# Expanding Ligand Space: Preparation, Characterization and Synthetic Applications of Air-Stable, Odorless Di-*tert*-alkylphosphine Surrogates

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**ABSTRACT:** The di-*tert*-alkylphosphino motif is common to many best-in-class ligands for late transition metal catalysis. However, the structural diversity of these privileged substructures is currently limited by the need to manipulate highly toxic, highly reactive reagents and intermediates in their synthesis. In response to this longstanding challenge, we report an umpolung strategy for the synthesis of structurally diverse di-*tert*-alkylphosphine building blocks *via* $S_N1$ alkylation of *in situ* generated $PH_3$ gas. We show that the products – which are isolated as air-stable, odorless phosphonium salts – can be used directly in the preparation of key synthetic intermediates and ligand classes. The di-*tert*-alkylphosphino building blocks that are accessible using our methodology therefore enable facile expansion of extant ligand classes by modification of a previously invariant vector; we demonstrate that these modifications impact the steric and electronic properties of the ligands, and can be used to tune their performance in catalysis.

**Keywords:** phosphorus, phosphines, ligand synthesis, catalysis, cross-coupling.

## Introduction

Advances in homogeneous transition metal catalysis have been underpinned by the rational design of sophisticated, application-specific phosphine ligands. Sterically demanding, electron-rich phosphines bearing *tert*-alkyl substituents have emerged as especially privileged in polymerization,[1] strong-bond activation[2] and cross-coupling[3] chemistries. While tri-*tert*-alkylphosphines have huge historical[4] and contemporary[5] significance, structural modification of this ligand class is extremely challenging.[6] In contrast, phosphines featuring two *tert*-alkyl substituents share many of the desirable attributes of their homoleptic counterparts, but can be conveniently tuned to meet reaction-specific demands through variation of the third, unique substituent.[7] As a consequence of this versatility, the di-*tert*-alkylphosphino (DTAP) motif forms the basis of many current best-in-class ligands (Scheme 1A).[7,8,9]

Despite the importance of DTAP motifs, the diversity in their *tert*-alkyl substituents is extremely limited. Indeed, all commercial phosphines featuring this substructure are based on either *tert*-butyl or 1-adamantyl (Ad) substituents,[10] with just a handful of other examples documented in the patent and primary literature.[11] Further exploration of this privileged region of ligand space is currently hampered by the practical challenges associated with the synthesis of new DTAP building blocks. As a case in point, the conventional "P+/C–" approach to di-*tert*-alkylphosphines (Scheme 1B)[12] involves manipulation of highly hazardous, air-sensitive reagents and intermediates over multiple steps, is redox-inefficient and is ultimately limited in scope by the diversity of the *tert*-alkylmetal reagents that are available.

## Scheme 1. Occurrence, Conventional Synthesis and Proposed Synthesis of *tert*-Alkylphosphines
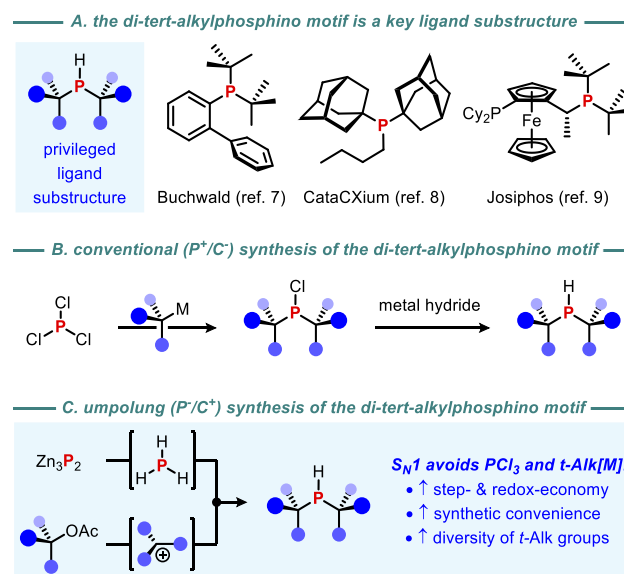


We anticipated that an umpolung strategy ("P–/C+", Scheme 1C) would provide unrivalled access to structurally diverse DTAP building blocks, and would eliminate the need for wasteful redox adjustments at phosphorus. $S_N1$ alkylation would enable facile installation of sterically demanding substituents and would open up a much wider pool of alkylating agents than is available to the conventional P+/C– approach. In situ generation of both the *P*-nucleophile and the *C*-electrophile would ultimately minimize the need to handle reactive reagents and intermediates.

Herein we report realization of this umpolung approach to secondary phosphine synthesis. By exploiting an $S_N1$ manifold, we demonstrate that di-*tert*-alkylphosphines can be prepared selectively from readily available, bench stable precursors. The products are obtained as air-stable, odorless phosphonium salts which can be isolated conveniently by filtration. The DTAP building blocks that are accessible in this way enable facile expansion of extant ligand classes by modification of a previously invariant vector; we show that these modifications impact the steric and electronic properties of the new ligands, and can be used to tune their performance in catalysis.

## Results and Discussion

Our proposed $S_N1$ strategy (Scheme 1C) requires a synthon of the type "HP$^{2-}$". While phosphine gas (PH$_3$) is an atom-economic and readily available synthetic equivalent to this synthon, we were cognizant of the risks and practical challenges associated with handling high-pressure, cylinderized PH$_3$.[13] We therefore sought to generate the gas on demand and in precise stoichiometries by protonolysis of a metal phosphide. Specifically, we identified zinc phosphide (Zn$_3$P$_2$) as a convenient source of PH$_3$ because, unlike other metal phosphides, it is both bench stable and cheap (£48 /kg).[14] While Zn$_3$P$_2$ can be stored and handled under an ambient atmosphere, it is readily protonolyzed to PH$_3$ under acidic conditions. We anticipated that this reactivity could be exploited in the two chamber 'CO-ware' reactor system developed by Skrydstrup,[15] with PH$_3$ generated in the first chamber from Zn$_3$P$_2$ and consumed in the second chamber by $S_N1$ alkylation (Scheme 2A).

To explore the viability of this strategy, we first confirmed that generation of PH$_3$ from Zn$_3$P$_2$ is indeed facile. As determined by volumetric gas titration (Scheme 2B), complete hydrolysis of Zn$_3$P$_2$ occurs within 10 minutes of adding excess aqueous HCl. Under these conditions, gas evolution exhibits *pseudo* first order kinetics with an effective half-life of 110 s (Scheme 2B, inset), providing sufficient time for addition of the acid before full gas pressure is achieved.

Subsequently, we sought to identify conditions for $S_N1$ alkylation of the *ex situ* generated PH$_3$ gas (Scheme 2C). Prior attempts to alkylate PH$_3$ or its synthetic equivalents[16] have exploited $S_N2$[17] or hydrophosphination[18] reactivity manifolds,

neither of which allow installation of *tert*-alkyl substituents.[19] A single example of $S_N1$-type alkylation was recently reported by Carrow, although a secondary phosphine nucleophile – rather than PH$_3$ – was employed in order to generate the homoleptic tertiary phosphine, PAd$_3$.[20] As illustrated in entries 1-4, we found that combination of *tert*-amyl alcohol or *tert*-amyl methyl ether with either HOTf or TMSOTf failed to afford appreciable amounts of alkylphosphine products. While the combination of *tert*-amyl acetate and HOTf proved similarly unsuccessful (entry 5), use of *tert*-amyl acetate and TMSOTf resulted in high-yielding alkylation of PH$_3$ (entry 6).[21] Notably, >95% of the phosphonium salt formed in this way was recovered conveniently *via* precipitation and filtration under air. The isolated material proved to be a free-flowing, non-hygroscopic and odorless solid that is soluble in organic media,[22] and that can be stored on the bench for at least a year without noticeable degradation. Although the yield of **1a** suffered slightly when a lower stoichiometry of *tert*-amyl acetate was employed (entry 7), these more economic conditions proved generally applicable in subsequent studies (*vide infra*).

The conditions outlined in entries 6 and 7 of Scheme 2C confer excellent selectivity for dialkylation, with neither mono- nor trialkylation products observed by $^{31}$P NMR spectroscopy. This remarkable selectivity can be explained by considering the different basicities of primary, secondary and tertiary phosphines.[23] The first-formed primary phosphine is, presumably, insufficiently basic to be fully protonated by the HOTf co-product. A second alkylation may therefore occur, affording a more-basic secondary phosphine which is fully protonated under the reaction conditions. This innate alkylation-dependent change in protonation state constitutes an effective self-regulation mechanism that prevents over-alkylation, and ensures that the product is obtained as a stable, crystalline phosphonium salt rather than an air-sensitive phosphine.[24]

The optimized reaction conditions were applied successfully to a range of diverse *tert*-alkyl esters (Scheme 3),[25] thereby providing convenient access to structurally unique di-*tert*-alkyl phosphonium salts. All products were isolated as air-stable, odorless solids on preparatively useful scales of up to 2.0 g.

**Scheme 2. Validation and Optimization of $S_N1$ Alkylation of PH$_3$ Gas Generated Within a Two-Chamber Reactor System**[a,b]
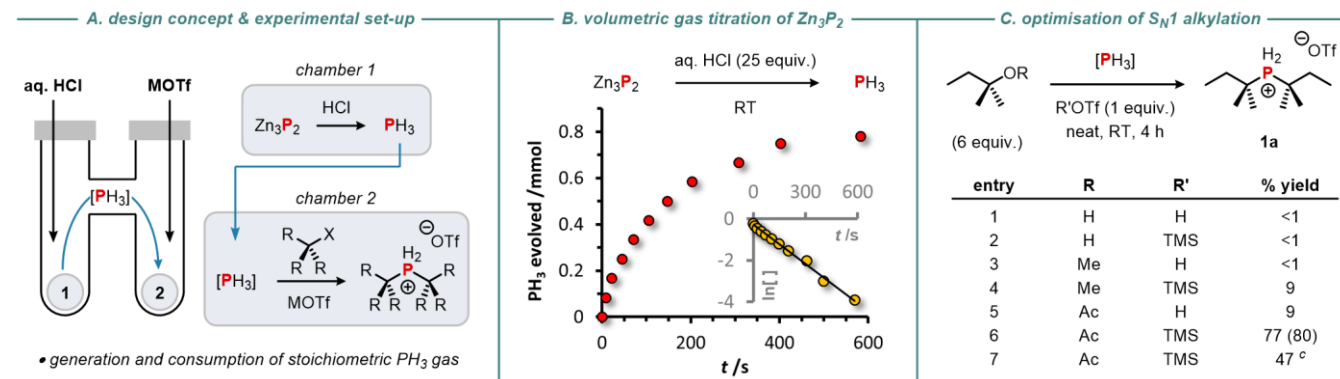


[a] Gas titration data are an average of 2 independent measurements and exhibit *pseudo* first order kinetics (Scheme 2B, inset). [b] $S_N1$ alkylation conditions: aq. HCl (5.0 M, 10 equiv.) added to Zn$_3$P$_2$ (0.5 equiv.) at RT in chamber 1 to generate 1 equiv. PH$_3$; R′OTf (1 equiv.) added to *tert*-amyl-OR (6 equiv.) at RT in chamber 2. Yields are of isolated, pure material; yields in parentheses determined by $^{31}$P NMR spectroscopic analysis *vs* internal standard. [c] Using 3 equiv. *tert*-amyl acetate.

**Scheme 3. Synthesis of Di-*tert*-alkylphosphonium Salts via S$_N$1 Alkylation of PH$_3$ Gas[a]**
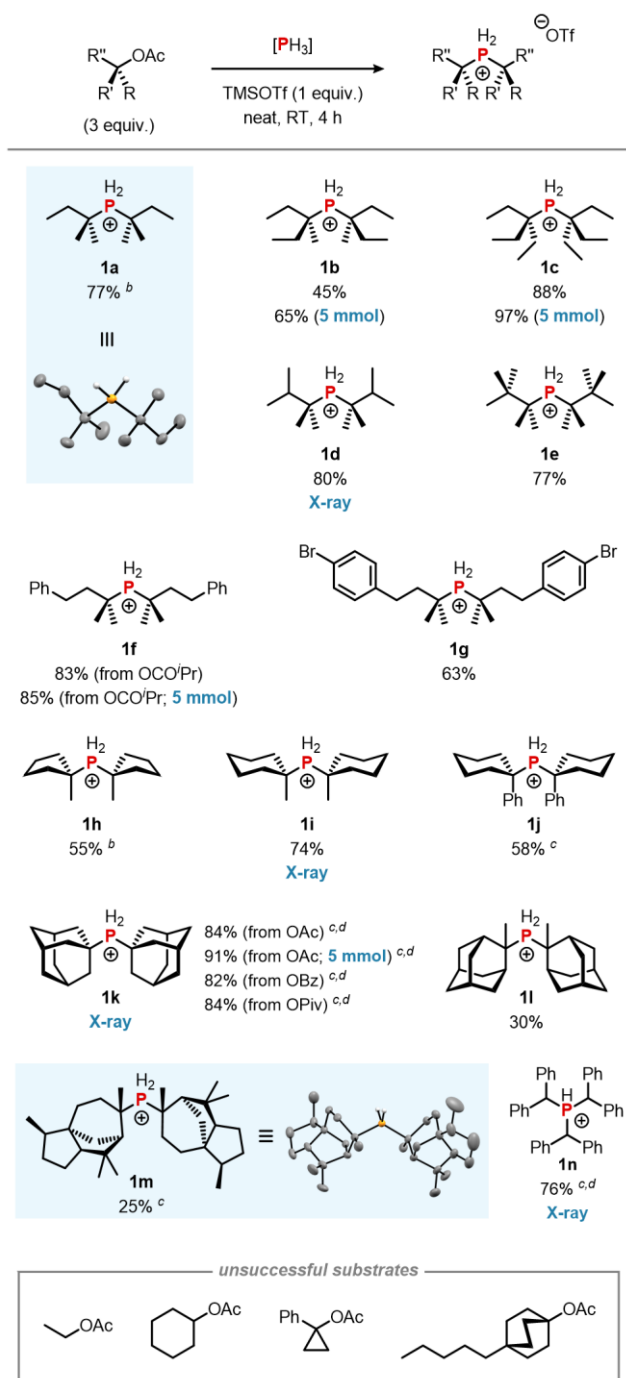
[a] Conditions: aq. HCl (5.0 M, 10 equiv.) added to Zn$_3$P$_2$ (0.5 equiv.) at RT in chamber 1 to generate 1 equiv. PH$_3$; TMSOTf (1 equiv.) added to ester (3 equiv.; acetate ester unless stated otherwise) at RT in chamber 2. Reactions were performed at a 1 mmol scale, unless indicated otherwise; yields are of isolated, pure material. [b] Using 6 equiv. *tert*-alkyl acetate. [c] Chamber 2 heated at 40 °C. [d] CH$_2$Cl$_2$ (2 mL) added to chamber 2. Thermal ellipsoids shown at 50% probability; triflate counterion and hydrogen atoms bonded to carbon omitted for clarity.
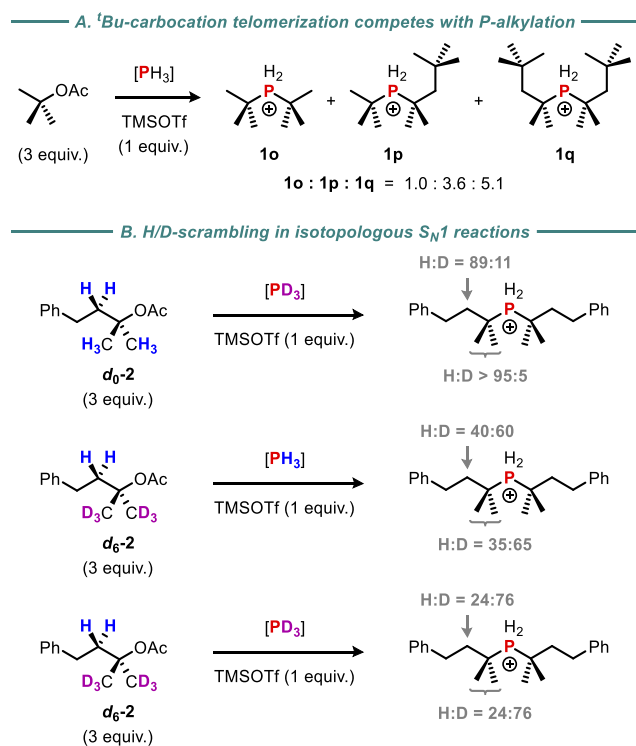
Using this methodology, two homologous series featuring increasing methylation at all C$_\beta$-positions (**1a-1c**: CMe$_2$Et, CMeEt$_2$ and CEt$_3$), or at a single C$_\beta$-position (**1a**, **1d** and **1e**: CMe$_2$Et, CMe$_2^i$Pr, CMe$_2^t$Bu), of each *tert*-alkyl substituent were prepared. We envisage that such facile access to series of these types will enable systematic variation of ligand properties during catalyst development campaigns. Our P$^-$/C$^+$ approach also allows installation of substituents featuring steric bulk distal to the phosphorus center (**1f**, **1g**), and is compatible with alkylating agents derived from both cyclic (**1h-1j**) and polycyclic (**1k-1m**) alkanols. Notably, aryl bromides (**1g**) are tolerated by our methodology, which illustrates its complementarity to conventional organometallic strategies. The ability to incorporate this functionality provides a useful synthetic handle that could ultimately be exploited for further elaboration of the ligands.

As demonstrated for phosphonium salt **1k**, esters other than acetates can be used with no detriment to reaction efficiency. Combined with the ready availability of tertiary alcohols and their esters, this synthetic flexibility increases the pool of viable alkylating agents that can be employed in our methodology. For example, salt **1f** is prepared from papaya isobutyrate, a commercial fragrance ingredient, whereas salt **1m** is derived from cedrol, which is produced on a kiloton scale each year as the main component of cedar wood oil.[26] Notably, salt **1m** is the first example of a *C*-stereogenic di-*tert*-alkylphosine, and is produced here as a single stereoisomer from a cheap, chiral-pool alcohol.

Within the context of our proposed S$_N$1 pathway, it is essential that a carbocationic electrophile is accessible, and that it is sufficiently long-lived for bimolecular nucleophilic trapping to compete with unimolecular elimination. Thus – in addition to *tert*-alkyl esters – benzhydryl acetate reacts cleanly to give phosphonium salt **1n**,[27] whereas primary, secondary and conformationally-constrained tertiary alkyl esters are unreactive (Scheme 3, bottom).[28] In contrast, while *tert*-butyl acetate ionizes efficiently, a well-documented and industrially important E1/S$_N$1 telomerization process[29] competes with trapping of the resulting carbocation by PH$_3$, affording an inseparable mixture of the desired di-*tert*-butylphosphonium salt **1o** and homologs **1p** and **1q** (Scheme 4A).

## Scheme 4. Evidence for an S$_N$1 Mechanism[a]

— *A. $^t$Bu-carbocation telomerization competes with P-alkylation* —



1o : 1p : 1q = 1.0 : 3.6 : 5.1

— *B. H/D-scrambling in isotopologous S$_N$1 reactions* —



[a] Conditions: HCl in H$_2$O *or* DCl in D$_2$O (5.0 M, 10 equiv.) added to Zn$_3$P$_2$ (0.5 equiv.) at RT in chamber 1 to generate 1 equiv. PH$_3$ *or* PD$_3$; TMSOTf (1 equiv.) added to ester (3 equiv.) at RT in chamber 2. Product distributions determined by NMR spectroscopic and mass spectrometric analysis of crude mixtures.

Deuterium labelling studies (Scheme 4B) provided further evidence that the reaction progresses via a carbocationic intermediate. Reaction of the isotopologous acetates *d$_0$*-2 and *d$_6$*-2 with either PH$_3$ or PD$_3$ resulted in isotopic exchange at the C$_\beta$-positions, indicating that reversible elimination of the carbocation to an alkene precedes nucleophilic trapping. Moreover, the comparable extent of environment-weighted exchange (*ca* 5%)[30] at the β-methyl and β-methylene substituents suggests that E1 elimination is equally statistically likely to give the exomethylene or the internal alkene. In contrast, the absence of deuterium incorporation at the γ-methylene position implies that migration of the internal alkene into conjugation with the phenyl ring is negligible.

Having identified general conditions for the preparation of structurally diverse di-*tert*-alkyl phosphonium salts, we sought to demonstrate their utility in ligand synthesis (Scheme 5). As illustrated for **1c**, treatment of the phosphonium salt with base enables *in situ* release of the corresponding air-sensitive secondary phosphine. This can then be exploited in conventional *P*-functionalization chemistry, including (*a*) protection as the phosphine-borane complex, (*b*) polarity inversion via *P*-chlorination, (*c*) selective oxidation to the secondary phosphine oxide, and (*d*) S$_N$2 alkylation to give an analog of Beller's cataXCium ABn ligand.[8,31] Our phosphonium salts can therefore be employed as convenient precursors to versatile synthetic intermediates (via pathways *a-c*) or can be converted directly to important ligand classes (via pathways *c* or *d*).[32]

Notably, the synthesis of tertiary phosphines via pathway *d* constitutes a low cost and redox-efficient route to privileged DTAP-based ligands that entirely avoids the use of PCl$_3$.
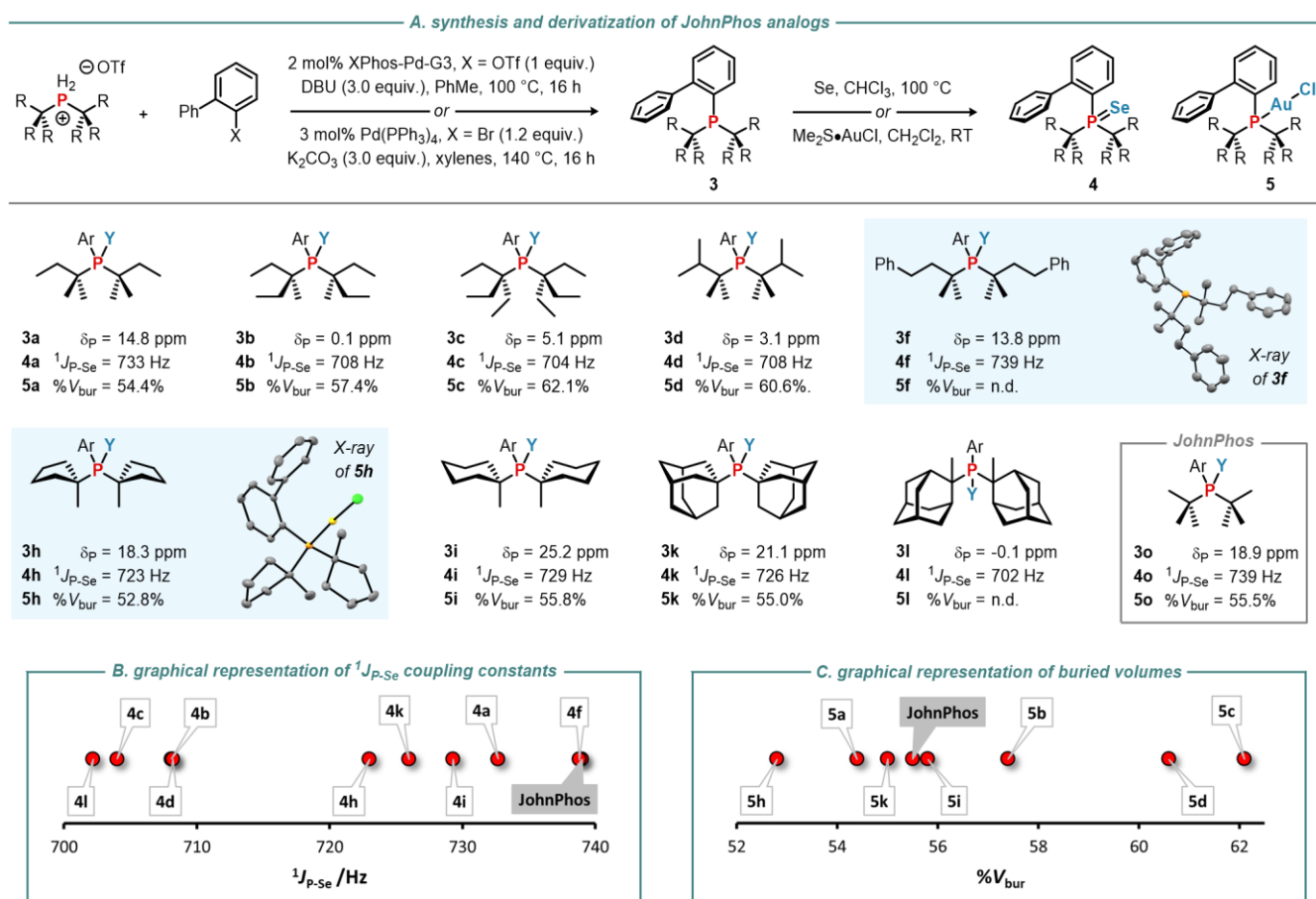
## Scheme 5. Di-*tert*-alkylphosphonium Salts are Convenient Synthetic Surrogates for Secondary Phosphines in Common *P*-Functionalization Reactions[a]
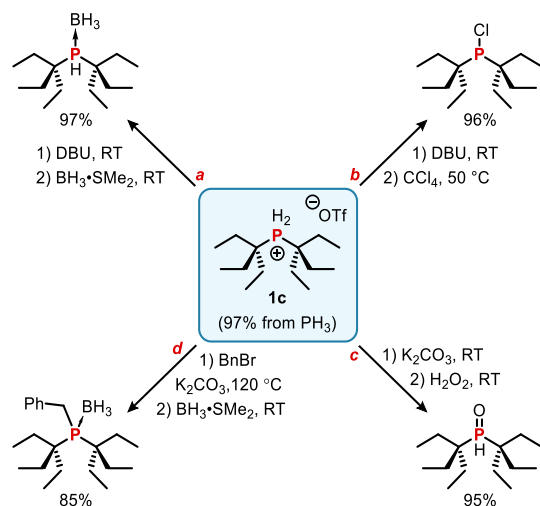


[a] *Pathway a*: (1) DBU (1.2 equiv.), THF, RT, 10 min; (2) BH$_3$•SMe$_2$ (2 equiv.), RT, 16 h. *Pathway b*: DBU (1 equiv.), CCl$_4$, 50 °C, 27 h. *Pathway c*: (1) K$_2$CO$_3$ (3 equiv.), MeOH, RT, 0.5 h; (2) H$_2$O$_2$ (30% aqueous; 2.5 equiv.), RT, 2 h. *Pathway d*: (1) BnBr (1 equiv.), K$_2$CO$_3$ (3 equiv.), toluene, 120 °C, 16 h; (2) BH$_3$• SMe$_2$ (2 equiv.), RT, 2 h.

Installation of an aryl group at phosphorus can be achieved via Pd-catalyzed P-C cross-coupling of the phosphonium salts (Scheme 6). In this way, a library of novel (2-biphenyl)di-*tert*-alkylphosphines **3** was prepared without the use of either PCl$_3$ or reactive *tert*-alkyllithium / Grignard reagents at any stage. Although cross-coupling with the sterically demanding *o*-biphenyl(*pseudo*)halide proved successful for the majority of phosphonium salts, those featuring especially large *tert*-alkyl substituents (**1e** and **1j**) could not be engaged effectively. The resulting phosphines are analogs of JohnPhos **3o**[33] – a member of the privileged Buchwald ligand class[7a-c] – and constitute a standardized, catalysis-relevant platform with which to investigate the stereoelectronic properties of the *tert*-alkyl groups.

**Scheme 6. Synthesis and Characterization of JohnPhos Analogs, their Selenides and their Gold(I) Chloride Complexes**[a]



*A. synthesis and derivatization of JohnPhos analogs*

2 mol% XPhos-Pd-G3, X = OTf (1 equiv.)
DBU (3.0 equiv.), PhMe, 100 °C, 16 h
— or —
3 mol% Pd(PPh₃)₄, X = Br (1.2 equiv.)
K₂CO₃ (3.0 equiv.), xylenes, 140 °C, 16 h

Se, CHCl₃, 100 °C
— or —
Me₂S•AuCl, CH₂Cl₂, RT

| | | |
|---|---|---|
| **3a** $\delta_P$ = 14.8 ppm | **3b** $\delta_P$ = 0.1 ppm | **3c** $\delta_P$ = 5.1 ppm |
| **4a** $^1J_{P\text{-}Se}$ = 733 Hz | **4b** $^1J_{P\text{-}Se}$ = 708 Hz | **4c** $^1J_{P\text{-}Se}$ = 704 Hz |
| **5a** %$V_{bur}$ = 54.4% | **5b** %$V_{bur}$ = 57.4% | **5c** %$V_{bur}$ = 62.1% |

| | |
|---|---|
| **3d** $\delta_P$ = 3.1 ppm | **3f** $\delta_P$ = 13.8 ppm |
| **4d** $^1J_{P\text{-}Se}$ = 708 Hz | **4f** $^1J_{P\text{-}Se}$ = 739 Hz |
| **5d** %$V_{bur}$ = 60.6%. | **5f** %$V_{bur}$ = n.d. |

X-ray of **3f**

| | | | | |
|---|---|---|---|---|
| **3h** $\delta_P$ = 18.3 ppm | **3i** $\delta_P$ = 25.2 ppm | **3k** $\delta_P$ = 21.1 ppm | **3l** $\delta_P$ = -0.1 ppm | **3o** $\delta_P$ = 18.9 ppm |
| **4h** $^1J_{P\text{-}Se}$ = 723 Hz | **4i** $^1J_{P\text{-}Se}$ = 729 Hz | **4k** $^1J_{P\text{-}Se}$ = 726 Hz | **4l** $^1J_{P\text{-}Se}$ = 702 Hz | **4o** $^1J_{P\text{-}Se}$ = 739 Hz |
| **5h** %$V_{bur}$ = 52.8% | **5i** %$V_{bur}$ = 55.8% | **5k** %$V_{bur}$ = 55.0% | **5l** %$V_{bur}$ = n.d. | **5o** %$V_{bur}$ = 55.5% |

X-ray of **5h**

*JohnPhos*

*B. graphical representation of $^1J_{P\text{-}Se}$ coupling constants*

4c 4b 4k 4a 4f
4l 4d 4h 4i JohnPhos

700 710 720 730 740
$^1J_{P\text{-}Se}$ /Hz

*C. graphical representation of buried volumes*

5a JohnPhos 5b 5c
5h 5k 5i 5d

52 54 56 58 60 62
%$V_{bur}$

[a] ³¹P NMR spectroscopic data refer to dilute solutions in CDCl₃; %$V_{bur}$ determined using SambVca2.[40] Ar = *o*-biphenylyl; n.d. = not determined because single crystals of sufficient quality for X-ray diffraction could not be obtained; **3f**: thermal ellipsoids at 30%; **5h**: thermal ellipsoids at 50%, and a molecule of water omitted for clarity.

With ligand series **3** in hand, we sought to demonstrate that the different *tert*-alkyl substituents have a measurable impact on the electronic and steric properties of the phosphorus center (Scheme 6), and that these differences can have significant consequences for catalysis (Scheme 7).[34]

The ³¹P NMR chemical shifts for the free ligands **3** exhibit the expected steric shielding effect from increased substitution at the C$_\beta$-position, and correlate well against the group contribution calculated for the individual *tert*-alkyl substituents.[35] Notably, however, this correlation does not hold for ligands in which the *tert*-alkyl groups feature two substituents at the C$_\beta$-position (**3b**, **3d**, **3h** and **3i**).[36] Following selenation, the one-bond $J_{P\text{-}Se}$ coupling constant was measured as an indicator of the net electron-donating ability of each ligand (Scheme 6B).[37] While some caution must be exercised when interpreting the absolute values of the $J_{P\text{-}Se}$ constants,[38] the difference between the most- and least-electron donating JohnPhos analogs (**4l** and **4o**; $\Delta J_{P\text{-}Se}$ = 37 Hz) is significant, and is the same as the difference between triphenylphosphine and Buchwald's RuPhos.[39] To obtain a measure of sterics, gold(I) chloride complexes **5** were synthesized, and the buried volumes were calculated from crystal structure data using the SambVca2 program (Scheme 6C).[40] Again, a significant difference is

observed across the ligand series, with a span between the largest and the smallest ligands (**5c** and **5h**; $\Delta$%$V_{bur}$(2Å) = 9.3%) that is comparable to the difference between tri-phenylphosphine and tri-*tert*-butylphosphine ($\Delta$%$V_{bur}$(2Å) = 9.1%).[41] The *tert*-alkyl groups that can be installed using our methodology therefore confer distinct physical and spectro-scopic properties on the resulting phosphines, and significantly extend the range of accessible ligand space beyond that occupied by the commercially-available 1-adamantyl and *tert*-butyl substituents (Scheme 6B and 6C).

Finally, we sought to demonstrate that modification of a ligand through its DTAP substructure can have a direct and meaningful impact on catalysis. As one possible indicator of catalyst performance, we investigated the chemoselectivity of oxidative addition under Suzuki-Miyaura conditions. To this end, the effect of JohnPhos analogs **3** on product distribution was measured by intermolecular competition between regioisomeric aryl bromides (Scheme 7). Notably, data concerning intermolecular competitions between unbiased systems are absent from the literature, although the chemoselectivity of oxidative addition has been studied and exploited in the context of intramolecular competitions.[42] As illustrated in Scheme 7, simply changing the *tert*-alkyl substituents on a common

JohnPhos core resulted in chemoselectivities ranging from 2.0:1 to 5.5:1, which corresponds to 0.6 kcal mol$^{-1}$ difference in relative activation energies.

That the observed selectivity trend does not correlate to simple ligand descriptors, such as $J_{P-Se}$ or %$V_{bur}$, reinforces the fact that prediction of catalyst activity is non-trivial,[39] and highlights the value of being able to access new ligand structures for laboratory assessment. More importantly, we have demonstrated that modification of a pre-existing ligand architecture by variation of its DTAP substructure can have significant consequences for its catalytic properties. By using our methodology to vary ligands through this previously inaccessible vector, it is thus now possible to access new regions of ligand space and, ultimately, reaction space.

**Scheme 7. Application of JohnPhos Analogs to Suzuki-Miyaura Cross-Coupling: Chemoselectivity of Oxidative Addition Depends on Di-*tert*-alkylphosphino Substructure**[a]
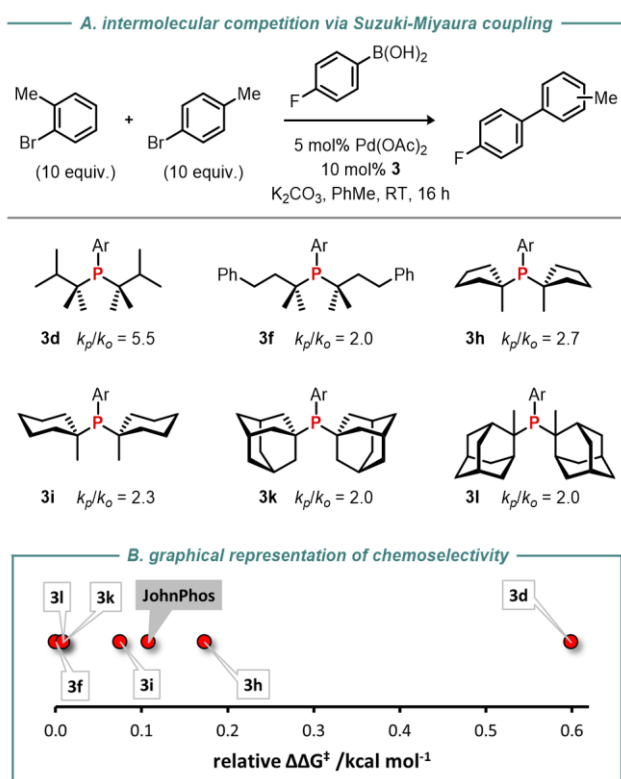


[a] Product distribution determined by $^{19}$F NMR spectroscopic analysis *vs* authentic samples. Ar = *o*-biphenylyl.

**Conclusions**

We have developed an umpolung (P$^-$/C$^+$) approach to P-C bond formation that enables the scalable, redox-efficient synthesis of di-*tert*-alkylphosphines from readily available *tert*-alkyl esters and bench stable $Zn_3P_2$. In this way, the conventional dependence on $PCl_3$ is avoided and an unprecedented variety of *tert*-alkyl substituents can be installed at phosphorus. The resulting DTAP building blocks can be used in the preparation of diverse new analogs of established ligand classes, thereby providing facile access to uncharted regions of ligand space. We show that even apparently minor variations in the DTAP substructure can have a dramatic impact on the

steric and electronic properties of a ligand, and ultimately on its performance in catalysis. This study therefore demonstrates that the DTAP motif need no longer be considered an immutable component of a ligand, but should now be treated as another vector for optimization in ligand design. We are actively seeking to exploit the opportunities that this methodology presents.

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**Notes**

The authors declare no competing financial interest.

## ASSOCIATED CONTENT

**Supporting Information**

The Supporting Information is available free of charge at

Additional discussion, experimental procedures, characterization data and NMR spectra (PDF); cif files for **1a**, **1d**, **1i**, **1k**, **1m**, **1n**, **3f**, **5a-d**, **5h**, **5i** and **5k** (CIF).

**Accession Codes**

CCDC 1990404−1990417 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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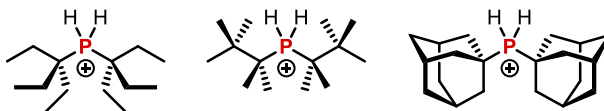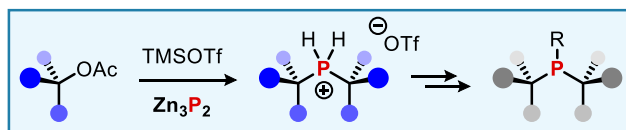


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