of PhZnBr at room temperature in CD_2Cl_2/THF solution and analyzed by $^{31}P\{^1H\}$ NMR spectroscopy 18 min later. In the case of the dppe, depe, dfppe, and dppf complexes (derived from sterically undemanding ligands), quantitative reactions had occurred to give [Pt(diphosphine)Ph_2] complexes as the only phosphorus-containing products. [Pt(dcype)(Ph)Br] only reacted to 62% conversion (to [Pt(dcype)Ph_2]) during this time period, and more strikingly, [Pt(dtbpx)(Ph)Br] did not show any product whatsoever, even after several days.

The reactions of the C2 diphosphine complexes were then monitored over time using $^{31}P\{^1H\}$ NMR. Figure 1 shows that the complexes derived from the smaller ligands all react at a faster rate than [Pt(dcype)(Ph)Br].

From this study, we can conclude that steric properties have a pronounced effect on the transmetalation of organozincs to platinum aryl halide complexes. This infers that the specific transmetalations discussed here involve a tight transition state during the Pt−C bond forming process. There does not appear to be a significant bite angle effect, since the complex of large bite angle ligand, dppf, did not suffer from the slow transmetalation observed with the dtbpx ligand. Ligand electronic effects on the reactions studied here represent a direct electronic effect on the halide for aryl substitution and are probably not as important as steric effects, since platinum complexes of electron-donating depe did not suffer from slow transmetalation in the same way as the two *bulky* electron-donating ligands. However, the beneficial effect of the fluorine substitution in the dfppe ligand suggested by Figure 1 does appear to be genuine, since a reaction between [Pt(dfppe)(Ph)Br] and 5 equiv of PhZnBr started at −78 °C gave 80% yield within 30 min, but required 100 min for 80% conversion with the analagous dppe complex.

We also note here the effect of the halide ligand in reactions of [Pt(dppe)(Ph)X] with PhZnBr. PhZnBr and [Pt(dppe)(Ph)Cl] react, under the conditions in Scheme 2, quantitatively to give [Pt(dppe)Ph_2] within 5 min, which is faster than reactions with [Pt(dppe)(Ph)Br]. Scheme 3 shows reaction times for a reaction conducted at low temperature and confirms that the transmetalation to the chloride complex is significantly faster. There are several possible explanations for this reactivity difference: formation of a zincate species between the chloride ligand and zinc reagent, reduced steric

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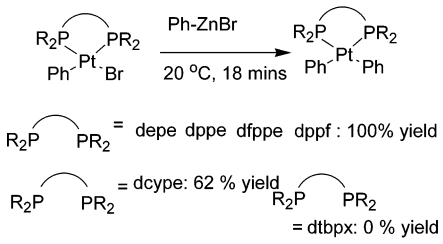
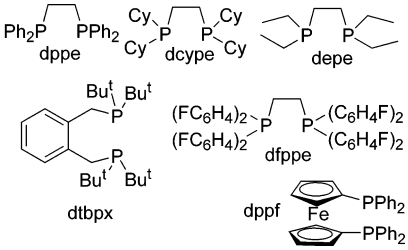
Scheme 2. [Pt(P∧P)(Ph)Br] Complexes Investigated in Reactions with PhZnBr





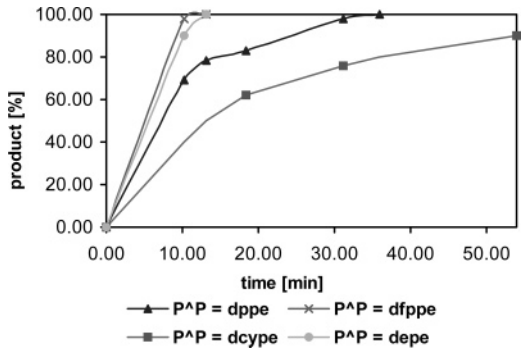
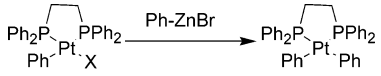


Figure 1. Rates of reaction between PhZnBr and [Pt(diphos)(Ph)Br].

Scheme 3. Halide Effect on Reaction of PhZnBr with [Pt(dppe)(Ph)X]



time reqd: (min.)	Br	Cl
50 % yield	17	8
80 % yield	100	12

demand of the chloride ligand, the greater electronegativity of chloride making the Pt center more electrophilic, or a stronger Pt−Br bond. Studies to fully evaluate the effect of every ligand, L, Ar, and halide, on the transmetalation on a range of different late transition metal complexes are required in the future to facilitate further developments in cross-coupling chemistry.

The results reported here suggest that if the transmetalation of organometallics to metal(phosphine)halide complexes is proving inefficient, less sterically demanding diphosphine ligands could be used advantageously. If one makes the (widely used) assumption that platinum complexes are suitable models for Pd catalysts, then it is likely that very bulky ligands, which promote oxidative addition and reductive elimination, could inhibit transmetalation in cross-coupling catalysis, as has already been observed in the Hiyama cross-coupling reactions catalyzed by palladium complexes of the dtbpx ligands. It is envisaged that the insights from mechanistic studies on transmetalation will guide future catalyst design for cross-coupling reactions that are limited by inefficient transmetalation.

Experimental Section

General Procedures. All experiments were carried out on a vacuum-nitrogen Schlenk line using dried Schlenk glassware. Dry, degassed solvents were used for reactions unless otherwise indicated. Carbon, proton, and phosphorus NMR spectra were recorded on a Bruker Avance 300 (automated) spectrometer. ^{1}H and ^{13}C NMR spectra were referenced internally to deuterated solvents, which were referenced relative to TMS (external). Electrospray ionization mass spectra (ESI) were acquired using the VG Platform I instrument. FAB analyses were run by the EPSRC national mass spectrometry service. [Pt(dppe)(Ph)Br] and [Pt(dcype)(Ph)Br] were prepared according to the literature.[38,39]

Table 1. ^{31}P NMR Data for Complexes Used in This Study[a]

complex	multiplicity	^1J P trans X	^1J P trans Ar	$^2J_{P-P}$
[Pt(dppe)(Ph)Br]	2 × (d + Pt sats)	4150 Hz	1650 Hz	3 Hz
[Pt(dfppe)(Ph)Br]	2 × (d + Pt sats)	4164 Hz	1610 Hz	3 Hz
[Pt(dtbpx)(Ph)Br]	2 × (d + Pt sats)	4498 Hz	1714 Hz	17 Hz
[Pt(dppe)(Ph)$_2$]	1 × (s + Pt sats)	N/A	1704 Hz	N/A
[Pt(dfppe)(Ph)$_2$]	1 × (s + Pt sats)	N/A	1630 Hz	N/A
[Pt(depe)(Ph)Br]	2 × (d + Pt sats)	3974 Hz	1620 Hz	unres
[Pt(depe)(Ph)$_2$]	1 × (s + Pt sats)	N/A	1726 Hz	N/A
[Pt(dcype)(Ph)Br]	2 × (d + Pt sats)	4022 Hz	1708 Hz	unres
[Pt(dcype)(Ph)$_2$]	1 × (s + Pt sats)	N/A	1754 Hz	N/A
[Pt(dppf)(Ph)Br]	2 × (d + Pt sats)	4492 Hz	1666 Hz	16 Hz
[Pt(dppf)(Ph)$_2$]	1 × (s + Pt sats)	N/A	1784 Hz	N/A

[a] N/A = not applicable, unres = unresolved, sats = ^{195}Pt satellites.

General Procedure for Synthesis of [Pt(diphos)(Ph)X]. A solution of the ligand in dichloromethane was added to a dichloromethane solution of [Pt(COD)(Ph)(Br)]. After 1 h stirring at room temperature the solvent was evaporated until 1 mL remained. The clean product was obtained by slowly adding *n*-hexane and filtering.

[Pt(dfppe)(Ph)Br]. Anal. Calcd: C 46.73, H 3.06. Found: C 46.68, H 2.98. ^{31}P{^{1}H} NMR (CD_2Cl_2): δ 38.5 (d of t, $^1J_{(PtP)}$ = 4163 Hz, $^2J_{(PP)}$ = 2.3 Hz, $^3J_{(PF)}$ = 3.8); 39.6 (d, $^1J_{(PtP)}$ = 1609 Hz, $^2J_{(PP)}$ = 2.3 Hz, $^3J_{(PF)}$ = 3.8). ^{1}H NMR ($CDCl_3$): δ 2.2−2.6 (m, 4 H, CH_2), 6.5−7.9 (m, 25 H, ArH). ^{19}F NMR ($CDCl_3$): δ −110 (m). MS-FAB: 844 (M + Na), 818 (M), 745 (M − Br), 665 (M − Ph − Br) (peaks show expected isotope pattern).

[Pt(dppf)(Ph)Br]. ^{31}P{^{1}H} NMR ($CDCl_3$): δ 14.3 (d, $^1J_{PtP}$ = 1666 Hz, $^2J_{PP}$ = 16 Hz), 16.3 (d, $^1J_{PtP}$ = 4492 Hz, $^2J_{PP}$= 16 Hz). ^{1}H NMR ($CDCl_3$): δ 3.7 (q (apparent), J = 2 Hz, 2H), 4.1 (s, apparent, 2H), 4.5 (s, apparent), 2H), 4.8 (m, 2H), 6.5 (m, 2H), 7.0 (m, 2H), 7.1−8.1 (m, 21H). MS (FAB+): 826 (M − Br), 749 (M − Br − Ph). Good isotope matches and no peaks corresponding to dimeric complexes were observed. HRMS (ES+): 826.1049; M − Br requires = 826.1046. This compound required several days stirring at room temperature for the reaction to reach completion.

[Pt(dtbpx)(Ph)Br]. Anal. Calcd: C 48.3, H 6.61. Found: C 48.0, H 6.79. ^{31}P{^{1}H} NMR (CD_2Cl_2): δ 11.4 (d, $^1J_{(PtP)}$ = 1714 Hz, $^2J_{(PP)}$ = 17 Hz), 16.4 (d, $^1J_{(PtP)}$ = 4498 Hz, $^2J_{(PP)}$ = 17 Hz). ^{1}H NMR ($CDCl_3$): δ 1.2 (m, br, 18H, Bu^t), 1.5 (d, J_{H-P} = 13 Hz, 18 H, Bu^t), 3.5 (s (apparent), br, 2H, CH_2), 3.7 (s (app), br, 2H, CH_2), 6.7−7.2 (m, 9H, ArH). MS-ES+ 666.3 (M − Br), 610.2 (M − Br − Ph) + Na), 588.2 (M − Br − Ph). Good isotope matches and no peaks corresponding to dimeric complexes

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were observed. Long reaction times are required for this reaction to go to completion.

[Pt(depe)(Ph)Br]. All the syntheses of this complex gave a second species that shows a complex NMR spectra in solution. The exact structure of this impurity is under investigation. Addition of [Pt(COD)Ph(Br)] or more ligand changed the relative concentrations of the two species, suggesting an equilibrium. The impure compound gives the diphenyl compound with high purity within minutes irrespective of the relative proportions of compounds in the starting Pt(depe)(Ph)Br complex, also consistent with the observations above. The results reported in Figure 1 used material that was ~90% pure and are corrected on this basis. In any case the results clearly show that this ligand does not inhibit transmetalation in the same way as the two bulky electron-donating ligands.

The identity of the diphenylplatinum species was confirmed by comparison with NMR data from authentic samples prepared by stirring the ligand with [Pt(COD)Ph_2] at room temperature. NMR data are reported in Table 1. [Pt(dppe)Ph_2],[40] [Pt(dcype)Ph_2],[41] and [Pt(dppf)Ph_2],[42] have been reported previously.

Transmetalation at Room Temperature. The reaction was carried out with 0.019 mmol of the Pt halide compound, which was dissolved in 0.8 mL of dry DCM in a Schlenck tube. After everything was dissolved the PhZnBr (0.5 M solution in THF) was added (13.5 equiv, 0.500 mL) and a stopwatch started. The reaction was syringed into a NMR tube, and the reaction was monitored in the NMR spectrometer.

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