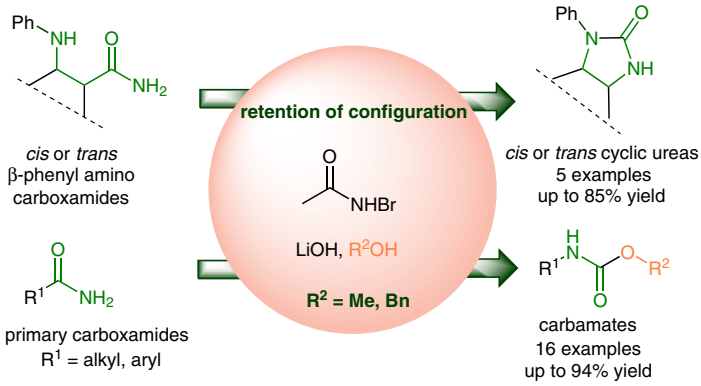
Synthesis I. I. Jevtić et al. Paper

# Hofmann Rearrangement of Carboxamides Mediated by *N*-Bromoacetamide

**Ivana I. Jevtić**[a]
**Ljiljana Došen-Mićović**[a]
**Evica R. Ivanović**[b]
**Milovan D. Ivanović**[*a]

[a] Faculty of Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia
misai@chem.bg.ac.rs
[b] Faculty of Agriculture, University of Belgrade, Nemanjina 6, 11080 Belgrade-Zemun, Serbia

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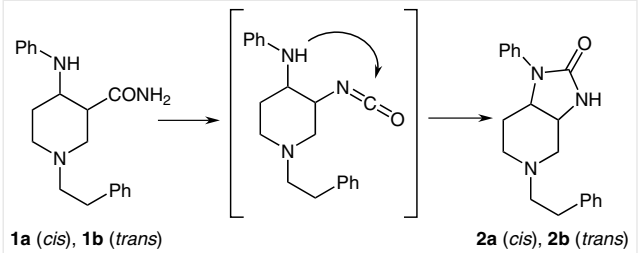
**Abstract** An efficient, one-pot procedure for the Hofmann rearrangement of aromatic and aliphatic amides has been developed. Methyl and benzyl carbamates are produced with *N*-bromoacetamide in the presence of lithium hydroxide or lithium methoxide, in high yields. β-Phenylamino amides gave five-membered cyclic ureas stereospecifically. Side products of aryl or benzyl bromination were minimized. This procedure offers an easy access to various protected amines or diamines, which represent important synthetic precursors.

**Key words** Hofmann rearrangement, amides, stereoselectivity, cyclization, heterocycles

The Hofmann rearrangement presents a useful method for the conversion of primary carboxamides into amines with one carbon atom fewer than the reactant.[1,2] The reaction typically occurs via formation of an isocyanate intermediate. Many different reagents have been used to promote the Hofmann rearrangement. While the classical protocol using alkaline hypohalites is still the method of choice for simple substrates,[3,4] it often suffers from low yields, intolerance to many functional groups and side products, particularly symmetrical acyclic ureas and *N*-acylureas.[2] The scope of the reaction has been significantly expanded by introducing a number of more selective and efficient reagents, particularly *N*-bromosuccinimide (NBS),[5–7] 1,3-dibromo-5,5-dimethylhydantoin,[8] $TsNBr_2$[9] and trichloroisocyanuric acid.[10] The reaction is usually performed in alcohols, producing carbamates rather than the free amines. Several organohypervalent iodine species have been used extensively, including [bis(trifluoroacetoxy)iodo]benzene (PIFA),[11] (tosylimino)phenyl-λ³-iodane (PhINTs),[12] (diacetoxyiodo)benzene (PIDA)[13,14] and others.[15–17] Cyclic imides are also useful substrates.[18] A number of aromatic five-membered cyclic ureas were prepared by intramolecular Hofmann rearrangement,[19–24] while five- and six-membered ureas resulted from protected asparagine and glutamine respectively.[25] Cyclic ureas are synthetically useful intermediates, particularly as precursors to pharmacologically active imidazoles.[20] In addition, cyclic ureas are protective groups for 1,2-diamines, providing the free amines after acid or base hydrolysis. Nevertheless, a range of sensitive substrates, including amides possessing an activated aromatic ring, often provide low yields in the Hofmann rearrangement due to side reactions. Thus, organohypervalent iodine reagents often result in oxidation, while chlorine- and bromine-containing reagents tend to halogenate the substrates.[2] Hence, there is a need to explore new, more selective reagents for the Hofmann rearrangement.

During the course of our research on opioid anilidopiperidines, we intended to introduce a primary amino group at the piperidine ring of diastereomeric amides **1a** and **1b**. Surprisingly, when the Hofmann rearrangement was attempted using NBS/MeONa,[5] the respective cyclic ureas **2a** and **2b** were obtained in modest yields (50–60%)[26] (Scheme 1; Table 1, entry 1). The diastereomeric ureas **2a**




**Scheme 1** Stereospecific formation of diastereomeric ureas **2a** and **2b**

**Table 1** Examination of the Stereospecific Formation of Ureas **2a** and **2b**

| Entry | Reagent[a] | Base | Solvent | Time (h) | Temp (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | NBS (6.0 equiv) | MeONa (6.0 equiv) | MeOH | 0.5–2 | 65 | 50–60[b,c] |
| 2 | NBS (2.0 equiv) | *i*-PrONa (2.5 equiv) | *i*-PrOH | 3–24 | 20–80 | <10[d] |
| 3 | NBS (3.5 equiv) | DBU (2.8 equiv) | MeOH | 3–24 | 20–65 | <10[d] |
| 4 | NBS (2.0 equiv) | $Cs_2CO_3$ (2.5 equiv) | MeOH | 3–24 | 20–65 | <10[d] |
| 5 | NBS (1.2 equiv) | aq KOH (2.5 equiv) | MeCN | 3 | 80 | <10[d] |
| 6 | NBS (10.0 equiv) | $LiOH·H_2O$ (15.0 equiv) | MeOH | 1–3 | 65 | 70–80[b,c] |
| 7 | NBS (10.0 equiv) | $LiOH·H_2O$ (10.0 equiv) | EtOH | 3–5 | 80 | <10[d] |
| 8 | PIDA (1.2 equiv) | aq KOH (2.5 equiv) | MeOH | 5 | –10 to 20 | – |
| 9 | PIFA (1.0 equiv) | – | $MeCN–H_2O$ | 4 | 20 | – |
| 10 | PhINTs (3.0 equiv) | – | $CH_2Cl_2$ | 24–48 | 20 | – |
| 11 | NBA (3.0 equiv) | $LiOH·H_2O$ (6.0 equiv) | MeOH | 48 | 0 to 20 | 75–85[b] |

[a] Various molar ratios of reagents and bases were examined, with optimal values given.
[b] Both isomers were obtained in comparable yields from several runs; isolated by flash or dry-column flash chromatography.
[c] Contaminated with 5–10% of brominated side products after chromatography, as estimated by NMR and HPLC/HRMS analysis.
[d] Slow conversion rate, estimated from $^1$H NMR spectroscopy, HPLC/HRMS and TLC.

and **2b** are structurally closely related to highly active opioid agonists, including fentanyl,[27] 3-methylfentanyl[28] and 3-carbomethoxyfentanyl.[29]

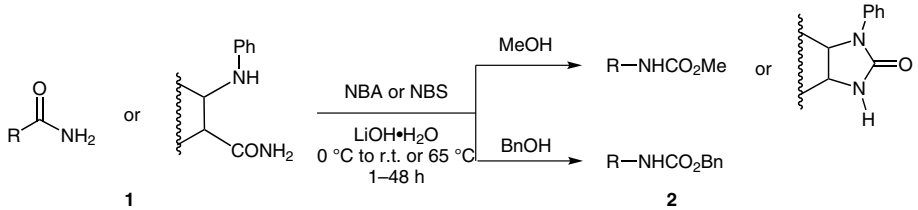
These new compounds originate from Hofmann rearrangement of the carboxamido group, followed by intramolecular nucleophilic addition of the β-amino group to the isocyanate, with complete retention of the configuration (Scheme 1). While the reaction is stereospecific, brominated contaminants were always present (~30%), regardless of the stoichiometric ratio of the reactants.

Several base/solvent combinations did not produce significant yields of any product (Table 1, entries 2–5). An improvement was observed when $LiOH·H_2O$ in MeOH was used as a base (Table 1, entry 6). $LiOH·H_2O$ reduced the amount of aryl brominated side products to 10–20%, even though a large excess of NBS was used. Apparently, lithium hydroxide is more selective than MeONa. Interestingly, the reaction was exceedingly slow in EtOH (Table 1, entry 7). It is important to mention that aryl brominated side products could not be completely removed chromatographically.

Organohypervalent iodine reagents (PIDA, PIFA and PhINTs) invariably gave complex mixtures (Table 1, entries 8–10), likely due to oxidative decomposition of the arylamino group.[2] In contrast, *N*-bromoacetamide (NBA) secured good yields of **2a** and **2b**, with only 0–5% of side products (Table 1, entry 11). Thus, the combination of NBA and $LiOH·H_2O$ in MeOH emerged as the reagent of choice for this particular transformation. It is noteworthy that other products of the Hofmann rearrangement (i.e., carbamates, free amines, acyclic ureas or *N*-acylureas) were never detected, regardless of the reagents or conditions.

Having established the efficiency and selectivity of NBA, we then tested the reagent on structurally diverse amides. Comparative experiments were also performed with NBS (Scheme 2,Table 2).

Amides possessing a β-phenylamino group gave the corresponding cyclic ureas **2c**–**e** in good yields (Table 2, entries 1–3). NBA gave higher yields and only trace amounts of side products, while NBS resulted in significant aromatic bromination (50% in the case of urea **2e**; Table 2, entry 3). However, β-alkylamino amides **1f**, **1g** and **1o** had slow conversion rates and gave complex mixtures (Table 2, entries 4, 5 and 16). Apparently, secondary alkylamines form stable brominated adducts with NBA, suggesting that the reagent is limited to β-arylamino precursors.




**Scheme 2** Hofmann rearrangement mediated by NBA

**Table 2** Hofmann Rearrangement of Carboxamides with NBA and LiOH·$H_2O$[a]

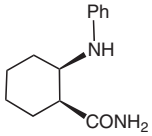
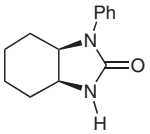
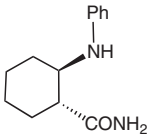
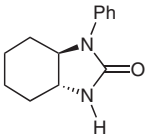
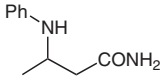
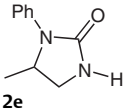
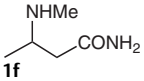
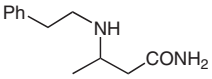
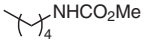
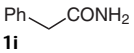
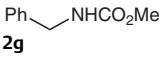
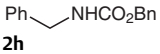
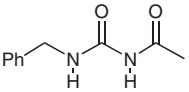
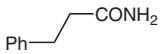
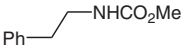
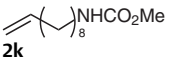
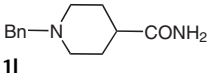
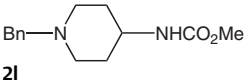
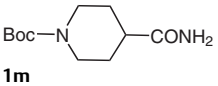
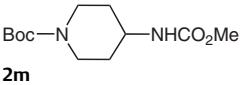
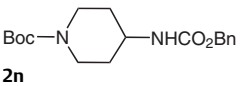
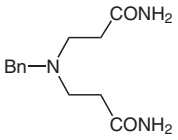
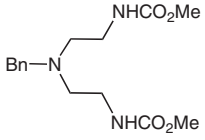
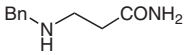
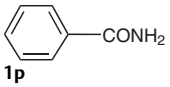
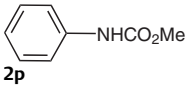
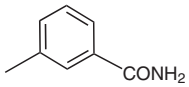
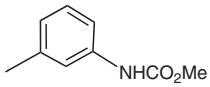
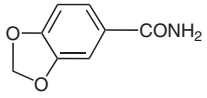
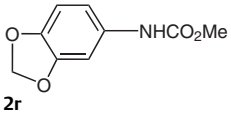
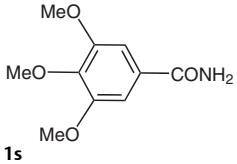
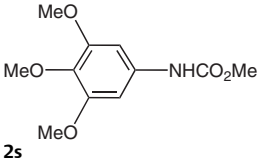
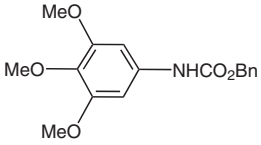
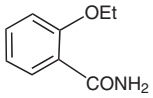
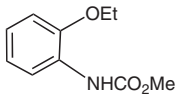
| Entry | Carboxamide **1** | Product **2**[b] | NBA/LiOH (equiv) | Yield[c] (%) |
|---|---|---|---|---|
| 1 |  **1c** |  **2c** | 3/15 | 80 (73)[d] |
| 2 |  **1d** |  **2d** | 2/14.6 | 85 (75)[d] |
| 3 |  **1e** |  **2e** | 2/6.1 | 85 (80)[d] |
| 4 |  **1f** | – | – | – |
| 5 |  **1g** | – | – | – |
| 6 |  **1h** |  **2f** | 2/5.9 | 81 (69) |
| 7 |  **1i** |  **2g** | 1/4.9 | 82[e] (60) |
| 8 | **1i** |  **2h** | 1/5 | 76 |
| 9 | **1i** |  **2i** | 1.5/1.5[f] | 82 |
| 10 |  **1j** |  **2j** | 2.5/6 | 83 |
| 11 |  **1k** |  **2k** | 2.5/6 | 94 (87) |
| 12 |  **1l** |  **2l** | 2/6 | 88 |
| 13 |  **1m** |  **2m** | 1.5/9.1 | 92 |
| 14 | **1m** |  **2n** | 2/5.2 | 69 |

Table 2 (continued)

| Entry | Carboxamide **1** | Product **2**[b] | NBA/LiOH (equiv) | Yield[c] (%) |
|---|---|---|---|---|
| 15 |  **1n** |  **2o** | 8/10 | 77 (62) |
| 16 |  **1o** | – | – | – |
| 17 |  **1p** |  **2p** | 1.3/5.1 | 94 (82) |
| 18 |  **1q** |  **2q** | 2.5/6 | 89 (95)[d] |
| 19 |  **1r** |  **2r** | 2.5/6 | 93 |
| 20 |  **1s** |  **2s** | 2/5 | 90 (60)[d] |
| 21 | **1s** |  **2t** | 2/6 | 60 |
| 22 |  **1t** |  **2u** | 1/2 | 85 |

[a] Reaction conditions: MeOH or BnOH, 0 to 25 °C, 24 h.
[b] Unless stated otherwise, products were >95% pure after chromatography, as estimated from $^1$H NMR spectroscopy and/or HPLC/HRMS.
[c] Yields of isolated products prepared with NBS are given in parentheses.
[d] Isolated products were a mixture of ~30–55% of the desired product and ~30–50% of aryl brominated side products, according to $^1$H and $^{13}$C NMR spectroscopy and HPLC/HRMS.
[e] Identical yields were obtained with MeOLi as a base.
[f] Methanolic KOH was used as a base.

Most of the examined amides produced good yields of the respective methyl carbamates, with NBA consistently affording higher yields than NBS. Benzyl carbamates were smoothly prepared using NBA only, avoiding bromination and/or oxidation of benzyl alcohol with the more reactive NBS (Table 2, entries 8, 14 and 21). The synthetic significance of benzyl carbamates has been widely recognized, since they are readily cleaved by catalytic hydrogenolysis under mild and neutral conditions. Thus, the benzyloxycarbonyl group is one of the most extensively used *N*-protecting groups in organic synthesis.[30] Cleavage of simple carbamates (e.g., methyl, ethyl) requires vigorous acid or base hydrolysis or special reagents such as trimethylsilyl iodide.[30]

NBA was distinctly superior to NBS in the case of aromatic amides, both in terms of the yields and purity of the obtained methyl carbamates (Table 2, entries 17–20 and 22). The results parallel those with cyclic ureas.

In this method, MeOLi was as efficient as LiOH·$H_2O$, without offering any advantage as a base. However, KOH in MeOH furnished *N*-acetylurea **2i** only, indicating that the cation plays a critical role in the reaction chemoselectivity (Table 2, entry 9).

Initially, the experiments were carried out by a gradual addition of NBA or NBS and the base. Subsequently, it was determined that addition of the reagents in one portion was equally effective. In most cases we found that a moderate to large excess of LiOH·$H_2O$ was needed for complete conversion of reactants, probably due to its low solubility in MeOH and BnOH.

The procedure is compatible with several functional groups, including an isolated double bond, tertiary benzylic amine, *tert*-butyloxycarbonyl, carboxybenzyl, and various aryl groups. Experiments with other alcohols, including 2,2,2-trichloroethanol, allyl alcohol and *tert*-butyl alcohol, were unsuccessful, resulting in slow conversion rates and mixtures of products.

In summary, we have demonstrated that NBA/LiOH·$H_2O$ efficiently promotes the Hofmann rearrangement, comparing well to other reagents in terms of product yields, purity and cost-effectiveness. The preparation of NBA is simple and relatively inexpensive on a multigram scale. The procedure often allows simple, chromatography-free isolation of the products, while the byproducts are water-soluble.

Unless stated otherwise, all solvents and chemicals were used as supplied. $^1$H and $^{13}$C NMR spectra were recorded on Varian Gemini 200 and Bruker Avance III spectrometers at 200 or 500 MHz for the proton ($^1$H) and at 50 or 126 MHz for the carbon ($^{13}$C) acquisitions. Chemical shifts are given in parts per million from TMS as internal standard in $CDCl_3$ or referenced to the residual solvent signal of DMSO for DMSO-$d_6$ and MeCN for $CD_3CN$. 2D NMR spectra (HSQC, NOESY) were recorded at 500 MHz. Unless stated otherwise, all spectra were recorded at r.t. High-resolution mass spectra (HRMS) were obtained with an Agilent Technologies 6210 LC/MS ESI-TOF spectrometer. All reactions were monitored by TLC. Flash and dry-column flash chromatography were carried out using silica gel (0.018–0.032 mm). Melting points were obtained on a Rapido/Nagema PHMK 05 apparatus at a heating rate of 4 °C/min, and are uncorrected. IR spectra are given for selected compounds and were recorded using a Thermo Scientific Nicolet 6700 Fourier transform spectrometer operating in the ATR mode. NBA was prepared according to a literature procedure, protected from light and kept at –20 °C.[31] It can also be prepared by an alternative method.[32] PIDA,[33] PIFA[11] and PhINTs[12] were prepared according to the published protocols. All three organohypervalent iodine reagents were tested on hexanamide, dodecanamide and/or 1-benzylpiperidine-4-carboxamide, affording the expected carbamates or free amines, as reported in the literature.[11–14]

***cis*-1-Phenethyl-4-(phenylamino)piperidine-3-carboxamide (1a) and *trans*-1-Phenethyl-4-(phenylamino)piperidine-3-carboxamide (1b)**

To a magnetically stirred solution of formamide (6.10 g, 130 mmol) in THF (30 mL) was added MeONa (52 mmol, 12.8 mL of 4.05 M solution in MeOH) at r.t. After 5 min, a solution of methyl *cis*/*trans*-1-phenethyl-4-(phenylamino)piperidine-3-carboxylate[29] (4.60 g, 13 mmol) in THF (7 mL) was added in one portion and the stirring was continued at r.t. The initially clear solution became turbid after 1–3 h, followed by the gradual formation of a white precipitate. The reaction progress was monitored by TLC (reactant consumption; $CH_2Cl_2$–MeOH, 9:1). After 24 h, the mixture was concentrated (30 °C, 1 h, rotary evaporator) and the syrupy residue was partitioned between brine (75 mL) and $CHCl_3$ (3 × 25 mL). The combined organic layers were concentrated by rotary evaporator, yielding the **1a**/**1b** mixture (4.05 g, 96%) as an off-white solid. The mixture was separated by flash column chromatography on silica gel ($CH_2Cl_2$–MeOH, 95:5).

**1a**

Yield: 1.6 g (38%); off-white solid; mp 141–142 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 7.57 (s, 1 H), 7.22 (qdd, *J* = 8.6, 5.1, 1.4 Hz, 5 H), 7.07 (dd, *J* = 8.4, 7.3 Hz, 2 H), 6.96 (s, 1 H), 6.60 (d, *J* = 7.8 Hz, 2 H), 6.53 (t, *J* = 7.3 Hz, 1 H), 5.20 (d, *J* = 7.9 Hz, 1 H), 3.65 (s, 1 H), 2.92 (br s, 1 H), 2.75 (t, *J* = 7.3 Hz, 2 H), 2.71–2.61 (m, 2 H), 2.60–2.53 (m, 2 H), 2.48 (br s, 1 H, partially overlapped), 2.34 (br s, 1 H), 1.86–1.61 (m, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 174.2, 147.5, 140.4, 128.9, 128.6, 128.2, 125.8, 115.8, 112.7, 59.5, 52.4, 49.9, 49.4, 44.2, 32.7, 28.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{26}N_3O$: 324.20704; found: 324.20698. (Note: HRMS was measured on the **1a**/**1b** mixture, prior to separation.)

**1b**

Yield: 1.9 g (45%); off-white solid; mp 153–154 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 7.29 (s, 1 H, partially overlapped), 7.28–7.15 (m, 5 H), 7.04 (dd, *J* = 8.4, 7.4 Hz, 2 H), 6.84 (s, 1 H), 6.60 (d, *J* = 7.7 Hz, 2 H), 6.49 (t, *J* = 7.2 Hz, 1 H), 5.19 (d, *J* = 8.9 Hz, 1 H), 3.47 (dd, *J* = 9.1, 3.3 Hz, 1 H), 2.99 (d, *J* = 10.0 Hz, 1 H), 2.90 (d, *J* = 11.0 Hz, 1 H), 2.79–2.68 (m, 2 H), 2.60–2.52 (m, 2 H), 2.44 (td, *J* = 10.1, 3.2 Hz, 1 H), 2.25 (t, *J* = 10.8 Hz, 1 H), 2.13 (t, *J* = 10.9 Hz, 1 H), 2.04–1.93 (m, 1 H), 1.31 (td, *J* = 14.2, 3.4 Hz, 1 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 174.2, 147.9, 140.3, 128.8, 128.6, 128.2, 125.8, 115.5, 112.6, 59.4, 55.4, 51.6, 51.0, 48.6, 32.9, 30.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{26}N_3O$: 324.20704; found: 324.20698. (Note: HRMS was measured on the **1a**/**1b** mixture, prior to separation.)

***cis*-2-(Phenylamino)cyclohexanecarboxamide (1c) and *trans*-2-(Phenylamino)cyclohexanecarboxamide (1d)**

Prepared from methyl *cis*/*trans*-2-(phenylamino)cyclohexanecarboxylate[34] (7.60 g, 32 mmol), according to the procedure for **1a**/**1b**. Yield of the **1c**/**1d** mixture: 6.05 g (87%); off-white solid. The mixture was separated by dry-column flash chromatography on silica gel ($CH_2Cl_2$–MeOH gradient, 100:0 to 90:10).

**1c**

Yield: 2.40 g (34%); white solid; mp 124 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 7.20 (s, 1 H), 7.10–7.00 (m, 2 H), 6.75 (s, 1 H), 6.62 (dd, *J* = 8.5, 0.9 Hz, 2 H), 6.51 (t, *J* = 7.2 Hz, 1 H), 5.10 (d, *J* = 8.3 Hz, 1 H), 3.77 (d, *J* = 3.1 Hz, 1 H), 2.56–2.51 (m, 1 H), 1.96–1.80 (m, 2 H), 1.65–1.48 (m, 3 H), 1.47–1.22 (m, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 175.6, 147.9, 128.8, 115.7, 112.8, 50.2, 44.8, 28.7, 24.4, 23.6, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}N_2O$: 219.14919; found: 219.14983. (Note: HRMS was measured on the **1c**/**1d** mixture, prior to separation.)

**1d**

Yield: 2.75 g (39%); white solid; mp 175–176 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 7.09 (s, 1 H), 7.02 (dd, *J* = 8.4, 7.4 Hz, 2 H), 6.68 (s, 1 H), 6.55 (d, *J* = 7.7 Hz, 2 H), 6.46 (t, *J* = 7.2 Hz, 1 H), 5.02 (d, *J* = 9.3 Hz, 1 H), 3.40 (dd, *J* = 10.5, 3.7 Hz, 1 H), 2.13 (td, *J* = 11.7, 3.6 Hz, 1 H), 2.02 (dd, *J* = 12.8, 2.5 Hz, 1 H), 1.79 (d, *J* = 12.8 Hz, 1 H), 1.67 (d, *J* = 12.1 Hz, 2 H), 1.48 (qd, *J* = 13.0, 3.2 Hz, 1 H), 1.29 (qd, *J* = 12.8, 3.1 Hz, 1 H), 1.17 (qd, *J* = 12.7, 3.3 Hz, 1 H), 1.05–0.93 (m, 1 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 176.1, 148.0, 128.8, 115.3, 112.5, 52.3, 50.2, 32.1, 29.4, 24.8, 24.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}N_2O$: 219.14919; found: 219.14983. (Note: HRMS was measured on the **1c**/**1d** mixture, prior to separation.)

**3-(Phenylamino)butanamide (1e)**

Prepared from methyl 3-(phenylamino)butanoate (6.00 g, 31 mmol), according to the procedure for **1a**/**1b**.

Yield: 5.10 g (92%); yellow oil.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.08 (m, 2 H), 6.82–6.56 (m, 3 H), 6.26 (br s, 1 H, partially overlapped), 6.17 (br s, 1 H, partially overlapped), 4.00–3.77 (m, 2 H), 2.46 (dd, *J* = 14.7, 6.2 Hz, 1 H, partially overlapped), 2.32 (dd, *J* = 14.8, 5.6 Hz, 1 H, partially overlapped), 1.25 (d, *J* = 6.3 Hz, 3 H).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 174.2, 146.7, 129.3, 117.9, 113.8, 46.3, 42.1, 20.5.

The spectra were in accordance with the previously reported data.[35]

***tert*-Butyl 4-Carbamoylpiperidine-1-carboxylate (1m)**

Prepared from 1-*tert*-butyl 4-methyl piperidine-1,4-dicarboxylate (1.22 g, 5 mmol), according to the procedure for **1a**/**1b**.

Yield: 0.70 g (61%); off-white solid; mp 154 °C.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 6.09 (br s, 1 H), 5.77 (br s, 1 H), 4.13 (d, *J* = 13.1 Hz, 2 H), 2.91–2.62 (m, 2 H), 2.31 (tt, *J* = 11.5, 3.8 Hz, 1 H), 1.84 (dd, *J* = 12.9, 2.8 Hz, 2 H), 1.74–1.54 (m, 2 H), 1.45 (s, 9 H).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 177.3, 154.6, 79.6, 43.2 (partially overlapped), 43.1 (partially overlapped), 42.5, 28.5.

The spectra were in accordance with the previously reported data.[36]

**3,3′-(Benzylazanediyl)dipropanamide (1n)**

A solution of dimethyl 3,3′-(benzylazanediyl)dipropanoate (2.0 g, 7.1 mmol) in 7 M methanolic ammonia (20 mL) was stirred magnetically in a stoppered flask for 48 h at r.t. The solution was concentrated on a rotary evaporator at 40 °C and the residue was stirred with hexane–EtOAc (2:1, 20 mL) for 1 h. The precipitated solid was collected by suction filtration and vacuum-dried.

Yield: 0.86 g (49%); white flakes; mp 102–103 °C. (Note: the filtrate contained methyl 3-[(3-amino-3-oxopropyl)(benzyl)amino]propanoate, 0.55 g, 2.1 mmol.)

$^1$H NMR (200 MHz, DMSO-$d_6$): δ = 7.31 (s, 2 H, partially overlapped), 7.29–7.24 (m, 4 H), 7.24–7.17 (m, 1 H), 6.74 (s, 2 H), 3.52 (s, 2 H), 2.61 (t, *J* = 7.3 Hz, 4 H), 2.21 (t, *J* = 7.3 Hz, 4 H).

$^{13}$C NMR (50 MHz, DMSO-$d_6$): δ = 173.8, 139.6, 128.9, 128.3, 127.0, 57.4, 49.3, 33.0.

The spectra were in accordance with the previously reported data.[37]

**Benzo[*d*][1,3]dioxole-5-carboxamide (1r)**

Benzo[*d*][1,3]dioxole-5-carboxylic acid (8.00 g, 48.1 mmol), $SOCl_2$ (10.4 mL, 144 mmol) and DMF (0.15 mL, 2 mmol) were mixed together in a flask protected with $CaCl_2$ trap and stirred magnetically at r.t. After 24 h, the homogeneous mixture was diluted with toluene (100 mL) and concentrated on a rotary evaporator at 40 °C; the residue was diluted with $CHCl_3$ (20 mL) at –10 °C and added dropwise to stirred aqueous ammonia (25%, 30 mL) at –10 °C. The layers were separated, the aqueous layer was extracted with $CHCl_3$ (2 × 25 mL) and the combined organic extracts were concentrated on a rotary evaporator at 20–80 °C. The residue was used without further purification.

Yield: 7.20 g (91%); off-white solid; mp 166 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 7.81 (br s, 1 H), 7.47 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.40 (d, *J* = 1.6 Hz, 1 H), 7.23 (br s, 1 H), 6.96 (d, *J* = 8.1 Hz, 1 H), 6.08 (s, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 167.0, 149.7, 147.3, 128.3, 122.5, 107.7, 107.6, 101.6.

The spectra were in accordance with the previously reported data.[38]

**2-Ethoxybenzamide (1t)**

Prepared from 2-ethoxybenzoic acid (5.00 g, 30.1 mmol), according to the procedure for **1r**.

Yield: 4.46 g (90%); off-white solid; mp 132 °C.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 8.22 (dd, *J* = 7.8, 1.9 Hz, 1 H), 7.89 (br s, 1 H), 7.45 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1 H), 7.16–6.87 (m, 2 H), 6.58 (br s, 1 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 1.51 (t, *J* = 7.0 Hz, 3 H).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 167.4, 157.3, 133.2, 132.4, 121.0, 120.8, 112.2, 64.6, 14.8.

The spectra were in accordance with the previously reported data.[39]

**Cyclic Ureas and Carbamates 2; General Procedure**

To a solution of a carboxamide **1** (0.6–7 mmol) in MeOH (0.2–0.9 M) was added LiOH·$H_2O$ (2–15 equiv), with the flask protected from light and cooled to 0 °C with stirring. Solid NBA (1–8 equiv) was added in one portion and the heterogeneous mixture was stirred, while the temperature gradually attained r.t. The reaction progress was monitored by TLC, requiring 24–48 h for completion. The reaction mixture was added to 10% aqueous $Na_2S_2O_5$ (2 volumes) and concentrated on a rotary evaporator (30 °C, 30 min). The liquid residue was diluted with 5% aqueous NaOH (15 volumes) and extracted with $CH_2Cl_2$ (3 × 8 volumes). The combined extracts were concentrated on a rotary evaporator and vacuum-dried (0.2 mmHg, 40 °C, 1 h). Further purification, when necessary, was achieved by dry-column flash chromatography, using the solvent gradient as indicated. When BnOH was used instead of MeOH, the procedure was modified as follows: After reaction completion, the mixture was diluted with $CH_2Cl_2$ (25 volumes) and extracted successively with 10% aqueous $Na_2S_2O_5$ (2 volumes) and 5% aqueous NaOH (15 volumes). The organic layer

was concentrated on a rotary evaporator and the excess BnOH was removed under reduced pressure (0.2 mmHg, 80 °C, 45 min). When necessary, the product was purified by dry-column flash chromatography.

Comparative experiments in which NBA was replaced with NBS were typically performed by adding NBS (1–4 equiv) and LiOH·$H_2O$ (6–15 equiv) to a solution of the carboxamide **1** (0.6–7 mmol) in MeOH (0.2–1.2 M). The heterogeneous mixture, protected from light, was stirred at r.t. or heated to reflux (65 °C). The reaction progress was monitored by TLC, requiring 1–24 h for completion. Workup and purification were the same as for the NBA procedure.

### *cis*-5-Phenethyl-1-phenylhexahydro-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)-one (2a)

Prepared according to the general procedure for NBA from *cis*-1-phenethyl-4-(phenylamino)piperidine-3-carboxamide (**1a**; 0.20 g, 0.6 mmol) in MeOH (3 mL), LiOH·$H_2O$ (0.39 g, 9.3 mmol) and NBA (0.34 g, 2.4 mmol), over 48 h. The crude product was purified by dry-column flash chromatography ($CH_2Cl_2$–MeOH gradient, 100:0 to 80:20).

Yield: 0.14 g (75%); pale yellow, amorphous solid; mp 99–100 °C.

IR (neat): 3281.1, 3027.0, 2947.0, 2812.2, 1705.9, 1599.6, 1499.0, 1403.8, 1309.9, 1253.8, 753.2, 698.2 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.39–7.12 (m, 10 H), 6.10 (s, 1 H), 4.21 (dt, *J* = 6.5, 4.6 Hz, 1 H), 3.82 (dd, *J* = 12.6, 7.1 Hz, 1 H), 2.87 (ddd, *J* = 11.7, 5.3, 1.0 Hz, 1 H), 2.81–2.71 (m, 2 H), 2.67–2.54 (m, 2 H), 2.45 (dd, *J* = 11.8, 7.7 Hz, 2 H), 2.39–2.25 (m, 1 H), 2.05–1.88 (m, 2 H).

$^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 161.1, 139.9, 137.8, 128.8, 128.6, 128.3, 126.0, 124.7, 123.2, 60.0, 55.8, 54.0, 49.2, 48.6, 33.4, 25.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{24}N_3O$: 322.19139; found: 322.18990. (Note: HRMS was measured on a **2a**/**2b** mixture, obtained in an earlier experiment where the precursors **1a**/**1b** were not separated.)

Compound **2a** was also prepared according to the general procedure for NBS; yield: 70%, contaminated with ~10% brominated side products which were not isolated, as determined via $^1H$ and $^{13}C$ NMR spectroscopy and HPLC/HRMS.

### *trans*-5-Phenethyl-1-phenylhexahydro-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)-one (2b)

Prepared according to the general procedure for NBA from *trans*-1-phenethyl-4-(phenylamino)piperidine-3-carboxamide (**1b**; 0.20 g, 0.6 mmol) in MeOH (3 mL), LiOH·$H_2O$ (0.30 g, 7.1 mmol) and NBA (0.24 g, 1.7 mmol), over 48 h. The crude product was purified by dry-column flash chromatography ($CH_2Cl_2$–MeOH gradient, 100:0 to 80:20).

Yield: 0.16 g (85%); pale yellow, amorphous solid; mp 136–138 °C.

IR (neat): 3228.7, 3105.0, 3027.8, 2953.4, 2808.2, 1702.6, 1601.3, 1498.3, 1351.9, 1236.1, 1165.7, 1139.3, 753.9, 698.0 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.37 (t, *J* = 7.9 Hz, 2 H), 7.32–7.22 (m, 4 H), 7.22–7.14 (m, 4 H), 5.74 (s, 1 H), 3.52–3.46 (m, 1 H), 3.42 (td, *J* = 11.1, 3.1 Hz, 1 H), 3.30 (dd, *J* = 9.9, 2.8 Hz, 1 H), 3.08 (d, *J* = 11.9 Hz, 1 H), 2.84–2.67 (m, 4 H), 2.37–2.29 (m, 2 H), 2.08 (dd, *J* = 12.2, 2.6 Hz, 1 H), 1.73 (qd, *J* = 11.8, 4.0 Hz, 1 H).

$^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 162.6, 139.9, 138.3, 128.8, 128.6, 128.3, 126.0, 125.0, 123.2, 63.6, 59.6, 56.6, 55.5, 51.8, 33.6, 28.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{24}N_3O$: 322.19139; found: 322.18990. (Note: HRMS was measured on a **2a**/**2b** mixture, obtained in an earlier experiment where the precursors **1a**/**1b** were not separated.)

Compound **2b** was also prepared according to the general procedure for NBS; yield: 80%, contaminated with ~5% brominated side products which were not isolated, as determined via $^1H$ and $^{13}C$ NMR spectroscopy and HPLC/HRMS.

### *cis*-1-Phenylhexahydro-1*H*-benzo[*d*]imidazol-2(3*H*)-one (2c)

Prepared according to the general procedure for NBA from *cis*-2-(phenylamino)cyclohexanecarboxamide (**1c**; 0.20 g, 0.90 mmol) in MeOH (3 mL), LiOH·$H_2O$ (0.58 g, 13.8 mmol) and NBA (0.38 g, 2.7 mmol), over 24 h.

Yield: 0.16 g (80%); white powder; mp 114–115 °C.

IR (neat): 3220.9, 2941.8, 2860.4, 1694.4, 1494.4, 1405.2, 1318.0, 1273.9, 1238.2, 758.6, 690.9 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.46–7.39 (m, 2 H), 7.34 (ddd, *J* = 8.6, 5.8, 1.9 Hz, 2 H), 7.10 (tt, *J* = 7.6, 1.2 Hz, 1 H), 5.35 (s, 1 H), 4.15 (dd, *J* = 12.1, 6.8 Hz, 1 H), 3.79 (dd, *J* = 11.6, 5.7 Hz, 1 H), 1.86–1.65 (m, 4 H), 1.64–1.56 (m, 1 H), 1.55–1.46 (m, 1 H), 1.44–1.35 (m, 1 H), 1.33–1.23 (m, 1 H).

$^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 160.8, 138.4, 128.8, 123.9, 122.0, 56.1, 49.8, 28.3, 25.5, 20.5, 20.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O$: 217.13354; found: 217.13352. (Note: HRMS was measured on a **2c**/**2d** mixture, obtained in an earlier experiment where the precursors **1c**/**1d** were not separated.)

Compound **2c** was also prepared according to the general procedure for NBS; yield: 73%, contaminated with ~40% brominated side products which were not isolated, as determined via $^1H$ and $^{13}C$ NMR spectroscopy and HPLC/HRMS.

### *trans*-1-Phenylhexahydro-1*H*-benzo[*d*]imidazol-2(3*H*)-one (2d)

Prepared according to the general procedure for NBA from *trans*-2-(phenylamino)cyclohexanecarboxamide (**1d**; 0.30 g, 1.4 mmol) in MeOH (4 mL), LiOH·$H_2O$ (0.86 g, 20.5 mmol) and NBA (0.37 g, 2.8 mmol), over 24 h.

Yield: 0.26 g (85%); white powder; mp 140–141 °C.

IR (neat): 3198.0, 3092.8, 2934.6, 2861.9, 1699.0, 1597.5, 1496.8, 1372.4, 1233.1, 772.0, 693.1 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 2 H), 7.24 (dt, *J* = 6.4, 4.0 Hz, 2 H), 7.19–7.10 (m, 1 H), 5.59 (s, 1 H), 3.50–3.40 (m, 1 H), 3.24 (tdd, *J* = 11.3, 3.3, 1.6 Hz, 1 H), 2.19–2.00 (m, 2 H), 1.91–1.77 (m, 2 H), 1.59–1.28 (m, 4 H).

$^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 162.4, 138.4, 128.7, 124.9, 123.5, 64.3, 58.9, 29.5, 28.3, 24.1, 24.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O$: 217.13354; found: 217.13352. (Note: HRMS was measured on a **2c**/**2d** mixture, obtained in an earlier experiment where the precursors **1c**/**1d** were not separated.)

Compound **2d** was also prepared according to the general procedure for NBS; yield: 75%, contaminated with ~30% brominated side products which were not isolated, as determined via $^1H$ and $^{13}C$ NMR spectroscopy and HPLC/HRMS.

**5-Methyl-1-phenylimidazolidin-2-one (2e)**

Prepared according to the general procedure for NBA from 3-(phenylamino)butanamide (**1e**; 0.70 g 3.9 mmol) in MeOH (7 mL), LiOH·$H_2O$ (1.00 g, 23.8 mmol) and NBA (1.08 g, 7.88 mmol), over 24 h.

Yield: 0.59 g (85%); pale yellow oil.

IR (neat): 3289.7, 3063.8, 2974.3, 1685.3, 1497.6, 1441.1, 1258.4, 1154.2, 1007.9, 760.6 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.46–7.29 (m, 4 H), 7.10 (tt, *J* = 7.4, 1.3 Hz, 1 H), 6.34 (s, 1 H), 4.44–4.34 (m, 1 H), 3.67 (t, *J* = 8.7 Hz, 1 H), 3.11 (dd, *J* = 8.6, 6.3 Hz, 1 H), 1.26 (d, *J* = 6.2 Hz, 3 H).

$^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 160.5, 138.1, 128.8, 123.9, 121.9, 52.3, 45.5, 18.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{13}N_2O$: 177.10224; found: 177.10194.

Compound **2e** was also prepared according to the general procedure for NBS; yield: 80%, contaminated with ~50% brominated side products which were not isolated, as determined via $^1H$ and $^{13}C$ NMR spectroscopy and HPLC/HRMS.

**Methyl Pentylcarbamate (2f)**

Prepared according to the general procedure for NBA from hexanamide (**1h**; 0.30 g, 2.6 mmol) in MeOH (3 mL), LiOH·$H_2O$ (0.65 g, 15.4 mmol) and NBA (0.72 g, 5.2 mmol), over 24 h.

Yield: 0.30 g (81%); pale yellow oil.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 4.89 (br s, 1 H), 3.66 (s, 3 H), 3.16 (dd, *J* = 13.2, 6.6 Hz, 2 H), 1.50 (dt, *J* = 13.4, 6.8 Hz, 2 H), 1.30 (dt, *J* = 7.5, 3.6 Hz, 4 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 157.1, 51.8, 40.9, 29.6, 28.7, 22.2, 13.8.

The spectra were in accordance with the previously reported data.[40]

Compound **2f** was also prepared according to the general procedure for NBS; yield: 69%.

**Methyl Benzylcarbamate (2g)**[9]

Prepared according to the general procedure for NBA from 2-phenylacetamide (**1i**; 0.30 g, 2.2 mmol) in MeOH (3 mL), LiOH·$H_2O$ (0.46 g, 10.9 mmol) and NBA (0.30 g, 2.2 mmol), over 24 h.

Yield: 0.30 g (82%); white amorphous solid; mp 65 °C.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.46–7.10 (m, 5 H), 5.19 (br s, 1 H), 4.34 (d, *J* = 6.0 Hz, 2 H), 3.67 (s, 3 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 157.1, 138.5, 128.5, 127.4, 52.0, 44.9.

The spectra were in accordance with the previously reported data.[9]

Compound **2g** was also prepared according to the general procedure for NBS; yield: 60%.

**Benzyl Benzylcarbamate (2h)**

Prepared according to the general procedure for NBA from 2-phenylacetamide (**1i**; 0.20 g, 1.5 mmol) in BnOH (3 mL), LiOH·$H_2O$ (0.32 g, 7.5 mmol) and NBA (0.21 g, 1.5 mmol), over 24 h.

Yield: 0.27 g (76%); colorless oil. (Note: the product was contaminated with 10% BnOH.)

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.45–7.30 (m, 10 H), 5.22 (br s, 1 H, partially overlapped), 5.10 (s, 2 H), 4.33 (d, *J* = 5.9 Hz, 2 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 156.4, 140.9, 138.3, 128.6, 128.4, 128.1, 127.5, 127.4, 126.9, 66.8, 45.0.

The spectra were in accordance with the previously reported data.[41]

***N*-(Benzylcarbamoyl)acetamide (2i)**

To a stirred solution of 2-phenylacetamide (**1i**; 1.00 g, 7.3 mmol) in MeOH (10 mL) at 0 °C, NBA (1.51 g, 10.9 mmol) was added in one portion. The flask was protected from light; a solution of KOH (0.60 g, 10.6 mmol) in MeOH (5 mL) was added to the mixture over a 1 h period and the stirring was continued for 24 h at 0 °C to r.t. The mixture was concentrated on a rotary evaporator, partitioned between brine (20 mL) and $CH_2Cl_2$ (60 mL), and the organic layer was concentrated. The solid residue was dissolved in $CHCl_3$ (20 mL), triturated with petroleum ether (5 mL) and the precipitated impurities removed. The filtrate was concentrated to afford the product with 5–10% impurity.

Yield: 1.16 g (82%); white solid; mp 130 °C.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 10.38 (s, 1 H), 8.91 (s, 1 H), 7.39–7.22 (m, 5 H), 4.48 (d, *J* = 6.0 Hz, 2 H), 2.09 (s, 3 H).

$^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 172.6, 155.0, 138.0, 128.6, 127.4, 127.3, 43.5, 23.8.

The spectra were in accordance with the previously reported data.[42]

**Methyl Phenethylcarbamate (2j)**

Prepared according to the general procedure for NBA from 3-phenylpropanamide (**1j**; 0.30 g, 2.0 mmol) in MeOH (4 mL), LiOH·$H_2O$ (0.50 g, 12 mmol) and NBA (0.64 g, 5 mmol), over 24 h.

Yield: 0.29 g (83%); white amorphous solid; mp 30 °C.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.41–7.08 (m, 5 H), 4.86 (br s, 1 H), 3.64 (s, 3 H), 3.42 (dd, *J* = 13.3, 6.7 Hz, 2 H), 2.79 (t, *J* = 7.0 Hz, 2 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 156.9, 138.7, 128.7, 128.5, 126.4, 51.9, 42.1, 36.0.

The spectra were in accordance with the previously reported data.[43]

**Methyl Dec-9-en-1-ylcarbamate (2k)**

Prepared according to the general procedure for NBA from undec-10-enamide (**1k**; 0.50 g, 2.7 mmol) in MeOH (4 mL), LiOH·$H_2O$ (0.68 g, 16.3 mmol) and NBA (0.94 g, 6.7 mmol), over 24 h.

Yield: 0.54 g (94%); pale yellow oil.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 5.81 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1 H), 5.08–4.87 (m, 2 H), 4.80 (br s, 1 H), 3.66 (s, 3 H), 3.16 (dd, *J* = 13.1, 6.5 Hz, 2 H), 2.13–1.94 (m, 2 H), 1.61–1.17 (m, 12 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 157.1, 139.1, 114.1, 51.9, 41.0, 33.7, 29.9, 29.2, 29.1, 28.9, 28.8, 26.6.

The spectra were in accordance with the previously reported data.[44]

Compound **2k** was also prepared according to the general procedure for NBS; yield: 87%.

**Methyl 1-Benzylpiperidin-4-ylcarbamate (2l)**

Prepared according to the general procedure for NBA from 1-benzylpiperidine-4-carboxamide (**1l**; 0.15 g, 0.7 mmol) in MeOH (2 mL), LiOH·$H_2O$ (0.17 g, 4.2 mmol) and NBA (0.19 g, 1.4 mmol), over 24 h.

Yield: 0.15 g (88%); off-white solid; mp 78–79 °C.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.49–7.09 (m, 5 H), 4.78 (d, *J* = 6.9 Hz, 1 H), 3.64 (s, 3 H), 3.48 (s, 3 H), 2.87–2.69 (m, 2 H), 2.09 (td, *J* = 11.6, 2.3 Hz, 2 H), 1.90 (d, *J* = 11.0 Hz, 2 H), 1.59–1.30 (m, 2 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 156.2, 138.1, 129.0, 128.1, 126.9, 62.9, 52.0, 51.8, 48.0, 32.3.

The spectra were in accordance with the previously reported data.[45]

**tert-Butyl 4-[(Methoxycarbonyl)amino]piperidine-1-carboxylate (2m)**

Prepared according to the general procedure for NBA from *tert*-butyl 4-carbamoylpiperidine-1-carboxylate (**1m**; 0.20 g, 0.9 mmol) in MeOH (4 mL), LiOH·$H_2O$ (0.31 g, 7.3 mmol) and NBA (0.15 g, 1.2 mmol), over 24 h.

Yield: 0.21 g (92%); colorless oil.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 4.91 (d, *J* = 7.0 Hz, 1 H), 4.02 (d, *J* = 13.4 Hz, 2 H), 3.66 (s, 4 H), 2.97–2.73 (m, 2 H), 1.91 (dd, *J* = 12.6, 3.0 Hz, 2 H), 1.45 (s, 9 H), 1.38–1.19 (m, 2 H).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 156.2, 154.6, 79.5, 51.9, 48.2, 42.4, 32.2, 28.3, 28.2.

The spectra were in accordance with the previously reported data.[46]

**tert-Butyl 4-{[(Benzyloxy)carbonyl]amino}piperidine-1-carboxylate (2n)**

Prepared according to the general procedure for NBA from *tert*-butyl 4-carbamoylpiperidine-1-carboxylate (**1m**; 0.20 g, 0.9 mmol) in BnOH (4 mL), LiOH·$H_2O$ (0.2 g, 4.7 mmol) and NBA (0.24 g, 1.8 mmol), over 24 h.

Yield: 0.20 g (69%); white powder; mp 88 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.28 (m, 5 H), 5.08 (s, 2 H), 4.82 (d, *J* = 5.9 Hz, 1 H), 4.00 (br s, 2 H), 3.64 (br s, 1 H), 2.84 (br s, 2 H), 1.91 (d, *J* = 11.1 Hz, 2 H), 1.45 (s, 9 H), 1.36–1.22 (m, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 155.5, 154.6, 136.4, 128.5, 128.1, 79.6, 66.6, 48.3, 42.5, 32.2, 28.3.

The spectra were in accordance with the previously reported data.[47]

**Methyl 2-{Benzyl[2-(methoxycarbonylamino)ethyl]amino}ethylcarbamate (2o)**

Prepared according to the general procedure for NBA from 3,3′-(benzylazanediyl)dipropanamide (**1n**; 0.30 g, 1.2 mmol) in MeOH (3 mL), LiOH·$H_2O$ (0.50 g, 12.0 mmol) and NBA (1.32 g, 9.6 mmol), over 24 h.

Yield: 0.28 g (77%); pale yellow oil.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.08 (m, 5 H), 5.16 (br s, 2 H), 3.58 (s, 6 H), 3.50 (s, 2 H), 3.15 (dd, *J* = 11.5, 5.7 Hz, 4 H), 2.49 (t, *J* = 5.9 Hz, 4 H).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 156.4, 137.8, 127.9, 127.4, 126.2, 57.6, 52.4, 51.0, 37.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{24}N_3O_4$: 310.17613; found: 310.17585.

Compound **2o** was also prepared according to the general procedure for NBS; yield: 62%.

**Methyl Phenylcarbamate (2p)**

Prepared according to the general procedure for NBA from benzamide (**1p**; 0.31 g, 2.5 mmol) in MeOH (4 mL), LiOH·$H_2O$ (0.54 g, 12.8 mmol) and NBA (0.46 g, 3.3 mmol), over 24 h.

Yield: 0.36 g (94%); white powder; mp 47 °C.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.67 (br s, 1 H), 7.37 (ddd, *J* = 4.4, 3.3, 1.8 Hz, 2 H), 7.30–7.12 (m, 2 H), 7.03–6.90 (m, 1 H), 3.63 (s, 3 H).

$^{13}$C NMR (50 MHz, $CD_3CN$): δ = 155.6, 140.2, 130.2, 124.3, 119.9, 52.9.

The spectra were in accordance with the previously reported data.[10]

Compound **2p** was also prepared according to the general procedure for NBS; yield: 82%.

**Methyl *m*-Tolylcarbamate (2q)**

Prepared according to the general procedure for NBA from 3-methylbenzamide (**1q**; 0.30 g, 2.2 mmol) in MeOH (4 mL), LiOH·$H_2O$ (0.56 g, 13.3 mmol) and NBA (0.76 g, 5.5 mmol), over 24 h.

Yield: 0.33 g (89%); pale yellow solid; mp 57–58 °C.

$^1$H NMR (500 MHz, $CD_3CN$): δ = 7.60 (br s, 1 H), 7.22–7.14 (m, 2 H), 7.10 (t, *J* = 7.8 Hz, 1 H), 6.83–6.76 (m, 1 H), 3.62 (s, 3 H), 2.23 (s, 3 H).

$^{13}$C NMR (126 MHz, $CD_3CN$): δ = 155.6, 140.2, 140.1, 130.1, 125.0, 120.5, 117.1, 52.9, 21.9.

The spectra were in accordance with the previously reported data.[48]

Compound **2q** was also prepared according to the general procedure for NBS; yield: 95%, contaminated with ~40% brominated side products which were not isolated, as determined via $^1$H and $^{13}$C NMR spectroscopy and HPLC/HRMS.

**Methyl Benzo[*d*][1,3]dioxol-5-ylcarbamate (2r)**

Prepared according to the general procedure for NBA from benzo[*d*][1,3]dioxole-5-carboxamide (**1r**; 0.30 g, 1.8 mmol) in MeOH (4 mL), LiOH·$H_2O$ (0.46 g, 10.9 mmol) and NBA (0.63 g, 4.5 mmol), over 24 h.

Yield: 0.33 g (93%); off-white solid; mp 65 °C.

$^1$H NMR (500 MHz, $CD_3CN$): δ = 7.59 (br s, 1 H), 7.07 (d, *J* = 5.2 Hz, 1 H), 6.77 (dt, *J* = 15.3, 5.1 Hz, 2 H), 5.91 (s, 2 H), 3.67 (s, 3 H).

$^{13}$C NMR (126 MHz, $CD_3CN$): δ = 155.8, 149.1, 144.7, 134.5, 113.1, 112.8, 109.2, 102.7, 53.0.

The spectra were in accordance with the previously reported data.[49]

**Methyl 3,4,5-Trimethoxyphenylcarbamate (2s)**

Prepared according to the general procedure for NBA from 3,4,5-trimethoxybenzamide (**1s**; 0.30 g, 1.4 mmol) in MeOH (2 mL), LiOH·$H_2O$ (0.30 g, 7.1 mmol) and NBA (0.36 g, 2.8 mmol), over 24 h.

Yield: 0.31 g (90%); white amorphous solid; mp 88 °C.

$^1$H NMR (500 MHz, $CD_3CN$): δ = 7.65 (br s, 1 H), 6.79 (s, 2 H), 3.77 (s, 6 H), 3.69 (s, 3 H), 3.66 (s, 3 H).

$^{13}$C NMR (126 MHz, $CD_3CN$): δ = 155.6, 154.8, 136.4, 135.0, 97.7, 61.3, 56.9, 53.0.

The spectra were in accordance with the previously reported data.[49]

Compound **2s** was also prepared according to the general procedure for NBS; yield: 60%, contaminated with ~30% brominated side products which were not isolated, as determined via $^1$H and $^{13}$C NMR spectroscopy and HPLC/HRMS.

**Benzyl 3,4,5-Trimethoxyphenylcarbamate (2t)**

Prepared according to the general procedure for NBA from 3,4,5-trimethoxybenzamide (**1s**; 0.50 g, 2.3 mmol) in BnOH (5 mL), LiOH·$H_2O$ (0.58 g, 13.8 mmol) and NBA (0.65 g, 4.6 mmol), over 24 h. The crude product was purified by dry-column flash chromatography (hexane–EtOAc gradient, 100:0 to 80:20).

Yield: 0.44 g (60%); white powder; mp 110–111 °C.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.43–7.26 (m, 5 H), 6.91 (br s, 1 H), 6.67 (s, 2 H), 5.18 (s, 2 H), 3.79 (s, 3 H, partially overlapped), 3.78 (s, 6 H, partially overlapped).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 153.4, 153.3, 135.9, 134.0, 133.8, 128.5, 128.3, 128.1, 96.3, 66.8, 60.8, 55.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}NO_5$: 318.13360; found: 318.13374.

**Methyl 2-Ethoxyphenylcarbamate (2u)**

Prepared according to the general procedure for NBA from 2-ethoxybenzamide (**1t**; 0.20 g, 1.2 mmol) in MeOH (3 mL), $LiOH·H_2O$ (0.10 g, 2.4 mmol) and NBA (0.16 g, 1.2 mmol), over 24 h. The crude product was dissolved in hexane, the impurities were removed by filtration and the filtrate was concentrated.

Yield: 0.20 g (85%); colorless oil.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 8.08 (br s, 1 H), 7.26 (br s, 1 H), 7.07–6.70 (m, 3 H), 4.06 (q, *J* = 7.0 Hz, 2 H), 3.78 (s, 3 H), 1.42 (t, *J* = 7.0 Hz, 3 H).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 153.9, 146.9, 127.6, 122.6, 120.9, 118.0, 110.8, 64.0, 52.1, 14.7.

The spectra were in accordance with the previously reported data.[50]

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## Supporting Information

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