The effect of steric bulk in Sonogashira coupling reactions†

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Received (in Cambridge, UK) 14th November 2006, Accepted 29th November 2006
First published as an Advance Article on the web 11th December 2006
DOI: 10.1039/b616608c

The rates of Sonogashira coupling reactions using [Pd–PR_3] complexes depend on a combination of the steric bulk of phosphines and substrates; however, below a critical cone angle of *ca.* 170° the catalytic activity drops drastically.

The optimisation of catalysts for a given chemical transformation is an extremely time consuming task.[1] However, uncovering the "best" catalyst for a certain reaction primarily relies on an empirical trial-and-error approach; the increasing use of high throughput techniques underlines this basic problem.[2–6]

The enormous progress in cross-coupling reactions.[7] during the last decade resulted in a few rules of thumb, which aid the design of new phosphine ligands for palladium: (a) sterically demanding and electron-rich phosphines form high activity catalysts,[8,9] (b) an interaction of Pd(0) with a neighbouring π-system seems to be an important factor in Buchwald type phosphines, (c) sp^3-CH units next to the Pd are favourable to avoid cyclopalladation reactions with sp^2-CH units.[10]

While the *a posteriori* rationalisation of a successful catalyst is possible,[11] the rational design of catalysts remains the exception.[12] Furthermore, despite the availability of powerful computational methods the predictive power of such techniques appears to be limited.[13–15]

We wish to demonstrate here the use of high throughput techniques to obtain a better understanding of the factors governing carbon–carbon coupling,[16,17] especially that of the Sonogashira reaction.[18] Our approach makes use of a technique, termed one-pot multisubstrate screening, introduced by Kagan.[19] In this HTS approach a single catalyst acts upon numerous substrates to simultaneously effect a large number of coupling reactions in a single reaction vessel. We have now extended and modified this method in order to allow the collection of a large number of kinetic data in a short time. The advantages of this approach are obvious. All reactions are carried out under truly identical reaction conditions, a requirement urgently needed to understand subtle catalytic effects, which is only met with difficulty in standard procedures. Furthermore, the large number of reactions carried out simultaneously result in enormous time savings, concerning the coupling reactions as well as the quantitative analysis of the reaction products by gas chromatography. A few potential disadvantages of multisubstrate screening need to be taken care of: (a) the reactions under study must produce the desired products with only negligible amounts of by-products; fortunately the Sonogashira reaction is well behaved in this respect, apart from the desired coupling products only minute amounts (≪1%) of the homocoupling product diphenylbutadiyne are formed in the strict absence of oxygen; (b) the relative rates at which the respective coupling products are formed must be the same as in the single substrate screens;[20] (c) the ratio of the initial rates at which the individual coupling products are synthesized should be smaller than a factor of 100 since otherwise the effective catalyst concentration per substrate is not constant, leading to an overestimation of the observed rates.

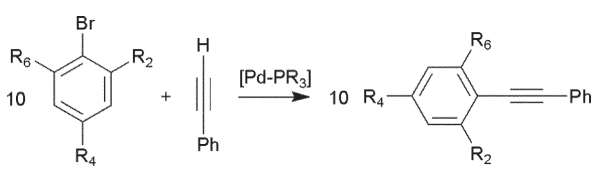
Using parallel multisubstrate screening‡ we wish to demonstrate how systematic variation of steric parameters in both substrate and catalyst influence the rates at which the individual coupling products are formed.

We have simultaneously reacted ten different aryl bromides with phenyl acetylene in a single reaction vessel in the presence of one phosphine (Ad_2PtBu, tBu_3P, tBu_2PCy, $tBuPCy_2$, PCy_3, Ad_2PBn or tBu_2PBn) (Ad = 1-adamantyl), Na_2PdCl_4 and CuI (molar ratio 4 : 4 : 3) in $HNiPr_2$ solvent to result in the formation of ten different tolanes (Scheme 1). In total, applying seven different phosphines the rates of 70 coupling reactions were determined.

All of the initial reaction rates determined at low substrate conversion *via* multisubstrate experiments are listed in Table 1. The data illustrate that the most active palladium catalysts are formed with bulky phosphines such as $AdPtBu_2$, tBu_3P, Ad_2PBn or tBu_2PBn. Within the series tBu_3P, tBu_2PCy, $tBuPCy_2$, PCy_3 the rates of tolane formation decrease by a factor of 26 (T = 80 °C). The Pd–PCy_3 complexes are much less efficient than Pd complexes of the other phosphines, while $tBuPCy_2$ is only 2.4 times slower than tBu_3P for the reaction of bromobenzene.

However, the order of reactivity is not straightforward. In Fig. 1 the relative rates (normalized to H = 1) for the coupling of various 2-substituted aryl bromides are plotted. For the palladium complex of Ad_2PtBu the catalytic activity decreases in the series R = 2-Me, 2-Et, 2-*i*Pr. With tBu_3P and tBu_2PCy the situation is less clear cut and the three different aryl bromides display roughly the same reactivity, while with $tBuPCy_2$ and PCy_3 increasing steric bulk at the aryl bromides translates into an unexpected increase in the reaction rates!

What happens if the bulk of substituents around the C–Br bond is increased further, *i. e.* when instead of a single substituent in the 2-position, both the 2- and the 6-position are occupied by alkyl groups? The palladium complexes of Ad_2PtBu, tBu_3P and



Scheme 1 Parallel Sonogashira reactions.

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† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b616608c

Table 1 Absolute rates (h^{-1})[a] for the Sonogashira coupling of aryl bromides using the respective Pd–phosphine complexes

	Aryl bromide[b]									
Phosphine[c]	H	2-Me	2-Et	2-*i*Pr	2,6-Me_2	2,4-Me_2	2,4,6-Me_3	2,4,6-Et_3	2,4,6-*i*Pr_3	2,6-Me_2,4-*t*Bu
Ad_2PtBu	3560	2060	2000	1890	760	1350	360	183	18	262
tBu_3P	3270	2130	2210	2270	1300	1570	394	307	56	278
tBu_2PCy	2350	1530	1630	1580	860	934	397	311	79	307
$tBuPCy_2$	1390	950	1010	1050	560	495	318	279	202	215
PCy_3	125	83	96	112	50	52	30	32	24	25
Ad_2PBn	3550	2190	2220	2120	1430	1610	731	607	194	564
tBu_2PBn	3290	2120	2200	2220	1210	1550	980	541	95	522

[a] Absolute rates are at low conversion TOF. [b] Headings indicate substituents on the phenyl ring. [c] Na_2PdCl_4 + CuI + $PR_3 \cdot HBF_4$ (molar ratio Pd : Cu : P = 4 : 3 : 4, 0.1 mol% Pd), HN*i*Pr_2 solvent and base, T = 80 °C

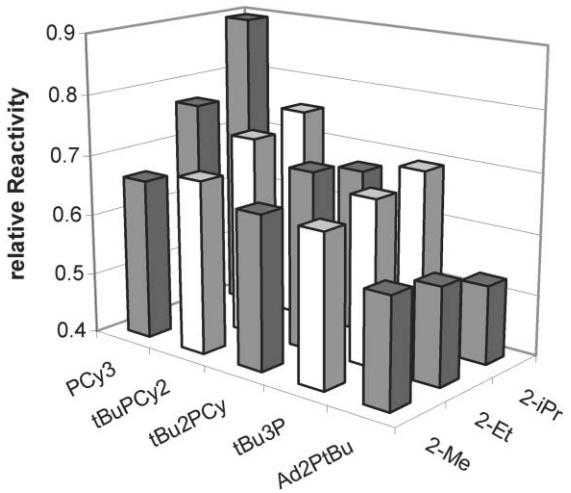

Fig. 1 Relative rates (k_R/k_H) of Sonogashira reactions of 2-substituted aryl bromides using the respective Pd-phosphine complexes.

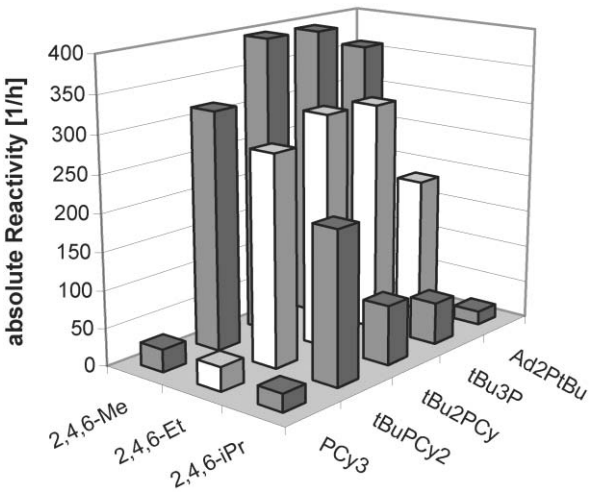

Fig. 3 Absolute rates of Sonogashira reaction of 2,4,6-substituted aryl bromides using the respective Pd-phosphine complexes.

tBu_2PCy experience a drastic decrease in the rates of product formation, which is much less pronounced with *t*$BuPCy_2$ and PCy_3 (Fig. 2).

Up until now we have only discussed relative rates, which are only of limited practical value for catalytic transformations. The absolute rates listed in Fig. 3 reveal that the best catalyst for a given substrate depends crucially on the nature of substrates. For the reactions of phenyl acetylene with the 2,4,6-Me_3 substituted bromobenzene the activity of the palladium complexes of *t*Bu_2PCy, *t*Bu_3P and Ad_2PtBu are roughly similar; with 2,4,6-Et_3 substituents the complexes with *t*Bu_3P, *t*Bu_2PCy and *t*$BuPCy_2$ are the top performers; for 2,4,6-*i*Pr_3 the palladium complex of *t*$BuPCy_2$ is the most active catalyst.

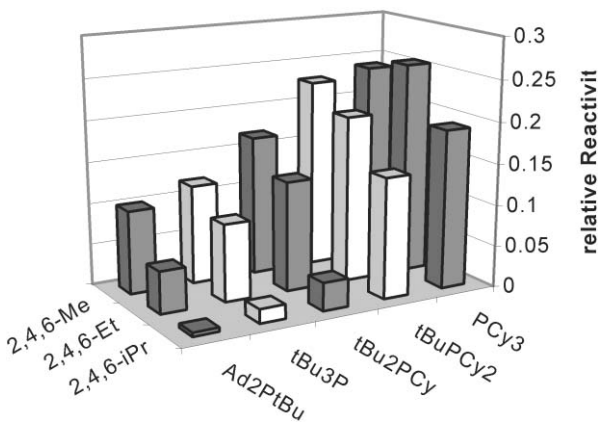

Fig. 2 Relative rates (k_R/k_H) of Sonogashira reactions of 2,4,6-substituted aryl bromides using the respective Pd-phosphine complexes.

What could be the reason for the decrease in the rate of the cross-coupling reaction on increasing the number of alkyl groups next the C–Br bond? The obvious answer seems to be the increase in the steric bulk around the C–Br bond. However, this is not true with phosphines of lower steric bulk (*t*Bu_2PCy, *t*$BuPCy_2$ and PCy_3) the decrease in the rate of the Sonogashira reaction is mainly due to the electron donating (inductive) effect of the methyl group, the steric effect appears to be negligible (Table 2). Only with very bulky phosphines (Ad_2PtBu and *t*Bu_3P) the steric and electronic effects of the methyl group seem to contribute equally to the retardation of the coupling reaction.

Table 2 Relative rates (k_{RB}/k_{HB}) of Sonogashira product formation of various methylated aryl bromides with phenylacetylene using the respective Pd-phosphine complexes

Substituent(s)	Ad_2tBu	tBu_3	tBu_2PCy	$tBuPCy_2$	PCy_3
H	1	1	1	1	1
2-Me	0.58	0.65	0.65	0.69	0.66
2,4-Me_2	0.38	0.48	0.40	0.36	0.42
2,6-Me_2	0.21	0.40	0.37	0.40	0.40
2,4,6-Me_3	0.10	0.12	0.17	0.23	0.24

The reliability and sensitivity of the multisubstrate screening becomes obvious on comparing the rates for the 2,4,6-Me_3 substituted bromobenzene with 2,6-Me_2,4-*t*Bu relative. The slightly stronger electron-donating capacity of *t*Bu *vs.* Me consistently leads to slower product formation rates with all seven phosphines.

The lower activities observed in coupling reactions utilizing very bulky phosphines may help to explain why certain phosphines of intermediate steric bulk, such as tBu_2PMe,[21,22] Ad_2PnBu[23–26] or Ad_2PBn[27–29] are highly effective ligands in numerous cross-coupling reactions for a wide range of substrates. This is also observed here (Table 1) with Ad_2PBn based catalysts.

In conclusion, the rate of a given Sonogashira reaction depends on a combination of the steric bulk of the reactants *and* the steric bulk of the phosphines coordinated to the catalytically active palladium. We have now systematically studied this effect, which had been hinted in previous studies to be of significance for coupling reactions.[30,31] Our experiments have shown that normal substrates are most efficiently coupled with palladium complexes of large phosphines with cone angles of 182° (tBu_3P) to 190° (Ad_2PtBu). However, with very bulky substrates the best results are obtained with palladium–phosphine complexes of slightly smaller steric demand, such as for example in tBu_2PCy (178°) or $tBuPCy_2$ (174°). This simple rule can aid the optimisation of catalysts for various Pd-catalyzed cross-coupling reactions.

Nonetheless, it should be noted that Sonogashira reactions with normal substrates (*i.e.* without high steric demand) show approximately the same conversion rates with a range of Pd-PR_3 complexes (Ad_2PtBu, tBu_3P, tBu_2PCy, $tBuPCy_2$, Ad_2PBn, tBu_2PBn) with cone angles of between 174 and 190°. However, once the cone angle decreases below a critical threshold the activity of the respective Pd-catalysts goes down drastically. Compared to $tBuPCy_2$ (174°) the cone angle of PCy_3 (170°) is only slightly smaller, while the decrease in activity of the Pd-complex is 10-fold.

We believe these effects to be even more pronounced in other cross-coupling reactions since acetylenes utilized in the Sonogashira coupling are reactants of low steric demand, while aryl boronic acids used in the Suzuki coupling are more bulky substrates.

Notes and references

‡ *Experimental*: *Screening of the bulky aryl bromides*. Separate-component catalyst: Palladium composition: Na_2PdCl_4 (26.4 mg, 89.8 μmol) was finely ground with the inert salt $HNiPr_2{\cdot}HBr$ (420.0 mg). Copper composition: CuI (14.8 mg, 77.7 μmol) was finely ground with the inert salt $HNiPr_2{\cdot}HBr$ (504.6 mg). Phosphine composition: The respective phosphonium tetrafluoroborate salt (89.8 μmol) was finely ground with the inert salt $HNiPr_2{\cdot}HBr$.[32] Aryl bromides were weighed with the appropriate amount of the internal GC standard and then filled up with $HNiPr_2$ to reach the required concentration of substrate stock solutions. The solution was then siphoned into a Schlenk tube and carefully degassed by freeze and thaw. The final concentration of the aryl bromide stock solutions was 1 M for the sum of all components and $1/n_{components}$ M for each of the internal GC standards (dibenzofuran and naphthalene).

Sonogashira coupling: The respective catalyst component mixtures (palladium-, copper- and the phosphine-composition), were weighed in a Schlenk tube (each composition: 5.0 mg = 1 μmol of Pd, 0.75 μmol Cu, 1 μmol P). This mixture and the aryl bromide stock solution (500 μL, 0.5 mmol in $HNiPr_2$ (4.5 mL) was carefully degassed (freeze and thaw) and then heated to 80 °C with vigorous stirring for 10 min. Initiation of reaction is done by the addition of phenyl acetylene (150 μL, 1.37 mmol), the precipitation of $HNiPr_2{\cdot}HBr$ indicates the start of the reaction and stirring was continued until full conversion, and monitored by GC. The rates listed in Table 1 represent the average of at least three independent experiments.

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