Synthesis of Novel Heterocycles by Amide Activation and Umpolung Cyclization

Haoqi Zhang, Margaux Riomet, Alexander Roller and Nuno Maulide*

Institute of Organic Chemistry, Faculty of Chemistry, University of Vienna, Währinger Straße 38, 1090 Vienna, Austria.
Institute of Inorganic Chemistry, Faculty of Chemistry, University of Vienna, Währinger Straße 42, 1090 Vienna, Austria.
1. General Information

Unless otherwise stated, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon with anhydrous solvents. Triflic anhydride was distilled over P2O5 prior to use. All other reagents were used as received from commercial suppliers unless otherwise stated. Reaction requiring higher temperature were heated in an oil bath. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F254 with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). DMA mixture for column chromatography was made of DCM, MeOH, concentrated ammonia (90:10:1). Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (vmax) are reported in cm⁻¹. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All 1H NMR and 13C NMR spectra were recorded using a Bruker AV-400, AV-600 and AV-700 spectrometer at 300K. Chemical shifts were given in parts per million (ppm, δ) and coupling constants (J) are quoted in Hz, referenced to the solvent peak of CDCl3, defined at δ = 7.26 ppm (1H NMR) and δ = 77.16 (13C NMR). Coupling constants are quoted in Hz (J). 1H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Selected 13C NMR spectra were recorded using the attached proton test (APT) to facilitate the confirmation and assignment of the structure.
2. Optimization

2.1. Amidine

![Chemical Structure](image.png)

| Entry | x (eq) | t (min) | y (eq) | Quinoline | z (eq) | T    | Yield |
|-------|--------|---------|--------|-----------|--------|------|-------|
| 1     | 2      | 15      | 2      |           | 5      | rt   | 48%   |
| 2     | 2      | 15      | 2      |           | 5      | rt   | -     |
| 3     | 2      | 15      | 2      |           | 5      | rt   | -     |
| 4     | 2      | 15      | 2      |           | 2      | rt   | 63%   |
| 5     | 2      | 15      | 2      |           | 2      | rt   | 75%   |
| 6     | 2      | 15      | 2      |           | 2      | 40 °C| 63%   |
| 7     | 2      | 15      | 2      |           | 2      | rt   | 66%   |
| 8     | 2      | 15      | 1.1    |           | 2      | rt   | 78%   |
| 9     | 1.1    | 15      | 1.1    |           | 2      | rt   | 53%   |
| 10    | 1.1    | 30      | 1.1    |           | 2      | rt   | 59%   |
| 11    | 1.4    | 15      | 1.1    |           | 2      | rt   | 67%   |

Table S1 Reaction optimization. Yields refer to isolated product. Reactions were carried out on 0.2 mmol scale.

2.2. Hydrolysis of Amidine

To a solution of 3a in [solvent] was added aqueous [base]. The mixture was stirred for [time] under reflux. After cooling down and quenching with NH₄Cl (sat.), the layers were separated and the aqueous phase was washed with DCM (3x). The combined organic layers were dried over Na₂SO₄ and
concentrated under reduced pressure. The product was purified via column chromatography (silica, DMA-DCM gradient, 0 to 20%).

![Diagram](image)

| Entry | Base                        | Solvent | Time | Yield$^a$ |
|-------|-----------------------------|---------|------|-----------|
| 1     | 1.0 mL NaOH (1 M, 5 eq)     | 1.0 mL THF | 15 h | 56 %      |
| 2     | 2.0 mL NaOH (1 M, 10 eq)    | 2.0 mL THF | 24 h | 43 %      |
| 3     | 1.0 mL NaOH (5 M, 25 eq)    | 1.0 mL THF | 24 h | 5 %       |
| 4     | 1.0 mL NaOH (1 M, 5 eq)     | 1.0 mL EtOH | 15 h | 7 %       |
| 5     | 1.0 mL KOH (1 M, 5 eq)      | 1.0 mL THF | 15 h | 10 %      |
| 6     | 1.0 mL NaOH (1 M, 5 eq)     | 1.0 mL Dioxane | 15 h | 22 %      |
| 7     | 1.0 mL NaOH (1 M, 5 eq)     | 5.0 mL THF | 15 h | 0 %       |
| 8     | 1.0 mL NaOH (1 M, 5 eq)     | 1.0 mL THF | 15 h | 63 %      |
|       | TPA-OH (0.1 eq)             |         |      |           |

Table S2 Hydrolysis optimization. Yields refer to isolated product. Reactions were carried out on 0.2 mmol scale.

Reaction conditions: A mixture of 3a (0.2 mmol, 1 eq.), solvent and base were stirred under reflux for 15 h. $^a$Isolated yields.
3. Substrates
3.1. Amide Synthesis

General Procedure A
To a solution of the amine (1.0 eq.) and triethylamine (2.0 eq.) in DCM (0.1 M) at 0 °C, the corresponding acyl chloride (1.2 eq.) was added dropwise and the resulting reaction mixture was allowed to warm up to room temperature while stirring for 14 h. Afterwards, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the biphasic system was separated. After extraction of the aqueous phase with DCM (2×), the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate, 40:60) to afford the desired compound.

General Procedure B
The acyl chloride was first prepared via addition of oxalyl chloride (3 eq.) to a mixture of carboxylic acid (1 eq.) and catalytic amount of N,N-dimethylformamide (0.1 eq.) in DCM (0.2 M) at room temperature. After stirring for 14 h, the solvent and excess of oxalyl chloride were removed under reduced pressure. The crude acyl chloride was directly dissolved in DCM (0.2 M) and pyrrolidine (5 eq.) was added. The mixture was stirred for 5 h at room temperature. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate. After separation, the organic layer was washed with HCl (1 M), NaHCO$_3$ (sat.) and brine. The product was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The pure product was used without further purification.

General Procedure C
To a solution of carboxylic acid (1.0 eq.), HOBt (1.0 eq.) and EDCI (1.0 eq.) in DCM (0.5 M) were added the secondary amine (1.0 eq.) and triethylamine (1.0 eq.). The mixture was stirred for 16 h under argon atmosphere at room temperature. The mixture was diluted with EtOAc (5 DCM volumes). The organic layer was washed with HCl 1M. then a saturated solution of NaHCO$_3$ then brine. The organic layer was dried over MgSO$_4$; filtered and evaporated under reduced pressure.

General Procedure D
HATU (1.2 eq.) was added to a solution of secondary amine (1.2 eq.), carboxylic acid (1 eq.) and triethylamine (2.4 eq.) in 0.4 M DMF. The reaction was stirred overnight at room temperature before quenching with 1M NaOH. The mixture was then extracted with ether, washed with sat. NH$_4$Cl solution, dried over Na$_2$SO$_4$, and then evaporated.
2-phenyl-1-([pyrrolidin-1-yl]ethan-1-one 1a

The desired amide was prepared using procedure A with 10.0 mmol pyrrolidine (821 µL), 12.0 mmol phenylacetyl chloride (1.62 mL) and 20.0 mmol of Et$_3$N (2.79 mL).

Yield (yellow-white solid): 91 % (1.72 g).

Spectroscopic data are in agreement with the literature.$^1$

$N,N$-Diethyl-2-phenylacetamide 1b

The desired amide was prepared using procedure C with 7.34 mmol diethylamine (760 µL), 7.34 mmol phenylacetic acid (1.00 g), 7.34 mmol HOBt (992 mg), 7.34 mmol EDCI.HCl (1.41 g) and 7.34 mmol of Et$_3$N (1.02 mL). The crude product was purified by column chromatography (Heptane /EtOAc, from 80%/20% to 0%/100%).

Yield (colourless oil): 82 % (1.15 g).

Spectroscopic data are in agreement with the literature.$^2$

1-(azetidin-1-yl)-2-phenylethan-1-one 1c

The desired amide was prepared using procedure C with 10 mmol azetidine hydrochloride (936 µL), 10 mmol phenylacetic acid (1.36 g), 10 mmol HOBt (1.35 g), 10 mmol EDCI.HCl (1.92 g) and 20 mmol of Et$_3$N (2.79 mL). The crude product was purified by column chromatography (Heptane /EtOAc, from 80%/20% to 0%/100%).

Yield (colourless oil): 29 % (505 mg).

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.35 – 7.21 (m, 5H), 4.14 – 4.08 (m, 2H), 4.06 – 4.00 (m, 2H), 3.45 (s, 2H), 2.28 – 2.17 (m, 2H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ (ppm) 170.8, 134.7, 129.0 (2C), 128.6 (2C), 126.8, 50.6, 48.1, 39.1, 15.1.

HRMS (ESI) m/z calculated for [M+H]$^+$ C$_{11}$H$_{14}$N.O$: 176.1070, found 176.1073.

ATR-FTIR (cm$^{-1}$): 2951, 1638, 1424, 1298, 1118, 720, 695.

$^1$ Pintori, D. G.; Greaney, M. F. Org. Lett. 2011, 13, 5713–5715.

$^2$ Bannwart, L.; Abele, S.; Tortoioli, S. Synthesis 2016, 48, 2069–2078.
2-(2-bromophenyl)-1-(pyrrolidin-1-yl)ethan-1-one 1d

The desired amide was prepared using procedure C with 3.06 mmol pyrrolidine (251 µL), 3.06 mmol 2-bromophenylacetic acid (658 mg), 3.06 mmol HOBT (468 mg), 3.06 mmol EDCI.HCl (586 mg) and 3.06 mmol of Et3N (426 µL). The crude product was purified by column chromatography (Heptane/EtOAc, from 80%/20% to 0%/100%).

Yield (colourless oil): 97% (780 mg).

\[ ^1H \text{NMR} \text{ (400 MHz, CDCl}_3 \text{): } \delta \text{ (ppm)} \text{ 7.55 (d, } J = 8.0 \text{ Hz, 1H), 7.33 (d, } J = 7.6 \text{ Hz, 1H), 7.27 (dd, } J = 10.8, 3.4 \text{ Hz, 1H), 7.13 \text{ – 7.09 (m, 1H), 3.77 (s, 2H), 3.52 (t, } J = 6.9 \text{ Hz, 2H), 3.48 (t, } J = 6.8 \text{ Hz, 2H), 1.96 (m, 2H), 1.87 (m, 2H).} \]

\[ ^13C \text{NMR} \text{ (151 MHz, CDCl}_3 \text{): } \delta \text{ (ppm)} \text{ 168.6, 135.4, 132.7, 131.1, 128.6, 127.7, 125.0, 47.0, 46.1, 42.2, 26.3, 24.6.} \]

HRMS (ESI) m/z calculated for [M+Na]+ C_{12}H_{14}BrNNaO+: 290.0151, found 290.0149.

ATR-FTIR (cm\(^{-1}\)): 2951, 2880, 1638, 1424, 1118, 720, 695.

2-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)ethan-1-one 1e

The desired amide was prepared using procedure B with 1.0 mmol 4-Methoxyphenylacetic Acid (166 mg), 0.10 mmol DMF (7.7 µL), 3.00 mmol oxalyl chloride (254 µL) and 5.0 mmol pyrrolidine (411 µL).

Yield (yellow oil): 95% (209 mg).

Spectroscopic data are in agreement with the literature.\(^3\)

2-(4-nitrophenyl)-1-(pyrrolidin-1-yl)ethan-1-one 1f

The product was obtained using general procedure D from 5.0 mmol 4-nitrophenylacetic acid (906 mg), 6.00 mmol pyrrolidine (493 µL), 6.00 mmol HATU (2.28 g) and 12 mmol triethylamine (1.67 mL). The crude product was purified by column chromatography (Heptane/EtOAc, from 80%/20% to 0%/100%).

Yield (yellow oil): 81% (945 mg)

Spectroscopic data are in agreement with the literature.\(^4\)

---

\(^3\) Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. J. Org. Chem. 1991, 56, 1058–1067.

\(^4\) Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. Tetrahedron 2002, 58, 9925–9932.
1-(pyrrolidin-1-yl)-2-(4-(trifluoromethyl)phenyl)ethan-1-one 1g

The desired amide was prepared using modified procedure C with THF as solvent and 3.76 mmol pyrrolidine (309 µL), 2.89 mmol 4-trifluorophenylacetic acid (590 mg), 3.76 mmol HOBt (508 mg), 3.76 mmol EDCI.HCl (720 mg) and 7.51 mmol of Et₃N (1.05 mL). The crude product was purified by column chromatography (Heptane/EtOAc, from 80%/20% to 0%/100%).

Yield (white solid): 88 % (653 mg).

Spectroscopic data are in agreement with the literature.⁴

N,N-diethylnonanamide S1

The desired amide was prepared using procedure A with 6.0 mmol diethylamine (621 µL), 5.0 mmol nonanoyl chloride (901 µL) and 10.0 mmol of Et₃N (1.39 mL).

Yield (yellow oil): quant. (1.01 g).

Spectroscopic data are in agreement with the literature.⁵

N,N-dimethyl-4-phenylbutanamide S2

The product was prepared according to general procedure C from 2.46 g 4-phenylbutyric acid and 4-nitrobenzenesulfonyl chloride (15.0 mmol) and 7.5 mL dimethylamine (2.0 M in THF), (15.0 mmol). The crude product was purified by column chromatography (Heptane/EtOAc, from 80%/20% to 0%/100%).

Yield (yellow oil): 71% (2.04 g). in 71% (2.04 g) yield.

Spectroscopic data are in agreement with the literature.⁶

---

⁴ Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. Org. Lett. 2006, 8, 1383–1386.
⁵ Zhou, X.; Zhang, G.; Gao, B.; Huang, Org. Lett. 2018, 20, 2208–2212.
3.2. Bromide Synthesis

2-bromo-1-(4-nitrophenyl)ethan-1-one S3

A solution of 6 mmol bromine (307 µL) in chloroform (2 mL) was slowly added to a solution of 5 mmol 4-nitroacetophenone (826 mg) in chloroform (5 mL) at 0°C under continuous stirring. The temperature of the reaction mixture was maintained at 0–5 °C during the addition. After stirring for 14 h at r.t., the solvent was removed under reduced pressure. The product was purified by recrystallization in EtOH (ca. 10 mL) to yield pure compound.

Yield (yellow-white solid): 32 % (386 mg).

Spectroscopic data are in agreement with the literature.⁷

3.3. Azide Synthesis

General Procedure E

A solution of bromide (1 eq.) and NaN₃ (1.5 eq.) in DMF (0.2 M) was stirred at 80 °C overnight. After 14 h, the reaction mixture was cooled to r.t., diluted with Et₂O or EtOAc. The biphasic system was separated and the organic layer was washed with ice-cooled H₂O (4x) and brine (1x). The pure product was obtained after drying over anhydrous Na₂SO₄ and evaporation of the solvent under reduced pressure to obtain the pure product which was used without further purifications.

General Procedure F

The corresponding halide was added to a solution of NaN₃ (1.5 eq. or 3 eq.) in DMSO (0.5 M) at 0 °C and the reaction mixture was stirred at 23 °C for 10 min or 14 h. Ice-cooled H₂O was added to the mixture and the mixture was extracted with diethyl ether (3x). The combined organic layers were washed with ice-cooled H₂O (4x) and brine (1x), dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure to obtain the pure product which was used without further purifications.

General Procedure G

The corresponding chloride was added to a suspension of NaN₃ (1.5 eq.) in acetone (0.2 M) and stirred for 36 h. Afterwards, the mixture was filtered. The filtrate was evaporated under reduced pressure to obtain the pure product which was used without further purification.

⁷ Tada, N.; Ban, K.; Hirashima, S.; Miura, T.; Itoh, A. Direct Synthesis of α-Bromoketones from Alkylarenes by Aerobic Visible Light Photooxidation. Org. Biomol. Chem. 2010, 8, 4701–4704.
(2-azidoethyl)benzene 2a

The product was prepared using procedure E with 10 mmol (2-Bromoethyl)benzene (1.37 mL) and 15 mmol sodium azide (975 mg) in DMF.

Yield (yellow oil): 87 % (1.29 g).

Spectroscopic data are in agreement with the literature.  

1-(2-azidoethyl)-2-methylbenzene 2b

The product was prepared using procedure E with 1 mmol 2-Methylphenethyl bromide (169 µL) and 1.5 mmol sodium azide (97.5 mg) in DMF.

Yield (yellow oil): 93 % (150 mg).

Spectroscopic data are in agreement with the literature.  

1-(2-azidoethyl)-3-methoxybenzene 2c

The product was prepared using procedure E with 1 mmol 3-methoxyphenethyl bromide (215 mg) and 1.5 mmol sodium azide (97.5 mg) in DMF.

Yield (clear oil): 90 % (160 mg).

Spectroscopic data are in agreement with the literature.  

---

8 Kalkeren, H. A. van; Bruins, J. J.; Rutjes, F. P. J. T.; van Delft, F. L. Advanced Synthesis & Catalysis 2012, 354, 1417–1421.
9 Suzuki, T.; Ota, Y.; Ri, M.; Bando, M.; Gotoh, A.; Itoh, Y.; Tsumoto, H.; Tatum, P. R.; Mizukami, T.; Nakagawa, H.; et al. J. Med. Chem. 2012, 55, 9562–9575.
1-(2-azidoethyl)-4-fluorobenzene 2d

To a 0.5 M solution of NaN$_3$ (1.1 eq., 2.2 mmol, 143 mg) in 4 mL DMSO was added p-Fluorophenethyl bromide (1.0 eq., 2 mmol, 0.28 mL), and the mixture was stirred at 80 °C and periodically monitored by TLC. When the reaction was completed, the mixture was quenched with water and stirred until it cooled down to room temperature and then extracted with Et$_2$O. The organic layer was separated, washed with water and brine, and dried over Na$_2$SO$_4$. Filtration, concentration in vacuo, and purification of the residue by silica gel flash column chromatography gave the corresponding alkyl azide.

Yield (clear oil): quantitative (330 mg).

Spectroscopic data are in agreement with the literature. 9

1-(2-azidoethyl)-3-nitrobenzene 2e

The product was prepared using procedure E with 1 mmol bromide (230 mg) and 1.5 mmol sodium azide (97.5 mg) in DMF.

Yield (yellow oil): 99% (191 mg).

Spectroscopic data are in agreement with the literature. 9

Benzyl azide 2f

The product was obtained using general procedure E from 10 mmol benzyl bromide (1.19 mL) and 15 mmol sodium azide (975 mg).

Yield (yellow oil): quantitative (1.35 g).

Spectroscopic data are in agreement with the literature. 10

1-(azidomethyl)-3-methoxybenzene 2g

The product was prepared using procedure E with 1 mmol 3-Methoxybenzyl bromide (143 µL) and 1.5 mmol sodium azide (97.5 mg) in DMF.

Yield (clear oil): 93% (151 mg).

Spectroscopic data are in agreement with the literature. 11

---

9 Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Eur. J. Org. Chem. 2010, 2010 (10), 1875–1884
10 Montanari, S.; Scalvini, L.; Bartolini, M.; Belluti, F.; Gobbi, S.; Andrisano, V.; Ligresti, A.; Di Marzo, V.; Rivara, S.; Mor, M.; et al. J. Med. Chem. 2016, 59, 6387–6406.
2-azido-1-phenylethan-1-one 7a

The product was prepared using procedure F with 5 mmol phenacyl bromide (995 mg) and 15 mmol sodium azide (975 mg) in DMSO.

Yield (orange oil): 92% (743 mg).

Spectroscopic data are in agreement with the literature. 9

2-azido-1-(naphthalen-2-yl)ethan-1-one 7b

The product was prepared using procedure F with 1 mmol 2-Bromo-2′-acetonaphthone (249 mg) and 3 mmol sodium azide (195 mg) in DMSO.

Yield (orange solid): 94 % (198 mg).

Spectroscopic data are in agreement with the literature. 12

2-azido-1-(4-methoxyphenyl)ethan-1-one 7c

The product was prepared using procedure F with 1 mmol 2-Bromo-4′-methoxyacetophenone (229 mg) and 3 mmol sodium azide (195 mg) in DMSO.

Yield (yellow solid): 95 % (181 mg).

Spectroscopic data are in agreement with the literature. 13

2-azido-1-(4-nitrophenyl)ethan-1-one 7d

The product was prepared using procedure F with 1 mmol S3 (244 mg) and 3 mmol sodium azide (195 mg) in DMSO.

Yield (red oil): 74 % (153 mg).

Spectroscopic data are in agreement with the literature. 14

12 Neyyappadath, R. M.; Chisholm, R.; Greenhalgh, M. D.; Rodríguez-Escrich, C.; Pericàs, M. A.; Hähner, G.; Smith, A. D. ACS Catal. 2018, 8, 1067–1075.
13 Yokoi, T.; Tanimoto, H.; Ueda, T.; Morimoto, T.; Kakiuchi, K. J. Org. Chem. 2018, 83, 12103–12121.
14 Gong, P. K.; Blough, B. E.; Brieaddy, L. E.; Huang, X.; Kuhar, M. J.; Navarro, H. A.; Carroll, F. I. J. Med. Chem. 2007, 50 (15), 3686–3695.
**1-azido-3,3-dimethylbutan-2-one 7e**

![1-azido-3,3-dimethylbutan-2-one](image)

The product was prepared using procedure G with 1 mmol 1-Chloropinacoline (131 µL) and 1.5 mmol sodium azide (97.5 mg) in acetone.

Yield (yellow oil): 79 % (153 mg)

Spectroscopic data are in agreement with the literature.\(^{15}\)

**3-azidobutan-2-one 7f**

![3-azidobutan-2-one](image)

The product was prepared using procedure G with 2 mmol 3-Chloro-2-butanone (202 µL) and 3 mmol sodium azide (195 mg) in acetone.

Yield (yellow oil): 90 % (203 mg).

Spectroscopic data are in agreement with the literature.\(^{16}\)

**2-azidocyclohexan-1-one 7g**

![2-azidocyclohexan-1-one](image)

The product was prepared using procedure F with 5 mmol 2-Chlorocyclohexanone (572 µL) and 7.5 mmol sodium azide (488 mg) in DMSO and stirring for 14 h.

Yield (brown oil): 78 % (545 mg).

Spectroscopic data are in agreement with the literature.\(^{17}\)

---

\(^{15}\) Streefkerk, D. E.; Schmidt, M.; Ippel, J. H.; Hackeng, T. M.; Nuijens, T.; Timmerman, P.; van Maarseveen, J. H. *Org. Lett.* **2019**, *21*, 2095–2100.

\(^{16}\) Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62* (8), 1864–1876.

\(^{17}\) Myers, E. L.; Raines, R. T. *Angew. Chem. Int. Ed.* **2009**, *48* (13), 2359–2363.
3-azido-1-phenylpropan-1-one 7h

The product was prepared using procedure F with 5 mmol 3-Chloropropiophenone (843 mg) and 7.5 mmol sodium azide (488 mg) in DMSO and stirring for 14 h. Additional purification via column chromatography on silica gel (heptane/EtOAc 9:1) was performed.

Yield (yellow oil): 68 % (598 mg).
Spectroscopic data are in agreement with the literature.18

tert-butyl 2-azidoacetate 7i

The product was prepared using procedure F with 5 mmol tert-butyl bromoacetate (729 µL) and 7.5 mmol sodium azide (488 mg) in DMSO and stirring for 14 h.

Yield (yellow oil): 56 % (442 mg).
Spectroscopic data are in agreement with the literature.19

18 Singh, P. N. D.; Muthukrishnan, S.; Murthy, R. S.; Klima, R. F.; Mandel, S. M.; Hawk, M.; Yarbrough, N.; Gudmundsdóttir, A. D. Tetrahedron Lett. 2003, 44, 9169–9171.
19 Asano, K.; Matsubara, S. Org. Lett. 2010, 12, 4988–4991.
4. Amidines, Oxazines and Oxazinones

General Procedure H

To a mixture of amide (1.0 eq.), 2,4-dichloroquinoline (2.0 eq.) in anhydrous DCM (0.1 M), triflic anhydride (2.0 eq.) was added dropwise under vigorous stirring at 0 °C. After 15 min, the azide (1.1 eq.) was added and the mixture was stirred at r.t. for 14 h. The reaction was then quenched with a saturated aqueous solution of sodium bicarbonate for 1 h. After separation of the biphasic system and extraction of the aqueous phase with DCM (3×), the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure.
4.1. Amidines

5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium- trifluoromethanesulfonate 3a

The amidine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf2O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2a (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange solid): 78 % (69 mg).

Gram Scale Reaction

To a mixture of amide 1a (757 mg, 4.0 mmol, 1.0 eq.), 2,4-dichloroquinoline (1.58 g, 8.0 mmol, 2.0 eq.) in anhydrous DCM (40 mL), triflic anhydride (1.35 mL, 8.0 mmol, 2.0 eq.) was added dropwise under vigorous stirring at 0 °C. After 15 min, azide 2a (648 mg, 4.4 mmol, 1.1 eq.) was added and the mixture was stirred at r.t. for 14 h. The reaction was then quenched with a saturated aqueous solution of sodium bicarbonate for 1 h. After separation of the biphasic system and extraction of the aqueous phase with DCM (3 ×), the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70). The product was obtained as an orange solid (1.45 g, 83%).

1H NMR (600 MHz, CDCl3): δ (ppm) 8.94 (br. s, 1H), 7.38 (m, 1H), 7.34 (m, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.27 – 7.23 (m, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 5.44 (s, 1H), 4.01 – 3.86 (m, 2H), 3.75 – 3.65 (m, 1H), 3.53 – 3.41 (m, 2H), 3.17 (m, 1H), 2.96 (dt, J = 17.8, 3.5 Hz, 1H), 2.30 – 2.03 (m, 4H).

13C NMR (151 MHz, CDCl3): δ (ppm) 164.8, 137.7, 137.0, 133.0, 132.4, 129.8 (2C), 129.7, 129.6, 128.4, 127.6, 125.8 (2C), 52.6, 51.1, 49.6, 40.5, 32.1, 25.5, 25.1.

19F NMR (565 MHz, CDCl3): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]+ C20H23N2+: 291.1856, found 291.1858.

ATR-FTIR (cm−1): 3295, 3233, 3066, 2962, 2929, 1642, 1496, 1451, 1279, 1157, 1030, 672.

Mp.: 178–180 °C

4-(diethylamino)-5-phenyl-2,5-dihydro-1H-benzo[d]azepin-3-ium- trifluoromethanesulfonate 3b

The amidine was prepared using procedure H with 0.20 mmol amide 1b (38.3 mg), 0.40 mmol Tf2O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2a (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 51 % (45 mg)

1H NMR (600 MHz, CDCl3): δ (ppm) 9.13 (br.s, 1H), 7.43 – 7.38 (m, 1H), 7.38 – 7.29 (m, 4H), 7.28 (m, 1H), 7.18 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 7.7 Hz, 2H), 5.42 (s, 1H), 3.95 – 3.76 (m, 2H), 3.68 (m, 1H), 3.61 (m, 2H), 3.49 – 3.34 (m, 1H), 3.32 – 3.16 (m, 1H), 2.99 – 2.91 (m, 1H), 1.43 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).

13C NMR (151 MHz, CDCl3): δ (ppm) 166.4, 137.7 (2C), 133.2, 132.8, 129.9 (2C), 129.7, 129.3, 128.4, 127.7, 125.5 (2C), 50.3, 47.7, 46.2, 40.0, 32.1, 14.9, 11.7.

19F NMR (565 MHz, CDCl3): δ (ppm) –78.2.
HRMS (ESI) m/z calculated for [M-TfO]+ C_{20}H_{25}N_2+: 293.2012, found 293.2013.

**ATR-FTIR (cm⁻¹):** 3280, 3229, 2982, 2928, 16,31, 1584, 1495, 1449, 1243, 1224, 1198, 1154, 1029, 748, 636.

4-(azetidin-1-yl)-5-phenyl-2,5-dihydro-1H-benzo[d]azepin-3-ium-trifluoromethanesulfonate 3c

The amidine was prepared using procedure H with 0.20 mmol amide 1c (35.0 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2a (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange solid): 69 % (59 mg).

**1H NMR** (600 MHz, CDCl₃): δ (ppm) 8.90 (s, 1H), 7.34 – 7.27 (m, 3H), 7.25 (m, 2H), 7.16 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 7.9 Hz, 2H), 4.86 (s, 1H), 4.52 (m, 3H), 4.43 (m, 1H), 3.37 (m, 2H), 3.00 (ddd, J = 15.5, 10.5, 4.6 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.53 (m, 1H), 2.48 – 2.37 (m, 1H).

**13C NMR** (151 MHz, CDCl₃): δ (ppm) 164.6, 137.6, 136.5, 132.5, 132.1, 130.1, 129.7 (2C), 129.6, 128.4, 127.7, 126.2 (2C), 53.2, 52.3, 49.3, 40.8, 32.0, 14.8.

**19F NMR** (565 MHz, CDCl₃): δ (ppm) –78.3.

HRMS (ESI) m/z calculated for [M-TfO]+ C_{18}H_{23}N_2+: 277.1699, found 277.1697.

**ATR-FTIR (cm⁻¹):** 3219, 3092, 2950, 1656, 1495, 1448, 1244, 1157, 1029, 725, 636, 517.

Mp.: 163–165 °C.

5-(2-bromophenyl)-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium-trifluoromethanesulfonate 3d

The amidine was prepared using procedure H with 0.20 mmol amide 1d (53.6 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2a (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (yellow solid): 70 % (73 mg).

**1H NMR** (600 MHz, CDCl₃) δ (ppm) 8.81 (br.s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.34 (m, 2H), 7.28 – 7.22 (m, 2H), 7.19 (d, J = 7.4 Hz, 1H), 6.76 – 6.61 (m, 1H), 5.21 (s, 1H), 4.29 (m, 1H), 3.75 (m, 2H), 3.63 – 3.52 (m, 2H), 3.44 – 3.30 (m, 2H), 3.01 (m, 1H), 2.23 – 2.01 (m, 4H).

**13C NMR** (151 MHz, CDCl₃): δ (ppm) 163.8, 138.0, 137.1, 134.6, 133.0, 132.0, 131.1, 130.4, 130.1, 128.3, 128.1, 121.6, 53.2, 50.7, 49.7, 38.9, 32.3, 25.4, 24.9.

**19F NMR** (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]+ C_{20}H_{22}BrN_2+: 371.0940, found 371.0954.

**ATR-FTIR (cm⁻¹):** 3287, 3220, 3071, 2980, 2960, 2929, 1637, 1466, 1244, 1157, 1029, 757, 729, 636.

Mp.: 212–215 °C.
5-(4-methoxyphenyl)-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-i um- trifluoromethane-sulfonate 3e

The amidine was prepared using procedure H with 0.20 mmol amide 1e (43.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2a (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 45 % (42 mg)

\( ^1H \text{NMR} \) (400 MHz, CDCl₃): \( \delta \) (ppm) 9.03 (br. s, 1H), 7.39 – 7.22 (m, 3H), 7.16 (d, \( J = 7.6 \) Hz, 1H), 6.87 (d, \( J = 8.8 \) Hz, 2H), 6.79 (d, \( J = 8.2 \) Hz, 2H), 5.36 (s, 1H), 3.95 – 3.85 (m, 2H), 3.85 – 3.80 (m, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.54 (m, 2H), 3.24 – 3.10 (m, 1H), 2.98 (m, 1H), 2.26 – 2.06 (m, 4H).

\( ^13C \text{NMR} \) (151 MHz, CDCl₃): \( \delta \) (ppm) 164.9, 159.5, 137.8, 132.8, 132.4, 130.0, 129.6, 128.7, 127.5, 127.0 (2C), 115.1 (2C), 55.5, 52.0, 51.0, 49.6, 40.5, 32.1, 25.5.

\( ^19F \text{NMR} \) (565 MHz, CDCl₃): \( \delta \) (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₇H₇N₂O₂⁺: 321.1961, found 321.1962.

ATR-FTIR (cm⁻¹): 3293, 3226, 3064, 2959, 2935, 1639, 1510, 1455, 1242, 1153, 1027, 732, 635, 516.

5-(4-nitrophenyl)-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-i um- trifluoromethane-sulfonate 3f

The amidine was prepared using procedure H with 0.20 mmol amide 1f (46.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2a (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 0:100 to 30:70).

Yield (orange-brown oil): 13 % (13 mg)

\( ^1H \text{NMR} \) (600 MHz, CDCl₃): \( \delta \) (ppm) 9.18 (br. s, 1H), 8.20 (d, \( J = 12.5 \) Hz, 2H), 7.49 – 7.41 (m, 1H), 7.36 (dd, \( J = 7.5 \), \( J = 7.5 \) Hz, 1H), 7.31 (d, \( J = 6.6 \) Hz, 1H), 7.21 (d, \( J = 10.1 \) Hz, 1H), 7.16 (d, \( J = 8.5 \) Hz, 2H), 5.46 (s, 1H), 3.97 (m, 1H), 3.95 – 3.88 (m, 2H), 3.81 – 3.72 (m, 1H), 3.57 (m, 1H), 3.34 (m, 1H), 3.29 – 3.17 (m, 1H), 2.98 (m, 1H), 2.36 – 2.06 (m, 4H).

\( ^13C \text{NMR} \) (151 MHz, CDCl₃): \( \delta \) (ppm) 163.7, 147.8, 144.1, 137.6, 132.9 (2C), 130.4, 128.4, 128.0, 127.2 (2C), 124.9 (2C), 52.5, 51.3, 50.0, 40.7, 32.1, 25.5, 25.1.

\( ^19F \text{NMR} \) (565 MHz, CDCl₃): \( \delta \) (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₁₁H₁₁N₃O₂⁺: 336.1707, found 336.1711.

ATR-FTIR (cm⁻¹): 3230, 3080, 2960, 2931, 16,45, 1521, 1347, 1159, 1030, 637.
2-(4-nitrophenyl)-2-(phenethylamino)-1-(pyrrolidin-1-yl)ethan-1-one S4

The α-aminated product was formed as the major product during the synthesis of 3f. Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 0:100 to 30:70).

Yield (orange oil): 37 % (26 mg).

1H NMR (600 MHz, CDCl3): δ (ppm) 8.16 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 7.27 (m, 2H), 7.23 – 7.12 (m, 3H), 4.43 (s, 1H), 3.59 – 3.51 (m, 1H), 3.47 (m, 1H), 3.43 – 3.35 (m, 1H), 3.09 (m, 1H), 2.88 – 2.74 (m, 3H), 2.65 (m, 1H), 2.37 – 2.17 (br.s, 1H), 1.98 – 1.71 (m, 4H).

13C NMR (151 MHz, CDCl3): δ (ppm) 169.4, 147.7, 146.1, 139.8, 128.9 (2C), 128.8 (2C), 128.6 (2C), 126.4, 124.1 (2C), 64.1, 49.3, 46.3, 46.2, 36.9, 26.1, 24.1.

HRMS (ESI) m/z calculated for [M-H]– C20H24N3O3+: 354.1812, found 354.1813.

ATR-FTIR (cm⁻¹): 3330, 3026, 2949, 2877, 1640, 1604, 1519, 1429, 1345, 1109, 842, 752, 731, 700.

4-(pyrrolidin-1-yl)-5-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-benzo[d]azepin-3-ium trifluoromethanesulfonate 3g

The amidine was prepared using procedure H with 0.20 mmol amide 1g (51.5 mg), 0.40 mmol Tf2O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2a (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 45 % (46 mg).

1H NMR (600 MHz, CDCl3): δ (ppm) 9.01 (br.s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.36 (m, 1H), 7.27 (m, 1H), 7.21 (d, J = 6.4 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 2H), 5.38 (s, 1H), 3.96 – 3.73 (m, 3H), 3.73 – 3.61 (m, 1H), 3.51 – 3.39 (m, 1H), 3.32 (m, 1H), 3.18 – 3.04 (m, 1H), 2.90 (m, 1H), 2.28 – 1.97 (m, 4H).

13C NMR (151 MHz, CDCl3): δ (ppm) 164.0, 141.1, 137.6, 132.9, 132.6, 130.8 (q, J = 33.2 Hz, 1C), 130.1, 128.9, 126.7 (q, J = 3.0 Hz, 2C), 122.2 (dd, J = 320.1 Hz, J = 487.7 Hz, 1C), 52.5, 51.2, 49.9, 40.7, 32.0, 25.4, 25.1.

19F NMR (565 MHz, CDCl3): δ (ppm) –62.76, –78.3.

HRMS (ESI) m/z calculated for [M-TfO]+ C21H22F3N2+: 359.1730, found 359.1729.

ATR-FTIR (cm⁻¹): 3295, 3229, 3080, 2961, 2930, 1644, 1327, 1246, 1161, 1121, 1069, 1030, 638.
9-methyl-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium-trifluoromethanesulfonate 3h

The amidine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2b (35.5 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown solid): 61 % (55 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.14 (br.s, 1H), 7.38 – 7.27 (m, 4H), 7.22 (dd, J = 17.4, 9.8 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.89 (d, J = 8.1 Hz, 2H), 5.43 (1H), 3.95 (m, 2H), 3.89 – 3.79 (m, 2H), 3.79 – 3.68 (m, 1H), 3.59 (m, 1H), 3.52 – 3.43 (m, 1H), 3.31 (dd, J = 28.7 Hz, 10.5 Hz, 1H), 3.02 (ddd, J = 17.9, 12.8, 5.0 Hz, 1H), 2.74 (m, 1H), 2.32 – 2.23 (m, 3H), 2.41 – 2.07 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 165.0, 140.3, 137.2, 136.1, 131.7, 131.2, 129.8 (2C), 129.0, 128.4, 127.3, 125.7 (2C), 53.0, 50.9, 49.6, 39.9, 30.0, 25.5, 25.2, 20.7.

¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M–TfO]+ C₂₁H₂₅N₂O: 305.2017, found 305.2017.

ATR-FTIR (cm⁻¹): 3220, 3060, 1632, 1443, 1243, 1158, 1029, 731, 700, 636, 517.

Mp.: 243–245 °C.

8-methoxy-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium-trifluoromethanesulfonate 3i

The amidine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2c (39.0 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown solid): 93 % (88 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 8.97 (br.s, 1H), 7.39 – 7.28 (m, 3H), 7.10 (d, J = 8.5, 1H), 6.88 (d, J = 9.4 Hz, 2H), 6.84 (dd, J = 8.5, 2.8 Hz, 1H), 6.76 (d, J = 2.6 Hz, 1H), 5.38 (s, 1H), 3.96 – 3.86 (m, 2H), 3.82 (s, 3H), 3.80 (m, 1H), 3.72 (m, 1H), 3.55 – 3.35 (m, 2H), 3.24 – 3.05 (m, 1H), 2.94 (m, 1H), 2.28 – 2.03 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 165.0, 160.3, 139.1, 137.4, 134.2, 129.7 (2C), 128.3, 125.8 (2C), 121.4, 116.9, 113.6, 55.5, 51.8, 51.0, 49.6, 40.3, 32.4, 25.5, 25.2.

¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M–TfO]+ C₂₁H₂₁N₂O: 321.1961, found 321.1961.

ATR-FTIR (cm⁻¹): 3291, 3229, 3062, 2960, 2937, 1639, 1499, 1451, 1242, 1156, 1028, 731, 700, 635, 517.

Mp.: 160–162 °C.
7-fluoro-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium- trifluoromethanesulfonate 3j

The amidine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 2d (36.3 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 39 % (36 mg).

1H NMR (600 MHz, CDCl₃): δ (ppm) 9.13 (br. s, 1H), 7.43 – 7.29 (m, 3H), 7.26 – 7.22 (m, 1H), 7.12 (m, 1H), 6.97 – 6.92 (m, 1H), 6.88 (m, 2H), 5.37 (s, 1H), 3.97 – 3.86 (m, 2H), 3.81 (m, 2H), 3.55 (m, 1H), 3.46 (m, 1H), 3.17 (m, 1H), 2.95 (m, 1H), 2.33 – 2.02 (m, 4H).

13C NMR (151 MHz, CDCl₃): δ (ppm) 164.2, 161.5 (d, J = 24.7 Hz, 1C), 136.3, 134.2 (d, J = 7.5 Hz, 1C), 133.5 (d, J = 4.5 Hz, 1C), 131.25 (d, J = 6.0 Hz, 1C), 130.0 (2C), 128.7, 125.7 (2C), 119.3 (d, J = 22.6 Hz, 1C), 116.9 (d, J = 21.1 Hz, 1C), 52.3, 51.1, 49.8, 40.6, 31.5, 25.5, 25.2.

19F NMR (565 MHz, CDCl₃): δ (ppm) –78.3, –115.1.

HRMS (ESI) m/z calculated for [M–TfO]+ C₂₀H₂₂FN₂+: 309.1762, found 359.1773.

ATR-FTIR (cm⁻¹): 3295, 3229, 3064, 2961, 2928, 1640, 1498, 1450, 1241, 1152, 1060, 733, 699, 635, 516.

4-phenyl-3-(pyrrolidin-1-yl)-1,4-dihydroisoquinolin-2-ium-trifluoro-methanesulfonate 3l

The amidine was prepared using procedure H with 0.40 mmol amide 1a (75.7 mg), 0.80 mmol Tf₂O (135 µL), 0.80 mmol 2,4-dichloroquinoline (158 mg) and 0.44 mmol azide 2f (64.8 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 49 % (87 mg).

1H NMR (600 MHz, CDCl₃): δ (ppm) 9.74 (br. s, 1H), 7.40 – 7.29 (m, 6H), 7.24 (d, J = 7.3 Hz, 1H), 7.19 (d, J = 7.5 Hz, 2H), 5.15 (s, 1H), 4.86 (d, J = 15.9 Hz, 1H), 4.65 (d, J = 17.2 Hz, 1H), 3.87 – 3.78 (m, 3H), 3.53 – 3.46 (m, 1H), 2.18 – 2.05 (m, 3H), 2.00 – 1.93 (m, 1H).

13C NMR (151 MHz, CDCl₃): δ (ppm) 161.7, 135.5, 132.0, 130.2 (2C), 129.8, 128.9, 128.8, 128.5, 127.8, 126.7 (2C), 126.5, 49.9, 49.5, 47.9, 45.4, 25.5, 24.9.

19F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M–TfO]+ C₁₉H₁₂FN₂+: 277.1699, found 277.1712.

ATR-FTIR (cm⁻¹): 3213, 2859, 1653, 1457, 1223, 1154, 1027, 910, 727, 601.
The amidine was prepared using procedure H with 0.40 mmol amide 1a (75.7 mg), 0.80 mmol Tf₂O (135 µL), 0.80 mmol 2,4-dichloroquinoline (158 mg) and 0.44 mmol azide 2f (64.8 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70) to obtain a mixture of regioisomer.

Yield (orange-brown oil): 84% (77 mg).

¹H NMR (600 MHz, CDCl₃) δ (ppm) 9.57 (s, 0.4H), 9.54 (s, 0.6H), 7.39 – 7.20 (m, 5H), 7.17 (d, J = 7.4 Hz, 1H), 6.89 – 6.82 (m, 1.4H), 6.72 (m, 0.6H), 5.55 (s, 0.4H), 5.15 (s, 0.6H), 4.81 (m, 0.4H), 4.79 (m, 0.6H), 4.65 (d, J = 5.6 Hz, 0.6H), 4.62 (d, J = 5.5 Hz, 0.4H), 3.91 (s, 1H), 3.89 – 3.82 (m, 1H), 3.76 (s, 4H), 3.55 (m, 0.6H), 3.47 (m, 0.4H), 2.14 – 2.00 (m, 3H), 2.00 – 1.88 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ (ppm) {162.1}, 162.0, 159.5, (155.8), 136.2, (135.1), (131.7), 130.9, 130.1 (2C), (129.7), (129.5), 129.1, 128.7, (128.6), (127.3), 126.6 (2C), 124.0, (120.9), (118.5), 115.4, 110.7, (110.1), (55.8), 55.6, 50.0, (49.9), 49.3, 47.1, 45.5, (45.4), (41.4), 25.4, (25.4), (24.9), 24.8. When distinguishable, the signals of the second minor are reported in brackets.

¹⁹F NMR (565 MHz, CDCl₃) δ (ppm) -78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₀H₂₃N₂O⁺: 307.1805, found 307.1806.
4.2. α-Amination

\( \alpha \)-Aminated amide was prepared using procedure H with 0.20 mmol amide \( S1 \) (42.7 mg), 0.40 mmol \( \text{Tf}_2 \text{O} \) (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide \( 2a \) (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (orange-brown oil): 39% (36 mg).

\(^1\text{H NMR} \) (600 MHz, CDCl\(_3\)): \( \delta \) (ppm) 7.26 (m, 2H), 7.18 (m, 3H), 3.54 (m, 1H), 3.36 (m, 2H), 3.26 – 3.13 (m, 2H), 2.86 – 2.75 (m, 2H), 2.72 (m, 1H), 2.65 – 2.56 (m, 1H), 2.27 – 1.89 (br.s, 1H), 1.57 – 1.45 (m, 2H), 1.41 (m, 1H), 1.31 – 1.22 (m, 9H), 1.20 – 1.13 (t, \( J = 7.1 \text{ Hz} \), 3H), 0.87 (t, \( J = 7.0 \text{ Hz} \), 3H).

\(^{13}\text{C NMR} \) (151 MHz, CDCl\(_3\)): \( \delta \) (ppm) 174.4, 140.3, 128.8 (2C), 128.4 (2C), 126.1, 58.1, 50.1, 41.4, 40.5, 37.2, 34.5, 31.9, 29.8, 29.3, 26.1, 22.7, 15.0, 14.2, 13.2.

HRMS (ESI) m/z calculated for [M+H]+ \( \text{C}_{21}\text{H}_{37}\text{N}_2\text{O} \): 333.2900, found 333.2901.

ATR-FTIR (cm\(^{-1}\)): 2954, 2926, 2854, 1636, 1454, 1427, 1378, 1362, 1259, 1128, 845, 749, 699.

\( \alpha \)-Aminated amide was prepared using procedure H with 0.20 mmol amide \( S2 \) (35.5 mg), 0.40 mmol \( \text{Tf}_2 \text{O} \) (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide \( 2a \) (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (orange-brown oil): 63% (39 mg).

\(^1\text{H NMR} \) (600 MHz, CDCl\(_3\)): \( \delta \) (ppm) 7.32 – 7.24 (m, 4H), 7.24 – 7.13 (m, 6H), 3.40 (dd, \( J = 7.6, 5.4 \text{ Hz} \), 1H), 2.94 (s, 3H), 2.87 – 2.79 (m, 2H), 2.79 – 2.76 (m, 1H), 2.75 (s, 3H), 2.75 – 2.69 (m, 2H), 2.58 (m, 1H), 1.99 (br.s, 1H), 1.85 – 1.73 (m, 2H).

\(^{13}\text{C NMR} \) (151 MHz, CDCl\(_3\)): \( \delta \) (ppm) 175.0, 141.8, 140.4, 128.9 (2C), 128.7 (2C), 128.5 (2C), 128.4 (2C), 126.1, 126.0, 57.1, 50.2, 37.2, 36.5, 35.8, 35.2, 32.0.

HRMS (ESI) m/z calculated for [M+H]+ \( \text{C}_{20}\text{H}_{27}\text{N}_2\text{O} \): 311.2118, found 311.2117.

ATR-FTIR (cm\(^{-1}\)): 3025, 2927, 2855, 1640, 1495, 1454, 1397, 1258, 1121, 1030, 750, 699.
4.3. Oxazines and Oxazinone

2,6-diphenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine \(8a\)

The oxazine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7a (35.5 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow solid): 90% (55 mg).

\(^1\)H NMR (600 MHz, CDCl₃): δ (ppm) 7.47 – 7.43 (m, 2H), 7.41 (m, 2H), 7.36 – 7.30 (m, 3H), 7.25 – 7.20 (m, 2H), 7.12 (m, 1H), 6.78 (s, 1H), 5.87 (s, 1H), 3.80 – 3.05 (m, 4H), 2.05 – 1.79 (m, 4H).

\(^{13}\)C NMR (151 MHz, CDCl₃): δ (ppm) 151.7, 135.5, 135.3, 134.4, 129.1, 128.8 (2C), 128.3 (2C), 128.0 (2C), 126.7, 123.5 (2C), 116.0, 71.6, 46.5 (2C), 25.1 (2C).

HRMS (ESI) m/z calculated for [M+H]+ C₂₀H₂₁N₂O+: 305.1648, found 305.1651.

ATR-FTIR (cm\(^{-1}\))): 3071, 3025, 2962, 2872, 1599, 1567, 1488, 1447, 1342, 1055, 1026, 951, 761, 750, 690, 479.

Mp.: 218 – 221 °C.

6-(naphthalen-2-yl)-2-phenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine \(8b\)

The oxazine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7b (46.5 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow solid): 81% (57 mg).

\(^1\)H NMR (600 MHz, CDCl₃): δ (ppm) 7.88 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.53 (dd, J = 8.7, 1.4 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.42 (m, 1H), 7.38 – 7.28 (m, 4H), 6.94 (s, 1H), 5.93 (s, 1H), 3.82 – 3.07 (m, 4H), 2.07 – 1.81 (m, 4H).

\(^{13}\)C NMR (151 MHz, CDCl₃): δ (ppm) 152.0, 135.5, 135.3, 133.7, 132.5, 131.7, 129.1, 128.8 (2C), 128.1, 127.8 (2C), 127.7, 127.6, 126.1, 125.4, 121.8, 121.4, 116.9, 71.7, 46.4 (2C), 24.9 (2C).

HRMS (ESI) m/z calculated for [M+H]+ C₂₄H₂₃N₂O+: 355,1805, found 355,1798.

ATR-FTIR (cm\(^{-1}\))): 3058, 2968, 2869, 1561, 1448, 1338, 1212, 1060, 857, 817, 747, 699, 476.

Mp.: 179 – 181 °C.
6-(4-methoxyphenyl)-2-phenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine 8c

The oxazine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 μL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7c (42.1 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow solid): 56% (37 mg).

H NMR (600 MHz, CDCl₃): δ 7.45 (d, J = 6.7 Hz, 2H), 7.35 – 7.29 (m, 5H), 6.82 – 6.74 (m, 2H), 6.63 (s, 1H), 5.85 (s, 1H), 3.75 (s, 3H), 3.37 – 3.4 (m, 4H), 2.03 – 1.80 (m, 4H).

13C NMR (151 MHz, CDCl₃): δ (ppm) 158.8, 151.3, 135.6, 135.4, 129.1, 128.8 (2C), 127.9 (2C), 127.2, 125.0 (2C), 114.4, 113.8 (2C), 71.6, 55.4, 46.4 (2C), 24.9 (2C).

HRMS (ESI) m/z calculated for [M+H]+ C₂₁H₂₃N₂O₂+: 335.1754, found 335.1758.

ATR-FTIR (cm⁻¹): 3061, 2966, 2870, 1606, 1576, 1509, 1458, 1446, 1339, 1248, 1175, 1059, 1031, 829, 750.

Mp.: 159–162 °C.

6-(4-nitrophenyl)-2-phenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine 8d

The oxazine was prepared using procedure H with 0.2 mmol amide 1a (37.9 mg), 0.4 mmol Tf₂O (67.3 μL), 0.4 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7d (45.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (red solid): 81% (57 mg).

H NMR (600 MHz, CDCl₃): δ (ppm) 8.09 – 7.99 (m, 2H), 7.51 – 7.46 (m, 2H), 7.41 – 7.38 (m, 2H), 7.36 – 7.32 (m, 3H), 7.01 (s, 1H), 5.88 (s, 1H), 3.70 (m, 2H), 3.53 (m, 1H), 3.19 (m, 1H), 2.04 – 1.84 (m, 4H).

13C NMR (151 MHz, CDCl₃): δ (ppm) 152.9, 145.6, 140.8, 134.5, 133.6, 129.5, 129.0 (2C), 127.8 (2C), 123.9 (2C), 122.7 (2C), 120.8, 71.6, 47.1, 46.5, 25.9, 24.5.

HRMS (ESI) m/z calculated for [M+H]+ C₂₀H₂₀N₃O₃+: 350,1499, found 350,1500.

ATR-FTIR (cm⁻¹): 3061, 2966, 2870, 1559, 1503, 1460, 1333, 1257, 1182, 1112, 1058, 947, 838, 750.

Mp.: 187–190 °C.
6-(tert-butyl)-2-phenyl-3-(pyrrolidin-1-yl)-2H,1,4-oxazine 8e

The oxazine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7e (31.1 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow oil): 88% (50 mg).

¹H NMR (600 MHz, CDCl₃): δ 8 ppm) 7.39 – 7.31 (m, 5H), 5.99 (s, 1H), 5.69 (s, 1H), 3.50 (m, 4H), 2.01 – 1.69 (m, 4H), 0.83 (s, 9H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 150.5, 145.3, 134.2, 129.3, 128.7 (2C), 128.6 (2C), 109.8, 71.6, 46.6 (2C), 33.0, 27.3 (3C), 25.0 (2C).

HRMS (ESI) m/z calculated for [M+H]+ C₁₈H₂₅N₂O: 285.1861, found 285.1866.

ATR-FTIR (cm⁻¹): 2963, 2869, 1659, 1623, 1582, 1447, 1341, 1358, 1341, 1158, 1030, 762, 699, 638, 518.

5,6-dimethyl-2-phenyl-3-(pyrrolidin-1-yl)-2H,1,4-oxazine 8f

The oxazine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7f (24.9 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow oil): 59% (30 mg).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.42 – 7.28 (m, 5H), 5.64 (s, 1H), 3.51 (m, 4H), 2.04 – 1.86 (m, 4H), 1.85 (app.d, J = 0.8 Hz, 3H), 1.66 (app.d, J = 0.8 Hz, 3H).

¹³C NMR (151 MHz, DMSO): δ (ppm) 150.2, 136.3, 128.7, 128.6 (2C), 128.1, 127.2 (2C), 118.7, 69.9, 46.6 (2C), 24.7 (2C), 17.1, 15.4.

HRMS (ESI) m/z calculated for [M+H]+ C₁₆H₂₁N₂O: 257.1648, found 257.1650.

ATR-FTIR (cm⁻¹): 2950, 2869, 1725, 1585, 1444, 1340, 1279, 1156, 1140, 1031, 752, 737, 638.

2-phenyl-3-(pyrrolidin-1-yl)-5,6,7,8-tetrahydro-2H-benzo[b][1,4]oxazine 8g

The oxazine was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7g (30.6 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow oil): 70% (40 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.41 – 7.28 (m, 5H), 5.59 (s, 1H), 3.37 (m, 4H), 2.35 – 2.25 (m, 1H), 2.15 (m, 1H), 2.06 (m, 1H), 1.97 – 1.88 (m, 2H), 1.87 – 1.77 (m, 3H), 1.70 – 1.64 (m, 1H), 1.61 – 1.47 (m, 2H), 1.42 – 1.31 (m, 1H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 150.9, 136.0, 131.4, 128.9, 128.7 (2C), 127.7 (2C), 121.6, 71.5, 46.7 (2C), 28.2, 26.5, 25.1 (2C), 23.2, 23.0.
2,7-diphenyl-3-(pyrrolidin-1-yl)-2,5-dihydro-1,4-oxazepin-4-ium-trifluoromethanesulfonate 8h

The oxazine was prepared using procedure H with 0.2 mmol amide 1a (37.9 mg), 0.40 mmol Tf2O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7h (38.5 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (yellow solid): 72 % (67 mg).

$^1$H NMR (600 MHz, CDCl3): $\delta$ (ppm) 9.48 (br.s, 1H), 7.54 (m, 2H), 7.47 (m, 3H), 7.42 – 7.34 (m, 5H), 6.15 (s, 1H), 5.78 (dd, $J = 6.9, 4.4$ Hz, 1H), 4.22 (dd, $J = 16.9, 4.4$ Hz, 1H), 4.11 (dd, $J = 16.9, 4.4$ Hz, 1H), 3.83 (m, 2H), 3.66 (m, 1H), 3.28 (m, 1H), 2.15 – 1.95 (m, 4H).

$^{13}$C NMR (151 MHz, CDCl3): $\delta$ (ppm) 161.5, 154.7, 133.9, 132.5, 130.5, 130.0 (2C), 129.7, 128.8 (2C), 126.1 (2C), 125.1 (2C), 105.0, 77.5, 50.6, 50.1, 40.6, 25.7, 24.6.

$^{19}$F NMR (565 MHz, CDCl3): $\delta$ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]$^+$ C_{21}H_{23}N_2O$: 319.1805, found 319.1804.

ATR-FTIR (cm$^{-1}$): 3218, 3080, 2956, 1653, 1452, 1246, 1159, 1030, 757, 697, 574, 518

Mp.: 217–219 °C.

6-phenyl-5-(pyrrolidin-1-yl)-3,6-dihydro-2H-1,4-oxazin-2-one 8i

The oxazinone was prepared using procedure H with 0.20 mmol amide 1a (37.9 mg), 0.40 mmol Tf2O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide 7i (37.6 mg). Due to its high sensitivity, the purification was performed by dissolving the crude product in ACN and washing with heptane (5x).

Yield (yellow oil): 70 % (34 mg).

$^1$H NMR (600 MHz, CDCl3): $\delta$ (ppm) 7.41 (m, 3H), 7.37 – 7.32 (m, 2H), 6.07 (s, 1H), 4.30 (d, $J = 19.9$ Hz, 1H), 3.81 (d, $J = 19.9$ Hz, 1H), 3.41 (m, 4H), 2.01 – 1.84 (m, 4H).

$^{13}$C NMR (151 MHz, CDCl3): $\delta$ (ppm) 170.1, 156.1, 133.4, 129.9, 129.6 (2C), 127.4 (2C), 77.3, 49.0, 46.9 (2C), 25.4 (2C).

HRMS (ESI) m/z calculated for [M+H]$^+$ C_{14}H_{17}N_2O_2$: 245.1285, found 245.1286.

ATR-FTIR (cm$^{-1}$): 2968, 2870, 2106, 1744, 1620, 1446, 1312, 1236, 1186, 1028, 911, 739, 697, 637, 517.
5. Derivatisation of Amidines

5.1. Hydrolysis

General Procedure I

A mixture of amidine (0.2 mmol, 1 eq.), THF (1 mL), NaOH (1 mL, 5 M, 5 eq.) and TPA-OH (4 µL, 0.02 mmol, 0.1 eq) were stirred under reflux for 15 h. Purification was performed via addition of NH₄Cl and extraction with (3x) DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure.

1-phenyl-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one 4a

The benzoazepinone was obtained using procedure I with amidine 3a (88.1 mg). The crude product was further purified by flash chromatography on silica gel (DMA/DCM gradient, 0:100 to 10:90).

Yield (yellow oil): 63 % (30 mg).

1H NMR (600 MHz, CDCl₃): δ (ppm) 7.28 (m, 3H), 7.27 – 7.24 (m, 1H), 7.23 (m, 1H), 7.20 (m, 1H), 7.18 – 7.16 (m, 1H), 7.12 – 7.08 (m, 2H), 6.71 (br.s, 1H), 5.15 (s, 1H), 3.37 (ddd, J = 19.2, 9.6, 4.7 Hz, 1H), 3.12 – 3.05 (m, 1H), 3.04 – 2.95 (m, 2H).

13C NMR (151 MHz, CDCl₃): δ (ppm) 175.1, 139.8, 137.8, 133.5, 132.9, 131.2, 128.8 (2C), 127.9, 127.1, 126.9, 126.9 (2C), 60.5, 39.7, 33.8.

HRMS (ESI) m/z calculated for [M+H]+ C₁₆H₁₆NO+: 238.1226, found 238.1228.

ATR-FTIR (cm⁻¹): 3199, 3081, 2935, 1666, 1493, 1342, 806, 759, 749, 706.

7-methoxy-4-phenyl-1,4-dihydroisoquinolin-3(2H)-one 4ba

The isolated, hydrolysed regioisomer was obtained using procedure I with isomere mixture 3m. The crude product was further purified by flash chromatography on silica gel (DMA/DCM gradient, 0:100 to 10:90).

Yield (brown amorphous solid): 17 % (8.6 mg).

1H NMR (600 MHz, CDCl₃): δ (ppm) 7.28 (m, 2H), 7.23 (m, 1H), 7.19 – 7.13 (m, 2H), 7.03 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.5 Hz, 1H), 6.75 (d, J = 2.5 Hz, 1H), 6.71 (br.s, 1H), 4.76 (s, 1H), 4.54 (d, J = 15.8 Hz, 1H), 4.35 (dd, J = 15.8, 4.1 Hz, 1H), 3.82 (s, 3H).

13C NMR (151 MHz, CDCl₃): δ (ppm) 173.0, 158.8, 139.0, 132.9, 130.1, 128.8 (2C), 128.1 (2C), 127.4, 127.3, 113.9, 110.7, 55.5, 51.8, 45.4.

HRMS (ESI) m/z calculated for [M+H]+ C₁₆H₁₆NO₂+: 254.1176, found 254.1177.

ATR-FTIR (cm⁻¹): 3219, 3061, 2930, 2838, 1668, 1613, 1493, 1324, 1272, 1240, 1035, 738, 706.
The isolated, hydrolysed regioisomer was obtained using procedure I with isomere mixture 3m. The crude product was further purified by flash chromatography on silica gel (DMA/DCM gradient, 0:100 to 10:90).

Yield (white amorphous solid): 7% (3.5 mg).

\[ \text{1H NMR (600 MHz, CDCl}_3\text{): } \delta \text{ (ppm) 7.28 (m, 1H), 7.24 (m, 2H), 7.21 (m, 3H), 6.84 (m, 2H), 6.27 (br.s, 1H), 5.17 (s, 1H), 4.61 (d, } J = 15.7 \text{ Hz, 1H), 4.32 (dd, } J = 15.7, 4.8 \text{ Hz, 1H), 3.75 (s, 3H).} \]

\[ \text{13C NMR (151 MHz, CDCl}_3\text{): } \delta \text{ (ppm) 172.8, 156.9, 138.3, 133.3, 128.7 (2C), 128.4, 127.7 (2C), 127.2, 124.1, 117.7, 109.6, 55.7, 46.6, 45.3.} \]

HRMS (ESI) m/z calculated for [M+H\(^+\)]\(^+\) C\(_{16}\)H\(_{16}\)NO\(_2\): 254.1176, found 254.1177.

ATR-FTIR (cm\(^{-1}\)): 3210, 3059, 2931, 2839, 1671, 1595, 1471, 1256, 1072, 782, 745, 700.

5.2. Deprotonation

5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepine 5a

The free base of 3a was obtained by extraction DCM/NaOH 4 M. The organic layer was dried over \( \text{K}_2\text{CO}_3\), filtered and evaporated.

Yield (brown oil): 99% (58 mg).

\[ \text{1H NMR (600 MHz, CDCl}_3\text{): } \delta \text{ (ppm) 7.26 (m, 3H), 7.23 \text{–} 7.16 (m, 3H), 7.12 (d, } J = 7.2 \text{ Hz, 1H), 7.04 (d, } J = 8.1 \text{ Hz, 2H), 5.24 (s, 1H), 3.63 \text{–} 3.52 (m, 5H), 3.32 (ddd, } J = 13.8, 4.4, 4.4 \text{ Hz, 1H), 2.99 \text{–} 2.92 (m, 2H), 1.99 \text{–} 1.91 (m, 4H).} \]

\[ \text{13C NMR (151 MHz, CDCl}_3\text{): } \delta \text{ (ppm) 162.1, 142.2, 140.6, 134.5, 132.6, 131.7, 128.6 (2C), 127.6, 126.4 (2C), 126.3, 125.9, 53.2, 47.5 (2C), 45.1, 33.9, 25.7.} \]

HRMS (ESI) m/z calculated for [M+H\(^+\)]\(^+\) C\(_{20}\)H\(_{23}\)N\(_2\): 291.1856, found 291.1858.

ATR-FTIR (cm\(^{-1}\)): 3058, 3022, 2921, 2867, 1611, 1493, 1421, 1362, 1336, 1263, 950, 909, 748, 721, 696, 636, 569.
5.3. Methylation

3-methyl-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium 6a

The methylated product 6a was obtained by dropwise addition of Mel (50 µL, 0.80 mmol, 3.0 eq) to a mixture of 5a (47.5 mg, 0.20 mmol, 1.0 eq) in ACN (0.1 M). The reaction progress was followed by LCMS. After 40h, the mixture was diluted with MeOH and concentrated under reduced pressure. Purification was performed by flash column chromatography on silica gel (DMA/DCM gradient, 0:100 to 20:80).

Yield (brown-yellow oil): 56 % (48 mg); 61% brsm

**¹H NMR** (600 MHz, CDCl₃): δ (ppm) 7.35 (m, 3H), 7.32 – 7.26 (m, 2H), 7.25 – 7.20 (m, 2H), 7.03 (d, J = 7.8 Hz, 2H), 5.67 (s, 1H), 4.30 (m, 1H), 4.18 – 3.88 (m, 4H), 3.58 (s, 3H), 3.39 – 3.29 (m, 1H), 3.20 (m, 1H), 2.33 (m, 1H), 2.12 (m, 3H).

**¹³C NMR** (151 MHz, CDCl₃): δ (ppm) 170.0, 137.6, 136.8, 133.1, 131.8, 129.8 (2C), 129.7, 129.5, 128.2, 127.7, 126.2 (2C), 55.8, 53.3, 51.4, 51.3, 45.2, 31.0, 25.4, 25.3.

**HRMS (ESI) m/z calculated for [M⁺] C₂₁H₂₅N₂⁺:** 305.2012, found 305.2014.

**ATR-FTIR** (cm⁻¹): 3144, 3042, 2954, 2924, 2874, 1726, 1634, 1494, 1447, 1338, 1268, 1159, 759, 731, 701

31
6. X-ray Analysis

The X-ray intensity data were measured on Bruker D8 Venture diffractometer equipped with multilayer monochromators, Mo K/α INCOATEC micro focus sealed tubes and Oxford system. The structure was solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted at calculated positions and refined with riding model. The following software was used: Bruker SAINT software package\(^{20}\) using a narrow-frame algorithm for frame integration, SADABS\(^{21}\) for absorption correction, OLEX2\(^{22}\) for structure solution, refinement, molecular diagrams and graphical user-interface, Shelxi\(^{23}\) for refinement and graphical user-interface SHELXS-2015\(^{24}\) for structure solution, SHELXL-2015\(^{25}\) for refinement, Platon\(^{26}\) for symmetry check and π-π Interactions. Experimental data and CCDC-Codes (Available online: http://www.ccdc.cam.ac.uk/conts/retrieving.html) can be found in Table 1. Crystal data, data collection parameters and structure refinement details are given in Tables 2 to 5. Crystal structures and Packing views are visualized in Figures 1 to 4.

**Table S3** Experimental parameter and CCDC-Codes.

| Sample | Machine | Source | Temp. | Detector Distance | Time/Frame | #Frames | Frame width | CCDC |
|--------|---------|--------|-------|-------------------|------------|---------|-------------|-------|
| 8a     | D8      | Mo     | 120   | 40                | 15         | 1176    | 0.500       | 1983046 |
| 3a     | D8      | Mo     | 100   | 40                | 10         | 360     | 0.500       | 1983045 |

\(^{20}\) Bruker SAINT v8.38A/B & SAINT v7.56/7.68A Copyright © 2005–2019 Bruker AXS.

\(^{21}\) Krause, L.; Herbst-Irmer, R.; Sheldrick G. M.; Stalke D. J. Appl. Cryst., 2015, 48, 3–10.

\(^{22}\) Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J; Howard, J.A.K.; Puschmann, H. OLEX2, J. Appl. Cryst. 2009, 42, 339–341.

\(^{23}\) Huebschle, C. B.; Sheldrick G. M.; Dittrich B.; ShelXle: a Qt graphical user interface for SHELXL, J. Appl. Cryst. 2011, 44, 1281–1284.

\(^{24}\) Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122.

\(^{25}\) Sheldrick, G. M. Acta Cryst. 2015, C71, 3–8.

\(^{26}\) A. L. Spek, Acta Cryst. 2009, D65, 148–155.
-2,6-diphenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine

Figure S1 Crystal structure, drawn with 50% displacement ellipsoid. The bond precision for C-C single bonds is 0.0032Å.
Figure S2 Packing view.
### Table S4 Sample and crystal data.

| Property                        | Value                      |
|--------------------------------|----------------------------|
| Chemical formula               | C20H20N2O                 |
| Formula weight [g/mol]         | 304.38                    |
| Temperature [K]                | 120                       |
| Measurement method             | f and w scans             |
| Crystal system                 | monoclinic                |
| Formula weight [g/mol]         | 304.38                    |
| Space group                    | C2/c                      |
| Z                              | 8                         |
| Volume [Å³]                    | 3128.3(3)                 |
| Radiation (Wavelength [Å])     | MoKα (λ = 0.71073)        |
| Unit cell dimensions [Å] and [°]| 31.2597(15) 90           |
| Crystal size / [mm³]           | 0.581 × 0.148 × 0.046     |
| Crystal habit                  | clear yellow plate        |
| Density (calculated) / [g/cm³] | 1.293                     |
| Absorption coefficient / [mm⁻¹]| 0.08                      |
| Abs. correction Tmin           | 0.3486                    |
| Abs. correction Tmax           | 0.746                     |
| Abs. correction type           | multiscan                 |
| F(000) [e⁻]                   | 1296                      |

### Table S5 Data collection and structure refinement.

| Property                        | Value                      |
|--------------------------------|----------------------------|
| Index ranges                   | -37 ≤ h ≤ 37, -6 ≤ k ≤ 6, -23 ≤ l ≤ 21 |
| Theta range for data collection [°]| 4.688 to 50.678             |
| Reflections number             | 26343                      |
| Data / restraints / parameters  | 2846/6/212                 |
| Refinement method              | Least squares              |
| Final R indices                | all data | R1 = 0.0682, wR2 = 0.1648 |
|                               | I>2σ(I) | R1 = 0.0625, wR2 = 0.1588 |
| Goodness-of-fit on F²          | 1.054                      |
| Weighting scheme               | w=1/[(σ²(Fo²)+(0.0747P)² +7.3558P)] |
| Largest diff. peak and hole [e Å⁻³]| 0.65/-0.57               |
Figure S3 Crystal structure, drawn with 50% displacement ellipsoid. The bond precision for C-C single bonds is 0.0043Å.
Figure S4 In the packing view one hydrogen bond on trifluoromethanesulfonate was detected with a bond length 2.083 Å.

Table S6 Sample and crystal data.

| Chemical formula | C21H23F3N2O3S | Crystal system | orthorhombic |
|------------------|----------------|----------------|--------------|
| Formula weight [g/mol] | 440.47 | Space group | P212121 |
| Temperature [K] | 100 | Z | 4 |
| Measurement method | χf and χw scans | Volume [Å³] | 2034.84(8) |
| Radiation (Wavelength [Å]) | MoKα (λ = 0.71073) | Unit cell dimensions [Å] and [°] | 6.48180(10) 90 |
| Crystal size / [mm³] | 0.579 × 0.244 × 0.144 | 12.5595(3) 90 |
| Crystal habit | clear colourless block | Abs. correction | 24.9955(6) 90 |
| Density (calculated) / [g/cm³] | 1.438 | Absorption coefficient / [mm⁻¹] | 0.212 |
| Abs. correction Tmin | 0.6553 | Abs. correction Tmax | 0.7467 |
| Abs. correction type | multiscan | F(000) [e⁻] | 920 |
Table S7 Data collection and structure refinement.

| Index ranges      | -9 ≤ h ≤ 8, -17 ≤ k ≤ 19, -38 ≤ l ≤ 39 | Theta range for data collection [°] | 4.598 to 68.018 |
|-------------------|----------------------------------------|--------------------------------------|------------------|
| Reflections number| 21905                                   | Data / restraints / parameters        | 7198/0/271       |
| Refinement method | Least squares                           | Final R indices                       | all data         |
| Function minimized| Σ w(Fo^2 - Fc^2)^2                       |                                      | R1 = 0.0615, wR2 = 0.1365 |
| Goodness-of-fit on F^2 | 1.185                           | Weighting scheme                      | w=1/(σ2(Fo2)+2.4717P) |
| Largest diff. peak and hole [e Å^-3] | 0.59/-0.72                       |                                      | where P=(Fo^2+2Fc^2)/3 |
6. NMR

$^1$H NMR (400 MHz, CDCl₃)

$^{13}$C NMR (151 MHz, CDCl₃)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{19}$F NMR (565 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^{19}$F NMR (565 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{19}$F NMR (565 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^{19}$F NMR (565 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
\( ^1H \text{NMR} \) (600 MHz, CDCl\(_3\))

\[ \text{S4} \]

\( ^{13}C \text{NMR} \) (151 MHz, CDCl\(_3\))

\[ \text{S4} \]
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{19}$F NMR (565 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^{19}$F NMR (565 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{19}\text{F NMR (565 MHz, CDCl}_3$)

$^{1}\text{H NMR (600 MHz, CDCl}_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^{19}$F NMR (565 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{19}$F NMR (565 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
\( ^{13}\text{C NMR} \ (151 \text{ MHz, CDCl}_3) \)

\( ^{19}\text{F NMR} \ (565 \text{ MHz, CDCl}_3) \)
$^1$H NMR (600 MHz, CDCl$_3$)

\[
\text{C}_6\text{H}_{15}\text{NH} - \text{C}_6\text{H}_{15}\text{O}
\]

$^13$C NMR (151 MHz, CDCl$_3$)

\[
\text{C}_6\text{H}_{15}\text{NH} - \text{C}_6\text{H}_{15}\text{N}
\]
$^1$H NMR (600 MHz, CDCl₃)

$^{13}$C NMR (151 MHz, CDCl₃)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
HSQC

$^1$H NMR (600 MHz, CDCl$_3$), $^{13}$C NMR (151 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$), $^{13}$C NMR (151 MHz, CDCl$_3$)

HSQC
$^1$H NMR (600 MHz, CDCl₃)

$^{13}$C NMR (151 MHz, CDCl₃)
HSQC

$^1$H NMR (600 MHz, CDCl$_3$), $^{13}$C NMR (151 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^2$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR ($151$ MHz, CDCl$_3$)

![NMR spectrum](image1)

$^1$H NMR ($600$ MHz, CDCl$_3$), $^{13}$C NMR ($151$ MHz, CDCl$_3$)

![NMR spectrum](image2)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, DMSO)
HSQC

$^1\text{H NMR}$ (600 MHz, CDCl$_3$), $^{13}\text{C NMR}$ (151 MHz, DMSO)

HMBC

$^1\text{H NMR}$ (600 MHz, CDCl$_3$), $^{13}\text{C NMR}$ (151 MHz, DMSO)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{19}\text{F NMR} \ (565 \text{ MHz, CDCl}_3)$

$^1\text{H NMR} \ (600 \text{ MHz, CDCl}_3)$
$^{13}\text{C NMR (151 MHz, CDCl}_3\text{)}$

$^1\text{H NMR (600 MHz, CDCl}_3\text{)}$
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

![Carbon NMR spectrum of 5a]

$^1$H NMR (600 MHz, CDCl$_3$)

![Hydrogen NMR spectrum of 6a]
$^{13}$C NMR (151 MHz, CDCl$_3$)