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Intramolecular and intermolecular Schmidt reactions of alkyl azides with aldehydes

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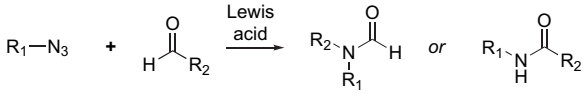
Abstract—Despite recent advances in the use of alkyl azides in ring expansion reactions of ketones, there has been little work done on the corresponding chemistry of aldehydes. In the present study, the Lewis acid-promoted reactions of alkyl azides with aldehydes were studied in both intermolecular and intramolecular contexts. The intramolecular reactions of azidoalkyl aldehydes in which the azide and carbonyl groups were separated by 2–5 carbons were examined. Although the examples having the shortest tether failed (3-azidopropanals), each of the other systems gave good yields of either NH-substituted lactams (resulting from hydride migration in the initially formed azidohydrin adduct) or formamides (alkyl migration). The product formed was dependent on the chain length of the starting azido aldehyde. The intermolecular reactions were less efficient, requiring $TiCl_4$ promotion for even moderate yields, and in each case gave mixtures of products resulting from hydride and alkyl migration.

1. Introduction

The amide bond is one of the most important linkages in chemistry. Although majority of the amide bonds are formed by the condensation of an amine and a carboxylic acid equivalent, alternative approaches to amide synthesis are of continuing interest.[1] In particular, aldehydes are attractive precursors to amides due to their ready availability and reactivity. A number of ways of accomplishing this conversion have been reported.[2,3]

Another way of preparing amides is through rearrangement.[4] In this regard, the Schmidt reaction has long been known to provide amides from aldehydes or ketones, with nitriles as commonly observed side products when aldehydes are used as the carbonyl component.[5] Although the Schmidt reaction classically uses hydrazoic acid as a nitrogen source, it is now known that alkyl azides can be used in Schmidt chemistry as well.[6,7]

Our own work in this area has focused on the acid-promoted reactions of alkyl azide with ketones.[8] In contrast, only a few examples of useful azide/aldehyde reactions to afford amides have been reported (Scheme 1). In 1950s, Boyer and co-workers showed that certain aromatic aldehydes could react with azides to afford amides under the influence of H_2SO_4, albeit in poor yield.[9] Much later, we reported the intramolecular reactions of one γ-azido aldehyde and one δ-azido aldehyde, the latter using a variety of protic and Lewis acid conditions.[8d]



Scheme 1.

In the work described herein, we reinvestigated the reactions of azides with aldehydes to determine whether this potentially useful transformation could be realized using modern Lewis acid conditions. In the intermolecular framework, we focused both on possible Lewis acids and on the issue of alkyl group versus hydride migration in the Schmidt reaction step. It has been amply established that the intramolecular reactions of azides with ketones are much more facile than their intermolecular counterparts.[8] Accordingly, we began the present study by examining the intramolecular reactions of ω-azido alkyl aldehydes in greater detail than previously reported,[8d] again focusing on the matter of regioselectivity.

2. Intramolecular reactions

A series of azidoalkyl aldehydes containing a 2–5 carbon chain connecting the two functional group were prepared for examination under protic (TFA) and Lewis acid ($TiCl_4$) conditions. Electronically neutral substituents were added

Keywords: Schmidt reaction; Alkyl azide; Aldehyde.
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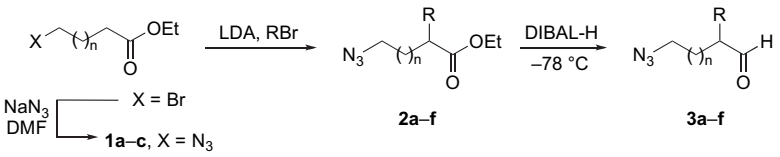
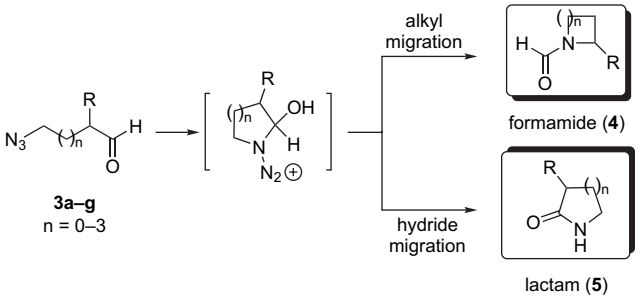
Table 1. Synthesis of azidoalkyl aldehydes



Entry	Compd	*n*	**1** (yield, %)	Compd	R	**2** (yield, %)	Compd	**3** (yield, %)
1	**1a**	1	96	**2a**	Allyl	84	**3a**	59
2	**1a**	1	96	**2b**	Benzyl	79	**3b**	41
3	**1b**	2	99	**2c**	Allyl	44	**3c**	66
4	**1b**	2	99	**2d**	Benzyl	65	**3d**	83
5	**1c**	3	99	**2e**	Allyl	83	**3e**	81
6	**1c**	3	99	**2f**	Benzyl	54	**3f**	78

α to the aldehyde to facilitate product isolation and identification. Except for the case of β-azidoalkyl aldehyde (**3g**), which was prepared via the Michael addition of hydrazoic acid to acrylaldehyde (Table 1),[10] the azidoalkyl aldehydes were synthesized from commercially available bromoalkyl esters. Thus, the bromide was first displaced by sodium azide, followed by α-alkylation of the ester[11] and reduction using DIBAL–H.[12] As suggested by precedent,[12] the azides typically survived the conditions required for the reduction of the ester group.

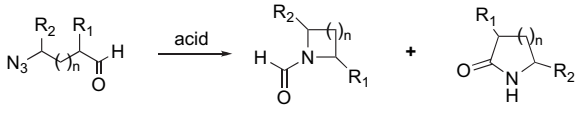
Treatment of the azido aldehydes **3a–g** with acid can in principle afford two kinds of products, depending on the mechanism. First, azide adds to the aldehyde to form an azidohydrin intermediate, which can lead to formamide **4** or lactam **5** by carbon–carbon bond migration or 1,2-hydride shift (followed by tautomerization), respectively (Scheme 2).



Scheme 2.

When the azido aldehydes were exposed to either protic or Lewis acid at room temperature, gas evolution was observed and products isolated following workup as summarized in Table 2. A successful Schmidt reaction of β-azido aldehyde would in principle afford a β-lactam; however, no tractable products were detected upon protic or Lewis acid treatment of **3g** (entries 1 and 2). Increasing tether length by one carbon led to the exclusive formation of lactam **5a** or **5b** in good yields (entries 3–6), while further increase in chain length switched the product profile such that only formamides were observed (entries 7–14). In general, all of these reactions were efficient, although higher yields were usually observed when $TiCl_4$ was used. In addition, the yields obtained in this study were generally improved over the two examples we reported previously.[8d]

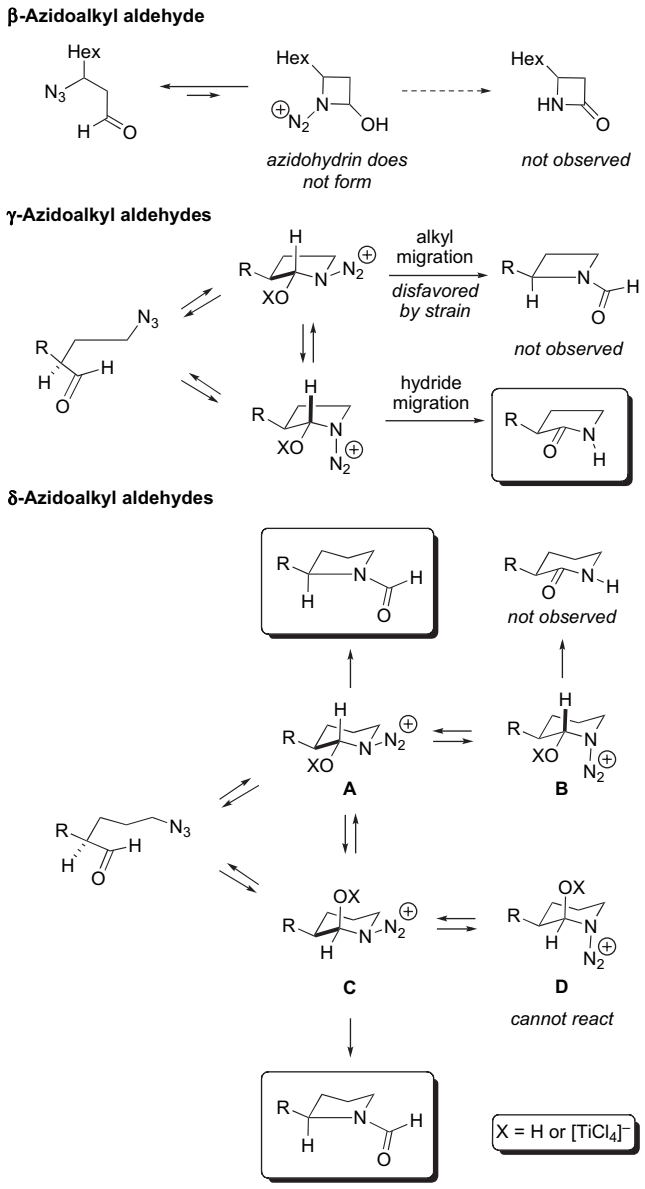
Table 2. Intramolecular reactions of azides with aldehydes



Entry	Compd	*n*	R_1	R_2	Acid	Product (yield, %)	
						4	**5**
1	**3g**	0	H	C_6H_{13}	TFA	—	—
2	**3g**	0	H	C_6H_{13}	$TiCl_4$	—	—
3	**3a**	1	Allyl	H	TFA	—	63
4	**3a**	1	Allyl	H	$TiCl_4$	—	90
5	**3b**	1	Benzyl	H	TFA	—	77
6	**3b**	1	Benzyl	H	$TiCl_4$	—	94
7	**3c**	2	Allyl	H	TFA	60	—
8	**3c**	2	Allyl	H	$TiCl_4$	96	—
9	**3d**	2	Benzyl	H	TFA	68	—
10	**3d**	2	Benzyl	H	$TiCl_4$	85	—
11	**3e**	3	Allyl	H	TFA	53	—
12	**3e**	3	Allyl	H	$TiCl_4$	41	—
13	**3f**	3	Benzyl	H	TFA	71	—
14	**3f**	3	Benzyl	H	$TiCl_4$	49	—

In general, these results can be rationalized by strain considerations (Scheme 3). The lack of β-lactam formation (entries 1 and 2) is ascribed to the nonformation of a necessary four-membered cyclic azidohydrin intermediate from the β-azido aldehyde. In contrast, a γ-azidoalkyl aldehyde readily forms a five-membered cyclic azidohydrin that can in principle lead to migration of either an *endo*cyclic bond (affording formamide **4**) or hydride (affording lactam **5**). Two of the stereoisomeric possibilities for this intermediate are shown where X=H (protic acid promotion) or complexed $TiCl_4$ (two epimers at the aminol carbon are also possible but in this case do not affect the regiochemical outcome of the Schmidt reaction). Assuming antiperiplanar migration in the azidohydrin (darkened bonds indicate the bond antiperiplanar to the N_2^+ leaving group), either alkyl or hydride migration is possible on stereoelectronic grounds, but it appears in the present case that developing strain in the four-membered azetidine product disfavors alkyl migration and so valerolactam is exclusively formed (entries 3–6).

In the larger ring sizes, ring strain is less of consideration (entries 7–14). Of four possible azidohydrins, antiperiplanar alkyl migration from either **A** or **C** affords the formamide products that are solely observed in these series. It is not clear if the reason for this is (1) intrinsic preference for or greater

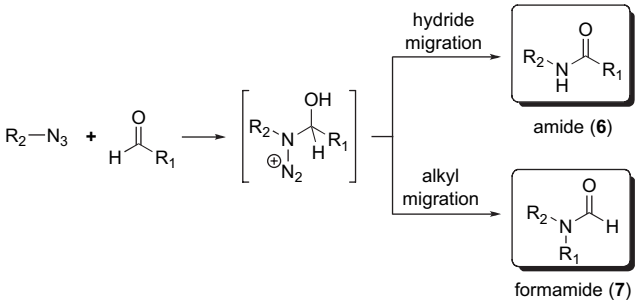


Scheme 3.

reactivity of **A** or **C** (equatorial N_2^+) versus **B** or **D** (axial N_2^+), (2) greater migratory aptitude of an alkyl group over a hydride, or (3) preferred formation of **C** or **D** (axial OX, conceivably preferred due to the anomeric effect in **C**) over **A** or **B** (equatorial OX) coupled with the lack of a mechanism for hydride migration from **D** (oxaziridines or products therefrom have never been observed in the azido-Schmidt reaction[8]). Although not shown, similar considerations apply for the ε-azido aldehyde series. The relatively modest yields in this series suggest that either cyclization or orbital alignment for the migration step is less ideal for the seven-membered azidohydrin intermediate. In none of the cases examined were products of intermolecular reactions identified.

3. Intermolecular reactions

We sought to expand the reaction to its intermolecular variant using different aldehydes and alkyl azides as depicted in Scheme 4. As above, it was expected that an acid-activated aldehyde would react with the alkyl azide to form an azidohydrin intermediate that would ultimately afford either formamide resulting from alkyl migration or simple amide resulting from hydride migration/tautomerization.

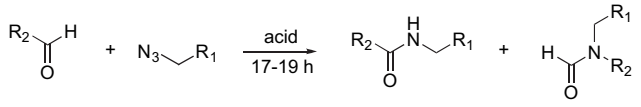


Scheme 4.

Although low yields of amides had been reported to result from treatment of aromatic aldehydes with H_2SO_4,[9] we had hoped to achieve superior results using Lewis acid promotion. To this end, a variety of Lewis acid conditions were initially tried for reaction of *n*-hexyl azide with either heptanal or phenylacetaldehyde ($SnBr_4$, $BF_3 \cdot OEt_2$, Ti(O-*i*-Pr)$_3$, Sc(OTf)$_3$, CF_3SO_3H, and 1 N HCl). Unfortunately, none of these conditions provided useful quantities of amide. Only two acid promoters, TFA and $TiCl_4$, provided sufficient yields of products so that they were further examined with a series of reactants (Table 3). In general, the reactions proceeded best when $TiCl_4$ was used to promote them.

Benzyl azide gave the lowest yields among those examined in these reactions (entries 1–6). This was not surprising as

Table 3. Intermolecular reactions of alkyl azides with aldehydes



Entry	R_1	R_2	Acid	Compds **6** and **7**	Yield, %[a]	
					6	**7**
1	Ph	$PhCH_2$	TFA	**a**	Trace	Trace
2	Ph	$PhCH_2$	$TiCl_4$	**a**	21	10
3	Ph	*n*-Hex	TFA	**b**	Trace	Trace
4	Ph	*n*-Hex	$TiCl_4$	**b**	16	10
5	Ph	$Ph(CH_3)CH$	TFA	**c**	Trace	Trace
6	Ph	$Ph(CH_3)CH$	$TiCl_4$	**c**	33[b]	11[b]
7	$PhCH_2$	$PhCH_2$	TFA	**d**	16	16
8	$PhCH_2$	$PhCH_2$	$TiCl_4$	**d**	22	19
9	$PhCH_2$	*n*-Hex	TFA	**e**	9	9
10	$PhCH_2$	*n*-Hex	$TiCl_4$	**e**	45	39
11	$PhCH_2$	$Ph(CH_3)CH$	TFA	**f**	13	5
12	$PhCH_2$	$Ph(CH_3)CH$	$TiCl_4$	**f**	20	30
13	$CH_3(CH_2)_3CH_2$	$PhCH_2$	TFA	**g**	19	13
14	$CH_3(CH_2)_3CH_2$	$PhCH_2$	$TiCl_4$	**g**	29	26
15	$CH_3(CH_2)_3CH_2$	*n*-Hex	TFA	**h**	28	12
16	$CH_3(CH_2)_3CH_2$	*n*-Hex	$TiCl_4$	**h**	37	26
17	$CH_3(CH_2)_3CH_2$	$Ph(CH_3)CH$	TFA	**i**	23	8
18	$CH_3(CH_2)_3CH_2$	$Ph(CH_3)CH$	$TiCl_4$	**i**	35	27

[a] Isolated products, unless otherwise noted.
[b] Inseparable mixture. Yields estimated from ^{1}H NMR.

benzylic azides are known to decompose under acidic conditions.[13] In contrast, use of azidoethylbenzene or azidohexane afforded increased yields. Although the combined yields of products were in some cases reasonable (i.e., entries 10, 12, 14, 16, and 18), selectivities of products resulting from hydride and alkyl migration were low throughout. This suggests that the intrinsic migratory preference for alkyl and hydride is comparable in this system, which in turn suggests that the considerably better selectivities noted for the intramolecular examples in Table 2 could well arise from the stereoelectronic effects imposed in those reactions.

4. Summary

The intramolecular reaction of azides and aldehydes, like the version using azidoketone substrates, is a useful tool for the synthesis of nitrogenous heterocycles. In those reactions, the product profile was shown to entirely depend on the length of the tether between the azide and aldehyde. Although in some cases the intermolecular reaction of azides and aldehydes proceeds with useful efficiency, especially in the presence of $TiCl_4$, the lack of regiochemical control in the migration step is a drawback.

5. Experimental section

5.1. General

Unless otherwise stated, all reactions were performed under an argon atmosphere in flame-dried glassware. All chromatography was performed using Sorbent Technologies silica gel (230–400 mesh) with the indicated solvent mixtures. Infrared spectra were recorded on a Perkin–Elmer 1420 spectrometer or a Nicolet Fourier transform infrared spectrometer and are expressed in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform using a Bruker AV-400 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.24 ppm ^1H NMR, 77.0 ppm ^{13}C NMR). Coupling constants (J values) are given in hertz (Hz). Low-resolution mass spectra were obtained using a Ribermag R10-10 quadrupole instrument. High-resolution mass spectra (HRMS) were obtained using a VG Analytical ZAG double focusing spectrometer.

Tetrahydrofuran, dichloromethane, and ether (when used as reaction solvents) were purchased from Fisher Scientific and purified using an Innovative Technologies solvent purification system. All other reagents were commercially available and were used without further purification. The azido esters **1a–c** were prepared according to a modified procedure of Khoukhi and co-workers.[11,14]

5.2. General procedure for the synthesis of azido esters 2a–f

Diisopropylamine (1.30 equiv) was dissolved in THF (50 mL) at 0 °C, followed by the addition of *n*-butyllithium (1.10 equiv). The mixture was allowed to stir for 40 min. The temperature was decreased to −78 °C and the azido ester **1** (1.00 equiv) was added. After 30 min of stirring, allyl bromide (1.10 equiv) was added into the reaction mixture. Then, the temperature was allowed to slowly increase to room temperature over 3.5 h before the reaction mixture was diluted with Et_2O (50 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (1×30 mL), dried ($NaSO_4$), and concentrated to give the crude product, which was purified by flash chromatography to afford the azido ester **2**.

5.2.1. Ethyl 2-(2′-azidoethyl)pent-4-enoate (2a). Compound **2a** (1.25 g, 84%) was isolated after chromatography (5% EtOAc/hexanes) as a pale yellow oil. R_f=0.50 (30% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.07 (m, 2H), 4.16 (q, J=7.2 Hz, 2H), 3.32 (m, 2H), 2.56 (m, 1H), 2.63 (m, 1H), 2.41 (m, 1H), 1.93 (m, 1H), 1.75 (m, 1H), 1.27 (t, J=3.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.6, 134.7, 117.4, 60.6, 49.4, 42.3, 36.4, 30.5, 14.3; IR (NaCl) 3000, 2100, 1740; MS (ES^+) m/z 198.2 (M^++H); HRMS calcd for $C_9H_{16}N_3O_2$ (M^++H) 198.1242, found 198.1516.

5.2.2. Ethyl 4-azido-2-benzylbutanoate (2b). Compound **2b** (1.62 g, 79%) was isolated after chromatography (10% EtOAc/hexanes) as a pale yellow oil. R_f=0.50 (30% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (m, 5H), 4.07 (q, J=7.12 Hz, 2H), 3.30 (m, 2H), 2.95 (m, 1H), 2.75 (m, 2H), 1.94 (m, 1H), 1.75 (m, 1H), 1.55 (t, J=7.12 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.7, 138.5, 130.1, 128.9, 128.5, 126.6, 60.6, 49.5, 44.8, 38.5, 30.8, 14.1; IR (NaCl) 3100, 3000, 2100, 1730; MS (ES^+) m/z 248.2 (M^++H); HRMS calcd for $C_{13}H_{18}N_3O_2$ (M^++H) 248.1399, found 248.1682.

5.2.3. Ethyl 2-(3′-azidopropyl)pent-4-enoate (2c). Compound **2c** (0.38 g, 44%) was isolated after chromatography (10% EtOAc/hexanes) as a pale yellow oil. R_f=0.50 (30% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.06 (m, 2H), 4.16 (q, J=7.1 Hz, 2H), 3.29 (t, J=6.5 Hz, 2H), 2.41 (m, 2H), 2.26 (m, 1H), 1.60 (m, 4H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1, 135.1, 117.1, 60.4, 51.2, 44.8, 36.5, 28.7, 26.7, 14.3; IR (NaCl) 2020, 1660; MS (ES^+) m/z 184.1 (M^+−2N+H); HRMS calcd for $C_{10}H_{18}NO_2$ (M^+−2N+H) 184.1338, found 184.1337.

5.2.4. Ethyl 5-azido-2-benzylpentanoate (2d). Compound **2d** (0.69 g, 65%) was isolated after chromatography (10% EtOAc/hexanes) as a pale yellow oil. R_f=0.50 (30% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5H), 4.09 (q, J=7.1 Hz, 2H), 3.27 (t, J=6.6 Hz, 2H), 2.97 (m, 1H), 2.76 (dd, J=6.8, 6.7 Hz, 1H), 2.68 (m, 1H), 1.65 (m, 4H), 1.18 (t, J=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1, 139.0, 128.9, 128.4, 126.4, 60.4, 51.2, 47.2, 38.6, 29.0, 26.7, 14.2; IR (NaCl) 2000, 1680, 1450; MS (ES^+) m/z 262.2 (M^++H); HRMS calcd for $C_{14}H_{20}N_3O_2$ (M^++H) 262.1555, found 262.1553.

5.2.5. Ethyl 2-allyl-6-azidohexanoate (2e). Compound **2e** (0.50 g, 83%) was isolated after chromatography (10% EtOAc/hexanes) as a pale yellow oil. R_f=0.50 (30% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (m,

1H), 4.96 (m, 2H), 4.07 (q, J=4.9 Hz, 2H), 3.19 (t, J=6.8 Hz, 2H), 2.33 (m, 2H), 2.16 (m, 1H), 1.51 (m, 4H), 1.32 (m, 2H), 1.19 (t, J=4.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1, 135.3, 116.7, 60.1, 51.1, 45.0, 36.4, 31.1, 28.7, 34.4, 14.2; IR (NaCl) 2950, 2060, 1710; MS (ES$^+$) m/z 200.2 (M$^+$−2N+3H); HRMS calcd for $C_{11}H_{22}NO_2$ (M$^+$−2N+3H) 200.1650, found 200.1644.

5.2.6. Ethyl 6-azido-2-benzylhexanoate (2f). Compound **2f** (0.80 g, 54%) was isolated after chromatography (20% EtOAc/hexanes) as a pale yellow oil. R_f=0.60 (50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 5H), 4.06 (q, J=7.1 Hz, 2H), 3.17 (t, J=6.8 Hz, 2H), 2.95 (m, 1H), 2.70 (m, 2H), 1.67 (m, 1H), 1.51 (m, 3H), 1.35 (m, 2H), 1.13 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1, 139.3, 128.9, 128.3, 126.3, 60.1, 51.1, 47.4, 38.6, 31.5, 28.7, 24.5, 14.2; IR (NaCl) 2880, 2020, 1700; MS (ES$^+$) m/z 298.2 (M$^+$+Na); HRMS calcd for $C_{15}H_{21}N_3O_2Na$ (M$^+$+Na) 298.1531, found 298.1532.

5.3. General procedure for the synthesis of azido aldehydes 3a–f

DIBAL–H (1.08 equiv) was slowly added to a solution of the azido ester **2** (1.00 equiv) in anhydrous Et_2O (10.0 mL) at −70 °C. The reaction mixture was stirred for 1 h and quenched with MeOH (0.50 mL) followed by the addition of saturated aqueous potassium sodium tartrate solution (10 mL). The reaction mixture was then passed through a thin layer of Celite. After the separation of organic layer, the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (1×30 mL), dried ($NaSO_4$), and concentrated to give the crude product, which was purified by flash chromatography to afford the azido ester **3**.

5.3.1. 2-(2′-Azidoethyl)pent-4-enal (3a). Compound **3a** (0.32 g, 41%) was isolated after chromatography (20% EtOAc/hexanes) as a pale yellow oil. R_f=0.40 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, J=1.5 Hz, 1H), 5.74 (m, 1H), 5.13 (m, 2H), 3.35 (m, 2H), 2.50 (m, 2H), 2.28 (m, 1H), 1.97 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 203.1, 134.1, 118.1, 49.1, 48.3, 32.9, 27.3; IR (NaCl) 2960, 2140, 1730; MS (ES$^+$) m/z 126.1 (M$^+$−2N+H); HRMS calcd for $C_7H_{12}NO$ (M$^+$−2N+H) 126.0919, found 126.0911.

5.3.2. 4-Azido-2-benzylbutanal (3b). Compound **3b** (0.73 g, 59%) was isolated after chromatography (5% EtOAc/hexanes) as a pale yellow oil. R_f=0.35 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, J=1.5 Hz, 1H), 7.27 (m, 5H), 3.32 (m, 2H), 3.06 (dd, J=5.5, 7.0 Hz, 1H), 2.77 (m, 2H), 1.96 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 203.1, 137.9, 128.9, 128.8, 126.8, 50.5, 49.1, 35.1, 27.6; IR (NaCl) 2960, 2120, 1740; MS (ES$^+$) m/z 178.1 (M$^+$−2N+3H); HRMS calcd for $C_{11}H_{16}NO$ (M$^+$−2N+3H) 178.1232, found 178.1227.

5.3.3. 2-(3′-Azidopropyl)pent-4-enal (3c). Compound **3c** (0.25 g, 66%) was isolated as a pale yellow oil. R_f=0.60 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 5.76 (m, 1H), 5.13 (m, 2H), 3.33 (t, J=6.0 Hz, 2H), 2.47 (m, 2H), 2.29 (m, 1H), 1.68 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.0, 134.4, 117.7, 51.3, 50.7, 33.1, 26.3, 25.3; IR (NaCl) 2880, 2010, 1660, 1600; MS (ES$^+$) m/z 140.1 (M$^+$−2N+H); HRMS calcd for $C_8H_{14}NO$ (M$^+$−2N+H) 140.1075, found 140.1078.

5.3.4. 5-Azido-2-benzylpentanal (3d). Compound **3d** (0.54 g, 83%) was isolated as a pale yellow oil. R_f=0.50 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, J=2.2 Hz, 1H), 7.26 (m, 5H), 3.28 (t, J=6.5 Hz, 2H), 3.04 (q, J=7.2, 6.7 Hz, 1H), 2.76 (dd, J=7.2, 6.7 Hz, 1H), 2.68 (m, 1H), 1.65 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 203.9, 138.3, 128.9, 128.7, 126.6, 52.9, 51.3, 35.2, 26.4, 25.5; IR (NaCl) 3000, 2010, 1700, 1650; MS (ES$^+$) m/z 217.1 (M$^+$); HRMS calcd for $C_{12}H_{15}N_3O$ (M$^+$) 217.1215, found 217.1056.

5.3.5. 2-Allyl-6-azidohexanal (3e). Compound **3e** (97 mg, 81%) was isolated as a pale yellow oil. R_f=0.50 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, J=2.2 Hz, 1H), 5.69 (m, 1H), 5.04 (m, 2H), 3.23 (t, J=6.8 Hz, 2H), 2.35 (m, 2H), 2.23 (m, 1H), 1.59 (m, 3H), 1.40 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.3, 134.7, 117.3, 51.1, 50.9, 32.9, 29.0, 27.6, 24.0; IR (NaCl) 2850, 2040, 1680; MS (ES$^+$) m/z 154.1 (M$^+$−2N+H); HRMS calcd for $C_9H_{16}NO$ (M$^+$−2N+H) 154.1232, found 154.1236.

5.3.6. 6-Azido-2-benzylhexanal (3f). Compound **3f** (0.52 g, 78%) was isolated as a pale yellow oil. R_f=0.50 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, J=2.1 Hz, 1H), 7.24 (m, 5H), 3.21 (t, J=6.7 Hz, 2H), 3.00 (dd, J=7.0, 6.9 Hz, 1H), 2.73 (dd, J=7.0, 6.9 Hz, 1H), 2.62 (m, 1H), 1.67 (m, 1H), 1.38 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.1, 138.8, 138.2, 129.3, 129.0, 128.8, 128.6, 128.4, 127.6, 126.8, 126.5, 53.2, 51.1, 35.0, 28.8, 27.9, 24.1; IR (NaCl) 2960, 2020, 1680, 1660; MS (ES$^+$) m/z 204.1 (M$^+$); HRMS calcd for $C_{13}H_{18}NO$ (M$^+$−2N+H) 204.1388, found 204.1389.

5.3.7. 3-Azidononanal (3g). To a solution of NaN_3 (1.46 g, 22.5 mmol) in aqueous acetic acid (21.6 mmol in 2.0 mL of H_2O) was added nonenal (1.20 mL, 7.23 mmol) at 0 °C. After 1 h of consistent stirring, the reaction mixture was diluted with Et_2O (20 mL) before washing with $NaHCO_3$ (3×5 mL) and brine (10 mL). The organic layer was dried ($NaSO_4$) and concentrated to give the crude product, which was purified by flash chromatography (2% EtOAc/hexanes) to afford **3g** (1.14 g, 87%). R_f=0.30 (10% EtOAc/hexanes) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (m, 1H), 3.87 (m, 1H), 2.62 (m, 2H), 1.41 (m, 10H), 0.88 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.9, 57.4, 48.6, 34.9, 32.0, 29.3, 26.2, 22.9, 14.4; IR (NaCl) 2115, 1731; MS (FAB$^+$) m/z 184 (M$^+$+H).

5.4. General procedures for intramolecular Schmidt reactions using $TiCl_4$ and TFA

$TiCl_4$ procedure: The azido aldehyde (1.0 equiv) was activated by $TiCl_4$ (1.3 equiv) in CH_2Cl_2 (2.0 mL) at room temperature. After 17–19 h of stirring, the mixture was quenched with saturated $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were

washed with brine, dried ($NaSO_4$), and concentrated to give crude product, which was purified by chromatography.

TFA procedure: The azido aldehyde was dissolved in TFA (1.0 mL) at room temperature and quenched after 17–19 h of stirring. Workup as described above afforded crude product, which was purified by chromatography.

5.4.1. 3-Allylpyrrolidin-2-one (5a). Compound **5a** (81 mg, 90% with $TiCl_4$ and 57 mg, 63% with TFA) was afforded after chromatography (75% EtOAc/hexanes) as a pale yellow oil. R_f=0.20 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 5.75 (m, 1H), 5.07 (m, 2H), 3.31 (m, 2H), 2.55 (m, 1H), 2.46 (m, 1H), 2.20 (m, 2H), 1.81 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.3, 135.6, 116.8, 40.6, 40.5, 35.0, 26.6; IR (NaCl) 3000, 1710, 1660; MS (ES^+) *m/z* 126.1 (M^++H); HRMS calcd for $C_7H_{12}NO$ (M^++H) 126.0919, found 126.0917.

5.4.2. 3-Benzylpyrrolidin-2-one (5b). Compound **5b** (89 mg, 94% with $TiCl_4$ and 100 mg, 77% with TFA) was afforded after chromatography (70% EtOAc/hexanes) as a pale yellow oil. R_f=0.20 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.30 (m, 5H), 3.23 (m, 3H), 2.65 (m, 2H), 2.09 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.2, 139.6, 129.0, 128.8, 128.5, 126.3, 43.0, 40.5, 36.7, 21.1; IR (NaCl) 3240, 3020, 1660; MS (ES^+) *m/z* 176.1 (M^++H); HRMS calcd for $C_{11}H_{14}NO$ (M^++H) 176.1075, found 176.1071.

5.4.3. 2-Allylpyrrolidine-1-carbaldehyde (4c). Compound **4c** (80 mg, 96% with $TiCl_4$ and 50 mg, 60% with TFA) was isolated as a mixture of rotamers in a 6:4 ratio after chromatography (50% EtOAc/hexanes) as a pale yellow oil. R_f=0.10 (50% EtOAc/hexanes). IR (NaCl) 2900, 1620; MS (ES^+) *m/z* 140.1 (M^++H); HRMS calcd for $C_8H_{14}NO$ (M^++H) 140.1075, found 140.1070. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 5.76 (m, 1H), 5.09 (m, 2H), 3.55 (m, 1H), 3.84 (m, 1H), 3.39 (m, 1H), 2.28 (m, 2H), 1.90 (m, 3H), 1.77 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.1, 134.3, 118.7, 57.1, 46.7, 40.5, 30.2, 23.7. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 5.76 (m, 1H), 5.09 (m, 2H), 3.84 (m, 1H), 3.55 (m, 1H), 3.39 (m, 1H), 2.28 (m, 2H), 1.90 (m, 3H), 1.77 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.0, 133.6, 117.6, 54.7, 43.5, 37.5, 29.5, 22.4.

5.4.4. 2-Benzylpyrrolidine-1-carbaldehyde (4d). Compound **4d** (74 mg, 85% with $TiCl_4$ and 59 mg, 68% with TFA) was isolated as rotamers in a 2:1 ratio after chromatography (50% EtOAc/hexanes) as a pale yellow oil. R_f=0.10 (50% EtOAc/hexanes). IR (NaCl) 2950, 1650, 750, 690; MS (ES^+) *m/z* 190.1 (M^++H); HRMS calcd for $C_{12}H_{16}NO$ (M^++H) 190.1232, found 190.1227. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.22 (m, 5H), 4.02 (m, 1H), 3.52 (m, 1H), 3.40 (m, 1H), 2.74 (m, 2H), 1.85 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.1, 137.5, 129.6, 129.4, 128.8, 128.4, 126.8, 56.5, 46.8, 38.7, 30.3, 22.3; Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.22 (m, 5H), 4.24 (m, 1H), 3.52 (m, 1H), 3.30 (m, 1H), 2.74 (m, 2H), 1.85 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.1, 138.3, 129.6, 129.4, 128.8, 128.4, 126.3, 59.1, 43.4, 42.4, 29.2, 23.5.

5.4.5. 2-Allylpiperidine-1-carbaldehyde (4e). Compound **4e** (35 mg, 41% with $TiCl_4$ and 45 mg, 53% with TFA) was isolated as rotamers in a 1:1 ratio after chromatography (40% EtOAc/hexanes) as a pale yellow oil. R_f=0.15 (50% EtOAc/hexanes). IR (NaCl) 3000, 2860, 1620; MS (ES^+) *m/z* 154.1 (M^++H); HRMS calcd for $C_9H_{16}NO$ (M^++H) 154.1232, found 154.1230. Rotamer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 5.66 (m, 1H), 5.05 (m, 2H), 4.21 (dd, *J*=3.4, 9.6 Hz, 1H), 3.60 (m, 1H), 2.70 (t, *J*=3.0, 10.4 Hz, 1H), 2.52 (m, 1H), 2.27 (m, 1H), 1.69 (m, 5H), 1.39 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.3, 134.9, 118.2, 54.5, 42.5, 34.9, 29.4, 26.3, 19.9. Rotamer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 5.66 (m, 1H), 5.05 (m, 2H), 4.60 (q, *J*=6.4 Hz, 1H), 3.36 (dd, *J*=4.2, 9.2 Hz, 1H), 3.14 (t, *J*=2.8, 10.5 Hz, 1H), 2.41 (m, 1H), 2.27 (m, 1H), 1.69 (m, 5H), 1.39 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.2, 134.1, 117.1, 46.8, 36.3, 34.1, 27.1, 25.0, 19.5.

5.4.6. 2-Benzylpiperidine-1-carbaldehyde (4f). Compound **4f** (43 mg, 49% with $TiCl_4$ and 62 mg, 71% with TFA) was isolated as rotamers in a 3:2 ratio after chromatography (40% EtOAc/hexanes) as a pale yellow oil. R_f=0.20 (50% EtOAc/hexanes). IR (NaCl) 2880, 1620; MS (ES^+) *m/z* 226.1 (M^++Na); HRMS calcd for $C_{13}H_{17}NONa$ (M^++Na) 226.1208, found 226.1204. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.23 (m, 5H), 4.29 (dd, *J*=4.3, 9.2 Hz, 1H), 3.76 (m, 1H), 3.07 (q, *J*=4.3 Hz, 1H), 2.85 (m, 2H), 1.69 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.2, 138.2, 138.0, 129.2, 129.0, 128.8, 126.8, 56.6, 42.7, 37.0, 29.5, 26.4, 20.0. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.23 (m, 5H), 4.81 (q, *J*=7.2 Hz, 1H), 3.43 (dd, *J*=4.9, 8.4 Hz, 1H), 3.28 (t, *J*=2.7, 10.3 Hz, 1H), 2.85 (m, 2H), 1.69 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.2, 138.2, 138.0, 129.2, 129.0, 128.5, 126.4, 48.6, 36.3, 35.7, 26.1, 25.1, 19.5.

5.5. General procedures for intermolecular Schmidt reactions using $TiCl_4$ and TFA

$TiCl_4$ procedure: The aldehyde (1.0 equiv) was activated by $TiCl_4$ (1.3 equiv) in CH_2Cl_2 (2.0 mL) at room temperature, followed by slow addition of alkyl azide (1.1 equiv). After 17–19 h of consistent stirring, the mixture was quenched with saturated $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine, dried ($NaSO_4$), and concentrated to give the crude product, which was purified by flash chromatography.

TFA procedure: The aldehyde was reacted with the alkyl azide in TFA (1.0 mL) at room temperature and quenched after 17–19 h of stirring. Workup as described above gave crude product, which was purified by flash chromatography.

5.5.1. *N*-Benzyl-2-phenylacetamide (6a) and *N*,*N*-dibenzylformamide (7a). Compounds **6a** (40 mg, 21%) and **7a** (20 mg, 10%) were isolated after chromatography (20% EtOAc/hexanes) as pale yellow oils. *Compound* **6a**: R_f=0.35 (50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.90 (s, 1H), 4.43 (d, *J*=5.8 Hz, 2H), 3.64 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.0, 138.2, 134.9, 129.5, 129.1, 128.7, 127.5, 127.4, 127.4,

60.4, 43.8, 43.6; IR (NaCl) 3320, 3100, 1660, 1070; MS (ES^+) *m/z* 226.1 (M^++H); HRMS calcd for $C_{15}H_{16}NO$ (M^++H) 226.1232, found 226.1245. *Compound* **7a**: R_f=0.30 (50% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.31 (m, 10H), 4.44 (s, 2H), 4.29 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.9, 136.0, 135.6, 129.0, 128.7, 128.5, 128.2, 127.7, 127.7, 50.3, 44.7; IR (NaCl) 3080, 2980, 1680, 1210; MS (ES^+) *m/z* 226.1 (M^++H); HRMS calcd for $C_{15}H_{16}NO$ (M^++H) 226.1232, found 226.1245.

5.5.2. *N*-Benzylheptanamide (6b) and *N*-benzyl-*N*-hexylformamide (7b). Compounds **6b** (30 mg, 16%) and **7b** (20 mg, 10%, rotamers in a 5:6 ratio) were isolated after chromatography (30% EtOAc/hexanes) as pale yellow oils. *Compound* **6b**: R_f=0.30 (50% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.88 (s, 1H), 4.44 (d, *J*=5.7 Hz, 2H), 2.22 (t, *J*=7.4 Hz, 2H), 1.66 (t, *J*=7.1 Hz, 2H), 1.32 (m, 6H), 0.896 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1, 138.5, 128.7, 127.8, 127.5, 43.6, 36.8, 31.5, 29.0, 25.8, 22.5, 14.0; IR (NaCl) 3320, 3100, 1700, 1200; MS (ES^+) *m/z* 220.2 (M^++H); HRMS calcd for $C_{14}H_{22}NO$ (M^++H) 220.1701, found 220.1703. *Compound* **7b**: R_f=0.45 (50% EtOAc/hexanes). IR (NaCl) 3000, 2960, 2900, 1680; MS (ES^+) *m/z* 220.2 (M^++H); HRMS calcd for $C_{14}H_{22}NO$ (M^++H) 220.1701, found 220.1694. Rotamer 1: ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.31 (m, 5H), 4.41 (s, 2H), 3.24 (t, *J*=7.5 Hz, 2H), 1.50 (m, 2H), 1.27 (m, 6H), 0.89 (q, *J*=6.7 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.9, 136.3, 128.9, 128.6, 128.2, 128.1, 127.5, 51.2, 45.2, 31.5, 28.1, 26.8, 26.1, 14.0. Rotamer 2: ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.31 (m, 5H), 4.55 (s, 2H), 3.14 (t, *J*=7.1 Hz, 2H), 1.50 (m, 2H), 1.27 (m, 6H), 0.89 (q, *J*=6.7 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.8, 136.3, 128.9, 128.6, 128.2, 128.1, 127.5, 46.8, 42.0, 31.3, 28.1, 26.5, 22.5, 14.0.

5.5.3. *N*-Benzyl-2-phenylpropanamide (6c) and *N*-benzyl-*N*-(1′-phenylethyl)-formamide (7c). Compounds **6c**[15] and **7c** (86 mg, 44%) were isolated as inseparable product in mixture a 1:3 ratio after chromatography (20% EtOAc/hexanes) as pale yellow oils. *Compound* **7c**: exists as an inseparable mixture in a 1:3 ratio of rotamers. R_f=0.15 (25% EtOAc/hexanes). IR (NaCl) 3320, 3100, 1660; MS (ES^+) *m/z* 240.1 (M^++Na); HRMS calcd for $C_{16}H_{17}NONa$ (M^++Na) 262.1208, found 262.1204. Major rotamer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.15 (m, 10H), 4.40 (m, 2H), 4.07 (m, 1H), 1.54 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.6, 141.4, 139.7, 138.4, 137.7, 128.9, 128.6, 128.5, 128.0, 127.8, 127.7, 127.3, 126.8, 56.7, 48.3, 20.2. Minor rotamer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J*=10.6 Hz, 1H), 7.15 (m, 10H), 4.40 (m, 2H), 3.61 (m, 1H), 1.54 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.5, 140.4, 139.7, 138.4, 137.5, 128.7, 128.6, 128.5, 128.0, 127.8, 127.7, 127.3, 126.8, 50.6, 45.3, 17.0.

5.5.4. *N*-Phenethyl-2-phenylacetamide (6d) and *N*-benzyl-*N*-phenethyl-formamide (7d). Compounds **6d** (40 mg, 22% with $TiCl_4$ and 28 mg, 16% with TFA) and **7d** (33 mg, 19% with $TiCl_4$ and 28 mg, 16% with TFA, rotamers in a 1:1 ratio) were isolated after chromatography (30% EtOAc/hexanes) as pale yellow oils. *Compound* **6d**: R_f=0.10 (25% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 8H), 7.01 (m, 2H), 5.37 (s, 1H), 3.52 (s, 2H), 3.44 (q, *J*=6.8 Hz, 2H), 2.71 (t, *J*=6.8 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.9, 138.7, 134.8, 129.5, 129.0, 128.7, 128.6, 127.3, 126.4, 43.9, 40.7, 35.5; IR (NaCl) 3260, 3000, 1620; MS (ES^+) *m/z* 240.1 (M^++H); HRMS calcd for $C_{16}H_{18}NO$ (M^++H) 240.1388, found 240.1380. *Compound* **7d**: R_f=0.15 (25% EtOAc/hexanes). IR (NaCl) 3000, 1650; MS (ES^+) *m/z* 240.1 (M^++H); HRMS calcd for $C_{16}H_{18}NO$ (M^++H) 240.1388, found 240.1377. Rotamer 1: ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.18 (m, 10H), 4.55 (s, 2H), 3.44 (t, *J*=7.4 Hz, 2H), 2.78 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.9, 138.8, 136.4, 129.9, 129.2, 128.9, 128.7, 128.3, 127.7, 126.9, 126.5, 51.9, 45.5, 35.1. Rotamer 2: ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.18 (m, 10H), 4.22 (s, 2H), 3.37 (t, *J*=7.0 Hz, 2H), 2.78 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.8, 137.8, 136.1, 129.4, 129.1, 128.8, 128.6, 128.1, 127.6, 126.9, 126.5, 48.4, 43.9, 33.5.

5.5.5. *N*-Phenethylheptanamide (6e) and *N*-hexyl-*N*-phenethylformamide (7e). Compounds **6e** (77 mg, 45% with $TiCl_4$ and 16 mg, 9% with TFA) and **7e** (68 mg, 39% with $TiCl_4$ and 16 mg, 9% with TFA, rotamers in a 5:4 ratio) were isolated after chromatography (20% EtOAc/hexanes) as pale yellow oils. *Compound* **6e**: R_f=0.10 (25% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 5.74 (s, 1H), 3.52 (m, 2H), 2.82 (t, *J*=7.0 Hz, 2H), 2.13 (t, *J*=7.4 Hz, 2H), 1.60 (m, 2H), 1.31 (m, 6H), 0.89 (t, *J*=6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.3, 139.0, 128.8, 128.6, 126.5, 40.5, 36.8, 35.7, 31.6, 29.0, 25.7, 22.5, 14.2, 14.0; IR (NaCl) 3350, 2880, 1620; MS (ES^+) *m/z* 234.2 (M^++H); HRMS calcd for $C_{15}H_{24}NO$ (M^++H) 234.1858, found 234.1843. *Compound* **7e**: R_f=0.20 (25% EtOAc/hexanes). IR (NaCl) 2880, 1650, 1620; MS (ES^+) *m/z* 234.2 (M^++H); HRMS calcd for $C_{15}H_{24}NO$ (M^++H) 234.1858, found 234.1847. Major rotamer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.24 (m, 5H), 3.53 (t, *J*=7.6 Hz, 2H), 3.11 (t, *J*=7.2 Hz, 2H), 2.86 (m, 2H), 1.50 (m, 2H), 1.33 (m, 6H), 0.91 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.9, 138.8, 137.8, 128.8, 128.7, 128.5, 126.8, 49.1, 44.2, 35.5, 31.5, 28.6, 26.6, 22.6, 14.0. Minor rotamer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.24 (m, 5H), 3.46 (t, *J*=7.2 Hz, 2H), 3.34 (t, *J*=7.6 Hz, 2H), 2.86 (m, 2H), 1.50 (m, 2H), 1.33 (m, 6H), 0.91 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.8, 138.8, 137.8, 128.8, 128.6, 128.5, 126.5, 48.0, 42.4, 33.7, 31.3, 27.3, 26.1, 22.5, 14.0.

5.5.6. *N*-Phenethyl-2-phenylpropanamide (6f) and *N*-phenethyl-*N*-(1′-phenylethyl)-formamide (7f). Compounds **6f** (38 mg, 20% with $TiCl_4$ and 24 mg, 13% with TFA) and **7f** (57 mg, 30% with $TiCl_4$ and 9 mg, 5% with TFA, rotamers in a 2:1 ratio) were isolated as pale yellow oil after chromatography (20% EtOAc/hexanes). *Compound* **6f**: R_f=0.15 (25% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 8H), 6.99 (d, *J*=6.3 Hz, 2H), 5.39 (s, 1H), 3.48 (m, 2H), 3.38 (m, 1H), 2.69 (t, *J*=1.6, 5.1 Hz, 2H), 1.49 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1, 141.3, 138.8, 128.9, 128.7, 128.5, 127.7, 127.2, 126.4, 47.1, 40.7, 35.5, 18.3; IR (NaCl) 3320, 3000, 1650, 1550; MS (ES^+) *m/z* 254.1 (M^++H); HRMS calcd for $C_{17}H_{20}NO$ (M^++H) 254.1545, found 254.1533. *Compound* **7f**: R_f=0.10 (25% EtOAc/hexanes). IR (NaCl) 3000,

2860, 1620; MS (ES$^+$) *m/z* 254.2 (M$^+$+H); HRMS calcd for $C_{17}H_{20}NO$ (M$^+$+H) 254.1545, found 254.1537. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.25 (m, 10H), 4.67 (q, *J*=7.0 Hz, 1H), 3.23 (m, 2H), 2.79 (m, 1H), 2.56 (m, 1H), 1.59 (dd, *J*=2.2, 5.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.1, 141.3, 140.1, 138.9, 128.9, 128.7, 128.5, 128.3, 128.0, 127.8, 127.2, 126.7, 126.4, 51.1, 49.8, 44.2, 34.5, 16.8. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.25 (m, 10H), 5.79 (q, *J*=7.2 Hz, 1H), 3.36 (m, 2H), 2.69 (t, *J*=1.3, 5.3 Hz, 1H), 2.42 (m, 1H), 1.49 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.5, 140.2, 139.1, 138.0, 128.8, 128.7, 128.5, 128.3, 128.0, 127.8, 127.2, 126.7, 126.4, 51.1, 46.0, 37.9, 19.3, 16.8.

5.5.7. *N*-Hexyl-2-phenylacetamide (6g) and *N*-benzyl-*N*-hexylformamide (7g). Compounds **6g** (51 mg, 29% with $TiCl_4$ and 32 mg, 19% with TFA) and **7g** (45 mg, 26% with $TiCl_4$ and 22 mg, 13% with TFA rotamers in a 1:1 ratio) were isolated after chromatography (20–25% EtOAc/hexanes) as pale yellow oils. *Compound* **6g**: R_f=0.50 (50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.39 (s, 1H), 3.58 (s, 2H), 3.21 (q, *J*=6.9 Hz, 2H), 1.42 (t, *J*=7.0 Hz, 2H), 1.25 (m, 6H), 0.87 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.8, 135.1, 129.5, 129.0, 127.3, 43.9, 39.7, 31.4, 29.4, 26.4, 22.5, 14.0; IR (NaCl) 3300, 2980, 1640; MS (ES$^+$) *m/z* 220.2 (M$^+$+H); HRMS calcd for $C_{14}H_{22}NO$ (M$^+$+H) 220.1701, found 220.1692.

5.5.8. Hexylheptanamide (6h) and *N*,*N*-dihexylformamide (7h). Compounds **6h** (68 mg, 37% with $TiCl_4$ and 51 mg, 28% with TFA) and **7h** (48 mg, 26% with $TiCl_4$ and 22 mg, 12% with TFA) were isolated after chromatography (20% EtOAc/hexanes) as pale yellow oils. *Compound* **6h**: R_f=0.50 (50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H), 3.22 (q, *J*=6.9 Hz, 2H), 2.15 (t, *J*=7.5 Hz, 2H), 1.60 (q, *J*=6.5 Hz, 2H), 1.48 (q, *J*=6.2 Hz, 2H), 1.32 (s, 12H), 0.88 (t, *J*=5.0 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1, 39.5, 36.9, 31.6, 31.5, 29.6, 29.0, 26.6, 25.8, 22.5, 22.5, 14.0, 14.0; IR (NaCl) 3300, 2960, 1650; MS (ES$^+$) *m/z* 214.2 (M$^+$+H); HRMS calcd for $C_{13}H_{28}NO$ (M$^+$+H) 214.2171, found 214.2161. *Compound* **7h**: R_f=0.25 (50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 3.28 (t, *J*=6.4 Hz, 2H), 3.18 (t, *J*=6.9 Hz, 2H), 1.52 (s, 4H), 1.29 (s, 12H), 0.89 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.7, 47.4, 42.1, 31.5, 31.4, 28.6, 27.3, 26.6, 26.1, 22.6, 22.5, 14.0, 14.0; IR (NaCl) 2980, 1660; MS (ES$^+$) *m/z* 214.2 (M$^+$+H); HRMS calcd for $C_{13}H_{28}NO$ (M$^+$+H) 214.2171, found 214.2147.

5.5.9. *N*-Hexyl-2-phenylpropanamide (6i) and *N*-hexyl-*N*-(1-phenylethyl)-formamide (7i). Compounds **6i** (70 mg, 35%) and **7i** (55 mg, 27%, rotamers in a 2:1 ratio) were isolated as pale yellow oils after chromatography (20% EtOAc/hexanes). *Compound* **6i**: R_f=0.35 (25% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.51 (s, 1H), 3.56 (q, *J*=7.2 Hz, 1H), 3.18 (m, 2H), 1.53 (d, *J*=7.2 Hz, 3H), 1.40 (m, 2H), 1.24 (m, 6H), 0.86 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1, 141.6, 128.8, 128.4, 127.9, 127.5, 127.2, 126.8, 47.1, 39.6, 31.4, 29.4, 26.4, 22.5, 18.5, 14.0; IR (NaCl) 3500, 3300, 1650; MS (ES$^+$) *m/z* 234.2 (M$^+$+H); HRMS calcd for $C_{15}H_{24}NO$ (M$^+$+H) 234.1858, found 234.1847. *Compound* **7i**: R_f=0.30 (25% EtOAc/hexanes). IR (NaCl) 3500, 2980, 1670; MS (ES$^+$) *m/z* 234.2 (M$^+$+H); HRMS calcd for $C_{15}H_{24}NO$ (M$^+$+H) 234.1858, found 234.1847. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.30 (m, 5H), 4.72 (q, *J*=7.1 Hz, 1H), 3.10 (t, *J*=2.0, 5.0 Hz, 2H), 1.67 (d, *J*=7.1 Hz, 3H), 1.42 (m, 2H), 1.20 (m, 6H), 0.85 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.2, 140.5, 128.8, 128.4, 127.6, 127.5, 126.8, 56.8, 44.6, 31.4, 29.4, 26.8, 22.5, 19.6, 14.0. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.30 (m, 5H), 5.73 (q, *J*=7.2 Hz, 1H), 3.00 (m, 2H), 1.57 (d, *J*=7.2 Hz, 3H), 1.42 (m, 2H), 1.20 (m, 6H), 0.85 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.4, 140.2, 128.7, 127.8, 127.5, 127.2, 126.8, 49.8, 44.6, 31.2, 28.3, 26.4, 22.4, 16.8, 13.9.

Compounds **6i** and **7i** were also obtained using TFA (62 mg, 31%). The compounds were not separated in this experiment (**6i**/**7i**=1:3 by NMR).

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