JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2019, 84, 2012−2021
Article
pubs.acs.org/joc

# Schmidt Reaction of ω-Azido Valeryl Chlorides Followed by Intermolecular Trapping of the Rearrangement Ions: Synthesis of Assoanine and Related Pyrrolophenanthridine Alkaloids

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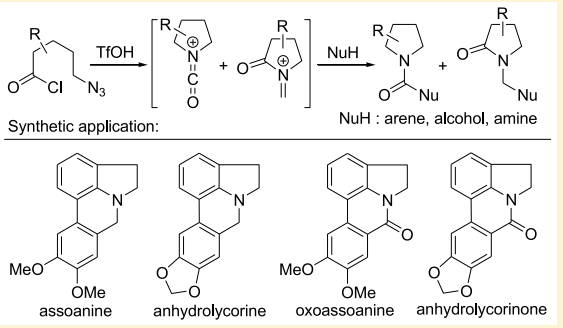
Supporting Information

**ABSTRACT:** The Schmidt reaction of ω-azido valeryl chlorides in the presence of an additional nucleophile was explored. The arenes, alcohols, and amines were demonstrated as the intermolecular trapping reagents for isocyanate ion and *N*-acyliminium ion from the Schmidt rearrangement, affording the corresponding products with moderate to excellent yields. Two 2-oxoindoles from the reaction were successfully converted into four natural alkaloids, namely, assoanine, anhydrolycorine, oxoassoanine, and anhydrolycorinone.




## INTRODUCTION

The Schmidt−Aubé reaction is involved with the rearrangement of alkyl azides with ketones or aldehydes (Scheme 1), and it has been used as a powerful strategy for synthesis of various *N*-heterocycles.[1,2] The analogue reaction of alkyl azides with acyl chlorides was reported in our group, and it proceeded through the *N*-diazonium ion amide intermediate, which was different from the Schmidt−Aubé reaction.[3] Rearrangement of the intermediate would produce isocyanate ion and *N*-acyliminium ion as the primary products. Therefore, a nucleophile was preinstalled in the ω-azido acyl chloride for intramolecular capture of the ions, resulting in electroneutral products for isolation. In the meantime, Chaturvedi's group reported[4] that the ω-azido acyl chlorides and arenes reacted through an intermolecular Friedel−Crafts acylation followed by an intramolecular Schmidt−Aubé reaction, producing *N*-aryl lactams with good to excellent yields (Scheme 1). The similar hypothesis for the process had been excluded with the reaction of aryl substituted ω-azido acyl chlorides in our previous research,[3a] where the **intramolecular** Friedel−Crafts acylation failed in competition with the intramolecular Schmidt reaction of alkyl azides with acyl chlorides. It made it confusing that the **intermolecular** Friedel−Crafts acylation was preferred over the intramolecular Schmidt reaction in Chaturvedi's research, where only catalytic Lewis acid was employed. To clarify it, we reported here the Schmidt reaction of ω-azido valeryl chlorides followed by trapping the rearrangement ions with several different nucleophiles (arenes, alcohols, and amines) and application of the conversion in synthesis of assoanine and related alkaloids.

## RESULTS AND DISCUSSION

The reaction of ω-azido valeryl chloride with benzene was selected for the initial exploration, and the ω-azido valeryl chloride was *in situ* prepared from 5-azidopentanoic acid **1a**[5] with oxalyl chloride (Table 1). According to our previous research, generation of isocyanate ion **I** and *N*-acyliminium ion **II** would be efficient under acidic conditions. It might be very reasonable to apply the nucleophile after the ω-azido valeryl chloride was treated with the acid promoter. By doing this, the competitive Friedel−Crafts acylation of the acyl chloride with benzene could be avoided. In consideration of the potential chelation between the nitrogen-containing product and the acid promoter, generally the reaction was examined with 2.0 equiv of the promoter, and excessive benzene was used to ensure that the trapping reaction could be efficient.

Several acid promoters including $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, $AlCl_3$, $EtAlCl_2$, TFA, and TfOH were examined. In screening the acid promoters, we found that in most cases the ω-azido acyl chloride was consumed in 15 min when the acid promoter was applied, so benzene was added after that. The capture process with 5.0 equiv of benzene seemed to be very slow, and all of the trapping reactions were kept for 46 h (entries 1−7, Table 1). TfOH was shown as a good candidate, where the benzamide **3aa** and lactam **4aa** were produced in a ratio of about 1.3/1.0 with a combined yield of 78% (entry 7, Table 1). Both the **3aa** and **4aa** were known compounds, and the NMR data were identified with those reported in the literature.[6,7] If the capture process was shortened to 22 h, formation of **3aa** and **4aa** was slightly reduced (entry 8 vs entry 7, Table 1). The

**Received:** November 26, 2018
**Published:** January 14, 2019







DOI: 10.1021/acs.joc.8b03018
J. Org. Chem. 2019, 84, 2012−2021

**Scheme 1. Reaction of ω-Azido Acid Chloride with an Arene**

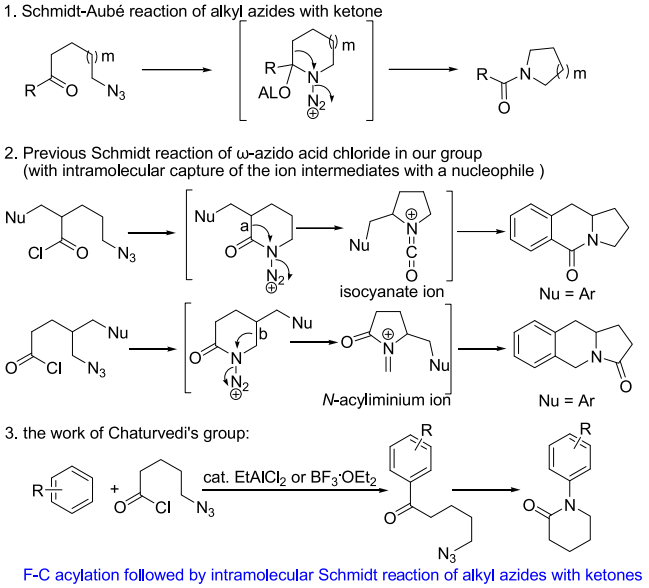
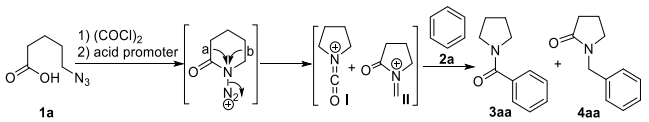



**Table 1. Optimization of the Reaction of 5-Azidopentanoic Acid 1a and Benzene 2a**[a]




| entry | acid promoter | reaction time[b] (h) | 3aa/4aa | combined yield[c] (%) |
|---|---|---|---|---|
| 1 | $TiCl_4$ | 46 | -/37 | 37 |
| 2 | $SnCl_4$ | 46 | 6/19 | 25 |
| 3 | $BF_3{\cdot}OEt_2$ | 46 | -/- | 0 |
| 4 | $AlCl_3$ | 46 | -/24 | 24 |
| 5 | $EtAlCl_2$ | 46 | -/- | 0 |
| 6 | TFA | 46 | -/- | 0 |
| 7 | TfOH | 46 | 44/34 | 78 |
| 8 | TfOH | 22 | 36/26 | 62 |
| 9 | TfOH[d] | 46 | 34/28 | 62 |
| 10 | TfOH[e] | 46 | 43/34 | 77 |
| 11 | TfOH[f] | 46 | 51/35 | 86 |
| 12 | TfOH[e,f] | 46 | 53/32 | 85 |

[a]Treatment of **1a** (1.0 mmol) in DCM (1.5 mL) with $(COCl)_2$ (1.4 mmol) at 30 °C for 1.5 h followed with the acid (2.0 equiv) promoter at 0 °C and then benzene **2a** (5.0 mmol) was applied and kept the mixture at refluxing for capture reaction. [b]Time for the capture process. [c]Isolated combined yield. [d]Benzene (3.0 equiv) employed. [e]TfOH (4.0 equiv) employed. [f]Benzene was applied before TfOH.

conversion was dropped if the benzene was cut down (entry 9, Table 1). Even if more TfOH was employed, the yields for **3aa** and **4aa** were not improved (entry 10, Table 1). To our great surprise, the reaction could be a bit more efficient if the benzene was employed before TfOH (entries 11 and 12, Table 1), in which the benzamide **3aa** and lactam **4aa** were isolated in 51 and 35% yield from the reaction promoted by 2.0 equiv of TfOH for 46 h. With these two cases, we did not observe any aromatic ketone from the competitive Friedel−Crafts acylation.

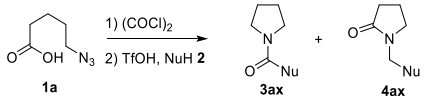
After demonstrating the process, a series of nucleophiles **2** including arenes, alcohols, and amines were examined with the reaction of 5-azidopentanoic acid **1a** (Table 2). Three arenes were further explored with **1a** using the conditions of entry 11 in Table 1. When the *p*-xylene **2b** was used, aryl amide **3ab** and lactam **4ab** were produced in a ratio of 35/38 with the combined yield of 73% (entry 1, Table 2). However, the trapping reaction with 1,4-dichlorobenzene **2c** gave lactam **4ac** as a sole product with 38% yield, indicating only the *N*-acyliminium ion is captured (entry 2, Table 2), where the isocyanate ion might be hydrolyzed into pyrrolidine and lost in the workup procedure. The reaction with naphthalene **2d** was successful, and the 1-naphthyl amide **3ad** and lactam **4ad** were observed with a combined yield of 67% (entry 3, Table 2). Further, the oxygen nucleophiles and nitrogen nucleophiles were employed with the rearrangement of **1a** (entries 4−7, Table 2), where the TfOH was applied before these nucleophiles to avoid the reaction of the acyl chloride with alcohols and amines. The reaction of **1a** and ethanol **2e** afforded the ethyl carbamate **3ae** in a yield of 58%, and in the meantime, 2-pyrrolidinone **4ae** was isolated with a yield of 15%. 1-Hexanol **2f** was also employed for trapping the reaction of **1a**, and the carbamate **3af** and 2-pyrrolidinone **4af** were isolated with 37 and 36% yields, respectively. Only the carbamides **3ag** and **3ah** could be isolated when the nitrogen nucleophiles **2g** and **2h** were used as the nucleophiles, and they were both derived from the capture of isocyanate ion.

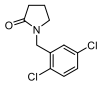
Then, the 5-azido-2-ethylpentanoic acid **1b** and 5-azido-4-ethylpentanoic acid **1c** were investigated (Table 3). 1,2-Migration of the methine carbon would be preferred over the methylene carbon;[3a,b] therefore, an isocyanate ion would be expected as the major one from the Schmidt reaction of **1b**. The inseparable benzamide **3ba** and lactam **4ba** in a ratio of 6/1 were obtained with 72% yield when the benzene **2a** was used as the capture nucleophile for the Schmidt reaction of **1b** (entry 1, Table 3). Only the carbamate **3bf** from isocyanate ion could be separated if the 1-hexanol **2f** was applied with the reaction of **1b** (entry 2, Table 3), and similar results were observed with butanamine **2g** and piperidine **2h** (entries 3 and 4, Table 3), which indicated that the trapping of *N*-acyliminium ion with oxygen nucleophiles and nitrogen nucleophiles was a bit difficult or the corresponding products were unstable under the conditions. By contrast, the *N*-acyliminium ion intermediate would be mainly participated from the reaction of **1c**, and it could be quenched by benzene for 46 h with 82% yield (entry 5, Table 3). The capture of the major *N*-acyliminium ion and the trace isocyanate ion from the reaction of **1c** could be both achieved with the *p*-xylene **2b**, where the aryl amide **3cb** and lactam **4cb** were afforded in a combined yield of 79% (entry 6, Table 3). The trapping reaction of **1c** with 1,4-dichlorobenzene **2c** gave amide **4cc** with only moderate yield (entry 7, Table 3).

Schmidt reaction of the 2-(2-(azidomethyl)phenyl)acetic acid **1d**[8] was also explored (Scheme 2). The TfOH-promoted reaction of **1d** was quenched with benzene at refluxing dichloromethane, and the 1-benzyl-2-oxoindole **4da** was obtained with 96% yield, indicating the exclusive migration of aryl group in the process of Schmidt reaction. Then, the 1,2-


DOI: 10.1021/acs.joc.8b03018
J. Org. Chem. 2019, 84, 2012−2021

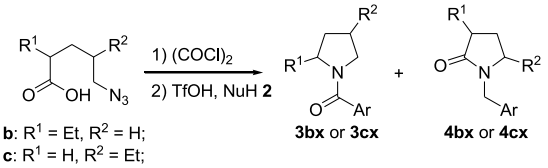
**Table 2. Schmidt Reaction of 1a Followed by Trapping the Rearrangement Ions with Nucleophiles**[a]




| entry | 2 | Time (h)[b] | 3 and 4 | yield (3/4)[c] |
|---|---|---|---|---|
| 1 |  **2b** | 46 |  **3ab**  **4ab** | 73% (35/38) |
| 2 |  **2c** | 46 |  **4ac** | 38% (-/38) |
| 3 |  **2d** | 46 |  **3ad**  **4ad** | 67% (27/40) |
| 4[d] |  **2e** | 4 |  **3ae**  **4ae** | 73% (58/15) |
| 5[d] |  **2f** | 22 |  **3af**  **4af** | 73% (37/36) |
| 6[d] |  **2g** | 4 |  **3ag** | 58% (58/-) |
| 7[d] |  **2h** | 4 |  **3ah** | 59% (59/-) |

[a]Treatment of **1a** (1.0 mmol) in DCM (1.5 mL) with $(COCl)_2$ (1.4 mmol) at 30 °C for 1.5 h followed with TfOH (2.0 mmoL) at 0 °C and then nucleophile **2** (5.0 mmol) was applied and kept the mixture at refluxing for capture reaction. [b]Time for the capture process. [c]Isolated combined yield and ratio of **3** and **4**. [d]TfOH (4.0 equiv) employed and the capture reaction at room temperature.

**Table 3. Schmidt Reaction of 1b and 1c Followed by Trapping the Rearrangement Ions with Nucleophiles**[a]




| entry | 1 | 2 | Time (h)[b] | 3 and 4 | Yield (3/4)[c] |
|---|---|---|---|---|---|
| 1 | | **2a** | 46 |  **3ba**  **4ba** | 72 (6:1) |
| 2[d] |  **1b** | **2f** | 22 |  **3bf** | 62 (62/-) |
| 3[d] | | **2g** | 4 |  **3bg** | 75 (75/-) |
| 4[d] | | **2h** | 4 |  **3bh** | 56 (56/-) |
| 5 | | **2a** | 46 |  **4ca** | 82 (-/82) |
| 6 |  **1c** | **2b** | 46 |  **3cb**  **4cb** | 79 (1:5) |
| 7 | | **2c** | 46 |  **4cc** | 35 (-/35) |

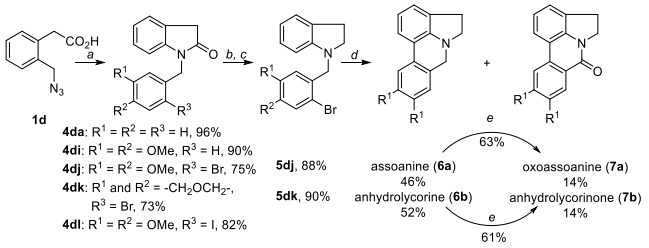
[a]Treatment of **1b** or **1c** (1.0 mmol) in DCM (1.5 mL) with $(COCl)_2$ (1.4 mmol) at 30 °C for 1.5 h followed with TfOH (2.0 mmol) at 0 °C and then the corresponding nucleophile **2** (5.0 mmol) was applied and kept the mixture at refluxing for capture reaction. [b]Time for the capture process. [c]Isolated combined yield and ratio of **3** and **4**. [d]TfOH (4.0 equiv) employed and the capture reaction at room temperature.

dimethoxybenzene **2i**, 4-bromo-1,2-dimethoxybenzene **2j**, 5-bromobenzo[*d*][1,3]dioxole **2k**, and 4-iodo-1,2-dimethoxybenzene **2l** were employed for trapping the promised *N*-acyliminium ion, and all gave the corresponding 2-oxoindoles with good to excellent yields.

To demonstrate the synthetic utility, the 2-oxoindoles **4dj** and **4dk** were efficiently reduced by 9-BBN,[9] and the crude reaction mixtures were further treated with $NaBH_3CN$,[10] affording the indolines **5dj** and **5dk** with 88 and 90% yields, respectively. Then, Harayama's procedure[11] was applied for the biaryl coupling reaction of the indoline **5dj**, and it gave the pyrrolophenanthridine alkaloid assoanine **6a**[11,12] in 46% yield and oxoassoanine **7a**[13] in 14% yield. Similarly, the Pd-catalyzed coupling of **5dk** furnished the anhydrolycorine **6b**[14] in 52% yield and anhydrolycorinone **7b**[15] in 14% yield. Furthermore, assoanine **6a** and anhydrolycorine **6b** could be oxidized with


DOI: 10.1021/acs.joc.8b03018
J. Org. Chem. 2019, 84, 2012−2021

**Scheme 2. Schmidt Reaction of 1d and Synthesis of Assoanine and Related Alkaloids**[a]




[a]Reaction conditions: (a) $(COCl)_2$, then **2**, TfOH, $CH_2Cl_2$; (b) 9-BBN, THF; (c) $NaBH_3CN$, AcOH; (d) $Pd(OAc)_2$, $PCy_3$, $K_2CO_3$, DMF; (e) $KMnO_4$, NaOH, $CH_2Cl_2$.

$KMnO_4$ into oxoassoanine **7a** in 63% yield and anhydrolycorinone **7b** in 61% yield.[14b]

In summary, the Schmidt reaction of several $\omega$-azido valeryl chlorides was well demonstrated, and the intermolecular capture of isocyanate ion and *N*-acyliminium ion from the rearrangement with variable arenes, alcohols, and amines was explored. Generally, the isocyanate ion could be efficiently captured with oxygen nucleophiles and nitrogen nucleophiles, and the arenes were excellent nucleophiles for trapping the *N*-acyliminium ion. Two lactam products were readily converted into four alkaloids, and they were assoanine, anhydrolycorine, oxoassoanine, and anhydrolycorinone, respectitively. The conversion might be very useful in synthesis of natural products, and further application was explored in the laboratory.

## EXPERIMENTAL SECTION

All reagents were purchased from Titan, Acros, Sigma-Aldrich, Alfa-Aesar, Aladdin, or Adamas, and they were used as received. All solvents were distilled using the classic method before use. The reactions were monitored by thin layer chromatography (TLC) on 3.0 cm × 10 cm, 200−250 $\mu$m analytical plates coated with silica gel 60 F254, and the plates were purchased from Qingdao Haiyang Chemical Co. Ltd. The thin layer chromatography plates were visualized by exposure to ultraviolet light (UV, 254 nm) or phosphomolybdic acid. Purification of the synthetic compounds by flash column chromatography employed neutral silica gel (200−300 mesh or 300−400 mesh), which was purchased from Qingdao Haiyang Chemical Co. Ltd. The NMR spectra were recorded on a Bruker 400 MHz spectrometer, and tetramethylsilane ($\delta$ = 0 and $\delta$ = 7.26) was used as an internal standard for $^1$H NMR (400 MHz) and $CDCl_3$ ($\delta$ = 77.16) for $^{13}C\{^1H\}$ NMR (100 MHz).

**$^{13}C\{^1H\}$ NMR Was Performed with an APT Technique [Methyl and Methine Were Assigned *down*; Methylene and Quaternary Carbon Were Assigned *up*].** The IR spectra were recorded on a PerkinElmer spectrometer with a potassium bromide crystal optic rectangle. High-resolution mass spectra (HRMS) were measured on a LTQ Orbitrap XL Domain 35A (Thermo Fisher) spectrometer, and electrospray ionization (ESI) was used as the ion source. All alkylation reactions and the Schmidt reactions were carried out in dry reaction vessels or flasks under a positive pressure of nitrogen or argon.

*5-Azidopentanoic Acid (**1a**).* To a stirred solution of ethyl 5-bromopentanoate **8a** (6.27 g, 30.0 mmol) in the combined solvent (MeOH/$H_2O$ = 1/1, 40 mL) was added $NaN_3$ (2.46 g, 37.8 mmol), and then, the mixture was heated to 75 °C for 5.5 h. The reaction mixture was extracted by $CH_2Cl_2$ (40 mL × 3), and the combined organic phase was washed with water (20 mL × 3), dried over anhydrous $Na_2SO_4$, and concentrated to afford the ethyl 5-azidopentanoate **9a** as a colorless oil (5.08 g, 98% yield from **8a**). **9a**: $R_f$ = 0.67 (EtOAc/PE = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.13 (q, $J$ = 7.2 Hz, 2 H), 3.29 (t, $J$ = 6.4 Hz, 2 H), 2.34 (t, $J$ = 7.2 Hz, 2 H), 1.61−1.73 (m, 4 H), 1.26 (t, $J$ = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 173.0, 60.3, 51.0, 33.6, 28.2, 22.0, $\delta$ (down) 14.1. To a stirred solution of the above ethyl 5-azidopentanoate **9a** (5.14 g, 30.0 mmol) in the combined solvent (THF/$H_2O$ = 1/1, 200 mL) was added LiOH·$H_2O$ (12.59 g, 300.0 mmol), and the mixture was heated to 80 °C for 24 h. Then, the reaction mixture was cooled to room temperature and treated with 1 N HCl for adjusting the mixture to pH < 3. The mixture was extracted by EtOAc (40 mL × 3), washed with brine (10 mL × 3), dried over $Na_2SO_4$, and concentrated, and then, the residue was purified by flash column chromatography to afford the 5-azidopentanoic acid **1a** as a light yellow oil (4.18 g, 96% yield from **9a**). **1a**: known compound,[16] $R_f$ = 0.57 (EtOAc/PE = 1/5); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.31 (t, $J$ = 6.4 Hz, 2 H), 2.41 (t, $J$ = 7.2 Hz, 2 H), 1.65−1.77 (m, 4 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 179.8, 51.1, 33.5, 28.3, 21.9; IR (film) 2943, 2099, 1709, 1277 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_5H_9N_3O_2Na$ 166.0587, found 166.0588.

*Ethyl 5-Bromo-2-ethylpentanoate and Ethyl 5-Iodide-2-ethylpentanoate (**8b**).* To a stirred solution of *N*,*N*-diisopropylamine (2.64 g, 26.0 mmol) in dry THF (60 mL) at 0 °C was added a solution of *n*-BuLi (15.0 mL, 1.6 M in hexane, 24.0 mmol). The reaction mixture was kept at 0 °C for 15 min, and then, it was cooled to −78 °C for 30 min. A solution of ethyl 5-bromopentanoate **8a** (5.02 g, 24 mmol) in THF (10 mL) was added dropwise into the mixture. The reaction mixture was kept at −78 °C for 45 min, and then, a solution of iodoethane **10** (3.18 g, 20.0 mmol) in THF (10 mL) was added dropwise. The mixture was slowly warmed to room temperature and kept stirring for overnight; then, it was quenched with saturated $NH_4Cl$ (60 mL), extracted with EtOAc (40 mL × 3), washed with brine (20 mL × 3), dried over anhydrous $Na_2SO_4$, and concentrated; then, the residue was purified by flash column chromatography to afford a mixture of ethyl 5-bromo-2-ethylpentanoate and ethyl 5-iodide-2-ethylpentanoate **8b** as a colorless oil (3.26 g, 61% yield from **8a**). Mixture of **8b**: $R_f$ = 0.56 (EtOAc/PE = 1/3); $^1$H NMR ($CDCl_3$, 400 MHz) (iodide/bromide = about 1/2) $\delta$ 4.14 (q, $J$ = 7.2 Hz, 2 H for bromide and iodide), 3.38−3.42 (m, 2 H for bromide), 3.16−3.19 (m, 2 H for iodide), 2.26−2.30 (m, 1 H for bromide and iodide), 1.51−1.87 (m, 6 H for bromide and iodide), 1.26 (t, $J$ = 7.2 Hz, 3 H for bromide and iodide), 0.903 (t, $J$ = 7.2 Hz, 3 H for bromide and iodide); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 175.9 (bromide and iodide), 60.3 (bromide and iodide), 33.5 (bromide), 32.8 (iodide), 31.3 (iodide), 30.6 (bromide), 30.5 (bromide and iodide), 25.6 (bromide), 6.4 (iodide), $\delta$ (down) 46.5 (bromide), 46.4 (iodide), 14.5 (bromide and iodide), 11.8 (bromide and iodide); IR (film) 1732 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_9H_{17}BrO_2Na$ 259.0304, found 259.0307.

*5-Azido-2-ethylpentanoic Acid (**1b**).* To a stirred mixture of ethyl 5-bromo-2-ethylpentanoate and ethyl 5-iodide-2-ethylpentanoate **8b** (2.65 g, 10.5 mmol) in DMF (45 mL) was added $NaN_3$ (2.05 g, 31.5 mmol), and the mixture was heated to 80 °C (oil bath) for 11 h. Then, the mixture was treated with water (10 mL) and extracted by $CH_2Cl_2$ (50 mL × 3). The combined organic phase was washed with water (20 mL × 3), dried over anhydrous $Na_2SO_4$, and concentrated; then, the residue was purified by flash column chromatography to afford the ethyl 5-azido-2-ethylpentanoate **9b** as a light yellow oil (1.92 g, 92% yield from **8b**). **9b**: $R_f$ = 0.73 (EtOAc/PE = 1/10); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.14 (q, $J$ = 7.2 Hz, 2 H), 3.27 (t, $J$ = 6.4 Hz, 2 H), 2.26−2.28 (m, 1 H), 1.50−1.70 (m, 6 H), 1.26 (t, $J$ = 7.2 Hz, 3 H), 0.898 (t, $J$ = 7.6 Hz 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 175.8, 60.3, 51.3, 29.0, 26.8, 25.6, $\delta$ (down) 46.8, 14.4, 11.8. The 5-azido-2-ethylpentanoic acid **1b** (1.33 g, 81% yield from **9b**) was prepared from the above ethyl 5-azido-2-ethylpentanoate **9b** (1.92 g, 9.6 mmol) with LiOH·$H_2O$ (8.08 g, 193.0 mmol) in the combined solvent (THF/$H_2O$ = 1/1, 80 mL) by the above procedure for preparation of **1a**, and the reaction time was 48 h. **1b**: $R_f$ = 0.50 (EtOAc/PE = 1/5); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.30 (t, $J$ = 6.4 Hz, 2 H), 2.31−2.35 (m, 1 H), 1.54−1.72 (m, 6 H), 0.956 (t, $J$ = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus


DOI: 10.1021/acs.joc.8b03018
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APT) δ (up) 182.6, 51.3, 28.7, 26.8, 25.3, δ (down) 46.6, 11.7; IR (film) 2967, 2099, 1706, 1460, 1259 $cm^{-1}$; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_7H_{13}N_3O_2Na$ 194.0900, found 194.0902.

*Diethyl 2-(2-Cyanoethyl)malonate (**13**).* To a stirred solution of diethyl malonate **11** (5.77 g, 36.0 mmol) in dry THF (80 mL) was added NaH (60% dispersion in oil, 1.68 g, 42.0 mmol) at room temperature. After 1 h, a solution of 3-bromopropanenitrile **12** (5.34 g, 40.0 mmol) in dry THF (20 mL) was added dropwise. Then, the mixture was allowed to vigorously stir for 16 h. The reaction mixture was quenched by slow addition of saturated $NH_4Cl$ (20 mL), extracted with EtOAc (60 mL × 3), washed with brine (20 mL × 3), dried over anhydrous $Na_2SO_4$, and concentrated; then, the residue was purified by flash column chromatography to afford the diethyl 2-(2-cyanoethyl)malonate **13** (6.03 g, 78% yield from **11**). **13**: known compound,[17] $R_f$ = 0.29 (EtOAc/PE = 1/5); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 4.18−4.27 (m, 4 H), 3.48−3.52 (m, 1 H), 2.49−2.52 (m, 2 H), 2.22−2.27 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 168.3 (2), 118.6, 62.1 (2), 24.6, 15.2, δ (down) 50.2, 14.1 (2).

*Diethyl 2-(2-Cyanoethyl)-2-ethylmalonate (**14**).* The diethyl 2-(2-cyanoethyl)-2-ethylmalonate **14** (5.42 g, 80% yield from **13**) was prepared from the diethyl 2-(2-cyanoethyl)malonate **13** (6.03 g, 28.3 mmol) with iodoethane **10** (4.80 g, 30.2 mmol) in the presence of NaH (60% dispersion in oil, 1.17 g, 29.3 mmol) according to the above procedure for preparation of **13**. **14**: known compound,[18] $R_f$ = 0.37 (EtOAc/PE = 1/5); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 4.18−4.25 (m, 4 H), 2.37−2.41 (m, 2 H), 2.21−2.25 (m, 2 H), 1.95 (q, *J* = 7.6 Hz, 2 H), 1.26 (t, *J* = 7.2 Hz, 6 H), 0.861 (t, *J* = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 170.5 (2), 119.2, 61.7 (2), 57.1, 28.3, 26.3, 13.0, δ (down) 14.1 (2), 8.5.

*Ethyl 4-Cyano-2-ethylbutanoate (**15**).* To a stirred solution of diethyl 2-(2-cyanoethyl)-2-ethylmalonate **14** (5.43 g, 22.5 mmol) in DMSO (73 mL) was added LiCl (4.76 g, 112.3 mmol) at room temperature. Then, the reaction was heated to refluxing (oil bath at 140 °C) for 48 h; the mixture was cooled to room temperature and quenched by water (20 mL). The mixture was extracted by EtOAc (60 mL × 3), washed with water (20 mL × 3) and brine (10 mL × 3), dried over anhydrous $Na_2SO_4$, and concentrated to afford the ethyl 4-cyano-2-ethylbutanoate **15** as a yellow oil (3.62 g, yield 95% from **14**). **15**: $R_f$ = 0.30 (EtOAc/PE = 1/5); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 4.09−4.17 (m, 2 H), 2.27−2.43 (m, 3 H), 1.90−1.99 (m, 1 H), 1.72−1.84 (m, 1 H), 1.48−1.70 (m, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 0.87 (t, *J* = 6.8 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 174.5, 119.2, 60.6, 27.1, 25.1, 15.3, δ (down) 45.5, 14.2, 11.3; IR (film) 2335, 1731 $cm^{-1}$; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_9H_{15}NO_2Na$ 192.0995, found 192.0995.

*4-Cyano-2-ethylbutyl 4-Methylbenzenesulfonate (**17**).* To a stirred solution of ethyl 4-cyano-2-ethylbutanoate **15** (3.76 g, 22.2 mmol) in dry THF (100 mL) was added $KBH_4$ (1.43 g, 26.6 mmol) and LiCl (1.13 g, 26.6 mmol) at room temperature. Then, the reaction was heated to 75 °C for 22 h, quenched with saturated $NH_4Cl$ (10 mL), and treated with 1 N HCl for adjusting the mixture to pH ≈ 3−4. The mixture was extracted with $CH_2Cl_2$ (40 mL × 3), washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated; then, the residue was purified by flash column chromatography to afford the 4-(hydroxymethyl)hexanenitrile **16** as a colorless oil (1.83 g, 64% yield from **15**). **16**: $R_f$ = 0.45 (EtOAc/PE = 1/2); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 3.66 (dd, *J* = 4.8 and 4.8 Hz, 1 H), 3.56 (dd, *J* = 6.0 and 6.0 Hz, 1 H), 2.39−2.48 (m, 2 H), 1.66−1.83 (m, 2 H), 1.54−1.63 (m, 1 H), 1.30−1.45 (m, 3 H), 0.933 (t, *J* = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 120.2, 64.1, 26.8, 23.1, 15.1, δ (down) 40.9, 11.1. To a stirred solution of the above 4-(hydroxymethyl)hexanenitrile **16** (1.82 g, 14.3 mmol)) in dry DCM (65 mL) was added $NEt_3$ (2.18 g, 21.5 mmol), DMAP (174.7 mg, 1.43 mmol), and TsCl (5.45 g, 28.6 mmol), and the reaction mixture was kept for 22 h at room temperature. Then, the mixture was concentrated and purified by flash column chromatography to afford the 4-cyano-2-ethylbutyl 4-methylbenzenesulfonate **17** as a yellow oil (3.38 g, 84% yield from **16**). **17**: $R_f$ = 0.53 (EtOAc/PE = 1/2); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 3.99 (dd, *J* = 10.0 and 3.6 Hz, 1 H), 3.92 (dd, *J* = 10.0 and 4.8 Hz, 1 H), 2.46 (s, 3 H), 2.32 (t, *J* = 6.8 Hz, 2 H), 1.64−1.75 (m, 3 H), 1.32−1.40 (m, 2 H), 0.843 (t, *J* = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 145.2, 132.6, 119.3, 70.8, 26.4, 22.9, 14.8, δ (down) 130.1 (2), 127.9 (2), 38.2, 21.7, 10.8; IR (film) 2246, 1176 $cm^{-1}$; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}NO_3SNa$ 304.0978, found 304.0980.

*4-(Azidomethyl)hexanenitrile (**18**).* To a stirred solution of 4-cyano-2-ethylbutyl 4-methylbenzenesulfonate **17** (3.38 g, 12.0 mmol) in DMF (70 mL) was added $NaN_3$ (1.56 g, 24.0 mmol), and the mixture was heated to 50 °C (oil bath) for 10 h. Then, the mixture was treated with water (10 mL) and extracted by EtOAc (30 mL × 3). The combined organic phase was washed with water (20 mL × 3) and brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated; then, the residue was purified by flash column chromatography to afford the 4-(azidomethyl)hexanenitrile **18** as a light yellow oil (1.78 g, 97% yield from **17**). **18**: $R_f$ = 0.63 (EtOAc/PE = 1/1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 3.40 (dd, *J* = 12.4 and 4.0 Hz, 1 H), 3.31 (dd, *J* = 12.4 and 5.2 Hz, 1 H), 2.40 (t, *J* = 7.2 Hz, 2 H), 1.64−1.76 (m, 3 H), 1.37−1.43 (m, 2 H), 0.941 (t, *J* = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 119.5, 53.9, 27.3, 23.9, 14.9, δ (down) 38.7, 10.9; IR (film) 2246, 2099 $cm^{-1}$; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_7H_{12}N_4Na$ 175.0954, found 175.0953.

*4-(Azidomethyl)hexanoic Acid (**1c**).* The 4-(azidomethyl)-hexanenitrile **18** (1.78 g, 11.7 mmol) was added into the combined solvent (EtOH/15% aqueous NaOH = 1/1, 90 mL), and it was heated to refluxing for 10 h. Then, the reaction mixture was cooled to room temperature and treated with 1 N HCl for adjusting the mixture to pH < 3. The mixture was extracted by EtOAc (30 mL × 3), washed with brine (20 mL × 3), dried over $Na_2SO_4$, and concentrated; then, the residue was purified by flash column chromatography to afford the 4-(azidomethyl)hexanoic acid **1c** as a light yellow oil (1.77 g, 89% yield from **18**). **1c**: $R_f$ = 0.42 (EtOAc/PE = 1/5); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 3.24−3.34 (m, 2 H), 2.39 (t, *J* = 7.6 Hz, 2 H), 1.67−1.72 (m, 2 H), 1.53−1.59 (m, 1 H), 1.36−1.43 (m, 2 H), 0.92 (t, *J* = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 180.2, 54.4, 31.5, 26.3, 24.1, δ (down) 39.0, 10.8; IR (film) 2935, 2100, 1710, 1285 $cm^{-1}$; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_7H_{13}N_3O_2Na$ 194.0900, found 194.0900.

*Ethyl 2-(2-(Bromomethyl)phenyl)acetate (**20**).* The ethyl 2-(2-(bromomethyl)phenyl)acetate **20** (17.00 g, 98% yield from **19**) was prepared from the isochroman-3-one **19** (10.00 g, 67.5 mmol) according to the reported procedure.[19] **20**: known compound,[19] $R_f$ = 0.56 (EtOAc/PE = 1/20); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.27−7.38 (m, 4 H), 4.60 (s, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 3.79 (s, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 170.8, 136.2, 133.4, 61.0, 38.2, 31.8, δ (down) 131.1, 130.6, 129.0, 127.8, 14.1.

*Ethyl 2-(2-(Azidomethyl)phenyl)acetate (**21**).* The ethyl 2-(2-(azidomethyl)phenyl)acetate **21** (10.64 g, 97% yield from **20**) was prepared from the ethyl 2-(2-(bromomethyl)phenyl)acetate **20** (12.86 g, 50.0 mmol) according to the reported procedure.[8] **21**: known compound,[8] $R_f$ = 0.41 (EtOAc/PE = 1/20); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.28−7.36 (m, 4 H), 4.42 (s, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.71 (s, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 171.2, 134.0, 133.3, 61.2, 52.9, 38.6, δ (down) 131.3, 130.0, 129.0, 127.8, 14.2.

*2-(2-(Azidomethyl)phenyl)acetic Acid (**1d**).* The 2-(2-(azidomethyl)phenyl)acetic acid **1d** (8.94 g, 97% yield from **21**) was prepared from the ethyl 2-(2-(azidomethyl)phenyl)acetate **21** (10.64 g, 48.5 mmol) with $LiOH·H_2O$ (10.18 g, 242.5 mmol) in the combined solvent ($THF/H_2O$ = 1/1, 360 mL) by the above procedure for preparation of **1a**, and the reaction was carried out at 70 °C for 19 h. **1d**: known compound,[8] a white solid, Mp 113.3−115.5 °C, $R_f$ = 0.48 (EtOAc/PE = 1/1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.29−7.37 (m, 4 H), 4.41 (s, 2 H), 3.76 (s, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 177.6, 134.2, 132.4, 52.9, 38.2, δ (down) 131.4, 130.1, 129.1, 128.2. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_9H_9N_3O_2H$ 192.0768, found 1942.0778.



DOI: 10.1021/acs.joc.8b03018
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*Phenyl(pyrrolidin-1-yl)methanone (**3aa**) and 1-Benzylpyrrolidin-2-one (**4aa**). Procedure A.* To a stirred solution of 5-azidopentanoic acid **1a** (143.2 mg, 1.0 mmol) in DCM (1.5 mL) was treated with $(COCl)_2$ (177.7 mg, 1.4 mmol) for 1.5 h at 30 °C; then, the benzene **2a** (390.6 mg, 5.0 mmol) was applied. TfOH (300.1 mg, 2.0 mmol) was slowly added into the reaction mixture at 0 °C, and the mixture was heated to reflux (oil bath at 60 °C) for 46 h. After that, the mixture was cooled to room temperature and quenched with 5% aqueous KOH (4 mL). The mixture was extracted by $CH_2Cl_2$ (10 mL × 4), and the combined organic phase was dried over $Na_2SO_4$ and concentrated; then, the residue was purified by flash column chromatography to afford the phenyl(pyrrolidin-1-yl)methanone **3aa** (90.0 mg, 51% yield from **1a**) and 1-benzylpyrrolidin-2-one **4aa** (61.2 mg, 35% yield from **1a**). **3aa** known compound:[6] a light yellow oil, $R_f$ = 0.59 (EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.36−7.52 (m, 5 H), 3.64 (t, $J$ = 7.2 Hz, 2 H), 3.42 (t, $J$ = 6.8 Hz, 2 H), 1.92−1.99 (m, 2 H), 1.83−1.89 (m, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 169.7, 137.3, 49.6, 46.2, 26.4, 24.5, $\delta$ (down) 129.8, 128.2 (2), 127.1 (2); IR (film) 2971, 2876, 1623, 1575, 700 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{11}H_{13}NONa$ 198.0889, found 198.0893. Further elution gave the **4aa**, known compound,[21] a light yellow oil, $R_f$ = 0.31 (EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.23−7.35 (m, 5 H), 4.46 (s, 2 H), 3.26 (t, $J$ = 7.2 Hz, 2 H), 2.45 (t, $J$ = 8.0 Hz, 2 H), 1.96−2.03 (m, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 174.9, 136.6, 46.61, 46.58, 31.0, 17.8, $\delta$ (down) 128.7 (2), 128.1 (2), 127.6; IR (film) 2918, 1685, 1495, 1463, 702 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{11}H_{13}NONa$ 198.0889, found 198.0893.

*Ethyl Pyrrolidine-1-carboxylate (**3ae**) and 1-(Ethoxymethyl)-pyrrolidin-2-one (**4ae**). Procedure B.* To a stirred solution of 5-azidopentanoic acid **1a** (143.2 mg, 1.0 mmol) in DCM (1.5 mL) was treated with $(COCl)_2$ (177.7 mg, 1.4 mmol) for 1.5 h at 30 °C; then, the TfOH (600.2 mg, 4.0 mmol) was slowly added into the reaction mixture at 0 °C. Fifteen min later, ethanol **2e** (230.3 mg, 5.0 mmol) was applied, and the mixture was kept for 4 h at room temperature. After that, the mixture was quenched with 5% aqueous KOH (4 mL) and extracted by $CH_2Cl_2$ (10 mL × 4), and the combined organic phase was dried over $Na_2SO_4$ and concentrated; then, the residue was purified by flash column chromatography to afford the ethyl pyrrolidine-1-carboxylate **3ae** (83.3 mg, 58% yield from **1a**) and **4ae** (21.7 mg, 15% yield from **1a**). **3ae** known compound:[22] a colorless oil, $R_f$ = 0.62 (MTBE); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.12 (q, $J$ = 7.2 Hz, 2 H), 3.34 (m, 4 H), 1.84 (m, 4 H), 1.24 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 155.3, 60.8, 46.1, 45.7, 25.8, 25.0, $\delta$ (down) 14.9; IR (film) 2979, 1700, 1423, 1382, 1181 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + H]$^+$ calcd for $C_7H_{13}NO_2H$ 144.1019, found 144.1015. Further elution gave the **4ae**: a colorless oil, $R_f$ = 0.30 (MTBE); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.72 (s, 2 H), 3.44−3.50 (m, 4 H), 2.42 (t, $J$ = 8.0 Hz, 2 H), 2.02−2.08 (m, 2 H), 1.18 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 176.1, 72.5, 63.9, 46.0, 31.3, 18.0, $\delta$ (down) 15.1; IR (film) 3473, 2975, 1701, 1423, 1283 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_7H_{13}NO_2Na$ 166.0839, found 166.0837.

*(2,5-Dimethylphenyl)(pyrrolidin-1-yl)methanone (**3ab**) and 1-(2,5-Dimethylbenzyl)pyrrolidin-2-one (**4ab**).* The **3ab** (70.3 mg, 35% yield from **1a**) and **4ab** (78.6 mg, 38% yield from **1a**) were prepared from the Schmidt reaction of **1a** (143.2 mg, 1.0 mmol) with the nucleophile *p*-xylene **2b** (530.8 mg, 5.0 mmol) according to **Procedure A** for the preparation of **3aa** and **4aa**, and the reaction time for the capture process was 46 h. **3ab**: a light yellow oil, $R_f$ = 0.67 (EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.04−7.09 (m, 2 H), 7.00 (s, 1 H), 3.65 (t, $J$ = 7.2 Hz, 2 H), 3.13 (t, $J$ = 6.4 Hz, 2 H), 2.30 (s, 3 H), 2.25 (s, 3 H), 1.92−1.99 (m, 2 H), 1.82−1.89 (m, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 170.1, 137.8, 135.3, 130.3, 48.2, 45.2, 25.9, 24.6, $\delta$ (down) 130.2, 129.4, 126.0, 20.8, 18.4; IR (film) 2918, 1632, 1435, 814 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{13}H_{17}NONa$ 226.1202, found 226.1203. Further elution gave **4ab**: a colorless oil, $R_f$ = 0.52 (EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.05 (d, $J$ = 8.0 Hz, 1 H), 7.00 (d, $J$ = 8.0 Hz, 1 H), 6.95 (s, 1 H), 4.43 (s, 2 H), 3.20 (t, $J$ = 7.2 Hz, 2 H), 2.45 (t, $J$ = 8.0 Hz, 2 H), 2.30 (s, 3 H), 2.25 (s, 3 H), 1.94−2.02 (m, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 174.5, 135.4, 133.9, 133.3, 46.4, 44.5, 30.8, 17.6, $\delta$ (down) 130.3, 129.5, 128.2, 20.8, 18.5; IR (film) 2922, 1685, 1425, 1287, 814 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{13}H_{17}NONa$ 226.1202, found 226.1203.

*1-(2,5-Dichlorobenzyl)pyrrolidin-2-one (**4ac**).* The **4ac** (93.6 mg, 38% yield from **1a**) was prepared from the Schmidt reaction of **1a** (143.2 mg, 1.0 mmol) with the nucleophile 1,4-dichlorobenzene **2c** (735.0 mg, 5.0 mmol) according to **Procedure A** for preparation of **3aa** and **4aa**, and the reaction time for the capture process was 46 h. **4ac**: a colorless oil, $R_f$ = 0.41 (EtOAc/PE = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.18−7.31 (m, 3 H), 4.55 (s, 2 H), 3.33 (t, $J$ = 6.8 Hz, 2 H), 2.46 (t, $J$ = 8.0 Hz, 2 H), 2.02−2.09 (m, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 175.1, 135.7, 132.9, 131.7, 46.9, 43.6, 30.4, 17.7, $\delta$ (down) 130.6, 129.1, 128.8; IR (film) 2949, 1689, 1493, 1285, 814 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{11}H_{11}Cl_2NONa$ 266.0110, found 266.0108.

*Naphthalen-1-yl(pyrrolidin-1-yl)methanone (**3ad**) and 1-(Naphthalen-1-ylmethyl)pyrrolidin-2-one (**4ad**).* The **3ad** (61.0 mg, 27% yield from **1a**) and **4ad** (89.0 mg, 40% yield from **1a**) were prepared from the Schmidt reaction of **1a** (143.2 mg, 1.0 mmol) with the nucleophile naphthalene **2d** (640.9 mg, 5.0 mmol) according to **Procedure A** for preparation of **3aa** and **4aa**, and the reaction time for the capture process was 46 h. **3ad**, known compound,[23] a yellow oil, $R_f$ = 0.56 (EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.86−7.88 (m, 3 H), 7.45−7.54 (m, 4 H), 3.80 (t, $J$ = 7.2 Hz, 2 H), 3.13 (t, $J$ = 6.8 Hz, 2 H), 1.97−2.04 (m, 2 H), 1.80−1.87 (m, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 169.2, 135.8, 133.5, 129.2, 48.5, 45.6, 26.0, 24.6, $\delta$ (down) 129.1, 128.4, 126.9, 126.3, 125.2, 124.9, 123.7; IR (film) 3051, 2974, 2877, 1630, 1439, 800 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{15}H_{15}NONa$ 248.1046, found 248.1045. Further elution gave the **4ad**: a yellow oil, $R_f$ = 0.41 (EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.14 (d, $J$ = 8.0 Hz, 1 H), 7.85 (d, $J$ = 8.0 Hz, 1 H), 7.80 (d, $J$ = 8.0 Hz, 1 H), 7.36−7.56 (m, 4 H), 4.89 (s, 2 H), 3.12 (t, $J$ = 7.2 Hz, 2 H), 2.43 (t, $J$ = 8.0 Hz, 2 H), 1.84−1.91 (m, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 174.4, 133.7, 132.0, 131.5, 46.4, 44.8, 31.0, 17.5, $\delta$ (down) 128.6, 128.5, 127.3, 126.6, 126.0, 125.1, 123.8; IR (film) 2949, 1680, 1423, 1259, 784 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{15}H_{15}NONa$ 248.1046, found 248.1042.

*Hexyl Pyrrolidine-1-carboxylate (**3af**) and 1-((Hexyloxy)methyl)-pyrrolidin-2-one (**4af**).* The **3af** (74.0 mg, 37% yield from **1a**) and **4af** (70.6 mg, 36% yield from **1a**) were prepared from the Schmidt reaction of **1a** (143.2 mg, 1.0 mmol) with the nucleophile 1-hexanol **2f** (510.9 mg, 5.0 mmol) according to **Procedure B** for the preparation of **3ae** and **4ae**, and the capture process was carried out at room temperature for 22 h. **3af**: a colorless oil, $R_f$ = 0.57 (EtOAc/DCM/PE = 1/5/10); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.06 (t, $J$ = 6.8 Hz, 2 H), 3.31−3.40 (m, 4 H), 1.85 (m, 4 H), 1.58−1.65 (m, 2 H), 1.25−1.44 (m, 6 H), 0.87−0.90 (m, 3 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 155.5, 65.3, 46.0 (2), 31.5, 29.1, 25.7, 25.4 (2), 22.6, $\delta$ (down) 14.0; IR (film) 3493, 2956, 1705, 1423, 1105, 770 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{11}H_{21}NO_2Na$ 222.1465, found 222.1463. Further elution gave the **4af**: a colorless oil, $R_f$ = 0.54 (EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.72 (s, 2 H), 3.48 (t, $J$ = 7.2 Hz, 2 H), 3.40 (t, $J$ = 6.8 Hz, 2 H), 2.43 (t, $J$ = 8.0 Hz, 2 H), 2.00−2.08 (m, 2 H), 1.51−1.56 (m, 2 H), 1.25−1.34 (m, 6 H), 0.875 (t, $J$ = 6.8 Hz, 3 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 176.0, 72.6, 68.5, 45.9, 31.6, 31.2, 29.5, 25.8, 22.6, 17.9, $\delta$ (down) 14.0; IR (film) 3484, 2932, 2243, 1703, 1422, 1267, 1089, 732 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{11}H_{21}NO_2Na$ 222.1465, found 222.1464.

*N-Butylpyrrolidine-1-carboxamide (**3ag**).* The **3ag** (98.7 mg, 58% yield from **1a**) was prepared from the Schmidt reaction of **1a** (143.2 mg, 1.0 mmol) with the nucleophile *n*-butylamine **2g** (365.7 mg, 5.0 mmol) according to **Procedure B** for the preparation of **3ae** and **4ae**, and the capture process was carried out at room temperature for 4 h. **3ag**, known compound,[24] $R_f$ = 0.48 (EtOAc); $^1$H NMR ($CDCl_3$, 400


DOI: 10.1021/acs.joc.8b03018
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MHz) δ 4.25 (bs, 1 H), 3.14−3.32 (m, 6 H), 1.75−1.85 (m, 4 H), 1.39−1.46 (m, 2 H), 1.24−1.33 (m, 2 H), 0.86 (t, $J$ = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 156.9, 47.8, 45.3, 40.2, 32.5, 25.43, 25.40, 19.9, δ (down) 13.7; IR (film) 3338, 2956, 2933, 2871, 2225, 2096, 1631, 1538, 733 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_9H_{18}N_2ONa$ 193.1311, found 193.1311.

*Piperidin-1-yl(pyrrolidin-1-yl)methanone (**3ah**).* The **3ah** (107.9 mg, 59% yield from **1a**) was prepared from the Schmidt reaction of **1a** (143.2 mg, 1.0 mmol) with the nucleophile piperidine **2h** (425.8 mg, 5.0 mmol) according to **Procedure B** for the preparation of **3ae** and **4ae**, and the capture process was carried out at room temperature for 4 h. **3ah**: a light yellow oil, $R_f$ = 0.31 (EtOAc/PE = 1/5); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 3.33−3.38 (m, 4 H), 3.16−3.21 (m, 4 H), 1.76−1.84 (m, 4 H), 1.54−1.62 (m, 6 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 163.2, 48.3 (2), 47.1 (2), 25.8 (2), 25.5 (2), 24.7; IR (film) 3479, 2934, 1639, 1412, 1252 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{10}H_{18}N_2ONa$ 205.1311, found 205.1308.

*(2-Ethylpyrrolidin-1-yl)(phenyl)methanone (**3ba**) and Benzyl-3-ethylpyrrolidin-2-one (**4ba**).* The mixture of **3ba** and **4ba** (**3ba**/**4ba** = 6/1 from $^1H$ NMR, 145.5 mg, 72% combined yield from **1b**) was prepared from the Schmidt reaction of **1b** (171.2 mg, 1.0 mmol) with the nucleophile benzene **2a** (390.6 mg, 5.0 mmol) according to **Procedure A** for the preparation of **3aa** and **4aa**, and the reaction time for the capture process was 46 h. The **3ba** and **4ba** could be partly separated by careful column chromatography, and the pure samples were used for further characterization. **3ba**: a colorless oil, mixture of rotamer (3:1 from $^1H$ NMR), $R_f$ = 0.69 (EtOAc/PE = 1/2); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.35−7.51 (m, 5 H for major rotamer and minor rotamer), 4.21 (m, 1 H for major rotamer), 3.79 (m, 2 H for minor rotamer), 3.44 (m, 1 H for minor rotamer), 3.40−3.42 (m, 2 H for major rotamer), 1.86−2.11 (m, 3 H for major rotamer and 3 H for minor rotamer), 1.65−1.77 (m, 2 H for major rotamer and 2 H for minor rotamer), 1.48−1.55 (m, 1 H for major rotamer), 1.23−1.25 (m, 1 H for minor rotamer), 0.95 (t, $J$ = 7.6 Hz, 3 H for major rotamer), 0.62 (m, 3 H for minor rotamer); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 169.8, 137.6, 50.3, 29.7, 26.3, 25.1, δ (down) 129.7, 128.1 (2), 127.3 (2), 58.5, 10.0; IR (film) 2966, 1627, 1413, 701 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{13}H_{17}NONa$ 226.1202, found 226.1204. **4ba**: $R_f$ = 0.65 (EtOAc/PE = 1/2); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.14−7.26 (m, 5 H), 4.41 (d, $J$ = 14.4 Hz, 1 H), 4.33 (d, $J$ = 14.4 Hz, 1 H), 3.07−3.11 (m, 2 H), 2.31−2.34 (m, 1 H), 2.04−2.10 (m, 1 H), 1.81−1.87 (m, 1 H), 1.54−1.62 (m, 1 H), 1.34−1.41 (m, 1 H), 0.88 (t, $J$ = 6.8 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 176.6, 136.7, 46.6, 44.9, 24.3, 24.1, δ (down) 128.6 (2), 128.1 (2), 127.5, 43.3, 11.4; IR (film) 2963, 1687, 1426, 700 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{13}H_{17}NONa$ 226.1202, found 226.1202.

*Hexyl 2-Ethylpyrrolidine-1-carboxylate (**3bf**).* The **3bf** (141.0 mg, 62% yield from **1b**) was prepared from the Schmidt reaction of **1b** (171.2 mg, 1.0 mmol) with the nucleophile 1-hexanol **2f** (510.9 mg, 5.0 mmol) according to the **Procedure B** for preparation of **3ae** and **4ae**, and the capture process was carried out at room temperature for 22 h. **3bf**: a light yellow oil, $R_f$ = 0.58 (EtOAc/PE = 1/10); mixture of rotamers, (1:1 from $^{13}C\{^1H\}$ NMR) $^1H$ NMR ($CDCl_3$, 400 MHz) δ 4.00−4.06 (m, 2 H), 3.69−3.75 (m, 1 H), 3.35−3.44 (m, 2 H), 1.75−1.89 (m, 3 H), 1.56−1.68 (m, 4 H), 1.25−1.35 (m, 7 H), 0.84−0.94 (m, 6 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 155.6 (rotamer A and rotamer B), 64.9 (rotamer A and rotamer B), 46.6 (rotamer A), 46.3 (rotamer B), 31.5 (rotamer A and rotamer B), 30.1 (rotamer A), 29.3 (rotamer B), 29.1 (rotamer A and rotamer B), 27.4 (rotamer A), 26.6 (rotamer B), 25.7 (rotamer A and rotamer B), 23.9 (rotamer A), 23.1 (rotamer B), 22.6 (rotamer A and rotamer B), δ (down) 59.1 (rotamer A), 58.6 (rotamer B), 14.0 (rotamer A and rotamer B), 10.5 (rotamer A and rotamer B); IR (film) 3497, 2959, 1700, 1462, 1416, 1108, 732 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{13}H_{25}NO_2Na$ 250.1778, found 250.1773.

*N-Butyl-2-ethylpyrrolidine-1-carboxamide (**3bg**).* The **3bg** (149.1 mg, 75% yield from **1b**) was prepared from the Schmidt reaction of **1b** (171.2 mg, 1.0 mmol) with the nucleophile *n*-butylamine **2g** (365.7 mg, 5.0 mmol) according to **Procedure B** for the preparation of **3ae** and **4ae**, and the capture process was carried out at room temperature for 4 h. **3bg**: a colorless oil, $R_f$ = 0.57 (EtOAc/PE = 1/1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 4.12 (m, 1 H), 3.76 (m, 1 H), 3.19−3.30 (m, 4 H), 1.85−1.94 (m, 3 H), 1.69−1.78 (m, 2 H), 1.45−1.52 (m, 2 H), 1.25−1.39 (m, 3 H), 0.92 (t, $J$ = 7.2 Hz, 3 H), 0.87 (t, $J$ = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 157.0, 45.9, 40.2, 32.6, 29.4, 27.2, 23.7, 20.1, δ (down) 58.5, 13.8, 10.5; IR (film) 3338, 2962, 2097, 1629, 1535, 737 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{11}H_{22}N_2ONa$ 221.1624, found 221.1619.

*(2-Ethylpyrrolidin-1-yl)(piperidin-1-yl)methanone (**3bh**).* The **3bh** (117.7 mg, 56% yield from **1b**) was prepared from the Schmidt reaction of **1b** (171.2 mg, 1.0 mmol) with the nucleophile piperidine **2h** (425.8 mg, 5.0 mmol) according to **Procedure B** for the preparation of **3ae** and **4ae**, and the capture process was carried out at room temperature for 4 h. **3bh**: a colorless oil, $R_f$ = 0.34 (EtOAc/PE = 1/5); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 3.96−3.99 (m, 1 H), 3.16−3.33 (m, 6 H), 2.03−2.07 (m, 1 H), 1.29−1.81 (m, 11 H), 0.84 (t, $J$ = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 163.1, 50.7, 47.0 (2), 30.4, 27.3, 25.7 (2), 25.5, 24.7, δ (down) 58.9, 9.7; IR (film) 3478, 2965, 2096, 1631, 1413, 734 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{12}H_{22}N_2ONa$ 233.1624, found 233.1618.

*1-Benzyl-5-ethylpyrrolidin-2-one (**4ca**).* The **4ca** (166.6 mg, 82% yield from **1c**) was prepared from the Schmidt reaction of **1c** (171.2 mg, 1.0 mmol) with the nucleophile benzene **2a** (390.6 mg, 5.0 mmol) according to **Procedure A** for the preparation of **3aa** and **4aa**, and the reaction time for the capture process was 46 h. **4ca**: a colorless oil, $R_f$ = 0.75 (EtOAc); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.22−7.33 (m, 5 H), 4.99 (d, $J$ = 14.8 Hz, 1 H), 3.95 (d, $J$ = 14.8 Hz, 1 H), 3.38−3.40 (m, 1 H), 2.40−2.48 (m, 2 H), 2.04−2.11 (m, 1 H), 1.65−1.74 (m, 2 H), 1.34−1.41 (m, 1 H), 0.82 (t, $J$ = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 175.2, 136.8, 44.0, 30.3, 25.4, 23.2, δ (down) 128.5 (2), 127.9 (2), 127.3, 57.9, 8.4; IR (film) 2965, 1689, 1417, 1257, 703 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{13}H_{17}NONa$ 226.1202, found 226.1202.

*Dimethylphenyl)(3-ethylpyrrolidin-1-yl)methanone (**3cb**) and 1-(2,5-Dimethylbenzyl)-5-ethylpyrrolidin-2-one (**4cb**).* The **3cb** and **4cb** (**3cb**/**4cb** = 1/5 from $^1H$ NMR, 183.7 mg, 79% combined yield from **1c**) were prepared from the Schmidt reaction of **1c** (171.2 mg, 1.0 mmol) with the nucleophile *p*-xylene **2b** (530.8 mg, 5.0 mmol) according to **Procedure A** for the preparation of **3aa** and **4aa**, and the reaction time for the capture process was 46 h. The **3cb** and **4cb** could be partly separated by careful column chromatography, and the pure samples were used for further characterization. **3cb**: a light yellow oil, mixture of rotamer A and rotamer B (1:1 from $^1H$ NMR), $R_f$ = 0.47 (EtOAc/PE = 1/1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.04−7.10 (m, 2 H), 6.99 (s, 1 H), 3.86−3.91 (m, 0.5 H), 3.76−3.81 (m, 0.5 H), 3.52−3.59 (m, 0.5 H), 3.09−3.27 (m, 2 H), 2.73−2.78 (m, 0.5 H), 2.30 (s, 3 H), 2.25 (s, 3 H), 1.95−2.12 (m, 2 H), 1.43−1.59 (m, 2 H), 1.31−1.38 (m, 1 H), 0.97 (t, $J$ = 7.2 Hz, 1.5 H), 0.87 (t, $J$ = 7.6 Hz, 1.5 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 170.1, 170.0, 137.7, 137.5, 135.34, 135.32, 130.3, 130.2, 53.5, 50.6, 48.0, 44.9, 31.7, 30.2, 26.2, 25.6, δ (down) 130.2 (2, rotamers), 129.3 (2, rotamers), 126.0 (2, rotamers), 41.0, 39.7, 20.8, 18.4, 12.5, 12.4; IR (film) 3482, 2960, 1634, 1434, 1192, 813 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{15}H_{21}NOH$ 232.1696, found 232.1698. **4cb**: a light yellow oil, $R_f$ = 0.45 (EtOAc/PE = 1/1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.04 (d, $J$ = 7.6 Hz, 1 H), 6.98 (d, $J$ = 7.6 Hz, 1 H), 6.91 (s, 1 H), 4.97 (d, $J$ = 15.2 Hz, 1 H), 3.92 (d, $J$ = 15.2 Hz, 1 H), 3.33−3.35 (m, 1 H), 2.42−2.48 (m, 2 H), 2.29 (s, 3 H), 2.24 (s, 3 H), 2.06−2.14 (m, 1 H), 1.63−1.74 (m, 2 H), 1.36−1.43 (m, 1 H), 0.83 (t, $J$ = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) δ (up) 174.8, 135.5, 134.1, 133.2, 42.1, 30.3, 25.4, 23.1, δ (down) 130.5, 129.0, 128.2, 57.8, 21.1, 18.8, 8.6; IR (film) 2966, 1689, 1496, 1422, 813 $cm^{-1}$; HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{15}H_{21}NONa$ 254.1515, found 254.1510.



DOI: 10.1021/acs.joc.8b03018
J. Org. Chem. 2019, 84, 2012−2021

*1-(2,5-Dichlorobenzyl)-5-ethylpyrrolidin-2-one (**4cc**).* The **4cc** (96.1 mg, 35% yield from **1c**) was prepared from the Schmidt reaction of **1c** (171.2 mg, 1.0 mmol) with the nucleophile 1,4-dichlorobenzene **2c** (735.0 mg, 5.0 mmol) according to **Procedure A** for the preparation of **3aa** and **4aa**, and the reaction time for the capture process was 46 h. **4cc**: a colorless oil, $R_f$ = 0.65 (EtOAc/PE = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.24 (d, $J$ = 8.4 Hz, 1 H), 7.16 (s, 1 H), 7.13 (d, $J$ = 8.4 Hz, 1 H), 4.77 (d, $J$ = 16.0 Hz, 1 H), 4.24 (d, $J$ = 16.0 Hz, 1 H), 3.38−3.44 (m, 1 H), 2.36−2.50 (m, 2 H), 2.09−2.19 (m, 1 H), 1.63−1.75 (m, 2 H), 1.30−1.37 (m, 1 H), 0.82 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 175.5, 136.3, 133.0, 131.3, 41.4, 30.0, 25.9, 23.5, $\delta$ (down) 130.6, 129.0, 128.7, 58.8, 8.7; IR (film) 2966, 1691, 1463, 1421, 1270, 1097, 813 cm$^{-1}$; HRMS (ESI-TOF) $C_{13}H_{15}Cl_2NOH$ $m/z$ [M + H]$^+$ calcd for 272.0604, found 272.0603.

*1-Benzylindolin-2-one (**4da**).* The **4da** (215.2 mg, 96% yield from **1d**) was prepared from the Schmidt reaction of **1d** (191.2 mg, 1.0 mmol) in DCM (2 mL) with the nucleophile benzene **2a** (390.6 mg, 5.0 mmol) according to **Procedure A** for the preparation of **3aa** and **4aa**, and the *in situ* formation of acyl chloride was carried out at 45 °C for 1 h, where the reaction time for the capture process was 23 h. **4da**, known compound,[25] $R_f$ = 0.69 (EtOAc/PE = 1/5), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.25−7.32 (m, 6 H), 7.17 (t, $J$ = 7.6 Hz, 1 H), 7.01 (t, $J$ = 7.2 Hz, 1 H), 6.72 (d, $J$ = 7.6 Hz, 1 H), 4.92 (s, 2 H), 3.63 (s, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 174.9, 144.1, 135.8, 124.3, 43.5, 35.6, $\delta$ (down) 128.6 (2), 127.6, 127.5, 127.2 (2), 124.3, 122.2, 108.9.

*1-(3,4-Dimethoxybenzyl)indolin-2-one (**4di**).* The **4di** (254.0 mg, 90% yield from **1d**) was prepared from the Schmidt reaction of **1d** (191.2 mg, 1.0 mmol) in DCM (2 mL) with the nucleophile 1,2-dimethoxybenzene **2i** (690.8 mg, 5.0 mmol) according to **Procedure B** for the preparation of **3aa** and **4aa**, and the *in situ* formation of acyl chloride was carried out at 45 °C for 1 h, where the capture reaction was promoted with TfOH (300.1 mg, 2.0 mmol) at 0 °C for 6 h. **4di**: $R_f$ = 0.39 (EtOAc/PE = 1/1), Mp 119.7−120.2 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.25 (d, $J$ = 7.6 Hz, 1 H), 7.18 (t, $J$ = 8.0 Hz, 1 H), 7.01 (t, $J$ = 7.2 Hz, 1 H), 6.86−6.88 (m, 2 H), 6.76−6.80 (m, 2 H), 4.85 (s, 2 H), 3.84 (s, 6 H), 3.61 (s, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 174.8, 148.9, 148.2, 144.0, 128.2, 124.2, 43.2, 35.4, $\delta$ (down) 127.5, 124.1, 122.1, 119.5, 110.8, 110.5, 108.8, 55.6, 55.5. IR (film) 2950, 2837, 1707, 1616, 1518, 1467, 1142, 749 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{17}H_{17}NO_3Na$ 306.1102, found 306.1102.

*1-(2-Bromo-4,5-dimethoxybenzyl)indolin-2-one (**4dj**).* Two different capturing conditions were employed for preparation of the **4dj** from the reaction of **1d** with **2j**,[20] and the following were the results: The **4dj** (271.0 mg, 75% yield from **1d**) was prepared from the Schmidt reaction of **1d** (191.2 mg, 1.0 mmol) in DCM (2 mL) with the nucleophile 4-bromo-1,2-dimethoxybenzene **2j** (1.09 g, 5.0 mmol) according to **Procedure A** for the preparation of **4da**, and the *in situ* formation of acyl chloride was carried out at 45 °C for 1 h, where the capture reaction was promoted with TfOH (300.1 mg, 2.0 mmol) at 60 °C for 23 h. The **4dj** (247.9 mg, 68% yield from **1d**) was prepared from the Schmidt reaction of **1d** (191.2 mg, 1.0 mmol) in DCM (2 mL) with the nucleophile 4-bromo-1,2-dimethoxybenzene **2j** (1.09 g, 5.0 mmol) according to **Procedure B** for the preparation of **4di**, and the *in situ* formation of acyl chloride was carried out at 45 °C for 1 h, where the capture reaction was promoted with TfOH (300.1 mg, 2.0 mmol) at 0 °C for 6 h. **4dj**, known compound,[12d] $R_f$ = 0.61 (EtOAc/PE = 1/1), Mp 156.3−158.0 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.25 (s, 1 H), 7.19 (t, $J$ = 7.6 Hz, 1 H), 7.03 (t, $J$ = 7.2 Hz, 2 H), 6.90 (d, $J$ = 8.0 Hz, 1 H), 6.70 (s, 1 H), 4.97 (s, 2 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.66 (s, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 175.3, 149.0, 148.8, 143.9, 126.8, 124.2, 112.9, 43.3, 35.8, $\delta$ (down) 127.9, 124.3, 122.6, 115.3, 111.1, 109.3, 56.1, 56.0.

*1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)indolin-2-one (**4dk**).* The **4dk** (251.2 mg, 73% yield from **1d**) was prepared from the Schmidt reaction of **1d** (191.2 mg, 1.0 mmol) in DCM (2 mL) with the nucleophile 5-bromobenzo[*d*][1,3]dioxole **2k** (1.01 g, 5.0 mmol) according to **Procedure B** for the preparation of **4di**, and the *in situ* formation of acyl chloride was carried out at 45 °C for 1 h, where the capture reaction was promoted with TfOH (300.1 mg, 2.0 mmol) at 0 °C for 6 h. **4dk**, known compound,[12d] $R_f$ = 0.62 (EtOAc/PE = 1/2), Mp 145.2−145.3 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.28 (d, $J$ = 7.2 Hz, 1 H), 7.20 (t, $J$ = 7.8 Hz, 1 H), 7.03−7.06 (m, 2 H), 6.71 (d, $J$ = 8.0 Hz, 1 H), 6.56 (s, 1 H), 5.92 (s, 2 H), 4.93 (s, 2 H), 3.66 (s, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 175.6, 147.9, 147.8, 143.7, 127.6, 124.3, 113.1, 101.9, 43.6, 35.8, $\delta$ (down) 128.0, 124.5, 122.8, 112.7, 109.3, 107.7.

*(2-Iodo-4,5-dimethoxybenzyl)indolin-2-one (**4dl**).* The **4dl** (335.9 mg, 82% yield from **1d**) was prepared from the Schmidt reaction of **1d** (191.2 mg, 1.0 mmol) in DCM (2 mL) with the nucleophile 4-iodo-1,2-dimethoxybenzene **2l** (1.32 g, 5.0 mmol) according to **Procedure B** for the preparation of **4di**, and the *in situ* formation of acyl chloride was carried out at 45 °C for 1 h, where the capture reaction was promoted with TfOH (300.1 mg, 2.0 mmol) at 0 °C for 0.5 h. **4dl**: a white solid, Mp 161.5−161.7 °C, $R_f$ = 0.44 (EtOAc/PE = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.24−7.27 (m, 2 H), 7.17 (t, $J$ = 7.6 Hz, 1 H), 7.02 (t, $J$ = 7.6 Hz, 1 H), 6.71 (d, $J$ = 7.6 Hz, 1 H), 6.61 (s, 1 H), 4.89 (s, 2 H), 3.84 (s, 3 H), 3.67 (s, 5 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 175.2, 149.7, 148.9, 143.9, 130.0, 124.2, 86.0, 48.4, 35.8, $\delta$ (down) 128.0, 124.4, 122.6, 121.4, 110.4, 109.6, 56.1, 55.8; IR (film) 3433, 2938, 1695, 1614, 1508, 1253, 745 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{17}H_{16}INO_3Na$ 432.0067 found 432.0070.

*1-(2-Bromo-4,5-dimethoxybenzyl)indoline (**5dj**).* To a stirred solution of 1-(2-bromo-4,5-dimethoxybenzyl)indolin-2-one **4dj** (724.4 mg, 2.0 mmol) in THF (10 mL) was added borane−dimethylsulfide compex 9-BBN (0.5 M in THF, 8.8 mL, 4.4 mmol); then, the mixture was kept for 1 h at room temperature. The mixture was concentrated to afford the crude product, and then, the crude mixture was dissolved in AcOH (6 mL). $NaBH_3CN$ (377.0 mg, 6.0 mmol) was added into the mixture, and it was kept for 2 h at room temperature. Then, the reaction was treated with 0.5 N KOH for adjusting the mixture to pH > 7 and the mixture was extracted by $CH_2Cl_2$ (15 mL × 3), dried over $Na_2SO_4$, and concentrated; then, the residue was purified by flash column chromatography to afford the 1-(2-bromo-4,5-dimethoxybenzyl)indoline **5dj** (609.4 mg, 88% yield from **4dj**). **5dj**: known compound,[11] $R_f$ = 0.36 (EtOAc/PE = 1/10); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.14 (d, $J$ = 7.2 Hz, 1 H), 7.07−7.10 (m, 2 H), 7.02 (s, 1 H), 6.72 (t, $J$ = 7.2 Hz, 1 H), 6.52 (d, $J$ = 7.6 Hz, 1 H), 4.26 (s, 2 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 3.39 (t, $J$ = 8.4 Hz, 2 H), 3.03 (t, $J$ = 8.0 Hz, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 152.4, 148.43, 148.41, 129.8, 129.3, 113.2, 54.0, 53.7, 28.5, $\delta$ (down) 127.2, 124.4, 117.9, 115.3, 112.0, 107.2, 56.1, 56.0.

*1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)indoline (**5dk**).* The **5dk** (623.2 mg, 90% yield from **4dk**) was prepared from the **4dk** (692.4 mg, 2.0 mmol) with the 9-BBN (0.5 M in THF, 8.8 mL, 4.4 mmol) according to the procedure for preparation of **5dj**, and the reaction time for the reduction process with $NaBH_3CN$ (377.0 mg, 6.0 mmol) was 1 h. **5dk**: known compound,[11] $R_f$ = 0.64 (EtOAc/PE = 1/10); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.12 (d, $J$ = 7.2 Hz, 1 H), 7.04−7.08 (m, 2 H), 6.97 (s, 1 H), 6.69 (t, $J$ = 7.2 Hz, 1 H), 6.40 (d, $J$ = 8.0 Hz, 1 H), 5.96 (s, 2 H), 4.22 (s, 2 H), 3.41 (t, $J$ = 8.4 Hz, 2 H), 3.02 (t, $J$ = 8.4 Hz, 2 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 152.3, 147.7, 147.4, 130.9, 129.9, 113.5, 101.8, 54.1, 54.0, 28.7, $\delta$ (down) 127.5, 124.6, 117.9, 112.8, 109.3, 107.0.

*Assoanine (**6a**) and Oxoassoanine (**7a**).* To a stirred solution of 1-(2-bromo-4,5-dimethoxybenzyl)indoline **5dj** (104.5 mg, 0.3 mmol) in DMF (8 mL) was added $Pd(OAc)_2$ (6.8 mg, 3% mmol), $PCy_3$ (16.8 mg, 6% mmol), and $K_2CO_3$ (82.8 mg, 0.6 mmol), and the mixture was heated to 125 °C (oil bath) for 1 h. Then, the mixture was cooled to room temperature, treated with water (2 mL), extracted by EtOAc (8 mL × 3), washed with water (10 mL × 3) and brine (10 mL × 3), dried over $Na_2SO_4$, and concentrated; then, the residue was purified by flash column chromatography to afford **6a** (37.8 mg, 46% yield from **5dj**) and **7a** (12.8 mg, 14% yield from **5dj**). Assoanine **6a**: known compound,[11] $R_f$ = 0.58 (EtOAc/PE = 1/5); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.33 (d, $J$ = 8.0 Hz, 1 H), 7.19 (s, 1 H), 7.00 (d, $J$ = 7.2 Hz, 1 H), 6.78 (d, $J$ = 7.6 Hz, 1 H), 6.66 (s, 1 H), 4.11 (s, 2 H), 3.95


DOI: 10.1021/acs.joc.8b03018
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(s, 3 H), 3.90 (s, 3 H), 3.34 (t, $J$ = 8.0 Hz, 2 H), 3.03 (t, $J$ = 8.0 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 149.6, 148.7, 148.4, 128.6, 124.8, 124.3, 119.1, 55.5, 53.3, 29.1, $\delta$ (down) 123.4, 119.7, 119.4, 110.4, 105.4, 56.1 (2). Oxoassoanine **7a**: known compound,[11] $R_f$ = 0.63 (EtOAc); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.91 (s, 1 H), 7.90 (d, $J$ = 8.0 Hz, 1 H), 7.51 (s, 1 H), 7.28 (d, $J$ = 7.2 Hz, 1 H), 7.20 (t, $J$ = 7.6 Hz, 1 H), 4.47 (t, $J$ = 8.0 Hz, 2 H), 4.08 (s, 3 H), 4.04 (s, 3 H), 3.42 (t, $J$ = 8.0 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 159.7, 152.9, 149.7, 139.5, 131.0, 128.6, 121.4, 116.8, 46.6, 27.5, $\delta$ (down) 123.6, 123.2, 119.3, 108.8, 103.0, 56.3, 56.2, and the sample was found to be congruent ($^1H$ NMR) to the substance previously reported.

*Oxoassoanine (**7a**).* The **7a** (17.8 mg, 63% yield from **6a**) could also be achieved from the **6a** (26.7 mg, 0.1 mmol) via the following oxidation according to the reported procedure.[14b] The sample was found to be congruent ($^1H$, $^{13}C\{^1H\}$ NMR) to the substance from the biaryl coupling reaction of **5dj**.

*Anhydrolycorine (**6b**) and Anhydrolycorinone (**7b**).* The **6b** (39.3 mg, 52% yield from **5dk**) and **7b** (7.9 mg, 14% yield from **5dk**) were prepared from the **5dk** (99.6 mg, 0.3 mmol) with the $Pd(OAc)_2$ (6.8 mg, 3% mmol), $PCy_3$ (16.8 mg, 6% mmol), and $K_2CO_3$ (82.8 mg, 0.6 mmol) according to the procedure for preparation of **6a** and **7a**, and the reaction time for the process was 1 h. Anhydrolycorine **6b**: known compound,[11] $R_f$ = 0.60 (EtOAc/PE = 1/5); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.20 (d, $J$ = 7.2 Hz, 1 H), 7.17 (s, 1 H), 7.02 (d, $J$ = 7.6 Hz, 1 H), 6.76 (t, $J$ = 7.2 Hz, 1 H), 6.64 (s, 1 H), 5.97 (s, 2 H), 4.07 (s, 2 H), 3.32 (t, $J$ = 8.0 Hz, 2 H), 3.02 (t, $J$ = 8.0 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 149.7, 147.6, 146.8, 128.6, 126.2, 125.8, 119.2, 101.2, 55.5, 53.7, 29.2, $\delta$ (down) 123.6, 119.8, 119.7, 107.6, 102.8. Anhydrolycorinone **7b**: known compound,[11] $R_f$ = 0.60 (EtOAc); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.90 (s, 1 H), 7.73 (d, $J$ = 8.0 Hz, 1 H), 7.52 (s, 1 H), 7.28 (d, $J$ = 7.2 Hz, 1 H), 7.18 (t, $J$ = 7.2 Hz, 1 H), 6.13 (s, 2 H), 4.46 (t, $J$ = 8.0 Hz, 2 H), 3.42 (t, $J$ = 8.0 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, plus APT) $\delta$ (up) 159.5, 151.9, 148.4, 139.4, 130.9, 130.7, 123.1, 116.8, 102.1, 46.6, 27.5, $\delta$ (down) 123.8, 123.3, 119.5, 106.8, 100.9, and the sample was found to be congruent ($^1H$ NMR) to the substance previously reported.

*Anhydrolycorinone (**7b**).* The **7b** (16.2 mg, 61% yield from **6b**) was prepared from the **6b** (25.1 mg, 0.1 mmol) with the aqueous NaOH (3 mol/L, 1 mL) and $KMnO_4$ (30.0 mg, 0.2 mmol) according to the above oxidation procedure for the preparation of **7a**, and the reaction time for the process was 2 h. The sample was found to be congruent ($^1H$, $^{13}C\{^1H\}$ NMR) to the substance from the biaryl coupling reaction of **5dk**.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b03018.

Copies of NMR spectra for the key compounds (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 21662027), the Program for Leading Talents of Ningxia Province (KJT2015002), and the Natural Science Foundation of Ningxia (NZ17035).

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DOI: 10.1021/acs.joc.8b03018
*J. Org. Chem.* 2019, 84, 2012−2021