Computational Design

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Computational Ligand Design for the Reductive Elimination of $ArCF_3$ from a Small Bite Angle Pd^{II} Complex: Remarkable Effect of a Perfluoroalkyl Phosphine**

*Mads C. Nielsen, Karl. J. Bonney, and Franziska Schoenebeck**

Abstract: *To date only three ligands are known to trigger the challenging reductive elimination of $ArCF_3$ from Pd^{II}. We report the computational design of a bidentate trifluoromethylphosphine ligand that although exhibiting a generally ineffective small bite angle is predicted to give facile reductive elimination. Our experimental verification gave quantitative formation of $ArCF_3$ at 80°C within 2 h. This highlights the distinct effect of P-CF_3 in organometallic reactivity and constitutes a proof-of-principle study of computational reactivity design.*

There are various approaches to chemical innovation and advances. These may vary between serendipitous discoveries, high-throughput screening, or insight-driven developments.[1] The complexity of the problem frequently dictates the approach. In this context, the application of computational tools in addition to experimental investigations has shown promise in delivering the key molecular information necessary to make reactivity predictions.[2,3] Yet, there have been only a few reports of effective computational reactivity designs.[4]

We herein report a proof-of-principle study of a successful computational ligand design for the inherently difficult reductive elimination of $ArCF_3$ from a counterintuitive, small bite angle bidentate Pd^{II} complex. To date, only three ligands are known to give efficient reductive elimination of $ArCF_3$ from a Pd^{II} center—the wide bite angle ligand Xantphos[5] and two of Buchwald's biaryl ligands[6] (RuPhos and BrettPhos). Small bite angle phosphine ligands were previously found to be ineffective.[7] As such, our computational design contrasts the general reactivity trend.

The reductive elimination of $ArCF_3$ from a Pd^{II} center constitutes a key step in Pd^0/Pd^{II}-catalyzed trifluoromethylation of arenes, an area that has recently received considerable interest.[9,10] In this context, elegant experimental studies by

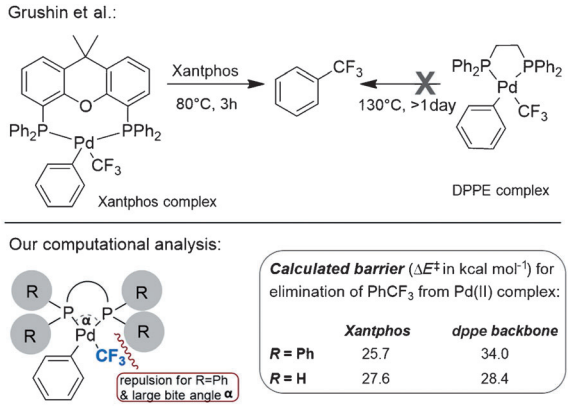

Figure 1. Reductive elimination of $PhCF_3$ from [(Xantphos)Pd^{II}(Ph)(CF_3)] demonstrated by Grushin et al.[5] (top) and our computational analysis of the origins of reactivity (bottom).[8,12]

Grushin et al. had demonstrated[5] that the large bite angle ligand Xantphos gave rise to the relatively facile reductive elimination of $ArCF_3$, while the small bite angle phosphine ligand DPPE[7] was ineffective (Figure 1). In 2011 our research group reported a detailed computational analysis of the origins of this reactivity difference.[8] We had compared the propensity to reductively eliminate $ArCF_3$ from Pd(II) for DPPE and Xantphos, and predicted a constant reactivity difference of $\triangle\triangle E^{\ddagger} =$ ca. 8 kcal mol^{-1} for a variety of different computational methods.[8] A key finding in this analysis was when we replaced the R = Ph substituents in the ligand frameworks by R = H (Figure 1). In these cases, the essentially identical activation barriers for the reductive elimination of $PhCF_3$ were predicted for the two ligands, despite the very different bite angles.[8] This suggested that the reactivity was not directly correlated with the bite angle, but instead with the interaction of the ligand substituents R with the "to-be-eliminated groups" (Figure 1). For Xantphos, R was relatively close to the CF_3 group (ca. 2.7 Å versus ca. 3.3 Å for DPPE), thereby leading to a greater destabilization of the reactant complex relative to the transition state. By contrast, for DPPE the transition state was found to be more strongly destabilized by larger R substituents than the reactant complex.[8]

The computational analysis suggested that a ligand with a small bite angle could only give rise to a relatively low barrier for reductive elimination if R was small, but ideally also repelled the "to-be-eliminated groups" in the reactant complex and hence destabilized the latter. We envisioned that these properties would be combined in the $R = CF_3$ substituent, that is, $(CF_3)_2PC_2H_4P(CF_3)_2$ (dfmpe), as the fluorine

[*] Dr. K. J. Bonney, Prof. Dr. F. Schoenebeck
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52056 Aachen (Germany)
E-mail: franziska.schoenebeck@rwth-aachen.de
Homepage: http://www.schoenebeck.oc.rwth-aachen.de/
Dr. M. C. Nielsen, Prof. Dr. F. Schoenebeck
ETH Zürich, Laboratory for Organic Chemistry
Vladimir-Prelog-Weg 3, 8093 Zürich (Switzerland)

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atoms should electrostatically repel the "to-be-eliminated" CF_3 group and in addition should not be too bulky.

We subsequently explored this computationally. For comparability with our previous study, we initially applied the ONIOM(B3LYP:HF)[12] method, as the predicted barrier for [(Xantphos)Pd^{II}(Ph)(CF_3)] at this level of theory (ΔE^{+} = 25.7 kcal mol^{-1} [8,12]) was in agreement with the activation barrier experimentally determined by Grushin and co-workers ($\Delta H^{+} = 25.9 \pm 2.6$ kcal mol^{-1}).[11]

Pleasingly, we predicted an activation barrier of ΔE^{+} = 24.8 kcal mol^{-1} [12,13] for the reductive elimination of $PhCF_3$ from [(dfmpe)Pd^{II}(Ph)(CF_3)] complex **1** (Figure 2). This suggests that the designed complex **1** should be capable of the efficient elimination of $ArCF_3$. The envisioned electrostatic repulsion between the CF_3 groups of the ligand and the Pd-CF_3 group, therefore, seems viable,[14] and is supported by the electrostatic potential surface of the reactant complex (Figure 2 top right, with highly negative potentials shown in red) and the calculated CF_3-Pd-Ph angle. The repulsion between the Pd-CF_3 and the ligand-CF_3 groups appears to push the "to-be-eliminated groups" together. The CF_3-Pd-Ph angles and bite angles are given in Figure 2. In comparison to the dppe-derived Pd^{II} complex, our designed complex **1** is calculated to have a smaller bite angle (83° versus 84.5°), and yet the CF_3-Pd-Ph angle is also smaller (84.9° versus 86.3°). This contrasts the general trend that larger bite angle ligands push the "to-be-eliminated" groups together more strongly and demonstrates the counterintuitive effect of the CF_3-P substituents.

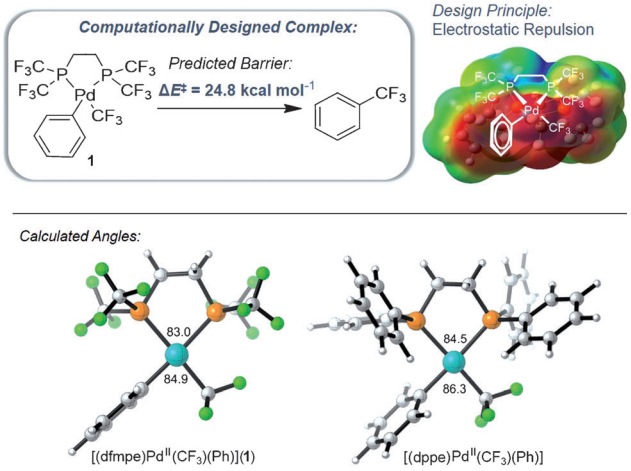

Figure 2. Computationally designed [(dfmpe)Pd^{II}(Ph)(CF_3)] complex **1** (top left); the predicted activation barrier for the elimination of $PhCF_3$ is ΔE^{+} = 24.8 kcal mol^{-1}.[12] Top right: the electrostatic potential surface of **1**. Bottom: calculated characteristic angles in DPPE-derived Pd^{II} complexes versus **1**.[25]

We subsequently set out to prepare complex **1**. There are few examples of organometallic complexes with the desired dfmpe ligand, and none with Pd.[15] More extensive work has been conducted with higher fluorinated bisphosphines, in particular by Roddick and co-workers, involving $(CF_3CF_2)_2PC_2H_4P(CF_2CF_3)_2$.[16] The interest in the latter has been largely concerned with its π-acceptor properties as a CO-binding mimic. There has been little exploration regarding the reactivities of organometallic complexes carrying such perfluoroalkyl bisphosphine ligands.[15b,16] The introduction of CF_3 into alternative ligand scaffolds has received greater interest because of its potential in asymmetric catalysis.[17] A challenge in relation to this field is the frequently cumbersome synthesis of polytrifluoromethylated phosphine ligands.[18] However, a straightforward route was recently reported by Caffyn and co-workers, who demonstrated the in situ formation of dfmpe by functionalization of $(PhO)_2P(CH_2)_2P(OPh)_2$ with KF and $TMSCF_3$.[19] We followed this route to synthesize the desired dfmpe ligand (Figure 3). Purification of the ligand was achieved using preparative gas chromatography. However, treating the purified ligand with [(tmeda)Pd^{II}(CF_3)(Ph)] (tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine or [(pyridine)$_2Pd^{II}$-(CF_3)(Ph)]—both complexes that have previously been employed as precursors in syntheses of [L_nPd^{II}(CF_3)(Ph)] complexes[7a,20]—did not yield the desired complex **1**. We hypothesized that a more weakly binding ligand in the Pd^{II} precursor complex might be necessary and identified the 3-fluoropyridine-derived Pd^{II} complex **2** as an ideal precursor: its X-ray structure is illustrated in Figure 3. The subsequent ligand-exchange reaction with dfmpe was conducted in CH_2Cl_2 at room temperature, followed by precipitation of the desired complex **1** with hexane.

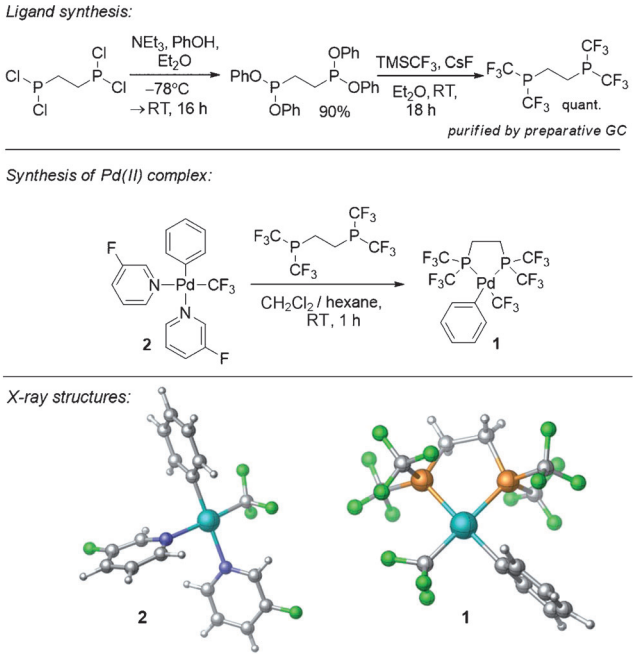

Figure 3. Synthesis of computationally designed [dfmpe)Pd^{II}(Ph)(CF_3)] complex **1** and X-ray structures of **1** and **2**.[21] (**1** crystallized as a twin and could therefore not be resolved with 100% certainty.)

The ^{19}F NMR spectroscopic analysis of complex **1** showed resonances at −54.2 and −54.8 ppm, each appearing as a doublet, which would be expected for the PCF_3 groups in a *cis*-bidentate Pd^{II} complex in which the phosphorus atoms are no longer chemically equivalent. The CF_3 group bound to

the palladium center resonates at −13.3 ppm, and appears as a double doublet, with coupling constants of 57.7 and 23.3 Hz.[22] Attempts to obtain high-resolution crystallographic data were unsuccessful, as complex **1** crystallized as a twin, thus allowing us to only show a lower resolution X-ray structure in Figure 3. However, the various collected spectroscopic data unambiguously confirmed the identity of the Pd^{II} complex **1**.

With complex **1** in hand, its ability to reductively eliminate $PhCF_3$ was subsequently explored. We studied the reductive elimination of Pd^{II} complex **1** in the presence of an additional equivalent of ligand in toluene at four different temperatures (between 60 °C and 90 °C). The conversions were monitored by ^{19}F NMR spectroscopy. To our delight, the designed complex **1** indeed gave rise to clean formation of $PhCF_3$, and quantitative reductive elimination was achieved in 100 min at 80 °C. Thus, the computational reactivity design was successful. Figure 4 illustrates the kinetic profiles. Further

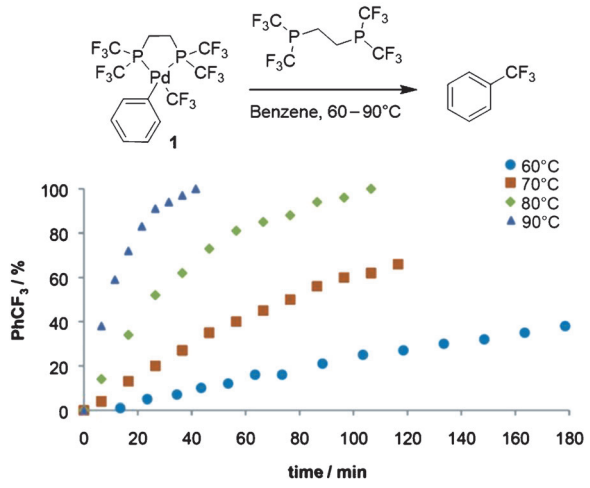

Figure 4. Reductive elimination from [(dfmpe)Pd^{II}(Ph)(CF_3)] complex **1** in toluene in the presence of one equivalent of ligand.

analysis of the kinetic data gave an activation free enthalpy of $\Delta H^{\ddagger} = 27.9 \pm 1.6$ kcal mol^{-1} for the reductive elimination of $PhCF_3$ from complex **1** in toluene. This value is slightly above the computationally predicted barrier at the ONIOM level of theory (see the Supporting Information for alternative computational methods, namely activation barriers at DFT-D3, M06L, M062X and solvation corrected values).

Within error margins, the observed reactivity of complex **1** is similar to that of the Xantphos-derived Pd^{II} complex and exceptionally greater than that of analogous small bite angle phosphine ligands, such as the completely ineffective dppe. This highlights the special properties imposed by the CF_3 substituents. Perfluoroalkyl phosphine ligands have previously been ascribed to have excellent π-acceptor properties,[23] and electron-poor metal centers have been found to favor reductive elimination.[7b,24] To examine whether this is also the predominant factor triggering facile reductive elimination in our designed complex **1**, we calculated the carbonyl stretching frequencies of bis-CO-bound Pd complexes for $R_2PCH_2CH_2PR_2$, with R = Ph (dppe), R = CF_3 (dfmpe), and R = F (dfpe).[13,25] The ν(CO) stretch is widely used as a measure of the electronic properties of phosphine ligands. Our designed ligand dfmpe (R = CF_3) indeed gives rise to a higher frequency ν(CO) stretch (2116 cm^{-1}) than dppe (R = Ph, 2049 cm^{-1}), which indicates that it is a better acceptor. Dfpe (R = F) is the strongest π acceptor in the series (ν(CO) = 2120 cm^{-1}). We hypothesized that if the sole reason for higher reactivity of **1** over other small bite angle derived Pd^{II} complexes was the greater π-acceptor properties of dfmpe (R = CF_3), then there should be an even greater reactivity predicted for the R = F (dfpe) substituted phosphine Pd^{II} complex, since it is the better π-acceptor. However, we predict a 2 kcal mol^{-1} greater energy barrier for the reductive elimination of $PhCF_3$ from [($R_2PCH_2CH_2PR_2$)Pd^{II}-(CF_3)(Ar)] with R = F than for R = CF_3 at the B3LYP level of theory (and 1.4 kcal mol^{-1} at B3LYP-D3).[25] This suggests that the electron-withdrawing properties of dfmpe can only in part be responsible for its success, and that its electrostatic repulsion with the "to-be-eliminated" CF_3 (as described above), together with low steric demand, is a crucial component of its reactivity.[26]

In conclusion, this study presents an example of how computational explorations can allow for the design of ligands that trigger reactions which are not self-evident and may upon first inspection contrast the generally accepted trends. We report the first synthesis of a {Pd^{II}(Ph)(CF_3)} complex with a bidentate trifluoromethylphosphine ligand, and demonstrate its high reactivity towards the reductive elimination of $PhCF_3$. Kinetic studies revealed the activation parameter $\Delta H^{\ddagger} = 27.9 \pm 1.6$ kcal mol^{-1}. The key design principles in the ligand are: 1) the low steric demand of $P(CF_3)_2$ (large substituents destabilize the TS); 2) electrostatic repulsion of $P(CF_3)_2$ with the "to-be-eliminated" groups, which results in reactant destabilization (and hence energy-barrier lowering); and 3) the electron-withdrawing properties of CF_3. This study is a proof-of-principle of a successful computational reactivity design and underlines the distinct properties of the CF_3 group in organometallic reactivity. Our future efforts are directed at exploring these effects in catalysis.[27]

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[21] Selected X-ray data for **2**: crystal data for $C_{17}H_{13}N_2F_5Pd$ (M_r = 446.69): triclinic, space group $P\bar{1}$ (no. 2), $a = 9.4005(9)$, $b = 10.0258(9)$, $c = 10.0977(9)$ Å, $\alpha = 62.265(2)$, $\beta = 74.832(2)$, $\gamma = 82.248(2)°$, $V = 812.90(13)$ Å^3, $Z = 2$, $T = 100$ K, μ(MoKα) = 1.196 mm^{-1}, $\rho_{calcd} = 1.825$ g m^{-1} m^3, 6912 reflections measured ($4.48 \le 2\Theta \le 54.8$), 3543 unique ($R_{int} = 0.0251$) which were used in all calculations, the final R1 was 0.0303 (> 2 sigma(I)) and wR2 was 0.0663 (all data). The Supporting Information contains the supplementary crystallographic data. CCDC 982794 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[26] This is also manifested by the CF_3-Pd^{II}-Ph angles in the Pd^{II} complexes, which are smaller for $R = CF_3$ (84.9°) than for R = F (86.1°), consistent with the fact that greater electrostatic repulsion pushes the "to-be-eliminated" groups together.

[27] Although reductive elimination is one challenging component of Pd^0/Pd^{II}-catalyzed trifluoromethylation of aryl halides, the transmetalation step is also highly challenging, as reactive CF_3 anions frequently displace phosphine ligands and lead to catalyst deactivation. Trace amounts of water introduced in fluoride sources to activate the transmetalation agents also lead to side reactions. See Ref. [5b] for further information.

