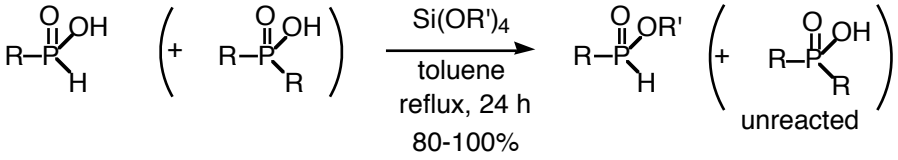
Montchamp, Jean-Luc
Summer 2015

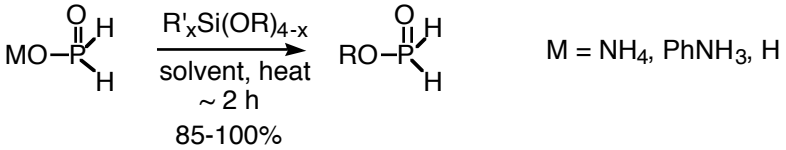
Research Highlights - New Chemical Reactions & Synthetic Methodology

1) Selective Esterification of H-Phosphinic Acids (*Org. Lett.* **2000**, *2*, 3341)



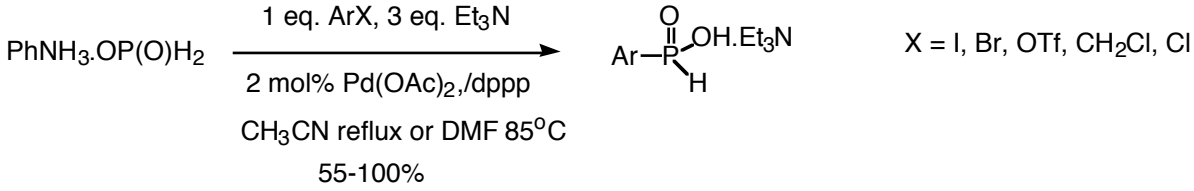
- alternative to the traditional methods (diazomethane, DCC, PivCl)
- inexpensive and scalable
- selective for H-phosphinic acids in the presence of symmetrically-substituted phosphinic acids
- can be purified by simple extraction

2) Esterification of Hypophosphorous Compounds (*J. Organomet. Chem.* **2002**, *643-644*, 154)



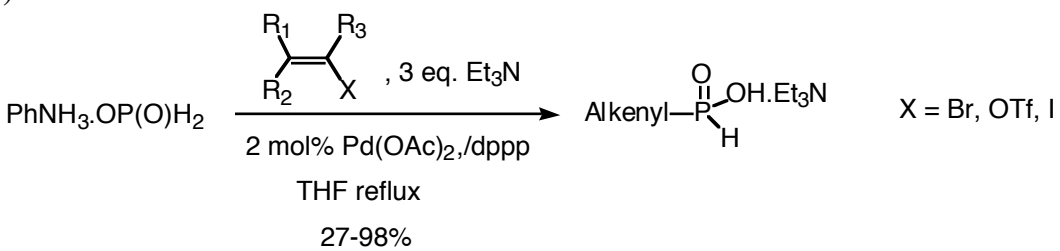
- literature methods are lower-yielding and limited to a handful of solvents
- the products have unusual thermal stability under these conditions
- a variety of ester R can be prepared

3) Palladium-Catalyzed Phosphorus-Carbon Bond Formation – Aryl Electrophiles (*J. Am. Chem. Soc.* **2001**, *123*, 510)



- novel P-C bond forming reaction
- literature alternatives require several steps to obtain the same products
- wide scope (even certain aryl chlorides undergo the reaction)
- convenient reaction conditions (reagent grade solvents and air are tolerated) "beaker reaction"
- as little as 0.2 mol% Pd can be used to afford comparable yields
- anilinium hypophosphite introduced as a convenient and inexpensive reagent

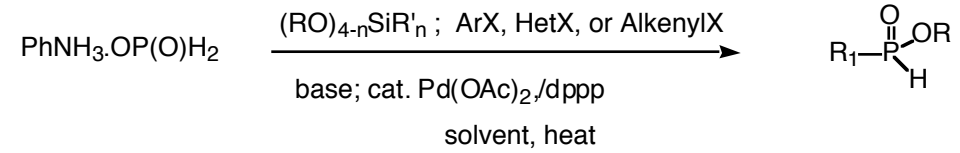
4) Palladium-Catalyzed Phosphorus-Carbon Bond Formation – Alkenyl Electrophiles (*J. Organomet. Chem.* **2002**, *653*, 252)



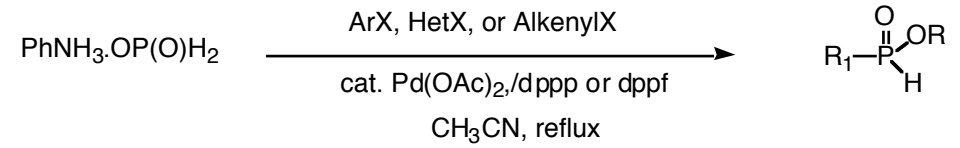
- extension of our cross-coupling chemistry to alkenyl substrates

- applied to the expeditious synthesis of TPMPA (a selective antagonist of $GABA_B$ receptors)
- broad scope (various substitution patterns are tolerated)
- literature alternatives require several steps to obtain the same products

5) Palladium-Catalyzed Phosphorus-Carbon Bond Formation – Reaction of Aryl and Alkenyl Electrophiles with Hypophosphite Esters (*Comptes Rendus Chimie* **2004**, *7/8-9*, 763, *Tetrahedron* **2005**, *61*, 6315)

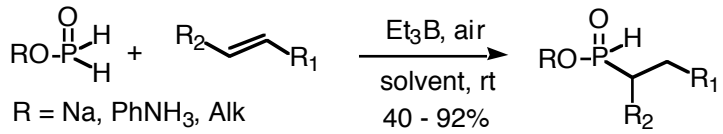


X = I, Br, OTf, CH_2Cl R_1 = Ar, Het, Alkenyl



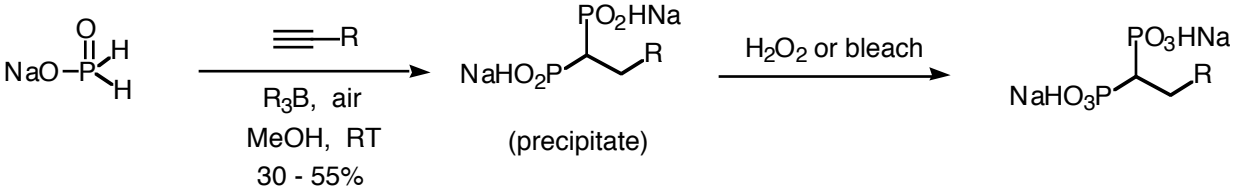
- extension of our Pd-catalyzed coupling to directly form alkyl H-phosphinates
- aminopropyl(trialkoxy)silane can be used as both the base and the ester source, and allows purification by extraction
- scope is unprecedented in the literature

6) Room-Temperature Radical Hydrophosphinylation (*J. Org. Chem.* **2001**, *66*, 6745)



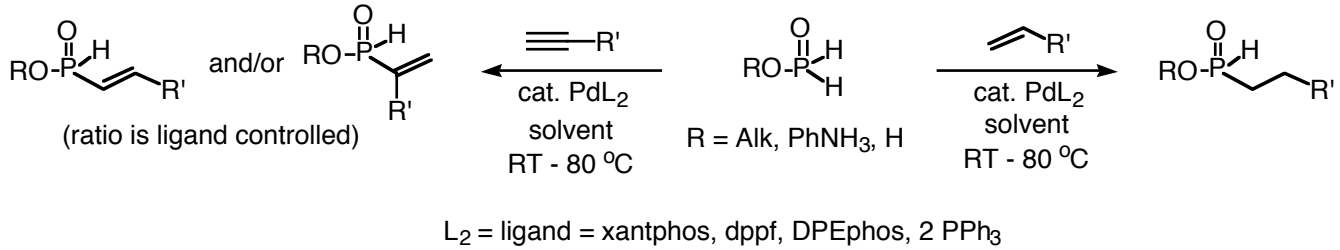
- extremely broad scope
- neutral conditions
- functional group tolerant
- practical and scalable ("beaker reaction")

7) Radical Hydrophosphinylation of Alkynes (*Org. Lett.* **2005**, *7*, 5909; United States Patent: "Bis-H-Phosphinic Acid Derivatives as Precursors to Therapeutic Bisphosphonates and Uses Thereof" US Patent Number US 6,781,011 B2, August 24, 2004)



- novel class of compounds
- precursors to medicinally important bisphosphonates
- reaction can be conducted easily on very large scales and is convenient ("beaker reaction")
- the products can be easily purified
- mild conditions
- no protecting groups necessary

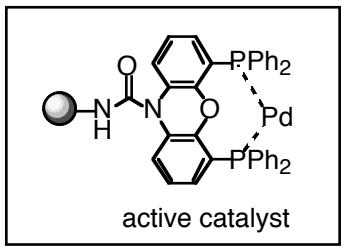
8) Palladium-Catalyzed Hydrophosphinylation of Unsaturated Compounds (*J. Am. Chem. Soc.* **2002**, *124*, 9386; *J. Org. Chem.* **2008**, *73*, 2292)

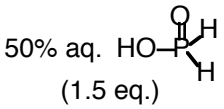


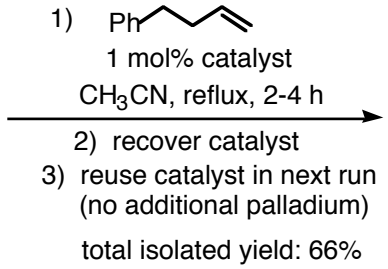
L_2 = ligand = xantphos, dppf, DPEphos, 2 PPh_3

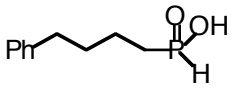
- Fundamentally novel reaction-type
- very general reaction (broad scope of unsaturated substrates: alkynes, alkenes, dienes, enynes, allenes; broad scope of hypophosphorous reagents and solvents)
- highly catalytic (even 0.02 mol% Pd gives high yields)
- the reaction can proceed even in the presence of water
- the reaction can proceed at room temperature
- the normal transfer-hydrogenation pathway is completely suppressed
- another "beaker reaction"

9) Environmentally Benign Palladium-Catalyzed Hydrophosphinylation (*Org. Lett.* **2004**, *6*, 3805)

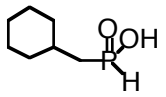




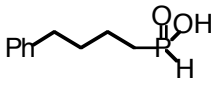




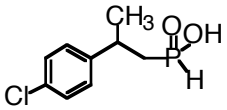
Run 1: 92%
Run 2: 81%
Run 3: 79%
Run 4: 84%
Run 5: 74%



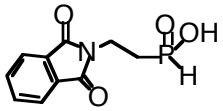
2 eq. conc. H_3PO_2
CH_3CN, reflux
92 % isolated



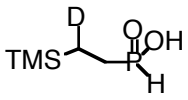
2 eq. 50 % aq. H_3PO_2
CH_3CN, reflux
97 % isolated

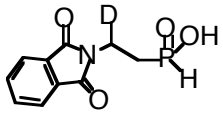


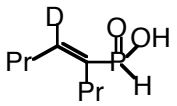
2 eq. 50 % aq. H_3PO_2
CH_3CN, reflux
91 % isolated



2 eq. conc. H_3PO_2
CH_3CN, reflux
61 % isolated



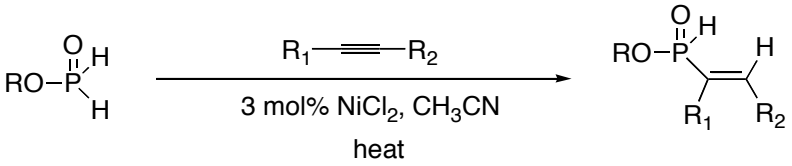




yields: 60-90%
% D incorporation > 75%

- reusable polymeric catalyst, available in one step from commercially available reagents
- mild conditions (water-tolerant, low reaction temperatures, atom-economical)
- high yields and straightforward product isolation
- alternative for the preparation of a heart drug precursor
- can be used for labeling (potentially including radio-labeling)

10) Nickel Chloride-Catalyzed Hydrophosphinylation (*J. Org. Chem.* **2005**, *70*, 4064)

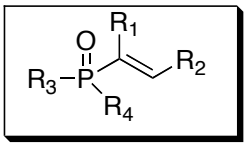


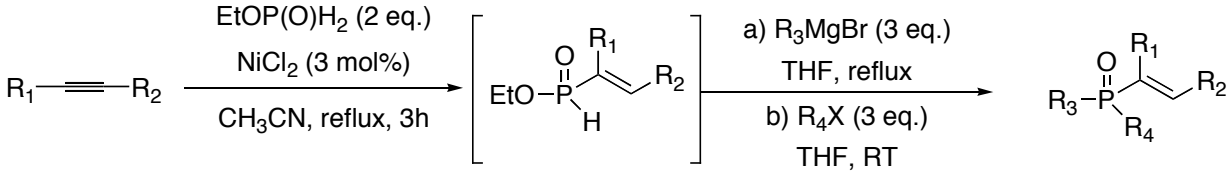
- broad scope and practical conditions
- 3 mol% or less $NiCl_2$ or even $NiCl_2.6H_2O$
- can be conducted in 5 min under microwave heating
- high yields

One-pot triple P-C bond-forming sequence:

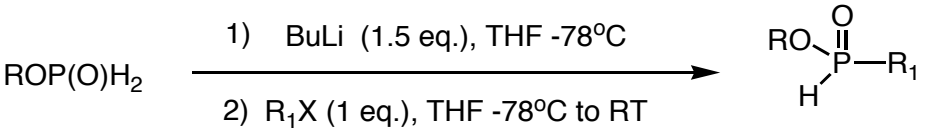
tertiary phosphine oxides

(one-pot, three P-C bond formations)

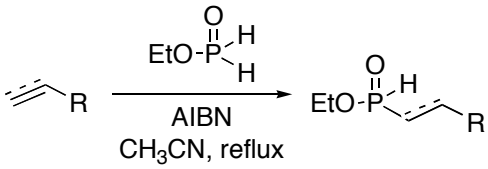




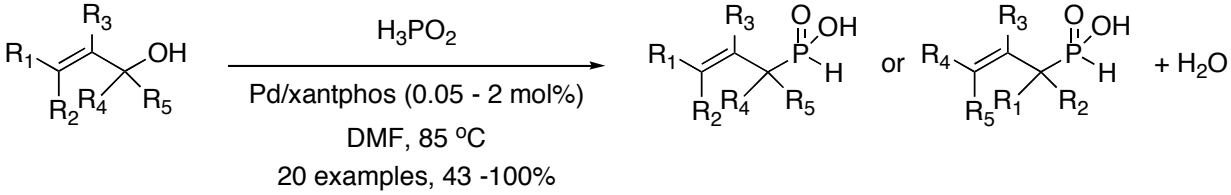
11) Direct Alkylation of Alkylphosphinates $ROP(O)H_2$ (*Synthesis* **2006**, *2*, 325)



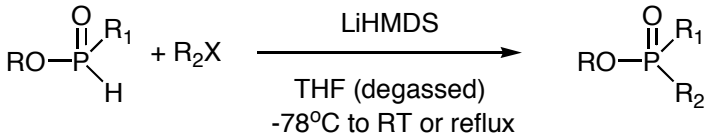
12) AIBN-Initiated Radical Reactions of Ethyl Phosphinate (*Synthesis* **2006**, 3080)



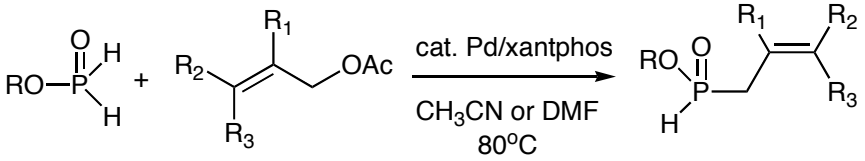
13) Palladium-Catalyzed Dehydrative Allylation of Hypophosphorous Acid with Allylic Alcohols (*Org. Lett.* **2006**, *8*, 4169; *Org. Synth.* **2008**, *85*, 96)



14) Base-Promoted Alkylation of H-Phosphinate Esters: Synthesis of Disubstituted Phosphinates (*J. Org. Chem.* **2007**, *72*, 2851)

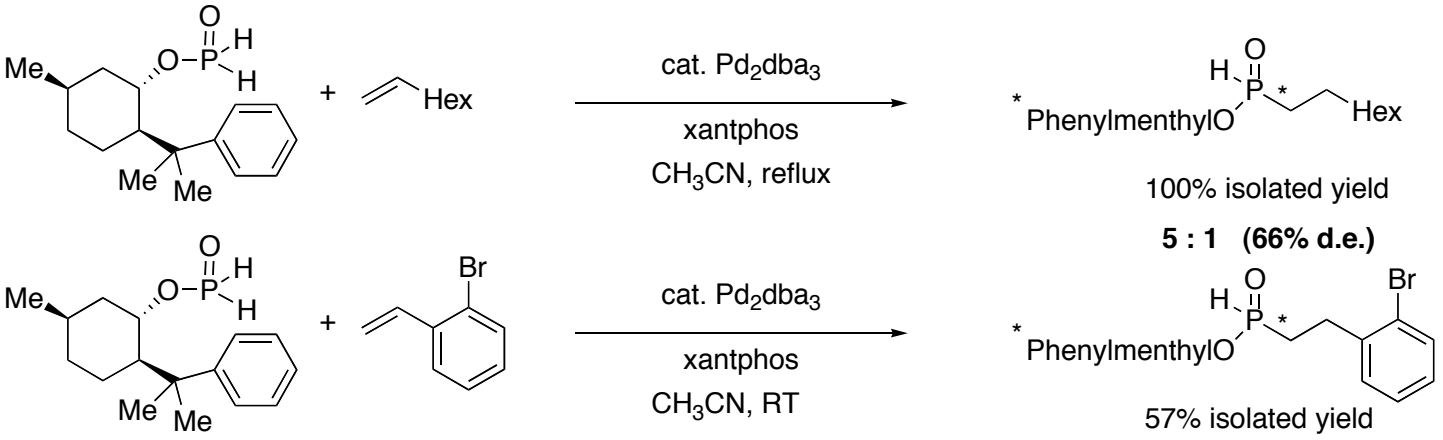


15) Palladium-Catalyzed Allylation of Hypophosphorous Compounds with Allylic Acetates (*J. Org. Chem.* **2008**, *73*, 2292)

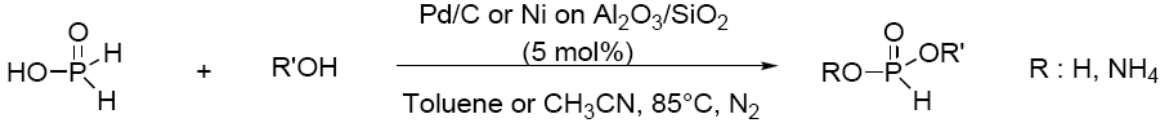


R = $PhNH_3$, Et_3NH, Alk

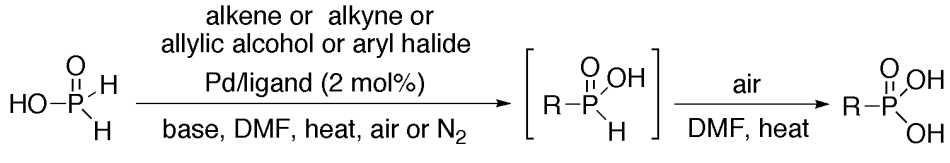
16) Desymmetrization of Phosphinate Esters Using a Chiral Auxiliary: Synthesis of P-Chiral H-Phosphinic Acid Esters (Unpublished results)



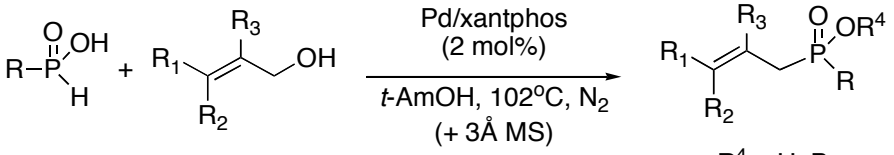
17) Catalytic Phosphorus-Oxygen Bond-Formation (*Tetrahedron Lett.* **2007**, *48*, 6505)



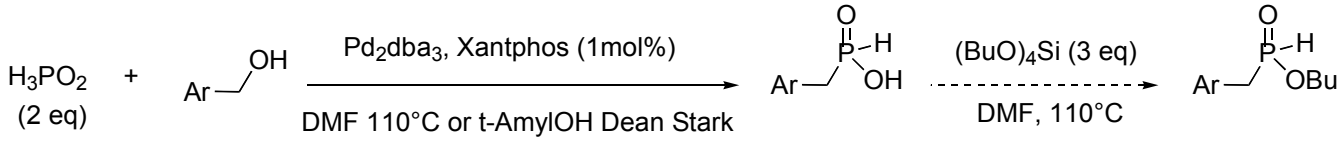
18) Catalytic Synthesis of Phosphonic Acids from H_3PO_2 (*Tetrahedron Lett.* **2007**, *48*, 5755)



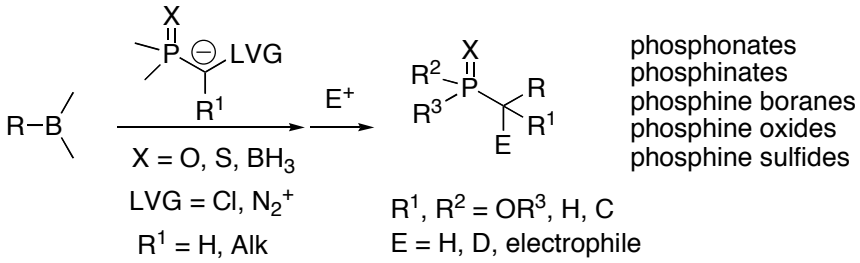
19) Palladium-Catalyzed Allylation of H-Phosphinic Acids using Allylic Alcohols (*Org. Lett.* **2008**, *10*, 1123)



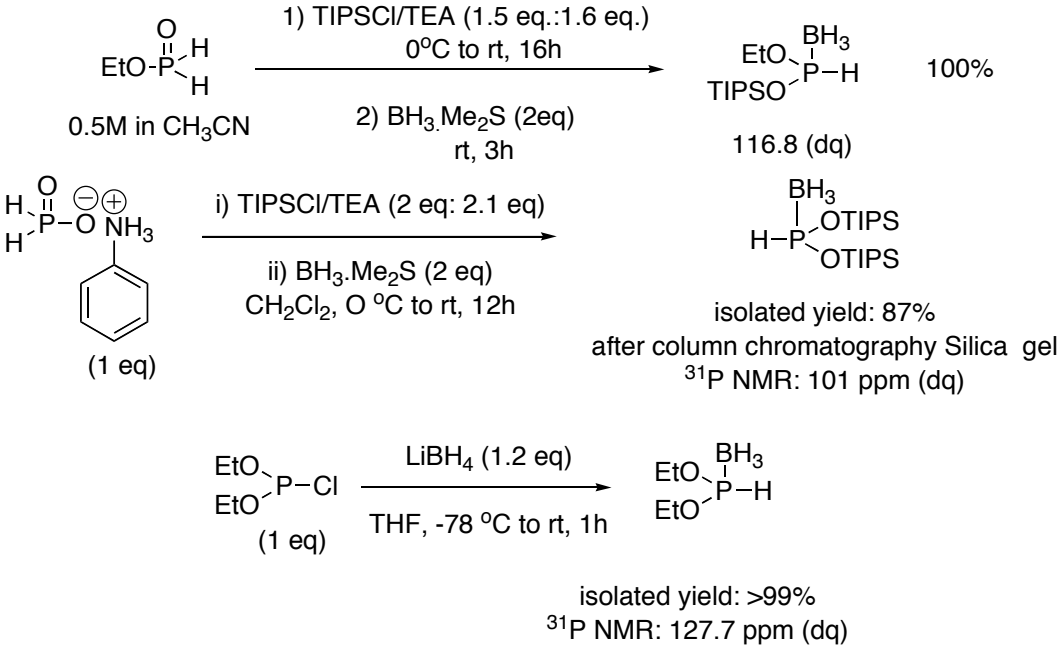
20) Palladium-Catalyzed Benzylation of H_3PO_2 using Benzylic Alcohols (*Eur. J. Org. Chem.* **2008**, 4101)



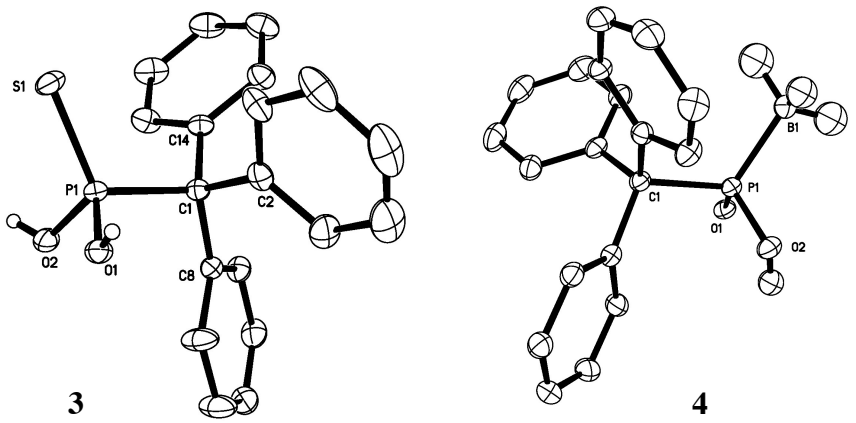
21) Mild Synthesis of Organophosphorus Compounds: Reaction of Phosphorus-Containing Carbenoids with Organoboranes (*Org. Lett.* **2008**, *10*, 977)

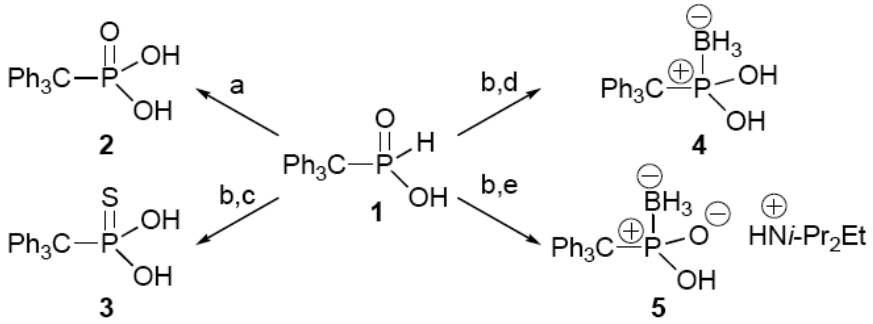


22) Borane Complexes of Hypophosphorous Acid's P(III) Tautomer: Useful Phosphinate Equivalents (*Tetrahedron* **2008**, *64*, 9181)



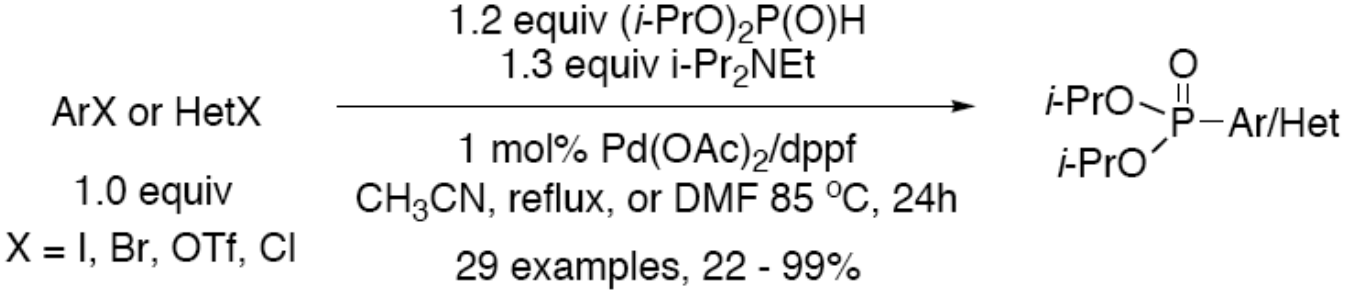
23) First Crystal Structure Characterization of Phosphonothioic and Boranophosphonic Acids (*Phosphorus, Sulfur and Silicon and the Related Elements* **2008**, *183*, 2214) [see also *J. Chem. Cryst.* **2009**, *39*, 337]



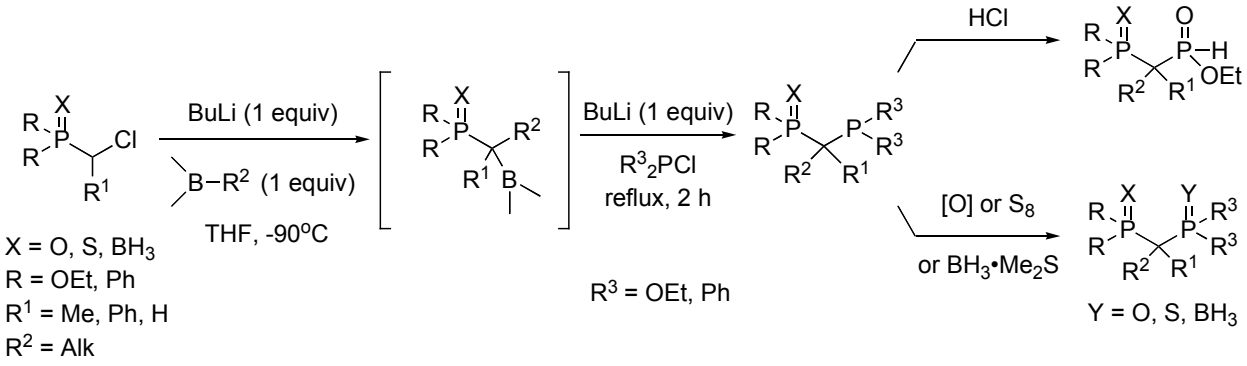


Scheme Synthesis of compounds **2-5**: (a) O_3, MeOH, 0°C, 82%; (b) N,O-bis(trimethylsilyl)acetamide, THF, rt, 1h; (c) S_8, rt, then MeOH; (d) $BH_3{\cdot}Me_2S$, rt, then MeOH; (e) $BH_3{\cdot}EtNiPr_2$, then NH_4OH, MeOH.

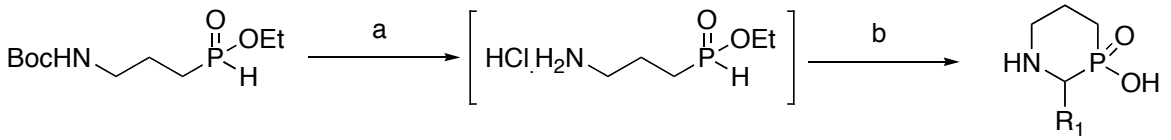
24) Revisiting the Hirao Cross-Coupling (*J. Organomet. Chem.* **2008**, *693*, 3171)



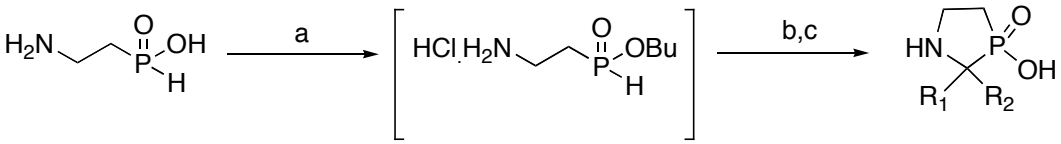
25) Synthesis of 1,1-Bis-Phosphorus Compounds from Organoboranes (*Tetrahedron Lett*. **2008**, *49*, 5909)



26) Heterocyclization of Aminoalkyl-H-Phosphinates: Aminoacid Analogs (*J*. *Org*. *Chem*. **2008**, *73*, 8987)



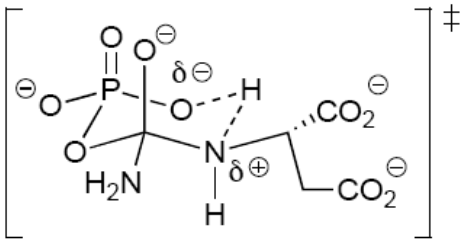
a) HCl_g, CH_2Cl_2, r.t. 12h; b) RCHO 1eq., BuOH, MW, 200°C 3-6 min, purification by simple filtration



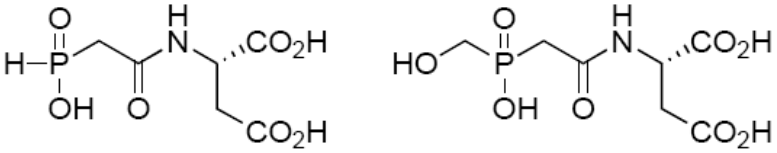
a) 2 eq. 1 N HCl, BuOH with Dean-Stark system, reflux 12h; b) $R_1C(O)R_2$ 1 eq., DIEA 1 eq., MW 200°C, 3 min; c) TMSBr 3 eq., CH_2Cl_2, r.t. 12h.

27) Inhibition of Aspartate Transcarbamoylase (ATCase) (*Bioorg*. *Med*. *Chem*. *Lett*. **2009**, *19*, 900; *Bioorg. Med. Chem.* **2009**, *17*, 7680)

The design, syntheses, and enzymatic activity of two submicromolar competitive inhibitors of aspartate transcarbamoylase (ATCase) are described. The phosphinate inhibitors are analogs of N-phosphonacetyl-L-aspartate (PALA) but have a reduced charge at the phosphorus moiety. The mechanistic implications are discussed in terms of a possible cyclic transition-state during enzymatic catalysis.

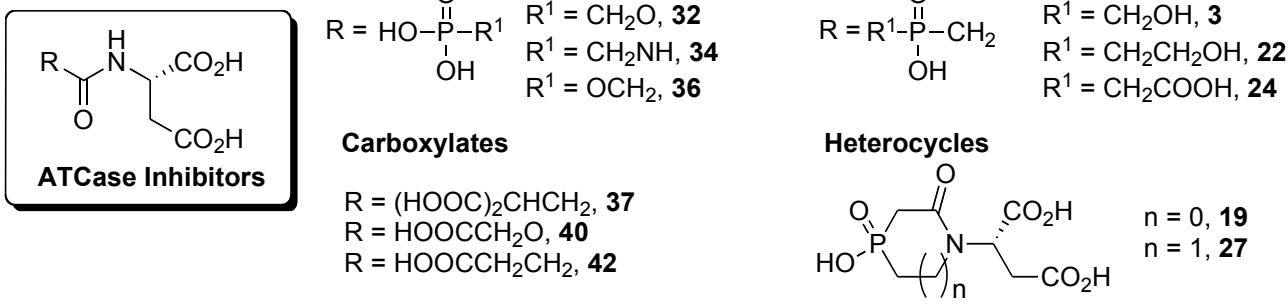


postulated transition-state

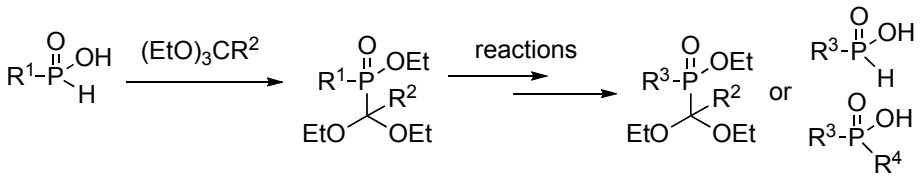


phosphinate inhibitors

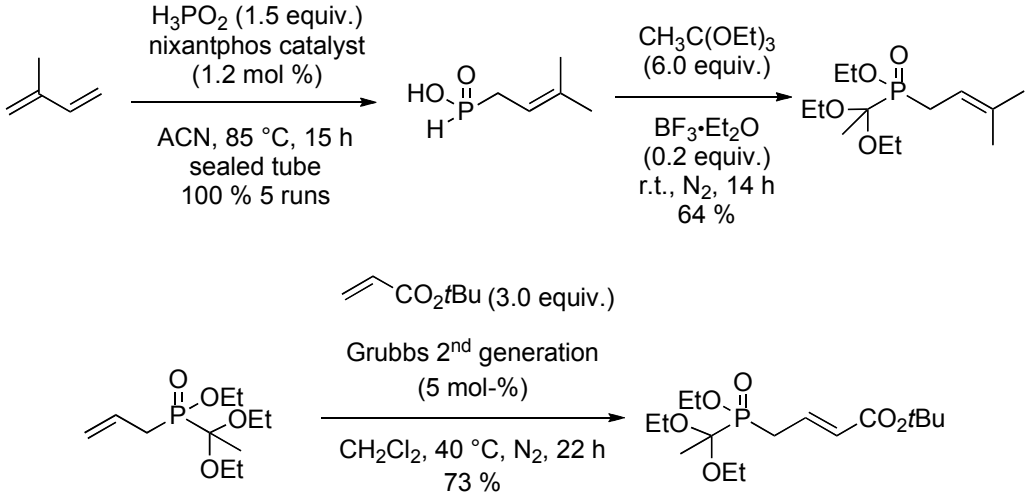
The full study includes the synthesis and evaluation for a full range of inhibitors:



28) Temporary Protection of *H*-Phosphinic Acids as a Synthetic Strategy (*Eur. J. Org. Chem.* **2009**, 4646)

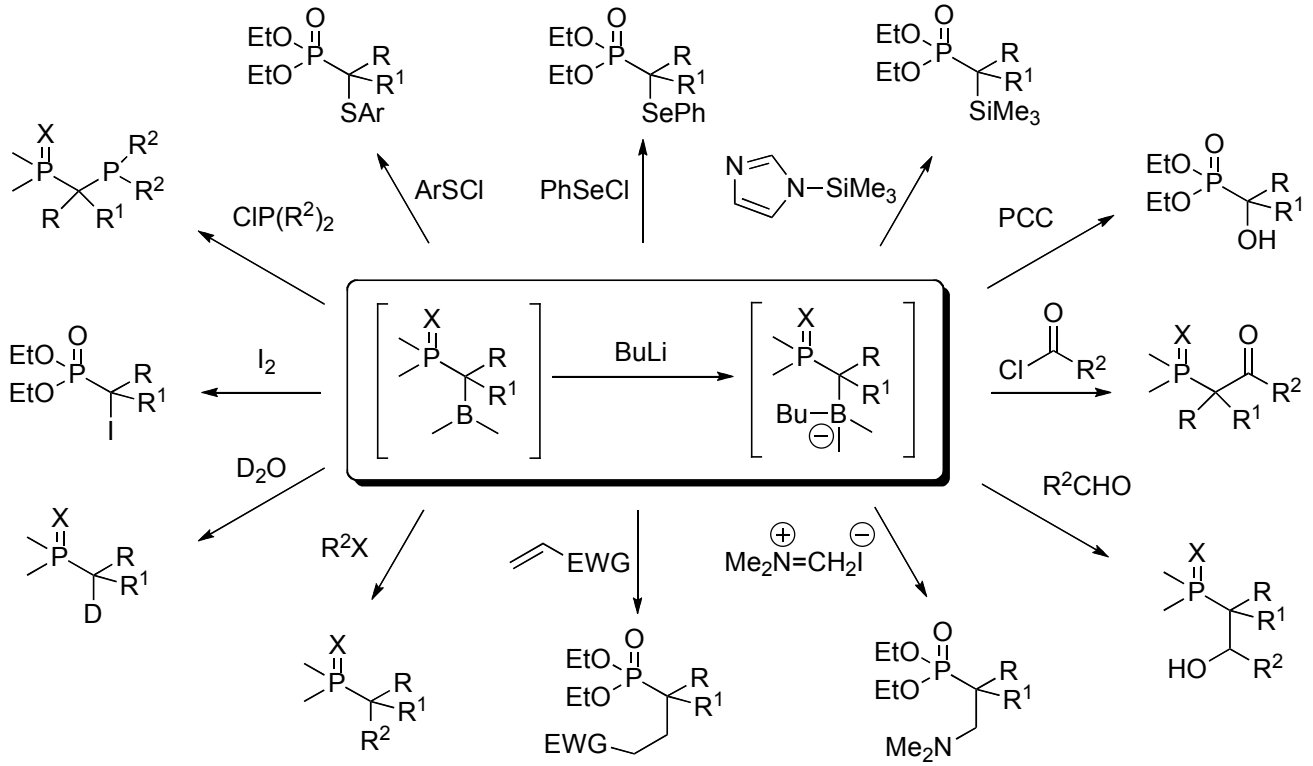


H-Phosphinates obtained through various methodologies are protected directly via reaction with triethyl orthoacetate. The resulting products can be manipulated easily, and various synthetic reactions are presented. For example, application to the synthesis of aspartate transcarbamoylase (ATCase) or kynureninase inhibitors are illustrated. Other reactions, such as Sharpless' asymmetric dihydroxylation, or Grubbs' olefin cross-metathesis are also demonstrated.



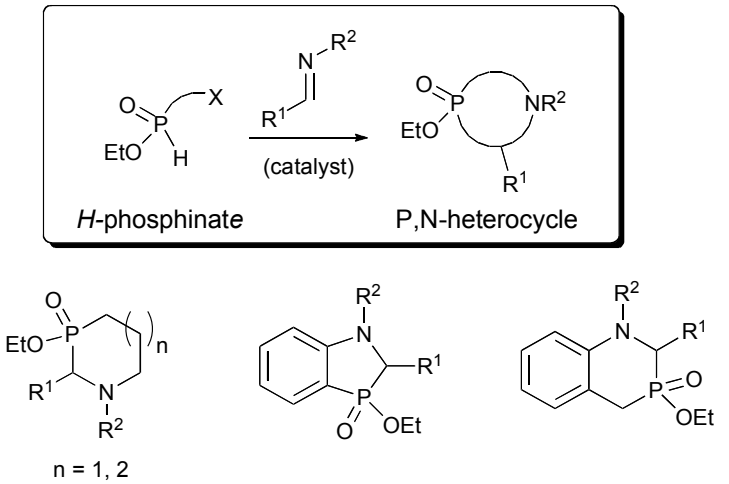
29) Reactions of α-Boranophosphorus Compounds with Electrophiles: Alkylation, Acylation, and other Reactions (*J. Org. Chem.* **2009**, *74*, 3758)

The homologation of phosphorus carbenoids with organoboranes leads to α-boranophosphorus compounds, which can be further functionalized through reactions with various electrophiles, either directly or after activation to the corresponding borate. A variety of substituted organophosphorus compounds can be obtained in one-pot via reaction with many electrophiles. Complex structures are prepared in a single step using simple building blocks.

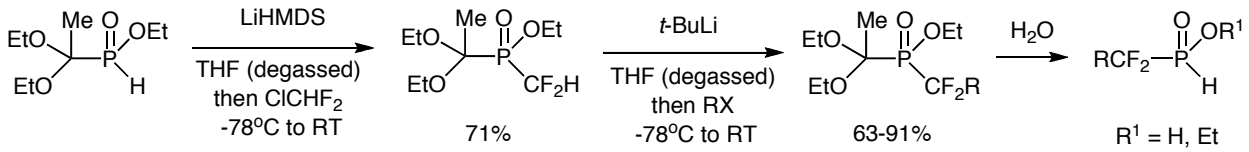


30) Facile P,N-heterocycles synthesis via tandem aminomethylation-cyclization of *H*-phosphinates building blocks (*Org. Biomol. Chem.* **2010**, *8*, 267)

Various heterocycles containing phosphorus and nitrogen are synthesized easily from readily available *H*-phosphinate building blocks. Aminomethylation of these *H*-phosphinates is followed by in situ cyclization through substitution or cross-coupling to produce novel heterocycles in moderate to good yields.

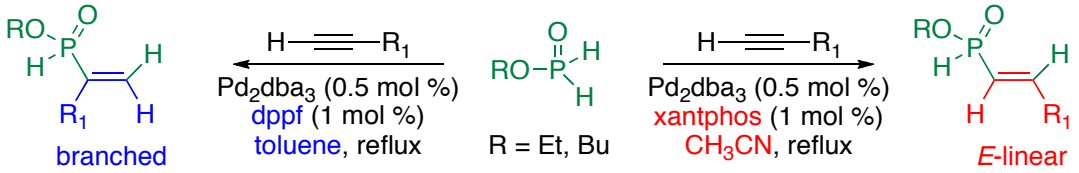


31) Synthesis and Reactivity Studies of α,α-Difluoromethylphosphinates (*Tetrahedron* **2010**, *66*, 4434)



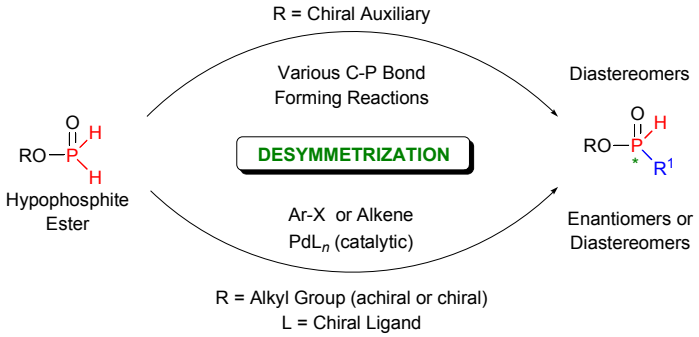
The preparation and reactivity of some α,α-difluorophosphinates is investigated. Alkylation of *H*-phosphinates with LiHMDS and $ClCF_2H$ gives the corresponding α,α-difluorophosphinates in good yield. Deprotonation of these reagents with alkyllithium or LDA is then studied. Subtle electronic effects translate into significant differences in the deprotonation/alkylation of the two "Ciba-Geigy reagents" $(EtO)_2CRP(O)(OEt)H$ (R = H, Me). On the other hand, attempted methylation of difluoromethyl-octyl-phosphinic acid butyl ester resulted in the exclusive alkylation of the octyl chain. Finally, reaction with carbonyl compounds results in the formation of 1,1-difluoro-2-phosphinoyl compounds.

32) Regiocontrol in the Palladium-Catalyzed Hydrophosphinylation of Terminal Alkynes (*J. Organomet. Chem.* **2010**, *in press*)



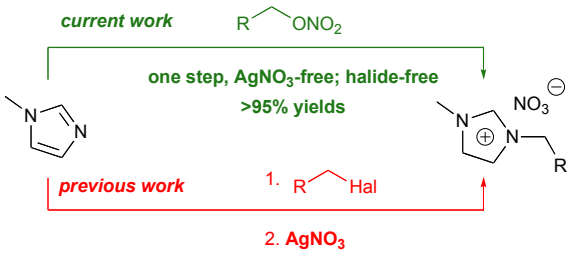
The regioselectivity of the palladium-catalyzed hydrophosphinylation of terminal alkynes was investigated. Complementary conditions to achieve the predominant formation of either the linear or the branched alkenyl-*H*-phosphinate products were identified. With Pd/xantphos in acetonitrile, the linear isomer is generally obtained with good to excellent selectivity, and *E*-stereospecificity. On the other hand, using Pd/dppf in the non-polar solvent toluene, good selectivity for the branched alkenyl-*H*-phosphinate is typically observed. The role of various reaction parameters is studied.

33) Strategies for the asymmetric synthesis of *H*-phosphinate esters (*Org. Biomol. Chem.* **2010**, *in press*)

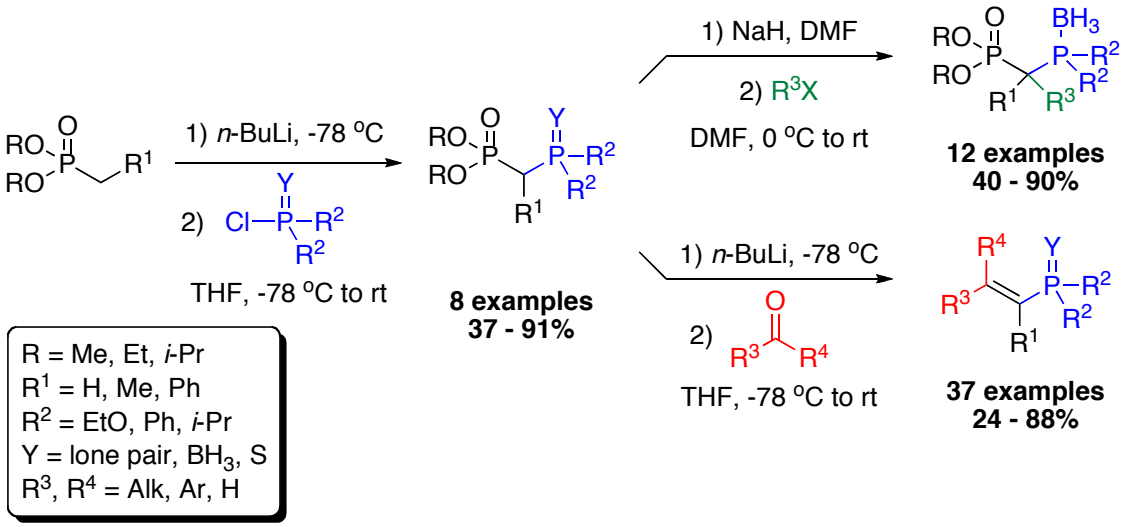


Access to *P*-chiral *H*-phosphinates via desymmetrization of hypophosphite esters was investigated. The use of chiral auxiliaries, chiral catalysts, and of a bulky prochiral group that could lead to kinetic resolution was explored. A chiral NMR assay for enantiomeric excess determination of *H*-phosphinates was developed. An asymmetric route to *C*-chiral *H*-phosphinates is also examined and an assay was developed.

34) Silver nitrate-free synthesis of nitrate-containing room-temperature ionic liquids (*New J. Chem.* **2011**, *35*, 909).

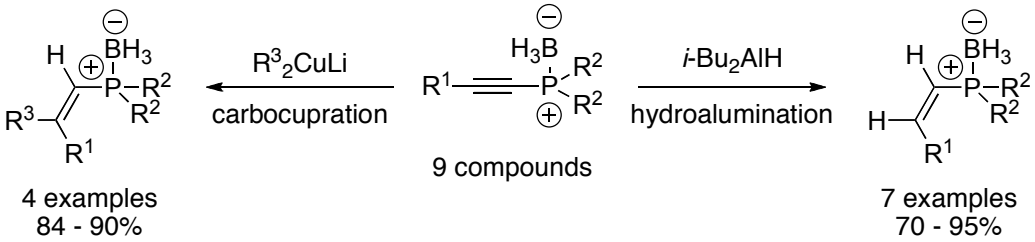


35) Mixed 1,1-Bis-Phosphorus Compounds: Synthesis, Alkylation, and Horner-Wadsworth-Emmons Olefination Reactions (*J. Org. Chem.* **2010**, *75*, 8166).



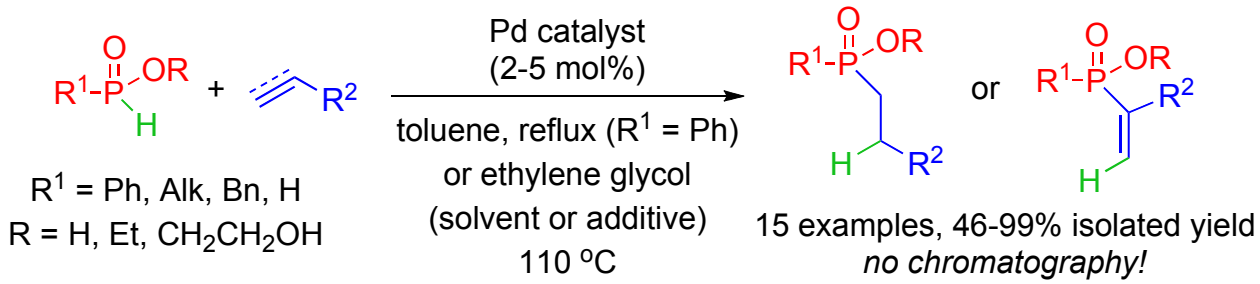
Mixed 1,1-bisphosphorus compounds were prepared by the reaction between a phosphonate diester anion and a P(III) chlorophosphine, or its P(V) borane complex. After deprotonation either *in situ* or in a separate step, the resulting products can be alkylated or reacted with carbonyl compounds. A variety of olefination products were obtained, generally with high *E*-stereoselectivity. The reaction is competitive with other methods for the synthesis of alkenyl phosphorus compounds, and in the case of trisubstituted alkenes, regio- and stereo-controlled olefination provides products not easily accessible via any other process. The deprotection of phosphine-borane adducts was also demonstrated. Overall, a variety of novel organophosphorus reagents and products were synthesized easily and in good yields.

36) Synthesis of *Z*-Alkenyl Phosphorus Compounds Through Hydroalumination and Carbocupration of Alkynyl Precursors (*Org. Lett.* **2011**, *13*, 3134).



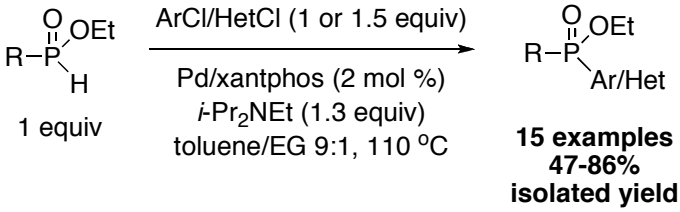
The stereocontrolled synthesis of *Z*-alkenyl phosphine-borane complexes is easily accomplished via the hydroalumination or carbocupration of alkynyl precursors. *Z*/*E* ratios are generally higher than 95/5. These reactions are stereocomplementary to our olefination approach.

37) Synthesis of Disubstituted Phosphinates via Palladium-Catalyzed Hydrophosphinylation of *H*-Phosphinic Acids (*Adv. Synth. Catal.* **2011**, *353*, 1883).



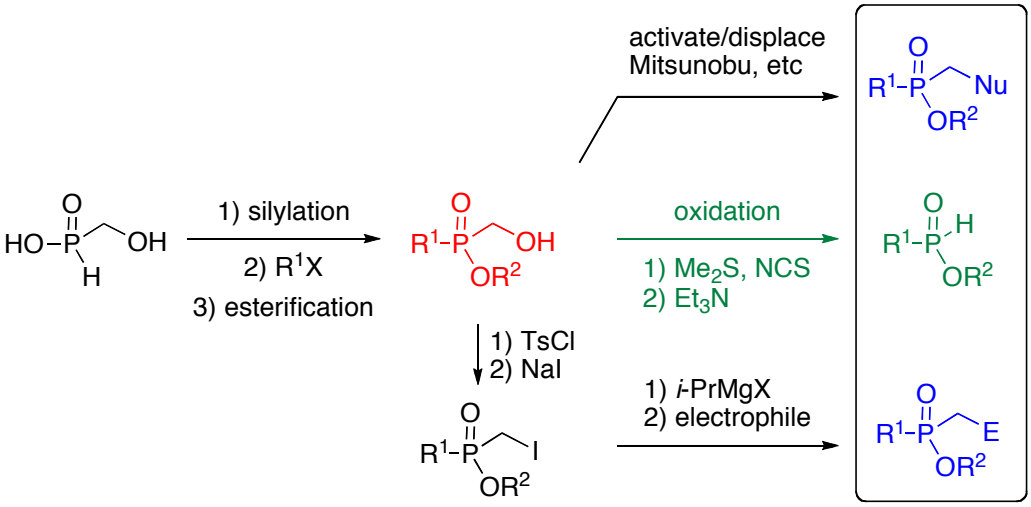
The first metal-catalyzed hydrophosphinylation of unsaturated hydrocarbons with *H*-phosphinic acids is described. A strategy to activate the P-H bond through control of the tautomeric equilibrium using ethylene glycol is described. The reactions also avoid chromatographic purification.

38) Palladium-Catalyzed Cross-Coupling of H-Phosphinate Esters with Chloroarenes (*Org. Lett.* **2011**, *13*, 3270).



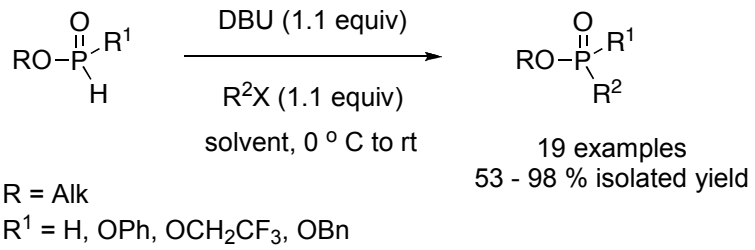
The palladium-catalyzed cross-coupling reaction between *H*-phosphinate esters and chloroarenes or chloroheteroarenes is described. This reaction is the first general metal-catalyzed phosphorus-carbon bond-forming reaction between a phosphorus nucleophile and chloroarenes.

39) Chemistry of the Versatile (Hydroxymethyl)phosphinyl P(O)CH_2OH Functional Group (*Org. Lett.* **2012**, *14*, 3404)



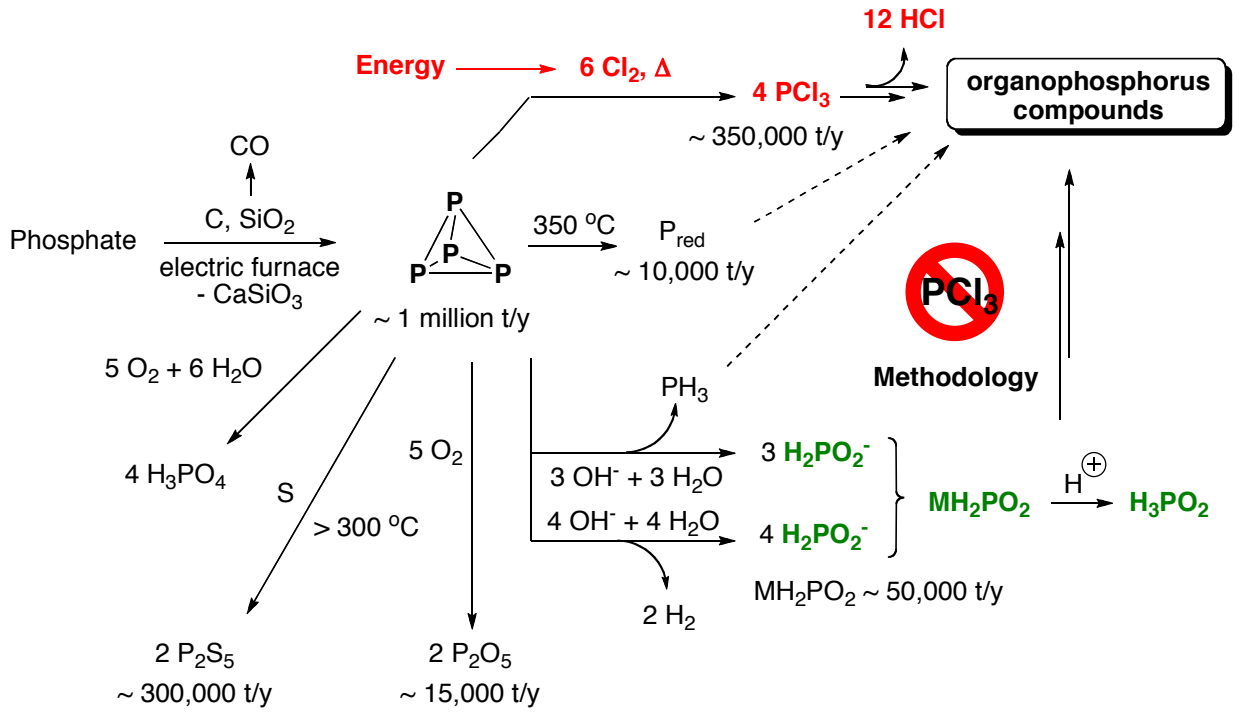
(Hydroxymethyl)phosphorus compounds are well-known and valuable compounds in general, however the use of (hydroxymethyl)phosphinates $R^1P(O)(OR^2)CH_2OH$ in particular has been much more limited. The potential of this functionality has not yet been fully realized because the mild unmasking of the hydroxymethyl group was not available. The mild *oxidative* conversion of $R^1P(O)(OR^2)CH_2OH$ into $R^1P(O)(OR^2)H$ using the Corey-Kim oxidation is described. Other reactions preserving the methylene carbon are also reported.

40) DBU-Promoted Alkylation of Alkyl Phosphinates and *H*-Phosphonates (*Tetrahedron Lett*. **2012**, *53*, 5000)



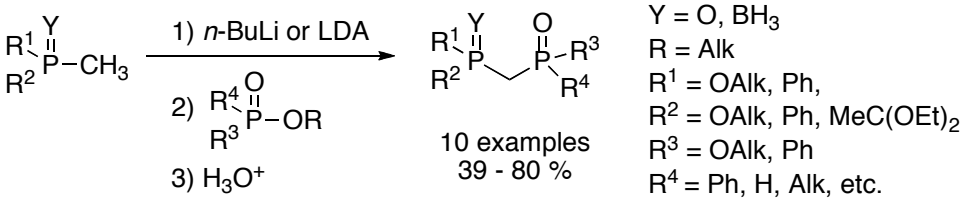
The alkylation of alkyl phosphinates and some *H*-phosphonate diesters is promoted by the base DBU. Only more reactive alkyl halides react in preparatively useful yields. However, the method provides easy access to important *H*-phosphinate building blocks, without the need for a protecting group strategy or metal catalysts. The reaction is conveniently conducted at, or below, room temperature. The preparation of methyl-*H*-phosphinate esters is particularly interesting as it avoids the heretofore more common use of methyldichlorophosphine $MePCl_2$.

41) Organophosphorus Synthesis Without Phosphorus Trichloride: The Case For The Hypophosphorous Pathway (*Phosphorus, Sulfur, Silicon and the Related Elements* **2013**, *188*, 66)



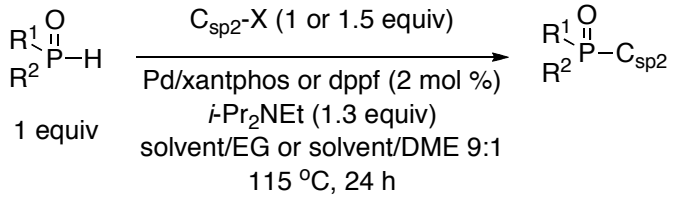
The vast majority of organophosphorus compounds is currently synthesized from phosphorus trichloride (PCl_3), even though the final consumer products do not contain reactive phosphorus-chlorine bonds. In order to bypass phosphorus trichloride, significant interest has been devoted to functionalizing elemental phosphorus (P_4, the precursor to PCl_3), red phosphorus (P_{red}), or phosphine (PH_3). Yet, other industrial scale precursors are hypophosphorous derivatives (H_3PO_2 and its alkali salts), but their use as phosphorus trichloride replacements has been completely overlooked. Here, the case is made for an alternative approach to the industrial synthesis of organophosphorus compounds based on hypophosphites.

42) The Phosphorus-Claisen Condensation (*Tetrahedron Lett*. **2013**, *54*, 817)



1,1-Bisphosphorus compounds are easily synthesized through the phosphorus-Claisen (phospha-Claisen) condensation between a phosphorus-stabilized anion and a phosphorus electrophile. The preliminary scope of this reaction is investigated in terms of employable phosphorus reagents. Valuable intermediates are conveniently prepared in a single step. Overall, the method is competitive with multistep procedures which require the preparation of PCl intermediates derived from the P(OR) reagents we instead employ directly, and it delivers complex organophosphorus compounds in moderate to good isolated yields. An example of the intramolecular version of the reaction, the phospha-Dieckmann condensation, is also reported.

43) Phosphorus-Carbon Bond Formation: Palladium-Catalyzed Cross-Coupling of *H*-Phosphinates and Other P(O)H-Containing Compounds (*Adv*. *Synth*. *Catal*. **2013**, *355*, 1361)

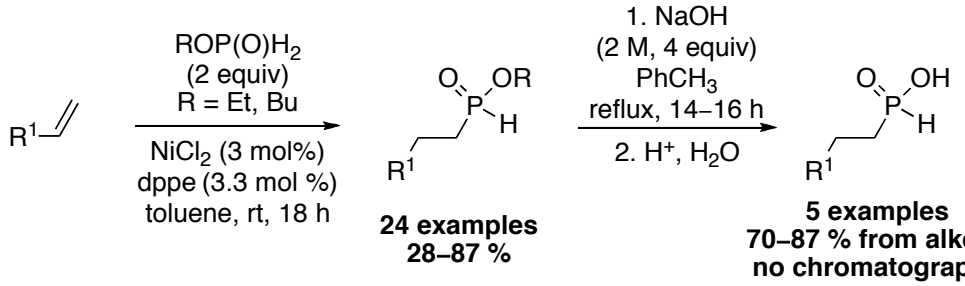


X = I, Br, Cl, OTf

H-phosphinate: R^1 = Alk, Ar; R^2 = OR	**> 30 examples, 55-95 %**
H-phosphonate: $R^1 = R^2$ = OR	**5 examples, 52-87 %**
diphenylphosphine oxide: $R^1 = R^2$ = Ph	**4 examples, 78-96 %**

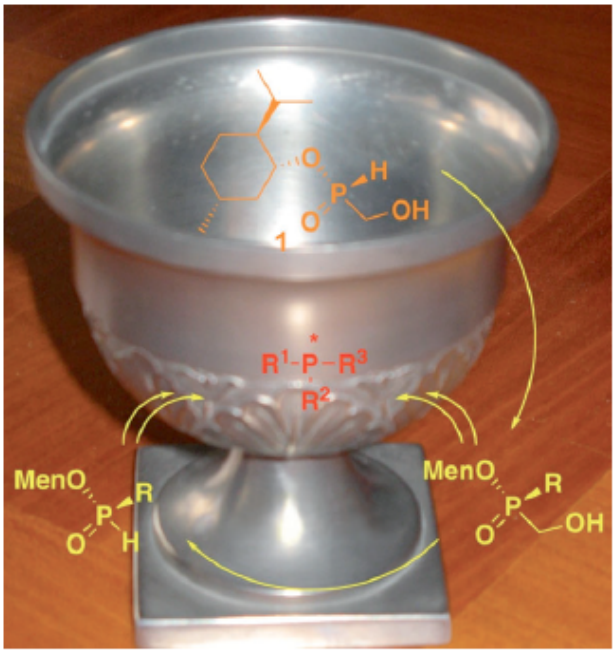
Two generally applicable systems have been developed for the cross-coupling of P(O)-H compounds with C_{sp2}-X and related partners. Palladium catalysis using a ligand/additive combination, typically either xantphos/ethylene glycol or 1,1'-bis(diphenylphosphino)ferrocene/1,2-dimethoxyethane, with diisopropylethylamine as the base, proved to be generally useful for the synthesis of numerous P-C containing compounds. Routinely, 2 mol % of catalyst is employed (less than half the amount typically employed in most other literature reports). In most cases, excellent results are obtained with a variety of electrophiles (RX, where R = alkeny, allyl, alkynyl, etc.). The full account of our studies is disclosed, including tandem hydrophosphinylation/coupling and coupling/coupling for doubly catalytic phosphorus-carbon bond formation. The methodology compares favorably with any existing literature report. The use of an additive appears to be a generally useful strategy to control the reactivity of phosphinylidene compounds.

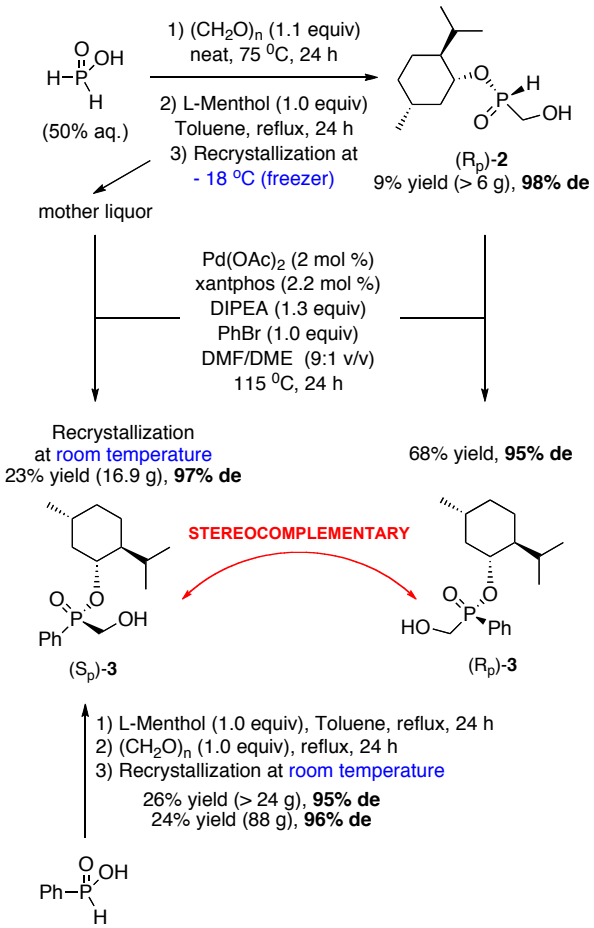
44) Hydrophosphinylation of Unactivated Terminal Alkenes Catalyzed by Nickel Chloride (*J. Org. Chem.* **2013**, *78*, 6599)



The room-temperature hydrophosphinylation of unactivated monosubstituted alkenes using phosphinates ($ROP(O)H_2$) and catalytic $NiCl_2$ in the presence of dppe is described. The method is competitive with prior palladium-catalyzed reactions and uses a much cheaper catalyst and simple conditions. The scope of the reaction is quite broad in terms of unactivated terminal olefins, proceeds at room temperature, often avoids chromatographic purification, and allows one-pot conversion to various organophosphorus compounds

45) A General Strategy for the Synthesis of *P*-Stereogenic Compounds (*Angew. Chem. Int. Ed.* **2013**, *52*, 11377)

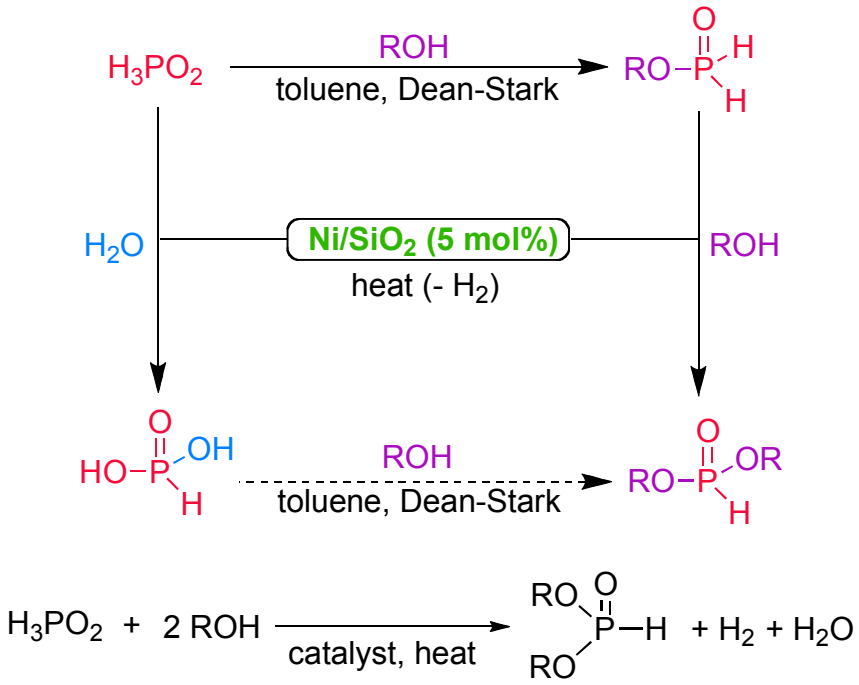




A general solution to the long-standing problem of *P*-chiral synthesis has been found. Heating H_3PO_2 with (-)-menthol and paraformaldehyde gives easily crystallized menthyl (hydroxymethyl)-*H*-phosphinate. From this molecule, virtually any *P*-chiral compound can be synthesized.

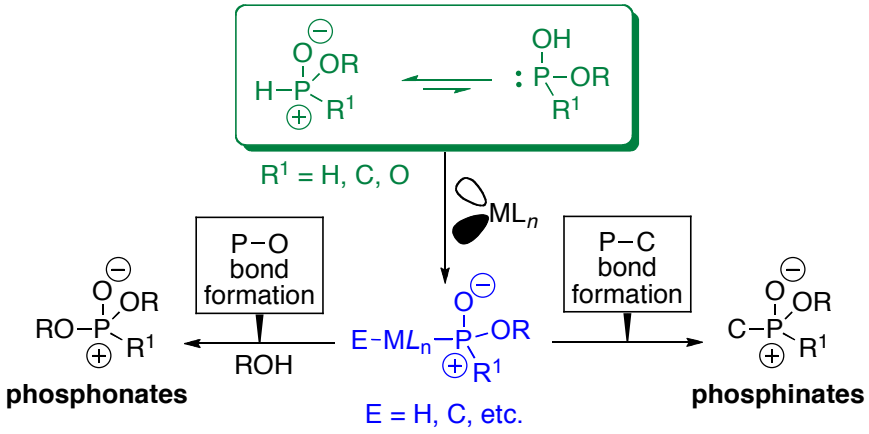
Based on US Patent application on June 7, 2013: US *2013/0331594* Al published Dec. 12, 2013, STREM is now offering two of our compounds: STREM #15-2915, #15-2928 (http://www.strem.com/catalog/v/15-2915/phosphorus, http://www.strem.com/catalog/v/15-2928/phosphorus_1508260-88-5).

46) Organophosphorus Chemistry Without PCl_3: A Bridge From Hypophosphorous Acid to *H*-Phosphonate Diesters (*Eur. J. Org. Chem.* **2013**, 7973)



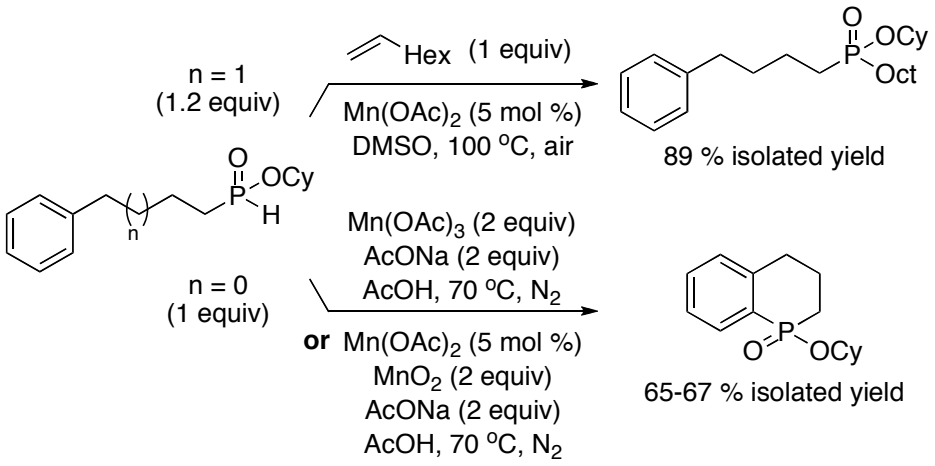
A process for the conversion of hypophosphorous acid (H_3PO_2, HPA) and alcohols into various *H*-phosphonate diesters $(RO)_2P(O)H$ is described. The new reaction provides a missing bridge between HPA and important *H*-phosphonates, completely avoiding PCl_3. Nickel chloride or nickel on silica catalyze the oxidative phosphorylation of alkyl phosphinates with various alcohols or water. The reaction is environmentally benign because it is atom economical and the Ni/SiO_2 catalyst can be reused. The current need for both chlorine and base is completely avoided.

47) Phosphinate Chemistry in the 21st Century: A Viable Alternative to the Use of Phosphorus Trichloride in Organophosphorus Synthesis (*Acc. Chem. Res.* **2014**, *47*, 77)



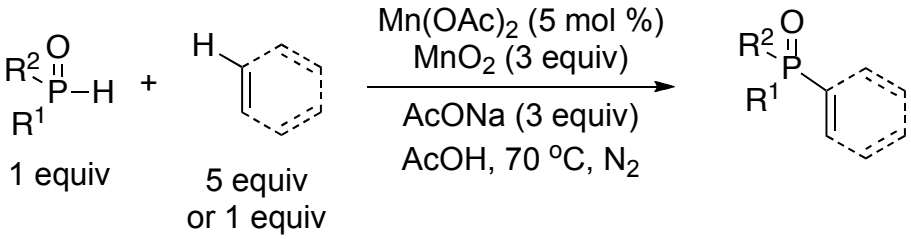
Organophosphorus compounds are important in a variety of everyday applications ranging from flame-retardants, to agriculture and medicine. To date, the most important industrial organophosphorus compounds have a phosphorus atom bonded to three oxygens (phosphonates, *H*-phosphonate diesters, and phosphite triesters) or to four oxygens (phosphate triesters). The vast majority of organophosphorus compounds (defined herein as containing a phosphorus-carbon bond) are currently manufactured through the intermediacy of phosphorus trichloride (PCl_3). However, the avoidance of phosphorus trichloride has become a significant area of research to improve sustainability and safety, as well as to decrease energy consumption and waste formation. Two major strategies based on elemental phosphorus (P_4 or P_{red}) or on phosphine (PH_3) have attracted considerable attention as ways to circumvent PCl_3. This account discusses the heretofore neglected potential of phosphinates, especially that of their simplest members: the already industrially relevant hypophosphites ($H_2P(O)(OR)$) as replacements of PCl_3 for the preparation of organophosphorus compounds. Phosphinates are an important class of phosphorus compounds defined as any compound with a phosphorus atom attached to only two oxygens: $R^1R^2P(O)(OR)$ (R^1/R^2 = hydrogen/carbon). Hypophosphites offer many advantages over other proposed PCl_3-surrogates, in terms of stability, toxicity, solubility, and atom economy. Based on their strong reducing properties, hypophosphites are currently used industrially (~50,000 metric tons per year) for electroless plating. These compounds are also excellent precursors to organophosphorus compounds, if their reducing power is harnessed in order to form phosphorus-carbon or phosphorus-oxygen bonds. The chemistry of phosphinates is rich and versatile, even more so since recent advances that have been made in the author's laboratory. This article examines the potential of phosphinates to replace PCl_3 in the formation of the major organophosphorus functionalities. Particular attention is placed on transition metal-catalyzed reactions such as cross-coupling and hydrophosphinylation for phosphorus-carbon bond formation, and controlled transfer hydrogenation for phosphorus-oxygen bond formation. The article hopes to promote research in this novel and exciting, yet much underdeveloped area, which could be coined "phosphinate activation".

48) Manganese-Catalyzed and Promoted Reactions of *H*-Phosphinate Esters (*Adv. Synth. Catal.* **2014**, *356*, 1199)



H-Phosphinates react with alkenes and alkynes using catalytic manganese(II) acetate. Under stoichiometric conditions with manganese(III) acetate or with catalytic manganese(II) acetate + excess manganese(II) oxide various reactions like arylation or cyclization through radical oxidative arylation can take place. Whereas the chemistry of manganese is already well developed for the functionalization of *H*-phosphonates, the present methodology provides an unprecedented access to functionalized phosphinates in acceptable to good yields.

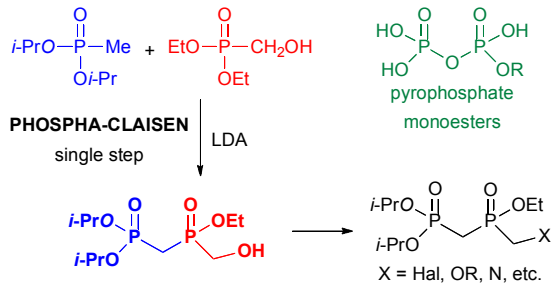
49) Manganese-Mediated Intermolecular Arylation of *H*-Phosphinates and Related Compounds (*Chem. Eur. J.* **2014**, *20*, 12385)



H-phosphinates: R^1 = C, R^2 = O, 27 examples: 37 - 97 % yield
diphenylphosphine oxide: R^1 = R^2 = Ph, 6 examples: 40 - 96 % yield
H-phosphonates R^1 = R^2 = O, 5 examples: 37 - 94 % yield

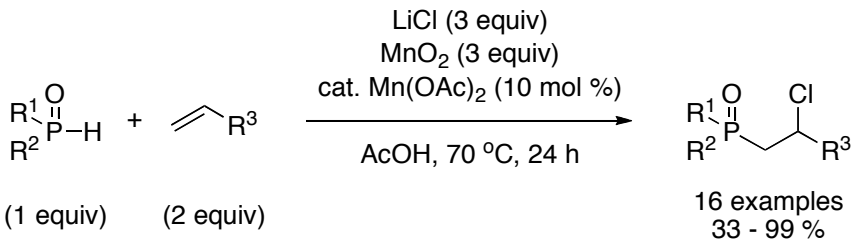
The intermolecular radical functionalization of arenes with aryl and alkyl H-phosphinate esters, as well as diphenylphosphine oxide and H-phosphonate diesters is described. The novel catalytic Mn(II)/excess Mn(IV) system is a convenient and inexpensive solution to directly convert C_{sp2}-H into C-P bonds. The reaction can be employed to functionalize P-stereogenic H-phosphinates since it is stereospecific. With monosubstituted aromatics, the selectivity for para-substitution increases in the order $(RO)_2P(O)H < R^1P(O)(OR)H < Ph_2P(O)H$, a trend that may be explained by steric effects.

50) Synthesis of (phosphonomethyl)phosphinate pyrophosphate analogues via the phospha-Claisen condensation (*Org. Biomol. Chem.* **2015**, *13*, 825)



Pyrophosphate analogues are of great importance especially for the design of biologically active molecules. The Phospha-Claisen condensation allows for the rapid synthesis of (phosphonomethyl)phosphinate pyrophosphate analogues and building blocks that can be employed in numerous applications.

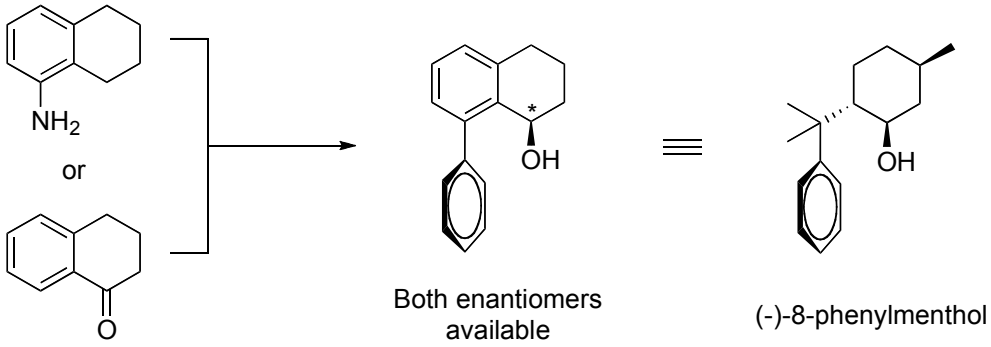
51) Manganese-Mediated Alkene Chloro-Phosphinoylation (*Tetrahedron Lett.* **2015**, *56*, 3197)



The Mn(II)/Mn(IV) system was used to achieve the bisfunctionalization of alkenes with phosphorus and chlorine in moderate to good yields. A variety of phosphinylidene-containing (P(O)H) compounds were

examined. When the phosphorus reagent is limiting, the reaction yield is generally in the 40-50 % range, although the structure of the organophosphorus starting material greatly influences it. The reaction is simple and inexpensive and the β-chloro-phosphinoyl products are versatile intermediates. For example, elimination with DBU gave the corresponding α,β-unsaturated phosphorus compound stereoselectively.

52) Development of a New Family of Chiral Auxiliary (*Org. Lett.* **2015**, *17*, 1819)



A new family of chiral auxiliaries designed on a conformationally restricted version of (-)-8-phenylmenthol has been developed. Both enantiomers are available from an inexpensive synthesis conducted on multigram scale. A first application has showed comparable diastereoselectivity between the novel auxiliary and (-)-8-phenylmenthol.