Communication

Tri(1-adamantyl)phosphine: Expanding the Boundary of Electron-Releasing Character Available to Organophosphorus Compounds

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Tri(1-adamantyl)phosphine: Expanding the Boundary of Electron-Releasing Character Available to Organophosphorus Compounds

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Supporting Information Placeholder

ABSTRACT:We report here the remarkable properties of PAd_3, a crystalline air-stable solid accessible through a scalable S_N1 reaction. Spectroscopic data reveal that PAd_3, benefiting from the polarizability inherent to large hydrocarbyl groups, exhibits unexpected electron releasing character that exceeds other alkylphosphines and falls within a range dominated by*N*-heterocyclic carbenes. Dramatic effects in catalysis are also enabled by PAd_3duringSuzuki-Miyaura reactions of chloro(hetero)arenes (40 examples) at low Pd loading, including the late-stage functionalization of commercial drugs. Exceptional space-time yieldsare demonstrated for the syntheses of industrial precursors to valsartan and boscalid from chloroarenes with ca. 2×10^4 turnoversin 10 min.

The capacity of ancillary ligands to tune the activity, selectivity, and stability of homogeneousmetal catalystshas played a central role in the development of many modern synthetic methods.[1]Phosphines constituteone of the most utilized among various ligand types due in large part to thesensitivity of the electron density and steric environment about phosphorus towardssubstituent perturbations. The many areas of synthetic chemistrythat utilize organophosphines,including emerging fieldssuch as organocatalysis,[2]bioorthogonal reactions,[3] nanomaterials,[4] polymerization,[5]and frustrated Lewis pairs,[6]could thus benefit from expansion of accessible stereoelectronic properties beyond classical boundaries. Several recent discoveries that highlight this potential include Alcarazo's phosphine cations' ability to greatly accelerate π-acid catalysis,[7]Radosevich's T-shaped phosphines' oxidative additions,[8]and Dielmann's imidazolin-2-ylidenaminophosphines' reversible CO_2 fixation.[9]

Another enabling aspect of organophosphine chemistry has been the development of quantitative descriptors oftheir electronicand steric properties such as Tolman's electronic parameter (TEP) and cone angle, respectively,[10]which aids both inmechanistic understanding and predictionof reactivity. A typical response of the TEP to increased α-carbon branching in the homoleptic series $P\{C[(H)_{3-n}(CH_3)_n]\}_3$ (n = 0-3) can be seen in Figure 1a (open circles).Tolman rationalized such a trend as arising from steric repulsion of larger substituents, whichraises the HOMO energy as phosphorus adopts a more planar geometry (Figure 1b). However,a curious enhancement in donor strengththat is not readily explained by geometric effects is evident for phosphines that possessalkyl substituents at the more distant β-position(e.g. PBu_3 and PCy_3) rather thanβ-methylgroups (e.g. PEt_3 and $P(i\text{-}Pr)_3$).We report here the first synthesis of tri(1-adamantyl)phosphine (PAd_3), which appears to capitalize on this effect more than existing phosphinesto access electron-releasing properties exceeding a boundary for organophosphines that has persisted over many decades.[11]

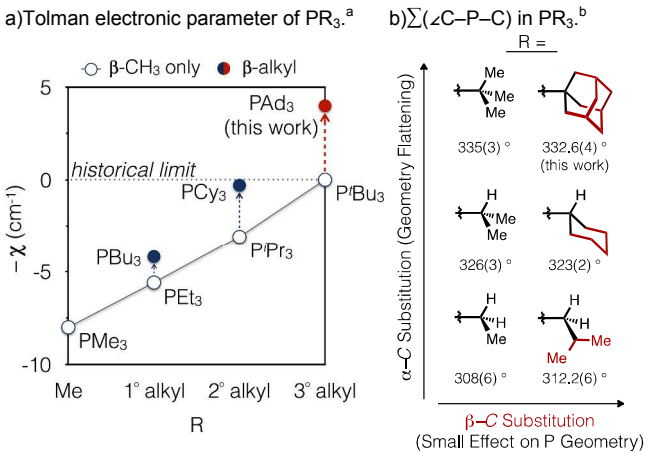
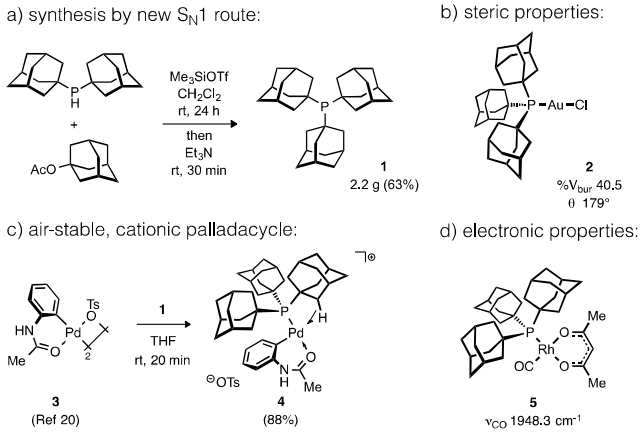


Figure 1. Examples of β–substituenteffects on the (a) TEPand (b) geometry of homoleptic phosphines. [a]$\chi = \nu_{CO}(A_1)$–2056.1 cm^{-1} for $Ni(CO)_3(PR_3)$. [b]From solid-state data for $Au(PR_3)Cl$.[12]

Numerous syntheses of phosphines with two 1-adamantyl (Ad) substituents have been developed, many of which have found wide success in catalysis.[13]Installation of a third hindered Adgroup, however, has remained challenging. In fact, any tri-*tert*-alkylphosphine for which all β-carbon positions are alkyl rather than methyl groupsisto the best of our knowledge unprecedented. We found that reaction of

$ClPAd_2$ and AdMgBr in the presence of a CuI/LiBr catalyst[14] led to complete consumption of the electrophile over 15 h but gave only trace amounts of PAd_3 (**1**). This is consistent with a non-catalyzed S_N2 route attempted by Whitesides.[15]An alternative strategy (Scheme 1a) to forge the final hindered P–C bond in PAd_3 that proved surprisingly facile involved instead an S_N1 reaction withAd cation.[16,17]A mixture of the commercial reagent $HPAd_2$,AdOAc (1.1 equiv), and Me_3SiOTf (1.2 equiv) cleanly generated protonated PAd_3 over 24 h at rt. Neutralization of **1**·HOTf with Et_3Nformed a colorless precipitate, pure PAd_3, that was simplyfilteredunder air in good yield (63 %)on a multi-gram scale. We were surprised to then discover that negligible oxidation of solid PAd_3occurred during storage under air over a period of three months as determined from periodic analysis of aliquots by ^{31}P NMR spectroscopy.[18] This behavior contrasts starkly with many other alkylphosphines that are air-sensitive and in the case of P(*t*-Bu)$_3$, pyrophoric.

Scheme 1. Synthesis and properties of PAd_3 (1).



Comparison ofthe Charton steric parameter (υ) for the Adgroup (1.33) compared to, for instance, a *t*-Bu group (1.24) intuitively suggests that PAd_3 should be more sterically hindered than other trialkylphosphines.[19]We thus synthesized (PAd_3)AuCl (**2**) (Scheme 1b) and the air-stable cationic complex **4**, prepared in one step by coordination of **1** to palladacycle **3**(Scheme 1c),[20]to quantitatively establish the steric properties of PAd_3.Thecone angle (θ) calculated from the solid state structure of **2**(179°) is similar to the reported value for P(*t*-Bu)$_3$ (182°).[10b] Similarly, the buried volume parameter (%V_{bur}) of PAd_3in **2** (40.5) calculated using the SambVca program[21]is close to that for P(*t*-Bu)$_3$(40.0) in an analogous gold complex.[10b,22]Values for PAd_3 in**4**(40.3) versus P(*t*-Bu)$_3$ inPd[P(*t*-Bu)$_3$](Ph)(Br) (39.3)[23] are also similar. We thus conclude $PAd_3$and P(*t*-Bu)$_3$are best described as isosteric, which contrasts common proposals about the differences of Ad- and *t*-Bu-phosphine congeners.[24]

The electronic properties of PAd_3 (Scheme 1d) were next established from the carbonyl stretching frequency of **5** (ν_{CO} 1948.3 cm^{-1}), which occurs at a uniquely low frequency among alkylphosphines. Analogous Rh complexes (**S3**-**S5**) ligated by P(*t*-Bu)$_3$(ν_{CO}1956.4 cm^{-1}),PAd_2(*n*-Bu) (ν_{CO}1956.9 cm^{-1}), or PCy_3 (ν_{CO}1958.7 cm^{-1}) all exhibit distinctly higher frequencies indicative ofreduced electron releasing ability of these compared to PAd_3.[25] The TEP for PAd_3(2052.1 cm^{-1}), indirectly calculated from the relationship between ν_{CO} for Ni(CO)$_3$(L) and Rh(acac)(CO)(L) complexes (Figure S5),[26] is significantly red shifted compared to P(*t*-Bu)$_3$(2056.1cm^{-1}) and other alkylphosphines.[10a,10c] In fact, PAd_3approachesarange typical of*N*-heterocyclic carbenes(e.g. IPr; 2051.5 cm^{-1})[27] that are generally regarded as superiorσ donors to transition metals.[28]Additional theoretical and experimental data that corroborate this spectroscopic datainclude ahigher calculated HOMO energyfor PAd_3(+0.20 eV)relative to P(*t*-Bu)$_3$, a larger pK_α^{THF} of the conjugate acid of PAd_3(11.6)compared to P(*t*-Bu)$_3$(10.7),[29]and a smaller $^1J(^{31}P\text{-}^{77}Se)$coupling constant for$Ad_3PSe$ (669.9 Hz) than for(*t*-Bu)$_3$PSe (688.2 Hz).[30]

Several effectswere considered that might account for the unique electronic properties of PAd_3. The average C_α–$C_\beta$bond length of PAd_3 in **2** (1.551(4) Å) is slightly longer than the average C_β–C_γ and (1.537(4) Å)andC_γ–C_δ (1.530(4)Å) bond lengths, respectively. A hyperconjugative effect would be expected to contract the C_α–$C_\beta$bonds,[31] which is clearly not the case.The sum of the C–P–Cangles about PAd_3(332.6(4)°) determined from solid state data for**2** areslightlylesscomparedto P(*t*-Bu)$_3$inthe analogous gold complex (335(3)°).[12a]The C–P–Cangles in **4**andthe known complex Pd[P(*t*-Bu)$_3$](Ph)(Br) are also similar.[20]These data show that planarization of phosphorus also does not account for the properties of PAd_3. However,London dispersion could explainthe slight contraction of theC–P–Cbond angles in PAd_3,[11]and this possibility led us to further consider van der Waals forces.[11,32]The larger Taft polarizability parameter (σ_α) of Ad(– 0.95) compared to *t*-Bu(– 0.75) indicates the former is better able to facilitate electron donation from phosphorus by stabilizing a more polarizedP−M dative bond.[33]In fact, a general correlation is observed between $\sigma_\alpha$and the TEP of a series of homoleptic alkylphosphines(Eq 1). Thiscorrelation suggests to us that van der Waals forces mightaccount for the trendthatphosphines possessing largeβ-alkyl groupsare more electron-releasing thanthe β-methyl analogues (Figure 1a).[11]

$$\nu_{CO}(A_1) = (20.234 \times \sigma_\alpha) + 2071.5; \quad R^2 = 0.995 \quad (1)$$

Because transition states are generally more polarizable than are ground states,[34] we wanted to assess effects ofPAd_3within a catalytic manifold. We chose as a challenging test case the room temperature Suzuki-Miyaura cross-coupling (SMC) of *p*-chloroanisole (0.50 mmol), 1-napthylboronic acid (0.55 mmol) and KOH (1.1 mmol) in the presence of palladacycle **3** and a phosphine (0.05 mol% Pd; L:Pd = 1:1 in all cases) in THF/toluene (Eq2). The use of$P(t\text{-Bu})_3$, PAd_2(*n*-Bu), or PCy_3, each of whichis used extensively for SMC,[35]led to low yields(<10%) of 1-(*p*-anisyl)naphthalene (**6**)over 8 h

(Figure 2).In contrast, the reaction catalyzed by the combination of **3** and PAd_3 under identical conditions proceeded to 99% yield within 4 h. The yield of **6** at 10 min (99%) using0.25 mol%**3** and 0.5 mol% PAd_3corresponds to a turnover frequency (TOF) of 1.2×10^4 h^{-1} at rteven with this quintessential deactivated substrate for SMC; an analogous reaction using P(*t*-Bu)$_3$was slower andstalled at ca. 33% yield (Figure S3). The reactivity of **3** and PAd_3 compared favorably even head-to-head againststate-of-the-art precatalystssuch as SPhos-Pd G2, XPhos-Pd G3, and PEPPSI-IPr.[36]Note that these data only sample the ensemble of ligand effects on catalyst initiation, innate reactivity, and stabilitythat affect the overall catalyst performance.We do believe the high reactivity of the PAd_3-Pd catalyst in this SMC reflects the donicity and polarizability of PAd_3, but a related PAd_3-Pd complex (**S1**) was also found to beverystable towards cyclometalation (Figure S1). Thus,catalyst stability differences might also contribute to these observations.

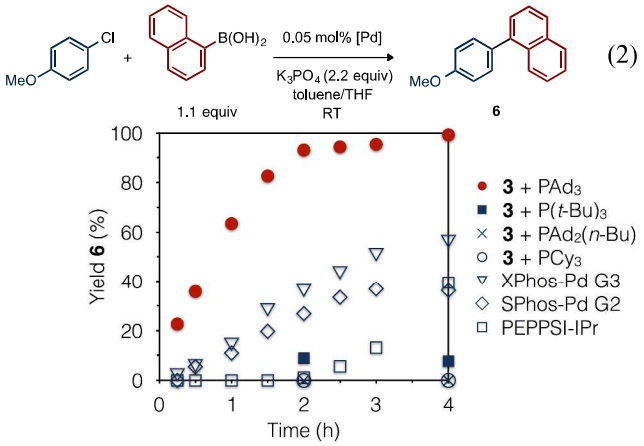


Figure 2. Yield of **6** from reactions in Eq 2.L/Pd = 1 in all cases.

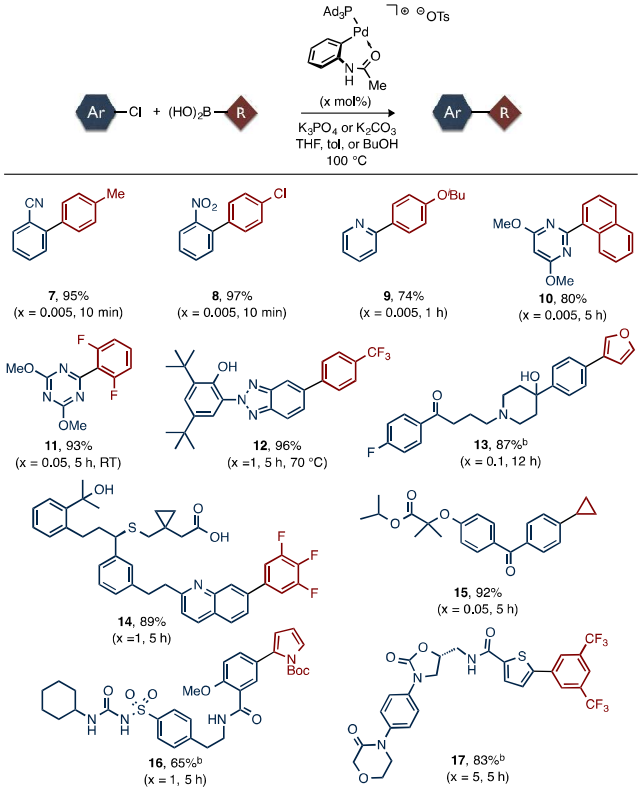
The stark contrast of the catalytic effects of PAd_3 versus, for instance, PAd_2(*n*-Bu)in this SMC is surprising given the structural similarities.We considered that Tolman's proposal of substituent additivity (Eq 3)[10a]could be used toevaluateif in fact the number of Ad groups exerts a proportional effect on the phosphine properties. We thus determinedχ_{Ad} (Eq 4) in PAd_3 (− 1.3 cm^{-1}), PAd_2(*n*-Bu)(− 0.20 cm^{-1}), and PAd_2Bn(−1.0cm^{-1}) using known$\chi_R$and TEP values.[10a] The variance in χ_{Ad} indicates that, contrary to Tolman's proposal,[10c]the influence of the Ad group is actually dependent on the exact phosphine structureand also that phosphorus apparently gains more electron density per Ad group in the case of PAd_3.

$$\nu_{CO}(A_1) - 2056.1\ cm^{-1} = \chi = \sum_{i=1}^{3} \chi_i \quad (3)$$

$$\text{For } P(Ad)_2R: \chi_{Ad} = \frac{(\chi - \chi_R)}{2} \quad (4)$$

Lastly, we broadenedour investigation of the SMCto establish if PAd_3-Pd catalysts might be broadly applicable at low Pd loading (≤0.1 mol%),[37] which is desirable for industrial applications yet remains challenging using chloroarenes.[38]A limited selection of solvents (THF, toluene, or *n*-BuOH) and bases (K_3PO_4 or K_2CO_3) using **4**as catalyst was sufficient to achieve high yields across 40 diverse combinations of chloro(hetero)arene and organoboronic acid. Representative examples are shown in Scheme 2 with the remainder listed in the Supporting Information (Figure S4). Complex **4** retained high activity in the presence of *N*-heteroaryl substrates including pyridine, pyrrole, pyrazine,pyrimidine, isoxazole, triazine, and thiadiazole fragments giving high yields within 1-12 h using 0.05-0.1 mol% Pd. Products from reactions with organoboron compounds that are notoriously sensitive to protodeboronation such as 2-pyrrolyl, 2-furyl,2-thienyl, and 2,6-difluorophenyl boronic acids alsoformed in high yields even at low catalyst loadings.[39]Reactions that formed industrial precursors (**7**, **8**)to valsartan and boscalid proceeded to high yield (95-97 %) within 10 minat 100 ºC using 0.005 mol% Pd.[37b]These turnover numbers (TON) of ca. 2×10^4 and exceptionalTOFsexceeding$1 \times 10^5 h^{-1}$ highlight that high space-time yield are accessible using less reactive chloroarenes and low Pd loading. High TON within1-5 h are also observed for reactions of *N*-heterocycles (**9**-**11**). Lastly, functionalization by SMC of the C–Cl bond in haloperidol, fenofibrate, montelukast, glibenclamide, and 5-*R*-rivaroxaban with methyl, cyclopropyl, heteroaromatic, or fluoroaromatic fragments occurred in uniformly good yields (65-92%). We were very encouraged by the observations that PAd_3, a simple compound readily prepared from inexpensive reagents, engenders catalytic properties rivaling some of the most important methods developed for SMC reactions.

Scheme 2. Illustrative examples of 4 as a general catalyst for Suzuki-Miyaura coupling of chloro(hetero)arenes.[a]



[a]See Supporting Information for 28 additional examples and full experimental details. [b]Yield determined by NMR.

In conclusion, a facile and scalable synthesis of PAd_3 has been developed. Spectroscopic data reveal $PAd_3$is significantly more donating than P(*t*-Bu)$_3$, thus redefining the limit of electron-releasing characteraccessible to alkylphosphines that has persisted for half a century.Preliminary investigations to establish how the electronic properties and chemical stabilityof PAd_3might be leveraged revealedthat a PAd_3-palladacyclecatalyzes Suzuki-Miyaura coupling of chloro(hetero)arenes with exceptionalTOF and high TON. A strong correlation between the Tolman electronic and Taft $\sigma_\alpha$parametersargues the special properties of PAd_3originate from the substantialpolarizabilityinherent to large hydrocarbyl groups like adamantyl. These results support the hypothesis that access to phosphine steric or electronic properties beyond historical limits can enableunique reactivity in catalysis and also contribute to a growing number of examples for whichweak van der Waals forces can in fact contribute significantly to both structure and reactivity.[11]

ASSOCIATED CONTENT

Details of experimental conditions and characterization, crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest: a patent application was filed by Princeton University.

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