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Using Catalysts To Make Catalysts: Titanium-Catalyzed Hydroamination To Access *P,N*-Ligands for Assembling Catalysts in One Pot

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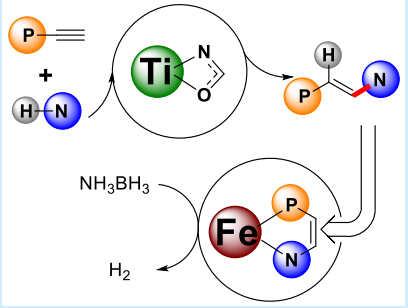
ABSTRACT: Using a diamido-bis(amidate) titanium precatalyst, the hydroamination of alkynylphosphines afforded phosphinoenamine products. After reduction, 2-aminophosphines are prepared in excellent yield and on gram scale. A broad variety of alkynylphosphines and primary amines with different electronic and steric features are tolerated in this sequential transformation, enabling the rapid assembly of a collection of ligands. Additionally, intermediate phosphinoenamines can be used directly as proligands for coordination to transition metals using protonolysis or salt metathesis reactions. These transformations result in easy-to-use one pot protocols to prepare metal *P,N*-complexes for catalysis or small molecule activation.



2-Aminophosphines are useful chelating ligands in transition-metal coordination chemistry. With both a σ-donating *N* "hard" donor and a π-accepting *P* "soft" donor, 2-aminophosphines can stabilize transition metals at low oxidation state while also supporting oxidative addition at the reactive metal centers.[1] Both the steric and electronic features of *P* and *N* can be modified to give various 2-aminophosphine ligands. The ligands are featured in an array of transition metal catalyzed transformations, such as asymmetric hydrogenation, carbon−carbon bond forming reactions, and small molecule activation.[2−10]

Several approaches are used to synthesize 2-aminophosphines with different steric and electronic features (Scheme 1). Commonly, stoichiometric strong bases and pyrophoric phosphines (R_2PH) are required in the 2-haloamine nucleophilic attack pathway.[11−17] Alternatively, *ortho*-lithiated aryl amines can be used for nucleophilic substitution reactions with halo phosphines (R_2PX).[18] However, only phenyl tethered aminophosphines have been prepared using this method. Another strategy focuses on C−N bond forming reactions, rather than C−P bond formation. For example, a vinyl-phosphine-oxide ($R_2P(=O)CH=CH_2$) can be used as a Michael acceptor for 1,4-addition of an amine to give 2-aminophosphine oxides.[19,20] This transformation, featuring an activated alkene, is a formal hydroamination reaction to give an intermediate phosphine oxide product that can be reduced to furnish the desired 2-aminophosphines. However, the vinyl-phosphine-oxide starting material takes multiple steps to access. A new synthetic protocol to access 2-aminophosphines features ring opening of phosphiranium salts with aniline derivatives.[21] Here, the mesityl phosphiranium salt required also demands specialized synthesis.

Hydroamination is a powerful tool for making carbon−nitrogen bonds with excellent atom economy.[22] Advances in alkyne hydroamination include regioselective reactions of both alkyl and aryl alkynes with a range of primary and secondary amines as well as *N*-heterocycles.[23−29] However, α-heteroatom-substituted alkyne hydroamination is rare with few reported examples.[30−42] To date the catalytic hydroamination of simple alkynylphosphines is unknown.

In addition to commonly used saturated aminophosphines, examples with unsaturated backbones also attract interest as ligands. The conjugated moiety decreases the π-donating feature and basicity of alkyl amido donors and offers a more sterically rigid backbone.[43,44] However, due to synthetic challenges, only *ortho*-phosphinoanilines have been widely utilized (Scheme 1 b).[18] Phosphinoenamines (Scheme 1e) as ligands in catalysis have rarely been investigated.[45−51]

Our group has developed a commercially available diamido-bis(amidate) Ti alkyne hydroamination precatalyst [Ti] for anti-Markovnikov terminal alkyne hydroamination.[52−59] It has good functional group tolerance, and a broad scope of alkynes containing heteroatoms can be used.[55,58] Here we show that this catalyst promotes regioselective hydroamination of alkynylphosphines to make *P,N*-ligands in one atom-economic, catalytic step (Scheme 1 e). The phosphinoenamine/imine

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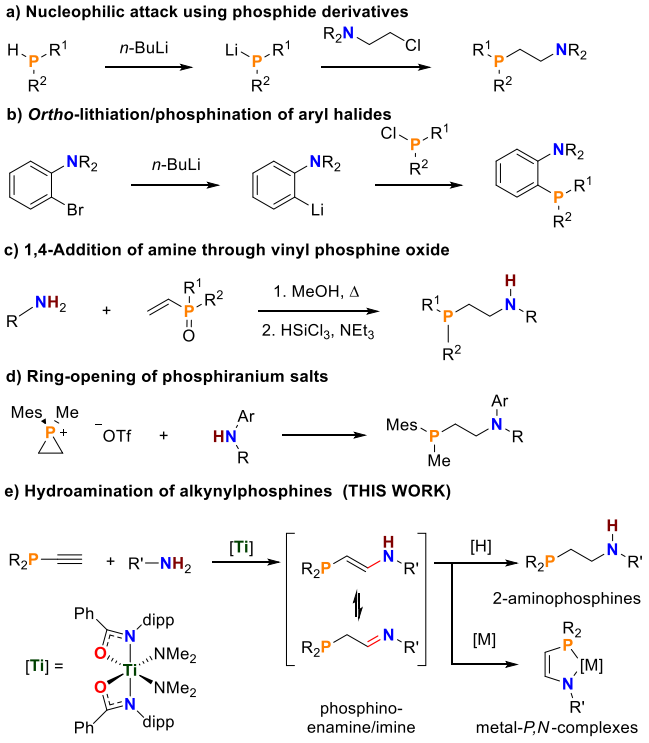
Scheme 1. Synthesis of 2-Aminophosphine Ligands



product of the hydroamination reaction can be reduced to 2-aminophosphines for isolation, or alternatively these reactive intermediates can be installed directly onto catalytically relevant metal centers using a one-pot approach using salt metathesis reactions. This synthetic approach can incorporate a variety of phosphine and amine substrates to afford a modular and atom efficient assembly of *P,N*-ligands or *P,N*-ligated complexes with different electronic and/or steric features. As a proof of concept, an iron bis-phosphinoenamido complex was prepared using sequential hydroamination-salt metathesis in one pot, to access a new Fe(II) ammonia borane dehydrogenation catalyst.

One-Pot Hydroamination: Reduction for *P,N*-Ligands. $Ph_2P-C{\equiv}CH$ (**1**) was prepared following a literature procedure,[60] and initial hydroamination reactions were performed using *sec*-$BuNH_2$ with 5 mol % [Ti] (Figure 1). After 30 min at 70 °C, the diagnostic peak of **1** (−33 ppm) disappeared in the $^{31}P\{^1H\}$ NMR spectrum (Figure S9 vs S12), and three new peaks emerged at −11, −20, and −35 ppm with a ratio of 55:35:10. Based on 2D-NMR experiments (Supporting Information (SI)), the most intense peak at −11 ppm was determined to be the *E*-enamine product of anti-Markovnikov hydroamination (**2a**). Meanwhile the peak at −20 ppm was assigned to the imine tautomer **2a′**, and the minor peak at −35 ppm corresponded to the *Z*-enamine tautomer **2a″**. Most importantly, there were no peaks that could be assigned to the Markovnikov product. On the contrary, using the known $Ti(NMe_2)_4$ hydroamination catalyst,[61] a complicated mixture of phosphorus containing compounds was recovered, as established by a complex $^{31}P\{^1H\}$ spectrum of the reaction mixture (Figure S122). Thus, this regioselective reactivity with phosphinoalkynes is consistent with the established unique regioselectivity trends of bis(amidate)titanium precatalyst **1**. To further confirm the regioisomer assignment, compound **2a** was recrystallized from

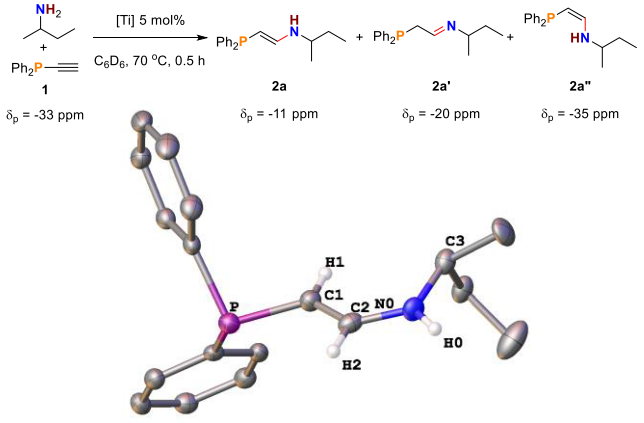


Figure 1. Hydroamination of $Ph_2P-C{\equiv}CH$ and *sec*-$BuNH_2$. The $^{31}P\{^1H\}$ chemical shifts of the starting material and three tautomerizing products along with the solid-state molecular structure of the product phosphino-*E*-enamine **2a**.

hexanes at −40 °C and analyzed by single crystal X-ray diffraction (Figure 1).[62]

Attempts to purify the 2-phosphinoenamine product by column chromatography resulted in decomposition, presumably due to hydrolysis of the imine tautomer. To avoid decomposition the enamine/imine mixture was directly reduced with $NaBH_4$ to afford the corresponding 2-aminophosphine **3a** in 61% isolated yield after column chromatography.

To improve the atom economy of the reaction, catalytic hydrogenation reactions were attempted using Pd/C catalysts with H_2 gas. Such catalytic hydrogenation reactions have been used to advantage in one-pot protocols with [Ti] previously, as reported for the atom-economic synthesis of amines and morpholines from terminal alkynes directly.[54−57] Unfortunately, only complicated mixtures resulted in this case. The disappointing results here can be attributed to the *P,N*-ligands generated in this sequence that may bind the reactive Pd metal surface and inhibit desirable hydrogenation catalytic reactivity.

With a one-pot hydroamination−reduction sequence in hand, the substrate scope for preparing a range of *P,N*-ligands was explored. Both alkyl and aryl amine substrates can be used with alkyne **1** (Scheme 2). Aliphatic primary amines with 2°, 3°, and 4° α-carbons all react well (**3a**−**3c**), with benzyl amine being the most sluggish (120 vs 30 min). Commercially available chiral amines can be used (**3d**), which could lead to chiral *P,N*-ligands. Notably racemization of the chiral amine does not occur with Ti precatalyst **1**,[63] in contrast to other reported Ti hydroamination catalysts.[64] Similar to the hydroamination of regular alkynes,[54,55] aromatic amines are more reactive substrates (**3e**−**3h**). Consistent with the mechanistic understanding of this reaction, which invokes turnover limiting associative protonolysis of intermediate metallacycles,[65] more electron-rich 4-methoxyaniline is more reactive, while electron-poor 4-(trifluoromethyl)aniline requires longer reaction times (**3f** vs **3g**). The hydroamination step using 4-bromoaniline went smoothly, although subsequent reduction and purification resulted in a reduced yield (**3h**). The sterically hindered 2,6-dimethylaniline required a longer reaction time of up to 1 day (**3i**). Although purification of **3i** by column chromatography on the benchtop was challenging, a modified protocol featuring isolation by filtration of the reaction mixture under N_2 after $NaBH_4$ reduction gave

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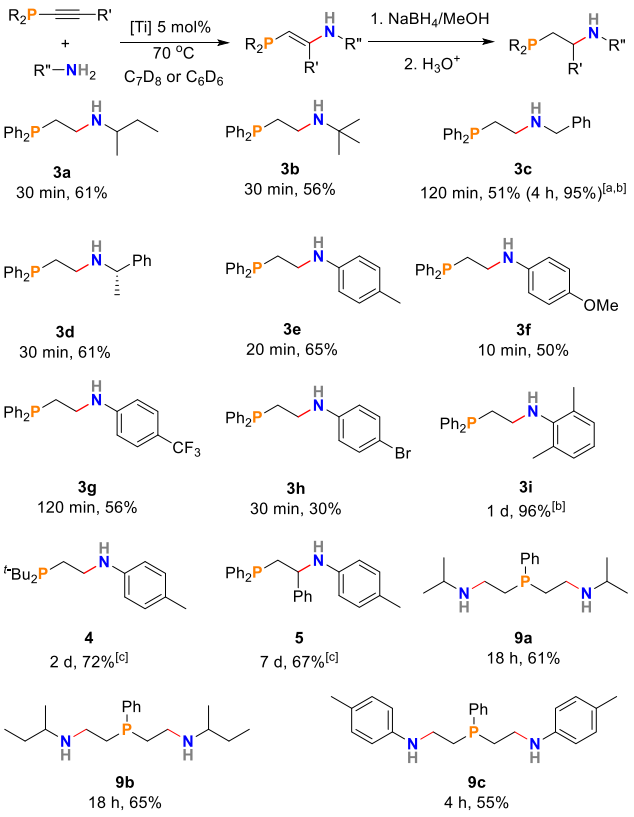
Scheme 2. Sequential Hydroamination–Reduction Synthesis of 2-Aminophosphines[a]



[a]Reaction time and isolated yields are listed.

an almost quantitative yield of the crude product. This column-free isolation protocol has proven to be broadly useful, and **3c** (95% yield at 1 g scale) is provided as another example.[14,15]

The known alkyl substituted phosphine starting material *t*-Bu_2P–C≡CH[60] was less reactive requiring a longer reaction time (48 h) and elevated temperature (120 °C) for the reaction with 4-methylaniline. Subsequent reduction and purification gave **4** in 72% yield. This can be attributed to the bulky *t*-Bu groups on the phosphorus atom and the reduced electronic polarization of the alkyne with the change to an alkyl phosphine.[65] However, the less reactive *sec*-$BuNH_2$ showed no hydroamination reactivity, even with heating at 120 °C for 3 days.

Internal alkynylphosphines, such as Ph_2P–C≡CPh, are challenging substrates, demanding a one-week reaction to achieve >80% conversion in hydroamination (Figure S20 vs S19). Further $NaBH_4$ reduction also required gentle heating to give aminophosphine **5** in 67% yield. Once again, only one regioisomer was formed, which highlights the regioselectivity of the [Ti] precatalyst in internal alkyne hydroamination.[56] Less reactive alkyl-substituted internal alkynylphosphines, such as Ph_2P–C≡C^{n}Bu did not react with 4-methylaniline under similar conditions.

Interestingly, by reacting 2 equiv of amine with a dialkynylphosphine $PhP(C{\equiv}CH)_2$, symmetric *β,β′*-phosphinodienamines were successfully prepared. Noteworthy, a mixture of tautomerizing phosphino-enamine and imines was observed according to the ^{31}P NMR spectrum of the product (Figure S26), with the major component being the enamine (−32 ppm). Subsequent reduction gives the corresponding *NPN* type 2,2′-diaminophosphine products **9a–c** in approximately 60% yield over the two steps, slightly higher than an analog with a cyclopentene backbone.[49] Similar to the trend observed in phosphinoalkyne hydroamination, aromatic amines react faster than alkyl amines in the hydroamination step (4 h vs 18 h).

These results demonstrate the flexible synthesis of diverse *P,N*-saturated proligands using regioselective catalytic hydroamination and subsequent reduction. These proligands can then be isolated and stored for later use. These results show that *P,N*-chelating ligands with strong *σ*- and *π*-donating amido substituents, coupled with *π*-accepting phosphines, can be readily accessed using this approach. Alternatively, the intermediate phosphinoenamine/imine products of hydroamination can be used as ligands directly, and to date, this is a class of chelating *P,N*-ligands that is largely unexplored. Additionally, *NPN* type molecules could also be prepared using the same strategy, providing an efficient synthetic route to such kind of multidentate ligands.

One-Pot Synthesis of P,N-Ligated Catalysts. The reaction of phosphinoalkynes in anti-Markovnikov hydroamination generates phosphinoenamine/imine ligands in an atom-economic approach. Most importantly, this intermediate product that cannot be easily isolated can be used directly in a ligand substitution reaction onto reactive metal centers. This *in situ* ligand preparation avoids the stoichiometric reduction step and offers direct access to phosphinoenamine ligands. Related *ortho*-P,N substituted arenes have been used to advantage in a range of catalytic transformations.[46,49,66–69] Here we can access rarely investigated analogues without the aromatic backbone.[45–51] The handful of previous reports of such chelating ligands reveal tedious syntheses, unlike the one-pot method developed here.

Ammonia borane (H_3BNH_3) has been extensively studied as a promising material for hydrogen storage due to its high hydrogen capacity (19.6 wt %).[70,71] A variety of catalysts have been developed to facilitate dehydrogenation of ammonia borane, which includes Fe complexes as inexpensive and earth-abundant-metal catalysts for this desirable transformation. Specifically, a saturated bis(2-phosphinoamido) ligated Fe(II) complex has been developed for the dehydrogenation of ammonia borane.[72] Catalyst development efforts found that it showed good reactivity for ammonia borane dehydropolymerization; however, the ligand synthesis involved a multistep sequence, including protection and deprotection protocols, and could not be easily modified to accommodate diverse substituents.[72] Furthermore, low turnover numbers were observed, due to proposed proton abstraction resulting in catalyst decomposition. Here we show that by using a one-pot hydroamination–deprotonation–complexation sequence complementary unsaturated phosphinoenamido ligands can be used to generate new catalysts for ammonia borane dehydrogenation (Figure 2). Furthermore, this class of unsaturated phosphinoenamido ligand may not be resistant to complex degradation by deprotonation.

Complex **6** can be easily prepared by direct deprotonation of the hydroamination product, intermediate phosphinoenamine **2e**, using a strong base like KHMDS to give 2-phosphinoenamide monoanionic ligand salts. These ligand salts can then be directly installed onto transition metals using a salt

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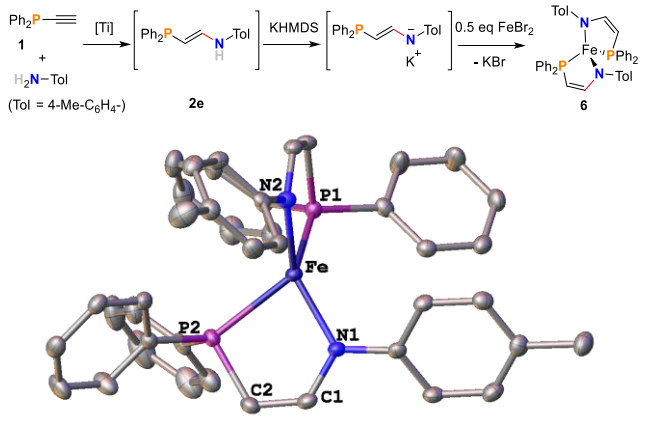

Figure 2. Synthetic route (top) and the ORTEP representation of the molecular structure of **6**. Drawn in 50% probability. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Fe−N1, 1.968(2); Fe−P1, 2.4238(8); N1−C1, 1.357(4); C1−C2, 1.351(4); N1−Fe−P1, 85.35(7); N1−Fe−N2, 133.95(9); P1−Fe−P2, 109.51(3); N1−Fe−P2, 122.59(7).

metathesis reaction with $FeBr_2$ (Figure 2). This one-pot protocol goes from simple phosphinoalkyne and amine through to an isolable *P,N*-ligated Fe(II) complex that is obtained in 42% yield of crystalline material.

Structure analysis of **6** using NMR spectroscopy was challenging due to its paramagnetic nature (Figure S114). The μ_B of **6** was determined to be 4.16 at 298 K using the Evans method (Figure S115),[73] consistent with a high-spin Fe(II) complex. Furthermore, the molecular structure of complex **6** was established by single crystal X-ray diffraction. In the solid state, complex **6** is a pseudotetrahedral iron complex with two β-phosphinoenamido ligands (Figure 2). Interestingly, the *P,N*-ligand that contains *trans*-enamine as the major isomer successfully binds to Fe in the *cis*-conformation. The coordination environment around iron in **6** is similar to the previously reported catalytically active complex disclosed by Baker.[72] The effect of the unsaturated ligand backbone featured here, as well as phenyl substituents of **6** rather than the cyclohexyl substituents of the Baker complex, shows that **6** has a smaller P1−Fe−P2 angle (109.51° vs 116.55°). Additionally, although the Fe−P distances in both cases are all about 2.423 Å, in **6** the N1−C1 (1.357 Å vs 1.461 Å) and C1−C2 (1.351 Å vs 1.514 Å) distances are all shorter due to the unsaturated and conjugated ligand backbone. To explore this new system in catalytic ammonia-borane dehydrogenation catalysis, a proof-of-concept investigation of the catalytic activity of complex **6** was completed.

Following the previously published protocol,[72] a quartz NMR tube with a rubber cap was loaded with a dry THF solution of H_3BNH_3 (0.33 M) and $NaBPh_4$ (0.067 M) as an internal standard. Next 5 mol % **6** in THF was added using a syringe. The mixture rapidly turned dark, and small bubbles started to evolve, consistent with H_2 generation.[74] The reaction mixture was heated at 45 °C for 3 h, and 90% of the starting H_3BNH_3 was consumed as determined by $^{11}B\{^1H\}$ NMR spectroscopy. Meanwhile, white precipitate formed in the NMR tube, as would be consistent with the formation of polyaminoborane. These results show that the more sterically accessible **6** is more catalytically active than the previously reported saturated catalyst (complete conversation in 3 h vs 20 h). Furthermore, the reaction conditions used with **6** were milder than the previous report (45 °C vs 60 °C).

To test the recyclability and turnover number of **6**, a second portion of H_3BNH_3 was added to the catalytic reaction mixture. Reduced catalytic activity was observed, as a longer reaction time was required to consume the second portion (12 h for 90% overall consumption). Finally, a third portion was added; however, only approximately half of the newly added H_3BNH_3 was consumed after 2 days. Overall, the turnover number of **6** was found to be more than 50. This is a comparable catalyst turnover number as was observed for the previously reported complex.[72] These preliminary results demonstrate the promise of using catalytic hydroamination to make new catalysts for investigation.

In conclusion, we report the regioselective, catalytic hydroamination of alkynylphosphines with our titanium precatalyst. A broad scope of terminal alkynylphosphines and amines bearing different electronic and steric substituents are tolerated. Subsequent reduction yields 2-aminophosphines in high overall yields, or the intermediate phosphinoenamines can be installed directly onto reactive metal centers by salt metathesis. This one-pot reaction represents a new, modular, step- and atom-economic approach for preparing this unsaturated chelating *P,N*-ligand motif. Additionally, preliminary studies showed that new catalytic active complexes could be synthesized efficiently using a sequential hydroamination−complexation strategy. This new approach enables the rapid assembly of a range of metal complexes to be explored in catalysis and stoichiometric organometallic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04212.

Experimental details and crystallography data (PDF)

Accession Codes

CCDC 2051563 and 2051565 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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Notes

The authors declare no competing financial interest.

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(74) ***ATTENTION!*** A needle was left on the cap for venting.

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