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Regioselective Preparation of Saturated Spirocyclic and Ring-Expanded Fused Pyrazoles

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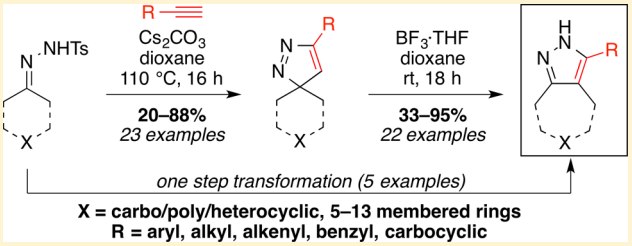
Supporting Information

ABSTRACT: Saturated bicyclic pyrazoles represent an important class of biologically active molecules, but their preparation can be hampered by labor-intensive synthesis of required starting materials. A convenient one- or two-step procedure for the synthesis of saturated spirocyclic and fused pyrazoles is reported. The synthesis benefits from the use of readily available alkynes and bench-stable tosylhydrazones, which are easily prepared from their parent ketones. Sigmatropic rearrangement of spirocyclic pyrazoles to fused analogues occurs with concomitant one-carbon expansion of the saturated ring, allowing rapid access to a range of pharmaceutically and agrochemically relevant polycyclic structures featuring a broad scope of saturated ring sizes.

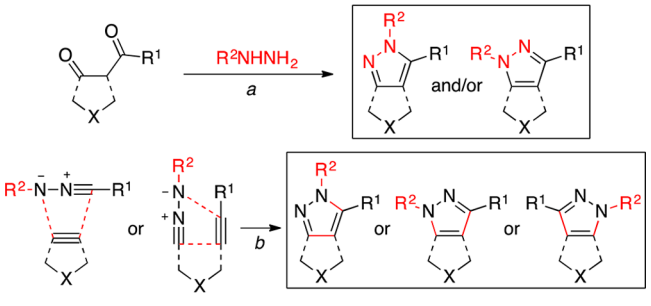


INTRODUCTION

The structural and electronic properties of the pyrazole motif have found widespread application in the development of diverse compound classes, such as metal chelators, dyes, agrochemicals, and pharmaceuticals.[1,2] There is a current drive in the industry toward improving the three-dimensional character of molecules by increasing the proportion of saturated (sp^3) carbon, and as such, the joining of a pyrazole motif with a saturated ring system represents an attractive building block.[3,4] Indeed, saturated fused bicyclic pyrazoles have demonstrated a broad range of biological activities,[5−22] but their preparation is not always straightforward.[5−11] General and robust methods for the generation of saturated polycyclic pyrazoles are, therefore, highly valuable synthetic processes.

Saturated bicyclic pyrazoles are typically prepared by the Knorr condensation of a hydrazine derivative with a 1,3-dicarbonyl compound[5−8,13−45] (Scheme 1a) or an equivalent substrate.[11,46−50] Alternative procedures involve variations of the 1,3-dipolar cycloaddition (Scheme 1b).[8−10,51−60] The main drawback of these methods lies in the often laborious preparation of the required starting materials, which can limit the available functionality in the product and precludes the late-stage introduction of structural diversity. In addition, some saturated heterocyclic systems have been noted to give unexpected rearrangement products under Knorr condensation conditions.[61]

Scheme 1. General Syntheses of Fused Pyrazoles via (a) Knorr Condensation or (b) 1,3-Dipolar Cycloaddition



The Valdés group recently reported a synthesis of substituted pyrazoles from tosylhydrazones and alkynes.[62] The reaction was proposed to proceed via a cycloaddition to give a 3,3,5-trisubstituted pyrazole intermediate, followed by spontaneous sigmatropic rearrangement to the 3,4,5-substituted pyrazole. Performing this procedure with cyclic tosylhydrazones would be expected to give the ring-expanded fused pyrazole. However, the authors found that saturated cycloalkyl substrates gave no desired product, and only examples involving an aryl or alkenyl (sp^2 carbon) migration from the 3,3-spirocyclic intermediate gave the desired ring-expanded fused product (Scheme 2a). In addition, although the 3,3,5-trisubstituted (or 3,3-spirocyclic) pyrazole intermediate was invoked mechanistically, it was not isolated. Despite this, saturated 3,3-spirocyclic pyrazoles have previously been synthesized from both aryl[63−67] and acyl stabilized[68,69] diazo compounds or from the gold catalyzed cyclization of propargylic tosylhydrazines (Scheme 2b).[70] The sigmatropic rearrangement of 3,3-disubstituted pyrazoles is well-established[71−77] and was demonstrated for spirocyclic

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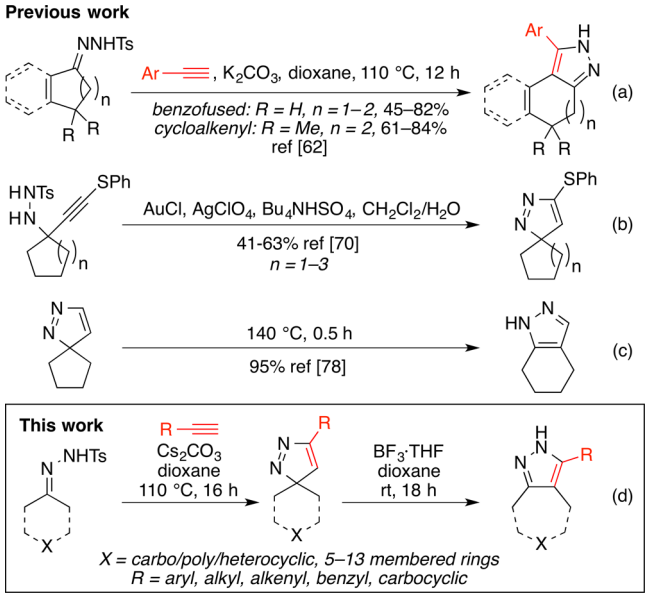
Scheme 2. Selected Studies in the Formation of Bicyclic Pyrazoles



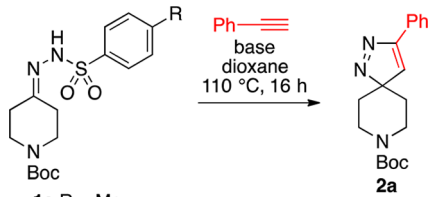
substrates in a report from Yen et al. (Scheme 2c), although the reaction requires relatively harsh conditions (150 °C).[78]

We have previously described a number of reactions using a range of structurally diverse, bench-stable saturated cyclic tosylhydrazones, which are trivial to prepare in one step from their parent ketones without the need for chromatographic purification.[79,80] On the basis of the aforementioned reports and our own experiences, we envisaged that diazo intermediates generated in situ from these compounds would undergo [3 + 2] cycloaddition with alkynes, providing access to a wide range of saturated spirocyclic pyrazoles (Scheme 2d). We then proposed to induce sigmatropic rearrangement of these spirocyclic species to give a collection of medicinally and agrochemically relevant ring-expanded fused pyrazoles (Scheme 2d). Because of the presence of a ring-expansion mechanism, this reaction allows the preparation of saturated polycyclic frameworks incorporating unusual ring sizes, which are typically challenging to obtain using conventional methods.

RESULTS AND DISCUSSION

To begin our investigations, piperidinone tosylhydrazone **1a** was heated at 110 °C with phenylacetylene and K_2CO_3 in dioxane. This led to recovery of a compound that was confirmed by 2D NMR as spirocyclic pyrazole **2a**, in a 7% yield (Table 1, entry 1). Pleasingly, this yield was vastly improved to 78% upon changing the base to Cs_2CO_3 (Table 1, entry 2). The significant increase in yield upon switching from potassium to cesium carbonate is consistent with observations from our previous studies on cross-coupling and ketone synthesis using sulfonylhydrazones.[79,80] A short screen of other bases revealed no further improvement in yield (Table 1, entries 3–5). We have previously reported the modulation of sulfonylhydrazone electronics as a route to slowing or accelerating diazo release in cross-coupling reactions.[79] However, in this instance, an equivalent yield was obtained using the electron-rich PMP-sulfonylhydrazone **1b** (Table 1, entry 6), while a highly electron-deficient sulfonylhydrazone **1c** gave a very low yield (Table 1, entry 7). Finally, the yield was moderately reduced by

Table 1. Optimization of Reaction Conditions for Cycloaddition of Sulfonylhydrazone 1 with Phenylacetylene To Form 2a[a]



entry	1	base	yield 2a (%)[b]
1	1a	K_2CO_3	7
2	1a	Cs_2CO_3	78
3	1a	$CsOH·H_2O$	57
4	1a	^tBuOK	12
5	1a	DBU	8
6	1b	Cs_2CO_3	77
7	1c	Cs_2CO_3	3
8	1a	Cs_2CO_3	52[c]

[a]Reaction conditions: 0.5 mmol of **1**, 0.75 mmol of phenylacetylene, 0.75 mmol of base, 2 mL of dioxane, 110 °C, sealed tube. [b]Isolated yield. [c]Reaction carried out in a round-bottom flask.

performing the reaction in an unsealed system (Table 1, entry 8), which is also consistent with our previous findings.[79]

With an optimized process for the formation of spirocyclic pyrazole **2a** in hand, we sought conditions for the regioselective sigmatropic rearrangement of **2a** into ring-expanded fused pyrazole **3a**. Initially, an attempt to promote the rearrangement thermally by dissolving **2a** in toluene and heating to 110 °C in air for 12 h led to exclusive recovery of the starting material (Table 2, entry 1). We then speculated that perturbing the electron density of the conjugated system via binding of a Lewis acid to one of the nitrogen atoms in the pyrazole ring may induce the rearrangement. To test this hypothesis, a range of Lewis acidic promoters were screened at room temperature (Table 2, entries 2–7). Gratifyingly, four Lewis acids facilitated conversion to the desired product **3a**, with the BF_3·THF complex emerging as the optimal candidate with a 58% yield. It has been previously documented that sigmatropic rearrangements of 3,3-disubstituted pyrazoles may give mixtures of products arising from migration to either the carbon or the nitrogen atoms of the pyrazole ring.[71,75,76] After confirmation of the product structure by NMR studies, this procedure was found to be entirely selective for C–C bond formation, and the *N*-substituted fused pyrazole was not observed in any case. A screen of different reaction temperatures demonstrated no further improvement to the yield (Table 2, entries 8–11), and significant decomposition of the starting material was observed. Consequently, room temperature was adopted as a fixed parameter. The reaction proved to be acutely sensitive to the stoichiometry of BF_3·THF used, with exactly 1.0 equiv giving the best results, while yields fell away sharply below 0.75 and above 1.25 equiv (Table 2, entries 4 and 12–17). The poorer yields observed were due to lower conversion and decomposition of the starting material, respectively. These results may indicate that 1 equiv of BF_3 binds to both the starting material and the product (until workup) and that binding of additional equivalents of BF_3 is detrimental. A short solvent screen (Table 2, entries 18–22) revealed that trifluorotoluene and dioxane

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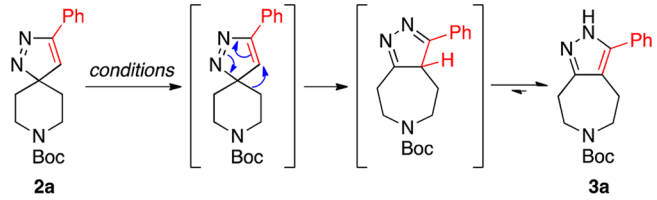
Table 2. Optimization of Reaction Conditions for Sigmatropic Rearrangement of Spirocyclic Pyrazole 2a to Ring-Expanded Fused Pyrazole 3a[a]



2a **3a**

entry	LA	equiv LA	T (°C)	solvent	[**2a**] (M)	t (h)	yield **3a** (%)[b]
1	none	N/A	110	toluene	0.1	12	0[c]
2	$Cu(OTf)_2$	1.0	25	toluene	0.1	24	28
3	$ZnCl_2$	1.0	25	toluene	0.1	24	0
4	BF_3·THF	1.0	25	toluene	0.1	24	58
5	$Sc(OTf)_3$	1.0	25	toluene	0.1	24	21
6	$Yb(OTf)_3$	1.0	25	toluene	0.1	24	0
7	$AlCl_3$	1.0	25	toluene	0.1	24	trace
8	BF_3·THF	1.0	−40	toluene	0.1	24	trace
9	BF_3·THF	1.0	0	toluene	0.1	24	7
10	BF_3·THF	1.0	60	toluene	0.1	24	35
11	BF_3·THF	1.0	110	toluene	0.1	24	21
12	BF_3·THF	0.5	25	toluene	0.1	24	16
13	BF_3·THF	0.75	25	toluene	0.1	24	49
14	BF_3·THF	1.25	25	toluene	0.1	24	50
15	BF_3·THF	1.5	25	toluene	0.1	24	36
16	BF_3·THF	2.0	25	toluene	0.1	24	25
17	BF_3·THF	4.0	25	toluene	0.1	24	5
18	BF_3·THF	1.0	25	$PhCF_3$	0.1	24	52
19	BF_3·THF	1.0	25	dioxane	0.1	24	56
20	BF_3·THF	1.0	25	THF	0.1	24	20
21	BF_3·THF	1.0	25	CH_2Cl_2	0.1	24	47
22	BF_3·THF	1.0	25	MeCN	0.1	24	33
23	BF_3·THF	1.0	25	dioxane	0.025	24	64
24	BF_3·THF	1.0	25	dioxane	0.05	24	70
25	BF_3·THF	1.0	25	dioxane	0.075	24	65
26	BF_3·THF	1.0	25	dioxane	0.2	24	58
27	BF_3·THF	1.0	25	dioxane	1.0	24	44
28	BF_3·THF	1.0	25	dioxane	0.05	6	50
29	BF_3·THF	1.0	25	dioxane	0.05	12	72
30	BF_3·THF	1.0	25	dioxane	0.05	18	74
31	BF_3·THF	1.0	25	dioxane	0.05	18	52[c]

[a]Reaction conditions: 0.25 mmol of **2a** under argon, sealed tube. [b]Isolated yield. [c]Performed under air. Abbreviations: LA, Lewis acid.

gave very similar results to toluene (Table 2, entries 4, 18−19). In the interests of continuity with the cycloaddition reaction and a superior solubility profile, dioxane was retained in further experiments (Table 2, entry 19). As the reaction is an intramolecular process, the concentration was expected to be critical to the performance. Indeed, dilution experiments (Table 2, entries 19, 23−27) revealed the optimal concentration to be 0.05 M, giving an improved 70% yield of **3a** (Table 2, entry 24), which is presumably due to fewer competing intermolecular interactions in the more dilute system. While a reduced yield was obtained after 6 h (Table 2, entry 28), the reaction appeared to be complete after 12 h and was relatively insensitive beyond this, with similar yields being obtained for 12, 18, and 24 h reactions (Table 2, entries 24, 29−30). Taking reaction rate variability across substrates into consideration and in the interests of practicality, 18 h was taken forward as the standard reaction time. Finally, a reaction run under an atmosphere of air provided a slightly reduced yield (Table 2, entry 31), and so an argon atmosphere was retained.

Following optimization, the scope of the alkyne partner in both reaction components was explored. First, tosylhydrazone **1a** was used to probe the viability of the cycloaddition reaction with a range of structurally diverse alkynes (Scheme 3). Good-to-excellent yields of spirocyclic pyrazoles derived from electron-neutral (**2a−b**), electron-rich (**2c**), and electron-poor (**2d−e**) aromatic alkynes were obtained. Similarly good results were observed from reactions involving *ortho*-substituted (**2f−g**) and heterocyclic (**2h−i**) alkynes. Finally, benzylic (**2j**), alkenyl (**2k**), cycloalkyl (**2l−m**), and alkyl (**2n**) spirocyclic products were isolated in moderate yields. These results show that higher yields are observed for conjugated alkynes but that their specific electronic density is largely unconnected to the outcome. This effect may be due to better stabilization of the transition state compared with unconjugated alkynes, particularly if the cycloaddition is asynchronous. The alternative regioisomer was not observed in any instance, suggesting that the piperidine ring exerts a sufficiently strong steric bias in the

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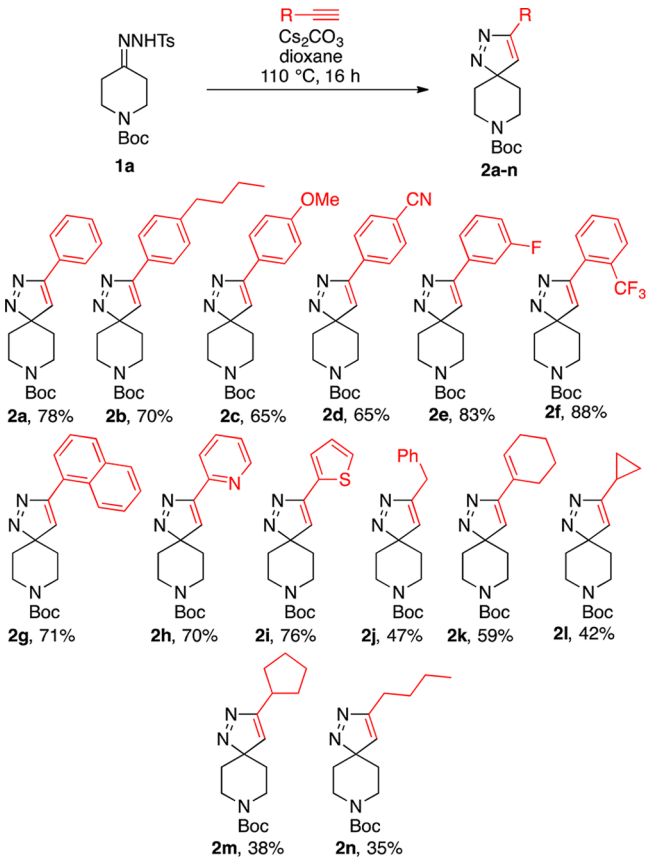
Scheme 3. Isolated Yields of Spirocyclic Pyrazoles 2a–n from Reaction of 1a with a Range of Alkynes

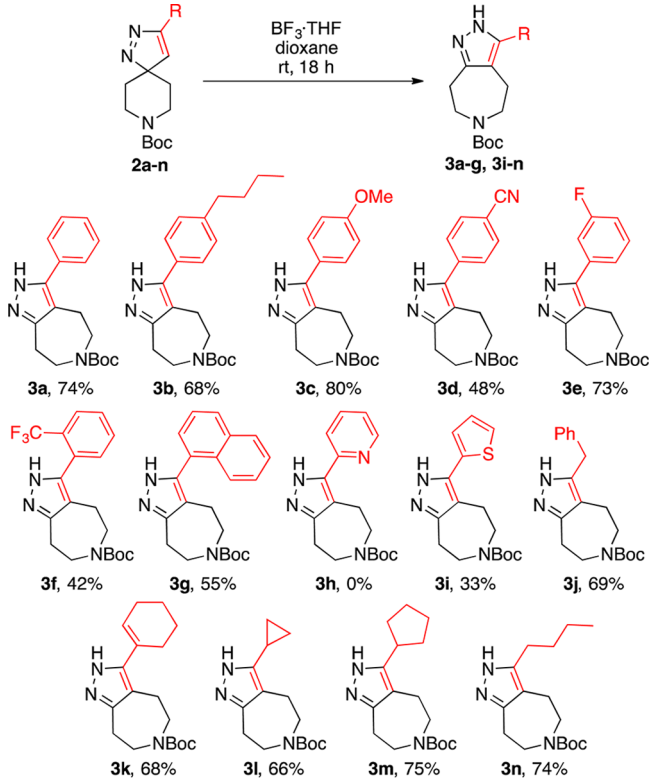


transition state as to give rise to the observed products exclusively.

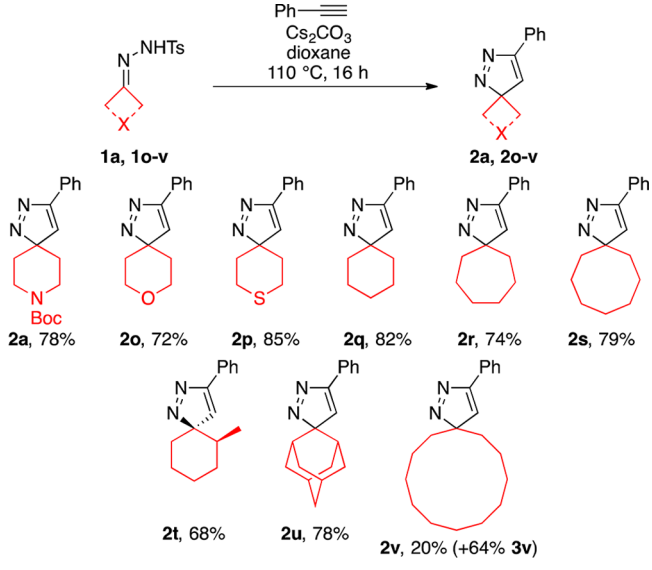
The library of spirocyclic pyrazoles thus obtained (**2a–n**) were subjected to the optimized reaction conditions (Table 2, entry 30) for sigmatropic rearrangement to the corresponding ring-expanded fused compounds (Scheme 4). The reaction was found to proceed in good yield with electron-neutral (**3a–b**), electron-rich (**3c**), and electron-poor (**3e**) aromatic substrates. Lower yields were observed with nitrile substrate **3d** and thiophene **3i**, whereas pyridine **3h** was not obtained in any amount. This is presumably due to disruptive interactions between the heteroatoms in the compound and the Lewis acid.[81] *Ortho*-substituted pyrazoles **3f** and **3g** were prepared in moderate yield, which was postulated to be due to increased steric hindrance in the transition state. Finally, good yields were observed for benzyl (**3j**), alkenyl (**3k**), cycloalkyl (**3l–m**), and alkyl (**3n**) substrates.

To evaluate the tosylhydrazone component of the cycloaddition, a range of saturated cyclic tosylhydrazones (**1a**, **1o–v**) were prepared and submitted to the established reaction conditions (Table 1, entry 2) with phenylacetylene as a common reaction partner (Scheme 5). High yields of spirocyclic cycloaddition products were observed for heterocyclic (**2a**, **2o–p**) and six- (**2q**), seven- (**2r**), and eight-membered (**2s**) cycloalkyl substrates. α-Methyl cyclohexanone tosylhydrazone (**1t**) underwent diastereoselective cycloaddition to afford **2t** as the major diastereoisomer in 68% yield[82] while adamantanone tosylhydrazone **1u** gave an excellent yield of the complex polycyclic structure **2u**. Interestingly, only 20% of the cyclododecanyl product **2v** was isolated, as the majority (64%)

Scheme 4. Isolated Yields of Fused Pyrazoles 3a–g and 3i–n from Sigmatropic Rearrangement of Spirocyclic Pyrazoles 2a–n



Scheme 5. Isolated Yields of Spirocyclic Pyrazoles 2a and 2o–v from Reaction of Tosylhydrazones 1a and 1o–v with Phenylacetylene



had spontaneously rearranged under the reaction conditions to the corresponding ring-expanded fused product **3v**, although the specific driving force for this process is currently unclear.

A number of additional substrates were found to undergo spontaneous sigmatropic rearrangement to give the fused pyrazole product (Scheme 6). As described previously, the 13-membered fused pyrazole **3v** was recovered in 64% yield along with 20% of the spirocyclic adduct **2v**. The four- and five-

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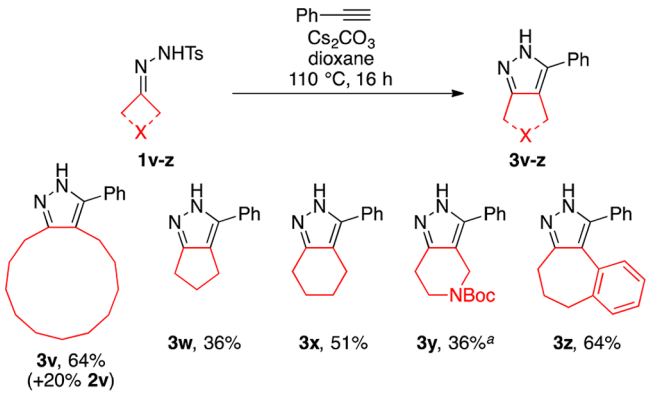
Scheme 6. Isolated Yields of Fused Pyrazoles 3v–z from Reaction of Sulfonylhydrazones 1v–z with Phenylacetylene[a]

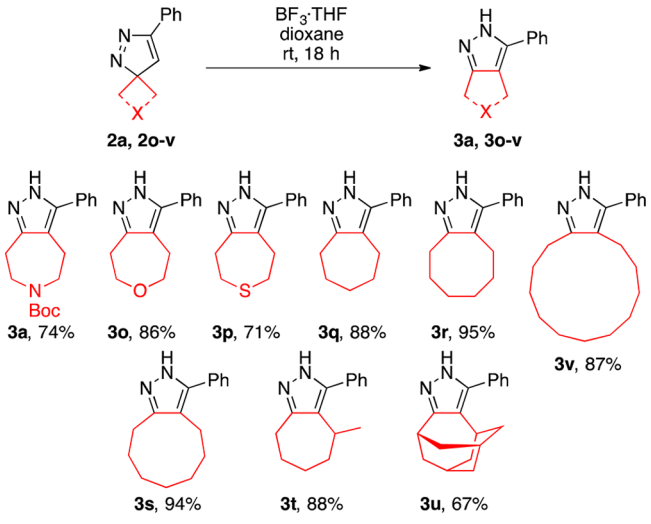


[a]Reaction performed using *p*-methoxyphenylsulfonyl hydrazone **1y′**.

membered cyclic tosylhydrazones **1w–x** provided exclusively ring-expanded products **3w–x** in low-to-moderate yield. Spontaneous rearrangement in this manner might be anticipated, based on the angle strain in the respective spirocyclic intermediates and the temperature of the reaction. In the case of compound **3y**, no product was observed from the reaction with the tosylhydrazone **1y**, but a 36% yield was obtained by switching to the analogous electron-rich *p*-methoxyphenylsulfonyl hydrazone **1y′**, consistent with our prior observations.[79] An example involving migration of an sp^2-hybridized carbon was also shown to form the fused pyrazole **3z** directly, in line with the observations of Valdés, albeit in a marginally improved yield (64% vs 45%).[62]

The spirocyclic substrates that did not spontaneously rearrange were subjected to the optimized reaction conditions for sigmatropic rearrangement (Table 2, entry 30). Heterocyclic (**3a**, **3o–p**), carbocyclic (**3q–t**, **3v**), and polycyclic (**3u**) examples all proceeded in good-to-excellent yields (Scheme 7). In the case of compound **3t**, the more substituted carbon center was found to migrate exclusively. We tentatively suggest that this is due to a higher migratory aptitude derived from the

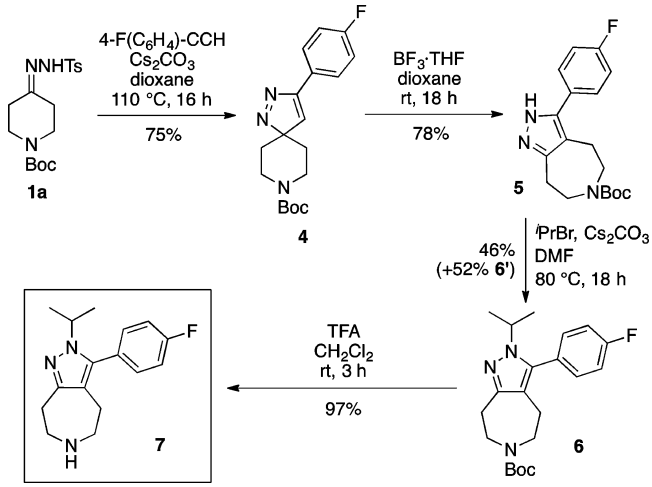
Scheme 7. Isolated Yields of Fused Pyrazoles 3a and 3o–v from Sigmatropic Rearrangement of Spirocyclic Pyrazoles 2a and 2o–v



electronic nature of the substrate, but steric effects cannot be ruled out at this stage.

In order to demonstrate the utility of this methodology, a synthesis of $5HT_7/HT_2$ dual antagonist **7** was then performed (Scheme 8).[5] Cycloaddition of **1a** with 4-fluorophenylacetylene

Scheme 8. Synthesis of $5HT_7/HT_2$ Dual Antagonist 7



proceeded in 75% yield, followed by BF_3-promoted sigmatropic rearrangement in 78% yield to give the ring-expanded core structure **5** in short order. Compound **5** was subsequently alkylated to give a 46% of the desired regioisomer **6**, along with a 52% yield of the undesired regioisomer **6′**. Finally, removal of the Boc protecting group with TFA provided **7** in a total of five steps, starting from commercially available materials. In addition to delivering compound **7** in a short sequence, this route is conducive to rapid analogue synthesis via late stage introduction of structural complexity and application to a broad range of saturated cyclic motifs.

CONCLUSION

In summary, we present a procedurally simple method for the regioselective preparation of pharmaceutically and agrochemically useful pyrazoles. The cycloaddition reaction gives high yields of functionalized 3,3-spirocyclic pyrazoles from a range of commercially available alkynes and bench-stable tosylhydrazones, which are easily prepared in one step from their parent ketones. Several examples undergo spontaneous sigmatropic rearrangement to ring-expanded fused systems, and the isolable spirocycles may be similarly transformed via a BF_3-mediated process. These reactions enable the rapid assembly of partially saturated polycyclic systems, including those featuring unusual ring sizes, which would otherwise require a more challenging multistep synthesis.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were conducted using standard Schlenk techniques. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated glass-backed plates and visualized by ultraviolet radiation (254 nm) and/or potassium permanganate as appropriate. Flash column chromatography was performed using silica gel (particle size 40–63 nm) under air pressure. ^1H NMR spectra were recorded in $CDCl_3$ on 600 or 400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) with the resonance resulting from incomplete deuteration of the solvent as the internal standard ($CHCl_3$: 7.26 ppm). Signal

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multiplicities are denoted using standard abbreviations with the exception of app = apparent. ^{13}C NMR spectra were recorded in $CDCl_3$ on 150 or 100 MHz spectrometers with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.0 ppm, t). HRMS was performed using electrospray ionization with time-of-flight mass analysis. HRMS signals are reported to four decimal places and are within ±5 ppm of theoretical values. Infrared spectra were recorded neat as thin films, and only selected peaks are reported.

General Procedure A: Preparation of Sulfonylhydrazones. Compounds were prepared according to a known procedure.[79] To a solution of sulfonylhydrazide (1.0 equiv) in MeOH (0.5 M) was added ketone (1.0 equiv). The reaction mixture was stirred at room temperature until complete conversion was observed by TLC. Solvents were removed in vacuo to give the title compound. Sulfonylhydrazones **1a**−**c**, **1o**−**q**, **1x**−**y**, and **1y′** were prepared according to previously reported conditions, with matching spectral data.[79,80]

*N′-Cycloheptylidene-4-methylbenzenesulfonohydrazide (**1r**).* Isolated as a white amorphous solid (1.40 g, 4.99 mmol, quant.) according to general procedure A: ^1H NMR δ 1.49−1.53 (6H, m), 1.63 (2H, m), 2.34 (2H, t, J 5.9 Hz), 2.37−2.39 (2H, m), 2.41 (3H, s), 7.29 (2H, d, J 8.1 Hz), 7.64 (1H, br), 7.84 (2H, d, J 8.2 Hz); ^{13}C NMR δ 21.7, 24.4, 27.4, 30.2, 30.3, 30.5, 37.1, 128.1, 129.6, 135.7, 143.9, 164.3 (br); FTIR (υ_{max} cm^{-1}) 3237, 2917, 2851, 1627, 1595, 1447, 1385, 1339, 1326, 1165, 1029, 929, 812, 719, 663; R_f 0.43 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{14}H_{21}N_2O_2S$ [M + H]$^+$ 281.1324, found 281.1327.

*N′-Cyclooctylidene-4-methylbenzenesulfonohydrazide (**1s**).* Isolated as a white amorphous solid (1.47 g, 4.99 mmol, quant.) according to general procedure A: ^1H NMR δ 1.15−1.19 (2H, m), 1.38−1.41 (4H, m), 1.64−1.66 (4H, m), 2.20−2.23 (2H, m), 2.29−2.30 (2H, m), 2.41 (3H, s), 7.29 (2H, d, J 8.1 Hz), 7.50 (1H, br), 7.83 (2H, d, J 8.3 Hz); ^{13}C NMR δ 21.7, 24.3, 24.8, 25.1, 26.4, 27.2, 28.0, 36.4, 128.1, 129.6, 135.8, 144.0, 160.5 (br); FTIR (υ_{max} cm^{-1}) 3215, 2940, 1598, 1489, 1460, 1391, 1329, 1156, 1091, 902, 818, 744, 672; R_f 0.46 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{15}H_{23}N_2O_2S$ [M + H]$^+$ 295.1480, found 295.1476.

*4-Methyl-N′-(2-methylcyclohexylidene)benzenesulfonohydrazide (**1t**).* Isolated as a white amorphous solid (1.40 g, 4.99 mmol, quant.) according to general procedure A: ^1H NMR δ 1.01 (3H, d, J 6.7 Hz), 1.15−1.22 (1H, m), 1.35−1.45 (2H, m), 1.67−1.83 (4H, m), 2.21 (1H, m), 2.41 (3H, s), 2.56 (1H, td, J 14.4, 4.4 Hz), 7.28 (2H, d, J 8.1 Hz), 7.77 (1H, br), 7.84 (2H, d, J 8.3 Hz); ^{13}C NMR δ 16.1, 17.0, 21.7, 24.6, 26.2, 26.5, 26.6, 29.3, 31.5, 35.5, 39.3, 128.1, 128.3, 129.4, 129.6, 135.4, 135.6, 143.8, 164.7 (br); FTIR (υ_{max} cm^{-1}) 3204, 2954, 2866, 1598, 1447, 1406, 1333, 1164, 1152, 1092, 1015, 994, 922, 874, 847, 805, 742, 686; R_f 0.46 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{14}H_{20}N_2O_2SNa$ [M + Na]$^+$ 303.1143, found 303.1148.

*N′-(Adamantan-2-ylidene)-4-methylbenzenesulfonohydrazide (**1u**).* Isolated as a white amorphous solid (1.59 g, 4.99 mmol, quant.) according to general procedure A: ^1H NMR δ 1.64−1.73 (4H, m), 1.79 (2H, br), 1.86−1.90 (6H, m), 2.40 (3H, s), 2.56 (1H, br), 3.01 (1H, br), 7.28 (2H, d, J 8.0 Hz), 7.75 (1H, br), 7.82 (2H, d, J 7.1 Hz); ^{13}C NMR δ 21.7, 27.6, 31.5, 36.2, 37.7, 39.0, 39.4, 128.1, 129.5, 135.6, 143.8, 170.7 (br); FTIR (υ_{max} cm^{-1}) 3222, 2917, 2853, 1597, 1447, 1403, 1346, 1321, 1292, 1211, 1166, 1158, 1122, 1090, 1007, 989, 933, 922, 812, 731, 703, 675; R_f 0.47 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{17}H_{23}N_2O_2S$ [M + H]$^+$ 319.1480, found 319.1470.

*N′-Cyclododecylidene-4-methylbenzenesulfonohydrazide (**1v**).* Isolated as a white amorphous solid (1.75 g, 4.99 mmol, quant.) according to general procedure A: ^1H NMR δ 0.78−0.83 (4H, m), 0.88−0.91 (2H, m), 1.13 (8H, m), 1.43−1.47 (2H, m), 1.61 (2H, quint, J 6.0 Hz), 2.12 (2H, t, J 6.5 Hz), 2.21 (2H, t, J 6.1 Hz), 2.39 (3H, s), 7.27 (2H, d, J 8.0 Hz), 7.46 (1H, br), 7.82 (2H, d, J 8.3 Hz); ^{13}C NMR δ 21.66, 21.74, 22.0, 22.8, 22.9, 23.1, 23.4, 24.0, 26.1, 26.2, 29.0, 31.6, 128.4, 129.7, 135.6, 144.0, 159.6 (br); FTIR (υ_{max} cm^{-1}) 3256, 2924, 2847, 1648, 1597, 1471, 1442, 1376, 1335, 1164, 918, 814, 723, 663; R_f 0.55 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{19}H_{31}N_2O_2S$ [M + H]$^+$ 351.2106, found 351.2105.

*N′-Cyclobutylidene-4-methylbenzenesulfonohydrazide (**1w**).* A solution of tosylhydrazide (186 mg, 1.0 mmol, 1.0 equiv) and cyclobutanone (74.7 μL, 1.0 mmol, 1.0 equiv) in DMSO-d_6 (0.75 mL) was heated to 60 °C until complete conversion was observed by ^1H NMR. The solution was cooled to room temperature and poured into stirring water (5 mL). The resulting white precipitate was filtered and dried in vacuo to give the title compound (194 mg, 0.814 mmol, 81%) as a white amorphous solid: ^1H NMR δ 1.94 (2H, quint, J 8.0 Hz), 2.42 (3H, s), 2.78 (2H, t, J 8.0 Hz), 2.88 (2H, t, J 7.8 Hz), 7.31 (2H, d, J 8.1 Hz), 7.71 (1H, br), 7.83 (2H, d, J 8.2 Hz); ^{13}C NMR δ 13.6, 21.7, 32.1, 34.1, 128.1, 129.8, 135.5, 144.2, 161.1; FTIR (υ_{max} cm^{-1}) 3208, 2969, 1678, 1597, 1448, 1402, 1332, 1159, 1090, 1015, 917, 814, 709, 668; R_f 0.43 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{11}H_{15}N_2O_2S$ [M + H]$^+$ 239.0854, found 239.0856.

*N′-(3,4-Dihydronaphthalen-1(2H)-ylidene)-4-methylbenzenesulfonohydrazide (**1z**).* Isolated as a white amorphous solid (1.57 g, 4.99 mmol, quant.) according to general procedure A: ^1H NMR δ 1.87 (2H, quint, J 6.5 Hz), 2.41 (3H, s), 2.49 (2H, t, J 6.6 Hz), 2.70 (2H, t, J 6.1 Hz), 7.08 (1H, d, J 7.4 Hz), 7.19 (1H, t, J 7.4 Hz), 7.24 (1H, dt, J 7.3, 1.3 Hz), 7.32 (2H, d, J 8.0 Hz), 7.95 (2H, d, J 8.3 Hz), 7.98 (1H, dd, J 7.7, 0.8 Hz), 8.08 (1H, br); ^{13}C NMR δ 21.5, 21.7, 25.6, 29.4, 125.1, 126.5, 128.2, 128.4, 129.6, 129.7, 131.7, 135.6, 139.9, 144.2, 152.8 (br); FTIR (υ_{max} cm^{-1}) 3245, 2859, 1595, 1481, 1435, 1393, 1341, 1315, 1166, 1079, 1054, 1012, 928, 813, 777, 718, 661; R_f 0.38 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{17}H_{19}N_2O_2S$ [M + H]$^+$ 315.1167, found 315.1165.

General Procedure B: Reaction of Tosylhydrazones with Alkynes To Give Spirocyclic or Fused Pyrazoles. Tosylhydrazone (1.0 mmol, 1.0 equiv), Cs_2CO_3 (1.5 mmol, 1.5 equiv), and alkyne (if solid at room temperature, 1.5 mmol, 1.5 equiv) were placed in an oven-dried tube in vacuo for 30 min. The tube was backfilled with argon and evacuated (3 cycles), before addition of 1,4-dioxane (4 mL) under an argon atmosphere, followed by addition of alkyne (if liquid at room temperature, 1.5 mmol, 1.5 equiv). The tube was sealed and heated to 110 °C for 16 h before being cooled to room temperature, quenched with NH_4Cl (4 mL of a saturated aqueous solution), and extracted with CH_2Cl_2 (3 × 4 mL). The organic phase was dried over $MgSO_4$, and solvents were removed in vacuo to give a residue, which was purified by flash column chromatography (10−30% EtOAc/hexane) to give the title compounds.

*tert-Butyl 3-Phenyl-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2a**).* Isolated as a tan amorphous solid (245 mg, 0.782 mmol, 78%) from **1a** according to general procedure B: ^1H NMR δ 1.51 (9H, s), 1.77 (4H, br), 3.80 (2H, br), 3.96 (2H, ddd, J 12.9, 8.8, 3.7 Hz), 7.06 (1H, s), 7.42 (1H, t, J 7.3 Hz), 7.46 (2H, t, J 7.5 Hz), 8.04 (2H, d, J 7.6 Hz); ^{13}C NMR δ 28.6, 30.7 (br), 42.9 (br), 80.1, 96.6, 127.3, 129.1, 129.5, 130.8, 135.0, 154.9, 155.7; FTIR (υ_{max} cm^{-1}) 3195, 2974, 1688, 1458, 1412, 1365, 1298, 1277, 1243, 1160, 1106, 1073, 1025, 1001, 984, 923, 895, 860, 818, 771, 744, 699, 666; R_f 0.25 (20% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{18}H_{24}N_3O_2$ [M + H]$^+$ 314.1869, found 314.1864.

*tert-Butyl 3-(4-Butylphenyl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2b**).* Isolated as a white amorphous solid (129 mg, 0.349 mmol, 70%) from **1a** according to general procedure B. ^1H NMR δ 0.94 (3H, t, J 7.4 Hz), 1.37 (2H, sext, J 7.6 Hz), 1.51 (9H, s), 1.63 (2H, quint, J 7.7 Hz), 1.78 (4H, br), 2.67 (2H, t, J 7.6 Hz), 3.79 (2H, br), 3.96 (2H, ddd, J 13.2, 8.6, 3.8 Hz), 7.00 (1H, s), 7.28 (1H, d, J 8.2 Hz), 7.95 (2H, t, J 8.2 Hz); ^{13}C NMR δ 13.9, 22.3, 28.5, 30.6 (br), 33.5, 35.5, 42.7 (br), 80.0, 96.3, 127.1, 128.0, 129.0, 133.8, 144.5, 154.8, 155.7; FTIR (υ_{max} cm^{-1}) 3088, 2928, 1680, 1623, 1509, 1424, 1366, 1276, 1262, 1247, 1179, 1156, 1104, 1019, 952, 921, 864, 834, 812, 770, 699; R_f 0.51 (20% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{22}H_{32}N_3O_2$ [M + H]$^+$ 370.2495, found 370.2484.

*tert-Butyl 3-(4-Methoxyphenyl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2c**).* Isolated as a white amorphous solid (112 mg, 0.326 mmol, 65%) from **1a** according to general procedure B: ^1H NMR δ 1.51 (9H, s), 1.77 (4H, br), 3.77 (2H, br), 3.86 (3H, s), 3.95 (2H, ddd, J 12.9, 8.7, 3.7 Hz), 6.91 (1H, s), 6.99 (1H, d, J 8.8 Hz), 7.98 (2H, t, J 8.8 Hz); ^{13}C NMR δ 28.6, 30.8 (br), 42.1 (br), 55.5, 80.1, 96.5, 114.5, 123.5, 128.7, 132.5, 154.9, 155.4, 160.6; FTIR (υ_{max}

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cm^{-1}) 3086, 2925, 1691, 1628, 1560, 1510, 1464, 1439, 1418, 1368, 1309, 1279, 1251, 1226, 1178, 1160, 1115, 1069, 1037, 1014, 996, 974, 950, 900, 862, 823, 792, 767; R_f 0.37 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{19}H_{26}N_3O_3$ $[M + H]^+$ 344.1974, found 344.1970.

*tert-Butyl 3-(4-Cyanophenyl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2d**).* Isolated as a bright yellow amorphous solid (110 mg, 0.325 mmol, 65%) from **1a** according to general procedure B: ^1H NMR δ 1.49 (9H, s), 1.76 (4H, br), 3.81 (2H, br), 3.92 (2H, br), 7.24 (1H, s), 7.74 (2H, d, J 8.0 Hz), 8.14 (2H, d, J 7.9 Hz); ^{13}C NMR δ 28.5, 30.5 (br), 42.5 (br), 80.2, 97.5, 112.7, 118.6, 127.8, 132.8, 134.9, 138.5, 153.8, 154.8; FTIR (υ_{max} cm^{-1}) 3087, 2955, 2225, 1686, 1601, 1414, 1366, 1314, 1249, 1173, 1152, 1101, 1016, 973, 951, 856, 823, 770, 730, 677; R_f 0.16 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{19}H_{23}N_4O_2$ $[M + H]^+$ 339.1821, found 339.1836.

*tert-Butyl 3-(3-Fluorophenyl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2e**).* Isolated as a white amorphous solid (138 mg, 0.416 mmol, 83%) from **1a** according to general procedure B: ^1H NMR δ 1.51 (9H, s), 1.76 (4H, br), 3.81 (2H, br), 3.94 (2H, br), 7.09 (1H, s), 7.09–7.12 (1H, m), 7.43 (1H, q, J 7.9 Hz), 7.74 (1H, d, J 9.8 Hz), 7.80 (1H, d, J 7.7 Hz); ^{13}C NMR δ 28.6, 30.6 (br), 42.7 (br), 80.2, 97.0, 114.2 (d, J 22.8 Hz), 116.4 (d, J 21.1 Hz), 123.0 (d, J 2.9 Hz), 130.7 (d, J 8.2 Hz), 132.9 (d, J 8.2 Hz), 136.3, 154.6 (d, J 2.7 Hz), 154.9, 163.2 (d, J 244.9 Hz); FTIR (υ_{max} cm^{-1}) 3105, 2980, 1676, 1602, 1581, 1453, 1426, 1366, 1251, 1228, 1176, 1151, 1003, 961, 952, 902, 860, 843, 830, 795, 762, 707, 689; R_f 0.37 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{18}H_{23}N_3O_2F$ $[M + H]^+$ 332.1774, found 332.1778.

*tert-Butyl 3-(2-(Trifluoromethyl)phenyl)-1,2,8-triazaspiro[4.5]-deca-1,3-diene-8-carboxylate (**2f**).* Isolated as a yellow oil (168 mg, 0.440 mmol, 88%) from **1a** according to general procedure B: ^1H NMR δ 1.48 (9H, s), 1.75 (4H, br), 3.79 (2H, br), 3.92 (2H, br td, J 12.1, 5.7 Hz), 7.05 (1H, s), 7.51 (1H, t, J 7.5 Hz), 7.63 (1H, t, J 7.5 Hz), 7.75 (1H, dd, J 7.9, 1.3 Hz), 7.90 (1H, dd, J 7.6, 2.5 Hz); ^{13}C NMR δ 28.5, 30.1 (br), 42.7 (br), 80.0, 97.6, 124.0 (q, J 271.7 Hz), 126.5 (q, J 5.5 Hz), 128.7 (q, J 30.1 Hz), 129.1, 130.0 (d, J 6.1 Hz), 131.3, 131.9, 141.5 (q, J 3.0 Hz), 152.9, 154.8; FTIR (υ_{max} cm^{-1}) 2975, 1688, 1601, 1421, 1366, 1313, 1247, 1151, 1126, 1064, 1035, 950, 861, 767, 736, 691; R_f 0.31 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{19}H_{23}N_3O_2F_3$ $[M + H]^+$ 382.1742, found 382.1739.

*tert-Butyl 3-(Naphthalen-1-yl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2g**).* Isolated as an orange amorphous solid (129 mg, 0.355 mmol, 71%) from **1a** according to general procedure B: ^1H NMR δ 1.53 (9H, s), 1.88 (4H, br), 3.87 (2H, br), 4.01 (2H, ddd, J 13.3, 7.3, 5.6 Hz), 7.14 (1H, s), 7.53–7.58 (3H, m), 7.92–7.94 (2H, m), 7.97 (1H, dd, J 7.1, 1.0 Hz), 8.09–8.11 (1H, m); ^{13}C NMR δ 28.5, 30.6 (br), 42.1 (br), 80.0, 96.6, 125.1, 125.3, 126.1, 126.8, 127.9, 128.5, 128.7, 129.8, 131.3, 133.8, 140.1, 154.8, 155.4; FTIR (υ_{max} cm^{-1}) 3083, 2935, 1683, 1509, 1427, 1389, 1363, 1278, 1246, 1152, 1093, 1019, 935, 899, 863, 798, 771, 705, 663; R_f 0.32 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{22}H_{26}N_3O_2$ $[M + H]^+$ 364.2025, found 364.2011.

*tert-Butyl 3-(Pyridin-2-yl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2h**).* Isolated as a yellow amorphous solid (110 mg, 0.350 mmol, 70%) from **1a** according to general procedure B: ^1H NMR δ 1.45 (9H, s), 1.66 (2H, br), 1.83 (2H, br), 3.67 (2H, br), 3.94 (2H, br), 7.27 (1H, s), 7.57 (1H, m), 7.80 (1H, m), 8.38 (1H, m), 8.60 (1H, m); ^{13}C NMR δ 28.5, 30.3 (br), 41.8 (br), 80.0, 96.7, 122.4, 123.9, 137.1, 139.5, 149.7, 150.2, 154.7, 156.1; FTIR (υ_{max} cm^{-1}) 2970, 2244, 1678, 1580, 1563, 1449, 1425, 1365, 1277, 1249, 1225, 1175, 1144, 1107, 1000, 973, 951, 923, 865, 781, 725; R_f 0.27 (50% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{17}H_{23}N_4O_2$ $[M + H]^+$ 315.1821, found 315.1811.

*tert-Butyl 3-(Thiophen-2-yl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2i**).* Isolated as a yellow amorphous solid (120 mg, 0.376 mmol, 76%) from **1a** according to general procedure B: ^1H NMR δ 1.46 (9H, s), 1.66–1.77 (4H, m), 3.72 (2H, m), 3.89 (2H, ddd, J 13.1, 8.7, 3.5 Hz), 6.84 (1H, s), 7.08 (1H, dd, J 5.0, 3.7 Hz), 7.35 (1H, dd, J 5.0, 0.8 Hz), 7.68 (1H, dd, J 3.6, 0.6 Hz); ^{13}C NMR δ 28.4, 30.6 (br), 41.7 (br), 79.9, 97.1, 127.0, 127.1, 127.9, 132.2, 133.5, 150.2, 154.7; FTIR (υ_{max} cm^{-1}) 3098, 2951, 2258, 1694, 1618, 1455, 1403, 1364, 1275, 1246, 1146, 1099, 962, 943, 914, 859, 817, 771, 723; R_f 0.28 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{16}H_{22}N_3O_2S$ $[M + H]^+$ 320.1433, found 320.1434.

*tert-Butyl 3-Benzyl-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2j**).* Isolated as an off-white amorphous solid (76.8 mg, 0.235 mmol, 47%) from **1a** according to general procedure B: ^1H NMR δ 1.48 (9H, s), 1.60 (2H, br) 1.67 (2H, br), 3.68 (2H, br), 3.89 (2H, ddd, J 13.4, 8.8, 3.7 Hz), 4.16 (2H, s), 6.40 (1H, s), 7.24–7.27 (3H, m), 7.31–7.34 (2H, m); ^{13}C NMR δ 28.6, 30.4 (br), 34.1, 42.0 (br), 80.0, 95.5, 126.9, 128.9, 129.0, 137.8, 138.0, 154.9, 157.7; FTIR (υ_{max} cm^{-1}) 2972, 1694, 1405, 1366, 1275, 1244, 1151, 1098, 1036, 964, 939, 862, 821, 773, 720, 695; R_f 0.24 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{19}H_{26}N_3O_2$ $[M + H]^+$ 328.2025, found 328.2013.

*tert-Butyl 3-(Cyclohex-1-en-1-yl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2k**).* Isolated as a yellow amorphous solid (93.6 mg, 0.295 mmol, 59%) from **1a** according to general procedure B: ^1H NMR δ 1.44 (9H, s), 1.58–1.71 (8H, br), 2.17 (2H, br), 2.25 (2H, br), 3.66 (2H, br), 3.88 (2H, br), 6.37 (1H, s), 7.20 (1H, br); ^{13}C NMR δ 22.1, 22.3, 25.7, 26.0, 28.5, 30.7, 42.7, 79.8, 95.5, 128.1, 130.7, 130.9, 154.8, 157.1; FTIR (υ_{max} cm^{-1}) 3091, 2926, 1698, 1650, 1588, 1407, 1365, 1274, 1244, 1173, 1150, 1097, 1018, 961, 942, 863, 832, 815, 769, 732, 685; R_f 0.45 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{18}H_{28}N_3O_2$ $[M + H]^+$ 318.2182, found 318.2191.

*tert-Butyl 3-Cyclopropyl-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2l**).* Isolated as a white amorphous solid (57.5 mg, 0.207 mmol, 42%) from **1a** according to general procedure B: ^1H NMR δ 1.00 (4H, m), 1.46 (9H, s), 1.56 (2H, br), 1.65 (2H, br), 2.00 (1H, br), 3.65 (2H, br), 3.86 (2H, br), 6.39 (1H, s); ^{13}C NMR δ 7.7, 8.7, 28.5, 30.5 (br), 42.1 (br), 80.0, 95.3, 133.7, 154.9, 159.7; FTIR (υ_{max} cm^{-1}) 3081, 2949, 1688, 1630, 1470, 1417, 1365, 1276, 1246, 1154, 1098, 1025, 975, 958, 937, 855, 771, 760, 684; R_f 0.33 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{15}H_{24}N_3O_2$ $[M + H]^+$ 278.1869, found 278.1858.

*tert-Butyl 3-Cyclopentyl-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2m**).* Isolated as a white amorphous solid (57.1 mg, 0.187 mmol, 38%) from **1a** according to general procedure B: ^1H NMR δ 1.49 (9H, s), 1.59 (2H, br), 1.69 (6H, br), 1.77 (2H, br), 2.11 (2H, br), 3.26 (1H, quint, J 7.9 Hz), 3.69 (2H, br), 3.91 (2H, ddd, J 12.8, 8.8, 3.7 Hz), 6.42 (1H, s); ^{13}C NMR δ 25.4, 28.6, 30.5 (br), 32.1, 38.3, 42.0 (br), 80.0, 94.8, 134.6, 155.0, 162.7; FTIR (υ_{max} cm^{-1}) 3096, 2956, 1685, 1628, 1425, 1362, 1279, 1246, 1161, 1094, 968, 938, 906, 863, 763; R_f 0.38 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{17}H_{28}N_3O_2$ $[M + H]^+$ 306.2182, found 306.2174.

*tert-Butyl 3-Butyl-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**2n**).* Isolated as a yellow amorphous solid (50.3 mg, 0.171 mmol, 35%) from **1a** according to general procedure B: ^1H NMR δ 0.95 (3H, t, J 7.4 Hz), 1.40 (2H, sext, J 7.5 Hz), 1.50 (9H, s), 1.61 (2H, br), 1.69 (4H, br), 2.80 (2H, td, J 7.6, 1.3 Hz), 3.70 (2H, br), 3.91 (2H, ddd, J 13.4, 8.7, 3.7 Hz), 6.47 (1H, d, J 1.4 Hz); ^{13}C NMR δ 14.0, 22.4, 27.3, 28.6, 30.1, 30.5 (br), 42.8 (br), 80.3, 95.2, 136.4, 155.0, 158.7; FTIR (υ_{max} cm^{-1}) 3093, 2928, 1694, 1627, 1467, 1407, 1365, 1275, 1244, 1177, 1154, 1093, 1037, 963, 938, 861, 821, 771, 728; R_f 0.35 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{16}H_{27}N_3O_2Na$ $[M + Na]^+$ 316.2001, found 316.1986.

*3-Phenyl-8-oxa-1,2-diazaspiro[4.5]deca-1,3-diene (**2o**).* Isolated as a white amorphous solid (77.2 mg, 0.360 mmol, 72%) from **1o** according to general procedure B: ^1H NMR δ 1.83 (4H, br), 3.92 (2H, td, J 11.9, 3.9 Hz), 4.32 (2H, m), 7.11 (1H, s), 7.40 (1H, t, J 7.3 Hz), 7.46 (2H, t, J 7.2 Hz), 8.05 (2H, d, J 7.1 Hz); ^{13}C NMR δ 30.9, 65.9, 95.7, 127.2, 129.0, 129.4, 130.7, 135.1, 155.5; FTIR (υ_{max} cm^{-1}) 3079, 2923, 2862, 1597, 1494, 1450, 1242, 1097, 1033, 1012, 956, 913, 851, 814, 762, 691, 681; R_f 0.14 (20% EtOAc/hexane); HRMS (ESI^+) calculated for $C_{13}H_{15}N_2O$ $[M + H]^+$ 215.1184, found 215.1192.

*3-Phenyl-8-thia-1,2-diazaspiro[4.5]deca-1,3-diene (**2p**).* Isolated as a white amorphous solid (97.3 mg, 0.422 mmol, 85%) from **1p** according to general procedure B: ^1H NMR δ 1.85 (2H, m), 2.09 (2H, br m), 2.76 (2H, ddd, J 13.6, 8.0, 3.1 Hz), 3.25 (2H, m), 7.10 (1H, s),

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7.39 (1H, t, *J* 7.3 Hz), 7.45 (2H, t, *J* 7.3 Hz), 8.02 (2H, d, *J* 7.2 Hz); ^{13}C NMR δ 26.5, 32.0, 97.2, 127.1, 128.9, 129.3, 130.6, 135.5, 155.4; FTIR (υ_{max} cm^{-1}) 3672, 3092, 2912, 1625, 1491, 1445, 1394, 1271, 1073, 946, 901, 853, 764, 693; R_f 0.51 (20% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{13}H_{15}N_2S$ [M + H]$^+$ 231.0956, found 231.0958.

*3-Phenyl-1,2-diazaspiro[4.5]deca-1,3-diene (**2q**).* Isolated as a white amorphous solid (87.0 mg, 0.410 mmol, 82%) from **1q** according to general procedure B: ^{1}H NMR δ 1.42 (2H, br m), 1.62 (2H, m), 1.72 (2H, br m), 2.07 (4H, m), 7.20 (1H, s), 7.37 (1H, t, *J* 7.6 Hz), 7.44 (2H, t, *J* 7.7 Hz), 8.03 (2H, d, *J* 7.7 Hz); ^{13}C NMR δ 24.6, 25.5, 31.3, 99.2, 127.0, 128.8, 128.9, 131.2, 136.3, 154.7; FTIR (υ_{max} cm^{-1}) 3090, 2935, 2849, 1596, 1493, 1449, 1334, 1261, 1171, 1029, 951, 902, 866, 765, 694, 681; R_f 0.62 (20% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{14}H_{17}N_2$ [M + H]$^+$ 213.1392, found 213.1400.

*3-Phenyl-1,2-diazaspiro[4.6]undeca-1,3-diene (**2r**).* Isolated as a white amorphous solid (84.2 mg, 0.372 mmol, 74%) from **1r** according to general procedure B: ^{1}H NMR δ 1.47 (2H, dq, *J* 8.3, 2.2 Hz), 1.67 (2H, br), 1.76 (2H, br), 1.83 (2H, br), 2.09 (2H, br), 2.15 (2H, dq, *J* 10.3, 2.2 Hz), 7.14 (1H, s), 7.38 (1H, t, *J* 7.4 Hz), 7.45 (2H, t, *J* 7.4 Hz), 8.02 (2H, d, *J* 7.2 Hz); ^{13}C NMR δ 25.8, 29.6, 33.1, 102.4, 127.2, 128.9, 129.0, 131.2, 137.6, 154.4; FTIR (υ_{max} cm^{-1}) 3093, 2919, 2857, 1596, 1493, 1456, 1446, 1243, 1073, 1018, 921, 863, 844, 759, 690; R_f 0.65 (20% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{15}H_{19}N_2$ [M + H]$^+$ 227.1548, found 227.1549.

*3-Phenyl-1,2-diazaspiro[4.7]dodeca-1,3-diene (**2s**).* Isolated as a white amorphous solid (94.9 mg, 0.395 mmol, 79%) from **1s** according to general procedure B: ^{1}H NMR δ 1.43 (2H, m), 1.58−1.88 (8H, m), 2.06 (4H, m), 7.13 (1H, s), 7.37 (1H, t, *J* 7.4 Hz), 7.44 (2H, t, *J* 7.5 Hz), 8.03 (2H, d, *J* 7.3 Hz); ^{13}C NMR δ 25.1, 28.4, 29.0, 102.2, 127.1, 128.8, 128.9, 131.2, 137.6, 154.8; FTIR (υ_{max} cm^{-1}) 3671, 3087, 2910, 1596, 1495, 1473, 1450, 1243, 1229, 1075, 966, 943, 915, 866, 759, 691, 677; R_f 0.53 (10% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{16}H_{21}N_2$ [M + H]$^+$ 241.1705, found 241.1703.

*6-Methyl-3-phenyl-1,2-diazaspiro[4.5]deca-1,3-diene (**2t**).* Isolated as a white amorphous solid (76.5 mg, 0.338 mmol, 68%) from **1t** according to general procedure B: ^{1}H NMR δ 0.51 (3H, d, *J* 6.6 Hz), 1.29 (1H, d, *J* 13.0 Hz), 1.61 (1H, app tq, *J* 12.8, 3.7 Hz), 1.84 (3H, m), 2.06−2.22 (4H, m), 6.92 (1H, s), 7.38 (1H, t, *J* 7.4 Hz), 7.45 (2H, t, *J* 7.4 Hz), 8.06 (2H, d, *J* 7.1 Hz); ^{13}C NMR δ 15.7, 24.6, 26.2 (br), 32.7, 33.3 (br), 38.0, 101.6, 127.0, 128.81, 128.83, 131.2, 138.5, 154.3; FTIR (υ_{max} cm^{-1}) 3093, 2926, 1596, 1492, 1444, 1232, 1075, 932, 876, 762, 690; R_f 0.61 (17% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{15}H_{19}N_2$ [M + H]$^+$ 227.1548, found 227.1540.

*5′-Phenylspiro[adamantane-2,3′-pyrazole] (**2u**).* Isolated as a white amorphous solid (104 mg, 0.393 mmol, 78%) from **1u** according to general procedure B. ^{1}H NMR δ 1.55 (2H, br), 1.90 (4H, br), 2.02 (4H, br), 2.13 (1H, br), 2.24 (1H, br), 2.94 (2H, br d, *J* 10.9 Hz), 7.39 (1H, tt, *J* 7.4, 1.2 Hz), 7.43 (1H, s), 7.47 (2H, t, *J* 7.3 Hz), 8.07 (2H, dd, *J* 7.1, 1.3 Hz); ^{13}C NMR δ 27.5, 27.6, 35.8, 36.1, 37.8, 38.0, 104.0, 127.2, 128.96, 129.01, 131.5, 136.7, 154.5; FTIR (υ_{max} cm^{-1}) 3660, 2901, 2849, 1596, 1496, 1451, 1354, 1233, 1100, 1075, 946, 856, 848, 766, 697; R_f 0.64 (20% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{18}H_{21}N_2$ [M + H]$^+$ 265.1705, found 265.1704.

*3-Phenyl-1,2-diazaspiro[4.11]hexadeca-1,3-diene (**2v**).* Isolated as a white amorphous solid (29.1 mg, 0.0982 mmol, 20%) from **1v** according to general procedure B: ^{1}H NMR δ 1.31−1.48 (16H, br m), 1.83 (6H, br m), 7.08 (1H, s), 7.38 (1H, t, *J* 7.4 Hz), 7.46 (2H, t, *J* 7.4 Hz), 8.02 (2H, d, *J* 7.3 Hz); ^{13}C NMR δ 22.1, 22.3, 22.7, 26.1, 26.7, 28.9, 101.9, 127.9, 128.9, 129.0, 131.3, 137.7, 154.7; FTIR (υ_{max} cm^{-1}) 3081, 2927, 2870, 1596, 1491, 1470, 1445, 1248, 1071, 1023, 947, 864, 851, 760, 689; R_f 0.36 (5% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{20}H_{29}N_2$ [M + H]$^+$ 297.2331, found 297.2334.

*3-Phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazole (**3w**).* Isolated as a white amorphous solid (33.0 mg, 0.179 mmol, 36%) from **1w** according to general procedure B: ^{1}H NMR δ 2.49 (2H, quint, *J* 7.1 Hz), 2.70 (2H, t, *J* 7.2 Hz), 2.82 (2H, t, *J* 7.0 Hz), 7.28 (1H, t, *J* 7.4 Hz), 7.38 (2H, t, *J* 7.6 Hz), 7.63 (2H, d, *J* 7.6 Hz), 11.25 (1H, br); ^{13}C NMR δ 24.2, 24.4, 30.7, 122.9, 125.5, 127.5, 128.9, 131.3, 138.2 (br), 160.4 (br); FTIR (υ_{max} cm^{-1}) 3062, 2926 (br, m), 1592, 1493, 1444, 1325, 1091, 951, 763, 690; R_f 0.33 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{12}H_{13}N_2$ [M + H]$^+$ 185.1073, found 185.1067.

*3-Phenyl-4,5,6,7-tetrahydro-2H-indazole (**3x**).* Isolated as a pale yellow amorphous solid (50.4 mg, 0.254 mmol, 51%) from **1x** according to general procedure B. ^{1}H NMR δ 1.77−1.80 (4H, m), 2.58 (2H, t, *J* 5.1 Hz), 2.72 (2H, t, *J* 5.0 Hz), 7.28 (1H, tt, *J* 7.4, 1.1 Hz), 7.36 (2H, t, *J* 7.4 Hz), 7.65 (2H, dd, *J* 7.3, 1.0 Hz), 11.37 (1H, br); ^{13}C NMR δ 22.1, 22.3 (br), 22.8, 23.7, 113.0 (br), 126.7, 127.3, 128.6, 133.1 (br), 144.2 (br), 144.7 (br); FTIR (υ_{max} cm^{-1}) 3127, 2927, 1595, 1509, 1444, 1323, 1162, 1110, 992, 822, 769, 734, 695; R_f 0.29 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{13}H_{15}N_2$ [M + H]$^+$ 199.1235, found 199.1243.

*tert-Butyl 3-Phenyl-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate (**3y**).* Isolated as a white gum (54.3 mg, 0.181 mmol, 36%) from **1y′** according to general procedure B. ^{1}H NMR δ 1.49 (9H, s), 2.80 (2H, br), 3.75 (2H, br), 4.68 (2H, br), 7.35 (1H, br), 7.43 (2H, br), 7.55 (2H, d, *J* 7.4 Hz); ^{13}C NMR δ 28.6, 28.7 (br), 29.8, 41.2 (br), 41.8 (br), 80.3, 110.1, 110.8, 126.3, 128.1, 129.1, 133.3 (br), 141.5 (br), 147.5 (br), 155.2; FTIR (υ_{max} cm^{-1}) 3245, 2927, 1675, 1416, 1366, 1239, 1157, 908, 728, 694; R_f 0.23 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{17}H_{22}N_3O_2$ [M + H]$^+$ 300.1712, found 300.1705.

*1-Phenyl-2,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-c]pyrazole (**3z**).* Isolated as a white gum (82.7 mg, 0.318 mmol, 64%) from **1z** according to general procedure B: ^{1}H NMR δ 2.14 (2H, quint, *J* 7.4 Hz), 2.55 (2H, t, *J* 7.4 Hz), 2.76 (2H, t, *J* 6.8 Hz), 7.10−7.11 (2H, m), 7.17−7.20 (1H, m), 7.31−7.32 (4H, m), 7.57−7.58 (2H, m), 12.60 (1H, br); ^{13}C NMR δ 22.9, 30.5, 32.7, 116.3, 126.1, 126.2, 128.0, 128.3, 128.6, 128.8, 129.5, 132.0 (br), 133.6, 140.6, 144.4 (br), 147.7 (br); FTIR (υ_{max} cm^{-1}) 3660, 2928, 1508, 1442, 1264, 1073, 977, 906, 761, 728, 695; R_f 0.25 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{18}H_{17}N_2$ [M + H]$^+$ 261.1392, found 261.1388.

General Procedure C: Sigmatropic Rearrangement of Spirocyclic Pyrazoles to Fused Pyrazoles. Spirocyclic pyrazole (0.25 mmol, 1.0 equiv) was placed in an oven-dried tube in vacuo for 30 min. The tube was backfilled with argon and evacuated (3 cycles), before addition of 1,4-dioxane (5.0 mL, 0.05 M) under an argon atmosphere, followed by addition of BF_3·THF (0.25 mmol, 1.0 equiv). The tube was sealed and stirred at room temperature for 18 h before being quenched with $NaHCO_3$ (2 mL, saturated aqueous solution) and extracted with CH_2Cl_2 (3 × 4 mL). The organic phase was dried over $MgSO_4$, and solvents were removed in vacuo to give a residue, which was purified by flash column chromatography (20−40% acetone/CH_2Cl_2) to give the title compounds.

*tert-Butyl 3-Phenyl-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (**3a**).* Isolated as a white gum (57.9 mg, 0.185 mmol, 74%) from **2a** according to general procedure C: ^{1}H NMR δ 1.50 (9H, s), 2.66 (2H, br), 2.77 (2H, br), 3.45 (4H, br), 7.33 (1H, m), 7.37 (2H, m), 7.44 (2H, m), 11.20 (1H, br); ^{13}C NMR δ 25.2, 25.8, 28.6, 28.8 (br), 29.4 (br), 47.0, 47.6, 48.9, 49.5, 79.8, 115.4 (br), 115.6 (br), 128.0, 128.1, 128.4, 128.5, 128.7, 132.0 (br), 141.9 (br), 146.7 (br), 154.9, 155.0; FTIR (υ_{max} cm^{-1}) 3195, 2935, 1688, 1459, 1412, 1365, 1277, 1244, 1164, 1107, 984, 924, 860, 771, 744, 698; R_f 0.27 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{18}H_{24}N_3O_2$ [M + H]$^+$ 314.1869, found 314.1880.

*tert-Butyl 3-(4-Butylphenyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(2H)-carboxylate (**3b**).* Isolated as a white gum (63.1 mg, 0.171 mmol, 68%) from **2b** according to general procedure C: ^{1}H NMR δ 0.94 (3H, t, *J* 7.3 Hz), 1.38 (2H, sext, *J* 7.4 Hz), 1.49 (9H, s), 1.62 (2H, quint, *J* 7.4 Hz), 2.63 (2H, t, *J* 7.7 Hz), 2.78 (4H, br), 3.48 (4H, br), 7.20 (2H, d, *J* 7.1 Hz), 7.32 (1H, d, *J* 8.0 Hz), 7.34 (1H, d, *J* 7.8 Hz), 10.76 (1H, br); ^{13}C NMR δ 14.1, 22.5, 25.2, 25.8, 28.6, 28.9 (br), 29.5 (br), 33.7, 35.5, 47.0, 47.6, 48.9, 49.5, 79.7, 115.3 (br), 115.5 (br), 128.1, 128.2, 128.7, 129.2 (br), 142.9, 143.0, 145.9 (br), 147.4 (br), 155.0; FTIR (υ_{max} cm^{-1}) 3180, 2931, 1682, 1458, 1413, 1366, 1244, 1164, 1106, 987, 923, 909, 836, 773, 729; R_f 0.61 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{22}H_{32}N_3O_2$ [M + H]$^+$ 370.2495, found 370.2492.

*tert-Butyl 3-(4-Methoxyphenyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (**3c**).* Isolated as a white gum (69.1

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mg, 0.201 mmol, 80%) from **2c** according to general procedure C: ^{1}H NMR δ 1.48 (9H, s), 2.77 (4H, br m), 3.48 (4H, br m), 3.81 (3H, s), 6.89 (2H, t, *J* 6.9 Hz), 7.32 (2H, dd, *J* 14.6, 8.2 Hz), 10.15 (1H, br); ^{13}C NMR δ 25.2, 25.8, 28.6, 28.8 (br), 29.4 (br), 47.0, 47.7, 48.9, 49.5, 55.4, 79.7, 114.1, 115.0, 115.2, 124.2 (br), 124.5 (br), 129.5, 129.6, 145.4 (br), 147.6 (br), 154.9, 159.5; FTIR (υ_{max} cm^{-1}) 3181, 2934, 1680, 1616, 1513, 1458, 1414, 1366, 1298, 1246, 1164, 1106, 1035, 985, 922, 908, 834, 773, 728; R_f 0.27 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{19}H_{26}N_3O_3$ [M + H]$^+$ 344.1974, found 344.1993.

*tert-Butyl 3-(4-Cyanophenyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(2H)-carboxylate (**3d**).* Isolated as a white gum (40.4 mg, 0.119 mmol, 48%) from **2d**, according to general procedure C: ^{1}H NMR δ 1.49 (9H, s), 2.83 (4H, br), 3.55 (4H, br), 7.57 (1H, d, *J* 7.9 Hz), 7.60 (1H, d, *J* 8.0 Hz), 7.68 (2H, d, *J* 7.8 Hz), 10.96 (1H, br); ^{13}C NMR δ 25.3, 25.9, 28.1 (br), 28.65, 28.72 (br), 46.7, 47.3, 48.6, 49.2, 80.2, 111.4, 111.5, 116.1, 116.5, 118.8 (br), 128.7, 128.8, 132.4, 132.5, 137.6 (br), 145.0 (br), 154.8, 154.9; FTIR (υ_{max} cm^{-1}) 3218, 2975, 2228, 1666, 1610, 1461, 1414, 1366, 1340, 1243, 1161, 1106, 985, 923, 844, 773, 728; R_f 0.54 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{19}H_{22}N_4O_2Na$ [M + Na]$^+$ 361.1635, found 361.1626.

*tert-Butyl 3-(3-Fluorophenyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(2H)-carboxylate (**3e**).* Isolated as a white gum (60.1 mg, 0.181 mmol, 73%) from **2e**, according to general procedure C: ^{1}H NMR δ 1.49 (9H, s), 2.73 (4H, br), 3.49 (4H, br), 7.02 (1H, t, *J* 7.9 Hz), 7.15 (1H, m), 7.21 (1H, dd, *J* 17.6, 7.2 Hz), 7.33 (1H, br m), 12.14 (1H, br); ^{13}C NMR δ 25.1, 25.8, 28.5 (br), 28.6, 29.4 (br), 46.8, 47.5, 48.8, 49.4, 79.9, 114.8 (br d, *J* 8.9 Hz), 114.9 (br d, *J* 9.3 Hz), 115.3 (d, *J* 21.8 Hz), 115.7 (d, *J* 29.8 Hz), 124.1, 130.2 (d, *J* 7.5 Hz), 134.7 (br), 146.5 (br), 154.88, 154.94, 162.9 (d, *J* 244.9 Hz); FTIR (υ_{max} cm^{-1}) 3183, 2934, 1668, 1589, 1457, 1414, 1366, 1241, 1162, 1115, 1103, 1005, 924, 907, 861, 788, 728; R_f 0.50 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{18}H_{23}N_3O_2F$ [M + H]$^+$ 332.1769, found 332.1767.

*tert-Butyl 3-(2-(Trifluoromethyl)phenyl)-4,5,7,8-tetrahydro-pyrazolo[3,4-d]azepine-6(2H)-carboxylate (**3f**).* Isolated as a white gum (39.9 mg, 0.105 mmol, 42%) from **2f**, according to general procedure C: ^{1}H NMR δ 1.47 (9H, app d, *J* 23.6 Hz), 2.44 (2H, br), 2.75 (2H, br), 3.47 (4H, br), 7.34 (1H, t, *J* 7.7 Hz), 7.53 (1H, t, *J* 7.6 Hz), 7.58 (1H, t, *J* 7.4 Hz), 7.76 (1H, d, *J* 7.8 Hz), 10.76 (1H, br); ^{13}C NMR δ 24.9, 25.6, 28.63, 28.67, 28.72 (br), 47.1, 47.8, 48.8, 49.4, 79.8, 117.5 (br), 117.7 (br), 123.9 (q, *J* 272.3 Hz), 126.4 (q, *J* 4.5 Hz), 128.9, 129.0 (q, *J* 6.0 Hz), 131.2 (q, *J* 32.9 Hz), 131.6, 133.0, 143.6 (br), 146.6 (br), 154.9, 155.0; FTIR (υ_{max} cm^{-1}) 3195, 2931, 1683, 1460, 1413, 1367, 1314, 1247, 1162, 1127, 1108, 1059, 1034, 991, 925, 859, 769, 730; R_f 0.59 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{19}H_{23}N_3O_2F_3$ [M + H]$^+$ 382.1737, found 382.1740.

*tert-Butyl 3-(Naphthalen-1-yl)-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(2H)-carboxylate (**3g**).* Isolated as a white gum (49.8 mg, 0.137 mmol, 55%) from **2g**, according to general procedure C: ^{1}H NMR δ 1.44 (9H, app d, *J* 33.7 Hz), 2.44 (4H, br m), 3.36 (4H, br m), 7.42−7.49 (4H, m), 7.77 (1H, dd, *J* 12.7, 8.6 Hz), 7.87−7.89 (2H, m), 11.54 (1H, br); ^{13}C NMR δ 25.2, 25.8, 28.3 (br), 28.6, 28.7, 47.0, 47.6, 48.8, 49.4, 79.6, 117.4 (br), 125.3, 125.90, 125.92, 126.2, 126.6, 126.7, 128.3, 128.4, 129.0 (br), 129.5 (br), 132.4 (br), 133.7, 143.4 (br), 147.2 (br), 154.8, 154.9; FTIR (υ_{max} cm^{-1}) 3182, 2930, 1682, 1413, 1366, 1295, 1243, 1162, 1111, 1046, 961, 923, 908, 803, 777, 727; R_f 0.55 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{22}H_{26}N_3O_2$ [M + H]$^+$ 364.2020, found 364.2011.

*tert-Butyl 3-(Thiophen-2-yl)-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(2H)-carboxylate (**3i**).* Isolated as a pale yellow amorphous solid (26.3 mg, 0.0823 mmol, 33%) from **2i**, according to general procedure C: ^{1}H NMR δ 1.49 (9H, s), 2.85 (4H, br), 3.54 (4H, br), 7.08 (1H, t, *J* 4.5 Hz), 7.16 (1H, app dd, *J* 14.3, 2.6 Hz), 7.31 (1H, d, *J* 5.0 Hz); ^{13}C NMR δ 25.2, 25.8, 28.2 (br), 28.7, 28.9 (br), 46.9, 47.5, 48.6, 49.2, 79.9, 115.6 (br), 116.0 (br), 125.5, 125.6, 125.65, 125.74, 127.6, 127.7, 134.4 (br), 141.2 (br), 145.4 (br), 154.9, 155.0; FTIR (υ_{max} cm^{-1}) 3455, 2968, 1654, 1467, 1419, 1366, 1246, 1168, 1119, 1023, 941, 924, 846, 775, 727, 694; R_f 0.56 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{16}H_{22}N_3O_2S$ [M + H]$^+$ 320.1427, found 320.1421.

*tert-Butyl 3-Benzyl-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (**3j**).* Isolated as a white gum (56.5 mg, 0.173 mmol, 69%) from **2j**, according to general procedure C: ^{1}H NMR δ 1.47 (9H, app d, *J* 6.4 Hz), 2.56 (2H, br), 2.85 (2H, br), 3.45−3.55 (4H, br m), 3.90 (1H, s), 3.92 (1H, s), 7.14−7.27 (5H, m), 7.95 (1H, br); ^{13}C NMR δ 24.7, 25.2, 28.7, 28.8 (br), 29.6 (br), 31.6 (br), 31.8 (br), 47.2, 47.8, 48.8, 49.3, 79.8, 115.6, 115.8, 126.55, 126.62, 128.5, 128.7, 128.8, 138.5 (br), 138.7 (br), 143.6 (br), 146.9 (br), 154.9; FTIR (υ_{max} cm^{-1}) 3182, 2928, 1679, 1458, 1415, 1366, 1248, 1163, 1112, 1054, 923, 909, 858, 726, 696; R_f 0.55 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{19}H_{26}N_3O_2$ [M + H]$^+$ 328.2025, found 328.2017.

*tert-Butyl 3-(Cyclohex-1-en-1-yl)-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (**3k**).* Isolated as a white gum (53.5 mg, 0.169 mmol, 68%) from **2k**, according to general procedure C: ^{1}H NMR δ 1.48 (9H, s), 1.64 (2H, br), 1.72 (2H, br), 2.17 (2H, br), 2.29 (2H, br), 2.70 (2H, br), 2.89 (2H, br), 3.52 (4H, br), 5.84 (1H, m), 8.65 (1H, br); ^{13}C NMR δ 22.0, 22.8, 25.5, 25.6, 26.1, 28.06, 28.10, 28.7, 29.3 (br), 30.0 (br), 47.1, 47.7, 48.7, 49.4, 79.7, 114.6, 114.8, 128.2 (br), 128.6 (br), 128.7, 128.9, 145.3 (br), 148.8 (br), 155.0; FTIR (υ_{max} cm^{-1}) 3181, 2932, 1674, 1459, 1414, 1366, 1247, 1163, 1113, 914, 728; R_f 0.57 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{18}H_{28}N_3O_2$ [M + H]$^+$ 318.2182, found 318.2174.

*tert-Butyl 3-Cyclopropyl-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(2H)-carboxylate (**3l**).* Isolated as a white gum (45.8 mg, 0.165 mmol, 66%) from **2l**, according to general procedure C: ^{1}H NMR δ 0.70 (2H, m), 0.86 (2H, m), 1.48 (9H, s), 1.71 (1H, m), 2.71 (2H, br), 2.84 (2H, br), 3.53 (4H, br), 8.67 (1H, br); ^{13}C NMR δ 6.06 (br), 6.14, 6.2, 24.5, 25.1, 28.7, 28.8 (br), 29.5 (br), 47.3, 47.8, 48.9, 49.5, 79.7, 116.2, 116.5, 142.6 (br), 146.8 (br), 154.96, 154.99; FTIR (υ_{max} cm^{-1}) 3129, 2932, 1675, 1460, 1413, 1366, 1248, 1164, 1112, 1037, 1019, 924, 908, 859, 773, 729; R_f 0.44 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{15}H_{24}N_3O_2$ [M + H]$^+$ 278.1869, found 278.1862.

*tert-Butyl 3-Cyclopentyl-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(2H)-carboxylate (**3m**).* Isolated as a white gum (57.9 mg, 0.190 mmol, 75%) from **2m**, according to general procedure C: ^{1}H NMR δ 1.47 (9H, s), 1.64 (4H, br), 1.76 (2H, br), 1.99 (2H, br), 2.61 (2H, m), 2.86 (2H, m), 3.00 (1H, quint, *J* 8.1 Hz), 3.53 (4H, br m), 9.14 (1H, br); ^{13}C NMR δ 24.7, 25.3, 25.4, 28.6, 29.0 (br), 29.8 (br), 32.5, 36.5 (br), 36.7 (br), 47.2, 47.8, 48.9, 49.4, 79.7, 114.6 (br), 114.8 (br), 147.6 (br), 148.3 (br), 155.0; FTIR (υ_{max} cm^{-1}) 3182, 2948, 1675, 1459, 1413, 1366, 1247, 1164, 1111, 925, 908, 859, 773, 729; R_f 0.55 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{17}H_{28}N_3O_2$ [M + H]$^+$ 306.2176, found 306.2174.

*tert-Butyl 3-Butyl-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (**3n**).* Isolated as a white gum (54.6 mg, 0.186 mmol, 74%) from **2n**, according to general procedure C: ^{1}H NMR δ 0.89 (3H, app q, *J* 7.4 Hz), 1.33 (2H, quint, *J* 7.9 Hz), 1.48 (9H, s), 1.53 (2H, q, *J* 7.6 Hz), 2.53 (2H, t, *J* 7.8 Hz), 2.58 (2H, td, *J* 21.4, 4.5 Hz), 2.87 (2H, td, *J* 19.3, 4.5 Hz), 3.52 (4H, app tt, *J* 19.0, 4.7 Hz), 9.35 (1H, br); ^{13}C NMR δ 14.0, 22.5, 22.6, 24.6, 24.9, 25.1, 25.2, 28.7, 29.1 (br), 29.8 (br), 31.8, 47.3, 47.9, 49.0, 49.5, 79.7, 114.9 (br), 115.1 (br), 145.0 (br), 147.8 (br), 155.0; FTIR (υ_{max} cm^{-1}) 3196, 2932, 1677, 1459, 1414, 1366, 1247, 1165, 1112, 963, 923, 909, 859, 773, 728; R_f 0.38 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{16}H_{28}N_3O_2$ [M + H]$^+$ 294.2176, found 294.2179.

*3-Phenyl-4,5,7,8-tetrahydro-2H-oxepino[4,5-c]pyrazole (**3o**).* Isolated as a white amorphous solid (45.8 mg, 0.214 mmol, 86%) from **2o**, according to general procedure C: ^{1}H NMR δ 2.77 (2H, dd, *J* 5.0, 4.9 Hz), 2.84 (2H, dd, *J* 5.0, 4.9 Hz), 3.75 (2H, dd, *J* 5.1, 5.0 Hz), 3.79 (2H, dd, *J* 5.0, 4.9 Hz), 7.34 (1H, t, *J* 7.3 Hz), 7.39 (2H, t, *J* 7.1 Hz), 7.44 (2H, d, *J* 7.0 Hz), 10.52 (1H, br); ^{13}C NMR δ 27.8, 31.3 (br), 70.9, 73.0, 116.1 (br), 128.1, 128.3, 128.8, 131.9 (br), 145.2 (br), 148.4 (br); FTIR (υ_{max} cm^{-1}) 3126, 2855, 1499, 1446, 1383, 1333, 1167, 1101, 1041, 1009, 933, 804, 774, 750, 701; R_f 0.42 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{13}H_{15}N_2O$ [M + H]$^+$ 215.1184, found 215.1194.

*3-Phenyl-4,5,7,8-tetrahydro-2H-thiepino[4,5-c]pyrazole (**3p**).* Isolated as a white amorphous solid (41.0 mg, 0.178 mmol, 71%) from **2p**, according to general procedure C: ^{1}H NMR δ 2.58 (2H, m), 2.67 (2H, m), 2.94 (2H, d, J 3.9 Hz), 3.06 (2H, m), 7.35−7.41 (5H, m), 10.84 (1H, br); ^{13}C NMR δ 29.0, 30.1, 32.0, 32.9 (br), 116.5 (br), 128.2, 128.7, 132.1 (br), 146.5 (br), 148.6 (br); FTIR (υ_{max} cm^{-1}) 3117, 2905, 1588, 1507, 1444, 1412, 1347, 1334, 1167, 1073, 989, 923, 880, 774, 739, 704; R_f 0.31 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{13}H_{15}N_2S$ [M + H]$^+$ 231.0956, found 231.0956.

*3-Phenyl-2,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole (**3q**).* Isolated as a white amorphous solid (46.7 mg, 0.220 mmol, 88%) from **2q**, according to general procedure C. ^{1}H NMR δ 1.63 (4H, br), 1.83 (2H, br), 2.63−2.68 (4H, m), 7.33 (1H, t, J 7.3 Hz), 7.38 (2H, t, J 7.3 Hz), 7.46 (2H, d, J 7.6 Hz), 10.31 (1H, br); ^{13}C NMR δ 24.9, 27.6, 28.4 (br), 29.2, 32.4, 117.6 (br), 127.7, 128.4, 128.6, 132.7 (br), 145.6 (br), 149.8 (br); FTIR (υ_{max} cm^{-1}) 3126, 2921, 1591, 1508, 1437, 1334, 1229, 1141, 987, 846, 770, 741, 699; R_f 0.40 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{14}H_{17}N_2$ [M + H]$^+$ 213.1392, found 213.1393.

*3-Phenyl-4,5,6,7,8,9-hexahydro-2H-cycloocta[c]pyrazole (**3r**).* Isolated as a white amorphous solid (53.8 mg, 0.238 mmol, 95%) from **2r**, according to general procedure C: ^{1}H NMR δ 1.50 (4H, br), 1.61 (2H, br), 1.72 (2H, br), 2.63 (2H, t, J 6.1 Hz), 2.68 (2H, t, J 6.2 Hz), 7.31 (1H, t, J 7.3 Hz), 7.37 (2H, t, J 7.3 Hz), 7.54 (2H, d, J 7.2 Hz), 11.06 (1H, br); ^{13}C NMR δ 21.7, 24.7 (br), 25.6, 25.8, 29.6, 30.4, 115.1 (br), 127.5, 127.7, 128.5, 132.9 (br), 145.7 (br), 147.3 (br); FTIR (υ_{max} cm^{-1}) 3118, 2926, 1587, 1506, 1456, 1443, 1357, 1153, 1070, 945, 840, 770, 732, 700; R_f 0.43 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{15}H_{19}N_2$ [M + H]$^+$ 227.1548, found 227.1554.

*3-Phenyl-2,4,5,6,7,8,9,10-octahydrocyclonona[c]pyrazole (**3s**).* Isolated as a white solid (56.7 mg, 0.236 mmol, 94%) from **2s**, according to general procedure C: ^{1}H NMR δ 1.41−1.50 (6H, m), 1.57 (2H, m), 1.67 (2H, m), 2.59 (2H, dd, J 6.2, 6.0 Hz), 2.65 (2H, dd, J 6.0, 5.9 Hz), 7.32 (1H, tt, J 7.3, 1.2 Hz), 7.38 (2H, t, J 7.2 Hz), 7.56 (2H, dd, J 7.1, 1.3 Hz), 11.03 (1H, br); ^{13}C NMR δ 22.4, 24.5, 24.7, 24.9, 26.1, 27.4, 28.3, 116.1 (br), 127.5, 128.1, 128.5, 133.6 (br), 146.0 (br), 147.5 (br); FTIR (υ_{max} cm^{-1}) 3121, 2922, 1584, 1505, 1470, 1443, 1140, 1070, 863, 773, 751, 733, 699; R_f 0.47 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{16}H_{21}N_2$ [M + H]$^+$ 241.1705, found 241.1705.

*4-Methyl-3-phenyl-2,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole (**3t**).* Isolated as a white amorphous solid (49.8 mg, 0.220 mmol, 88%) from **2t**, according to general procedure C: ^{1}H NMR δ 1.24 (3H, d, J 7.3 Hz), 1.32 (1H, q, J 12.6 Hz), 1.60 (1H, t, J 12.1 Hz), 1.81−1.92 (4H, m), 2.55 (1H, dt, J 13.2, 2.4 Hz), 2.65 (1H, br), 3.14−3.18 (1H, m), 7.34 (1H, t, J 7.3 Hz), 7.39 (2H, t, J 7.2 Hz), 7.48 (2H, d, J 7.1 Hz), 10.72 (1H, br); ^{13}C NMR δ 20.0, 25.4, 27.88, 27.90, 28.1 (br), 35.1, 122.1 (br), 127.7, 128.4, 128.6, 132.9 (br), 145.5 (br), 148.3 (br); FTIR (υ_{max} cm^{-1}) 3113, 2906, 1572, 1506, 1444, 1412, 1333, 1154, 1124, 1110, 1073, 986, 880, 774, 741, 698; R_f 0.41 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{15}H_{19}N_2$ [M + H]$^+$ 227.1548, found 227.1546.

*3-Phenyl-2,4,5,6,7,8,9,10-octahydro-4,8:6,10-dimethano-cyclonona[c]pyrazole (**3u**).* Isolated as a white amorphous solid (44.0 mg, 0.166 mmol, 67%) from **2u**, according to general procedure C: ^{1}H NMR δ 1.79−1.85 (6H, m), 1.93−2.00 (4H, m), 2.16 (2H, br), 2.96 (1H, t, J 4.9 Hz), 3.07 (1H, t, J 5.5 Hz), 7.33 (1H, tt, J 7.0, 1.6 Hz), 7.38−7.43 (4H, m), 9.18 (1H, br); ^{13}C NMR δ 27.2, 29.0, 31.9 (br), 34.8, 36.0, 36.6, 123.7, 127.8, 128.0, 128.8, 131.9 (br), 141.0 (br), 147.4 (br); FTIR (υ_{max} cm^{-1}) 3068, 2898, 1459, 1441, 1263, 1119, 1086, 987, 800, 778, 750, 733, 698; R_f 0.40 (50% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{18}H_{21}N_2$ [M + H]$^+$ 265.1705, found 265.1712.

*3-Phenyl-2,4,5,6,7,8,9,10,11,12,13,14-dodecahydrocyclotrideca-[c]pyrazole (**3v**).* Isolated as a white amorphous solid (64.8 mg, 0.219 mmol, 87%) from **2v**, according to general procedure C or as a white amorphous solid (94.2 mg, 0.318 mmol, 64%) from **1v**, according to general procedure B: ^{1}H NMR δ 1.33−1.42 (14H, m), 1.62 (4H, br), 2.54 (4H, ddd, J 16.1, 8.3, 7.7 Hz), 7.32 (1H, t, J 7.3 Hz), 7.38 (2H, t, J 7.3 Hz), 7.54 (2H, d, J 7.4 Hz), 11.73 (1H, br); ^{13}C NMR δ 22.0, 24.2 (br), 24.6, 24.8, 24.9, 25.1, 25.9, 26.4, 26.5, 26.9, 27.8, 115.2 (br), 127.5, 128.1, 128.5, 133.3 (br), 146.3 (br), 146.9 (br); FTIR (υ_{max} cm^{-1}) 3108, 2929, 1570, 1506, 1465, 1443, 1329, 1158, 1074, 978, 766, 729, 698; R_f 0.40 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{20}H_{29}N_2$ [M + H]$^+$ 297.2331, found 297.2331.

*tert-Butyl 3-(4-Fluorophenyl)-1,2,8-triazaspiro[4.5]deca-1,3-diene-8-carboxylate (**4**).* Isolated as a white amorphous solid (124 mg, 0.374 mmol, 75%) from **1a**, according to general procedure B: ^{1}H NMR δ 1.51 (9H, s), 1.76 (4H, br), 3.80 (2H, br), 3.94 (2H, ddd, J 13.0, 8.0, 4.4 Hz), 7.00 (1H, s), 7.16 (1H, t, J 8.5 Hz), 8.02 (2H, dd, J 8.0, 5.6 Hz); ^{13}C NMR δ 28.6, 30.7 (br), 42.5 (br), 80.1, 96.9, 116.1 (d, J 21.7 Hz), 127.0 (d, J 3.3 Hz), 129.2 (d, J 8.2 Hz), 134.6 (d, J 1.9 Hz), 154.7, 154.9, 163.4 (d, J 248.2 Hz); FTIR (υ_{max} cm^{-1}) 3086, 2947, 1694, 1626, 1507, 1446, 1408, 1364, 1276, 1244, 1226, 1176, 1149, 1100, 1016, 972, 954, 860, 837, 822, 810, 771, 720, 687; R_f 0.31 (20% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{18}H_{23}N_3O_2F$ [M + H]$^+$ 332.1774, found 332.1779.

*tert-Butyl 3-(4-Fluorophenyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(2H)-carboxylate (**5**).* Isolated as a white gum (64.7 mg, 0.195 mmol, 78%) from **4**, according to general procedure C: ^{1}H NMR δ 1.48 (9H, s), 2.73 (4H, br), 3.49 (4H, br), 7.05 (2H, dd, J 8.3, 5.7 Hz), 7.38 (2H, m), 11.38 (1H, br); ^{13}C NMR δ 25.1, 25.8, 28.3 (br), 28.6, 28.8 (br), 46.9, 47.5, 48.8, 49.4, 79.9, 115.4 (br), 115.6 (br d, J 18.0 Hz), 128.3 (br), 130.1 (d, J 8.1 Hz), 142.7 (br), 146.0 (br), 154.88, 154.94, 162.6 (d, J 246.4 Hz); FTIR (υ_{max} cm^{-1}) 3191, 2932, 1685, 1511, 1458, 1414, 1366, 1223, 1157, 1106, 987, 923, 839, 815, 773, 729; R_f 0.47 (33% acetone/CH_2Cl_2); HRMS (ESI$^+$) calculated for $C_{18}H_{23}N_3O_2F$ [M + H]$^+$ 332.1774, found 332.1773.

*tert-Butyl 3-(4-Fluorophenyl)-2-isopropyl-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (**6**) and tert-Butyl 3-(4-Fluorophenyl)-1-isopropyl-4,5,7,8-tetrahydropyrazolo[3,4-d]-azepine-6(1H)-carboxylate (**6′**).* To **5** (166 mg, 0.500 mmol, 1.0 equiv) and Cs_2CO_3 (489 mg, 1.50 mmol, 3.0 equiv) in DMF (2 mL) was added 2-bromopropane (0.140 mL, 1.50 mmol, 3.0 equiv). The resulting solution was heated to 80 °C for 18 h before being cooled to room temperature and concentrated in vacuo. The resulting residue was partitioned between H_2O (2 mL) and CH_2Cl_2 (2 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography (20% EtOAc/hexane) to give the desired product **6** (85.7 mg, 0.229 mmol, 46%) as a white gum and the undesired regioisomer **6′** (97.1 mg, 0.260 mmol, 52%) as a white amorphous solid: **6**: ^{1}H NMR δ 1.37 (6H, d, J 6.7 Hz), 1.46 (9H, app d, J 15.4 Hz), 2.47 (2H, br app d, J 27.1 Hz), 2.95 (2H, br app d, J 21.4 Hz), 3.43 (2H, br app d, J 11.3 Hz), 3.56 (2H, br app d, J 11.5 Hz), 4.22 (1H, sept, J 6.5 Hz), 7.14 (2H, m), 7.19 (2H, m); ^{13}C NMR δ 22.9, 25.0, 25.8, 28.6, 30.3, 30.7, 47.5, 47.9, 48.9, 49.5, 49.9, 79.5, 79.6, 115.9 (d, J 21.5 Hz), 116.76 (br), 116.85 (br), 126.7 (br), 126.8 (br), 131.9 (d, J 8.0 Hz), 139.5 (br), 139.7 (br), 150.0 (br), 150.3 (br), 154.9 (br), 155.0 (br), 161.8 (d, J 247.2 Hz); FTIR (υ_{max} cm^{-1}) 2977, 1684, 1509, 1458, 1413, 1366, 1242, 1159, 1110, 927, 841, 729; R_f 0.51 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{21}H_{29}N_3O_2F$ [M + H]$^+$ 374.2244, found 374.2259. **6′**: ^{1}H NMR δ 1.48 (15H, app d, J 7.8 Hz), 2.79 (2H, br app d, J 23.8 Hz), 2.90 (2H, br app d, J 23.3 Hz), 3.52 (2H, br app d, J 19.9 Hz), 3.64 (2H, br app d, J 19.5 Hz), 4.43 (1H, sept, J 5.7 Hz), 7.06 (2H, t, J 8.2 Hz), 7.46 (2H, m); ^{13}C NMR δ 22.6, 24.9, 25.4, 26.5, 27.0, 28.5, 45.4, 46.0, 48.2, 48.9, 49.9, 79.7, 115.2 (d, J 21.2 Hz), 115.3 (br), 130.2 (d, J 7.9 Hz), 130.46 (br), 130.52 (br), 138.8 (br), 139.2 (br), 148.1 (br), 148.2 (br), 154.7 (br), 155.0 (br), 162.2 (d, J 244.4 Hz); FTIR (υ_{max} cm^{-1}) 2979, 1683, 1528, 1462, 1421, 1271, 1221, 1167, 1109, 1041, 929, 838, 771; R_f 0.68 (33% EtOAc/hexane); HRMS (ESI$^+$) calculated for $C_{21}H_{29}N_3O_2F$ [M + H]$^+$ 374.2244, found 374.2238.

*3-(4-Fluorophenyl)-2-isopropyl-2,4,5,6,7,8-hexahydropyrazolo-[3,4-d]azepine (**7**).* To **6** (33.0 mg, 0.0884 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL) dropwise, and the reaction mixture was stirred at room temperature for 2 h before being concentrated in vacuo. The resulting residue was partitioned between $NaHCO_3$ (4 mL, saturated aqueous solution) and EtOAc (4 mL), and the aqueous phase was extracted with EtOAc (3 × 4 mL). The organic

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phase was dried over $MgSO_4$ and concentrated in vacuo to give the title compound (23.4 mg, 0.0856 mmol, 97%) as an off-white amorphous solid without further purification: ^{1}H NMR δ 1.33 (6H, d, J 6.8 Hz), 2.43 (2H, dd, J 5.1, 5.0 Hz), 2.87 (2H, dd, J 5.1, 4.9 Hz), 2.90 (2H, m), 2.99 (2H, m), 3.74 (1H, br), 4.19 (1H, sept, J 6.7 Hz), 7.08 (2H, t, J 8.6 Hz), 7.16 (2H, m); ^{13}C NMR δ 22.8, 27.3, 32.5, 48.6, 49.7, 50.2, 115.7 (d, J 21.4 Hz), 117.6, 126.7 (d, J 3.4 Hz), 131.7 (d, J 8.1 Hz), 139.1, 151.2, 162.6 (d, J 247.0 Hz); FTIR (υ_{max} cm^{-1}) 3254, 2934, 1674, 1509, 1445, 1219, 1149, 960, 839, 811, 721; HRMS (ESI$^+$) calculated for $C_{16}H_{21}N_3F$ $[M + H]^+$ 274.1720, found 274.1708.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(81) The reactions to form **3d** and **3h−i** were also attempted with superstoichiometric amounts of BF_3·THF. However, this promoted significant decomposition of the starting materials and lowered the isolated yields.
(82) ^{1}H NMR of the crude reaction mixture showed a mixture of diastereoisomers in a 3.6:1 ratio. The major diastereoisomer **2t** was isolated in 68% yield by chromatography.