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Modification and Optimization of the Bis-picolylamide-Based Relay Protection for Carboxylic Acids to be Cleaved by Unusual Complexation with Cu^{2+} Salts

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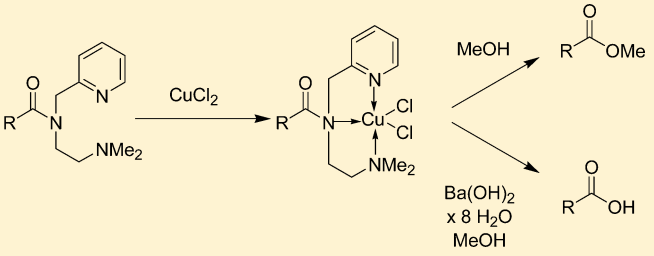
Supporting Information

ABSTRACT: A simple modification of our recently published protection scheme for carboxylic acids as amides resulted in a new protecting group with significantly improved properties. It requires shorter reaction times for deprotection and allows us to replace $Cu(OTf)_2$ by $CuCl_2$, indicating at the same time the importance of the nature of the anion of the Cu^{2+} source. Since the new scheme fulfills all criteria required for an ideal protection group it should find widespread application in synthetic organic chemistry.



INTRODUCTION

The preparation of complex organic molecules in most cases encompasses the need for protecting groups.[1,2] Common requirements for them are straightforward introduction and robustness to a variety of reaction conditions combined with the possibility for selective and efficient cleavage, preferably under mild conditions. There is only a small number of protection schemes fulfilling all these criteria.

Recently, we reported on two new linker systems for solid-phase chemistry which are based on chelating amides.[3,4] These activities led us to the development of a relay protection scheme for carboxylic acids **1a** as amides of bispicolylamine (bpa, **2**) (Scheme 1).[5] The protection group is easily removed from amide **3** by treatment with $Cu(OTf)_2$ in MeOH, which leads to quantitative formation of methyl ester **4**. The reaction is based on the unusual involvement of the amide nitrogen in the complexation to Cu^{2+} leading to a weakening of the amide bond which makes it accessible to the nucleophilic attack by MeOH.

Alternatively, the methanolysis was performed in the presence of $Ba(OH)_2{\cdot}8H_2O$[6−8] which yielded after acidic workup the pertinent carboxylic acid **1b**.

Compared to the commonly used protection of carboxylic acids as esters, the protection as amides shows a significantly higher stability due to the high resonance energy of about 80 kJ/mol. Despite its robustness it allowed for a cleavage under mild conditions. In addition, the cleavage process was orthogonal to most conditions employed for the deprotection of esters. Furthermore, bpa protection could be successfully applied to aliphatic, aromatic, and amino acids. A disadvantage though was the relatively long reaction time required for the methanolysis step which took between 16 and about 30 h and the use of the rather expensive $Cu(OTf)_2$ as copper source which had to be used in equimolar amounts.

RESULTS AND DISCUSSION

To widen the scope of the new protection scheme and to overcome the disadvantage of the long reaction times we carried out a systematic investigation of the influence of pendant coordinating groups on the rate of methanolysis of amides. Therefore, we prepared an array of variants to the original bpa entity (Scheme 2). The modifications involved the replacement of one or both pyridine rings of bis-picolylamine (bpa) by other coordinating entities, as well as variations of the distances between the pyridyl donor sites.[9,10]

Compounds **6**−**25** were then submitted to a cleavage process using $Cu(OTf)_2$ in MeOH at rt for 24 h. The amount of the released benzoic acid methyl ester was quantified by HPLC using phenol as standard. As a benchmark for the methanolysis we used the transformation of the original bpa-protected benzoic acid amide **5** to its methyl ester (Table 1).

Omitting one pyridine ring and hence omitting one coordination site as in **6** led only to a marginal cleavage rate, indicating that at least three coordinating sites are necessary to obtain decent methanolysis rates. Replacing one pyridine ring by other heterocycles was to no avail as well. Of all investigated compounds, derivatives **9**, **10**, and **25** revealed quantitative cleavage and were superior compared to the benchmark amide **5**. Since the parent amine of derivative **9** is most easily obtained, very robust and structurally very simple, we focused on the application of amine **9a** namely dimethylaminoethyl-picolylamine (dmepa) for the protection of carboxylic acids.

For this reason, we performed a side by side evaluation of **9** with the bpa amide **5** using $Cu(OTf)_2$ as copper source. In the methanolysis of **9** at rt a quantitative conversion was already observed after about 5 h compared to the more than 30 h

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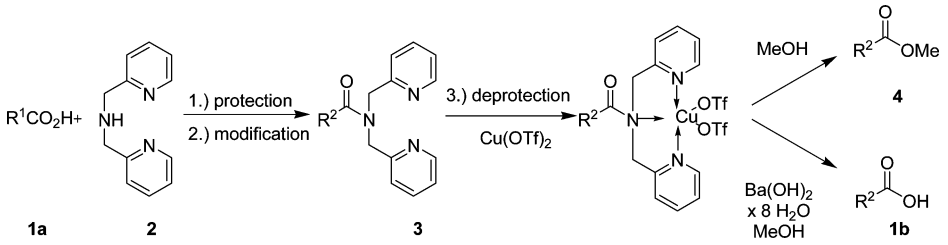
Scheme 1. Principle of the bpa-Based Protection for Carboxylic Acids As Chelating Amides



needed for derivative **5**. Variations of the experimental conditions led to further enhancements. Addition of diisopropylethylamine (DIEA, Hünig's base) turned out to have a positive effect on the cleavage rate which was also true for elevated temperatures. Hence, we also carried out the comparison at 50 °C and in the presence or absence of Hünig's base (Figure 1).

Quantitative cleavage of **9** was now possible within about 1 h.

Next we investigated the cleavage rate of an aliphatic amide. For this purpose, benzoylpropionic acid was first coupled to the parent dimethylaminoethylpicolylamine (dmepa) **9a** using TBTU as coupling reagent (Scheme 3). The resulting amide **27** was then subjected to the methanolysis reactions and compared to the one of **26**.

It turned out that formation of the expected methyl ester was at rt significantly slower than for the aromatic amide **9**. Again, increasing the temperature to 50 °C and/or adding DIEA led to much faster cleavage of the amide and complete conversion was achieved within 2−3 h (Figure 2).

No differences were observed in the methanolysis rate of **28** and **29** (Scheme 4) applying $CuCl_2$ when compared to the one of **9**. This indicated that electronic factors on the aromatic system had virtually no influence on this reaction.

A previous kinetic study involving bpa-amide **5** with either $Cu(OTf)_2$ and $CuCl_2$ had revealed that the reaction with the former proceeded much faster. For this reason, we had originally devised $Cu(OTf)_2$ as source for the Cu^{2+} being aware of the fact that this salt is rather expensive and that this would become an issue especially in large-scale synthesis employing equimolar amounts. To our delight, we discovered that the order of reactivity concerning the Cu source is reversed for the new derivative **9** (Figure 3). Complete transfer into the methyl ester was observed with $CuCl_2$ at rt already after about 1 h. This result emphasizes the importance of the nature of the anion of the Cu^{2+} source, a topic of ongoing investigations. Application of $Ba(OH)_2{\cdot}8H_2O$ in combination with the Cu^{2+} salt, furnished after acidic workup the carboxylic acid.

CONCLUSIONS

In summary, by investigating a number of structural variants of our original bpa protecting group for carboxylic acids we have developed a new and more versatile protecting group in which one pyridine entity of bpa was replaced by a simple tertiary amine and which we have dubbed as "dmepa" protecting group. The synthesis of the parent amine **9a** was performed by a simple reductive amination between pyridine-2-carboxaldehyde and *N,N*-dimethylethylenediamine, both of which are commercially available. The methanolysis reaction of pertinent carboxylic acid amides was significantly faster compared to the one resulting from bpa and it could be further increased by running the reactions at 50 °C or in the presence of DIEA. Furthermore, the commonly used $Cu(OTf)_2$ could be replaced by the much more effective and significantly cheaper $CuCl_2$. The new protection scheme works for aromatic as well as aliphatic carboxylic acids, and complete methanolysis can be achieved in both cases in less than 1 h. Thus, the newly developed protecting group for carboxylic acids fulfills virtually all requirements for an ideal protection scheme: The synthesis of the parent dmep-amine **9a** comprises only one step starting from cheap starting materials. The protection of carboxylic acids is easily performed using TBTU as coupling reagent,[11] the protection itself is very robust, the rather fast cleavage is performed under mild conditions with high yields and leads optionally to the methyl ester or the free carboxylic acid, and the procedure for cleavage is orthogonal to most deprotection schemes for carboxylic acids. Hence, we believe that the newly developed protection scheme should find widespread application in synthetic organic chemistry.

EXPERIMENTAL SECTION

General Methods. All reactions with air- and moisture-sensitive compounds were carried out under an argon atmosphere. All solvents were analytical grade or better. Dry DCM and 1,2-DCE were distilled from CaH_2. ^1H NMR and ^{13}C NMR spectra were recorded with Me_4Si as internal reference. Mass spectrometry was carried out using chemical ionization (CI) methods. High-resolution masses were recorded with a double-focusing sector-field as analyzer (mass resolution up to 50.000) or an orbitrap as mass analyzer (HRMS of compounds **17**, **19**, and **23**).

General Procedure for Reductive Aminations (General Procedure a). The amino compound (1.0 equiv) and the aldehyde (1.0 equiv) were dissolved in dry 1,2-DCE and then treated with solid sodium triacetoxyborohydride (1.5 equiv). The reaction mixture was stirred at room temperature, and completion of the reaction was easily monitored by TLC (using DCM/MeOH 9:1). Most of the reactions were already complete after 2 or 3 h. The reaction mixture was then quenched with saturated sodium hydrogen carbonate solution which was then extracted three times with DCM. The combined organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure with a rotatory evaporator. The products were purified either via distillation (parent secondary amines of compounds **9**, **14**, and **22**) or via column chromatography (parent secondary amines of compounds **6**−**8**, **10**, **13**, **15**−**21**, **25**) or used without further purification (parent amines of **11**, **12**, **23**, and **24**) in the following acylation reaction.

General Procedure for the Acylation with TBTU and the Carboxylic Acid (General Procedure b). The carboxylic acid (1.5 equiv, either benzoic acid or 3-benzoyl propionic acid) and TBTU (1.4 equiv) were suspended in DCM, and DIEA (6.0 equiv) was added. After 10 min, the secondary amine (1.0 equiv) was added. After stirring overnight at rt, the mixture was washed with water 2× and dried over Na_2SO_4. The organic solvent was evaporated, and the crude product was purified via flash chromatography (silica gel using CH_2Cl_2/MeOH 98:2 → 85:15 or aluminum oxide with CH/EE mixtures).

General Procedure for the Acylation Using Benzoyl Chloride and NEt_3 (General Procedure c). The secondary amine (1.0 equiv) and NEt_3 (3.0 equiv) were dissolved in DCM and cooled to 0 °C.

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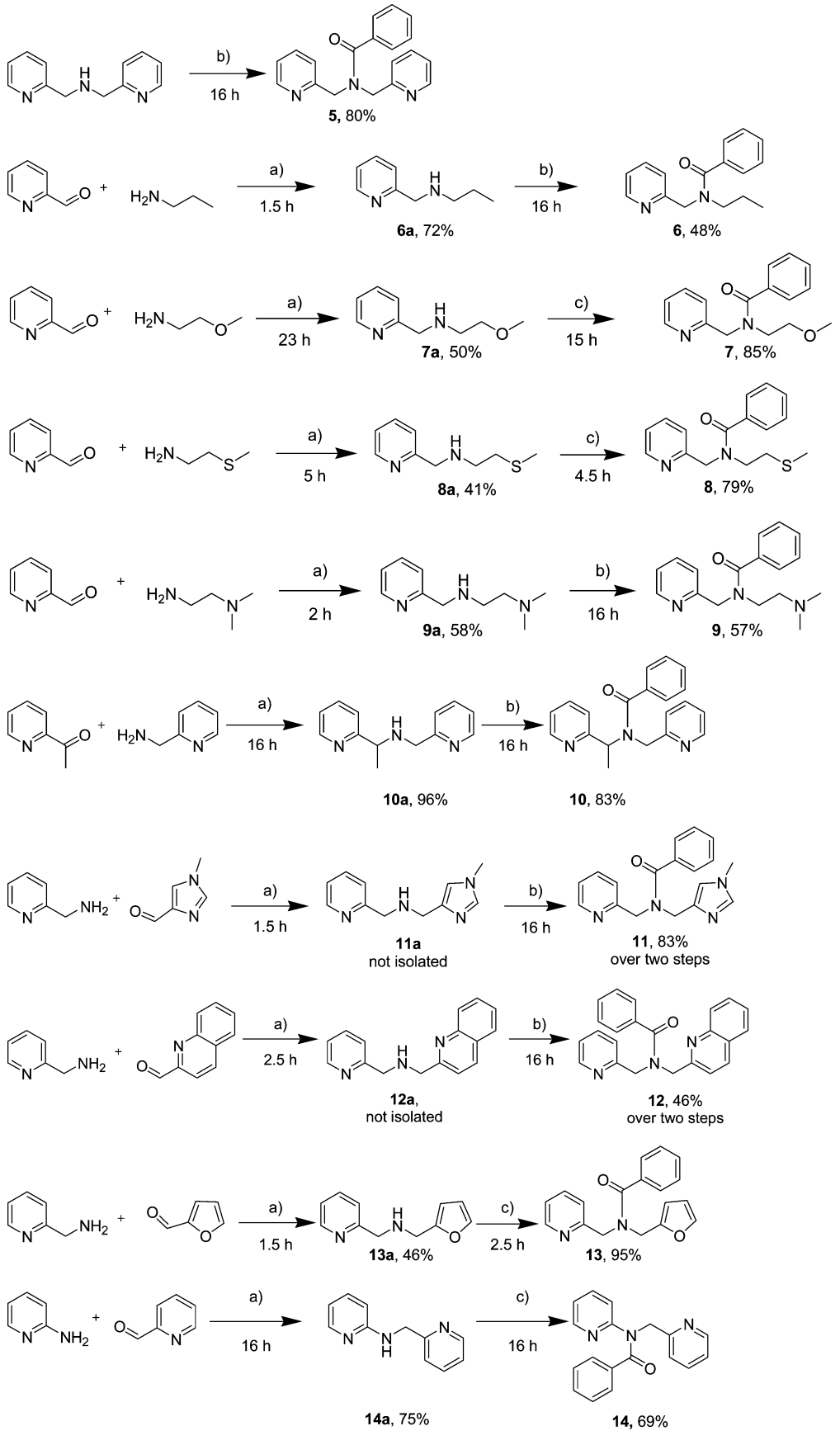
Scheme 2. Overview of Synthesized Chelating Amides



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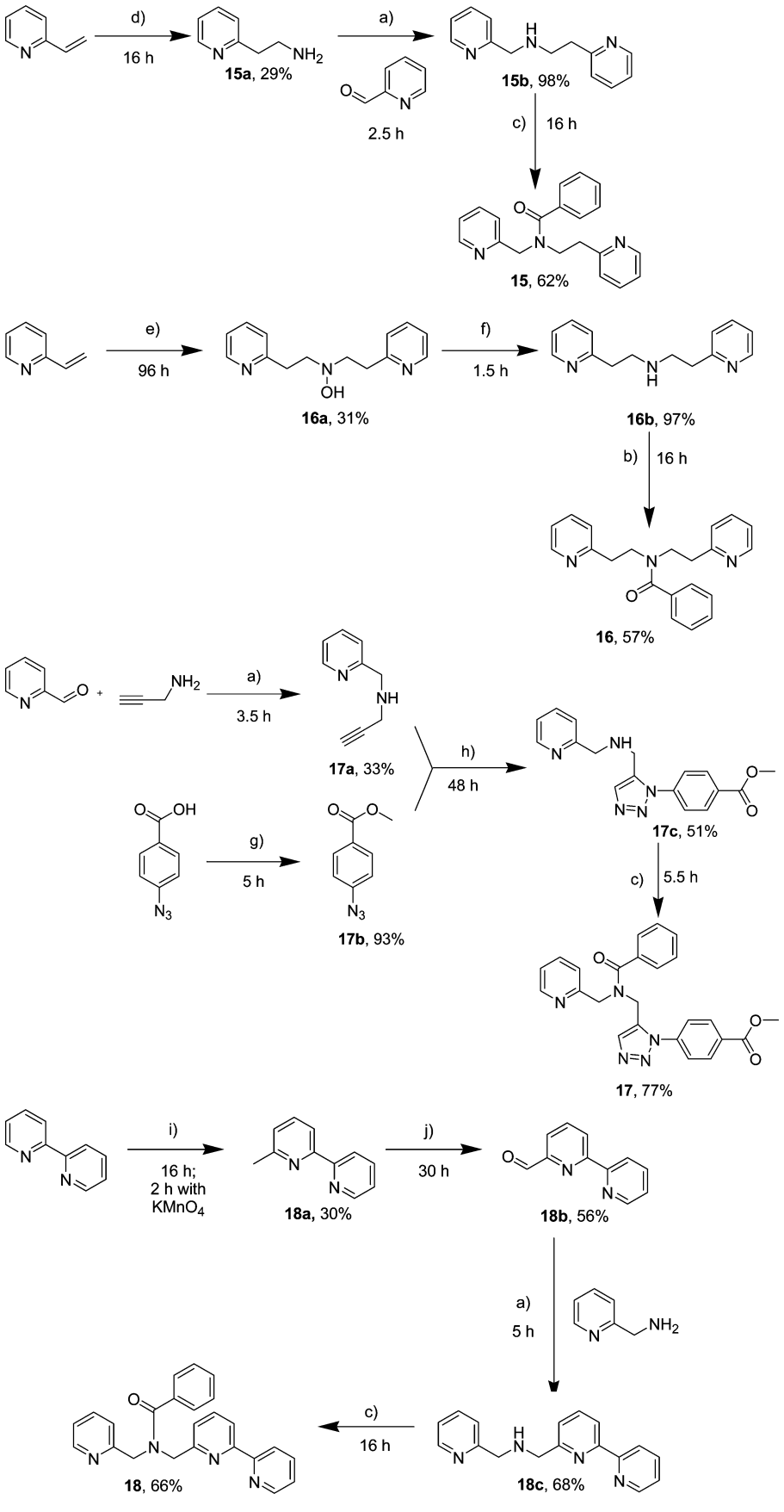

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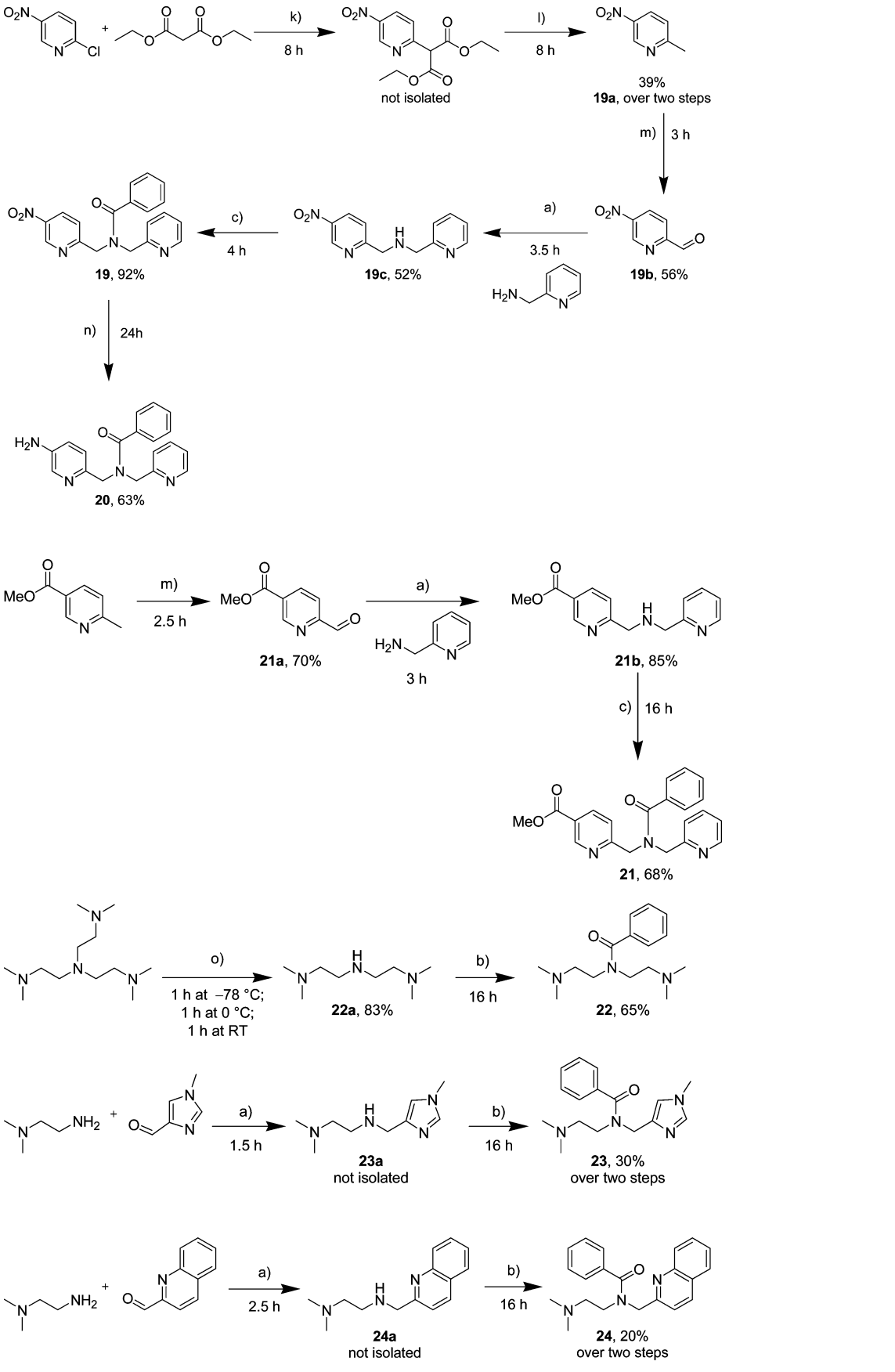

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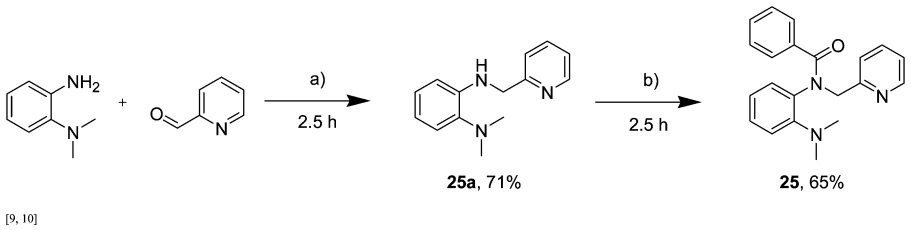
Scheme 2. continued



[9, 10]

[a]Key: (a) $NaBH(OAc)_3$ (1.40 equiv), 1,2-DCE, rt; (b) TBTU (1.40 equiv), benzoic acid (1.40 equiv), DIEA (6.00 equiv), DCM, rt; (c) benzoyl chloride (3.00 equiv), NEt_3 (3.00 equiv), DCM, rt; (d) NH_4Cl (2.00 equiv), MeOH/water, reflux; (e) hydroxylammonium hydrochloride (1.00 equiv), rt; (f) Zn (5.00 equiv), HCl (2 M), reflux; (g) DMAP (0.09 equiv), DCC (1.00 equiv), MeOH (3.00 equiv), DCM, rt; (h) pyridinium-2-carboxaldehyde (1.30 equiv), CuI (0.10 equiv), NEt_3 (0.40 equiv), MeCN, rt; (i) MeLi (1.00 equiv), Et_2O, −78 °C to rt; $KMnO_4$, acetone, 2 h, rt; (j) SeO_2 (1.50 equiv), dioxane, reflux; (k) diethyl malonate (1.55 equiv), NaH (1.04 equiv), toluene, 120 °C; (l) H_2SO_4 (50%), 120 °C; (m) I_2 (1.00 equiv), TFA (3.00 equiv), *t*-BuI (0.40 equiv), DMSO, 170 °C; (n) H_2 (1 bar), Pd/C (10%), MeOH/toluene (1:2), rt; (o) *n*-BuLi (1.00 equiv), *n*-pentane, 1 h, −78 °C; 1 h, 0 °C; 1 h, rt.

Table 1. Yield of Methanolysis Product after 24 h at rt

compd	methanolysis (%) after 24 h at rt	compd	methanolysis (%) after 24 h at rt
5	89	**16**	5
6	4	**17**	1
7	3	**18**	0
8	16	**19**	22
9	100	**20**	24
10	100	**21**	75
11	1	**22**	25
12	14	**23**	0
13	1	**24**	5
14	59	**25**	100
15	77		

Benzoyl chloride (3.0 equiv) was then added dropwise within 15 min. After removal of the ice bath, the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with water, and the organic phase was washed with water one more time. After the mixture was dried over sodium sulfate, the solvent was removed under reduced pressure and the compounds were purified via column chromatography (over silica gel using CH_2Cl_2/MeOH 98:2 → 85:15 or over basic aluminum oxide using CH/EE 4:1→ EE → EE/EtOH 98:2).

General Procedure of the Cleavage of the Chelating Amide to the Methyl Ester with $Cu(OTf)_2$ at rt. To a solution of the chelating amide (1.0 equiv) in MeOH (volume was added in order to get a concentration of 0.28 M) was added $Cu(OTf)_2$ (1.1 equiv), and the resulting mixture was stirred at rt. During the reaction, samples for HPLC measurements were taken with Hamilton syringes (10 μL, diluted with 100 μL of phenol standard solution and 180 μL of MeOH). Alternatively, the reaction was performed at 50 °C and/or in the presence of DIEA (1.1 equiv). The samples for the HPLC measurements were taken in an analytical way.

Analytical Data. *Benzylbis[(2-pyridyl)methyl]amine (**5**).* Benzamide **5** was synthesized according to the general procedure b described above. The resulting dark oil was purified via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 95:5). The resulting yellow gum (0.97 g, 3.2 mmol, 80%) crystallized overnight.

Benzylbis[(2-pyridyl)methyl]amine (**5**): mp 58−59 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.70 (s, 2H), 4.90 (s, 2H), 7.15 − 7.20 (m, 3H), 7.32−7.45 (m, 4H), 7.53 −7.57 (m, 2H), 7.66 (m, 2 H), 8.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 50.5, 54.6, 121.4, 122.4, 122.5, 127.0, 128.5, 129.8, 136.0, 136.8, 149.4, 149.9, 156.8, 157.2, 172.6 ppm, MS (CI, NH_3): *m*/*z* = 304.1 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) *m*/*z* [$(M + 1)^+$] calcd for $C_{19}H_{17}N_3O$ 303.13716, found 303.13720. Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.06; H, 5.62; N, 13.81.

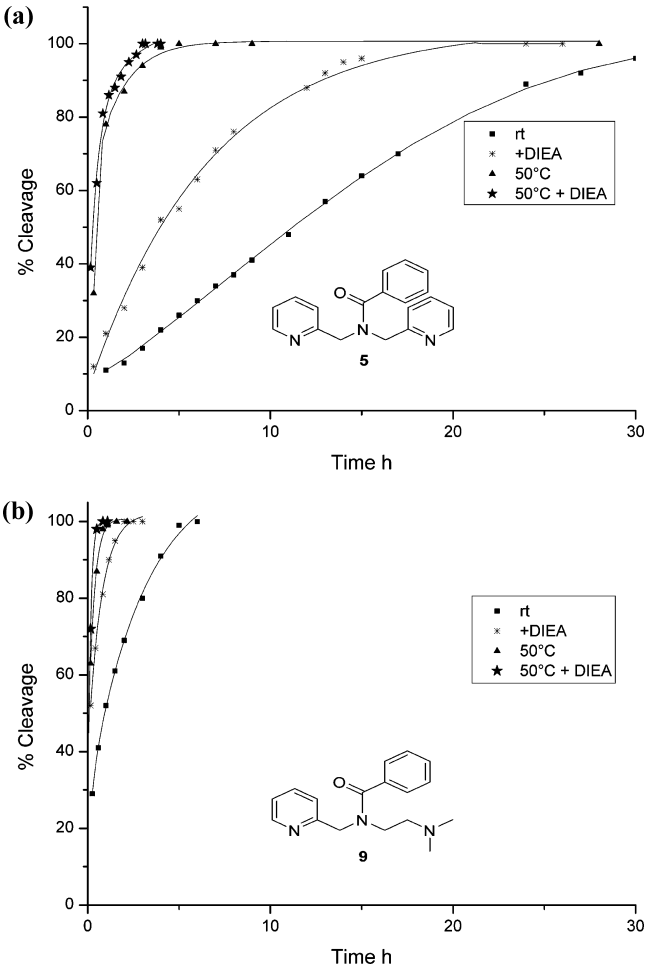


Figure 1. (a) Methanolysis of benzamide **5** at rt, at 50 °C or/and in the presence of DIEA. (b) Methanolysis of benzamide **9** at rt, at 50 °C or/and in the presence of DIEA.

*N-Propyl-N-pyridin-2-ylmethylbenzamide (**6**).* The precursor amine **6a** was synthesized by the general procedure a described above. A yellow liquid (0.93 g, 6.2 mmol, 72%) with the following analytical data was obtained after purification with column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 80:20).

N-((Pyridin-2-yl)methyl)propan-1-amine (**6a**):[12] ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.95 (t, 3H, *J* = 7.4 Hz), 1.59−1.73 (m, 2H), 2.76 (t, 2H, *J* = 7.4 Hz), 4.07 (s, 2H), 7.22 (m_c, 1H), 7.33 (d, 1H, *J* = 7.7 Hz), 7.69 (ddd, 1H, *J* = 7.7 Hz, *J* = 7.7 Hz, *J* = 1.8 Hz), 8.57 (m_c, 1H); ^{13}C

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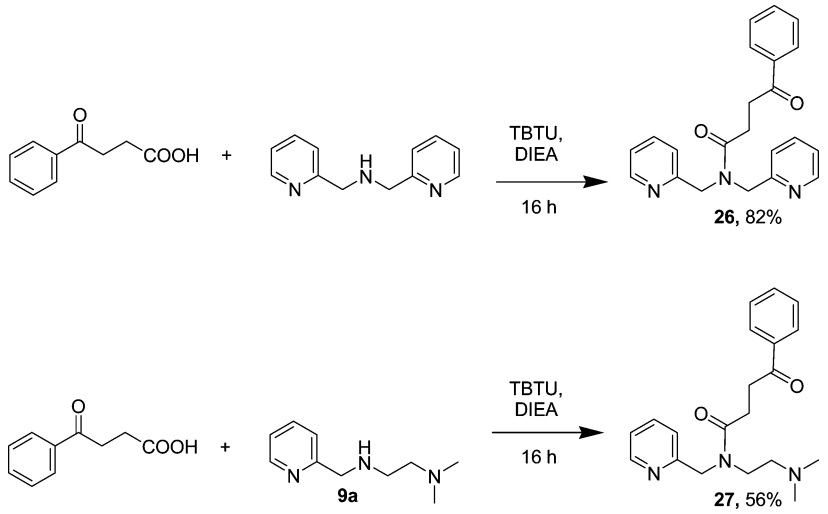
Scheme 3. Synthetic Steps for the Preparation of Aliphatic Amides 26 and 27



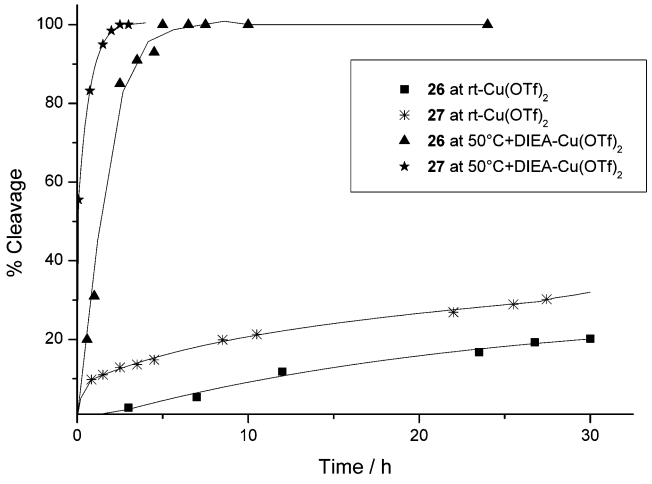


Figure 2. Methanolysis of **26** and **27** in the presence of $Cu(OTf)_2$ at rt or at 50 °C in the presence of $Cu(OTf)_2$ and DIEA.

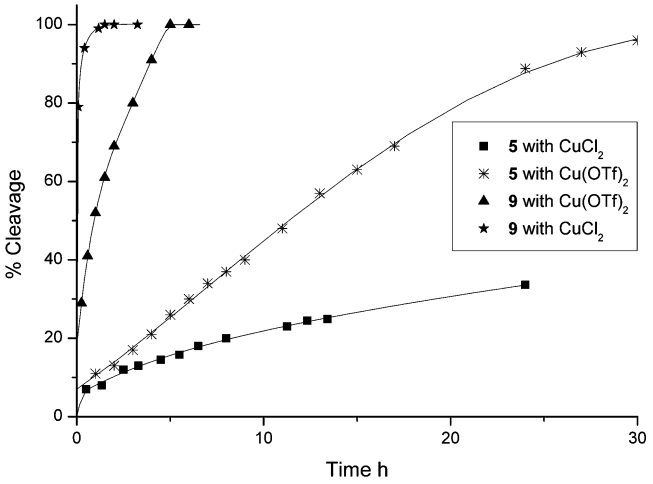


Figure 3. Comparison of the cleavage rate of **5** and **9** with $CuCl_2$ and $Cu(OTf)_2$ at rt.

NMR ($CDCl_3$, 100 MHz) δ = 11.8, 23.1, 51.5, 55.1, 121.9, 122.3, 136.5, 149.3, 159.6; MS (CI, NH_3) m/z = 151.1 (100) $[(M + 1)^+]$; HRMS (CI, NH_3) m/z $[(M + 1)^+]$ calcd for $C_9H_{14}N_2$ 151.12352, found 151.12370.

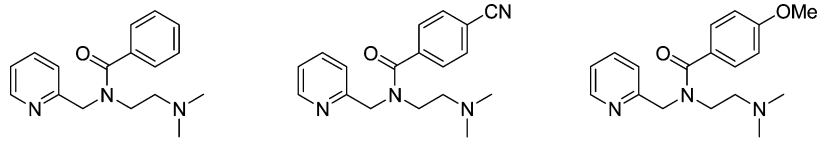
Amine **6a** was then acylated according to literature procedure b, and benzamide **6** was obtained as a yellow gum (0.74 g, 2.9 mmol, 48%) after purification via column chromatography (silica gel, DCM/MeOH 99:1 → DCM/MeOH 98:2).

N-Propyl-*N*-pyridine-2-ylmethyl-benzamide (**6**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.63−1.00 (m, 3H), 1.48−1.77 (m, 2H), 3.19−3.54 (m, 2H), 4.58−4.96 (m, 2H), 7.20 (m_c, 1H), 7.29−7.47 (m, 6H), 7.68 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.5 Hz), 8.55 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.2, 21.6, 47.1, 50.2, 51.2, 54.4, 121.1, 122.4, 126.5, 128.4, 129.4, 136.5, 136.9, 149.3, 157.4, 172.3; MS (CI, NH_3) m/z = 255.1 (100) $[(M + 1)^+]$; HRMS (CI, NH_3) m/z $[(M + 1)^+]$ calcd for $C_{16}H_{18}N_2O$ 255.14974, found 255.14930.

N-(2-Methoxyethyl)-N-pyridin-2-ylmethylbenzamide (7). The precursor amine **7a** was synthesized according to the general procedure a) described above. A yellow liquid (0.79 g, 4.7 mmol, 50%) with the following analytical data was obtained after purification with column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 90:10).

2-Methoxy-*N*-((pyridin-2-yl)methyl)ethanamine (**7a**):[13] ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.64 (br s, 1H), 2.87 (t, 2H, J = 5.2 Hz), 3.36 (s, 3H), 3.55 (t, 2H, J = 5.2 Hz), 3.93 (s, 2H), 7.16 (m_c, 1H), 7.32 (d, 1H, J = 7.7 Hz), 7.63 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 8.55 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 49.0, 55.2, 59.0, 72.0, 122.1, 136.6, 159.4, 159.6; MS (CI, NH_3) m/z = 167.1 (100) $[(M + 1)^+]$.

Scheme 4. Benzamide 9 and Structurally Related Benzamides



9 **28** **29**

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Amine **7a** was then acylated according to literature procedure c, and benzamide **7** was obtained as a brown gum (0.67 g, 2.5 mmol, 85%) after purification via column chromatography (silica gel, DCM/MeOH 98:2).

N-(2-Methoxyethyl)-*N*-pyridin-2-ylmethylbenzamide (**7**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.14−3.27 (m, 2H), 3.30−3.43 (m, 2H), 3.47−3.79 (m, 3H), 4.69−5.02 (m, 2H), 7.19 (m$_c$, 1H), 7.28−7.75 (m, 7H), 8.56 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.3, 49.1, 50.7, 55.7, 58.9, 70.0, 122.5, 127.0, 128.4, 129.6, 136.4, 172.6; MS (CI, NH_3) m/z = 271.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{16}H_{18}N_2O_2$ 271.14520, found 271.14465.

*N-(2-Methylsulfanylethyl)-N-pyridine-2-ylmethylbenzamide (**8**).* The precursor amine **8a** was synthesized according to the general procedure a described above. A dark yellow liquid (0.210 g, 1.14 mmol, 41%) with the following analytical data was obtained after purification with column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 90:10).

2-(Methylthio)-*N*-((pyridin-2-yl)methyl)ethanamine (**8a**):[14] ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.09 (s, 3H), 2.41 (br s, 1H), 2.71 (t, 2H, J = 6.5 Hz), 2.89 (t, 2H, J = 6.5 Hz), 3.96 (s, 2H), 7.16 (m$_c$, 1H), 7.33 (d, 1H, J = 7.7 Hz), 7.65 (dd, 1H, J = 7.7 Hz, J = 7.7 Hz), 8.56 (d, 1H, J = 4.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 15.4, 34.4, 48.7, 54.9, 122.2, 136.5, 149.5, 159.6; MS (CI, NH_3) m/z = 183.1 (100) [$(M + 1)^+$].

This amine was then acylated according to the general procedure c, and benzamide **8** was obtained as a brown gum (0.26 g, 0.92 mmol, 79%) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 95:5).

N-(2-Methylsulfanylethyl)-*N*-pyridin-2-ylmethylbenzamide (**8**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (m$_c$, 3H), 2.70 (m$_c$, 2H), 3.63 (m$_c$, 2H), 4.79 (m$_c$, 2H), 7.12−7.24 (m, 1H), 7.27−7.66 (m, 6H), 7.66−7.84 (m, 1H), 8.57 (m$_c$, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 32.5, 45.0, 48.9, 50.3, 55.3, 122.9, 126.9, 128.6, 129.8, 134.6, 149.9, 136.2, 157.0, 172.4; MS (CI, NH_3) m/z = 287.0 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{16}H_{18}N_2OS$ 287.12180, found 287.12181.

*N-(2-Dimethylaminoethyl)-N-pyridin-2-ylmethylbenzamide (**9**).* The precursor amine **9a** was synthesized by the general procedure a described above. A liquid with the following analytical data was obtained after distillation ($bp_{6.5*10^{-2}mbar}$ = 95−100 °C) as a yellow liquid (2.42 g, 13.5 mmol, 58%).

N^1,N^1-Dimethyl-N^2-((pyridin-2-yl)methyl)ethane-1,2-diamine (**9a**):[15] ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.28 (s, 6H), 2.58 (t, 2H, J = 6.2 Hz), 2.82 (t, 2H, J = 6.2 Hz), 3.96 (s, 2H), 7.16 (ddd, 1H, J = 7.7 Hz, J = 4.8 Hz, J = 1.2 Hz), 7.32−7.34 (m, 1H), 7.64 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 8.54 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.7, 47.0, 55.5, 59.3, 122.0, 122.3, 136.5, 149.3, 159.9; MS (CI, NH_3) m/z = 180.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{10}H_{17}N_3$ 180.15007, found 180.15020.

Amine **9a** was then acylated according to the general procedure b, and benzamide **9** was obtained as a yellow gum (0.54 g, 1.9 mmol, 57%) after purification with column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 80:20).

N-(2-Dimethylamino-ethyl)-*N*-pyridine-2-ylmethylbenzamide (**9**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.94−2.36 (m, 6H), 2.35−2.70 (m, 2H), 3.32−3.71 (m, 2H), 4.64−4.99 (m, 2H), 7.19 (m$_c$, 1H), 7.29−7.43 (m, 4H), 7.44−7.47 (m, 2H), 7.67 (m, 1H), 8.55 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.7, 122.6, 126.9, 128.5, 129.6, 137.0, 172.5; MS (CI, NH_3) m/z = 284.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{17}H_{21}N_3O$ 284.17629, found 284.17640.

*N-(1-Pyridin-2-yl)ethyl)-N-((pyridin-2-yl)methyl)benzamide (**10**).* The precursor amine **10a** was synthesized according to the general procedure a described above. A brown liquid (2.08 g, 9.6 mmol, 96%) with the following analytical data was obtained without further purification.

1-(Pyridin-2-yl)-*N*-((pyridin-2-yl)methyl)ethanamine (**10a**):[16] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.43 (d, 3H, J = 6.7 Hz), 3.10 (br s, 1H), 3.77 (s, 2H, CH_2), 3.94 (q, 1H, J = 6.7 Hz), 7.08−7.14 (m, 2H), 7.25 (d, 1H, J = 7.7 Hz), 7.36 (ddd, 1H, J = 7.8 Hz, J = 7.8 Hz, J = 1.1 Hz), 7.58 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.9 Hz), 7.62 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.9 Hz), 8.53 (m$_c$, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.9, 53.1, 59.2, 121.1, 121.9, 122.0, 122.3, 136.4, 136.6, 149.2, 149.3, 159.7, 164.4; MS (CI, NH_3) m/z = 214.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{13}H_{15}N_3$ 214.13442, found 214.13420.

This amine was then acylated according to general procedure b, and **10** was obtained as a yellow gum (1.29 g, 4.05 mmol, 83%) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 90:10). The yellow gum crystallized after several days.

N-(1-Pyridin-2-yl)ethyl)-*N*-((pyridin-2-yl)methyl)benzamide (**10**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.58 (d, 3H, J = 5.5 Hz), 4.32−6.10 (m, 3H), 6.90−7.70 (m, 11H), 8.47 (m$_c$, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 17.7, 47.8, 59.3, 121.6, 121.7, 122.4, 126.7, 128.7, 129.6, 136.5, 148.7, 149.5, 158.5, 172.9; MS (CI, NH_3) m/z = 318.2 (100) [$(M + 1)^+$]. Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.60; H, 6.14; N, 13.32.

*N-(1-Methyl-1H-imidazol-4-ylmethyl)-N-pyridin-2-ylmethylbenzamide (**11**).* The precursor amine **11a** was synthesized according to the general procedure a described above. The pale yellow liquid **11a** was then acylated according to the general procedure b, and **11** was obtained as a brown gum (0.27 g, 0.8 mmol, 83% over two steps) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 90:10). *N*-(1-Methyl-1*H*-imidazol-4-ylmethyl)-*N*-pyridin-2-ylmethylbenzamide (**11**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.64 (s, 3H), 4.36−4.67 (m, 2H), 4.67−4.95 (m, 2H), 6.70−6.99 (m, 1H), 7.14−7.25 (m, 1H), 7.28−7.51 (m, 6H), 7.64−7.72 (m, 2H), 8.51−8.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 33.5, 42.6, 49.6, 118.5, 119.3, 121.45, 122.3, 127.0, 127.4, 128.4, 129.4, 136.8, 138.0, 138.3, 149.2, 149.8; MS (CI, NH_3) m/z = 307.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{18}H_{18}N_4O$ 307.15589, found 307.15570.

*N-Pyridin-2-ylmethyl-N-quinolin-2-ylmethylbenzamide (**12**).* The precursor amine **12a** was synthesized according to the general procedure a described above. Amine **12a** was then acylated according to literature procedure b, and **12** was obtained as a brown gum (0.44 g, 1.23 mmol, 46% over two steps) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 97:3). *N*-Pyridin-2-ylmethyl-*N*-quinolin-2-ylmethylbenzamide (**12**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.69−4.90 (m, 2H), 4.94−5.11 (m, 2H), 7.15 (m$_c$, 1H), 7.17−7.28 (m, 1H), 7.28−7.39 (m, 3H), 7.45 (m$_c$, 1H), 7.48−7.73 (m, 6H), 7.80 (dd, 1H, J = 8.1 Hz, J = 1.4 Hz), 7.99−8.05 (m, 1H), 8.09−8.16 (m, 1H), 8.52 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 48.9, 49.2, 52.7, 53.2, 117.2, 118.5, 119.6, 120.4, 120.7, 124.5, 125.1, 125.5, 125.7, 126.5, 127.3, 127.6, 127.8, 134.2, 134.8, 135.0, 147.4, 147.9, 170.9; MS (CI, NH_3) m/z = 354.1 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{23}H_{19}N_3O$ 354.16064, found 354.16080.

*N-Furan-2-yl-methyl-N-pyridin-2-ylmethylbenzamide (**13**).* The precursor amine **13a** was synthesized according to the general procedure a described above. A brown liquid (0.80 g, 4.25 mmol, 46%) with the following analytical data was obtained after purification with column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 85:15).

(Furan-2-yl)-*N*-((pyridin-2-yl)methyl)methanamine (**13a**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.78 (br s, 1H), 3.85 (s, 2H), 3.93 (s, 2H), 6.20 (dd, 1H, J = 3.1 Hz, J = 0.7 Hz), 6.30 (dd, 1H, J = 3.1 Hz, J = 1.8 Hz), 7.16 (m$_c$, 1H), 7.28 (d, 1H, J = 7.7 Hz), 7.37 (dd, 1H, J = 1.8 Hz, J = 0.7 Hz), 7.63 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 8.56 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.8, 54.1, 107.3, 110.2, 122.3, 136.6, 142.0, 149.4, 153.6, 159.4; MS (CI, NH_3): m/z = 189.2 (100) [$(M + 1)^+$].

Amine **13a** was then acylated according to literature procedure b, and **13** was obtained as a brown gum (0.59 g, 2.0 mmol, 95%) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 90:10).

N-Furan-2-yl-methyl-*N*-pyridin-2-ylmethyl-benzamide (**13**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.58 (m$_c$, 2H), 4.80 (m$_c$, 2H), 6.15−6.32 (m, 2H), 7.20 (dd, 1H, J = 7.4 Hz, J = 4.9 Hz), 7.31−7.76 (m,

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8H), 8.57 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 46.4, 49.7, 109.2, 110.4, 122.4, 127.1, 128.3, 129.8, 132.9, 135.9, 142.7, 149.2; MS (CI, NH_3) = 293.0 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{18}H_{16}N_2O_2$ 293.12950, found 293.12900.

*N-(Pyridin-2-yl)-N-((pyridin-2-yl)methyl)benzamide (**14**).* The precursor amine **14a** was synthesized by the general procedure a described above. A yellow liquid (1.53 g, 8.27 mmol, 75%) with the following analytical data was obtained after purification with column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 95:5).

N,N-(2-Pyridyl)(2-pyridylmethyl)amine (**14a**):[17,18] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.63 (s, 2H), 4.76 (s, 1H), 6.46 (d, 1H, J = 8.5 Hz), 6.58 (ddd, 1H, J = 6.1 Hz, J = 5.2 Hz, J = 0.9 Hz), 6.77 (s, 1H), 7.36 (d, 1H, J = 7.7 Hz), 7.42 (ddd, 1H, J = 8.6 Hz, J = 7.4 Hz, J = 2.0 Hz), 7.64 (ddd, 1H, J = 7.6 Hz, J = 7.6 Hz J = 1.8 Hz), 8.02 (m_c, 1H), 8.55 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 47.4, 108.2, 113.1, 121.8, 122.3, 136.8, 138.0, 148.6, 149.2, 157.9, 158.1 ppm.

This amine was then acylated according to the general procedure c and **14** was obtained as a crystalline powder (0.82 g, 2.84 mmol, 70%) after purification via column chromatography (aluminum oxide, CH/EE 4:1).

N-(Pyridin-2-yl)-*N*-((pyridin-2-yl)methyl)benzamide (**14**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.45 (s, 2H), 6.92 (ddd, 1H, J = 8.1 Hz, J = 8.1 Hz, J = 0.9 Hz), 6.99 (ddd, 1H, J = 7.5 Hz, J = 4.9 Hz, J = 1.0 Hz), 7.13 (m_c, 1H), 7.19–7.24 (m, 2H), 7.28–7.33 (m, 1H), 7.39–7.44 (m, 3H), 7.46 (ddd, 1H, J = 7.9 Hz, J = 7.9 Hz, J = 1.0 Hz), 7.63 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 8.36 (ddd, 1H, J = 4.9 Hz, J = 1.9 Hz, J = 0.9 Hz), 8.50 (ddd, 1H, J = 4.1 Hz, J = 1.9 Hz, J = 1.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 53.6, 121.0, 122.0, 122.1, 128.1, 128.8, 130.4, 136.0, 136.7, 137.3, 148.8, 149.2, 156.2, 157.7; MS (CI, NH_3) m/z = 290.1 (100) [$(M + 1)^+$]. Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.50; H, 5.24; N, 14.50.

*N-(2-(Pyridin-2-yl)ethyl)-N-((pyridin-2-yl)methyl)benzamide (**15**).* Benzamide **15** was synthesized via a multistep reaction. The first step was the addition of ammonium chloride to 2-vinylpyridine which was commercially available.[19] The primary amine **15a** was obtained as a colorless liquid (1.76 g, 14.3 mmol, 29%) after distillation (bp_{16mbar} = 88 °C).

2-(Pyridin-2-yl)ethanamine (**15a**):[20] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.54 (s, 2H), 2.91 (t, 2H, J = 6.7 Hz), 3.10 (t, 2H, J = 6.7 Hz), 7.09 (ddd, 1H, J = 7.5 Hz, J = 6.1 Hz, J = 1.1 Hz), 7.14 (ddd, 1H, J = 7.9 Hz, J = 0.9 Hz, J = 0.9 Hz), 7.57 (ddd, 1H, J = 7.6 Hz, J = 7.2 Hz, J = 1.9 Hz), 8.51 (ddd, 1H, J = 4.9 Hz, J = 1.9 Hz, J = 1.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 41.9, 121.2, 123.3, 136.3, 149.3, 160.0; MS (CI, NH_3) m/z = 123.1 (100) [$(M + 1)^+$].

The secondary amine **15b** was then synthesized via the general procedure a described above. 2-Pyridine-carboxaldehyde was used as the carbonyl compound. The secondary amine was obtained as a yellow liquid (1.47 g, 6.95 mmol, 97%) without further purification.

2-(Pyridin-2-yl)-*N*-((pyridin-2-yl)methyl)ethanamine (**15b**):[21,22] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.01 (s, 1H), 3.16 (m, 4H), 4.10 (s, 2H), 7.13–7.22 (m, 3H), 7.37 (ddd, 1H, J = 7.7 Hz, J = 1.0 Hz), 7.62 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 7.67 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 8.51 (ddd, J = 4.9 Hz, J = 1.8 Hz, J = 0.9 Hz), 8.54 (ddd, 1H, J = 4.9 Hz, J = 1.8 Hz, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.8, 48.3, 55.7, 121.8, 122.8, 122.9, 123.5, 136.8, 136.9, 149.1, 149.5, 156.3, 159.4; MS (CI, NH_3) m/z = 214.1 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{13}H_{15}N_3$ 214.13442, found 214.13430.

The secondary amine **15b** was then acylated according to general procedure b. The benzamide **15** was obtained as yellow gum (0.55 g, 1.74 mmol, 62%) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 97:3).

N-(2-(Pyridin-2-yl)ethyl)-*N*-((pyridin-2-yl)methyl)benzamide (**15**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.12 (m_c, 2H), 3.84 (m_c, 2H), 4.70 (m_c, 2H), 6.84–7.71 (m, 11H), 8.50 (m_c, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.6, 37.0, 45.9, 49.4, 50.2, 55.0, 121.1, 121.7, 122.4, 124.0, 126.7, 128.2, 128.5, 129.5, 129.9, 136.4, 136.7, 149.0, 149.8; MS (CI, NH_3) m/z = 318.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{20}H_{19}N_3O$ 318.16064, found 318.16050.

*N,N-Bis(2-(pyridin-2-yl)ethyl)benzamide (**16**).* The parent secondary amine of benzamide **16** was prepared according to a literature process[23] in a two-step reaction. In the first step, hydroxylammonium hydrochloride was added to 2-vinylpyridine. The hydroxylamine derivative **16a** (2.17 g, 9.11 mmol, 31%) was obtained after recrystallization (*n*-hexane/DCM) as a brown solid.

Bis[2-(pyridin-2-ylethyl)]hydroxylamine (**16a**): mp 100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.10 (s, 8H), 7.06 (ddd, 2H, J = 6.2 Hz, J = 5.0 Hz, J = 1.2 Hz), 7.12 (ddd, 2H, J = 7.8 Hz, J = 1.0 Hz, J = 1.0 Hz), 7.53 (ddd, 2H, J = 7.7 Hz, J = 7.7 Hz, J = 1.9 Hz), 8.44 (ddd, 2H, J = 4.9 Hz, J = 1.9 Hz, J = 1.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 36.0, 60.0, 121.2, 123.5, 136.5, 148.9, 160.4 ppm.

In the second step, **16a** was reduced to the corresponding amine with zinc and hydrochloric acid. After the solution was stirred at 95 °C for 90 min, the suspension was allowed to cool down and made basic with a solution of sodium hydroxide. The secondary amine **16b** was obtained after extraction with DCM (3×) as yellow oil (0.70 g, 2.35 mmol, 97%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.16 (br s, 1H), 3.00 (t, 4H, J = 6.5 Hz), 3.08 (t, 4H, J = 6.5 Hz), 7.10 (dd, 2H, J = 5.8 Hz, J = 5.8 Hz), 7.15 (d, 2H, J = 7.7 Hz), 7.57 (ddd, 2H, J = 7.8 Hz, J = 7.8 Hz, J = 1.8 Hz), 8.49 (d, 2H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 49.2, 121.4, 123.4, 136.5, 149.4, 160.2 ppm.

Benzamide **16** was then synthesized according to general procedure b. Compound **16** was obtained as a yellow oil (0.32 g, 0.97 mmol, 57%) after purification via column chromatography (silica gel, DCM/MeOH 99:1 → 97:3).

N,N-Bis(2-(pyridin-2-yl)ethyl)benzamide (**16**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.41 (m_c, 8H), 6.90 (br s, 1H), 7.04–7.20 (m, 4H), 7.26–7.36 (m, 4H), 7.58 (m_c, 2H), 8.47 (m_c, 2H); MS (CI, NH_3) m/z = 332.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{21}H_{21}N_3O$ 332.17629, found 332.17630.

*4-[5-[(Benzoylpyridin-2-ylmethylamino)methyl][1,2,3]triazol-1-yl]benzoic Acid Methyl Ester (**17**).* Benzamide **17** was synthesized in a multistep reaction. Its triazol unit was built up via a [2 + 3]-cycloaddition. The propargyl amine **17a** was synthesized by a reductive amination step according to the general procedure a. The propargyl amine was a dark brown oil (0.91 g, 6.23 mmol, 33%) purified via column chromatography (silica gel, DCM/MeOH 98:2 → 90:10). Prop-2-ynylpyridin-2-ylmethylamine (**17a**):[24] ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.12 (br s, 1H), 2.24 (t, 1H, J = 2.4 Hz), 3.51 (d, 2H, J = 2.4 Hz), 4.01 (s, 2H), 7.17 (m_c, 1H), 7.33 (d, 1H, J = 7.7 Hz), 7.64 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 8.56 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 37.8, 53.7, 71.7, 81.9, 122.4, 136.5, 149.5, 159.2; MS (CI, NH_3) m/z = 147.1 (100) [$(M + 1)^+$].

The azido building block **17b** was prepared via a methylester formation using the commercially available carboxylic acid (1.0 equiv), dry MeOH, DMAP (0.09 equiv), and DCC (1.0 equiv). The reaction mixture was stirred at rt for 4 h. The methyl ester was isolated as a yellow solid (2.02 g, 11.4 mmol, 93%) after purification via column chromatography (silica gel, DCM/MeOH 99:1).

4-Azido-benzoic acid methyl ester (**17b**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.91 (s, 3H), 7.06 (m_c, 2H), 8.03 (m_c, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.0, 52.2, 118.9, 126.9, 131.5, 144.8, 166.4 ppm.

The [2 + 3]-cycloaddition resulting in amine **17c** was achieved by stirring azide **17b** (1.3 equiv) and propargyl amine **17a** (1.0 equiv) in CH_3CN in the presence of CuI (0.1 equiv) and NEt_3 (0.4 equiv) for 48 h. Amine **17c** was obtained as a brown gum (0.15 g, 0.45 mmol, 51%) after purification via column chromatography (silica gel, DCM/MeOH 99:1 → DCM/MeOH 90:10).

4-[5-[[(Pyridin-2-ylmethyl)amino]methyl][1,2,3]triazol-1-yl]-benzoic acid methyl ester (**17c**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.53 (s, 1H), 3.96 (s, 3H), 4.04 (s, 2H), 4.11 (s, 2H), 7.18 (m_c, 1H), 7.34 (d, 1H, J = 7.7 Hz), 7.66 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 7.84 (m_c, 2H), 8.12 (s, 1H), 8.19 (m_c, 2H), 8.57 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.3, 52.5, 54.5, 119.9, 120.0, 122.2, 122.5, 130.2, 130.7, 131.4, 136.6, 140.3, 148.0, 149.5, 159.0, 166.0; MS (CI, NH_3) m/z = 324.0 (100) [$(M + 1)^+$].

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Amine **17c** was then acylated according to the general procedure c, and benzamide **17** was isolated as a brown solid (0.12 g, 0.28 mmol, 77%) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 95:5).

4-[5-[(Benzoyl-pyridin-2-ylmethylamino)methyl][1,2,3]triazol-1-yl]benzoic acid methyl ester (**17**): mp 107 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.97 (s, 3H), 4.75 (s, 2H), 4.85 (s, 2H), 7.24 (m_c, 1H), 7.31−7.89 (m, 7H), 7.87 (m_c, 2H), 8.21 (m_c, 2H), 8.29 (s, 1H), 8.63 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 41.0, 52.5, 54.5, 119.9, 121.9, 122.0, 127.3, 128.5, 130.1, 131.4, 135.6, 136.9, 140.2, 145.2, 150.0, 156.4, 166.0, 172.7; MS (CI, NH_3) m/z = 428.2 (100) [$(M + 1)^+$]; HRMS (APCI, MeOH) m/z [$(M + 1)^+$] calcd for $C_{24}H_{22}N_5O_3$ 428.17226, found 428.17220.

*N-((Pyridin-2-yl)methyl)-N-(6-(pyridine-2-yl)pyridin-2-yl)methyl)-benzamide (**18**).* Benzamide **18** was synthesized in a multistep reaction using commercially available 2,2′-bipyridine as starting material. 2,2′-Bipyridine was methylated according to a literature process,[25] and **18a** was obtained as a yellow gum (1.83 g, 10.6 mmol, 30%) after purification via column chromatography (silica gel, DCM/MeOH 97:3).

2-Methyl-6-(pyridin-2-yl)pyridine (**18a**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.61 (s, 3H), 7.13 (d, 1H, J = 7.7 Hz), 7.23−7.29 (m, 1H), 7.66 (t, 1H, J = 7.8 Hz), 7.74−7.81 (m, 1H), 8.15 (d, 1H, J = 7.6 Hz), 8.38 (m, 1H), 8.64−8.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 24.6, 118.1, 121.2, 123.3, 123.5, 136.8, 137.1, 149.2, 155.6, 156.5, 157.9 ppm.

Compound **18a** was then oxidized to the corresponding carboxaldehyde **18b** according to literature.[26] Carboxaldehyde **18b** was then isolated as yellow powder (1.06 g, 5.76 mmol, 56%) after purification via column chromatography (silica gel, DCM/EE 90:10).

6-(Pyridin-2-yl)pyridin-2-carbaldehyde (**18b**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36 (ddd, 1H, J = 7.7 Hz, J = 4.8 Hz, J = 1.1 Hz), 7.87 (ddd, 1H, J = 7.8 Hz, J = 7.8 Hz, J = 1.8 Hz), 7.95−8.02 (m, 2H), 8.55 (ddd, 1H, J = 7.8 Hz, J = 7.8 Hz, J = 1.0 Hz), 8.66 (dd, 1H, J = 6.7 Hz, J = 2.3 Hz), 8.71 (ddd, 1H, J = 4.7 Hz, J = 1.8 Hz, J = 0.9 Hz), 10.17 (d, 1H, J = 0.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 121.4, 121.5, 124.4, 125.3, 137.2, 138.0, 149.3, 152.4, 155.0, 156.7, 193.7; MS (CI, NH_3): m/z = 184.0 (100) [$(M + 1)^+$].

The secondary amine was then prepared via a reductive amination step according to general procedure a, and amine **18c** was obtained as a brown oil (1.04 g, 3.75 mmol, 68%) without further purification.

(Pyridin-2-yl)-*N*-((6-(pyridin-2-yl)pyridin-2-yl)methyl)-methanamine (**18c**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.33 (br s, 1H), 4.07 (s, 2H), 4.09 (s, 2H), 7.16 (dd, 1H, J = 7.7 Hz, J = 4.9 Hz), 7.28 (ddd, 1H, J = 7.5 Hz, J = 4.8 Hz, J = 1.2 Hz), 7.35 (d, 1H, J = 7.8 Hz), 7.38 (d, 1H, J = 7.8 Hz), 7.64 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 7.73−7.82 (m, 2H), 8.26 (d, 1H, J = 7.9 Hz), 8.45 (ddd, 1H, J = 8.0 Hz, J = 8.0 Hz, J = 1.0 Hz), 8.57 (ddd, 1H, J = 4.8 Hz, J = 1.5 Hz, J = 0.8 Hz), 8.66 (ddd, 1H, J = 4.8 Hz, J = 1.7 Hz, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 54.5, 54.6, 119.5, 121.3, 122.2, 122.3, 122.4, 123.7, 136.6, 136.9, 137.5, 149.2, 149.4, 155.7, 156.2, 158.4, 159.2; MS (CI, NH_3): m/z = 277.2 (100) [$(M + 1)^+$].

Amine **18c** was then acylated according to the general procedure c. Benzamide **18** was obtained as a yellow gum (0.98 g, 2.57 mmol, 66%) after purification via column chromatography (aluminum oxide, CH/EE 4:1 → CH/EE 1:1).

N-((Pyridin-2-yl)methyl)-*N*-(6-(pyridine-2-yl)pyridin-2-yl)methyl)-benzamide (**18**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.79 (s, 2H), 4.97 (d, 2H, J = 10.8 Hz), 7.10−7.53 (m, 10H), 7.66 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.9 Hz), 7.73−7.86 (m, 2H), 8.31 (d, 1H, J = 7.8 Hz), 8.36−8.46 (dd, 1H, J = 18.8 Hz, J = 8.0 Hz), 8.49−8.59 (m, 1H), 8.67 (ddd, 1H, J = 4.8 Hz, J = 1.8 Hz, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 50.5, 50.8, 54.6, 77.3, 119.6, 119.8, 121.3, 121.7, 122.5, 122.6, 123.0, 123.7, 124.0, 149.2, 127.0, 127.1, 128.4, 129.8, 136.2, 137.1, 137.7, 149.1, 149.9; MS (CI, NH_3) m/z = 381.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{24}H_{18}N_4O$ 381.17154, found 381.17130.

*N-(5-Nitropyridin-2-ylmethyl)-N-pyridin-2-ylmethylbenzamide (**19**) and N-(5-Aminopyridin-2-ylmethyl)-N-pyridin-2-ylmethylbenzamide (**20**).* Benzamide **19** was prepared in a multistep reaction sequence. In the first step, malonic acid diethylester was added dropwise to a suspension of sodium hydride (1.1 equiv). The resulting white suspension was then stirred for 30 min at 120 °C. Then, 2-chloro-5-nitropyridine (1.0 equiv) in toluene was added dropwise, and the reaction mixture stirred for 8 h at 120 °C. After the mixture was cooled to rt, the solvent was removed at reduced pressure using the rotatory evaporator. The oily residue was then resolved in sulfuric acid (50%), and the reaction mixture was refluxed for 8 h. After the mixture was cooled to rt and water was added, a concentrated sodium hydroxide solution was added slowly at 0 °C. Furthermore, a solution of saturated $NaHCO_3$ was added. After the water phases were extracted with Et_2O, the organic layers were dried over sodium sulfate and the picoline derivative **19a** was obtained as a pink solid (2.15 g, 15.6 mmol, 39%) after purification via column chromatography (silica gel, DCM).

2-Methyl-5-nitropyridine (**19a**):[27] mp 102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.70 (s, 3H), 7.34 (d, 1H, J = 8.6 Hz), 8.36 (dd, 1H, J = 2.7 Hz, J = 8.6 Hz), 9.33 (d, 1H, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 24.9, 123.4, 131.3, 144.8, 165.5; MS (CI, NH_3) m/z = 139.1 (100) [$(M + 1)^+$]. Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.34; H, 4.47; N, 20.00.

The picoline derivative **19a** was dissolved in DMSO, and iodine (1.0 equiv), *tert*-butyliodine (0.4 equiv), and TFA (3.0 equiv) were added. The resulting reaction mixture was then stirred for 3 h at 170 °C. After cooling down to rt, a $NaHCO_3$ solution (10%) and a $Na_2S_2O_3$ solution (1 M) were added. The combined water phases were extracted with DCM several times, and the combined organic phases were dried over sodium sulfate. The carbaldehyde **19b** was obtained as yellow crystals (1.11 g, 7.23 mmol, 56%) after purification via column chromatography (silica gel, DCM).

5-Nitropyridine-2-carbaldehyde (**19b**):[28] mp 55 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.16 (dd, 1H, J = 8.5 Hz, J = 0.6 Hz), 8.66 (dd, 1H, J = 8.5 Hz, J = 2.4 Hz), 9.59 (d, 1H, J = 2.4 Hz), 10.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 121.8, 132.6, 145.8, 146.1, 155.8, 191.3; MS (CI, NH_3) m/z = 153.1 (100) [$(M + 1)^+$]. Anal. Calcd for $C_6H_4N_2O_3$: C, 47.38; H, 2.65; N, 18.42. Found: C, 46.91; H, 2.67; N, 18.76.

The secondary amine **19c** was prepared according to the general procedure a, and **19c** was obtained as a dark brown gum (0.15 g, 0.61 mmol, 52%) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 90:10).

(5-Nitropyridine-2-ylmethyl)pyridin-2-ylmethylamine (**19c**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.02 (s, 2H), 4.14 (s, 2H), 7.19 (m_c, 1H), 7.32 (d, 1H, J = 7.8 Hz), 7.62−7.70 (m, 2H), 8.44 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz), 8.58 (m_c, 1H), 9.38 (d, 1H, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 54.6, 60.5, 122.3, 122.4, 131.6, 136.7, 143.2, 144.8, 149.5, 159.1, 166.9 ppm.

Benzamide **19** was prepared according to the general procedure c. Benzamide **19** was obtained as a brown gum (0.18 g, 0.52 mmol, 92%) after purification via column chromatography (silica gel, DCM/MeOH 98:2).

N-(5-Nitropyridin-2-ylmethyl)-*N*-pyridin-2-ylmethylbenzamide (**19**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.74−4.86 (m, 2H), 4.87−4.97 (m, 2H), 7.20 (m_c, 2H), 7.28−7.73 (m, 8H), 8.44 (m_c, 1H), 9.35 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 50.9, 55.4, 121.8, 122.9, 127.2, 128.7, 130.2, 131.7, 135.5, 136.9, 143.4, 144.8, 150.0, 156.3, 164.0; MS (CI, NH_3) m/z = 349.2 (100) [$(M + 1)^+$]; HRMS (APCI, MeOH) m/z [$(M + 1)^+$] calcd for $C_{19}H_{16}N_4O_3$ 349.13007, found 349.13000. Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.12; H, 4.71; N, 16.18.

Benzamide **20** was prepared via a hydrogenation of benzamide **19**. Benzamide **20** was dissolved in MeOH/toluene (1:2) and Pd/C was added. The resulting black suspension was then stirred for 24 h in a hydrogen atmosphere (1 bar). The suspension was then filtrated over kieselguhr and washed with MeOH. After the solvent was removed under reduced pressure and purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 95:5), **20** was obtained as yellow gum (0.25 g, 0.78 mmol, 63%).

N-(5-Aminopyridin-2-ylmethyl)-*N*-pyridin-2-ylmethylbenzamide (**20**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.56 (br s, 2H), 4.53 (m_c,

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2H), 4.74 (m$_c$, 2H), 6.82−6.94 (m, 2H), 7.07−7.62 (m, 8 H) 7.94 (m$_c$, 1H), 8.47 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 50.1, 59.1, 66.3, 122.3, 127.0, 128.4, 129.7, 136.2, 136.8, 137.2, 141.8, 145.7, 146.5, 149.3, 149.8, 156.8, 157.3; MS (CI, NH_3) m/z = 319.2 (100) [(M + 1)$^+$], HRMS (CI, NH_3) m/z [(M + 1)$^+$] calcd for $C_{19}H_{18}N_4O$ 319.15589, found 319.15660.

*Methyl 6-((N-((Pyridine-2-yl)methyl)benzamido)methyl)pyridine-3-carboxylate (**21**).* Benzamide **21** was prepared via a multistep reaction beginning with the oxidation of 6-methyl-nicotinic acid leading to carbaldehyde **21a**. Carbaldehyde **21a** was obtained as a pale yellow solid (1.54 g, 9.28 mmol, 62%) after purification via column chromatography (silica gel, CH/EE 3:1).

Methyl 6-formylpyridin-3-carboxylate (**21a**):[29] mp 107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.00 (s, 3H), 8.03 (dd, 1H, J = 8.1 Hz, J = 0.9 Hz), 8.46 (ddd, 1H, J = 8.1 Hz, J = 2.0 Hz, J = 0.9 Hz), 9.36 (dd, 1H, J = 2.0 Hz, J = 0.9 Hz), 10.14 (d, 1H, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 52.9, 121.2, 129.3, 138.4, 151.3, 155.0, 164.9, 192.7; MS (CI, NH_3) m/z = 166.0 (100) [(M + 1)$^+$].

A reductive amination step according to the general procedure a using **21a** as carbonyl compound and 2-picolylamine as amine lead to the secondary amine **21b** which was obtained as dark brown oil (0.41 g, 1.59 mmol, 93%) without further purification.

Methyl 6-(((pyridine-2-yl)methylamino)methyl)pyridine-3-carboxylate (**21b**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.94 (s, 3H), 4.01 (s, 2H), 4.07 (s, 2H), 7.17 (ddd, 1H, J = 7.5 Hz, J = 4.9 Hz, J = 1.2 Hz), 7.33 (d, 1H, J = 7.9 Hz), 7.47 (dd, 1H, J = 8.2 Hz, J = 0.8 Hz), 7.64 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.9 Hz), 8.24 (dd, 1H, J = 8.1 Hz, J = 2.2 Hz), 8.56 (ddd, 1H, J = 4.8 Hz, J = 1.7 Hz, J = 0.8 Hz), 9.15 (dd, 1H, J = 2.2 Hz, J = 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 52.4, 54.5, 54.6, 121.8, 122.3, 122.5, 124.6, 136.6, 137.7, 149.5, 150.7, 159.0, 164.0, 165.9 ppm.

The secondary amine **21b** was the acylated according to the general procedure c, and **21** was obtained as a pale yellow gum (0.33 g, 0.91 mmol, 58%) after purification via column chromatography (silica gel, DCM/MeOH 97:3).

Methyl 6-((*N*-((pyridine-2-yl)methyl)benzamido)methyl)pyridine-3-carboxylate (**21**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.95 (s, 3H), 4.71 (br s, 1H), 4.80 (br s, 1H), 4.92 (br s, 2H), 7.13−7.59 (m, 8H), 7.70 (ddd, 1H, J = 6.5 Hz, J = 6.5 Hz, J = 3.3 Hz), 8.25 (m$_c$, 1H), 8.54 (m$_c$, 1H), 8.54 (d, 1H, J = 12.4 Hz), 9.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 48.7, 50.5, 52.8, 53.0, 119.2, 119.7, 120.1, 120.7, 125.0, 125.2, 126.6, 128.0, 133.8, 134.9, 135.9, 148.0, 148.7, 149.1, 154.6, 159.3, 159.8; MS (CI, NH_3) m/z = 362.1 (100) [(M + 1)$^+$]; HRMS (CI, NH_3) m/z [(M + 1)$^+$] calcd for $C_{23}H_{21}N_3O$ 362.15047, found 362.15040.

*N,N-Bis(2-dimethylaminoethyl)benzamide (**22**).* Compound **22a** was prepared according to a literature procedure[30] followed by distillation (bp_{16mbar} = 90 °C) to obtain a colorless liquid (1.72 g, 10.8 mmol, 83%).

N,N,N′,N′-Tetramethyldiethylamine (**22a**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.22 (s, 12H), 2.41 (t, 4H, J = 6.4 Hz), 2.71 (t, 4H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.7, 47.8, 59.4; MS (CI, NH_3) m/z = 160.2 (100) [(M + 1)$^+$]; HRMS (CI, NH_3) m/z [(M + 1)$^+$] calcd for $C_8H_{21}N_3$ 160.18150, found 160.18137.

Benzamide **22** was prepared out of amine **22a** according to the general procedure b. Benzamide **22** was obtained as a yellow gum (0.57 g, 2.2 mmol, 65%) after purification via bulb to bulb distillation ($bp_{6.8*10^{-2}mbar}$ = 240 °C).

N,N-Bis(2-dimethylaminoethyl)benzamide (**22**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.98−2.35 (m, 12H), 2.35−2.64 (m, 4H), 3.29−3.69 (m, 4H), 7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.7, 47.0, 55.5, 59.3, 122.0, 122.3, 136.5, 149.3, 159.9; MS (CI, NH_3) m/z = 264.2 (100) [(M + 1)$^+$]; HRMS (CI, NH_3) m/z [(M + 1)$^+$] calcd for $C_{15}H_{25}N_3O$ 264.20810, found 264.20759.

*N-(2-Dimethylamino-ethyl)-N-(1-methyl-1H-imidazol-4-ylmethyl)benzamide (**23**).* The secondary amine **23a** was prepared according to the general procedure a and than the secondary amine **23a** was acylated according to the general procedure b. The benzamide **23** was obtained as a yellow gum (0.07 g, 0.2 mmol, 30% over two steps) after purification via column chromatography (aluminum oxide, EE → EE/EtOH 98:2).

N-(2-Dimethylaminoethyl)-*N*-(1-methyl-1*H*-imidazol-4-ylmethyl)-benzamide (**23**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.90−2.29 (m, 6H), 2.29−2.56 (m, 2H), 3.26−3.57 (m, 2H), 3.58 (s, 3H), 4.31−4.62 (m, 2H), 6.59−6.94 (m, 1H), 7.2−7.38 (m, 5H), 7.38−7.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 42.6, 45.6, 46.9, 47.7, 56.6, 57.6, 117.9, 119.0, 126.6, 126.9, 128.3, 129.3, 136.8, 137.8, 138.8, 171.8; MS (pos ESI) m/z = 287.3 (100) [(M + 1)$^+$]; HRMS (APCI, MeOH/NH_4) m/z [(M + 1)$^+$] calcd for $C_{16}H_{22}N_4O$ 287.18730, found 287.18719.

*N-(2-Dimethylaminoethyl)-N-quinolin-2-ylmethylbenzamide (**24**).* Benzamide **24** was prepared via a reductive amination step according to general procedure a followed by an acylation according to general procedure b. Benzamide **24** was then obtained as a brown gum (0.16 g, 0.48 mmol, 20% over two steps) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 85:15).

N-(2-Dimethylaminoethyl)-*N*-quinolin-2-ylmethylbenzamide (**24**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.71−2.86 (m, 2H), 3.41 (s, 6H), 3.97−4.15 (m, 1H), 4.88−5.06 (m, 2H) 7.12−7.31 (m, 3H), 7.23−7.57 (m, 4H), 7.68−7.74 (m, 1H), 7.76−7.82 (m, 1H), 8.01−8.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.1, 40.9, 43.5, 53.6, 55.1, 62.7, 120.1, 126.6, 126.7, 126.8, 127.3, 127.6, 127.7, 128.3, 128.9, 129.8, 130.0, 135.3, 137.1, 147.6, 156.0, 173.4; MS (CI, NH_3) m/z = 334.2 (100) [(M + 1)$^+$]; HRMS (CI, NH_3) m/z [(M + 1)$^+$] calcd for $C_{21}H_{23}N_3O$ 334.19194, found 334.19250.

*N-(2-Dimethylaminophenyl)-N-pyridin-2-ylmethylbenzamide (**25**).* The precursor amine was synthesized by the general procedure a described above. A yellow liquid (0.58 g, 2.6 mmol, 71%) with the following analytical data was obtained after column chromatography (silica gel, CH/EE 5:1 → CH/EE 2:1).

N,N-Dimethyl-*N*-pyridin-2-ylmethylbenzene-1,2-diamine (**25a**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.70 (s, 6H), 4.50 (s, 2H), 6.52 (dd, 1H, J = 8.0 Hz, J = 1.4 Hz), 6.68 (ddd, 1H, J = 7.6 Hz, J = 7.6 Hz, J = 1.4 Hz), 6.93 (dddd, 1H, J = 7.4 Hz, J = 7.4 Hz, J = 1.5 Hz, J = 0.5 Hz), 7.05 (dd, 1H, J = 7.7 Hz, J = 1.5 Hz), 7.14 (m, 1H), 7.34 (m, 1H), 7.61 (ddd, 1H, J = 7.6 Hz, J = 7.6 Hz, J = 1.8 Hz), 8.58 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.2, 50.0, 110.6, 117.0, 119.2, 121.2, 122.1, 124.8, 136.8, 140.7, 142.9, 149.4, 159.8; MS (CI, NH_3) m/z = 228.2 (100) [(M + 1)$^+$]; HRMS (CI, NH_3) m/z [(M + 1)$^+$] calcd for $C_{14}H_{17}N_3$ 228.15007, found 228.14970.

The secondary amine **25a** was then acylated according to the general procedure b, and **25** was isolated as a yellow gum (0.24 g, 0.7 mmol, 65%) after purification via column chromatography (silica gel, DCM/MeOH 98:2 → 97:3).

N-(2-Dimethylaminophenyl)-*N*-pyridin-2-ylmethylbenzamide (**25**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.52 (s, 6H), 4.26 (d, 1H, J = 15.2 Hz), 5.89 (d, 1H, J = 15.2 Hz), 6.78 (dd, 1H, J = 8.2 Hz, J = 1.4 Hz), 6.84 (dddd, 1H, J = 7.4 Hz, J = 7.4 Hz, J = 1.5 Hz, J = 0.3 Hz), 7.07 (dddd, 1H, J = 7.4 Hz, J = 7.4 Hz, J = 1.6 Hz, J = 0.7 Hz), 7.10−7.23 (m, 5H), 7.38−7.42 (m, 2H), 7.50−7.54 (m, 1H), 7.67 (ddd, 1H, J = 7.7 Hz, J = 7.7 Hz, J = 1.8 Hz), 8.58 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 42.8, 54.7, 120.1, 122.1, 122.4, 122.5, 127.1, 127.9, 128.3, 182.8, 129.5, 136.2, 136.8, 148.5, 149.2, 158.1, 171.2; MS (CI, NH_3) m/z = 332.2 (100) [(M + 1)$^+$]; HRMS (CI, NH_3) m/z [(M + 1)$^+$] calcd for $C_{21}H_{21}N_3O$ 332.17629, found 332.17640.

*4-Oxo-4-phenyl-N,N-bis-pyridin-2-ylmethylbutyramide (**26**).* Amine **2** was acylated according to the general procedure b, and the aliphatic amide **26** was obtained as a brown gum (0.52 g, 1.44 mmol, 82%) after purification with column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 90:10).

4-Oxo-4-phenyl-*N,N*-bis-pyridin-2-ylmethyl-butyramide (**26**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.93 (t, 2H, J = 6.4 Hz), 3.41 (t, 2H, J = 6.4 Hz), 4.78 (s, 2H), 4.82 (s, 2H), 7.14 (ddd, 1H, J = 7.6 Hz, J = 4.9 Hz, J = 1.2 Hz), 7.18 (ddd, 1H, J = 7.6 Hz, J = 4.9 Hz, J = 1.2 Hz), 7.31 (m$_c$, 2H), 7.41−7.47 (m, 2H), 7.51−7.56 (m, 2H), 7.62 (td, 1H, J = 7.7 Hz, J = 1.8 Hz), 7.69 (td, 1H, J = 7.7 Hz, J = 1.8 Hz), 7.98−8.02 (m, 2H), 8.48 (m$_c$, 1H), 8.56 (m$_c$, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 27.6, 34.1, 51.9, 53.2, 120.9, 122.3, 122.4, 128.1, 128.7, 133.0,

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136.9, 149.2, 149.9, 156.8, 157.4, 172.8, 199.2; MS (CI, NH_3) m/z = 360.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{22}H_{21}N_3O_2$ 360.17120, found 360.17100.

*N-(2-Dimethylaminoethyl)-4-oxo-4-phenyl-N-pyridin-2-ylmethylbutyramide (**27**).* Amine **9a** was acylated according to the general procedure b, and the aliphatic amide **27** was obtained as a brown gum (0.42 g, 1.22 mmol, 56%) after purification with column chromatography (silica gel, DCM/MeOH 98:2 → DCM/MeOH 80:20).

N-(2-Dimethylaminoethyl)-4-oxo-4-phenyl-*N*-pyridin-2-ylmethylbutyramide (**27**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.23−2.27 (m, 6H), 2.45 (t, 1H, J = 7.4 Hz), 2.55 (t, 1H, J = 7.3 Hz), 2.83 (t, 1H, J = 6.4 Hz), 2.91 (t, 2H, J = 6.4 Hz), 3.37 (t, 1H, J = 6.4 Hz), 3.43 (t, 1H, J = 6.4 Hz), 3.53−3.61 (m, 2H), 4.74−4.80 (m, 2H), 7.13−7.23 (m, 1H), 7.25−7.38 (m, 1H), 7.42−7.48 (m, 2H), 7.52−7.58 (m, 1H), 7.61−7.73 (m, 1H), 7.98−8.04 (m, 2H), 8.49−8.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 27.0, 27.5, 33.7, 33.9, 44.6, 45.6, 45.8, 46.5, 51.8, 53.8, 56.9, 57.8, 120.8, 122.2, 122.6, 128.1, 128.6, 133.1, 136.8, 137.1, 149.2, 149.8, 157.2, 158.0, 172.2, 172.5, 199.2; MS (CI, NH_3) m/z = 340.2 (100) [$(M + 1)^+$]; HRMS (CI, NH_3) m/z [$(M + 1)^+$] calcd for $C_{20}H_{25}N_3O_2$ 340.20250, found 340.20260.

*4-Cyano-N-(2-dimethylaminoethyl)-N-(2-iminobut-3-enyl)-benzamide (**28**).* Amine **9a** was acylated according to the general procedure b, and benzamide **28** was obtained as a yellow gum (0.22 g, 0.7 mmol, 40%) after purification with column chromatography (silica gel, DCM/MeOH/Et_3N 99:1:0.1 → DCM/MeOH/Et_3N 97:3:0.1).

4-Cyano-*N*-(2-dimethylaminoethyl)-*N*-(2-iminobut-3-enyl)-benzamide (**28**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.96−2.32 (m, 6H), 2.32−2.62 (m, 2H), 3.30−3.67 (m, 2H), 4.56−4.97 (m, 2H), 7.07−7.46 (m, 1H), 7.22 (ddd, 1H), 7.55−7.76 (m, 5H), 8.58 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.7, 113.4, 118.3, 122.7, 127.8, 132.3, 136.9, 141.0, 170.4; MS (CI, NH_3) m/z = 309.2 (100) [$(M + 1)^+$]; HRMS (APCI, MeOH) m/z [$(M + 1)^+$] calcd for $C_{18}H_{20}N_4O$ 309.17154, found 309.17090.

*N-(2-Dimethylaminoethyl)-4-methoxy-N-pyridin-2-ylmethylbenzamide (**29**).* Amine **9a** was acylated according to the general procedure b and benzamide **29** was obtained as a yellow gum (0.31 g, 1.0 mmol, 37%) after purification with column chromatography (silica gel, DCM/MeOH/Et_3N 99:1:0.1 → DCM/MeOH/Et_3N 97:3:0.1).

N-(2-Dimethylaminoethyl)-4-methoxy-*N*-pyridin-2-ylmethylbenzamide (**29**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.97−2.34 (m, 6H), 2.34−2.65 (m, 2H), 3.36−3.67 (m, 2H), 3.81 (s, 3H), 4.64−4.97 (m, 2H), 6.89 (m_c, 2H), 7.19 (ddd, 1H), 7.22−7.47 (m, 3H), 7.68 (dt, 1H), 8.56 (m_c, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.7, 55.5, 113.7, 122.5, 128.8, 136.9, 160.7, 172.2; MS (pos ESI) m/z = 314.2 (100) [$(M + 1)^+$]; HRMS (pos ESI, MeCN) m/z [$(M + 1)^+$] calcd for $C_{18}H_{23}N_3O_2$ 314.18685, found 314.18630.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra and theoretical calculation data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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