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Simultaneous Formation and Functionalization of Aryliminophosphoranes Using 1,3-Dihydro-1*H*-benzimidazol-2-ones as Precursors

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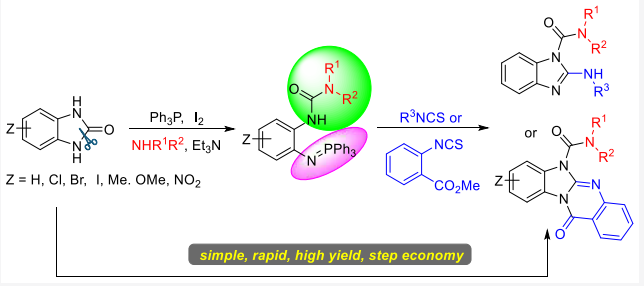
ABSTRACT: An atom- and step-economic synthesis of aryliminophosphoranes bearing *ortho* urea was achieved via unprecedented Ph_3P-I_2 mediated ring-opening of 1,3-dihydro-1*H*-benzimidazol-2-ones with secondary amines. Tandem aza-Wittig/heterocyclization of the functionalized aryliminophosphoranes upon treatment with isothiocyanates enables a facile access to a single regioisomer of N^1-substituted 2-aminobenzimidazoles as well as fused tetracyclic quinazolinone derivatives in one-pot. $^{31}P\{^1H\}$ NMR studies suggested that the urea C−N bond of benzimidazolone is weakened by *N*-phosphorylation, leading to aminolysis rather than the expected deoxygenative amination.

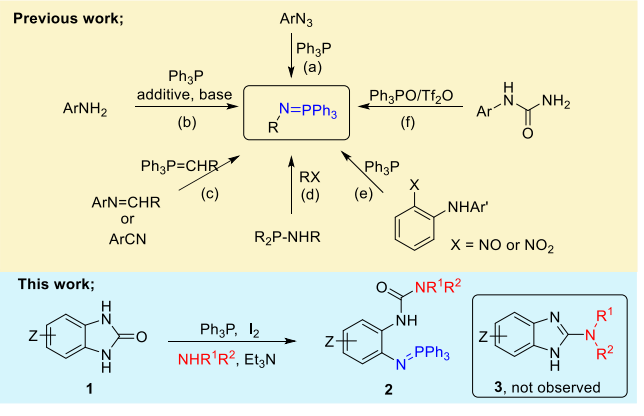


Aryliminophosphoranes are versatile reagents in C═N bond formation which have found numerous applications in the synthesis of diverse *N*-containing molecules.[1] Their use in an aza-Wittig type reaction offers practical approaches toward a vast number of interesting derivatives with pharmacological and biological significances.[2] Moreover, a highly polarized P═N bond makes them valuable ligands for catalysis applications.[3]

Owning to their synthetic potential, the synthesis and application of iminophosphoranes have attracted considerable attention among organic and medicinal chemists. Since it was first introduced in 1919,[4] the Staudinger reaction between aromatic azides and phosphines has been the most commonly used method for the preparation of aryliminophosphoranes (Scheme 1a).[1,5] Other alternative approaches include the reaction of amines with phosphines in the presence of halogenating agents,[6] azodicarboxylates,[7] or ethylenedicarboxylates (Scheme 1b),[8] the reaction of ylides with Schiff bases[9] or nitriles[10] (Scheme 1c), alkylation of aminophosphanes (Scheme 1d),[11] condensation of *N*-aryl-2-nitrosoanilines[12] or 2-nitrodiarylamines[13] with triphenylphosphine (Scheme 1e), as well as condensation of triphenylphosphine oxide with *N*-monosubstituted arylureas (Scheme 1f).[14] These methods have their own merits; however, the preparation of complex iminophosphorane structures often requires a tedious synthetic and purification process involving multistep functionalization which may hinder their practical utility toward challenging targets.

In our ongoing work involving phosphonium-mediated synthesis of 2-aminoheterocycles using Ph_3P-I_2 as an activator,[15] rather than the expected deoxygenative amination toward **3** as has been observed in the $POCl_3$-mediated reaction,[16] 1,3-dihydro-1*H*-benzimidazol-2-ones **1** underwent an unprecedented aminolysis at the cyclic urea C−N bond to yield aryliminophosphoranes bearing an *ortho* urea moiety **2**

Scheme 1. Synthetic Approaches toward Iminophosphoranes



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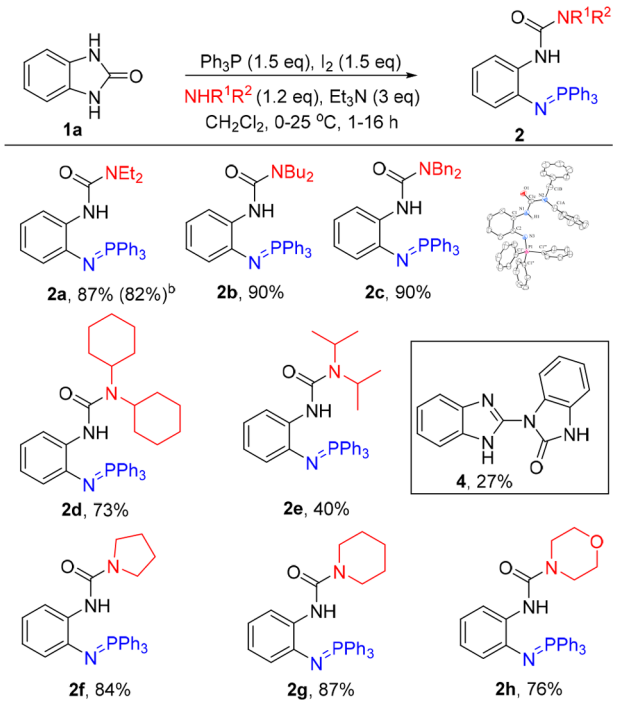
exclusively (Scheme 1). Although a similar ring-opening reaction of the urethane derivatives has previously been observed,[15d] this discovery is still rather surprising since the urea bonds are extremely stable due to the conjugation stabilization effects of its dual amide structure.[17]

Since *ortho*-functionalized aryliminophosphoranes would enable a straightforward and step-economic construction of a vast number of *N*-heterocyclic frameworks, while the bifunctional derivatives are potentially useful in asymmetric catalysis,[3,18] this prompted us to explore the reaction in detail in order to better understand the reaction mechanism and factors governing their formation. Presented here is a novel pathway toward a new type of aryliminophosphoranes. Their application in aza-Wittig/heterocyclization furnishing N^1-substituted 2-aminobenzimidazoles as well as tetracyclic quinazolinone derivatives is also demonstrated.

In our preliminary study, 1,3-dihydro-1*H*-benzimidazol-2-one **1a** was treated with a series of amines under our previously reported conditions.[15d] According to Scheme 2, compound **1a**

Scheme 2. Substrate Scope with Respect to Amines[a]



[a]Reaction conditions: **1a** (0.74 mmol), PPh_3 (1.11 mmol), I_2 (1.11 mmol), amine (0.89 mmol), Et_3N (2.22 mmol), CH_2Cl_2 (5 mL). [b]Reaction performed in gram scale using **1a** (10 mmol).

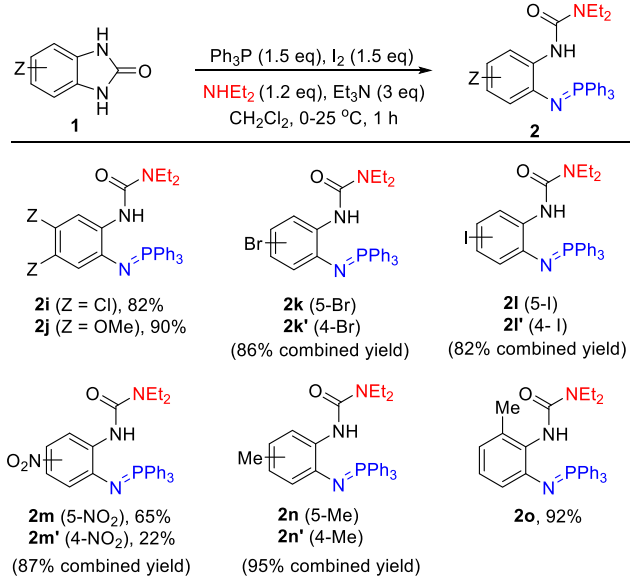
underwent ring-opening with secondary aliphatic amines both acyclic and cyclic systems to furnish aryliminophosphoranes **2** at room temperature. Products **2a**–**2c** were afforded in high yields within a short reaction time when using dialkylamines with different carbon chain lengths. The preparation of **2a** is also feasible under gram-scale synthesis (see parentheses).

Steric hindrance caused by the alkyl substituent of the amine lowered the yield of the product **2d** slightly. To our delight, the reaction is still compatible with highly hindered diisopropylamine, albeit with long reaction time and low yield of **2e** due to competing formation of pseudo-dimerized product **4**. The reaction of **1a** also proceeded effectively with less hindered cyclic amines, furnishing the products **2f**–**2h** in high yields without detectable formation of the corresponding 2-aminobenzimidazoles **3**. Unfortunately, **1a** failed to react with all the tested primary amines (benzylamine, cyclohexylamine, and aniline, *data not shown*). This could be attributed to a competitive substitution reaction at the phosphorus center of the formed phosphonium intermediate(s) by these nucleophiles. Indeed, cyclohexylaminophosphonium salt was isolated (79% yield) from the reaction of **1a** with cyclohexylamine.

The identities of all the products were consistent with the NMR and MS data. In the case of compound **2c**, the proposed iminophosphorane structure was unambiguously confirmed by X-ray crystallography. As illustrated in Figures S1 and S2 (Supporting Information (SI)), the N–P–C and C–P–C bond angles within the range of 106.9–114.6° indicate the distorted tetrahedral arrangement about the phosphorus and are in the expected range. Noteworthy, the short P1–N3 bond distance, 1.573 Å, suggests the double bond character (1.54 Å) rather than a single bond (1.78 Å).[19] An intramolecular hydrogen bonding interaction of 2.115 Å also exists between the N–H of the urea residue and N3 of the iminophosphorane **2c**.

Electronic and steric effects of the substrates on the yield and regioselectivity of the reaction were next examined using different substituted benzimidazol-2-one derivatives **1**. As summarized in Scheme 3, the electronic properties of the

Scheme 3. Substrate Scope with Respect to Benzimidazolone Precursors[a]



[a]Reaction conditions: **1** (0.74 mmol), PPh_3 (1.11 mmol), I_2 (1.11 mmol), diethylamine (0.89 mmol), Et_3N (2.22 mmol), CH_2Cl_2 (5 mL).

substituents at the phenyl ring of **1** exert little influence on the product yield and regioselectivity. While symmetrically substituted substrates **1b** and **1c** gave rise to high yield of the corresponding products **2i** and **2j**, the reaction of unsymmetrical substrates generally provides an approximately 1:1 mixture of the inseparable regioisomers **2k**–**2n** based on the NMR analysis of the crude product mixture. Only for the nitro containing substrate **1f**, isomer **2m** having the nitro group *para* to the N=P bond was isolated as a major product.

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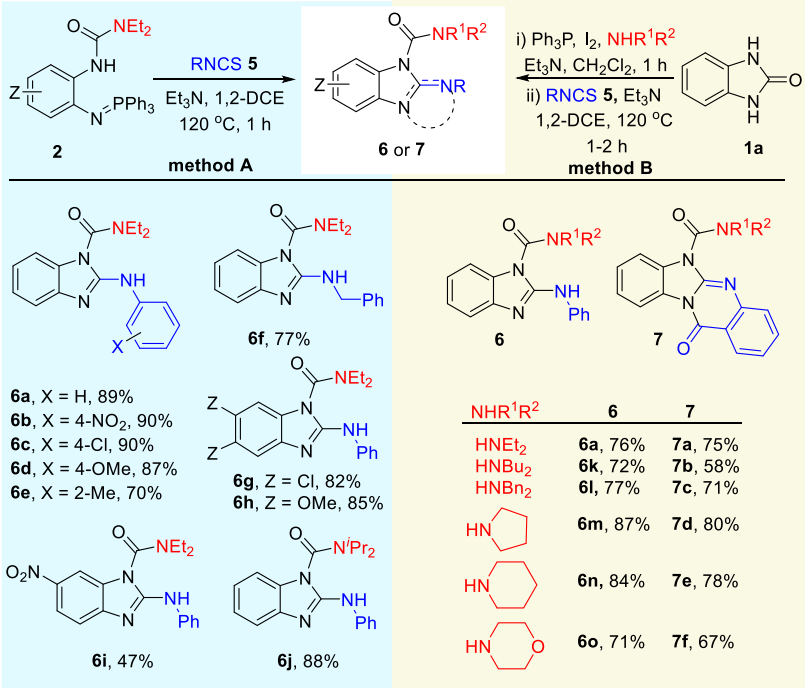
Scheme 4. Aza-Wittig/Heterocyclization



By comparing the two benzimidazolone derivatives that exhibit complementary substitution patterns, **1g** and **1h**, the regioselectivity of the reaction was found to be highly sensitive to steric factor. In contrast to the 1:1 mixture of the products **2n** and **2n′** obtained from the reaction of **1g**, the formation of sterically less hindered product **2o** was preferred with **1h** having an *ortho* methyl group.

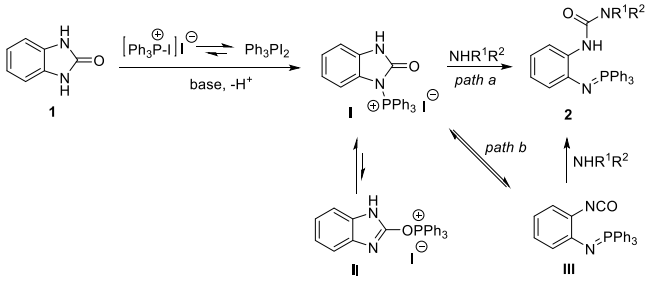
Most of the iminophosphoranes **2** are stable compounds which can be purified by column chromatography and stored at room temperature without detectable decomposition. As a representative, compound **2a** remained unchanged even when stirring in wet THF or in 1 M HCl in MeOH (16 h) as neither hydrolysis nor reduction to the corresponding aryl amine was observed.

To demonstrate the synthetic utility of **2**, aza-Wittig/heterocyclization toward fused *N*-heterocycles was examined in the reaction with isothiocyanates **5** as shown in Scheme 4. Under thermal conditions, the aza-Wittig reaction of **2** with the isothiocyanate group initially provides carbodiimides.[12] These intermediates then undergo intramolecular cyclization with the *ortho* urea NH to afford N^1-substituted 2-aminobenzimidazoles **6** (method A).

The reaction proceeded smoothly with aryl isothiocyanates containing an electron-withdrawing or electron-donating group as well as alkyl isothiocyanate to provide **6a**−**6f** in high yields. The reaction also appears to be compatible with various substituents on the aryl ring of **2**, and even the presence of a bulky *ortho* urea group can be tolerated (e.g., **6g**−**6j**). Remarkably, under method B, benzimidazole **6a** along with **6k**−**6o** could be prepared directly from **1a** in good overall yields through in situ formation of **2**, followed by a sequential aza-Wittig-cyclization reaction upon addition with phenyl isothiocyanate. Furthermore, a single regioisomer of fused tetracyclic quinazolinone derivatives **7** was readily afforded in high yield through a one-pot reaction of **1a** with amines and methyl 2-isothiocyanatobenzoate. It is noteworthy that, in all the tested reactions, competitive formation of self-condensed products **3** was not observed.

To gain insight into the mechanism for the formation of **2**, progress of the reaction between **1a** and dibenzylamine ($NHBn_2$) was monitored using $^{31}P\{^1H\}$ NMR (see Figures S3−S5 and discussion in SI). On the basis of the above results and the NMR data, the mechanism of the reaction was proposed as depicted in Scheme 5. Treatment of **1** with the

Scheme 5. Proposed Mechanism



Ph_3P-I_2 mixture in the presence of base gives rise to predominant formation of *N*-phosphorylated intermediate **I** which could be in equilibrium with an aryloxyphosphonium species **II**. Triggered by the presence of the *N*-phosphonium group, **I** could undergo C−N bond cleavage upon attacking by an amine, leading directly to aryliminophosphorane **2** (path *a*). Although no other prominent signals were observed under the $^{31}P\{^1H\}$ NMR time scale, **2** could possibly be obtained through an addition of an amine to an isocyanate **III** derived from bond dissociation of **I** as observed in the reaction of hindered urea bonds (path *b*).[20]

In conclusion, we have disclosed a novel unconventional route toward *ortho*-functionalized aryliminophosphoranes through phosphonium-mediated ring-opening of 1,3-dihydro-1*H*-benzimidazol-2-ones with amines. This step- and atom-

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economic approach allows a convenient access to various iminophosphoranes, which enables the direct one-pot regioselective synthesis of N^1-substituted 2-aminobenzimidazoles as well as fused tetracyclic quinazolinones via tandem aza-Wittig/heterocyclization. With an increasing number of potent *N*-heterocycles with endocyclic urea being discovered,[21] it is anticipated that this protocol would open a new avenue toward valuable structural motifs that are otherwise inaccessible or difficult to obtain with the existing methodologies. Further studies based on this strategy are currently underway.

EXPERIMENTAL SECTION

General Information. All reagents including 1,3-dihydro-1*H*-benzimidazol-2-ones **1** (**1a**, **1b**, **1f**) were purchased from Sigma-Aldrich or TCI and used without further purification. Compounds **1c**,[22a] **1d**,[22b] **1e**,[22c] **1g**,[22d] and **1h**[22e] were synthesized according to the reported procedures. All reactions were run in flame- or oven-dried glassware under N_2 gas. The reaction was monitored by thin-layer chromatography carried out on silica gel plates ($60F_{254}$, MERCK, Germany) and visualized under UV light (254 nm). Column chromatography was performed over silica gel 60 (70−230 mesh, MERCK, Germany). Melting points were determined using Mettler Toledo DSC equipment at a heating rate of 6 °C/min and are uncorrected. NMR spectra were recorded using a Bruker AVANCE (400 and 500 MHz for ^{1}H). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS). Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qui), sextet (sex), septet (sep), multiplet (m), broad (br), doublet of doublets (dd), triplet of doublets (td), and doublet of doublet of doublets (ddd). High-resolution mass spectra (HRMS) were recorded using time-of-flight (TOF) via the atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI).

General Procedure for the Synthesis of 2. To a solution of iodine (281 mg, 1.11 mmol) and triphenylphosphine (291 mg, 1.11 mmol) in freshly distilled dichloromethane (5 mL) was added amine (0.89 mmol) at 0 °C under N_2. After that, 1,3-dihydro-1*H*-benzimidazol-2-ones **1** (0.74 mmol) and triethylamine (0.31 mL, 2.22 mmol) were sequentially added, followed by warming up to room temperature with continuous stirring. After completion of the reaction, the crude mixture was concentrated under reduced pressure before purification by column chromatography (CC) using ethyl acetate/hexanes as the eluent.

1,1-Diethyl-3-(2-((triphenyl-λ^5-phosphanylidene)amino)phenyl)-urea (Scheme 2, ***2a****).* Yellow oil; (0.3011 g, 87% yield[a]; 3.8337 g, 82% yield[b]); R_f 0.32 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.27 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 3H), 7.70 (d, J = 7.5 Hz, 3H), 7.54 (t, J = 7.5 Hz, 3H), 7.46−7,44 (m, 6H), 6.67 (t, J = 7.5 Hz, 1H), 6.49 (t, J = 7.5 Hz, 1H), 6.40 (d, J = 7.5 Hz, 1H), 3.37 (q, J = 7.0 Hz, 4H), 1.12 (t, J = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.2, 138.7, 134.6, 134.5 (d, $^3J_{pc}$ = 20.0 Hz), 132.5, 132.4 (d, $^2J_{pc}$ = 10.0 Hz), 132.03, 132.00 (d, $^4J_{pc}$ = 3.75 Hz), 130.9, 130.1 (d, $^1J_{pc}$ = 100.0 Hz), 128.81, 128.71 (d, $^3J_{pc}$ = 12.5 Hz), 120.5, 119.01, 118.94 (d, $^3J_{pc}$ = 8.75 Hz), 118.1, 116.5, 41.5, 14.0; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$) δ 8.56; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{29}H_{31}N_3OP$ 468.2199, found 468.2195.

1,1-Dibutyl-3-(2-((triphenyl-λ^5-phosphanylidene)amino)phenyl)-urea (Scheme 2, ***2b****).* Off-white solid; (0.3489 g, 90% yield); R_f 0.30 (20% EtOAc/hexanes); mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.26 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 3H), 7.70 (d, J = 8.0 Hz, 3H), 7.54 (t, J = 8.0 Hz, 3H), 7.47−7.43 (m, 6H), 6.66 (t, J = 7.5 Hz, 1H), 6.47 (t, J = 7.5 Hz, 1H), 6.37 (d, J = 7.5 Hz, 1H), 3.28 (t, J = 7.5 Hz, 4H), 1.52 (qui, J = 7.5 Hz, 4H), 1.18 (sex, J = 7.5 Hz, 4H), 0.79 (t, J = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.3, 138.7, 134.6, 134.5 (d, $^3J_{pc}$ = 20.0 Hz), 132.56, 132.48 (d, $^2J_{pc}$ = 10.0 Hz), 131.94, 131.92 (d, $^4J_{pc}$ = 2.5 Hz), 131.1, 130.3 (d, $^1J_{pc}$ = 98.75 Hz), 128.77, 128.68 (d, $^3J_{pc}$ = 11.25 Hz), 120.4, 119.04, 118.97 (d, $^3J_{pc}$ = 8.75 Hz), 118.2, 116.7, 47.4, 30.8, 20.2, 14.0; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$) δ 8.11; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{33}H_{39}N_3OP$ 524.2825, found 524.2829.

1,1-Dibenzyl-3-(2-((triphenyl-λ^5-phosphanylidene)amino)-phenyl)urea (Scheme 2, ***2c****).* Pale yellow solid; (0.3942 g, 90% yield); R_f 0.35 (30% EtOAc/hexanes); mp 190−192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.39 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.0 Hz, 3H), 7.53 (d, J = 8.0 Hz, 3H), 7.46 (t, J = 8.0 Hz, 3H), 7.32−7.29 (m, 6H), 7.25−7.20 (m, 10H), 6.70 (t, J = 7.5 Hz, 1H), 6.51 (t, J = 7.5 Hz, 1H), 6.37 (d, J = 7.5 Hz, 1H), 4.52 (s, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.7, 138.9, 137.7, 134.30, 134.14 (d, $^3J_{pc}$ = 20.0 Hz), 132.41, 132.34 (d, $^2J_{pc}$ = 8.75 Hz), 131.87, 131.84 (d, $^4J_{pc}$ = 3.75 Hz), 130.8, 130.0 (d, $^1J_{pc}$ = 98.75 Hz), 128.73, 128.63 (d, $^3J_{pc}$ = 12.50 Hz), 128.6, 127.7, 127.0, 120.9, 118.95, 118.88 (d, $^3J_{pc}$ = 8.75 Hz), 118.1, 116.7, 49.2; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$) δ 8.55; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{39}H_{35}N_3OP$ 592.2512, found 592.2517.

1,1-Dicyclohexyl-3-(2-((triphenyl-λ^5-phosphanylidene)amino)-phenyl)urea (Scheme 2, ***2d****).* Colorless oil (0.3112 g, 73% yield); R_f 0.39 (40% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.10 (ddd, J = 8.0, 2.8, 1.5 Hz, 1H), 7.74−7.69 (m, 6H), 7.53 (td, J = 7.5, 1.5 Hz, 3H), 7.46−7.42 (m, 6H), 6.65 (td, J = 8.0, 1.5 Hz, 1H), 6.44 (td, J = 8.0, 1.5 Hz, 1H), 6.34 (dt, J = 8.0, 1.5 Hz, 1H), 3.41−3.35 (m, 2H), 1.83 (q, J = 12.5 Hz, 4H), 1.63 (t, J = 12.5 Hz, 8H), 1.46 (br d, J = 13.0 Hz, 2H), 1.19−1.09 (m, 4H), 0.98−0.89 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.5, 138.9, 134.7, 134.5 (d, $^3J_{pc}$ = 20.0 Hz), 132.7, 132.6 (d, $^2J_{pc}$ = 10.0 Hz), 131.85, 131.82 (d, $^4J_{pc}$ = 3.8 Hz), 131.1, 130.3 (d, $^1J_{pc}$ = 98.8 Hz), 128.8, 128.7 (d, $^3J_{pc}$ = 12.5 Hz), 120.2, 119.40, 119.32 (d, $^3J_{pc}$ = 10.0 Hz), 118.0, 117.3, 55.7, 31.7, 26.4, 25.4; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$) δ 8.04; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{37}H_{43}N_3OP$ 576.3138, found 576.3135.

1,1-Diisopropyl-3-(2-((triphenyl-λ^5-phosphanylidene)amino)-phenyl)urea (Scheme 2, ***2e****).* Yellow oil; (0.1470 g, 40% yield); R_f 0.41 (40% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.5 Hz, 6H), 7.54 (t, J = 7.5 Hz, 3H), 7.44 (t, J = 7.5 Hz, 6H), 6.66 (t, J = 8.0 Hz, 1H), 6.46 (t, J = 8.0 Hz, 1H), 6.37 (d, J = 8.0 Hz, 1H), 3.94 (sep, J = 6.5 Hz, 2H), 1.23 (d, J = 6.5 Hz, 12H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.8, 138.8, 134.92, 134.76, (d, $^3J_{pc}$ = 20.25 Hz), 132.70, 132.63 (d, $^2J_{pc}$ = 9.1 Hz), 131.92, 131.90 (d, $^4J_{pc}$ = 3.25 Hz), 130.93, 130.13 (d, $^1J_{pc}$ = 99.0 Hz), 128.75, 128.65 (d, $^3J_{pc}$ = 11.9 Hz), 120.3, 119.23, 119.15 (d, $^3J_{pc}$ = 10.0 Hz), 118.1, 116.9, 45.4, 21.3; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$) δ 8.95; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{31}H_{35}N_3OP$ 496.2512, found 496.2516.

1′H-[1,2′-Bibenzo[d]imidazol]-2(3H)-one (Scheme 2, ***4****).* Gray powder; (0.0504 g, 27% yield); R_f 0.35 (30% EtOAc/hexanes); mp > 300 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) 12.46 (s, 1H), 11.72 (s, 1H), 8.47−8.144(m, 1H), 7.76−7.58 (m, 2H), 7.26−7.18 (m, 5H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 152.9, 144.5, 129.1, 127.5, 123.9, 121.15, 121.09, 114.0, 109.9.

N-(2-((Triphenyl-λ^5-phosphanylidene)amino)phenyl)pyrrolidine-1-carboxamide (Scheme 2, ***2f****).* Pale yellow solid; (0.2897 g, 84% yield); R_f 0.28 (40% EtOAc/hexanes); mp 222−225 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 8.35 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.5 Hz, 6H), 7.56 (br s, 3H), 7.70−7.66 (m, 6H), 7.53 (s, 1H), 6.90 (t, J = 8.0 Hz, 1H), 6.74 (t, J = 8.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 3.66 (br s, 4H), 2.14 (br s, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 154.8, 138.5, 134.01, 133.86 (d, $^3J_{pc}$ = 18.8 Hz), 132.45, 132.38 (d, $^2J_{pc}$ = 8.8 Hz), 132.1, 130.79, 129.99 (d, $^1J_{pc}$ = 100.0 Hz), 128.76, 128.66 (d, $^3J_{pc}$ = 12.5 Hz), 121.6, 121.0, 119.35, 119.28 (d, $^3J_{pc}$ = 8.8 Hz), 118.2, 116.6, 109.42, 45.6, 25.5; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$) δ 8.75; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{29}H_{29}N_3OP$ 466.2043, found 466.2043.

N-(2-((Triphenyl-λ^5-phosphanylidene)amino)phenyl)piperidine-1-carboxamide (Scheme 2, ***2g****).* Pale yellow solid; (0.3091 g, 87% yield); R_f 0.28 (30% EtOAc/hexanes); mp 177−179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.18 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 3H), 7.70 (d, J = 8.0 Hz, 3H), 7.55 (t, J = 8.0 Hz, 4H), 7.47−7.43 (m, 6H), 6.68 (t, J = 7.5 Hz, 1H), 6.50 (t, J = 7.5 Hz, 1H), 6.40 (t, J = 7.5 Hz, 1H), 3.48 (t, J = 5.0 Hz, 4H), 1.61−1.56 (m, 6H);

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$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.2, 138.6, 134.4, 134.2 (d, $^3J_{pc}$ = 20.0 Hz), 132.5, 132.4 (d, $^2J_{pc}$ = 8.75 Hz), 131.99, 131.97 (d, $^4J_{pc}$ = 2.5 Hz), 131.0, 130.2 (d, $^1J_{pc}$ = 100.0 Hz), 128.78, 128.69 (d, $^3J_{pc}$ = 11.25 Hz), 120.7, 118.91, 118.84 (d, $^3J_{pc}$ = 8.75 Hz), 118.2, 116.7, 45.1, 25.8, 24.7; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 7.73; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{30}H_{31}N_3OP$ 480.2199, found 480.2201.

*N-(2-((Triphenyl-λ⁵-phosphanylidene)amino)phenyl)-morpholine-4-carboxamide (Scheme 2, **2h**).* White solid; (0.2711 g, 76% yield); R_f 0.30 (40% EtOAc/hexanes); mp 179−180 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.5 Hz, 3H), 7.68 (d, J = 7.5 Hz, 3H), 7.55 (t, J = 7.5 Hz, 3H), 7.47−7.44 (m, 6H), 6.69 (t, J = 8.0 Hz, 1H), 6.53 (t, J = 8.0, 1H), 6.41 (d, J = 8.0 Hz, 1H), 3.68 (t, J = 5.0 Hz, 4H), 3.47 (t, J = 5.0 Hz, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.2, 138.8, 133.8, 133.6 (d, $^3J_{pc}$ = 20.0 Hz), 132.5, 132.1 (d, $^2J_{pc}$ = 10.0 Hz), 132.13, 132.11 (d, $^4J_{pc}$ = 2.5 Hz), 130.9, 130.1 (d, $^1J_{pc}$ = 100.0 Hz), 128.82, 128.73 (d, $^3J_{pc}$ = 11.25 Hz), 121.2, 118.95, 118.88 (d, $^3J_{pc}$ = 8.75 Hz), 118.2, 116.8, 66.7, 44.1; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 8.52; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{29}N_3O_2P$ 482.1992, found 482.1994.

(Cyclohexylamino)triphenylphosphonium iodide. White solid; (0.2849 g, 79% yield); R_f 0.34 (10% MeOH/EtOAc); mp 188−189 °C; ^1H NMR (500 MHz, $CDCl_3$) NMR δ 7.85−7.81 (m, 6H), 7.77−7.73 (m, 3H), 7.65−7.61 (m, 6H), 6.89 (t, J = 10.1 Hz, 1H), 2.85−2.76 (m, 1H), 2.10−2.02 (m, 2H), 1.70−1.66 (m, 4H), 1.47−1.43 (m, 1H), 1.19−1.12 (m, 1H), 0.99−0.89 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 134.79, 134.77 (d, $^4J_{pc}$ = 3.1 Hz), 133.87, 133.78 (d, $^3J_{pc}$ = 11.2 Hz), 129.86, 129.76 (d, $^2J_{pc}$ = 13.2 Hz), 122.24, 121.42 (d, $^1J_{pc}$ = 103.0 Hz), 54.48, 54.46 (d, $^2J_{pc}$ = 2.8 Hz), 35.23, 35.19 (d, $^3J_{pc}$ = 4.4 Hz), 25.8, 24.6; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 36.07; HRMS (ESI) m/z $[M - I]^+$ calcd for $C_{24}H_{27}N_3P$ 360.1876, found 360.1873.

*3-(4,5-Dichloro-2-((triphenyl-λ⁵-phosphanylidene)amino)-phenyl)-1,1-diethylurea (Scheme 3, **2i**).* Yellow solid; (0.3255 g, 82% yield); mp 170−172 °C; R_f 0.32 (30% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.42 (s, 1H), 7.69−7.66 (m, 6H), 7.58 (t, J = 7.5 Hz, 3H), 7.49 (t, J = 7.5 Hz, 6H), 6.32 (s, 1H), 3.35 (q, J = 7.0 Hz, 4H), 1.12 (t, J = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.4, 138.8, 134.3, 134.1 (d, $^3J_{pc}$ = 20.0 Hz), 132.44, 132.36 ($^2J_{pc}$ = 9.9 Hz), 132.40, 132.38 (d, $^4J_{pc}$ = 2.8 Hz), 129.9, 129.1 (d, $^1J_{pc}$ = 99.9 Hz), 129.0, 128.9 (d, $^3J_{pc}$ = 11.25 Hz), 122.5, 120.5, 119.05, 118.97 (d, $^3J_{pc}$ = 8.75 Hz), 117.4, 41.5, 13.9; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 10.49; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{29}{}^{35}ClN_3OP$ 536.1420, found 536.1419; calcd for $C_{29}H_{29}{}^{37}ClN_3OP$ 540.1360, found 540.1363.

*3-(4,5-Dimethoxy-2-((triphenyl-λ⁵-phosphanylidene)amino)-phenyl)-1,1-diethylurea (Scheme 3, **2j**).* Yellow oil; (0.3516 g, 90% yield) ; R_f 0.30 (15% acetone/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.11 (s, 1H), 7.73−7.69 (m, 6H), 7.57−7.54 (m, 3H), 7.48−7.45 (m, 6H), 6.01 (s, 1H), 3.84 (s, 3H), 3.36 (d, J = 7.0 Hz, 4H), 3.30 (s, 3H), 1.13 (d, J = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.9, 142.2, 141.2, 132.5, 132.4 (d, $^2J_{pc}$ = 9.5 Hz), 132.0, 131.97 (d, $^4J_{pc}$ = 2.8 Hz), 131.2, 130.4 (d, $^1J_{pc}$ = 97.0 Hz), 128.78, 128.68 (d, $^3J_{pc}$ = 11.9 Hz), 127.93, 127.77 (d, $^3J_{pc}$ = 20.0 Hz), 105.38, 105.31 (d, $^3J_{pc}$ = 8.9 Hz), 102.7, 56.1, 55.9, 41.4, 13.9; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 7.14; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{31}H_{35}N_3O_3P$ 528.2411, found 528.2409.

*3-(5-Bromo-2-((triphenyl-λ⁵-phosphaneylidene)amino)phenyl)-1,1-diethylurea and 3-(4-Bromo-2-((triphenyl-λ⁵-phosphaneylidene)amino)phenyl)-1,1-diethylurea (Scheme 3, **2k** and **2k′**).* Yellow oil; (0.3479 g, 86% yield, ratio **2k**:**2k′** 1:1); R_f 0.37 (30% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.66 (s, 1H), 8.50−8.43 (t, J = 2.5 Hz 1H), 8.14 (dd, J = 8.5, 2.5 Hz, 1H), 7.71−7.66 (m, 12H), 7.59−7.54 (m, 6H), 7.50−7.44 (m, 12H), 6.76 (dd, J = 8.5, 2.0 Hz, 1H), 6.57 (dd, J = 8.5, 2.5 Hz, 1H), 6.42 (d, J = 2.0 Hz, 1H), 6.20 (d, J = 8.5 Hz, 1H), 3.37−3.33 (m, 8H), 1.13−1.10 (m, 12H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.7, 154.6, 140.5, 137.8, 135.76, 135.60 (d, $^3J_{pc}$ = 20.0 Hz), 133.79, 133.63 (d, $^2J_{pc}$ = 20.0 Hz), 132.49, 132.41 (d, $^2J_{pc}$ = 10.0 Hz), 132.47, 132.39 (d, $^2J_{pc}$ = 10.0 Hz), 132.26, 132.24 (d, $^4J_{pc}$ = 2.5 Hz), 132.17, 132.15 (d, $^4J_{pc}$ = 2.5 Hz), 130.50, 129.70 (d, $^1J_{pc}$ = 100.0 Hz), 130.27, 129.48 (d, $^1J_{pc}$ = 98.75 Hz), 128.9, 128.88, 128.83 (d, $^3J_{pc}$ = 6.25 Hz), 128.78 (d, $^3J_{pc}$ = 12.5 Hz), 123.0, 121.22, 121.14 (d, $^3J_{pc}$ = 10.0 Hz), 120.6, 119.61, 119.54 (d, $^3J_{pc}$ = 8.75 Hz), 119.2, 117.5, 112.9, 110.4, 41.53, 41.46, 13.90; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 7.81, 7.62; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{30}{}^{79}BrN_3OP$ 546.1304, found 546.1307; calcd for $C_{29}H_{30}{}^{81}BrN_3OP$ 548.1284, found 548.1288.

*1,1-Diethyl-3-(5-iodo-2-((triphenyl-λ⁵-phosphaneylidene)-amino)phenyl)urea and 1,1-Diethyl-3-(4-iodo-2-((triphenyl-λ⁵-phosphaneylidene)amino)phenyl)urea (Scheme 3, **2l** and **2l′**).* Yellow oil; (0.3603 g, 82% yield, ratio **2l**:**2l′** 1.4:1); R_f 0.35 (30% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.66 (s, 1H), 8.62 (t, J = 2.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.71−7.66 (m, 12H), 7.59−7.54 (m, 6H), 7.50−7.44 (m, 12H), 6.95 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.59 (s, 1H), 6.10 (d, J = 8.0 Hz, 1H), 3.35 (q, J = 7.2 Hz, 8H), 1.11 (t, J = 7.2 Hz, 12H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.7, 154.6, 140.8, 138.7, 136.09, 135.93 (d, $^3J_{pc}$ = 20.0 Hz), 134.53, 134.37 (d, $^2J_{pc}$ = 20.0 Hz), 132.49, 132.40, (d, $^2J_{pc}$ = 10.0 Hz), 132.47, 132.40 (d, $^2J_{pc}$ = 8.75 Hz), 132.28, 132.25 (d, $^4J_{pc}$ = 3.75 Hz), 132.21, 132.18 (d, $^4J_{pc}$ = 3.75 Hz), 130.41,129.62 (d, $^1J_{pc}$ = 98.75 Hz), 130.24, 129.44 (d, $^1J_{pc}$ = 100.0 Hz), 129.3, 128.93, 128.83 (d, $^3J_{pc}$ = 12.5 Hz), 128.90, 128.80 (d, $^3J_{pc}$ = 12.5 Hz), 127.11, 127.03 (d, $^3J_{pc}$ = 10.0 Hz), 126.9, 124.7, 120.47, 120.39 (d, $^3J_{pc}$ = 10.0 Hz), 118.2, 83.6, 80.1, 41.55, 41.48, 14.0; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 9.89, 9.70; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{30}IN_3OP$ 594.1166, found 594.1161.

*1,1-Diethyl-3-(4-nitro-2-((triphenyl-λ⁵-phosphanylidene)amino)-phenyl)urea (Scheme 3, **2m**).* Yellow oil; (0.2463 g, 65% yield); R_f 0.34 (40% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.72 (s, 1H), 7.69 (t, J = 7.5 Hz, 6H), 7.62 (t, J = 7.5 Hz, 3H), 7.53−7.50 (m, 6H), 7.47 (dd, J = 9.0, 2.0 Hz, 1H), 6.25 (d, J = 9.0 Hz, 1H), 3.39 (q, J = 7.0 Hz, 4H), 1.15 (t, J = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.4, 147.0, 138.7, 134.10, 133.94 (d, $^3J_{pc}$ = 20.0 Hz), 132.76, 132.73 (d, $^4J_{pc}$ = 3.8 Hz), 132.46, 132.38 (d, $^2J_{pc}$ = 10.0 Hz), 129.19, 129.09 (d, $^3J_{pc}$ = 12.5 Hz), 129.0, 128.2 (d, $^1J_{pc}$ = 100.0 Hz), 117.8, 116.95, 116.86 (d, $^3J_{pc}$ = 11.3 Hz), 111.8, 41.6, 13.9; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 13.29; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{30}N_4O_3P$ 513.2050, found 513.2054.

*1,1-Diethyl-3-(4-nitro-2-((triphenyl-λ⁵-phosphanylidene)amino)-phenyl)urea (Scheme 3, **2m′**).* Yellow solid; (0.0831 g, 22% yield); R_f 0.34 (40% EtOAc/hexanes); mp 158−160 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.5 Hz, 6H), 7.61 (d, J = 7.5 Hz, 3H), 7.52−7.49 (m, 6H), 7.17 (s, 1H), 3.40 (q, J = 7.0 Hz, 4H), 1.15 (t, J = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.2, 141.16, 141.00 (d, $^3J_{pc}$ = 20.0 Hz), 140.95, 139.2, 132.58, 132.56 (d, $^4J_{pc}$ = 2.5 Hz), 132.47, 132.40 (d, $^2J_{pc}$ = 8.75 Hz), 129.4, 128.5 (d, $^1J_{pc}$ = 100.0 Hz), 129.11, 129.02 (d, $^3J_{pc}$ = 11.25 Hz), 115.1, 114.5, 112.33, 112.25 (d, $^3J_{pc}$ = 10.0 Hz), 41.7, 13.9; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 13.29; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{30}N_4O_3P$ 513.2050, found 513.2054.

*1,1-Diethyl-3-(5-methyl-2-((triphenyl-λ⁵-phosphaneylidene)-amino)phenyl)urea and 1,1-Diethyl-3-(4-methyl-2-((triphenyl-λ⁵-phosphaneylidene)amino)phenyl)urea (Scheme 3, **2n** and **2n′**).* Yellow oil; (0.3384 g, 95% yield, ratio **2n**:**2n′**; 1:1); Rf 0.35 (40% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.68 (s, 1H), 8.16 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.74−7.69 (m, 12H), 7.56−7.52 (m 6H), 7.47−7.43 (m, 12H), 6.49 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 8.5 Hz, 1H), 6.29 (d, J = 8.5 Hz, 1H), 6.20 (s, 1H), 3.36 (qui, J = 6.8 Hz, 8H), 2.21 (s, 3H), 1.94 (s, 3H), 1.12 (q, J = 6.8 Hz, 12H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.9, 154.9, 138.5, 136.0, 134.3, 134.2 (d, $^3J_{pc}$ = 20.0 Hz), 132.56, 132.49 (d, $^2J_{pc}$ = 8.75 Hz), 132.54, 132.46 (d, $^2J_{pc}$ = 10.0 Hz), 131.97, 131.95 (d, $^4J_{pc}$ = 2.5 Hz), 131.92 (d, $^4J_{pc}$ = 3.75 Hz), 131.10, 130.30 (d, $^1J_{pc}$ = 100.0 Hz), 131.08, 130.28 (d, $^1J_{pc}$ = 100.0 Hz), 129.5, 128.77, 128.67 (d, $^3J_{pc}$ = 12.50 Hz), 127.4, 120.8, 120.02, 119.94 (d, $^3J_{pc}$ = 10.0 Hz), 118.60, 118.52 (d, $^3J_{pc}$ = 10.0 Hz), 118.58, 117.4, 116.3, 41.5, 41.4, 21.3, 21.0, 14.0; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ 7.81, 7.62; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{30}H_{33}N_3OP$ 482.2356, found 482.2351.

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*1,1-Diethyl-3-(2-methyl-6-((triphenyl-λ⁵-phosphanylidene)-amino)phenyl)urea (Scheme 3, **2o**).* Yellow oil; (0.3274 g, 92% yield); R_f 0.28 (10% acetone/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.69 (m, 6H), 7.53−7.50 (m, 3H), 7.44−7.41 (m, 6H), 7.33 (s, 1H), 6.58−6.54 (m, 2H), 6.27−6.25 (m, 1H), 3.40 (q, *J* = 7.0 Hz, 4H), 2.26 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.5, 143.4, 133.14, 132.68, 132.61 (d, $^2J_{pc}$ = 9.8 Hz), 132.61, 132.55 (d, $^3J_{pc}$ = 7.5 Hz), 131.79, 131.77 (d, $^4J_{pc}$ = 2.8 Hz), 131.29, 130.49 (d, $^1J_{pc}$ = 100.0 Hz), 128.67, 128.58 (d, $^3J_{pc}$ = 11.9 Hz), 123.6, 120.3, 117.58, 117.50 (d, $^3J_{pc}$ = 9.6 Hz), 41.5, 19.5, 14.0; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$) δ 5.53; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{33}N_3OP$ 482.2356, found 482.2357.

Scale-Up for the Synthesis of 2a. To a mixture of iodine (3.8075 g, 15 mmol) and triphenylphosphine (3.9049 g, 15 mmol) in freshly distilled dichloromethane (50 mL) was added diethylamine (1.25 mL, 12 mmol) at 0 °C under N_2. After that, **1a** (1.3415 g, 10 mmol) and triethylamine (4.20 mL, 30 mmol) were sequentially added, followed by warming up to room temperature with continuous stirring for 16 h. Then, the reaction mixture was quenched with water and extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, and the product **2a** was obtained as a yellow oil (3.8337 g, 82% yield).

Synthesis of *N*^{1}-Substituted 2-Aminobenzimidazoles 6 from 2 (Method A). In a 10 mL pressure tube, iminophosphorane **2** (0.38 mmol) was added with 1,2-dichloroethane (5 mL), followed by isothiocyanate **5** (0.45 mmol) and triethylamine (0.16 mL, 1.14 mmol). The tightly capped vessel was then subjected to heating in a preset oil bath at 120 °C until reaction completion. After cooling down, the mixture was concentrated under reduced pressure before column chromatography using ethyl acetate/hexanes as the eluent to afford the product **6**.

Synthesis of 6 or 7 from 1a (Method B). To a solution of iodine (144 mg, 0.57 mmol) and triphenylphosphine (150 mg, 0.57 mmol) in freshly distilled dichloromethane (2 mL), amine (0.45 mmol), 2-hydroxybenzimidazole **1a** (0.0510 g, 0.38 mmol), and triethylamine (0.16 mL, 1.14 mmol) were sequentially added at 0 °C under N_2. After stirring at 25 °C for 1 h, the mixture was transferred into a pressure tube before concentrated, followed by adding 1,2-dichloroethane (5 mL) and isothiocyanate **5** or methyl 2-isothiocyanatobenzoate (0.45 mmol). The tightly capped vessel was heated in a preset oil bath at 120 °C until reaction completion. After cooling down, the crude mixture was concentrated under reduced pressure before purified by CC.

*N,N-Diethyl-2-(phenylamino)-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6a**).* Coloress oil (0.1045 g, 89% yield (A); 0.0889g, 76% yield (B); R_f 0.48 (40% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.19−7.12 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 3.62 (sex, *J* = 7.0 Hz, 2H), 3.48 (sex, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.6, 149.8, 142.0, 139.0, 130.2, 129.2, 123.4, 122.6, 121.3, 118.7, 118.0, 110.2, 42.8, 13.7; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}N_4O$ 309.1710, found 309.1714.

*N,N-Diethyl-2-((4-nitrophenyl)amino)-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6b**).* Yellow solid (0.1207 g, 90% yield); mp 188−189 °C; R_f 0.37 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 3.65 (sex, *J* = 7.0 Hz, 2H), 3.48 (sex, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.3, 148.1, 144.8, 142.1, 141.2, 130.0, 125.4, 123.9, 122.4, 118.6, 117.7, 110.6, 42.9, 13.6; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_5O_3$ 354.1561, found 354.1558.

*N,N-Diethyl-2-((4-chlorophenyl)amino)-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6c**).* White solid (0.1170 g, 90% yield); mp 103−105 °C; R_f 0.25 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.27 (t, *J* = 9.0 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 3.65 (sex, *J* = 7.0 Hz, 2H), 3.48 (sex, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.3, 148.1, 144.8, 142.1, 141.2, 130.0, 125.4, 123.9, 122.4, 118.6, 117.6, 110.6, 42.9, 13.6; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}{}^{35}ClN_4O$ 343.1320, found 343.1317, calcd for $C_{18}H_{20}{}^{37}ClN_4O$ 345.1290, found 345.1289.

*N,N-Diethyl-2-((4-methoxyphenyl)amino)-1H-benzo[d]-imidazole-1-carboxamide (Scheme 4, **6d**).* Yellow oil (0.1119 g, 87% yield); R_f 0.36 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.13−7.07 (m, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 3.58 (sex, *J* = 7.0 Hz, 2H), 3.44 (sex, *J* = 7.0 Hz, 2H), 1.23 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.6, 153.6, 150.7, 142.1, 132.2, 130.4, 123.3, 121.0, 120.9, 117.8, 114.5, 110.1, 55.6, 42.8, 13.6; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{23}N_4O_2$ 339.1816, found 339.1816.

*N,N-Diethyl-2-(o-tolylamino)-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6e**).* Red oil; (0.0859 g, 70% yield); R_f 0.32 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.0 Hz, 1H), 8.14 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.25−7.22 (m, 2H), 7.16−7.15 (m, 2H), 7.04 (t, *J* = 8.0 Hz, 1H), 3.62 (sex, *J* = 7.5 Hz, 2H), 3.50 (sex, *J* = 7.0 Hz, 2H), 2.38 (s, 3H), 1.28 (t, *J* = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.9, 150.3, 142.0, 137.3, 130.4, 130.3, 127.1, 126.6, 123.4, 123.0, 121.2, 119.7, 118.0, 110.2, 43.0, 17.7, 13.7; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{23}N_4O$ 323.1866, found 323.1863.

*2-(Benzylamino)-N,N-diethyl-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6f**).* Yellow oil (0.0944 g, 77% yield); R_f 0.26 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.08−7.02 (m, 2H), 5.96 (t, *J* = 5.5 Hz 1H), 4.73 (d, *J* = 5.5 Hz, 2H), 3.53 (sex, *J* = 7.0 Hz, 2H), 3.40 (sex, *J* = 7.0 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.3, 153.4, 142.3, 138.3, 131.3, 128.7, 127.7, 127.5, 123.2, 120.5, 117.1, 109.9, 47.1, 42.7, 13.7; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{23}N_4O$ 323.1866, found 323.1868.

*5,6-Dichloro-N,N-diethyl-2-(phenylamino)-1H-benzo[d]-imidazole-1-carboxamide (Scheme 4, **6g**).* White solid; (0.1176 g, 82% yield); mp 115−116 °C; R_f 0.38 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.15 (s, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 3.60−3.53 (m, 2H), 3.45−3.38 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.9, 151.0, 141.8, 138.3, 129.6, 129.2, 127.2, 124.6, 123.2, 119.1, 118.9, 111.5, 43.0, 13.6; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}{}^{35}Cl_2N_4O$ 377.0930, found 377.0926, calcd for $C_{18}H_{19}{}^{37}Cl_2N_4O$ 381.0870, found 381.0866.

*N,N-Diethyl-5,6-dimethoxy-2-(phenylamino)-1H-benzo[d]-imidazole-1-carboxamide (Scheme 4, **6h**).* Green oil; (0.1194 g, 85% yield); R_f 0.30 (60% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.65 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.16 (s, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.72 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.57 (sex, *J* = 7.0 Hz, 2H), 3.47 (sex, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.7, 148.9, 147.0, 145.3, 139.1, 135.4, 129.1, 123.2, 122.3, 118.3, 101.7, 95.9, 56.9, 56.3, 42.6, 13.6; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}N_4O_3$ 369.1921, found 369.1915.

*N,N-Diethyl-6-nitro-2-(phenylamino)-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6i**).* Yellow oil; (0.0629 g, 47% yield); R_f 0.37 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.5 Hz, 1H), 8.09 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.02 (br s, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.12 (t *J* = 8.5 Hz, 1H), 3.64−3.57 (m, 2H), 3.46−3.39 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.4, 151.8, 144.5, 142.2, 138.1, 134.8, 129.3, 123.6, 119.1, 117.4, 113.7, 109.4, 43.1, 13.6; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{19}N_5NaO_3$ 376.1380, found 376.1379.

*N,N-Diisopropyl-2-(phenylamino)-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6j**).* Colorless oil; (0.1127 g, 88% yield); R_f 0.46 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl3) δ 7.65 (d,

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J = 7.5 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.15−7.11 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 3.81 (sep, J = 6.5 Hz, 1H), 1.48 (d, J = 6.5 Hz, 3H), 1.34 (d, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 151.4, 149.5, 141.7, 139.1, 130.9, 129.2, 123.1, 122.6, 121.2, 118.8, 118.0, 109.2, 49.3, 21.6, 20.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{25}N_4O$ 337.2023, found 337.2024.

*N,N-Dibutyl-2-(phenylamino)-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6k**).* White solid; (0.0992 g, 72% yield); mp 105−106 °C; R_f 0.25 (5% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.68 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.09−7.04 (m, 2H), 3.62−3.56 (m, 2H), 3.34−3.29 (m, 2H), 1.65−1.57 (m, 4H), 1.35−1.26 (m, 4H), 0.86 (d, J = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.0, 149.9, 141.9, 139.0, 130.2, 129.2, 123.3, 122.6, 121.3, 118.8, 118.1, 110.3, 48.0, 30.1, 19.9, 13.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{29}N_4O$ 365.2336, found 365.2336.

*N,N-Dibenzyl-2-(phenylamino)-1H-benzo[d]imidazole-1-carboxamide (Scheme 4, **6l**).* Red oil; (0.1263 g, 77% yield); R_f 0.30 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.67 (d, J = 7.5 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.40−7.31 (m, 9H), 7.23−7.17 (m, 4H), 7.11−7.06 (m, 3H), 4.68 (d, J = 12.0 Hz, 2H), 4.36 (d, J = 15.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.7, 150.0, 142.1, 138.9, 135.5, 130.3, 129.2, 129.1, 128.4, 128.2, 123.7, 122.8, 121.6, 119.1, 118.2, 110.4, 51.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_4O$ 433.2023, found 433.2028.

*(2-(Phenylamino)-1H-benzo[d]imidazol-1-yl)(pyrrolidin-1-yl)-methanone (Scheme 4, **6m**).* Brown oil; (0.1013 g, 87% yield); R_f 0.19 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 3.60 (br s, 4H), 2.00 (br s, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 152.7, 149.3, 142.1, 138.9, 129.6, 129.2, 123.2, 122.5, 121.1, 118.5, 118.0, 111.1, 48.7, 25.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_4O$ 307.1553, found 307.1548.

*(2-(Phenylamino)-1H-benzo[d]imidazol-1-yl)(piperidin-1-yl)-methanone (Scheme 4, **6n**).* Red oil; (0.1019 g, 84% yield); R_f 0.35 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.20−7.14 (m, 2H), 7.08 (t, J = 8.0 Hz, 1H), 3.69−3.65 (m, 2H), 3.46−3.41 (m, 2H), 1.76−1.69 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.9, 150.3, 142.0, 137.3, 130.4, 130.3, 127.1, 126.6, 123.4, 123.0, 121.2, 119.7, 118.0, 110.2, 43.0, 17.7, 13.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{21}N_4O$ 321.1710, found 321.1712.

*Morpholino(2-(phenylamino)-1H-benzo[d]imidazol-1-yl)-methanone (Scheme 3, **6o**).* Yellow oil; (0.0871 g, 71% yield); R_f 0.23 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.18−7.12 (m, 2H), 7.06 (t, J = 7.5 Hz, 1H), 3.85−3.80 (m, 2H), 3.77−3.72 (m, 2H), 3.64−3.55 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.8, 149.8, 142.0, 138.7, 129.7, 129.2, 123.9, 122.8, 121.5, 118.7, 118.2, 110.6, 66.6, 47.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_4O_2$ 323.1503, found 323.1502.

*N,N-Diethyl-12-oxobenzo[4,5]imidazo[2,1-b]quinazoline-6-(12H)-carboxamide (Scheme 4, **7a**).* White solid; (0.0954 g, 75% yield); mp 162−164 °C; R_f 0.44 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 7.5 Hz, 1H), 8.40 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.43−7.35 (m, 3H), 3.73 (br s, 2H), 3.51 (br s, 2H), 1.43 (br s, 3H), 1.25 (br s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.7, 149.6, 148.6, 144.4, 134.5, 130.2, 126.9, 126.6, 126.4, 126.3, 124.0, 123.5, 117.6, 116.3, 111.0, 43.8, 42.2, 14.4, 12.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{19}N_4O_2$ 335.1503, found 335.1505.

*N,N-Dibutyl-12-oxobenzo[4,5]imidazo[2,1-b]quinazoline-6-(12H)-carboxamide (Scheme 4, **7b**).* White solid; (0.0863 g, 58% yield); mp 107−108 °C; R_f 0.45 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.46−7.35 (m, 4H), 3.93−3.34 (m, 4H), 1.81 (br s, 2H), 1.61 (br s, 4H), 1.26−1.13 (m, 2H), 1.06 (br s, 3H), 0.73 (br s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.7, 150.2, 148.6, 144.3, 134.5, 130.2, 127.0, 126.7, 126.5, 126.3, 124.0, 123.5, 117.6, 116.3, 111.3, 49.1, 47.0, 30.7, 29.5, 20.0, 19.8, 13.9, 13.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{27}N_4O_2$ 391.2129, found 391.2133.

*N,N-Dibenzyl-12-oxobenzo[4,5]imidazo[2,1-b]quinazoline-6-(12H)-carboxamide (Scheme 4, **7c**).* White solid; (0.1235 g, 71% yield). mp 143−144 °C; R_f 0.43 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H) 7.62 (t, J = 8.0 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.35−7.25 (m, 10H), 7.15 (t, J = 7.5 Hz, 1H), 4.72 (s, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.9, 154.5, 151.0, 136.8, 136.4, 133.3, 132.6, 132.34, 132.26, 131.59, 131.57, 128.80, 128.76, 128.6, 128.5, 128.04, 127.79, 124., 123.4, 112.6, 49.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{23}N_4O_2$ 459.1816, found 459.18.17.

*6-(Pyrrolidine-1-carbonyl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (Scheme 4, **7d**).* White solid; (0.1013 g, 80% yield). mp 148−149 °C; R_f 0.43 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 8.0 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.46−7.36 (m, 3H), 3.85 (t, J = 6.5 Hz, 2H), 3.71 (br s, 2H), 2.11 (t, J = 6.5 Hz, 2H), 1.99 (t, J = 6.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.7, 148.4, 148.3, 143.8, 134.6, 129.6, 127.0, 126.5, 126.4, 126.2, 124.1, 123.6, 117.6, 116.2, 112.0, 48.4, 47.8, 25.9, 24.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_4O_2$ 333.1346, found 333.1342.

*6-(Piperidine-1-carbonyl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (Scheme 4, **7e**).* White solid; (0.1027 g, 78% yield); mp 236−237 °C; R_f 0.43 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.40−7.35 (m, 2H), 3.85 (br s, 2H), 3.61 (br s, 1H), 3.41 (br s, 1H), 1.90 (br s, 2H), 1.75 (br s, 3H), 1.56 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.6, 149.0, 148.5, 144.2, 134.5, 130.1, 127.0, 126.6, 126.4, 126.2, 124.1, 123.6, 117.6, 116.2, 111.8, 48.9, 45.8, 26.3, 25.6, 24.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{19}N_4O_2$ 347.1503, found 347.1508.

*6-(Morpholine-4-carbonyl)benzo[4,5]imidazo[2,1-b]-quinazoline-6(12H)-carboxamide (Scheme 4, **7f**).* White solid; (0.0889 g, 67% yield); mp 146−147 °C; R_f 0.41 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.45−7.35 (m, 3H), 4.12−3.70 (m, 8H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.5, 149.4, 148.1, 144.0, 134.7, 129.9, 127.0, 126.7, 126.5, 126.1, 124.4, 123.9, 117.7, 116.2, 112.3, 66.7, 48.3, 45.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_4O_3$ 349.1295, found 349.1297.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01979.

Copies of ^1H NMR, $^{13}C\{^1H\}$ NMR spectra of all products and $^{31}P\{^1H\}$ NMR spectra of selected products, X-ray data of **2c**, and $^{31}P\{^1H\}$ NMR reaction monitoring studies (PDF)

Structure with X-ray data of **2c** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Molina, P.; Vilaplana, M. J. Iminophosphoranes: useful building blocks for the preparation of nitrogen-containing heterocycles. *Synthesis* **1994**, *1994*, 1197. Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. Synthetic applications of intramolecular aza-Wittig reaction for the preparation of heterocyclic compounds. *Curr. Org. Chem.* **2009**, *13*, 810. Eguchi, S.; Matsushita, Y.; Yamashita, K. The aza-Wittig reaction in heterocyclic synthesis. A review. *Org. Prep. Proced. Int.* **1992**, *24*, 209. Lao, Z.; Toy, P. H. Catalytic Wittig and aza-Wittig reactions. *Beilstein J. Org. Chem.* **2016**, *12*, 2577.

(2) Wamhoff, H.; Richardt, G.; Stoelben, S. Iminophosphoranes: Versatile Tools in Heterocyclic Synthesis. *Adv. Heterocycl. Chem.* **1995**, *64*, 159. Fresneda, P. M.; Molina, P. Application of iminophosphorane-based methodologies for the synthesis of natural products. *Synlett* **2004**, 1. Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. The aza-Wittig reaction. An efficient tool for the construction of carbon-nitrogen double bonds. *Tetrahedron* **2007**, *63*, 523. Cai, L.; Zhang, K.; Chen, S.; Lepage, R. J.; Houk, K. N.; Krenske, E. H.; Kwon, O. Catalytic Asymmetric Staudinger-aza-Wittig Reaction for the Synthesis of Heterocyclic Amines. *J. Am. Chem. Soc.* **2019**, *141*, 9537. Tryniszewski, M.; Bujok, R.; Cmoch, P.; Ganczarczyk, R.; Kulszewicz-Bajer, I.; Wrobel, Z. Direct Reductive Cyclocondensation of the Nitro Group with the Amido Group: Key Role of the Iminophosphorane Intermediate in the Synthesis of 1,4-Dibenzodiazepine Derivatives. *J. Org. Chem.* **2019**, *84*, 2277. Tukhtaev, H. B.; Ivanov, K. L.; Bezzubov, S. I.; Cheshkov, D. A.; Melnikov, M. Y.; Budynina, E. M. aza-Wittig Reaction with Nitriles: How Carbonyl Function Switches from Reacting to Activating. *Org. Lett.* **2019**, *21*, 1087.

(3) Garcia-Alvarez, J.; Garcia-Garrido, S. E.; Cadierno, V. Iminophosphorane-phosphines: Versatile ligands for homogeneous catalysis. *J. Organomet. Chem.* **2014**, *751*, 792. Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. Phosphine Organocatalysis. *Chem. Rev.* **2018**, *118*, 10049. Krawczyk, H.; Dziegielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, L. Chiral Iminophosphoranes-An Emerging Class of Superbase Organocatalysts. *Chem. - Eur. J.* **2015**, *21*, 10268. Nunez, M. G.; Farley, A. J. M.; Dixon, D. J. Bifunctional Iminophosphorane Organocatalysts for Enantioselective Synthesis: Application to the Ketimine Nitro-Mannich Reaction. *J. Am. Chem. Soc.* **2013**, *135*, 16348.

(4) Staudinger, H.; Meyer, J. New organic compounds of phosphorus. III. Phosphinemethylene derivatives and phosphinimines. *Helv. Chim. Acta* **1919**, *2*, 635.

(5) Eguchi, S. Recent progress in the synthesis of heterocyclic natural products by the Staudinger/intramolecular aza-wittig reaction. *ARKIVOC* **2005**, *2005*, 98. Gololobov, Y. G.; Kasukhin, L. F. Recent advances in the Staudinger reaction. *Tetrahedron* **1992**, *48*, 1353. van Berkel, S. S.; van Eldijk, M. B.; van Hest, J. C. M. Staudinger Ligation as a Method for Bioconjugation. *Angew. Chem., Int. Ed.* **2011**, *50*, 8806. Hartung, R.; Paquette, L. Recent synthetic applications of the tandem Staudinger/Aza-Wittig reaction. *Chemtracts* **2004**, *17*, 72.

(6) Omran, O. A.; Sayed, S. M.; Raslan, M. A. Iminophosphoranes in Heterocyclic Synthesis: A Facile Synthesis of Pyrido[4,3-*D*]-Pyrimidine and Pyrido[4,3-*D*][1,3]Oxazine Derivatives via Intermolecular aza-Wittig Reactions. *J. Heterocycl. Chem.* **2017**, *54*, 1103. Alvarez-Sarandes, R.; Peinador, C.; Quintela, J. M. Iminophosphoranes in heterocyclic chemistry. A simple one-pot synthesis of pyridothienopyridazines and pyrimidothienopyridazines. *Tetrahedron* **2001**, *57*, 5413. Zeng, F.; Alper, H. Tandem Palladium-Catalyzed Addition/Cyclocarbonylation: An Efficient Synthesis of 2-Heteroquinazolin-4(3*H*)-ones. *Org. Lett.* **2010**, *12*, 1188.

(7) Adib, M.; Sheikhi, E.; Deljoush, A. Reaction between triphenylphosphine and aromatic amines in the presence of diethyl azodicarboxylate: an efficient synthesis of aryliminophosphoranes under neutral and mild conditions. *Tetrahedron* **2011**, *67*, 4137.

(8) Yavari, I.; Adib, M.; Hojabri, L. Vinyltriphenylphosphonium salt mediated serendipitous synthesis of aryliminophosphoranes. *Tetrahedron* **2002**, *58*, 7213.

(9) Bestmann, H. J.; Seng, F. Reaction of phosphinealkylenes with Schiff bases. *Angew. Chem.* **1963**, *75*, 475.

(10) Ciganek, E. Iminophosphoranes from the reaction of ylides with nitriles. *J. Org. Chem.* **1970**, *35*, 3631.

(11) Alajarin, M.; Lopez-Leonardo, C.; Llamas-Lorente, P. The alkylation of aminophosphanes: A new synthesis of iminophosphoranes. *Synlett* **2003**, 0801.

(12) Lukasik, E.; Wrobel, Z. Simple Synthesis of 2-Aminoaryliminophosphoranes from *N*-Aryl-2-nitrosoanilines and Their Application in 2-Aminobenzimidazole Synthesis. *Synlett* **2014**, *25*, 217.

(13) Lukasik, E.; Wrobel, Z. 2-(Arylamino)aryliminophosphoranes from 2-nitrodiarylamines. *Heteroat. Chem.* **2016**, *27*, 372. Tryniszewski, M.; Bujok, R.; Cmoch, P.; Ganczarczyk, R.; Kulszewicz-Bajer, I.; Wrobel, Z. Direct Reductive Cyclocondensation of the Nitro Group with the Amido Group: Key Role of the Iminophosphorane Intermediate in the Synthesis of 1,4-Dibenzodiazepine Derivatives. *J. Org. Chem.* **2019**, *84*, 2277.

(14) Min, X.; Liu, J. An Approach to P:N Bond Formation: Straightforward Synthesis of Arylurea-Derived Phosphazenes via Condensation of Ph_3P:O with *N*-Monosubstituted Arylureas. *ChemistrySelect* **2018**, *3*, 6840.

(15) (a) Pattarawarapan, M.; Yamano, D.; Wiriya, N.; Phakhodee, W. Metal-Free Synthesis of 2-*N*,*N*-Dialkylaminobenzoxazoles Using Tertiary Amines as the Nitrogen Source. *J. Org. Chem.* **2019**, *84*, 6516. (b) Phakhodee, W.; Duangkamol, C.; Wiriya, N.; Pattarawarapan, M. A convenient one-pot synthesis of *N*-substituted amidoximes and their application toward 1,2,4-oxadiazol-5-ones. *RSC Adv.* **2018**, *8*, 38281. (c) Phakhodee, W.; Wangngae, S.; Pattarawarapan, M. Approach to the Synthesis of 2,3-Disubstituted-3*H*-quinazolin-4-ones Mediated by Ph_3P-I_2. *J. Org. Chem.* **2017**, *82*, 8058. (d) Pattarawarapan, M.; Wiriya, N.; Yimklan, S.; Wangngae, S.; Phakhodee, W. Zwitterionic Ring-Opened Oxyphosphonium Species from the Ph_3P-I_2 Mediated Reactions of Benzo[*d*]oxazol-2(3*H*)-ones with Secondary Amines. *J. Org. Chem.* **2020**, *85*, 6151.

(16) Deng, X.; Roessler, A.; Brdar, I.; Faessler, R.; Wu, J.; Sales, Z. S.; Mani, N. S. Direct, metal-free amination of heterocyclic amides/

ureas with NH-heterocycles and *N*-substituted anilines in $POCl_3$. *J. Org. Chem.* **2011**, *76*, 8262.
(17) Akester, J.; Cui, J.; Fraenkel, G. Efficient Synthesis of Diastereomerically Pure Vicinal Diamines: meso-2,3-Bis-(methylamino)butane and *cis*-1,2-Bis(methylamino)cycloalkanes. *J. Org. Chem.* **1997**, *62*, 431. Hutchby, M.; Houlden, C. E.; Ford, J. G.; Tyler, S. N. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. Hindered Ureas as Masked Isocyanates: Facile Carbamoylation of Nucleophiles under Neutral Conditions. *Angew. Chem., Int. Ed.* **2009**, *48*, 8721. Blakeley, R. L.; Treston, A.; Andrews, R. K.; Zerner, B. Nickel(II)-promoted ethanolysis and hydrolysis of *N*-(2-pyridylmethyl)urea. A model for urease. *J. Am. Chem. Soc.* **1982**, *104*, 612.
(18) Farley, A. J. M.; Sandford, C.; Dixon, D. J. Bifunctional Iminophosphorane Catalyzed Enantioselective Sulfa-Michael Addition to Unactivated α-Substituted Acrylate Esters. *J. Am. Chem. Soc.* **2015**, *137*, 15992. Formica, M.; Sorin, G.; Farley, A. J. M.; Diaz, J.; Paton, R. S.; Dixon, D. J. Bifunctional iminophosphorane catalysed enantioselective sulfa-Michael addition of alkyl thiols to alkenyl benzimidazoles. *Chem. Sci.* **2018**, *9*, 6969. Goldys, A. M.; Nunez, M. G.; Dixon, D. J. Creation through Immobilization: A New Family of High Performance Heterogeneous Bifunctional Iminophosphorane (BIMP) Superbase Organocatalysts. *Org. Lett.* **2014**, *16*, 6294. Thomson, C. J.; Barber, D. M.; Dixon, D. J. Catalytic Enantioselective Direct Aldol Addition of Aryl Ketones to α-Fluorinated Ketones. *Angew. Chem., Int. Ed.* **2020**, *59*, 5359.
(19) Klaehn, J. R.; Rollins, H. W.; McNally, J. S.; Arulsamy, N.; Dufek, E. J. Phosphoranimines containing cationic *N*-imidazolinium moieties. *Inorg. Chim. Acta* **2017**, *466*, 254. Azouzi, K.; Duhayon, C.; Benaissa, I.; Lugan, N.; Canac, Y.; Bastin, S.; Cesar, V. Bidentate Iminophosphorane-NHC Ligand Derived from the Imidazo[1,5-*a*]pyridin-3-ylidene Scaffold. *Organometallics* **2018**, *37*, 4726. Chen, H.; Yan, K. 6-Benzyl-2-[(triphenyl-λ^5-phosphanylidene)amino]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carbonitrile. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2011**, *67*, o2548.
(20) Ying, H.; Cheng, J. Hydrolyzable Polyureas Bearing Hindered Urea Bonds. *J. Am. Chem. Soc.* **2014**, *136*, 16974. Ying, H.; Yang, Y.; Cai, K.; Cheng, J. Hindered Urea Bond: A Bilaterally Responsive Chemistry to Hydrogen Peroxide. *Eur. J. Org. Chem.* **2019**, *2019*, 728. Ying, H.; Zhang, Y.; Cheng, J. Dynamic urea bond for the design of reversible and self-healing polymers. *Nat. Commun.* **2014**, *5*, 3218.
(21) Ghosh, A. K.; Brindisi, M. Urea Derivatives in Modern Drug Discovery and Medicinal Chemistry. *J. Med. Chem.* **2020**, *63*, 2751. Jagtap, A. D.; Kondekar, N. B.; Sadani, A. A.; Chern, J.-W. Ureas: Applications in Drug Design. *Curr. Med. Chem.* **2017**, *24*, 622. Pizzirani, D.; Bach, A.; Realini, N.; Armirotti, A.; Mengatto, L.; Bauer, I.; Girotto, S.; Pagliuca, C.; De Vivo, M.; Summa, M.; Ribeiro, A.; Piomelli, D. Benzoxazolone Carboxamides: Potent and Systemically Active Inhibitors of Intracellular Acid Ceramidase. *Angew. Chem., Int. Ed.* **2015**, *54*, 485. Bach, A.; Pizzirani, D.; Realini, N.; Vozella, V.; Russo, D.; Penna, I.; Melzig, L.; Scarpelli, R.; Piomelli, D. Benzoxazolone Carboxamides as Potent Acid Ceramidase Inhibitors: Synthesis and Structure-Activity Relationship (SAR) Studies. *J. Med. Chem.* **2015**, *58*, 9258. Di Martino, S.; Tardia, P.; Cilibrasi, V.; Caputo, S.; Mazzonna, M.; Russo, D.; Penna, I.; Realini, N.; Margaroli, N.; Migliore, M.; Pizzirani, D.; Ottonello, G.; Bertozzi, S. M.; Armirotti, A.; Nguyen, D.; Sun, Y.; Bongarzone, E. R.; Lansbury, P.; Liu, M.; Skerlj, R.; Scarpelli, R. Lead Optimization of Benzoxazolone Carboxamides as Orally Bioavailable and CNS Penetrant Acid Ceramidase Inhibitors. *J. Med. Chem.* **2020**, *63*, 3634. Ortega, J. A.; Arencibia, J. M.; La Sala, G.; Borgogno, M.; Bauer, I.; Bono, L.; Braccia, C.; Armirotti, A.; Girotto, S.; Ganesan, A.; De Vivo, M. Pharmacophore Identification and Scaffold Exploration to Discover Novel, Potent, and Chemically Stable Inhibitors of Acid Ceramidase in Melanoma Cells. *J. Med. Chem.* **2017**, *60*, 5800. Tapia, I.; Alonso-Cires, L.; Lopez-Tudanca, P. L.; Mosquera, R.; Labeaga, L.; Innerarity, A.; Orjales, A. 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxamides with Selective Affinity for the 5-HT4 Receptor: Synthesis and Structure-Affinity and Structure-Activity Relationships of a New Series of Partial Agonist and Antagonist Derivatives. *J. Med. Chem.* **1999**, *42*, 2870.
(22) (a) Kametani, T.; Fujimoto, Y.; Mizushima, M. Novel formation of the benzimidazo[2,1-*a*]isoquinoline and benz[*c*]acridine from the 1,2,3,4-tetrahydro-1-(2-nitrophenethyl)isoquinoline with triethyl phosphite. *Heterocycles* **1975**, *3*, 619. (b) Yao, X.; Sun, X.; Jin, S.; Yang, L.; Xu, H.; Rao, Y. Discovery of 4-Aminoquinoline-3-carboxamide Derivatives as Potent Reversible Bruton's Tyrosine Kinase Inhibitors for the Treatment of Rheumatoid Arthritis. *J. Med. Chem.* **2019**, *62*, 6561. (c) Alberti, M. N.; Polyhach, Y.; Tzirakis, M. D.; Toedtli, L.; Jeschke, G.; Diederich, F. Exploring the Strength of the H-Bond in Synthetic Models for Heme Proteins: The Importance of the N-H Acidity of the Distal Base. *Chem. - Eur. J.* **2016**, *22*, 10194. (d) Nakao, S.; Mabuchi, M.; Shimizu, T.; Itoh, Y.; Takeuchi, Y.; Ueda, M.; Mizuno, H.; Shigi, N.; Ohshio, I.; Jinguji, K.; Ueda, Y.; Yamamoto, M.; Furukawa, T.; Aoki, S.; Tsujikawa, K.; Tanaka, A. Design and synthesis of prostate cancer antigen-1 (PCA-1/ALKBH3) inhibitors as anti-prostate cancer drugs. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1071. (e) Kilchmann, F.; Marcaida, M. J.; Kotak, S.; Schick, T.; Boss, S. D.; Awale, M.; Gonczy, P.; Reymond, J.-L. Discovery of a Selective Aurora A Kinase Inhibitor by Virtual Screening. *J. Med. Chem.* **2016**, *59*, 7188.

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