Conference paper

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Challenges and solutions in phosphinate chemistry

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Abstract: Several major challenges still remain in organophosphorus chemistry. Organophosphorus compounds are currently synthesized from phosphorus trichloride (PCl_3), even though the final consumer products (such as pesticides, flame-retardants, extractants) 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, phosphinates (ROP(O)H_2) are already available on an industrial scale and are the most environmentally benign, but their use as phosphorus trichloride replacements has been completely overlooked until a few years ago. An overview of some of the methodologies developed in my laboratory for P–C and P–O bond-forming reactions through phosphinate chemistry, as well as some selected applications, are presented. Another significant challenge remains the synthesis of *P*-stereogenic compounds. My group's recent progress in this area is also discussed. Based on menthol as an inexpensive chiral auxiliary, various menthyl phosphinates can be synthesized. These phosphinates are precursor to *P*-stereogenic phosphines through well-established literature transformations.

Keywords: asymmetric synthesis; ICPC-22; organophosphorus chemistry; phosphinate; phosphorus trichloride; synthetic methods; tautomerism.

Introduction

In spite of phosphorus chemistry being an old and well-established area, tremendous progress continues to be made, as was seen during the 22nd ICPC conference. Nonetheless, significant problems and challenges remain. In this paper, several challenges will be discussed and some solutions provided. Perhaps the most challenging of all problems remains the realm of industrial chemistry of phosphorus: the need for more economical and environmentally responsible stewardship and recycling of phosphorus.

The spelling of the word phosphorus

During various lectures, manuscript reviews, and sometimes even reading already published works, I have noticed an increasing number of misspelling of the word phosphorus. In some cases, authors are trying to hedge their bet by peppering in their manuscript the word spelled both incorrectly and correctly.

The element is ALWAYS spelled phosphorUS. PhosphorOUS is only employed to describe a lower oxidation state of phosphorus: phosphorous acid = $(HO)_2P(O)H$ and hypophosphorous acid = $HOP(O)H_2$. Sulfurous

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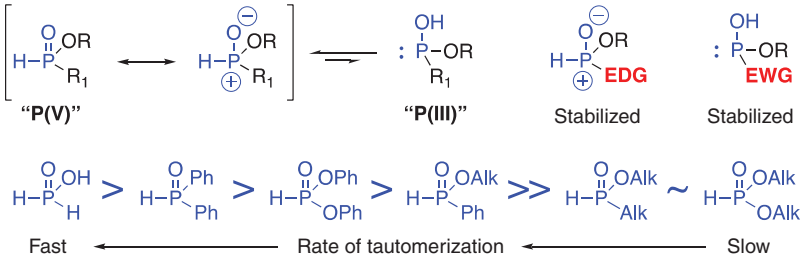
similarly denotes a lower oxidation state of sulfur, but of course here there is no confusion because there is a clear pronunciation difference between sulfurous and sulfur. Phosphorous is also not a British English spelling. Most of these issues are already discussed in Hairston Jr.'s excellent letter to nature [1]. Let us try to eradicate the misspelling of phosphorus once and for all! This problem has a simple solution.

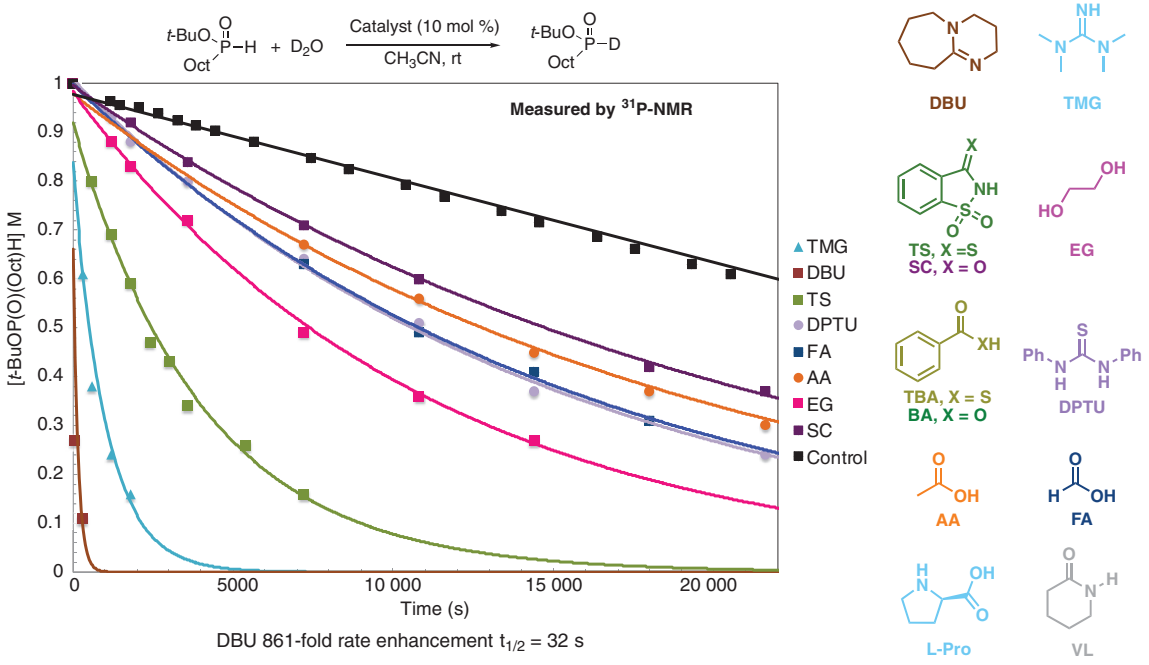
The P(=O)H to P–OH tautomeric equilibrium

A few years ago, with my colleague Ben Janesko, I published a combined experimental and theoretical study of the prototropic tautomerism, which exists in compounds containing a P(O)H moiety [4]. The P(=O)H form is customarily referred to as P(V) whereas the P(–OH) form as P(III). In other words, in this case the numbers do not correspond to oxidation states but simply to the number of bonds around phosphorus. Of course, both tautomers are in the same oxidation state: for *H*-phosphonate diesters $(RO)_2P(O)H$ +3.

As may be expected, the consideration of very simple electronic effects is sufficient to rank the various compounds: electron-donating groups (EDG) will stabilize the phosphonium ion while electron-withdrawing groups will delocalize/stabilize the lone pair (Scheme 1). In almost all cases, the so-called P(V) form is very major even in the presence of a P(III)-stabilizing EWG. At any rate, an experimental/computational ranking of various compounds was made [4]. The important lesson is that there is a very large difference in equilibrium



Scheme 1: Not all phosphinylidenes [2, 3] are created equal: tautomeric equilibrium.



Scheme 2: Catalysis of the tautomeric equilibrium in *tert*-butyl octyl-*H*-phosphinate.

between various phosphinylidenes [2, 3] $R^1R^2P(O)H$ (secondary phosphine oxides SPOs, *H*-phosphinates, *H*-phosphonates) and authors should not make claims for all these classes of compounds, when, for example, only $Ph_2P(O)H$ is tested. Furthermore, even within the same class, striking differences exist: indeed $Ph_2P(O)H$ tautomerizes rapidly whereas $Bu_2P(O)H$ does not. Thus, authors are urged to either try various phosphinylidene compounds or to not make broad claims if only one compound is tested.

Since the vast majority of the reactions of P(O)H compounds involves the P(III) form (exceptions are reaction with a very strong base and silylation) the ability to access the P(III) tautomer is key. Thus, I became interested in investigating the catalysis of this tautomeric equilibrium. Again, good agreement between experimental measurements and computational studies was obtained. Experimentally, a *tert*-butyl group was chosen to avoid the nucleophilic dealkylation of the ester.

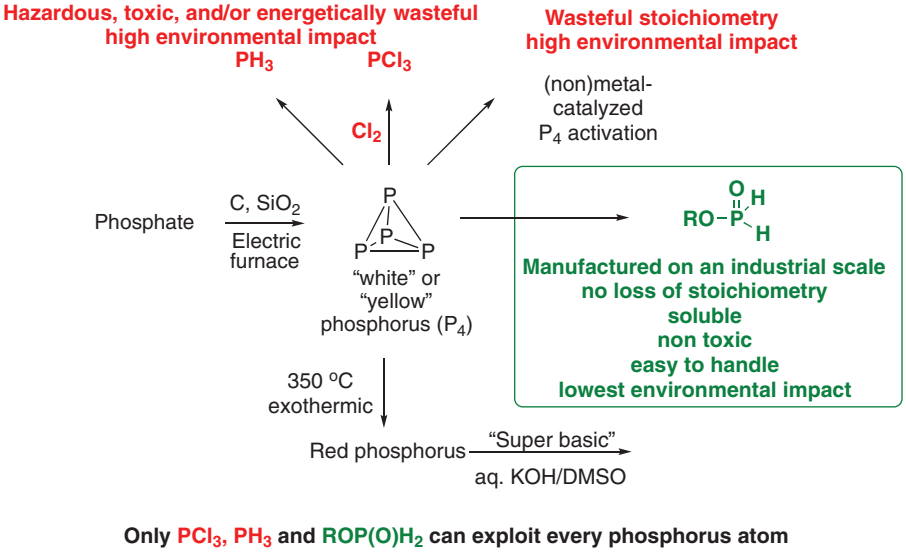
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,1,3,3-tetramethylguanidine (TMG), the stronger bases tested in our screen were powerful catalysts (Scheme 2). Interestingly, neutral thiosaccharin (TS) was a good catalyst. A study of $(t\text{-BuO})_2P(O)H$ gave similar results although thiosaccharin was much less successful there.

It was previously known [5] that DBU was a superior base to accomplish the alkylation of various phosphinylidenes, which tautomerize more easily. Thus, *H*-phosphonate diesters $(PhO)_2P(O)H$, and $(BnO)_2P(O)H$ could be alkylated, whereas $(EtO)_2P(O)H$ was unreactive, correlating with their half-lives of deuteration of 5.2 min, 4.1 h, and 21 h, respectively [5].

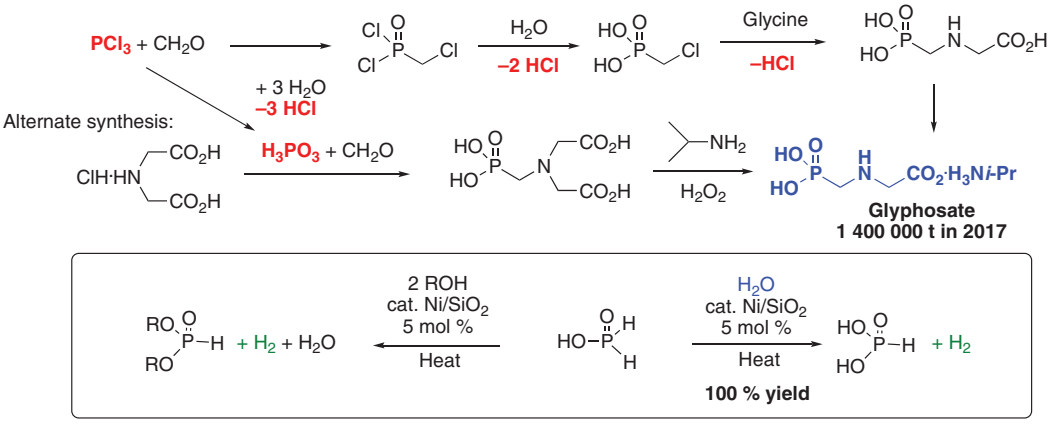
Avoiding the use of chlorine and phosphorus trichloride

Avoiding chlorine in the manufacture of organic phosphorus compounds via phosphorus trichloride has been a goal for some time (Scheme 3). The production of chlorine is energy demanding (~3 MW/t). Chlorine is also a toxic gas that has been involved in various transportation accidents, not to mention in chemical warfare. Various approaches have been envisioned in order to avoid Cl_2 and PCl_3: (1) "P_4-activation" [6–13], (2) red phosphorus [14, 15], (3) PH_3 [16], and (4) hypophosphorous derivatives $ROP(O)H_2$ [17, 18]. The latter approach being the one my laboratory has chosen.

The P_4-activation strategy (Scheme 3) is based on the fact that P_4 is currently the obligatory intermediate (850 000 t/year) for the preparation of PCl_3 and derived organophosphorus compounds, although less than 5% of P_4 is used for this purpose. Additionally, the P_4-tetrahedron is very reactive. In my opinion, however, this general approach suffers from a number of drawbacks. First, P_4 is insoluble in virtually everything except carbon disulfide, a solvent which, although used industrially, is highly flammable. Second, the reactivity of P_4 drops



Scheme 3: PCl_3 and its alternatives.



Scheme 4: The *H*-phosphinate to *H*-phosphonate bridge and PCl_3-free glyphosate synthesis.

with each bond broken as the strain is relieved more and more, making it difficult to incorporate all the phosphorus atoms into the product. Third, P_4 is not only pyrophoric but also very toxic (LD_{50} human/oral = 1.4 mg/kg) [19], more toxic than sodium cyanide (LD_{50} rat/oral = 6.4 mg/kg)! [20].

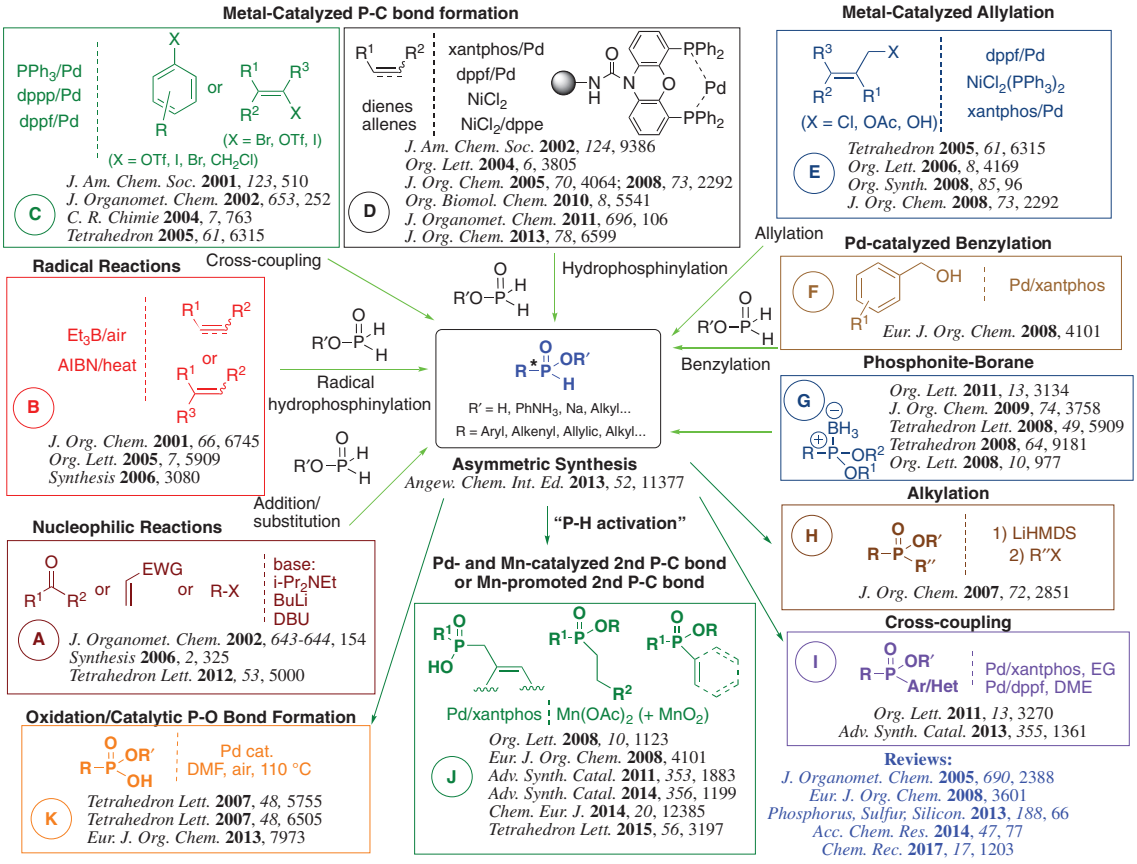
Red phosphorus (~10 000 t/year) is considerably safer than P_4. However, two disadvantages remain: insolubility and the difficulty in incorporating all atoms of phosphorus into a product. Typically red phosphorus is used under superbasic conditions (KOH/DMSO).

Phosphine (PH_3) is a highly toxic gas (this property is used to kill rodents – LD_{50} rat/1 h inhalation = 22 ppm) [21] that may be pyrophoric if impure. Still, PH_3 is already used industrially for the manufacture of tertiary phosphines (R_3P) or tetra(hydroxymethyl)phosphonium salts. The main advantage is that its reactions involve only one phosphorus atom.

Hypophosphorous derivatives (phosphinates, $ROP(O)H_2$) are already produced industrially (~50 000 t/year), especially sodium hypophosphite and calcium hypophosphite [8]. They are currently manufactured as reducing agents for a single application called electroless plating (Kanigen process). The hypophosphite salts are prepared through "P_4-activation", namely alkaline hydrolysis (Scheme 3). The reaction is complex, in all likelihood because of solubility problems with P_4, as it also produces PH_3 and some hydrogen. Aside from the fact that phosphinates are already available on a large scale, several advantages exist over other possible PCl_3 replacements. Sodium hypophosphite and hypophosphorous acid are soluble in water, glycerol, ethylene glycol and lower alcohols. As with PH_3 and PCl_3 only one atom of phosphorus must be transferred. Importantly, phosphinates are not toxic ($NaOP(O)H_2$ LD_{50} rat/oral = 7.6 g/kg [22]; 50 % aqueous $HOP(O)H_2$ LD_{50} rat/oral > 90 g/kg) [23] and in fact, several hypophosphites are listed as Generally Recognized as Safe (GRAS), with sodium hypophosphite approved as a food additive [24]. Therefore, phosphinates are arguably the best already existing replacement for PCl_3. The main use of PCl_3 (~50 %) is for the manufacture of the herbicide glyphosate, of which ~1.4 million tons were produced in 2017. Thus, any potential PCl_3-replacement should be able to be used for making glyphosate. My approach to create the bridge between phosphinates and glyphosate relies on the nickel-catalyzed conversion of hypophosphorous acid into phosphorous acid and *H*-phosphonate diesters (Scheme 4) [25]. Hypophosphorous acid is a strong enough reducing agent to reduce water to hydrogen in the presence of a nickel catalyst. Since glyphosate has been manufactured from phosphorous acid our approach constitutes a chlorine-free alternative to the use of PCl_3.

Synthetic methodologies in organophosphorus chemistry

Over the past 20 years, my laboratory has invented and developed a number of reactions for the synthesis of phosphinates (Scheme 5) [26]. Initially, reactions employed hypophosphorous acid derivatives (phosphinates) as starting materials to prepare *H*-phosphinates. As a result, a portfolio of synthetic methods has been



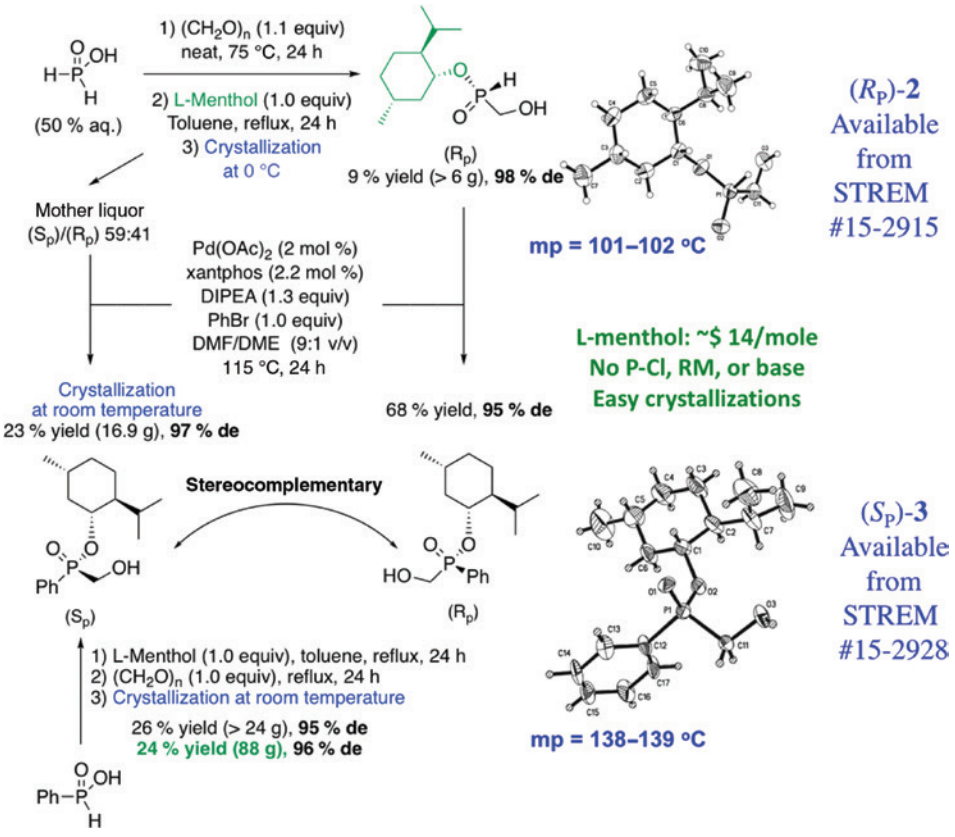
Scheme 5: Various methodologies for P–C and P–O bond-formation from the Montchamp laboratory [17, 18, 26].

assembled including palladium-catalyzed cross-couplings with (hetero)aryl halides (including chlorides) and benzylic and allylic alcohols, and addition to unactivated alkenes and alkynes using palladium- and nickel-catalyzed or radical-initiated processes. This topic was reviewed in 2014 [17]. Since *H*-phosphinates are less reactive than hypophosphorous derivatives, the reactions could stop cleanly there. Subsequently, I became interested in the second P–C bond-forming reaction of *H*-phosphinates to form disubstituted phosphinates. Since these reactions are generally more difficult than when hypophosphite derivatives are employed, conditions are more forcing (higher temperature, use of a drying agent) and the catalyst loadings are also higher (typically 2 mol% palladium).

Recently, focus shifted away from palladium and nickel, to manganese and the free-radical arylation of phosphinylidenes [27–29]. Many oxidation states of manganese are available and inexpensive. But a significant exception is manganese triacetate $Mn(OAc)_3 \cdot 2H_2O$, which is often employed in the free-radical arylation reactions of *H*-phosphonates [30], but it costs 1000 $/mol and typically 2–3 equivalents are used [31]. My laboratory's alternative system [27–29, 31] is 5 mol% $Mn(OAc)_2$ and excess (2–3 equiv) MnO_2. This generally gives comparable or better results than Mn(III) but it costs 100 times less. In order to be able to compare various synthetic methodologies, we have introduced the concepts of Cost of Academic Methodologies (CAM) and aggregate molecular weight (AMW). The details will be reported elsewhere.

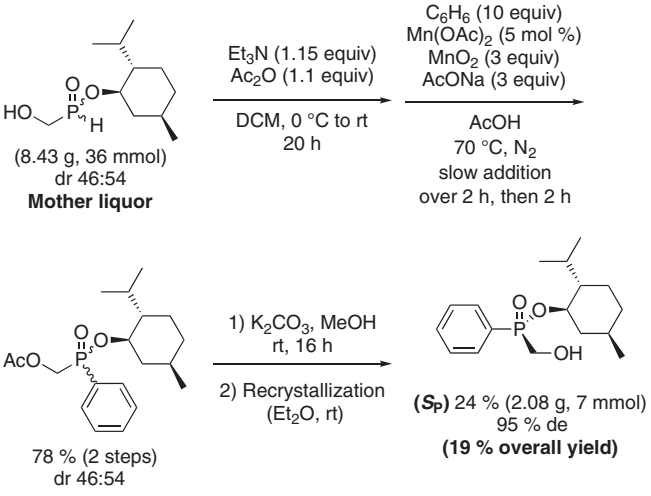
Menthyl phosphinates as *P*-stereogenic building blocks

In keeping with our initial goal of using hypophosphites in the place of PCl_3, a synthesis of *P*-stereogenic compounds was devised from H_3PO_2 (Scheme 6) [32, 33]. Hypophosphorous acid is heated with paraform-



Scheme 6: *P*-Chirogenic menthyl phosphinates and X-ray crystal structures.

aldehyde to form (hydroxymethyl)-*H*-phosphinic acid as an intermediate, which is then esterified with menthol using a Dean-Stark trap. This one-pot reaction delivers $HOCH_2P(O)(OMen)H$ as a mixture of diastereoisomers. Crystallization at 0 °C or in a freezer provides one isomer in good purity (98 % de). The absolute stereochemistry at phosphorus was established by X-ray crystallography. However, the yield is low (around 10 %). In order to obtain more material, the leftover mother liquor undergoes a palladium-catalyzed cross-



Scheme 7: Replacing the Pd-catalyzed cross-coupling by the Mn-promoted arylation to convert the mother liquor (mixture of diastereoisomer) into $PhP(O)(OMen)CH_2OH$.

coupling to form $PhP(O)(OMen)CH_2OH$, which crystallizes easily in about 20–25 % yield and >95 % de. Thus, approximately a total 30–35 % of the starting H_3PO_2 becomes a useful *P*-stereogenic product, and without the use of PCl_3, Grignard reagents, etc. Initially, the mother liquor underwent our palladium-catalyzed cross-coupling (Scheme 6), but later on the more economical manganese-promoted arylation chemistry was used instead (Scheme 7) [27].

Acetylation of $HOCH_2P(O)(OMen)H$ is necessary because $P(O)CH_2OH$ is not compatible with the free-radical manganese chemistry. After arylation and cleavage of the acetate, $PhP(O)(OMen)CH_2OH$ is crystallized as before. Acetylation and deacetylation add extra steps but those are high yielding. In the end a recovery of 19 % from the mother liquor [27], whereas it was 23 % for the palladium-catalyzed cross-coupling (Scheme 6) [32, 33].

The overall success of this approach to menthyl phosphinates relies on two results: (1) (hydroxymethyl) phosphinates are much more easily handled and crystallized than other phosphinates, and (2) the hydroxymethyl moiety of $P(O)CH_2OH$ can be cleaved stereospecifically to unmask a P(O)H through Corey-Kim oxidation. Taken together, our approach delivers menthyl phosphinates conveniently and inexpensively. Efforts to improve the chemical yield of $HOCH_2P(O)(OMen)H$ are currently underway.

Conclusion

Many challenges remain in organophosphorus chemistry. My laboratory has invented several reactions in order to convert hypophosphorous acid and its derivatives into compounds containing new P–O and P–C bonds. In some cases, the current industrial intermediacy of PCl_3 could be avoided and hypophosphorous derivatives be used instead. Another challenge is the synthesis of *P*-stereogenic compounds. There, good progress has been made although further improvements are desirable.

One of the most important challenges in phosphorus chemistry that was not discussed in this paper is the recycling of phosphorus and the avoidance of elemental phosphorus.

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