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Article

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TITLE

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Brett C. Bookser*, †, Michael I. Weinhouse†, Aaron C. Burns†, Andrew N. Valiere†, Lino J. Valdez†, Pawel Stanczak‡, Jim Na∫, Arnold L. Rheingold§, Curtis E. Moore§ and Brian Dyck†

Departments of †Medicinal Chemistry, ‡Structural Biology and ∫Scientific Computing, Dart NeuroScience LLC, 12278 Scripps Summit Dr., San Diego, CA 92131.

§Department of Chemistry, Crystallography Laboratory, University of California, San Diego, Urey Hall 5128, mail code 0358, 9500 Gilman Drive, La Jolla, CA 92093-0358.

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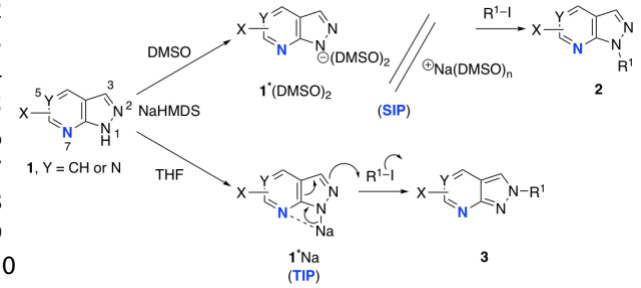


ABSTRACT

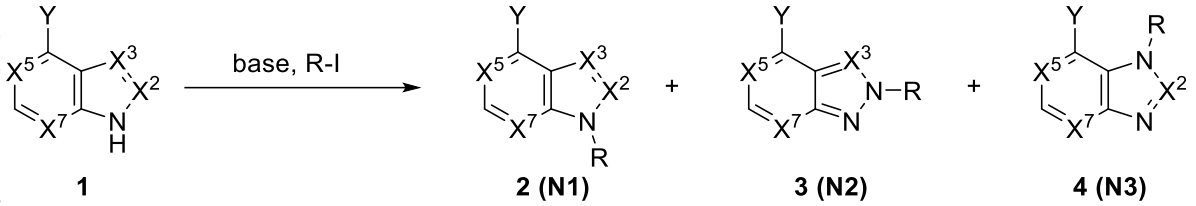
Alkylation of 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) with iodomethane in THF using NaHMDS as base selectively provided N2-methyl product 4-methoxy-2-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine (**3b**) in 8/1 ratio over N1-methyl product (**2b**). Interestingly, conducting the reaction in DMSO reversed selectivity to provide a 4/1 ratio of N1/N2 methylated products. Crystal structures of product **3b** with N1 and N7 coordinated to sodium indicated a potential role for the latter reinforcing the N2-selectivity. Limits of selectivity were tested with 26 heterocycles which revealed that N7 was a controlling element directing alkylations to favor N2 for pyrazolo- and N3 for imidazo- and triazolo-fused ring heterocycles when conducted in THF. Use of ^{1}H-detected pulsed field gradient-stimulated echo (PFG-STE) NMR defined the molecular weights of ionic reactive complexes. This data and DFT charge distribution calculations suggest close ion pairs (CIPs) or tight ion pairs (TIPs) control alkylation selectivity in THF and solvent separated ion pairs (SIPs) are the reactive species in DMSO.

INTRODUCTION

Fused 5,6-ring systems are found in 52 of the 100 top selling drugs.[1] In addition, nitrogen containing heterocycles are contained in 59% of small-molecule drugs.[2] Of these ring systems, the purine ring is the second most common fused ring nitrogen heterocycle.[2] The prevalence is so common in drug discovery[3] that the purine ring and similar 5,6-fused ring heterocycles have been described as "privileged structures".[4] This may be a logical consequence of the importance of purine rings in a myriad of biological processes. Many drug discovery efforts towards purine recognizing targets involve creative mimicking of the endogenous purine core. This is the case for kinases,[5] purine

receptors,[6] phosphodiesterases[7] and other important biological targets. Additionally, it has been observed that incorporation of an N atom to replace an aromatic CH group may provide substantial gains in potency and physical chemical properties in drug discovery lead compounds.[8] Synthetic access to these types of compounds often involves substitution reactions of commercially available N-containing heteroaryls. Perhaps the simplest of these reactions is *N*-alkylation of a heteroaryl NH-position. Our understanding of how to perform this reaction in a site-selective manner on purine and purine-like ring systems continues to grow.[9] Yet, challenges remain, as the ambident nature of the azole ring anion complicates the ability to achieve site-selective *N*-alkylation (see Table 1).

Table 1. Azolo-Fused Ring Heterocycle *N*-Alkylations Explored.



1 **2 (N1)** **3 (N2)** **4 (N3)**

ring name (**1**)	X^2	X^3	X^5	X^7
1*H*-Indazole	N	CH	CH	CH
1*H*-Pyrazolo[4,3-*c*]pyridine	N	CH	N	CH
1*H*-Pyrazolo[3,4-*b*]pyridine	N	CH	CH	N
1*H*-Pyrazolo[3,4-*d*]pyrimidine	N	CH	N	N
1*H*-Benzo[*d*]imidazole	CH	N	CH	CH
1*H*-Imidazo[4,5-*c*]pyridine	CH	N	N	CH
3*H*-Imidazo[4,5-*b*]pyridine	CH	N	CH	N
9*H*-Purine	CH	N	N	N
1*H*-Benzo[*d*][1,2,3]triazole	N	N	CH	CH
1*H*-[1,2,3]Triazolo[4,5-*c*]pyridine	N	N	N	CH
3*H*-[1,2,3]Triazolo[4,5-*b*]pyridine	N	N	CH	N

In medicinal chemistry these ring systems can become central core structural elements. In the example depicted in Figure 1, combining N1-, N2-, and N3-alkylations with the three possible mono-substitutions of the six-member ring, minimally nine different two-vector combinations are conceivable. Having site-control of the azole ring alkylation provides the ability to design compound structures to have specific size, shape and electronic features to complement protein binding pockets and achieve the highly potent, and specific binding interactions necessary to impact the biological function desired for a pharmacological effect. On the contrary, compound library synthesis methods which produce an equal distribution of alkylation products from each core heterocycle, *i.e.* all azole nitrogen sites being alkylated equally, may also be an advantage.

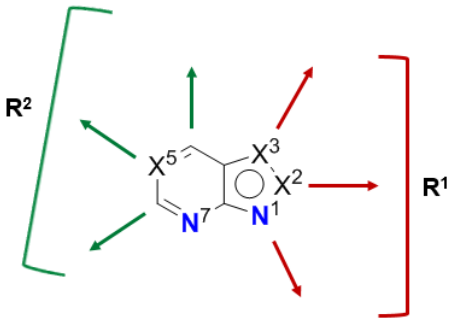


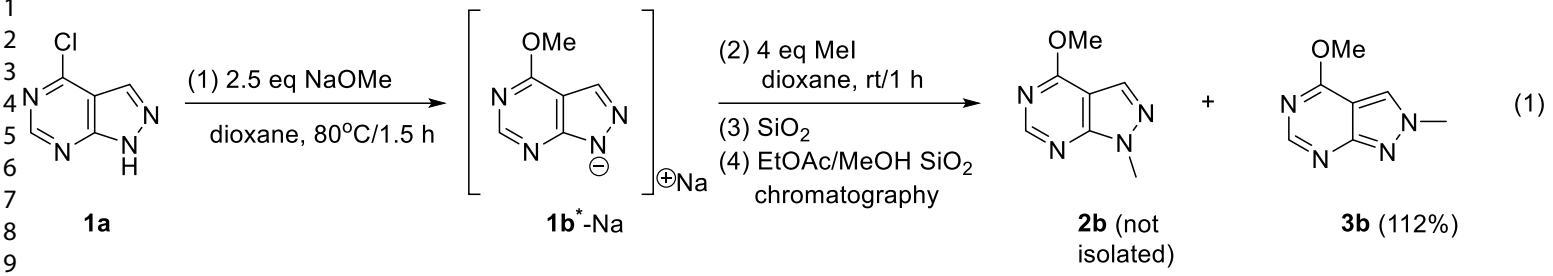
Figure 1. Possible Vector Substitution Patterns in a 6-5 Ring System.

This report presents our study of the alkylation of the ring systems in Table 1 and how the X-ray crystal structure determination of one of the reaction products inspired a strategy to predict alkylation outcomes depending on the nature of the azole, the solvent and the presence or absence of a N7 nitrogen atom.

RESULTS AND DISCUSSION

The alkylation of 1*H*-pyrazolo[3,4-*d*]pyrimidines has typically been observed to be selective for N1 in various conditions such as phase transfer catalysis in benzene,[10] Cs_2CO_3 in DMF,[11] or Mitsunobu conditions in THF.[12] One exception to this trend showed N2-alkylation selectivity for the specific heterocycle, 4,6-bis(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidine, under conditions of NaH in THF.[13] In our investigations of the one-pot S_NAr/alkylation reaction of **1a**, selective production of **3b**[10] was observed and gravimetrically determined to be produced in greater than

100% yield (Equation 1, **2b** was not isolated in this experiment). Various NMR experiments (^{1}H, ^{13}C, 2D NOESY and 2D HMBC experiments in DMSO-d_6, $CDCl_3$, THF-d_8, and methanol-d_4) on the product produced identical data to that observed for authentic compound **3b**.[10] However, X-ray crystallography (see Figure 2) and microanalysis revealed this product to be **3b** complexed with sodium iodide and water in the variable formula $[\mathbf{3b}]_x[NaI]_y[H_2O]_z$ (**5**) which corrected the observed yield to 65% based on the heavier of the two complexes, **5b**.



Upon ethyl acetate/hexane recrystallization, two different crystal forms were identified with defined oligomer complexes $[\mathbf{3b}]_3[NaI]_2[H_2O]_6$ (**5a**) and $[\mathbf{3b}]_4[NaI]_3[H_2O]_2$ (**5b**) (Figure 2). These structures represent the first reported pyrazolo[3,4-*d*]pyrimidine complexes with sodium ions. The exact nature of the complex seems to be dependent on the availability of water with the higher hydrated complex **5a** fully separating the sodium and iodide ions. The relative geometry of N1 to N7 is nearly ideal to form neighboring apical ligand bonds both above and below two sodium ions in C_{2h} symmetric orientation in **5a**.[14] Six water molecules occupy the equatorial binding sites of the side-by-side octahedral sodium binding complexes. The N1-Na1 and N7-Na1' bond distances average 2.540 Å which agrees with previously published coordination complexes of sodium with pyrazolo[15]or pyrimidinyl[16] nitrogens. The Na-Na distance in **5a**, of 3.292 Å is more compressed, enforced by the N1 and N7 bonds, compared to that of the simple water bridged NaI complex $(NaI)_2(H_2O)_4$ which is 3.56 Å.[17] By comparison, complex **5b** with only two water molecules, instead of the six as in **5a**, contains sodium atoms bridged by iodides and water molecules similar to the reference compound $(NaI)_2(H_2O)_4$.[17] Yet similar to complex **5a**, the pyrazolopyrimidine N1 and N7 of **5b** occupy apical ligand bonds with N1-Na1 and N7B-Na2 bond distances averaging 2.511 Å. Interestingly, in order to accommodate bridging iodides, the heterocycles turn 90 degrees on the apical axis relative to complex **5a**. Also, in another striking difference, apical bonding is N1-Na1-N1' in **5b** but is N1-Na1-N7' in **5a**. The Na1-Na2 intra-atomic distance is 3.951 Å in **5b** where the sodium atoms are bridged simultaneously by water and iodide. This distance, 0.656 Å longer than the Na1-Na1' length

in **5a**, is appropriate since it falls approximately in the middle of Na-Na distances bridged individually by water (3.56 Å) or iodide (4.51 Å) in the reference compound $(NaI)_2(H_2O)_4$.[17]

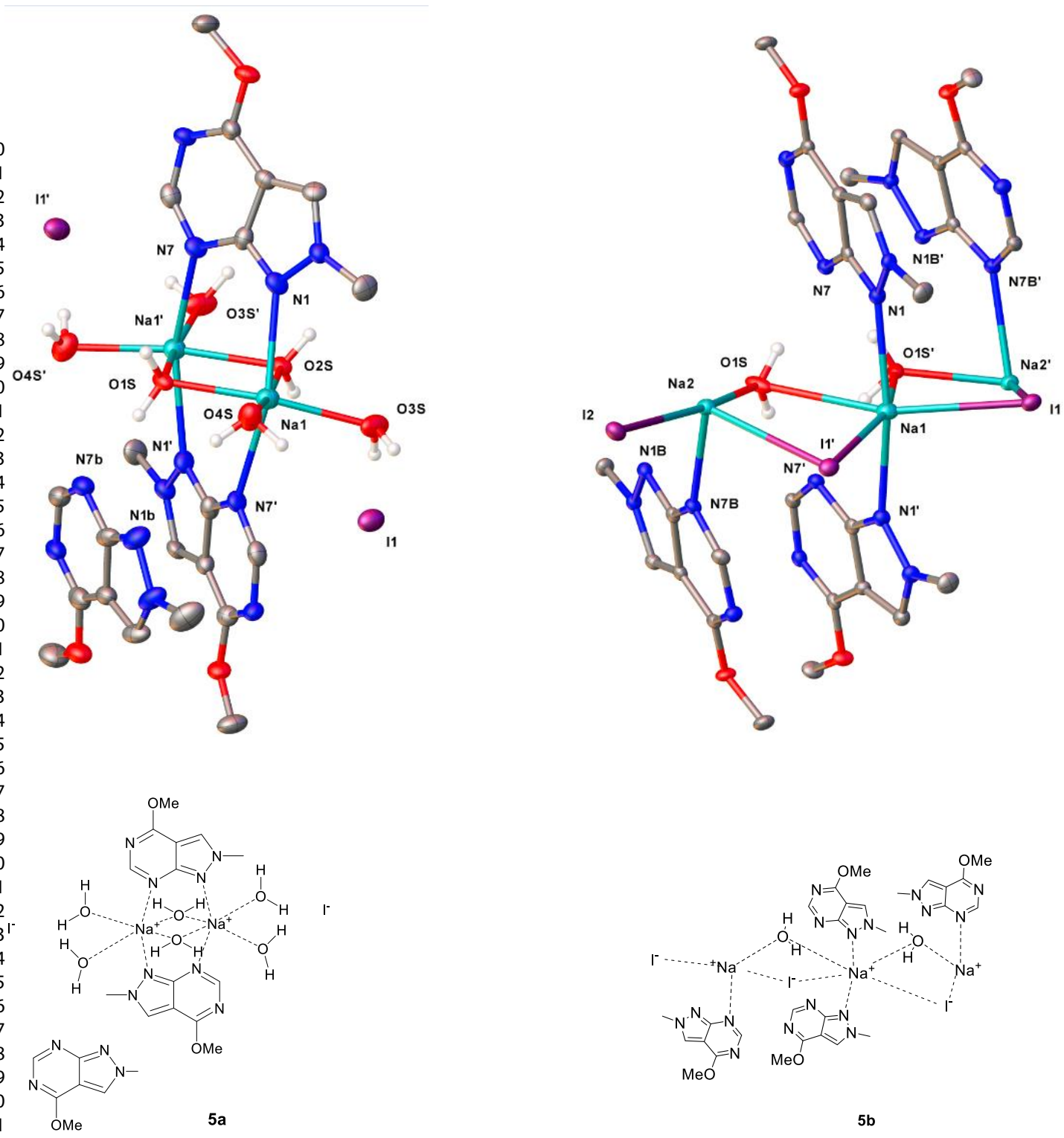
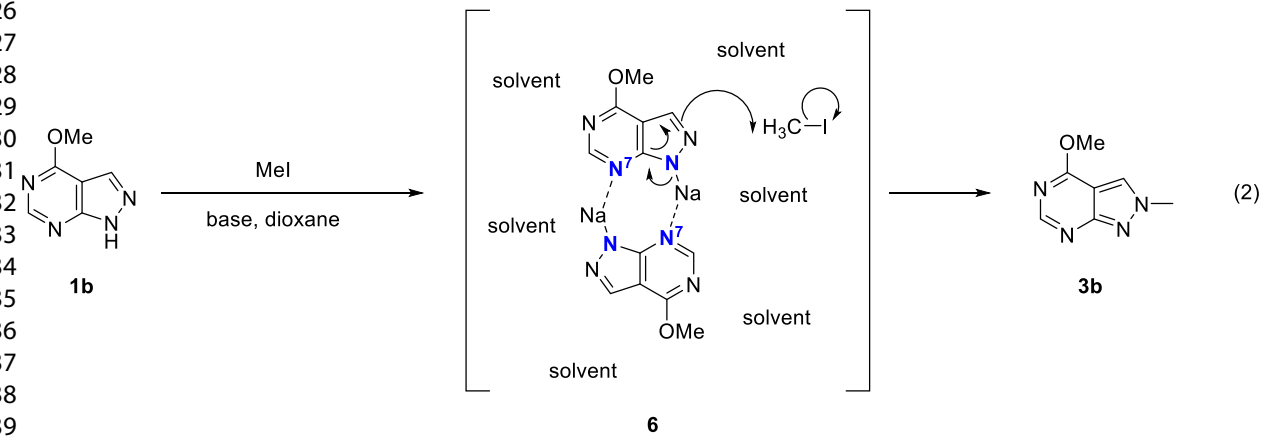


Figure 2. X-ray Crystal Structure Forms of $[3b]_x[NaI]_y[H_2O]_z$ (5), ellipsoid contours for each at 50% probability. Selected bond lengths (Å), **5a**: Na1-Na1' 3.295(5), Na1-N1 2.534(6), Na1-N7' 2.546(5); **5b**: Na1-Na2

3.951(11), Na2-N7B 2.502 (2), Na1-N1 2.519(2). Selected bond angles (deg), **5a**: O1S-Na1-O3S 170.03(19), O2S-Na1-O4S 172.04(17), N1-Na1-N7' 158.88(19), Na1'-O1S-Na1 89.9(3), Na1'-O2S-Na1 87.7(3); **5b**: Na1-I1-Na2' 77.26(3), N1'-Na1-N1 165.45(11), Na2-O1S-Na1 93.96(7), O1S-Na2-I2 173.46(6), O1S'-Na1-I1' 158.14(5).

These crystal structures indicate that N1 and N7 of compound **3b** can have ligand bonding interactions with sodium in the solid state. The association with sodium iodide is maintained through silica gel chromatography indicating solution state association as well. These observations resulted in a hypothesis that the selective N2 alkylation of **1b** to form **3b** required N7 as a controlling factor. A mnemonic based on the crystal structure **5a** was thus created to help rationalize the selectivity (see Equation 2). In less polar solvents like dioxane or THF, if the anion **1b*** forms a tight ion pair or ion pair dimer (see intermediate **6** for example, Equation 2), then N1-alkylation is limited and thus N2-alkylation preferred. This observed N2-selectivity was optimized on **1b** and the hypothesis tested on heterocycles with and without N7.



(2)

In the optimization study, the alkylation of **1b** with iodomethane was studied in detail with N1/N2 (**2b**/**3b**) alkylation product ratios determined by HPLC of the crude products then confirmed by chromatographic purification. Solvent choice proved to be the primary factor determining alkylation selectivity under a variety of conditions as shown in Table 2. Less polar solvents like dioxane (entries 1-3) and THF (entries 4-5) favored production of the N2-methyl product **3b** with the N1/N2 (**2b**/**3b**) product ratios varying from 1/5 to 1/10. Toluene and acetonitrile were ineffective as solvents perhaps due to solubility limitations (entries 9-10). Polar solvents DMSO (entries 6-7), DMF (entry 11) and DMPU (entry 12) reversed the selectivity to favor production of the N1-product **2b** with ratios of **2b**/**3b**

of 2/1 to 5/1. Thus, for substrate **1b**, N2-site-selectivity can be effected by choosing THF or dioxane to preferentially provide **3b** (69% yield, entry 4) consistent with a tight ion pair (similar to **6**) favoring reactivity at N2. Use of DMSO and other polar solvents selectively provided **2b** (55% yield, entry 6) consistent with a solvent separated ion pair and permitting the more reactive solvated nitrogen anion to be alkylated. Notably, conducting the reaction in 10:1 THF/DMSO produced a 1:1 distribution of **2b**/**3b** (entry 8).

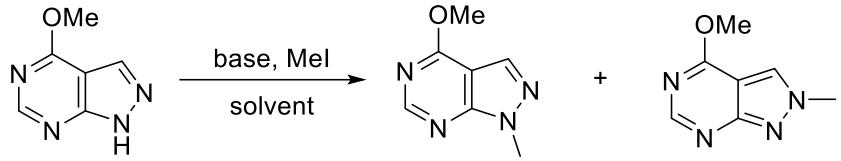
In this table and subsequent tables, most often 3 equivalents of iodomethane or other electrophile were used as the alkylating reagent. The reaction also occurs with essentially the same product composition when 1.5 equivalents of electrophile are used, compare entries 4 to 5 and 6 to 7, except more time is required for the reactions to go to completion.

Like NaHMDS, other strong bases with counter-ions Li, Na, and K, which can irreversibly deprotonate **1b**, provided similar product ratios in THF or DMSO (entries 13-19). Since the bases typically were THF solutions, each DMSO reaction was technically 3:1 DMSO/THF. Moreover, rigorously excluding THF by employing solid NaO*t*-Bu in DMSO, resulted in no further N1 selectivity, (see entries 17 and 18).

Larger cations, such as those derived by reactions with bases DBU (entry 23), P_2-Et (entries 24-26) and Cs_2CO_3 (entries 30-31) also did not provide selectivity for the N2 product **3b** and instead favored N1 (**2b**) in THF and provided increased N1/N2 product ratios when conducted in DMSO (entries 26 and 31). This is consistent with the cation being too large to form an effective tight ion-pair with N1.

Grignard reagents such as *t*-BuMgCl and MeMgCl were not effective bases (entries 20-21) providing for complete recovery of the heterocycle **1b**. Compare this to the use of MeMgCl to provide selective N7-alkylpurine products.[9] Other weak bases such as Hünig's base, Li_2CO_3, Na_2CO_3, and K_2CO_3 were ineffective in THF (entries 22, 27-29).

Table 2. Regioselective *N*-Alkylation Optimization[a]



1b **2b** **3b**

entry	base	solvent	temp/time	**2b**[b] (yield)[c]	**3b**[b] (yield)[c]	**1b**[b]	**2b**/**3b**[d]
1	NaOMe	dioxane	80 ˚C/24h	8	72 (60)	5	1/9
2	NaHMDS	dioxane	80 ˚C/0.5h	8	82 (48)	10	1/10
3	NaHMDS	dioxane	20 ˚C/7h	11 (8)	77 (45)	5	1/7
4	NaHMDS	THF	20 ˚C/1h	11 (8)	89 (69)	0	1/8
5[e]	NaHMDS	THF	20 ˚C/24h	16 (0)	84 (68)	1 (2)	1/5
6	NaHMDS	DMSO	20 ˚C/1h	73 (55)	22 (13)	5 (6)	3/1
7[e]	NaHMDS	DMSO	20 ˚C/48h	65 (52)	29 (18)	6 (9)	2/1
8	NaHMDS	10-1 THF/DMSO	20 ˚C/1h	44 (38)	55 (40)	0	1/1
9	NaHMDS	toluene	20 ˚C/3h	0	0	100	--
10	NaHMDS	acetonitrile	20 ˚C/3h	0	11	89	--
11	NaHMDS	DMF	20 ˚C/1h	69	27	4	3/1
12	NaHMDS	DMPU	20 ˚C/1h	63	14	0	5/1
13	LiHMDS	THF	20 ˚C/7h	15	85	0	1/6
14	KHMDS	THF	20 ˚C/4h	17 (9)	81 (54)	2	1/5
15	LiO*t*-Bu	THF	20 ˚C/5h	14 (6)	86 (47)	0	1/6
16	NaO*t*-Bu	THF	20 ˚C/0.5h	9 (8)	89 (58)	2	1/10
17	NaO*t*-Bu	DMSO	20 ˚C/1h	62 (29)	25 (15)	12 (15)	2/1
18	NaO*t*-Bu[f]	DMSO	20 ˚C/1h	70 (37)	30 (18)	0	2/1
19	KO*t*-Bu	THF	20 ˚C/5h	11 (11)	84 (48)	3	1/8
20	*t*-BuMgCl	THF	20 ˚C/6h	0	1	99	--
21	MeMgCl	THF	50 ˚C/24h	0	0	100	--
22	Hünig's base	THF	66 ˚C/7h	1	1	97	--
23	DBU	THF	66 ˚C/5h	61	31	8	2/1
24	P_2-Et[g]	THF	20 ˚C/5min	80 (55)	20	0	4/1

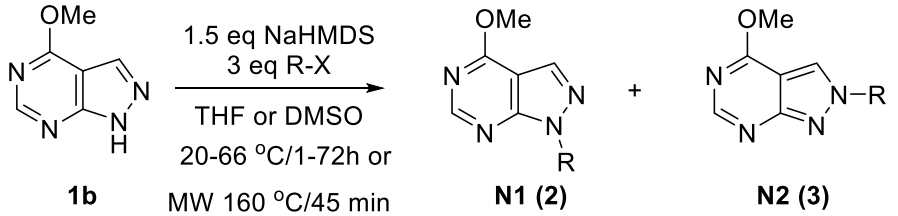
25	P_2-Et[g]	THF	-78 ˚C/0.5h	60 (27)	36 (2)	4	2/1
26	P_2-Et[g]	DMSO	20 ˚C/0.5h	85 (63)	15 (16)	0	6/1
27	Li_2CO_3	THF	65 ˚C/24h	0.4	0.6	99	--
28	Na_2CO_3	THF	66 ˚C/5h	2	6	92	--
29	K_2CO_3	THF	66 ˚C/5h	13	53	32	1/4
30	Cs_2CO_3	THF	66 ˚C/1h	40	57	3	1/1
31	Cs_2CO_3	DMSO	20 ˚C/3h	77	18	5	4/1

[a]Standard reaction conditions: compound **1b** (100 mg, 0.67 mmol) was dissolved or suspended in 3.3 mL of solvent at 0 ˚C (except DMSO reactions were started at 15 ˚C), base (1 mmol) as a solution or solid (MHMDS and MO*t*-Bu with M = Li, Na, K; and *t*-BuMgCl were 1 or 2 M solutions in THF unless noted otherwise) was added followed by iodomethane (0.12 mL, 2 mmol) and the mixture was stirred at the designated temperature for the designated time. Then the mixture was diluted with CH_2Cl_2 and aqueous 1 M NH_4Cl, the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3×). The combined organic extracts were dried ($MgSO_4$) and evaporated to crude product residue. [b]HPLC % composition determined from the crude product residue at 220 nm. [c]Isolated % yield after subjecting the crude product residue to SiO_2 chromatography through a 12 g SiO_2 column eluted with a gradient of 10-100% ethyl acetate in heptane. [d]Ratio of HPLC peak areas. [e]Performed with 1.5 instead of 3 equivalents of MeI (1 mmol). [f]Solid NaO*t*-Bu was used. [g]N'''-[bis(dimethylamino)(ethylimino)phosphoranyl]-N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide.

With the systems NaHMDS/THF and NaHMDS/DMSO established to selectively produce either **2b** or **3b** upon reaction of **1b** with iodomethane, the scope of the alkylation of **1b** was investigated with other electrophiles (Table 3).[18] As expected, in THF, the alkylations generally occurred selectively on the N2 position with isolated yield ratios of N1/N2 (**2**/**3**) ranging from 1:2 (entry 9) to 1:17 (entry 2). Some THF reactions with hindered alkyl halide electrophiles, entries 3, 4, 6, 7, and 10, were slow to react at room temperature (20 ˚C) and required higher temperatures (microwave heating at 160 ˚C/0.75 h) to reach completion. Isolated yields of the major N2-products (**3**) from reactions conducted in THF were mostly > 50%. With very reactive electrophiles, entries 9 and 11, N2 selectivity became weaker. In the glycosylation reaction in THF (entry 11), no selectivity was observed and yet a higher yield of N2-product was obtained (1:1 N1/N2 ratio) compared to previous reports.[19]

By comparison, reactions in DMSO, with all but two electrophiles (entries 6 and 10) showed N1-selectivity (N1/N2, **2**/**3** ratios of 2:1 up to 19:1, see Table 3). All DMSO reactions were performed at 20 ˚C. In general, yields of the major products, **2**, were satisfactory except for the challenging 4-iodotetrahydro-2*H*-pyran electrophile, entry 10.

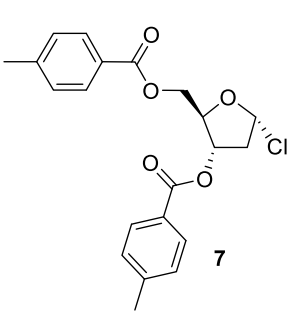
Table 3. Alkylation of 4-Methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (1b)[a]

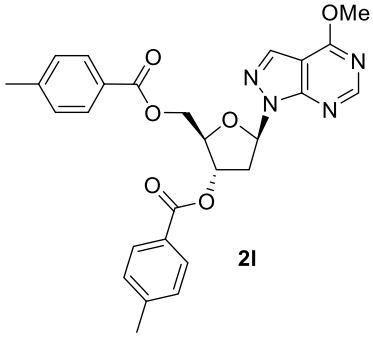


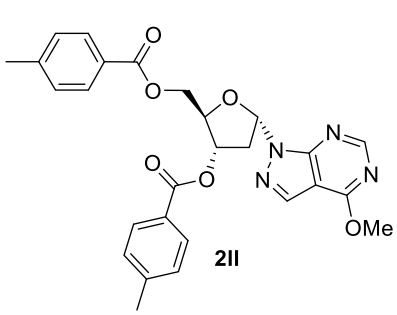
			THF/DMSO		in THF[b]			in DMSO[b]		
entry	**R-X**	**temp (°C)**	**time (h)**	**N1 (%)**	**N2 (%)**	**N1/N2**	**N1 (%)**	**N2 (%)**	**N1/N2**
1	Me-I	20/20	1/1	**2b** (8)	**3b** (69)	1/9	**2b** (55)	**3b** (13)	4/1
2	Et-I	20/20	24/0.5	**2c** (4)	**3c** (66)	1/17	**2c** (67)	**3c** (13)	5/1
3	*i*-Pr-I	160/20	0.75/1.5	**2d** (6)	**3d** (32)	1/5	**2d** (41)	**3d** (9)	5/1
4[c]	1-iodo-2-methylpropane	160/20	0.75/144	**2e** (7)	**3e** (57)	1/8	**2e** (37)	**3e** (11)	3/1
5	(bromomethyl)cyclopropane	65/20	48/144	**2f** (10)	**3f** (50)	1/5	**2f** (42)	**3f** (9)	5/1
6	benzyl chloride	160/20	0.75/1	**2g** (4)	**3g** (56)	1/14	**2g** (40)	**3g** (41)	1/1
7	1-bromo-2-methoxyethane	160/20	0.75/20	**2h** (18)	**3h** (48)	1/3	**2h** (57)	**3h** (3)	19/1
8	3,3-dimethylallyl bromide	20/20	2/3	**2i** (4)	**3i** (56)	1/14	**2i** (50)	**3i** (0)	>10/1
9	ethyl 2-chloroacetate	20/20	16/3	**2j** (28)	**3j** (57)	1/2	**2j** (59)	**3j** (24)	2/1
10	4-iodotetrahydro-2*H*-pyran	160/20	0.75/19	**2k** (0)	**3k** (10)	<1/10	**2k** (6)	**3k** (4)	1/1
11[d]	compound **7**	20/20	4/1	**2l** (32) **2ll** (2)	**3l** (28)	1/1	**2l** (24) **2ll** (7)	**3l** (12)	2/1

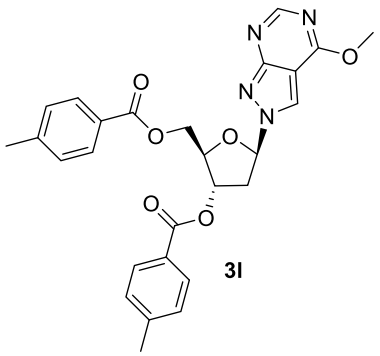
[a]See standard reaction conditions as described in Table 1 substituting R-X for methyl iodide. [b]Chromatographically isolated yields. [c]Experiment in THF conducted with 3 mmol **1b**. [d]Only 1.5 equivalents of compound **7** was used.

Structures:





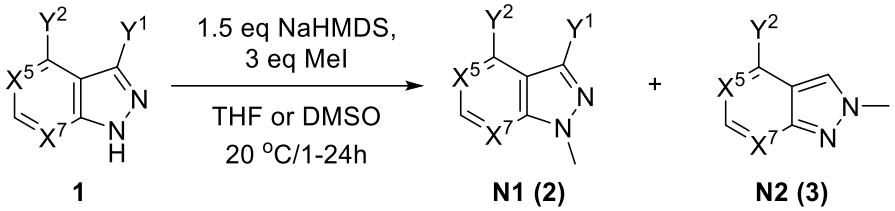


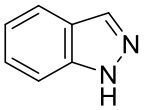
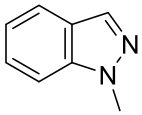
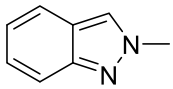
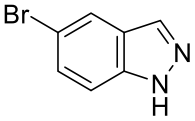
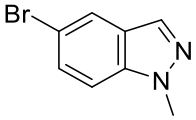
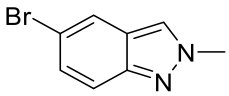
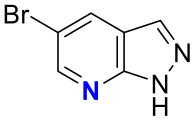
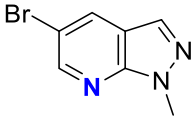
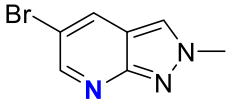
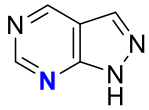
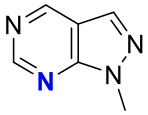
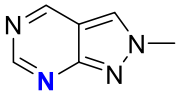
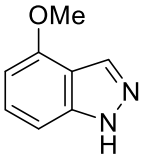
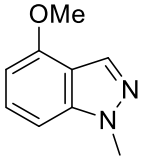
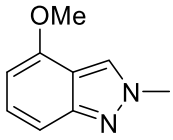


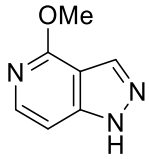
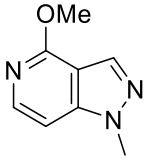
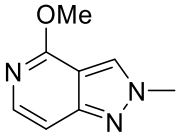
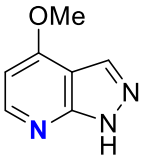
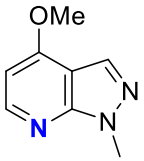
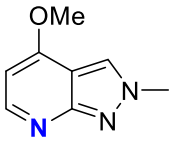
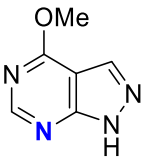
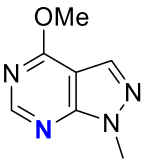
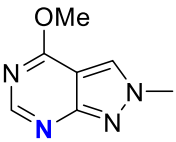
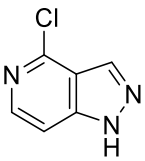
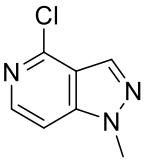
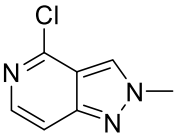
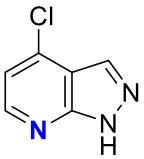
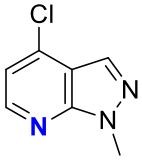
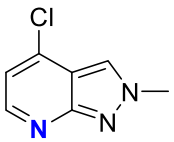
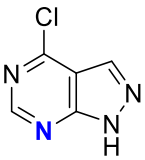
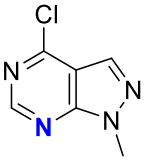
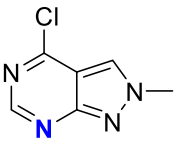
The N7-atom contributes key ligand-bonding interactions with sodium in the crystal structures **5a** and **5b** (Figure 2). To gauge the role of N7 in N2-alkylation site-selectivity in THF, 15 pyrazolo-fused rings with either CH or

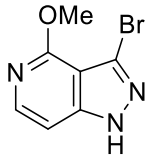
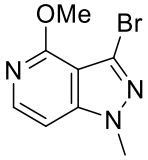
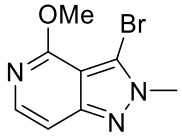
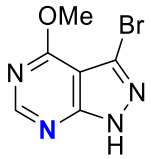
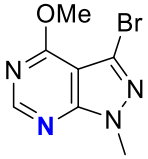
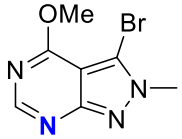
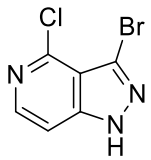
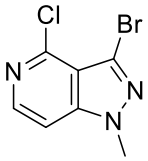
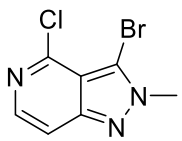
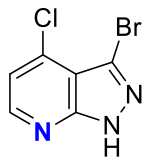
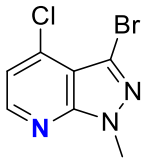
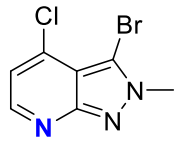
N at position 7 were compared (see Table 4).[18] Heterocycles were chosen with additional substituents that would be of interest in medicinal chemistry for exploring a variety of substitution vectors (see Figure 1). In entries 1-4, heterocycles with CH instead of N in position 7 (**1m** and **1n**), showed no N2-selectivity in THF. Introduction of N7 in similar heterocycles **1o** and **1p**, entries 5-8, in THF showed 1:10 and 1:5 N1/N2 ratios, respectively; while in DMSO the selectivity reversed to 15:1 and 9:1 N1/N2, respectively. Heterocycles with a 4-methoxy substituent, entries 9-16, showed similar N1/N2 selectivity effects when comparing THF to DMSO which was dependent on the presence of N7. Heterocycles having CH instead of N in position 7, **1q** and **1r**, provided N1-selective alkylation in both solvents. But heterocycles containing N7, **1s** and **1b** (*vida supra*) provided for N2-selectivity in THF, which again reversed to N1 when conducted in DMSO. Heterocycles containing a 4-chloro substituent had the same selectivity profile (entries 17-22). Finally, the influence of steric hindrance from a 3-bromo substituent did little to redirect the THF alkylation away from N2 when N7 was present (entries 25 and 29) giving 1:2 N1/N2 alkylation selectivity while heterocycles having CH in position 7 showed good N1-selectivity (4:1 to >10:1) in both THF and DMSO (entries 23, 24, 27 and 28). This study emphasized the importance of N7 to achieving N2-selective alkylation in THF. When CH was present instead of N in position 7, alkylation almost always favored N1 in both solvents. Moreover, all of these heterocycles favored N1-alkylation in DMSO.

Table 4. Application to Other Pyrazolo-fused Ring Heterocycles[a]



entry	heterocycle	time (h)	solvent	N1 (%)[b]	N2 (%)[b]	N1/N2
						
1	**1m**	96	THF	**2m** (49)	**3m** (31)	2/1
2	**1m**	1	DMSO	**2m** (45)	**3m** (17)	3/1
						
3[c]	**1n**	5	THF	**2n** (44)	**3n** (42)	1/1
4	**1n**	4	DMSO	**2n** (48)	**3n** (15)	3/1
						
5	**1o**	2	THF	**2o** (7)	**3o** (69)	1/10
6	**1o**	4	DMSO	**2o** (46)	**3o** (3)	15/1
						
7	**1p**	4	THF	**2p** (8)	**3p** (38)	1/5
8	**1p**	4	DMSO	**2p** (27)	**3p** (3)	9/1
						
9	**1q**	2	THF	**2q** (57)	**3q** (25)	2/1
10	**1q**	2	DMSO	**2q** (65)	**3q** (23)	3/1

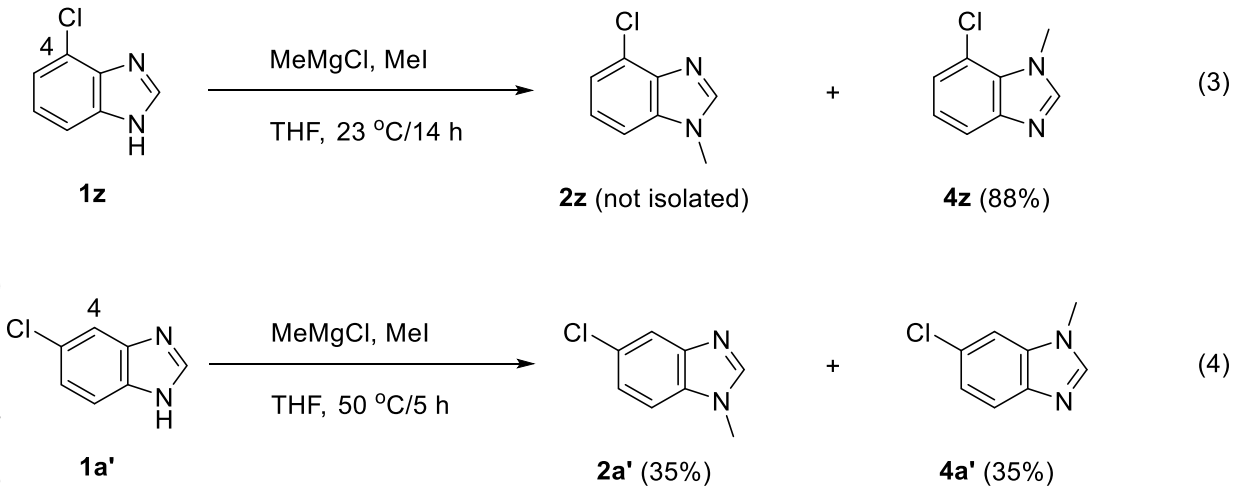
						
11	**1r**	2	THF	**2r** (50)	**3r** (35)	3/2
12	**1r**	2	DMSO	**2r** (46)	**3r** (18)	3/1
						
13	**1s**	2	THF	**2s** (5)	**3s** (30)	1/6
14	**1s**	2	DMSO	**2s** (67)	**3s** (5)	13/1
						
15	**1b**	1	THF	**2b** (8)	**3b** (69)	1/8
16	**1b**	1	DMSO	**2b** (55)	**3b** (13)	4/1
						
17	**1t**	16	THF	**2t** (43)	**3t** (39)	1/1
18	**1t**	1	DMSO	**2t** (52)	**3t** (27)	2/1
						
19	**1u**	4	THF	**2u** (11)	**3u** (81)	1/8
20	**1u**	1	DMSO	**2u** (44)	**3u** (0)	>10/1
						
21	**1a**	1.5	THF	**2a** (6)	**3a** (36)	1/6
22	**1a**	1.5	DMSO	**2a** (47)	**3a** (11)	4/1

						
23	**1v**	4	THF	**2v** (63)	**3v** (15)	4/1
24	**1v**	4	DMSO	**2v** (56)	**3v** (7)	8/1
						
25	**1w**	24	THF	**2w** (27)	**3w** (47)	1/2
26	**1w**	1	DMSO	**2w** (80)	**3w** (7)	11/1
						
27	**1x**	16	THF	**2x** (61)	**3x** (10)	6/1
28	**1x**	4	DMSO	**2x** (67)	**3x** (0)	>10/1
						
29	**1y**	16	THF	**2y** (25)	**3y** (43)	1/2
30	**1y**	16	DMSO	**2y** (66)	**3y** (0)	>10/1

[a]See standard reaction conditions as described in Table 1. [b]Chromatographically isolated yields.
[c]See ref. 20a for methylation of **1n** in THF.

In a recent report on selective N3-alkylation of imidazo-fused heterocycles using MeMgCl and THF,[9] it was observed that a steric component was necessary to drive the selectivity (see Scheme 1). For example, 4-chloro substrate **1z** exhibited complete N3-selectivity to product **4z** while 4-H substrate **1a'** was alkylated with no selectivity to products **2a'** and **4a'** (see Equations 3 and 4). Thus, it was of interest to evaluate whether N1 *vs* N3 alkylation site selectivity could be influenced in imidazo-fused ring heterocycles when a proximal nitrogen atom (N7) was present, and especially test whether selectivity would be independent of steric influence.

Scheme 1. **Literature N3-Selective Imidazo-Fused Ring Alkylation**[a]

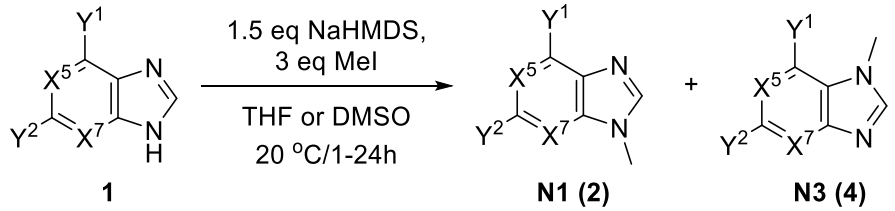


[a]See ref. 9.

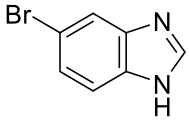
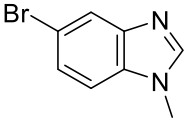
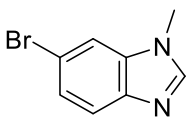
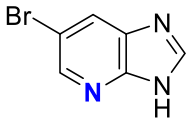
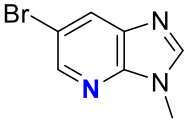
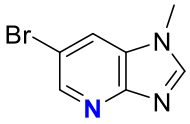
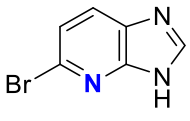
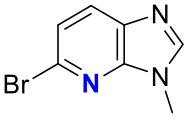
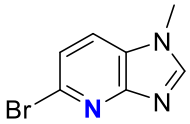
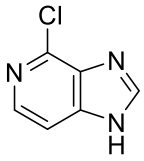
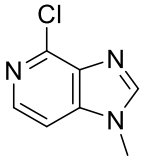
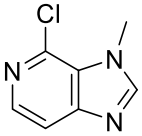
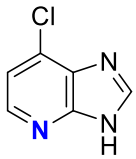
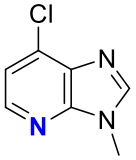
Table 5 shows the application of our method to imidazo-fused ring heterocycles.[18] Entries 1-6 confirmed the N7-effect also applies to this ring type with heterocycles unsubstituted at C4. Alkylation of N3 is preferred with N7-containing heterocycles in THF where heterocycles **1c'** and **1d'** provided 1:4 and 1:3 N1/N3-alkylation ratios, respectively, with major products **4c'** (54%) and **4d'** (66%) thus adding a N3-selective alkylation to this structure type. The N7 effect was further confirmed with 4-chloro substituted ring systems in entries 7-15. Heterocycles **1f'** and **1h'** selectively provided **4f'** (56%) and **4h'** (55%) in THF reactions while heterocycle **1g'** provided the lowest N1 to N3 selectivity switch going from DMSO (3:1) to THF (1:1). Of note, heterocycles **1e'**, **1f'**, **1g'** and **1h'** have been demonstrated to selectively alkylate N3 with the MeMgCl/THF method.[9]

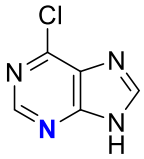
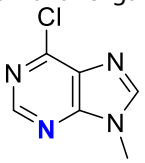
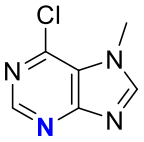
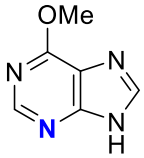
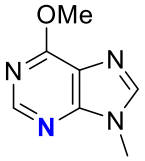
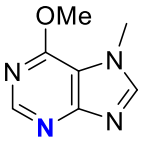
The reaction in DMSO favored the N1 products with heterocycles **1c'**, **1f'**, **1g'** and **1h'**. Also, similar to entry 8 in Table 2, with heterocycles **1e'**[21] and **1f'**, a 10:1 THF/DMSO solvent ratio provided a 1:1 N1/N3 ratio for product pairs **2e'**/**4e'** and **2f'**/**4f'**.

Table 5. Application to Imidazo-fused Ring Heterocycles[a]



1 **N1 (2)** **N3 (4)**

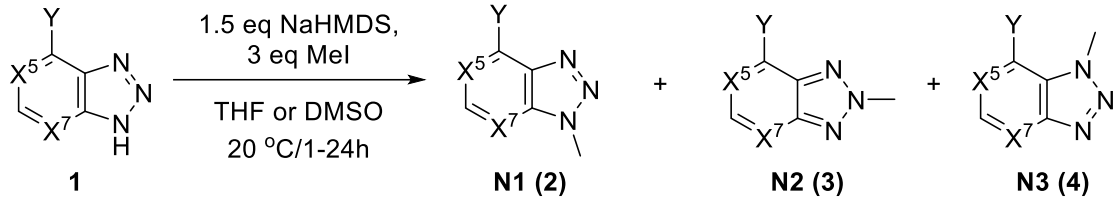
entry	heterocycle	time (h)	solvent	N1 (%)[b]	N3 (%)[b]	N1/N3
						
1	**1b'**	2	THF	**2b'** (52)	**4b'** (52)	1/1
2	**1b'**	2	DMSO	**2b'** (33)	**4b'** (33)	1/1
						
3	**1c'**	2	THF	**2c'** (14)	**4c'** (54)	1/4
4	**1c'**	2	DMSO	**2c'** (37)	**4c'** (6)	6/1
						
5	**1d'**	1.5	THF	**2d'** (19)	**4d'** (66)	1/3
6	**1d'**	1.5	DMSO	**2d'** (46)	**4d'** (37)	1/1
						
7[c]	**1e'**	3	THF/DMSO	**2e'** (42)	**4e'** (32)	1/1
8	**1e'**	3	DMSO	**2e'** (28)	**4e'** (24)	1/1
						
9	**1f'**	2	THF	**2f'** (18)	**4f'** (56)	1/3
10[c]	**1f'**	1.5	THF/DMSO	**2f'** (33)	**4f'** (29)	1/1
11	**1f'**	96	DMSO	**2f'** (34)	**4f'** (14)	2/1

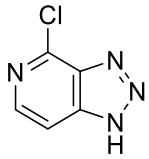
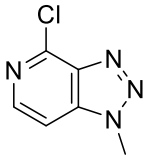
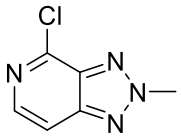
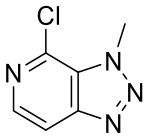
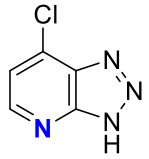
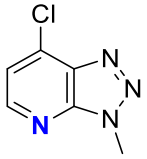
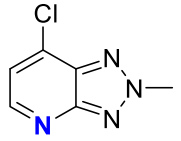
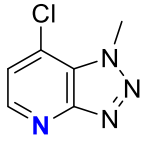
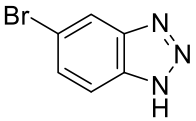
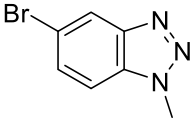
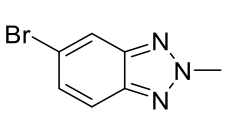
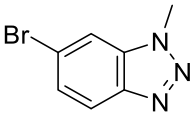
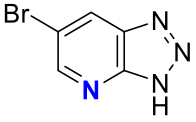
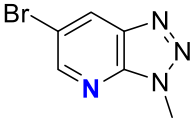
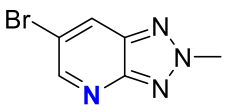
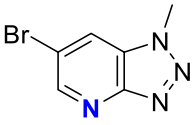
						
12	**1g'**	5	THF	**2g'** (33)	**4g'** (42)	1/1
13	**1g'**	5	DMSO	**2g'** (40)	**4g'** (15)	3/1
						
14	**1h'**	1.5	THF	**2h'** (25)	**4h'** (55)	1/2
15	**1h'**	1.5	DMSO	**2h'** (41)	**4h'** (23)	2/1

[a]See standard reaction conditions as described in Table 1. [b]Chromatographically isolated yields. [c]Conducted in 10:1 THF/DMSO.

Finally, very little study has been made of the alkylation of triazolo-fused ring heterocycles.[22] To conclude this study several triazolo-fused ring alkylations were examined in THF and DMSO and a small effect was observed favoring N3-alkylation in THF when an N7 nitrogen atom was present (Table 6).[18] Alkylation of heterocycles **1j'** and **1l'** in THF favorably produced N3-alkyl products **4j'** (43%) and **4l'** (24%), respectively, with 1:1:2 N1/N2/N3 alkylation ratios in both cases (entries 3 and 6). In DMSO, those heterocycles gave statistically distributed 1:1:1 N1/N2/N3 product ratios (entries 4 and 7). Triazolo-fused ring heterocycles having CH instead of the N7 atom gave different product distributions (entries 1, 2 and 5).

Table 6. Application to Triazolo-fused Ring Heterocycles[a]



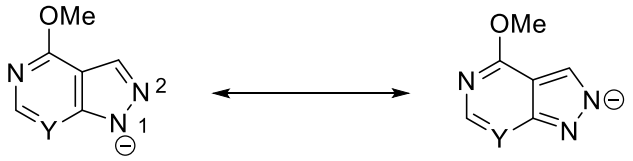
entry	heterocycle	time (h)	solvent	N1 (%)[b]	N2 (%)[b]	N3 (%)[b]	N1/N2/N3
							
1[c]	**1i'**	24	THF	**2i'** (45)	**3i'** (17)	**4i'** (18)	3/1/1
2	**1i'**	2	DMSO	**2i'** (29)	**3i'** (25)	**4i'** (15)	2/2/1
							
3[c]	**1j'**	48	THF	**2j'** (19)	**3j'** (17)	**4j'** (43)	1/1/2
4	**1j'**	4	DMSO	**2j'** (24)	**3j'** (25)	**4j'** (20)	1/1/1
							
5[d]	**1k'**	4	THF	**2k'** (25)	**3k'** (26)	**4k'** (25)	1/1/1
							
6	**1l'**	4	THF	**2l'** (11)	**3l'** (14)	**4l'** (24)	1/1/2
7	**1l'**	24	DMSO	**2l'** (19)	**3l'** (12)	**4l'** (14)	1/1/1

[a]See standard reaction conditions as described in Table 1. [b]Chromatographically isolated yields. [c]Product structures confirmed by X-ray crystallography, see Supporting Information. [d]See ref. 20a.

MECHANISM

Solvent polarity is known to have a dramatic effect on the regioselectivity of reactions in which the mechanism involves close ion pairs (CIPs) or solvent separated ion pairs (SIP).[23, 24, 25] In order to probe whether ion pairs play a role in the selectivities observed for alkylation reactions of azolo-fused ring heterocycles, especially those containing N7 instead of CH at that position, computational analysis of anion charge density was performed on **1b*** and **1r*** (Table 7). Comparative analysis of calculated charge density using density functional theory (DFT) calculations at the B3LYP/6-31G**(d) level of theory for these anions (as well as tautomer anions **1b**** and **1r****) show charge density is focused more on N1 than on N2 by about 0.2 charge units for each.[26] Importantly, the DFT calculations indicate that substitution of N for CH at position 7 (variable Y in Table 7) does not influence charge density concentration at N1 in both compounds, thus the N1-anion should be more reactive in each compound especially in a polar ion solvating solvent like DMSO. This is supported experimentally with the N1-methyl derivative determined as the major product in methylation reactions of **1b** and **1r** conducted in DMSO with N1/N2 ratios of 4:1 and 3:1 (Table 4, entries 16 and 12, respectively).[23] However, the product distribution for reactions conducted in THF are 8-fold N2-selective for **1b** and nonselective for **1r** (Table 4, entries 15 and 11, respectively), which indicates a separate THF solvent effect that is much more enhanced for molecules containing N7.

Table 7. Density functional theory (DFT) charge distribution (vacuum).[a]



1b*, Y = N
1r*, Y = CH

1b**, Y = N
1r**, Y = CH

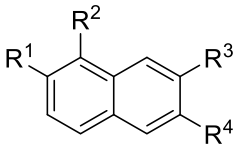
		charge		
entry	anion	N1	N2	N1-N2
1	**1b***	-0.642	-0.418	-0.224
2	**1b****	-0.571	-0.395	-0.176
3	**1r***	-0.588	-0.394	-0.194
4	**1r****	-0.587	-0.394	-0.193

[a]Calculations at the B3LYP/6-31G**(d) level of theory with the net charge set to -1.

To better understand the specific role of THF in reversing N1/N2 alkylation selectivities with azolo-fused ring heterocycles containing N7, the ^{1}H-detected pulsed field gradient-stimulated echo (PFG-STE) NMR method was applied to examine the solution N-sodio species of these two compounds and their neutral counterparts in THF-d_8 and DMSO-d_6.[27, 28, 29, 30] The method efficiently measures the diffusion coefficient D_t of molecules in solution. Since LogD_t relates directly to LogMW, this MW information can be used to interpret aggregation and solvation states of molecules[31] which in turn can be applied to mechanistic reasoning for the reactivity difference. Example applications on *N*-lithio-complexes[29, 31b, 31d] indicate its potential for providing insight into how solution aggregates relate to reactive intermediates.

Each PFG-STE NMR experiment was conducted in THF-d_8 or DMSO-d_6 solutions containing naphthalene analogs **7a**, **7b** and **7c** as internal MW standards. The naphthalenes, because of their planar structural similarity to **1b** and **1r** and their chemical inertness, served as suitable standards to form internal calibration curves (ICCs).[29] For each compound examined, the MW of its solution species aggregate (MW_{det}) as a NMR time average form[28c] was determined

by plotting Log$D_{t,obs}$ to respective ICCs, (see Figure 3 for an example analysis). Table 8 lists the results of this analysis with proposed time average solution species having calculated MW (MW_{calc}) values that agree to within 10% or better (MW_{err}) with the MW_{det} of the test compound in solution.[31]



7a, $R^1 = R^3 = R^4 = H$; $R^2 = Me$; MW 142
7b, $R^1 = H$; $R^2 = R^3 = R^4 = Me$; MW 170
7c, $R^1 = R^4 = Et$; $R^2 = R^3 = H$; MW 184

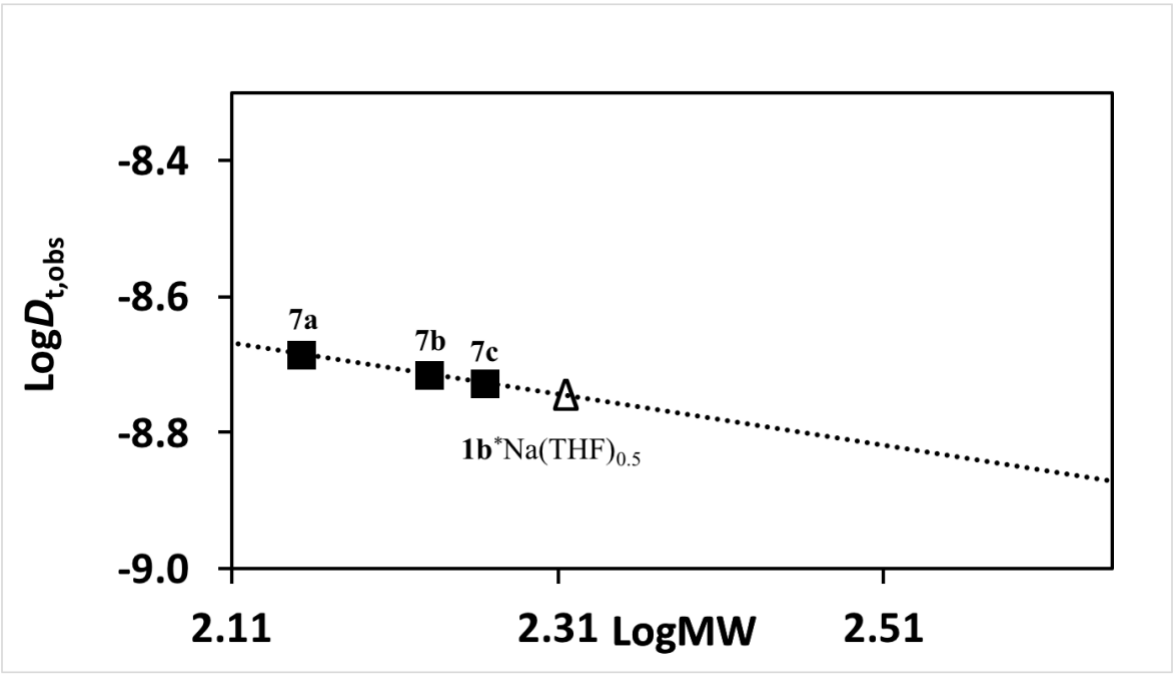
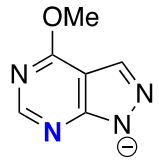
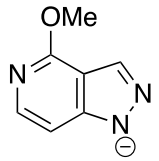


Figure 3. ^{1}H-detected pulsed field gradient-stimulated echo (PFG-STE) NMR MW_{det} analysis of *N*-sodio form of heterocycle 1b* in THF-d_8 based on internal calibration curve (ICC) with standards 7a, 7b and 7c. ICC: y = -0.3800x – 7.8670; R^2 = 1.0000. See Supporting Information for all PFG-STE analysis of **1b, 1r, 1b*** and **1r*** in THF-d_8 and DMSO-d_6.

Table 8. Solution species MW_{det} from PFG-STE NMR determined diffusion coefficients $D_{t,obs}$ of 1b, 1r, 1b* and 1r* measured in THF-d_8 and DMSO-d_6.[a]



1b*



1r*

entry	heterocycle	solvent[b]	$D_{t,obs}$ (10^{-9} m^2/s)	MW_{det} (g/mol)	time average sol'n species	MW_{calc} (g/mol)	MW_{err} (%)
1	**1b**	THF	1.8510	187	**1b**$(THF)_{0.5}$	186	-1
2	**1r**	THF	2.4405	195	**1r**$(THF)_{0.5}$	185	+5
3	**1b**	DMSO	0.36733	246	**1b**(DMSO)	228	+10
4	**1r**	DMSO	0.38243	239	**1r**(DMSO)	227	+5
5	**1b***	THF	1.7840	209	**1b***$Na(THF)_{0.5}$	208	+0.5
6	**1r***	THF	1.5633	404	**1r***$Na(THF)_3$	387	+4
7	**1b***	DMSO	0.36170	278	**1b***$(Na)_{0.5}(DMSO)_{1.5}$	278	0
8	**1r***	DMSO	0.37283	260	**1r***$(Na)_{0.5}(DMSO)_{1.5}$	277	-7

[a]Values $D_{t,obs}$ for compounds are the average of at least 2 determinations from separate resolvable ^1H resonances for 94% of samples; 89% of $D_{t,obs}$ SD values were $\leq$ 5%. See Supporting Information for all curves and data. [b]For $D_{t,obs}$ based MW_{det} calculations, the protio-form of the NMR solvents are used since it was previously determined that deuterium containing solvents have MW_{det} values that agree with their protio-form MWs, see ref. 31d.

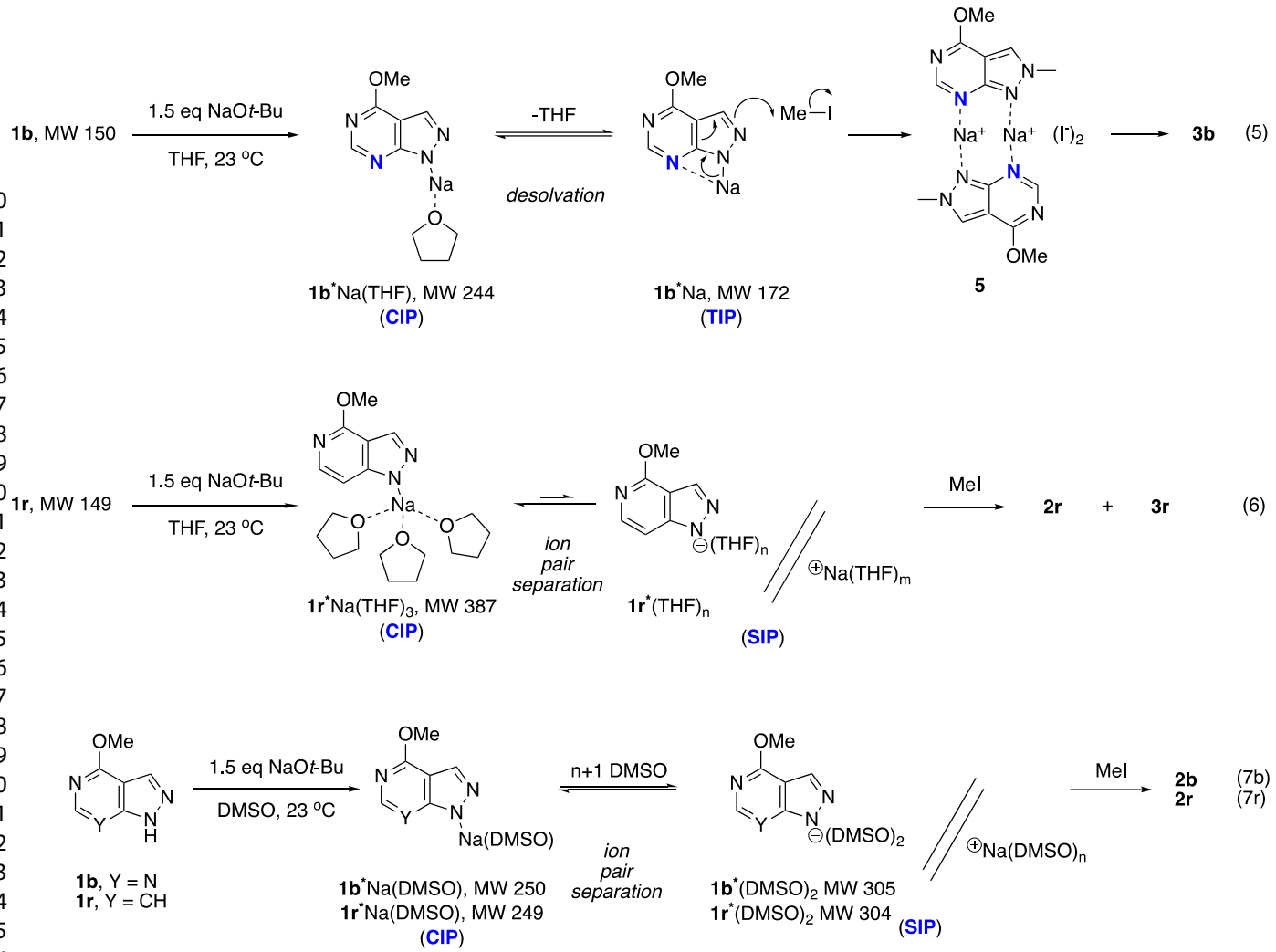
PFG-STE NMR analysis of the neutral compounds **1b** and **1r** revealed similar solution solvation states for the compound pair in THF and DMSO. In THF **1b** and **1r** are in equilibrium between desolvated and mono-THF solvated molecular aggregates (Table 8, entries 1-2). While in DMSO, the compounds are each associated with one molecule of solvent (entries 3-4).[32]

Remarkably, in THF the ionic compounds **1b*** and **1r*** exhibit starkly different aggregate forms with the former having MW_{det} = 209 g/mol and the latter with MW_{det} = 404 (Table 8, entries 5-6). These values agree with time average solution species **1b***$Na_{0.5}(THF)_{0.5}$ and **1r***$Na(THF)_3$.[33, 34] These proposed aggregates support a mechanistic explanation

for why **1b*** in THF is more selective for N2-alkylation (1:8 N1/N2) compared to **1r*** (3:2 N1/N2) and by extension how other N7 containing azolo-fused ring heterocycles are selective for N2 or N3 (Tables 4-6). As described in Scheme 2, Equation 5, the N7 containing heterocycle **1b*** in THF exists as an aggregate with MW_{det} = 209 representing the 1:1 equilibrium of the close ion pair (CIP) **1b***Na(THF) (MW = 244) with the desolvated tight ion pair (TIP) **1b***Na (MW = 172).[35] This lack of solvent to coordinate the Na^+ ion in the TIP enforces a tighter N1-Na bond because of additional through-space ligand bonding of N7 to Na and/or simply because N7 contributes, within the heterocycle bonding network, a through-bond electronic force to stabilize the N1-Na interaction. The resulting TIP N1-Na bond does not separate enough to allow N1 alkylation and instead N2 is alkylated. Additionally, invoking a N7-Na ligand bond allows rationalization for the formation of complex **5** containing the same bonding as observed by X-ray crystallography of the isolated product (see **5a** in Figure 2). The contrasting alkylation behavior of **1r*** is understandable considering the much different aggregate in THF, **1r***Na(THF)$_3$.[34] The extra coordinating solvent likely contributes to a small degree of ion pair separation and increased reactivity of the resulting SIP form **1r***(THF)$_n$, providing little discrimination between alkylation of N1 *vs.* N2 (3:2 N1/N2).

PFG-STE NMR of the ionic species **1b*** and **1r*** in DMSO-d_6 produced similar MW_{det} values of 278 and 260 g/mol (Table 8, entries 7-8), respectively. These values are consistent with the same mechanism being in effect in DMSO regardless of the presence of N7. The MW_{det} values describe time-averaged ion pairs **1b***(Na)$_{0.5}$(DMSO)$_{1.5}$ and **1r***(Na)$_{0.5}$(DMSO)$_{1.5}$ that represent 1:1 equilibrium mixtures of CIP/SIP forms (Scheme 2, Equations 7b and 7r). The stable CIP forms **1b***Na(DMSO) and **1r***Na(DMSO) each accept another molecule of DMSO which aids in the formation of SIPs containing solvated Na^+ ions separate from **1b***(DMSO)$_2$ and **1r***(DMSO)$_2$, respectively. Then as predicted by DFT calculations (Table 7) and in agreement with ion pair theory[23, 24] the SIP anions alkylate primarily at the nitrogen with the most negative charge, N1, producing products **2b** and **2r** (4:1 **2b**/**3b** and 3:1 **2r**/**3r**).

Scheme 2. Ion Pair Theory Mechanisms for Solvent Controlled Site-Selective Pyrazolo-Fused Ring Heterocycle Alkylations[a]



[a]Molecular weights (MW) are expressed in units of g/mol.

CONCLUSION

Understanding and controlling azolo-heterocycle alkylation site-selectivity is critical to many medicinal chemistry programs. This study has demonstrated that in THF, pyrazolo-, imidazo- and triazolo-fused ring heterocycles that contain N7 will preferentially alkylate at N2 (for pyrazolo-) or N3 (for imidazo- and triazolo-) in good to excellent selectivity. When conducted in DMSO, high selective alkylation of N1 is observed with pyrazolo- and imidazo-fused ring heterocycles containing N7. Even with CH instead of N7, pyrazolo-fused ring heterocycles exhibit generally good N1-selectivity in DMSO. However, imidazo-fused ring heterocycles lacking N7 show no selectivity in DMSO. In DMSO, alkylation of triazolo-fused ring heterocycles is not selective with or without N7. Finally, equal alkylation product distribution amongst azole nitrogens, of interest for compound library production, can be achieved with 10-1 THF/DMSO solvent mixtures.

X-ray crystal structures of sodium iodide complexes **5a** and **5b** and DFT calculations coupled with PFG-STE NMR MW analysis of the ionic reactive intermediates in solution support ion pair mechanistic interpretations. Interestingly, these data suggest that in THF, N7 contributes to a tight N1-Na bond in the intermediate TIP **1b***(Na) (Equation 5); which, as applied to pyrazolo-, imidazo- and triazolo-fused heterocycles, blocks N1 alkylation and forces alkylation to the N2- or N3-azolo-nitrogen. This agrees with early ion pair theory[23] which determined that in THF, solvent separated anions with sodium cations (SIPs) make up less than 1% of the ionic species when compared to polar solvents such as HMPA or DMSO and that CIPs or TIPs predominate in THF. In further agreement with ion-pair theory, the inability to form SIPs in THF led to decreased reactivity as witnessed in alkylations with bulky electrophiles that required higher temperatures to go to completion as compared to DMSO (Table 3).

This work has uncovered a new principle of alkylation site control in azolo-fused ring heterocycles containing the N7 atom. Reactions performed in THF will predictably alkylate preferentially at N2 or N3 and this is expected to provide new opportunities for drug discovery projects to examine substituent effects into vector directions not previously recognized as being accessible from such a simple reaction.

EXPERIMENTAL SECTION

General Information. All starting materials and reagents were purchased from commercial sources and used as received unless otherwise noted. Microwave reactions were performed with a single mode operating Biotage Initiator^{+} in sealed reaction vials at the indicated fixed temperature held constant for the designated reaction time. The temperature within the microwave reaction vial was monitored by an IR sensor focused on a point on the reaction vial glass. Melting points were obtained on a Electrothermal IA-9100 Melting Point Apparatus and are uncorrected. The instrument was validated by melting a sample of 1-naphthoic acid, mp 160-161 ˚C (vendor reported mp 157-160 ˚C). NMR spectra were recorded on 400 MHz and 600 MHz instruments. All ^{1}H and ^{13}C NMR data were referenced to the internal deuterated solvent relative to TMS at 0 ppm. Analytical HPLC was performed with a C_{18} column (3 μm, 3 × 50 mm) and the solvent system A: pH 4.5 aqueous buffer (20 mM KH_2PO_4) and B: acetonitrile; eluting 0% B (2 min), 0-20% B (2.5 min), 20-75% B (3.5 min), 75% B (1 min) with a flow rate of 1.5 mL/min. Analytical LC/MS was performed on a UPLC-MS instrument equipped with a C_{18} column (1.7 μm, 2.1 × 50 mm) and the solvent system A: 0.1% HCOOH in H_2O and B: 0.1% HCOOH in acetonitrile, eluting 5-95% solvent B (0.75 min) with a flow rate of 1 mL/min at a column temperature of 45 ºC. Flash column chromatography (FCC) was performed on prepacked silica (SiO_2) columns eluted with the indicated solvents. Preparative HPLC Method 1: on a 30 mm × 100 mm × 2.5 μm (particle size) C_{18} column with a gradient of acetonitrile (B) in water (A) (15 min) and 0.05% trifluoroacetic acid added as a modifier to both phases with a flow rate of 60 mL/min. Elution profiles were monitored by UV at 254 and 220 nm. Preparative HPLC Method 2: on a 30 mm × 100 mm × 5 μm (particle size) C_{18} column and the solvent system with a 9 min gradient of acetonitrile (B) in water (A) and 0.1% trifluoroacetic acid added as a modifier to both phases with a flow rate of 60 mL/min. Fractions collected from preparative HPLC were diluted with aqueous 1 M Na_2CO_3 and extracted with CH_2Cl_2 (3 × 50 mL); organic extract dried ($MgSO_4$) and evaporated to product residue. The standard crystallization method to prepare samples for mp determination, microanalysis or X-ray crystallographic structure determination, unless specified otherwise, was to dissolve 50 mg of sample in 0.5 mL THF in a 4 mL vial, place this inside a 20 mL vial containing 5 mL pentane, cap the outer vial and after standing at rt for 24-72 h, the resulting crystals were collected. C, H, I, N, and Na microanalysis were performed at a vendor where %I and %Cl were

determined by ion chromatography and %Na was determined with ICP-OES. Single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Mo K_α radiation (λ = 0.71073 Å).

4-Methoxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2b) and 4-Methoxy-2-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine (3b). General Method 1. Methylation of Heterocycles in THF and DMSO. To 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) (100 mg, 0.67 mmol) suspended or dissolved, respectively, in 3.3 mL of THF (at 0 ˚C) or DMSO (at 15 ˚C), was added 1 mL of a 1 M solution of NaHMDS in THF (1 mmol) followed by iodomethane (0.12 mL, 2 mmol) and each mixture stirred at 20 ºC for 1h. Then the two reaction mixtures were separately diluted with CH_2Cl_2 and aqueous 1 M NH_4Cl, the organic layers separated and the aqueous layers extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts from each experiment were dried ($MgSO_4$) and concentrated to crude product residues. Purifications (FCC, SiO_2, 10-100% EtOAc/heptane) first afforded compound **2b** as a white solid (THF: 9 mg, 8% yield; DMSO: 60 mg, 55% yield): ^{1}H and ^{13}C NMR (DMSO-d_6) were identical to that reported;[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.00 (s, 1H), 4.14 (s, 3H), 4.08 (s, 3H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed no relevant crosspeaks. X-ray crystallography confirmed the structure; see CCDC 1825997.

Continued elution provided compound **3b** as a white solid (THF: 75 mg, 69% yield; DMSO: 14 mg, 13% yield): mp 177-180 ˚C (lit. mp 166-169 ˚C);[10] ^{1}H and ^{13}C NMR (DMSO-d_6) were identical to that reported;[10] HSQC (DMSO-d_6) showed cross peaks of δ 8.61-125.1 (H3-C3); 8.52 to 154.6 (H6-C6); 4.15 to 40.5 (NCH_3 C-H); 4.07 to 53.9 (OCH_3 C-H); NOESY (DMSO-d_6) showed cross peaks from δ 8.61 to 4.15 (H3 to NCH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.94 (s, 1H), 4.14 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 161.9, 155.6, 123.6, 103.5, 54.0, 40.9; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N2-CH_3 (δ 4.05) to H3 (δ 7.94); 1H NMR (400 MHz, THF-d_8) δ 8.43 (s, 1H), 8.20 (s, 1H), 4.14 (s, 3H), 4.06 (s, 3H); 13C NMR (101MHz, THF-d_8) δ 165.9, 163.1, 155.6, 124.5, 104.2, 54.1, 40.9; HSQC (THF-d_8) cross peaks of δ 8.25-123 (H3-C3); 8.48 to 154.5 (H6-C6); 4.18 to 39.5 (NCH_3 C-H); 4.10 to 53.0 (OCH_3 C-H); NOESY (THF-d_8) cross peaks of δ 4.18 to 8.24 (NCH_3 to H3); ^{1}H NMR

(400 MHz, methanol-d_4) δ 8.51 (s, 1H), 8.39 (s, 1H), 4.20 (s, 3H), 4.15 (s, 3H); X-ray crystallography confirmed the structure; see CCDC 1825993.

4-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2a) and 4-Chloro-2-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine (3a). Prepared from 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (**1a**) (100 mg, 0.64 mmol) and iodomethane as described in General Method 1. THF and DMSO conditions: 20 ºC/1.5 h. Purification (FCC, SiO_2, 10-100% EtOAc/heptane) first afforded compound **2a** as a white solid (THF: 7 mg, 6% yield; DMSO: 51 mg, 47% yield): ^{1}H and ^{13}C NMR (DMSO-d_6) were identical to that reported.[36]

Continued elution provided compound **3a** as a white solid (THF: 39 mg, 36% yield; DMSO: 12 mg, 11% yield): ^{1}H (DMSO-d_6) was identical to that reported;[37] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.16 (s, 1H), 4.31 (s, 3H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N2-CH_3 (δ 4.31) to H3 (δ 8.16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 156.2, 154.8, 124.9, 113.4, 41.6.

1-Ethyl-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (2c) and 2-Ethyl-4-methoxy -2*H*-pyrazolo[3,4-*d*]pyrimidine (3c). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and 2-iodoethane (0.16 mL, 2 mmol) as described in General Method 1. THF conditions: 20 ºC/24 h. DMSO conditions: 20 ºC/0.5 h. Purification (FCC, SiO_2, 10-100% EtOAc/heptane) first afforded first afforded compound **2c** as a white solid (THF: 5 mg, 4% yield; DMSO: 80 mg, 67% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (t, *J*=7.21 Hz, 3 H) 4.13 (s, 3 H) 4.48 (q, *J*=7.34 Hz, 2 H) 7.28 (s, 1 H) 8.00 (s, 1 H) 8.53 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 154.9, 154.1, 130.9, 102.8, 54.1, 42.5, 14.9. Anal. calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.99; H, 5.35; N, 31.53.

Continued elution provided compound **3c** as a white solid (THF: 78 mg, 66% yield; DMSO: 16 mg, 13% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (t, *J*=7.34 Hz, 3 H) 4.14 (s, 3 H) 4.47 (q, *J*=7.34 Hz, 2 H) 5.31 (s, 1 H) 7.29 (s, 1 H) 8.01 (s, 1 H) 8.63 (s, 1 H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N2-CH_2 (δ 4.47) to H3 (δ 8.01); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 161.5, 155.3, 122.0, 103.0, 53.9, 49.0, 15.3. Anal. calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 54.22; H, 5.61; N, 31.14.

1-Isopropyl-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (2d) and 2-Isopropyl-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (3d). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and 2-iodopropane (0.20 mL, 2 mmol) as described in General Method 1. THF conditions: microwave heating to 160 ºC/0.75 h. DMSO conditions: 20 ºC/1.5 h. Purification [FCC, SiO_2, 5-65% polar solvent (9-1 EtOAc:MeOH) in heptane] first afforded compound **2d** as a white solid (THF: 8 mg, 6% yield; DMSO: 53 mg, 41% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.03 (s, 1H), 5.18 (spt, *J*=6.7 Hz, 1H), 4.16 (s, 3H), 1.59 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 154.7, 153.7, 130.7, 102.8, 54.1, 49.3, 22.0. LC/MS (ESI+) calcd for $C_9H_{12}N_4O$ ([M + H]$^+$) *m/z* 193.1; found 193.1. Anal. calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 56.72; H, 6.16; N, 29.28.

Continued elution provided compound **3d** as a white solid (THF: 41 mg, 32% yield; DMSO: 11 mg, 9% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.00 (s, 1H), 4.74 (spt, *J*=6.7 Hz, 1H), 4.09 (s, 3H), 1.62 (d, *J*=6.6 Hz, 6H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed crosspeaks from N2-$CHCH_3$ (δ 4.74 and 1.62) to H3 (δ 8.00); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 161.4, 155.4, 120.1, 102.8, 56.3, 53.9, 23.0. LC/MS (ESI+) calcd for $C_9H_{12}N_4O$ ([M + H]$^+$) *m/z* 193.1; found 193.1. Anal. calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 56.32; H, 6.29; N, 29.31.

1-Isobutyl-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (2e) and 2-Isobutyl-4-methoxy-2*H*-pyrazolo[3,4-*d*]pyrimidine (3e). The reaction in THF was according to General Method 1 using reagents: 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b)** (450 mg, 3 mmol), 15 mL THF, 4.5 mL of 1 M NaHMDS in THF (4.5 mmol), and 1-iodo-2-methylpropane (1.0 mL, 9.0 mmol) with microwave heating at 160 ºC for 45 min. The reaction in DMSO was according to General Method 1 using reagents: **1b** (100 mg, 0.67 mmol), 3.3 mL DMSO, 1.0 mL of 1 M NaHMDS in THF (1 mmol), 1-iodo-2-methylpropane (0.23 mL, 2.0 mmol), 20 ºC/1.5 h. Purification [FCC, SiO_2, 5-50% polar solvent (9-1 EtOAc:MeOH) in heptane] first afforded compound **2e** as an oil (THF: 40 mg, 6% yield; DMSO: 51 mg, 37% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.03 (s, 1H), 4.26 (d, *J*=7.3 Hz, 2H), 4.16 (s, 3H), 2.38 (quint, *J*=6.9, 13.8 Hz, 1H), 0.92 (d, *J*=6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 155.0, 154.8, 130.9, 102.5, 54.6, 54.1, 29.2, 19.9. Anal. calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.17. Found: C, 57.94; H, 6.45; N, 26.90.

Continued elution provided compound **3e** as a white solid (THF: 350 mg, 57% yield; DMSO: 15 mg, 11% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.94 (s, 1H), 4.18 (d, *J*=7.3 Hz, 2H), 4.13 (s, 3H), 2.43 (quint, *J*=6.9, 13.7 Hz, 1H), 0.95 (d, *J*=6.7 Hz, 6H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed crosspeaks from N2-CH_2 (δ 4.18) to H3 (δ 7.94); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 161.7, 155.5, 123.2, 103.0, 61.7, 54.0, 29.5, 19.8. Anal. calcd for $C_9H_{12}N_4O$: C, 58.24; H, 6.84; N, 27.17. Found: C, 58.34; H, 6.84; N, 27.22.

1-(Cyclopropylmethyl)-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (2f) and 2-(Cyclopropylmethyl)-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (3f). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and (bromomethyl)cyclopropane (0.19 mL, 2 mmol) as described in General Method 1. THF conditions: 65 ºC/48 h. DMSO conditions: 20 ºC/144 h. Purification (FCC, SiO_2, 10-100% EtOAc in heptane) first afforded compound **2f** as an oil (THF: 14 mg, 10% yield; DMSO: 58 mg, 42% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.05 (s, 1H), 4.33 (d, *J*=7.1 Hz, 2H), 4.17 (s, 3H), 1.47 - 1.33 (m, 1H), 0.61 - 0.53 (m, 2H), 0.50 - 0.44 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 154.9, 154.5, 131.0, 103.7, 54.2, 52.4, 11.3, 3.9. LC/MS (ESI+) calcd for $C_{10}H_{12}N_4O$ ($[M + H]^+$) *m/z* 205.1; found 205.1. Anal. calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.93; H, 5.94; N, 26.73.

Continued elution provided compound **3f** as a white solid (THF: 69 mg, 50% yield; DMSO: 12 mg, 9% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.16 (m, 1H), 4.28 (d, *J*=7.3 Hz, 2H), 4.16 (s, 3H), 1.53 - 1.39 (m, 1H), 0.80 - 0.71 (m, 2H), 0.50 (s, 2H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed crosspeaks from N2-CH_2 (δ 4.28) to H3 (δ 8.16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 161.2, 155.4, 122.2, 103.3, 58.9, 54.1, 10.9, 4.4. LC/MS (ESI+) calcd for $C_{10}H_{12}N_4O$ ($[M + H]^+$) *m/z* 205.1; found 205.1. Anal. calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.12; H, 5.87; N, 27.36.

1-Benzyl-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (2g) and 2-Benzyl-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (3g). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and benzyl chloride (0.23 mL, 2 mmol) as described in General Method 1. THF conditions: microwave heating to 160 ºC/0.75 h. DMSO conditions: 20 ºC/1 h. Purification [FCC, SiO_2, 5-65% polar solvent (9-1 EtOAc:MeOH) in heptane] first afforded compound **2g** as a white solid (THF: 7 mg, 4% yield; DMSO: 64 mg, 40% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.07 (s,

1H), 7.38 - 7.29 (m, 5H), 5.65 (s, 2H), 4.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 155.3, 154.7, 136.3, 131.6, 128.7, 128.01, 127.97, 102.8, 54.2, 51.1; 2D HSQC and HMBC NMR (400 MHz, $CDCl_3$) confirmed the structure. Anal. calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.04; H, 4.70; N, 22.90.

Continued elution provided compound **3g** as a white solid (THF: 64 mg, 40% yield; DMSO: 66 mg, 41% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.91 (s, 1H), 7.44 - 7.33 (m, 5H), 5.59 (s, 2H), 4.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 161.7, 155.6, 134.5, 129.1, 128.8, 128.5, 123.0, 103.6, 58.0, 54.0; 2D HSQC and HMBC NMR (400 MHz, $CDCl_3$) confirmed the structure. Anal. calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.80; H, 5.05; N, 23.25.

4-Methoxy-1-(2-methoxyethyl)-1H-pyrazolo[3,4-d]pyrimidine (2h) and 4-Methoxy-2-(2-methoxyethyl)-2H-pyrazolo[3,4-d]pyrimidine (3h). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and 1-bromo-2-methoxyethane (0.19 mL, 2 mmol) as described in General Method 1. THF conditions: microwave heating to 160 °C/0.75 h. DMSO conditions: 20 °C/20 h. Purification, from THF reaction: (FCC, SiO_2, 20-100% EtOAc in heptane) first afforded compound **2h** as a white solid (25 mg, 18% yield): ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.12 (s, 1H), 4.62 (t, *J*=5.5 Hz, 2H), 4.18 (s, 3H), 3.88 (t, *J*=5.4 Hz, 2H), 3.29 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 164.2, 155.0, 154.8, 131.0, 102.5, 70.0, 57.5, 53.6, 46.6; 2D HSQC and HMBC NMR (400 MHz, CD_3OD) confirmed the structure. Anal. calcd for $C_{13}H_{12}N_4O$: C, 51.92; H, 5.81; N, 26.91. Found: C, 51.93; H, 5.81; N, 26.78.

Continued elution provided compound **3h** as a white solid (66 mg, 48% yield): ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.43 (s, 1H), 4.64 - 4.59 (m, 2H), 4.17 (s, 3H), 3.91 - 3.86 (m, 2H), 3.33 (s, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ 165.8, 160.7, 155.2, 125.5, 102.8, 70.0, 57.7, 53.6, 53.6; 2D HSQC and HMBC NMR (400 MHz, CD_3OD) confirmed the structure. Anal. calcd for $C_{13}H_{12}N_4O$: C, 51.92; H, 5.81; N, 26.91. Found: C, 51.76; H, 6.00; N, 26.56.

The DMSO reaction was purified using Preparative HPLC Method 1, 10-40% B in A, to provide first compound **3h** as a white solid (4 mg, 3%) and then compound **2h** (79 mg, 57%).

4-Methoxy-1-(3-methylbut-2-en-1-yl)-1H-pyrazolo[3,4-d]pyrimidine (2i) and 4-Methoxy-2-(3-methylbut-2-en-1-yl)-2H-pyrazolo[3,4-d]pyrimidine (3i). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and 3,3-dimethylallyl bromide (0.23 mL, 2 mmol) as described in General Method 1. THF conditions: 20 ºC/2 h. DMSO conditions: 20 ºC/3 h. Purification: (FCC, SiO_2, 0-50% EtOAc in heptane) first afforded compound **2i** as an oil (THF: 6 mg, 4% yield; DMSO: 73 mg, 50% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.05 (s, 1H), 5.68 - 5.41 (m, 1H), 5.07 (d, *J*=6.8 Hz, 2H), 4.18 (s, 3H), 1.88 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 155.0, 154.2, 137.4, 131.1, 118.7, 102.7, 54.1, 45.2, 25.7, 18.1. LC/MS (ESI+) calcd for $C_{11}H_{14}N_4O$ ($[M + H]^+$) *m/z* 219.1; found 219.2. Anal. calcd for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.32; H, 6.47; N, 25.77.

Continued elution provided compound **3i** as a white solid (THF: 81 mg, 56% yield; DMSO: 0 mg, 0% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.01 (s, 1H), 5.71 - 5.38 (m, 1H), 5.03 (d, *J*=7.3 Hz, 2H), 4.16 (s, 3H), 1.85 (d, *J*=12.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 161.7, 155.4, 140.7, 121.9, 117.0, 103.2, 53.9, 51.6, 25.8, 18.2; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N2-CH_2 (δ 5.03) to H3 (δ 8.01). Anal. calcd for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. LC/MS (ESI+) calcd for $C_{11}H_{14}N_4O$ ($[M + H]^+$) *m/z* 219.1; found 219.1. Found: C, 59.72; H, 6.08; N, 25.12.

Ethyl 2-(4-Methoxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetate (2j) and Ethyl 2-(4-Methoxy-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetate (3j). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and ethyl chloroacetate (0.21 mL, 2.0 mmol) as described in General Method 1. THF conditions: 20 ºC/16 h. DMSO conditions: 20 ºC/3 h. Purification: (FCC, SiO_2, 0-50% EtOAc in heptane) first afforded compound **2j** as a white solid (THF: 45 mg, 28% yield; DMSO: 97 mg, 59% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.08 (s, 1H), 5.22 (s, 2H), 4.22 (q, *J*=7.1 Hz, 2H), 4.15 (s, 3H), 1.25 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 164.1, 155.53, 155.45, 132.2, 102.9, 61.9, 54.3, 48.4, 14.1. Anal. calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.98; H, 4.92; N, 23.51.

Continued elution provided compound **3j** as a white solid (THF: 92 mg, 57% yield; DMSO: 40 mg, 24% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.14 (s, 1H), 5.20 (s, 2H), 4.28 (q, *J*=7.2 Hz, 2H), 4.15 (s, 3H), 1.30 (t,

J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 165.5, 161.5, 156.0, 124.9, 104.1, 62.5, 54.8, 54.1, 14.1; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N2-CH_2 (δ 5.20) to H3 (δ 8.14). Anal. calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.63; H, 4.94; N, 23.37.

4-Methoxy-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (2k) and 4-Methoxy-2-(tetrahydro-2*H*-pyran-4-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine (3k). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and 4-iodotetrahydro-2H-pyran (0.29 mL, 2 mmol) as described in General Method 1. THF conditions: microwave heating to 160 ºC/0.75 h. DMSO conditions: 20 ºC/19 h. Purification, from THF reaction: [FCC, SiO_2, 10-100% polar solvent (9-1 EtOAc:MeOH) in heptane]. From DMSO reaction: [FCC, SiO_2, 10-100% polar solvent (9-1 EtOAc:MeOH) in heptane] first afforded a mixture of **2k** and **1b**. This mixture was subjected to preparative HPLC Method 2, 15-40% B in A, to first afford compound **1b** (52 mg, 52% yield) and then compound **2k** as a white solid [THF: none isolated (compound **1b** 62 mg, 62% yield recovered); DMSO: 10 mg, 6% yield]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.04 (s, 1H), 5.00 (tt, *J*=4.2, 11.6 Hz, 1H), 4.20 - 4.12 (m, 5H), 3.63 (dt, *J*=2.0, 12.0 Hz, 2H), 2.42 (dq, *J*=4.6, 12.4 Hz, 2H), 1.96 (td, *J*=2.1, 10.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 154.8, 154.0, 131.0, 102.9, 67.1, 54.1, 53.8, 32.2. Anal. calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.25; H, 6.11; N, 23.91.

Continued elution provided compound **3k** as a white solid (THF: 15 mg, 10% yield; DMSO: 7 mg, 5% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.04 (s, 1H), 4.69 - 4.58 (m, 1H), 4.21 - 4.13 (m, 5H), 3.66 - 3.53 (m, 2H), 2.29 - 2.18 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 161.3, 155.6, 120.3, 103.0, 66.6, 60.3, 54.0, 33.2; 2D NOESY NMR (400 MHz, $CDCl_3$) showed crosspeaks from N2-CH (δ 4.69-4.58) as well as N2-CH**CH_2** (δ 2.29-2.18) to H3 (δ 8.04). Anal. calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.31; H, 6.11; N, 23.95.

1-[2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-erythro-pentofuranosyl]-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (2l), 1-[2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-erythro-pentofuranosyl]-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (2ll) and 2-[2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-erythro-pentofuranosyl]-4-methoxy-2*H*-pyrazolo[3,4-*d*]pyrimidine (3l). Prepared from 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) and 2-deoxy-3,5-di-O-(p-toluoyl)-a-D-erythro-

pentofuranosyl chloride (**7**) (388 mg, 1.0 mmol) as described in General Method 1. THF conditions: 20 ºC/4 h. DMSO conditions: 20 ºC/1 h. Purification, from THF reaction: (the first chromatography system, FCC, SiO_2, 10-80% EtOAc in heptane). From DMSO reaction: (the first chromatography system, FCC, SiO_2, 10-80% EtOAc in heptane) first afforded a mixture of **2l** and **2ll**. This mixture was subjected purification: (the second chromatography system, FCC, SiO_2, 0-10% EtOAc in CH_2Cl_2) first afforded compound **2l** as a white solid (THF: 108 mg, 32% yield; DMSO: 81 mg, 24% yield): ^{1}H and ^{13}C NMR (DMSO-d_6) were identical to that reported.[19b]

Continued elution from the DMSO reaction second chromatography system provided compound **2ll** as a white solid (THF: none isolated; DMSO: 23 mg, 7% yield): ^{1}H and ^{13}C NMR (DMSO-d_6) were identical to that reported.[19b]

Continued elution from the first chromatography system of the THF and DMSO derived products provided compound **3l** as a white solid (THF: 95 mg, 28% yield; DMSO: 39 mg, 12% yield): ^{1}H and ^{13}C NMR (DMSO-d_6) were identical to that reported;[19b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.27 (s, 1H), 7.96 (d, *J*=8.19 Hz, 2H), 7.76 (d, *J*=8.19 Hz, 2H), 7.28 (d, *J*=7.95 Hz, 2H), 7.12 (d, *J*=7.95 Hz, 2H), 6.47 (t, *J*=5.99 Hz, 1H), 5.82 (td, *J*=3.27, 6.42 Hz, 1H), 4.72-4.80 (m, 2H), 4.56-4.65 (m, 1H), 4.09 (s, 3H), 3.26-3.35 (m, 1H), 2.96 (ddd, *J*=3.79, 6.48, 14.43 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from H1' (δ 6.47), H5's (d 4.72-4.80), and H2' (3.26-3.35) to H3 (δ 8.27).

1-Methyl-1*H*-indazole (2m) and 2-Methyl-2*H*-indazole (3m). Prepared according to General Method 1 using reagents: 1H-indazole (**1m**) (100 mg, 0.85 mmol), 4.2 mL of THF or DMSO, 1.3 mL of 1 M NaHMDS in THF (1.3 mmol), and iodomethane (0.16 mL, 2.5 mmol). THF conditions: 20 ºC/96 h. DMSO conditions: 20 ºC/1 h. THF reaction purification (FCC, SiO_2, 0-40% EtOAc/heptane) first afforded compound **2m** as a white solid (55 mg, 49% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported.[38]

Continued elution provided compound **3m** as a white solid (35 mg, 31% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported.[39]

The DMSO reaction was purified using Preparative HPLC Method 2, 15-40% B in A, to provide first compound **3m** as a white solid (19 mg, 17%) and then compound **2m** (50 mg, 45%).

5-Bromo-1-methyl-1*H*-indazole (2n) and 5-Bromo-2-methyl-2*H*-indazole (3n). Prepared according to General Method 1 using reagents (note the THF reaction has been reported):[20a] 5-bromo-1*H*-indazole (**1n**) (150 mg, 0.76 mmol), 3.8 mL DMSO (the THF reaction has been reported),[20a] 1.1 mL of 1 M NaHMDS in THF (1.1 mmol), and iodomethane (0.15 mL, 2.3 mmol). Conditions: 23 ºC/4 h. Reaction purification (FCC, SiO_2, 0-40% EtOAc/heptane) first afforded compound **2n** as a white solid (77 mg, 48% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported;[20b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (s, 3 H) 7.29 (d, *J*=8.80 Hz, 1 H) 7.47 (dd, *J*=8.86, 1.77 Hz, 1 H) 7.87 (d, *J*=1.34 Hz, 1 H) 7.92 (d, *J*=0.73 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.6, 110.3, 113.5, 123.4, 125.4, 129.2, 131.9, 138.5; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N1-CH_3 (δ 4.07) to H7 (δ 7.29).

Continued elution provided compound **3n** as a white solid (24 mg, 15% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported;[20b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (s, 3 H) 7.34 (dd, *J*=9.17, 1.83 Hz, 1 H) 7.58 (d, *J*=9.05 Hz, 1 H) 7.81 (d, *J*=1.71 Hz, 1 H) 7.85 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 40.4, 115.0, 118.9, 122.1, 123.0, 123.20, 129.4, 147.3; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N1-CH_3 (δ 4.22) to H3 (δ 7.85).

5-Bromo-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (2o) and 5-Bromo-2-methyl-2*H*-pyrazolo[3,4-*b*]pyridine (3o). Prepared according to General Method 1 using reagents: 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine (**1o**) (150 mg, 0.76 mmol), 3.8 mL of THF or DMSO, 1.1 mL of 1 M NaHMDS in THF (1.1 mmol), and iodomethane (0.14 mL, 2.3 mmol). THF conditions: 20 ºC/2 h. DMSO conditions: 20 ºC/4 h. Purification [FCC, SiO_2, 10-100% polar solvent (9-1 EtOAc:MeOH) in heptane] first afforded compound **2o** as a white solid (THF: 12 mg, 7% yield; DMSO: 74 mg, 46% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J*=2.2 Hz, 1H), 8.16 (d, *J*=2.2 Hz, 1H), 7.93 (s, 1H), 4.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 148.6, 131.6, 130.9, 116.8, 112.3, 34.1. Anal. calcd for $C_7H_6BrN_3$: C, 39.65; H, 2.85; N, 19.82. Found: C, 39.87; H, 2.71; N, 19.68.

Continued elution provided compound **3o** as a white solid (THF: 111 mg, 69% yield; DMSO: 5 mg, 3% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J*=2.3 Hz, 1H), 8.13 (d, *J*=2.3 Hz, 1H), 7.87 (s, 1H), 4.23 (s, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 156.5, 152.2, 130.8, 122.8, 115.3, 113.2, 41.1; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N2-CH_3 (δ 4.23) to H3 (δ 8.13). Anal. calcd for $C_7H_6BrN_3$: C, 39.65; H, 2.85; N, 19.82. Found: C, 39.90; H, 2.72; N, 19.78.

1-Methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2p) and 2-Methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine (3p). Prepared according to General Method 1 using reagents: 1*H*-pyrazolo[3,4-*d*]pyrimidine (**1p**) (150 mg, 1.25 mmol), 6.2 mL of THF or DMSO, 1.9 mL of 1 M NaHMDS in THF (1.9 mmol), and iodomethane (0.23 mL, 3.8 mmol). THF and DMSO conditions: 20 ºC/4 h. Purification [FCC, SiO_2, 10-100% polar solvent (9-1 EtOAc:MeOH) in heptane] first afforded compound **2p** as a white solid (THF: 13 mg, 8% yield; DMSO: 45 mg, 27% yield): ^1H and ^{13}C NMR ($CDCl_3$) were identical to that reported.[40] LC/MS (ESI+) calcd for $C_6H_6N_4$ ($[M + H]^+$) *m/z* 135.1; found 135.0.

Continued elution provided compound **3p** as a white solid (THF: 63 mg, 38% yield; DMSO: 5 mg, 3% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 9.11 (s, 1H), 8.12 (s, 1H), 4.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.03, 155.64, 154.71, 124.70, 113.33, 41.35; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N2-CH_3 (δ 4.31) to H3 (δ 8.12). LC/MS (ESI+) calcd for $C_6H_6N_4$ ($[M + H]^+$) *m/z* 135.1; found 135.0. Anal. calcd for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 52.67; H, 4.22; N, 39.93.

4-Methoxy-1-methyl-1*H*-indazole (2q) and 4-Methoxy-2-methyl-2*H*-indazole (3q). Prepared according to General Method 1 using reagents: 4-methoxy-1H-indazole (**1q**) (100 mg, 0.67 mmol), 3.4 mL of THF or DMSO, 1.0 mL of 1 M NaHMDS in THF (1.0 mmol), and iodomethane (0.12 mL, 2.0 mmol). THF and DMSO conditions: 20 ºC/2 h. Purification (FCC, SiO_2, 0-50% EtOAc in heptane) first afforded compound **2q** as a white solid (THF: 62 mg, 57% yield; DMSO: 71 mg, 65% yield): ^1H and ^{13}C NMR ($CDCl_3$) were identical to that reported.[38] LC/MS (ESI+) calcd for $C_9H_{10}N_2O$ ($[M + H]^+$) *m/z* 163.1; found 163.1.

Continued elution provided compound **3q** as a white solid (THF: 27 mg, 25% yield; DMSO: 25 mg, 23% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3 H) 4.21 (s, 3 H) 6.36 (d, *J*=7.34 Hz, 1 H) 7.19 - 7.24 (m, 1 H) 7.30 (d, *J*=8.32 Hz, 1 H) 7.96 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 150.7, 126.7, 122.1, 115.8, 109.7, 98.4, 55.2, 40.2.

LC/MS (ESI+) calcd for $C_9H_{10}N_2O$ ($[M + H]^+$) *m/z* 163.1; found 163.1. Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 65.73; H, 6.24; N, 17.00.

4-Methoxy-1-methyl-1*H*-pyrazolo[4,3-*c*]pyridine (2r) and 4-Methoxy-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine (3r). Prepared according to General Method 1 using reagents: 4-methoxy-1*H*-pyrazolo[4,3-*c*]pyridine (**1r**) (149 mg, 1.00 mmol), 5 mL of THF or DMSO, 1.5 mL of 1 M NaHMDS in THF (1.5 mmol), and iodomethane (0.19 mL, 3.0 mmol). THF and DMSO conditions: 20 ºC/2 h. Purification (FCC, SiO_2, 0-20% EtOAc in CH_2Cl_2) first afforded compound **2r** as a white solid (THF: 81 mg, 50% yield; DMSO: 75 mg, 46% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J*=0.73 Hz, 1H), 7.93 (d, *J*=6.11 Hz, 1H), 6.89 (dd, *J*=0.86, 6.11 Hz, 1H), 4.10 (s, 3H), 4.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 145.1, 141.7, 132, 109.9, 99.0, 53.3, 35.7; 2D HSQC NMR (400 MHz, $CDCl_3$) supported ^{1}H NMR assignment of N1-CH_3 (δ 4.03) and H8 (δ 6.89); 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N1-CH_3 (δ 4.03) to H8 (δ 6.89). LC/MS (ESI+) calcd for $C_8H_9N_3O$ ($[M + H]^+$) *m/z* 164.1; found 164.1. Anal. calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.73; H, 5.40; N, 25.59.

Continued elution provided compound **3r** as a white solid (THF: 57 mg, 35% yield; DMSO: 30 mg, 18% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.79 (d, *J*=6.36 Hz, 1H), 7.11 (dd, *J*=0.67, 6.42 Hz, 1H), 4.18 (s, 3H), 4.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 152.9, 139.9, 124.2, 110.1, 105.7, 53.2, 40.3; 2D HSQC NMR (400 MHz, $CDCl_3$) supported ^{1}H NMR assignment of N2-CH_3 (δ 4.18) and H3 (δ 7.98); 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from N2-CH_3 (δ 4.18) to H3 (δ 7.98). LC/MS (ESI+) calcd for $C_8H_9N_3O$ ($[M + H]^+$) *m/z* 164.1; found 164.1. Anal. calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.19; H, 5.49; N, 25.30.

4-Methoxy-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (2s) and 4-Methoxy-2-methyl-2*H*-pyrazolo[3,4-*b*]pyridine (3s). Prepared according to General Method 1 using reagents: 4-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine (**1s**) (150 mg, 1.0 mmol), 5 mL of THF or DMSO, 1.5 mL of 1 M NaHMDS in THF (1.5 mmol), and iodomethane (0.19 mL, 3.0 mmol). THF and DMSO conditions: 20 ºC/2 h. Purification [FCC, SiO_2, 0-100% polar solvent (9-1 EtOAc:MeOH) in heptane] first afforded compound **2s** as a white solid (THF: 9 mg, 5% yield; DMSO: 110 mg, 67% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J*=5.38 Hz, 1H), 8.04 (s, 1H), 6.51 (d, *J*=5.50 Hz, 1H), 4.14 (s, 3H), 4.05

(s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 152.6, 150.6, 129.6, 107.4, 97.9, 55.8, 34.1; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from O-CH_3 (δ 4.05) to H5 (δ 6.51). LC/MS (ESI+) calcd for $C_8H_9N_3O$ ($[M + H]^+$) *m/z* 164.1; found 164.0. Anal. calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.74; H, 5.46; N, 25.32.

Continued elution provided compound **3s** as a white solid (THF: 50 mg, 30% yield; DMSO: 9 mg, 5% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.64 (d, *J*=5.87 Hz, 1H), 6.81 (d, *J*=5.87 Hz, 1H), 4.19 (s, 3H), 4.12 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1, 154.9, 149.4, 125.3, 107.8, 97.8, 57.3, 40.7; 2D NOESY NMR (400 MHz, DMSO-d_6) showed a crosspeak from O-CH_3 (δ 4.12) to H5 (δ 6.81) and N2-CH_3 (δ 4.19) to H3 (δ 8.73). LC/MS (ESI+) calcd for $C_8H_9N_3O$ ($[M + H]^+$) *m/z* 164.1; found 164.0. Anal. calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 43.39; H, 5.26; N, 18.36.

4-Chloro-1-methyl-1*H*-pyrazolo[4,3-*c*]pyridine (2t) and 4-Chloro-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine (3t). Prepared according to General Method 1 using reagents: 4-chloro-1H-pyrazolo[4,3-c]pyridine (**1t**) (150 mg, 0.98 mmol), 5 mL of THF or DMSO, 1.5 mL of 1 M NaHMDS in THF (1.5 mmol), and iodomethane (0.18 mL, 2.9 mmol). THF conditions: 20 ºC/16 h. DMSO conditions: 20 ºC/1 h. Purification (FCC, SiO_2, 0-50% EtOAc in heptane) first afforded compound **2t** as a white solid (THF: 70 mg, 43% yield; DMSO: 85 mg, 52% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J*=6.0 Hz, 1H), 8.10 (s, 1H), 7.22 (dd, *J*=0.7, 6.0 Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 143.9, 143.1, 133.0, 120.1, 103.6, 36.1; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from δ 4.07 to δ 7.22. LC/MS (ESI+) calcd for $C_7H_6ClN_3$ ($[M + H]^+$) *m/z* 168.0; found 168.0. Anal. calcd for $C_7H_6ClN_3$: C, 50.17; H, 3.61; N, 25.07. Found: C, 50.38; H, 3.37; N, 24.68.

Continued elution provided compound **3t** as a white solid (THF: 64 mg, 39% yield; DMSO: 45 mg, 27% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.04 (d, *J*=6.2 Hz, 1H), 7.44 (dd, *J*=0.9, 6.2 Hz, 1H), 4.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 145.2, 141.4, 125.2, 119.5, 110.7, 40.8; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from δ 4.26 to δ 8.10. LC/MS (ESI+) calcd for $C_7H_6ClN_3$ ($[M + H]^+$) *m/z* 168.0; found 168.0. Anal. calcd for $C_7H_6ClN_3$: C, 50.17; H, 3.61; N, 25.07. Found: C, 50.08; H, 3.48; N, 24.43.

4-Chloro-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (2u) and 4-Chloro-2-methyl-2*H*-pyrazolo[3,4-*b*]pyridine (3u). Prepared according to General Method 1 using reagents: 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine (**1u**) (150 mg, 0.98 mmol), 5 mL of THF or DMSO, 1.5 mL of 1 M NaHMDS in THF (1.5 mmol), and iodomethane (0.19 mL, 2.9 mmol). THF conditions: 20 ºC/4 h. DMSO conditions: 20 ºC/1 h. Purification (FCC, SiO_2, 0-80% EtOAc in heptane) first afforded compound **2u** as a white solid (THF: 17 mg, 11% yield; DMSO: 72 mg, 44% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J*=4.9 Hz, 1H), 8.06 (s, 1H), 7.11 (d, *J*=5.0 Hz, 1H), 4.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 148.9, 137.7, 130.3, 116.6, 115.3, 34.3. Anal. calcd for $C_7H_6ClN_3$: C, 50.17; H, 3.61; N, 25.07. Found: C, 50.14; H, 3.42; N, 24.79.

Continued elution provided compound **3u** as a white solid (THF: 132 mg, 81% yield; DMSO: no product isolated): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J*=4.6 Hz, 1H), 7.99 (s, 1H), 7.04 (d, *J*=4.8Hz, 1H), 4.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 151.1, 137.0, 123.0, 117.2, 115.0, 41.3; 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from δ 4.25 to δ 7.99. Anal. calcd for $C_7H_6ClN_3$: C, 50.17; H, 3.61; N, 25.07. Found: C, 50.05; H, 3.52; N, 24.81.

3-Bromo-4-methoxy-1-methyl-1*H*-pyrazolo[4,3-*c*]pyridine (2v) and 3-Bromo-4-methoxy-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine (3v). Prepared according to General Method 1 using reagents: 3-bromo-4-methoxy-1*H*-pyrazolo[4,3-*c*]pyridine (**1v**) (110 mg, 0.48 mmol), 2.4 mL of THF or DMSO, 0.72 mL of 1 M NaHMDS in THF (0.72 mmol), and iodomethane (0.090 mL, 1.45 mmol). THF and DMSO conditions: 20 ºC/4 h. Purification [FCC, SiO_2, 10-100% (10% EtOAc in CH_2Cl_2) to heptane] first afforded compound **2v** as a white solid (THF: 73 mg, 63% yield; DMSO: 65 mg, 56% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J*=6.11 Hz, 1H), 6.87 (d, *J*=6.24 Hz, 1H), 4.12 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 146.7, 142.8, 119.1, 109.3, 99.1, 53.6, 36.1. 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from δ 3.99 to δ 6.87. LC/MS (ESI+) calcd for $C_8H_8BrN_3O$ ($[M + H]^+$) *m/z* 242.0/244.0; found 242.1/244.1. Anal. calcd for $C_8H_8BrN_3O$: C, 39.69; H, 3.33; N, 17.36. Found: C, 39.65; H, 3.09; N, 16.98.

Continued elution provided compound **3v** as a white solid (THF: 18 mg, 15% yield; DMSO: 8 mg, 7% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J*=6.36 Hz, 1H), 7.08 (d, *J*=6.36 Hz, 1H), 4.15 (s, 3H), 4.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 152.3, 140.3, 109.8, 107.9, 106.0, 53.5, 38.9. LC/MS (ESI+) calcd for $C_8H_8BrN_3O$ ([M + H]$^+$) *m/z* 242.0/244.0; found 242.1/244.1 Anal. calcd for $C_8H_8BrN_3O$: C, 39.69; H, 3.33; N, 17.36. Found: C, 40.29; H, 3.39; N, 16.94.

3-Bromo-4-methoxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2w) and 3-Bromo-4-methoxy-2-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine (3w). Prepared according to General Method 1 using reagents: 3-bromo-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1w**) (100 mg, 0.44 mmol), 2.2 mL of THF or DMSO, 0.65 mL of 1 M NaHMDS in THF (0.65 mmol), and iodomethane (0.082 mL, 1.3 mmol). THF conditions: 20 ºC/24 h. DMSO conditions: 20 ºC/1 h. Purification (FCC, SiO_2, 10-100% EtOAc in heptane) first afforded compound **2w** as a white solid (THF: 29 mg, 27% yield; DMSO: 85 mg, 80% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 4.20 (s, 3H), 4.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 156.0, 155.3, 117.9, 103.0, 54.7, 34.4. 2D HMBC crosspeaks from δ 4.08 to 119.7 (NMe to C3, 1,4 weak), δ 4.08 to 155.9 (NMe to C7a, 1,3 strong). Anal. calcd for $C_7H_7BrN_4O$: C, 34.59; H, 2.90; N, 23.05. Found: C, 34.70; H, 2.53; N, 22.81.

Continued elution provided compound **3w** as a white solid (THF: 50 mg, 47% yield; DMSO: 7 mg, 7% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 4.18 (s, 3H), 4.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 160.4, 155.9, 107.2, 104.0, 54.4, 39.2. 2D HMBC crosspeaks from δ 4.18 to 106.8 (NMe to C3, 1,3 strong). Anal. calcd for $C_7H_7BrN_4O$: C, 34.59; H, 2.90; N, 23.05. Found: C, 34.65; H, 2.66; N, 22.80.

3-Bromo-4-chloro-1-methyl-1*H*-pyrazolo[4,3-*c*]pyridine (2x) and 3-Bromo-4-chloro-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine (3x). Prepared according to General Method 1 using reagents: 3-bromo-4-chloro-1*H*-pyrazolo[4,3-*c*]pyridine (**1x**) (140 mg, 0.60 mmol), 3 mL of THF or DMSO, 0.9 mL of 1 M NaHMDS in THF (0.90 mmol), and iodomethane (0.11 mL, 1.8 mmol). THF conditions: 20 ºC/16 h. DMSO conditions: 20 ºC/4 h. Purification (FCC, SiO_2, 0-30% EtOAc in heptane) first afforded compound **3x** as a white solid (THF: 15 mg, 10% yield; DMSO: 0 mg, 0% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=6.2 Hz, 1H), 7.37 (d, *J*=6.2 Hz, 1H), 4.15 (s, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 151.0, 144.9, 141.6, 117.2, 111.2, 109.3, 39.6. Anal. calcd for $C_7H_5BrClN_3$: C, 34.11; H, 2.04; N, 17.05. Found: C, 34.02; H, 1.83; N, 16.97.

Continued elution provided compound **2x** as a white solid (THF: 88 mg, 61% yield; DMSO: 100 mg, 67% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J*=6.1 Hz, 1H), 7.26 (d, *J*=6.0 Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 145.2, 143.9, 120.2, 117.8, 104.0, 36.4. 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from δ 4.07 to δ 7.26. Anal. calcd for $C_7H_5BrClN_3$: C, 34.11; H, 2.04; N, 17.05. Found: C, 34.19; H, 1.79; N, 17.08.

3-Bromo-4-chloro-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (2y) and 3-Bromo-4-chloro-2-methyl-2*H*-pyrazolo[3,4-*b*]pyridine (3y). Prepared according to General Method 1 using reagents: 3-bromo-4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine (**1y**) (145 mg, 0.62 mmol), 3.1 mL of THF or DMSO, 0.94 mL of 1 M NaHMDS in THF (0.94 mmol), and iodomethane (0.12 mL, 1.9 mmol). THF and DMSO conditions: 20 ºC/16 h. Purification (FCC, SiO_2, 0-50% EtOAc in heptane) first afforded compound **2y** as a white solid (THF: 39 mg, 25% yield; DMSO: 102 mg, 66% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J*=4.9 Hz, 1H), 7.13 (d, *J*=5.0 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 149.9, 138.3, 118.1, 117.0, 112.9, 34.5; 2D HSQC and HMBC NMR (400 MHz, $CDCl_3$) confirmed the structure. Anal. calcd for $C_7H_5BrClN_3$: C, 34.11; H, 2.04; N, 17.05. Found: C, 34.26; H, 1.86; N, 16.97.

Continued elution provided compound **3y** as a white solid (THF: 66 mg, 43% yield; DMSO: 0 mg, 0% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br. s., 1H), 7.27 (d, *J*=4.9 Hz, 1H), 4.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 148.8, 141.22, 118.0, 107.9, 39.8; 2D HSQC and HMBC NMR (400 MHz, $CDCl_3$) confirmed the structure. Anal. calcd for $C_7H_5BrClN_3$: C, 34.11; H, 2.04; N, 17.05. Found: C, 34.4; H, 1.78; N, 16.82.

5-Bromo-1-methyl-1*H*-benzo[*d*]imidazole (2b') and 6-Bromo-1-methyl-1*H*-benzo[*d*]imidazole (4b'). Prepared according to General Method 1 using reagents: 5-bromo-1*H*-benzo[*d*]imidazole (**1b'**) (150 mg, 0.76 mmol), 3.8 mL of THF or DMSO, 1.1 mL of 1 M NaHMDS in THF (1.1 mmol), and iodomethane (0.14 mL, 2.3 mmol). THF and DMSO conditions: 20 ºC/2 h. Purification [FCC, SiO_2, 10-100% (9-1 EtOAc/MeOH) to heptane] afforded a 1:1 mixture of compounds **2b'** and **4b'** as a white solid (THF: 167 mg, 104% yield; DMSO: 105 mg, 65% yield): ^{1}H NMR

(400 MHz, $CDCl_3$) for the 1:1 mixture of compounds **2b'** and **4b'** matched that observed for individual commercial samples.

6-Bromo-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (2c') and 6-Bromo-1-methyl-1*H*-imidazo[4,5-*b*]pyridine (4c'). Prepared according to General Method 1 using reagents: 6-bromo-3*H*-imidazo[4,5-*b*]pyridine (**1c'**) (150 mg, 0.76 mmol), 3.8 mL of THF or DMSO, 1.1 mL of 1 M NaHMDS in THF (1.1 mmol), and iodomethane (0.14 mL, 2.3 mmol). THF and DMSO conditions: 20 ºC/2 h. Purification [FCC, SiO_2, 10-100% (9-1 EtOAc/MeOH) to heptane] first afforded compound **2c'** as a white solid (THF: 23 mg, 14% yield; DMSO: 60 mg, 37% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported;[40] ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 145.7, 145.1, 136.4, 130.2, 113.8, 29.9; 2D NOESY NMR (400 MHz, $CDCl_3$) confirmed.

Continued elution provided compound **4c'** as a white solid (THF: 86 mg, 54% yield; DMSO: 10 mg, 6% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported;[41] ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 146.3, 145.8, 127.6, 120.2, 114.1, 31.5; 2D NOESY NMR (400 MHz, $CDCl_3$) confirmed.

5-Bromo-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (2d') and 5-Bromo-1-methyl-1*H*-imidazo[4,5-*b*]pyridine (4d'). Prepared according to General Method 1 using reagents: 5-bromo-3*H*-imidazo[4,5-*b*]pyridine (**1d'**) (150 mg, 0.76 mmol), 3.8 mL of THF or DMSO, 1.1 mL of 1 M NaHMDS in THF (1.1 mmol), and iodomethane (0.14 mL, 2.3 mmol). THF and DMSO conditions: 20 ºC/1.5 h. Purification [FCC, SiO_2, 10-100% (9-1 EtOAc/MeOH) to heptane] first afforded compound **2d'** as a white solid (THF: 30 mg, 19% yield; DMSO: 74 mg, 46% yield): ^{1}H NMR ($CDCl_3$) ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.91 (d, *J*=8.4 Hz, 1H), 7.38 (d, *J*=8.3 Hz, 1H), 3.90 (s, 3H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from δ 3.90 to δ 8.00; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 144.7, 135.9, 134.4, 130.1, 122.1, 30.0. Anal. calcd for $C_7H_6BrN_3$: C, 39.65; H, 2.85; N, 19.82. Found: C, 40.12; H, 2.77; N, 19.65.

Continued elution provided compound **4d'** as a white solid (THF: 106 mg, 66% yield; DMSO: 60 mg, 37% yield): ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.35 (d, *J*=8.3 Hz, 1H), 3.88 (s, 3H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed crosspeaks from δ 3.88 to δ 7.58 and 7.35; ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0,

146.2, 135.7, 125.9, 121.8, 119.9, 31.7. Anal. calcd for $C_7H_6BrN_3$: C, 39.65; H, 2.85; N, 19.82. Found: C, 40.09; H, 2.80; N, 19.76.

4-Chloro-1-methyl-1*H*-imidazo[4,5-*c*]pyridine (2e') and 4-Chloro-3-methyl-3*H*-imidazo[4,5-*c*]pyridine (4e'). Prepared according to General Method 1 with a modification using reagents: 4-chloro-1H-imidazo[4,5-c]pyridine (**1e'**) (150 mg, 0.98 mmol) was dissolved in 0.45 mL of DMSO and then 4.9 mL of THF or DMSO were added, then 1.5 mL of 1 M NaHMDS in THF (1.5 mmol), and finally iodomethane (0.18 mL, 2.9 mmol). THF/DMSO and DMSO conditions: 20 ºC/3 h. Purification [FCC, SiO_2, 10-100% (9-1 EtOAc/MeOH) to heptane] first afforded compound **4e'** as a white solid (THF/DMSO: 53 mg, 32% yield; DMSO: 40 mg, 24% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported;[42] ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 147.5, 141.0, 134.0, 128.7, 114.9, 34.0.

Continued elution provided compound **2e'** as a white solid (THF/DMSO: 68 mg, 42% yield; DMSO: 46 mg, 28% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported;[43] ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 142.7, 141.3, 140.4, 137.6, 104.9, 31.5.

7-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (2f') and 7-Chloro-1-methyl-1*H*-imidazo[4,5-*b*]pyridine (4f'). Prepared according to General Method 1 using reagents: 7-chloro-3*H*-imidazo[4,5-*b*]pyridine (**1f'**) (100 mg, 0.65 mmol), 3 mL of THF or DMSO were added, then 1.0 mL of 1 M NaHMDS in THF (1.0 mmol), and finally iodomethane (0.12 mL, 2.0 mmol). In a third experiment (designated THF/DMSO) compound **1f'** (100 mg, 0.65 mmol) was dissolved in 0.3 mL of DMSO and then 3 mL of THF was added followed by 1.0 mL of 1 M NaHMDS in THF (1.0 mmol), and finally iodomethane (0.12 mL, 2.0 mmol). THF conditions 20 ºC/2 h. DMSO conditions: 20 ºC/96 h. THF/DMSO conditions: 20 ºC/1.5 h. Purification [FCC, SiO_2, 10-100% (9-1 EtOAc/MeOH) to heptane] first afforded compound **2f'** as a light yellow solid (THF: 20 mg, 18% yield; DMSO: 37 mg, 34% yield; THF/DMSO: 36 mg, 33%): ^{1}H NMR ($CDCl_3$) was identical to that reported.[44]

Continued elution provided compound **4f'** as a light yellow solid (THF: 61 mg, 56% yield; DMSO: 15 mg, 14% yield; THF/DMSO: 32 mg, 29% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported.[44]

6-Chloro-9-methyl-9*H*-purine (2g') and 6-Chloro-7-methyl-7*H*-purine (4g'). Prepared according to General Method 1 using reagents: 6-chloro-9*H*-purine (**1g'**) (150 mg, 1.0 mmol), 5.0 mL THF or DMSO were added, then 1.5 mL of 1 M NaHMDS in THF (1.5 mmol), and finally iodomethane (0.19 mL, 3.0 mmol). THF and DMSO conditions 20 ºC/5 h. Purification [FCC, SiO_2, 30-100% (9-1 EtOAc/MeOH) to heptane] first afforded compound **2g'** as a light yellow solid (THF: 55 mg, 33% yield; DMSO: 68 mg, 40% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported;[45] ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 151.9, 150.9, 145.6, 131.4, 30.2.

Continued elution provided compound **4g'** as a light yellow solid (THF: 70 mg, 42% yield; DMSO: 26 mg, 15% yield); ^{1}H NMR (DMSO-d_6) was identical to that reported;[45] ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 162.3, 151.3, 142.4, 122.7, 33.9.

6-Methoxy-9-methyl-9*H*-purine (2h') and 6-Methoxy-7-methyl-7*H*-purine (4h'). Prepared according to General Method 1 using reagents: 6-methoxy-9*H*-purine (**1h'**) (150 mg, 1.0 mmol), 5.0 mL THF or DMSO were added, then 1.5 mL of 1 M NaHMDS in THF (1.5 mmol), and finally iodomethane (0.19 mL, 3.0 mmol). THF and DMSO conditions 20 ºC/1.5 h. Purification [FCC, SiO_2, 0-100% (9-1 EtOAc/MeOH) to heptane] first afforded compound **2h'** as a light yellow solid (THF: 41 mg, 25% yield; DMSO: 67 mg, 41% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported.[45]

Continued elution provided compound **4h'** as a light yellow solid (THF: 90 mg, 55% yield; DMSO: 38 mg, 23% yield): ^{1}H NMR ($CDCl_3$) was identical to that reported.[45]

4-Chloro-1-methyl-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (2i'), 4-Chloro-2-methyl-2*H*-[1,2,3]triazolo[4,5-*c*]pyridine (3i') and 4-Chloro-3-methyl-3*H*-[1,2,3]triazolo[4,5-*c*]pyridine (4i'). Prepared according to General Method 1 using reagents: 4-chloro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (**1i'**) (154 mg, 1.0 mmol), 5.0 mL THF or DMSO were added, then 1.5 mL of 1 M NaHMDS in THF (1.5 mmol), and finally iodomethane (0.19 mL, 3.0 mmol). THF conditions 20 ºC/24 h. DMSO conditions 20 ºC/2 h. Purification (FCC, SiO_2, 0-10% EtOAc to heptane) first afforded compound **3i'** as a white solid (THF: 28 mg, 17% yield; DMSO: 42 mg, 25% yield): mp 97-99 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J=5.99 Hz, 1H), 7.95 (d, J=5.99 Hz, 1H), 4.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.6,

142.0, 141.4, 139.1, 111.9, 44.2; 2D-NMR experiments HSQC and HMBC defined ^{13}C and ^{1}H chemical shift assignments. LC/MS (ESI+) calcd for $C_6H_5ClN_4$ ([M + H]$^+$) *m/z* 169.0; found 169.1. Anal. calcd for $C_6H_5ClN_4$: C, 42.75; H, 2.99; N, 33.23. Found: C, 43.04; H, 2.94; N, 32.45. X-ray crystallography confirmed the structure; see CCDC 1825992.

Continued elution provided compound **4i'** as a white solid (THF: 30 mg, 18% yield; DMSO: 25 mg, 15% yield): mp 120-121 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J*=5.87 Hz, 1H), 8.10 (d, *J*=5.75 Hz, 1H), 4.55 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.3, 141.3, 134.2, 128.3, 113.5, 37.1; 2D-NMR experiments HSQC and HMBC defined ^{13}C and ^{1}H chemical shift assignments. LC/MS (ESI+) calcd for $C_6H_5ClN_4$ ([M + H]$^+$) *m/z* 169.0; found 169.0. Anal. calcd for $C_6H_5ClN_4$: C, 42.75; H, 2.99; N, 33.23. Found: C, 43.23; H, 2.89; N, 32.61. X-ray crystallography confirmed the structure; see CCDC 1825994.

Continued elution (10-75% EtOAc to heptane) provided compound **2i'** as a white solid (THF: 76 mg, 45% yield; DMSO: 49 mg, 29% yield): mp 149-150 ˚C (lit.[46] mp 150-152 ˚C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J*=5.87 Hz, 1H), 7.95 (d, *J*=5.87 Hz, 1H), 4.37 (s, 3H); 2D NOESY NMR (400 MHz, DMSO-d_6) showed crosspeaks from δ 4.37 to δ 7.95; ^{13}C NMR (101 MHz, DMSO-d_6) δ 143.6, 141.7, 139.5, 138.7, 106.2, 35.0; 2D-NMR experiments HSQC and HMBC defined ^{13}C and ^{1}H chemical shift assignments. LC/MS (ESI+) calcd for $C_6H_5ClN_4$ ([M + H]$^+$) *m/z* 169.0; found 169.1. Anal. calcd for $C_6H_5ClN_4$: C, 42.75; H, 2.99; N, 33.23. Found: C, 42.96; H, 2.80; N, 32.89. X-ray crystallography confirmed the structure; see CCDC 1826000.

7-Chloro-3-methyl-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine (2j'), 7-Chloro-2-methyl-2*H*-[1,2,3]triazolo[4,5-*b*]pyridine (3j') and 7-Chloro-1-methyl-1*H*-[1,2,3]triazolo[4,5-*b*]pyridine (4j'). Prepared according to General Method 1 using reagents: 7-chloro-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine (**1j'**) (100 mg, 0.65 mmol), 3.2 mL THF or DMSO were added, then 0.97 mL of 1 M NaHMDS in THF (0.97 mmol), and finally iodomethane (0.12 mL, 2.0 mmol). THF conditions 20 ºC/48 h. DMSO conditions 20 ºC/4 h. Purification (FCC, SiO_2, 0-5% EtOAc to CH_2Cl_2) first afforded compound **2j'** as a white solid (THF: 21 mg, 19% yield; DMSO: 26 mg, 24% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J*=4.89 Hz, 1H), 7.35-7.43 (m, 1H), 4.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 147.1, 136.5,

135.5, 119.9, 33.5; 2D-NMR experiments HSQC and HMBC defined ^{13}C and ^{1}H chemical shift assignments with cross peaks indicating a strong 3-bond CH_3 (δ 4.39) to C3a (δ 147.1) and a weak 4-bond CH_3 (δ 4.39) to C7a (δ 135.5) connectivity. Anal. calcd for $C_6H_5ClN_4$: C, 42.75; H, 2.99; N, 33.23. Found: C, 42.61; H, 2.54; N, 32.87. X-ray crystallography confirmed the structure; see CCDC 1825996.

Continued elution provided compound **3j'** as a white solid (THF: 19 mg, 17% yield; DMSO: 28 mg, 25% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 - 8.63 (m, 1H), 7.42 (s, 1H), 4.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 151.5, 135.9, 134.5, 121.7, 44.4; 2D-NMR experiments HSQC and HMBC defined ^{13}C and ^{1}H chemical shift assignments with cross peaks indicating a weak 4-bond CH_3 (δ 4.62) to C3a (δ 156.6) and a weak 4-bond CH_3 (δ 4.62) to C7a (δ 135.9) connectivity. Anal. calcd for $C_6H_5ClN_4$: C, 42.75; H, 2.99; N, 33.23. Found: C, 42.56; H, 2.86; N, 32.77. X-ray crystallography confirmed the structure; see CCDC 1825999.

Continued elution (5-50% EtOAc to CH_2Cl_2) provided compound **4j'** as a white solid (THF: 46 mg, 43% yield; DMSO: 22 mg, 20% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J=4.77 Hz, 1H), 7.46 (d, J=4.77 Hz, 1H), 4.60 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8, 148.5, 127.6, 124.0, 122.6, 37.4; 2D-NMR experiments HSQC and HMBC defined ^{13}C and ^{1}H chemical shift assignments with cross peaks indicating a weak 4-bond CH_3 (δ 4.60) to C3a (δ 158.8) and a strong 3-bond CH_3 (δ 4.60) to C7a (δ 124.0) connectivity. Anal. calcd for $C_6H_5ClN_4$: C, 42.75; H, 2.99; N, 33.23. Found: C, 42.92; H, 2.80; N, 32.94. X-ray crystallography confirmed the structure; see CCDC 1825995.

6-Bromo-3-methyl-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine (2l'), 6-Bromo-2-methyl-2*H*-[1,2,3]triazolo[4,5-*b*]pyridine (3l') and 6-Bromo-1-methyl-1*H*-[1,2,3]triazolo[4,5-*b*]pyridine (4l'). Prepared according to General Method 1 using reagents: 6-bromo-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine (**1l'**) (150 mg, 0.75 mmol), 3.8 mL THF or DMSO were added, then 1.1 mL of 1 M NaHMDS in THF (1.1 mmol), and finally iodomethane (0.14 mL, 2.3 mmol). THF conditions 20 ºC/4 h. DMSO conditions 20 ºC/24 h. Purification (FCC, SiO_2, 0-5% EtOAc to CH_2Cl_2) first afforded compound **2l'** as a white solid (THF: 18 mg, 11% yield; DMSO: 30 mg, 19% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J=2.0 Hz, 1H), 8.51 (d, J=2.0 Hz, 1H), 4.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 144.7, 137.9, 130.5, 115.5, 33.2; 2D-NMR experiment HMBC defined ^{13}C and ^{1}H chemical shift assignments with cross

peaks indicating a strong 3-bond CH_3 (δ 4.36) to C3a (δ 144.7) and a weak 4-bond CH_3 (δ 4.36) to C7a (δ 137.9) connectivity. Anal. calcd for $C_6H_5BrN_4$: C, 33.83; H, 2.37; N, 26.30. Found: C, 34.15; H, 2.39; N, 26.24.

Continued elution provided compound **3l'** as a white solid (THF: 23 mg, 14% yield; DMSO: 20 mg, 12% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J*=2.2 Hz, 1H), 8.38 (d, *J*=2.2 Hz, 1H), 4.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 153.0, 137.5, 128.5, 117.8, 44.2; 2D-NMR experiment HMBC defined ^{13}C and ^{1}H chemical shift assignments with cross peaks indicating a weak 4-bond CH_3 (δ 4.55) to C3a (δ 154.3) and a weak 4-bond CH_3 (δ 4.55) to C7a (δ 137.5) connectivity. Anal. calcd for $C_6H_5BrN_4$: C, 33.83; H, 2.37; N, 26.30. Found: C, 34.22; H, 2.06; N, 26.37.

Continued elution provided compound **4l'** as a white solid (THF: 39 mg, 24% yield; DMSO: 22 mg, 14% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J*=2.0 Hz, 1H), 8.13 (d, *J*=2.1 Hz, 1H), 4.32 (s, 3H); 2D NOESY NMR (400 MHz, $CDCl_3$) showed a crosspeak from δ 4.32 to δ 8.13; ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 149.4, 126.6, 120.4, 119.1, 35.0; 2D-NMR experiment HMBC defined ^{13}C and ^{1}H chemical shift assignments with cross peaks indicating a weak 4-bond CH_3 (δ 4.32) to C3a (δ 156.0) and a strong 3-bond CH_3 (δ 4.32) to C7a (δ 126.6) connectivity. Anal. calcd for $C_6H_5BrN_4$: C, 33.83; H, 2.37; N, 26.30. Found: C, 34.00; H, 2.14; N, 26.01.

Tris-[4-Methoxy-2-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine]-bis-[sodium iodide] hexahydrate (5a) and Tetrakis-[4-Methoxy-2-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine]-tris-[sodium iodide] dihydrate (5b). To a heterogeneous mixture of 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1a**) (4.01 g, 26.0 mmol) in 104 mL dioxane was added 15 mL of a 25 weight % solution of sodium methoxide in methanol (65 mmol) and the mixture stirred at 80 ˚C for 1.5 h, then cooled to 20 ˚C. Then iodomethane (6.5 mL, 104 mmol) was added and the mixture stirred at 20 ˚C for 1 h. Then silica gel (23 g) was added and the solvent evaporated. The resulting solid was loaded into a pre-column and subjected to purification [FCC, SiO_2 (120 g column), 1-20% methanol in EtOAc] and afforded compound **5** (4.79 g, 65% yield based on a monomeric unit of the higher molecular oligomer **5b**) as a white solid: mp 158-160 ˚C; ^{1}H NMR (400 MHz) ^{13}C NMR (101 Hz), 2D NOESY and 2D HMBC NMR experiments in DMSO-d_6, $CDCl_3$, THF-d_8, and methanol-d_4 were all identical to that observed for compound **3b**.

Complex $[C_7H_8N_4O]_3[NaI]_2[H_2O]_6$ (**5a**) single crystal X-ray diffraction studies. Crystals of compound **5a** were grown by slow cooling of an EtOAc/hexane solution in an 80 ˚C sand bath. A 0.053 × 0.021 × 0.005 mm piece of an orange plank was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm and exposure time was 20 seconds per frame using a scan width of 1.0˚. Data collection was 100% complete to 25.00° in θ. A total of 16912 reflections were collected covering the indices, -33<=h<=33, -41<=k<=54, -8<=l<=8. 3922 reflections were found to be symmetry independent, with a R_{int} of 0.0642. Indexing and unit cell refinement indicated an *F*-centered, orthorhombic lattice. The space group was found to be *F*dd2. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure. All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL- 2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. There relative positions were restrained using DFIX commands and their thermals fixed to that of the parent atom. Crystallographic data are summarized in the Supporting Information; see CCDC 1825998.

Complex $[C_7H_8N_4O]_4[NaI]_3[H_2O]_2$ (**5b**) single crystal X-ray diffraction studies and microanalysis. Crystals of compound **5b** were prepared by dissolving 86 mg of the white solid **5** into 6 mL of EtOAc in a 20 mL sealed vial at 80 ˚C. Then 3 mL of hexane were added while maintaining 80 ˚C which formed a small amount of white solid. An additional 2 mL of EtOAc was added and the mixture heated at 80 ˚C for 10 min, then cooled to 60 ˚C and let sit at 60 ˚C for 2 h. Then cooled to 40 ˚C and then let sit at 40 ˚C for 2h. Finally, the mixture was cooled to 20 ˚C and crystals collected under solution for X-ray diffraction and microanalysis. The microanalysis sample was prepared by decanting the solvent and drying the sample under a stream of N_2 and then high vacuum at 20 ˚C for 16 h to provide 41 mg of **5b** as a white crystalline solid: mp 160-162 ˚C. C, H, N microanalysis was conducted in a glovebox. Anal. calcd for $C_{28}H_{36}I_3N_{16}Na_3O_6$: C, 29.44; H, 3.18; I, 33.33; N, 19.62; Na, 6.04. Found: C, 29.60; H, 3.05; I, 27.03; N, 19.58; Na, 5.90. Extra analysis found: Cl, 0.0090%.

A 0.157 × 0.053 × 0.049 mm piece of a colorless block of crystalline **5b** was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm and exposure time was 2 seconds per frame using a scan width of 1.0˚. Data collection was 99.9% complete to 25.00˚ in *θ*. A total of 26596 reflections were collected covering the indices, -20<=h<=19, -22<=k<=22, -17<=l<=17. 4089 reflections were found to be symmetry independent, with a R_{int} of 0.0539. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be *P*bcn. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure. All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. Crystallographic data are summarized in the Supporting Information; see CCDC 1826001.

Theoretical Calculations. The Density Functional Theory (DFT) calculations were carried out at the B3LYP/6-31G**(d) level of theory using Jaguar1 which is part of the Schrödinger Software.[47] All calculations were set to full minimization at the above level of theory, and the net charge is set to -1.

^{1}H Pulsed Field Gradient-Stimulated Echo (PFG-STE) NMR Experiments in THF-d_8 and DMSO-d_6. All NMR glass sample tubes were pre-rinsed with appropriate solutions **A** or **B** prior to transfer of 0.5 mL of each Sample **A-J** solution to respective NMR tubes. Samples **A-J** were prepared with compositions as described in the following.

Sample **A**. Compounds **7a, 7b,** and **7c** in THF-d_8. Compounds **7a** (43 mg, 0.3 mmol), **7b** (51 mg, 0.3 mmol), and **7c** (55 mg, 0.3 mmol) were dissolved in 6 mL of THF-d_8 and 4A molecular sieves were added. Then the mixture let sit at rt for 24 h.

Sample **B**. Compounds **7a, 7b,** and **7c** in DMSO-d_6. Compounds **7a** (43 mg, 0.3 mmol), **7b** (51 mg, 0.3 mmol), and **7c** (55 mg, 0.3 mmol) were dissolved in 6 mL of DMSO-d_6 and 4A molecular sieves were added. Then the mixture let sit at rt for 24 h.

Sample **C**. Compounds **1b, 7a, 7b,** and **7c** in THF-d_8. Compound **1b** (4.5 mg, 0.03 mmol) was dissolved in 0.6 mL of Sample **A**.

Sample **D**. Compounds **1r, 7a, 7b,** and **7c** in THF-d_8. Compound **1r** (4.5 mg, 0.03 mmol) was dissolved in 0.6 mL of Sample **A**.

Sample **E**. Compounds **1b, 7a, 7b,** and **7c** in DMSO-d_6. Compound **1b** (4.5 mg, 0.03 mmol) was dissolved in 0.6 mL of Sample **B**.

Sample **F**. Compounds **1r, 7a, 7b,** and **7c** in DMSO-d_6. Compound **1r** (4.5 mg, 0.03 mmol) was dissolved in 0.6 mL of Sample **B**.

Sample **G**. Compounds **1b*, 7a, 7b,** and **7c** in THF-d_8. Compound **1b** (15 mg, 0.1 mmol) was dissolved in 2 mL of Sample **A**, then NaO*t*-Bu (14.4 mg, 0.15 mmol) was added with mixing.

Sample **H**. Compounds **1r*, 7a, 7b,** and **7c** in THF-d_8. Compound **1r** (15 mg, 0.1 mmol) was dissolved in 2 mL of Sample **A**, then NaO*t*-Bu (14.4 mg, 0.15 mmol) was added with mixing.

Sample **I**. Compounds **1b*, 7a, 7b,** and **7c** in DMSO-d_6. Compound **1b** (15 mg, 0.1 mmol) was dissolved in 2 mL of Sample **B**, then NaO*t*-Bu (14.4 mg, 0.15 mmol) was added with mixing.

Sample **J**. Compounds **1r*, 7a, 7b,** and **7c** in DMSO-d_6. Compound **1r** (15 mg, 0.1 mmol) was dissolved in 2 mL of Sample **B**, then NaO*t*-Bu (14.4 mg, 0.15 mmol) was added with mixing.

All samples were homogeneous except for Sample **G**. Sample **G** (0.5 mL) was filtered through a small plug of Celite on cotton in a glass pipette directly into an NMR sample tube. Some concentrations were not as expected due to mechanical errors during the transfer of the volatile naphthalene reagents **7a**, **7b**, and **7c**. The internal standards **7a**, **7b**

and **7c** were 75 mM in each solution as determined by ^{1}H NMR integral comparison with known 50 mM concentrations of **1b** and **1r** in samples **C**, **D** and **E**. Sample **F** had a 60 mM concentration of **1r** by comparison to **7a**, **7b** and **7c** (as determined in **C**-**E**). Based on the determined concentrations of internal standards **7a**, **7b** and **7c**, as determined by integral comparison, the solution concentrations of the *N*-anionic compounds were as follows: Sample **G**, 9 mM **1b***; Sample **H**, 75 mM **1r***; Sample **I**, 50 mM **1b***; Sample **J**, 75 mM **1r***. To each of the remainder of Samples **G**-**J** not used for an NMR sample was added iodomethane (0.019 mL, 0.3 mmol) and the mixtures stirred 1 h and then analyzed by LC/MS. Each was found to contain the same composition of products previously described in Table 4, entries 14, 10, 15, and 11, respectively, as identified by retention times and [M+H] signals.

4-Methoxypyrazolo[3,4-*d*]pyrimidin-1-ide (1b*). Sample G, ^{1}H NMR (600MHz, THF-d_8) δ 8.23 (s, 0.12H), 8.01 (s, 0.12H), 4.02 (s, 0.37H); **Sample I**, ^{1}H NMR (600MHz, DMSO-d_6) δ 8.08 (s, 0.62H), 7.88 (s, 0.54H), 3.94 (s, 3H).

4-Methoxypyrazolo[4,3-*c*]pyridin-1-ide (1r*). Sample H, ^{1}H NMR (600MHz, THF-d_8) δ 8.03 (s, 1H), 7.44 (d, J=5.9 Hz, 1H), 6.94 (d, J=6.1 Hz, 1H), 3.95 (s, 3H); **Sample J**, ^{1}H NMR (600MHz, DMSO-d_6) δ 7.85 (m, 1H), 7.30 - 7.26 (m, 1H), 6.92 - 6.87 (m, 1H), 3.87 (m, 3H).

^{1}H PFG-STE NMR data were acquired at 27 ºC on Bruker Avance III HD 600 equipped with a triple resonance inverse detection TCI cryo-probe head (Bruker, Billerica, MA). In 1D ^{1}H NMR experiments for observation of signals of each of the compounds **1b**, **1b***, **1r**, **1r***, **7a**, **7b**, and **7c** in Samples **A**-**J** was used a data size of 65,536 complex points, a sweep width of 9615 Hz, an acquisition time of 3.41 s, and 16 scans were accumulated. Translational diffusion constants, D_t, were measured by pulsed gradient simulated-echo (PFG-STE) NMR experiments.[27b, 27c] For each experiment, a series of 16 diffusion-weighted 1D ^{1}H PFG-STE spectra were recorded in a two-dimensional manner, using a pair of gradient pulses of duration δ = 2.5 ms that were separated by a delay of Δ = 100 ms, with gradient strengths, G_D, ranging from 0.5 to 30 Gcm^{-1}. All NMR data were processed with the software TOPSPIN 3.2 (Bruker). Translational diffusion coefficients, D_t, for particles in solution were determined using Equation 8 for the signal attenuation, Ψ_Q, in PFG-STE NMR experiments,[27a, 48]

$$\Psi_Q,=\exp\{-QD_tT_{diff}\}, \quad (8)$$

With $Q = (\gamma s G_D \delta)^2$, where γ is the proton gyromagnetic ratio and s described the shape of the diffusion gradient, and $T_{diff} = \Delta - \delta/3$. G_D was calibrated with the residual ^1H resonance in 99% ^2H_2O by use of a self-diffusion coefficient for HDO at 25 °C of (1.902 ± 0.002) x 10^{-9} m^2s^{-1}.[48]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^1H, ^{13}C, and 2D NMR spectra, LC/MS chromatograms, X-ray crystallographic structures, DFT calculations, ^1H PFG-STE NMR analysis (PDF).

AUTHOR INFORMATION

Corresponding Author

*E-mail: brettbookser@gmail.com

ORCID

Brett C. Bookser: 0000-0002-0822-7029

Notes

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33. As expected, the anionic compounds **1b*** and **1r*** have ^{1}H NMR shift assignments in THF-d_8 and DMSO-d_6 distinct from the neutral compounds **1b** and **1r**. See the PFG-STE NMR analysis within the Experimental Section and Supporting Information for detailed comparative information.

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