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Remodeling and Enhancing Schmidt Reaction Pathways in Hexafluoroisopropanol

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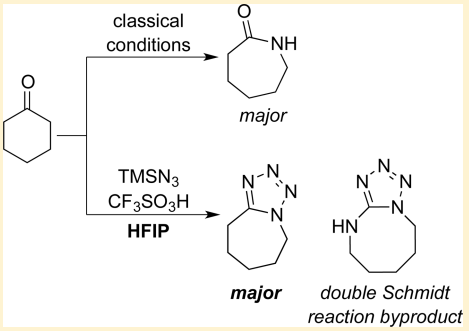
Supporting Information

ABSTRACT: The effect of carrying out two variations of the Schmidt reaction with ketone electrophiles in hexafluoroisopropanol (HFIP) solvent has been studied. When $TMSN_3$ is reacted with ketones in the presence of triflic acid (TfOH) promoter, tetrazoles are obtained as the major products. This observation is in contrast to established methods, which usually lead to amides or lactams arising from formal NH insertion as the major products. The full product profiles of several examples of this reaction are also reported and found to include mechanistically interesting products (e.g., double ring expansion). Application of TfOH promoter in HFIP was also found to promote the reaction of a hydroxyalkyl azide with a ketone, which affords lactams following nucleophilic opening of initially formed iminium ether more efficiently than previously reported methods.



INTRODUCTION

The classical Schmidt reaction, first introduced in 1923,[1] entails the treatment of a carbonyl compound (or, less commonly, a cationic species) with hydrazoic acid (HN_3) or, more recently, $TMSN_3$.[2] Although most commonly used to prepare amide-bond-containing products, it has long been appreciated that other conversions can be effected under these conditions (Figure 1a). For example, reacting aldehydes with HN_3 often affords a mixture of amide products, resulting from a C → N migration step, accompanied by formal elimination of the initially formed azidohydrin intermediate to give a nitrile (Figure 1b). In ketones, the usually desired lactam product may be accompanied by a tetrazole byproduct resulting from the addition of a second molecule of HN_3 to the nitrilium ion intermediate proposed for such reactions (Figure 1a). Tetrazoles become more prevalent when excess amounts of HN_3 are used and represent valuable synthetic objectives in their own right. Today, the Schmidt reaction is understood to include alkyl azides as the nucleophilic component under certain conditions, with synthetically useful examples being the reactions of hydroxyalkyl azides with ketones and the intramolecular version shown in Figure 1c,d, respectively.[3]

A practical issue affecting nearly every version of the Schmidt reaction has been the necessity of using superstoichiometric amounts of acid catalysts, often as solvent, for high conversion.[3,5] Attributable to inhibition of catalyst turnover by the strongly basic amide product, this limits the reaction's application to acid-sensitive substrates and contributes to acid or metal waste. Recently, we discovered that the strong hydrogen-bond-donating solvent, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), promotes catalysis in the intramolecular Schmidt reaction (Figure 1d), dramatically reducing the number of equivalents of acid needed for good conversion.[4] Moreover, reactions carried out under these conditions were uniformly cleaner with respect to side product formation and afforded lactams that required little final purification.

We set about the present study with the straightforward goal of seeing whether other types of Schmidt reactions would benefit similarly from being carried out in HFIP. To this end, we chose to study the intermolecular reactions of ketones with $TMSN_3$ and hydroxyalkyl azides, respectively. One main conclusion of this paper will be that HFIP does indeed represent a highly attractive medium for carrying out these synthetically important variations of the Schmidt reaction. Unexpectedly, we also found that modifying the reaction conditions in this way can lead to changes in product profile or previously unobserved reaction pathways that suggest further extensions of this rich reaction manifold.

RESULTS AND DISCUSSION

Effect of HFIP Solvent on the Reaction Profile of Schmidt Reactions of Ketones with $TMSN_3$. A typical Schmidt reaction of a ketone with hydrazoic acid or $TMSN_3$ usually affords amides or lactams, but K.F. Schmidt himself reported that tetrazoles may also arise under some conditions.[1b] This form of the Schmidt reaction has received considerably less attention, with the main limitations being the usual need for large excesses of hydrazoic acid and long reaction times, often rendering it unsuitable for functionalized substrates.[6] Nonetheless, the conversion of ketones to tetrazoles remains an attractive transformation given the utility of the product. For

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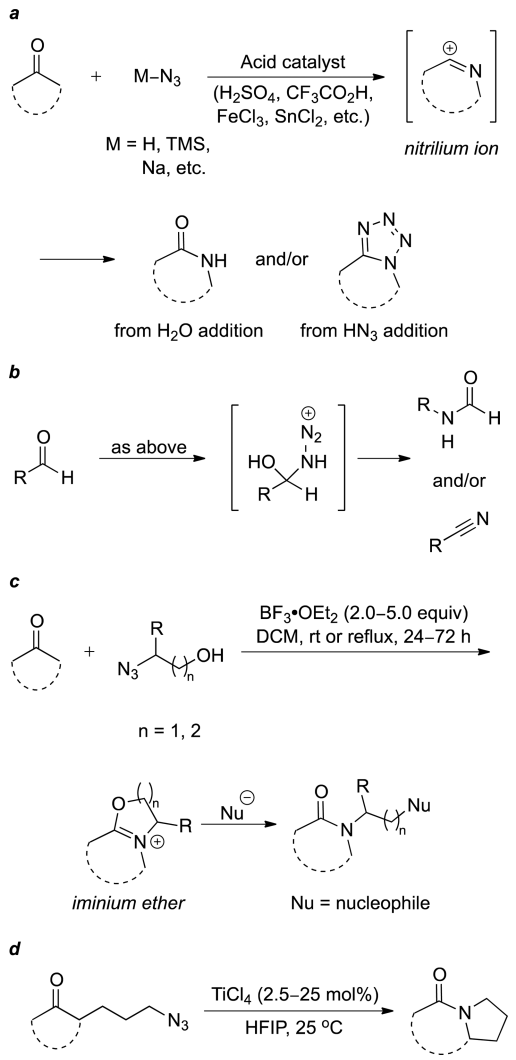

Figure 1. Selected variants of the Schmidt reaction: (a) Schmidt reaction of ketones and hydrazoic acid or equivalents, (b) Schmidt reactions of aldehydes, (c) reaction of hydroxyalkyl azides with ketones (followed by nucleophilic ring opening of the first-formed iminium ether product), and (d) the intramolecular Schmidt reaction of an azidoalkyl ketone using recently reported catalytic conditions.[4]

example, tetrazoles have found widespread applications as organocatalysts,[7] ligands,[8] and precursors for other nitrogen-containing heterocycles[9] and in materials science.[10] From a medicinal chemistry perspective, tetrazoles are extensively used as carboxylic acid bioisosteres or conformational mimics of cis amide bonds and appear in a variety of biologically active compounds (Figure 2).[11]

The present study was instituted to determine whether carrying out the Schmidt reaction of $TMSN_3$ with a ketone would benefit from carrying out the reaction in HFIP. Nishiyama had previously reported that the reaction of ketones with $TMSN_3$ with $SnCl_2{\cdot}2H_2O$ at room temperature provided diazides, which could be converted to tetrazoles upon treatment with Lewis acids or by carrying out the initial reaction at elevated temperatures (diazido compounds are potentially explosive[3,13]).[14] Upon treatment of cyclohexanone **1a** with $TMSN_3$ and 10 mol % of $SnCl_2{\cdot}2H_2O$ under solvent-free conditions, we directly obtained tetrazole **2a** in 87% yield after heating at 55 °C for 16 h (entry 1, Table 1). Similar

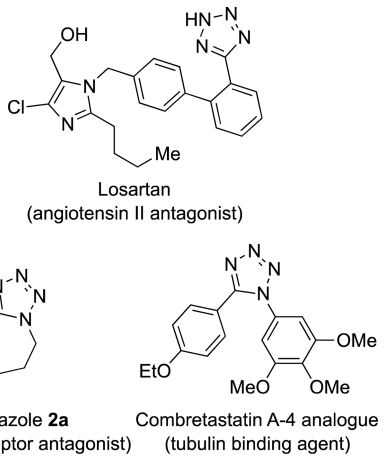

Figure 2. Representative examples of pharmacologically active tetrazoles.[11f,12]

reaction with 5 mol % of $SnCl_2{\cdot}2H_2O$ in the presence of HFIP was slightly less effective (entry 2).

Sensing the potential to develop an attractive route to tetrazoles, we carried out optimization studies using 4-phenylcyclohexanone **1b** as a substrate. Screening of different protic and Lewis acids in HFIP identified triflic acid (TfOH) as the optimal acid catalyst for this transformation; 25 mol % of TfOH provided the maximum yield of 84% for tetrazole **2b** and 7% of aminotetrazole **4b** in just 1 h (entries 3–9). Triflic acid was chosen over other strong acids known to facilitate Schmidt reactions, such as sulfuric acid, as it has been reported to minimize side reactions in some cases.[15] The reaction of **1b** with 1.5 equiv of $TMSN_3$ in HFIP afforded **2b** as the major product, albeit in moderate yield due to incomplete conversion (entry 3). This result was noteworthy because previous reports show that two or more equivalents of an azide nucleophile are usually needed to obtain tetrazole as a major product.[5,6,16] The reaction with $FeCl_3$ in HFIP also delivered tetrazole **2b** (entry 7), in contrast to previous reports that reactions of ketones with 1.5 equiv of $TMSN_3$ in 1,2-dichloroethane provide lactams.[2c] However, reaction with 2.5 equiv of $TMSN_3$ in the presence of 50 μL of water afforded lactam **3b** as a major product (entry 10). Reaction of **1a** with 5 mol % of TfOH in HFIP at 55 °C provided a yield comparable to that with 10 mol % of $SnCl_2{\cdot}2H_2O$ without solvent (cf. entries 11 and 1). Conversely, when the neat reaction of **1b** was carried out with 25 mol % of $SnCl_2{\cdot}2H_2O$ at room temperature, only a trace amount of tetrazole **2b** in addition to unidentified byproducts and some unreacted **1b** was observed by crude ^1H NMR (entry 12). The poor conversion could be due to the heterogeneity of the reaction mixture in this case. Finally, the neat reaction with 25 mol % of TfOH at room temperature afforded a low yield of **2b** (entry 13).

The formation of aminotetrazole **4b** is intriguing. It presumably arises via two consecutive Schmidt reactions to afford an aminonitrilium ion intermediate **B** (Scheme 1). Subsequent addition of a third molecule of azide leads to the formation of aminotetrazole **4b**, the structure of which was confirmed by single-crystal X-ray diffraction analysis. Substituted 5-aminotetrazoles have been prepared via a variety of synthetic methods,[17] but aside from Schmidt's 1924 report that benzophenone formed the tautomeric iminodihydrotetrazole upon treatment with HN_3,[1b] aminotetrazoles have not been observed to arise from Schmidt reaction manifolds until now.

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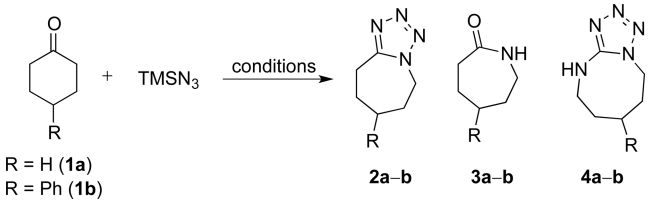
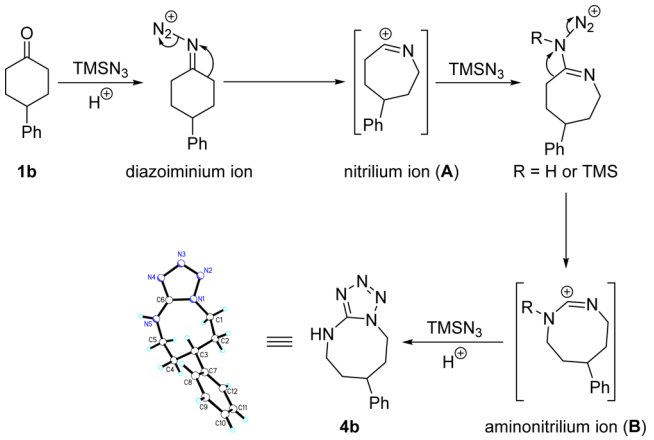
Table 1. Optimization of Reaction Conditions for Tetrazole Synthesis[a,b]



entry	R	$TMSN_3$ (equiv)	catalyst	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%)[c] 2	3b	4b
1	H	3.0	$SnCl_2{\cdot}2H_2O$	10	neat	55	16	87(71)[d]	ND	ND
2	H	3.0	$SnCl_2{\cdot}2H_2O$	5	HFIP	55	16	66	ND	ND
3	Ph	1.5	CF_3SO_3H	10	HFIP	rt	20	49	~7[e]	~6[e]
4	Ph	2.5	CF_3SO_3H	20	HFIP	rt	2	75	ND	ND
5	Ph	2.5	CH_3COCl[f]	20	HFIP	rt	18	31	ND	ND
6	Ph	2.5	$BF_3{\cdot}OEt_2$	20	HFIP	rt	22	16	ND	ND
7	Ph	2.5	$FeCl_3{\cdot}6H_2O$	20	HFIP	rt	22	60	ND	ND
8	Ph	3.0	$ClSO_3H$[g]	20	HFIP	rt	2	51	ND	ND
9	**Ph**	**2.5**	**CF_3SO_3H**	**25**	**HFIP**	**rt**	**1**	**84**	**ND**	**7**
10	Ph	2.5	CF_3SO_3H	25	HFIP	rt	5	13	53[h]	ND
11	H	3.0	CF_3SO_3H	5	HFIP	55	16	85	ND	ND
12	Ph	2.5	$SnCl_2{\cdot}2H_2O$	25	neat	rt	2	trace		
13	Ph	2.5	CF_3SO_3H	25	neat	rt	2	34	~12[e]	~3[e]

[a]To a solution or suspension of a ketone **1a** (0.400 mmol) or **1b** (0.200 mmol) and $TMSN_3$ in HFIP (1.0 or 0.5 mL) or under neat conditions was added a catalyst, and the reaction was allowed to stir at a specified temperature (rt is ≈22−23 °C) for a designated period of time unless otherwise mentioned (see the Experimental Section for details). [b]Concentration of ketone was ≈0.40 M. [c]Isolated yields. [d]Yield in parentheses refers to the reported yield in ref 14. [e]Corrected yield for **3b** and **4b** from a slightly impure inseparable mixture as determined by ^1H NMR. [f]Could generate 20 mol % of in situ HCl (ref 4). [g]Reaction was carried out under an argon atmosphere. [h]50 μL of deionized water was added before the addition of TfOH. ND = Not determined.

Scheme 1. Proposed Mechanism for Aminotetrazole formation



The scope of the tetrazole synthesis was investigated under the optimized reaction conditions (Table 2). Substituted cyclohexanones worked well with 25 mol % of TfOH, delivering good yields of tetrazoles and <15% combined yields of aminotetrazoles and lactams (entries 1−4). Functionalized and sterically hindered cyclohexanones required 45−65 mol % of TfOH to afford tetrazoles in good yields (entries 5−7). A single tetrazole product **2f** was obtained from the potentially epimerizable L-menthone **1f** with high regio- and diastereoselectivity (entry 6). The requirement of 65 mol % of TfOH for piperidone substrate **1g** may reflect decreased turnover due to catalyst binding to the amide (entry 7). Reactions of smaller and medium ring ketones provided moderate to excellent yields of tetrazoles (entries 8−10). However, the reaction of aliphatic ketones required close to a stoichiometric amount of acid catalyst to afford the corresponding tetrazoles in moderate to good yields (entries 11−13). Nonetheless, this represents an improvement over previous work given the poor availability of these products using the Nishiyama protocol.[14]

The diversion of the reaction pathway to favor tetrazoles over lactams as the primary reaction product suggests that nitrilium ions **A** (Scheme 1) are better stabilized in HFIP than in traditional Schmidt reaction solvents. This possibility is consistent with the high polarity and poor nucleophilicity of HFIP (Scheme 1). This consideration should also favor increased amounts of "double Schmidt" products **4**. Another possibility is that carrying out the reaction in HFIP instead of more traditional solvents favors the formation of nitrilium ion **A** as opposed to a direct rearrangement pathway of azidohydrin leading to lactam, but again, we have no evidence to make a firm mechanistic conclusion on this point.

The Schmidt reaction of aromatic ketones, in particular, chromanones and flavanones, has been extensively studied with respect to the synthesis of benzoheterazepine analogues as potential psychotropic agents.[16,18] These less reactive ketones often require excess acid catalysts as solvents and long reaction times.[16,18e] Although the reaction of flavanone **1n** using our HFIP methodology required a full equivalent of TfOH, the reaction time was much shorter and tetrazole **2n** was furnished in moderate yield along with only a small amount of lactam regioisomers **3na** and **3nb** (Scheme 2). Moreover, three unusual minor products **5**, **6**, and **7** were obtained through intra- and intermolecular trapping of the nitrilium ion with different nucleophiles en route to the tetrazole and aminotetrazole.

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Table 2. Substrate Scope for Tetrazole Synthesis[a,b]

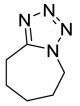
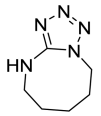
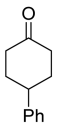
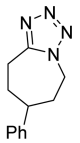
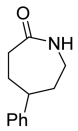
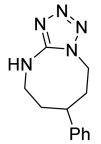
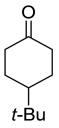
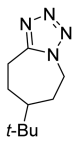
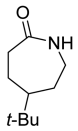
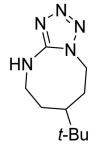
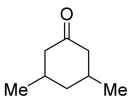
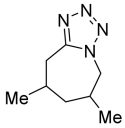
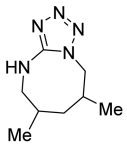
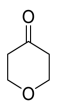
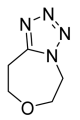
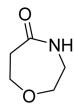
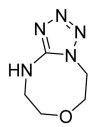
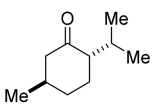
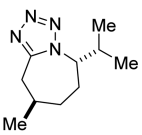
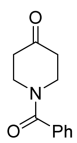
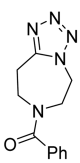
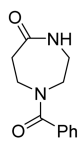
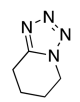
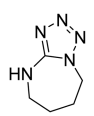
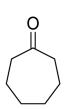
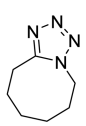
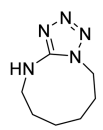
entry	ketone **1**	catalyst (mol %)	time (h)	yield (%)[c] **2**	**3**	**4**
1	 **1a**	25	2	 **2a** (91%)	–	 **4a** (4%)
2	 **1b**	25	2	 **2b** (84%)	 **3b** (3%)	 **4b** (9%)
3	 **1c**	25	2	 **2c** (83%)	 **3c** (~2%)[d]	 **4c** (9%)
4	 **1d**[e]	25	1.5	 **2d** (83%)[f]	–	 **4d** (3%)[f]
5	 **1e**	45	2.5	 **2e** (53%)	 **3e** (3%)[g]	+  **4e** (7%)[g]
6	 **1f**	50	6	 **2f** (87%)	–	–
7	 **1g**	65	2.5	 **2g** (50%)[h]	 **3g** (14%)[h]	–
8	 **1h**	50	6	 **2h** (51%)	–	 **4h** (7%)
9	 **1i**	60	2	 **2i** (93%)	–	 **4i** (ca. 2%)

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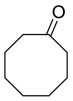
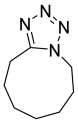
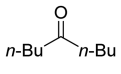
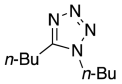
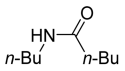
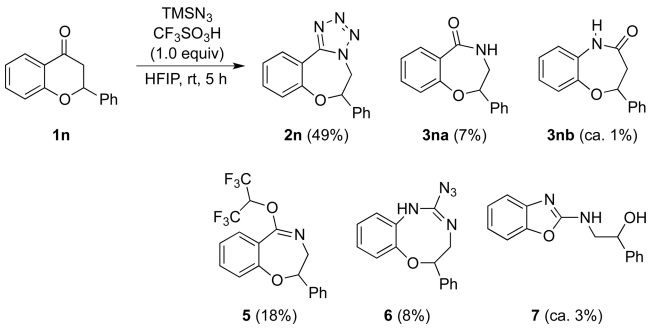
Table 2. continued

entry	ketone 1	catalyst (mol %)	time (h)	yield (%)[c] 2	3	4
10	 **1j**	60	2	 **2j** (86%)	–	–
11	 **1k**	80	3	 **2k** (40%)[i]	 **3k** (19%)[i]	–
12	 **1l**	90	6	 **2l** (74%)[j]	–	–
13	 **1m**	90	6	 **2m** (66%)	–	–

[a]To a solution of ketone (1.0 equiv) and $TMSN_3$ (2.5 equiv) in HFIP (1.0 mL) was added TfOH, and the reaction was allowed to stir at room temperature for a specified period. [b]Concentration of ketone was ≈0.40 M. [c]Isolated yields. [d]Impure lactam **3d** (~2%) was obtained (see the Experimental Section for details). [e]Mixture of isomers (~95% major isomer, presumably cis). [f]Corrected yield of major isomer from a mixture of isomers (presumably cis; see the Experimental Section for details). [g]Corrected yield for **3e** and **4e** from an inseparable mixture as determined by ^{1}H NMR. [h]Mixture of rotamers (see the Experimental Section for details). [i]Corrected yield for **2k** and **3k** from an inseparable mixture as determined by ^{1}H NMR (see the Experimental Section for details). [j]Corrected yield of **2l**; contains a small amount of byproduct (probably amide) as determined by ^{1}H NMR and HRMS (see the Experimental Section). ND = Not determined. Cy = Cyclohexyl.

Scheme 2. Products Obtained from Flavanone 1n



Iminoether **5** arises from HFIP trapping of a nitrilium ion. The formation of iminoesters as a major product upon treatment of flavanone with NaN_3 in trifluoroacetic acid has been documented.[16] Intermolecular trapping of the aminonitrilium ion **C** with $TMSN_3$ led to the formation of guanyl azide **6**, which could, in principle, cyclize to afford the aminotetrazole. However, the aminotetrazole product was not observed in this instance (Scheme 3). This result was counterintuitive because cyclization into the aminotetrazole is generally the thermodynamically more favored process,[19] believed to arise via thermal isomerization of the transient guanyl azide intermediate.[19a,b] Guanyl azide **6** was subsequently subjected to copper-promoted reaction with phenyl acetylene to provide guanidino triazole **8**, which further confirmed the structure of **6**. The formation of aminobenzoxazole **7**, although in small amounts, is mechanistically fascinating (Schemes 2 and 3). The aminonitrilium ion **C** formed after two sequential Schmidt reactions could intramolecularly interact with the oxygen atom attached to the ring to generate an oxonium ion **D** (lacking detailed structural information, we have drawn the two limiting stereoisomeric forms of **C**, while recognizing the possible existence of a linear carbodiimidium cation form).[20] Subsequent hydration of benzylic carbocation **E** eventually leads to **7**. Misiti has previously reported aminobenzoxazole products arising from Schmidt reactions of substituted flavanones and NaN_3.[18b]

The Schmidt reaction of β-tetralone **1o** with hydrazoic acid was reported to provide only low yields of tetrazoles (Scheme 4).[18c] Using the current conditions, tetrazoles **2oa** and **2ob** were isolated in modest yield in addition to small amounts of lactams **3oa** and **3ob** and aminotetrazoles **4oa** and **4ob**. In contrast, the reaction of 2-indanone **1p** afforded a complex mixture from which tetrazole **2p** and aminotetrazole **4p** were isolated in low yields.

Effect of HFIP Solvent on Efficiencies of Reactions of *N*-Hydroxyalkyl Azides. We examined the Schmidt reaction of ketones with hydroxyalkyl azides toward the synthesis of *N*-hydroxyalkyl lactams.[21] This variant was originally developed to overcome the poor scope of the $TiCl_4$-promoted intermolecular reaction of simple azides with ketones[22] and has been used for nitrogen asymmetric ring expansion reactions,[23] construction of γ-turn-like peptidomimetic libraries,[24] and synthesis of functionalized lactams[25] and *N*-alkyl heterocycles[26] via nucleophilic addition to iminium ethers.

Typically, this intermolecular Schmidt reaction requires 2−5 equiv of $BF_3{\cdot}OEt_2$ or another acidic reagent in DCM to achieve successful iminium ether formation over extended reaction times (Scheme 5).[21,27] However, in principle, only 1 equiv of

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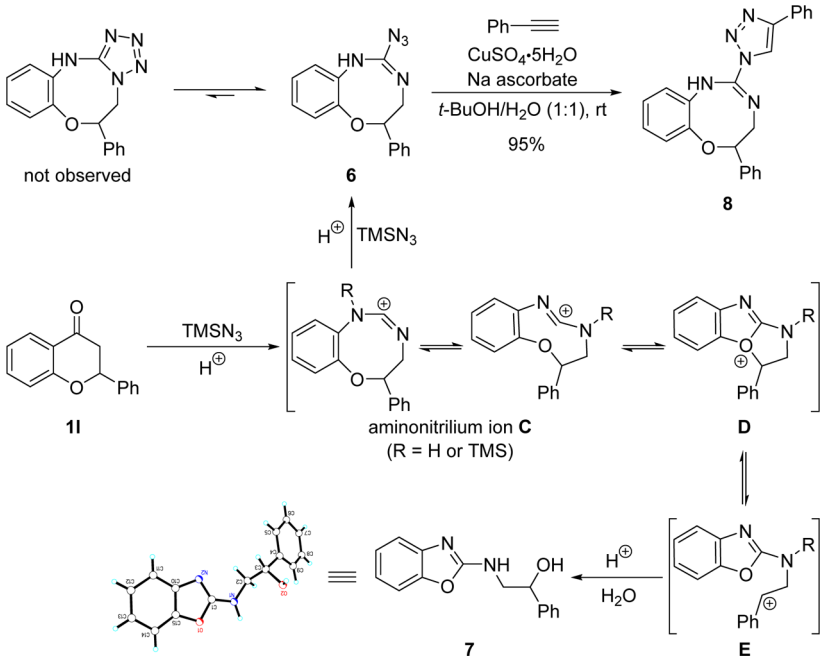
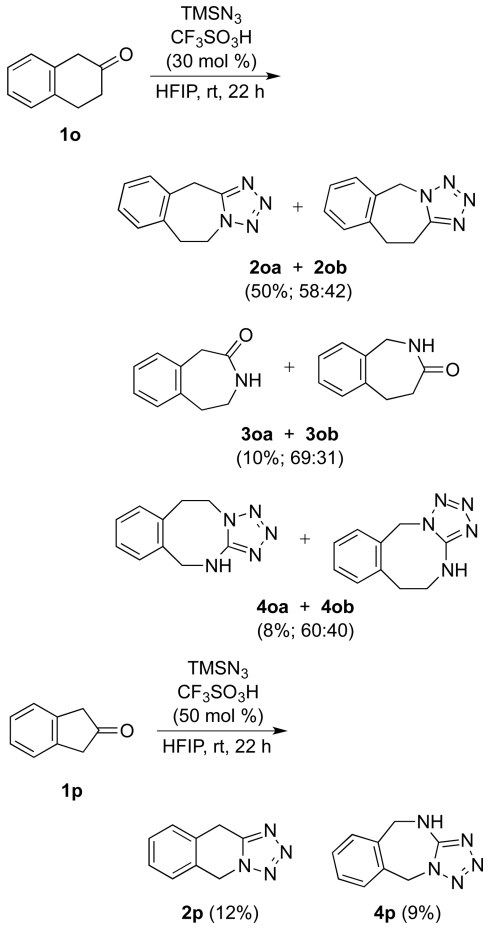
Scheme 3. Proposed Mechanism for the Formation of Guanyl Azide 6 and Aminobenzoxazole 7

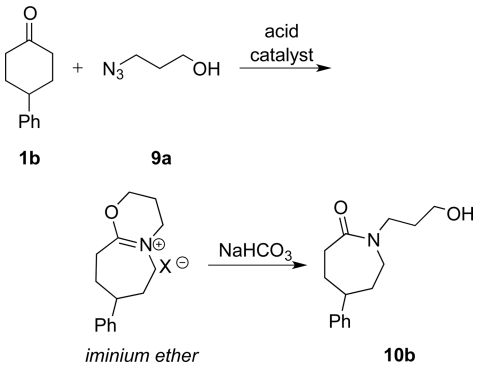


Scheme 4. Schmidt Reactions of β-Tetralone and 2-Indanone



acid catalyst should be sufficient to promote the reaction to completion as only 1 equiv of the counterion is required in the isolable iminium ether intermediate.[21a,b] Thus, carrying out this

Scheme 5. Formation of *N*-Hydroxyalkyl Lactam via an Intermediate of Iminium Ether



transformation with 1 equiv of protic acid catalyst in a short period would constitute a significant practical improvement by lowering catalyst loading and would also provide easy access to the intermediate iminium ethers for further functionalization when necessary (in this case, hydrolysis to afford *N*-hydroxyalkyl lactam).

We compared a standard $BF_3{\cdot}OEt_2$-promoted reaction of 4-phenylcyclohexanone **1b** with 3-azidopropanol **9a** in the presence of either DCM or HFIP at room temperature (entries 1−3, Table 3). Compared to DCM,[21a,b] the use of HFIP efficiently promoted the reaction in 6 h with just 1.1 equiv of $BF_3{\cdot}OEt_2$ (cf. entries 1 and 2 with entry 3). Previously, we reported that other Lewis and protic acids could be used in place of $BF_3{\cdot}OEt_2$, albeit affording product in slightly lower yields.[21b] Expanding our screen to other acids revealed that 1 equiv of TfOH in HFIP was sufficient to afford complete conversion of **1b** to the corresponding iminium ether within 1 h, which after basic hydrolysis and purification afforded *N*-hydroxyalkyl lactam **10b** in excellent yield (cf. entry 7 with entries 4−6).

Encouraged by these initial results, we subjected a selection of ketones to the optimized conditions (Table 4). Reaction of

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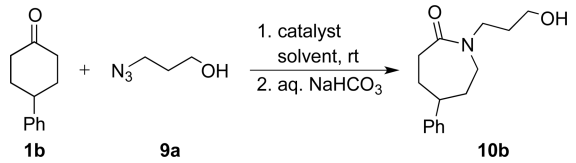
Table 3. Optimization of Conditions for Intermolecular Schmidt Reaction of 1b with 9a[a,b]



entry	9a (equiv)	catalyst	catalyst (equiv)	solvent	time (h)	^{1}H NMR ratio (10b/1b)[c]	yield (%)[d]
1	2.0	$BF_3{\cdot}OEt_2$	2.0	DCM	24	88:12	82[e]
2	1.5	$BF_3{\cdot}OEt_2$	1.1	DCM	6	73:27	62
3	1.5	$BF_3{\cdot}OEt_2$	1.1	HFIP	6	>98:2	92
4	1.5	H_2SO_4	0.55[f]	HFIP	6	71:29	62
5	1.5	$TiCl_4$	0.28[f]	HFIP	6	>97:3	89
6	1.5	CH_3COCl	1.1[f]	HFIP	6	>95:5	85
7	1.5	CF_3SO_3H	1.0	HFIP	1	>98:2[g]	95

[a]To a solution of 4-phenylcyclohexanone **1b** (1.0 equiv) and 3-azidopropanol **9a** in solvent (0.75 mL) at room temperature was added a catalyst, and reaction mixture was allowed to stir for a specified time. Further hydrolysis with aqueous $NaHCO_3$ for 12−14 h followed by purification on a silica gel afforded **10b**. [b]Concentration of **1b** was ≈0.40 M. [c]^{1}H NMR ratio of the crude reaction mixture. [d]Isolated yield. [e]Yield of 88% has been reported when the reaction was allowed to stir for 48 h (ref 21b). [f]Acetyl chloride is known to generate an equimolar amount of HCl upon dissolution in HFIP (ref 4). [g]Complete conversion of **1b** to **10b** was observed as determined by ^{1}H NMR of a crude reaction mixture.

simple cyclohexanones afforded very high yields of *N*-hydroxyalkyl lactams in just 1 h (entries 1 and 2). Functionalized six-membered cyclic ketones such as tetrahydropyran-4-one **1e** and 1-benzoyl-4-piperidone **1g**, each having a functional group capable of catalyst deactivation, still underwent facile conversion within 6 h to their corresponding lactams in good yields (entries 3 and 4). Previously, seven- and eight-membered cyclic ketones required relatively harsh conditions (5 equiv of $BF_3{\cdot}OEt_2$ in refluxing DCM for 72 h) to get either lactam or aminolactone depending on the base ($NaHCO_3$/NaOH) used in the hydrolysis step.[27] Application of the present methodology to cycloheptanone **1i** provided a moderate yield of corresponding lactam **10i** upon hydrolysis with NaOH (entry 5). However, the reaction of cyclooctanone **1j** afforded the corresponding macrocyclic aminolactone **11j** exclusively, in higher yield than that previously reported (entry 6).[27] The reaction of benzylic ketones smoothly provided lactams in excellent yield, with unsymmetrical β-tetralone **1o** giving rise to a mixture of two lactam isomers in a ∼2:1 ratio (entries 7 and 8). The increased electrophilicity of the C-3 carbonyl in isatin **1q** was expected to override the potential problem of product inhibition presented by the adjacent amide functionality. Accordingly, the reaction of **1q** proceeded well in 6 h, providing products with two different ring systems, quinoxaline dione **10qa** and quinazoline dione **10qb** as a mixture in ∼2:1 ratio in an overall 76% yield (entry 9). This example represents a new mode for this version of the Schmidt reaction, constituting the first time that the acyl group has been observed to migrate in this chemistry (affording **10qb**).

The reaction with bicyclic ketones proceeded smoothly in 1−2 h to afford the corresponding lactams in excellent yields as mixtures of two regioisomers (entries 10 and 11). Adamantanone **1t** also required just 1 h to provide the corresponding tricyclic lactam **10t** in 96% yield (entry 12). In the case of acyclic ketone **1k**, 1.5 equiv of TfOH was required for successful iminium ether formation, which upon hydrolysis with $NaHCO_3$ provided a mixture of amino ester **11k** as a major product in 69% yield and hydroxypropylamide **10k** as a minor product in 15% yield (entry 13).[27] Overall, good to excellent yields were obtained with only 1 equiv of TfOH in a relatively short period.

CONCLUSION

Two useful variations of the Schmidt reaction were studied to determine whether using the strong hydrogen-bonding solvent HFIP led to improvements in efficiency or convenience. For one of these reactions, the two-stage reaction of a ketone with a hydroxyalkyl azide followed by hydrolysis of the initially formed iminium ether, it proved possible to dramatically decrease the amount of acid promoter needed for the initial reaction. In addition, better yields of lactams resulting from the overall reaction were obtained. More interestingly, for the classical Schmidt reaction of ketones with a hydrazoic acid equivalent, $TMSN_3$, we found that the course of the reaction was modified relative to previous reports. Thus, tetrazoles were the major products under conditions in the absence of large excesses of $TMSN_3$, rendering this one of the most attractive synthetic pathways for converting ketones to ring-expanded tetrazoles. In separate work, we have disclosed that similar enhancements of efficiency and selectivity are possible for yet another reaction of $TMSN_3$ with carbonyls, in which aromatic aldehydes are converted cleanly to nitriles accompanied by little or no formamide formation (Scheme 1b).[28] Taken together, this body of work demonstrates that practical utility, for example, higher yields and often purer products, as well as changes in reaction pathways and selectivity, results from carrying out Schmidt reactions in HFIP relative to more traditional solvents.

EXPERIMENTAL SECTION

General Information. Reactions were performed under a nitrogen atmosphere in glass sample vials with a TFE-lined cap. Plastic syringes were flushed with nitrogen before use. All chemicals were used as received from a commercial source without further purification, except L-menthone and β-tetralone, which were purified on normal-phase silica flash columns using an automated chromatography system. New containers of boron trifluoride diethyl etherate, triflic acid, and HFIP were used. Methylene chloride was dried by passage through neutral alumina columns using a commercial solvent purification system prior to use. Thin-layer chromatography (TLC) was performed using commercial glass-backed silica plates (250 μm) with an organic binder. Preparative TLC was carried out using silica gel GF TLC plates (UV 254 nm, 1000 μm). Visualization was accomplished with UV light and Seebach's stain or aqueous $KMnO_4$ by heating. Purification was carried out on an automated flash chromatography/medium-pressure liquid chromatography system using normal-phase silica flash columns (4 or

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Table 4. Synthesis of *N*-Hydroxyalkyl Lactams[a,b]

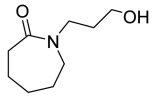
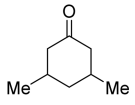
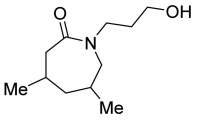
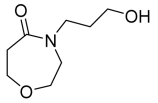
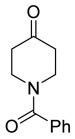
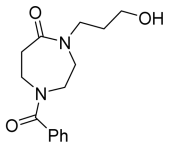
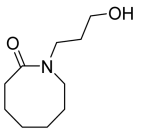
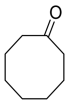
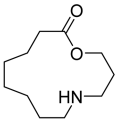
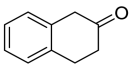
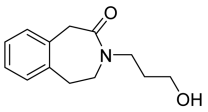
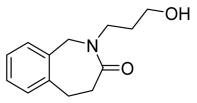
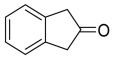
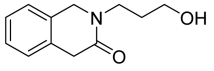
entry	ketone **1**	time (h)	product **10**	yield (%)[c]
1	 **1a**	1	 **10a**	95
2	 **1d**[d]	1	 **10d**[d]	94[e]
3	 **1e**	6	 **10e**	84
4	 **1g**	6	 **10g**	80
5	 **1i**	6	 **10i**	61[f]
6	 **1j**	6	 **11j**	56
7	 **1o**	3	 **10oa**  **10ob** **10oa**:**10ob** = 63:37[g]	94
8	 **1p**	1	 **10p**	90

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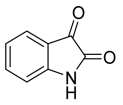
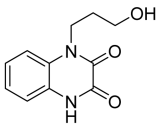
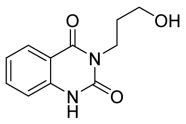
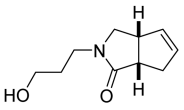
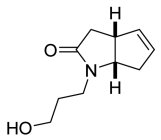
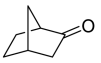
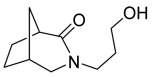
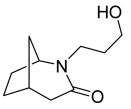
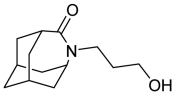
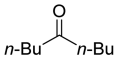
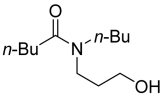
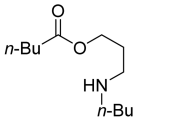
Table 4. continued

entry	ketone **1**	time (h)	product **10**	yield (%)[c]
9		6	 	76
	1q		**10qa** **10qb**	
			10qa:**10qb** = 63:37[g]	
10		1	 	95
	1r		**10ra** **10rb**	
			10ra:**10rb** = 74:26[g]	
11		2	 	90
	1s		**10sa** **10sb**	
			10sa:**10sb** = 58:42[g]	
12		1		96
	1t		**10t**	
13		6	 	84[h,i]
	1k		**10k** (15%)[j] **11k** (69%)	

[a]To a solution of a ketone (1.0 equiv) and **9a** (1.5 equiv) in HFIP (1.0 mL) at room temperature was added TfOH (1.0 equiv), and the reaction was allowed to stir at room temperature for the specified time (time indicated in the table refers to the time required for the formation of iminium ether). Further hydrolysis with aqueous $NaHCO_3$/NaOH for 12−24 h followed by purification on a silica gel afforded products (see the Experimental Section for details). [b]Concentration of ketone was ≈0.40 M. [c]Isolated yield. [d]Mixture of isomers (~95% major isomer, presumably cis). [e]Corrected yield of major isomer from a mixture of isomers (presumably cis; see the Experimental Section for details). [f]Similar reaction of cycloheptanone with 1.5 equiv of TfOH provided **10i** in 69% yield (see the Experimental Section for details). [g]Ratio of two inseparable isomers from a purified mixture as determined by ^{1}H NMR. [h]The reaction was carried out with 1.5 equiv of TfOH. [i]Combined yield of **10k** and **11k**. [j]Mixture of rotamers (ratio = 79:21).

12 g). Infrared spectra were acquired as thin films or solids. All nuclear magnetic resonance spectra (^{1}H, ^{13}C, APT, COSY, HSQC, HMBC, and NOESY) were recorded on either a 400 MHz or a 500 MHz with a dual carbon/proton cryoprobe instrument. NMR samples were recorded in deuterated chloroform, deuterated methanol, or deuterated dimethyl sulfoxide. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent (for $CDCl_3$, δ 7.26 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR; and for C_2D_6SO, δ 2.50 ppm for ^{1}H NMR and 39.52 ppm for ^{13}C NMR). Coupling constants are given in hertz (Hz). HRMS data were collected with a time-of-flight mass spectrometer and an electrospray ion source (ESI). Melting points were determined in open capillary tubes using an automated melting point apparatus and are uncorrected. Sample concentrator using nitrogen gas was utilized for concentration of reaction mixtures. Microsyringes (flushed with nitrogen prior to use) were used to measure and deliver volumes between 1.00 and 100 μL. Spectroscopic data for the known compounds prepared according to the methodology described in this paper match with those reported in the literature.

CAUTION: Researchers should employ extreme care whenever using azide sources, especially in the presence of acids or protic solvents. Minimally, the use of blast shields and careful control of temperature and scale should be exercised. We do not recommend distillation of reaction mixtures that may contain residues of azide sources.

General Procedure for the Optimization of Reaction Conditions for Tetrazole Formation. Procedure for Reactions Carried out under Heating at 55 °C (Table 1). Either to a neat suspension of cyclohexanone **1a** (39.3 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (138 mg, 1.20 mmol, 3.0 equiv) or to a solution of **1a** (0.400 mmol) and $TMSN_3$ (1.20 mmol) in HFIP (1.0 mL) in a nitrogen-flushed microwave reaction vial (2−5 mL capacity) was added catalyst (5−10 mol %). The vial was sealed, and the reaction mixture was allowed to stir at 55 °C for 16 h (effervescence due to nitrogen gas evolution was observed upon addition of a catalyst). The reaction mixture was cooled to room temperature and concentrated under nitrogen using a sample concentrator. The residue obtained was diluted with DCM and loaded on silica gel in a 5 g sample cartridge. Purification was carried out using a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0

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to 5% MeOH/DCM over 50 min. Concentration of the appropriate fractions afforded tetrazole **2a**.

Procedure for Reactions Carried out at Room Temperature (Table 1). Either to a neat suspension of 4-phenylcyclohexanone **1b** (34.9 mg, 0.200 mmol, 1.0 equiv) and $TMSN_3$ (57.6 mg, 0.500 mmol, 2.5 equiv) or to a solution of **1b** (0.200 mmol) and $TMSN_3$ (1.5−3.0 equiv) in HFIP (0.5 mL) in a nitrogen-flushed two-dram vial was added catalyst (10−25 mol %) unless otherwise noted (see Table 1 footnotes). The vial was capped, and the reaction mixture was allowed to stir at room temperature for 1−22 h (slight exotherm and effervescence due to nitrogen gas evolution were immediately observed upon addition of a catalyst for a successful reaction). The reaction mixture was concentrated under nitrogen. The residue obtained was diluted with DCM and loaded on silica gel in a 5 g sample cartridge. Purification was carried out using a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0 to 5% MeOH/DCM over 30−50 min. Concentration of appropriate fractions afforded products **2b**, **3b**, and **4b**.

General Procedure A for Tetrazole Formation (Table 2). To a solution of ketone (0.400 mmol, 1.0 equiv) and $TMSN_3$ (1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) in a nitrogen-flushed two-dram vial was added triflic acid (0.100−0.400 mmol, 0.25−1.0 equiv). The vial was capped, and the reaction mixture was allowed to stir at room temperature for 2−22 h (exotherm and brisk effervescence due to nitrogen gas evolution were immediately observed). The reaction mixture was concentrated under nitrogen. The residue obtained was diluted with DCM (unless otherwise noted) and loaded on a silica gel in a 5 g sample cartridge. Purification was carried out using a 4 or 12 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0 to 5% MeOH/DCM over 50 min (unless otherwise noted). Concentration of appropriate fractions afforded products. In most cases, recrystallization of products from solvents afforded, after solvent evaporation, plate-like crystals or crystalline solids, which were utilized for determining melting point and, in two cases, for acquiring single-crystal X-ray diffraction data. In general, when the reaction did not go to completion, no attempt was made to recover starting ketone.

6,7,8,9-Tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine 2a and 4,5,6,7,8,9-Hexahydrotetrazolo[1,5-*a*][1,3]diazocine 4a. Following the general procedure A, a solution of cyclohexanone **1a** (39.3 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (8.90 μL, 0.100 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded tetrazole **2a** (eluted between 1.2 and 2.7% MeOH/DCM) as a colorless partially crystalline semisolid (50.3 mg, 0.364 mmol, 91% yield) and aminotetrazole **4a** (eluted between 3.4 and 3.5% MeOH/DCM) as a colorless waxy solid (2.5 mg, 0.016 mmol, 4% yield). Recrystallization of **2a** from a EtOAc−hexanes mixture under cold conditions afforded, after solvent evaporation, colorless plate-like crystals. Tetrazole **2a**: R_f = 0.53 (2% MeOH/DCM, run twice); mp 57−59.5 °C (lit.[14] mp 57−58 °C and lit.[29] mp 59 °C). Aminotetrazole **4a**: R_f = 0.14 (2% MeOH/DCM, run twice); IR (neat) 3263, 1601, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.60−1.65 (m, 2H), 1.87 (m, 2H), 2.04 (p, J = 6.4 Hz, 2H), 3.57 (q, J = 6.1 Hz, 2H), 4.58 (t, J = 6.5 Hz, 2H), 6.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 28.7, 30.2, 42.2, 46.5, 157.0; HRMS (ESI) m/z calcd for $C_6H_{12}N_5$ $[M + H]^+$ 154.1093, found 154.1086.

7-Phenyl-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine 2b, 5-Phenylazepan-2-one 3b,[30] and 7-Phenyl-4,5,6,7,8,9-hexahydrotetrazolo[1,5-*a*][1,3]diazocine 4b. Following the general procedure A, a solution of 4-phenylcyclohexanone **1b** (69.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (8.90 μL, 0.100 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded tetrazole **2b** (eluted between 1.3 and 2.6% MeOH/DCM) as a colorless solid (71.7 mg, 0.335 mmol, 84% yield) and an impure mixture of lactam **3b** and aminotetrazole **4b** (eluted between 3.3 and 3.5% MeOH/DCM) as a colorless solid. The impure mixture of **3b** and **4b** was purified by preparative TLC developing two times with 2% MeOH/DCM and one time with 60% EtOAc/hexanes. Bands corresponding to **4b** (top band) and **3b** (bottom band) were scraped from the plate and eluted separately with 2% MeOH/DCM through a phase separator tabless. Concentration afforded **3b** as a colorless solid (2.4 mg, 0.013 mmol, 3% yield) and **4b** as a colorless solid (8.6 mg, 0.038 mmol, 9% yield). Recrystallization of **4b** from a DCM−EtOH mixture through slow solvent evaporation afforded colorless fine crystals, which were used for X-ray diffraction analysis. Tetrazole **2b**: R_f = 0.53 (2% MeOH/DCM, run twice); mp 128−130 °C; IR (neat) 1602, 1531, 1244, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71 (m, 1H), 1.89 (m, 1H), 2.19−2.28 (m, 2H), 2.84 (ddd, J = 15.5, 12.9, 2.3 Hz, 1H), 2.96 (tt, J = 11.8, 2.4 Hz, 1H), 3.61 (ddd, J = 15.7, 5.8, 1.9 Hz, 1H), 4.20 (m, 1H), 5.01 (ddd, J = 14.6, 5.1, 2.3 Hz, 1H), 7.15 (m, 2H), 7.23 (m, 1H), 7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 32.2, 34.5, 48.2, 48.4, 126.6, 127.1, 129.1, 145.8, 156.2; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_4$ $[M + H]^+$ 215.1297, found 215.1275. Lactam **3b**: R_f = 0.18 (80% EtOAc/hexanes); mp 193−195 °C (lit.[30] mp 199−200 °C); IR (neat) 3194, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68−1.85 (m, 2H), 1.98−2.04 (m, 2H), 2.53−2.67 (m, 2H), 2.76 (tt, J = 12.1, 3.4 Hz, 1H), 3.26−3.42 (m, 2H), 6.72 (br s, 1H), 7.16−7.23 (m, 3H), 7.29−7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 36.1, 37.6, 42.3, 49.0, 126.7, 126.8, 128.8, 146.5, 178.7; HRMS (ESI) m/z calcd for $C_{12}H_{16}NO$ $[M + H]^+$ 190.1232, found 190.1238. Aminotetrazole **4b**: R_f = 0.32 (80% EtOAc/hexanes); mp 190−192 °C; IR (neat) 3245, 1624, 1605, 1491, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.02 (ddt, J = 15.5, 12.1, 3.7 Hz, 1H), 2.11 (ddt, J = 16.3, 12.6, 3.8 Hz, 1H), 2.17−2.23 (m, 1H), 2.32−2.40 (m, 1H), 2.86 (tt, J = 12.2, 3.3 Hz, 1H), 3.51 (dtd, J = 15.6, 6.3, 3.5 Hz, 1H), 3.87 (m, 1H), 4.62 (ddd, J = 15.3, 6.0, 3.5 Hz, 1H), 4.75 (m, 1H), 6.65 (t, J = 6.3 Hz, 1H), 7.12 (d, J = 7.3 Hz, 2H), 7.18 (m, 1H), 7.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.7, 38.3, 40.1, 41.6, 46.0, 127.0, 127.1, 129.0, 145.4, 156.8; HRMS (ESI) m/z calcd for $C_{12}H_{16}N_5$ $[M + H]^+$ 230.1400, found 230.1391.

7-(*tert*-Butyl)-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine 2c and 7-(*tert*-Butyl)-4,5,6,7,8,9-hexahydrotetrazolo[1,5-*a*]-[1,3]diazocine 4c. Following the general procedure A, a solution of 4-*tert*-butylcyclohexanone **1c** (61.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (8.9 μL, 0.100 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded tetrazole **2c** (eluted between 1.0 and 2.4% MeOH/DCM) as a colorless crystalline solid (64.5 mg, 0.332 mmol, 83% yield) and aminotetrazole **4c** (eluted between 2.8 and 3.0% MeOH/DCM) as a colorless solid (7.6 mg, 0.036 mmol, 9% yield). A small amount of impure lactam **3c** (~2%) was also obtained and characterized on the basis of its ^1H NMR spectrum.[31] Recrystallization of **2c** from EtOAc−DCM mixture afforded colorless, long plate-like crystals. Tetrazole **2c**: R_f = 0.39 (2% MeOH/DCM); mp 131−132 °C (lit.[32] mp 132.5−133 °C); IR (neat) 1537, 1476, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.10 (m, 1H), 1.23−1.38 (m, 2H), 2.14−2.24 (m, 2H), 2.58 (ddd, J = 15.4, 12.6, 2.4 Hz, 1H), 3.46 (ddd, J = 15.8, 6.3, 1.9 Hz, 1H), 3.92−3.99 (m, 1H), 4.88 (ddd, J = 14.4, 5.6, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 25.8, 27.7, 28.4, 33.9, 48.5, 52.2, 156.4; HRMS (ESI) m/z calcd for $C_{10}H_{19}N_4$ $[M + H]^+$ 195.1610, found 195.1607. Aminotetrazole **4c**: R_f = 0.12 (2% MeOH/DCM); mp 164−165 °C; IR (neat) 3264 (br), 3071, 1621, 1604, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.22 (m, 1H), 1.44 (m, 1H), 1.60 (m, 1H), 2.09 (m, 1H), 2.29 (m, 1H), 3.33 (m, 1H), 3.71 (m, 1H), 4.50−4.61 (m, 2H), 5.73 (br m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 30.0, 30.8, 33.6, 43.4, 44.1, 45.8, 157.2; HRMS (ESI) m/z calcd for $C_{10}H_{20}N_5$ $[M + H]^+$ 210.1719, found 210.1704.

6,8-Dimethyl-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine 2d and 6,8-Dimethyl-4,5,6,7,8,9-hexahydrotetrazolo[1,5-*a*]-[1,3]diazocine 4d. Following the general procedure A, a solution of 3,5-dimethylcyclohexanone **1d** (mixture of isomers, ~95% trans,

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50.5 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (8.9 μL, 0.100 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 1.5 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded a mixture of tetrazole isomers, ∼97% of major isomer **2d** (eluted between 1.0 and 2.2% MeOH/DCM) as a colorless solid and an impure aminotetrazole **4d** (eluted between 3.0 and 3.1% MeOH/DCM). Further purification of tetrazole isomers using a 4 g flash column on an automated MPLC system (0−3% MeOH/DCM over 45 min) afforded a partial separation of major tetrazole isomer **2d** as a colorless crystalline solid and remaining as a mixture of tetrazole isomers (∼97% of **2d**) as a colorless solid (**2d**: 55.0 mg, 0.331 mmol, 83% corrected yield). Recrystallization of **2d** from EtOAc afforded large, colorless, rectangular plate-like crystals. Impure aminotetrazole **4d** was purified by preparative TLC developing two times with 3% MeOH/DCM. The band corresponding to **4d** was scraped from the plate and eluted with 5% MeOH/DCM through a phase separator tabless. Concentration afforded a slightly impure sample of **4d** as a colorless waxy solid film (2.2 mg, 0.012 mmol, ∼3% yield). Recrystallization of **4d** from EtOAc−DCM mixture afforded partial recrystallization into colorless, tiny plate-like crystals and an off-white solid film (quantity of **4d** was not sufficient for determining the melting point). Tetrazole **2d**: R_f = 0.38 (2% MeOH/DCM); mp 152−155 °C (lit.[32] mp 156 °C); IR (neat) 1525, 1455, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (dd, *J* = 8.3, 6.8 Hz, 6H), 1.30 (m, 1H), 1.65−1.76 (m, 1H), 1.77−1.89 (m, 1H), 1.96 (dp, *J* = 14.2, 2.2 Hz, 1H), 2.48 (dd, *J* = 15.3, 11.7 Hz, 1H), 3.34 (dt, *J* = 15.3, 2.0 Hz, 1H), 3.78 (dd, *J* = 14.2, 11.0 Hz, 1H), 4.72 (dt, *J* = 14.2, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 24.1, 31.5, 31.7, 33.3, 47.9, 54.7, 155.3; HRMS (ESI) *m*/*z* calcd for $C_8H_{15}N_4$ $[M + H]^+$ 167.1297, found 167.1306. Aminotetrazole **4d**: R_f = 0.10 (2% MeOH/DCM); IR (neat) 3259, 1599, 1385 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, *J* = 6.6 Hz, 6H), 1.04−1.11 (m, 1H), 1.54 (dt, *J* = 15.2, 3.6 Hz, 1H), 2.00 (m, 1H), 2.20 (m, 1H), 3.10 (d, *J* = 15.6 Hz, 1H), 3.91 (dd, *J* = 15.6, 3.6 Hz, 1H), 4.36 (dd, *J* = 15.2, 1.6 Hz, 1H), 4.70 (dd, *J* = 15.2, 4.8 Hz, 1H), 5.79 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.1, 34.3, 34.8, 37.7, 47.5, 51.9 (peak for a quaternary carbon of tetrazole ring was not observed); HRMS (ESI) *m*/*z* calcd for $C_8H_{16}N_5$ $[M + H]^+$ 182.1406, found 182.1399.

5,6,8,9-Tetrahydrotetrazolo[1,5-*d*][1,4]oxazepine 2e, 1,4-Oxazepan-5-one 3e[33] and 5,6,8,9-Tetrahydro-4*H*-tetrazolo[1,5-*d*][1,4,6]oxadiazocine 4e. Following the general procedure A, a solution of tetrahydro-4*H*-pyran-4-one **1e** (40.1 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (15.9 μL, 0.180 mmol, 0.45 equiv). The reaction mixture was stirred at room temperature for 2.5 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded tetrazole **2e** (eluted between 1.1 and 3.1% MeOH/DCM) as a colorless solid (30.0 mg, 0.214 mmol, 53% yield) and a slightly impure mixture of lactam **3e** and aminotetrazole **4e** (eluted between 3.9 and 4.3% MeOH/DCM) as a colorless solid (for **3e**, ≈3.4 mg, 0.30 mmol, 7% corrected yield; for **4e**, ≈1.8 mg, 0.012 mmol, 3% corrected yield; ratio of **3e**/**4e** = 66:34 by ^1H NMR).

Similarly, the solution of **1e** (40.1 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (17.7 μL, 0.200 mmol, 0.50 equiv) at room temperature for 1 h. Concentration, followed by quenching with triethylamine (≈0.1 mL), and purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded tetrazole **2e** (eluted between 2.4 and 2.7% MeOH/DCM) as a colorless solid (26.5 mg, 0.189 mmol, 47% yield) and a mixture of lactam **3e** and aminotetrazole **4e** (eluted between 3.6 and 3.7% MeOH/DCM, pure fractions only) as a colorless solid (for **3e**, ≈0.50 mg, 0.0043 mmol, 1% corrected yield; for **4e**, ≈1.3 mg, 0.0084 mmol, 2% corrected yield; ratio of **3e**/**4e** = 29:71 by ^1H NMR). Tetrazole **2e**: R_f = 0.36 (2% MeOH/DCM); mp 157−159 °C; IR (neat) 1530, 1468, 1143, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.30 (m, 2H), 3.90 (m, 2H), 3.96 (m, 2H), 4.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 51.4, 68.3, 69.4, 155.5; HRMS (ESI) *m*/*z* calcd for $C_5H_9N_4O$ $[M + H]^+$ 141.0776, found 141.0787. Mixture of lactam **3e** and aminotetrazole **4e** (**3e**/**4e** = 29:71): R_f = 0.31 (4% MeOH/DCM); IR (neat) 3261, 3130, 3074, 1665 (lactam), 1633 (aminotetrazole), 1547 cm^{-1}. For lactam **3e** in a mixture: ^1H NMR (500 MHz, $CDCl_3$) δ 2.72 (m, 2H), 3.35 (m, 2H), 3.77 (m, 2H), 3.81 (m, 2H), 6.14 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.1, 45.0, 65.7, 71.8, 177.5; HRMS (ESI) *m*/*z* calcd for $C_5H_{10}NO_2$ $[M + H]^+$ 116.0712, found 116.0711. For aminotetrazole **4e** in a mixture: ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (apparent q, *J* = 5.2 Hz, 2H), 3.90 (apparent t, *J* = 5.0 Hz, 2H), 3.98 (t, *J* = 5.5 Hz, 2H), 4.61 (t, *J* = 5.5 Hz, 2H), 5.61 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.3, 47.5, 68.3, 71.2, 157.6; HRMS (ESI) *m*/*z* calcd for $C_5H_{10}N_5O$ $[M + H]^+$ 156.0885, found 156.0896.

(5*S*,8*R*)-5-Isopropyl-8-methyl-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine 2f.[32,34] Following the general procedure A, a solution of purified L-menthone **1f** (61.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (17.7 μL, 0.200 mmol, 0.50 equiv). The reaction mixture was stirred at room temperature for 6 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded a single tetrazole regioisomer **2f** (eluted between 1.1 and 2.0% MeOH/DCM) as a colorless oil (67.6 mg, 0.348 mmol, 87% yield). Tetrazole **2f**: R_f = 0.50 (2% MeOH/DCM); IR (neat) 2962, 1520, 1459, 1429, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.58 (m, 1H), 1.79−1.87 (m, 1H), 1.91−1.99 (m, 1H), 2.05−2.13 (complex, 2H), 2.40 (m, 1H), 3.03 (d, *J* = 4.1 Hz, 2H), 4.33 (ddd, *J* = 9.0, 6.1, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 18.9, 19.9, 23.9, 28.6, 28.9, 30.2, 31.6, 65.8, 154.1; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{19}N_4$ $[M + H]^+$ 195.1610, found 195.1620.

Phenyl(5,6,8,9-tetrahydro-7*H*-tetrazolo[1,5-*d*][1,4]diazepin-7-yl)methanone 2g (Mixture of Rotamers) and 1-Benzoyl-1,4-diazepan-5-one 3g[35] (Mixture of Rotamers). Following the general procedure A, a solution of 1-benzoyl-4-piperidone **1g** (81.3 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (23.0 μL, 0.260 mmol, 0.65 equiv). The reaction mixture was stirred at room temperature for 2.5 h. Purification using a 12 g flash column on an automated MPLC system (0−5% MeOH/DCM over 45 min) afforded impure tetrazole **2g** as a mixture of rotamers (eluted between 3.5 and 3.7% MeOH/DCM) and impure lactam **3g** as a mixture of rotamers (eluted between 4.5 and 4.9% MeOH/DCM). The impure tetrazole **2g** was purified by preparative TLC developing four times with 2% MeOH/DCM. The band corresponding to **2g** was scraped from the plate and eluted with 5% MeOH/DCM through a phase separator tabless. Concentration afforded **2g** (mixture of rotamers) as a colorless crystalline solid (49.0 mg, 0.201 mmol, 50% yield; ratio of rotamers = 70:30). Recrystallization of **2g** with a DCM−MeOH mixture afforded almost colorless large plate-like crystals. Similarly, the impure lactam **3g** was purified twice by preparative TLC developing three times each with 3% MeOH/DCM. The band corresponding to **3g** was scraped from the plate and eluted with 5% MeOH/DCM through a phase separator tabless. Concentration afforded **3g** (mixture of rotamers) as a colorless amorphous solid (12.5 mg, 0.0573 mmol, 14% yield; ratio of rotamers = 65:35). Recrystallization of **3g** with DCM afforded colorless small plate-like crystals. Tetrazole **2g**: R_f = 0.37 (3% MeOH/DCM, run twice); mp 197−199 °C; IR (neat) 1631, 1423, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 3.17 and 3.41 (br s, 2H, rotamers), 3.72 and 3.94 (br s, 2H, rotamers), 3.85 and 4.08 (br s, 2H, rotamers), 4.49 and 4.75 (br s, 2H, rotamers), 7.41−7.43(m, 2H), 7.46−7.51 (complex, 3H); ^1H NMR (major rotamer, diagnostic peaks only) δ 3.17 (br s, 1.4 H), 3.72 (br s, 1.4 H), 4.08 (br s, 1.4 H), 4.75 (br s, 1.4 H); ^1H NMR (minor rotamer, diagnostic peaks only) δ 3.41 (br s, 0.6 H), 3.85 (br s, 0.6 H), 3.94 (br s, 0.6 H), 4.49 (br s, 0.6 H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 25.4, 27.0, 43.4, 45.3, 47.6, 49.3, 49.9, 50.8, 126.8, 129.2, 130.6, 135.1, 154.6, 155.5, 171.9; ^{13}C NMR (major rotamer, diagnostic peaks only) δ 27.0, 45.3, 47.6, 49.9, 154.6; ^{13}C NMR (minor rotamer,

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diagnostic peaks only) δ 25.4, 43.4, 49.3, 50.8, 155.5; HRMS (ESI) m/z calcd for $C_{12}H_{14}N_5O$ $[M + H]^+$ 244.1198, found 244.1219. Lactam **3g**: R_f = 0.15 (3% MeOH/DCM, run twice); mp 170−173 °C, with softening observed above 155 °C; IR (neat) 3280, 1659, 1626, 1433, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 2.59 and 2.75 (br s, 2H, rotamers), 3.25 and 3.42 (br s, 2H, rotamers), 3.58 (br s, 2H, rotamers), 3.91 (br s, 2H, rotamers), 6.44 (br s, 1H), 7.37−7.39 (complex, 2H), 7.41−7.45 (complex, 3H); ^1H NMR (major rotamer, diagnostic peaks only) δ 2.59 (br s, 1.3 H), 3.42 (br s, 1.3 H); ^1H NMR (minor rotamer, diagnostic peaks only) δ 2.75 (br s, 0.7 H), 3.25 (br s, 0.7 H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 38.5, 39.4, 40.4, 43.2, 44.1, 45.4, 46.9, 52.1, 127.0, 129.0, 130.2, 135.7, 171.4, 176.4, 177.3; ^{13}C NMR (major rotamer, diagnostic peaks only) δ 39.4, 43.2, 45.4, 46.9, 176.4; ^{13}C NMR (minor rotamer, diagnostic peaks only) δ 38.5, 40.4, 44.1, 52.1, 177.3; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2O_2$ $[M + H]^+$ 219.1134, found 219.1134.

5,6,7,8-Tetrahydrotetrazolo[1,5-*a*]pyridine 2h[29] and 5,6,7,8-Tetrahydro-4*H*-tetrazolo[1,5-*a*][1,3]diazepine 4h. Following the general procedure A, a solution of cyclopentanone **1h** (33.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (17.7 μL, 0.200 mmol, 0.50 equiv). The reaction mixture was stirred at room temperature for 6 h. Concentration, followed by quenching with triethylamine (≈0.1 mL), and purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded tetrazole **2h** (eluted between 1.9 and 2.8% MeOH/DCM) as a colorless solid (25.3 mg, 0.204 mmol, 51% yield) and aminotetrazole **4h** (eluted between 3.2 and 3.4% MeOH/DCM) as a colorless waxy solid film (3.8 mg, 0.027 mmol, 7% yield). Recrystallization of **4h** from DCM afforded small, almost colorless crystals. Tetrazole **2h**: R_f = 0.32 (2% MeOH/DCM); mp 114−116 °C (lit.[29] mp 116 °C and lit.[14] mp 115−116 °C); IR (neat) 1532, 1448, 913, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98−2.05 (m, 2H), 2.07−2.14 (m, 2H), 3.02 (t, J = 6.4 Hz, 2H), 4.35 (t, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 20.9, 22.4, 45.7, 152.1; HRMS (ESI) m/z calcd for $C_5H_9N_4$ $[M + H]^+$ 125.0827, found 125.0825. Aminotetrazole **4h**: R_f = 0.26 (4% MeOH/DCM); mp 100−104 °C, with softening observed 92 °C; IR (neat) 3250, 3063, 1591, 1397 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.92−1.98 (complex, 4H), 3.23 (m, 2H), 4.32 (m, 2H), 5.58 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 29.7, 45.7, 49.0, 159.6; HRMS (ESI) m/z calcd for $C_5H_{10}N_5$ $[M + H]^+$ 140.0936, found 140.0940.

5,6,7,8,9,10-Hexahydrotetrazolo[1,5-*a*]azocine 2i[29] and 5,6,7,8,9,10-Hexahydro-4*H*-tetrazolo[1,5-*a*][1,3]diazonine 4i. Following the general procedure A, a solution of cycloheptanone **1i** (44.9 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (21.2 μL, 0.240 mmol, 0.60 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded tetrazole **2i** (eluted between 1.3 and 2.9% MeOH/DCM) as a colorless waxy solid (56.5 mg, 0.371 mmol, 93% yield) and an impure aminotetrazole **4i** (eluted between 3.2 and 3.5% MeOH/DCM), which was purified by preparative TLC developing one time with 3% MeOH/DCM and one time with 60% EtOAc/hexanes. The band corresponding to **4i** was scraped from the plate and eluted with 5% MeOH/DCM through a phase separator tabless. Concentration afforded **4i** as a colorless solid film (1.1 mg, 0.0066 mmol, ∼2% yield). Tetrazole **2i**: R_f = 0.34 (2% MeOH/DCM); mp 66.5−68.5 °C (lit.[36] mp 68 °C and lit.[14] mp 66−67 °C); IR (neat) 1525, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28−1.36 (m, 2H), 1.38−1.46 (m, 2H), 1.84 (m, 2H), 1.91 (m, 2H), 3.01 (m, 2H), 4.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 23.7, 25.0, 29.7, 30.5, 45.8, 155.8; HRMS (ESI) m/z calcd for $C_7H_{13}N_4$ $[M + H]^+$ 153.1140, found 153.1140. Aminotetrazole **4i**: R_f = 0.14 (2% MeOH/DCM); IR (neat) 3253, 3074, 1616, 1390 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (m, 2H), 1.67 (m, 4H), 1.92 (m, 2H), 3.55 (m, 2H), 4.52 (m, 2H), 5.35 (br m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 24.2, 30.8, 32.3, 42.4, 47.5, 156.6; HRMS (ESI) m/z calcd for $C_7H_{14}N_5$ $[M + H]^+$ 168.1249, found 168.1249.

6,7,8,9,10,11-Hexahydro-5*H*-tetrazolo[1,5-*a*]azonine 2j.[29] Following the general procedure A, a solution of cyclooctanone **1j** (50.5 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (21.2 μL, 0.240 mmol, 0.60 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded tetrazole **2j** (eluted between 1.2 and 2.7% MeOH/DCM) as a colorless viscous oil (57.5 mg, 0.346 mmol, 86% yield). Tetrazole **2j**: R_f = 0.38 (2% MeOH/DCM); IR (neat) 1520, 1474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25−1.32 (m, 2H), 1.33−1.40 (m, 2H), 1.43−1.49 (m, 2H), 1.85−1.91 (m, 2H), 1.97 (m, 2H), 3.04 (m, 2H), 4.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.5, 25.6, 25.8, 26.4, 28.5, 47.6, 156.3; HRMS (ESI) m/z calcd for $C_8H_{15}N_4$ $[M + H]^+$ 167.1297, found 167.1297.

1,5-Dibutyl-1*H*-tetrazole 2k[37] and *N*-Butylpentanamide 3k.[38] Following the general procedure A, a solution of 5-nonanone **1k** (56.9 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (28.3 μL, 0.320 mmol, 0.80 equiv). The reaction mixture was stirred at room temperature for 3 h. Purification using a 12 g flash column on an automated MPLC system (0−2% MeOH/DCM over 45 min) afforded tetrazole **2k** (eluted between 0.4 and 0.7% MeOH/DCM) as a pale yellow oil and a mixture of **2k** and amide **3k** (eluted between 0.7 and 1.0% MeOH/DCM; ≈41:59 ratio of **2k**/**3k** by ^1H NMR) as a pale yellow oil (for **2k**, 29.4 mg, 0.161 mmol, 40% corrected yield; for **3k**, 11.8 mg, 0.0750 mmol, 19% corrected yield). For amide **3k** in a mixture of **2k** and **3k** (**2k**/**3k** = 41:59 by ^1H NMR): R_f = 0.36 (2% MeOH/DCM); IR (neat) 3303, 1648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, amide **3k**) δ 0.89 (td, J = 7.3, 3.9 Hz, 6H), 1.28−1.38 (complex, 4H, partially obscured by peaks of **2k**), 1.39−1.49 (complex, 2H, partially obscured by peaks of **2k**), 1.59 (m, 2H), 2.14 (t, J = 7.7 Hz, 2H), 3.22 (m, 2H), 5.57 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, amide **3k**) δ 13.9, 14.0, 20.2, 22.6, 28.1, 31.9, 36.8, 39.4, 173.3; HRMS (ESI) m/z calcd for $C_9H_{20}NO$ $[M + H]^+$ 158.1545, found 158.1561.

1,5-Dicyclohexyl-1*H*-tetrazole 2l.[39] Following the general procedure A, a solution of dicyclohexylketone **1l** (77.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (31.9 μL, 0.360 mmol, 0.90 equiv). The reaction mixture was stirred at room temperature for 6 h. Concentration, followed by quenching with triethylamine (≈0.05 mL), and purification using a 12 g flash column on an automated MPLC system (0−5% MeOH/DCM over 55 min) afforded tetrazole **2l** (eluted between 1.0 and 1.2% MeOH/DCM) as a colorless crystalline solid, followed by a mixture of **2l** and an unidentified byproduct (eluted between 1.2 and 1.9% MeOH/DCM; ≈88:12 ratio of **2l**/byproduct by ^1H NMR) and an impure mixture of **2l** and byproduct (eluted between 1.9 and 2.6% MeOH/DCM). Further purification of the impure mixture of **2l** and byproduct using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 25 min) afforded **2l** with a trace amount of byproduct (eluted between 2.4 and 3.2% MeOH/DCM) as a colorless solid (for **2l**, 69.8 mg, 0.298 mmol, 74% corrected overall yield) and an impure mixture of byproduct with a little bit of **2l** (eluted between 3.2 and 3.4% MeOH/DCM). Subsequent purification of the impure mixture in order to obtain an analytically pure sample of byproduct for characterization was unsuccessful. HMRS of a mixture of **2l** and byproduct showed molecular ion peaks $[M + H]^+$ for both **2l** and amide (for amide, HRMS (ESI) m/z calcd for $C_{13}H_{24}NO$ $[M + H]^+$ 210.1858, found 210.1828). The byproduct could not be confirmed as amide due to lack of complete spectroscopic analysis. Tetrazole **2l**: R_f = 0.56 (2% MeOH/DCM); mp 173−177 °C (lit.[39] mp 179.5−180 °C); IR (neat) 2928, 1501, 1450, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 1.27−1.48 (complex, 6H), 1.70−1.80 (complex, 4H), 1.85−2.08 (complex, 10H), 2.75 (tt, J = 11.6, 3.5 Hz, 1H), 4.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.57, 25.63, 26.1, 31.6, 33.4, 33.7, 57.5, 157.7; HRMS (ESI) m/z calcd for $C_{13}H_{23}N_4$ $[M + H]^+$ 235.1923, found 235.1904.

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1,5-Diethyl-1*H*-tetrazole 2m.[14,40] Following the general procedure A, a solution of 3-pentanone **1m** (34.5 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (31.9 μL, 0.360 mmol, 0.90 equiv). The reaction mixture was stirred at room temperature for 6 h. Concentration, followed by quenching with triethylamine (≈0.05 mL), and purification using a 12 g flash column on an automated MPLC system (0−10% MeOH/DCM over 55 min) afforded tetrazole **2m** (eluted between 1.1 and 1.9% MeOH/DCM) as a pale yellow oily solid (33.6 mg, 0.266 mmol, 66% yield). Tetrazole **2m**: R_f = 0.50 (2% MeOH/DCM); IR (neat) 2985, 1521, 1456, 1426, 1094, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.6 Hz, 3H), 1.51 (t, *J* = 7.3 Hz, 3H), 2.84 (q, *J* = 7.6 Hz, 2H), 4.28 (q, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 15.1, 16.9, 42.2, 155.5; HRMS (ESI) *m*/*z* calcd for $C_5H_{11}N_4$ $[M + H]^+$ 127.0984, found 127.0961. A small amount of impure amide was also obtained during this purification.

6-Phenyl-5,6-dihydrobenzo[*f*]tetrazolo[1,5-*d*][1,4]oxazepine 2n,[18a] **2-Phenyl-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one 3na,**[18a] **2-Phenyl-2,3-dihydrobenzo[*b*][1,4]oxazepin-4(5*H*)-one 3nb,**[18a] **5-((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)-2-phenyl-2,3-dihydrobenzo[*f*][1,4]oxazepine 5, (*E*)-2-Azido-5-phenyl-4,5-dihydro-1*H*-benzo[*b*][1,4,6]oxadiazocine 6, and 2-(Benzo[*d*]oxazol-2-ylamino)-1-phenylethan-1-ol 7.** Following the general procedure A, a solution of flavanone **1n** (89.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (35.4 μL, 0.400 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 5 h. Reaction mixture was concentrated under nitrogen, the residue obtained was diluted with a hexanes−DCM mixture, and loaded on silica gel in a 5 g sample cartridge. Purification using a 12 g flash column on an automated MPLC system (0−90% EtOAc/hexanes over 55 min) afforded iminoether **5** (eluted between 100% hexanes) as a colorless oil (28.1 mg, 0.0722 mmol, 18% yield), tetrazole **2n** (eluted between 3.0 and 5.0% EtOAc/hexanes) as a colorless amorphous solid (52.0 mg, 0.197 mmol, 49% yield), an impure mixture of guanyl azide **6** and lactam **3nb** (eluted between 15 and 35% EtOAc/hexanes), and an impure mixture of aminobenzoxazole **7** and lactam **3na** (eluted between 40 and 60% EtOAc/hexanes). Recrystallization of **2n** from EtOAc afforded colorless, thick plate-like crystals. The impure mixture of guanyl azide **6** and lactam **3nb** was purified by preparative TLC developing two times with 30% EtOAc/hexanes. Bands corresponding to **6** and **3nb** were scraped from the plate and separately eluted with 1% MeOH/DCM through a phase separator tabless. Concentration afforded **6** as a pale orange amorphous solid (8.5 mg, 0.030 mmol, 8% yield) and **3nb** as a colorless waxy solid film (1.1 mg, 0.0046 mmol, ∼1% yield). Recrystallization of **6** from DCM−hexanes afforded colorless, thread-like, fine crystals. Similarly, the impure mixture of aminobenzoxazole **7** and lactam **3na** was purified by preparative TLC developing two times with 40% EtOAc/hexanes. Bands corresponding to **7** and **3na** were scraped from the plate and separately eluted with 2% MeOH/DCM through a phase separator tabless. Concentration afforded a slightly impure sample of **7** as a colorless waxy solid film (2.8 mg, 0.011 mmol, ∼3% yield) and **3na** as colorless viscous oil (7.0 mg, 0.029 mmol, 7% yield). Recrystallization of **7** from EtOAc−hexanes mixture afforded partial recrystallization into almost colorless, thin plate-like crystals and a pale brownish residue. Crystals were utilized for acquiring a single-crystal X-ray diffraction data and for determining the melting point. Recrystallization of **3na** from DCM afforded partially crystalline, off-white waxy solid. Tetrazole **2n**: R_f = 0.33 (20% EtOAc/hexanes); mp 124.5−126.5 °C (lit.[16] mp 136−137 °C and lit.[18a] mp 137−138 °C); IR (neat) 1609, 1484, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (dd, *J* = 14.6, 9.8 Hz, 1H), 5.12 (dd, *J* = 14.6, 1.5 Hz, 1H), 5.26 (dd, *J* = 9.8, 1.3 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.26 (m, 1H), 7.44−7.56 (m, 6H), 8.57 (dd, *J* = 8.0, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 79.1, 113.1, 121.7, 124.2, 126.2, 129.3, 129.4, 130.5, 133.4, 136.5, 152.1, 157.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{13}N_4O$ $[M + H]^+$ 265.1089, found 265.1071. Lactam **3na**: R_f = 0.34 (50% EtOAc/hexanes); mp 122.5−125.5 °C (lit.[18a] mp 125−126 °C); IR (neat) 3222, 1654, 1603, 1459, 1209 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (dt, *J* = 15.4, 5.8 Hz, 1H), 3.67 (ddd, *J* = 15.4, 6.2, 3.5 Hz, 1H), 5.46 (dd, *J* = 6.1, 3.5 Hz, 1H), 6.87 (br s, 1H), 7.09 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1H), 7.34−7.42 (m, 5H), 7.48 (m, 1H), 7.87 (dd, *J* = 7.8, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.6, 86.0, 122.7, 124.0, 126.1, 126.5, 128.8, 128.9, 131.2, 133.6, 139.2, 154.8, 171.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}NO_2$ $[M + H]^+$ 240.1025, found 240.1012. Lactam **3nb**: R_f = 0.21 (30% EtOAc/hexanes); IR (neat) 3214, 1673, 1597, 1497 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.99 (ddd, *J* = 14.8, 4.1, 0.8 Hz, 1H), 3.09 (dd, *J* = 14.8, 8.8 Hz, 1H), 5.66 (dd, *J* = 8.8, 4.1 Hz, 1H), 6.95−6.98 (m, 1H), 7.05−7.13 (complex, 3H), 7.34−7.44 (complex, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.1, 83.3, 122.1, 123.8, 124.6, 126.2, 126.3, 128.8, 128.9, 130.2, 140.2, 148.4, 171.1; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}NO_2$ $[M + H]^+$ 240.1025, found 240.1039. Iminoether **5**: R_f = 0.78 (20% EtOAc/hexanes); IR (neat) 1685, 1605, 1223, 1190, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (dd, *J* = 15.5, 7.8 Hz, 1H), 4.05 (dd, *J* = 15.5, 2.2 Hz, 1H), 5.35 (dd, *J* = 7.8, 2.2 Hz, 1H), 6.51 (hept, *J* = 6.5 Hz, 1H), 7.16−7.21 (m, 2H), 7.38−7.43 (m, 1H), 7.45 (m, 4H), 7.50 (m, 1H), 7.91 (dd, *J* = 7.9, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.9, 66.2−67.6 (p, *J* = 135.1 Hz, 1C), 85.7, 118.2, 120.1, 121.9, 122.7, 122.9, 126.3, 128.5, 128.9, 129.8, 133.7, 139.5, 155.4, 158.2; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{14}F_6NO_2$ $[M + H]^+$ 390.0929, found 390.0900. Guanyl azide **6**: R_f = 0.43 (30% EtOAc/hexanes); mp 99.5−101 °C; IR (neat) 3209, 2101, 1643, 1583, 1459, 1242 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.62 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.81 (dd, *J* = 14.0, 5.1 Hz, 1H), 4.92 (dd, *J* = 8.8, 5.1 Hz, 1H), 5.46 (br s, 1H), 7.07 (td, *J* = 7.8, 1.1 Hz, 1H), 7.19 (td, *J* = 7.7, 1.0 Hz, 1H), 7.27 (m, 1H), 7.36−7.44 (complex, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.4, 65.2, 109.2, 116.8, 121.5, 124.3, 127.3, 129.2, 129.3, 136.7, 142.7, 148.7, 161.5; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}N_5O$ $[M + H]^+$ 280.1198, found 280.1183. Aminobenzoxazole **7**: R_f = 0.39 (50% EtOAc/hexanes); mp 118−121 °C; IR (neat) 3255, 1647, 1585, 1461, 1244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (dd, *J* = 14.1, 8.0 Hz, 1H), 3.84 (dd, *J* = 14.0, 3.4 Hz, 1H), 5.05 (dd, *J* = 7.9, 3.4 Hz, 1H), 5.45 (br s, 1H), 7.05 (td, *J* = 7.8, 1.1 Hz, 1H), 7.18 (td, *J* = 7.7, 1.0 Hz, 1H), 7.24−7.26 (m, 2H), 7.31 (m, 1H), 7.36−7.39 (complex, 3H), 7.42−7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.8, 73.7, 109.1, 116.7, 121.4, 124.3, 126.1, 128.3, 128.9, 141.6, 142.5, 148.8, 162.6; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{15}N_2O_2$ $[M + H]^+$ 255.1134, found 255.1136.

(*E*)-5-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-4,5-dihydro-1*H*-benzo[*b*][1,4,6]oxadiazocine 8. Following a slight modification of the reported procedure,[41] in a one-dram vial, to a clear colorless solution of guanyl azide **6** (4.0 mg, 0.014 mmol, 1.0 equiv) and phenyl acetylene (1.8 mg, 0.017 mmol, 1.2 equiv) in *tert*-butanol and deionized water mixture (0.6 mL, 1:1) were added copper(II) sulfate pentahydrate (3.6 mg, 0.014 mmol, 1.0 equiv) and (+)-sodium L-ascorbate (5.7 mg, 0.029 mmol, 2.0 equiv). The vial was capped, and the resulting pale yellowish-blue turbid suspension was stirred at room temperature for 18 h. The reaction mixture was partially concentrated under N_2, diluted with DCM (1 mL), and quenched with NH_4OH solution (five drops). After being stirred at room temperature for 5 min, the biphasic mixture was passed through a hydrophobic phase separator tabless, which allowed the DCM layer to pass through the tabless. The blue aqueous layer was further washed with DCM (2 × 1 mL), and the DCM layer was allowed to pass through the tabless. The combined DCM layer was concentrated, and the residue was purified by preparative TLC developing one time with 2% MeOH/DCM. The band corresponding to guanidino triazole **8** was scraped from the plate and eluted with 5% MeOH/DCM through a phase separator tabless. Concentration afforded **8** as a colorless amorphous solid (5.2 mg, 0.014 mmol, 95% yield). Guanidino triazole **8**: R_f = 0.18 (2% MeOH/DCM); mp 216.5−218.5 °C; IR (neat) 3087, 1668, 1641, 1586, 1459, 1246 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 4.31 (dd, *J* = 14.6, 4.3 Hz, 1H), 4.51 (dd, *J* = 14.6, 9.9 Hz, 1H), 6.03 (dd, *J* = 9.8, 4.4 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.30 (m, 1H), 7.34−7.40 (complex, 8H), 7.74−7.76 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 47.1, 64.3, 109.3, 116.5, 121.1, 121.6, 124.3, 125.9, 127.0, 128.6, 129.0, 129.3, 129.4, 130.2, 136.8, 142.2, 148.2, 148.6, 161.6; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{20}N_5O$ $[M + H]^+$ 382.1668, found 382.1647.

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6,11-Dihydro-5*H*-benzo[*d*]tetrazolo[1,5-*a*]azepine 2oa,[18c] 10,11-Dihydro-5*H*-benzo[*e*]tetrazolo[1,5-*a*]azepine 2ob,[18c] 1,3,4,5-Tetrahydro-2*H*-benzo[*d*]azepin-2-one 3oa,[42] 1,2,4,5-Tetrahydro-3*H*-benzo[*c*]azepin-3-one 3ob,[43] 4,5,10,11-Tetrahydrobenzo[*e*]tetrazolo[1,5-*a*][1,3]diazocine 4oa, and 4,5,6,11-Tetrahydrobenzo[*f*]tetrazolo[1,5-*a*][1,3]diazocine 4ob. Following the general procedure A, a solution of β-tetralone **1o** (58.5 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (10.6 μL, 0.120 mmol, 0.30 equiv). The reaction mixture was stirred at room temperature for 22 h. Purification with a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0 to 35% EtOAc/hexanes over 60 min afforded tetrazole regioisomer **2oa** (eluted between 25 and 28% EtOAc/hexanes) as a pale cream-orange solid, followed by a mixture of tetrazole regioisomers **2oa** and **2ob** (eluted between 28 and 30% EtOAc/hexanes) as an off-white solid and tetrazole regioisomer **2ob** (eluted between 30 and 32% EtOAc/hexanes) as a creamy solid (combined yield of **2oa** and **2ob**: 37.3 mg, 0.200 mmol, 50% yield; ratio of **2oa**/**2ob** = 58:42). Recrystallization of **2oa** from DCM−hexanes mixture afforded colorless square-shaped, plate-like crystals. Recrystallization of **2ob** from EtOAc afforded colorless plate-like crystals. Continuation with the chromatography by changing to a more polar solvent system (0−5% MeOH/DCM over 30 min) afforded an impure mixture of lactams **3oa** and **3ob** and aminotetrazoles **4oa** and **4ob** (eluted between 3.0 and 3.3% MeOH/DCM) as an orange semisolid. This mixture of four compounds was further purified by preparative TLC developing three times with 70% EtOAc/hexanes. Bands corresponding to aminotetrazoles (high R_f two overlapping bands) and lactams (low R_f two overlapping bands) were scraped from the plate and eluted separately with 5% MeOH/DCM through a phase separator tabless. Concentration of elutions containing low R_f bands afforded lactam **3oa** as a colorless amorphous solid and a slightly impure mixture of lactams **3oa** and **3ob** as a colorless waxy solid (combined yield of **3oa** and **3ob**: 5.0 mg, 0.031 mmol, 8% yield; ratio of **3oa**/**3ob** = 69:31). Recrystallization of **3oa** from DCM afforded colorless fine crystals. Concentration of elutions containing high R_f bands afforded a slightly impure aminotetrazole **4oa** as a colorless waxy solid and a mixture of aminotetrazoles **4oa** and **4ob** as a colorless solid (combined yield of **4oa** and **4ob**: 8.0 mg, 0.040 mmol, 10% yield; ratio of **4oa**/**4ob** = 60:40). Recrystallization of **4oa** from a DCM−MeOH mixture afforded partial recrystallization into colorless fine plate-like crystals and an off-white solid film. Tetrazole **2oa**: R_f = 0.42 (50% EtOAc/hexanes); mp 148−151 °C (lit.[18c] mp 156−157 °C); IR (neat) 1525, 1471, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.37 (m, 2H), 4.40 (s, 2H), 4.61 (m, 2H), 7.25−7.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 30.5, 49.3, 128.4, 128.9, 129.4, 129.5, 134.5, 137.0, 151.6; HRMS (ESI) m/z calcd for $C_{10}H_{11}N_4$ $[M + H]^+$ 187.0984, found 187.0978. Tetrazole **2ob**: R_f = 0.32 (50% EtOAc/hexanes); mp 135.5−137 °C (lit.[18c] mp 145−146 °C); IR (neat) 1524, 1417, 1123, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.22−3.25 (m, 2H), 3.35−3.38 (m, 2H), 5.63 (s, 2H), 7.27−7.31 (m, 1H), 7.34−7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 29.0, 51.5, 127.9, 129.3, 129.6, 130.3, 132.7, 139.9, 153.1; HRMS (ESI) m/z calcd for $C_{10}H_{11}N_4$ $[M + H]^+$ 187.0984, found 187.0981. Lactam **3oa**: R_f = 0.39 (70% EtOAc/hexanes, run three times); mp 154−157 °C, softening observed above 125 °C (lit.[42] mp 159−160 °C); IR (neat) 3176, 1660, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.13 (m, 2H), 3.58 (m, 2H), 3.85 (s, 2H), 6.05 (br s, 1H), 7.11−7.22 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.5, 41.7, 42.7, 127.1, 127.5, 130.0, 130.6, 132.0, 137.0, 173.7; HRMS (ESI) m/z calcd for $C_{10}H_{12}NO$ $[M + H]^+$ 162.0919, found 162.0920. For lactam **3ob** in a mixture of **3oa** and **3ob** (ratio of **3oa**/**3ob** = 14:86 by ^1H NMR): R_f = 0.34 (70% EtOAc/hexanes, run three times); IR (neat, for a mixture) 3247, 1661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, lactam **3ob**) δ 2.82 (m, 2H), 3.11 (m, 2H, partially obscured by peaks of **3oa**), 4.37 (d, J = 5.4 Hz, 2H), 6.38 (br s, 1H), 7.11−7.12 (m, 1H, partially obscured by peaks of **3oa**), 7.16−7.21 (m, 2H, partially obscured by peaks of **3oa**), 7.25−7.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, lactam **3ob**) δ 28.7, 34.6, 46.2, 126.7, 128.4, 128.5, 129.8, 136.1, 139.2, 175.4; HRMS (ESI) m/z calcd for $C_{10}H_{12}NO$ $[M + H]^+$ 162.0919, found 162.0929. Aminotetrazole **4oa**: R_f = 0.67 (70% EtOAc/hexanes, run three times); mp 174−180 °C, softening observed above 140 °C; IR (neat) 3231, 1585 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.52 (t, J = 6.6 Hz, 2H), 4.51 (s, 2H), 4.78 (t, J = 6.6 Hz, 2H), 5.91 (br s, 1H), 7.14−7.17 (m, 1H), 7.21−7.26 (complex, 3H; partially obscured by solvent peak); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.4, 46.4, 48.6, 128.4, 129.3, 131.0, 131.6, 135.3, 135.9 (peak for a quaternary carbon of tetrazole ring was not observed); HRMS (ESI) m/z calcd for $C_{10}H_{12}N_5$ $[M + H]^+$ 202.1093, found 202.1096. For aminotetrazole **4ob** in a mixture of **4oa** and **4ob** (ratio of **4oa**/**4ob** = 37:63 by ^1H NMR): R_f = 0.62 (70% EtOAc/hexanes, run three times); IR (neat, for a mixture) 3246, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, aminotetrazole **4ob**) δ 3.26 (m, 2H), 3.51 (m, 2H, partially obscured by peaks of **4oa**), 5.44 (s, 2H), 5.59 (br s, 1H), 7.18−7.23 (m, 1H, partially obscured by peaks of **4oa**), 7.25−7.34 (m, 2H), 7.45 (dd, J = 7.3, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, aminotetrazole **4ob**) δ 36.8, 46.6, 50.1, 128.1, 130.1, 130.8, 131.4, 132.3, 139.7, 157.7 (crossover peaks for the quaternary carbon of tetrazole ring for **4oa** and **4ob** were observed in HMBC); HRMS (ESI) m/z calcd for $C_{10}H_{12}N_5$ $[M + H]^+$ 202.1093, found 202.1088.

5,10-Dihydrotetrazolo[1,5-*b*]isoquinoline 2p and 5,10-Dihydro-4*H*-benzo[*e*]tetrazolo[1,5-*a*][1,3]diazepine 4p. Following the general procedure A, a solution of 2-indanone **1p** (52.9 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (17.7 μL, 0.200 mmol, 0.50 equiv). The reaction mixture was stirred at room temperature for 22 h. Purification using a 4 g flash column on an automated MPLC system (0−5% MeOH/DCM over 50 min) afforded impure tetrazole **2p** (eluted between 1.4 and 2.6% MeOH/DCM) and impure aminotetrazole **4p** (eluted between 3.2 and 3.5% MeOH/DCM). Subsequent purification of impure tetrazole **2p** using a 4 g flash column on an automated MPLC system (0−40% EtOAc/hexanes over 35 min) afforded **2p** (eluted between 30 and 36% EtOAc/hexanes) as a colorless solid (8.4 mg, 0.049 mmol, 12% yield). The impure aminotetrazole **4p** was further purified by preparative TLC developing two times with 2% MeOH/DCM and one time with 60% EtOAc/hexanes. The band corresponding to **4p** was scraped from the plate and eluted with 2% MeOH/DCM through a phase separator tabless. Concentration afforded **4p** as a colorless crystalline solid (6.7 mg, 0.036 mmol, 9% yield). Tetrazole **2p**: R_f = 0.43 (2% MeOH/DCM); mp 164−167 °C; IR (neat) 1544, 1500, 1088, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.41 (t, J = 2.6 Hz, 2H), 5.63 (t, J = 2.5 Hz, 2H), 7.35−7.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 48.0, 127.0, 127.6, 128.2, 128.6, 128.9, 129.5, 150.9; HRMS (ESI) m/z calcd for $C_9H_9N_4$ $[M + H]^+$ 173.0827, found 173.0857. Aminotetrazole **4p**: R_f = 0.14 (2% MeOH/DCM); mp 177−180 °C; IR (neat) 3245, 1611, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.55 (d, J = 4.7 Hz, 2H), 5.60 (s, 2H), 7.24 (br m, 1H), 7.33−7.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.4, 50.2, 129.0, 129.2 (2C), 130.2, 133.0, 136.8, 155.7; HRMS (ESI) m/z calcd for $C_9H_{10}N_5$ $[M + H]^+$ 188.0936, found 188.0932.

General Procedure B for the Optimization of Reaction Conditions for the Synthesis of 1-(3′-Hydroxypropyl)-5-phenylazepan-2-one 10b (Table 3). To a solution of 4-phenylcyclohexanone **1b** (0.300 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (0.450 mmol−0.600 mmol, 1.5−2.0 equiv) in solvent (0.75 mL) in a nitrogen-flushed two-dram vial was added Lewis acid or Bronsted acid (0.300−0.600 mmol, 1.0−2.0 equiv). The vial was capped, and the reaction mixture was stirred at room temperature for 1−24 h. The solution was concentrated under nitrogen using a sample concentrator and dried under vacuum. The residual oil was diluted with DCM and treated with saturated $NaHCO_3$ solution (1.5 mL) at room temperature for 12−14 h. The reaction mixture was further diluted with DCM (50 mL), dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. Purification was carried out using a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0−10% MeOH/DCM over 40 min. Concentration of the appropriate fractions afforded **10b**.

General Procedure C for the Synthesis of *N*-Hydroxyalkyl Lactams (Table 4). To a solution of ketone (0.400 mmol, 1.0 equiv)

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and 3-azido-1-propanol **9a** (0.600 mmol, 1.5 equiv) in HFIP (1.0 mL) in a nitrogen-flushed two-dram vial was added triflic acid (0.400−0.600 mmol, 1.0−1.5 equiv) (immediate gas evolution was noted upon addition of acid for most substrates). The vial was capped, and the reaction mixture was stirred at room temperature for 1−6 h. The solution was concentrated under nitrogen using a sample concentrator and dried under vacuum. The residual oil was diluted with DCM and treated with either saturated $NaHCO_3$ solution (1.5 mL) or 1 M NaOH solution (1.5 mL) at room temperature for 12−24 h. The reaction mixture was further diluted with DCM (50 mL), dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. Purification was carried out either by elution with 10% MeOH/DCM through a short bed of silica gel packed in a phase separator tabless or by using a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0 to 25% MeOH/DCM over 30−75 min. Concentration of appropriate fractions afforded products.

1-(3′-Hydroxypropyl)azepan-2-one 10a.[21b] Following the general procedure C, to a solution of cyclohexanone **1a** (39.3 mg, 0.400 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.7 mg, 0.600 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.395 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 1 h. Subsequently, hydrolysis was carried out with saturated $NaHCO_3$ solution for 12 h. The crude oil obtained was eluted through a short bed of silica gel using 10% MeOH/DCM. Concentration of solvents afforded **10a** as a colorless oil (64.8 mg, 0.378 mmol, 95%).

1-(3′-Hydroxypropyl)-5-phenylazepan-2-one 10b.[21b] The compound was prepared as described in the general procedure B, as a colorless oil (70.5 mg, 0.285 mmol, 95%).

1-(3′-Hydroxypropyl)-4,6-dimethylazepan-2-one 10d. Following the general procedure C, to a solution of 3,5-dimethylcyclohexanone **1d** (50.6 mg, 0.401 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.4 mg, 0.597 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 1 h. Subsequently, hydrolysis was carried out by treatment with 1 M NaOH solution for 14 h. Purification was carried out on an automated MPLC system (0−10% MeOH/DCM over 40 min) to afford **10d** as a colorless oil (76.8 mg, 0.385 mmol, 94%): R_f = 0.40 (5% MeOH/DCM); IR (neat) 3390, 1619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (m, 4H), 0.92 (m, 3H), 1.58 (m, 3H), 1.70 (m, 1H), 1.79 (m, 1H), 2.25 (m, 1H), 2.35−2.42 (dd, J = 13.6, 11.2 Hz, 1H), 2.84 (m, 1H), 3.20−3.26 (dd, J = 14.9, 10.1 Hz, 1H), 3.42 (m, 4H), 4.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.5, 30.1, 30.2, 34.0, 44.6, 44.9, 48.0, 56.3, 58.0, 175.9; HRMS (ESI) m/z calcd for $C_{11}H_{22}NO_2$ $[M + H]^+$ 200.1651, found 200.1656.

4-(3′-Hydroxypropyl)-1,4-oxazepan-5-one 10e. Following the general procedure C, to a solution of tetrahydro-4*H*-pyran-4-one **1e** (37.0 μL, 0.401 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.6 mg, 0.599 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 6 h. Subsequently, hydrolysis was carried out with saturated $NaHCO_3$ solution for 13 h. Purification was carried out on an automated MPLC system (0−5% MeOH/DCM over 30 min) to afford **10e** as a colorless oil (58.5 mg, 0.338 mmol, 84%): R_f = 0.51 (5% MeOH/DCM); IR (neat) 3394, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66 (m, 2H), 2.75 (m, 2H), 3.45 (m, 2H), 3.52 (m, 4H), 3.72 (m, 2H), 3.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 41.1, 45.3, 52.1, 58.2, 65.6, 70.4, 175.9; HRMS (ESI) m/z calcd for $C_8H_{16}NO_3$ $[M + H]^+$ 174.1130, found 174.1134.

1-Benzoyl-4-(3′-hydroxypropyl)-1,4-diazepan-5-one 10g. Following the general procedure C, to a solution of 1-benzoyl-4-piperidone **1g** (81.3 mg, 0.400 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.4 mg, 0.597 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 6 h. Subsequently, hydrolysis was carried out with saturated $NaHCO_3$ solution for 12 h. Purification was carried out on an automated MPLC system (0−10% MeOH/DCM over 50 min) to afford **10g** as a colorless oil (88.9 mg, 0.322 mmol, 80%): R_f = 0.20 (5% MeOH/DCM); IR (neat) 3408, 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (br s, 2H), 2.71 (br s, 2H), 3.51−3.84 (complex, 10H), 7.32−7.42 (complex, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 39.0, 45.2, 45.4, 50.1, 50.7, 58.3, 127.0, 128.9, 130.2, 135.4, 171.3, 174.5; HRMS (ESI) m/z calcd for $C_{15}H_{21}N_2O_3$ $[M + H]^+$, 277.1552, found 277.1562.

1-(3′-Hydroxypropyl)-1-azacyclooctan-2-one 10i.[27] Following the procedure C, to a solution of cycloheptanone **1i** (44.7 mg, 0.399 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.8 mg, 0.601 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397, 1.0 equiv). The reaction mixture was stirred at room temperature for 6 h. Subsequently, hydrolysis was carried out with 1 M NaOH solution for 24 h. The crude oil obtained was eluted through a short bed of silica gel using 10% MeOH/DCM. Concentration of solvents afforded **10i** as a yellow oil (45.2 mg, 0.244 mmol, 61%).

Similarly, the solution of cycloheptanone **1i** (44.9 mg, 0.400 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.7 mg, 0.600 mmol, 1.5 equiv) in HFIP (1.0 mL) was treated with triflic acid (53.0 μL, 0.600 mmol, 1.5 equiv) for 6 h. Subsequent hydrolysis and purification as described above afforded **10i** as a yellow oil (51.0 mg, 0.275 mmol, 69%).

1-Oxa-5-azacyclotridecan-13-one 11j.[27] Following the general procedure C, to a solution of cyclooctanone **1j** (50.8 mg, 0.403 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.9 mg, 0.602 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 6 h. Subsequently, hydrolysis was carried out with saturated $NaHCO_3$ solution for 12 h. Purification was carried out on an automated MPLC system (0−25% MeOH/DCM over 40 min) to afford **11j** as an orange low melting solid (45.3 mg, 0.227 mmol, 56%).

3-(3′-Hydroxypropyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one 10oa and 2-(3′-Hydroxypropyl)-4,5-dihydro-1*H*-benzo[*c*]azepin-3(2*H*)-one 10ob. Following the general procedure C, to a solution of β-tetralone (58.5 mg, 0.400 mmol, 1.0 equiv) **1o** and 3-azido-1-propanol **9a** (60.7 mg, 0.600 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 3 h. Subsequently, hydrolysis was carried out with saturated $NaHCO_3$ solution for 13 h. Purification was carried out on an automated MPLC system (0−10% MeOH/DCM over 50 min) to afford a mixture of lactams **10oa** and **10ob** as an orange oil (combined yield of **10oa** and **10ob**: 82.3 mg, 0.375 mmol, 94%; ratio of **10oa**/**10ob** = 63:37): R_f = 0.39 (5% MeOH/DCM); IR (neat) 3382, 1625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (m, 2H), 1.72 (m, 2H), 2.94 (m, 2H), 3.13 (m, 2H), 3.18 (t, J = 6.68 Hz, 2H), 3.35 (t, J = 5.52 Hz, 2H), 3.48 (t, J = 5.52 Hz, 2H), 3.57 (m, 2H), 3.61 (m, 2H), 3.72 (m, 2H), 3.92 (s, 2H), 4.49 (s, 2H), 7.04−7.25 (complex, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 30.4, 30.5, 32.4, 33.5, 42.9, 43.6, 44.5, 46.9, 53.1, 58.0, 58.2, 126.2, 126.7, 127.3, 128.3 128.7, 130.4, 130.6, 131.0, 131.3, 134.3, 135.6, 137.4, 173.4, 175.0. Diagnostic peaks of **10oa**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (m, 2H), 3.13 (m, 2H), 3.48 (t, J = 5.52 Hz, 2H), 3.57 (m, 2H), 3.72 (m, 2H), 3.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 32.4, 42.9, 43.6, 46.9, 58.2, 131.3, 135.6, 173.4. Diagnostic peaks of **10ob**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (m, 2H), 2.94 (m, 2H), 3.18 (m, J = 6.68 Hz, 2H), 3.35 (t, J = 5.52 Hz, 2H), 3.61 (m, 2H), 4.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 30.4, 33.5, 44.5, 53.1, 58.0, 175.0; HRMS (ESI) m/z calcd for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1338, found 220.1346. One-dimensional and two-dimensional NMR techniques were employed to determine the structures of the individual regioisomers from the mixture.

2-(3′-Hydroxypropyl)-1,2-dihydroisoquinolin-3(4*H*)-one 10p.[21b] Following the procedure C, to a solution of 2-indanone **1p** (39.7 mg, 0.300 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (45.5 mg, 0.450 mmol, 1.5 equiv) in HFIP (0.75 mL) was added triflic acid (27.0 μL, 0.306, 1.0 equiv). The reaction mixture was stirred at room temperature for 1 h. Subsequently, hydrolysis was carried out with saturated $NaHCO_3$ solution for 24 h. Purification was carried out on an automated MPLC system (0−10% MeOH/DCM over 40 min) to afford **10p** as a brown oil (55.4 mg, 0.270 mmol, 90%).

1-(3′-Hydroxypropyl)quinoxaline-2,3(1*H*,4*H*)-dione 10qa and 3-(3′-Hydroxypropyl)quinazoline-2,4(1*H*,3*H*)-dione 10qb.

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Following the general procedure C, to a solution of isatin **1o** (58.9 mg, 0.400 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.7 mg, 0.600 mmol, 1.5 equiv) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 6 h. Subsequently, hydrolysis was carried out with saturated $NaHCO_3$ solution for 12 h. The precipitate was filtered, washed with water, and dried under vacuum to obtain a mixture of lactams **10qa** and **10qb** as a cream-colored solid (combined yield of **10qa** and **10qb**: 67.2 mg, 0.305 mmol, 76%; ratio of **10qa**/**10qb** = 63:37): R_f = 0.21 and 0.48 (5% MeOH/DCM); IR (neat) 3410, 1673, 1601; ^{1}H NMR (400 Hz, DMSO-*d*) δ 1.72−1.77 (m, 4H), 3.47 (t, *J* = 6.40 Hz, 2H), 3.52 (t, *J* = 6.1 Hz, 2H), 3.94 (m, 2H), 4.14 (m, 2H), 7.19 (m, 5H), 7.39 (m, 1H), 7.63 (ddd, *J* = 8.4, 7.3, 1.5 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*) δ 30.8, 31.8, 38.8, 40.9, 59.2, 59.8, 114.7, 115.8, 116.0, 116.7, 123.4, 124.2, 124.4, 126.8, 127.2, 128.3, 135.8, 140.3, 151.1, 154.5, 156.0, 162.9. Diagnostic peaks of **10qa**: ^{1}H NMR (400 Hz, DMSO-*d*) δ 3.52 (t, *J* = 6.08 Hz, 2H), 4.14 (m, 2H), 7.39 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d*) δ 31.8, 40.9, 59.2, 126.8, 127.3, 154.5, 156.0; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{13}N_2O_3$ $[M + H]^+$ 221.0926, found 221.0937. Diagnostic peaks of **10qb**: 3.47 (t, *J* = 6.40 Hz, 2H), 3.94 (m, 2H), 7.63 (ddd, *J* = 8.4, 7.3, 1.5 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*) δ 30.8, 38.8, 59.8, 114.7, 128.3, 135.8, 140.3, 151.1, 162.9; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{13}N_2O_3$ $[M + H]^+$ 221.0926, found 221.0928. One-dimensional and two-dimensional NMR methods were employed to elucidate the structures of the individual regioisomers in a mixture.

(3a*R,6a*S**)-2-(3′-Hydroxypropyl)-2,3,3a,4-tetrahydrocyclopenta[*c*]pyrrol-1(6a*H*)-one 10ra and (3a*R**,6a*S**)-1-(3′-Hydroxypropyl)-3,3a,6,6a-tetrahydrocyclopenta[*b*]pyrrol-2(1*H*)-one 10rb.** Following the general procedure C, to a solution of (±)-*cis*-bicyclo[3.2.0]hept-2-en-6-one **1r** (42.0 μL, 0.398 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.7 mg, 0.600 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 1 h. Subsequently, hydrolysis was carried out with saturated $NaHCO_3$ solution for 12 h. The crude oil obtained was eluted through a short bed of silica gel using 10% MeOH/DCM. Concentration of solvents afforded a mixture of lactams **10ra** and **10rb** as a brown oil (combined yield of **10ra** and **10rb**: 69.0 mg, 0.381 mmol, 95%; ratio of **10ra**/**10rb** = 74:26): R_f = 0.25 (5% MeOH/DCM); IR (neat) 1652, 3382 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56−1.71 (complex, 4H), 2.28 (dd, *J* = 17.5, 2.9, 1H), 2.48 (m, 1H), 2.53 (m, 1H), 2.67−2.56 (complex, 2H), 2.69 (m, 1H), 2.74 (m, 1H), 3.09−3.17 (complex, 2H), 3.20 (m, 1H), 3.29 (m, 1H), 3.40−3.34 (complex, 3H), 3.52−3.42 (complex, 3H), 3.60 (m, 2H), 4.24 (td, *J* = 6.9, 1.8 Hz, 1H), 5.58 (m, 1H), 5.65 (m, 1H), 5.67 (m, 1H), 5.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 29.4, 30.2, 35.8, 36.2, 37.3, 37.4, 38.8, 42.3, 42.5, 44.6, 51.9, 58.1, 58.5, 61.6, 128.7, 131.8, 132.0, 133.1, 175.5, 178.3. Diagnostic peaks of **10ra**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (m, 1H), 5.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.4, 36.2, 38.8, 42.5, 44.6, 51.9, 58.1, 131.8, 132.0, 178.3; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{16}NO_2$ $[M + H]^+$ 182.1181, found 182.1184. Diagnostic peaks of **10rb**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (dd, *J* = 17.5, 2.9, 1H), 2.48 (m, 1H), 2.53 (m, 1H), 2.74 (m, 1H), 3.20 (m, 1H), 4.24 (td, *J* = 6.9, 1.8 Hz, 1H), 5.65 (m, 1H), 5.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 35.8, 37.3, 37.4, 42.3, 58.5, 61.6, 128.7, 133.1, 175.5; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{16}NO_2$ $[M + H]^+$ 182.1181, found 182.1180. One-dimensional and two-dimensional NMR methods were employed to elucidate the structures of the individual regioisomers in a mixture.

(1*R,5*S**)-3-(3′-Hydroxypropyl)-3-azabicyclo[3.2.1]octan-2-one 10sa and (1*R**,5*S**)-2-(3′-Hydroxypropyl)-2-azabicyclo-[3.2.1]octan-3-one 10sb.** Following the general procedure C, to a solution of norcamphor **1s** (44.9 mg, 0.408 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (61.0, 0.603 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 2 h. Subsequently, hydrolysis was carried out with 1 M NaOH solution for 12 h. Purification was carried out on an automated MPLC system (0−10% MeOH/DCM over 40 min) to afford a mixture of lactams **10sa** and **10sb** as orange oil (combined yield of **10sa** and **10sb**: 67.1 mg, 0.366 mmol, 90%; ratio of **10sa**/**10sb** = 58:42): R_f = 0.32 (5% MeOH/DCM); IR (neat) 3380, 1616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49−1.81 (complex, 10 H), 1.82−1.97 (complex, 6H), 2.24 (m, 1H), 2.51 (m, 2H), 2.59 (m, 1H), 2.75 (br, s, 1H), 2.92 (m, 1H), 3.07 (m, 1H), 3.20 (m, 1H), 3.31 (dd, *J* = 11.4, 4.04 Hz, 1H), 3.36−3.43 (m, 1H), 3.45 (m, 1H), 3.50−3.64 (m, 2H), 3.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1, 29.21 (2C), 29.3, 30.2, 31.4, 32.6, 32.9, 33.5, 33.6, 36.6, 41.6, 42.1, 42.8, 43.5, 55.7, 58.1, 58.7, 170.8, 176.2. Diagnostic peaks of **10sa** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (br, s, 1H), 2.92 (m, 1H), 3.20 (m, 1H), 3.31 (dd, *J* = 11.4, 4.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.6, 43.5, 55.7, 176.2. Diagnostic peaks of **10sb**: δ 2.24 (m, 1H), 2.59 (m, 1H), 3.07 (m, 1H), 3.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.6, 42.1, 42.8, 58.7, 170.8; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{18}NO_2$ $[M + H]^+$ 184.1338, found 184.1341. One-dimensional and two-dimensional NMR methods were employed to elucidate the structures of the individual regioisomers in a mixture.

(1*R,3*R**,8*S**)-4-(3′-Hydroxypropyl)-4-azatricyclo[4.3.1.1^{3,8}]-]undecan-5-one 10t.** Following the general procedure C, to a solution of 2-adamantanone **1t** (60.0 mg, 0.399 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.7 mg, 0.600 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 1 h. Subsequently, hydrolysis was carried out with 1 M NaOH solution for 12 h. The crude oil obtained was eluted through a short bed of silica gel using 10% MeOH/DCM. Concentration of solvents afforded **10r** as a yellow oil (85.6 mg, 0.383 mmol, 96%): R_f = 0.21 (5% MeOH/DCM); IR (neat) 3387, 1604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (m, 2H), 1.70−1.95 (complex, 10H), 2.05 (m, 2H), 2.86 (m, 1H), 3.33 (m, 1H), 3.51 (m, 4H), 4.26 (t, *J* = 7.16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4 (2C), 30.2, 31.3 (2C), 34.5, 35.7 (2C), 42.4, 45.4, 53.7, 58.1, 180.6; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{22}NO_2$ $[M + H]^+$ 224.1651, found 224.1645.

***N*-(3′-Hydroxypropyl)-*N*-butylpentanamide (Mixture of Rotamers) 10k and 3-Butylaminopropylpentanoate 11k.**[27] Following the general procedure C, to a solution of 5-nonanone **1k** (57.5 mg, 0.404 mmol, 1.0 equiv) and 3-azido-1-propanol **9a** (60.7 mg, 0.600 mmol, 1.5 equiv) in HFIP (1.0 mL) was added triflic acid (35.0 μL, 0.397 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 6 h, and was followed by hydrolysis with saturated $NaHCO_3$ solution for 24 h. Purification was carried out on an automated MPLC system (0−25% MeOH/DCM over 75 min) to afford **10k** (mixture of rotamers) as a colorless oil (13.1 mg, 0.0610 mmol, 15%; ratio of rotamers = 79:21) and **11k** as a yellow oil (59.9 mg, 0.278 mmol, 69%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02764.

X-ray data for **4b** (CIF)

X-ray data for **7** (CIF)

^{1}H and ^{13}C NMR spectra for new compounds and known compounds prepared by the present method (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Schmidt, K. F. *Angew. Chem.* **1923**, *36*, 511−524. (b) Schmidt, K. F. *Ber. Dtsch. Chem. Ges. B* **1924**, *57*, 704−706.
(2) (a) Birkofer, L.; Wegner, P. *Org. Synth.* **1970**, *50*, 107. (b) Jafarzadeh, M. *Synlett* **2007**, *2007*, 2144−2145. (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S.; Praneeth, K. *Tetrahedron Lett.* **2008**, *49*, 4742−4745.
(3) Wrobleski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aubé, J. *Org. React.* **2012**, *78*, 1−320.
(4) Motiwala, H. F.; Fehl, C.; Li, S.-W.; Hirt, E.; Porubsky, P.; Aubé, J. *J. Am. Chem. Soc.* **2013**, *135*, 9000−9009.
(5) Wolff, H. *Org. React.* **1946**, *3*, 307−332.
(6) Koldobskii, G. I.; Ostrovskii, V. A.; Gidaspov, B. Z. *Chem. Heterocycl. Compd.* **1975**, *11*, 626−635.
(7) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897−3900.
(8) Aromí, G.; Barrios, L. A.; Roubeau, O.; Gamez, P. *Coord. Chem. Rev.* **2011**, *255*, 485−546.
(9) (a) Huisgen, R.; Sauer, J.; Sturm, H. J.; Markgraf, J. H. *Chem. Ber.* **1960**, *93*, 2106−2124. (b) Frija, L. M. T.; Ismael, A.; Cristiano, M. L. S. *Molecules* **2010**, *15*, 3757−3774.
(10) (a) Ostrovskii, V. A.; Pevzner, M. S.; Kofman, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets Heterocycl. Syst.* **1999**, *3*, 467−526. (b) Gaponik, P. N.; Voitekhovich, S. V.; Ivashkevich, O. A. *Russ. Chem. Rev.* **2006**, *75*, 507.
(11) (a) Yu, K. L.; Johnson, R. L. *J. Org. Chem.* **1987**, *52*, 2051−2059. (b) Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499−531. (c) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379−3393. (d) Hajra, S.; Sinha, D.; Bhowmick, M. *J. Org. Chem.* **2007**, *72*, 1852−1855. (e) Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl. Compd.* **2007**, *43*, 1−9. (f) Mohapatra, D. K.; Maity, P. K.; Ghorpade, R. V.; Gurjar, M. K. *Heterocycles* **2009**, *77*, 865−872. (g) Ostrovskii, V. A.; Trifonov, R. E.; Popova, E. A. *Russ. Chem. Bull.* **2012**, *61*, 768−780.
(12) (a) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149−191. (b) Jung, M. E.; Lal, H.; Gatch, M. B. *Neurosci. Biobehav. Rev.* **2002**, *26*, 429−439.
(13) (a) Benson, F. R. *The High-Nitrogen Compounds*; Wiley-Interscience: New York, 1984. (b) Huynh, M. H. V.; Hiskey, M. A.; Chavez, D. E.; Naud, D. L.; Gilardi, R. D. *J. Am. Chem. Soc.* **2005**, *127*, 12537−12543.
(14) Nishiyama, K.; Watanabe, A. *Chem. Lett.* **1984**, *13*, 455−458.
(15) Howells, R. D.; Mc Cown, J. D. *Chem. Rev.* **1977**, *77*, 69−92.
(16) Litkei, G.; Patonay, T. *Acta Chim. Hung.* **1983**, *114*, 47−56.
(17) Benson, F. R. *Chem. Rev.* **1947**, *41*, 1−61.
(18) (a) Misiti, D.; Rimatori, V. *Tetrahedron Lett.* **1970**, *11*, 947−950. (b) Misiti, D.; Rimatori, V. *Ann. Ist Super Sanita* **1973**, *9*, 150−159. (c) Sudan, S.; Gupta, R.; Kachroo, P. L.; Gupta, D. K.; Bhutani, K. K. *Indian J. Chem., Sect B* **1992**, *31B*, 610−612. (d) Daya, S.; Kaye, P. T.; Mphahlele, M. J. *Med. Sci. Res.* **1996**, *24*, 137−141. (e) Mphahlele, M. J. *Trends Org. Chem.* **2009**, *13*, 1−10.
(19) (a) Finnegan, W. G.; Henry, R. A.; Lieber, E. *J. Org. Chem.* **1953**, *18*, 779−791. (b) Henry, R. A.; Finnegan, W. G.; Lieber, E. *J. Am. Chem. Soc.* **1954**, *76*, 88−93. (c) Boyer, J. H.; Miller, E. J., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 4671−4673.
(20) (a) Molina, P.; Alajarín, M.; Sánchez-Andrada, P.; Carrió, J. S.; Martínez-Ripoll, M.; Anderson, J. E.; Jimeno, M. L.; Elguero, J. *J. Org. Chem.* **1996**, *61*, 4289−4299. (b) Richter, R.; Tucker, B.; Ulrich, H. *J. Org. Chem.* **1983**, *48*, 1694−1700. (c) Richter, R.; Barsa, E. A. *J. Org. Chem.* **1986**, *51*, 417−419. (d) Wentrup, C.; Thétaz, C.; Tagliaferri, E.; Lindner, H. J.; Kitschke, B.; Winter, H.-W.; Reisenauer, H. P. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 566−567.
(21) (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047−8048. (b) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241−16252. (c) Smith, B. T.; Gracias, V.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 3771−3774.
(22) (a) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226−7232. (b) Aube, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637.
(23) (a) Furness, K.; Aubé, J. *Org. Lett.* **1999**, *1*, 495−498. (b) Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914−7922.
(24) Fenster, E.; Rayabarapu, D. K.; Zhang, M.; Mukherjee, S.; Hill, D.; Neuenswander, B.; Schoenen, F.; Hanson, P. R.; Aubé, J. *J. Comb. Chem.* **2008**, *10*, 230−234.
(25) Treece, J. L.; Goodell, J. R.; Velde, D. V.; Porco, J. A.; Aubé, J. *J. Org. Chem.* **2010**, *75*, 2028−2038.
(26) (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 10−11. (b) Fenster, E.; Smith, B. T.; Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **2008**, *73*, 201−205.
(27) Forsee, J. E.; Aubé, J. *J. Org. Chem.* **1999**, *64*, 4381−4385.
(28) Motiwala, H. F.; Yin, Q.; Aubé, J. *Molecules* **2016**, *21*, 45.
(29) Eshghi, H.; Hassankhani, A. *Synth. Commun.* **2005**, *35*, 1115−1120.
(30) Mitsuhashi, K.; Shiotani, S.; Ohuchi, R.; Shiraki, K. *Chem. Pharm. Bull.* **1969**, *17*, 434−453.
(31) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879−4891.
(32) Harvill, E. K.; Roberts, C. W.; Herbst, R. M. *J. Org. Chem.* **1950**, *15*, 58−67.
(33) Evans, P. A.; Modi, D. P. *J. Org. Chem.* **1995**, *60*, 6662−6663.
(34) Sakakida, Y.; Kumanireng, A. S.; Kawamoto, H.; Yokoo, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 478−480.
(35) Arya, V. P.; Kaul, C. L.; Grewal, R. S.; David, J.; Talwalker, P. K.; Shenoy, S. J. *Indian J. Chem., Sect. B* **1977**, *15*, 720−726.
(36) D'Itri, F. M.; Popov, A. I. *J. Am. Chem. Soc.* **1968**, *90*, 6476−6481.
(37) Aridoss, G.; Laali, K. K. *Eur. J. Org. Chem.* **2011**, *2011*, 6343−6355.
(38) (a) Kametani, T.; Umezawa, O. *Chem. Pharm. Bull.* **1966**, *14*, 369−375. (b) Goh, K. S.; Tan, C.-H. *RSC Adv.* **2012**, *2*, 5536−5538.
(39) Harvill, E. K.; Herbst, R. M.; Schreiner, E. C.; Roberts, C. W. *J. Org. Chem.* **1950**, *15*, 662−670.
(40) Lee, L. A.; Crabtree, E. V.; Lowe, J. U., Jr; Cziesla, M. J.; Evans, R. *Tetrahedron Lett.* **1965**, *6*, 2885−2887.
(41) Coombs, T. C.; Lushington, G. H.; Douglas, J.; Aubé, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2734−2737.
(42) Clark, R. D.; Jahangir. *Tetrahedron* **1993**, *49*, 1351−1356.
(43) Katoh, M.; Inoue, H.; Honda, T. *Heterocycles* **2007**, *72*, 497−516.

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