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A Two-step Procedure for the Overall Transamidation of 8-Aminoquinoline Amides Proceeding via the Intermediate *N*-Acyl-Boc-Carbamates

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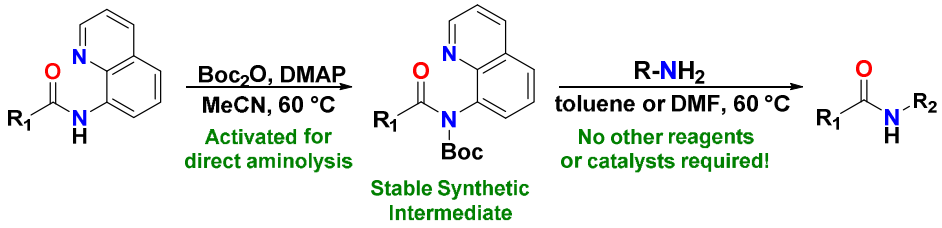
ABSTRACT GRAPHICS



ABSTRACT

Herein, a two-step strategy for achieving overall transamidation of 8-aminoquinoline amides has been explored. In this protocol, the 8-aminoquinoline amides were first treated with Boc_2O and DMAP to form the corresponding *N*-acyl-Boc-carbamates, which were found to be sufficiently reactive to undergo subsequent aminolysis with different amines in the absence of any additional reagents or catalysts. To demonstrate the utility of this approach, it was applied on a number of 8-aminoquinoline amides from the recent C–H functionalization literature, enabling access to a range of elaborate amide derivatives in good to high yields.

INTRODUCTION

The combination of transition-metal catalysis and bidentate directing groups has recently emerged as a powerful and broadly applicable strategy for achieving the functionalization of

unactivated C–H bonds.[1] A particularly appealing feature of this approach from a synthetic chemistry point of view is that it allows for rapid build-up of molecular complexity while offering high control of regio- and stereochemistry. Among the assorted bidentate directing groups available today, 8-aminoquinoline (8-AQ) introduced by Daugulis and co-workers in 2005,[2] constitutes one of the most successful auxiliaries for carrying out the activation and functionalization of C(sp^2)–H and C(sp^3)–H bonds.[1a,1b,3] Taking the functionalization of aromatic C(sp^2)–H bonds as one illustrative example, one can find a variety of catalytic protocols employing different transition metals and the 8-AQ directing group for the formation of new carbon-carbon[2,4] and carbon-heteroatom bonds.[5] However, it is important to point out that 8-AQ-directed C–H functionalization has also been successfully used for other, more challenging, classes of substrates.[1] As a result, this synthetic approach has found extensive use in the preparations of natural products and other drug-like compounds,[6] where it often allows for precise control of the stereochemistry and step-efficient syntheses.

For synthetic strategies that rely on directed C–H functionalization to be practical, the auxiliary must be readily removed when it is no longer needed. In pursuit of this goal, a number of methods have been reported for the cleavage of the 8-AQ directing group (Figure 1). The most straightforward approach to cleave the 8-AQ auxiliary is to carry out a direct hydrolysis at high temperatures to afford the free carboxylic acid under either strongly acidic[4h,5b,6d] or strongly basic conditions.[5j,6a] Unfortunately, this approach requires that the substrate is robust and does not contain any other acid- or base-labile functional groups, otherwise the yield of the desired acid product will be low. Another commonly used strategy that enables milder hydrolysis conditions involves activation of the 8-AQ amides by either *N*-methylation[4g,5g,6e,7] or Boc-protection.[6a,6b,6d,8] Maulide and co-workers have also shown that the 8-AQ directing group can be activated through

an ozonolysis/reductive quenching-sequence to form a labile imide intermediate that can subsequently be converted to either the corresponding carboxylic acid or primary amide depending on whether $LiOH/H_2O_2$ or NH_4OH is used.[9]

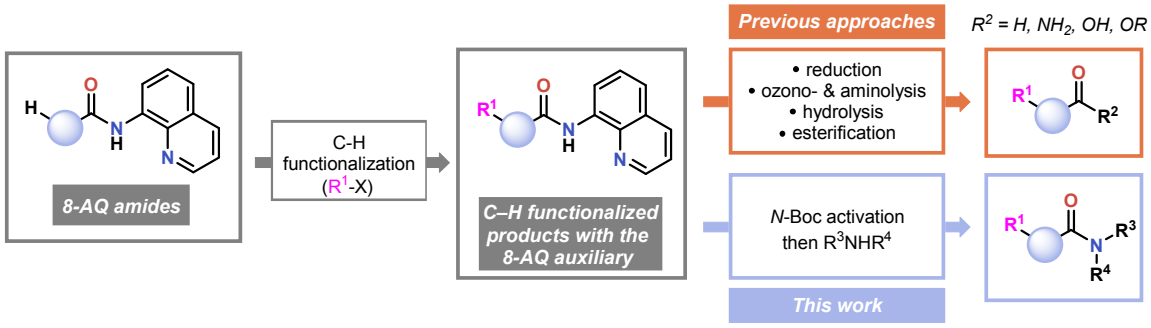


Figure 1. Approaches for the transformation of C–H functionalized products with the 8-AQ auxiliary into different classes of compounds.

Different ways to transform 8-AQ amides include reduction to the corresponding aldehydes[4g,6e,6f,10] and various esterification protocols that provide the corresponding esters.[4k,11] However, to the best of our knowledge, there is no prior study that has thoroughly evaluated the potential of 8-AQ amides to undergo transamidation. After surveying the literature on transamidation chemistry,[12] we were particularly inspired by a recent metal-free protocol developed by the Szostak group[13] and were keen to investigate if it was also feasible to transamidate 8-AQ amides in a similar fashion. This metal-free approach to achieve overall transamidation relies on destabilization of the amide bond through the generation of an intermediate *N*-acyl-Boc-carbamate with a highly twisted amide bond with diminished capability for amidic resonance (*cf.* the resonance energy of *N*-Boc-benzanilide on 7.2 kcal/mol to that of acetamide of 19.1 kcal/mol).[13,14] In the context of this proposed strategy to transamidate 8-AQ amides, it is also worth highlighting a recent Zn-catalyzed protocol reported by the group of

Maes to transform amides carrying a related nicotinate auxiliary into different ester or amide derivatives.[15]

RESULTS AND DISCUSSION

Preliminary trials were performed on the simple Boc-protected model substrate **2a** using piperonylamine as the amine nucleophile with the initial aim of studying the overall feasibility of this methodology (see Supporting Information (SI), Figures S1 and S2). In accordance with the *N*-acyl-Boc-carbamates studied by the Szostak group,[13] model substrate **2a** was found to be readily converted to amide product **3a** even at ambient temperature without any added catalyst.[16] However, the aminolysis of **2a** was found to be most efficient at 60 °C and when it was performed with 1.5 equiv piperonylamine in toluene (0.5 M) product **3a** could be isolated in 98% yield after 7 h.

After establishing that the transamidation of 8-AQ amides was indeed a feasible transformation, we wanted to evaluate the efficiency of this reaction on more elaborate substrates selected from the recent C–H functionalization literature.[17] We envisioned that such a transamidation strategy would provide rapid access to a diverse set of amide derivatives if it were to be used in conjunction with various C–H functionalization methods or other 8-AQ directed transformations. To demonstrate this concept, *N*-Boc protection of the selected substrates was first carried out (typically done in 74-98% yield using Boc_2O/DMAP in MeCN for 1-2 h at 60 °C, see experimental section for details). The obtained *N*-acyl-Boc-carbamates were then subjected to piperonylamine in toluene at 60 °C (Scheme 1). Attempts to extend the transamidation methodology to *ortho*-substituted 8-AQ benzamides, such as carbamates **2b** and **2c**, worked poorly as the aminolysis step furnished low yields of the desired products **3b** and **3c**. These results suggest that an increased steric bulk around the Boc-amide moiety was detrimental

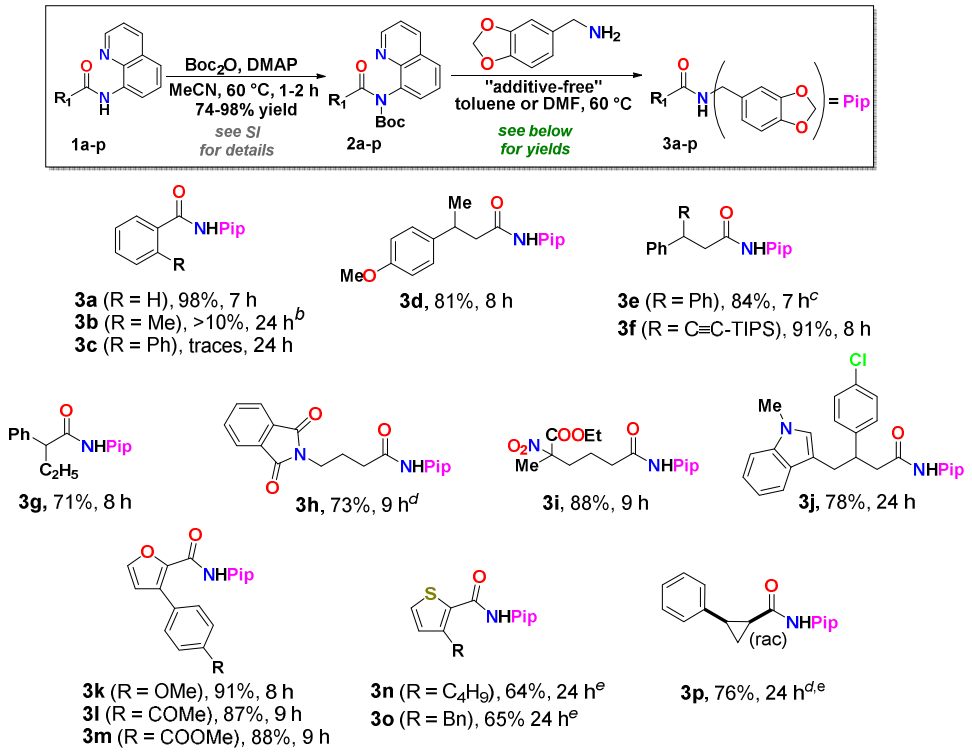
to the aminolysis reaction. Instead, the major product from these reactions were the *N*-Boc-deprotected compounds **1b** and **1c**, resulting from the transfer of the Boc group to piperonylamine.[18]

To our delight, the protocol was found to be significantly more effective when extended to several other classes of 8-AQ amides. For example, a variety of aliphatic 8-AQ amides could efficiently be transamidated by this two-step approach. Carbamates **2d** and **2e**, which are accessible *via* synthetic routes involving directed *β*-arylation of linear aliphatic 8-AQ amides (precursors D and E, Table S1), were converted to the corresponding amides **3d** and **3e** in 81% and 84% yield, respectively. The presence of a TIPS-protected alkyne moiety in the substrate was also well-tolerated, as demonstrated by the reaction of carbamate **2f** to provide product **3f** in 91% yield after 8 h. Carbamate **2g** was included in our substrate scope investigation as a surrogate for more elaborate linear 8-AQ amides carrying substituents in the α-position, and it was found to undergo significant aminolysis after 8 h, allowing product **3g** to be isolated in 71% yield. Carbamates **2h** and **2i**, obtained through synthetic routes involving directed alkene hydroamination of a homoallylic 8-AQ amide (precursor G, Table S1) with either phthalimide or ethyl 2-nitropropionate, could be converted into products **3h** and **3i** in 73% and 88% yield, respectively, after 9 h. Here, product **3i** obtained in 88% yield is worth particular mentioning as it demonstrates that this transamidation chemistry can be carried out selectively in the presence of an ester group. In contrast, chemoselective cleavage of the 8-AQ auxiliary from **3i** through hydrolysis would be challenging as the ester group would also be prone to hydrolyze under such reaction conditions.

The same homoallylic 8-AQ amide (precursor G) could also be used to access carbamate **2h** through Pd-catalyzed *β*,*γ*-vicinal dicarbofunctionalization followed by Boc protection, which in

turn was transformed into product **3h** in 78% yield after 24 h. Noteworthily, all the reactions involving the less hindered aliphatic carbamates **2d-j** were found to produce low amounts of the Boc deprotected byproducts **1d-j**, which further supported the hypothesis that significant steric bulk around the *N*-Boc amide moiety favors this undesired reaction path.

Scheme 1. Scope of the transamidation strategy in terms of different 8-aminoquinoline amides.[a]



[a]Reaction conditions unless otherwise noted: *N*-Boc protection step: Substrate **1a-p** (1 equiv), Boc_2O (2 equiv) and DMAP (0.1 equiv) in MeCN (0.1 M), 60 °C, 1-2 h. Aminolysis step: Carbamate **2a-p** (1 equiv), piperonylamine (1.5 equiv), toluene (0.5 M), 60 °C. All yields refer to isolated yields following column chromatography (from **2a-p** to **3a-p**) unless otherwise stated. [b]Product **3b** was not isolated, instead the yield was estimated by ^{1}H-NMR from the ratio of **1b**, **2b** and **3b**. [c]**3e** was isolated after precipitation from the reaction mixture. [d]Reaction was performed in DMF (0.5 M).[e]2 equiv of piperonylamine were used.

Interestingly, also furan carbamates **2k-m** prepared *via* directed C3-arylation chemistry could be efficiently converted to products **3k-m** in high yields. Here, the successful aminolysis of carbamate **2m** further demonstrates the compatibility of the present transamidation protocol towards ester-containing substrates, and highlights that it also can be applied to substrates

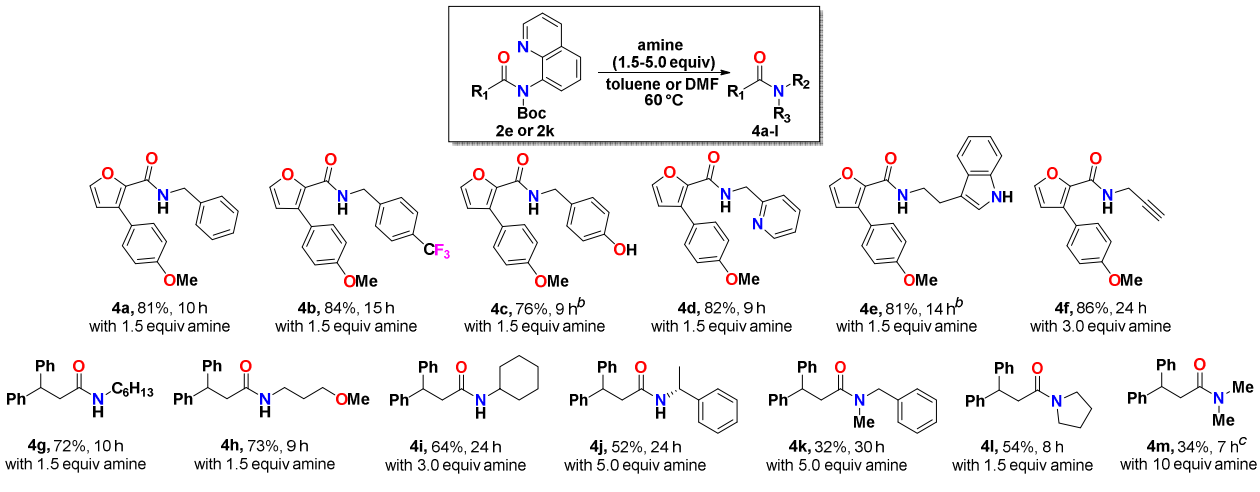
containing benzoate ester moieties. For the C3-alkylated thiophene carbamates **2n** and **2o** the transamidation was found to be slower, requiring 2 equiv of piperonylamine and extended reaction times to furnish satisfactory yields of products **3n** and **3o**. For these two reactions, Boc deprotection was found to occur to a greater extent and the side products **1n** and **1o** were obtained in ca 15% yield from each reaction. Also cyclopropane-type substrates were applicable for this method, as exemplified by the transformation of **2p** to **3p**, which was carried out in 76% yield when performed with 2 equiv of piperonylamine in DMF for 24 h.

After having surveyed a series of *N*-acyl-Boc carbamates, we then focused on investigating the efficiency of the aminolysis step with different amine nucleophiles, using carbamates **2e** and **2k** as the model substrates (Scheme 2). Benzylamine and 4-(trifluoromethyl)benzylamine reacted slower with furan carbamate **2k** than piperonylamine; however, by extending the reaction times both products **4a** and **4b** could be obtained in high yields (81% and 84%, respectively). The presence of a free phenol moiety did not have any significant negative effect on the reaction outcome and product **4c** was acquired in 76% yield when the aminolysis was performed in DMF for 9 h. Both 2-picolylamine and tryptamine proved to be competent nucleophiles for the reaction with substrate **2k** as well, and the corresponding amides **4d** and **4e** were acquired in 82% and 81% yield, respectively. Propargylamine could also be used for the aminolysis, but the high volatility of this reagent led to a less efficient reaction with carbamate **2k**. However, performing this reaction with 3 equiv of propargylamine for 24 h allowed amide **4f** to be isolated in 86% yield.

For other less volatile linear aliphatic primary amines, such as hexylamine or 3-methoxypropylamine, 1.5 equiv proved sufficient in the reactions with carbamate **2e**, giving products **4g** and **4h** in 72% and 73% yield, respectively, after shorter reaction times. More

hindered amines were found to produce substantial amounts of the Boc-deprotected byproduct, which reduced the yields of the desired amide products. The reactions between carbamate **2e** and the amines cyclohexylamine and (*R*)-1-phenylethylamine gave only 64% and 52% yield of products **4i** and **4j**, respectively, despite the reactions being pushed to >95% conversion with increased amine stoichiometry and extended reaction times. A similar outcome was also observed for the reaction between the secondary amine *N*-methylbenzylamine (5 equiv) and carbamate **2e**, where product **4k** was obtained in a low yield of 32% after 30 h and where the Boc-deprotected side product **1e** almost exclusively accounted for the remaining mass balance. Pyrrolidine was found to react more efficiently with carbamate **2e** and full conversion was reached already after 8 h, but also for this reaction the selectivity was low and product **4l** was isolated in merely 54% yield. Dimethylamine solution (2 M in THF, 10 equiv) could also be used to trigger aminolysis of carbamate **2e**, but in line with the other entries involving sterically encumbered amines nucleophiles the outcome of the reaction was disappointing as only 34% yield of product **4m** was obtained after 7 h.

Scheme 2. Aminolysis of **2e** and **2i** with different amine nucleophiles.[a]

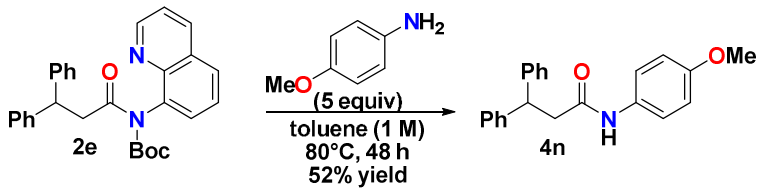


[a]Reaction conditions unless otherwise noted: 8-aminoquinoline amide substrate (1 equiv), amine (1.5-5.0 equiv), toluene (0.5 M), 60 °C. All yields refer to isolated yields following column

chromatography. [b]Reaction was performed in DMF (0.5 M).[c]Reaction was performed with 0.4 mmol **2e** in dimethylamine solution (2 M in THF, 2 mL).

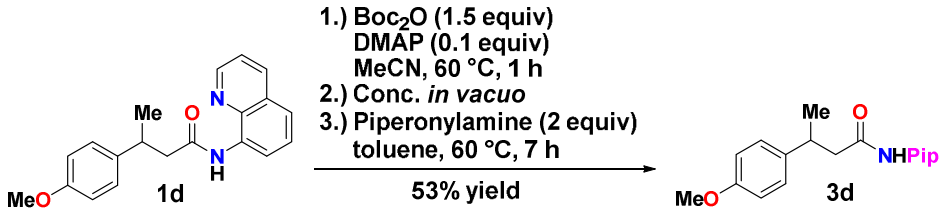
Interestingly, successful aminolysis could be achieved with an aniline-type nucleophile, which was beyond the scope of the earlier metal-free method reported by Szostak and co-workers.[13] However, this reaction was slow due to the low nucleophilicity of *p*-anisidine, requiring additional alterations of the reaction conditions. As shown in Scheme 3, when the aminolysis was performed at 80 °C for 48 h with 5 equiv of *p*-anisidine, product **4n** was obtained in 52% yield. Noteworthily, this reaction appeared to be very selective towards the formation of **4n**, as unreacted starting material accounted for most of the remaining material, and only trace amounts of the Boc-deprotected byproduct **1e** were observed from ^{1}H-NMR analysis of the crude reaction mixture. However, it is important to emphasize that previous transamidation protocols based on Pd-,[12a,12c] Ni-,[12b,12d,12e] Cu-,[12g] and Zn-catalysis[15] constitute more efficient and more general options for carrying out transamidations with aniline nucleophiles.

Scheme 3. Aminolysis with an aniline.



It is also important to highlight that for all entries shown in Schemes 1 and 2, the *N*-acyl-Boc carbamates had all been purified by column chromatography prior to the aminolysis step. However, as demonstrated by the overall transamidation of **1d**, it is also possible to perform both steps in one-pot (Scheme 4). With this one-pot procedure, amide **3d** was obtained in 53% yield after a single column chromatography purification.[19]

Scheme 4. One-pot protocol for overall transamidation.



CONCLUSION

In summary, the aminolysis of *N*-acyl-Boc-carbamates prepared from different 8-aminoquinoline amides has been evaluated, as this was identified as a convenient approach to achieve overall transamidation of these synthetically useful amide compounds. In many cases, the carbamates were found to undergo facile aminolysis under mild conditions to give a variety of amide products in good to high yields, without the need for any additional additives. Additional advantages of this method are that it tolerates substrates containing hydrolysis-sensitive functional groups as well as an aniline as the nucleophile, and moreover it can be modified to work in a one-pot fashion. However, the method also has limitations, as exemplified by the aminolysis reactions involving sterically-hindered substrates, which gave lower yields of the desired amide products, despite the use of more forcing reaction conditions. Overall, the method offers a useful and alternative way to transform 8-aminoquinoline amides into other more elaborate amide derivatives, and circumvents the need of proceeding *via* the intermediate carboxylic acid that is associated with the subsequent use of coupling reagents to form the desired amide bond.

EXPERIMENTAL SECTION

General Experimental Information

All reagents and solvents were purchased and used as received from commercial vendors or synthesized according to cited procedures. 8-Aminoquinoline amides **1a-p** were obtained using previously reported procedures (see Table S1 in the SI for further details). Oxygen and/or moisture sensitive reactions were carried out in oven or flame-dried glassware under nitrogen atmosphere using appropriately dried solvents. Yields refer to chromatographically isolated compounds, unless otherwise stated. Room temperature in laboratory (21-23 °C). Trace impurities of CH_2Cl_2 in some spectra originates from the process of transferring compounds between containers, where this solvent was used for washing. Flash chromatography was performed using 15-45 μm silica gel cartridges (60Å mesh) on a Teledyne Isco Combiflash Rf. SiliaSep SiO_2 cartridges used for these purifications were provided from SiliCycle. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates and visualized by UV light (254 nm) or suitable TLC stain. Chemical shifts are reported in parts per million (ppm) relative to the NMR solvent peaks. Nuclear Magnetic Resonance Spectroscopy (NMR) were recorded on a Bruker Advance spectrometer (^{1}H, ^{13}C and ^{19}F-NMR). Deuterated solvents for NMR analyses was obtained from Sigma-Aldrich. Data for ^{1}H-NMR are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, m =

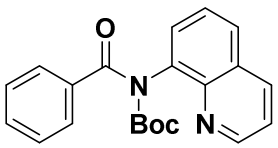
multiplet), coupling constants, and integration. High resolution mass spectroscopy (HRMS) was performed on Bruker microTOF/ESI mass spectrometer. Infrared spectra were obtained with a "Spectrum One" instrument from Perkin-Elmer or a Nicolet iS5 instrument with full-diamond crystal ATR from Thermo-Fisher.

General Procedure A for the *N*-Boc protection of substrates 1a-p

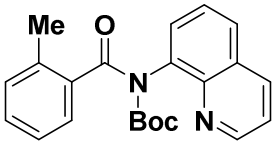
This general procedure was used for all *N*-Boc protection reactions unless otherwise stated. To a reaction vessel containing 8-aminoquinoline amide substrate **1a-p** (1 equiv) and 4-(dimethylamino)pyridine (DMAP, 0.1 equiv) were added Boc anhydride (Boc_2O, 2 equiv) in dry MeCN (0.1 M). The reactions were allowed to stir at 60 °C for 1-2 h, after which they were concentrated *in vacuo* and purified by column chromatography (SiO_2) to give the corresponding carbamates **2a-p**.

General Procedure B for the aminolysis of substrates 2a-p

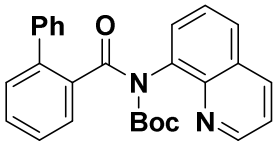
This general procedure was used for all aminolysis reactions described in Scheme 1 and Scheme 2, unless otherwise stated. To a sealed vial containing the Boc-protected substrates **2a-p** (0.20 mmol, 1 equiv), was added the amine (0.30-1.00 mmol, 1.5-5.0 equiv) in toluene or DMF, and the reaction was allowed to stir at 60 °C for 7-30 h. The reactions were then concentrated *in vacuo* and purified by column chromatography (SiO_2) to give products **3a-p** and **4a-l**.



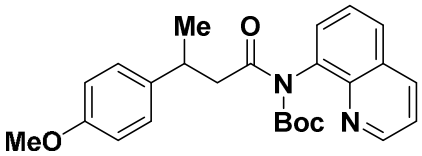
Tert-butyl benzoyl(quinolin-8-yl)carbamate (**2a**): The reaction was performed according to general procedure A with 4.0 mmol **1a** for 1 h. The product was isolated after column chromatography (gradient 0-50% EtOAc in pentane) in 1.30 g (93%) as a pale yellow amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.89 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.96–7.94 (m, 2H), 7.83 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.69 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.60–7.51 (m, 2H), 7.47–7.39 (m, 3H), 1.21 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 173.5, 153.5, 150.5, 144.1, 137.5, 137.3, 136.1, 131.3, 129.2, 129.1, 128.6, 128.2, 128.0, 126.2, 121.7, 83.1, 27.5. **IR** (thin film) ν_{max} 2980, 1737, 1683, 1369, 1349, 1275, 1260, 1153, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{20}N_2O_3Na$ 371.1372; Found 371.1366**.**



Tert-butyl (2-methylbenzoyl)(quinolin-8-yl)carbamate (**2b**). The reaction was performed according to general procedure A with 0.8 mmol **1b** for 1 h. The product was isolated after column chromatography (gradient 0-50% EtOAc in pentane) in 265 mg (91%) as a yellow amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.91 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.92–7.90 (m, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.72 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.60 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.42 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.36–7.33 (m, 1H), 7.28–7.25 (m, 2H + $CHCl_3$), 2.56 (s, 3H), 1.15 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 173.2, 153.1, 150.4, 144.2, 138.2, 136.7, 136.1, 136.0, 130.5, 129.7, 129.20, 129.18, 128.4, 127.3, 126.2, 125.3, 121.6, 83.1, 27.3, 19.6. **IR** (thin film) ν_{max} 2985, 1736, 1683, 1349, 1275, 1261, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{22}H_{22}N_2O_3Na$ 385.1528; Found 385.1522.

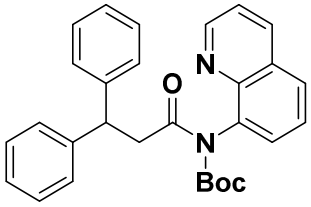


Tert-butyl ([1,1'-biphenyl]-2-carbonyl)(quinolin-8-yl)carbamate (**2c**). The reaction was performed according to general procedure A with 0.8 mmol **1c** for 1 h. No column chromatography purification was performed for **2c**, instead the product precipitated directly from the crude reaction solution and could be obtained in 299 mg (71%) as a colorless amorphous solid, after washing with cold MeCN. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.90 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.13 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.79 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.53–7.38 (m, 8H), 7.32–7.30 (m, 1H), 1.11 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 172.7, 152.4, 150.4, 144.4, 140.4, 139.5, 137.7, 136.4, 135.9, 129.8, 129.6, 129.2, 129.0, 128.8, 128.3, 128.2, 127.7, 127.5, 127.0, 126.1, 121.5, 83.0, 27.5. **IR** (thin film) ν_{max} 2987, 1742, 1683, 1368, 1352, 1275, 1261, 1154, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{27}H_{24}N_2O_3Na$ 447.1685; Found 447.1675.

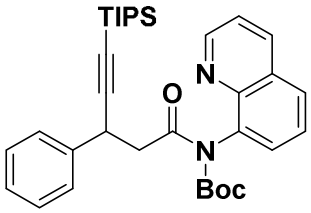


Tert-butyl (3-(4-methoxyphenyl)butanoyl)(quinolin-8-yl)carbamate (**2d**). The reaction was performed according to general procedure A with 1.5 mmol **1d** for 1 h. The product was isolated after column chromatography (gradient 0-50% EtOAc in pentane) in 501 mg (80%) as an orange foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.86 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.78 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.49 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.39 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.28–7.22 (m, 3H + $CHCl_3$), 6.87–6.83 (m, 2H), 3.80 (s, 3H), 3.49–3.32 (m, 3H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.21 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 175.2, 157.9,

153.0, 150.3, 144.2, 138.9, 137.0, 135.9, 128.9, 128.8, 128.0, 127.9, 126.1, 121.4, 113.8, 82.4, 55.3, 46.2, 35.6, 27.6, 22.3. **IR** (thin film) ν_{max} 2977, 1737, 1702, 1514, 1369, 1275, 1260, 1155, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{25}H_{28}N_2O_4Na$ 443.1947; Found 443.1938.

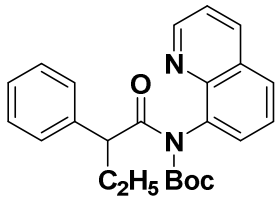


Tert-butyl (3,3-diphenylpropanoyl)(quinolin-8-yl)carbamate (**2e**). The reaction was performed according to general procedure A with 0.4 mmol **1e** for 1 h. The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 178 mg (97%) as a yellow foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.12 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.75 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.44 (dd, *J* = 8.1, 7.4 Hz, 1H), 7.39–7.28 (m, 9H), 7.20 (tt, *J* = 7.2, 1.3 Hz, 2H), 7.08 (dd, *J* = 7.4, 1.3 Hz, 1H), 4.76 (t, *J* = 7.7 Hz, 1H), 3.98 (d, *J* = 7.7 Hz, 2H), 1.24 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 174.7, 153.0, 150.3, 144.3, 144.2, 136.9, 135.9, 128.81, 128.79, 128.5, 128.1, 127.9, 126.3, 126.1, 121.4, 82.6, 47.2, 43.8, 27.7. **IR** (thin film) ν_{max} 2980, 1736, 1704, 1369, 1275, 1261, 1154, 1123, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{29}H_{28}N_2O_3Na$ 475.1998; Found 475.1986.

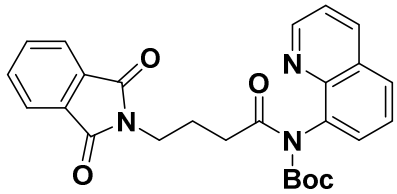


Tert-butyl (3-phenyl-5-(triisopropylsilyl)pent-4-ynoyl)(quinolin-8-yl)carbamate (**2f**). The reaction was performed according to general procedure A with 0.5 mmol **1f** for 1 h. The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 237 mg (85%)

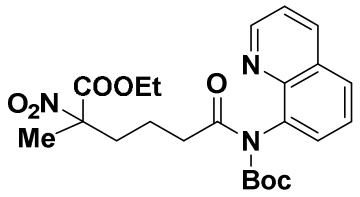
as a yellow gel. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.80 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.53–7.49 (m, 3H), 7.41–7.36 (m, 2H), 7.35–7.30 (m, 2H), 7.26–7.22 (m, 1H), 4.45 (t, *J* = 7.2 Hz, 1H), 3.63 (d, *J* = 7.2 Hz, 2H), 1.21 (s, 9H), 1.10–1.07 (m, 21H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 173.4, 152.8, 150.3, 144.2, 141.2, 136.8, 135.9, 129.0, 128.8, 128.4, 128.1, 127.9, 126.8, 126.1, 121.4, 109.6, 83.1, 82.7, 47.2, 35.1, 27.6, 18.7, 11.3. **IR** (thin film) ν_{max} 2942, 2865, 1739, 1708, 1296, 1259, 1156, 1124, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{34}H_{44}N_2O_3SiNa$ 579.3019; Found 579.3001.



Tert-butyl (2-phenylbutanoyl)(quinolin-8-yl)carbamate (**2g**). The reaction was performed according to general procedure A with 0.8 mmol **1g** for 2 h. The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 232 mg (74%) as a yellow foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.86 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.77 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.47 (dd, *J* = 8.1, 7.5 Hz, 1H), 7.41–7.30 (m, 5H), 7.29–7.23 (m, 2H), 4.87 (bs, 1H), 2.29–2.19 (m, 1H), 1.89–1.79 (m, 1H), 1.16 (s, 9H), 0.92 (t, 7.2 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 177.1, 152.7, 150.3, 144.4, 140.0, 137.3, 135.8, 128.80, 128.78, 128.6, 128.3, 127.8, 126.8, 126.0, 121.5, 82.3, 53.1, 27.5, 27.4, 12.1. **IR** (thin film) ν_{max} 2967, 1733, 1700, 1367, 1289, 1251, 1150, 1122, 789. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{24}H_{26}N_2O_3Na$ 413.1841; Found 413.1847.

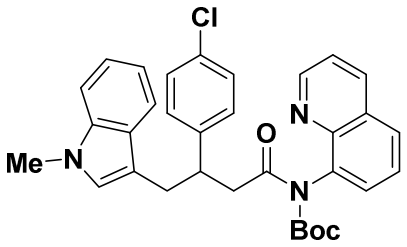


Tert-butyl (4-(1,3-dioxoisoindolin-2-yl)butanoyl)(quinolin-8-yl)carbamate (**2h**). The reaction was performed according to general procedure A with 0.4 mmol **1h** for 1 h. The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 165 mg (90%) as a yellow foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.86 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.84–7.82 (m, 2H), 7.78 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.70–7.67 (m, 2H), 7.58–7.51 (m, 2H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.82 (t, *J* = 6.9 Hz, 2H), 3.21 (t, *J* = 7.3 Hz, 2H), 2.16–2.09 (m, 2H), 1.19 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 175.3, 168.5, 152.8, 150.4, 144.1, 136.9, 136.0, 133.8, 132.3, 129.1, 128.9, 128.0, 126.1, 123.2, 121.4, 82.6, 37.4, 35.2, 27.6, 24.1. **IR** (thin film) ν_{max} 2977, 2932, 1738, 1712, 1396, 1369, 1296, 1272, 1255, 1157, 1125, 721. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{25}N_3O_5Na$ 482.1692; Found 482.1683.

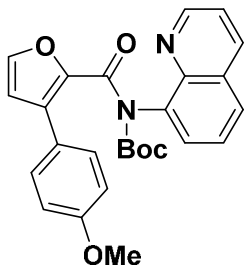


ethyl 6-((tert-butoxycarbonyl)(quinolin-8-yl)amino)-2-methyl-2-nitro-6-oxohexanoate (**2i**) The reaction was performed according to general procedure A with 0.39 mmol **1i** for 2 h. The product was isolated after column chromatography (gradient 10-50% EtOAc in pentane) in 159 mg (89%) as a yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.88 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.81 (dd, J = 8.1, 1.6 Hz, 1H), 7.57–7.49 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.41–2.26 (m, 2H), 1.85–1.74 (overlapping m and s, 1H + 3H), 1.72–1.61 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.22 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 175.3, 167.4, 152.9, 150.5, 144.0, 136.8, 136.0, 129.0, 128.9, 128.1, 126.1, 121.5, 92.8, 82.7, 62.7, 37.3, 35.7, 27.6, 21.1, 19.2, 13.8. **IR** (thin film) ν_{max} 2977,

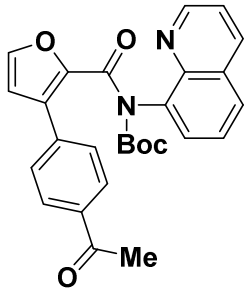
1734, 1700, 1549, 1251, 1153, 1123, 1022, 853, 792. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{23}H_{29}N_3O_7Na$ 482.1903; Found 482.1901.



Tert-butyl (3-(4-chlorophenyl)-4-(1-methyl-1H-indol-3-yl)butanoyl)(quinolin-8-yl)carbamate (**2j**). The reaction was performed according to general procedure A with 0.4 mmol **1j** for 2 h. The product was isolated after column chromatography (gradient 0-50% EtOAc in pentane) in 170 mg (76%) as a yellow foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.78 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 8.1, 7.4 Hz, 1H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.25–7.16 (m, 7H), 7.06–7.01 (m, 1H), 6.62 (s, 1H), 3.77–3.70 (m, 1H), 3.67 (s, 3H), 3.63–3.52 (m, 2H), 3.25 (dd, *J* = 14.2, 6.3 Hz, 1H), 3.03 (dd, *J* = 14.2, 8.3 Hz, 1H), 1.21 (s, 9H). **^{13}C-NMR** (100 MHz, CD_3CN, 298 K) δ 174.6, 152.8, 150.4, 144.0, 143.9, 137.02, 136.98, 136.2, 131.2, 129.6, 128.9, 128.8, 128.1, 128.04, 128.00, 127.6, 126.1, 121.7, 121.2, 118.9, 118.5, 112.0, 109.3, 82.4, 43.8, 42.5, 31.9, 31.8, 26.8. **IR** (thin film) ν_{max} 2979, 2932, 1736, 1701, 1492, 1474, 1369, 1322, 1296, 1255, 1156, 1124, 742. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{33}H_{32}ClN_3O_3Na$ 576.2030; Found 576.2023.

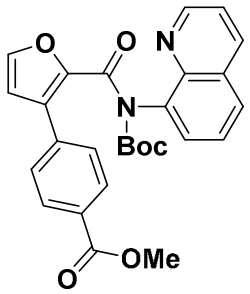


Tert-butyl (3-(4-methoxyphenyl)furan-2-carbonyl)(quinolin-8-yl)carbamate (**2k**). The reaction was performed according to general procedure A with 0.5 mmol **1k** for 1 h. The product was isolated after column chromatography (gradient 10-75% EtOAc in pentane) in 219 mg (98%) as an orange foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.87 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.80 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.71–7.67 (m, 2H), 7.64 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.57–7.53 (m, 2H), 7.39 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.90–6.87 (m, 2H), 6.70 (d, *J* = 1.8 Hz, 1H), 3.79 (s, 3H), 1.33 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 162.8, 159.6, 153.0, 150.4, 144.0, 143.2, 142.8, 137.0, 136.0, 132.6, 130.3, 129.1, 128.6, 128.0, 126.2, 124.1, 121.6, 113.9, 113.7, 82.8, 55.3, 27.6. **IR** (thin film) ν_{max} 2978, 1739, 1676, 1516, 1393, 1369, 1337, 1251, 1154, 876, 819, 765. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{24}N_2O_5Na$ 467.1583; Found 467.1575.

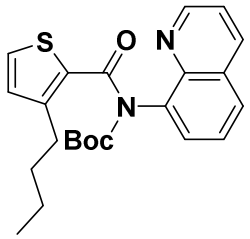


Tert-butyl (3-(4-acetylphenyl)furan-2-carbonyl)(quinolin-8-yl)carbamate (**2l**). The reaction was performed according to general procedure A with 0.34 mmol **1l** for 1 h. The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 131 mg (82%) as a yellow foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.88 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.95–7.92 (m, 2H), 7.84–7.80 (m, 3H), 7.65 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.60–7.54 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.76 (d, *J* =1.8, 1H), 2.58 (s, 3H), 1.32 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 197.7, 162.6, 152.8, 150.4, 144.0, 143.9, 143.4, 136.6, 136.5, 136.4, 136.1, 131.1, 129.12, 129.11, 128.6, 128.3, 128.2, 126.2, 121.7, 113.6, 83.1, 27.6, 26.6.

IR (thin film) ν_{max} 2979, 1742, 1681, 1337, 1268, 1154, 877, 819, 765. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{27}H_{24}N_2O_5Na$ 479.1583; Found 479.1578.

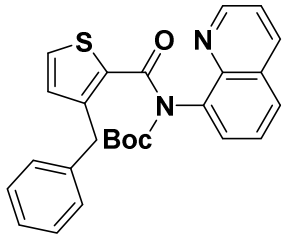


Methyl 4-(2-((tert-butoxycarbonyl)(quinolin-8-yl)carbamoyl)furan-3-yl)benzoate (**2m**). The reaction was performed according to general procedure A with 0.42 mmol **1m** for 1 h. The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 201 mg (93%) as a yellow foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.88 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.03–8.00 (m, 2H), 7.84–7.78 (m, 3H), 7.64 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.59–7.54 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.76 (d, *J* =1.8 Hz, 1H), 3.90 (s, 3H), 1.31 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 166.8, 162.6, 152.8, 150.4, 143.92, 143.89, 143.4, 136.7, 136.3, 136.1, 131.1, 129.6, 129.5, 129.1, 128.9, 128.6, 128.2, 126.2, 121.7, 113.7, 83.1, 52.1, 27.6. **IR** (thin film) ν_{max} 2981, 1740, 1721, 1679, 1337, 1276, 1154, 1113, 877, 818, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{27}H_{24}N_2O_6Na$ 495.1532; Found 495.1532.



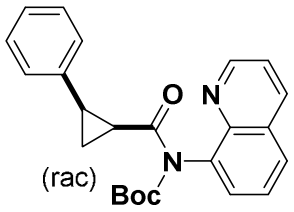
Tert-butyl (3-butylthiophene-2-carbonyl)(quinolin-8-yl)carbamate (**2n**). The reaction was performed according to general procedure A with 0.40 mmol **1n** for 1 h. The product was

isolated after column chromatography (gradient 0-30% EtOAc in pentane) in 156 mg (96%) as a yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.89 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.82 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.66 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.56 (dd, *J* = 8.1, 7.4 Hz, 1H), 7.42–7.38 (m, 2H), 6.96 (d, *J* = 5.1 Hz, 1H), 2.94 (t, *J* = 7.9 Hz, 2H), 1.70–1.58 (m, 2H), 1.46–1.35 (m, 2H), 1.30 (s, 9H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 167.1, 153.3, 150.3, 148.7, 144.0, 137.5, 136.0, 132.8, 129.5, 129.1, 128.7, 128.5, 128.0, 126.2, 121.6, 82.9, 32.8, 29.1, 27.6, 22.8, 14.0. **IR** (thin film) ν_{max} 2958, 1733, 1678, 1337, 1252, 1155, 1115, 817, 791, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{23}H_{26}N_2O_3SNa$ 433.1562; Found 433.1554.

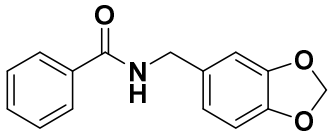


Tert-butyl (3-benzylthiophene-2-carbonyl)(quinolin-8-yl)carbamate (**2o**). The reaction was performed according to general procedure A with 0.38 mmol **1o** for 1 h. The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 140 mg (80%) as a colorless foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.60–7.52 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 (d, *J* = 5.1 Hz, 1H), 7.32–7.27 (m, 4H), 7.24–7.18 (m, 1H), 6.79 (d, *J* = 5.1 Hz, 1H), 4.35 (s, 2H), 1.31 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 166.9, 153.2, 150.3, 146.2, 144.0, 140.4, 137.4, 136.0, 133.5, 130.0, 129.2, 129.1, 128.8, 128.7, 128.4, 128.1, 126.19, 126.16, 121.7, 83.1, 35.2, 27.7. **IR** (thin film) ν_{max} 2920, 1735, 1671, 1337, 1275, 1261, 1152,

913, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{24}N_2O_3SNa$ 467.1405; Found 467.1394.

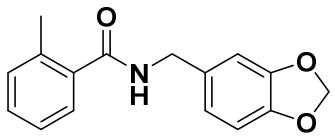


Tert-butyl ((cis)-2-phenylcyclopropane-1-carbonyl)(quinolin-8-yl)carbamate (**2p**). The reaction was performed according to general procedure A with 0.42 mmol **1p** for 2 h. The product was isolated after column chromatography (gradient 0-50% EtOAc in pentane) in 141 mg (90%) as a yellow foamy solid. Compound is racemic (single diastereomer). **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.84 (dd, *J* = 3.9, 1.3 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.39–7.18 (m, 7H + $CHCl_3$), 6.82 (br. s, 1H), 3.37 (br. s, 1H), 2.76 (q, J = 8.2 Hz, 1H), 1.94 (q, J = 5.8 Hz, 1H), 1.42–1.36 (m, 1H), 1.25 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 172.0, 152.9, 150.2, 144.1, 136.9, 136.8, 135.8, 129.3, 129.0, 128.7, 127.9, 127.7, 126.4, 126.0, 121.3, 82.3, 27.7, 26.7, 26.5, 11.3. **IR** (thin film) ν_{max} 2978, 1736, 1695, 1390, 1368, 1295, 1267, 1155, 1042, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{24}H_{24}N_2O_3Na$ 411.1685; Found 411.1675.

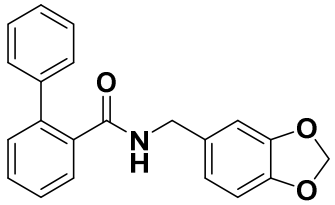


N-(benzo[d][1,3]dioxol-5-ylmethyl)benzamide (**3a**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 7 h in toluene (0.5 M with regard to **2a**). The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 50.5 mg (98%) as a colorless amorphous solid. The characterization data of **3a** was in

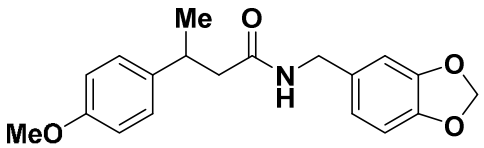
accordance with those preliminary reported in the literature.[20] **H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.79–7.75 (m, 2H), 7.51–7.45 (m, 1H), 7.45–7.37 (m, 2H), 6.84–6.75 (m, 3H), 6.48 (bs, 1H), 5.94 (s, 2H), 4.53 (d, J = 5.6 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) 167.3, 148.0, 147.1, 134.4, 132.1, 131.6, 128.6, 127.0, 121.2, 108.5, 108.4, 101.1, 44.0.



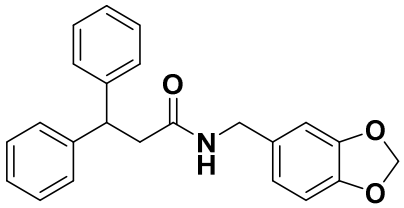
N-(benzo[d][1,3]dioxol-5-ylmethyl)-2-methylbenzamide (**3b**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 24 h in toluene (0.5 M with regard to **2b**). This reaction furnished **3b** in such a low yield that an isolation attempt was never pursued. Instead, the relative ratio of compounds **1b**, **2b** and **3b** was estimated by ^{1}H-NMR-analysis of the crude reaction mixture.



N-(benzo[d][1,3]dioxol-5-ylmethyl)-[1,1'-biphenyl]-2-carboxamide (**3c**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 24 h in toluene (0.5 M with regard to **2c**). This reaction furnished **3c** in such a low yield that an isolation attempt was never pursued. Only traces of **3c** were formed according to ^{1}H-NMR-analysis of the crude reaction mixture.

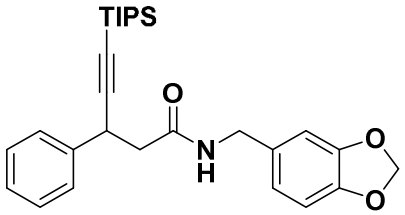


N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-methoxyphenyl)butanamide (**3d**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 8 h in toluene (0.5 M with regard to **2d**). The product was isolated after column chromatography (gradient 0-50% EtOAc in pentane) in 57.0 mg (81%) as a yellow amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.14–7.10 (m, 2H), 6.83–6.79 (m, 2H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.53–6.47 (m, 2H), 5.91 (s, 2H), 5.53 (br. t, 1H), 4.26 (dd, *J* = 14.7, 6.0 Hz, 1H), 4.15 (dd, *J* = 14.7, 5.5 Hz, 1H), 3.78 (s, 3H), 3.30–3.21 (m, 1H), 2.46–2.35 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 171.5, 158.2, 147.8, 146.8, 137.7, 132.0, 127.7, 120.9, 114.0, 108.3, 108.1, 101.0, 55.2, 46.1, 43.3, 36.3, 22.1. **IR** (thin film) ν_{max} 3286, 2923, 1645, 1514, 1490, 1444, 1249, 1038, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{19}H_{21}NO_4Na$ 350.1368; Found 350.1361.

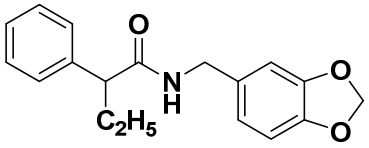


N-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-diphenylpropanamide (**3e**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 7 h in toluene (0.5 M with regard to **2e**). No column chromatography purification was performed for **3e**, instead the product precipitated directly from the crude reaction solution and could be obtained in 60.0 mg (84%) as a colorless amorphous solid, after washing with ice-cold toluene. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.30–7.18 (m, 10H + $CHCl_3$), 6.64 (d, *J* = 7.8 Hz, 1H), 6.40–6.36 (m, 2H), 5.92 (s, 2H), 5.46 (br. t, 1H), 4.60 (t, *J* = 7.9 Hz, 1H), 4.19 (d, *J* = 5.7 Hz, 2H), 2.92 (d, *J* = 7.9 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 170.8, 147.8, 146.8, 143.5, 131.8, 128.7, 127.8, 126.6, 120.7, 108.2, 108.1, 101.0, 47.6, 43.5, 43.3. **IR** (thin film) ν_{max} 3274, 2917, 1640, 1489, 1446, 1275,

1258, 1033, 749. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NO_3Na$ 382.1419; Found 382.1414.

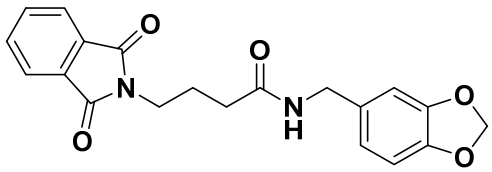


N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-phenyl-5-(triisopropylsilyl)pent-4-ynamide (**3f**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 8 h in toluene (0.5 M with regard to **2f**). The product was isolated after column chromatography (gradient 0-50% EtOAc in pentane) in 84.0 mg (91%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.42–7.40 (m, 2H), 7.34–7.30 (m, 2H), 7.27–7.23 (m, 1H + $CHCl_3$), 6.70 (d, *J* = 7.9 Hz, 1H), 6.63–6.59 (m, 2H), 5.93 (s, 2H), 5.92 (br. t, 1H), 4.38 (dd, *J* = 14.6, 6.2 Hz, 1H), 4.25 (dd, *J* = 8.2, 6.4 Hz, 1H), 4.18 (dd, *J* = 14.6, 5.2 Hz, 1H), 2.72 (dd, *J* = 14.2, 8.2 Hz, 1H), 2.59 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.06–1.03 (m, 21H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 169.7, 147.9, 147.0, 140.3, 131.8, 128.6, 127.4, 127.2, 121.1, 108.7, 108.5, 108.2, 101.1, 84.8, 46.2, 43.5, 35.6, 18.6, 11.2. **IR** (thin film) ν_{max} 3287, 2942, 2864, 1642, 1504, 1490, 1444, 1275, 1254, 1042, 750. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{28}H_{37}NO_3SiNa$ 486.2440; Found 486.2429.

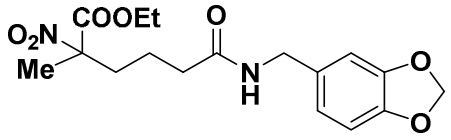


N-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2-phenylbutanamide (**3g**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 8 h in toluene (0.5 M with regard to **2g**). The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 42.0 mg (71%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K)

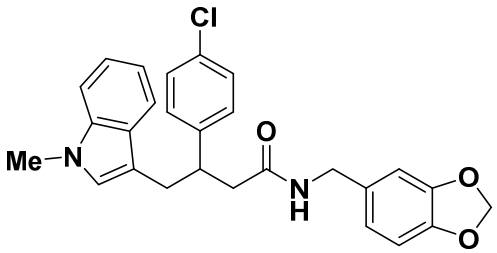
δ 7.35–7.23 (m, 5H + $CDCl_3$), 6.69 (d, *J* = 7.9 Hz, 1H), 6.63–6.59 (m, 2H), 5.91 (s, 2H), 5.64 (br. t, 1H), 4.34 (dd, *J* = 14.7, 5.9 Hz, 1H), 4.23 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.24 (t, *J* = 7.6 Hz, 1H), 2.27–2.17 (m, 1H), 1.87–1.76 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 173.3, 147.9, 146.9, 139.9, 132.2, 128.8, 128.0, 127.3, 120.8, 108.2, 108.1, 101.0, 55.3, 43.4, 26.4, 12.4. **IR** (thin film) ν_{max} 3300, 2955, 1640, 1541, 1487, 1444, 1248, 1213, 1038, 805. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{18}H_{19}NO_3Na$ 320.1263; Found 320.1254.



N-(benzo[d][1,3]dioxol-5-ylmethyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide (**3h**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 9 h in DMF (0.5 M with regard to **2h**). Prior to column chromatography purification, the reaction was diluted with EtOAc (10 mL) and washed with brine (5 × 5 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated *in vacuo*. The product was isolated after column chromatography (gradient 0-100% EtOAc in pentane) in 53.0 mg (73%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.85–7.82 (m, 2H), 7.73–7.71 (m, 2H), 6.80 (s, 1H), 6.75 (m, 2H), 6.16 (br. t, 1H), 5.93 (s, 2H), 4.32 (d, *J* = 5.7 Hz, 2H), 3.74 (t, *J* = 6.2 Hz, 2H), 2.23 (t, *J* = 7.3 Hz, 2H), 2.09–2.01 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 171.6, 168.7, 147.9, 146.9, 134.1, 132.2, 132.0, 123.3, 121.1, 108.5, 108.3, 101.0, 43.5, 37.2, 33.8, 25.0. **IR** (thin film) ν_{max} 3282, 3006, 1715, 1630, 1276, 1260, 1032, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{20}H_{18}N_2O_5Na$ 389.1113; Found 389.1107.

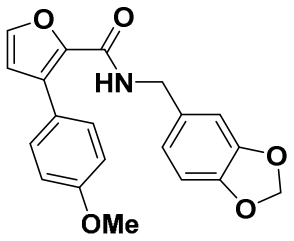


ethyl 6-((benzo[d][1,3]dioxol-5-ylmethyl)amino)-2-methyl-2-nitro-6-oxohexanoate (**3i**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 9 h in toluene (0.5 M with regard to **3i**). The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 64.0 mg (88%) as a yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 6.74–6.69 (m, 3H), 5.94 (br. t, 1H), 5.92 (s, 2H), 4.29 (d, *J* = 5.8 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.27–2.15 (m, 4H), 1.77 (s, 3H), 1.76–1.66 (m, 1H), 1.60–1.49 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 171.4, 167.3, 147.9, 147.0, 132.0, 121.1, 108.4, 108.3, 101.1, 92.5, 62.9, 43.5, 35.8, 35.6, 21.1, 19.7, 13.8. **IR** (thin film) ν_{max} 3284, 2898, 1744, 1642, 1547, 1488, 1249, 1182, 1035, 924, 808. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2O_7Na$ 389.1325; Found 289.1319.

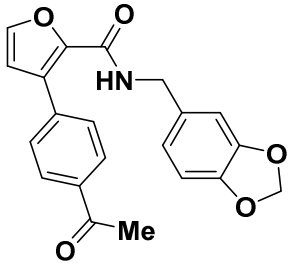


N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-chlorophenyl)-4-(1-methyl-1H-indol-3-yl)butanamide (**3j**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 24 h in toluene (0.5 M with regard to **2j**). The product was isolated after column chromatography (gradient 10-70% EtOAc in pentane) in 72.0 mg (78%) as a yellow foamy solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.52 (d, *J* = 8.1 Hz, 1H), 7.27–7.19 (m, 4H + $CHCl_3$), 7.13–7.07 (m, 3H), 6.68–6.65 (m, 2H), 6.48 (d, *J* = 1.3 Hz, 1H), 6.40 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.92 (s, 2H), 5.47 (br. t, 1H), 4.22 (dd, *J* = 14.6, 5.9 Hz, 1H), 4.06 (dd, *J* = 14.6, 4.8

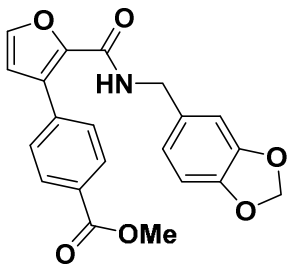
Hz, 1H), 3.68 (s, 3H), 3.58–3.50 (m, 1H), 3.11–3.00 (m, 2H), 2.66 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.37 (dd, *J* = 13.9, 9.6 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 171.1, 147.8, 146.9, 142.8, 136.9, 132.2, 132.0, 128.9, 128.6, 128.1, 127.3, 121.5, 120.8, 118.9, 118.8, 111.8, 109.2, 108.22, 108.17, 101.1, 43.21, 43.19, 43.1, 32.6, 32.0. **IR** (thin film) ν_{max} 3287, 2916, 1642, 1490, 1444, 1253, 1039, 747. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{27}H_{25}ClN_2O_3Na$ 483.1451; Found 483.1446.



N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-methoxyphenyl)furan-2-carboxamide (**3k**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 8 h in toluene (0.5 M with regard to **2k**). The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 64.0 mg (91%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.70–7.65 (m, 2H), 7.41 (d, *J* = 1.8 Hz, 1H), 6.95–6.92 (m, 2H), 6.82–6.74 (m, 3H), 6.60 (d, *J* = 1.8 Hz, 1H), 6.57 (br. t, 1H), 5.94 (s, 2H), 4.48 (d, *J* = 5.8 Hz, 2H), 3.83 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 159.6, 158.7, 147.9, 147.0, 142.7, 141.0, 132.1, 131.0, 130.7, 124.0, 121.2, 114.4, 113.6, 108.5, 108.3, 101.1, 55.3, 42.9. **IR** (thin film) ν_{max} 3290, 2932, 1655, 1516, 1489, 1249, 1179, 1037, 936, 834, 780. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}NO_5Na$ 374.1004; Found 374.0994.

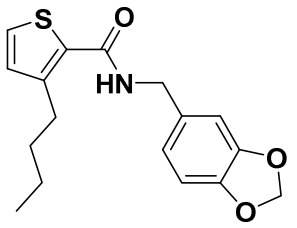


3-(4-Acetylphenyl)-N-(benzo[d][1,3]dioxol-5-ylmethyl)furan-2-carboxamide (**3l**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 9 h in toluene (0.5 M with regard to **2l**). The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 63.0 mg (87%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.00–7.97 (m, 2H), 7.83–7.80 (m, 2H), 7.45 (d, *J* = 1.8 Hz, 1H), 6.82–6.74 (m, 3H), 6.70 (br. t, 1H), 6.66 (d, *J* = 1.8 Hz, 1H), 5.94 (s, 2H), 4.48 (d, *J* = 5.9 Hz, 2H), 2.61 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 197.8, 158.3, 148.0, 147.1, 143.0, 141.9, 136.6, 136.4, 131.8, 130.3, 129.7, 128.1, 121.3, 114.3, 108.5, 108.4, 101.1, 43.0, 26.7. **IR** (thin film) ν_{max} 3336, 2917, 1677, 1524, 1489, 1260, 1039, 937, 843, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{17}NO_5Na$ 386.1004; Found 386.0995.

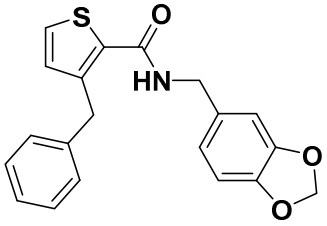


Methyl 4-(2-((benzo[d][1,3]dioxol-5-ylmethyl)carbamoyl)furan-3-yl)benzoate (**3m**). The reaction was performed according to general procedure B with 1.5 equiv piperonylamine for 9 h in toluene (0.5 M with regard to **2m**). The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 67.0 mg (88%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.08–8.05 (m, 2H), 7.81–7.78 (m, 2H), 7.44 (d, *J* = 1.8 Hz, 1H), 6.82–6.74 (m, 3H), 6.67 (br. t, 1H), 6.65 (d, *J* = 1.8 Hz, 1H), 5.94 (s, 2H), 4.48 (d, *J* = 5.8 Hz, 2H), 3.92 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 166.9, 158.3, 148.0, 147.1, 143.0, 141.9, 136.4, 131.8, 130.3, 129.6, 129.5, 129.4, 121.3, 114.4, 108.5, 108.4, 101.1, 52.1, 43.0. **IR**

(thin film) ν_{max} 3373, 2923, 1718, 1657, 1523, 1489, 1443, 1280, 1252, 1181, 1112, 1039, 936, 769. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{17}NO_6Na$ 402.0954; Found 402.0944.

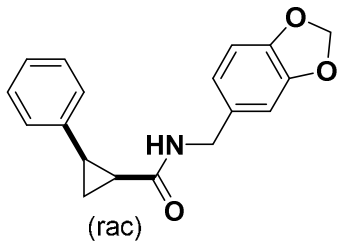


N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-butylthiophene-2-carboxamide (**3n**). The reaction was performed according to general procedure B with 2.0 equiv piperonylamine for 24 h in toluene (0.5 M with regard to **2n**). The product was isolated after column chromatography (gradient 0-20% EtOAc in pentane) in 40.5 mg (64%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.26–7.24 (m, 1H + $CHCl_3$), 6.94 (d, *J* = 5.1 Hz, 1H), 6.85–6.76 (m, 3H), 6.04 (br. t, 1H), 5.95 (s, 2H), 4.50 (d, *J* = 5.6 Hz, 2H), 2.94 (t, *J* = 7.8 Hz, 2H), 1.65–1.57 (m, 2H), 1.41–1.31 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 162.9, 148.0, 147.14, 147.07, 132.0, 130.9, 130.1, 126.2, 121.1, 108.43, 108.36, 101.1, 43.8, 32.9, 29.3, 22.6, 13.9. **IR** (thin film) ν_{max} 3307, 2929, 1637, 1542, 1505, 1489, 1276, 1260, 1040, 928, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{19}NO_3SNa$ 340.0983; Found 340.0978.

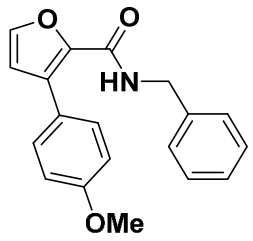


N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-benzylthiophene-2-carboxamide (**3o**). The reaction was performed according to general procedure B with 2.0 equiv piperonylamine for 24 h in toluene (0.5 M with regard to **2o**). The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 46.0 mg (65%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz,

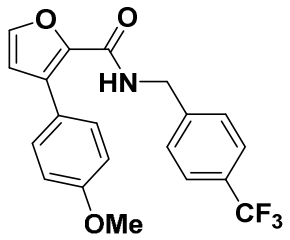
$CDCl_3$, 298 K) δ 7.28–7.23 (m, 3H + $CHCl_3$), 7.21–7.15 (m, 3H), 6.86 (d, *J* = 5.0 Hz, 1H), 6.76–6.69 (m, 3H), 6.05 (br. t, 1H), 5.95 (s, 2H), 4.44 (d, *J* = 5.6 Hz, 2H), 4.32 (s, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 162.6, 147.9, 147.1, 144.0, 139.9, 131.8, 131.6, 131.5, 128.67, 128.65, 126.8, 126.4, 121.2, 108.5, 108.3, 101.1, 43.9, 35.2. **IR** (thin film) ν_{max} 3308, 2920, 1637, 1541, 1501, 1489, 1444, 1276, 1255, 1039, 914, 764. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}NO_3SNa$ 374.0827; Found 374.0825.



(Cis)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-2-phenylcyclopropane-1-carboxamide (**3p**). The reaction was performed according to general procedure B with 2.0 equiv piperonylamine for 24 h in DMF (0.5 M with regard to **2p**). Prior to column chromatography purification, the reaction was diluted with EtOAc (10 mL) and washed with brine (5 × 5 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated *in vacuo*. The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 43.0 mg (73%) as a colorless amorphous solid. Compound is racemic (single diastereomer). **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.29–7.20 (m, 5H + $CHCl_3$), 6.63 (d, *J* = 7.7 Hz, 1H), 6.40–6.38 (m, 2H), 5.91 (m, 2H), 5.69 (br. s, 1H), 4.23 (dd, *J* = 14.7, 6.5 Hz, 1H), 4.03 (dd, *J* = 14.7, 5.3 Hz, 1H), 2.45 (q, *J* = 8.8 Hz, 1H), 1.96–1.90 (m, 1H), 1.76–1.72 (m, 1H), 1.31–1.26 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 169.2, 147.7, 146.7, 136.8, 132.3, 128.9, 128.1, 126.7, 120.8, 108.3, 108.1, 101.0, 43.3, 24.6, 24.0, 10.0. **IR** (thin film) ν_{max} 3291, 2923, 1647, 1545, 1489, 1444, 1252, 1237, 1039, 928, 913, 749. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{18}H_{17}NO_3Na$ 318.1106; Found 318.1105.

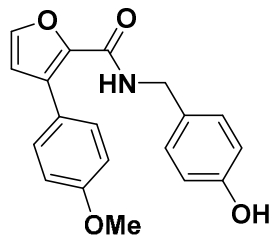


N-benzyl-3-(4-methoxyphenyl)furan-2-carboxamide (**4a**). The reaction was performed according to general procedure B with 1.5 equiv benzylamine for 10 h in toluene (0.5 M with regard to **2i**). The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 50.0 mg (81%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.70–7.65 (m, 2H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.36–7.27 (m, 5H), 6.95–6.92 (m, 2H), 6.63 (br. t, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 4.59 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 159.6, 158.8, 142.7, 141.1, 138.2, 131.0, 130.7, 128.7, 127.9, 127.5, 124.0, 114.4, 113.7, 55.3, 43.1. **IR** (thin film) ν_{max} 3321, 2925, 1655, 1612, 1516, 1249, 1179, 1030, 833. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{19}H_{17}NO_3Na$ 330.1106; Found 330.1102.

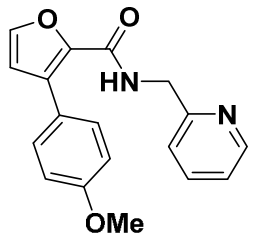


3-(4-Methoxyphenyl)-N-(4-(trifluoromethyl)benzyl)furan-2-carboxamide (**4b**). The reaction was performed according to general procedure B with 1.5 equiv 4-(trifluoromethyl)benzylamine for 15 h in toluene (0.5 M with regard to **2k**). The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 63.0 mg (84%) as a colorless amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.69–7.66 (m, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.46–7.41 (m, 3H), 6.95–6.92 (m, 2H), 6.74 (br. t, 1H), 6.62 (d, *J* = 1.8 Hz, 1H), 4.63 (d, *J* = 6.1 Hz, 2H), 3.83 (s, 3H). **^{19}F-NMR** (376 MHz, $CDCl_3$, 298 K) δ -62.5. **^{13}C-NMR** (100 MHz, $CDCl_3$,

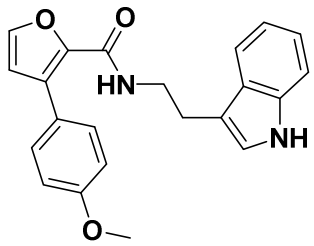
298 K) δ 159.7, 158.9, 142.9, 142.4 (q, J = 1.5 Hz), 140.8, 131.4, 130.7, 129.7 (q, J = 32.4 Hz), 128.0, 125.6 (q, J = 3.6 Hz), 124.1 (q, J = 272 Hz), 123.8, 114.5, 113.7, 55.3, 42.5. **IR** (thin film) ν_{max} 3320, 2921, 1654, 1618, 1517, 1327, 1251, 1179, 1162, 1125, 1067, 750. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{20}H_{16}F_3NO_3Na$ 398.0980; Found 398.0967.



N-(4-hydroxybenzyl)-3-(4-methoxyphenyl)furan-2-carboxamide (**4c**). The reaction was performed according to general procedure B with 1.5 equiv 4-hydroxybenzylamine for 9 h in DMF (0.5 M with regard to **2k**). Prior to column chromatography purification, the reaction was diluted with EtOAc (10 mL) and washed with brine (5 × 5 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated *in vacuo*. The product was isolated after column chromatography (gradient 0-70% EtOAc in pentane) in 49.0 mg (76%) as a pale yellow amorphous solid. **^{1}H-NMR** (400 MHz, d_6-DMSO, 298 K) δ 9.26 (br. s, 1H), 8.71 (t, J = 6.1 Hz, 1H), 7.82 (d, J = 1.8 Hz, 1H), 7.76–7.70 (m, 2H), 7.14–7.09 (m, 2H), 6.97–6.91 (m, 2H), 6.86 (d, J = 1.8 Hz, 1H), 6.72–6.67 (m, 2H), 4.29 (d, J = 6.3 Hz, 2H), 3.79 (s, 3H). **^{13}C-NMR** (100 MHz, d_6-DMSO, 298 K) δ 159.4, 158.9, 156.7, 144.0, 141.6, 131.0, 130.3, 129.7, 129.2, 124.4, 115.4, 114.3, 113.8, 55.6, 41.9. **IR** (thin film) ν_{max} 3353, 3124, 2968, 1627, 1614, 1512, 1295, 1243, 1179, 826, 788, 727. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{19}H_{17}NO_4Na$ 346.1055; Found 346.1043.

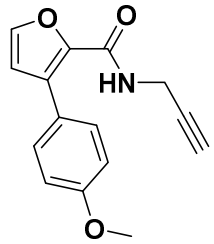


3-(4-Methoxyphenyl)-N-(pyridin-2-ylmethyl)furan-2-carboxamide (**4d**). The reaction was performed according to general procedure B with 1.5 equiv 2-picolylamine for 9 h in toluene (0.5 M with regard to **2k**). The product was isolated after column chromatography (gradient 0-100% EtOAc in pentane) in 52.0 mg (82%) as a yellow amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.55–8.52 (m, 1H), 7.70–7.63 (m, 3H), 7.50 (br. t, 1H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.30 (d, *J* = 7.9, 1H), 7.19 (dd, J = 7.6, 5.1 Hz, 1H), 6.95–6.92 (m, 2H), 6.60 (d, *J* = 1.8 Hz, 1H), 4.71 (d, J = 5.3 Hz, 2H), 3.83 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 159.6, 159.0, 156.6, 149.1, 142.9, 141.2, 136.8, 130.9, 130.7, 124.1, 122.4, 122.1, 114.3, 113.6, 55.3, 44.2. **IR** (thin film) ν_{max} 3350, 2934, 1643, 1590, 1517, 1478, 1253, 1177, 1036, 944, 830, 756. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{18}H_{16}N_2O_3Na$ 331.1059; Found 331.1055.

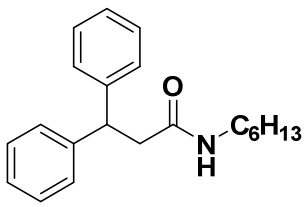


N-(2-(1H-indol-3-yl)ethyl)-3-(4-methoxyphenyl)furan-2-carboxamide (**4e**). The reaction was performed according to general procedure B with 1.5 equiv tryptamine for 14 h in DMF (0.5 M with regard to **2k**). Prior to column chromatography purification, the reaction was diluted with EtOAc (10 mL) and washed with brine (5 × 5 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated *in vacuo*. The product was isolated after column chromatography (gradient 0-60% EtOAc in pentane) in 58.0 mg (81%) as a brown foamy solid. **^{1}H-NMR** (400

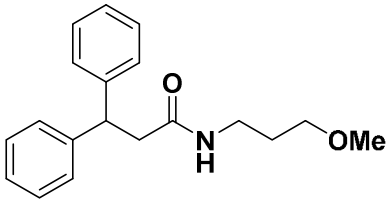
MHz, $CDCl_3$, 298 K) δ 8.21 (br. s, 1H), 7.64–7.59 (m, 3H), 7.37–7.34 (m, 2H), 7.23–7.19 (m, 1H), 7.14–7.10 (m, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 6.91–6.87 (m, 2H), 6.56 (d, *J* = 1.8 Hz, 1H), 6.46 (br. t, 1H), 3.81 (s, 3H), 3.75 (q, *J* = 3.75 Hz, 2H), 3.04 (dd, *J* = 7.2, 6.6 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 159.6, 159.1, 142.7, 141.3, 136.5, 130.7, 130.5, 127.3, 124.1, 122.13, 122.11, 119.4, 118.8, 114.3, 113.7, 112.9, 111.3, 55.3, 39.3, 25.5. **IR** (thin film) ν_{max} 3295, 2920, 1642, 1614, 1513, 1243, 1177, 1126, 832, 740. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{22}H_{20}N_2O_3Na$ 383.1372; Found 383.1365.



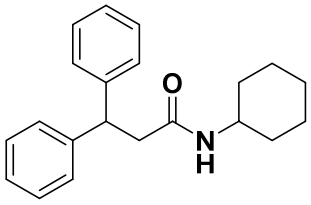
3-(4-Methoxyphenyl)-N-(prop-2-yn-1-yl)furan-2-carboxamide (**4f**). The reaction was performed according to general procedure B with 3.0 equiv propargylamine for 24 h in toluene (0.5 M with regard to **2k**). The product was isolated after column chromatography (gradient 0-70% EtOAc in pentane) in 44.0 mg (86%) as a pale yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.69–7.65 (m, 2H), 7.44 (d, *J* = 1.8 Hz, 1H), 6.96–6.92 (m, 2H), 6.61 (d, *J* = 1.8 Hz, 1H), 6.51 (br. t, 1H), 4.19 (dd, *J* = 5.4, 2.6 Hz, 2H), 3.83 (s, 3H), 2.25 (t, *J* = 2.6 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 159.7, 158.5, 143.0, 140.5, 131.5, 130.7, 123.8, 114.4, 113.7, 79.5, 71.6, 55.3, 28.8. **IR** (thin film) ν_{max} 3288, 2934, 1651, 1612, 1511, 1242, 1177, 1029, 890, 832, 777. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{15}H_{13}NO_3Na$ 278.0793; Found 278.0789.



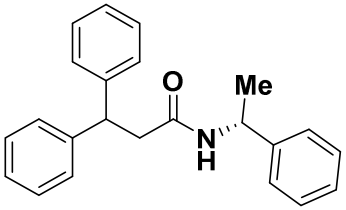
N-hexyl-3,3-diphenylpropanamide (**4g**). The reaction was performed according to general procedure B with 1.5 equiv hexylamine for 10 h in toluene (0.5 M with regard to **2e**). The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 44.5 mg (72%) as a yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.30–7.15 (m, 10H + $CHCl_3$), 5.21 (br. t, 1H), 4.56 (t, *J* = 7.9 Hz, 1H), 3.08 (q, *J* = 7.1 Hz, 2H), 2.87 (d, *J* = 7.9 Hz, 2H), 1.26–1.02 (m, 8H), 0.86 (t, *J* = 7.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 170.9, 143.7, 128.6, 127.8, 126.5, 47.6, 43.6, 39.4, 31.4, 29.4, 26.4, 22.5, 14.0. **IR** (thin film) ν_{max} 3290, 2927, 1637, 1552, 1450, 744. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{27}NONa$ 332.1990; Found 332.1983.



N-(3-methoxypropyl)-3,3-diphenylpropanamide (**4h**). The reaction was performed according to general procedure B with 1.5 equiv 3-methoxypropylamine for 9 h in toluene (0.5 M with regard to **2e**). The product was isolated after column chromatography (gradient 0-100% EtOAc in pentane) in 43.0 mg (73%) as a pale yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.30–7.16 (m, 10H + $CHCl_3$), 5.77 (br. t, 1H), 4.56 (t, *J* = 7.9 Hz, 1H), 3.25 (s, 3H), 3.24–3.18 (m, 4H), 2.87 (d, *J* = 7.9 Hz, 2H), 1.57–1.51 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 170.9, 143.8, 128.6, 127.8, 126.5, 71.3, 58.7, 47.5, 43.5, 37.7, 28.9. **IR** (thin film) ν_{max} 3292, 2924, 1639, 1552, 1449, 1116, 748. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{19}H_{23}NO_2Na$ 320.1626; Found 330.1615.

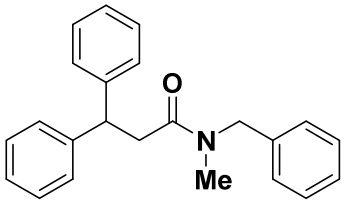


N-cyclohexyl-3,3-diphenylpropanamide (**4i**). The reaction was performed according to general procedure B with 3.0 equiv cyclohexylamine for 24 h in toluene (0.5 M with regard to **2e**). The product was isolated after column chromatography (gradient 0-35% EtOAc in pentane) in 39.0 mg (64%) as a pale yellow amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.31–7.16 (m, 10H + $CHCl_3$), 5.03 (br. d, 1H), 4.53 (d, J = 7.9 Hz, 1H), 3.66–3.59 (m, 1H), 2.85 (d, J = 7.9 Hz, 2H), 1.67–1.60 (m, 2H + H_2O), 1.58–1.48 (m, 3H), 1.32–1.20 (m, 2H), 1.11–1.00 (m, 1H), 0.89–0.78 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 170.1, 143.7, 128.6, 127.8, 126.5, 47.8, 47.7, 43.8, 32.8, 25.4, 24.6. **IR** (thin film) ν_{max} 3300, 2929, 1638, 1540, 1492, 1253, 744. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{25}NONa$ 330.1834; Found 330.1822.

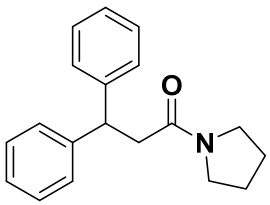


(R)-3,3-diphenyl-N-(1-phenylethyl)propanamide (**4j**). The reaction was performed according to general procedure B with 5.0 equiv (*R*)-1-phenylethylamine for 24 h in toluene (0.5 M with regard to **2e**). The product was isolated after column chromatography (gradient 0-40% EtOAc in pentane) in 34.0 mg (52%) as a yellow amorphous solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.32–7.16 (m, 13H + $CHCl_3$), 7.01–6.96 (m, 2H), 5.48 (br. d, 1H), 5.03–4.96 (m, 1H), 4.56 (t, J = 8.0 Hz, 1H), 2.90 (d, J = 8.0 Hz, 2H), 1.26 (d, J = 6.9 Hz, 3H). **^{13}C-NMR** (100 MHz, CD_3CN, 298 K) δ 169.7, 144.54, 144.51, 144.3, 128.51, 128.48, 128.3, 127.8, 127.6, 126.6, 126.4, 126.3, 125.7, 48.4, 47.5, 41.7, 21.7. **IR** (thin film) ν_{max} 3261, 2925, 1635, 1554, 1447, 1276, 748.

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{23}NONa$ 352.1677; Found 352.1677. $[\alpha]^{23}_D$ = +49.0 (c = 0.1, $CHCl_3$).

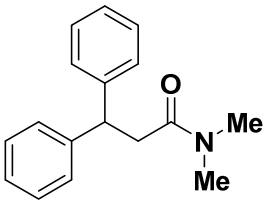


N-benzyl-N-methyl-3,3-diphenylpropanamide (**4k**). The reaction was performed according to general procedure B with 5.0 equiv *N*-benzylmethylamine for 30 h in toluene (0.5 M with regard to **2e**). The product was isolated after column chromatography (gradient 50-100% CH_2Cl_2 in Pentane) in 21.5 mg (32%) as a colorless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.32–7.17 (m, 13H + $CHCl_3$, both rotamers), 7.02–6.96 (m, 2H, both rotamers), 4.79–4.75 (m, 1H, both rotamers), 4.53 (s, 1.22H, major rotamer), 4.42 (s, 0.78H, minor rotamer), 3.13 (d, *J* = 7.6 Hz, 1.22H, major rotamer), 3.10 (d, *J* = 7.6 Hz, 0.78H, minor rotamer), 2.88 (s, 1.17H, minor rotamer), 2.83 (s, 1.83H, major rotamer). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K, both rotamers) δ 171.4, 171.2, 144.2, 144.1, 137.2, 136.6, 128.9, 128.50, 128.47, 127.92, 127.90, 127.85, 127.6, 127.2, 126.4, 126.33, 126.26, 53.1, 50.9, 47.3, 47.1, 39.2, 39.1, 34.9, 34.1. **IR** (thin film) ν_{max} 2852, 1641, 1493, 1450, 1402, 1265, 1154, 1118, 1079, 732. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{23}H_{23}NONa$ 352.1677; Found 352.1668.

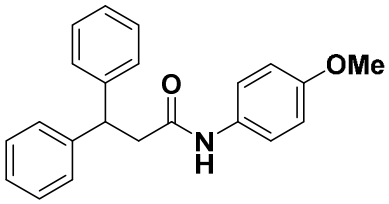


3,3-Diphenyl-1-(pyrrolidin-1-yl)propan-1-one (**4l**). The reaction was performed according to general procedure B with 1.5 equiv pyrrolidine for 8 h in toluene (0.5 M with regard to **2e**). The product was isolated after column chromatography (gradient 0-100% EtOAc in pentane) in 30.0

mg (64%) as a yellow amorphous solid.**^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.29–7.23 (m, 8H + $CHCl_3$), 7.20–7.15 (m, 2H), 4.71 (t, *J* = 7.5 Hz, 1H), 3.37 (t, *J* = 6.7 Hz, 2H), 3.20 (t, *J* = 6.7 Hz, 2H), 4.71 (d, *J* = 7.5 Hz, 2H), 1.81–1.69 (m, 4H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 169.7, 144.3, 128.4, 127.9, 126.3, 47.0, 46.6, 45.6, 41.0, 26.0, 24.3. **IR** (thin film) ν_{max} 2868, 1628, 1446, 1275, 1259, 913, 748. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{19}H_{21}NONa$ 302.1521; Found 302.1515.



N,N-dimethyl-3,3-diphenylpropanamide (**4m**). To a sealed vial containing carbamate **2e** (181.0 mg, 0.40 mmol, 1 equiv) was added 2 M dimethylamine solution in THF (2 mL, 4.0 mmol, 10 equiv) and the reaction was stirred for 7 h at 60 °C. The reaction mixture was then allowed to reach room temperature and was concentrated *in vacuo*. The obtained crude material was purified by column chromatography (SiO_2, 0-50% gradient of EtOAc in pentane) to afford the pure amide **4m** as a white amorphous solid (34.0 mg, 34%). The characterization data of **4m** was in accordance with those preliminary reported in the literature.[21]



N-(4-methoxyphenyl)-3,3-diphenylpropanamide (**4n**). To a sealed vial containing carbamate **2e** (90.5 mg, 0.20 mmol, 1 equiv) and *p*-anisidine (123.2 mg, 1.00 mmol, 5 equiv) was added toluene (0.2 mL, 1 M concentration with respect to **2e**) and the reaction was stirred at 80 °C for 48 h. The reaction was then allowed to reach room temperature and was diluted with EtOAc (15

mL). The EtOAc layer was transferred to a separation funnel and washed with 1 M aq. HCl (3 × 10 mL) to remove the excess *p*-anisidine. The organic layer was then washed once more with brine (10 mL), before being separated, dried over Na_2SO_4 and concentrated *in vacuo*. The obtained crude material was purified by column chromatography (SiO_2, 0-40% gradient of EtOAc in pentane) to afford the pure amide **4n** as a pale brown solid (34.5 mg, 52%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.32–7.26 (m, 8H), 7.23–7.18 (m, 2H), 7.15–7.11 (m, 2H), 6.83 (br. s, 1H), 6.79–6.76 (m, 2H), 4.63 (t, *J* = 7.7 Hz, 1H), 3.75 (s, 3H), 3.05 (d, *J* = 7.7 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 169.2, 156.5, 143.6, 130.5, 128.7, 127.8, 126.7, 122.1, 114.0, 55.5, 47.6, 44.3. **IR** (thin film) ν_{max} 3245, 3074, 2930, 1653, 1551, 1510, 1244, 1169, 1029, 830, 746. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{22}H_{21}NO_2Na$ 354.1470; Found 354.1464.

Procedure for the one-pot transamidation sequence depicted in Scheme 4

To a pear-shaped flask were added amide **1d** (80.1 mg, 0.25 mmol, 1 equiv) and DMAP (3.1 mg, 0.025 mmol, 0.1 equiv). Then, Boc_2O (81.8 mg, 0.375 mmol, 1.5 equiv) in dry MeCN (1.5 mL) was added and the reaction mixture was allowed to stir at 60 °C for 1 h. The reaction was then concentrated *in vacuo* by the use of a rotary evaporator and further dried by the use of a vacuum pump for 30 min. To the obtained crude was then added piperonylamine (75.5 mg, 0.50 mmol, 2 equiv) in toluene (1 mL), and the resulting solution was stirred at 60 °C for 7 h. The reaction mixture was allowed to reach room temperature and was then concentrated *in vacuo*. Purification by column chromatography (SiO_2, gradient of EtOAc in pentane, 0-50%) furnished amide product **3d** as a yellow amorphous solid (42 mg, 53% overall yield).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Methods for starting material preparation, initial aminolysis optimization reactions, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Addition of Ni-catalysts such as those described by the group of Garg in references 12d and 12e did not have any beneficial effect on the aminolysis reaction.

(17) For a list of to access the 8-AQ amide substrates **1a-p** shown in Scheme 1, please see Table S1 in the SI.

(18) The extent of this Boc-deprotection process during each reaction in Scheme 1-3 is summarized in Table S3 in the SI.

(19) The aminolysis step was cleaner when the transamidation was performed in a step-wise manner using purified carbamate **2d**. The overall yield for the corresponding two-step sequence was 65% which is slightly higher than that of the one-pot protocol.

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