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Nickel-catalysed diversification of phosphine ligands by formal substitution at phosphorus†

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We report a diversification strategy that enables the direct substituent exchange of tertiary phosphines. Alkylated phosphonium salts, prepared by standard alkylation of phosphines, are selectively dealkylated in a nickel-catalysed process to access alkylphosphine products *via* a formal substitution at the phosphorus center. The reaction can be used to introduce a wide range of alkyl substituents into both mono- and bisphosphines. We also show that the alkylation and dealkylation steps can be conducted in a one-pot sequence, enabling accelerated access to derivatives of the parent ligand. The phosphine products of the reaction are converted *in situ* to air-stable borane adducts for isolation, and versatile derivatisation reactions of these adducts are demonstrated.

Introduction

Many of the recent advances in transition metal catalysis have been driven by the design of bespoke ancillary ligands that modulate the catalyst's reactivity in an unprecedented fashion.¹ Despite the emergence of a large variety of ligand classes, phosphines remain the ligands of choice for many applications.^{2,3} A significant benefit of phosphines is that the ligand's electronic and steric properties can be tuned with precision by varying the substituents on the phosphorus centre. Taking advantage of a versatile toolbox of synthetic methods to access phosphines,⁴ many powerful phosphine ligand architectures have been developed.^{5–11} Phosphines have also been employed in numerous other applications such as organocatalysis,^{12,13} frustrated Lewis pair catalysis,¹⁴ or material sciences.^{15,16} It can be expected that the continued design of phosphines will lead to even more active ligands, opening further avenues for the application of this intriguing class of compounds.

Traditionally, phosphine ligands are prepared by *de novo* synthetic approaches such as nucleophilic substitution reactions of halophosphine substrates with organometallic reagents.⁴ Alternative strategies include the reduction of phosphine oxides^{17–20} or reactions of hydrophosphines such as the hydrophosphination of unsaturated systems,^{21–23} cross-coupling with aryl halides,^{24,25} or substitution reactions with electrophiles in the presence of base.^{4,26} Combined, these methods allow access to a plethora of diverse phosphine architectures. However, they typically require multi-step procedures involving toxic or pyrophoric reagents and air-sensitive intermediates that

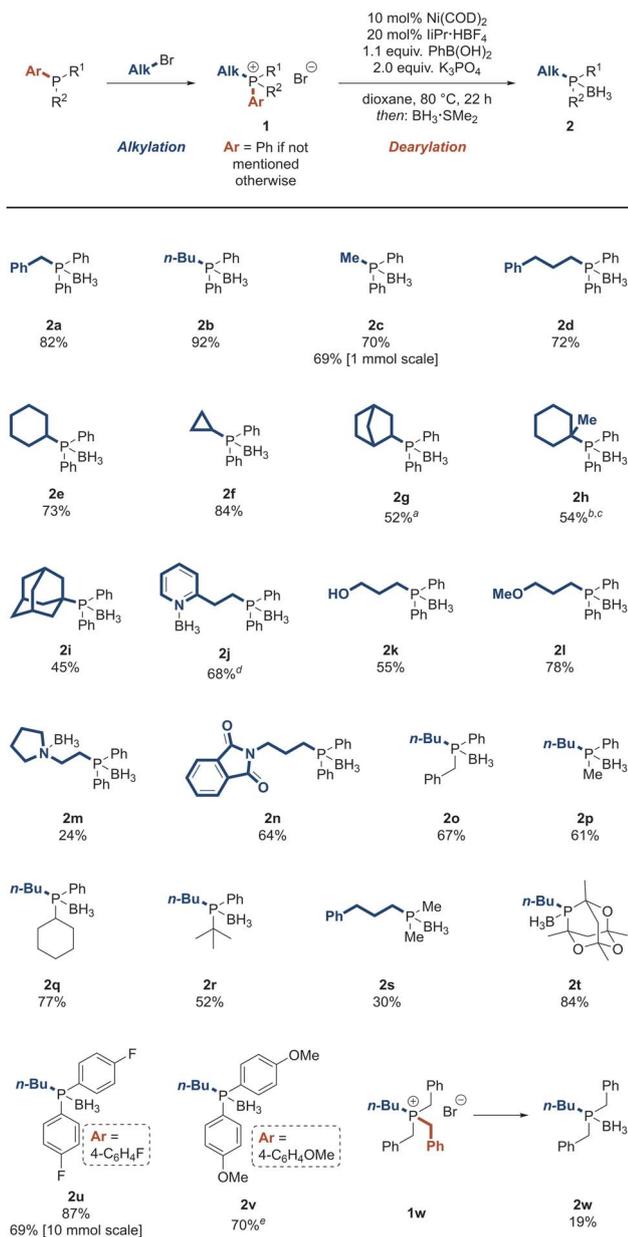
are challenging to isolate. These drawbacks can make the preparation of phosphines arduous and restrict ligand optimisation campaigns to the evaluation of the limited collection of commercially available phosphines. However, if chemists only evaluate commercially available phosphines, they might fail to identify more active and selective catalysts. Therefore, new approaches towards the straightforward synthesis of phosphines and other phosphorus-containing compounds are in critical demand.^{27–29}

A strategy to address this problem is the direct modification of tertiary phosphines (Scheme 1a). In this approach, substituents of phosphines are either altered or exchanged entirely, hence bypassing the need to handle toxic primary and secondary phosphines or even PH₃. It is also an efficient way to quickly generate libraries of ligands, which is a central endeavour for the rapid discovery and optimisation of new reactions. The direct access to ligand derivatives from a hit result also becomes increasingly important in light of recent advances in statistical and machine learning-based approaches that facilitate the *in silico* optimisation of ligand structures.^{9,30,31} Most efforts directed at the modification of tertiary phosphines have focused on altering substituents, for instance by C–H functionalisation approaches.^{32–34} Reactions that entirely replace one of the substituents of a phosphine remain rare although they would arguably be the most versatile tools to modify a wide range of phosphines. Such a strategy would be particularly useful to access underexplored alkylated phosphines. Approaches towards this goal are however limited and mainly rely on the formation and subsequent reaction of metal phosphides by engaging phosphines with highly reactive alkali metals (Scheme 1b).^{35–37} As an alternative, Wang and co-workers reported that acyl phosphines can be used as surrogates for secondary phosphines in metal-catalysed alkylation and arylation reactions.^{38–41} While these methods expand the toolbox of

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Scheme 2 Scope of monophosphines. Yields refer to isolated compounds for the dearylation process after derivatisation to the air-stable BH₃ adduct. ^adr = 12 : 1. The starting material 1g had a dr of 9 : 1. ^bFrom the iodide salt. ^c14 : 1 mixture with Ph₃P·BH₃. ^dFrom the chloride salt. ^eSiMe₃·HCl used instead of LiPr·HBF₄.

phosphine products were typically isolated after *in situ* conversion to the borane adducts. These adducts are air-stable, can be conveniently purified by column chromatography, and are easily deprotected (*vide infra*).^{62,63}

Phosphines containing both activated and unactivated primary alkyl groups were prepared in high yield by our dearylation strategy (2a–d). A cyclohexyl group was incorporated in 73% yield (2e). This moiety as well as the *tert*-butyl and adamantyl groups are arguably the most widespread alkyl substituents in modern ligands. Our reaction not only tolerates the presence of these moieties (2e, 2i, 2q–r), but also allows to

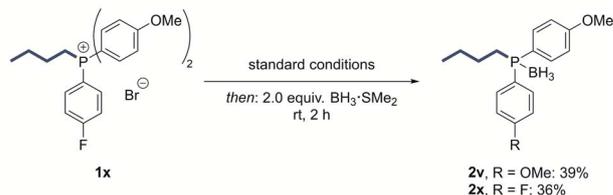
introduce other, less prevalent cyclic secondary alkyl groups (2f–g) or tertiary alkyl groups (2h). Alkyl groups containing coordinating moieties like pyridyl, primary alcohol, and ether groups were incorporated in good yield (2j–2l) and provide opportunities to use the reaction to prepare chelating ligands with two different coordinating atoms. A low, but synthetically useful yield was observed for a substrate containing a tertiary amine (2m, 24%). As an alternative, a phthalimide moiety, which can be used as a precursor for amines, was well tolerated (2n). The reaction can also be used to synthesize phosphines containing more than one alkyl group. Dialkylphosphonium salts with differing steric demand afforded the desired product in good yield (2o–r). Trialkylphosphine 2s was prepared in a lowered, but synthetically useful yield of 30%. In contrast, the caged trialkylphosphine 2t was obtained in high yield (84%).

Besides the introduced alkyl group, the nature of the removed aryl group can also be varied. Electron-rich and electron-poor aryl groups can be cleaved in the reaction in high yield (2u–2v). Notably, the reaction can also be conducted on a large scale, as demonstrated by the preparation of two grams of 2u. Besides the dearylation of phosphonium salts, the dealkylation is possible when the starting material does not contain an aryl group. Tetraalkylphosphonium salt 1w was selectively debenzylated in 19% yield without additional optimisation.

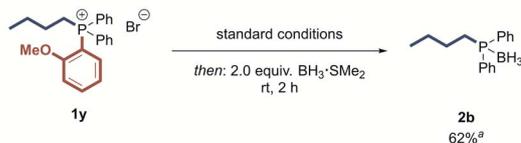
We next investigated reactions of phosphonium salts containing two different aryl groups (Scheme 3a). The transformation of phosphonium salt 1x, containing electron-

a) Dearylation of substrates containing two different aryl groups

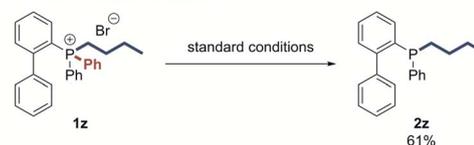
Generation of two modified phosphines in a single reaction



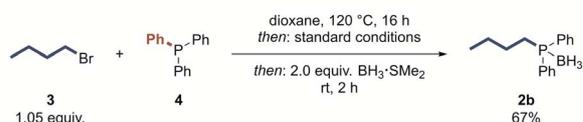
Selective removal of one type of aryl group



Synthesis of new Buchwald-type ligands



b) Direct substituent exchange in a one-pot process



Scheme 3 Further applications. ^a8 : 1 mixture with 2-methoxybiphenyl.

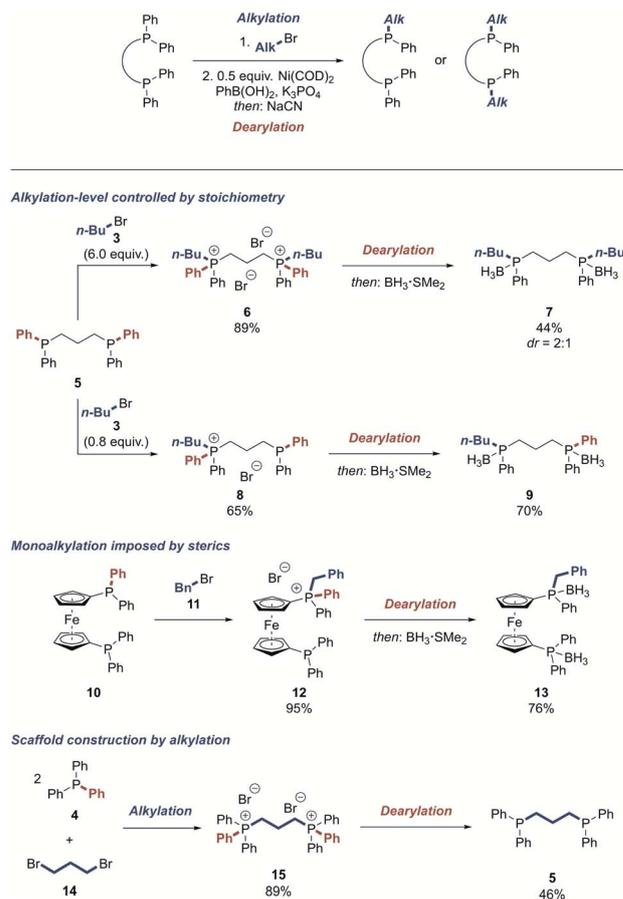


donating and electron-withdrawing aryl groups, resulted in partial cleavage of both aryl groups to deliver the two alkylated phosphines **2v** and **2x** in useful yields in a single reaction. The products could be conveniently separated by column chromatography. In contrast, the 2-methoxyphenyl group was exclusively removed from phosphonium salt **1y**, indicating a directing effect of the *ortho*-methoxy moiety. The reaction can also be used to modify Buchwald-type ligands, as demonstrated by the synthesis of the air-stable JohnPhos derivative **2z** in good yield.

Results of further substrates that were tested in the reaction are summarized in Fig. S3.† Generally, substrates with high steric hindrance performed worse in the reaction than less sterically hindered substrates. Additionally, substrates with strongly coordinating moieties did not perform well or even led to cleavage of the alkyl group.

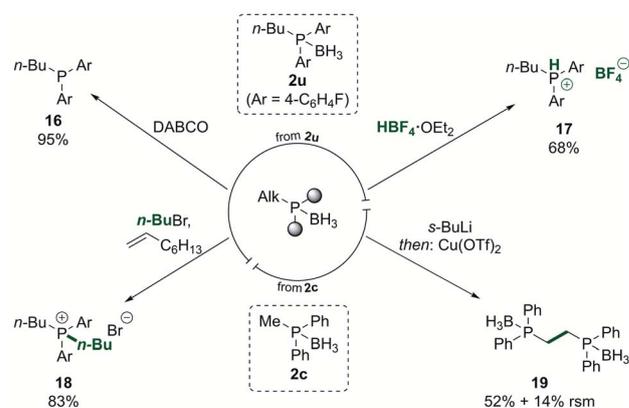
To further increase the utility of our strategy, we developed a one-pot protocol in which the phosphonium salt is first formed by the alkylation of a phosphine and then directly treated with the reagents for the nickel-catalysed dearylation. Applying this protocol, we were able to prepare *n*-butyldiphenylphosphine from triphenylphosphine (**4**) in 67% yield after converting the product to its air-stable borane adduct **2b** (Scheme 3b). Notably, no intermediate workup or solvent change is required, making this process a direct substitution at the phosphorus centre and enabling rapid access to alkylated phosphine ligands.

Due to the high importance of bidentate ligands in catalysis,² we attempted the synthesis of bisphosphines by the twofold dearylation of a bisphosphonium salt. However, no product was detected. Mechanistic experiments showed that the desired dearylation occurred, but the bidentate phosphine product **L** deactivated the catalyst by irreversibly coordinating to it in a NiL₂ complex (see ESI†). We thus tested a range of metal scavengers to de-coordinate the product from the nickel centre of this complex and found that sodium cyanide is highly active for this process.^{64–67} This insight enabled us to develop a strategy for the dearylative alkylation of bisphosphines. After an alkylation step, the nickel complexes NiL₂ of the desired dearylated ligand products were formed by a stoichiometric Suzuki reaction of the bisphosphonium salt and then directly exposed to sodium cyanide to afford the free bidentate phosphines. Notably, the protocol offers the possibility to modify the starting ligand selectively on both phosphorus centres or just one. 1,3-Bis(diphenylphosphino)propane (DPPP) (**5**) could be mono- or dialkylated in good yield, respectively, by simply changing the stoichiometry of the alkylation step (Scheme 4). The dearylation of the resulting phosphonium salts **6** and **8** proceeded smoothly to yield the symmetrically modified ligand **7** in 44% yield and the unsymmetric ligand **9** in 70% yield, respectively. Other privileged ligand scaffolds such as 1,1'-bis(diphenylphosphino)ferrocene (DPPF) (**10**) can also be altered using this process. Alkylation of **10** selectively yielded the monophosphonium salt **12** potentially because of the hindered nature of the second phosphino moiety after the first alkylation. The dearylation of **12** occurred in good yield to furnish the unsymmetric DPPF-type ligand **13** that would be



Scheme 4 Modification of bidentate ligands. See ESI† for detailed reaction conditions.

difficult to prepare by traditional means. The reaction can not only be used to modify bidentate ligands but also to construct them. DPPP (**5**) could be prepared in 46% yield by the reaction of triphenylphosphine (**4**) with the alkyl dihalide **14** and subsequent two-fold dearylation.



Scheme 5 Derivatization of the phosphine borane products. DABCO = 1,4-diazabicyclo[2.2.2]octane. RSM = recovered starting material. See ESI† for detailed reaction conditions.



The phosphine borane adducts, as which the phosphine products were typically isolated, can be used in versatile derivatisation reactions (Scheme 5). The free phosphine **16** was accessed in nearly quantitative yield by treatment of the phosphine borane adduct **2u** with DABCO and a subsequent simple filtration through Celite.⁶⁸ Conversion to the HBF₄ salt **17** was achieved in good yield.^{69,70} Such salts are air-stable and can be used directly as ligand precursors in catalysis by releasing the free phosphine *in situ* after treatment with a base.⁷¹

Phosphonium salt **18** was accessed in 83% yield from the phosphine borane adduct **2u** by treating it with an alkyl halide in the presence of 1-octene.⁷² The product phosphonium salt could then be used in the nickel-catalysed dearylation reaction again, allowing to quickly introduce multiple alkyl groups in a phosphine in a programmed fashion. As an additional way to modify the products, the alkyl group in the phosphine borane adduct **2c** was deprotonated in alpha-position to the phosphorus, and subsequent oxidative dimerisation yielded the bidentate product **19**, providing a means to extend the ligand diversification beyond the scope of the dearylation reaction.⁷³

Conclusions

In conclusion, we demonstrated a general strategy for the modification of phosphine ligands. The reaction enables the substitution of aryl groups in phosphines for alkyl groups in a protocol relying on the straightforward alkylation of a phosphine and a subsequent nickel-catalysed dearylation reaction. Besides the broad scope of the dearylation method, we demonstrate that the overall process can also be directly conducted as a one-pot protocol. Together with the development of a related strategy for the modification of bidentate ligands and versatile product derivatisation methods, this methodology provides a rapid entry into alkylphosphine ligand space. We expect that this strategy will streamline ligand optimisation campaigns and enable the identification of new powerful ligands for use in catalysis.

Data availability

Full experimental and characterization data is available in the ESI.†

Author contributions

S. R. conceived the project. S. R. and S. U. L. performed the experimental studies. B. M. supervised the research. S. R. wrote the original draft of the manuscript which was edited by all authors.

Conflicts of interest

There are no conflicts to declare.

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