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# Phosphonium Coupling in the Direct Bond Formations of Tautomerizable Heterocycles via C–OH Bond Activation

**Fu-An Kang,*[a] Zhihua Sui,[a] and William V. Murray[a]**

*Dedicated to Professor Xiao-Tian Liang on the occasion of his 85th birthday*

**Keywords:** Phosphonium coupling / Phosphonium salts / Direct bond formation / C–OH bond activation / Nucleosides / Tautomerizable heterocycles

Since the original report in 2004, phosphonium coupling has emerged as a new, mild, efficient, chemoselective and versatile methodology for the direct C–C, C–N, C–O, and C–S bond formations of *unactivated and unprotected* tautomerizable heterocycles. Phosphonium coupling proceeds via C–OH bond activation of a tautomerizable heterocycle with a phosphonium salt (e.g., PyBroP), and subsequent functionalization with either a nucleophile through $S_NAr$ displacement or an organometallic through transition-metal-catalyzed cross-coupling. As the first direct bond formation via C–OH bond activation, phosphonium coupling offers a powerful and practical methodology that features operational simplicity, functionality compatibility, and broad substrate scope. Its attractive protecting-group-free direct bond formation involving a domino multiple-step process in a single step provides unique and facile access to many biologically important heterocycles including macromolecules with sensitive functionalities (e.g., DNA, RNA and PNA building blocks). Consequently, the discovery of phosphonium coupling has finally enabled a single-step transformation in nucleoside chemistry, which has been an unsolved synthetic challenge in the past half-century.


## 1. Introduction

### 1.1. Traditional Cross-Couplings vs. Direct Bond Formations

In the art and practice of organic synthesis, chemical bond formations that create new C–C, C–N, C–O and C–S bonds play a central role in the construction of simple and complex molecules.[1] Biaryl molecules (Ar–Ar) and carbon or heteroatom linked biaryl molecules (Ar–Y–Ar) have become increasingly important templates and building blocks for material and life sciences.[2] Transition metal-catalyzed cross-couplings of arenes or heterocycles (Ar–H) via C–C (arylation), C–N (amination), C–O (etherification), and C–S (thioetherification) bond formations leading to Ar–Ar and Ar–Y–Ar have proven to be exceedingly valuable processes in contemporary organic synthesis.[3] Representative methodologies in the modern chemical technology toolbox related to this field have become name reactions, such as Kumada, Heck, Sonogashira, Negishi, Stille, Suzuki–Miyaura, Nozaki–Hiyama–Kishi, Hiyama, Buchwald–Hartwig, and Fukuyama coupling reactions. Traditional cross-coupling reactions involve the coupling of activated Ar–H (Ar–X), metalated Ar–H (Ar–M) or functionalized Ar–H (Ar–Y) (Scheme 1). Preparation of these coupling partners usually requires multiple steps including protection and deprotection of sensitive functional groups. This generates waste from reagents, solvents, and purification.

Direct bond formations, i.e., direct arylation, amination, etherification, and thioetherification, are new types of cross-couplings between *unactivated and unprotected* substrates and one of the traditional coupling partners (Ar–X, Ar–M or Ar–Y). In recent years, development of direct bond formation technologies has received considerable attention from the synthetic chemistry community, as they have become highly attractive alternative approaches to traditional cross-coupling methods in terms of efficiency, economy and environmental impact. Among these, direct arylation[4] and direct amination[5] of Ar–H via C–H bond activation are the most extensively explored reactions. These reactions utilize directing groups, steric interactions, electron-rich substrates or C–H bond acidity through the coupling of Ar–H with Ar–X, Ar–M or Ar–Y.

Ar–H and Ar–OH are both synthetic precursors of Ar–X. Like Ar–H, Ar–OH are widely available as arenols and tautomerizable heterocycles. Although direct bond formations of Ar–H via C–H bond activation have enjoyed explosive growth in the past several years, direct bond forma-

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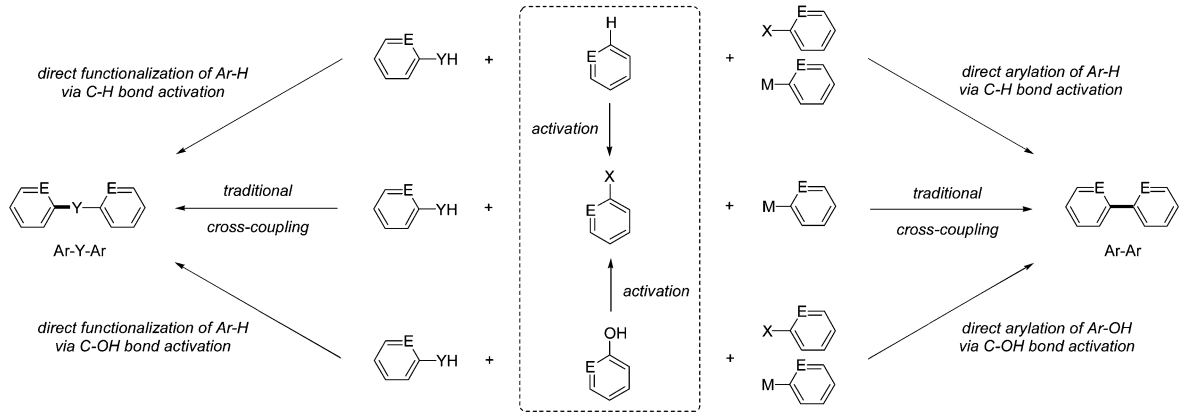


Ar-X: X = F, Cl, Br, I, $OSO_2R$, $OPO(OR)_2$; Ar-M: M = $B(OR)_2$, $SnR_3$, $SiR_3$, MgX, ZnX; Ar-Y: Y = C, N, O, S; E = N, C

Scheme 1. Traditional cross-couplings vs. direct bond formations.

tions of Ar–OH via C–OH bond activation, either catalytically or stoichiometrically, has remained largely undescribed. Direct arylation of aryl methyl ethers and direct alkylation of benzyl methyl ethers via C–OMe bond activation have been accomplished recently.[6] An advantage of direct bond formations of Ar–OH is that the C–OH bond activation and functionalization is regiospecific, while direct bond formations of Ar–H via C–H bond activation and functinalization is known to suffer from overfunctionalization or regioselectivity issues.[7]

### 1.2. Tautomerizable Heterocycles

More than half of the molecules produced by nature have heterocyclic rings incorporated into their structures, such as vitamins, hormones, antibiotics and alkaloids.[8] Many commercial therapeutic molecules are also derived from heterocyclic scaffolds. Therefore, as key building blocks in pharmaceutical research, heterocycles as well as their related bond formations have continued to be important subjects in organic chemistry.

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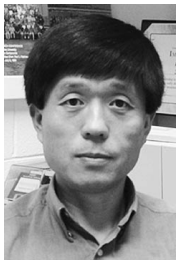

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*Bill Murray received his Ph.D. degree with Professor Francis Johnson at the State University of New York at Stony Brook. After a Postdoctoral Fellowship in Chemistry with Professor George Buchi at MIT, he joined Johnson & Johnson in 1980 as a synthetic organic chemist. He spent most of his career in drug discovery and process chemistry. During his career at J&J, he has held positions of increasing responsibility in medicinal chemistry, and chemical and pharmaceutical development. He has worked in numerous therapeutic areas including inflammation, cardiovascular, hematology, oncology and urology. His present role is Vice President of Chemistry for the East Coast Research and Early Development unit of J&J Pharmaceutical Group. He is author of over 80 refereed publications and inventor on over 50 issued US patents. He has also given many invited lectures in the areas of Synthetic Organic and Medicinal Chemistry.*

One of the basic approaches to prepare heterocyclic compounds relies on bond formations of readily available tautomerizable heterocycles. Tautomerization (or tautomerism) is defined as a phenomenon in which two or more molecular structures exist in a dynamic equilibrium with each other, where the energy barrier between them is usually small.[9] Tautomerizable heterocycles are mainly six-membered heterocycles that contain one or more nitrogen atoms, and possess the common interconvertible structural units, [–C(=O)–NH–] (lactam or keto form) ↔ [–C(–OH)=N–] (phenol or enol form) (Figure 1). Most tautomerizable heterocycles exist almost exclusively in the lactam form in solution as well as in solid state, as indicated by spectroscopic characterization and X-ray crystallography.[9] Tautomerization of the lactam form to the phenol form appears to be favored in the gas phase.[9] Since the nitrogen atom is more electronegative than the carbon atom, tautomerizable heterocycles are known to be electron-deficient systems.[8]

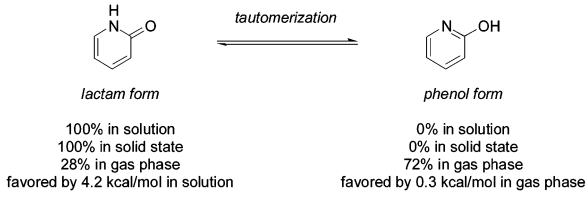



Figure 1. Lactam and phenol forms of tautomerizable heterocyles.

Tautomerizable heterocycles are ubiquitous in nature. As important building blocks of DNA and RNA, most of the nucleobases, nucleosides, and nucleotides contain tautomerizable heterocycles (Figure 2). In addition, tautomerizable heterocycles also exist in natural products, pharmaceuticals, biologicals and chemical building blocks.[10]

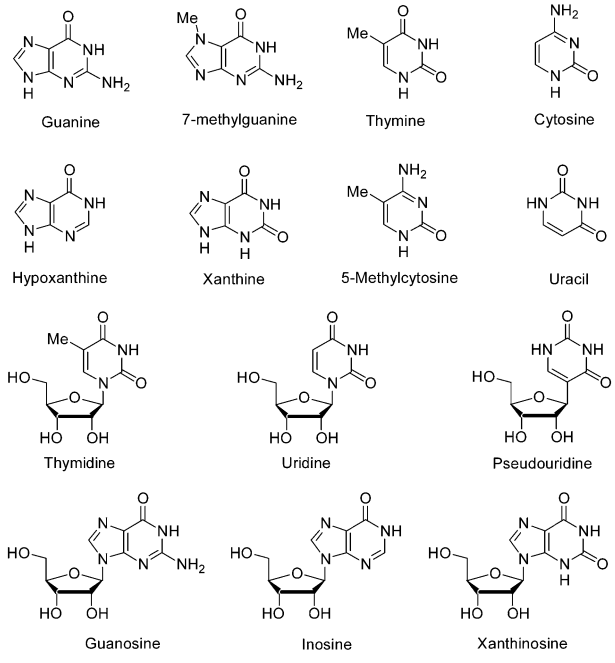
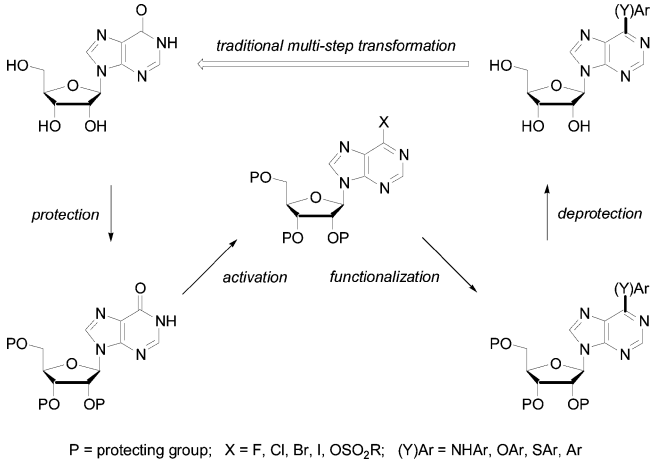



Figure 2. Tautomerizable heterocycles in nucleobases and nucleosides.

## 1.3. Traditional Bond Formations of Tautomerizable Heterocycles

Transformation of tautomerizable heterocycles to aromatic heterocycles via C–C, C–N, C–O, and C–S bond formations has been a basic and reliable approach utilized in the past decades. Traditionally, such bond formations are carried out in a multiple-step process that include tautomerization and activation via halogenation or sulfonylation. This is followed by functionalization with either nucleophiles via $S_NAr$ displacement or organometallics via transition-metal-catalyzed cross-coupling. For substrates with sensitive functionalities, such as alcoholic hydroxyl groups, two more steps of protection and deprotection have to be added to the process. Therefore, in the case of transformation of nucleosides, e.g., inosine, into the $C_6$-modified nucleosides via C–C, C–N, C–O, and C–S bond formations, the only practical way is by using existing $S_NAr$ displacemenst or cross-coupling technologies. It typically takes a nontrivial four-step process to complete such a conversion, including protection, activation, functionalization, and deprotection (Scheme 2).[11]




Scheme 2. Traditional multiple-step bond formations of nucleosides.

## 1.4. Coupling Reagents for Amide Bond Formation

The amide bond is one of the key functionalities that exist in natural products and drug molecules. Amide bond formation ($R^1CO\text{-}NHR^2$) between a carboxylic acid ($R^1CO_2H$) and an amine ($R^2NH_2$) has been enabled in a mild and efficient fashion thanks to the discovery of various useful and practical coupling reagents over the past half-century.[12] Among these, carbodiimides, phosphonium salts, and guanidinium/uronium salts are the most important and popular coupling reagents (Figure 3). The mechanism of the amide bond formation using these coupling reagents involves in situ activation of the carboxylic group by forming the corresponding highly reactive intermediates, i.e., *O*-acylurea from carbodiimide, *O*-acylphosphonium salt from phosphonium salt, and *O*-acylOBt from guanid-

ium/uronium salt. Subsequent nucleophilic attack on these intermediates by the amine results in the amide bond formation.

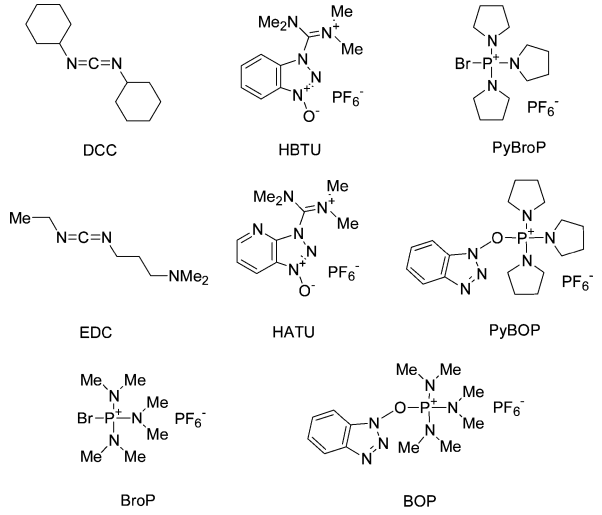



Figure 3. Common carbodiimides, guanidium/uronium salts, and phosphonium salts as coupling reagents for amide bond formation.

## 2. Phosphonium Coupling in the Direct Bond Formations via C–OH Bond Activation

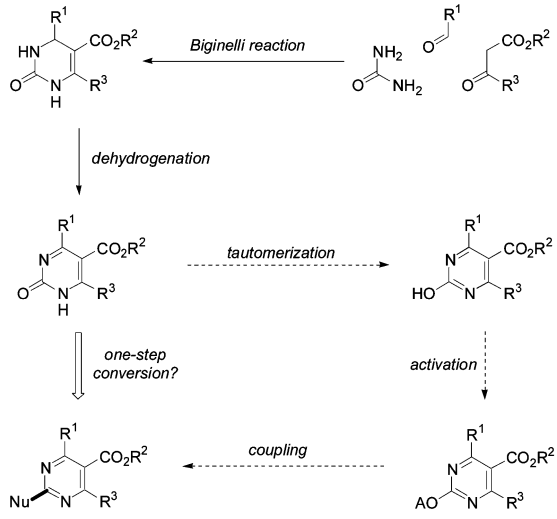
### 2.1. Discovery of Phosphonium Coupling

#### *2.1.1. Discovery of Base-Promoted Phosphonium Coupling*

In 2004,[13a] we presented the discovery of a new, mild, efficient, chemoselective and versatile phosphonium-mediated tautomerization-activation-coupling methodology (phosphonium coupling) for tautomerizable heterocycles. Part of the presentation was subsequently published.[13b] Phosphonium coupling affords direct bond formations of electron-deficient tautomerizable heterocycles with various nucleophiles via C–OH bond activation using phosphonium salts.

We became interested in an efficient transformation of readily accessible multifunctionalized Biginelli 2-dihydropyrimidinones into the multifunctionalized 2-pyrimidines, which can be adapted to a diversity-oriented synthesis[14] of compound libraries for high-throughput screening. The nonplanar 2-dihydropyrimidinones and the planar 2-pyrimidines are both favored templates for numerous bioactive compounds.[13] Although this conversion appeared to provide an ideal way for preparing this type of multifunctionalized 2-pyrimidines, this particular transformation remained largely undiscovered, due mainly to the lack of a practical dehydrogenation method.[13] It was not until 2001 that a useful but harsh dehydrogenation condition to convert 2-dihydropyrimidinones to 2-pyrimidinones became available.[15a] Interestingly, the demonstration[13] of this attractive facile access to the important multifunctionalized 2-pyrimidines has triggered recent development of more practical dehydrogenation methods under mild conditions.[15b–15e]

Next, to convert 2-pyrimidinone to 2-pyrimidines, a traditional approach required a multiple-step process. This included tautomerization, activation, and coupling, not to mention protection and deprotection of the sensitive functionalities in the substrate if that were necessary. Since the Biginelli 2-pyrimidinone is an electron-deficient tautomerizable heterocycle, we reasoned that direct bond formations leading to the functionalized 2-pyrimidines might be possible. It would require a highly reactive intermediate which could be formed in situ from the phenol form of the tautomerizable heterocycle via C–OH bond activation. The resulting highly reactive intermediate would be vulnerable enough to attack by a nucleophile via a $S_NAr$ pathway to complete the transformation in one pot (Scheme 3).



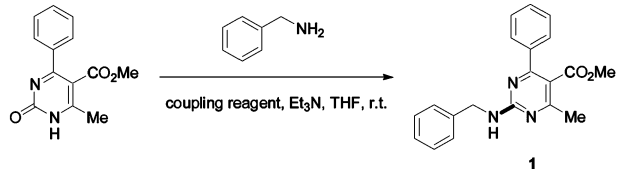

Scheme 3. Proposed one-step conversion of 2-pyrimidinones to 2-pyrimidines.

To test this hypothesis, we studied direct amination of the Biginelli 2-pyrimidinone with benzylamine in the presence of known in situ activating reagents. Considering the acidity of the phenol form of the tautomerizable heterocycle is similar to that of a carboxylic acid, we tested the common coupling reagents for amide bond formation, i.e., carbodiimides, phosphonium salts, and guanidinium/uronium salts. Interestingly, we discovered that, while carbodiimides and guanidinium/uronium salts were not effective, phosphonium salts (PyBroP, PyBOP) exhibited extraordinary in situ activating ability affording compound **1** in high yield (Table 1). Our screening of phosphonium salts, solvents and bases led to the optimal conditions for the direct C–N, C–O, C–S, and C–C bond formations of tautomerizable heterocycles with various nucleophiles in a single step.[13]

Initially, when considering the scope of this phosphonium coupling as a new synthetic methodology, we had discussed[13a] and predicted[13b] that these coupling conditions could be potentially applicable to other electron-deficient heterocyclic or aromatic systems. Indeed, shortly over a year after our initial disclosure,[13a] the utility and advantage of this new phosphonium coupling has been well demonstrated in recent applications.[16]

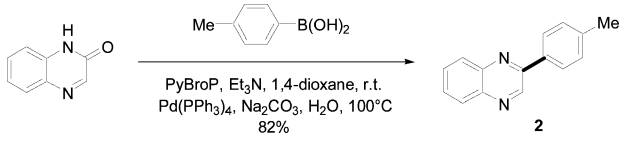
Table 1. Discovery of base-promoted phosphonium coupling.




| Reagent | DCC | EDC | HBTU | HATU | PyBOP | PyBroP |
|---|---|---|---|---|---|---|
| Yield (%) | 0 | 0 | 0 | 0 | 90 | 94 |

### *2.1.2. Discovery of Pd-Catalyzed Phosphonium Coupling*

In 2008,[17] we reported the first transition-metal-catalyzed version of phosphonium coupling, where it was extended to the Pd-catalyzed direct arylation of tautomerizable heterocycles with arylboronic acids. Since the phosphonium coupling was actually a combination of C–OH bond activation using a phosphonium salt, and subsequent functionalization with a nucleophile in one step, we envisioned that under the Suzuki–Miyaura cross-coupling conditions, the resulting heterocycle-phosphonium intermediate might behave chemically like the known pre-activated oxygen-containing cross-coupling partners, such as sulfonates[18] and phosphates.[19] This would undergo Pd-catalyzed direct arylation of the heterocycle with an arylboronic acid to furnish the biaryl product with new C–C bond formation. To explore this, we investigated the direct arylation of 2-quinoxalinone with *p*-tolylboronic acid by using a combination of two standard conditions: the phophonium coupling condition[13] (PyBroP, $Et_3N$, 1,4-dioxane, room temp.), and the Suzuki–Miyaura cross-coupling condition[3a] [$Pd(PPh_3)_4$, $Na_2CO_3$, water, heating] (Scheme 4). Again, we found that the Pd-catalyzed direct arylation of 2-quinoxalinone with *p*-tolylboronic acid successfully produced the biaryl product **2** in high yield. The optimal direct arylation conditions were obtained through screening of phosphonium salts, Pd catalysts, and bases. The Pd-catalyzed phosphonium coupling was found to tolerate a variety of electron-deficient tautomerizable heterocycles and arylboronic acids.

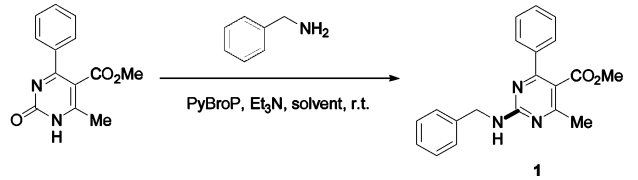



Scheme 4. Discovery of Pd-catalyzed phosphonium coupling.

## 2.2. Solvent Effect on Phosphonium Coupling

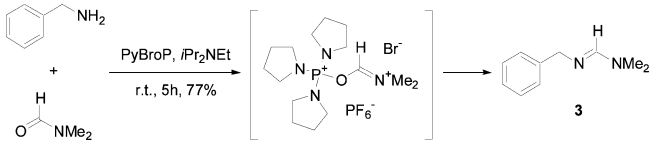
With PyBroP as the coupling reagent of choice, we studied the solvent effect on this phosphonium coupling.[13] We found that, among the common organic solvents, polar ethers (e.g., 1,4-dioxane, THF and DME) as well as acetonitrile led to faster and cleaner reactions than DCM and DMF. It is interesting to note that acetonitrile, DCM and DMF led to homogeneous reactions, while 1,4-dioxane, THF and DME resulted in heterogeneous reactions. 1,4-Dioxane produced a less heterogeneous, faster and cleaner reaction than THF and DME and proved to be the solvent of choice. It appeared that the heterocycle-phosphonium salts were readily soluble in all these polar solvents studied, and the heterogeneity may be caused by the byproduct salts (i.e., $Et_3NH^+Br^-$ and $Et_3NH^+PF_6^-$). Similar tetraarylphosphonium salts ($Ar_4P^+X^-$) are known to be soluble in solvents of moderate polarity (Table 2).[20]

Table 2. Solvent effect on phosphonium coupling.




| Solvent | DMF | DCM | MeCN | DME | THF | dioxane |
|---|---|---|---|---|---|---|
| Yield (%) | 20 | 45 | 80 | 90 | 94 | 96 |

It is not surprising that DMF was found to be the least effective solvent for the phosphonium coupling reaction, since it is known that PyBroP is an efficient activator in the synthesis of formamidines, such as benzyl formamidine **3**, from alkyl or aryl primary amines and DMF. (Scheme 5).[21]

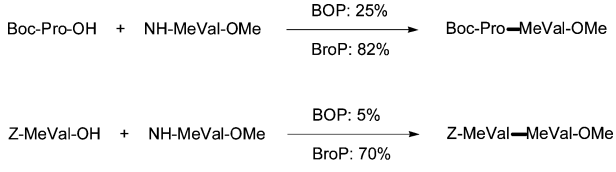



Scheme 5. PyBroP-mediated formamidine synthesis from amine and DMF.

In a recent application of the base-promoted phosphonium coupling to similar direct or indirect C–N, C–O, C–S, and C–C bond formations of tautomerizable heterocycles,[16f] the authors attempted to establish a structure-reactivity relationship among the phosphonium reagents in the coupling reactions. It is, however, somewhat puzzling that they concluded that the Br-derived reagents (PyBroP, BroP) were less reactive than the OBt-derived reagents (PyBOP, BOP). A closer look at the reaction conditions employed for the phosphonium couplings seems to provide a possible alternative explanation. Their studies on the phosphonium coupling reactions of the tautomerizable heterocycle and benzylamine were actually conducted in DMF. Based on the report mentioned above,[21] it seems reasonable to speculate that the reason the desired coupling reactions mediated by PyBroP and BroP were less efficient could be due to the competing side-reaction of the benzyl formamidine formation in these systems.

The unusual ability to activate DMF, a commonly used "inert" organic solvent, in the synthesis of formamidines under mild conditions reveals the remarkable activating power of the Br-derived phosphonium salts. The greater efficiency of the Br-derived reagent (BroP) over the OBt-derived reagent (BOP) in the peptide coupling of sterically hindered *N*-methylated amino acids has also been well documented (Scheme 6).[22d] The relative reactivity of these Br-derived and OBt-derived reagents may be due to their distinct steric and electronic effects (Figure 3). In the formation of the highly reactive phosphonium intermediates in peptide coupling and phosphonium coupling, the less hindered Br–$P^+$ bond in the Br-derived reagents is likely more prone to attack by carboxylate or phenolate, when compared to the more hindered OBt–$P^+$ bond in the OBt-derived reagents. Moreover, the $Br^-$ anion is also a better leaving group than the $OBt^-$ anion. Therefore, contrary to a recent comment,[16k] the anionic leaving groups ($Br^-$ vs. $OBt^-$) indeed seem to significantly influence the coupling reactions.

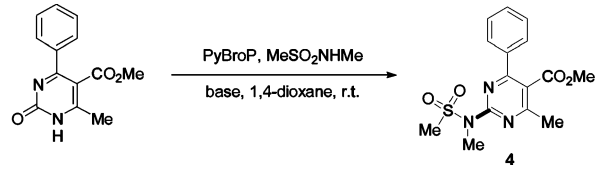



Scheme 6. Relative reactivity of BOP and BroP in peptide coupling.

### 2.3. Base Effect on Phosphonium Coupling

With PyBroP and 1,4-dioxane as the best reagent-solvent combination, we examined the base effect on this phosphonium coupling reaction.[13] We found that for strong nucleophiles, such as primary alkylamines, secondary alkylamines, cycloalkylamines, α-amino esters, α-amino alcohols and thiophenols, tertiary alkylamines ($Et_3N$ or $iPr_2NEt$) are suitable bases for achieving a smooth coupling reaction. In the case of weak nucleophiles such as *N*-methyl methanesulfonamide, no coupling reaction was observed with $Et_3N$ as the base. Our screening of different bases for the phosphonium coupling of the Biginelli 2-pyrimidinone and *N*-methyl methanesulfonamide indicated that NaO*t*Bu was an excellent base which led to a clean and complete reaction furnishing compound **4** in high yield (Table 3). Under these conditions, other weak or moderately strong nucleophiles such as *N*-methyl benzenesulfonamide, imidazole, indole, phenol, and diethyl malonate also coupled smoothly in highly yields in the corresponding coupling reactions. Consequently, with PyBroP and 1,4-dioxane as the best reagent and solvent, there are two standard conditions for the base-promoted phosphonium couplings, i.e., the $Et_3N$-promoted phosphonium coupling condition for strong nucleophiles, and the NaO*t*Bu-promoted phosphonium coupling condition for weak nucleophiles.[13]

Table 3. Base effect on phosphonium coupling with weak nucleophiles.

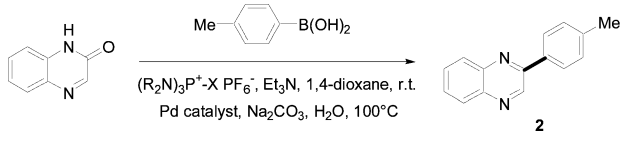



| Base | $Et_3N$ | DMAP | DBU | $Cs_2CO_3$ | DABCO | NaO*t*Bu |
|---|---|---|---|---|---|---|
| Yield (%) | 0 | 0 | 0 | 5 | 10 | 90 |

### 2.4. Phosphonium Salt, Catalyst, Base and Solvent Effects on Pd-Catalyzed Phosphonium Coupling

In the study of the first Pd-catalyzed phosphonium coupling of tautomerizable heterocycles with arylboronic acids, we compared the effectiveness of the common phosphonium salts (PyBroP, PyBOP, BroP, BOP).[17] We found that the Br-derived reagents (PyBroP, BroP) were far more effective than the OBt-derived reagents (PyBOP, BOP), probably because the latter simultaneously produced the heterocycle-OBt ethers as the side products[13] that virtually shut down the cross-coupling reaction. To investigate the Pd catalyst effect on direct arylation we screened a variety of Pd catalysts, and found that $PdCl_2(PPh_3)_2$ was the best catalyst. The reaction produced the biaryl product **2** in excellent yield (Table 4). In evaluating the bases involved in direct arylation, we observed that carbonates (Na, K, and Cs) were mild, effective, and advantageous over other common bases such as $iPr_2NEt$, DBU, DABCO, DMAP, CsF, NaOAc, $K_3PO_4$, NaOH, and NaO*t*Bu. In addition, we found the Pd-catalyzed phosphonium coupling appeared to be sluggish in the absence of water. Replacement of water with alkyl alcohols such as MeOH, EtOH, and *i*PrOH resulted in slower reactions as well as formation of the alkyloxy-heterocycle ethers as side products.[17]

Table 4. Phosphonium salt and Pd catalyst effects on Pd-catalyzed phosphonium coupling.

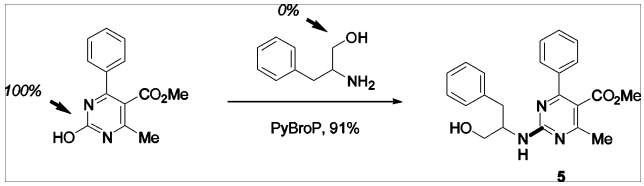



| Pd catalyst | Phosphonium salt | Yield (%) |
|---|---|---|
| $Pd(PPh_3)_4$ | PyBroP | 82 |
| $Pd(PPh_3)_4$ | BroP | 78 |
| $Pd(PPh_3)_4$ | PyBOP | 26 |
| $Pd(PPh_3)_4$ | BOP | 20 |
| $Pd(OAc)_2$ | PyBroP | 35 |
| $Pd(dppf)CH_2Cl_2$ | PyBroP | 42 |
| $Pd(dba)CHCl_3$ | PyBroP | trace |
| $PdCl_2(CH_3CN)_2$ | PyBroP | 11 |
| $Pd(OAc)_2(PPh_3)_2$ | PyBroP | 79 |
| $PdCl_2[P(o\text{-}Tol)_3]_2$ | PyBroP | 66 |
| $PdCl_2(PPh_3)_2$ | PyBroP | 94 |

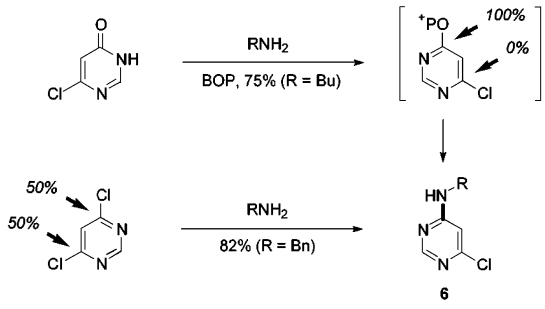
### 2.5. Chemoselectivity of Phosphonium Coupling

We found that the chemoselective nature of the phosphonium salts that are selectively bound to the acidic phenolic hydroxyl group of the tautomerizable heterocycles makes protection-deprotection operations on the sensitive functionalities, such as the alcoholic hydroxyl group, unnecessary. This was exemplified in the direct amination of the Biginelli 2-pyrimidinone with phenyl alaninol, affording compound **5** (Scheme 7), where the alcoholic hydroxyl group remained intact during the reaction.[13] This is a unique advantage of this methodology over existing technologies, and it is in line with the current trends of protecting-group-free synthesis[23] and green chemistry,[24] which are efficient, economical and environmentally friendly.



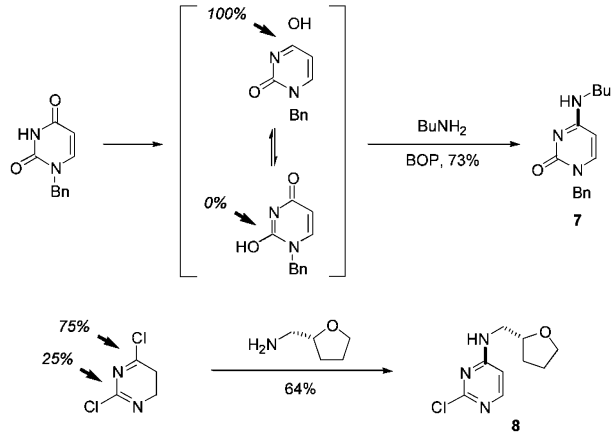

Scheme 7. Chemoselectivity of phenolic vs. alcoholic hydroxyl groups.

In addition to the chemoselectivity of a phenolic hydroxyl group over an alcoholic hydroxyl group in phosphonium coupling, the chemoselectivity of a C–$OP^+$ bond vs. a C–Cl bond was found in the same substrate. In the case of 6-chloro-*3H*-pyrimidin-4-one, direct amination could theoretically take place at either the $C_4$ position via phosphonium coupling or the $C_6$ position via $S_NAr$ displacement, which are equal positions with same reactivity in 4,6-dichloro-pyrimidine[25] affording compound **6** (Scheme 8). It turned out that direct amination proceeded exclusively at the $C_4$ position giving compound **6**.[16b] This suggested that the C–$OP^+$ bond is more reactive than the C–Cl bond in this substrate.




Scheme 8. Chemoselectivity of C–$OP^+$ bond vs. C–Cl bond.

The regioselectivity of phosphonium coupling was also observed in tautomerizable heterocycles with two possible phenol forms. For instance, 1-benzyl-pyrimidine-2,4-dione in principle has the 2-phenol form (Ar-$OH^2$) and the 4-phenol form (Ar-$OH^4$) through tautomerization (Scheme 9). Direct amination of this tautomerizable heterocycle via phosphonium coupling was found to occur only on the 4-phenol form giving compound **7**.[16b] This result apparently follows the trend in the amination of 2,4-dichloro-pyrimidine where $S_NAr$ displacement is known to occur preferably at the $C_4$ position yielding compound **8**.[26] These chemo- and regio-selectivity features of the phosphonium coupling could potentially allow sequential direct C–C, C–N, C–O or C–S bond formations within the same molecule with one or more tautomerizable heterocycles by tuning the reactivity of Ar–$OP^+$ vs. Ar–X, and Ar–$O^4P^+$ vs. Ar–$O^2P^+$.




Scheme 9. Chemoselectivity of 2-phenol form vs. 4-phenol form.

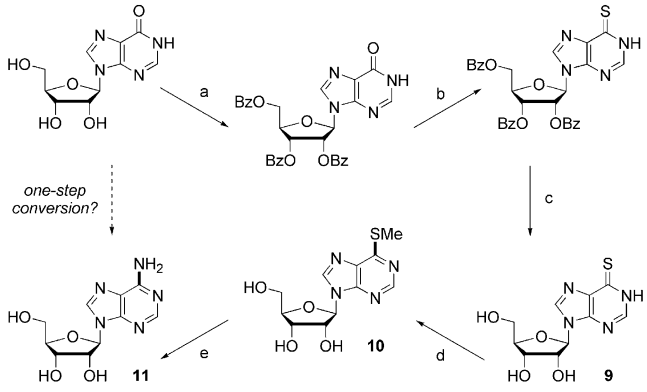
Due to the unique chemoselective nature of the phosphonium reagents (e.g., PyBroP), it is not surprising that the phosphonium coupling shows remarkable functionality compatibility. The target functionalities of PyBroP are carboxylic hydroxyl groups,[22] phenolic hydroxyl groups[13] and dialkyl formamides.[21] The C–$OP^+$ bond is readily attacked by strong or moderately strong nucleophilic functionalities, such as primary alkylamines, secondary alkylamines, phenols, thiols, and thiophenols. Therefore, under the standard $Et_3N$-promoted phosphonium coupling condition at ambient temperature[13] (see Section 2.3.), the following common functionalities should be compatible: alkenes, alkynes, allenes, imines, nitriles, alcohols, ethers, acetals, ketals, aldehydes, ketones, esters, amides, carbonates, carbamates, alkyl halides, aryl halides, tertiary alkylamines, arylamines, thioethers, sulfones, sulfoxides, sulfonamides, sulfonates, phosphanes, phosphates, silanes, silyl ethers, and nitrogen heterocycles.

### 2.6. A Long-Standing Synthetic Challenge of a Single-Step Transformation in Nucleoside Chemistry

Eventually, after 50 years, a synthetic challenge of a single-step transformation in nucleoside chemistry has been overcome. In 1958,[11a] Fox et al. conducted the pioneering work on the synthesis of biologically important $C_6$-modified nucleosides through $S_NAr$-type bond formations of naturally occurring commercially available nucleosides (e.g., inosine and guanosine). They worked out a multiple-step procedure to prepare the $C_6$-modified nucleosides **9**, **10** and **11** from natural nucleosides (e.g., inosine) (Scheme 10), in

which the sugar moieties bearing sensitive hydroxyl groups were protected (or blocked), so that they could survive the harsh activation conditions for subsequent $S_NAr$ displacements. In the past half-century, this multiple-step protocol in nucleoside chemistry (Scheme 2, Section 1.3.) has been the standard routine route used to access a variety of structurally modified nucleosides with important biological activities.[11] The groups that have been used to protect the sugar hydroxyl groups include acetate, benzoate, ketal and silyl ether. Apart from halo groups (F, Cl, Br, I), the $C_6$-activating groups (or leaving groups) have also been extended to other groups, such as sulfonyl, sulfone, pyridyl, imidazolyl and phenoxy groups.[11,16d] Installation of these functionalities onto nucleosides is nontrivial and often challenging. Thus, a highly desirable one-step conversion of natural nucleosides into $C_6$-modified nucleosides has been a long-standing synthetic challenge in nucleoside chemistry.

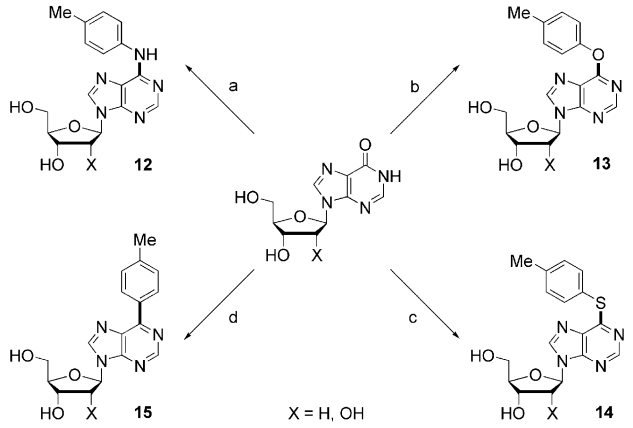



a) BzCl, pyridine,55°C, 82%; b) $PS_5$, pyridine, reflux, 88%;
c) NaOMe, MeOH, reflux, 77%; d) MeI, NaOH, $H_2O$, r.t., 74%; e) $NH_3$, MeOH,147°C, 69%

Scheme 10. Multiple-step nucleoside chemistry by Fox et al. in 1958.

After discovering phosphonium coupling (see Section 2.1.), recognizing its chemoselectivity (see Section 2.5.), and predicting its applications to existing tautomerizable heterocycles (see Sections 1.2. and 3.2.), we realized that this methodology could provide a unique solution to the long-standing synthetic challenge in nucleoside chemistry.[13a] To showcase this new, mild, efficient, chemoselective and versatile technology, we applied the base-promoted as well as Pd-catalyzed phosphonium coupling conditions to the direct amination, etherification, thioetherification and arylation of natural nucleosides (e.g., inosine and 2′-deoxyinosine),[13a,17] and found that these led to the $C_6$-modified nucleosides **12**, **13**, **14** and **15** in high yields (Scheme 11). It is noteworthy that, among these $C_6$-modified nucleosides that the $C_6$-aryl nucleosides displayed significant cytostatic and *anti*-HCV effect,[27] and have attracted considerable synthetic attention in recent years.[11j–11y]

Consequently, with the synthesis of the $C_6$-modified nucleosides being achieved via direct C–C, C–N, C–O and C–S bond formations of a natural nucleoside in a single step, the formidable synthetic challenge in nucleoside chemistry has been effectively overcome by this new phosphonium




a) PyBroP, $ArNH_2$, 70-75%; b) PyBroP, ArOH, 80-84%;
c) PyBroP, ArSH, 82-88%; d) PyBroP, $ArB(OH)_2$, $PdCl_2(PPh_3)_2$, 70-72%

Scheme 11. A single-step transformation in nucleoside chemistry enabled by phosphonium coupling.

coupling technology. Application of phosphonium coupling to the preparation of similar $C_6$-modified nucleosides via either direct or indirect C–N, C–O and C–S bond formations has also been reported recently.[16]

## 3. Mechanism and Scope of Phosphonium Coupling

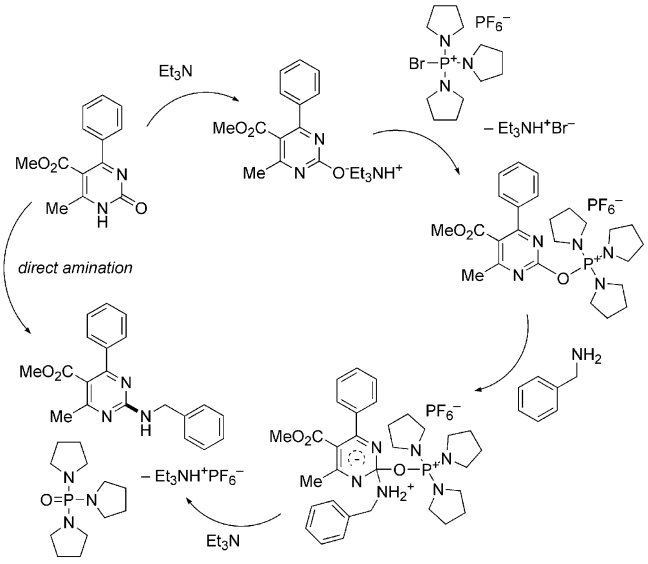
### 3.1. Mechanism of Phosphonium Coupling

#### *3.1.1. Mechanism of Phosphonium Coupling Using Br-Derived Reagents*

Phosphonium coupling of tautomerizable heterocycles and nucleophiles in the presence of the Br-derived reagents (PyBroP, BroP) leads to the coupling products in an efficient and high-yielding fashion. Based on the experimental evidence, we proposed the mechanism of direct amination via phosphonium coupling using PyBroP (Scheme 12).[13] It proceeds through the following four cascade steps: (1) tautomerization of 2-pyrimidinone to 2-hydroxypyrimidine in the presence of $Et_3N$; (2) activation of 2-hydroxypyrimidine with PyBroP generating the highly reactive heterocycle-phosphonium intermediate; (3) nucleophilic attack of benzylamine to the heterocycle-phosphonium intermediate forming the $S_NAr$-type transitional intermediate; and (4) displacement of trispyrolidino phosphonamide (TPPA) by benzylamine producing the coupling product. This reasonably straightforward mechanism was supported by the mass spectral analyses of the reaction mixture.[13] A mass peak of 484.2 $[M + H]^+$, corresponding to the cation of the heterocycle-phosphonium intermediate, was observed at the beginning of the reaction. This peak gradually disappeared, while mass peaks of 258.1 $[M + H]^+$ and 515.2 $[2 M + H]^+$, corresponding to TPPA, gradually increased. TPPA can also be isolated from the reaction mixture. According to this mechanism, two equivalents of base ($Et_3N$) are needed for the phosphonium coupling converting PyBroP into TPPA, $Et_3NH^+Br^-$ and $Et_3NH^+PF_6^-$.

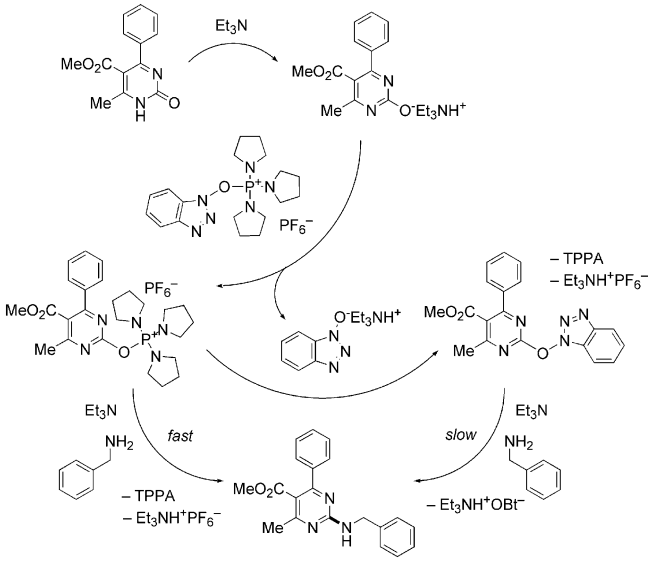
In two recent related studies,[16d,16f] diligent examination of this mechanism was carried out by sequential $^{31}P$ NMR studies tracking the release of HMPA from BOP and other species in a time course of 12–60 hours.




Scheme 12. Mechanism of phosphonium coupling using PyBroP.

### 3.1.2. Mechanism of Phosphonium Coupling Using OBt-Derived Reagents

Phosphonium coupling of tautomerizable heterocycles and nucleophiles using OBt-derived reagents (PyBOP, BOP) is more complicated than its counterpart using Br-derived reagents (PyBroP, BroP). We found that treatment of the Biginelli 2-pyrimidinone with PyBOP first formed the highly reactive heterocycle-phosphonium intermediate. Then, the released HOBt from PyBOP, as a competing nucleophile, simultaneously attacked the heterocycle-phosphonium intermediate yielding the heterocycle-OBt ether as a less reactive intermediate.[13] For direct amination with benzylamine, $S_NAr$ displacement of TPPA from the highly reactive heterocycle-phosphonium intermediate was a fast reaction, while $S_NAr$ displacement of HOBt from the less reactive heterocycle-OBt ether was a slow reaction. Usually, the less reactive heterocycle-OBt ethers can be isolated from the incomplete coupling reactions as side products.[13] Overall, phosphonium coupling using OBt-derived reagents often results in less efficient coupling reactions (longer times and lower yields). The mechanism of direct amination via phosphonium coupling using PyBOP is shown in Scheme 13.




Scheme 13. Mechanism of phosphonium coupling using PyBOP.

### 3.1.3. Scope of Phosphonium Salts

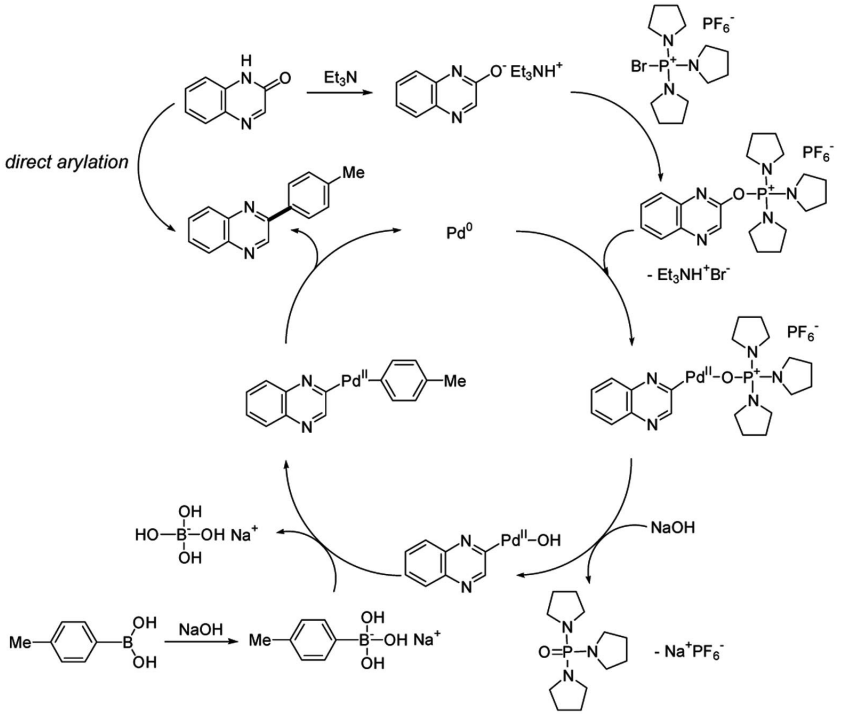
Castro et al. developed the seminal phosphonium salts for peptide coupling during 1970s–1990s.[22] BOP was the first generation of the OBt-derived phosphonium salt invented for this purpose. BOP was widely utilized as a coupling reagent in both solution phase and solid phase peptide synthesis in the past. The manufacture and utilization of BOP, however, involved the use and formation of the highly carcinogenic HMPA. Therefore, BOP was later replaced by its environmentally benign analogue, PyBOP. Subsequently, Castro et al. devised the more powerful BroP as the second generation of the Br-derived phosphonium salt that was not only more atom-economic but also displayed higher reactivity relative to the OBt-derived reagents (BOP, PyBOP). This was particularly evident in the peptide coupling of sterically hindered *N*-methylated amino acids (see Scheme 6, Section 2.2.). BroP was eventually substituted with PyBroP for similar environmental impact consideration. When commenting on the complications from the use of the OBt-derived reagents, Castro et al. pointed out that the HOBt residue in BOP and PyBOP appeared to be useless or even inadvisable due to the formation of the less reactive intermediates, and thereby they resulted in the poor performance of the peptide coupling.[22d] Consequently, from the standpoints of environmental impact, atom-economy, and relative reactivity, the order of the preferred phosphonium salts for coupling reactions should be: PyBroP > PyBOP >> BroP > BOP.

This preferred order of phosphonium salts in peptide coupling is apparently applicable to phosphonium coupling of tautomerizable heteocycles. The advantage of utilizing PyBroP over other reagents is obvious as mentioned above, because, without complications, the coupling reaction proceeds through a single heterocycle-phosphonium intermediate (Scheme 12) (see Section 3.1.1.). The chemical behaviour of BOP and its analogue PyBOP is similar in phosphonium couplings.[13,17] While BOP is still useful in $S_NAr$-type base-promoted phosphonium coupling,[16] it is much less effective in the transition-metal-catalyzed phosphonium coupling (see Section 2.4.).[17]

## 3.2. Mechanism of Pd-Catalyzed Phosphonium Coupling

Based on the modified Suzuki–Miyaura catalytic cycle,[28] we proposed a possible mechanism of the Pd-cata-




Scheme 14. Mechanism of Pd-catalyzed phosphonium coupling.

lyzed direct arylation of 2-quinoxalinone with *p*-tolylboronic acid (Scheme 14).[17] It most likely proceeds through the following seven cascade steps: (1) tautomerization of 2-quinoxalinone to 2-quinoxalinol in the presence of $Et_3N$; (2) activation of 2-quinoxalinol with PyBroP generating the heterocycle-phosphonium intermediate; (3) oxidative insertion of $Pd^0$ catalyst to the C–O bond of the heterocycle-phosphonium intermediate forming the unprecedented heterocycle-$Pd^{II}$-phosphonium species; (4) its reaction with a base (e.g., NaOH) producing the heterocycle-$Pd^{II}$-OH species; (5) activation of the arylboronic acid with the base affording the aryl boron-ate complex; (6) transmetallation of the heterocycle-$Pd^{II}$-OH species with the aryl boron-ate complex giving the heterocycle-$Pd^{II}$-aryl species; and (7) reductive elimination of the biaryl product and regeneration of the $Pd^0$ catalyst. According to this mechanism, three equivalents of bases ($Et_3N$, NaOH) are needed to convert PyBroP and $ArB(OH)_2$ into TPPA, $Et_3NH^+Br^-$, $Na^+PF_6^-$ and $Na^+B(OH)_4^-$.

### 3.3. Scope of Tautomerizable Heterocycles

Based on the evaluation of existing tautomerizable heterocycles with one or more nitrogen atoms, we reasoned that tautomerizable heterocycles containing type I–III core structures in any substituted or fused systems or electron-deficient arenols should be suitable substrates for phosphonium coupling (Figure 4).[13] Tautomerizable heterocycles with more electronegative nitrogen atoms (from type I to type III) or more electron-withdrawing groups (e.g., CN, COR, $CO_2R$, $SO_2R$, $NO_2$) should translate to more efficient phosphonium coupling reactions. The recent applications of the phosphonium coupling methodology along this line have demonstrated the utility, advantage and broad scope for a variety of tautomerizable heterocycles that are useful in the synthesis of many biologically interesting compounds.[16]

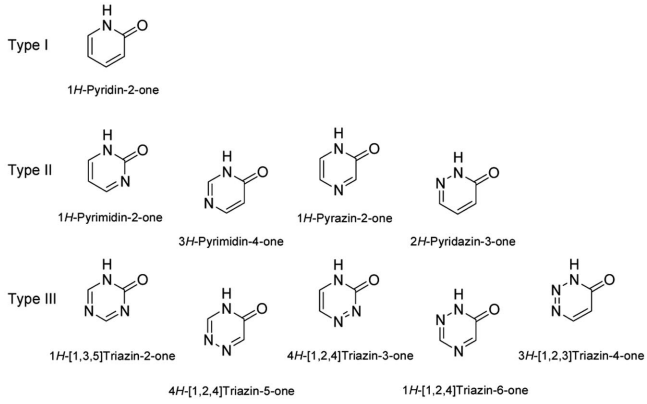



Figure 4. Core structures of electron-deficient tautomerizable heterocycles.

## 4. Phosphonium Coupling in the Direct Bond Formations of Tautomerizable Heterocycles

### 4.1. Direct Amination

#### *4.1.1 Direct Amination with Alkyl Amines*

Direct amination of tautomerizable heterocycles with alkylamines via phosphonium coupling produces aryl alkylamines (Ar–NH-R). Alkylamines are strong nucleophiles,

therefore the $Et_3N$-promoted phosphonium coupling conditions are suitable for their coupling reactions.[13] Application of direct amination of tautomerizable heterocycles with alkylamines has led to the facile synthesis of various aryl alkylamines whose structures are contained in the type I–III core structures (Figure 4) (see Section 3.3.). Included are pyridine, pyrimidine, pyrazine, triazine as well as electron-deficient five-membered heterocycles (Table 5).[13,16]

Table 5. Direct amination with alkylamines.

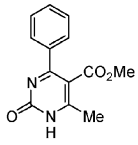
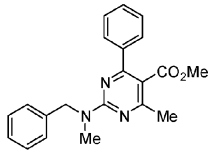
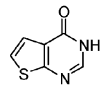
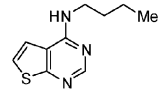
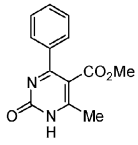
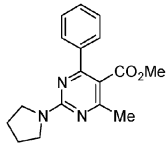
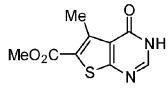
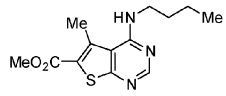
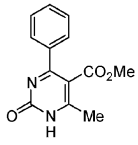
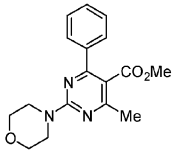
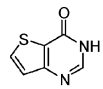
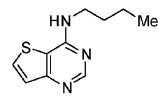
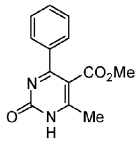
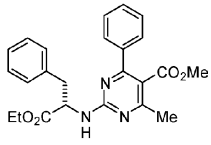
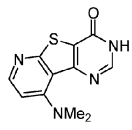
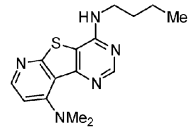
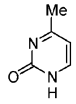
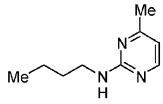
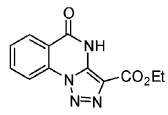
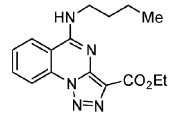
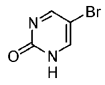
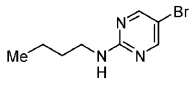
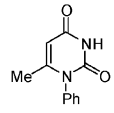
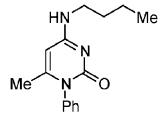
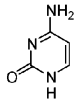
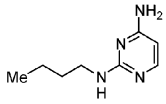
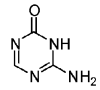
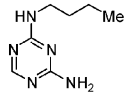
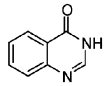
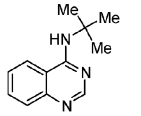
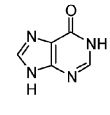
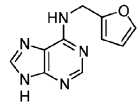
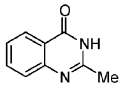
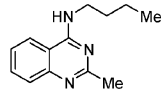
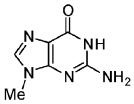
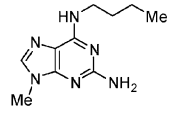
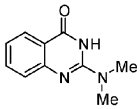
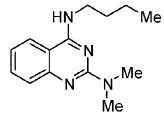
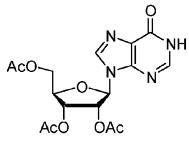
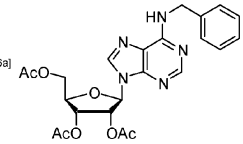
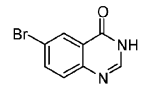
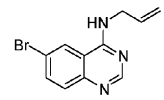
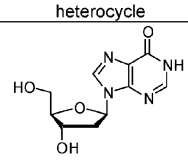
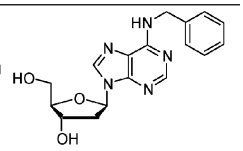
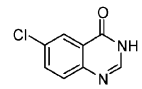
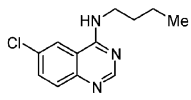
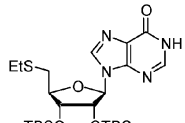
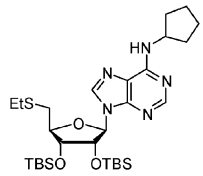
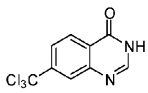
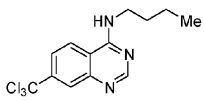
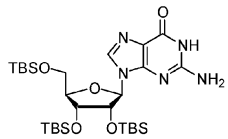
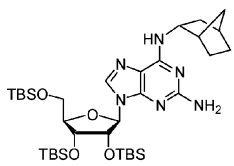
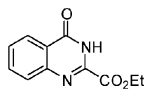
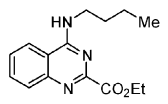
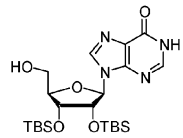
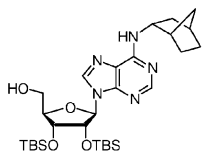
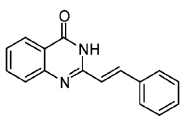
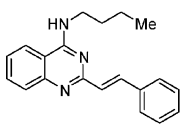
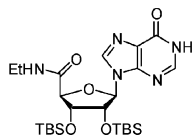
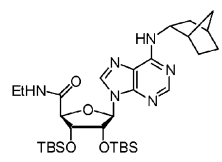
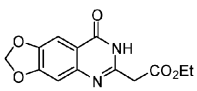
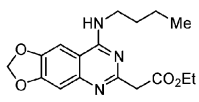
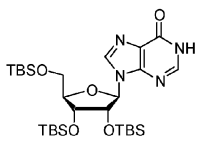
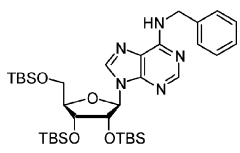
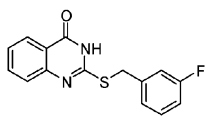
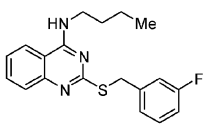
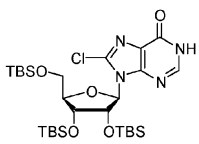
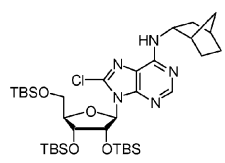
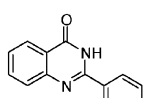
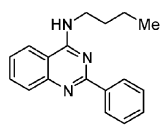
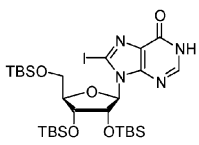
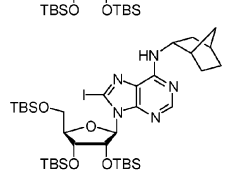
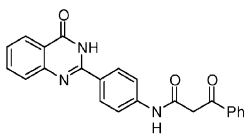
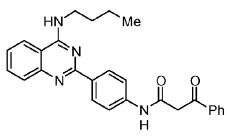
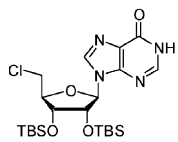
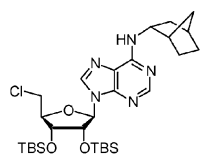
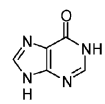
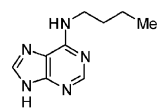
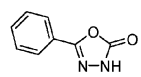
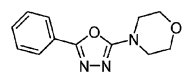
| Tautomerizable heterocycle | Yield | Coupling product | Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|---|---|---|
|  | **16** 94%[13] |  |  | **38** 94%[16f] |  |
|  | **17** 98%[13] |  |  | **39** 81%[16f] |  |
|  | **18** 92%[13] |  |  | **40** 94%[16f] |  |
|  | **19** 82%[13] |  |  | **41** 95%[16f] |  |
|  | **20** 68%[16f] |  |  | **42** 94%[16f] |  |
|  | **21** 95%[16f] |  |  | **43** 81%[16f] |  |
|  | **22** 0%[16f] |  |  | **44** 82%[16f] |  |
|  | **23** 64%[16f] |  |  | **45** 90%[16f] |  |
|  | **24** 99%[16f] |  |  | **46** 89%[16f] |  |
|  | **25** 99%[16f] |  |  | **47** 98%[16a] |  |
|  | **26** 95%[16f] |  |  | **48** 99%[16a] |  |

Table 5. *(continued)*.

| Tautomerizable heterocycle | Yield | Coupling product | Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|---|---|---|
|  | **27** 81%[16f] |  |  | **49** 99%[16a] |  |
|  | **28** 87%[16f] |  |  | **50** 92%[16g] |  |
|  | **29** 99%[16f] |  |  | **51** 52%[16g] |  |
|  | **30** 86%[16f] |  |  | **52** 68%[16g] |  |
|  | **31** 92%[16f] |  |  | **53** 75%[16g] |  |
|  | **32** 96%[16f] |  |  | **54** 78%[16g] |  |
|  | **33** 90%[16f] |  |  | **55** 67%[16g] |  |
|  | **34** 99%[16f] |  |  | **56** 57%[16g] |  |
|  | **35** 85%[16f] |  |  | **57** 80%[16g] |  |
|  | **36** 79%[16f] |  |  | **58** 92%[16k] |  |
|  | **37** 86%[16f] |  |  | **59** 50%[16k] |  |

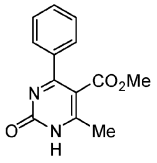
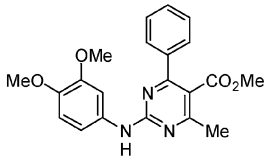
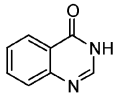
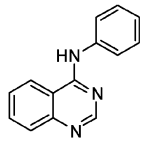
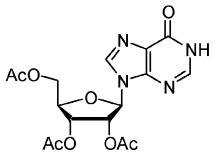
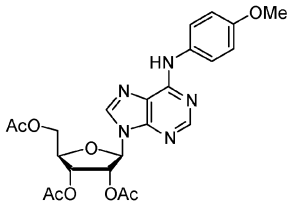
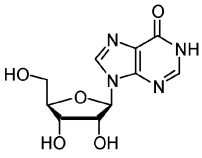
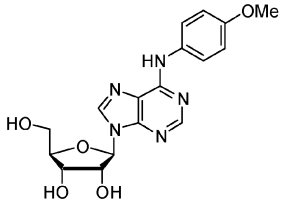
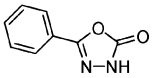
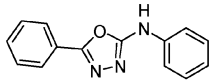
The reaction rate of the direct amination was found to be dependent on the electronic and steric nature of the amine nucleophiles.[13] For example, direct amination of tautomerizable heterocycles with primary or secondary alkylamines, and cycloalkylamines reached completion in a few hours at ambient temperature. While direct amination with sterically hindered and electron-deficient substrates, such as α-amino esters, as in the case of the Biginelli 2-pyrimidinone, took several days at ambient temperature.

In contrast to the successful direct amination of 2-pyrimidinones (entries **19**, **20**, **21**), direct amination of more electron-rich amino-substituted 2-pyrimidinone (entry **22**) using BOP failed to yield the coupling product. Other more electron-rich amino- or (dimethylamino)-substituted tautomerizable heterocycles (entries **25**, **44**, **46**, **51**) readily led to the desired coupling products. While these results may confirm the relative reactivity of 4-pyrimidiones over 2-pyrimidinones, direct amination of more electron-rich tautomerizable heterocycles could be accelerated by either using more powerful PyBroP or conducting the coupling reaction at elevated temperatures.

### *4.1.2. Direct Amination with Aryl Amines*

Direct amination of tautomerizable heterocycles with arylamines via phosphonium coupling produces biarylamines (Ar–NH–Ar). Arylamines are much weaker nucleophiles than alkylamines, therefore it is not surprising that even the NaO*t*Bu-promoted phosphonium coupling condition resulted in slow and low-yielding coupling reactions at ambient temperature.[13] We found that this limitation can be easily mitigated by conducting the coupling reactions at elevated temperatures. Similar results under similar conditions were also reported recently (Table 6).

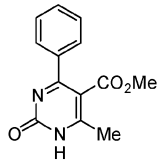
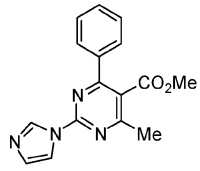
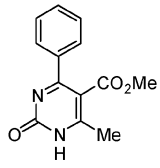
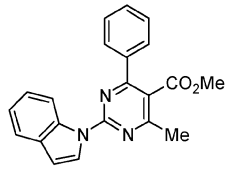
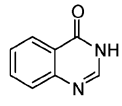
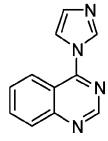
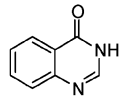
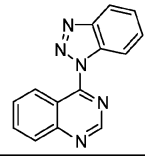
Table 6. Direct amination with arylamines.

| Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|
|  | **60** 26%[13] |  |
|  | **61** 78%[16f] |  |
|  | **62** 74%[16a] |  |
|  | **63** 81%[16a] |  |
|  | **64** 67%[16k] |  |

### *4.1.3. Direct Amination with Nitrogen Heterocycles*

Direct amination of tautomerizable heterocycles with nitrogen heterocycles via phosphonium coupling produces C–N bond linked biaryl compounds (Ar–$^{N}$Ar). Nitrogen heterocyles such as imidazole, indole and benzotriazole are also weak nucleophiles, therefore the NaO*t*Bu-promoted phosphonium coupling conditions are suitable for their coupling reactions.[13] Similar results under similar conditions were also reported recently (Table 7).

Table 7. Direct amination with nitrogen heterocycles.

| Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|
|  | **65** 84%[13] |  |
|  | **66** 78%[13] |  |
|  | **67** 92%[16f] |  |
|  | **68** 66%[16f] |  |

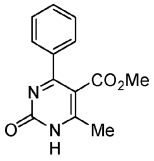
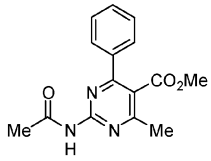
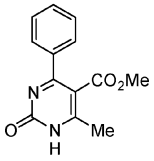
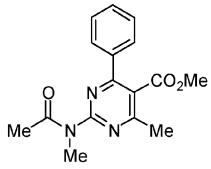
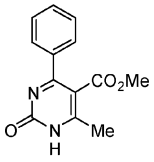
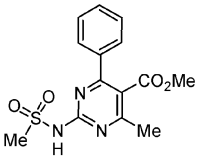
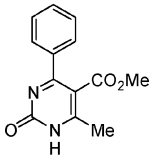
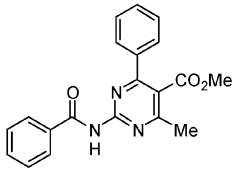
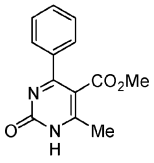
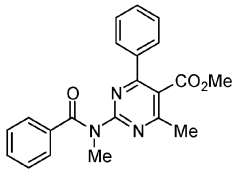
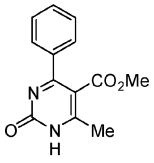
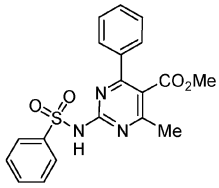
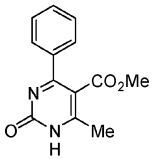
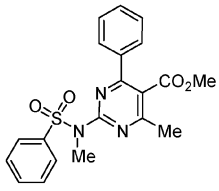
### *4.1.4. Direct Amination with Amides and Sulfonamides*

Direct amination of tautomerizable heterocycles with amides or sulfonamides via phosphonium couplings produce amide or sulfonamide bond linked biaryl compounds (Ar–CONR–Ar) or (Ar–$SO_2$NR–Ar). This direct amination seemed to be more challenging, since amides and sulfonamides are weaker nucleophiles.[13] Phosphonium coupling reactions with primary or secondary amides, and primary sulfonamides produced at most traces of coupling products in the presence of various strong bases at ambient or elevated temperatures.[13] Interestingly, we found that direct amination with secondary sulfonamides ($RSO_2$NHMe)

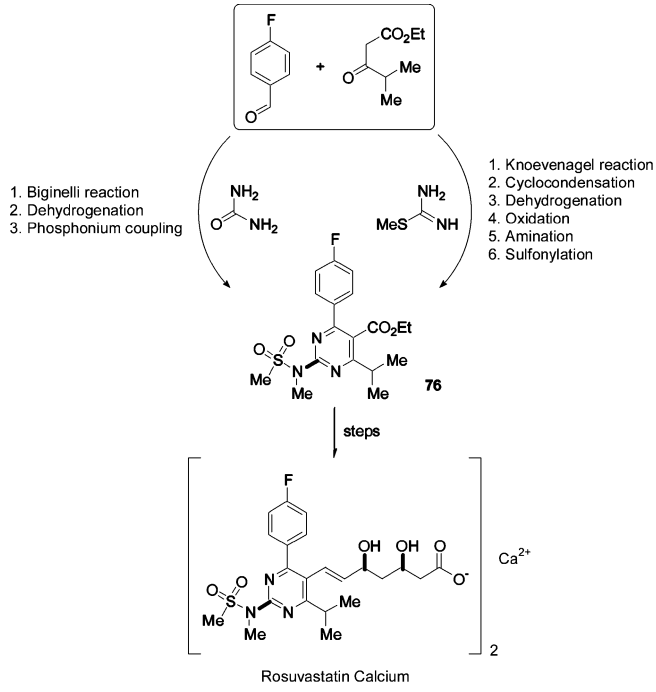
using the NaO*t*Bu-promoted phosphonium coupling conditions smoothly generated the coupling products in excellent yields (see Tables 3 and 8, Section 2.3.).

Table 8. Direct amination with amides and sulfonamides.

| Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|
|  | **69** 0%[13] |  |
|  | **70** trace[13] |  |
|  | **71** 0%[13] |  |
|  | **72** 0%[13] |  |
|  | **73** trace[13] |  |
|  | **74** 0%[13] |  |
|  | **75** 92%[13] |  |

The different reactivity of these amides and sulfonamides in the phosphonium coupling may be rationalized by the correlation of nucleophilicity and electron-delocalization. $RSO_2NHMe$ is a stronger nucleophile than $RSO_2NH_2$, because the electron-donating methyl group increases its nucleophilicity. In addition, $RSO_2NHMe$ is likely a stronger nucleophile than RCONHMe, because the non-planar tetrahedron-structure of the $SO_2NH$ group prevents electron-delocalization of the sulfonamide anion, which would otherwise decrease its nucleophilicity; and the planar structure of the CONH group facilitates electron-delocalization of the amide anion, which should decrease its nucleophilicity.

It is interesting to note that compound **4** is a close analogue of the key synthetic intermediate **76** of rosuvastatin calcium or Crestor®, a potent HMG-CoA reductase inhibitor used to treat hypercholesterolemia (Scheme 15). Compound **76**, a multifunctionalized 2-pyrimidine, was prepared in six steps in a synthetic route to rosuvastatin calcium.[29] On the basis of our facile synthesis of compound **4**, compound **76** could now be efficiently accessible in just three steps, including the Biginelli reaction, dehydrogenation and the phosphonium coupling.




Scheme 15. Phosphonium coupling vs. conventional transformations in the synthesis of Crestor®.

### 4.2. Direct Etherification

Direct etherification of tautomerizable heterocycles with phenols via phosphonium couplings produce biaryl ethers (Ar–O–Ar). Phenols are moderately strong nucleophiles, therefore the NaO*t*Bu-promoted phosphonium coupling conditions was found to be better than the $Et_3N$-promoted conditions.[13] Similar results under similar conditions were also reported recently (Table 9).

### 4.3. Direct Thioetherification

Direct thioetherification of tautomerizable heterocycles with thiophenols via phosphonium coupling produces biaryl thioethers (Ar–S–Ar). Thiophenols are strong nucleophiles, therefore the $Et_3N$-promoted phosphonium coupling condition is suitable for their coupling reactions.[13] Similar results under similar conditions were also reported recently (Table 10).

Table 9. Direct etherification with phenols.

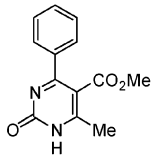
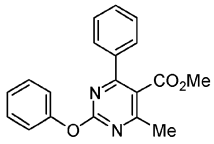
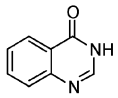
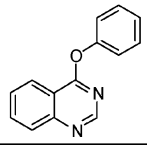
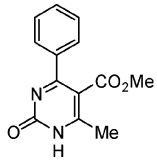
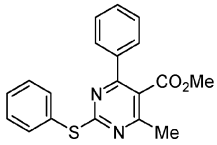
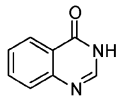
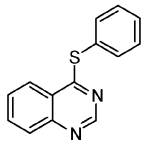
| Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|
|  | **77** 88%[13] |  |
|  | **78** 84%[16f] |  |

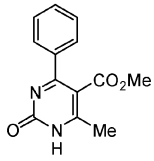
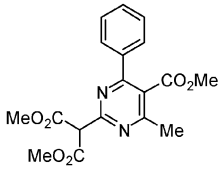
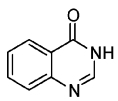
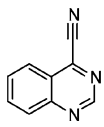
Table 10. Direct thioetherification with thiophenols.

| Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|
|  | **79** 95%[13] |  |
|  | **80** 93%[16f] |  |

### 4.4. Direct Alkylation

Direct alkylation of tautomerizable heterocycles with activated methylene compounds ($CH_2R_2$), e.g., malonate, via phosphonium coupling produces alkylated aryl compounds (Ar–$CHR_2$). Activated methylene compounds are weak nucleophiles, therefore the NaO*t*Bu-promoted phosphonium coupling condition is suitable for their coupling reactions.[13] Under similar conditions, direct cyanation with NaCN was also reported recently (Table 11).

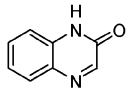
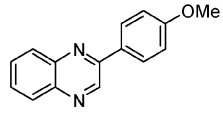
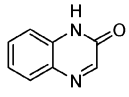
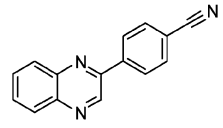
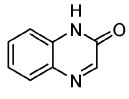
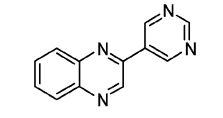
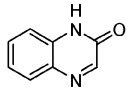
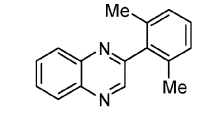
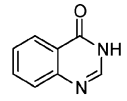
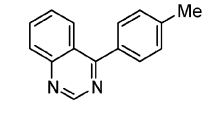
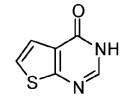
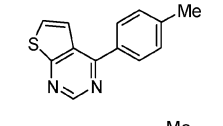
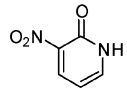
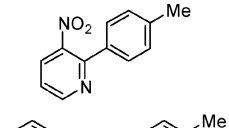
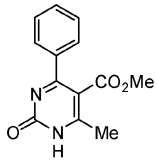
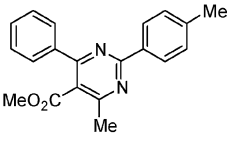
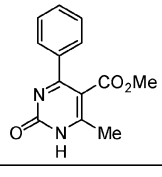
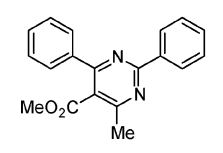
Table 11. Direct alkylation and cyanation with malonate and cyanide.

| Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|
|  | **81** 72%[13] |  |
|  | **82** 54%[16f] |  |

### 4.5. Direct Arylation

Direct arylation of tautomerizable heterocycles with arylboronic acids via Pd-catalyzed phosphonium coupling produces biaryl compounds (Ar–Ar). With the optimized direct arylation conditions available (see Section 2.4.), we embarked on an investigation of the reaction scope.[17] A variety of tautomerizable heterocycles were examined for the Pd-catalyzed direct arylation via C–OH bond activation using PyBroP (Tables 4 and 12). The Pd-catalyzed phosphonium coupling conditions proved to be general for the arylation of these heterocycles with *p*-tolylboronic acid. Complete conversion, and good to excellent isolated yields were observed for all the heterocycles employed. Both electron-rich and electron-poor arylboronic acids coupled well

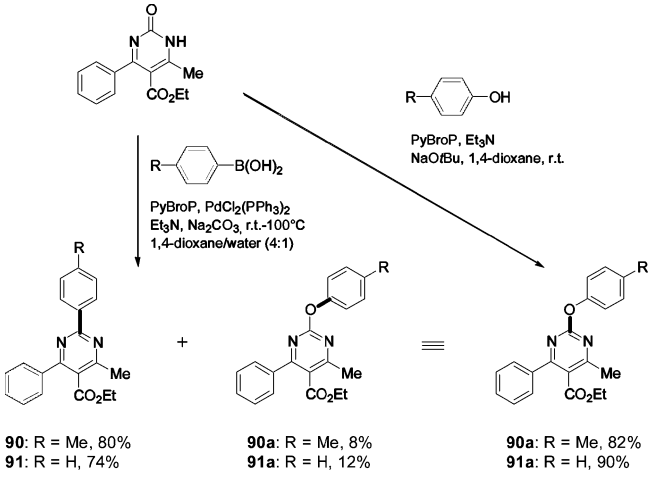
Table 12. Direct arylation with arylboronic acids.

| Tautomerizable heterocycle | Yield | Coupling product |
|---|---|---|
|  | **83** 92%[17] |  |
|  | **84** 90%[17] |  |
|  | **85** 89%[17] |  |
|  | **86** 84%[17] |  |
|  | **87** 82%[17] |  |
|  | **88** 91%[17] |  |
|  | **89** 85%[17] |  |
|  | **90** 80%[17] |  |
|  | **91** 74%[17] |  |

with the heterocycle-phosphonium intermediate to afford the biaryl products in excellent yields. Direct arylation using heteroaryl and sterically hindered arylboronic acids also efficiently furnished the biaryl products in high yields. The cross-coupling of the heterocycle-phosphonium salts behaved in contrast to the cross-coupling of phosphates, whose reactions were significantly impeded by both electronic and steric effects of the arylboronic acids.[19]

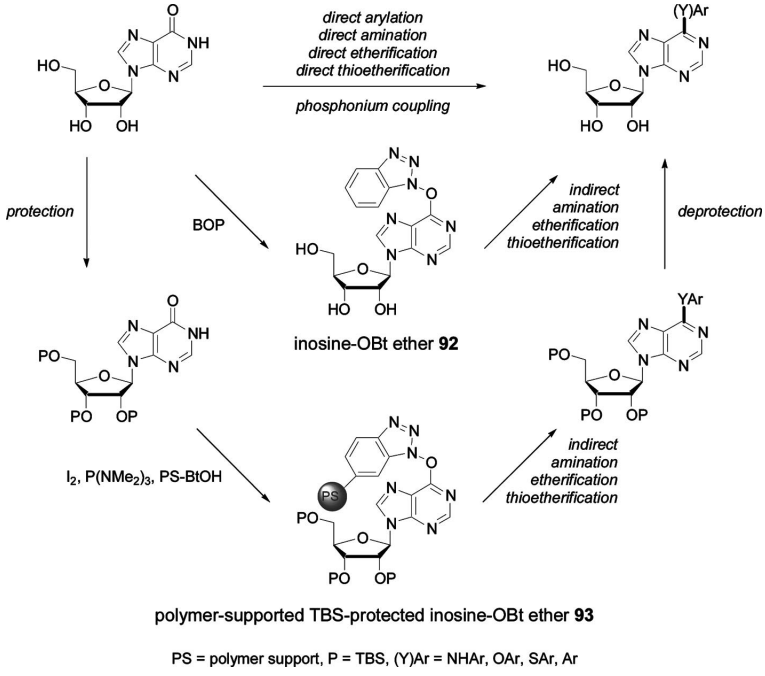
Interestingly, direct arylation of the Biginelli 2-pyrimidinone with arylboronic acids produced the unexpected biaryl ethers **90a** and **91a** via direct etherification as the minor side products, along with the desired biaryl products **90** and **91** (Scheme 16).[17] To confirm their structures, the identical biaryl ethers **90a** and **91a** were alternatively prepared via direct etherification (see Section 4.2.) using the corresponding phenols. The reason for the biaryl ether formation on this substrate was unclear, and neither C–C nor C–O bond formation was observed in the absence of PyBroP. Direct etherification of arenols with arylboronic acids furnishing biaryl ethers has been accomplished via Cu-mediated cross-coupling.[30]




Scheme 16. Pd-catalyzed direct arylation and etherification.

### 4.6. Indirect Phosphonium Coupling via Heterocycle-OBt Ethers

Phosphonium coupling offers an efficient and practical approach for the direct bond formations of various *unactivated and unprotected* tautomerizable heterocycles via $S_NAr$ displacement or transition-metal-catalyzed cross-coupling in a convenient single step. An alternative version of this methodology has appeared in some recent applications, where indirect phosphonium coupling and bond formation via the heterocycle-OBt ethers were carried out in several steps (Scheme 17).[16d,16f,16h–16j] In the presence of the OBt-derived reagent (BOP), phosphonium coupling of tautomerizable heterocycles with the in situ released HOBt was used to produce the isolable heterocycle-OBt ether, e.g., inosine-OBt ether **92**,[16d] which is a common side-product under this type of reaction conditions (see Sections 3.1.2 and 3.1.3). Compound **92** was then utilized as the intermediate for subsequent amination, etherification and thioetherification via $S_NAr$ displacement with the corresponding nucleophiles. Furthermore, the polymer-supported TBS-protected inosine-OBt ether **93**[16i] was developed via conventional halo-de-hydroxylation[31] involving the phosphonium intermediate under the halogenation conditions using $I_2$ and $P(NMe_2)_3$. A similar polymer-supported purine-OBt ether has been alternatively developed for the synthesis of purine derivatives.[32] Material **93** was then used




Scheme 17. Direct vs. indirect phosphonium couplings and bond formations.

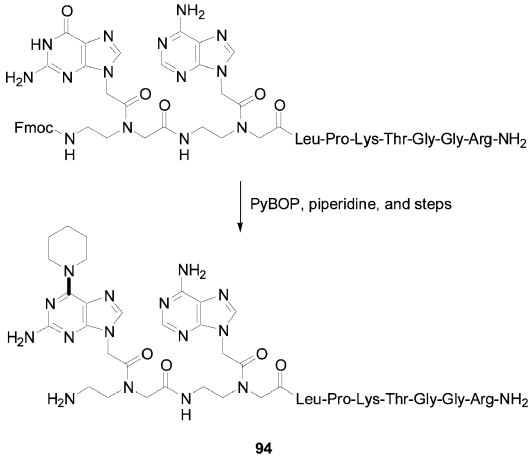
for subsequent amination, etherification and thioetherification via $S_NAr$ displacement, which would afford the inosine derivatives after deprotection.

This indirect phosphonium coupling provides an alternative useful approach to the functionalization of tautomerizable heterocycles, although its overall multiple-step sequence appears less straightforward. It is also interesting to note that, while the versatile phosphonium coupling enables direct arylation under the Suzuki–Miyaura cross-coupling condition,[17] the heterocycle-OBt ether failed to result in a C–C bond formation under similar conditions.[16h]

## 5. Summary and Outlook

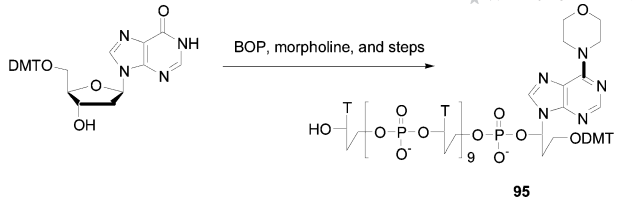
Over the past few years, phosphonium coupling has emerged as a mild, efficient, chemoselective and versatile technology for direct bond formations of many biologically important tautomerizable heterocycles via C–OH bond activation.[13,16,17] It features operational simplicity, functionality compatibility, and broad substrate scope. Its ability to create new C–C, C–N, C–O and C–S bonds from a common substrate makes it an ideal approach to develop diversity oriented-synthesis. Its attractive protecting-group-free, direct bond formation involving a cascade process in a single step provides unique and facile access to many biologically interesting molecules, which are not easily accessible using existing technologies. Accordingly, after 50 years of the pioneering work by Fox et al. in 1958, a long-standing synthetic challenge of a single-step transformation in nucleoside chemistry has been eventually solved.

The unique utility and advantage of phosphonium coupling has also been highlighted recently in the synthesis of structurally modified PNA oligomer **94**[16c] (Scheme 18) and DNA oligomer **95**[16d] (Scheme 19). This shows the considerable synthetic potential of this new technology in the assembly and post-synthetic modification of many structurally sensitive biologically important molecules in the future.




94

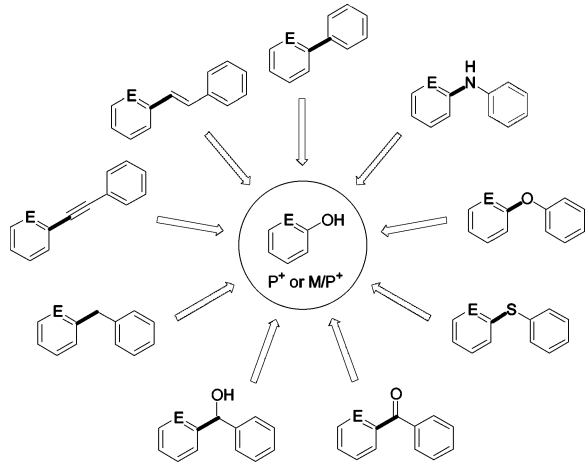
Scheme 18. Phosphonium coupling in the synthesis of PNA oligomer.




95

Scheme 19. Phosphonium coupling in the synthesis of DNA oligomer.

As the first direct bond formation via C–OH bond activation, phosphonium coupling opens up new synthetic avenues to the construction of molecules in a new efficient way. Since the C–$OP^+$ bond can be considered equivalent to the C–X bond, phosphonium coupling could potentially enable direct formation of all the major chemical bonds in chemical synthesis by using Ar–OH instead of Ar–X, such as $C(sp^2)$–N, $C(sp^2)$–O, $C(sp^2)$–S, $C(sp^2)$–C(sp), $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp^3)$ (Scheme 20).




Scheme 20. Potential applications of phosphonium coupling in direct formation of major chemical bonds.

In addition to the generally accepted reactivity order of the C–X bond in $S_NAr$ displacement, i.e., C–F > C–Cl > C–Br > C–I,[31a] Robin et al. recently discovered a new reactivity order of the C–X bond in activated nucleosides with strong nucleophiles such as butylamine, i.e., C–F > C–$SO_2R$ > C–Br > C–Cl > C–I.[33] The reactivity order of the C–X bond in Suzuki–Miyaura cross-couplings is known to be: C–I > C–Br, C–$OSO_2R$ > C–Cl > C–F.[3b] Since the C–$OP^+$ bond is more reactive than the C–Cl bond in $S_NAr$ displacement with butylamine (see Scheme 8, Section 2.5.), we think the complete reactivity order of the common C–X bonds in activated tautomerizable heterocyles in $S_NAr$ displacements with alkylamines should be: C–F > C–$SO_2R$ > C–$OP^+(NR_2)_3PF_6^-$, C–$OSO_2R$, C–$OPO(OR)_2$, C–Br > C–Cl > C–I. Similarly, the complete reactivity order in their transition-metal-catalyzed cross-couplings should be: C–I > C–$OP^+(NR_2)_3PF_6^-$, C–$OSO_2R$, C–$OPO(OR)_2$, C–Br >

C–Cl > C–$SO_2R$ > C–F. Obviously, the unique C–$OP^+$ bond is the only one that is generated in situ via C–OH bond activation, whereas the rest C–X bonds need to be pre-formed. We believe the reactivity of the C–$OP^+$ bond is similar to that of the C–Br bond, so that direct bond formations can be readily achieved via either $S_NAr$ displacement or transition-metal-catalyzed cross-coupling under mild conditions.

Besides tautomerizable heterocycles, phosphonium coupling is also likely applicable to arenols. The C–$OP^+$ bond of arenols is probably less reactive than its counterpart in tautomerizable heterocycles because the arenol is more electron-rich. Since the reactivity of the C–$OP^+$ and C–Br bonds are similar, and the cross-coupling of the inert Ar–Cl has been addressed,[34] phosphonium coupling of arenols could be feasible under similar conditions.

Finally, as phosphonium coupling[13,17] becomes a new synthetic tool for many applications,[16] credit should be given to Bertrand Castro who invented the seminal phosphonium reagents[22] (Castro's reagents).

## Acknowledgments

We thank Dr. Paul F. Jackson for helpful discussions.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