



Concise access to N9-mono-, N2-mono- and N2,N9-di-substituted guanines via efficient Mitsunobu reactions

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ABSTRACT

Guanine poses several problems to the synthetic chemist owing to its polyfunctional nature and poor solubility. Over the past few decades, synthetic guanines have found applications as anti-cancer and anti-viral agents. Coupled with the ever-growing interest in designer PNAs and G-quartets, simple and efficient synthetic routes to novel guanines would be of significant benefit. We herein report that, upon simple protection and/or activation step(s), the guanine precursor 2-amino-6-chloropurine is rendered an excellent substrate for Mitsunobu chemistry, furnishing, after subsequent hydrolytic dechlorination and appropriate deprotection step(s), the desired N9-mono-, N2-mono- or N2,N9-di-substituted guanines in excellent yields ($\geq 80\%$). Importantly, we demonstrate that N9-functionalization proceeds with very good N9/N7 regioselectivity and with complete inversion of stereochemistry.

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1. Introduction

Nucleotides are arguably the most fundamental biochemicals in living systems, playing several key roles in the cell. For example, in addition to serving as the structural units of DNA and RNA, they are also sources of chemical energy (as ATP and GTP), secondary messengers (cAMP and cGMP) and are incorporated into enzyme cofactors (e.g., coenzyme A). It is, therefore, little wonder that nucleosides and nucleotides have inspired the discovery of new drugs. In particular, modification of both the carbohydrate pentose portion and the nucleobase has led to the development of potent anti-cancer and anti-viral agents, such as the guanosine analogue acyclovir.¹ More recently, nucleobases have featured in Nielsen's peptide nucleic acids (PNAs),² which have attracted considerable attention owing to their potential for diagnostic as well as pharmaceutical applications, especially in anti-gene and anti-sense therapies.³ Indeed, we are currently developing novel PNAs that incorporate synthetic nucleobases as a new class of inhibitor of the oncogenic transcription factor protein Stat3.⁴

To aid in the further investigation and development of such nucleobase-containing drugs, synthetic protocols that allow for the facile and efficient derivatization of nucleobases would be of significant benefit. Of the main nucleobases, guanine, in particular,

poses several problems to the synthetic chemist, due to its notorious insolubility in organic solvents, along with its polyfunctional nature (imidazole, amide and guanidine sub-structures). Guanine analogues have found applications as anti-cancer and anti-viral compounds for decades.^{1d-f} Currently, a very popular area of research is centred on the ability of guanine to form hydrogen-bonded cyclic tetramers known as G-quartets,⁵ which are demonstrating special significance in ageing,⁶ cancer⁷ and genetic diseases,⁸ and in the development of nanodevices.⁹ For all these reasons, we believe that a study on the synthesis of novel guanine derivatives would be welcomed. We herein report concise, facile and efficient syntheses of novel guanines functionalized at the N9 and/or N2 positions, starting from 2-amino-6-chloropurine, and employing Mitsunobu reactions as key steps.

2. Results and discussion

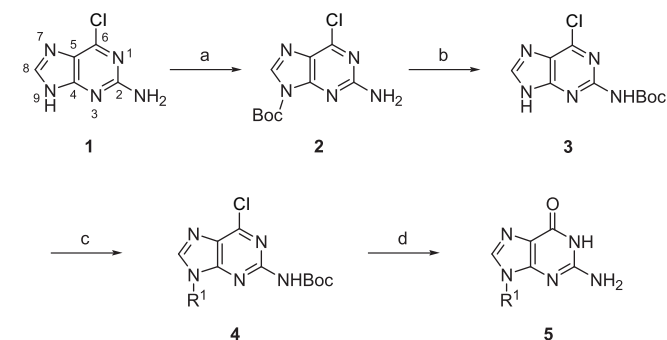
2.1. N9-Functionalization of guanine

The most popular approach towards N9-functionalization of purine bases is direct nucleophilic displacement of halides or activated alcohols, but considerable competition at the N9 and N7 sites is often reported.¹⁰ An alternative procedure takes advantage of the Mitsunobu reaction,¹¹ in which an alcohol is activated and then coupled to the purine nucleus *in situ*.¹² The Mitsunobu reaction has become a very popular chemical transformation, owing to its mildness, occurring under essentially neutral

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conditions, and its stereospecificity, proceeding with complete Walden inversion of stereochemistry.¹¹ To the best of our knowledge, there are no reports on the N9-functionalization of unprotected guanine with alcohols via the Mitsunobu reaction, likely owing to a combination of the limited solubility of the purine base as well as the potential for competing reactions at the N2, N7 and O6 positions. However, Lu et al. have recently described the N9-regioselective synthesis of guanine derivatives by reacting the O⁶-diphenylcarbamoyl, N²-acetyl protected analogue of guanine with a variety of alcohols under modified Mitsunobu conditions, followed by treatment with a 1:1 mixture of aqueous ammonia and methanol to remove the blocking groups.¹³ Whilst the authors report very good to excellent yields, two rounds of the Mitsunobu reaction are required in order to consume all of the starting purine, compounding the main drawback of Mitsunobu chemistry (poor atom economy). In addition, elevated temperatures are also necessary. We considered if a milder Mitsunobu approach to N9-functionalized guanines would be possible.

2-Amino-6-chloropurine (**1**) has become a popular guanine precursor since the chlorine atom can be effectively displaced with hydroxyl by nucleophilic aromatic substitution; one of the mildest of such approaches involves water as the nucleophile in an acid-catalyzed hydrolysis reaction.¹⁴ Although N9-functionalization of purine **1** has been achieved through Mitsunobu chemistry, its poor solubility in THF, the solvent of choice for such reactions, and the competing nucleophilicity of the exocyclic N2 amino group are likely primary reasons for the generally poor-to-moderate yields observed.¹⁵ In related work on the synthesis of 2,6,9-tri-substituted purines, we showed that the more soluble and N2-blocked purine **3**, prepared in two steps in near-quantitative yield from **1** (Scheme 1), is an excellent substrate for the Mitsunobu reaction, proceeding with very good N9-regioselectivity.¹⁶ Moreover, excellent chemoselectivity was also observed in the presence of the activated (acidic) but hindered NHBoc group. We demonstrated that hydrolytic dechlorination and Boc deprotection of subsequent purine **4a** (R¹=*n*-Bu) with a 3:1 mixture of TFA/H₂O for two days at room temperature furnished the corresponding guanine analogue **5a** (R¹=*n*-Bu) in quantitative yield. Alternatively, we herein report that the required hydrolytic dechlorination reaction of purines **4**, along with simultaneous Boc removal, can be accomplished conveniently and in near-quantitative yields by treatment with 80% formic acid¹⁷ at 75 °C for 2 h (Scheme 1).



Scheme 1. a) Boc₂O, cat. DMAP, DMSO, 0 °C → rt, 30 min, 99%; b) NaH, THF, rt, 2 h, 96%; c) (1) R¹OH, PPh₃, THF, rt, 2 min; (2) DIAD, rt, 15 min, 84–92%; d) 80% HCOOH, 75 °C, 2 h, 95–99%.

As illustrated in Table 1, purine **3** coupled in very good to excellent yields (the second step proceeded in yields of ≥95% in all cases) with a broad scope of alcohols, including benzylic, allylic, propargylic as well as primary and secondary aliphatic alcohols, under standard Mitsunobu conditions (triphenylphosphine (PPh₃)/diisopropylazodicarboxylate (DIAD) redox system). Elaborating on

our previous communication,¹⁶ we demonstrate here that this reaction is also compatible with the increasingly more hindered alcohols 2-indanol and (–)-menthol, and that no reaction occurs with *tert*-butanol, owing to steric hindrance at the tertiary carbon. The Mitsunobu reactions were especially mild and swift, proceeding to completion within 15 min at room temperature, and requiring only 1.1 equiv of reagents relative to the alcohol; these features suggest our protocol should also be compatible with related but more complex purine substrates. In fact, although yields are approximately the same, our reaction conditions are significantly milder and more cost effective than those reported by Lu et al.¹³—likely due in part to the enhanced solubility of our purine substrate—rendering our protocol particularly attractive. Moreover, due to the presence of the 6-chloro leaving group, our work is further appealing since it allows for the preparation of medicinally important 2,6,9-tri-substituted purines, as well as substituted guanines, from a common intermediate by nucleophilic aromatic substitution with either amines¹⁸ or water, respectively. Complete characterizations for purines **4** and guanines **5** are given in the Experimental section.

Table 1

R¹OH substrate scope for N9 Mitsunobu coupling with guanine precursor **3**^a

Entry	R ¹ OH	Regioselectivity N9/N7	Product	Yield ^b (%)
1		>7.3:1	5a	84
2		>9:1	5b	85
3		>5.3:1	5c	83
4		>6.1:1	5d	82
5		>5.7:1	5e	81
6		8.5:1	5f	82
7		>9:1	5g	86
8 ^c		>5.3:1	5h	81
9 ^c		>5.3:1	5i	80
10 ^c		>11.5:1	5j^d	88
11		—	5k	0

^a Reaction conditions: (1) To a solution of purine **3** (1 mmol) in anhydrous THF (7 mL) was added alcohol R¹OH (1.1 mmol) and PPh₃ (1.1 mmol). After 2 min, DIAD (1.1 mmol) was added dropwise at rt (over ~30 s to 1 min). The reaction was then stirred for 15 min at rt under a nitrogen atmosphere. (2) Purine **4** (0.5 mmol) was dissolved in 80% HCOOH (5 mL), and heated at 75 °C for 2 h.

^b Isolated overall yields.

^c Minor modifications to the experimental procedures were observed.

^d Structure confirmed by X-ray crystallography.

In order to confirm the N9-regioselectivity of the Mitsunobu reaction, the NMR spectral data of the N9 and N7 regioisomers of compound **4d** were compared. Since purification of the suspected N7 isomer of **4d** prepared by the Mitsunobu reaction was more complicated than for the N9 isomer, requiring pedantic flash chromatography conditions, the two regioisomers of **4d** were instead prepared by classical alkylation of purine **3** with benzyl bromide. Subsequently, comparison of the ^1H and ^{13}C NMR data of the readily separable N9 and N7 isomers of **4d** as described in the literature suggested that the less polar (TLC, silica gel) of the two products was the N9 regioisomer. This was further supported by excellent agreement of the NMR data of the Boc-protected regioisomers of **4d** with literature values.¹⁹ Furthermore, HMBC NMR experiments of N7-**4d** and N9-**4d** showed a long-range ^1H – ^{13}C coupling between H-8 and C-5 ($J_3=11.7$ Hz) for the less polar (TLC, silica gel) of the two isomers with a much weaker coupling between H-8 and C-4 ($J_3<4$ Hz), suggesting the N=CH double bond to be between N7 and C8, and this product to be the N9 isomer. Conversely, the more polar product exhibited couplings between H-8/C-5 and between H-8/C-4 of $J_3<4$ Hz and 13.3 Hz, respectively, indicating the double bond to be between N9 and C8, and the more polar product to be the N7 isomer. These relative polarities have been observed by others.²⁰ With all this data in hand, we thus deduced that the Mitsunobu reaction conducted on purine **3** with benzyl alcohol led to the N9 regioisomer of **4d** as the major product, and with a far superior N9/N7 regioselectivity than was observed with classical alkylation.²¹ Hence, the Mitsunobu reactions in Table 1 led to the N9 regioisomers of **4a–j**, as shown, in yields of 84–92%. Subsequently, hydrolytic dechlorination and Boc removal were accomplished almost quantitatively (95–99%) and in one pot by treatment with 80% formic acid for 2 h at 75 °C to afford the target, N9-functionalized guanine analogues **5a–j**. As a representative example, X-ray crystallography of compound **5j** confirmed the N9-regiochemical outcome of the Mitsunobu reaction (Fig. 1). Moreover, since a single diastereomer of compound **4j** was furnished, the X-ray crystal structure of **5j** (CCDC 771261) also confirmed that this reaction proceeded with complete inversion of the alcohol stereogenic centre of (–)-menthol. This finding is consistent with the $\text{S}_{\text{N}}2$ mechanism of the Mitsunobu reaction, suggesting our methodology is suitable for the stereospecific synthesis of non-sugar carbon guanosines.

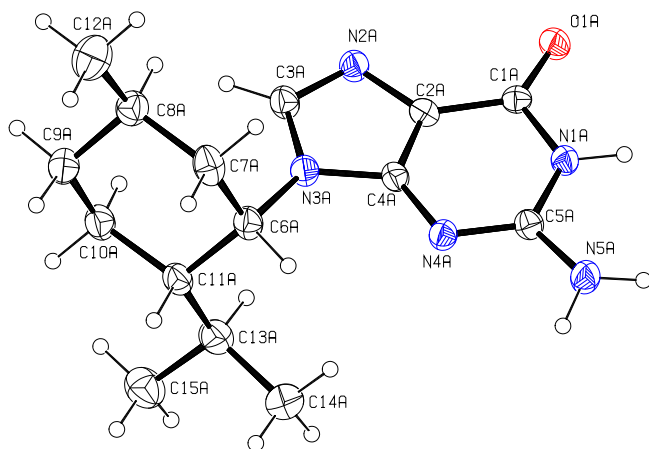


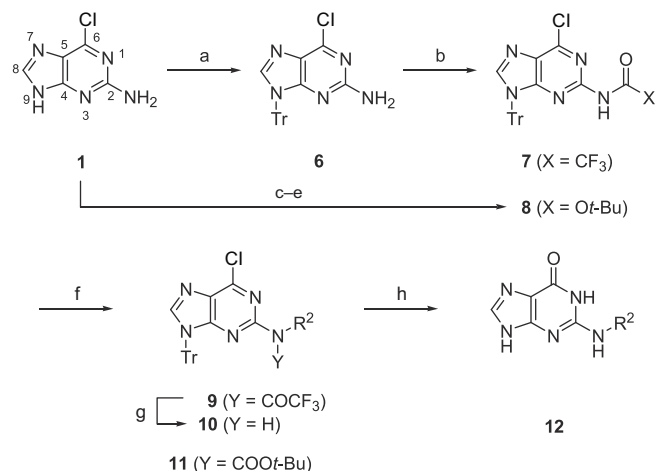
Figure 1. ORTEP drawing of the crystal structure of compound **5j**.

2.2. N2-Functionalization of guanine

N2-Functionalization of guanines is often accomplished by reacting a suitable 2-halopurine precursor with primary amines at elevated temperatures.²² Other approaches, employing suitable 2-aminopurine precursors, include reductive amination with an

aldehyde and *p*-thiocresol,²³ or classical N-alkylation of the corresponding amide followed by de-acylation.²⁴ Alternatively, we and others have shown that transformation of the exocyclic N2 amino group of guanine precursors, as well as the exocyclic N6 amino group of adenine, to an acetamide or a Boc carbamate renders the NH sufficiently acidic to participate in the Mitsunobu reaction.^{17,25–27} The resulting N2-functionalized purines may then undergo suitable synthetic transformations to reveal the target guanines. Due to the strongly electron-withdrawing nature of the trifluoroacetyl group, converting an amine to its trifluoroacetamide renders the resultant NH especially acidic. Indeed, Schultz et al. have reported using the trifluoroacetyl group to activate the N2 amino group of 2-amino-6-chloropurine derivatives, and demonstrated its reactivity in the Mitsunobu reaction.²⁸ Although the combined yield for the Mitsunobu reaction and the deprotection of the trifluoroacetyl group for their representative example was moderate, their work was not intended as an optimization study. To the best of our knowledge, there exists no comprehensive study on the Mitsunobu-mediated N2-substitution of such functionalized purines. We considered that, with suitable N9 protection, the trifluoroacetyl group would prove a convenient and efficient activating group to access N2-functionalized guanines via Mitsunobu chemistry.

To this end, 2-amino-6-chloropurine (**1**) was first trityl protected at the N9 position with TrCl to afford *N*⁹-trityl-2-amino-6-chloropurine **6**, analogous to the previously reported *N*⁹-trityl-persilylated guanine (Scheme 2).²⁹ Employing K_2CO_3 as the base in this reaction led to considerable *N*²-tritylation, but we found that this could be substantially reduced by forming the anion of **1** with NaH. Subsequently, the exocyclic N2 amino group was acylated with trifluoroacetic anhydride (TFAA) using an excess of pyridine as the base to ensure no inadvertent Tr cleavage occurred. As anticipated, the resulting amide of purine **7** was sufficiently acidic to undergo the Mitsunobu reaction with a wide range of alcohols (Table 2). After optimization, it was determined that this reaction required only a slight excess of reagents and proceeded to completion within 15 min at room temperature to furnish the series of N2-substituted trifluoroacetamides **9**. With only three exceptions, yields were very good to excellent (deprotection steps (1)(ii) and (2) in Table 2 were near-quantitative). However, compounds **9** slowly decomposed on the bench after purification by silica gel flash chromatography, likely initiated by attack of the N7 lone pair of electrons on the particularly electrophilic trifluoroacetyl carbonyl carbon. Thus, the

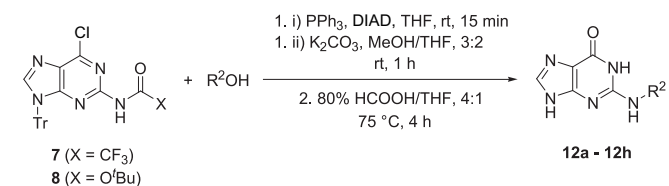


Scheme 2. a) (1) NaH, DMF, rt, 15 min; (2) TrCl, rt, 16 h, 85%; b) $(\text{CF}_3\text{CO})_2\text{O}$, pyridine, CHCl_3 , 0 °C, 30 min, 90%; c) Boc_2O , cat. DMAP, DMSO, 0 °C → rt, 30 min, 99%; d) NaH, THF, rt, 2 h, 96%; e) TrCl, DIPEA, DMF, rt, 4 h, 90%; f) (1) R^2OH , PPh_3 , THF, rt, 2 min; (2) DIAD, rt, 15 min; g) K_2CO_3 , MeOH/THF, 3:2, rt, 1 h, 35–90% (combined yields for steps (f) and (e) (g)); h) 80% HCOOH /THF, 4:1, 75 °C, 4 h, 95–99%.

trifluoroacetyl group was removed in situ with K_2CO_3 in MeOH/THF at room temperature to deliver the N2-functionalized guanine precursors **10**. Primary alcohols typically gave excellent yields for these two steps ($\geq 85\%$), and subsequent one pot hydrolytic dechlorination and de-tritylation with a 4:1 mixture of 80% HCOOH/THF proceeded almost quantitatively ($\geq 95\%$) to furnish the desired N2-functionalized guanines **12a–f** in excellent overall yields. 1H NMR in DMSO- d_6 at 293 K indicated that compounds **12a–f** were present as an approximate 4:1 mixture of the N9H/N7H tautomers. Both N9H and N7H tautomers of N2-acetylated guanines have also been observed on the NMR time-scale.³⁰ X-ray crystallography confirmed the structure of the major N9H tautomer of **12f** (Fig. 2; (CCDC 771260)).

Table 2

R²OH substrate scope for N2 Mitsunobu coupling with guanine precursors **7** (X=CF₃) or **8** (X=O^tBu)^a



Entry	X	R ² OH	Product	Yield ^b (%)
1	CF ₃		12a	88
2	CF ₃		12b	87
3	CF ₃		12c	80
4	CF ₃		12d	83
5	CF ₃		12e	83
6	CF ₃		12f^c	81
7 ^c	CF ₃		12g	64
8 ^{d,e}	O ^t -Bu		12g	82
9 ^c	CF ₃		12h	33
10 ^{d,e}	O ^t -Bu		12h	80
11	CF ₃		9i	0

^a Reaction conditions: (1) (i) To a solution of purine **7** (1 mmol) in anhydrous THF (14 mL) were added alcohol R²OH (1.2 mmol) and PPh₃ (1.3 mmol). After 2 min, DIAD (1.3 mmol) was added dropwise at rt (over ~30 s to 1 min). The reaction was then stirred for 15 min at rt under a nitrogen atmosphere. (1) (ii) Crude **9** (1 mmol) was dissolved in a 3:2 mixture of MeOH/THF (5 mL). K₂CO₃ (1.2 mmol) was added, and the reaction mixture was stirred for 1 h at rt. (2) Purine **10** (0.5 mmol) was dissolved in THF (1 mL). HCOOH (80%, 4 mL) was added, and the reaction was stirred under reflux at 75 °C for 4 h.

^b Isolated overall yields.

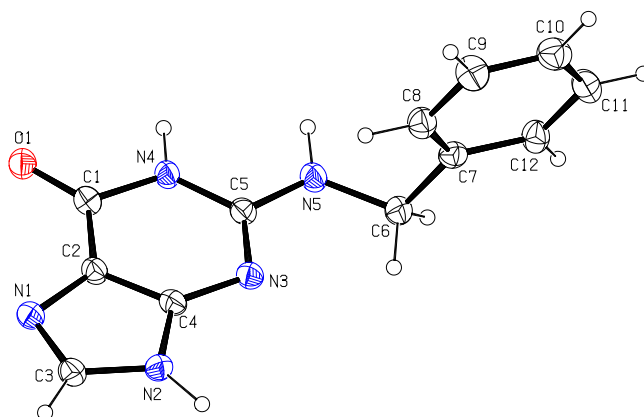
^c Trifluoroacetyl deprotection conditions: 1.2 equiv K₂CO₃, rt, 36 h.

^d Mitsunobu conditions as per method A, Table 3.

^e Step (e) was omitted and removal of the Boc group was accomplished in the formic acid hydrolytic dechlorination step.

^f Structure confirmed by X-ray crystallography.

On the other hand, the secondary alcohols *iso*-propanol and cyclopentanol generated the respective products **10g** and **10h** in much poorer yields (67% and 35%, respectively (combined yields for

**Figure 2.** ORTEP drawing of the crystal structure of compound **12f**.

the Mitsunobu reaction and trifluoroacetyl removal)), whilst *tert*-butanol once more did not react in the Mitsunobu reaction due to steric hindrance. Where R² was a primary alkyl moiety, removal of the trifluoroacetyl group in purines **9a–f** was typically complete within 1 h to furnish the corresponding purines **10a–f** in excellent yields. In contrast, where R² was a secondary alkyl group, 36 h were apparently required for complete removal of the trifluoroacetyl groups to afford **10g** and **10h**. Upon isolation and purification of the N²-trifluoroacetylated intermediates **9g** and **9h**, we discovered that the Mitsunobu reaction had generated a mixture of two inseparable products, which 1H NMR suggested to be the isomeric *N*- and *O*-alkylated trifluoroacetamides; such an observation has been reported previously with a related N2-acetylated substrate.³¹ The modified trifluoroacetyl group can no longer be removed from the *O*-alkylated trifluoroacetamides **9g** and **9h** by basic methanolysis, so presumably the extended reaction time to consume all of the trifluoroacetamides was due to a slower decomposition reaction (possibly addition/elimination displacement of the secondary alcohol by methanol), rather than removal of the modified trifluoroacetyl group in **9g** and **9h**. The promotion of the undesired *O*-alkylated product is probably a consequence of both steric (the hindered secondary alcohol as well as the nearby bulky trityl group) and electronic (the amide resonance $n_N \rightarrow \pi^*_{C=O}$ transition) factors. Since the resonance energy of a carbamate is less than that of an amide owing to competition of the $n_N \rightarrow \pi^*_{C=O}$ transition with the $n_O \rightarrow \pi^*_{C=O}$ transition, we considered that an N2 carbamate may generate more of the desired *N*-alkylated product with the hindered secondary alcohols. Indeed, we have previously shown that activation of the N2 amino group of N⁹-butyl-2-amino-6-chloropurine as its Boc carbamate allows the Mitsunobu reaction with *iso*-propanol to proceed in excellent yield,¹⁶ wherein the steric bulk of the Boc group may also contribute to offset undesired *O*-alkylation further still.

Thus, activation of the N2 amino group in **7** was alternatively achieved with Boc rather than with trifluoroacetyl to give purine **8**, and pleasingly this allowed the couplings with *iso*-propanol and cyclopentanol to proceed under modified Mitsunobu conditions (2.5 equiv of ROH, PPh₃ and DIAD, 35 °C, 30 min to 2 h) in much improved yields (**11g**: 86%; **11h**: 84%). Finally, de-tritylation, hydrolytic dechlorination and Boc removal were all accomplished almost quantitatively and in one pot with 80% HCOOH at 75 °C for 4 h, delivering the N2-functionalized guanines **12g** and **12h** in far superior overall yields than via the trifluoroacetamide route (Table 2, entries 8 and 10, cf. entries 7 and 9). Whilst 1H NMR of **12h** in DMSO- d_6 at 293 K demonstrated the existence of both N9H and N7H tautomers in a ratio of 81:19, there was minimal resolution of **12g** into its corresponding N9H and N7H tautomers on the NMR time-scale.

2.3. N2,N9-Di-functionalization of guanine

We have previously reported that purine **3** can undergo sequential Mitsunobu reactions, first at the endocyclic N9 position and then at the exocyclic N2 position.¹⁶ The second Mitsunobu reaction requires the use of either the DIAD/PPh₃ redox system with gentle heating or the 1,1'-(azodicarbonyl)dipiperidine (ADDP)/PBU₃ [CAUTION: PBU₃ is pyrophoric] redox system at room temperature, depending on the alcohol coupling partner (Table 3). Sterically hindered *tert*-butanol did not react under either set of conditions. As anticipated, subjecting the intermediate purines **13a–f** to formic acid at 75 °C effected both Boc deprotection and hydrolytic dechlorination. The targets **14a–f** were thus furnished in very good overall yields, illustrating that this facile approach to N2,N9-disubstituted guanines is also a very efficient approach.

Table 3

R²OH substrate scope for N2 Mitsunobu coupling with N9-butylylated guanine precursor **4a**^a

Entry	R ² OH	Method/Time	Product	Yield ^b (%)
1		A/30 min	14a	92
2		B/8 h	14b	83
3		B/8 h	14c	85
4		B/4 h	14d	83
5		A/30 min	14e	89
6		A/2 h	14f	85
7		A/16 h	14g	0

^a Reaction conditions: (1) Method (A) purine **4a** (0.5 mmol), R²OH (1.25 mmol) and PPh₃ (1.25 mmol) were dissolved in anhydrous THF (7 mL) at rt. After 2 min, DIAD (1.25 mmol) was added dropwise (over ~30 s), then reaction was heated at 35 °C under a nitrogen atmosphere for time indicated. Method (B) purine **4a** (1 equiv), R²OH (1.25 mmol) and PBU₃ (1.25 mmol) [CAUTION: PBU₃ is pyrophoric] were dissolved in anhydrous THF (7 mL). After 2 min, ADDP (1.25 mmol) was added in one portion. Reaction was stirred under a nitrogen atmosphere at rt for time indicated. (2) Resultant purine **13** (0.3 mmol) was dissolved in 80% HCOOH (3 mL), and heated at 75 °C for 2 h.

^b Isolated overall yields for two steps.

3. Conclusions

In conclusion, we have demonstrated that, after simple and high-yielding protection and/or activation steps, 2-amino-6-chloropurine is rendered a versatile reagent in the Mitsunobu reaction, allowing for the synthesis of novel guanines functionalized at the N9 endocyclic position and/or at the N2 exocyclic position. Reactions were mild and rapid, a large scope of alcohols was tolerated, and good to excellent yields were observed (>84%). Subsequent hydrolytic dechlorination and deprotection step(s) were accomplished near-quantitatively and in one pot, delivering the target guanines in overall yields of >80% (from the appropriate Mitsunobu substrate). Significantly, X-ray

crystallography confirmed that the Mitsunobu-mediated N9-functionalization of N²-Boc-2-amino-6-chloropurine proceeded with very good N9/N7 regiochemical control and excellent stereochemical control (complete inversion). We believe that all these factors render our two- and three-step protocols especially attractive routes to synthetic guanines. Indeed, we are currently investigating some novel guanine analogues as potential anti-cancer compounds (Stat3 inhibitors) and as guanine alternatives in PNA oligomers. Finally, it is noteworthy that our methodology may also be applied to the synthesis of 6,9-di- and 2,6,9-tri-substituted purines, such as the potent and selective cyclin-dependent kinase (CDK) inhibitor bohemine, through displacement of the 6-chloro group with amines.^{16,18}

4. Experimental section

4.1. General

Anhydrous solvents THF, MeOH, DMSO, CH₂Cl₂ and DMF were purchased from Sigma–Aldrich and used directly from their Sure-Seal bottles. Chemicals were purchased from Sigma–Aldrich of Alfa–Aesar. All reactions were performed under an atmosphere of dry nitrogen in oven-dried glassware and were monitored for completeness by thin-layer chromatography (TLC) using silica gel (visualized by UV light, or developed by treatment with KMnO₄ stain or Hanessian's stain). ¹H and ¹³C NMR spectra were recorded on a Bruker 400 MHz spectrometer in either CDCl₃ or DMSO-*d*₆. Chemical shifts (δ) are reported in parts per million after calibration to residual isotopic solvent (CHCl₃: δ_H=7.26 ppm, δ_C=77.00 ppm; DMSO: δ_H=2.50 ppm, δ_C=39.43 ppm). Coupling constants (*J*) are reported in hertz.

4.2. Typical procedure for Mitsunobu coupling of purine 3

To a stirred solution of purine **3** (270 mg, 1 mmol, 1 equiv) in anhydrous THF (14 mL) under a nitrogen atmosphere at room temperature were added the alcohol R¹OH (1.1 mmol, 1.1 equiv) and PPh₃ (289 mg, 1.1 mmol, 1.1 equiv). After ~2 min, DIAD (217 μL, 1.1 mmol, 1.1 equiv) was added dropwise (over ~30 s to 1 min). The reaction mixture was stirred at room temperature for 15 min, after which time TLC analysis indicated the reaction was complete. The reaction mixture was concentrated in vacuo, then adsorbed onto silica gel from CH₂Cl₂, and purified by silica gel flash column chromatography to afford purine **4**.

4.2.1. N²-Boc-9-butyl-6-chloro-9H-purin-2-ylamine (4a). R¹OH was 1-butanol. Flash column chromatography (eluent: hex/EtOAc, 2:3) afforded the title compound **4a** as a white foam (287 mg, 88%); R_f 0.36 (hex/EtOAc, 1:2); mp 102–105 °C; IR (KBr, cm⁻¹) 3425, 3257, 3186, 3105, 3011, 2963, 2932, 2875, 1749, 1720, 1608, 1578, 1518, 1473, 1442, 1403; δ_H (400 MHz, DMSO-*d*₆) 0.90 (t, *J*=7.3 Hz, 3H, CH₂CH₃), 1.17–1.31 (m, 2H, CH₂CH₃), 1.47 (s, 9H, C(CH₃)₃), 1.83 (app quintet, *J*=7.3 Hz, 2H, CH₂CH₂CH₃), 4.17 (t, *J*=7.3 Hz, 2H, CH₂CH₂CH₂CH₃), 8.51 (s, 1H, H-8), 10.33 (s, 1H, NHBoc); δ_C (100 MHz, CDCl₃) 13.4, 19.8, 28.2, 31.6, 43.9, 81.6, 127.6, 144.0, 150.2, 151.1, 152.3, 152.9; HRMS (ESI⁺) *m/z* calcd for C₁₄H₂₀ClN₅O₂Na [M+Na⁺] 348.1197, obsd 348.1196.

4.2.2. N²-Boc-9-(2-benzyloxyethyl)-6-chloro-9H-purin-2-ylamine (4b). R¹OH was 2-benzyloxyethanol. Flash column chromatography (eluent: hex/EtOAc, 2:3) to afford **4b** as a white foam (363 mg, 90%); R_f 0.37 (hex/EtOAc, 1:2); mp 86–91 °C; IR (KBr, cm⁻¹) 3451, 3225, 3089, 2978, 2923, 2853, 2359, 1744, 1607, 1576, 1520, 1445, 1407; δ_H (400 MHz, DMSO-*d*₆) 1.46 (s, 9H, C(CH₃)₃), 3.85 (t, *J*=5.0 Hz, 2H, CH₂CH₂OBn), 4.39 (t, *J*=5.0 Hz, 2H, CH₂CH₂OBn), 4.47 (s, 2H, CH₂Ph), 7.14–7.28 (m, 5H, Ph), 8.45 (s, 1H, H-8), 10.3 (s,

1H, *NHBoc*); δ_C (100 MHz, DMSO- d_6) 27.9, 43.3, 66.8, 71.5, 79.5, 126.7, 127.27, 127.32, 128.0, 137.8, 146.4, 148.7, 150.8, 152.2, 152.9; HRMS (ESI⁺) m/z calcd for C₁₉H₂₃ClN₅O₃ [M+H] 404.1483, obsd 404.1483.

4.2.3. *N*²-*Boc*-2-amino-6-chloro-purin-9-yl)-acetic acid ethyl ester (**4c**). R¹OH was ethyl glycolate. Flash column chromatography (eluent: hex/EtOAc, 1:2) to afforded **4c** as a white foam (299 mg, 84%); R_f 0.28 (hex/EtOAc, 1:2); mp 129–136 °C; IR (KBr, cm⁻¹) 3462, 3249, 3166, 3106, 2988, 2948, 2362, 1751, 1693, 1612, 1572, 1523, 1499, 1447, 1421; δ_H (400 MHz, DMSO- d_6) 1.22 (t, J =7.1 Hz, 3H, CH₃), 1.46 (s, 9H, C(CH₃)₃), 4.18 (q, J =7.1 Hz, 2H, CH₂CH₃), 5.11 (s, 2H, CH₂CO₂Et), 8.46 (s, 1H, H-8), 10.33 (s, 1H, *NHBoc*); δ_C (100 MHz, DMSO- d_6) 13.9, 27.8, 44.2, 61.6, 79.7, 126.3, 146.4, 149.0, 150.8, 152.6, 152.9, 167.3; HRMS (ESI⁺) m/z calcd for C₁₄H₁₈ClN₅O₄Na [M+Na⁺] 378.0939, obsd 378.0945.

4.2.4. *N*²-*Boc*-9-allyl-6-chloro-9H-purin-2-ylamine (**4d**). R¹OH was allyl alcohol. Flash column chromatography (eluent: hex/EtOAc, 2:3) afforded **4d** as a white foam (267 mg, 86%); R_f 0.34 (hex/EtOAc, 1:2); mp 106–112 °C; IR (KBr, cm⁻¹) 3428, 3258, 3189, 3091, 3010, 2982, 2933, 2359, 1753, 1721, 1645, 1607, 1578, 1511, 1444, 1400; δ_H (400 MHz, DMSO- d_6) 1.46 (s, 9H, C(CH₃)₃), 4.80–4.83 (m, 2H, CH₂CH=CH₂), 5.04–5.10 (m, 1H, CH=CH₂), 5.21–5.25 (m, 1H, CH=CH₂), 6.05–6.15 (m, 1H, CH=CH₂), 8.46 (s, 1H, H-8), 10.29 (s, 1H, *NHBoc*); δ_C (100 MHz, DMSO- d_6) 27.9, 45.3, 79.5, 117.9, 126.7, 132.5, 145.9, 148.8, 150.8, 152.4, 152.7; HRMS (ESI⁺) m/z calcd for C₁₃H₁₆ClN₅O₂Na [M+Na⁺] 332.0884, obsd 332.0886.

4.2.5. *N*²-*Boc*-9-(prop-2-ynyl)-6-chloro-9H-purin-2-ylamine (**4e**). R¹OH was propargyl alcohol. Flash column chromatography (eluent: hex/EtOAc, 2:3) afforded **4e** as a white foam (249 mg, 85%); R_f 0.32 (hex/EtOAc, 1:2); mp 129–136 °C; IR (KBr, cm⁻¹) 3425, 3231, 3154, 3112, 2977, 2358, 2128, 1722, 1591, 1533, 1497, 1450, 1426; δ_H (400 MHz, DMSO- d_6) 1.47 (s, 9H, C(CH₃)₃), 3.57 (t, J =2.4 Hz, 1H, C≡CH), 5.05 (d, J =2.4 Hz, 2H, CH₂C≡CH), 8.55 (s, 1H, H-8), 10.38 (s, 1H, H-1); δ_C (100 MHz, CDCl₃) 28.1, 33.5, 75.1, 75.8, 81.8, 127.4, 143.2, 150.2, 151.3, 152.2, 152.6; HRMS (ESI⁺) m/z calcd for C₁₃H₁₄ClN₅O₂Na [M+Na⁺] 330.0728, obsd 330.0731.

4.2.6. *N*²-*Boc*-9-benzyl-6-chloro-9H-purin-2-ylamine (**4f**). R¹OH was benzyl alcohol. Flash column chromatography (eluent: hex/EtOAc, 2:3) afforded **4f** as a white foam (305 mg, 85%); R_f 0.34 (hex/EtOAc, 1:2); mp 129–135 °C; IR (KBr, cm⁻¹) 3417, 2979, 2359, 1745, 1610, 1573, 1520, 1444, 1403; δ_H (400 MHz, DMSO- d_6) 1.46 (s, 9H, C(CH₃)₃), 5.40 (s, 2H, CH₂Ph), 7.28–7.41 (m, 5H, Ph), 8.58 (s, 1H, H-8), 10.32 (s, 1, *NHBoc*); δ_C (100 MHz, DMSO- d_6) 27.8, 46.6, 79.5, 126.7, 127.7, 127.8, 128.6, 136.1, 145.8, 149.0, 150.8, 152.5, 152.7; HRMS (ESI⁺) m/z calcd for C₁₇H₁₈ClN₅O₂Na [M+Na⁺] 382.1041, obsd 382.1044.

4.2.7. *N*²-*Boc*-9-benzyl-6-chloro-9H-purin-2-ylamine (**N9-4f**) and *N*²-*Boc*-7-benzyl-6-chloro-9H-purin-2-ylamine (**N7-4f**). Purine **3** (100 mg, 0.307 mmol, 1 equiv) was dissolved in anhydrous DMF (3 mL). K₂CO₃ (85 mg, 0.614 mmol, 2 equiv) was added and the reaction mixture was stirred for 1 h at room temperature, after which time benzyl bromide (40 μ L, 0.337 mmol, 1.1 equiv) was added dropwise. The reaction was allowed to stir overnight at room temperature. TLC indicated no starting material remaining and two clearly distinguishable products. Water (40 mL) was added to the reaction mixture, and the crude organics were extracted into EtOAc (3 \times 10 mL). The combined EtOAc extractions were washed with 5% NaHCO₃ (5 \times 10 mL), water (10 mL), brine (10 mL), dried (Na₂SO₄), filtered and concentrated. The two isomers were separated by silica gel flash column chromatography (EtOAc/MeOH, 98:2, then EtOAc/MeOH, 95:5), with the N9 isomer eluting first. **N9-4f**: 62% yield; R_f

0.48 (EtOAc/MeOH, 98:2); δ_H (400 MHz, DMSO- d_6) 1.46 (s, 9H, C(CH₃)₃), 5.40 (s, 2H, CH₂Ph), 7.28–7.41 (m, 5H, Ph), 8.58 (s, 1H, H-8), 10.32 (s, 1, *NHBoc*); δ_C (100 MHz, DMSO- d_6) 27.8, 46.6, 79.5, 126.7, 127.7, 127.8, 128.6, 136.1, 145.8, 149.0, 150.8, 152.5, 152.7; HRMS (ESI⁺) m/z calcd for C₁₇H₁₈ClN₅O₂Na [M+Na⁺] 382.1041, obsd 382.1041; **N7-4f**: 35% yield; R_f 0.20 (EtOAc/MeOH, 98:2); δ_H (400 MHz, DMSO- d_6) 1.46 (s, 9H, C(CH₃)₃), 5.68 (s, 2H, CH₂Ph), 7.16–7.17 (m, 2H, Ph), 7.30–7.38 (m, 3H, Ph), 8.85 (s, 1H, H-8), 10.21 (s, 1H, *NHBoc*); δ_C (100 MHz, DMSO- d_6) 27.8, 49.3, 79.3, 118.2, 126.3, 127.7, 128.7, 136.7, 142.0, 151.0, 151.3, 152.5, 162.9; HRMS (ESI⁺) m/z calcd for C₁₇H₁₈ClN₅O₂Na [M+Na⁺] 382.1041, obsd 382.1025. ¹H and ¹³C NMR data of the Boc-protected compounds (TFA/CH₂Cl₂, 1:1, room temperature, 45 min; concentration in vacuo; purine·TFA salt neutralized and purine extracted into CH₂Cl₂ by partitioning against a saturated aqueous solution of NaHCO₃) were consistent with the corresponding compounds **8a** and **8b** in Ref. 19 Boc-protected **N9-4f** (= **8a** in Ref. 19): R_f 0.54 (CH₂Cl₂/MeOH, 9:1); δ_H (400 MHz, DMSO- d_6) 5.29 (s, 2H, CH₂Ph), 6.95 (br s, 2H, NH₂), 7.23–7.36 (m, 5H, Ph), 8.23 (s, 1H, H-8); δ_C (100 MHz, DMSO- d_6) 46.0, 123.2, 127.1, 127.7, 128.6, 136.6, 143.1, 149.4, 154.0, 159.8; LRMS (ESI⁺) m/z calcd for C₁₂H₁₁ClN₅ [M+H⁺] 260.07, obsd 260.21; Boc-protected **N7-4f** (= **8b** in Ref. 19): R_f 0.37 (CH₂Cl₂/MeOH, 9:1); δ_H (400 MHz, DMSO- d_6) 5.56 (s, 2H, CH₂Ph), 6.67 (br s, 2H, NH₂), 7.13–7.15 (m, 2H, Ph), 7.29–7.37 (m, 3H, Ph), 8.56 (s, 1H, H-8); δ_C (100 MHz, DMSO- d_6) 49.1, 114.7, 126.3, 127.6, 128.7, 137.1, 142.3, 149.9, 160.0, 164.3; LRMS (ESI⁺) m/z calcd for C₁₂H₁₁ClN₅ [M+H⁺] 260.07, obsd 260.21.

4.2.8. *N*²-*Boc*-9-(iso-propyl)-6-chloro-9H-purin-2-ylamine (**4g**). R¹OH was iso-propanol. Flash column chromatography (eluent: hex/EtOAc, 2:3) afforded **4g** as a white solid (280 mg, 90%); R_f 0.33 (hex/EtOAc, 1:2); mp 164–165 °C; IR (KBr, cm⁻¹) 3417, 3252, 3021, 2975, 2934, 2360, 1712, 1603, 1570, 1523, 1503, 1482, 1462, 1439; δ_H (400 MHz, DMSO- d_6) 1.47 (s, 9H, C(CH₃)₃), 1.55 (d, J =6.8 Hz, 6H, CH(CH₃)₂), 4.75 (septet, J =6.8 Hz, 1H, CH(CH₃)₂), 8.59 (s, 1H, H-8), 10.27 (s, 1H, *NHBoc*); δ_C (100 MHz, DMSO- d_6) 21.7, 27.9, 47.3, 79.5, 127.1, 144.3, 148.7, 150.8, 151.9, 152.3; HRMS (ESI⁺) m/z calcd for C₁₃H₁₈ClN₅O₂Na [M+Na⁺] 334.1041, obsd 334.1047.

4.2.9. *N*²-*Boc*-9-cyclopentyl-6-chloro-9H-purin-2-ylamine (**4h**). To a stirred solution of purine **3** (269 mg, 1 mmol, 1 equiv) in anhydrous THF (14 mL) under an N₂ atmosphere at room temperature was added cyclopentanol (118 μ L, 1.3 mmol, 1.3 equiv) and PPh₃ (340 mg, 1.3 mmol, 1.3 equiv). After ~2 min (when all reagents had dissolved), DIAD (256 μ L, 1.3 mmol, 1.3 equiv) was added dropwise (over ~30 s to 1 min). The reaction mixture was stirred at room temperature for 15 min, after which time TLC analysis indicated the reaction was complete. The reaction mixture was concentrated in vacuo, then dry-loaded onto silica gel from CH₂Cl₂, and purified by flash column chromatography (eluent: hex/EtOAc, 2:3) to afford the title compound as a white foam (284 mg, 84%); R_f 0.36 (hex/EtOAc, 1:2); mp >198 °C (dec); IR (KBr, cm⁻¹) 3452, 3192, 3111, 2979, 2874, 2360, 1736, 1592, 1536, 1490, 1449; δ_H (400 MHz, DMSO- d_6) 1.47 (s, 9H, C(CH₃)₃), 1.60–1.71 (m, 2H, 2 \times CH), 1.85–1.94 (m, 2H, 2 \times CH), 1.95–2.06 (m, 2H, 2 \times CH), 2.12–2.22 (m, 2H, 2 \times CH), 4.84 (quintet, J =7.5 Hz, 1H, CH(CH₂)₂), 8.55 (s, 1H, H-8), 10.3 (s, 1H, *NHBoc*); δ_C (100 MHz, DMSO- d_6) 23.5, 27.9, 31.7, 55.9, 79.5, 127.2, 144.7, 148.7, 150.8, 151.9, 152.6; HRMS (ESI⁺) m/z calcd for C₁₅H₂₀ClN₅O₂Na [M+Na⁺] 360.1197, obsd 360.1208.

4.2.10. *N*²-*Boc*-9-(indan-2-yl)-6-chloro-9H-purin-2-ylamine (**4i**). To a stirred solution of purine **3** (269 mg, 1 mmol, 1 equiv) in anhydrous THF (14 mL) under an N₂ atmosphere at room temperature was added 2-indanol (201 mg, 1.5 mmol, 1.5 equiv) and PPh₃ (394 mg, 1.5 mmol, 1.5 equiv). After ~2 min (when all reagents had dissolved), DIAD (295 μ L, 1.5 mmol, 1.5 equiv) was added dropwise

(over ~30 s to 1 min). The reaction mixture was stirred at room temperature for 15 min, after which time TLC analysis indicated the reaction was complete. The reaction mixture was concentrated in vacuo, then dry-loaded onto silica gel from CH₂Cl₂, and purified by flash column chromatography (eluent: hex/EtOAc, 2:3) to afford the title compound as a white foam (324 mg, 84%); *R*_f 0.34 (hex/EtOAc, 1:2); mp 161–167 °C; IR (KBr, cm⁻¹) 3458, 3282, 3010, 2981, 2926, 1752, 1614, 1584, 1522, 1481, 1460, 1428; δ_{H} 1.44 (s, 9H, C(CH₃)₃), 3.43–3.54 (m, 4H, CH₂CHCH₂), 5.33 (quintet, *J*=7.5 Hz, 1H, CH(CH₂)₂), 7.20–7.25 (m, 2H, Ph), 7.28–7.33 (m, 2H, Ph), 8.43 (s, 1H, H-8), 10.30 (s, 1H, NHBoc); δ_{C} 27.8, 38.0, 55.4, 79.5, 124.4, 126.9, 127.1, 139.9, 144.4, 148.9, 150.8, 152.0, 152.7; HRMS (ESI⁺) *m/z* calcd for C₁₉H₂₀ClN₅O₂Na [M+Na⁺] 408.1197, obsd 408.1179.

4.2.11. N²-Boc-9-([1'S,2'S,5'R]-2'-isopropyl-5'-methylcyclohexyl)-6-chloro-9H-purin-2-ylamine (4j). To a stirred solution of purine **3** (269 mg, 1 mmol, 1 equiv) in anhydrous THF (14 mL) under an N₂ atmosphere at room temperature was added (–)-menthol (390 mg, 2.5 mmol, 2.5 equiv) and PPh₃ (658 mg, 2.5 mmol, 2.5 equiv). After ~2 min (when all reagents had dissolved), DIAD (492 μ L, 2.5 mmol, 2.5 equiv) was added dropwise (over ~30 s to 1 min). The reaction mixture was stirred for 1 h at 35 °C, after which time TLC analysis indicated the reaction was completed. The reaction mixture was concentrated in vacuo, then dry-loaded onto silica gel from CH₂Cl₂, and purified by flash column chromatography (eluent: hex/EtOAc, 2:3) to afford the title compound as a white foam (375 mg, 92%); *R*_f 0.65 (hex/EtOAc, 1:2); mp 170–173 °C; IR (KBr, cm⁻¹) 3414, 3252, 3191, 3145, 2964, 2917, 2883, 2841, 1728, 1609, 1573, 1511, 1479, 1463, 1444, 1416; δ_{H} (400 MHz, DMSO-*d*₆) 0.69 (d, *J*=6.4 Hz, 3H, CH₃), 0.74 (d, *J*=6.8 Hz, 3H, CH₃), 0.81 (d, *J*=6.0 Hz, 3H, CH₃), 0.97–1.12 (m, 2H, 2 \times CH), 1.42–1.57 (m, 11H, 2 \times CH, C(CH₃)₃), 1.62–1.78 (m, 3H, 3 \times CH), 1.81–1.93 (m, 2H, 2 \times CH), 5.13–5.17 (m, 1H, N9-CH), 8.73 (s, 1H, H-8), 10.29 (s, 1H, NHBoc); δ_{C} (100 MHz, DMSO-*d*₆) 20.3, 20.7, 22.0, 24.9, 25.7, 27.9, 29.0, 33.8, 39.9, 44.6, 51.8, 79.5, 125.8, 145.6, 149.1, 150.8, 152.3, 153.2; HRMS (ESI⁺) *m/z* calcd for C₂₀H₃₁ClN₅O₂ [M+H⁺] 408.2160, obsd 408.2175.

4.3. Typical procedure for hydrolytic dechlorination and Boc deprotection of purines 4

A solution of purine **4** (0.5 mmol) in 80% HCOOH (5 mL; 4:1 mixture of HCOOH/H₂O) was stirred at 75 °C for 2 h, by which time TLC indicated all starting material and Boc-protected intermediate had been consumed. The reaction mixture was concentrated under reduced pressure to dryness, adsorbed onto silica gel from CH₂Cl₂/MeOH, and then purified by silica gel flash column chromatography.

4.3.1. 2-Amino-9-butyl-1,9-dihydro-purin-6-one (5a). The substrate purine was **4a**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 9:1 \rightarrow 5:1) furnished **5a**¹³ as a white solid (98 mg, 95%); *R*_f 0.42 (CH₂Cl₂/MeOH, 5:1); mp>260 °C (dec); IR (KBr, cm⁻¹) 3474, 3150, 2930, 2873, 2670, 1688, 1630, 1572, 1543, 1477; δ_{H} (400 MHz, DMSO-*d*₆) 0.87 (t, *J*=7.3 Hz, 3H, CH₃), 1.23 (app sextet, *J*=7.3 Hz, 2H, CH₂CH₃), 1.69 (app quintet, *J*=7.3 Hz, 2H, CH₂CH₂CH₃), 3.92 (t, *J*=7.3 Hz, 2H, CH₂CH₂CH₂CH₃), 6.49 (s, 2H, NH₂), 7.68 (s, 1H, H-8), 10.59 (s, 1H, H-1); δ_{C} (100 MHz, DMSO-*d*₆) 13.3, 19.1, 31.4, 42.3, 116.4, 137.3, 151.0, 153.4, 156.7; HRMS (ESI⁺) *m/z* calcd for C₉H₁₄N₅O [M+H⁺] 208.1198, obsd 208.1195.

4.3.2. 2-Amino-9-(2-benzyloxyethyl)-1,9-dihydro-purin-6-one (5b). The substrate purine was **4b**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 9:1 \rightarrow 5:1) furnished **5b** as a white solid (135 mg, 95%); *R*_f 0.44 (CH₂Cl₂/MeOH, 5:1); mp>260 °C (dec); IR (KBr, cm⁻¹) 3327, 3161, 3034, 2859, 2744, 1686, 1647, 1602, 1576, 1543, 1489, 1436, 1416; δ_{H} (400 MHz, DMSO-*d*₆) 3.72 (t, *J*=5.4 Hz,

2H, CH₂CH₂OBn), 4.14 (t, *J*=5.4 Hz, 2H, CH₂CH₂OBn), 4.47 (s, 2H, CH₂Ph), 6.48 (s, 2H, NH₂), 7.21–7.33 (m, 5H, Ph), 7.66 (s, 1H, H-8), 10.60 (s, 1H, H-1); δ_{C} (100 MHz, DMSO-*d*₆) 42.9, 67.9, 72.0, 116.7, 127.7, 127.8, 128.5, 138.1, 138.4, 151.5, 153.8, 157.1; HRMS (ESI⁺) *m/z* calcd for C₁₄H₁₆N₅O₂ [M+H⁺] 286.1298, obsd 286.1290.

4.3.3. (2-Amino-6-oxo-1,6-dihydro-purin-9-yl)-acetic acid ethyl ester (5c). The substrate purine was **4c**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 7:1 \rightarrow 4:1) furnished **5c** as a white solid (117 mg, 99%); *R*_f 0.33 (CH₂Cl₂/MeOH, 5:1); mp>260 °C (dec); IR (KBr, cm⁻¹) 3442, 3136, 2988, 2733, 1749, 1690, 1634, 1604, 1542, 1481, 1425; δ_{H} (400 MHz, DMSO-*d*₆) 1.20 (t, *J*=7.2 Hz, 3H, CH₂CH₃), 4.15 (q, *J*=7.2 Hz, 2H, CH₂CH₃), 4.85 (s, 2H, CH₂CO₂CH₂CH₃), 6.55 (s, 2H, NH₂), 7.66 (s, 1H, H-8), 10.65 (s, 1H, H-1); δ_{C} (100 MHz, DMSO-*d*₆) 13.9, 43.7, 61.2, 116.0, 137.7, 151.4, 153.7, 156.7, 167.9; HRMS (ESI⁺) *m/z* calcd for C₉H₁₂N₅O₃ [M+H⁺] 238.0934, obsd 238.0942.

4.3.4. 9-Allyl-2-amino-1,9-dihydro-purin-6-one (5d).¹³ The substrate purine was **4d**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 9:1 \rightarrow 5:1) furnished **5d** as a white solid (91 mg, 95%); *R*_f 0.43 (CH₂Cl₂/MeOH, 5:1); mp>260 °C (dec); IR (KBr, cm⁻¹) 3452, 3398, 3165, 2923, 2879, 2697, 1689, 1663, 1634, 1606, 1573, 1541, 1523, 1487, 1475; δ_{H} (400 MHz, DMSO-*d*₆) 4.56–4.59 (m, 2H, CH₂CH=CH₂), 4.92–4.98 (m, 1H, CH=CH₂), 5.14–5.18 (m, 1H, CH=CH₂), 5.95–6.04 (m, 1H, CH=CH₂), 6.51 (s, 2H, NH₂), 7.64 (s, 1H, H-8), 10.34 (v br, H-1); δ_{C} (100 MHz, DMSO-*d*₆) 44.5, 116.4, 116.8, 133.5, 137.2, 151.0, 153.6, 156.7; HRMS (ESI⁺) *m/z* calcd for C₈H₁₀N₅O [M+H⁺] 192.0879, obsd 192.0877.

4.3.5. 2-Amino-9-(prop-2-ynyl)-1,9-dihydro-purin-6-one (5e).¹³ The substrate purine was **4e**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 9:1 \rightarrow 5:1) furnished **5e** as a white solid (90 mg, 95%); *R*_f 0.41 (CH₂Cl₂/MeOH, 5:1); mp>260 °C (dec); IR (KBr, cm⁻¹) 3459, 3194, 3112, 2851, 2721, 2100, 1698, 1636, 1608, 1579, 1543, 1531, 1482, 1428; δ_{H} (400 MHz, DMSO-*d*₆) 3.44 (t, *J*=2.5 Hz, 1H, C \equiv CH), 4.80 (d, *J*=2.5 Hz, 2H, CH₂C \equiv CH), 6.77 (s, 2H, NH₂), 7.73 (s, 1H, H-8), 10.85 (s, 1H, H-1); δ_{C} (100 MHz, DMSO-*d*₆) 31.9, 75.6, 78.4, 116.3, 136.5, 150.7, 153.9, 156.6; HRMS (ESI⁺) *m/z* calcd for C₈H₈N₅O [M+H⁺] 190.0723, obsd 190.0730.

4.3.6. 2-Amino-9-benzyl-1,9-dihydro-purin-6-one (5f).¹³ The substrate purine was **4f**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 9:1 \rightarrow 5:1) furnished **5f** as a white solid (117 mg, 97%); *R*_f 0.42 (CH₂Cl₂/MeOH, 5:1); mp>260 °C (dec); IR (KBr, cm⁻¹) 3453, 3134, 2954, 1694, 1651, 1607, 1584, 1538, 1480, 1412; δ_{H} (400 MHz, DMSO-*d*₆) 5.18 (s, 2H, CH₂Ph), 6.51 (s, 2H, NH₂), 7.21–7.36 (m, 5H, Ph), 7.78 (s, 1H, H-8), 10.65 (s, 1H, H-1); δ_{C} (100 MHz, DMSO-*d*₆) 45.7, 116.4, 127.0, 127.5, 128.6, 137.2, 137.4, 151.2, 153.6, 156.7; HRMS (ESI⁺) *m/z* calcd for C₁₂H₁₂N₅O [M+H⁺] 242.1036, obsd 242.1039.

4.3.7. 2-Amino-9-(iso-propyl)-1,9-dihydro-purin-6-one (5g).¹³ The substrate purine was **4g**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 9:1 \rightarrow 5:1) furnished **5g** as a white solid (93 mg, 96%); *R*_f 0.41 (CH₂Cl₂/MeOH, 5:1); mp>260 °C (dec); IR (KBr, cm⁻¹) 3416, 3145, 2976, 2739, 1689, 1620, 1604, 1574, 1533, 1475, 1405; δ_{H} (400 MHz, DMSO-*d*₆) 1.42 (d, *J*=6.8 Hz, 6H, CH(CH₃)₂), 4.48 (septet, *J*=6.8 Hz, 1H, CH(CH₃)₂), 6.44 (s, 2H, NH₂), 7.79 (s, 1H, H-8), 10.57 (s, 1H, H-1); δ_{C} (100 MHz, DMSO-*d*₆) 22.1, 45.6, 116.7, 134.9, 150.5, 153.2, 156.8; HRMS (ESI⁺) *m/z* calcd for C₈H₁₂N₅O [M+H⁺] 194.1036, obsd 194.1028.

4.3.8. 2-Amino-9-cyclopentyl-1,9-dihydro-purin-6-one (5h). The substrate purine was **4h**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 9:1 \rightarrow 5:1) furnished **5h** as a white solid (105 mg, 96%); *R*_f 0.44 (CH₂Cl₂/MeOH, 5:1); mp>260 °C (dec); IR (KBr, cm⁻¹)

3475, 3406, 3175, 3099, 2954, 2920, 2873, 2717, 1685, 1626, 1601, 1568, 1538, 1479, 1413; δ_{H} (400 MHz, DMSO- d_6) 1.59–1.70 (m, 2H, 2 \times CH), 1.77–1.91 (m, 4H, 4 \times CH), 2.01–2.09 (m, 2H, 2 \times CH), 4.59 (quintet, $J=7.2$ Hz, 1H, CH(CH₂)₂), 6.45 (s, 2H, NH₂), 7.75 (s, 1H, H-8), 10.58 (s, 1H, H-1); δ_{C} (100 MHz, DMSO- d_6) 23.3, 31.9, 54.6, 116.7, 135.4, 150.9, 153.2, 156.7; HRMS (ESI⁺) m/z calcd for C₁₀H₁₄N₅O [M+H⁺] 220.1192, obsd 220.1190.

4.3.9. 2-Amino-9-(indan-2-yl)-1,9-dihydro-purin-6-one (5i).¹³ The substrate purine was **4i**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 9:1 \rightarrow 5:1) furnished **5i** as a white solid (127 mg, 95%); R_f 0.43 (CH₂Cl₂/MeOH, 5:1); mp >260 °C (dec); IR (KBr, cm⁻¹) 3485, 3147, 2637, 1703, 1633, 1604, 1537, 1480; δ_{H} (400 MHz, DMSO- d_6) 3.36 (d, $J=7.7$ Hz, 4H, 2 \times CH₂), 5.11 (quintet, $J=7.7$ Hz, 1H, CH(CH₂)₂), 6.52 (s, 2H, NH₂), 7.19–7.23 (m, 2H, Ar), 7.26–7.29 (m, 2H, Ar), 7.60 (s, 1H, H-8), 10.62 (s, 1H, H-1); δ_{C} (100 MHz, DMSO- d_6) 38.3, 54.5, 116.9, 124.4, 126.8, 135.5, 140.2, 151.0, 153.3, 156.7; HRMS (ESI⁺) m/z calcd for C₁₄H₁₄N₅O [M+H⁺] 268.1192, obsd 268.1189.

4.3.10. 2-Amino-9-([1'S,2'S,5'R]-2'-isopropyl-5'-methylcyclohexyl)-1,9-dihydro-purin-6-one (5j). The substrate purine was **4j**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 10:1 \rightarrow 7:1) furnished **5j** as a white solid (139 mg, 96%); R_f 0.51 (CH₂Cl₂/MeOH, 5:1); mp >260 °C (dec); IR (KBr, cm⁻¹) 3416, 3134, 2953, 2844, 2729, 1698, 1644, 1603, 1567, 1536, 1474; δ_{H} (400 MHz, DMSO- d_6) 0.70 (d, $J=6.8$ Hz, 3H, CH₃), 0.77 (d, $J=6.4$ Hz, 3H, CH₃), 0.81 (d, $J=6.0$ Hz, 3H, CH₃), 0.96–1.05 (m, 1H, CH), 1.11–1.16 (m, 1H, CH), 1.33–1.44 (m, 2H, 2 \times CH), 1.53–1.66 (m, 3H, 3 \times CH), 1.81–1.88 (m, 2H, 2 \times CH), 4.86 (m, 1H, N9-CH), 6.46 (s, 2H, NH₂), 7.91 (s, 1H, H-8), 10.57 (s, 1H, H-1); δ_{C} (100 MHz, DMSO- d_6) 20.4, 20.6, 22.0, 25.2, 25.6, 28.9, 33.9, 39.9, 44.8, 50.2, 115.5, 137.0, 151.3, 153.3, 156.8; HRMS (ESI⁺) m/z calcd for C₁₅H₂₄N₅O [M+H⁺] 290.1975, obsd 290.1972. Slow vapour diffusion of ethyl ether into a solution of **5j** in DMF gave a single crystal suitable for X-ray diffraction analysis.

4.4. Typical procedure for Mitsunobu coupling of purine 7 and trifluoroacetyl deprotection of subsequent purines

To a stirred solution of purine **7** (507 mg, 1 mmol, 1 equiv) in anhydrous THF (14 mL) under a nitrogen atmosphere at room temperature was added the alcohol R²OH (1.2 mmol, 1.2 equiv) and PPh₃ (341 mg, 1.3 mmol, 1.3 equiv). After ~2 min, DIAD (256 μ L, 1.3 mmol, 1.3 equiv) was added dropwise (over ~30 s to 1 min). The reaction mixture was stirred at room temperature for 15 min, after which time TLC analysis indicated the reaction was complete. The reaction mixture was concentrated in vacuo. The crude residue was taken up in a 3:2 mixture of MeOH/THF (10 mL). K₂CO₃ (1.2 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h, when TLC analysis suggested all intermediate trifluoroacetamide (e.g., **9a**; R_f 0.40 (hex/EtOAc, 2:1)) had been deprotected (e.g., **10a**; R_f 0.34 (hex/EtOAc, 2:1)). The reaction mixture was diluted with water (150 mL) along with a small amount of brine (10 mL), then extracted into EtOAc (3 \times 30 mL). The combined EtOAc extractions were washed with water (20 mL), brine (20 mL), dried (Na₂SO₄), filtered and concentrated. The crude residue was adsorbed onto silica gel from CH₂Cl₂ at room temperature (heating was avoided in order to prevent trityl cleavage), then purified by flash column chromatography.

4.4.1. 9-Butyl-(6-chloro-9-trityl-9H-purin-2-yl)-amine (10a). R²OH was 1-butanol. Flash column chromatography (eluent: hex/EtOAc, 3:1) yielded **10a** as an off-white solid (416 mg, 89%); R_f 0.39 (hex/EtOAc, 1:1); mp >230 °C (dec); IR (KBr, cm⁻¹) 3472, 3297, 3063,

3027, 2961, 2932, 2869, 1784, 1632, 1580, 1552, 1490, 1446; δ_{H} (400 MHz, DMSO- d_6) 0.69 (t, $J=6.8$ Hz, 3H, CH₃), 0.92–1.10 (m, 4H, CH₂CH₂CH₃), 2.55–2.64 (m, 2H, NHCH₂), 7.19–7.23 (m, 6H, Trt), 7.28–8.28 (m, 10H, Trt, NH), 7.81 (s, 1H, H-8); δ_{C} (100 MHz, DMSO- d_6) 13.6, 19.5, 30.3, 40.6, 75.0, 124.0, 127.5, 127.9, 129.3, 141.0, 141.8, 149.7, 154.6, 157.8; HRMS (ESI⁺) m/z calcd for C₂₈H₂₇ClN₅ [M+H⁺] 468.1949, obsd 468.1942.

4.4.2. (2-Benzyloxyethyl)-(6-chloro-9-trityl-9H-purin-2-yl)-amine (10b). R²OH was 2-benzyloxyethanol. Flash column chromatography (eluent: hex/EtOAc, 3:1) yielded **10b** as a white, sticky foam (490 mg, 90%); R_f 0.39 (hex/EtOAc, 1:1); δ_{H} (400 MHz, DMSO- d_6) 2.80–2.88 (m, 2H, NHCH₂), 3.01–3.08 (m, 2H, CH₂CH₂OBn), 4.24 (s, 2H, CH₂Ph), 7.17–7.21 (m, 6H, Trt), 7.22–7.35 (m, 14H, Trt, Ph), 7.43–7.50 (m, 1H, NH), 7.82 (s, 1H, H-8); δ_{C} (100 MHz, DMSO- d_6) 67.4, 67.7, 71.6, 74.9, 124.0, 127.2, 127.5, 127.9 (2), 128.0, 129.2, 138.4, 140.8, 141.9, 149.8, 154.3, 157.5; HRMS (ESI⁺) m/z calcd for C₃₃H₂₉ClN₅O [M+H⁺] 546.2055, obsd 546.2043. Product was contaminated with a small amount of reduced DIAD (DIAD-H₂); yield was determined by analysis of the ¹H NMR spectrum.

4.4.3. (6-Chloro-9-trityl-9H-purin-2-ylamino)-acetic acid ethyl ester (10c). R²OH was ethyl glycolate. Flash column chromatography (eluent: hex/EtOAc, 3:1) yielded **10c** as a white powder (413 mg, 83%); R_f 0.34 (hex/EtOAc, 1:1); mp 195–201 °C; IR (KBr, cm⁻¹) 3451, 3283, 2937, 2355, 1751, 1613, 1585, 1550, 1489, 1449; δ_{H} (400 MHz, DMSO- d_6) 1.05 (t, $J=6.7$ Hz, 3H, CH₂CH₃), 3.30–3.32 (m, 2H, NHCH₂), 3.77 (br q, $J=6.7$ Hz, 2H, CH₂CH₃), 7.15–7.19 (m, 6H, Trt), 7.28–7.37 (m, 9H, Trt), 7.64–7.70 (m, 1H, NH), 7.88 (s, 1H, H-8); δ_{C} (100 MHz, DMSO- d_6) 13.8, 42.2, 59.8, 75.0, 124.5, 127.4, 127.8, 129.2, 140.8, 142.3, 149.8, 154.0, 157.3, 169.6; HRMS (ESI⁺) m/z calcd for C₂₈H₂₅ClN₅O₂ [M+H⁺] 498.1691, obsd 498.1678.

4.4.4. Allyl-(6-chloro-9-trityl-9H-purin-2-yl)-amine (10d). R²OH was allyl alcohol. Flash column chromatography (eluent: hex/EtOAc, 3:1) yielded **10d** as a white solid (390 mg, 86%); R_f 0.37 (hex/EtOAc, 1:1); mp 145–151 °C; IR (KBr, cm⁻¹) 3449, 3288, 3136, 3058, 2923, 2361, 1611, 1578, 1547, 1492, 1448, 1414; δ_{H} (400 MHz, DMSO- d_6) 3.23–3.32 (m, 2H, NHCH₂), 4.77–4.85 (m, 2H, CH=CH₂), 5.36–5.50 (m, 1H, CH=CH₂), 7.20–7.25 (m, 6H, Trt), 7.26–7.36 (m, 9H, Trt), 7.46–7.56 (m, 1H, NH), 7.85 (s, 1H, H-8); δ_{C} (400 MHz, DMSO- d_6) 43.1, 74.9, 114.9, 124.1, 127.4, 127.8, 129.2, 135.0, 140.9, 142.0, 149.7, 154.4, 157.4; HRMS (ESI⁺) m/z calcd for C₂₇H₂₂ClN₅Na [M+Na⁺] 474.1455, obsd 474.1461.

4.4.5. (6-Chloro-9-trityl-9H-purin-2-yl)-(prop-2-ynyl)-amine (10e). R²OH was propargyl alcohol. Flash column chromatography (eluent: hex/EtOAc, 3:1) yielded **10e** as a white solid (386 mg, 86%); R_f 0.37 (hex/EtOAc, 1:1); δ_{H} (400 MHz, DMSO- d_6) 2.89 (br t, 1H, C \equiv CH), 3.37–3.52 (m, 2H, CH₂C \equiv CH), 7.26–7.37 (m, 15H, Trt), 7.58–7.72 (m, 1H, NH), 7.97 (s, 1H, H-8); δ_{C} (100 MHz, DMSO- d_6) 30.0, 71.9, 75.1, 81.3, 124.5, 127.3, 127.9, 129.1, 141.0, 142.7, 149.8, 154.2, 156.9; HRMS (ESI⁺) m/z calcd for C₂₇H₂₀ClN₅Na [M+Na⁺] 472.1299, obsd 472.1308. Product was contaminated with a small amount of reduced DIAD (DIAD-H₂); yield was determined by analysis of the ¹H NMR spectrum.

4.4.6. Benzyl-(6-chloro-9-trityl-9H-purin-2-yl)-amine (10f). R²OH was benzyl alcohol. Flash column chromatography (eluent: hex/EtOAc, 3:1) yielded **10f** as a white solid (420 mg, 84%); R_f 0.37 (hex/EtOAc, 1:1); δ_{H} (400 MHz, DMSO- d_6) 3.82–3.90 (m, 2H, CH₂Ph), 6.80–6.90 (m, 2H, Ph), 7.14–7.30 (m, 18H, Trt, Ph), 7.89 (s, 1H, H-8), 7.85–7.98 (m, 2H, H-8, NH); δ_{C} (100 MHz, DMSO- d_6) 44.0, 74.9, 124.2, 126.3, 127.1, 127.3, 127.8, 127.9, 129.1, 139.8, 141.0, 142.2, 149.8, 154.3, 157.6; HRMS (ESI⁺) m/z calcd for C₃₁H₂₅ClN₅ [M+H⁺] 502.1793, obsd 502.1779. Product was contaminated with a small

amount of reduced DIAD (DIAD-H₂); yield was determined by analysis of the ¹H NMR spectrum.

4.4.7. (6-Chloro-9-trityl-9H-purin-2-yl)-(iso-propyl)-amine (10g). R²OH was *iso*-propanol. Flash column chromatography (eluent: hex/EtOAc, 3:1) yielded **10g** as a white solid (304 mg, 67%); *R*_f 0.38 (hex/EtOAc, 1:1); mp >140 °C (dec); IR (KBr, cm⁻¹) 3417, 3260, 3134, 3053, 2967, 2927, 2871, 2360, 1610, 1575, 1543, 1495, 1448; δ_{H} (400 MHz, DMSO-*d*₆) 0.77 (d, *J*=6.4 Hz, 6H, CH(CH₃)₂), 3.08–3.18 (m, 1H, CH(CH₃)₂), 7.18–7.22 (m, 7H, Trt, NH), 7.28–7.38 (m, 9H, Trt), 7.80 (s, 1H, H-8); δ_{C} (100 MHz, DMSO-*d*₆) 21.6, 42.2, 74.9, 123.7, 127.4, 127.8, 129.2, 140.9, 141.7, 149.7, 154.5, 157.0; HRMS (ESI⁺) *m/z* calcd for C₂₇H₂₅ClN₅ [M+H⁺] 454.1793, obsd 454.1783.

4.4.8. (6-Chloro-9-trityl-9H-purin-2-yl)-cyclopentyl-amine (10h). R²OH was cyclopentanol. Flash column chromatography (eluent: hex/EtOAc, 3:1) yielded **10h** as a white solid (168 mg, 35%); *R*_f 0.39 (hex/EtOAc, 1:1); mp 133–139 °C; IR (KBr, cm⁻¹) 3454, 3252, 3131, 3058, 2956, 2867, 2361, 1610, 1578, 1541, 1495, 1450; δ_{H} (400 MHz, DMSO-*d*₆) 1.10–1.20 (m, 2H, 2×CH), 1.24–1.52 (m, 6H, 6×CH), 3.20–3.29 (m, 1H, NHCH), 7.19–7.23 (m, 6H, Trt), 7.27–7.38 (m, 10H, Trt, NH), 7.81 (s, 1H, H-8); δ_{C} (100 MHz, DMSO-*d*₆) 23.1, 31.3, 52.5, 74.9, 123.7, 127.4, 127.8, 129.2, 140.9, 141.7, 149.5, 154.4, 157.3; HRMS (ESI⁺) *m/z* calcd for C₂₉H₂₇ClN₅ [M+H⁺] 480.1949, obsd 480.1954.

4.4.9. N²-Boc-(6-chloro-9-trityl-9H-purin-2-yl)-(iso-propyl)-amine (11g). To a stirring solution of **8** (256 mg, 0.5 mmol, 1 equiv) in anhydrous THF (7 mL) was added *iso*-propanol (95 μ L, 1.25 mmol, 2.5 equiv) and PPh₃ (328 mg, 1.25 mmol, 2.5 equiv). After ~2 min (when all reagents had dissolved), DIAD (246 μ L, 1.25 mmol, 2.5 equiv) was added dropwise (over ~30 s). The reaction mixture was then heated at 35 °C for 30 min, after which time TLC confirmed the reaction was complete. All THF was removed in vacuo, then the residue was dry-loaded onto silica gel from CH₂Cl₂ at room temperature, and purified by flash column chromatography (eluent: hex/EtOAc, 5:1) to give the title compound **11g** as a white foam (237 mg, 86%); *R*_f 0.55 (hex/EtOAc, 1:1); mp 172–177 °C; IR (KBr, cm⁻¹) 3414, 3132, 3057, 3026, 2973, 2927, 1711, 1590, 1553, 1495, 1470, 1447, 1427; δ_{H} (400 MHz, DMSO-*d*₆) 0.75 (d, *J*=6.8 Hz, 6H, CH(CH₃)₂), 1.23 (s, 9H, C(CH₃)₃), 4.05 (septet, *J*=6.8 Hz, 1H, CH(CH₃)₂), 7.20–7.25 (m, 6H, Trt), 7.27–7.37 (m, 9H, Trt), 8.35 (s, 1H, H-8); δ_{C} (100 MHz, DMSO-*d*₆) 20.0, 27.6, 48.6, 75.8, 79.7, 127.7, 128.0, 129.1, 129.8, 140.5, 146.8, 149.1, 151.9, 152.7, 153.1; HRMS (ESI⁺) *m/z* calcd for C₃₂H₃₃ClN₅O₂ [M+H⁺] 554.2317, obsd 554.2326.

4.4.10. N²-Boc-(6-chloro-9-trityl-9H-purin-2-yl)-cyclopentyl-amine (11h). To a stirring solution of **8** (256 mg, 0.5 mmol, 1 equiv) in anhydrous THF (7 mL) was added cyclopentanol (113 μ L, 1.25 mmol, 2.5 equiv) and PPh₃ (328 mg, 1.25 mmol, 2.5 equiv). After ~2 min (when all reagents had dissolved), DIAD (246 μ L, 1.25 mmol, 2.5 equiv) was added dropwise (over ~30 s). The reaction mixture was then heated at 35 °C for 2 h, after which time TLC confirmed the reaction was complete. All THF was removed in vacuo, then the residue was dry-loaded onto silica gel from CH₂Cl₂ at room temperature, and purified by flash column chromatography (eluent: hex/EtOAc, 5:1) to give the title compound **11h** as a white solid (243 mg, 84%); *R*_f 0.56 (hex/EtOAc, 1:1); mp 176–180 °C; IR (KBr, cm⁻¹) 3453, 3124, 3062, 3027, 2970, 2869, 2360, 1712, 1589, 1554, 1494, 1469, 1449, 1431; δ_{H} (400 MHz, DMSO-*d*₆) 1.10–1.19 (m, 3H, 3×CH (cyclopentyl)), 1.20–1.27 (m, 12H, 3×CH (cyclopentyl)), C(CH₃)₃), 1.39–1.50 (m, 2H, 2×CH (cyclopentyl)), 4.07 (quintet, *J*=8.4 Hz, 1H, CH(CH₂)₂), 7.17–7.22 (m, 6H, Trt), 7.29–7.38 (m, 9H, Trt), 8.34 (s, 1H, H-8); δ_{C} (100 MHz, DMSO-*d*₆) 22.8, 27.6, 28.6, 58.0, 75.8, 79.8, 127.7, 128.1, 129.1, 129.9, 140.5, 147.0, 149.2, 152.1, 153.0,

153.2; HRMS (ESI⁺) *m/z* calcd for C₃₄H₃₅ClN₅O₂ [M+H⁺] 580.2473, obsd 580.2472.

4.5. Typical procedure for hydrolytic dechlorination and trityl deprotection of purines **10**, **11g** and **11h**

To a solution of purine **10** or **11** (0.5 mmol) in THF (1 mL) was added 80% HCOOH (4 mL; 4:1 mixture of HCOOH/H₂O). The resulting mixture was stirred at 75 °C for 4 h, by which time TLC indicated all starting material and de-tritylated intermediate had been consumed. The reaction mixture was concentrated under reduced pressure to dryness, adsorbed onto silica gel from CH₂Cl₂/MeOH, and purified by silica gel flash column chromatography.

4.5.1. 2-Butylamino-1,9-dihydro-purin-6-one (12a). The substrate purine was **10a**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 7:1→4:1) afforded the title compound **12a** as a 78:22 mixture of N9H/N7H tautomers (103 mg, 99%); white solid; *R*_f 0.23 (CH₂Cl₂/MeOH, 5:1); mp >220 °C (dec); IR (KBr, cm⁻¹) 3457, 2955, 2824, 2360, 1695, 1616, 1505, 1472; δ_{H} (400 MHz, DMSO-*d*₆) 0.89 (t, *J*=7.2 Hz, 3H, CH₃), 1.32 (app sextet, *J*=7.2 Hz, 2H, CH₂CH₃), 1.49 (app quin, *J*=7.2 Hz, 2H, CH₂CH₂CH₃), 3.23 (app q, *J*=7.2 Hz, 2H, NHCH₂), 6.14–6.25 (m, 0.22H, NHCH₂), 6.40–6.50 (m, 0.78H, NHCH₂), 7.61 (s, 0.78H, H-8), 7.89 (s, 0.22H, H-8), 10.42–10.64 (m, 1H, H-1), 12.46 (s, 0.78H, imidazole NH), 12.86 (s, 0.22H, imidazole NH); δ_{C} (100 MHz, DMSO-*d*₆; only signals for major N9H tautomer given) 13.6, 19.5, 30.8, 40.0, 116.3, 135.1, 151.5, 152.5, 156.8; HRMS (ESI⁺) *m/z* calcd for C₉H₁₄N₅O [M+H⁺] 208.1198, obsd 208.1198.

4.5.2. 2-(2-Benzoyloxyethyl)amino-1,9-dihydro-purin-6-one (12b). The substrate purine was **10b**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 7:1→4:1) afforded the title compound **12b** as a 78:22 mixture of N9H/N7H tautomers (138 mg, 97%); white solid; *R*_f 0.29 (CH₂Cl₂/MeOH, 5:1); mp >250 °C (dec); IR (KBr, cm⁻¹) 3477, 3277, 3116, 3061, 2937, 2872, 2806, 2705, 1694, 1612, 1539, 1507, 1468, 1435; δ_{H} (400 MHz, DMSO-*d*₆) 3.47 (m, 2H, NHCH₂), 3.58 (t, *J*=5.2 Hz, 2H, CH₂CH₂OBn), 4.51 (s, 2H, CH₂Ph), 6.20–6.28 (m, 0.22H, NHCH₂), 6.42–6.49 (m, 0.78H, NHCH₂), 7.25–7.35 (m, 5H, Ph), 7.63 (s, 0.78H, H-8), 7.91 (s, 0.22H, NHCH₂), 10.55 (br s, 0.78H, H-1), 10.69 (br s, 0.22H, H-1), 12.47 (br s, 0.78H, imidazole NH), 12.88 (br s, 0.22H, imidazole NH); δ_{C} (100 MHz, DMSO-*d*₆; only signals for major N9H tautomer given) 40.2, 68.1, 71.9, 116.5, 127.4, 127.5, 128.1, 135.3, 138.2, 151.3, 152.4, 156.8; HRMS (ESI⁺) *m/z* calcd for C₁₄H₁₆N₅O₂ [M+H⁺] 286.1298, obsd 286.1288.

4.5.3. (6-Oxo-6,9-dihydro-1H-purin-2-ylamino)-acetic acid ethyl ester (12c). The substrate purine was **10c**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 7:1→4:1) afforded the title compound **12c** as a 71:29 mixture of N9H/N7H tautomers (114 mg, 96%); white solid; *R*_f 0.23 (CH₂Cl₂/MeOH, 5:1); mp >190 °C (dec); IR (KBr, cm⁻¹) 3452, 3283, 3124, 3069, 2935, 2674, 1726, 1708, 1613, 1584, 1515, 1475; δ_{H} (400 MHz, DMSO-*d*₆) 1.19 (t, *J*=7.1 Hz, 3H, CH₂CH₃), 4.04 (d, *J*=6.0 Hz, 2H, CH₂CO₂Et), 4.11 (q, *J*=7.1 Hz, 2H, CH₂CH₃), 6.53–6.62 (m, 0.29H, NHCH₂), 6.76–6.85 (m, 0.71H, NHCH₂), 7.63 (s, 0.71H, H-8), 7.91 (s, 0.29H, H-8), 10.85–11.20 (m, 1H, H-1), 12.55 (br s, 0.71H, imidazole NH), 12.94 (br s, 0.29H, imidazole NH); δ_{C} (100 MHz, DMSO-*d*₆; only signals for major N9H tautomer given) 14.0, 42.3, 60.4, 116.8, 135.5, 150.9, 152.3, 156.7, 170.2; HRMS (ESI⁺) *m/z* calcd for C₉H₁₂N₅O₃ [M+H⁺] 238.0934, obsd 238.0939.

4.5.4. 2-Allylamino-1,9-dihydro-purin-6-one (12d). The substrate purine was **10d**. Flash column chromatography (eluent: CH₂Cl₂/MeOH, 7:1→4:1) afforded the title compound **12d** as a 78:22 mixture of N9H/N7H tautomers (93 mg, 97%); white solid; *R*_f 0.23 (CH₂Cl₂/MeOH, 5:1); mp >250 °C (dec); IR (KBr, cm⁻¹) 3475, 3437,

3133, 2979, 2858, 1677, 1618, 1518, 1461; δ_{H} (400 MHz, DMSO- d_6) 3.90 (app t, $J=5.2$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.06–5.11 (m, 1H, $\text{CH}=\text{CH}_2$), 5.17–5.24 (m, 1H, $\text{CH}=\text{CH}_2$), 5.86–5.95 (m, 1H, $\text{CH}=\text{CH}_2$), 6.48–6.60 (s, 0.22H, NHCH_2), 6.74–6.88 (s, 0.78H, NHCH_2), 7.63 (s, 0.78H, H-8), 7.89 (s, 0.22H, H-8), 10.66–10.92 (m, 1H, H-1), 12.51 (br s, 0.78H, imidazole NH), 12.89 (br s, 0.22H, imidazole NH); δ_{C} (100 MHz, DMSO- d_6 ; only signals for major N9H tautomer given) 42.5, 115.2, 116.5, 135.1, 135.3, 151.3, 152.4, 156.8; HRMS (ESI^+) m/z calcd for $\text{C}_8\text{H}_{10}\text{N}_5\text{O}$ [$\text{M}+\text{H}^+$] 192.0879, obsd 192.0877.

4.5.5. 2-(Prop-2-ynyl)amino-1,9-dihydro-purin-6-one (12e). The substrate purine was **10e**. Flash column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 7:1→4:1) afforded the title compound **12e** as a 78:22 mixture of N9H/N7H tautomers (92 mg, 97%); white solid; R_f 0.24 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 5:1); mp >190 °C (dec); IR (KBr, cm^{-1}) 3448, 2857, 2361, 2328, 2127, 1689, 1611, 1520, 1463; δ_{H} (400 MHz, DMSO- d_6) 3.13 (t, $J=2.1$ Hz, 1H, $\text{C}\equiv\text{CH}$), 4.05 (dd, $J=5.6$, 2.1 Hz, 2H, $\text{CH}_2\text{C}\equiv\text{CH}$), 6.79–6.88 (m, 0.22H, NHCH_2), 7.12 (s, 0.78H, NHCH_2), 7.65 (s, 0.78H, H-8), 7.92 (s, 0.22H, H-8), 10.84–11.10 (m, 1H, H-1), 12.62 (br s, 0.78H, imidazole NH), 12.95 (br s, 0.22H, imidazole NH); δ_{C} (100 MHz, DMSO- d_6 ; only signals for major N9H tautomer given) 29.9, 73.1, 81.2, 116.7, 135.5, 150.9, 152.0, 156.7; HRMS (ESI^+) m/z calcd for $\text{C}_8\text{H}_8\text{N}_5\text{O}$ [$\text{M}+\text{H}^+$] 190.0723, obsd 190.0727.

4.5.6. 2-Benzylamino-1,9-dihydro-purin-6-one (12f). The substrate purine was **10f**. Flash column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 7:1→4:1) afforded the title compound **12f** as a 78:22 mixture of N9H/N7H tautomers (116 mg, 96%); white solid; R_f 0.28 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 5:1); mp >220 °C (dec); IR (KBr, cm^{-1}) 3444, 2966, 2360, 1673, 1614, 1515, 1456; δ_{H} (400 MHz, DMSO- d_6) 4.49 (d, $J=6.0$ Hz, 2H, CH_2Ph), 6.56–6.67 (m, 0.22H, NHCH_2), 6.79–6.60 (m, 0.78H, NHCH_2), 7.22–7.28 (m, 1H, Ph), 7.30–7.36 (m, 4H, Ph), 7.63 (s, 0.78H, H-8), 7.90 (s, 0.22H, H-8), 10.55–10.76 (m, 1H, H-1), 12.49 (br s, 0.78H, imidazole NH), 12.90 (br s, 0.22H, imidazole NH); δ_{C} (100 MHz, DMSO- d_6 ; only signals for major N9H tautomer given) 43.8, 116.6, 126.8, 127.0, 128.3, 135.3, 139.1, 151.3, 152.4, 156.8; HRMS (ESI^+) m/z calcd for $\text{C}_{12}\text{H}_{12}\text{N}_5\text{O}$ [$\text{M}+\text{H}^+$] 242.1036, obsd 242.1040. Slow vapour diffusion of ethyl ether into a solution of **12f** in DMF gave a single crystal suitable for X-ray diffraction analysis.

4.5.7. 2-(iso-Propyl)amino-1,9-dihydro-purin-6-one (12g). The substrate purine was **10g**. Flash column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 7:1→4:1) afforded the title compound **12g** as a white solid (92 mg, 95%); R_f 0.23 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 5:1); mp >220 °C (dec); IR (KBr, cm^{-1}) 3460, 2974, 2802, 1674, 1608, 1512, 1464; δ_{H} (400 MHz, DMSO- d_6) 1.15 (d, $J=6.5$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 3.93 (apparent octet, $J=6.5$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 6.22–6.33 (m, 1H, $\text{NHCH}(\text{CH}_3)_2$), 7.67 (br s, 1H, H-8), 10.35 (s, 1H, H-1), 12.37–12.89 (m, 1H, imidazole NH); δ_{C} aromatic signals too weak to allow reliable reporting, ^{13}C NMR spectrum is included in the [Supplementary data 3](#); HRMS (ESI^+) m/z calcd for $\text{C}_8\text{H}_{12}\text{N}_5\text{O}$ [$\text{M}+\text{H}^+$] 194.1036, obsd 194.1033. Hydrolytic dechlorination and deprotection of the Trt and Boc groups of **11g** in an identical manner gave a compound identical to **12g**.

4.5.8. 2-Cyclopentylamino-1,9-dihydro-purin-6-one (12h). The substrate purine was **10h**. Flash column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 7:1→4:1) afforded the title compound **12h** as a 81:19 mixture of N9H/N7H tautomers (52 mg, 95%); white solid; R_f 0.26 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 5:1); mp >220 °C (dec); IR (KBr, cm^{-1}) 3457, 2961, 2876, 2358, 1677, 1607, 1514, 1454; δ_{H} (400 MHz, DMSO- d_6) 1.38–1.70 (m, 6H, 6×CH), 1.86–1.94 (m, 2H, 2×CH), 4.03–4.12 (m, 1H, $\text{NHCH}(\text{CH}_3)_2$), 6.24–6.60 (m, 1H, $\text{NHCH}(\text{CH}_3)_2$), 7.52–8.00 (m, 1H, H-8), 10.20–10.44 (m, 1H, H-1), 12.49 (br s, 0.81H, imidazole NH), 12.86 (br s, 0.19H, imidazole NH); δ_{C} (100 MHz, DMSO- d_6 ; only signals for major N9H tautomer given) 23.1, 32.4, 51.9, 116.3, 135.2, 151.5, 152.0, 156.7; HRMS (ESI^+) m/z calcd for $\text{C}_{10}\text{H}_{14}\text{N}_5\text{O}$ [$\text{M}+\text{H}^+$]

220.1192, obsd 220.1191. Hydrolytic dechlorination and deprotection of the Trt and Boc groups of **11h** in an identical manner gave a compound identical to **12h**.

4.6. Typical procedure for Mitsunobu coupling of purine 4a: condition A

To a stirred solution of purine **4a** (163 mg, 0.5 mmol, 1 equiv) in anhydrous THF (7 mL) under an N_2 atmosphere at room temperature was added the alcohol R^2OH (1.25 mmol, 2.5 equiv) and PPh_3 (328 mg, 1.25 mmol, 2.5 equiv). After ~2 min, DIAD (246 μL , 1.25 mmol, 2.5 equiv) was added dropwise (over ~30 s). The reaction mixture was stirred at 35 °C for the specified time, at which point TLC analysis indicated the reaction was complete. The reaction mixture was concentrated in vacuo, then adsorbed onto silica gel from CH_2Cl_2 , and purified by flash column chromatography.

4.6.1. N^2 -Boc- N^2 -butyl-9-butyl-6-chloro-9H-purin-2-yl-amine (13a). R^2OH was *n*-butanol, and the reaction time was 30 min. Flash column chromatography (eluent: hex/EtOAc, 3:2) furnished **13a** as a pale yellow gum: (177 mg, 93%); R_f 0.50 (hex/EtOAc, 1:1); mp >101–103 °C; IR (KBr, cm^{-1}) 3453, 3094, 2962, 2935, 2874, 1713, 1608, 1561, 1509, 1451, 1429, 1403; δ_{H} (400 MHz, CDCl_3) 0.91 (t, $J=7.4$ Hz, 3H, CH_2CH_3), 0.97 (t, $J=7.2$ Hz, 3H, CH_2CH_3), 1.30–1.44 (m, 4H, 2× CH_2CH_3), 1.51 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.61–1.69 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.86–1.94 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.94 (t, $J=7.4$ Hz, 2H, $\text{N}2\text{-CH}_2$), 4.21 (t, $J=7.2$ Hz, 2H, $\text{N}9\text{-CH}_2$), 8.00 (s, 1H, H-8); δ_{C} (100 MHz, CDCl_3) 13.2, 13.6, 19.6, 19.8, 28.0, 30.7, 31.6, 43.8, 48.0, 81.1, 127.9, 144.6, 150.0, 152.4, 153.8, 155.1; HRMS (ESI^+) m/z calcd for $\text{C}_{18}\text{H}_{28}\text{ClN}_5\text{O}_2\text{Na}$ [$\text{M}+\text{Na}^+$] 404.1823, obsd 404.1824.

4.6.2. N^2 -Boc- N^2 -(iso-propyl)-9-butyl-6-chloro-9H-purin-2-yl-amine (13e). R^2OH was *iso*-propanol, and the reaction time was 30 min. Flash column chromatography (hex/EtOAc, 3:2) furnished **13e** as a white solid (169 mg, 92%); R_f 0.50 (hex/EtOAc, 1:1); mp 85–89 °C; IR (KBr, cm^{-1}) 3446, 3114, 2976, 2954, 2871, 1693, 1600, 1559, 1504, 1473, 1435, 1405; δ_{H} (400 MHz, DMSO- d_6) 0.89 (t, $J=7.2$ Hz, 3H, CH_3), 1.16–1.30 (m, 8H, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$), 1.35 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.84 (app quintet, $J=7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.26 (t, $J=7.2$ Hz, 2H, $\text{N}9\text{-CH}_2$), 4.46 (sextet, $J=6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)_2\text{CH}(\text{CH}_3)_2$), 8.69 (s, 1H, H-8); δ_{C} (100 MHz, CDCl_3) 13.4, 19.8, 20.9, 28.2, 31.8, 44.1, 49.9, 80.9, 128.8, 145.0, 150.3, 152.4, 153.9, 154.2; HRMS (ESI^+) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{ClN}_5\text{O}_2\text{Na}$ [$\text{M}+\text{Na}^+$] 390.1667, obsd 390.1669.

4.6.3. N^2 -Boc- N^2 -cyclopentyl-9-butyl-6-chloro-9H-purin-2-yl-amine (13f). R^2OH was cyclopentanol, and the reaction time was 2 h. Flash column chromatography (hex/EtOAc, 3:2) furnished the title compound **13f** as a white solid (175 mg, 89%); R_f 0.53 (hex/EtOAc, 1:1); mp 96–99 °C; IR (KBr, cm^{-1}) 3549, 3414, 3114, 2977, 2960, 2873, 2363, 1691, 1638, 1598, 1558, 1506, 1466, 1439, 1403; δ_{H} (400 MHz, DMSO- d_6) 0.87 (t, $J=7.3$ Hz, 3H, CH_3), 1.24 (app sextet, $J=7.3$ Hz, 2H, CH_2CH_3), 1.33 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.40–1.74 (m, 6H, 6×CH (cyclopentyl)), 1.78–1.92 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$, 2×CH (cyclopentyl)), 4.25 (t, $J=7.3$ Hz, 2H, $\text{N}9\text{-CH}_2$), 4.54 (app quintet, $J=8.3$ Hz, 1H, $\text{N}(\text{Boc})\text{CH}$), 8.70 (s, 1H, H-8); δ_{C} (100 MHz, DMSO- d_6) 13.2, 19.1, 23.6, 27.7, 29.4, 30.9, 43.4, 58.4, 80.0, 128.6, 147.9, 148.4, 152.6, 153.1, 153.4; HRMS (ESI^+) m/z calcd for $\text{C}_{19}\text{H}_{29}\text{ClN}_5\text{O}_2$ [$\text{M}+\text{H}^+$] 394.2004, obsd 394.2003.

4.7. Typical procedure for Mitsunobu coupling of purine 4a: condition B

To a stirred solution of purine **4a** (163 mg, 0.5 mmol, 1 equiv) in anhydrous THF (7 mL) under a nitrogen atmosphere at room

temperature was added the alcohol R^2OH (1.25 mmol, 2.5 equiv) and PBu_3 (308 μ l, 1.25 mmol, 2.5 equiv); *CAUTION: PBu_3 is pyrophoric.* After ~ 2 min, ADDP (315 mg, 1.25 mmol, 2.5 equiv) was added. The reaction mixture was stirred at room temperature for the time indicated, at which point TLC analysis indicated the reaction was complete. The reaction mixture was concentrated in vacuo, then adsorbed onto silica gel from CH_2Cl_2 , and purified by flash column chromatography.

4.7.1. N^2 -Benzyl- N^2 -Boc-9-butyl-6-chloro-9H-purin-2-yl-amine (13d). R^2OH was benzyl alcohol, and the reaction time was 4 h. Flash column chromatography (eluent: hex/EtOAc, 3:2) furnished **13d** as a pale yellow gum (181 mg, 87%); R_f 0.47 (hex/EtOAc, 1:1); mp >105–107 °C; IR (KBr, cm^{-1}) 3416, 3089, 3032, 2963, 2933, 2874, 1712, 1606, 1561, 1508, 1493, 1444, 1427, 1401; δ_H (400 MHz, $CDCl_3$) 0.93 (t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.31 (app sextet, $J=7.3$ Hz, 2H, CH_2CH_3), 1.47 (s, 9H, $C(CH_3)_3$), 1.83 (app quintet, $J=7.3$ Hz, 2H, $CH_2CH_2CH_3$), 4.15 (t, $J=7.3$ Hz, 2H, $N9-CH_2$), 5.18 (s, 2H, CH_2Ph), 7.16–7.27 (m, 3H, Ph), 7.36–7.38 (m, 2H, Ph), 7.96 (s, 1H, H-8); δ_C (100 MHz, $CDCl_3$) 13.4, 19.8, 28.1, 31.7, 44.0, 51.5, 81.8, 126.9, 127.5 (2), 128.2, 138.4, 144.5, 150.3, 152.4, 153.9, 155.0; HRMS (ESI^+) m/z calcd for $C_{21}H_{26}ClN_5O_2Na$ [$M+Na^+$] 438.1667, obsd 438.1675.

4.7.2. N^2 -Allyl- N^2 -Boc-9-butyl-6-chloro-9H-purin-2-yl-amine (13b). R^2OH was allyl alcohol, and the reaction time was 8 h. Flash column chromatography (hex/EtOAc, 3:2) furnished **13b** as a white solid (157 mg, 86%); R_f 0.48 (hex/EtOAc, 1:1); mp 87–92 °C; IR (KBr, cm^{-1}) 3448, 3089, 3010, 2978, 2958, 2933, 2873, 1822, 1701, 1643, 1604, 1560, 1510, 1441, 1401; δ_H (400 MHz, $DMSO-d_6$) 0.89 (t, $J=7.3$ Hz, 3H, CH_3), 1.25 (app sextet, $J=7.3$ Hz, 2H, CH_2CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 1.83 (app quintet, $J=7.3$ Hz, 2H, $CH_2CH_2CH_3$), 4.21 (t, $J=7.3$ Hz, 2H, $N9-CH_2$), 4.42–4.45 (m, 2H, $CH_2CH=CH_2$), 5.05–5.10 (m, 1H, $CH=CH_2$), 5.12–5.18 (m, 1H, $CH=CH_2$), 5.87–5.96 (m, 1H, $CH=CH_2$), 8.62 (s, 1H, H-8); δ_C (100 MHz, $CDCl_3$) 13.4, 19.8, 28.1, 31.7, 44.0, 50.5, 81.6, 116.7, 127.9, 133.8, 144.6, 150.2, 152.4, 153.6, 154.9; HRMS (ESI^+) m/z calcd for $C_{17}H_{24}ClN_5O_2Na$ [$M+Na^+$] 388.1510, obsd 388.1525.

4.7.3. N^2 -Boc- N^2 -(prop-2-ynyl)-9-butyl-6-chloro-9H-purin-2-yl-amine (13c). R^2OH was propargyl alcohol, and the reaction time was 8 h. Flash column chromatography (hex/EtOAc, 3:2) furnished **13c** as a white solid (160 mg, 88%); R_f 0.47 (hex/EtOAc, 1:1); mp 104–108 °C; IR (KBr, cm^{-1}) 3416, 3218, 3096, 2973, 2932, 2867, 2363, 2114, 1821, 1697, 1602, 1557, 1509, 1441, 1418; δ_H (400 MHz, $DMSO-d_6$) 0.90 (t, $J=7.3$ Hz, 3H, CH_3), 1.27 (app sextet, $J=7.3$ Hz, 2H, CH_2CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.85 (app quintet, $J=7.3$ Hz, 2H, $CH_2CH_2CH_3$), 3.12 (t, $J=2.4$ Hz, 1H, $C\equiv CH$), 4.23 (t, $J=7.3$ Hz, 2H, $N9-CH_2$), 4.61 (d, $J=2.4$ Hz, 2H, $CH_2C\equiv CH$), 8.65 (s, 1H, H-8); δ_C (100 MHz, $CDCl_3$) 13.4, 19.8, 28.1, 31.7, 37.6, 44.1, 70.9, 79.7, 82.4, 144.7, 128.1, 150.4, 152.4, 152.8, 154.1; HRMS (ESI^+) m/z calcd for $C_{17}H_{22}ClN_5O_2Na$ [$M+Na^+$] 386.1354, obsd 386.1355.

4.8. Typical procedure for hydrolytic dechlorination and Boc deprotection of purines 13

A solution of purine **13** (0.3 mmol) in 80% $HCOOH$ (3 mL; 4:1 mixture of $HCOOH/H_2O$) was stirred at 75 °C for 2 h, by which time TLC indicated all starting material and Boc-deprotected intermediate had been consumed. The reaction mixture was concentrated under reduced pressure to dryness, adsorbed onto silica gel from $CH_2Cl_2/MeOH$, and then purified by silica gel flash column chromatography.

4.8.1. 9-Butyl-2-butylamino-1,9-dihydro-purin-6-one (14a). The purine substrate was **13a**. Flash column chromatography (eluent: $CH_2Cl_2/MeOH$, 10:1 \rightarrow 7:1) delivered the title compound as a white powder (78 mg, 99%); R_f 0.58 ($CH_2Cl_2/MeOH$, 5:1); mp >310 °C

(dec); IR (KBr, cm^{-1}) 3465, 3273, 3063, 2957, 2930, 2872, 2688, 1712, 1608, 1576, 1514, 1470; δ_H (400 MHz, $DMSO-d_6$) 0.87–0.92 (m, 6H, $2\times CH_3$), 1.22 (app sextet, $J=7.0$ Hz, 2H, CH_2CH_3), 1.32 (app sextet, $J=7.3$ Hz, 2H, CH_2CH_3), 1.51 (app quintet, $J=7.0$ Hz, 2H, $CH_2CH_2CH_3$), 1.72 (app quintet, $J=7.3$ Hz, 2H, $CH_2CH_2CH_3$), 3.27 (app quartet, $J=7.0$ Hz, 2H, $NHCH_2$), 3.95 (t, $J=7.3$ Hz, 2H, $N9-CH_2$), 6.33 (t, $J=5.2$ Hz, 1H, $NHCH_2$), 7.68 (s, 1H, H-8), 10.34 (s, 1H, H-1); δ_C (100 MHz, $CDCl_3$ +few drops $MeOH-d_4$) 13.3, 13.7, 19.6, 20.0, 31.2, 31.7, 40.7, 43.3, 114.5, 137.3, 152.0, 152.6, 158.7; HRMS (ESI^+) m/z calcd for $C_{13}H_{22}N_5O$ [$M+H^+$] 264.1818, obsd 264.1816.

4.8.2. 2-Allylamino-9-butyl-1,9-dihydro-purin-6-one (14b). The purine substrate was **13b**. Flash column chromatography (eluent: $CH_2Cl_2/MeOH$, 10:1 \rightarrow 7:1) delivered **14b** as a white powder (72 mg, 97%); R_f 0.54 ($CH_2Cl_2/MeOH$, 5:1); mp >300 °C (dec); IR (KBr, cm^{-1}) 3449, 2958, 2927, 2865, 2363, 1719, 1609, 1516, 1473; δ_H (400 MHz, $DMSO-d_6$) 0.88 (t, $J=7.3$ Hz, 3H, CH_3), 1.22 (app sextet, $J=7.3$ Hz, 2H, CH_2CH_3), 1.71 (app quin, $J=7.3$ Hz, 2H, $CH_2CH_2CH_3$), 3.91–3.97 (m, 4H, $N9-CH_2$, $CH_2CH=CH_2$), 5.08–5.13 (m, 1H, $CH=CH_2$), 5.17–5.24 (m, 1H, $CH=CH_2$), 5.87–5.96 (m, 1H, $CH=CH_2$), 6.49 (t, $J=5.6$ Hz, 1H, $NHCH_2$), 7.70 (s, 1H, H-8), 10.52 (s, 1H, H-1); δ_C (100 MHz, $CDCl_3$ +few drops $MeOH-d_4$) 13.3, 19.5, 31.7, 43.3, 43.5, 115.2, 116.0, 134.4, 137.4, 151.7, 152.3, 158.8; HRMS (ESI^+) m/z calcd for $C_{12}H_{18}N_5O$ [$M+H^+$] 248.1505, obsd 248.1496.

4.8.3. 9-Butyl-2-(prop-2-ynyl)-amino-1,9-dihydro-purin-6-one (14c). The purine substrate was **13c**. Flash column chromatography (eluent: $CH_2Cl_2/MeOH$, 10:1 \rightarrow 7:1) delivered **14c** as a white powder (71 mg, 97%); R_f 0.50 ($CH_2Cl_2/MeOH$, 5:1); mp >250 °C (dec); IR (KBr, cm^{-1}) 3584, 3421, 3060, 2928, 2876, 2663, 1729, 1607, 1518, 1472; δ_H (400 MHz, $DMSO-d_6$) 0.88 (t, $J=7.3$ Hz, 3H, CH_3), 1.23 (app sextet, $J=7.3$ Hz, 2H, CH_2CH_3), 1.74 (quin, $J=7.3$ Hz, 2H, $CH_2CH_2CH_3$), 3.14 (t, $J=2.4$ Hz, 1H, $CH_2C\equiv CH$), 3.99 (t, $J=7.3$ Hz, 2H, $N9-CH_2$), 4.08 (dd, $J=5.6$, 2.4 Hz, 2H, $CH_2C\equiv CH$), 6.87 (t, $J=5.6$ Hz, 1H, $NHCH_2$), 7.83 (s, 1H, H-8), 10.83 (s, 1H, H-1); δ_C (100 MHz, $DMSO-d_6$) 13.3, 19.0, 30.0, 31.2, 42.3, 73.1, 81.0, 116.2, 137.6, 150.3, 151.8, 156.4; HRMS (ESI^+) m/z calcd for $C_{12}H_{16}N_5O$ [$M+H^+$] 246.1349, obsd 246.1347.

4.8.4. 2-Benzylamino-9-butyl-1,9-dihydro-purin-6-one (14d). The purine substrate was **13d**. Flash column chromatography (eluent: $CH_2Cl_2/MeOH$, 10:1 \rightarrow 5:1) delivered **14d** as a white powder (85 mg, 95%); R_f 0.56 ($CH_2Cl_2/MeOH$, 5:1); mp >280 °C (dec); IR (KBr, cm^{-1}) 3456, 2923, 2357, 1705, 1609, 1514, 1470; δ_H (400 MHz, $DMSO-d_6$) 0.84 (t, $J=7.2$ Hz, 3H, CH_3), 1.18 (app sextet, $J=7.2$ Hz, 2H, CH_2CH_3), 1.66 (app quintet, $J=7.2$ Hz, 2H, $CH_2CH_2CH_3$), 3.93 (t, $J=7.2$ Hz, 2H, $N9-CH_2$), 4.47 (d, $J=6.0$ Hz, 2H, CH_2Ph), 6.90–6.97 (m, 1H, $NHCH_2$), 7.21–7.38 (m, 5H, Ph), 7.68 (s, 1H, H-8), 10.54 (br s, 1H, H-1); δ_C insufficiently soluble; HRMS (ESI^+) m/z calcd for $C_{16}H_{20}N_5O$ [$M+H^+$] 298.1662, obsd 298.1667.

4.8.5. 2-(iso-Propyl)amino-9-butyl-1,9-dihydro-purin-6-one (14e). The purine substrate was **13e**. Flash column chromatography (eluent: $CH_2Cl_2/MeOH$, 10:1 \rightarrow 7:1) delivered **14e** as a white powder (72 mg, 97%); R_f 0.56 ($CH_2Cl_2/MeOH$, 5:1); mp >275 °C (dec); IR (KBr, cm^{-1}) 3452, 3260, 3072, 2967, 2930, 2863, 2750, 1699, 1599, 1578, 1519, 1465; δ_H (400 MHz, $DMSO-d_6$) 0.88 (t, $J=7.3$ Hz, 3H, CH_3), 1.20 (d, $J=6.4$ Hz, 6H, $CH(CH_3)_2$), 1.22 (app sextet, $J=7.3$ Hz, 2H, CH_2CH_3), 1.72 (quintet, $J=7.3$ Hz, 2H, $CH_2CH_2CH_3$), 3.92–4.00 (m, 3H, $N9-CH_2$, $CH(CH_3)_2$), 6.22 (d, $J=7.2$ Hz, 1H, $NHCH$), 7.68 (s, 1H, H-8), 10.21 (s, 1H, H-1); δ_C (100 MHz, $CDCl_3$ +few drops $MeOH-d_4$) 13.3, 19.5, 22.2, 31.7, 43.0, 43.3, 115.1, 137.4, 151.7, 152.0, 158.8; HRMS (ESI^+) m/z calcd for $C_{12}H_{20}N_5O$ [$M+H^+$] 250.1662, obsd 250.1655.

4.8.6. 9-Butyl-2-cyclopentylamino-1,9-dihydro-purin-6-one (14f). The purine substrate was **13f**. Flash column chromatography

(eluent: CH₂Cl₂/MeOH, 10:1 → 7:1) delivered **14f** as a white powder (78 mg, 95%); *R_f* 0.58 (CH₂Cl₂/MeOH, 5:1); mp > 320 °C (dec); IR (KBr, cm⁻¹) 3430, 3418, 2960, 2861, 2696, 1696, 1597, 1512, 1464; δ_H (400 MHz, DMSO-*d*₆) 0.88 (t, *J* = 7.4 Hz, 3H, CH₃), 1.22 (app sextet, *J* = 7.4 Hz, 2H, CH₂CH₃), 1.44 (m, 2H, 2×CH (cyclopentyl)), 1.50–1.77 (m, 6H, CH₂CH₂CH₃, 4×CH (cyclopentyl)), 1.95 (m, 2H, 2×CH (cyclopentyl)), 3.96 (t, *J* = 6.8 Hz, 2H, N9-CH₂), 4.09 (app sextet, *J* = 6.7 Hz, 1H, NHCH), 6.40 (d, *J* = 6.7 Hz, 1H, NHCH), 7.68 (s, 1H, H-8), 10.13 (s, 1H, H-1); δ_C (100 MHz, CDCl₃+few drops MeOH-*d*₄) 13.1, 19.4, 23.5, 31.6, 32.4, 43.2, 52.7, 115.0, 137.3, 151.8, 152.0, 158.3; HRMS (ESI⁺) *m/z* calcd for C₁₄H₂₂N₅O [M+H⁺] 276.1818, obsd 276.1824.

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Supplementary data

Experimental procedures for the syntheses of **2**, **3**, **6**, **7**, **8**, **9g** and **9h**, copies of ¹H and ¹³C NMR spectra for all compounds are provided. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 771261 (compound **5j**) and CCDC 771260 (compound **12f**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.03.118.

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