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Electronic and steric effects on the intramolecular Schmidt reaction of alkyl azides with secondary benzyl alcohols

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ABSTRACT

The intramolecular Schmidt reaction of simple azido secondary benzyl alcohols has been realized for the first time. Investigation of the electronic and steric effects of the substrates on the product outcome was conducted. Unique intramolecular Schmidt rearrangements were observed with the formation of a cinnamaldehyde derivative and aryl aldehydes, respectively. Using this protocol, an efficient synthesis of dihydrobenzotriazine derivatives was achieved. Moreover, a practical approach to 2-aryl-1-pyrrolines was also accessed.

1. Introduction

Two decades ago, the intramolecular Schmidt reaction of alkyl azides with ketones and tertiary carbocations was first reported by Aubé and Pearson independently.[1,2] Since then, a considerable amount of research has been conducted on the optimizations of the reaction conditions,[3] the applications in the synthesis of complex nitrogen-containing heterocycles,[4] and expanding the substrate scope.[5] Nevertheless, detailed studies are still warranted to address the steric and electronic effects of the substrates on these reactions.[5b,j,m,p] For example, Molina et al. showed that the azido benzylic carbocations with the tether length of four-carbon between the azido group and the phenyl group could readily undergo intramolecular Schmidt reaction to give five-membered cyclic imines.[5c] However, their attempts to make six-membered cyclic imines via Schmidt reaction of the azido benzylic carbocations with the tether length of five-carbon failed, without giving any explanation. On the other hand, although a variety of substrates have been explored in generating various electron-deficient systems for azide rearrangements,[5h] surprisingly, there is so far no report on intramolecular Schmidt reactions based on simple azido secondary benzyl alcohols.[5k,6]

This paper describes our study results on intramolecular Schmidt reaction of alkyl azides with secondary benzyl alcohols. Particularly, we address the substituent effects of the phenyl ring and the tether lengths of the azido alkyl chains on the product outcome. Detailed mechanistic analysis is also presented herein.

2. Results and discussion

As shown in Scheme 1, upon treatment of azido alcohols **1** with trifluoroacetic acid (TFA) at 0 °C, room temperature or 40 °C, products **2**–**6** were formed via paths i–v, respectively, depending on the length of azido alkyl chains and the electronic properties of the substituents at the phenyl ring. To test how the steric and electronic factors affected the product outcome, 19 substrates were examined (Table 1).

For azido alcohols **1** without substituents at the phenyl ring and with tether lengths of three-carbon (**1a**), five-carbon (**1l**), or six-carbon (**1p**), trifluoroacetic esters **2a**, **2l**, and **2p** were obtained as the major products (entries 1, 12, and 16) together with recovered starting materials, respectively. In contrast, for azido alcohol **1e** with tether length of four-carbon, five-membered cyclic imine **4e** was obtained as the major product (entry 5). This discrepancy might be due to that, given the instability of benzylic carbocations **7** without substitution at the phenyl ring, the steric difficulties in forming cyclic aminodiazonium ions **8** from **7** gave rise to the formation of trifluoroacetic esters **2a**, **2l**, and **2p**, respectively (Scheme 1, path i). For example, the strain of the four-membered cyclic intermediate **8** derived from **1a** might be so strong that, before its formation, an intermolecular nucleophilic trapping of **7** by TFA

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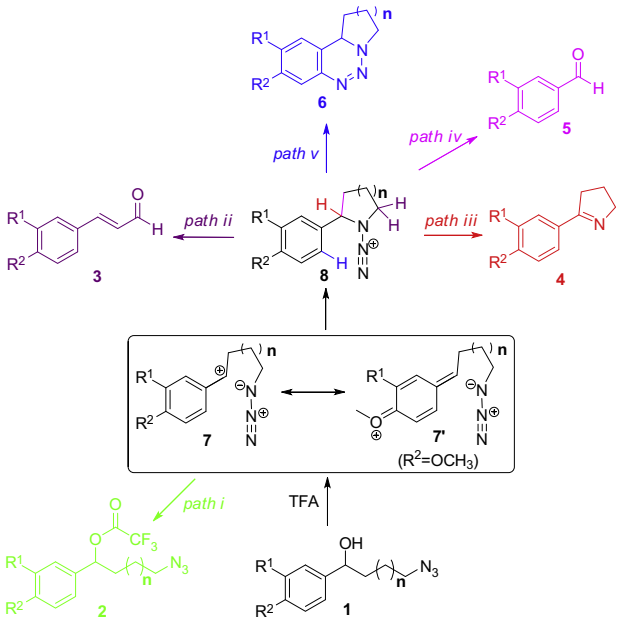


Scheme 1. Reactions of azido alcohols **1** with TFA.

Table 1
Product outcome of the reactions of azido alcohols **1** with TFA[a]

Entry	Azido alcohol	*n*	R^1	R^2	Product	Yield[b] (%)
1	**1a**	0	H	H	**2a**	44
2	**1b**	0	H	CF_3	—[c]	—[c]
3	**1c**	0	H	OCH_3	—[d]	—[d]
4	**1d**	0	OCH_3	OCH_3	**3d**	31
5	**1e**	1	H	H	**4e**	56
6	**1f**	1	H	CF_3	—[c]	—[c]
7	**1g**	1	H	CH_3	**4g**	75
8	**1h**	1	H	Ph	**4h**	58
9	**1i**	1	H	OCH_3	**4i**	74
10	**1j**	1	OCH_3	OCH_3	**4j**	65
11	**1k**	1	R[e]	OCH_3	**4k**	63
12	**1l**	2	H	H	**2l**	37
13	**1m**	2	H	CF_3	**2m**	58
14	**1n**	2	H	OCH_3	**5n**	54
15	**1o**	2	OCH_3	OCH_3	**5o**	61
16	**1p**	3	H	H	**2p**	55
17	**1q**	3	H	CF_3	—[c]	—[c]
18	**1r**	3	H	OCH_3	**5n**	52
19	**1s**	3	OCH_3	OCH_3	**6s**/**5o**[f]	73[f]

[a] Reaction temperature: rt for **1a**, **1e**, **1g**, **1h**, **1l**, and **1p**; 0 °C for **1c**, **1d**, **1i**–**k**, **1n**, **1o**, **1r**, **1s**; 40 °C for **1b**, **1f**, **1m**, and **1q**.
[b] Isolated yields.
[c] Starting materials recovered.
[d] The reaction was complex and no products could be identified.
[e] R=$O(CH_2)_3OCH_3$.
[f] **6s**/**5o**=6.3:1.

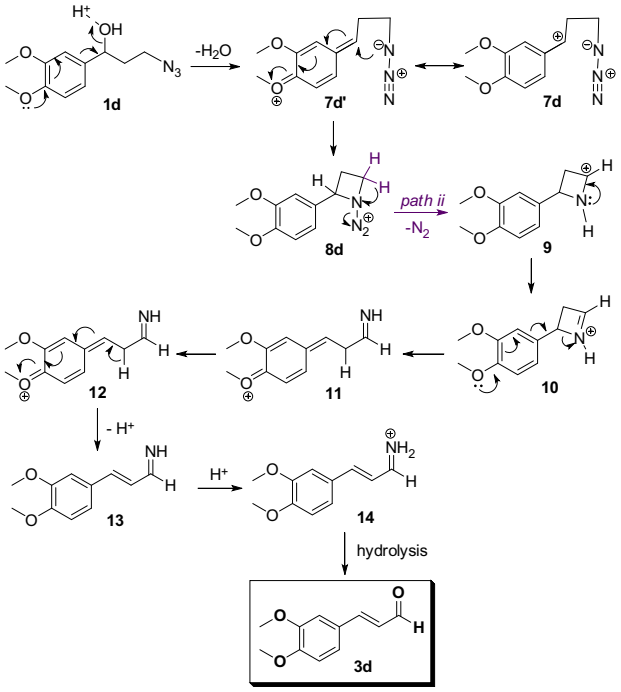
occurred, leading to ester **2a** as the major product. In addition, the longer tether lengths in **7** derived from **1l** and **1p** might delay and disfavor the azido attack at the benzylic carbocations so that esters **2l** and **2p** became the dominant products, respectively. This well explains why Molina et al. failed to make six-membered cyclic imines via intramolecular Schmidt reaction.[5c]

On the other hand, despite the instability of carbocation **7** derived from **1e**, the favored kinetics of five-membered ring formation readily gave rise to the corresponding aminodiazonium ion **8**, further leading to cyclic imine **4e** via benzylic hydride migration to the cyclic N atom with loss of nitrogen (Scheme 1, path iii).[5c]

To test the effect of electron-withdrawing substituents of the phenyl ring on the product profile, azido alcohols **1b**, **1f**, **1m**, and **1q** with different alkyl chain lengths were examined. Except for **1m** allowing for the formation of ester **2m** (entry 13), treatment of **1b**, **1f**, and **1q** with TFA at room temperature or at 40 °C all resulted in the recovery of the staring materials (entries 2, 6, 17), implying that electron-withdrawing groups disabled the generation of the corresponding benzylic carbocations **7**.

By contrast, azido alcohols **1** with electron-donating substituents at the phenyl ring were more susceptible to the Schmidt rearrangements (Scheme 1, paths ii, iii, iv), leading to different types of products **3**–**5**. This demonstrates that electron-donating groups promote the formation of stabilized benzylic carbocations **7** or *O*-methylated quinone methide cation **7′** (R^2=OCH_3), thus allowing for the formation of aminodiazonium ions **8** as the precursors to Schmidt reactions. The product profile still depends on the alkyl chain lengths and the electronic properties of the substituents (entries 3, 4, 7–11, 14, 15, 18, 19). The possible mechanisms are discussed as below.

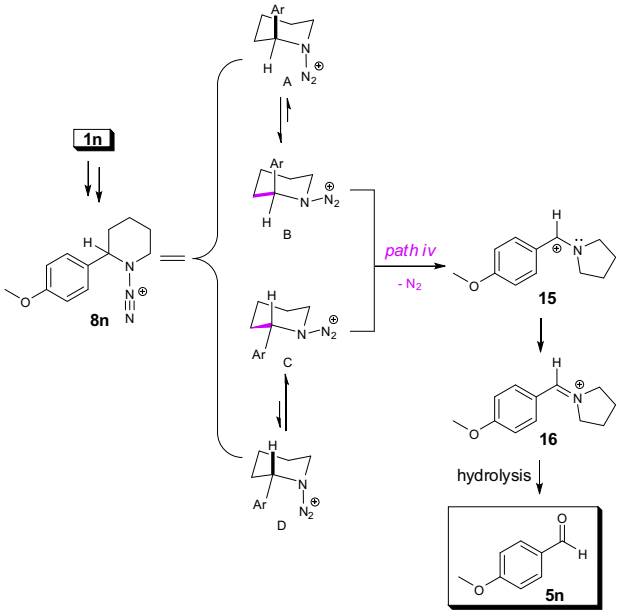
Scheme 2 elucidates the plausible mechanism for the formation of 3,4-dimethoxycinnamaldehyde **3d** from **1d** with tether length of three-carbon. We envisioned that, upon protonation of the benzylic hydroxyl group, the *p*-methoxy function in **1d** should play a key role as the secondary driving force through electron delocalization, leading to the quinone methide cation **7d′** as the first in situ generated species,[7] instead of benzylic carbocation **7d**. In comparison with **7d**, **7d′** is so stable that the unfavored four-membered cyclic intermediate **8d** could be formed. The strain in **8d** favors a nonbenzylic hydride shift to the cyclic N atom with loss of nitrogen, leading to carbocation **9**. After a series of electron transfer and proton transfer steps, hydrolysis of aldimine ion **14** results in **3d**. On the other hand, an alternative mechanism involving decomposition of a cinnamyl azide under acidic conditions cannot be excluded,[8] even though the generation of this cinnamyl azide in the presence of the *p*-methoxy function is questionable. To our knowledge, this is the first example for an intramolecular Schmidt reaction affording a cinnamaldehyde derivative as the major product.[5k]



Scheme 2. Mechanism of formation of **3d** from **1d**.

As mentioned above with **1e**, the Schmidt reactions of the azido alcohols with tether length of four-carbon afforded 2-aryl-1-pyrrolines **4** (entries 7–11). The putative mechanism for these reactions is similar to that proposed by Molina.[5c]

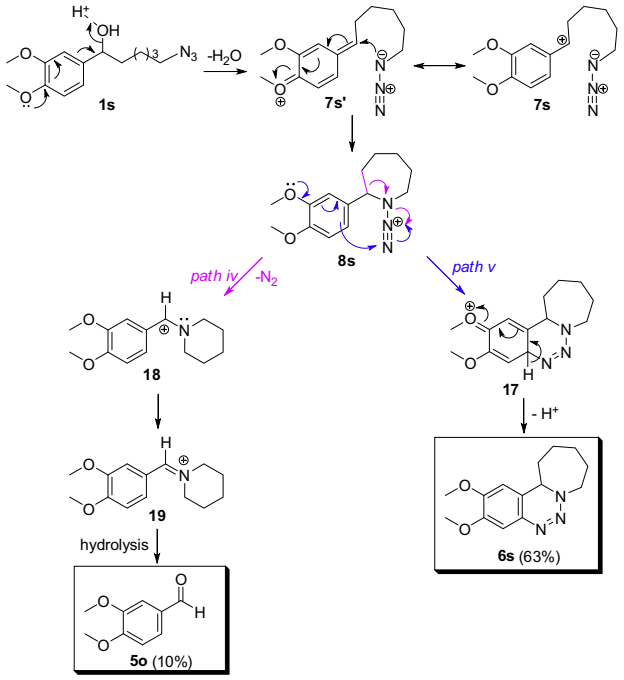
With further increasing in the tether length by one or two carbons, an alternative rearrangement pathway occurred, leading to aryl aldehydes **5** (Scheme 1, path iv) (entries 14, 15, 18, 19). A representative mechanism elucidation is shown in Scheme 3. Aminodiazonium ion **8n** derived from **1n** has four possible conformations **A**–**D**, among which conformer **C** with both the aromatic group and N_2 cation group in equatorial positions should be more stable than **A**, **B**, and **D**. According to Curtin–Hammett principle, although the interconversion of **A** to **B** and **C** to **D** could be very fast, the energy barrier for Schmidt rearrangement transition states of **A** and **D** might be much higher than that for **B** and **C**, thus leading to the dominance of path iv rearrangement products. Therefore, antiperiplanar 1,2-migration of the pinkened C–C bond in **B** or **C** to the cyclic N atom occurs with loss of nitrogen, leading to carbocation **15**, and then aldimine ion **16**. Hydrolysis of **16** afforded 4-methoxybenzaldehyde **5n**. This is the first example for such a transformation, and again explains why the corresponding six-membered cyclic imines could not be obtained via benzylic hydride shift-mediated Schmidt rearrangement.[5c]



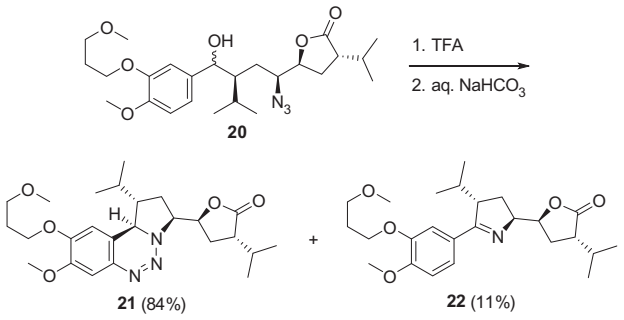
Scheme 3. Mechanism of formation of **5n** from **1n**.

Interestingly, for azido alcohol **1s** with tether length of six-carbon and 3,4-dimethoxy substituents, 3,4-dihydrobenzotriazine **6s** was obtained as the major product (63%), together with aldehyde **5o** as a minor product (10%) (entry 19). The formation of **6s** can be attributed to the enhanced nucleophilicity of the phenyl ring by the 3-methoxy function via electron resonance, toward the aminodiazonium group in **8s** (Scheme 4, path v, blue arrows).[9] This approach is more favored over the Schmidt rearrangement of **8s** allowing for the production of aldehyde **5o** (Scheme 4, path iv, pink arrows). We therefore have developed a novel approach to 3,4-dihydrobenzotriazines with potential pharmaceutical and agricultural utility.[10]

To further illustrate the utility of the above methodology, azido alcohol **20**, an important intermediate in the synthesis of aliskiren derivatives as renin inhibitors,[11] was examined (Scheme 5). Thus, treatment of **20** with TFA at 0 °C afforded 3,4-dihydrobenzotriazine



Scheme 4. Mechanism of formation of **6s** from **1s**.



Scheme 5. Reaction of aliskiren intermediate **20** with TFA.

21 in a good yield (84%), while cyclic imine **22** was isolated as a minor product (11%). In contrast to the reaction of **1k** carrying the same aryl moiety with **20**, where cyclic imine **4k** is the major product (entry 11), the lactone moiety and the isopropyl group near the benzylic carbon in **20** seem to disfavor the Schmidt rearrangement. The configuration of the benzylic carbon of **21** was confirmed by the ROESY spectrum. 3,4-Dihydrobenzotriazine **21** represents an interesting novel scaffold for the development of renin inhibitors as antihypertensive agents that is a part of our ongoing program.[12]

3. Conclusion

In conclusion, we have carried out the intramolecular Schmidt reactions of simple azido secondary benzyl alcohols. The substitution profile of the phenyl ring and the tether lengths of the azido alkyl chains had profound effects on the product outcome. Unique intramolecular Schmidt rearrangements led to the formation of a cinnamaldehyde derivative and aryl aldehydes, respectively. An efficient synthesis of 3,4-dihydrobenzotriazine derivatives has been realized and would provide novel scaffolds for pharmaceutical purpose. Moreover, a practical synthesis of 2-aryl-1-pyrrolines has also been developed. Further studies are

underway to explore the generality of these reactions and their applications in heterocyclic synthesis.

4. Experimental section

4.1. General information

Low- and high-resolution mass spectra (LRMS and HRMS) were recorded in electron impact mode. The mass analyzer type used for the HRMS measurements is TOF. Reactions were monitored by TLC on silica gel 60 F_{254} plates (Qingdao Ocean Chemical Company, China). Column chromatography was carried out on silica gel (200–300 mesh, Qingdao Ocean Chemical Company, China).

4.2. Procedure for the preparation of 1

*4.2.1. 3-Azido-1-phenylpropan-1-ol (**1a**).* To a solution of iodobenzene (5.77 g, 28.3 mmol) in anhydrous THF (60 mL) was added a 1.0 M solution of *i*-PrMgCl in anhydrous THF (28.3 mL, 28.3 mmol) over 20 min at −25 °C, and the resulting mixture was stirred for 1 h at −25 °C. After cooling to −75 °C, a solution of 3-azidopropanal (1.3 g, 13.0 mmol) in anhydrous THF (23 mL) was added dropwise over 20 min. After stirring for 1 h at −75 °C, the reaction mixture was quenched by saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 20:1 to 9:1) to give a brown oil, 1.20 g (52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90–2.10 (m, 2H), 2.14 (s, 1H), 3.33–3.53 (m, 2H), 4.80–4.84 (m, 1H), 7.25–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.3, 47.9, 71.3, 125.2, 127.4, 128.2, 143.3.

Following the procedure described for the preparation of **1a**, compounds **1c**, **1e**, **1g**, **1h**, **1i**, **1k**, **1l**, **1n**, **1o**, **1p**, **1r**, and **20** were prepared.

*4.2.2. 3-Azido-1-(4-methoxyphenyl)propan-1-ol (**1c**).* Brown oil, 0.92 g (30% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57–2.20 (m, 3H), 3.30–3.50 (m, 2H), 3.81 (s, 3H), 4.70–4.80 (m, 1H), 6.85–7.00 (m, 2H), 7.25–7.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.3, 48.0, 54.8, 71.0, 113.6, 126.5, 135.4, 158.7. ESI-MS *m*/*z* 206.1 $[M-H]^-$. HRMS calcd for $C_{10}H_{12}N_3O_2$ $[M-H]^-$ *m*/*z* 206.0930, found 206.0933.

*4.2.3. 4-Azido-1-phenylbutan-1-ol (**1e**).* Brown oil, 0.50 g (20% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55–1.67 (m, 1H), 1.69–1.92 (m, 3H), 2.04 (br s, 1H), 3.29 (t, 2H, *J*=5.7 Hz), 4.65–4.75 (m, 1H), 7.25–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 35.9, 51.3, 74.0, 125.7, 127.7, 128.5, 144.3. ESI-MS *m*/*z* 381.2 $[2M-H]^-$. HRMS calcd for $C_{20}H_{25}N_6O_2$ $[2M-H]^-$ *m*/*z* 381.2039, found 381.2043.

*4.2.4. 4-Azido-1-p-tolylbutan-1-ol (**1g**).* Brown oil, 0.82 g (31% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.87 (m, 4H), 1.96 (br s, 1H), 2.34(s, 3H), 3.23–3.30 (m, 1H), 3.50–3.60 (m, 1H), 4.60–4.70 (m, 1H), 7.10–7.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 25.4, 35.9, 51.4, 73.8, 125.7, 129.2, 137.4, 141.4. ESI-MS *m*/*z* 228.1 $[M+Na]^+$. HRMS calcd for $C_{11}H_{15}N_3ONa$ $[M+Na]^+$ *m*/*z* 228.1107, found 228.1098.

*4.2.5. 4-Azido-1-(biphenyl-4-yl)butan-1-ol (**1h**).* Brown oil, 0.75 g (34% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55–1.70 (m, 1H), 1.72–2.00 (m, 4H), 3.31 (t, 2H, *J*=5.8 Hz), 4.70–4.80 (m, 1H), 7.20–7.49 (m, 5H), 7.50–7.60 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 36.0, 51.4, 73.8, 126.2, 127.0, 127.2, 127.3, 128.8, 137.9, 140.7, 143.3. ESI-MS *m*/*z* 533.3 $[2M-H]^-$. HRMS calcd for $C_{32}H_{33}N_6O_2$ $[2M-H]^-$ *m*/*z* 533.2665, found 533.2670.

*4.2.6. 4-Azido-1-(4-methoxyphenyl)butan-1-ol (**1i**).* Brown oil, 0.30 g (46% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.60 (m, 1H), 1.65–1.80 (m, 3H), 1.99 (s, 1H), 3.25–3.40 (m, 2H), 3.80 (s, 3H), 4.60–4.70 (m, 1H), 6.85–7.00 (m, 2H), 7.20–7.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 35.9, 51.4, 55.3, 73.7, 114.0, 127.0, 136.5, 159.2. ESI-MS *m*/*z* 244.1 $[M+Na]^+$. HRMS calcd for $C_{11}H_{15}N_3O_2Na$ $[M+Na]^+$ *m*/*z* 244.1056, found 244.1061.

*4.2.7. 4-Azido-1-(4-methoxy-3-(3-methoxypropoxy)phenyl)butan-1-ol (**1k**).* Brown oil, 0.46 g (52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.70 (m, 1H), 1.72–2.00 (m, 4H), 2.05–2.20 (m, 2H), 3.25–3.33 (m, 2H), 3.36 (s, 3H), 3.59 (t, 2H, *J*=6.1 Hz), 3.86 (s, 3H), 4.13 (t, 2H, *J*=6.5 Hz), 4.60–4.66 (m, 1H), 6.82–6.90 (m, 2H), 6.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 29.0, 35.4, 50.9, 55.6, 58.1, 65.6, 68.8, 73.4, 110.4, 111.1, 117.7, 136.6, 148.2, 148.5. ESI-MS *m*/*z* 332.2 $[M+Na]^+$. HRMS calcd for $C_{15}H_{23}N_3O_4Na$ $[M+Na]^+$ *m*/*z* 332.1586, found 332.1589.

*4.2.8. 5-Azido-1-phenylpentan-1-ol (**1l**).* Brown oil, 1.41 g (44% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33–1.42 (m, 1H), 1.47–1.55 (m, 1H), 1.58–1.65 (m, 2H), 1.70–1.76 (m, 1H), 1.79–1.85 (m, 1H), 2.00 (br s, 1H), 3.20–3.30 (m, 2H), 4.63–4.70 (m, 1H), 7.20–7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0, 28.7, 38.4, 51.3, 74.3, 125.8, 127.6, 128.5, 144.6. ESI-MS *m*/*z* 228.1 $[M+Na]^+$. HRMS calcd for $C_{11}H_{15}N_3ONa$ $[M+Na]^+$ *m*/*z* 228.1107, found 228.1109.

*4.2.9. 5-Azido-1-(4-methoxyphenyl)pentan-1-ol (**1n**).* Brown oil, 1.20 g (43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.37 (m, 1H), 1.40–1.53 (m, 1H), 1.55–1.65 (m, 2H), 1.67–1.74 (m, 1H), 1.75–1.84 (m, 1H), 1.87 (br s, 1H), 3.24 (t, 2H, *J*=6.8 Hz), 3.80 (s, 3H), 4.60 (t, 1H, *J*=6.6 Hz), 6.87 (d, 2H, *J*=8.5 Hz), 7.25 (d, 2H, *J*=8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 28.7, 38.3, 51.3, 55.3, 74.0, 113.9, 127.1, 136.7, 159.1. ESI-MS *m*/*z* 258.1 $[M+Na]^+$. HRMS calcd for $C_{12}H_{17}N_3O_2Na$ $[M+Na]^+$ *m*/*z* 258.1218, found 258.1220.

*4.2.10. 5-Azido-1-(3,4-dimethoxyphenyl)pentan-1-ol (**1o**).* Brown oil, 0.91 g (53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32–1.41 (m, 1H), 1.45–1.55 (m, 1H), 1.58–1.65 (m, 2H), 1.67–1.75 (m, 1H), 1.79–1.85 (m, 2H), 3.25 (t, 2H, *J*=6.8 Hz), 3.87 (s, 3H), 3.89 (s, 3H), 4.61 (t, 1H, *J*=6.3 Hz), 6.82–6.87 (m, 2H), 6.90 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 28.7, 38.4, 51.3, 55.9, 56.0, 74.3, 109.0, 111.1, 118.1, 137.3, 148.6, 149.2. ESI-MS *m*/*z* 288.1 $[M+Na]^+$. HRMS calcd for $C_{13}H_{19}N_3O_3Na$ $[M+Na]^+$ *m*/*z* 288.1324, found 288.1327.

*4.2.11. 6-Azido-1-phenylhexan-1-ol (**1p**).* Brown oil, 1.40 g (45% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.50 (m, 4H), 1.50–1.65 (m, 2H), 1.66–1.83 (m, 2H), 1.98 (br s, 1H), 3.22 (t, 2H, *J*=6.8 Hz), 4.65 (t, 1H, *J*=6 Hz), 7.24–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 26.1, 28.3, 38.3, 50.8, 74.0, 125.4, 127.1, 128.0, 144.2. ESI-MS *m*/*z* 242.1 $[M+Na]^+$. HRMS calcd for $C_{12}H_{17}N_3ONa$ $[M+Na]^+$ *m*/*z* 242.1264, found 242.1263.

*4.2.12. 6-Azido-1-(4-methoxyphenyl)hexan-1-ol (**1r**).* Brown oil, 1.89 g (49% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23–1.33 (m, 1H), 1.35–1.47 (m, 3H), 1.55–1.63 (m, 2H), 1.65–1.71 (m, 1H), 1.74–1.80 (m, 1H), 1.87 (br s, 1H), 3.23 (t, 2H, *J*=6.9 Hz), 3.80 (s, 3H), 4.61 (t, 1H, *J*=5.1 Hz), 6.88 (d, 2H, *J*=8.5 Hz), 7.25 (d, 2H, *J*=8.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 26.6, 28.7, 38.7, 51.4, 55.3, 74.1, 113.9, 127.1, 136.9, 159.1. ESI-MS *m*/*z* 272.1 $[M+Na]^+$. HRMS calcd for $C_{13}H_{19}N_3O_2Na$ $[M+Na]^+$ *m*/*z* 272.1375, found 272.1381.

*4.2.13. (3S,5S)-5-((1S,3S)-1-Azido-3-(hydroxy(4-methoxy-3-(3-methoxypropoxy)phenyl)methyl)-4-methylpentyl)-3-isopropyldihydrofuran-2(3H)-one (**20**).*[11] Brown oil, 1.02 g (61%

yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78–2.65 (m, 23H), 3.34 (s, 3H), 3.58(t, 2H, J=6.0 Hz), 3.61–3.64 (m, 0.53H), 3.84 (s, 3H), 4.00–4.04 (m, 0.47H), 4.10 (t, J=6.0 Hz, 2H), 4.32–4.39 (m, 1H), 4.45 (d, 0.47H, J=8.6 Hz), 4.58 (d, 0.53H, J=8.2 Hz), 6.80–6.95 (m, 3H). ESI-MS m/z 500.2 $[M+Na]^+$.

*4.2.14. 3-Azido-1-(4-(trifluoromethyl)phenyl)propan-1-ol (**1b**).* To a solution of 1-bromo-4-(trifluoromethyl)benzene (7.3 g, 32.6 mmol) in anhydrous THF (90 mL) was added a 2.5 M solution of *n*-BuLi in hexane (13.04 mL, 32.6 mmol) over 20 min at −65 °C, and the resulting mixture was stirred for 1 h. Then, a solution of 3-azidopropanal (1.487 g, 15.0 mmol) in anhydrous THF (40 mL) was added dropwise to the mixture over 20 min. After stirring for 1 h at −65 °C, the reaction mixture was quenched by saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 10:1 to 3:1) to give a colorless oil, 1.73 g (47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90–2.10 (m, 2H), 2.40 (br s, 1H), 3.30–3.46 (m, 1H), 3.47–3.60 (m, 1H), 4.85–4.95 (m, 1H), 7.47 (d, 2H, J=8.0 Hz), 7.63 (d, 2H, J=8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.7, 48.1, 71.0, 122.1, 125.3, 125.3, 125.4, 125.5, 125.8, 126.6, 129.6, 130.0, 147.7. ESI-MS m/z 244.1 $[M-H]^-$. HRMS calcd for $C_{10}H_9N_3F_3O$ $[M-H]^-$ m/z 244.0698, found 244.0701.

Following the procedure described for the preparation of **1b**, compounds **1d**, **1f**, **1j**, **1m**, **1q**, and **1s** were prepared.

*4.2.15. 3-Azido-1-(3,4-dimethoxyphenyl)propan-1-ol (**1d**).* Brown oil, 1.87 g (39% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80–2.10 (m, 2H), 2.35 (br s, 1H), 3.25–3.37 (m, 1H), 3.38–3.42 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.70–4.80 (m, 1H), 6.70–6.90 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.8, 48.4, 55.8, 55.9, 71.5, 108.8, 111.1, 118.0, 136.5, 148.6, 149.2. ESI-MS m/z 260.1 $[M+Na]^+$. HRMS calcd for $C_{11}H_{15}N_3O_3Na$ $[M+Na]^+$ m/z 260.1011, found 260.1013.

*4.2.16. 4-Azido-1-(4-(trifluoromethyl)phenyl)butan-1-ol (**1f**).* Brown oil, 0.71 g (31% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.72 (m, 1H), 1.75–1.95 (m, 3H), 2.08 (br s, 1H), 3.31 (t, 2H, J=6.0 Hz), 4.78 (t, 1H, J=6.0 Hz), 7.45 (d, 2H, J=8.0 Hz), 7.61 (d, 2H, J=8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 36.1, 44.7, 73.1, 122.2, 125.3, 125.3, 125.4, 125.5, 126.0, 126.2, 128.1, 129.4, 162.4. ESI-MS m/z 258.1 $[M-H]^-$. HRMS calcd for $C_{11}H_{11}N_3F_3O$ $[M-H]^-$ m/z 258.0854, found 258.0856.

*4.2.17. 4-Azido-1-(3,4-dimethoxyphenyl)butan-1-ol (**1j**).* Brown oil, 1.14 g (26% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57–1.65 (m, 1H), 1.71–1.91 (m, 4H), 3.25–3.35 (m, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 4.60–4.68 (m, 1H), 6.80–6.87 (m, 2H), 6.90 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 36.0, 51.4, 55.9, 56.0, 74.0, 109.0, 111.2, 118.1, 137.1, 148.7, 149.2. ESI-MS m/z 274.1 $[M+Na]^+$. HRMS calcd for $C_{12}H_{17}N_3O_3Na$ $[M+Na]^+$ m/z 274.1168, found 274.1170.

*4.2.18. 5-Azido-1-(4-(trifluoromethyl)phenyl)pentan-1-ol (**1m**).* Brown oil, 1.25 g (35% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30–1.43 (m, 1H), 1.45–1.55 (m, 1H), 1.57–1.65 (m, 2H), 1.69–1.82 (m, 2H), 2.13 (br s, 1H), 3.27 (t, 2H, J=6.8 Hz), 4.70–4.77 (m, 1H), 7.44 (d, 2H, J=8.0 Hz), 7.62 (d, 2H, J=8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8, 28.6, 38.5, 51.2, 73.7, 122.3, 125.3, 125.4, 125.4, 125.5, 126.0, 129.6, 130.2, 148.5. ESI-MS m/z 274.1 $[M+H]^+$. HRMS calcd for $C_{12}H_{15}N_3OF_3$ $[M+H]^+$ m/z 274.1167, found 274.1171.

*4.2.19. 6-Azido-1-(4-(trifluoromethyl)phenyl)hexan-1-ol (**1q**).* Brown oil, 1.15 g (30% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30–1.50 (m, 4H), 1.55–1.65 (m, 2H), 1.68–1.80 (m, 2H), 1.98 (br s, 1H), 3.24 (t, 2H, J=6.8 Hz), 4.70–4.77 (m, 1H), 7.45 (d, 2H, J=8.0 Hz), 7.60 (d, 2H, J=8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 26.6, 28.7, 39.0, 51.3, 73.8, 123.1, 125.3, 125.3, 125.4, 125.4, 126.1, 129.6, 129.9, 148.7. ESI-MS m/z 545.2 $[2M-H-N_2]^-$. HRMS calcd for $C_{26}H_{31}N_4O_2F_6$ $[2M-H-N_2]^-$ m/z 545.2351, found 545.2358.

*4.2.20. 6-Azido-1-(3,4-dimethoxyphenyl)hexan-1-ol (**1s**).* Brown oil, 1.47 g (37% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.50 (m, 4H), 1.51–1.90 (m, 5H), 3.23 (t, 2H, J=6.8 Hz), 3.86 (s, 3H), 3.88 (s, 3H), 4.60 (t, 1H, J=6.1 Hz), 6.80–6.95 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 26.1, 28.3, 38.3, 50.9, 55.3, 55.4, 74.0, 108.3, 110.9, 118.1, 137.3, 148.0, 148.7. ESI-MS m/z 302.1 $[M+Na]^+$. HRMS calcd for $C_{14}H_{21}N_3O_3Na$ $[M+Na]^+$ m/z 302.1475, found 302.1476.

4.3. Procedure for the reaction of 1 with trifluoroacetic acid (TFA)

*4.3.1. Reaction of **1a** with TFA.* To a solution of **1a** (100 mg, 0.56 mmol) in dry CH_2Cl_2 (7.6 mL) was added dropwise TFA (0.28 mL, 3.36 mmol) at room temperature. The resulting mixture was kept at this temperature for 48 h. Then, a solution of aqueous saturated $NaHCO_3$ (7.9 mL) was added dropwise to the mixture at 0 °C and the resulting mixture was stirred at room temperature for 10 min. The mixture was extracted with CH_2Cl_2. The combined extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 100:1 to 5:1) to give 3-azido-1-phenylpropyl 2,2,2-trifluoroacetate (**2a**) as a colorless oil, 68 mg (44% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05–2.20 (m, 1H), 2.25–2.50 (m, 1H), 3.20–3.50 (m, 2H), 5.95–6.05 (m, 1H), 7.25–7.50 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.7, 48.2, 71.7, 125.6, 127.8, 128.6, 143.8. ESI-MS m/z 292.3 $[M+H_2O+H]^+$. HRMS calcd for $C_{11}H_{13}N_3O_3F_3$ $[M+H_2O+H]^+$ m/z 292.0909, found 292.0911.

*4.3.2. Reaction of **1e** with TFA.* Following the procedure described for the reaction of **1a** with TFA, 5-phenyl-3,4-dihydro-2*H*-pyrrole (**4e**) was obtained as a white solid, 24 mg (56% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95–2.10 (m, 2H), 2.95 (t, 2H, J=8.0 Hz), 4.07 (t, 2H, J=7.2 Hz), 7.40–7.50 (m, 3H), 7.80–7.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 34.9, 61.4, 127.6, 128.4, 130.3, 134.4, 173.2. ESI-MS m/z 146.1 $[M+H]^+$. HRMS calcd for $C_{10}H_{12}N$ $[M+H]^+$ m/z 146.0970, found 146.0972.

*4.3.3. Reaction of **1g** with TFA.* Following the procedure described for the reaction of **1a** with TFA, 5-*p*-tolyl-3,4-dihydro-2*H*-pyrrole (**4g**) was obtained as a light yellow solid, 58 mg (75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95–2.10 (m, 2H), 2.37 (s, 3H), 2.85–2.95 (m, 2H), 4.04 (t, 2H, J=7.3 Hz), 7.15–7.30 (d, 2H, J=8.1 Hz), 7.72 (d, 2H, J=8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 22.6, 34.8, 61.4, 127.5, 129.1, 131.9, 140.4, 173.1. ESI-MS m/z 160.1 $[M+H]^+$. HRMS calcd for $C_{11}H_{14}N$ $[M+H]^+$ m/z 160.1121, found 160.1120.

*4.3.4. Reaction of **1h** with TFA.* Following the procedure described for the reaction of **1a** with TFA, 5-(biphenyl-4-yl)-3,4-dihydro-2*H*-pyrrole (**4h**) was obtained as a white solid, 24 mg (58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95–2.15 (m, 2H), 2.93–3.03 (m, 2H), 4.09 (t, 2H, J=7.3 Hz), 7.20–7.50 (m, 3H), 7.55–7.70 (m, 4H), 7.85–7.95 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 34.9, 61.6, 127.0, 127.6, 128.0, 128.8, 133.5, 137.9, 140.3, 142.9, 172.9. ESI-MS m/z 222.1 $[M+H]^+$. HRMS calcd for $C_{16}H_{16}N$ $[M+H]^+$ m/z 222.1283, found 222.1285.

*4.3.5. Reaction of **1i** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 0 °C, 5-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyrrole (**4i**) was obtained as a white solid, 28 mg (74% yield). ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.95–2.10 (m, 2H), 2.92 (t, 2H, J=8.1 Hz), 3.84 (s, 3H), 4.04 (t, 2H, J=7.3 Hz), 6.92 (d, 2H, J=8.7 Hz), 7.81 (d, 2H, J=8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 34.9, 55.3, 61.1, 113.8, 127.2, 129.3, 161.5, 172.8. ESI-MS m/z 176.1 $[M+H]^+$. HRMS calcd for $C_{11}H_{14}NO$ $[M+H]^+$ m/z 176.1075, found 176.1077.

*4.3.6. Reaction of **1j** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 0 °C, 5-(3,4-dimethoxyphenyl)-3,4-dihydro-2*H*-pyrrole (**4j**) was obtained as a white solid, 85 mg (65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95–2.10 (m, 2H), 2.96 (t, 2H, J=8.1 Hz), 3.91 (s, 3H), 3.94 (s, 3H), 4.05 (t, 2H, J=7.3 Hz), 6.86 (d, 1H, J=8.3 Hz), 7.27 (dd, 1H, J=2.3, 8.9 Hz), 7.63 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 34.8, 55.9, 56.0, 60.7, 109.9, 110.3, 121.9, 127.2, 149.1, 151.6, 173.3. ESI-MS m/z 206.1 $[M+H]^+$. HRMS calcd for $C_{12}H_{16}NO_2$ $[M+H]^+$ m/z 206.1181, found 206.1183.

*4.3.7. Reaction of **1k** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 0 °C, 5-(4-methoxy-3-(3-methoxypropoxy)phenyl)-3,4-dihydro-2*H*-pyrrole (**4k**) was obtained as a white solid, 38 mg (63% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00–2.15 (m, 4H), 2.97 (t, 2H, J=5.0 Hz), 3.34 (s, 3H), 3.57 (t, 2H, J=5.0 Hz), 3.90 (s, 3H), 4.06 (t, 2H, J=6.7 Hz), 4.19 (t, 2H, J=6.4 Hz), 6.87 (d, 1H, J=8.2 Hz), 7.32 (d, 1H, J=8.0 Hz), 7.65 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 29.5, 34.8, 56.0, 58.6, 60.3, 66.3, 69.3, 110.7, 111.6, 122.0, 172.6. ESI-MS m/z 264.2 $[M+H]^+$. HRMS calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$ m/z 264.1600, found 264.1602.

*4.3.8. Reaction of **1l** with TFA.* Following the procedure described for the reaction of **1a** with TFA, 5-azido-1-phenylpentyl 2,2,2-trifluoroacetate (**2l**) was obtained as a colorless oil, 96 mg (37% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40–1.75 (m, 2H), 1.81–1.90 (m, 2H), 2.05–2.18 (m, 1H), 2.20–2.35 (m, 1H), 3.48 (t, 2H, J=6.7 Hz), 6.05–6.15 (m, 1H), 7.40–7.70 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 28.4, 35.3, 51.0, 80.5, 126.4, 128.8, 128.9, 130.0, 137.8. ESI-MS m/z 160.1 $[M-N_2-C_2O_2F_3]^+$. HRMS calcd for $C_{11}H_{14}N$ $[M-N_2-C_2O_2F_3]^+$ m/z 160.1126, found 160.1128.

*4.3.9. Reaction of **1m** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 40 °C, 5-azido-1-(4-(trifluoromethyl)phenyl)pentyl 2,2,2-trifluoroacetate (**2m**) was obtained as a colorless oil, 264 mg (58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30–1.70 (m, 4H), 1.89–2.00 (m, 1H), 2.03–2.10 (m, 1H), 3.30 (t, 2H, J=6.6 Hz), 5.90–5.94 (m, 1H), 7.49 (d, 2H, J=8.1 Hz), 7.68 (d, 2H, J=8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 28.3, 35.3, 50.9, 79.5, 125.8, 125.9, 125.9, 126.0, 126.7, 141.7. ESI-MS m/z 228.1 $[M-N_2-C_2O_2F_3]^+$. HRMS calcd for $C_{12}H_{13}NF_3$ $[M-N_2-C_2O_2F_3]^+$ m/z 228.1000, found 228.1003.

*4.3.10. Reaction of **1n** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 0 °C, 4-methoxybenzaldehyde (**5n**) was obtained as a light yellow oil, 63 mg (54% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.01 (d, 2H, J=8.6 Hz), 7.84 (d, 2H, J=8.6 Hz), 9.89 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 114.2, 129.9, 131.9, 164.5, 190.7. ESI-MS m/z 137.1 $[M+H]^+$. HRMS calcd for $C_8H_9O_2$ $[M+H]^+$ m/z 137.0603, found 137.0606.

*4.3.11. Reaction of **1o** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 0 °C, 3,4-dimethoxybenzaldehyde (**5o**) was obtained as a light yellow solid, 100 mg (61% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.93 (s, 3H), 6.95 (d, 2H, J=8.2 Hz), 7.43 (d, 2H, J=8.2 Hz), 9.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 56.1, 109.0, 110.4, 126.7, 130.1, 149.6, 154.5, 190.7. ESI-MS m/z 167.1 $[M+H]^+$. HRMS calcd for $C_9H_{11}O_3$ $[M+H]^+$ m/z 167.0708, found 167.0710.

*4.3.12. Reaction of **1p** with TFA.* Following the procedure described for the reaction of **1a** with TFA, 6-azido-1-phenylhexyl 2,2,2-trifluoroacetate (**2p**) was obtained as a colorless oil, 161 mg (55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30–1.50 (m, 4H), 1.50–1.65 (m, 2H), 1.80–2.00 (m, 1H), 2.02–2.15 (m, 1H), 3.24 (t, 2H, J=6.8 Hz), 5.85 (t, 1H, J=6.4 Hz), 7.24–7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 25.8, 28.1, 35.2, 50.7, 80.2, 126.0, 128.3, 128.4, 137.5. ESI-MS m/z 174.1 $[M-N_2-C_2O_2F_3]^+$. HRMS calcd for $C_{12}H_{16}N$ $[M-N_2-C_2O_2F_3]^+$ m/z 174.1283, found 174.1286.

*4.3.13. Reaction of **1r** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 0 °C, 4-methoxybenzaldehyde (**5n**) was obtained as a light yellow oil, 63 mg (52% yield).

*4.3.14. Reaction of **1s** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 0 °C, 2,3-dimethoxy-8,9,10,11,12,12a-hexahydrobenzo[4,5][1,2,3]triazino[1,6-*a*]azepine (**6s**) was obtained as a brown oil, 88 mg (63% yield). In addition, 3,4-dimethoxybenzaldehyde (**5o**) was obtained as a light yellow solid, 11 mg (10% yield). For **6s**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–1.63 (m, 3H), 1.65–1.80 (m, 4H), 2.05–2.15 (m, 1H), 3.47–3.56 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 4.16–4.25 (m, 1H), 4.41 (m, 1H), 6.37 (s, 1H), 6.98 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 26.6, 28.8, 37.2, 54.5, 54.8, 56.0, 56.1, 106.5, 107.4, 114.9, 132.1, 148.9, 150.0. ESI-MS m/z 262.1 $[M+H]^+$. HRMS calcd for $C_{14}H_{20}N_3O_2$ $[M+H]^+$ m/z 262.1556, found 262.1559.

*4.3.15. Reaction of **20** with TFA.* Following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 0 °C, (3*S*,5*S*)-3-isopropyl-5-((1*S*,3*S*,10b*R*)-1-isopropyl-8-methoxy-9-(3-methoxypropoxy)-1,2,3,10b-tetrahydrobenzo[*e*]pyrrolo[1,2-*c*][1,2,3]triazin-3-yl)dihydrofuran-2(3*H*)-one (**21**) was obtained as a colorless oil, 122 mg (84% yield). In addition, (3*S*,5*S*)-3-isopropyl-5-((2*S*,4*S*)-4-isopropyl-5-(4-methoxy-3-(3-methoxypropoxy)phenyl)-3,4-dihydro-2*H*-pyrrol-2-yl)dihydrofuran-2(3*H*)-one (**22**) was obtained as a colorless oil, 15 mg (11% yield). For **21**: $[\alpha]_D^{25}$ −111.2 (*c* 0.30, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, 3H, J=5.0 Hz), 0.91 (d, 3H, J=5.0 Hz), 0.95 (d, 3H, J=5.0 Hz), 1.06 (d, 3H, J=5.0 Hz), 1.95–2.15 (m, 7H), 2.20–2.27 (m, 1H), 2.33–2.43 (m, 1H), 2.45–2.55 (m, 1H), 3.35 (s, 3H), 3.57 (t, 2H, J=5.0 Hz), 3.89 (s, 3H), 3.91 (d, 1H, J=12.7 Hz), 4.14 (t, 2H, J=5.0 Hz), 4.25–4.30 (m, 1H), 4.81–4.86 (m, 1H), 6.61 (s, 1H), 7.10 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 18.1, 20.3, 22.3, 24.7, 27.5, 44.8, 44.9, 55.3, 56.1, 58.8, 61.2, 66.2, 69.0, 79.0, 106.1, 108.4, 117.0, 134.3, 149.1, 150.3, 178.6. ESI-MS m/z 460.2 $[M+H]^+$. HRMS calcd for $C_{25}H_{38}N_3O_5$ $[M+H]^+$ m/z 460.2811, found 460.2814. For **22**: $[\alpha]_D^{25}$=32.0 (*c* 0.13, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (d, 2H, J=6.8 Hz), 0.90–1.15 (m, 10H), 1.55–1.65 (m, 1H), 1.85–2.05 (m, 2H), 2.05–2.25 (m, 5H), 2.35–2.45 (m, 1H), 2.70–2.90 (m, 1H), 3.34 (s, 3H), 3.57 (t, 2H, J=6.1 Hz), 3.89 (s, 3H), 4.10–4.25 (m, 3H), 4.60–4.70 (m, 1H), 6.84 (d, 1H, J=8.3 Hz), 7.20–7.30 (m, 1H), 7.44–7.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 18.2, 20.6, 21.7, 25.6, 26.7, 28.6, 29.4, 29.5, 45.6, 54.1, 56.0, 58.7, 66.1, 69.3, 75.7, 80.0, 101.4, 109.6, 110.7, 112.3, 112.4, 121.7, 175.4. ESI-MS m/z 454.3 $[M+Na]^+$. HRMS calcd for $C_{25}H_{37}NO_5Na$ $[M+Na]^+$ m/z 454.2569, found 454.2573.

*4.3.16. Reaction of **1d** with TFA.* To a stirred solution of **1d** (130 mg, 0.55 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise TFA (0.25 mL, 3.3 mmol) at 0 °C. The resulting mixture was kept at this temperature for 1 h. The mixture was then warmed to room temperature and stirred for 11 h. A solution of aqueous saturated $NaHCO_3$ (3 mL) was added dropwise to the mixture at 0 °C and the resulting

mixture was stirred at room temperature for 10 min. Then, the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 10:1) to give (*E*)-3-(3,4-dimethoxyphenyl)acrylaldehyde **3d** as a yellow solid, 32 mg (31% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.93 (s, 3H), 6.60 (dd, 1H, *J*=7.7, 15.8 Hz), 6.89 (d, 1H, *J*=8.3 Hz), 7.08 (d, 1H, *J*=1.8 Hz), 7.15 (dd, 1H, *J*=3.0, 9 Hz), 7.41 (d, 1H, *J*=15.8 Hz), 9.66 (d, 1H, *J*=7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9, 56.0, 109.9, 111.1, 123.4, 126.7, 126.9, 149.3, 151.9, 152.8, 193.5. ESI-MS *m*/*z* 193.1 $[M+H]^+$. HRMS calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ *m*/*z* 193.0865, found 193.0867.

For the reactions of **1b**, **1f**, and **1q** with TFA, following the procedure described for the reaction of **1a** with TFA except that the reaction temperature was 40 °C, the starting materials were recovered, respectively. For the reaction of **1c** with TFA at 0 °C, the product was unstable and decomposed.

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Supplementary data

^{1}H NMR and ^{13}C NMR copies of all new compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.098.

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