Synthesis of triazolopyridines and triazolopyrimidines using a modified Mitsunobu reaction

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Dedicated to Professor Madeleine Joullie on the occasion of her 80th birthday

Abstract

Triazolopyridines and triazolopyrimidines were synthesized using a modified Mitsunobu reaction starting from acylated 2-hydrazinopyridines and acylated-hydrazinopyrimidines under mild conditions.

Keywords: Triazolopyridines, triazolopyrimidines, Mitsunobu reaction, intramolecular cyclization

Introduction

Triazolopyridines and fused triazoles are useful scaffolds for the generation of biologically interesting molecules.[1] The conventional synthesis of triazolopyridines involves the dehydration of a 2-hydrazidopyridine using refluxing phosphorus oxychloride, concentrated hydrochloric acid or refluxing acetic acid (Scheme 1).[2,1a] These relatively harsh reaction conditions are often incompatible with many acid or base labile functional and protecting groups such as esters or carbamates [t-butyloxycarbonyl (Boc), 9*H*-fluoren-9-ylmethyloxycarbonyl (Fmoc)], limiting the types of precursors that can be used in forming fused triazoles *via* these methods. Mild conditions for the formation of triazoles have been described in the literature,[3] however, significant variations in yields and reaction times limit the choice of substrates that can be utilized. For example, the use of Wamhoff and Zahran's conditions (2 eq. of triphenylphosphine dichloride, 2.8 eq. triethylamine in refluxing acetonitrile) to convert **1a** to **2a** gave less than 30% yield. Due to an interest in synthesizing fused [1,2,4]triazolo[4,3-*a*]pyridine heterocyclic systems for structure-activity relationship (SAR) studies, an effort was initiated to develop a general, mild and efficient method for the synthesis of triazolopyridines and other fused triazoles that would be compatible with amino acid substrates and other polar functional groups. As

shown conceptually in Scheme 1, it was postulated that a suitably mild dehydrating agent which could activate the carbonyl group of an acylated hydrazinopyridine under conditions that also maintained the nucleophilicity of the pyridine nitrogen could lead to intramolecular cyclization and provide the desired triazolopyridine.
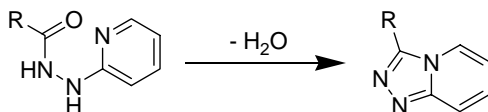
Scheme 1. Dehydrative Cyclization.

Results and Discussion

The Mitsunobu reaction has been one of the most extensively studied and applied reactions in organic synthesis, particularly in the formation of carbon-heteroatom bonds such as saturated heterocyclic rings, ethers, esters, azides and amines.[4] The Mitsunobu reaction has also been widely utilized in the formation of tetrazoles.[5] Activation of amides, including various cyclic amides such as pyridones and pyrimidinones, under Mitsunobu conditions has been well documented.[6] In addition, the Mitsunobu reaction has been used for the formation of benzoxazoles,[7] but its general utility in forming heteroaromatic rings, such as triazolopyridines, has not been explored.[8] Since the formation of triazolopyridines starting from acylated hydrazinopyridines, such as **1a** (Scheme 2), requires the loss of one water molecule, any appropriate dehydrating reagent should be able to mediate the cyclization if the reagent is suitably activating and if the pyridine nitrogen has sufficient nucleophilicity. The dehydrating nature of the Mitsunobu reaction suggested it might be effective in mediating the transformation outlined in Scheme 1. As shown in Scheme 2, subjecting acylated hydrazinopyridines **1a** and **1b** to the standard Mitsunobu reaction using triphenylphosphine (Ph$_3$P) and diethyl azodicarboxylate (DEAD) in THF afforded the desired products **2a** (5%) and **2b** (20%).
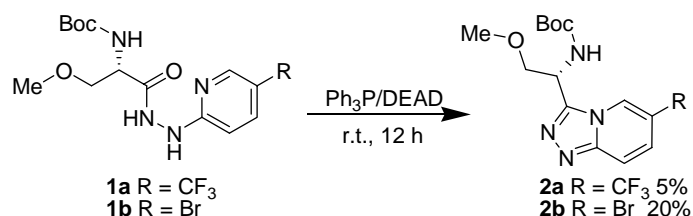
Scheme 2. Triazolopyridines: synthesis from classic Mitsunobu reaction conditions.

Although these initial attempts proceeded in low yields, the formation of the desired triazolopyridines under these mild reaction conditions provided sufficient justification for

optimizing the reaction.   Upon consideration of the proposed mechanism of the Mitsunobu reaction, it seemed reasonable to suggest a reaction mechanism proceeding through intermediate **5** (Scheme 3).[9,4d]   Addition of transient protecting groups might stabilize the intermediate and allow for the intramolecular attack of the pyridine nitrogen while preventing the decomposition of the starting material.
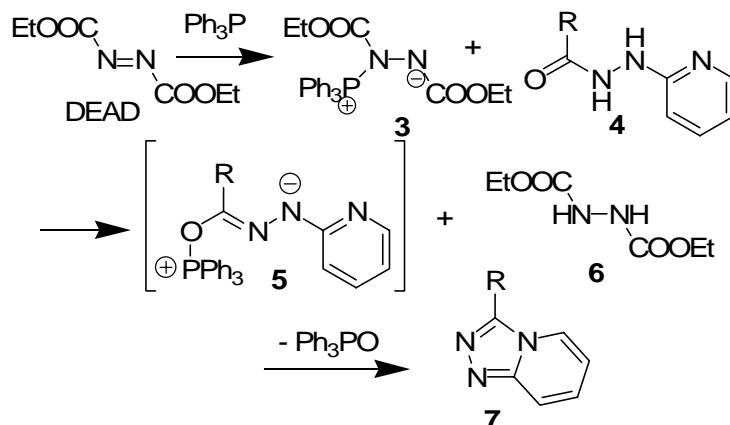
**Scheme 3.** Putative intermediate **5** from the Misunobu reaction.

To test this hypothesis, the effect on the product yield of incorporating an *in situ* transient protecting group like trimethylsilyl (TMS) was assessed. Duncia *et al*[5b] reported the use TMS-N_3 under Mitsunobu conditions to efficiently form tetrazoles. Based on this precedent, TMS-N_3 was the first additive that was tried, as shown in Scheme 4 proceeding to the triazolopyridine **7** via the putative intermediate **8**. The addition of TMS-N_3 and triphenylphosphine to the reaction mixture followed by DEAD enhanced the yield of triazolopyridine **2a** from ~5% to 90%, and of triazolopyridine **2b** from 20% to 95%.[10] In general, the reactions were complete in less than 10 minutes at room temperature. The formation of tetrazoles using Duncia's conditions is reported to require more than 24 h and excess azide to complete while in our case the cyclization is rapid and requires only one equivalent of the azide. This favorable outcome is probably due to the intramolecular nature of our reaction.

To understand the reaction further, other silylating agents and azide sources were tried, and it was found that TMS-N_3 is the optimal reagent (Table 1).[11] When no additive was used, less than 21% of the desired product was observed by LCMS (Entry 1). No starting material remained, as determined by TLC and LCMS, but no other major peaks other than triphenylphosphine oxide and the hydrazine dicarboxylate were observed. Multiple small peaks were observed over the length of the HPLC trace. When TMS-Cl was used, no desired product was observed and the starting material was not consumed (Entry 3). Similar results were also obtained with TMS-I (Entry 4). With TMS-OTf, a modest amount of product was observed (Entry 5, 24% yield), with the remainder of the mass balance being starting material.   With TMS-CN, *N,O*-bis trimethylsilylacetimidate or *N,O*-bis trimethylsilyltrifluoroacetimidate, low levels of product

were observed with complete consumption of the starting material (Entry 6-8).[12] The sequence of reagent addition is crucial for the success of the cyclization reaction. DEAD has to be added last, otherwise no difference in product yield was observed relative to those in Scheme 2 (37% product observed in the LCMS after 72h compared to 69%). ^{31}P NMR provided evidence that when **1a** was mixed with Ph_3P and TMS-N_3 at room temperature, the Ph_3P only reacted slowly in THF as evidenced by the disappearance of the ^{31}P signal of Ph_3P at -4.3 ppm and the appearance of the ^{31}P signal of Ph_3P=NTMS at δ -0.66 ppm over a period of 6 h. Furthermore, use of commercially available Ph_3P=NTMS (Entry 9) instead of Ph_3P and TMS-N_3, failed to effect the cyclization of **1a** and **1b**, presumably excluding the formation of Ph_3P=NTMS as a possible intermediate.

Addition of excess Bu_4NN_3 did not improve the reaction (Entry 10) but when sodium azide or the more THF-soluble cesium azide was added (Entry 11) a significant amount of triazolopyridine was formed. This suggests that the azide plays an important role in this reaction and the impact of the TMS group to the reaction might be only to provide a stable, soluble form of the azide for activation of the active species.[11,13]

Table 1. Additives for the dehydrative cyclization
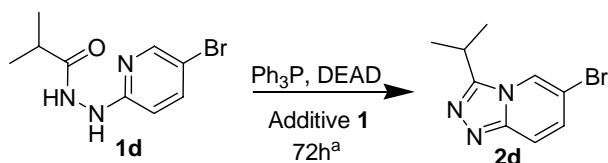
| Entry	Additive 1	% 1d[b]	% 2d
1	None	none	<21%
2	TMS-N_3	none	62% (62%)[c]
3	TMS-Cl	55%	none
4	TMS-I	35%	none
5	TMS-OTf	10%	24%
6	TMS-CN	none	<7%
7	$CH_3C(OTMS)$=NTMS	trace	<22%
8	$CF_3C(OTMS)$=NTMS	none	<26%
9	Ph_3P=NTMS	none	<2%
10	Bu_4NN_3	none	<1%
11	NaN_3	none	39%
12	CsN_3	none	45%

[a]DEAD (1.5 eq.) was added to a solution of the hydrazide (50 mg), Ph_3P (1.2 eq.) and the additive (1 eq.) in THF (0.2 M). All reactions were allowed to proceed for 72h. The reactions were monitored after 1, 6, 20, and 72h. No changes were observed between 6 and 72h. [b]The percentage of **1d** and **2d** was determined using reverse phase HPLC by integration of the area of

the signal by ultraviolet detection at 220 nm. The major peak was always Ph_3PO and was subtracted from the total integration before calculating the percentage of product. [c]Isolated yield.
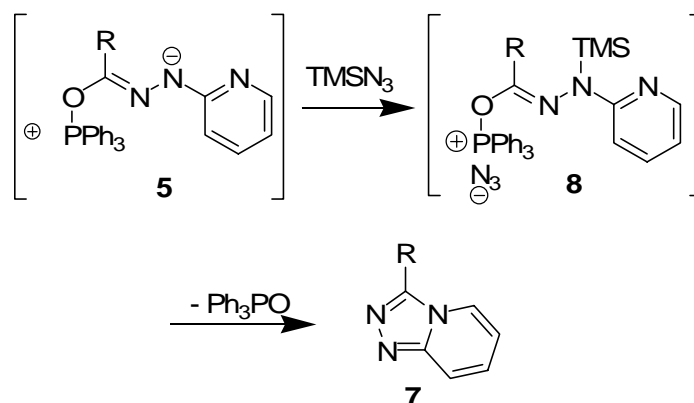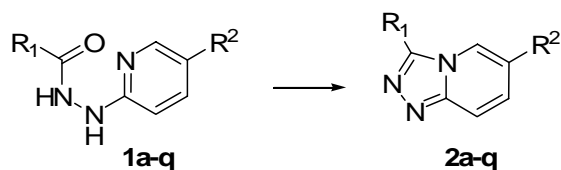

Scheme 4. TMS azide; possible role.

When diisopropylazodicarboxylate (DIAD) was used as an alternative to DEAD, it was found that in the absence of the acylated 2-hydrazinopyridines, a white precipitate formed upon addition of 1 eq. of DIAD to an equimolar mixture of Ph_3P and TMS-N_3 at 0.1 M, or in more concentrated solutions. No precipitate was formed with any of the other pairs of reagents at 0.1 M. This white solid also formed in ether, and was soluble in DCM or chloroform. The solid was found to be moisture sensitive and thermally unstable. NMR studies showed the presence of the phosphine, DIAD but no TMS group. When cesium azide was used instead of $TMSN_3$, a white precipitate also formed. The IR of the solid showed the presence of a band at 2100 cm^{-1}. This solid was able to perform the triazolopyridine cyclization but excess reagent was required to complete the reaction, indicating that this species might be involved in the cyclization reaction but another component is needed to make the conversion efficient, possibly the TMS group. Attempts to obtain crystals for an X-ray structure determination have been unsuccessful to date.[14] Other possible mechanisms are shown in Scheme 5. Pathway A shows the formation of a DEAD, triphenylphosphine and azide complex **9** in which the TMS group (or a metal) is associated with the negative charge on the DEAD. Displacement of the azide by nucleophilic attack of the carbonyl of the acyl hydrazine **4** results in a complex **10** that proceeds onto product **7**. Alternatively, as shown in Pathway B, attack of the acyl hydrazine **4** can displace the DEAD from the complex **9**. By this pathway, the triazolopyridine **7** is then formed through loss of triphenylphosphine oxide and azide.
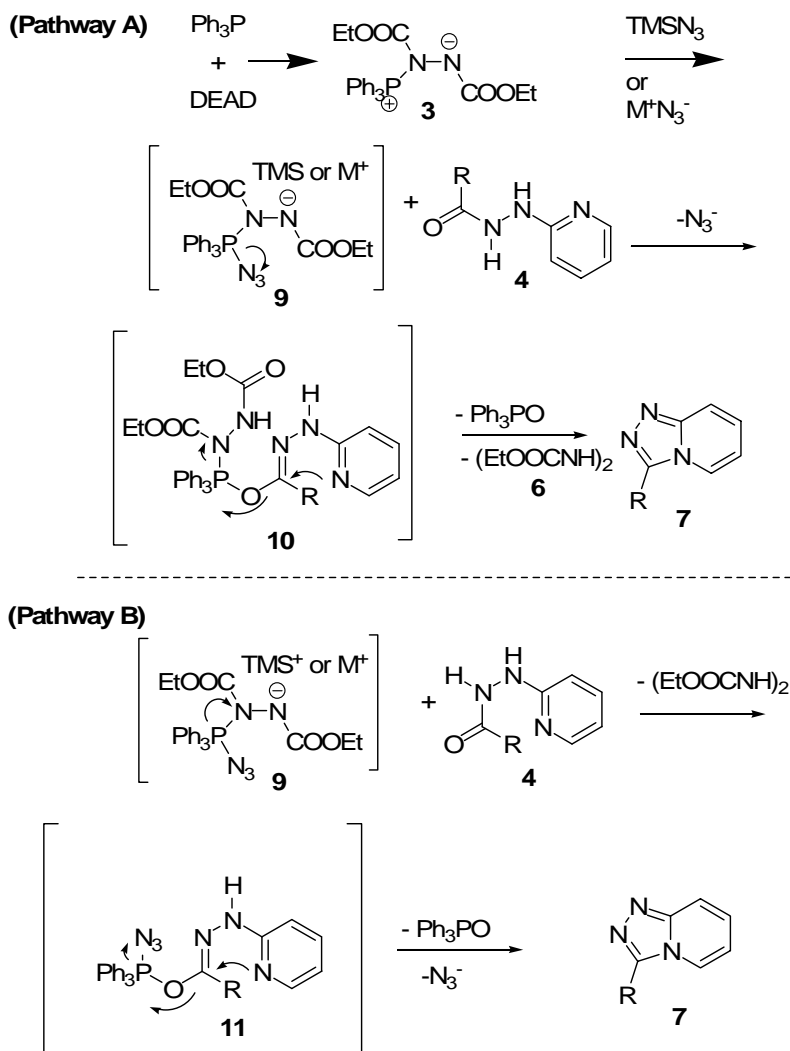
Scheme 5. Other possible reaction mechanisms.

The potential scope and application of the TMS-N_3 assisted Mitsunobu reaction to form triazolopyridines is shown in Table 2. Amino acid protecting groups such as Boc and Fmoc are compatible with the reaction conditions. Similarly, methyl ethers and benzyl, t-butyl, methyl and ethyl esters can also be used. Furthermore, Table 2 includes several examples of triazolopyridines derived from amino acids. These products have potential use as peptide mimetics as the triazolo ring can be envisioned to be an amide isostere. Triazolopyridines formed from amino acid precursors show a high retention of stereochemistry (ee = 99%) (examples **2a, 2k, 2l**, Table 2, as determined by using chiral HPLC or SFC, see experimental section for details). Acyl hydrazinopyridines in which R^1 is a secondary carbon were also found to undergo the modified Mitsunobu reaction (**2d**, **2g**, **2h**, **2i**, **2j**, Table 2). Table 3 shows that triazolopyrimidines (**2r-2u**) can be synthesized using this method, although higher reaction temperatures (50 °C) and longer times are needed.

Table 2. Synthesis of triazolopyridines[15]

Entry	R^1	R^2	Yield (%)
2a	(Me–O, NHBoc structure)	CF_3	90 ee = 99%
2b	(Me–O, NHBoc structure)	Br	95
2c	(Me–O, NHBoc structure)	CF_3	50
2d	iPr	Br	62
2e	3-pyridyl	CF_3	53
2f	3-pyridyl	Br	62
2g	4-*N*-Boc-piperidinyl	CF_3	69
2h	4-*N*-Boc-piperidinyl	Br	50
2i	2-*N*-Boc-pyrrolidinyl	CF_3	55
2j	2-*N*-Boc-pyrrolidinyl	Br	40
2k	(BocHN, tBuO structure)	CF_3	71 ee = 99%
2l	(BocHN, tBuO structure)	CF_3	55 ee = 99%
2m	(BnO, NHBoc structure)	CF_3	39
2n	(BnO, NHBoc structure)	Br	33
2o	(MeO, NHBoc structure)	CF_3	48
2p	(MeO, NHBoc structure)	Br	21
2q	(tBuO, NHFmoc structure)	CF_3	27

Table 3. Syntheses of triazolopyrimidines[16]

Entry	R^1	R^2	Yield (%)
2r	-CH$_2$OBn	Am[a]	31
2s	-COOMe	Am	53
2t	-CH$_2$COOEt	Am	60
2u	-COOMe	Bn	22

[a]Am: amyl (nC$_5$H$_{11}$)

Conclusions

In summary, a general application of the Mitsunobu reaction for the synthesis of triazolopyridines and triazolopyrimidines (Tables 2 and 3) has been developed using TMS-N$_3$ as an additive. The described methodology has general application for the formation of derivatized triazolopyridines under mild conditions, and for the generation of peptidomimetics when amino acids are used as precursors.

Acknowledgements

Experimental Section

General Procedures. Proton and carbon NMR spectra were recorded on one of the following instruments: Bruker DRX-400 MHz , Jeol ECL-400 or 500 MHz instrument. Analytical high pressure liquid chromatography (HPLC) and liquid chromatography/mass spectrometry (LC/MS) analyses were conducted using Shimadzu LC-10AS pumps and a SPD-10AV UV-vis detector. MS detection was performed with a Micromass Platform LC spectrometer. HPLC and LC/MS methods are detailed below. Preparative Reverse Phase (RP) HPLC was performed using two Shimadzu LC-8A pumps and a SPD-10AV UV-vis detector set at 220 nm on C18 RP columns (YMC Pack ODSA S5 20 × 100 mm or 30 × 250 mm) using methanol/water mixtures buffered

with 0.1% trifluoroacetic acid. Enantiomeric excess was determined using supercritical fluid chromatography (SFC, Berger) using a ChiralPak AD column (4.6 x 250 mm, 10 μm particles) at 2 mL/min flow rate of a 17% MeOH in CO_2 with UV detection at 260 nm or by HPLC with a Daicel Chiralcel AD column (4.6 x 250 mm) using an isocratic mixture of 6% isopropanol in hexanes at a flow of 1 mL/min with UV detection at 220 nm. High-resolution mass spectra (HMRS) were recorded on a JEOL SX102 mass spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories and the results obtained were within ±0.4% of the theoretical values, unless otherwise indicated. All non-aqueous reactions were carried out under an atmosphere of nitrogen or argon at ambient temperature unless otherwise noted. Commercial reagents and solvents were used without further purification.

2-Hydrazopyridines (5-Br and 5-CF3) were commercially availlable. Acylations of the hydrazopyridines were done using the mixed anhydride carbonate method or by using polymer supported IIDQ[17].

General procedure 1

Preparation of 1a. Polymer-supported IIDQ. 2-Hydrazinyl-5-(trifluoromethyl) pyridine (165 mg, 0.93 mmol) and (*S*)-2-(tert-butoxycarbonylamino)-3-methoxypropanoic acid (204 mg, 0.93 mmol) were added to PS-IIDQ (Novabiochem 1.8 mmol/g, 776 mg, 1.4 mmol) pre-swollen in acetonitrile (6 mL) and the reaction mixture was shaken at room temperature. The resin was filtered and washed with 3 cycles of DCM and MeOH. The filtrates were combined and concentrated *in vacuo* to give 425 mg of yellow oil. The oil was purified by flash (ISCO 12 g, hexane to ethyl acetate) to give a yellow solid (336.7 mg, 0.85 mmol, 91% yield); MH+ 379.2; ^{1}H NMR (500 MHz, CDCl3) δ ppm 9.39 (br. s., 1H), 8.40 (br. s., 1H), 8.32 (s, 1H), 7.66 (dd, J= 8.8, 2.2 Hz, 1H), 6.78 (d, J= 8.8 Hz, 1H), 6.47 (d, J= 7.7 Hz, 1H), 4.27 (dd, J= 13.2, 6.6 Hz, 1H), 3.61 (dd, J= 8.8, 4.9 Hz, 1H), 3.54 (dd, J= 9.1, 6.3 Hz, 1H), 3.35 (s, 3H), 1.44 (s, 9H).

General procedure 2

Preparation of 1d. Mixed anhydride. Isobutyl chloroformate (0.84 mL, 6.4 mmol) was added dropwise to a solution of isobutyric acid (0.59 mL, 6.4 mmol) and *N*-methylmorpholine (0.70 mL, 6.4 mmol) in THF (11 mL). A white precipitate formed and the mixture was stirred for 5 min. 5-Bromo-2-hydrazinopyridine (1.0 g, 5.3 mmol) was added and the mixture was stirred for 1h. The reaction was diluted with 200 mL water and was stirred overnight. The reaction was made basic with saturated sodium bicarbonate and the solid was filtered, washed with water and dried under reduced pressure overnight to give a white solid (1.17 g, 3.99 mmol, 75 % yield). LCMS (Phenominex, Luna C18, 4.6 X 50 mm, 4 min gradient from 10% MeOH, 90% water, 0.1% TFA to 90% MeOH, 10% water, 0.1% TFA) 1.54 min, >88%, MH+ 260.2; 2.40 min 13%, MH+ 288.2 isobutylcarbamate analog. TLC (70% EA/hex). The product was recrystalized from DCM. ^{1}H NMR (500 MHz, DMSO-D6) δ ppm 9.72 (s, 1H), 8.48 (s, 1H) , 8.11 (d, J= 2.2 Hz, 1H) , 7.67 (dd, J= 8.8, 2.2 Hz, 1H) , 6.49 (d, J=8.8 Hz, 1H), 2.43-2.49 (m, 1H), 1.05 (d, J= 7.1 Hz, 6H).

Preparation of 1u is representative for the preparation of the pyrimidines

(a) Benzylamine addition. A solution of benzylamine (3.02 mL, 27.6 mmol) and triethylamine (4.40 mL, 31.6 mmol) in ethanol (4 mL) was added drop-wise to a solution of 5-bromo-2,4-dichloropyrimidine (6.00 g, 26.3 mmol) in ethanol (13 mL) and the mixture was stirred for 1 h. A white precipitate formed. The reaction mixture was poured into water (100 mL) and the white solid was filtered washed with water and dried under reduced pressure to give 7.86 g (97% yield) of white solid: LCMS Pos/neg 3.30 min, 94% pure, MH+ 298.88, M-H 295.85 Phenominex ODS 4.6 X 50 mm, 4 mL min, 4 min gradient 100% A to 100% B (A: 10% methanol, 90% water, 10 mM NH$_4$OAc; B: 10% water, 90% methanol, 10 mM NH$_4$OAc, UV 220 nm), ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 8.33 (t, J=6.2, 1H), 8.27 (s, 1H), 7.2-7.35 (m, 5H), 4.56 (d, J= 6.2 Hz). ^{13}C NMR (100 MHz, DMSO-D6) δ ppm 159.37, 158.08, 156.84, 138.47, 128.27 (2C), 127.19 (2C), 126.90, 102.51, 43.88.

(b) Hydrazine addition. Hydrazine monohydrate (2.44 mL, 50.2 mmol) was added to a solution of N-benzyl-5-bromo-2-chloropyrimidin-4-amine (5.0 g, 16.7 mmol) and triethylamine (3.50 mL, 25.1 mmol) in ethanol (33 mL) and the mixture was refluxed for 3.5 h. The clear colorless solution was cooled to room temperature and was poured into iced water (200 mL). The white precipitate was filtered, washed with water to give 4.79 g (97% yield) of a pinkish solid after drying overnight under reduced pressure. LCMS Pos/neg 2.70 min, 90% pure (the rest was the starting chloride), MH+ 293.93, Phenominex ODS 4.6 X 50 mm, 4 mL min, 4 min gradient 100% A to 100% B (A: 10% methanol, 90% water, 10 mM NH$_4$OAc; B: 10% water, 90% methanol, 10 mM NH$_4$OAc, UV 220 nm); ^{1}H NMR (500 MHz, DMSO-D6) δ ppm 7.81 (s, 1H), 7.70 (s, 1H), 7.1-7.35 (m, 6H), 4.49 (d, J= 6.0 Hz, 2H), 3.97 (br. s, 2H); ^{13}C NMR (125 MHz, DMSO-D6) δ ppm 162.92, 157.76, 157.79, 139.99, 128.30 (2C), 127.50 (2C) 127.20, 126.56, 43.36.

(c) Acylation. Methyl 2-chloro-2-oxoacetate (0.62 mL, 6.7 mmol) was slowly added to a cold (– 20 °C) solution of N-benzyl-5-bromo-2-hydrazinylpyrimidin-4-amine (1.79 g, 6.1 mmol) and triethylamine (1.66 mL, 12.2 mmol) in THF (20 mL) and the mixture was slowly warmed to room temperature over 3 h. The mixture was poured into 50 mL of ice cold water and was stirred for 15 min. The solid was filtered to give 572.4 mg of yellow solid The filtrate was extracted with ethyl acetate (3 X 50 mL) washed with brine (30 mL) dried with sodium sulfate and concentrated to give ~ 900 mg of yellow foam. The foam dissolved in hot ethyl acetate (20-30 mL) and the product was precipitated by adding heptane (5-10 mL) to give 500 mg of white solid (98% pure by LCMS Pos/neg.2.48 min, MH+2 379.89, M-H 377.85). ^{1}H NMR (500 MHz, DMSO-D6) δ ppm 10.65 (s, 1H), 8.80 (s, 1H), 7.94 (s, 1H), 7.57 (t, J= 6.0, 1H), 7.15-7.3 (m, 6H), 4.50 (br.s, 2H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, DMSO-D6) δ ppm 160.68, 158.03, 155.92, 139.63, 128.07, 127.55, 126.63, 52.84, 43.35.

(R)-tert-butyl   2-methoxy-1-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethylcarbamate (2a). White solid, yield: 90%; ^{1}H NMR (500 MHz, CDC$_{l3}$) δ 8.80 (s, 1H), 7.86 (d, J= 10 Hz, 1H), 7.39 (d, J= 10 Hz, 1H), 5.58 (d, J= 10 Hz, 1H), 5.6-5.4 (m, 1H), 4.04-4.12 (m, 1H) 3.82-3.88 (m, 1H), 3.41 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ

155.58, 149.80, 147.45, 132.11, 131.88, 123.54, 118.32, 117.29, 80.91, 73.14, 59.20, 46.02, 28.15. Exact mass calcd. (M+H) for $C_{15}H_{19}F_3N_4O_3$: 361.1488; found: 361.1487. Elemental Analysis for $C_{15}H_{19}F_3N_4O_3$: calcd. C, 50.00%; H, 5.31%; F, 15.82%; N, 15.55%; O, 13.32%; found: C, 50.07%; H, 5.13%; F, 15.64%; N, 15.45%. Enantiomeric excess: 99% (supercritical fluid chromatography (SFC, Berger) using a ChiralPak AD column (4.6 x 250 mm, 10 μm particles) at 2 mL/min flow rate of a 17% MeOH in CO_2 with UV detection at 260 nm)

(R)-tert-butyl 2-methoxy-1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethylcarbamate (2b). White solid, yield: 95%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.67 (s, 1H), 7.98 (d, J= 10 Hz, 1H), 7.56 (d, J= 10 Hz, 1H), 5.89 (d, J= 10 Hz, 1H), 5.6-5.4 (m, 1H), 4.08-4.00 (m, 1H) 3.94-3.88 (m, 1H), 3.40 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.56, 147.02, 146.10, 134.09, 124.12, 115.63, 110.45, 81.06, 72.61, 59.18, 45.97, 28.10. Exact mass calcd. (M+H) for $C_{14}H_{19}BrN_4O_3$: 371.0719; found: 371.0736.

6-Bromo-3-isopropyl-[1,2,4]triazolo[4,3-a]pyridine (2d). White solid, yield 62%; ^{1}H NMR (500 MHz, CDCl3) δ ppm 8.09 (br. s., 1 H), 7.66 (d, J=8.8 Hz, 1 H), 7.27 (dd, J=9.9, 1.6 Hz, 1 H), 3.36 (dq, 1 H), 1.54 (d, J=7.1 Hz, 6 H); Litt.:[17] ^{1}H NMR (400 MHz, CDCl3): δ 8.06 (s, 1 H), 7.64 (d, J= 9.5 Hz, 1 H), 7.24 (d, J= 9.5 Hz, 1 H), 3.33 (m, J= 7.0 Hz, 1 H), 1.52 (d, J= 7.0 Hz, 6 H). ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 151.13, 148.40, 130.06, 121.93, 117.34, 108.48, 25.13, 20.12. (Exact mass calcd. (M+H) for $C_9H_{10}BrN_3$: 240.0136; found: 240.0146.

3-(Pyridin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (2e). White solid, yield 53%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.33 (s, 1H), 8.75 (d, J= 5 Hz, 1H), 8.52 (d, J= 10 Hz, 1H), 8.07 (d, J= 10Hz, 1H), 7.91-7.95 (m, 1H), 7.56 (d, J= 10 Hz, 1H), 7.43-7.46 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 149.98, 148.86, 147.12, 144.92, 137.34, 126.94, 126.89, 124.48, 122.83, 119.51, 119.24, 118.97, 118.68, 116.76. Exact mass calcd. (M+H) for $C_{12}H_7F_3N_4$: 265.0701; found: 265.0699.

3-(Pyridin-3-yl)-6-bromo -[1,2,4]triazolo[4,3-a]pyridine (2f). White solid, yield 62%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.12 (s, 1H), 8.77 (d, J= 5 Hz, 1H), 8.52 (d, J= 10 Hz, 1H), 7.90-7.94 (m, 2H), 7.50 (d, J= 10 Hz, 1H), 7.40-7.44 (m, 1H). ^{13}C NMR (125 MHz, CDCl3) δ 149.04, 148.86, 147.45, 143.87, 137.33, 132.53, 127.20, 124.31, 122.86, 116.22, 110.08. Exact mass calcd. (M+H) for $C_{11}H_7BrN_4$: 274.9932; found: 274.9930.

tert-Butyl 4-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)piperidine-1-carboxylate (2g). White solid, yield 69%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.25 (s, 1H), 7.83 (d, 1H, J= 9.90 Hz), 7.35-7.25 (dm, 1H, J= 9.90 Hz), 4.19 (br., 2H), 3.24-3.18 (m, 1H), 2.98 (br., 2H), 1.99 (br., 4H), 1.42 (s, 9H). ^{13}C NMR(125 MHz, CDCl$_3$) 154.59, 150.18, 149.22, 131.89, 122.82 (q, J= 272 Hz), 122.76, 118.47(q, J= 36 Hz), 118.05, 79.89, 32.55, 29.38, 28.39. Exact mass calcd. (M+H) for $C_{17}H_{22}N_4O_2F_3$: 371.1695; found: 371.1685.

tert-Butyl   4-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)piperidine-1-carboxylate   (2h). White solid, yield 50%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04 (s, 1H), 7.63 (d, 1H, J= 9.9 Hz), 7.24 (d, 1H, J= 9.4 Hz), 4.17 (br., 2H), 3.14 (br., 1H), 2.95 (br., 2H), 1.18 (br., 4H), 1.21 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) 154.62, 148.80, 148.37, 130.56, 121.75, 117.46, 109.00, 77.26, 32.68, 29.27, 28.41. Exact mass calcd. (M+H) for $C_{16}H_{22}BrN_4O_2$: 381.0926; found: 381.0890.

(*S*)-*tert*-Butyl 2-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)pyrrolidine-1-carboxylate (2i). White solid, yield 55%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.35 (s, 1H), 7.94 (d, 1H, J= 8.8 Hz), 7.45 (d, 1H, J= 8.8 Hz), 5.41 (m, 1H), 3.53 (m, 1H), 3.41 (m, 1H), 2.72 (br., 1H), 2.45 (br., 1H), 2.25 (br., 1H), 2.10 (br., 1H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) 155.50, 149.67, 149.07, 131.87, 123.05 (q, J= 272 Hz), 117.86 (q, J= 36 Hz), 116.96, 77.26, 51.54, 46.66, 31.53, 28.20, 22.59. Exact mass calcd. (M+H) for C$_{16}$H$_{19}$N$_4$O$_2$: 357.1538; found: 357.1554.

(*S*)-*tert*-Butyl 2-(6-bromo-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)pyrrolidine-1-carboxylate (2j). White solid, yield 40%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.83 (s, 1H), 7.60 (d, 1H, J= 8.8 Hz), 7.24 (d, 1H, J= 9.4 Hz), 5.30 (br., 1H), 3.48 (m, 1H), 3.42 (br., 1H), 2.60 (br., 1H), 2.45 (br., 1H), 2.25 (br., 1H), 2.03 (br., 1H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) 147.50, 131.50, 124.50, 116.00, 108.75, 77.25, 52.00, 46.64, 30.54, 28.33, 24.77. Exact mass calcd. (M+H) for C$_{15}$H$_{20}$BrN$_4$O$_2$: 368.0770; found: 368.0739.

(*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonylamino)-3-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)propanoate (2k). White solid, yield 71%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.53 (s, 1H), 7.82 (d, 1H, J= 9.9 Hz), 7.35 (d, 1H, J= 9.4 Hz), 5.67-5.62 (m, 1H), 4.65-4.60 (m, 1H), 3.74-3.60 (m, 2H), 1.37 (s, 18H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.28, 155.46, 149.38, 145.01, 122.87, 122.78, 122.23, 118.48, 117.59, 83.32, 77.25, 52.34, 28.17, 27.78. Exact mass calcd. (M+H) for C$_{19}$H$_{26}$N$_4$O$_4$F$_3$: 431.1906; found: 431.1888. Enantiomeric excess: 99% as determined with HPLC with a Daicel Chiralcel AD column (4.6 x 250 mm) using an isocratic mixture of 6% isopropanol in hexanes at a flow of 1 mL/min with UV detection at 220 nm.

(*R*)-*tert*-Butyl 2-(*tert*-butoxycarbonylamino)-3-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)propanoate (2l). White solid, yield 55%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.53 (s, 1H), 7.83 (d, 1H, J= 9.9 Hz), 7.36 (d, 1H, J= 9.4 Hz), 5.67-5.62 (m, 1H), 4.65-4.60 (m, 1H), 3.74-3.60 (m, 2H), 1.37 (s, 18H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.29, 155.46, 149.39, 145.01, 122.87, 122.77, 122.25, 118.48, 117.59, 83.33, 80.37, 76.75, 52.35, 28.18, 27.80. Exact mass calcd. (M+H) for C$_{19}$H$_{26}$N$_4$O$_4$F$_3$: 431.1906; found: 431.1909. Enantiomeric excess: 99% as determined with HPLC with a Daicel Chiralcel AD column (4.6 x 250 mm) using an isocratic mixture of 6% isopropanol in hexanes at a flow of 1 mL/min with UV detection at 220 nm.

(*S*)-Benzyl 4-(*tert*-butoxycarbonylamino)-4-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)butanoate (2m). White solid, 39% yield; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.86 (s, 1H), 7.81(d, 1H, J= 10 Hz), 7.42-7.3 (m, 6H), 5.5-5.4 (br, 1H), 5.32-5.25 (m, 1H), 5.12 (s, 2H), 2.8-2.58 (m, 3H), 2.53-2.4 (m, 1H), 1.42(s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.54, 155.78, 149.73, 148.32, 135.61, 128.51, 128.24, 123.34, 122.82(q, J= 272 Hz), 118.47 (q, J= 36 Hz), 117.24, 80.87, 66.58, 44.74, 30.23, 28.08, 27.92. Exact mass calcd. (M+H) for C$_{23}$H$_{25}$F$_3$N$_5$O$_4$: 479.1918; found: 479.1906.

(*S*)-Benzyl 4-(*tert*-butoxycarbonylamino)-4-(6-bromo-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)butanoate (2n). White solid, 33% yield; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.40 (s, 1H), 7.52 (d, 2H, J= 8.6 Hz), 7.27-7.19 (m, 6H), 5.29-5.2 (m, 1H), 5.2-5.1 (m, 1H), 5.02 (s, 2H), 2.58-2.52 (m, 1H), 2.5-2.48 (m, 2H), 2.33-2.28 (m, 1H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.53, 155.78,

148.86, 146.80, 135.66, 131.07, 128.53, 128.24, 123.37, 116.79, 109.06, 80.74, 66.54, 44.76, 30.22, 28.20. Exact mass calcd. (M+H) for $C_{22}H_{25}BrN_4O_4$: 489.1137; found: 489.1147.

(S)-*tert*-Butyl 2-(4-methoxyphenyl)-1-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)ethylcarbamate (2o). White solid, 48% yield; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (s, 1H), 7.77 (d, 1H, J= 10 Hz), 7.25 (d, 1H, J= 10 Hz), 7.04 (d, 2H, J= 8.8 Hz), 6.71 (d, 2H, J= 8.8 Hz), 5.65-5.55 (m, 1H), 5.5.45-5.35 (m, 1H), 3.70 (s, 3H), 3.5-3.4 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.81, 155.45, 149.44, 148.53, 130.32, 128.01, 122.99, 122.46 (q, J= 272 Hz), 117.94 (q, J= 36 Hz), 117.17, 114.06, 80.74, 55.12, 48.00, 39.80, 28.13. Exact mass calcd. (M+H) for for $C_{21}H_{23}F_3N_4O_3$: 437.1812; found: 437.1801. Elemental Analysis for $C_{21}H_{23}F_3N_4O_3$: calcd. C, 57.79%; H, 5.31%; N, 12.84%; found: C, 56.80%; H, 5.19%; N, 12.56%.

(S)-*tert*-Butyl 2-(4-methoxyphenyl)-1-(6-bromo-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)ethylcarbamate (2p). White solid, 21% yield; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 (s, 1H), 7.57 (d, 1H, J= 9.3 Hz), 7.19 (d, 1H, J= 10 Hz), 7.05 (d, 2H, J= 8.8 Hz), 6.73 (d, 2H, J= 8.2 Hz), 5.56-5.48 (m, 1H), 5.4-5.3 (m, 1H), 3.73 (s, 3H), 3.47-3.38 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) 158.74, 155.80, 149.00, 147.50, 130.74, 130.41, 128.22, 122.81, 116.65, 114.04, 108.68, 80.10, 55.23, 47.88, 39.79, 28.21. Exact mass calcd. (M+H) for $C_{20}H_{23}BrN_4O_3$: 447.1032; found: 447.1018. Elemental Analysis for $C_{20}H_{23}BrN_4O_3$: calcd. C, 53.70%; H, 5.18%; N, 12.52%; found: C, 53.63%; H, 4.88%; N, 12.49%.

(R)-(9*H*-Fluoren-9-yl)methyl 2-tert-butoxy-1-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)ethylcarbamate (2q). White solid, 27% yield; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.79 (br. s., 1H), 7.83 (d, 1H, J= 9.3 Hz), 7.74 (d, 2H, J= 7.7 Hz), 7.57 (d, 2H, J= 7.1 Hz), 7.34-7.42 (m, 3H), 7.26-7.30 (m, 2H), 6.36 (d, 1H, J=7.7 Hz), 5.44-5.50 (m, 1H), 4.43 (d, 2H, J= 7.1 Hz), 4.20 (t, 1H, J= 6.9 Hz), 4.00-4.07 (m, 1H), 3.64 (t, 1H, J= 8.5 Hz), 1.05 (s,9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ ppm 155.94, 149.76, 147.94, 143.61, 143.53, 141.22, 127.67, 126.99, 124.99, 124.09 - 124.41, 123.19, 119.93, 122.92 (q, J= 272 Hz), 117.08, 117.67 (q, 2C, J= 36 Hz), 74.35, 67.31, 64.89, 47.88, 47.03, 27.09. Exact mass calcd. (M+H) for $C_{28}H_{27}F_3N_4O_3$: 525.2114; found: 525.2102.

3-(Benzyloxymethyl)-6-bromo-*N*-pentyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-7-amine (2r). White solid, 31% yield; ^{1}H NMR (500 MHz, DMSO-D6) δ 8.80 (d, 1H, J= 2.6 Hz, 1H), 7.69 (br. s, 1H), 7.35-7.23 (m, 5H), 4.83 (s, 2H), 4.52 (s, 2H), 3.47-3.3 (m, 2H), 1.62-1.52 (m, 2H), 1.35-1.2 (m, 4H), 0.86 (t, 3H, J= 6.6 Hz). ^{13}C NMR (125 MHz, DMSO-D6) δ 153.30, 141.29, 137.58, 131.85, 128.22, 127.87, 127.63, 98.68, 71.41, 61.17, 41.43, 28.58, 27.67, 21.88, 13.88. Exact mass calcd. (M+H) for $C_{18}H_{22}BrN_5O$: 404.1086; found: 404.1096. Elemental Analysis for $C_{18}H_{22}BrN_5O$: calcd. C, 53.47%; H, 5.48%; N, 17.32%; found: C, 53.40%; H, 5.21%; N, 17.10%.

Methyl 6-bromo-7-(pentylamino)-[1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (2s). White solid, 53% yield; ^{1}H NMR (500 MHz, DMSO-D6) δ 9.02 (s, 1H), 8.43 (br. s, 1H), 3.96 (s, 3H), 3.5-3.4 (m, 2H), 1.60 (quintuplet, 2H, J= 7.4 Hz), 1.35-1.22 (m, 4H), 0.87 (t, 3H, J= 6.7 Hz). ^{13}C NMR (125 MHz, DMSO-D6) δ 156.96, 154.79, 152.60, 134.86, 133.20, 101.18, 52.92, 41.43,

28.52, 27.51, 21.83, 13.87. Exact mass calcd. (M+H) for $C_{12}H_{16}BrN_5O_2$: 342.0566; found: 342.0572.

Ethyl 2-(6-bromo-7-(pentylamino)-[1,2,4]triazolo[4,3-*a*]pyrimidin-3-yl)acetate (2t). White solid, 60% yield; ^{1}H NMR (500 MHz, DMSO-D6) δ 9.36 (s, 1H), 8.98-8.9 (m, 1H), 4.31 (s, 2H), 4.13 (q, 2H, J= 6.7 Hz), 3.52-3.44 (m, 2H), 1.61 (quintuplet, 2H, J= 7.4 Hz), 1.29 (m, 4H), 1.20 (t, 4H, J= 6.7 Hz), 0.87 (t, 3H, J= 6.7 Hz). ^{13}C NMR (125 MHz, DMSO-D6) δ 166.91, 156.30, 148.62, 139.70, 133.19, 101.01, 61.51, 41.85, 30.63, 28.45, 27.35, 21.8, 13.89. Exact mass calcd. (M+H) for $C_{14}H_{20}BrN_5O_2$: 370.0879; found: 370.0873.

Methyl 7-(benzylamino)-6-bromo-[1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (2u). White solid, 22% yield; ^{1}H NMR (500 MHz, DMSO-D6) δ 9.08 (s, 1H), 9.01-8.94 (m, 1H), 7.40-7.20 (m, 5H), 4.69 (d, 2H, J= 6.0 Hz), 3.96 (s, 3H). ^{13}C NMR (125 MHz, DMSO-D6) δ 156.94, 154.98, 152.42, 137.95, 134.97, 133.55, 128.34, 127.29, 127.04, 101.07, 52.95, 44.54. Exact mass calcd. (M+H) for $C_{14}H_{12}BrN_5O_2$: 362.0253; found: 362.0248.

References and Notes

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13. Zinc (II) azide bipyridine complex in combination with Ph_3P/DIAD has been used for azidation of alcohol see Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130.

14. A referee pointed out the following reference: Volante, R. P. *Tetrahedron Lett.* **1981,** *22*, 3119 where the formation of a precipitate was observed within 30 min upon adding DIAD to Ph_3P at a concentration of 0.4 M in THF at 0 °C. They reported that this precipitate was "essential for the success of this reaction." In our case, we observed the formation of the precipitate <u>only in the presence of TMS-N_3</u> at room temperature and a concentration of 0.1 M and as low as 0.05 M. When the substrate is present, the precipitate is often not observed or is seen only transiently. It is possible that we observed the formation of the same species as Volante and that the role of the TMS-N_3 is to speed the formation of this intermediate but the fact that we do see an azide band in the IR of the solid suggest that we have a different species.

15. General reaction conditions to form triazolopyridine **2a-2q**: DEAD (1.2 mmol, neat or 40% in toluene) was added to a solution of hydrazide (1.0 mmol), triphenylphosphine (1.2 mmol), and TMS-N_3 (1.1 mmol) in THF (0.1-1.0 M) at room temperature.   Diisopropyl azodicarboxylate (DIAD) works equally well. The reaction was found to be exothermic when performed on a larger scale (> 10 mmol). The resulting brown solution was stirred at room temperature until the reaction was complete (from minutes to 12 h). The products

were purified by silica gel chromatography using an appropriate solvent mixture (using gradients from CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2 or from hexanes to ethyl acetate).

16. General reaction conditions to form triazolopyrimidines (**2r-2u**) example **2r**: DEAD (370 µL, 2.3 mmol) was rapidly added to a solution of triphenylphosphine (493 mg, 1.88 mmol), TMS-N_3 (1.60 mmol) and 2-(benzyloxy)-N'-(5-bromo-4-(pentylamino)-pyrimidin-2-yl)acetohydrazide (661 mg, 1.57 mmol) in THF (8 mL, ~0.2 M). Gas evolution was observed and a white precipitate formed. The mixture was stirred 30 min at room temperature and at 50°C for 2 h during which time the precipitate disappeared. HCl (4N in dioxane, 5 mL) was added and the solvents were removed under a stream of nitrogen. The paste was suspended in CH_2Cl_2 (6 mL) and the white solid was filtered and dried under vacuum to give 317 mg of white solid (50% yield).

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