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The Scope and Mechanism of Phosphonium-Mediated S_NAr Reactions in Heterocyclic Amides and Ureas

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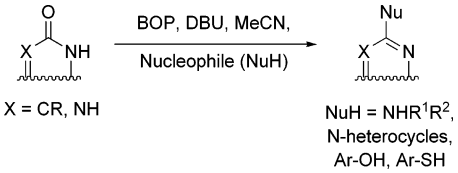

An efficient "one-step" synthesis of cyclic amidines and guanidines has been developed. Treatment of cyclic amides and ureas with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), base, and nitrogen nucleophiles leads to the formation of the corresponding cyclic amidines and guanidines, typically in good to excellent yields. This method has also been used to prepare heteroaryl ethers and thioethers using phenol and thiophenol nucleophiles. Time course NMR and HPLC-MS studies have facilitated explicit characterization of the proposed intermediates (the phosphonium salt and HOBt adduct); the data reveal a stepwise reaction pathway.

Introduction

Nitrogen-containing heterocycles are ubiquitous in nature and are well-represented among the desirable structures of modern medicinal chemistry. Considerable research is focused on the synthesis of nitrogenous heterocycles, including purines[1] and aminoquinazolines,[2,3] because of their varied biological activity. The latter have garnered particular interest, as numerous pharmaceuticals are aminoquinazoline derivatives, including a selection of well-known kinase inhibitors.[3]

The synthesis of functionalized heterocyclic compounds, such as cyclic amidines and guanidines, remains challenging. Frequently, amination of cyclic amides and ureas is achieved from aryl halides through S_NAr substitution[4] or by means of the recently developed Buchwald−Hartwig amination.[5] These strategies often involve four synthetic steps (Scheme 1). If present,

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(4) For a few representative examples, see: (a) Maruenda, H.; Chenna, A.; Liem, L.-K.; Singer, B. *J. Org. Chem*. **1998**, *63*, 4385. (b) Van Brocklin, H. F.; Lim, J. K.; Coffing, S. L.; Hom, D. L.; Negash, K.; Ono, M. Y.; Gilmore, J. L.; Bryant, I.; Riese, D. J., II. *J. Med. Chem*. **2005**, *48*, 7445. (c) Wissner, A.; Floyd, M. B.; Johnson, B. D.; Fraser, H.; Ingalls, C.; Nittoli, T.; Dushin, R. G.; Discafani, C.; Nilakantan, R.; Marini, J.; Ravi, M.; Cheung, K.; Tan, X.; Musto, S.; Annable, T.; Siegel, M. M.; Loganzo, F. *J. Med. Chem*. **2005**, *48*, 7560. (d) Mishani, E.; Abourbeh, G.; Jacobson, O.; Dissoki, S.; Daniel, R. B.; Rozen, Y.; Shaul, M.; Levitzki, A. *J. Med. Chem*. **2005**, *48*, 5337. (e) Domarkas, J.; Dudouit, F.; Williams, C.; Qiyu, Q.; Banerjee, R.; Brahimi, F.; Jean-Claude, B. J. *J. Med. Chem*. **2006**, *49*, 3544.

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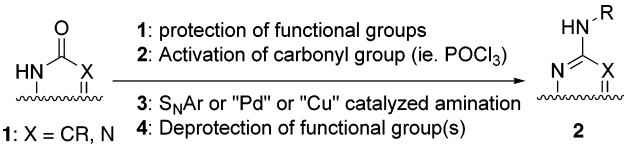
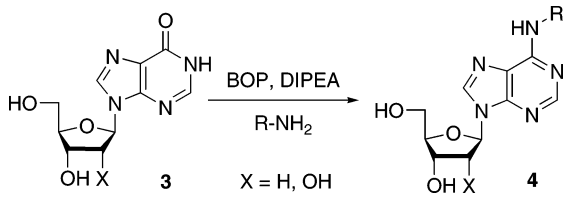
SCHEME 1



SCHEME 2



labile functional groups are protected. Next, the carbonyl group is activated by halogenation, often under harsh and acidic conditions with reagents such as $SOCl_2$, $POCl_3$, and PCl_5. These conditions may cause destruction of functionality or loss of protecting groups. After the key C−N bond-forming reaction, protecting groups are removed, generating the desired cyclic amidine or guanidine (e.g., structure **2**, Scheme 1).

Phosphonium reagents such as benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP) are widely used for amide bond formation[6] and other nucleophilic substitution reactions.[7] Reports on phosphonium-mediated transformations in heterocyclic systems are relatively rare by comparison.[8] We recently described a one-step synthesis of N^6-adenosine and N^6-deoxyadenosine derivatives **4** (Scheme 2) using BOP in the presence of a base; this amination was achieved without protection of the hydroxyl groups.[9] Further investigation revealed that this convenient bond-forming reaction could be used to functionalize a variety of substrates, including many with acid-labile functional groups.[10]

Our primary focus has been to expand the scope of this methodology. In this paper, we report the optimization of the reaction and provide numerous synthetic examples using a broad array of substrates and nucleophiles. These examples demonstrate that the mild conditions employed are tolerant of a variety of functional groups and help to illustrate the scope and limitations of this method. In addition, we disclose results of a more thorough examination of the reaction mechanism using data from ^{31}P NMR, ^1H NMR, and HPLC-MS experiments. On the basis of early observations, we proposed a mechanism where the substrate is converted to a phosphonium salt (e.g., structure **7**, Figure 1); the HOBt adduct (e.g., structure **8**, Figure 1) is formed when less reactive nucleophiles (such as aniline) are used.[10] The goals of the mechanism study were to (1) fully characterize the phosphonium intermediate, (2) determine whether formation of the HOBt adduct is a concerted process (route "b", Figure 1), and (3) determine under which circumstances the HOBt adduct participates in the reaction.

Results and Discussion

Reaction Condition Screening. In previous communications,[9,10] we showed that cyclic amides could be activated toward nucleophilic attack using BOP. Although PyBOP[11] or PyBrOP[12] were screened as reagents for amination at C-6 of purine nucleosides (i.e., 2′,3′,5′-tri-*O*-acetylinosine **10**), neither was as effective as BOP. Here, we present a more detailed comparison between the commercially available phosphonium coupling reagents illustrated in Figure 2.

Two model systems were chosen to screen the efficacy of each reagent; 2′,3′,5′-tri-*O*-acetylinosine **10** was selected as a substrate for the first model reaction (Scheme 3). The phosphonium reagents (Figure 2) were added to stirred solutions of **10**, benzylamine (1.5 equiv), DBU (2 equiv), and internal standard Ph_2O (1.0 equiv) in DMF at 0 °C.[13] The conversion to product **11** in each mixture was measured using HPLC-MS and calculated based on the UV absorbance of the internal standard. Percent conversion to **11** is plotted as function of time for each reagent in Figure 3. For each phosphonium reagent, there was a pronounced difference in the rate of formation of **11**. BOP and PyBOP performed very well; product formation was slightly faster with BOP, and at ∼2.5 h, the conversion with BOP was slightly greater (∼5%) than with PyBOP. Significantly less product was generated with PyAOP, BrOP, and PyBrOP.[14]

With **10** as the substrate (Scheme 3), the phosphonium intermediates were detected by HPLC-MS analysis. Tris-(dimethylamino)phosphonium intermediate **12** (Figure 4) was detected in the reactions using BOP and BrOP [ESI-MS *m*/*z* calcd for $C_{22}H_{35}N_7O_8P$ (M^+), 556.2, found 556.4], whereas tris-(pyrrolidino)phosphonium intermediate **13** (Figure 4) was detected when using PyBOP, PyAOP, and PyBrOP [ESI-MS *m*/*z* calcd for $C_{28}H_{47}N_7O_8P$ (M^+) 634.3, found 634.2]. The peaks corresponding to **12** and **13** in the HPLC-MS chromatograms

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(8) For work on amination in heteroaromatic systems through phosphonium intermediates via different phosphonium agents, see: (a) Lin, X.; Robins, M. J. *Org. Lett.* **2000**, *2*, 3497. (b) Véliz, E. A.; Beal, P. A. *Tetrahedron Lett.* **2000**, *41*, 1695. (c) Véliz, E. A.; Beal, P. A. *J. Org. Chem.* **2001**, *66*, 8592. (d) Janeba, Z.; Lin, X.; Robins, M. J. *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 137. (e) Clemens, J. J.; Davis, M. D.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4903. (f) Kang, F.-A.; Kodah, J.; Guan, Q.; Li, X.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 1957. (g) Zhang, M.; Nowak, I.; Cannon, J. F.; Robins, M. J. *J. Org. Chem.* **2006**, *71*, 4216. (h) Pritz, S.; Wolf, Y.; Klemm, C.; Bienert, M. *Tetrahedron Lett.* **2006**, *47*, 5893.

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(12) Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967.

(13) These reactions were performed under dilute conditions (0.02 M) to avoid problems with product or substrate solubility.

(14) Trace amounts of N^6-dimethylamino-2′,3′,5′-tri-*O*-acetyladenosine were occasionally observed, probably due to decomposition of DMF.

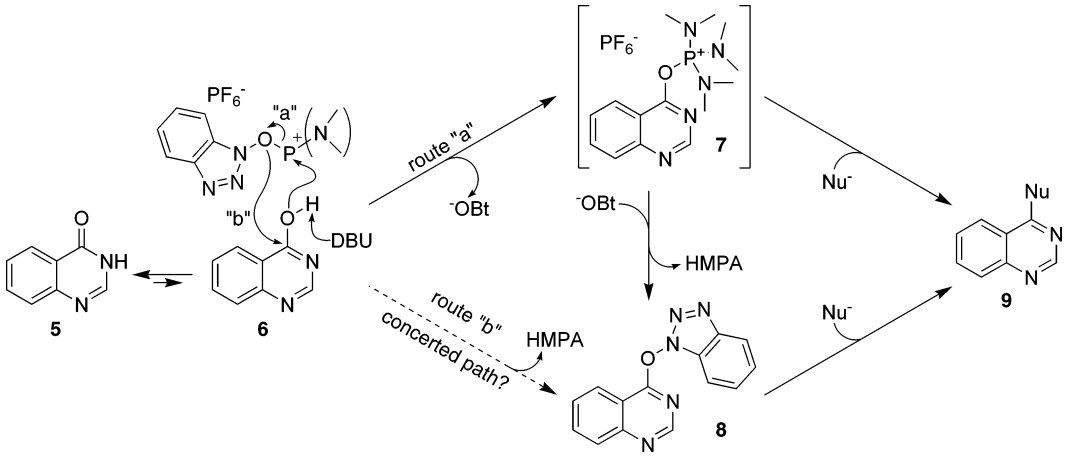


FIGURE 1. Proposed mechanism for BOP-mediated amination reaction.

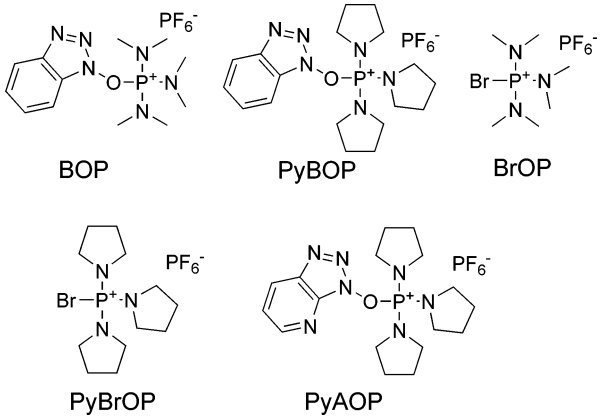
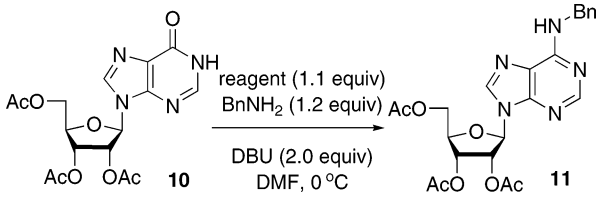


FIGURE 2. Representative phosphonium reagents.

SCHEME 3



of the reaction mixtures (at 254 nm) were integrated, normalized (relative to the internal standard, Ph_2O), and plotted as a function of time (Figure 5). Two observations suggest that the counterion (e.g., OBt^-) plays an important role in facilitating bond formation: (1) although formation of phosphonium intermediate **12** is rapid both with BOP and BrOP,[15] there is more complete conversion to the desired product **11** with BOP; (2) despite the fact that PyBOP, PyAOP,[16] and PyBrOP all generate intermediate **13**, conversion from **10** to **11** is faster using PyBOP. The HOBt or HOAt adducts (**14** and **15**, Figure 4) were not detected in the reaction mixtures by HPLC-MS analysis. The HOBt adducts accumulate only in the presence of poor nucleophiles or in the absence of an exogenous nucleophile (see below).

4-Hydroxyquinazoline **5** was chosen for a second model system to determine if reagent performance varies with substrate (Scheme 4). Benzotriazole was selected as the nucleophile because of its moderate reactivity (compared to benzylamine), making it easier to track the progress of the reaction by HPLC-MS analysis. As with the inosine model system, the reactions were performed under dilute conditions to avoid solubility problems.

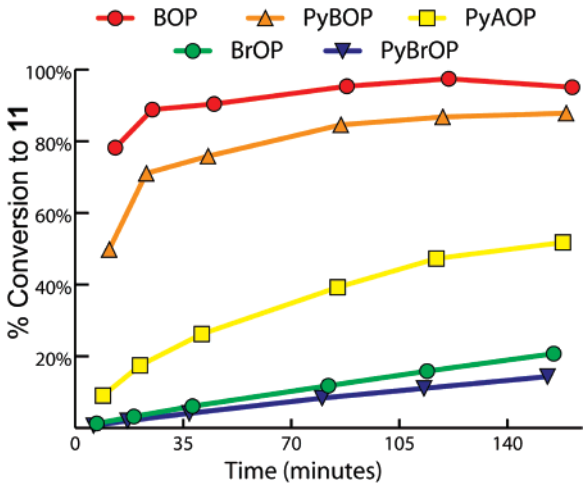


FIGURE 3. Conversion to product **11** as a function of time for model reaction with **10** (Scheme 3) at 0 °C.

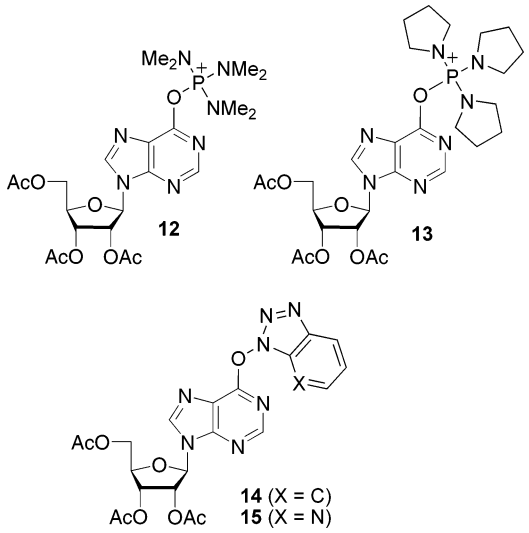


FIGURE 4. Phosphonium intermediates **12** and **13** from model reaction with **10** (Scheme 3).

(15) Castro, B.; Dormoy, J. R. *Tetrahedron Lett.* **1973**, *14*, 3243.
(16) Carpino, L.; El-Faham, A.; Minor, C.; Albericio, F. *J. Chem. Soc., Chem. Commun.* **1994**, *2*, 201.

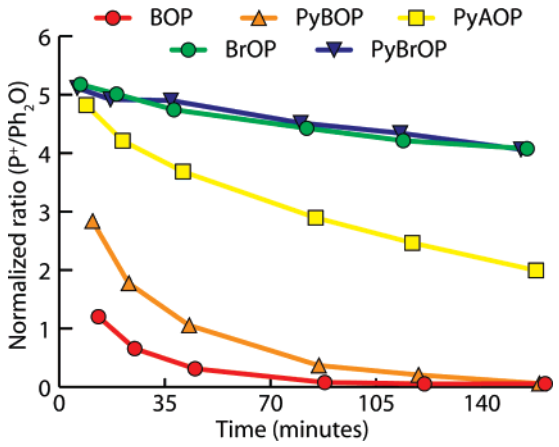
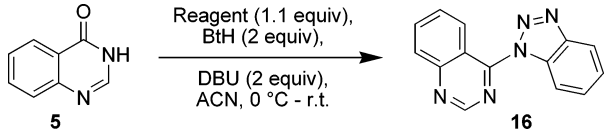


FIGURE 5. Normalized ratio of phosphonium intermediate to internal standard from the model reaction with **10** (Scheme 3) at 0 °C, plotted as a function of time.

SCHEME 4



BOP, PyBOP, PyAOP, and PyBrOP each affected a similar amount of conversion to **16** (Figure 6). BrOP was the least effective; only ~60% conversion to **16** was observed by the end of the time course. Interestingly, triphenylphosphine diiodide (PPh_3I_2, **17**) initially caused rapid conversion to product (~40%), but the reaction appeared to stall after ~1 h.

The tris(pyrrolidino)phosphonium reagents (PyBOP and PyAOP) generated an intermediate with an ESI-MS spectrum consistent with phosphonium salt **18** (Figure 7) (ESI-MS *m*/*z* calcd for $C_{19}H_{28}N_4OP$ (M − CHN) 359.2, found 359.3) The analogous phosphonium intermediate **7** (Figure 7) was not observed in the reactions of 4-hydroxyquinazoline **5** with BOP and BrOP. HOBt adduct **8** (Figures 1 and 7) was not observed when using BOP or PyBOP, and the HOAt adduct **19** (Figure 7) was not observed when using PyAOP under these conditions. HOBt or HOAt adducts **8** and **19** were observed, however, when a poor nucleophile (e.g., aniline) or no external nucleophile was used (see below). Attempts to compare reactivity of the

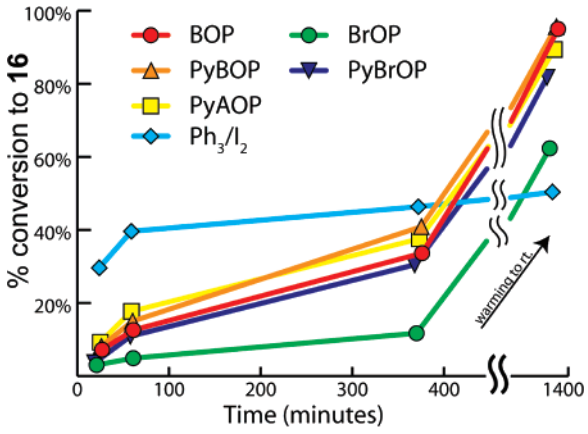


FIGURE 6. Product formation plotted as a function of time for model system shown in Scheme 4.

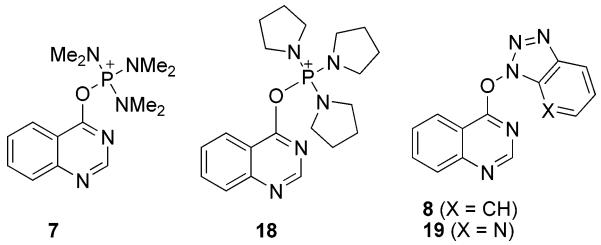


FIGURE 7. Phosphonium intermediates (**7**, **18**) and HOBt/HOAt adducts (**8**, **19**).

SCHEME 5

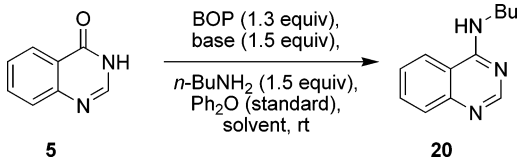


TABLE 1. Results of the Base and Solvent Screening for the BOP-Mediated Amination Reaction

entry	base	solvent	product **20** (%)[a]
1	DBU	NMP	95
2	TEA	NMP	87
3	DIPEA	NMP	78
4	collidine	NMP	74
5	proton sponge	NMP	54
6	*t*-BuONa	NMP	68
7	DBU	DMF	95
8	DBU	THF	99
9	DBU	CH_2Cl_2	93
10	DBU	MeCN	quant.

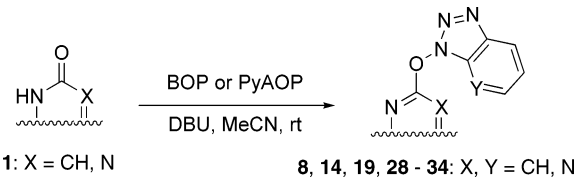
[a] Percent conversion determined by HPLC-MS analysis calibrated using an internal standard.

phosphonium intermediates with the HOBt/HOAt adducts were not successful.

Solvent and Base Effects. Amination of 4-hydroxyquinazoline **5** with butylamine was used as the model system for examining the effect of solvent and base on the reaction (Scheme 5). DBU is a superior base for this reaction (Table 1). Nearly complete conversion to product **20** was achieved within 1 h when 4-hydroxyquinazoline **5** was treated with BOP, *n*-butylamine, and DBU at room temperature in NMP (entry 1, Table 1). The conversion to product **20** was slightly less using TEA under similar conditions (entry 2, Table 1). DIPEA, proton sponge, collidine, and *t*-BuONa were not as effective (entries 3−6, Table 1). Similar results were obtained when these bases were screened in reactions with inosine derivatives (e.g, conversion of **10** to **11**, Scheme 3, data not shown). There was not a significant solvent effect for the reaction shown in Scheme 5, though there was slightly greater conversion in MeCN and THF. In practice, NMP, DMF, CH_2Cl_2, and MeCN may be interchanged as reaction solvent to accommodate the solubility of starting material and product without significant effect on reaction yield.

Performing the Reaction without Additional Nucleophiles. When stirred in solution with BOP and DBU, 4-hydroxyquinazoline **5** is rapidly converted to the HOBt adduct **8**; we isolated this compound in 86% yield.[10] The HOBt adducts first attracted our attention because of their apparent role in the mechanism of BOP-mediated nucleophilic substitution. These adducts are easily handled solids and are surprisingly shelf-stable (a sample of HOBt adduct **14** was stable in a closed vial

SCHEME 6



at room temperature for >2 years). Furthermore, the adducts are susceptible to nucleophilic attack and provide an alternate method to functionalize cyclic amides (nucleophilic addition to HOBt and HOAt adducts is explored below).

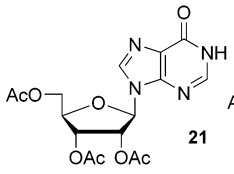
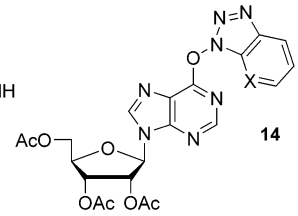
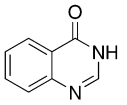
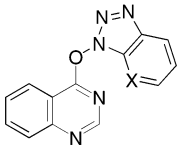
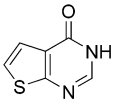
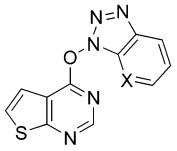
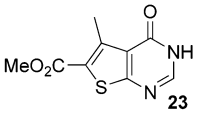
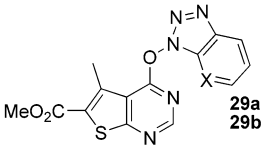
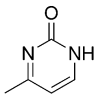
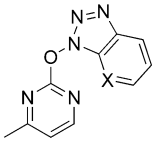
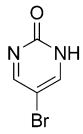
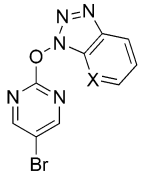
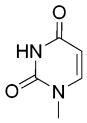
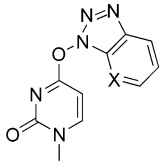
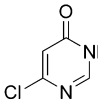
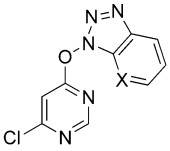
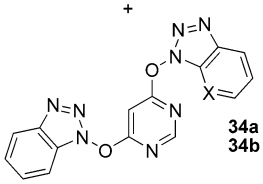
To explore the scope of this chemistry, HOBt and HOAt adducts from a variety of cyclic amides and ureas were prepared (Scheme 6 and Table 2). Each substrate was stirred in a solution containing DBU and either BOP or PyAOP; the desired adducts were isolated in good to excellent yields.[17] HOBt or HOAt adduct formation is usually very fast, and these reactions are typically complete within 1 h at room temperature. For analytical purposes, the products were purified by column chromatography. Synthetically useful products could also be easily obtained by diluting the crude reaction mixture with water and then filtering the precipitated product from the solution.

The major products of the reactions of 6-chloropyrimidin-4(3*H*)-one **27** with BOP and PyAOP were monosubstituted adducts **33a** and **33b**. Adducts **34a** (bis-HOBt adduct) and **34b** (bis-HOAt adduct) were isolated as minor products (Table 2, entry 8). This suggests that, for the phosphonium intermediate derived from **27**, the C-4 position (site of the phosphonium leaving group) is more electrophilic than C-6 (site of the chloride leaving group).

HOBt adduct **8** isomerized to **35** under acidic conditions. Treatment of 4-hydroxyquinazoline **5** with BOP (Scheme 7) and acidic workup resulted in the isolation of isomeric HOBt adduct **35** as the sole product. The structure of **35** was assigned by analogy to similar compounds reported in the literature.[18,19] In isomer **35**, the ^{13}C signal from C-4 of the quinazoline ring system is shifted upfield (see Scheme 7). To further confirm the isomerization, HOBt adduct **8** was dissolved in acetonitrile and treated with aqueous HCl solution; this affected partial isomerization to **35** (Scheme 7). Exposing **35** to similar conditions does not affect isomerization to **8**. Following purification, both **8** and **35** are stable at room temperature. Reese reported similar isomerization of an HOBt adduct (of a thymine nucleoside), though under basic conditions;[20] Carpino discussed the selective synthesis of the uronium and guanidinium salts of HATU in a recent report.[19]

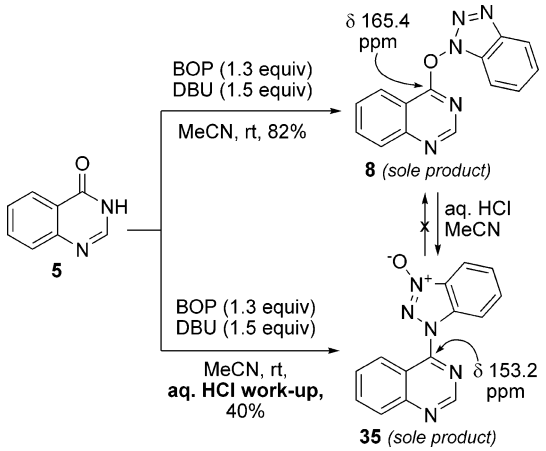
Nucleophile Scope. Having identified optimum reaction conditions, we performed the reaction with a variety of nucleophiles using 4-hydroxyquinazoline **5** as a substrate to

TABLE 2. Preparation of the HOBt and HOAt Adducts from Various Heterocyclic Amides

entry	substrate	product	X (yield %)[a]
1	 **21**	 **14**	CH (91)
2	 **5**	 **8** **19**	CH (82) N (99)
3	 **22**	 **28a** **28b**	CH (93) N (83)
4	 **23**	 **29a** **29b**	CH (76) N (96)
5	 **24**	 **30**	CH (70)
6	 **25**	 **31**	N (70)
7	 **26**	 **32**	N (58)
8	 **27**	 **33a** **33b**	CH (51) N (60)
		 **34a** **34b**	CH (31) N (26)

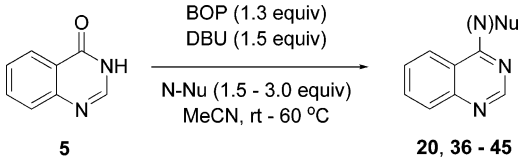
[a] Isolated yields are reported.

SCHEME 7



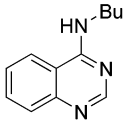
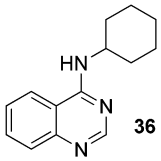
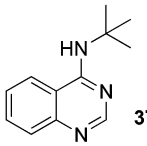
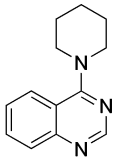
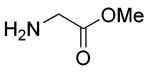
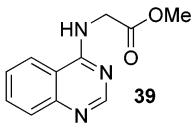
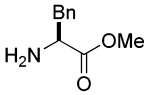
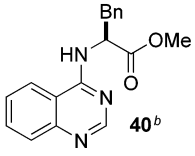
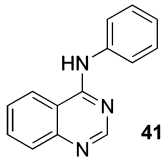
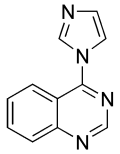
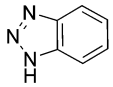
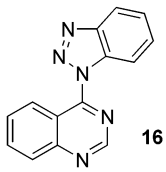
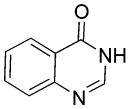
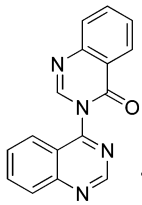
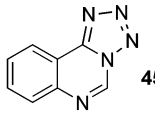
synthesize 4-aminoquinazolines, which are interesting because of their biological and pharmaceutical properties.[3,4b−e] Nitrogen nucleophiles of varying steric bulk and electronic properties were employed in these reactions. Each nucleophile was coupled to 4-hydroxyquinazoline **5** using BOP under the optimized reaction conditions (Scheme 8). The results of these experiments are summarized in Table 3.

SCHEME 8



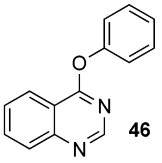
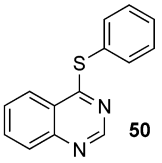
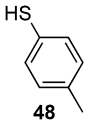
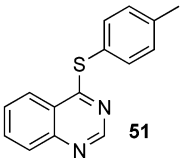
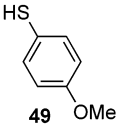
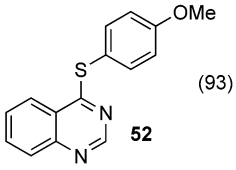
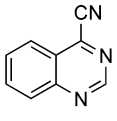
Unhindered primary and secondary amines (Table 3, entries 1, 2, and 4) as well as sodium azide (Table 3, entry 11) reacted rapidly with **5** at room temperature, giving the desired products with good isolated yields. HPLC-MS and TLC analysis revealed that the reactions proceeded smoothly; many were nearly complete within a few minutes. Amination with sterically hindered nucleophiles such as *t*-$BuNH_2$ (Table 3, entry 3) and phenylalanine methyl ester (Table 3, entry 6) was facilitated by increasing the excess of amine nucleophile and by heating

TABLE 3. Reactions of 4-Hydroxyquinazoline with Various Nitrogen Nucleophiles[a]

entry	nucleophile	temperature, equiv Nu	product	yield (%)
1	*n*-$BuNH_2$	rt, 1.5 equiv	 **20**	(86)
2		rt, 3 equiv	 **36**	(90)
3		rt - 60 °C, 1.3 equiv	 **37**	(64)
4		rt, 1.5 equiv	 **38**	(88)
5		rt, 3 equiv	 **39**	(84)
6		rt - 60 °C, 2.4 equiv	 **40**[b]	(75)
7		rt - 60 °C, 1.5 equiv	 **41**	(78)
8		rt - 80 °C, 4.5 equiv	 **42**	(92)
9		rt, 3 equiv	 **16**	(95)[c] (66)[d]
10		rt, 1 equiv[e]	 **44**	(82)
11	NaN_3	rt - 50 °C,[f] 2 equiv	 **45**	(82)

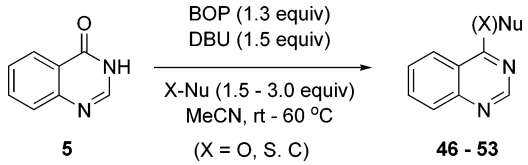
[a] Isolated yields are reported unless otherwise noted. All reactions were performed in MeCN with DBU as base. For details, see Experimental Section and Supporting Information. [b] Optical purity of **40** was not assessed. [c] Yield based on HPLC-MS analysis of crude reaction mixture relative to internal standard. [d] Isolated yield. [e] With 1.0 equiv of **5** and 0.5 equiv of BOP. [f] For 1 h at rt and 1.5 h at 50 °C.

TABLE 4. Reactions of 4-Hydroxyquinazoline with Various Non-Nitrogen-Containing Nucleophiles

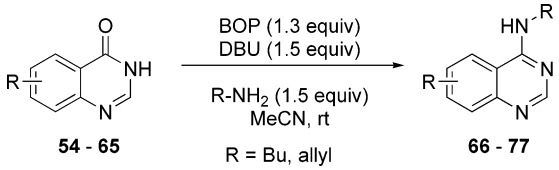
entry	nucleophile	temperature, equiv Nu	product	yield (%)[a]
1		rt, 1.5 equiv	 **46**	(84)
2	 **47**	rt, 1.5 equiv	 **50**	(93)
3	 **48**	rt, 4 equiv	 **51**	(64)
4	 **49**	rt, 2 equiv	 **52**	(93)
5	NaCN	rt, 2 equiv[b]	 **53**	(54)

[a] Isolated yields are reported; workup conditions were not optimized. [b] With 2 equiv of NaCN and 2 equiv of 18-crown-6.

SCHEME 9



SCHEME 10



the reaction mixture. Reactions with weaker nucleophiles such as aniline (Table 3, entry 7) and imidazole (Table 3, entry 8) were driven toward completion in a similar fashion.

When product formation was slow (e.g., Table 3, entry 7), a trace amount of asymmetrical dimer **44** was observed. The formation of **44** indicates that cyclic amides are suitable nucleophiles for coupling. This was confirmed by treating 4-hydroxyquinazoline **5** with 0.5 equiv of BOP (without an additional nucleophile), causing exclusive formation of **44**, which was isolated in 82% yield (Table 3, entry 10).

Next, the scope of the reaction was extended to non-nitrogen nucleophiles (Scheme 9); results of these experiments are summarized in Table 4. Phenol (Table 4, entry 1) was coupled to 4-hydroxyquinazoline **5** at room temperature, giving the desired product **46** in 84% isolated yield. Thiol nucleophiles (entries 2−4) reacted within minutes at room temperature, giving the desired thioethers **50**, **51**, and **52** in good to excellent yields. Carbon nucleophiles were also briefly examined. The reaction with sodium cyanide appeared (HPLC-MS) to proceed smoothly upon the addition of 18-crown-6, though the product **53** was recovered in only 54% yield (Table 4, entry 5).[21]

Functional Group Compatibility. The traditional method for derivatizing cyclic amides requires formation of aryl halides under relatively harsh conditions. Preservation of labile functionality under these conditions is a potential problem. To highlight the mild nature of the BOP-mediated coupling reaction, we chose 4-hydroxyquinazoline derivatives with a range of functional groups as substrates. Aminoquinazoline analogues have considerable pharmaceutical importance.[2,3] For example, compound **69** (81%, entry 4, Table 5) enhances autophagy and reduces toxicity in Huntington's and Parkinson's disease models.[22] *n*-BuNH$_2$ (allyl amine for **69**) was coupled to each substrate (Scheme 10); the results of each coupling reaction are indicated in Table 5. Product yields were excellent, demonstrating that many sensitive functional groups tolerate these reaction conditions. These include a ketal, olefin, and ketone (Table 5, entries 9, 10, and 12).

Substrate Scope. To further demonstrate the scope of this BOP-mediated reaction, a variety of cyclic amides (**22**, **23**, **27**, and **78**−**85**, Table 6) were subjected to the reaction conditions (Scheme 11). These substrates are commercially available heterocycles ranging from monocyclic to tricyclic systems. The solvent for each example in Table 6 was chosen to suit the properties of the starting material and product.

The expected products were obtained from each substrate in good to excellent yields (Table 6). The electronic properties

(17) We examined inosine HOBt adducts in conjunction with our earlier work (ref 9). During the preparation of this manuscript, another report on the HOBt adduct of inosine was disclosed (Bae, S.; Lakshman, M. K. *J. Am. Chem. Soc* **2007**, *129*, 782). Accordingly, we removed data from this manuscript regarding nucleophilic addition to the inosine HOBt adduct.

(18) Katritzky, A. R.; Kurz, T.; Zhang, S.; Voronkov, M. *Heterocycles* **2001**, *55*, 1703.

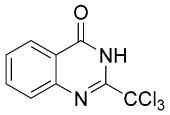
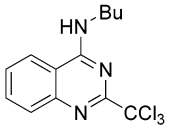
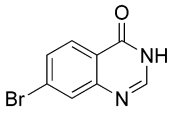
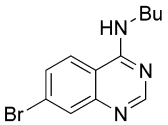
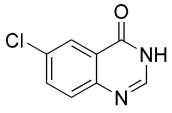
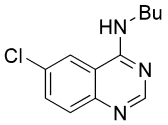
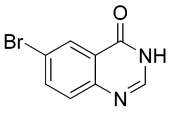
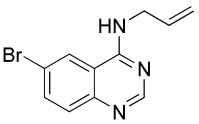
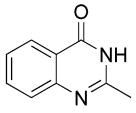
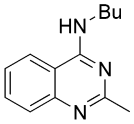
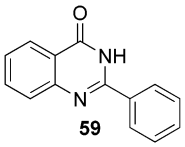
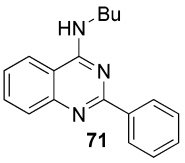
(19) Carpino, L. A.; Imazumi, H.; El-Faham, A.; Ferrer, F. J.; Zhang, C.; Lee, Y.; Foxman, M. M.; Henklein, P.; Hanay, C.; Mugge, C.; Wenschuh, H.; Klose, J.; Beyermann, M.; Bienert, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 442.

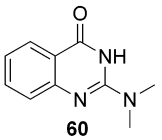
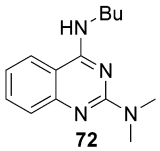
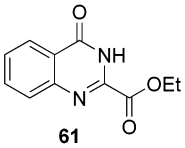
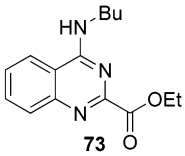
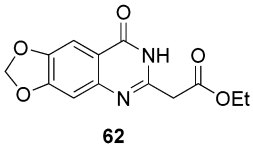
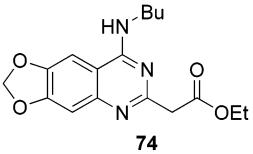
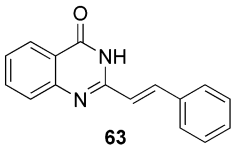
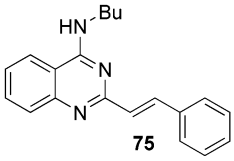
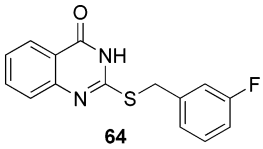
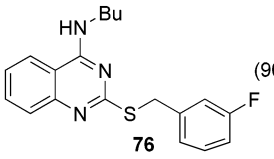
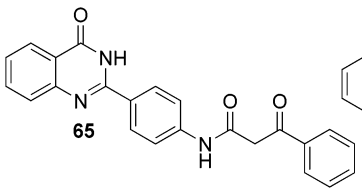
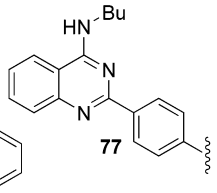
(20) Reese, C. B.; Richards, K. H. *Tetrahedron Lett.* **1985**, *26*, 2245.

(21) We attempted to use dimethyl malonate as a nucleophile (data not shown) but could not isolate the desired product under these conditions.

(22) Sakkar, S.; Perlstein, E. O.; Imarisio, S.; Pineau, S.; Cordenier, A.; Maglathlin, R. L.; Webster, J. A.; Lewis, T. A.; O'Kane, C. J.; Schreiber, S. L.; Rubinsztein, D. C. *Nat. Chem. Biol*. **2007**, *3*, 331.

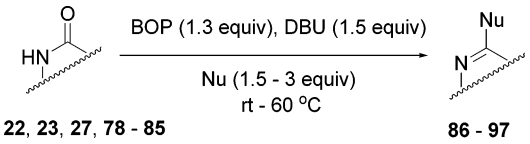
TABLE 5. Functional Group Tolerance of the BOP-Mediated Coupling Reaction[a]

entry	substrate	product	yield(%)
1	 **54**	 **66**	(99)
2	 **55**	 **67**	(95)
3	 **56**	 **68**	(86)
4	 **57**	 **69**	(81)
5	 **58**	 **70**	(99)
6	 **59**	 **71**	(99)

entry	substrate	method	product	yield(%)
7	 **60**		 **72**	(97)
8	 **61**		 **73**	(86)
9	 **62**		 **74**	(96)
10	 **63**		 **75**	(92)
11	 **64**		 **76**	(90)
12	 **65**		 **77**	(85)

[a] Isolated yields are reported for all entries. Procedure: the cyclic amide (1 equiv) and BOP (1.3 equiv) were dissolved in MeCN (0.2 M solution in amide). DBU (1.5 equiv) was added to the mixture, followed by *n*-$BuNH_2$ (1.5 equiv). The mixture was stirred until the reaction was complete.

SCHEME 11



and aromatization barrier of each substrate appears to dictate the facility of these BOP-mediated bond-forming reactions. For example, reactions of 6-chloropyrimidin-4(3*H*)-one **27** (Table 6, entry 1) and 3*H*-thieno[2,3-*d*]pyrimidin-4-one **22** (Table 6, entry 7) with *n*-$BuNH_2$ proceeded at room temperature to give the desired products **86** and **93** in 75 and 94% yield, respectively. However, the analogous reaction with hypoxanthine **80** (Table 6, entry 4) required heating to drive the reaction toward completion. Excellent chemoselectivity was achieved in the reaction with 6-chloropyrimidin-4(3*H*)-one **27** (Table 6, entry 1); addition at C-4, rather than at C-6, suggests that the phosphonium-mediated coupling is more facile than coupling with the analogous aryl chloride. For many of these examples, the reaction mixtures became homogeneous upon the addition of DBU. Nonetheless, the poor solubility of some of these heterocycles may have reduced the reaction rate (hypoxanthine **80** is only slightly soluble in DMSO or DMF). Excellent regioselectivity was observed with the uracil derivatives (Table 6, entries 2 and 3) due to the increased reactivity at the C-4 position.[23]

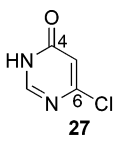
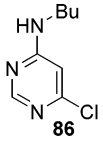
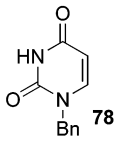
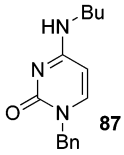
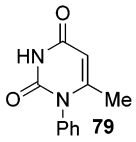
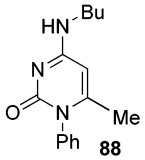
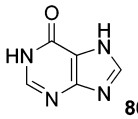
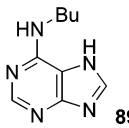
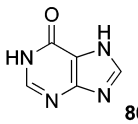
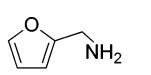
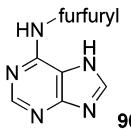
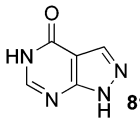
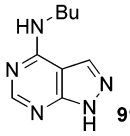
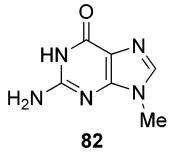
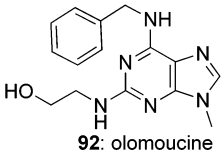
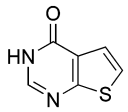
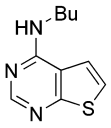
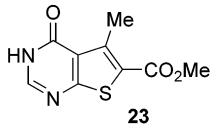
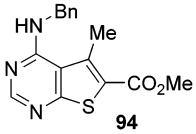
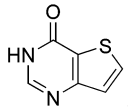
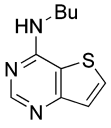
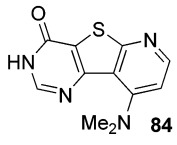
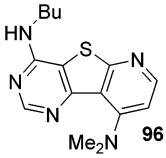
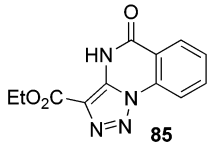
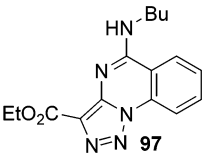
Two biologically interesting products were chosen to showcase this facile amination chemistry: kinetin **90** (commercially known as Verdan)[1j] and olomoucine **92**. Kinetin is a plant growth factor isolated from plant DNA[24] and, more recently, from human urine.[25] Kinetin affects a number of biological processes, including gene expression, auxin action, and the

(23) Peng, Z.-H.; Journet, M.; Humphrey, G. *Org. Lett.* **2006**, *8*, 395.

(24) Isolation: (a) Miller, C. O.; Skoog, F.; Von Saltza, M. H.; Strong, F. M. *J. Am. Chem. Soc.* **1955**, *77*, 1392. (b) Miller, C. O.; Skoog, F.; Okumura, F. S.; Von Saltza, M. H.; Strong, F. M. *J. Am. Chem. Soc.* **1956**, *78*, 1375. Syntheses: see ref 24b and: (c) Villar, J. D. F.; Motta, M. A. *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 1005.

(25) Barciszewski, J.; Mielcarek, M.; Stobiecki, M.; Siboska, G.; Clark, B. F. C. *Biochem. Biophys. Res. Commun.* **2000**, *279*, 69.

TABLE 6. BOP-Mediated Coupling with Various Heterocyclic Amides

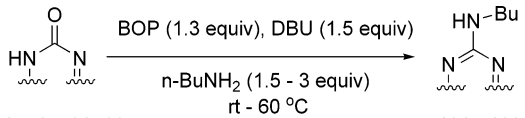
entry	substrate	amine (equiv), time, temp	product	yield (%)[a]
1	 **27**	*n*-$BuNH_2$ (3 equiv), rt, o.n.[b]	 **86**	(75)[c]
2	 **78**	*n*-$BuNH_2$ (2 equiv), rt, 3 days	 **87**	(73)
3	 **79**	*n*-$BuNH_2$ (1.5 equiv), rt, 3 days	 **88**	(81)
4	 **80**	*n*-$BuNH_2$ (5 equiv), rt, 2 days; 60 °C, 2h	 **89**	(79)[c]
5	 **80**	 (3 equiv), rt, 8 hr	 **90** (kinetin)	(90)
6	 **81**	*n*-$BuNH_2$ (1.5 equiv), rt, 2 days; 60 °C, 2 h	 **91**	(86)
7	 **82**	$BnNH_2$ (3 equiv), rt, 2 days; 60 °C, 2 h[d]	 **92**: olomoucine	(80)
8	 **22**	*n*-$BuNH_2$ (1.5 equiv), rt, 2 h	 **93**	(94)
9	 **23**	*n*-$BuNH_2$ (1.5 equiv), rt, 1 h	 **94**	(81)
10	 **83**	*n*-$BuNH_2$ (1.5 equiv), rt, 1 h	 **95**	(94)
11	 **84**	*n*-$BuNH_2$ (5 equiv), rt, 1 h	 **96**	(95)
12	 **85**	*n*-$BuNH_2$ (5.3 equiv), rt, 1 h	 **97**	(94)

[a] Isolated yields are reported unless otherwise noted. [b] Overnight, room temperature. [c] Yield based on HPLC analysis of crude reaction mixture relative to internal standard (Ph_2O). [d] Conditions: (i) BOP, DBU, $BnNH_2$, DMF/DMSO, rt (89%); (ii) $TBSOCH_2CHO$, HOAc, $NaBH_3CN$, then aq HCl, rt (90%).

reactions governing human DNA repair.[26] Kinetin was synthesized in one step from hypoxanthine **80** in 90% yield (Table 6, entry 5). Olomoucine is a potent and selective cyclin-dependent kinase inhibitor.[27] BOP-mediated amination of 1-methylguanine **82**, followed by one-pot reductive amination and in situ desilylation, afforded olomoucine **92** in 80% overall yield (Table 6, entry 7).

The BOP-mediated amination was also performed with several cyclic ureas (Scheme 12); results varied with the substitution and electronic properties of each substrate (Table 7). The reaction of 5-bromopyrimidin-2(1*H*)-one **25** with *n*-$BuNH_2$ proceeded to completion using BOP and DBU, affording cyclic guanidine **102** in 95% yield (Table 7, entry 2, method A); PyBOP and PyBrOP were far less effective for this transformation (Table 7, entry 2, methods B and C). While *n*-$BuNH_2$ was coupled to 4-methylpyrimidin-2-one **24** (Table 7, entry 1), providing **101** in modest yield (68%), none of the desired product could be detected in the reaction with relatively electron-rich 4-aminopyrimidin-2-one **98** (Table 7, entry 3).

SCHEME 12

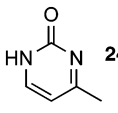
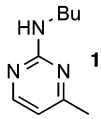
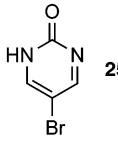
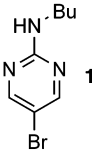
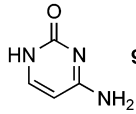
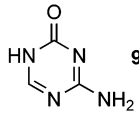
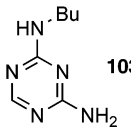


While screening cyclic ureas, the formation of an interesting side product was observed when 4-amino-5-bromopyrimidin-2(1*H*)-one **100** (Scheme 13) was treated with BOP and DBU at room temperature. Starting material **100** was converted to

(26) For a recent review on kinetin, see: Barciszewski, J.; Rattan, S. I. S.; Siboska, G.; Clark, B. F. C. *Plant Sci.* **1999**, *148*, 37.

(27) For representative biological activities, see: (a) Vesely, J.; Havlicek, L.; Strnad, M.; Blow, J.; Donella-Deana, A.; Pinna, L.; Letham, D.; Kato, J.; Detivaud, L.; Leclerc, S.; Meijer, L. *Eur. J. Biochem.* **1994**, *224*, 771. (b) Mistelli, T.; Warren, G. *J. Cell Sci.* **1995**, *108*, 2715. (c) Hartwell, L. H.; Kastan, M. B. *Science* **1994**, *266*, 1821. For recent 6−9 step syntheses, see: (d) Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J. Org. Chem.* **1997**, *62*, 201. (e) Dorff, P. H.; Garigipati, R. S. *Tetrahedron Lett.* **2001**, *42*, 2771. (f) Hammarström, L. G. J.; Smith, D. B.; Talamás, F. X.; Labadie, S. S.; Krauss, N. E. *Tetrahedron Lett.* **2002**, *43*, 8071.

TABLE 7. BOP-Mediated Coupling with Various Heterocyclic Ureas[a]

entry	substrate	method[b]	product	yield (%)
1	 **24**	A	 **101**	(68)
2	 **25**	A B C	 **102**	(95) (68) (45)
3	 **98**	E	No Product	(0)
4	 **99**	A	 **103**	(82)

[a] Isolated yields are reported. [b] Method summaries: (A) *n*-$BuNH_2$, BOP, DBU, MeCN, rt; (B) *n*-$BuNH_2$, PyBOP, DBU, MeCN; (C) *n*-$BuNH_2$, PyBrOP, DBU, MeCN; (D) *n*-$BuNH_2$, BOP, DBU, CH_2Cl_2, rt; (E) $BnNH_2$, BOP, DBU, MeCN.

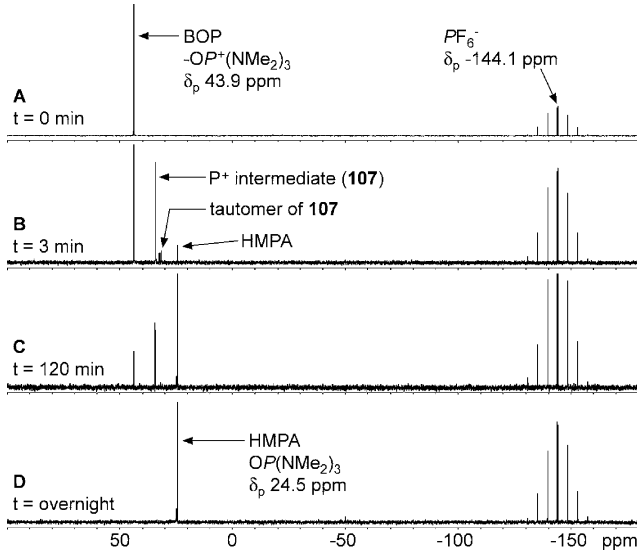


FIGURE 8. Sequential ^{31}P NMR spectra of the reaction mixture containing hypoxanthine, *n*-butylamine, BOP, and DBU in DMSO.

phosphonium intermediate **104** (ESI-MS *m*/*z* calcd for $C_{10}H_{21}BrN_6OP$ (M^+) 353.1, found 353.0) and a trace amount of cyclic trimer **105** (ESI-MS *m*/*z* calcd for $C_{12}H_7Br_3N_9$ ($M + H^+$) 513.8, found 514.1) along with a trace amount of HOBt adduct **106** within minutes (Scheme 13). After 2 days, much of the starting material had been converted to **106** (an analytical sample was isolated). This adduct did not self-react to form cyclic trimer **105** but did react with *n*-$BuNH_2$ to generate the desired guanidine product in moderate yield (structure not shown). These

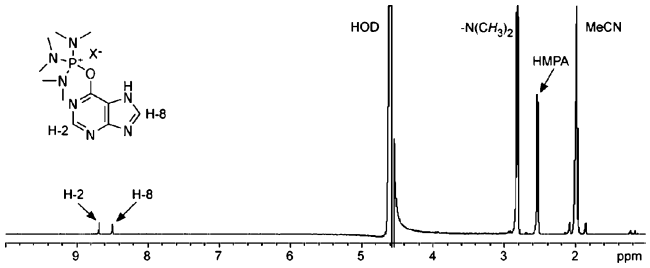


FIGURE 9. ^1H NMR spectrum of intermediate **107** obtained from the HPLC-NMR-MS experiment; HMPA (δ 2.82 ppm) coeluted with the intermediate. The signals at δ 2.07 and ~4.6 ppm are from MeCN and HOD, respectively.

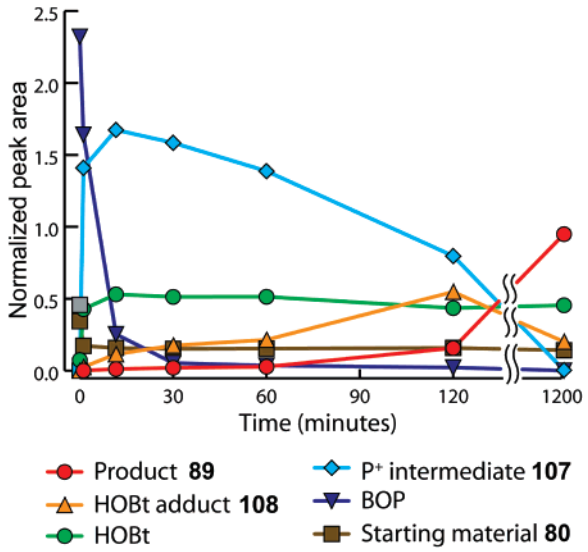


FIGURE 10. Plot illustrating the relative change of major reaction components with respect to time from the HPLC-MS time course study of hypoxanthine **80**. *Y*-axis is the ratio of peak area of a component to the peak area of DBU.

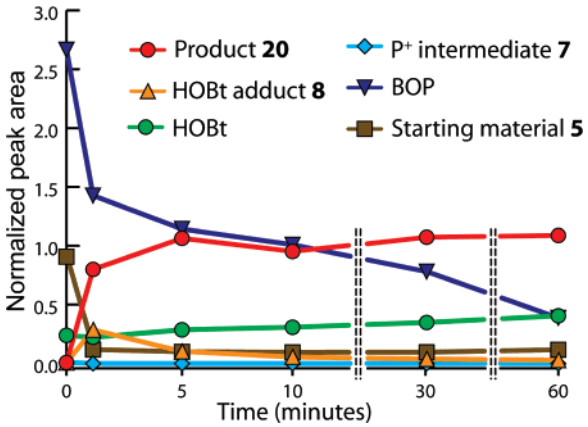


FIGURE 11. Plot illustrating the relative change of major reaction components with respect to time from the HPLC-MS time course study using 4-hydroxyquinazoline **5** as a substrate. *Y*-axis is the ratio of peak area of a component to the peak area of DBU.

results suggest that formation of **105** may be due to the higher reactivity of phosphonium intermediate **104** than of the corresponding HOBt adduct **106**.

Mechanistic Studies. In parallel with our synthetic efforts, we undertook a more systematic analysis of the reaction

SCHEME 13

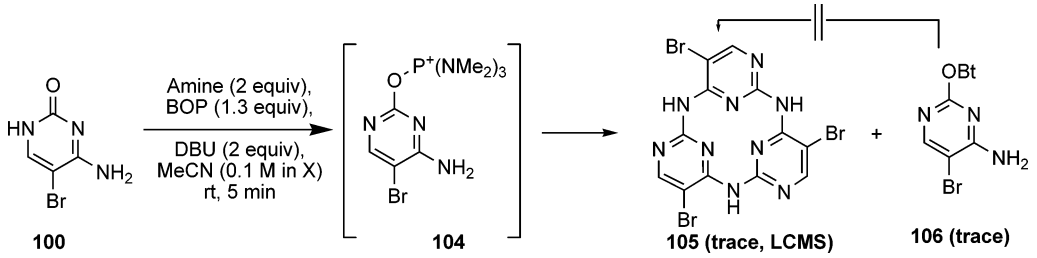


TABLE 8. Reaction of HOBt/HOAt Adducts (8 and 19) with Various Nucleophiles

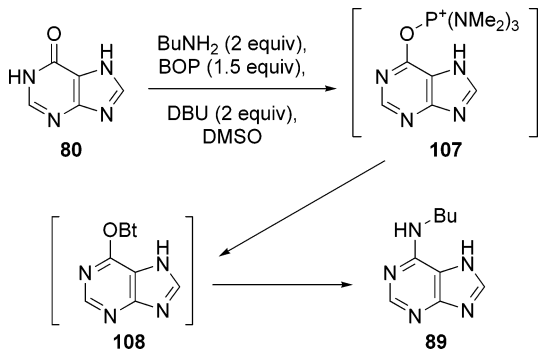
entry	nucleophile	X	equiv Nu (temp)	product (%)
1	Bu-NH_2	CH	1.5 equiv (rt)[b]	**20** (80)
2	H_2N CO_2Me	CH	3 equiv (rt)[b]	**39** (94)
3	H_2N	CH	3 equiv (rt - 60 °C)[b]	**41** (78)
4	HS	CH	2 equiv (rt)[c]	**50** (87)
5	HO	CH	2 equiv (rt)[c]	**46** (84)
6	HO	N	1.5 equiv (rt)[c]	**46** (86)
7	HO NO_2	N	3 equiv (rt)[c]	**109** (80)
8	HO OMe	N	3 equiv (rt - 60 °C)[c]	**49** (74)
9	MeO_2C CO_2Me	N	2 equiv (rt)[d]	**111** (91)
10	EtO_2C CO_2Et	N	2 equiv (rt)[d]	**112** (64)

[a] Isolated yields are reported. [b] No base, in MeCN. [c] Reaction performed with DBU in MeCN. [d] *t*-BuONa used as base in EtOH.

mechanism. The mechanism illustrated in Figure 1 was based on observation of the phosphonium intermediates[9,10] and on preliminary work with the S_NAr reaction between HOBt adduct **8** and aniline.[10,17] Along the proposed reaction pathway "a", treatment with BOP and base converts the cyclic amide/urea to a phosphonium intermediate (e.g., **7**) releasing 1 equiv of HOBt. Reactive nucleophiles might displace HMPA from the phosphonium intermediate, generating the final product (e.g., **9**). Alternatively, the HOBt anion displaces HMPA to generate the adduct (e.g., **8**); the HOBt adduct reacts with incoming nucleophiles giving the final product. Pathway "b" (Figure 1) was proposed as an alternate mechanism; a concerted four-centered bond-forming reaction[28] would directly provide the HOBt adduct (e.g., **8**) with simultaneous release of 1 equiv of HMPA. To confirm these hypotheses and to fully characterize the intermediates, several studies were performed with reaction progress monitored by ^{31}P NMR, ^{1}H NMR, and HPLC-MS. 4-Hydroxyquinazoline **5** and hypoxanthine **80** were selected as substrates for these studies based on our earlier observations.[29]

The BOP-mediated reaction of hypoxanthine **80** with *n*-$BuNH_2$ (Scheme 14) was monitored by ^{31}P NMR. These spectra are illustrated in Figure 8. Before the addition of hypoxanthine to the reaction mixture (**A**, $t = 0$ min), two resonances were detected corresponding to BOP: 43.9 ppm for $-OP^{+}(NMe_2)_3$ and the heptuplet centered at −144.1 ppm for PF_6^-. The second ^{31}P NMR spectrum was obtained 3 min following addition of

SCHEME 14



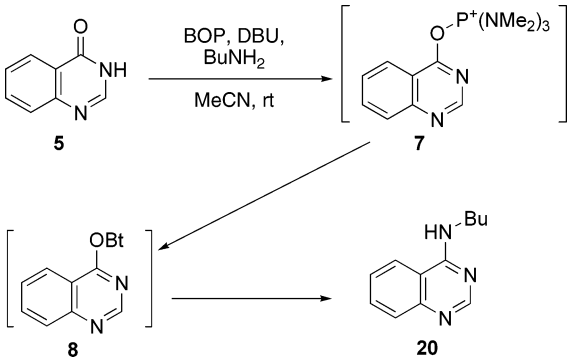
DBU and hypoxanthine. In this spectrum (**B**, $t = 3$ min), the intensity of the signal at 43.9 ppm (BOP) decreased relative to the signal from PF_6^-, and signals corresponding to HMPA (24.5 ppm) and to the phosphonium intermediate **107** (35.2 ppm) appeared. Over time, BOP concentration continues to decrease, while HMPA concentration increases (**C**, $t = 120$ min). A final ^{31}P NMR spectrum was obtained after leaving the reaction mixture at room temperature overnight (spectrum **D**). Signals corresponding to BOP and the phosphonium intermediate **107** disappeared; only the signal from HMPA remained.

Tautomers of **107** may be responsible for the small resonances at 32.8 and 33.5 ppm (e.g., from tautomerization between the 9*H*-purine and 7*H*-purine forms of **107**). This is suggested by data from HPLC-MS analysis of this reaction mixture (see below); we detected a small amount of compound with the same *m*/*z* ratio as **107**, but with slightly different retention time. These peaks also disappeared during the course of the reaction.

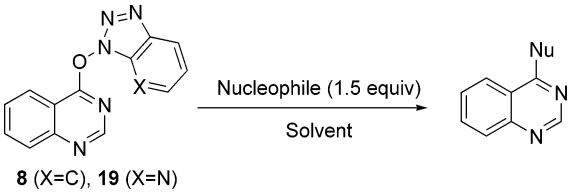
(28) A S_N2'-like pathway was also considered.

(29) We also conducted ^{31}P, ^{1}H NMR and time course HPLC-MS studies on triacetylinosine **10**, but due to the recent report (ref 17), these data have been removed from the original manuscript.

SCHEME 15



SCHEME 16



To further characterize the phosphonium intermediate, an HPLC-NMR-MS experiment was conducted; phosphonium intermediate **107** was sufficiently stable to allow analysis by LC-NMR. The reaction mixture was injected into the HPLC after 40 min.[30] The ^{1}H NMR spectrum of intermediate **107** is shown in Figure 9; the molecular weight of the component was confirmed by MS analysis. The ^{1}H spectrum shows two aromatic singlets (δ 8.49 and 8.68 ppm, 1H each) and the *N*-methyl signals (δ 2.82 ppm, 18H), consistent with the phosphonium intermediate **107** (Figure 9).

The ^{31}P NMR and HPLC-NMR-MS experiments facilitated characterization of the phosphonium intermediate **107**. To complement these experiments, we performed time-course HPLC-MS studies on the BOP-mediated coupling of *n*-butylamine to hypoxanthine **80** (Scheme 14) and to 4-hydroxyquinazoline **5** (Scheme 15). Samples were removed from the reaction mixtures at regular intervals and analyzed using HPLC-MS. The *m*/*z* ratio for the ion corresponding to each of the expected species in the reaction mixtures was extracted from the raw ion count data; these extracted ion counts were integrated and normalized (relative to the ion count from DBU). From this data, we determined the relative changes for each species in the reaction mixture over time. This method does not allow quantitative measure of concentration[31] but provides a means to observe the relative change of each component with respect to time.

The BOP-mediated coupling of *n*-$BuNH_2$ to hypoxanthine **80** (Scheme 14) was slow enough to reveal the reaction pathway from the HPLC-MS data (Figure 10). Pathway "b" (spontaneous formation of the HOBt adduct) was eliminated from consideration because of (1) the lack of evidence for spontaneous formation of the HOBt adduct **108**, and (2) the gradual increase in the concentration of **108** and gradual decrease in the concentration of the phosphonium intermediate **107**. The latter is also consistent with the results from the ^{31}P NMR study. Within the first few minutes, the concentration of BOP and hypoxanthine **80** decreased dramatically; this appeared to correlate with the rapid increase in concentration of phosphonium intermediate **107**. No product **89** was detected during this time (Figure 10). The concentration of **107** decreased over the next hours, whereas the concentration of HOBt adduct **108** and final product **89** increased steadily. By the final time point (at ~20 h), both the HOBt adduct **108** and phosphonium intermediate **107** appeared to have been consumed, leaving the final product **89**, as expected.

The BOP-mediated coupling of *n*-$BuNH_2$ to 4-hydroxyquinazoline **5** (Scheme 15) was nearly complete within a few minutes (Figure 11). Within 10 min, the data from the HPLC-MS time course of this reaction showed a striking decrease in the concentration of 4-hydroxyquinazoline **5** and BOP and a dramatic increase of the final product **20** (the persistence of the signal from the BOP ion is likely due to the slight excess of reagent and issues with the dynamic range of the detector). A small amount of HOBt adduct **8** could be detected early in the reaction; the corresponding phosphonium intermediate **7** was not detected. This is consistent with our observation that with similar substrates, and in the absence of other nucleophiles, formation of the HOBt adducts (e.g., **8**) is extremely rapid. As discussed above, the rate of the BOP-mediated coupling reaction is highly dependent on the electronics of the substrate; the differences between the reactions of 4-hydroxyquinazoline **5** and hypoxanthine **80** highlight this effect.

S_NAr Reactions of HOBt/HOAt Adducts. Finally, we examined the reactivity of isolated HOBt/HOAt adducts to further confirm their role in these phosphonium-mediated reactions. The isolated HOBt/HOAt adducts reacted readily with various nucleophiles (Scheme 16 and Table 8) to give the desired products in good to excellent yields.[32] For example, 4-(1*H*-benzo[*d*][1,2,3]triazol-1-yloxy)quinazoline **8** was isolated and treated with aniline to give 4-phenylaminoquinazoline **41** (Table 8) in good yield. The isomeric HOBt adduct **35** reacted more slowly with nucleophiles (i.e., thiophenol) than **8** (data not shown).

With this evidence in hand, the stepwise reaction mechanism is presented in Figure 12. Treatment of cyclic amide or urea **1** leads to the formation of phosphonium intermediate **114**. While **114** might react with the nucleophile directly to provide the desired product **116**, the HPLC-MS studies described above suggest that the HOBt adduct may play a role even in reactions with strong nucleophiles (e.g., *n*-$BuNH_2$). HOBt adducts can be isolated and may also be converted into the final product (**116**).[33]

Conclusion

A "one-step" S_NAr reaction of cyclic amides and ureas was developed employing BOP as activating agent. The facile and

(30) Five percent of the column effluent was diverted to a mass spectrometer for simultaneous MS analysis, while the remaining volume was directed to a LC-NMR probe.

(31) The constraints of the dynamic range of the MS detector prevented accurate quantification of each component in the reaction mixture. Also, it is expected that each component ionizes more or less efficiently; conclusions were only drawn regarding the relative changes of any individual component.

(32) We conducted S_NAr studies on the HOBt adduct of inosine; these data have been removed from this paper (see note 17). To the best of our knowledge, there are two examples in the literature where HOBt is used as a leaving group in heterocyclic systems; see ref 20 and: Scicinski, J. J.; Congreve, M. S.; Jamieson, C.; Ley, S. V.; Newman, E. S.; Vinader, V. M.; Carr, R. A. E. *J. Comb. Chem.* **2001**, *3*, 387.

(33) Although the phosphonium intermediate is presumably more reactive than the corresponding HOBt adduct, more experimental data are needed to explicitly confirm this assumption.

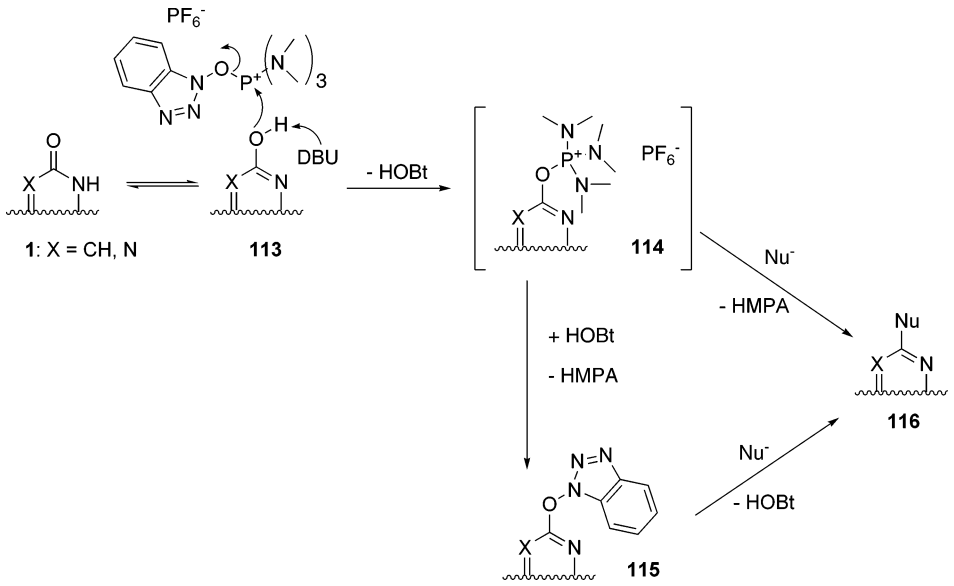


FIGURE 12. Mechanism of BOP-mediated activation of cyclic amides/ureas.

convenient bond-forming reactions facilitated syntheses of numerous biologically interesting heterocycles, including aryl amidines, guanidines, ethers, and thioethers in good to excellent yields. This method provides an alternative to methods involving aryl halides and, in some cases, a possible advantage over aryl halides (i.e., Cl) in terms of reactivity. Nonetheless, these BOP-mediated bond-forming reactions are still governed by the electronic properties of the reaction substrates. Therefore, it is realized that the limitation of this methodology is with electron-rich systems. NMR and HPLC-MS guided mechanistic studies were also conducted; data from these studies are consistent with the reaction mechanism involving stepwise formation of the HOBt adducts from the phosphonium intermediates. Further research into the scope of BOP-mediated bond formation is currently underway.

Experimental Section

General Method A: Preparation of HOBt Adducts. 4-(Benzotriazol-1-yloxy)quinazoline (8). To a room temperature solution of 4-hydroxyquinazoline (0.73 g, 5.0 mmol) and BOP (2.6 g, 6.0 mmol) in MeCN (40 mL) was added DBU (1.1 mL, 7.5 mmol). The mixture was stirred for 1 h at rt. The solvent was removed under vacuum, and the crude mixture was purified by chromatography on silica (elution with 1:1 EtOAc/hexanes) giving the desired product **8** as a white solid (1.08 g, 82%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.60 (d, J = 4.0 Hz, 1H), 8.25−8.16 (m, 3H), 8.00 (t, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 152.9, 151.5, 142.8, 135.8, 129.33, 129.30, 128.5, 127.8, 125.4, 122.7, 119.9, 112.7, 109.6; HRMS (ESI) m/z calcd for $C_{14}H_9N_5O$ (M + H$^+$) 264.0879, found 264.0879.

Acetic Acid (2*R*,3*R*,4*R*,5*R*)-3,4-Diacetoxy-5-[6-(benzotriazol-1-yloxy)purin-9-yl]tetrahydrofuran-2-ylmethyl Ester (14). To a solution of 2′,3′,5′-tri-*O*-acetylinosine (**21**, 100 mg, 0.253 mmol) and BOP (146 mg, 0.329 mmol, 1.3 equiv) in DMF (2.5 mL) was added DBU (57 μL, 0.38 mmol, 1.5 equiv) dropwise at 0 °C in an ice bath. The mixture was stirred for 1.3 h while warming to rt. The reaction mixture was diluted with H_2O (200 mL); the aqueous solution was extracted with EtOAc (4 × 30 mL). The EtOAc portions were combined, washed with brine (2 × 40 mL), dried over $MgSO_4$, and concentrated to an oil. The crude product was purified by chromatography on silica (gradient elution from hexanes to EtOAc) to give the desired product **14** (118 mg, 91%) as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01 (s, 3H), 2.06 (s, 3H), 2.12 (s, 3H), 4.21−4.33 (m, 1H), 4.37−4.51 (m, 2H), 5.66 (app t, J = 5.3 Hz, 1H), 6.06 (dd, J = 5.9, 5.2 Hz, 1H), 6.42 (d, J = 5.1 Hz, 1H), 7.56 (ddd, J = 8.3, 7.1, 1.0 Hz, 1H), 7.66 (ddd, J = 8.3, 7.1, 1.0 Hz, 1H), 7.83 (ddd, J = 8.3, 1.0, 1.0 Hz, 1H), 8.21 (ddd, J = 8.4, 1.0, 1.0 Hz, 1H), 8.57 (s, 1H), 8.91−8.93 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 169.3, 169.2, 158.4, 153.6, 151.4 (CH), 145.9 (CH), 142.7, 129.3 (CH), 128.5, 125.3 (CH), 119.9 (CH), 119.4, 109.4 (CH), 86.3 (CH), 79.7 (CH), 72.1 (CH), 69.9 (CH), 62.6 (CH_2), 20.4 (CH_3), 20.3 (CH_3), 20.2 (CH_3); ESI-MS m/z (relative intensity, ion) 512.1 (55%, [M + H$^+$]), 259.0 (100%, glycosidic bond cleavage); HRMS (ESI) m/z calcd for $C_{22}H_{22}N_7O_8$ (M + H$^+$) 512.1524, found 512.1540

General Method B: Preparation of HOAt Adducts. 4-(1,2,3-Triazolo[4,5-*b*]pyridin-3-yloxy)quinazoline (19). To a room temperature solution of 4-hydroxyquinazoline (2.94 g, 20.1 mmol) and PyAOP (11.4 g, 21.9 mmol, 1.1 equiv) in MeCN (100 mL) was added DBU (5.2 mL, 30 mmol). The mixture was stirred for 1 h at rt. The solvent was removed under vacuum, and the crude mixture was purified by chromatography on silica (elution with 4:1 EtOAc/hexanes) giving the desired product **19** (5.68 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, J = 1.2, 4.4 Hz, 1H), 8.64 (s, 1H), 8.53 (dd, J = 1.2, 8.0 Hz, 2H), 8.14−8.11 (m, 1H), 8.07−8.03 (m, 1H), 7.84−7.08 (m, 1H), 7.50 (dd, J = 4.4, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 152.9, 152.2, 151.8, 142.1, 135.1, 135.1, 129.7, 128.7, 128.2, 122.6, 121.0, 113.6; HRMS (ESI) m/z calcd for $C_{13}H_8N_6O$ (M + H$^+$) 265.0832, found 265.0836.

4-(Benzotriazol-1-yloxy)thieno[2,3-*d*]pyrimidine (28a). Synthesized according to General Method A (reaction mixture stirred for 12 h at rt) from 3*H*-thieno[2,3-*d*]pyrimidin-4-one **22** and purified by flash chromatography as a white solid (250 mg, 93%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.23−8.22 (m, 2H), 7.91 (d, J = 6.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.66−7.56 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.6, 162.5, 152.6, 143.1, 130.3, 129.7, 128.8, 125.7, 120.2, 117.9, 116.3, 109.9; HRMS (ESI) m/z calcd for $C_{12}H_7N_5OS$ (M + H$^+$) 270.0441, found 270.0441.

3-(Thieno[2,3-*d*]pyrimidin-4-yloxy)-3*H*-1,2,3-triazolo[4,5-*b*]-pyridine (28b). Synthesized according to General Method B (reaction mixture stirred for 2 h at rt) from 3*H*-thieno[2,3-*d*]-pyrimidin-4-one **22** and purified by flash chromatography as a white solid (980 mg, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, J = 1.2, 4.4 Hz, 1H), 8.61 (s, 1H), 8.51 (dd, J = 1.2, 8.0 Hz, 1H), 8.14 (s, 1H), 7.67 (s, 1H), 7.50 (dd, J = 4.8, 8.4 Hz, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 164.6, 163.5, 153.5, 151.9, 140.8, 136.9, 134.9, 129.7, 124.6, 121.0, 114.6; HRMS (ESI) *m*/*z* calcd for $C_{11}H_7N_6OS$ (M + H^+) 271.0397, found 271.0390.

4-(Benzotriazol-1-yloxy)-5-methylthieno[2,3-*d*]pyrimidine-6-carboxylic Acid Methyl Ester (29a). Synthesized according to General Method A (reaction mixture stirred for 12 h at rt) from 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid methyl ester **23** and purified by flash chromatography as a yellow solid (260 mg, 76%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.21 (dd, J = 0.8, 7.6 Hz, 1H), 7.92−7.90 (m, 1H), 7.67−7.56 (m, 2H), 3.96 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 164.7, 162.3, 155.0, 143.0, 138.7, 129.6, 128.7, 126.5, 125.8, 120.2, 118.3, 110.1, 53.2, 16.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}N_5O_3S$ (M + H^+) 342.0655, found 342.0659.

5-Methyl-4-(1,2,3-triazolo[4,5-*b*]pyridin-3-yloxy)thieno[2,3-*d*]-pyrimidine-6-carboxylic Acid Methyl Ester (29b). Synthesized according to General Method B (reaction mixture stirred for 12 h at rt) from 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid methyl ester **23** and purified by flash chromatography as a yellow solid (1.25 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, J = 0.8, 4.0 Hz, 1H), 8.52 (dd, J = 1.2, 8.0 Hz. 1H), 8.49 (s, 1H), 7.50 (dd, J = 4.0, 8.1 Hz, 1H), 4.00 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.6, 162.5, 154.1, 151.9, 140.8, 138.3, 135.0, 129.7, 127.5, 121.0, 118.1, 52.7, 15.9; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{11}N_6O_3S$ (M + H^+) 343.0608, found 343.0600.

1-(4-Methylpyrimidin-2-yloxy)-1*H*-benzotriazole (30). Synthesized according to General Method A (reaction mixture stirred for 12 h at rt) from 4-methylpyrimidin-2(1*H*)-one **24** and purified by flash chromatography as a white solid (160 mg, 70%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (dd, J = 4.8 Hz, 1H), 8.17 (dd, J = 8.4 Hz, 1H), 7.75 (dd, J = 8.4 Hz, 1H), 7.64−7.53 (m, 2H), 7.42 (dd, J = 5.2 Hz, 1H), 3.3 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.9, 164.1, 159.8, 142.7, 129.0, 128.0, 125.0, 119.7, 119.2, 109.2, 23.4; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{10}N_5O$ (M + H^+) 228.0880, found 228.0877.

3-(5-Bromopyrimidin-2-yloxy)-3*H*-1,2,3-triazolo[4,5-*b*]pyridine (31). Synthesized according to General Method B (reaction mixture stirred for 2 h at rt) from 5-bromo-1*H*-pyrimidin-2-one **25** and purified by flash chromatography as a white solid (820 mg, 70%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 2H), 8.81 (dd, J = 1.2, 4.4 Hz, 1H), 8.75 (dd, J = 0.8, 8.0 Hz, 1H), 7.66 (dd, J = 4.8, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9, 161.3, 152.5, 139.4, 134.4, 129.7, 121.6, 116.6; HRMS (ESI) *m*/*z* calcd for $C_9H_6BrN_6O$ (M + H^+) 292.9781, found 292.9783.

1-Methyl-4-(1,2,3-triazolo[4,5-*b*]pyridin-3-yloxy)-1*H*-pyrimidin-2-one (32). Synthesized according to General Method B (reaction mixture stirred for 12 h at rt) from 1-methyl-1*H*-pyrimidine-2,4-dione **26** and purified by flash chromatography as a white solid (400 mg, 77%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (dd, J = 1.2, 4.8 Hz, 1H), 8.75 (dd, J = 1.6, 8.4 Hz, 1H), 8.47 (d, J = 6.8 Hz, 1H), 7.66 (dd, J = 4.4, 8.4 Hz, 1H), 6.71 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 154.6, 152.9, 140.1, 134.6, 130.1, 122.0, 89.9, 38.1; HRMS (ESI) *m*/*z* calcd for $C_{10}H_9N_6O_2$ (M + H^+) 245.0781, found 245.0785.

1-(6-Chloropyrimidin-4-yloxy)-1*H*-benzotriazole (33a). Synthesized according to General Method A (reaction mixture stirred for 8 h at rt) from 6-chloro-3*H*-pyrimidin-4-one **27** and purified by flash chromatography as a white solid (125 mg, 51%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.7 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.05−8.04 (m, 1H), 7.82 (d, 1H), 7.69−7.66 (m, 1H), 7.57−7.55 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 162.3, 158.9, 129.8, 143.0, 128.4, 125.8, 120.3, 109.7, 107.0; HRMS (ESI) *m*/*z* calcd for $C_{10}H_7ClN_5O$ (M + H^+) 248.0334, found 248.0333.

3-(6-Chloropyrimidin-4-yloxy)-3*H*-1,2,3-triazolo[4,5-*b*]pyridine (33b). Synthesized according to General Method B (reaction mixture stirred for 8 h at rt) from 6-chloro-3*H*-pyrimidin-4-one **27** and purified by flash chromatography as a white solid (78 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, J = 1.6, 4.8 Hz, 1H), 8.50−8.48 (m, 2H), 7.49 (dd, J = 4.4, 8.8 Hz, 1H), 7.35 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 163.1, 158.3, 152.0, 141.1, 134.9, 129.7, 121.1, 106.7; HRMS (ESI) *m*/*z* calcd for $C_9H_6ClN_6O$ (M + H^+) 249.0286, found 249.0282.

4,6-Bis(1*H*-benzo[*d*][1,2,3]triazol-1-yloxy)pyrimidine (34a). Synthesized according to General Method A (reaction mixture stirred for 8 h at rt) from 6-chloro-3*H*-pyrimidin-4-one **27** and purified by flash chromatography as a white solid (110 mg, 31%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 0.8 Hz, 1H), 8.20 (d, J = 8.4 Hz, 2H), 7.87−7.86 (m, 2H), 7.84 (s, 1H), 7.71−7.67 (m, 2H), 7.58−7.56 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 158.7, 143.0, 129.8, 128.5, 125.8, 120.3, 109.7, 90.7; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{11}N_8O_2$ (M + H^+) 347.0999, found 347.1005.

4,6-Bis(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)pyrimidine (34b). Synthesized according to General Method B (reaction mixture stirred for 8 h at rt) from 6-chloro-3*H*-pyrimidin-4-one **27** and purified by flash chromatography as a white solid (89 mg, 26%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, J = 1.2, 4.4 Hz, 2H), 8.48 (dd, J = 1.2, 8.4 Hz, 2H), 8.17 (d, J = 0.8 Hz, 1H), 7.48 (dd, J = 4.0, 8.0 Hz, 1H), 7.15 (d, J = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 158.1, 152.0, 134.9, 129.7, 121.1, 89.5; HRMS (ESI) *m*/*z* calcd for $C_{14}H_9N_{10}O_2$ (M + H^+) 349.0904, found 349.0900.

4-(3-Oxybenzotriazol-1-yl)quinazoline (35). To a solution of 4-hydroxyquinazoline (**5**, 100 mg, 0.684 mmol) and BOP (393 mg, 0.889 mmol, 1.3 equiv) in MeCN (6.8 mL) was added DBU (156 μL, 1.03 mmol, 1.5 equiv) dropwise at 0 °C. The mixture was stirred while warming to room temperature. The mixture was diluted with EtOAc (250 mL); this solution was washed with 1:1 brine/1 M aq HCl (∼200 mL). The EtOAc layer was dried over $MgSO_4$ and concentrated under vacuum. The mixture was purified by chromatography on silica (gradient elution from hexanes (0.25% TEA) to EtOAc (0.25% TEA)); fractions containing the desired product were pooled and concentrated. Residual solvent was removed overnight, affording **35** (72.2 mg, 40%) as a white solid: mp 187 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (t, J = 7.8 Hz, 1H), 7.85−7.99 (m, 2H), 8.07−8.19 (m, 3H), 8.75 (d, J = 8.6 Hz, 1H), 8.99 (d, J = 8.6 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.2, 153.1, 152.5, 134.9, 133.6, 132.5, 131.2, 129.0, 128.5, 126.7, 126.4, 117.0, 115.8, 115.0; ESI-MS *m*/*z* (relative intensity, ion) 264 (100%, [M + H^+]); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{10}N_5O$ (M + H^+) 264.0880, found 264.0878.

Nitrogen Nucleophiles. 4-Benzotriazol-1-ylquinazoline (16). 4-Hydroxyquinazoline (**5**, 100 mg, 0.684 mmol, 1 equiv) and BOP (393 mg, 0.890 mmol, 1.3 equiv) were added to a 40 mL glass vial containing a magnetic stir bar. MeCN (27 mL) was added to the vial, then Ph_2O (108 μL, 0.684 mmol; HPLC standard) and DBU (205 μL, 1.37 mmol, 2 equiv). This solution was stirred for 1 min at room temperature. Benzotriazole (245 mg, 2.05 mmol, 3 equiv) was added to the reaction mixture. The slightly cloudy solution was stirred at room temperature overnight. Yield of **16** in the mixture was 95% (as determined by HPLC relative to internal standard). The reaction mixture was concentrated and then purified by chromatography on silica (gradient elution from hexanes to EtOAc). Fractions containing the product were pooled and concentrated; residual solvent was removed under reduced pressure, affording **16** (111 mg, 0.449 mmol, 66%) as a white solid: mp 169.5−169.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 7.81 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 7.93 (ddd, J = 8.3, 6.6, 1.8 Hz, 1H), 8.15−8.22 (m, 2H), 8.32 (app dt, J = 8.6, 0.9 Hz, 1H), 8.48 (app dt, J = 8.6, 0.9 Hz, 1H), 8.95 (dddd, J = 8.6, 1.8, 1.2, 0.5 Hz, 1H), 9.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.7, 153.6, 152.6, 145.2, 135.1, 132.1, 129.8, 129.3, 128.4, 126.7, 126.0, 119.7, 116.9, 114.7; ESI-MS *m*/*z* (relative intensity, ion) 248 (12%, [M + H^+]), 220 (100%, [M − N_2]); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{10}N_5$ (M + H^+) 248.0931, found 248.0931.

Cyclohexylquinazolin-4-ylamine (36). To a solution of 4-hydroxyquinazoline (**5**, 100 mg, 0.684 mmol) in MeCN (6.8 mL) were added Ph_2O (108 μL, 0.684 mmol; HPLC standard), cyclohexylamine (235 μL, 2.05 mmol, 3 equiv), DBU (205 μL, 1.37 mmol, 2 equiv), and BOP (393 mg, 0.889 mmol, 1.3 equiv). The reaction mixture was stirred for ~24 h. The mixture was concentrated by rotary evaporation and purified by chromatography on silica (gradient elution from hexanes (0.25% TEA) to EtOAc (0.25% TEA)) to give the desired product **36** (133 mg, 85%) as a white solid: mp 151.1−151.5 °C (lit.[34] 148−149 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07−1.25 (m, 1H), 1.26−1.47 (m, 4H), 1.60−1.70 (m, 1H), 1.72−1.81 (m, 2H), 1.91−1.99 (m, 2H), 4.11−4.24 (m, 1H), 7.48 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.65 (dd, 1H), 7.74 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 8.31 (dd, J = 8.3, 0.8 Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.5, 155.1, 149.2, 132.3, 127.4, 125.2, 122.9, 114.9, 49.3, 32.0 (2C), 25.3, 25.0 (2C); ESI-MS m/z (relative intensity, ion) 228 (100%, [M + H$^+$]); HRMS (ESI) m/z calcd for $C_{14}H_{18}N_3$ (M + H$^+$) 228.1495, found 228.1495.

[3,4′]Biquinazolinyl-4-one (44). To a solution of 4-hydroxyquinazoline (**5**, 50 mg, 0.34 mmol, 1 equiv) and BOP (75 mg, 0.17 mmol, 0.5 equiv) in MeCN (1.7 mL) were added Ph_2O (54.3 μL, 0.342 mmol; HPLC standard) and DBU (102 μL, 0.684 mmol, 2 equiv). After ~1.5 h, a significant amount of white precipitate had formed; CH_2Cl_2 (0.5 mL) was added to the vial to homogenize the reaction mixture. The mixture was stirred overnight, concentrated by rotary evaporation, and purified by chromatography on silica (gradient elution from hexanes (0.25% TEA) to EtOAc (0.25% TEA)) to afford **44** (38.6 mg, 82%) as a white solid: mp 229−230 °C (lit.[35] 232.5 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (ddd, J = 8.1, 7.33, 1.0 Hz, 1H), 7.80 (ddd, J = 8.3, 6.9, 1.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.99 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 8.01−8.05 (m, 1H), 8.15 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 8.22 (app d, J = 8.3, 1H), 8.26 (dd, J = 7.8, 1.5 Hz, 1H), 8.61 (s, 1H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 158.1, 154.5, 151.5, 147.6, 145.4, 135.5, 135.4, 129.2, 128.1, 128.0, 127.7, 126.5, 125.6, 121.4, 121.0; ESI-MS m/z (relative intensity, ion) 275 (100%, [M + H$^+$]); HRMS m/z calcd for $C_{16}H_{11}N_4O$ (M + H$^+$) 275.0927, found 275.0926.

Tetrazolo[1,5-*c*]quinazoline (45). To a solution of 4-hydroxyquinazoline (**5**, 100 mg, 0.684 mmol, 1 equiv) and BOP (363 mg, 0.821 mmol, 1.2 equiv) in MeCN (6.8 mL) were added Ph_2O (108 μL, 0.684 mmol; HPLC standard) and DBU (153 μL, 1.03 mmol, 1.5 equiv). After stirring the mixture for 5 min, NaN_3 (88.9 mg, 1.37 mmol) was added. The reaction mixture was stirred for 1.5 h, warmed to 50 °C, and stirred for 1 h. The mixture was concentrated by rotary evaporation and purified by chromatography on silica (gradient elution from hexanes to EtOAc) to give the desired product **45** (95.9 mg, 82%) as a white solid:[36] mp 214 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (ddd, J = 8.3, 7.3, 1.0 Hz, 1H), 8.07 (ddd, J = 8.3, 7.1, 1.5 Hz, 1H), 8.19 (app d, J = 8.1 Hz, 1H), 8.60 (ddd, J = 8.1, 1.5, 0.8 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.3, 142.5, 136.7, 133.6, 130.1, 128.7, 124.1, 115.3; ESI-MS m/z (relative intensity, ion) 172 (100%, [M + H$^+$]), 144 (75%, [M − N_2]).

Non-Nitrogen Nucleophiles. 4-*o*-Tolyloxyquinazoline (47). To a solution of 4-hydroxyquinazoline (**5**, 100 mg, 0.684 mmol) and BOP (393.4 mg, 0.890 mmol, 1.3 equiv) in MeCN (6.8 mL) were added Ph_2O (108 μL, 0.684 mmol; HPLC standard) and DBU (205 μL, 1.37 mmol, 2 equiv). The mixture was stirred for 10 min, and then *o*-cresol (211 μL, 2.05 mmol, 3 equiv) was added to the vial. The reaction mixture was stirred for 24 h at rt, then at 60 °C for 3 days. The mixture was concentrated and purified by chromatography on silica (gradient elution from hexanes to EtOAc) to give the desired product **47** (83.8 mg, 52%) as a white solid: mp 74−77 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.10 (s, 3H), 7.22−7.28 (m, 2H), 7.28−7.35 (m, 1H), 7.35−7.40 (m, 1H), 7.79 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 8.00 (ddd, J = 8.3, 1.5, 0.5 Hz, 1H), 8.05 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 8.42 (ddd, J = 8.3, 1.3, 0.8 Hz, 1H), 8.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 154.0, 151.1, 150.7, 134.6, 131.2, 130.1, 128.1, 127.5, 127.2, 126.0, 123.4, 122.3, 115.3, 15.8; ESI-MS m/z (relative intensity, ion) 236.9 (100%, [M + H$^+$]); HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O$ (M + H$^+$) 237.1022, found 237.1022.

4-*p*-Tolyloxyquinazoline (48). To a solution of 4-hydroxyquinazoline (**5**, 100 mg, 0.684 mmol) and BOP (393.4 mg, 0.890 mmol, 1.3 equiv) in MeCN (6.8 mL) were added Ph_2O (108 μL, 0.684 mmol; HPLC standard) and DBU (205 μL, 1.37 mmol, 2 equiv). The mixture was stirred for 5 min, and then *p*-cresol (~240 mg, 2.21 mmol, 3.2 equiv) was added to the vial. The reaction mixture was stirred for 24 h at rt and then warmed to 60 °C. The reaction mixture was stirred at 60 °C for 3 days. The mixture was concentrated and purified by chromatography on silica (gradient elution from hexanes to EtOAc) to give the desired product **48** (122.4 mg, 75%) as a white solid: mp 58.8−61.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H), 7.19 (d, J = 7.1 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.68−7.85 (m, 1H), 7.90−8.08 (m, 2H), 8.36 (d, J = 8.1 Hz, 1H), 8.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4, 153.8, 151.0, 149.9, 135.0, 134.5, 130.0, 127.9, 127.4, 123.3, 121.7, 115.6, 20.4; ESI-MS m/z (relative intensity, ion): 236.8 (100%, [M + H$^+$]); HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O$ (M + H$^+$) 237.1022, found 237.1022.

4-(4-Methoxyphenoxy)quinazoline (49). To a solution of 4-hydroxyquinazoline (**5**, 100 mg, 0.684 mmol) and BOP (393 mg, 0.890 mmol, 1.3 equiv) in MeCN (6.8 mL) were added Ph_2O (108 μL, 0.684 mmol; HPLC standard) and DBU (205 μL, 1.37 mmol, 2 equiv). The mixture was stirred for 5 min, and then *p*-hydroxyanisole (254 mg, 2.05 mmol, 3 equiv) was added to the vial. The reaction mixture was stirred for 4 h at rt and then at 60 °C for 2 days. The mixture was concentrated and purified by chromatography on silica (gradient elution from hexanes (0.25% TEA) to EtOAc (0.25% TEA)), giving a mixture of the desired product **49** (128 mg, 75%) and *p*-hydroxyanisole (122 mg) as a white crystalline solid (ratio of product to *p*-hydroxyanisole determined by ^{1}H NMR). An analytical sample was prepared by flash chromatography: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77 (s, 1H), 8.39−8.73 (m, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.94−7.90 (m, 1H), 7.68−7.64 (m, 1H), 7.20−7.17 (m, 2H), 7.01−6.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 157.3, 154.3, 151.5, 145.6, 134.0, 127.8, 127.5, 123.6, 122.6, 116.4, 114.8, 55.6; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O_2$ (M + H$^+$) 253.0971, found 253.0964

4-*p*-Tolylsulfanylquinazoline (51). To a solution of 4-hydroxyquinazoline (**5**, 100 mg, 0.684 mmol, 1 equiv) and BOP (393 mg, 0.890 mmol, 1.3 equiv) in MeCN (6.8 mL) were added Ph_2O (108 μL, 0.684 mmol; HPLC standard) and DBU (205 μL, 1.37 mmol, 2 equiv). The mixture was stirred for 5 min, and then 4-methylbenzenethiol (339 mg, 2.73 mmol, 4 equiv) was added to the vial. The mixture was stirred overnight, concentrated, and purified by chromatography on silica (gradient elution from hexanes to EtOAc) to afford **51** (110.4 mg, 64%) as a white solid:[37] mp 107−108 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.39 (s, 3H), 7.34 (app dt, J = 7.8, 0.8 Hz, 2H), 7.52 (app dt, J = 8.6, 2.0 Hz, 2H), 7.78 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 7.97 (ddd, J = 8.6, 1.5, 0.5 Hz, 1H), 8.03 (ddd, J = 8.6, 6.8, 1.5 Hz, 1H), 8.24 (ddd, J = 8.3, 1.3, 0.8 Hz, 1H), 8.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.7, 153.5, 147.7, 139.8, 135.8, 134.6, 130.2, 128.5, 128.3, 123.5, 122.9, 122.3, 20.9 (3C); ESI-MS m/z (relative intensity, ion) 253 (100%, [M +

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H^+]); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{13}N_2S$ (M + H^+) 253.0794, found 253.0792.

4-(4-Methoxyphenylsulfanyl)quinazoline (52). To a solution of 4-hydroxyquinazoline (**5**, 100 mg, 0.684 mmol), BOP (393 mg, 0.890 mmol, 1.3 equiv), and Ph_2O (108 μL, 0.684 mmol; HPLC standard) in MeCN (27 mL) was added DBU (205 μL, 1.37 mmol, 2 equiv). After stirring for 10 min at room temperature, 4-methoxybenzenethiol (252 μL, 2.05 mmol, 3 equiv) was added to the reaction mixture. The mixture was stirred overnight, concentrated, and purified by chromatography on silica (gradient elution from hexanes to EtOAc) to afford the desired product **52** (170.4 mg, 93%) as a white solid:[38] mp 136−137 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.84 (s, 3H), 7.07 (app dt, J = 9.9, 3.3 Hz, 2H), 7.54 (app dt, J = 9.9, 3.3 Hz, 2H), 7.77 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 7.96 (dd, J = 8.3, 1.0 Hz, 1H), 8.01 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 8.22 (ddd, J = 8.3, 1.3, 0.8 Hz, 1H), 8.81 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.0, 160.6, 153.5, 147.7, 137.5, 134.5, 128.4, 128.2, 123.5, 122.3, 116.6, 115.2, 55.3; ESI-MS *m*/*z* (relative intensity, ion): 268.9 (100%, [M + H^+]); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{13}N_2OS$ (M + H^+) 269.0743, found 269.0741.

Quinazoline-4-carbonitrile (53). To a solution of 4-hydroxyquinazoline (**5**, 200 mg, 1.37 mmol) and BOP (786 mg, 1.78 mmol, 1.3 equiv) in MeCN (13.7 mL) were added Ph_2O (217 μL, 1.37 mmol; HPLC standard) and DBU (307 μL, 2.05 mmol, 1.5 equiv). The mixture was stirred for 25 min at rt. NaCN (CAUTION: violent poison) (134 mg, 2.74 mmol, 2 equiv) was added to the vial. After stirring the mixture for 5 min, 18-crown-6 (722 mg, 2.74 mmol, 2 equiv) was added to the vial. The solution changed from pale yellow to dark red over 15 min; stirring was continued for an additional 22 h. The mixture was concentrated and purified by chromatography on silica (gradient elution from hexanes (0.25% TEA) to EtOAc (0.25% TEA)) to give the desired product **53** (115 mg, 0.743 mmol, 54%) as a white solid: mp 123.3−124.8 °C (lit.[39] 118.0−119.5 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98−8.04 (ddd, J = 8.0, 6.0, 2.0 Hz, 1H), 8.19−8.25 (m, 2H), 8.25−8.28 (m, 1H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.5, 150.1, 142.6, 136.5, 130.8, 128.7, 124.9, 123.8, 114.5; ESI-MS *m*/*z* (relative intensity, ion) 156.1 (100%, [M + H^+]).

Allyl-(6-bromoquinazolin-4-yl)amine (69). 6-Bromoquinazolin-4(3*H*)-one (**57**, 500 mg, 2.22 mmol) and DMF (660 μL) were added to a reaction vial. Ph_2O (352 μL, 2.22 mmol; HPLC reference), allyl amine (500 μL, 6.66 mmol, 3 equiv), and DBU (664 μL, 4.44 mmol) were added sequentially to the mixture in the vial. BOP (1.27 g, 2.88 mmol) was then added to the vial. The reaction mixture was stirred at room temperature for ~2 h and then added dropwise to cold water (175 mL). Brine was added to the aqueous solution, and the product was extracted multiple times with CH_2Cl_2. The CH_2Cl_2 portions were combined, washed with brine, and concentrated. The product was purified by chromatography on silica (gradient elution from hexanes to EtOAc); fractions containing the desired product were pooled and concentrated, affording **69** (473 mg, 1.79 mmol, 81%) as an off-white solid:[22] mp 171−173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.15−4.20 (dddd, J = 7.1, 5.6, 3.3, 1.5 Hz, 2H), 5.08−5.15 (ddd, J = 10.4, 3.3, 1.8 Hz, 1H), 5.22 (ddd, J = 17.2, 3.5, 1.8 Hz, 1H), 5.92−6.05 (dddd, J = 17.2, 10.4, 5.3, 5.3 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.89 (dd, J = 8.8, 2.0 Hz, 1H), 8.48 (s, 1H), 8.56 (t, J = 5.3 Hz, 1H), 8.59 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.8, 155.5 (CH), 148.0, 135.5 (CH), 134.7 (CH), 129.8 (CH), 125.2 (CH), 119.5, 116.2, 115.7 (CH_2), 42.8 (CH_2); ESI-MS *m*/*z* (relative intensity, ion) 265.9 (100%, M + H^+).

2-(Benzotriazol-1-yloxy)-5-bromopyrimidin-4-ylamine (106) and 5-Bromo-N^2-butylpyrimidine-2,4-diamine. To a suspension of 5-bromocytosine (**100**, 234 mg, 1.23 mmol), BOP (708 mg, 1.60 mmol, 1.3 equiv), and Ph_2O (195 μL, 1.23 mmol; HPLC standard) in MeCN (12.3 mL) was added DBU (368 μL, 2.46 mmol, 2 equiv). Upon addition of DBU, the mixture changed from cloudy and opaque to translucent pale yellow. After stirring the mixture for 2 h at rt, one-third of the mixture (4.1 mL) was removed in order to obtain an analytical sample of **106**. This smaller portion was concentrated and purified by chromatography on silica (gradient elution from hexanes (0.25% TEA) to EtOAc (0.25% TEA)); the desired fractions were pooled and concentrated, and residual solvent was removed under reduced pressure, affording the HOBt adduct **106** (7.9 mg, ~6%) as a white solid: mp 198 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (br s, 1H), 7.51 (ddd, J = 8.3, 7.1, 1.0 Hz, 1H), 7.63 (ddd, J = 8.3, 7.1, 1.0 Hz, 1H), 7.74 (app dt, J = 8.3, 1.0 Hz, 1H), 8.13 (app dt, J = 8.3, 1.0 Hz, 1H), 8.16 (s, 1H), 8.19 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.5, 162.2, 157.3, 142.7, 128.9, 128.1, 125.0, 119.7, 109.4, 98.9; ESI-MS *m*/*z* (relative intensity, ion) 307.0 (90%, M + H^+), 308.9 (100%); HRMS (ESI) *m*/*z* calcd for $C_{10}H_8BrN_6O$ (M + H^+) 306.9938, found 306.9937.

n-$BuNH_2$ (243 μL, 2.46 mmol, 3 equiv) was added to the remaining larger portion of the reaction mixture. The solution was stirred for 2 h at rt, and for 22 h at 60 °C. The mixture was concentrated and purified by chromatography on silica (hexanes (0.25% TEA) to EtOAc (0.25% TEA)) to give the desired product **103** (140 mg, 67%) as a white solid: mp 103−104 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (t, J = 7.3 Hz, 3H), 1.22−1.36 (m, 2H), 1.40−1.50 (m, 2H), 3.16 (app dt, J = 7.1, 5.9 Hz, 2H), 6.49 (br s, 1H), 6.53 (br s, 1H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 159.7, 156.5 (CH), 89.3 (*C*-Br), 40.4 (CH_2), 31.3 (CH_2), 19.6 (CH_2), 13.7 (CH_3); ESI-MS *m*/*z* (relative intensity, ion) 245.0 (85%, [M + H^+]); HRMS (ESI) *m*/*z* calcd for $C_8H_{14}BrN_4$ (M + H^+) 245.0396, found 245.0395.

Reaction between HOBt Adduct 8 and Nucleophiles. Butylquinazolin-4-ylamine (20): 4-(Benzotriazol-1-yloxy)quinazoline (**8**, 100 mg, 0.380 mmol), MeCN (15.2 mL), and Ph_2O (60.3 μL, 0.380 mmol; HPLC standard) were added to a 40 mL vial containing a magnetic stir bar. *n*-$BuNH_2$ (56.2 μL, 0.570 mmol, 1.5 equiv) and then DBU (114 μL, 0.760 mmol, 2 equiv) were added to the vial. The solution was stirred for 30 min at rt; the reaction was nearly complete (HPLC-MS). The reaction mixture was stirred overnight, concentrated, and purified by chromatography on silica (gradient elution from CH_2Cl_2 to 10% MeOH/CH_2Cl_2); fractions containing the desired product were pooled and concentrated, and residual solvent was removed under reduced pressure, affording **20** (61.1 mg, 80%) as a white solid. ^{1}H NMR and HPLC-MS analysis confirmed that this sample was identical to **20** as prepared using the one-pot method: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3H), 1.31−1.44 (m, 2H), 1.58−1.68 (m, 2H), 3.54 (dt, J = 7.2, 5.6 Hz, 2H), 7.49 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 7.66 (app dd, J = 8.3, 1.0 Hz, 1H), 7.74 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 8.19 (br s, 1H), 8.23 (ddd, J = 8.3, 1.5, 0.5 Hz, 1H), 8.44 (s, 1H); ESI-MS *m*/*z* (relative intensity, ion) 202.2 (100%, [M + H^+]).

(Quinazolin-4-ylamino)acetic Acid Methyl Ester (39): Prepared as described for **20** from 4-(benzotriazol-1-yloxy)quinazoline (**8**, 100 mg, 0.380 mmol), DBU (114 μL, 0.760 mmol, 2 equiv), and glycine methyl ester HCl (143 mg, 1.14 mmol, 3.0 equiv). The product was purified by chromatography on silica (gradient elution from CH_2Cl_2 to 10% MeOH/CH_2Cl_2); fractions containing the desired product were pooled and concentrated, and residual solvent was removed under reduced pressure, affording **39** (77.7 mg, 94%) as a white solid. ^{1}H NMR and HPLC-MS analysis confirmed that this sample was identical to **39** as prepared using the one-pot method: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.66 (s, 3H), 4.27 (d, J = 6.1 Hz, 1H), 7.56 (ddd, J = 8.3, 6.9, 1.5 Hz, 1H), 7.73 (dd, J = 8.3, 0.8 Hz, 1H), 7.81 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 8.25 (app d, J = 8.3 Hz, 1H), 8.46 (s, 1H), 8.74 (t, J = 5.8 Hz, 1H); ESI-MS *m*/*z* (relative intensity, ion) 218.2 (100%, [M + H^+]), 158.0 (23%, [M − CO_2Me]).

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Phenylquinazolin-4-ylamine (41): Prepared as described for **20** from 4-(benzotriazol-1-yloxy)quinazoline (**8**, 100 mg, 0.380 mmol), DBU (114 μL, 0.760 mmol, 2 equiv), and aniline (105 mg, 1.14 mmol, 3.0 equiv). The product was purified by chromatography on silica (gradient elution from CH_2Cl_2 to 10% MeOH/CH_2Cl_2); fractions containing the desired product were pooled and concentrated, and residual solvent was removed under reduced pressure, affording **41** (70 mg, 78%) as a white solid, purified by flash chromatography as a white solid (86 mg, 78%): mp 206−208 °C; ^{1}NMR (DMSO-d_6, 400 MHz) δ 9.38 (s, 1H), 8.66−8.57 (m, 2H), 7.88−7.89 (m, 4H), 7.64 (t, J = 1.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157.9, 154.5, 149.6, 139.2, 131.1, 128.6, 127.8, 126.5, 123.9, 123.1, 122.6, 115.2; HRMS (ESI) m/z calcd for $C_{14}H_{11}N_3$ 222.1025, found 222.1023.

4-Phenoxyquinazoline (46): Prepared as described for **20** from 4-(benzotriazol-1-yloxy)quinazoline (**8**, 100 mg, 0.380 mmol), DBU (114 μL, 0.760 mmol, 2 equiv), and phenol (72 mg, 0.76 mmol, 2 equiv). The product was purified by chromatography on silica (gradient elution from hexanes to EtOAc); fractions containing the desired product were pooled and concentrated, and residual solvent was removed under reduced pressure giving **46** (70.3 mg, 83%) as a white solid. ^{1}H NMR and HPLC-MS analysis confirmed that this sample was identical to **46** as prepared using the one-pot method: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.26 (d, J = 8.2 Hz, 1H), 8.05−8.00 (m, 2H), 7.80 (t, J = 6.3 Hz, 1H), 7.68−7.66 (m, 2H), 7.56−7.54 (m, 3H); ^{13}C NMR (100 Mhz, DMSO-d_6) δ 170.6, 153.8, 148.1, 136.1, 134.9, 130.2, 129.9, 128.8, 128.7, 126.8, 123.9, 122.7; HRMS (ESI) m/z calcd for $C_{14}H_{11}N_2O$ ($M + H^+$) 223.0866, found 223.0862.

4-(Phenylthio)quinazoline (50): Prepared as described for **20** from 4-(benzotriazol-1-yloxy)quinazoline (**8**, 100 mg, 0.380 mmol), DBU (114 μL, 0.760 mmol, 2 equiv), and thiophenol (78 μL, 0.76 mmol, 2 equiv). The product was purified by chromatography on silica (gradient elution from hexanes to EtOAc); fractions containing the desired product were pooled and concentrated, and residual solvent was removed under reduced pressure giving **50** (78.8 mg, 87%) as a white solid. ^{1}H NMR and HPLC-MS analysis confirmed that this sample was identical to **50** as prepared using the one-pot method: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52−7.57 (m, 3H), 7.64−7.69 (m, 2H), 7.80 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.99 (ddd, J = 8.3, 1.8, 1.0 Hz, 1H), 8.05 (ddd, J = 8.6, 6.9, 1.4 Hz, 1H), 8.27 (ddd, J = 8.3, 1.3, 0.8 Hz, 1H), 8.84 (s, 1H); ESI-MS m/z (relative intensity, ion) 239.0 (100%, [$M + H^+$]).

Reaction between HOAt Adduct 19 and Nucleophiles. 4-Phenoxyquinazoline (46) (preparation from HOAt adduct **19**). A mixture of 4-(1,2,3-triazolo[4,5-*b*]pyridin-3-yloxy)quinazoline **19** (27 mg, 0.10 mmol), phenol (14 mg, 0.15 mmol), and Cs_2CO_3 (43 mg, 0.15 mmol) was stirred for 1 h at rt. The solvent was removed, and the product was purified by chromatography on silica (elution with 1:4 EtOAc/hexanes), giving the desired product **46** (19 mg, 86%).

4-(3-Nitrophenoxy)quinazoline (111). Prepared from HOAt adduct **19** (as for **46**) in 80% isolated yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.39−8.37 (m, 1H), 8.22−8.20 (m, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.98−7.95 (m, 1H), 7.74−7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 153.7, 152.6, 151.9, 149.0, 130.2, 134.5, 128.4, 128.1, 128.0, 123.2, 120.9, 117.8, 116.0; HRMS (ESI) calcd for $C_{14}H_9N_3O_3$ ($M + H^+$) 268.0176, found 268.0174.

4-(4-Methoxyphenoxy)quinazoline (49). Prepared from HOAt adduct **19** according to the synthesis of **46** in 74% isolated yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.39−8.73 (m, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.94−7.90 (m, 1H), 7.68−7.64 (m, 1H), 7.20−7.17 (m, 2H), 7.01−6.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 157.3, 154.3, 151.5, 145.6, 134.0, 127.8, 127.5, 123.6, 122.6, 116.4, 114.8, 55.6; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2$ ($M + H^+$) 253.0971, found 253.0964

2-Quinazolin-4-ylmalonic Acid Dimethyl Ester (111). A stirred suspension of NaO*t*Bu (97 mg, 0.54 mmol) in dioxane (5 mL) was treated with dimethyl malonate (120 μL, 0.52 mmol) at 0 °C under a nitrogen atmosphere; stirring was continued for 15 min. 4-(1,2,3-Triazolo[4,5-*b*]pyridin-3-yloxy)quinazoline **8** (73 mg, 0.27 mmol) was added to the mixture. Stirring was continued at room temperature for 2 h. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 × 15 mL); the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by chromatography on silica (elution with 3:1 EtOAc/hexanes), giving the desired product **113** as a tautomeric mixture (70 mg, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.37 (s, 0.39H), 9.31 (s, 0.54H), 8.11−8.09 (m, 0.59H), 7.95−7.93 (m, 1.56H), 7.68−7.65 (m, 1.79H), 7.40−7.35 (m, 0.41H), 3.87−3.81 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 162.0, 154.4, 150.5, 148.7, 146.2, 141.8, 134.1, 133.6, 129.5, 128.5, 127.0, 125.1, 123.7, 123.6, 119.0, 57.7, 53.3, 52.7, 51.9; HRMS (ESI) calcd for $C_{13}H_{13}N_2O_4$ ($M + H^+$) 261.0870, found 261.0869.

2-Quinazolin-4-ylmalonic Acid Diethyl Ester (112).[40] Prepared according to the synthesis of **111**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.37 (s, 0.32H), 9.31 (s, 0.58H), 8.10 (d, J = 8.4 Hz, 0.72H), 7.97−7.90 (m, 1.60H), 7.71−7.63 (m, 0.66H), 7.37−7.34 (m, 0.33H), 5.51 (s, 0.63H), 4.33−4.27 (m, 4H), 1.34−1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 162.7, 157.7, 150.8, 148.4, 146.5, 142.3, 134.3, 133.8, 129.8, 128.7, 128.7, 127.3, 126.2, 124.2, 124.1, 119.5, 62.8, 62.0, 61.1, 58.5; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_4$ ($M + H^+$) 289.1183, found 289.1184.

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Supporting Information Available: Experimental procedures and characterization for those compounds not described above, and images of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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