COMMUNICATION

What makes for a good catalytic cycle? A theoretical study of the SPhos ligand in the Suzuki–Miyaura reaction†

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The Suzuki–Miyaura cross-coupling reaction with the SPhos ligand was studied with DFT and analyzed within the energetic span model. With this information, we designed a modification to the SPhos (the "InPhos"), which theoretically corrects the deficiencies of the prior ligand.

The cross-coupling reaction of Suzuki–Miyaura is a convenient way to generate C–C bonds by coupling an organic halide with an organoboron molecule, in the presence of a palladium catalyst.[1–3] In a recent paper[4] we studied theoretically the inability of a small phosphine (PMe₃) to develop a practical catalytic cycle, while bulkier ligands (PPh₃ and P*t*Bu₃) could correct its deficiencies. In the process we established, using the energetic span model,[5–8] the critical states (intermediates and transition states) that inhibit the reaction. Herein we will consider as ligand for the Suzuki–Miyaura reaction the dialkyl–biaryl phosphine SPhos (2-(2′,6′-dimethoxybiphenyl)–dicyclo-hexylphosphine), which has been found to generate stable and very efficient Pd catalysts.[9–11] Moreover, we will analyze the hypothetical catalytic cycle of a modified SPhos ligand, namely the "InPhos", which we predict will provide a more effective reaction.

According to the energetic span model, only the TOF determining states define the kinetics of the reaction. There-fore, based on the previously calculated systems,[4] we computed only the states that have the potential to be TOF determining (see ESI† for the DFT theoretical method). Fig. 1 shows the most important states and their Gibbs energies for the SPhos system. For such a big ligand the only possible pathway is the monophosphine mechanism.[4]

In this reaction profile the oxidative addition, the trans-metallation and the reductive elimination are not TOF deter-mining transition states (TDTS).[5,7,8] Although being a stable intermediate, the A₁ mono-phosphine Pd⁰ complex actually serves as the TDTS of the reaction (the actual barrier will be slightly higher, as it will refer not to A₁ but to the loose,
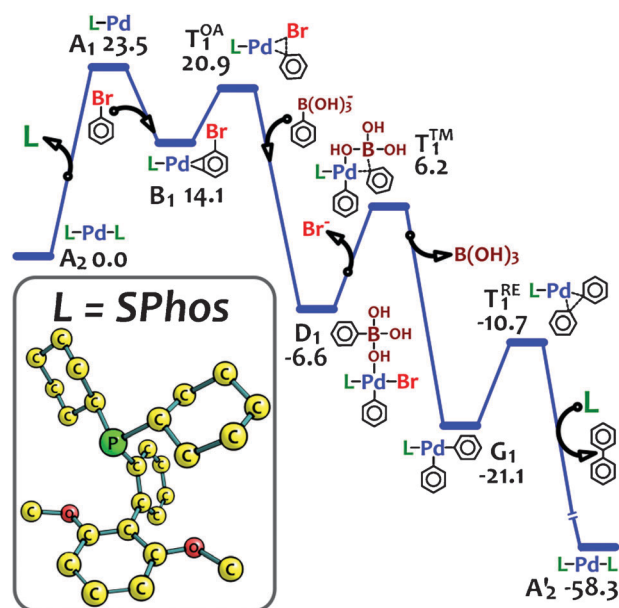

Fig. 1 Most important states in the calculated catalytic cycle for the SPhos system, and their Gibbs energies in kcal mol⁻¹.

entropy-only transition state between A₂ and A₁ + L). The A₁ state has an η² interaction between the metal center and the lower aryl ring, making it a more stable intermediate compared to other phosphines[4] (it can almost be considered a bidentate complex). The TDI (TOF determining intermediate) is the A₂ di-phosphine starting point. As in the P*t*Bu₃ case, the first phosphine dissociation is the critical step for this reaction;[4] however, in the present case we see a smaller energetic span (SPhos: 23.5 kcal mol⁻¹; P*t*Bu₃: 29.0 kcal mol⁻¹). At the same conditions, the SPhos system will have a theoretical TOF of four orders of magnitude faster compared to the P*t*Bu₃ system.

The "Away" and "In" conformations of SPhos[9,10,12,13] (see Fig. 2) play a critical role on the A₁ and A₂ species (the TOF determining states of the reaction); in general, the "In" species are more stable. In the free ligand it is mostly owing to steric reasons, but in the A₁ mono-phosphine complex the "In" situation is stabilized due to the η² interaction of the metal with the phenyl group. We found two almost isoenergetic di-phosphine conformations, the "In–In" and the "In–Away".

An important reason to desire the "In" geometry is the stability of this conformer towards oxidation by O₂.[14] It was proposed

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Pd-SPhos (A₁)

In: 0.0   Away: 7.3

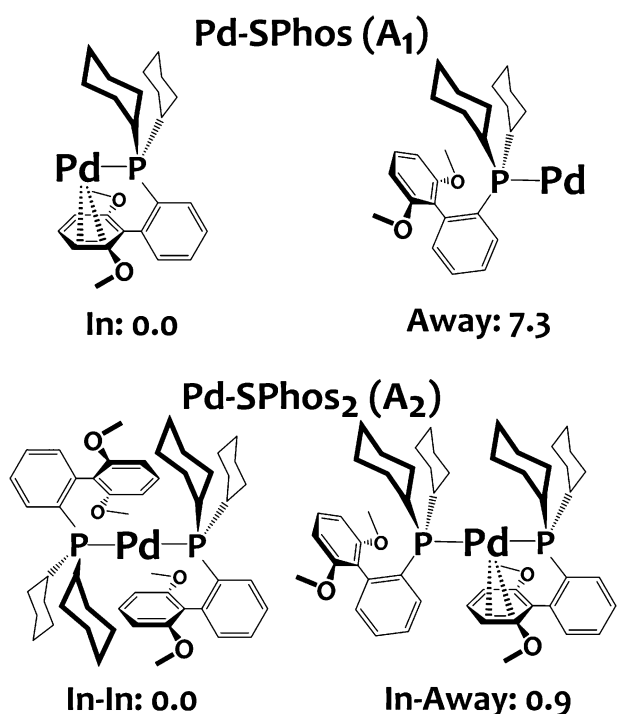## Pd-SPhos₂ (A₂)

In-In: 0.0   In-Away: 0.9

Fig. 2 Calculated "In" and "Away" mono- and di-phosphine species of the SPhos ligand, and their relative Gibbs energies in kcal mol⁻¹.

that changing the cyclohexyl groups for *tert*-butyls increases the rotational barrier, and experimentally resulted in a more stable to air system indeed.[14] To compare with the cyclohexyl SPhos system, we tested the effect of using methyl–cyclohexyl substituents. With this bulkier ligand the rotation to form the "Away" conformer was found to be strongly hampered, consequently we called this ligand "InPhos".

We speculated that the InPhos system will have a very similar energy profile compared to the SPhos. The expected difference was a slightly higher energy of the A_2 TDI, since the methyl addition may obstruct the parallel disposition of the different rings on the ligands. The destabilization of the TDI
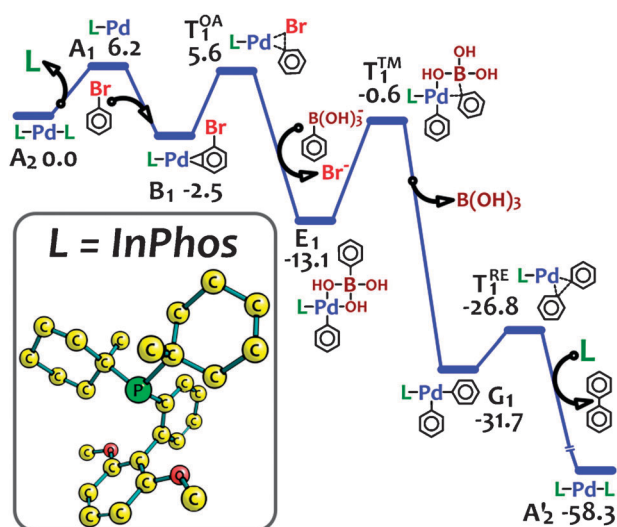

Fig. 3 Relevant states and Gibbs energies (in kcal mol⁻¹) for the InPhos theoretical system.

will accelerate the reaction by lowering the energetic span,[15] even though no transition state is expected to be affected. The resulting pathway appears in Fig. 3.

As expected, owing to the methyl substituent on the cyclohexyl groups the A_2 di-phosphine complex is now disrupted and destabilized. The Pd–P bond distance is elongated compared to all the previously studied systems[4] (Pd–P distances: PMe_3 = 2.29 Å, PPh_3 = 2.28 Å, $PtBu_3$ = 2.30 Å, SPhos = 2.29 Å, InPhos = 2.33 Å), and the van der Waals interaction between the different rings is weakened. However, the geometries, energies and characteristics of the mono-phosphine species are not affected compared to the SPhos ligand, thus providing a much lower activation energy for the phosphine dissociation.

The TOF determining states are not anymore at the ligand dissociation step for the InPhos system. The TDI and TDTS are now the E_1 and T_1^{TM} (see Fig. 3), with a calculated energetic span of only 12.5 kcal mol⁻¹; this is (theoretically) eight orders of magnitude faster than the SPhos system!

As the ligand dissociation is not TOF determining, the concentration of the phosphine should be irrelevant to the TOF. More than that, as the only kinetically influencing species are the ones that are consumed or produced between the TDI -E_1- and the TDTS -T_1^{TM}-, the TOF should not be affected by any reactant or product concentration at all (as long as the species are at "regular" concentrations).[5]

We must be cautious with these results, as other possible low lying intermediates not taken into account (such as anionic species)[16–18] may affect the experimental outcomes. Nonetheless, we can expect that the InPhos ligand will rectify one of the most deleterious problems of these systems, the low-lying poly-phosphine Pd⁰ complexes.[4]

In conclusion, we theoretically studied the mechanisms of a Pd catalyzed Suzuki–Miyaura cross-coupling reaction of bromobenzene and phenylboronate, using as ligands SPhos[9–14] and the hypothetical "InPhos" phosphine. The Gibbs energy profile was analyzed with the energetic span model,[4–7] and the TOF determining states (TDI and TDTS) located for each system. The SPhos system was found to give a fast and efficient catalysis; however, with the InPhos system a small modification (a methyl group) is predicted to generate an even faster reaction, less sensitive to the phosphine concentration. The "know-why" obtained from experimentally known Suzuki–Miyaura reactions provided us with the "know-how" to design a new, improved ligand, the InPhos.

Notes and references

1 J. Hartwig, *Organotransition metal chemistry: from bonding to catalysis*, University Science Books, Sausalito, CA, 2010.
2 X. Wu, P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2010, **49**, 9047–9050.
3 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483.
4 S. Kozuch and J. M. L. Martin, *ACS Catal.*, 2011, **1**, 246–253.
5 S. Kozuch and S. Shaik, *Acc. Chem. Res.*, 2011, **44**, 101–110.
6 S. Kozuch and S. Shaik, *J. Phys. Chem. A*, 2008, **112**, 6032–6041.
7 S. Kozuch and S. Shaik, *J. Am. Chem. Soc.*, 2006, **128**, 3355–3365.
8 A. Uhe, S. Kozuch and S. Shaik, *J. Comput. Chem.*, 2011, **32**, 978–985.
9 R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461–1473.
10 T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685–4696.

11 S. D. Walker, T. E. Barder, J. R. Martinelli and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2004, **43**, 1871–1876.

12 T. E. Barder and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 5096–5101.

13 T. E. Barder, M. R. Biscoe and S. L. Buchwald, *Organometallics*, 2007, **26**, 2183–2192.

14 T. E. Barder and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 12003–12010.

15 J. Wassenaar, E. Jansen, W. van Zeist, F. M. Bickelhaupt, M. A. Siegler, A. L. Spek and J. N. H. Reek, *Nat. Chem.*, 2010, **2**, 417–421.

16 C. Amatore and A. Jutand, *J. Organomet. Chem.*, 1999, **576**, 254–278.

17 S. Kozuch, S. Shaik, A. Jutand and C. Amatore, *Chem.–Eur. J.*, 2004, **10**, 3072–3080.

18 S. Kozuch, C. Amatore, A. Jutand and S. Shaik, *Organometallics*, 2005, **24**, 2319–2330.