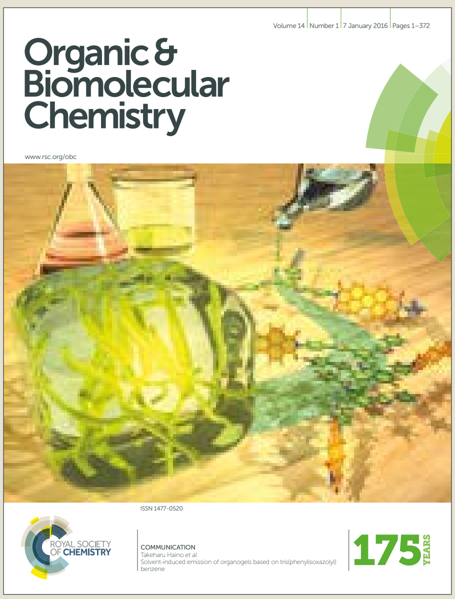
View Article Online
View Journal

Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Serafini, A. Griglio, S. Viarengo, S. Aprile and T. Pirali, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB01715D.



View Article Online
DOI: 10.1039/C7OB01715D

Journal Name

ARTICLE

An Aryne-Based Three-Component Access to α-Aroylamino Amides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Marta Serafini,[a] Alessia Griglio,[a] Sara Viarengo,[a] Silvio Aprile[a] and Tracey Pirali*[a]

Aryne chemistry has recently received widespread attention and isocyanides have been reported as efficient nucleophilic partners in a set of multicomponent transformations. In this study, we demonstrate that tertiary α-monosubstituted α-isocyanocetamides are efficaciously coupled with water and benzyne to offer the direct and metal-free access to densely functionalized α-benzoylamino amides, without competing with the intramolecular cyclization to 5-aminooxazoles. Despite the formation of the aryl anion as a key intermediate, the reaction displays a stereoconservative course, allowing for the preparation of enantiomerically pure α-benzoylamino amides. Finally, the synthetic utility of the reported MCR was exemplified by the preparation of proglumide, a cholecystokinin antagonist.

Introduction

Twenty years ago, the chemistry of arynes began to flourish encouraged by the discovery of the Kobayashi method,[1] a useful strategy to afford arynes *in situ* from stable and commercially available precursors. From that moment on, a plethora of reactions involving arynes have been discovered.[2] Among them, an important role is entrusted to isocyanide-mediated multicomponent reactions (MCRs)[3] where, for the most part, the first step is represented by nucleophilic attack of isocyanide to the highly electrophilic aryne. After formation of the zwitterionic moiety, the reaction can evolve with interception of the aryl anion by an electrophile[4] or with trapping of the nitrilium ion by a nucleophile. The latter event is the less represented in literature and a few nucleophiles have been reported. The nitrilium ion might be attacked by alkynyl bromides, polyfluoroaryl bromide,[5] terminal alkynes[6] or water,[7] leading to densely functionalized compounds.

Thanks to our recent discoveries that secondary α,α'-disubstituted α-isocyanoacetamides react with arynes *via* cascade reaction to afford 2-arylimidazolones[8] and with the aim to expand our knowledge over the reactivity of functionalized isocyanides,[9] the use of this bifunctional substrate in a MCR involving arynes and water was investigated. Indeed, we speculated that a α-isocyanoacetamide-triggered MCR could result in a new route to access highly functionalized α-aroylamino amides.

Results and discussion

Inspired by the synthesis of 2-arylimidazolones,[8] we initially performed the reaction employing secondary α,α'-disubstituted α-isocyanoacetamides **2**, but the main isolated product was the 2-arylimidazolone **3**, even in the presence of an excess of water.

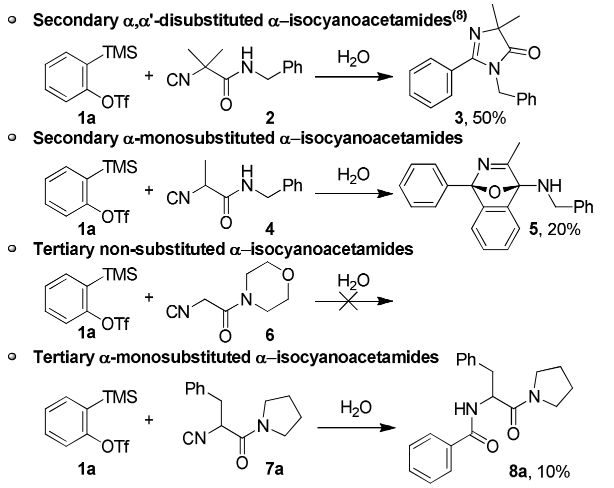
Next, we investigated the same reactivity involving different α-isocyanoacetamides, but neither secondary α-monosubstituted **4** nor tertiary non-substituted α-isocyanoacetamides **6** gave the expected product. While in case of **6** only unreacted isocyanoacetamide was recovered, secondary α-monosubstituted α-isocyanoacetamides **4** reacted with benzyne in an intramolecular *O*-cyclization to afford the corresponding 5-aminooxazole. The product immediately underwent a [4+2] cycloaddition, leading to the benzyne-oxazole cycloadduct **5**.[10] Delightfully, when we employed the tertiary α-monosubstituted α-isocyanoacetamide **7a**, no intramolecular cyclization occurred and the α-aroylamino amide **8a** was isolated, even if in low yield (Scheme 1).

An alternative to the use of coupling reagents for amide bond formation would represent an advantageous improvement in organic synthesis. Indeed, many efforts have been made to avoid the use of coupling procedures and improve the atom economy associated with the reaction, but most of the reported methods require the use of catalysts, activators or harsh reaction conditions, displaying occasional epimerization problems.[11]

a. Dipartimento di Scienze del Farmaco, Università degli Studi del Piemonte Orientale "A. Avogadro", Largo Donegani 2, 28100 Novara, Italy
†Electronic Supplementary Information (ESI) available: Deuterium-labelling studies,
HPLC chromatograms for enantioenriched compounds and spectra for all new compounds. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C7OB01715D

Scheme 1. Reaction with Different α-Isocyanoacetamides, Benzyne and Water[a]

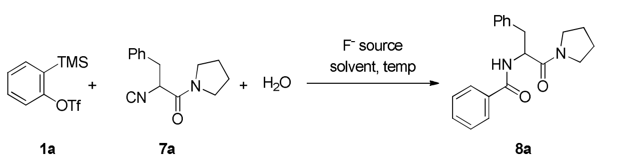


[a]Reaction conditions: **1a** (0.75 mmol, 1.5 equiv), α-isocyanoacetamide (0.50 mmol, 1 equiv), H_2O (1 mmol, 2 equiv), KF (1.50 mmol, 3 equiv), 18-crown-6 (1.50 mmol, 3 equiv), THF (2.5 mL), rt. Yields based on isolated product after gravimetric chromatography are given.

Encouraged by the challenge of a transition-metal-free α-aroylamino amide synthesis, other experimental conditions were investigated, as summarized in Table 1, to find out fluoride source, solvent and temperature affording the highest yield of **8a**.

During optimization phase, it was clear that the yield was lower when the reaction was conducted in the presence of cesium fluoride (entry 1-2), TBAF or TBAT and when the temperature was maintained below 60 °C (entry 3-8).

Table 1. Optimization of the Reaction Conditions[a]



entry	fluoride source	solvent	temp (°C)	yield[b] (%)
1	CsF	MeCN	rt	10
2	CsF	MeCN: toluene 1:3	82	22
3	TBAF	THF	40	17
4	TBAT	THF	40	23
5	TBAT	THF	60	28
6	KF, 18-crown-6	THF	rt	10
7	KF, 18-crown-6	THF	30	30
8	KF, 18-crown-6	THF	40	62
9	**KF, 18-crown-6**	**THF**	**60**	**70**

[a]Reaction conditions: **1a** (0.75 mmol, 1.5 equiv), **7a** (0.50 mmol, 1 equiv), H_2O (1 mmol, 2 equiv), fluoride source (3 equiv), 18-crown-6 (1.50 mmol, 3 equiv), and solvent (2.5 mL) for 3 h. [b]Yields based on isolated product after gravimetric chromatography are given.

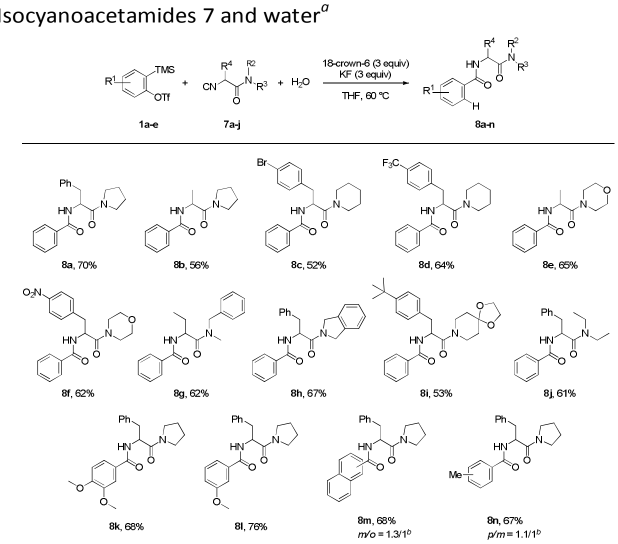
The best choice for the reaction was represented by KF and 18-crown-6 as fluoride source in THF at 60 °C (entry 9).

With optimized conditions in hand, the scope of the MCR was investigated with respect to the isocyanide and aryne substrates. Diverse α-isocyanoacetamides **7** were well tolerated, leading to α-aroylamino amides **8a-j** in good yields. As shown in Scheme 2, various cyclic amines as pyrrolidine (**8a, 8b**), piperidine (**8c, 8d**), morpholine (**8e, 8f**), isoindoline (**8h**) and 4-piperidone-ethylene ketal (**8i**) are well tolerated on the amide moiety. The cyclic amine may be also replaced by a linear one, leading to the desired product in good yields (**8g, 8j**). Furthermore, the *alpha*-substituent might be an alkyl moiety (**8b, 8e, 8g**) or a benzyl group (**8a, 8h, 8j**). In this case, different substituents are possible on the aromatic ring and α-isocyanoacetamides with halogen, CF_3, NO_2 and *tert*-butyl groups react efficiently with benzyne, affording the corresponding products **8c, 8d, 8f, 8i**.

Next, various substituted 2-(trimethylsilyl)aryl triflates **1** were exploited (Scheme 2). When symmetrical aryne was employed, the reaction afforded the expected product **8k** in good yield. If the reaction took place with 3-methoxyaryne, despite the possible formation of two different regioisomers, both the electron-withdrawing and steric effects of the methoxy group led to one product, **8l**.

Conversely, when 1-(trimethylsilyl)-2-naphthyl triflate was used, an inseparable mixture of two regioisomers (**8m**) was formed in 68% yield in a 1.3:1 ratio of *meta*/*ortho*, due to the slightly more accessible 2-position for the nucleophilic attack. Finally, the reaction among water, α-isocyanoacetamides **7** and 4-methyl aryne furnished a regioisomeric mixture of **8n** in a 1.1:1 ratio of *para/meta*, caused by irrelevant steric and electronic effects, in 67% yield.

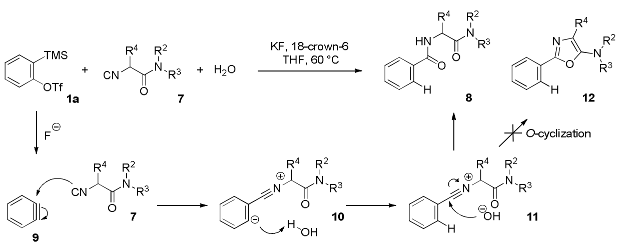
Scheme 2. Substrate Scope of the MCR Involving Aryne 1 α-Isocyanoacetamides 7 and water[a]



[a]Reaction conditions: **1** (0.75 mmol, 1.5 equiv), **7** (0.50 mmol, 1 equiv), H_2O (1 mmol, 2 equiv), KF (1.50 mmol, 3 equiv), 18-crown-6 (1.50 mmol, 3 equiv), THF (2.5 mL), 60 °C, 3 h. Yields based on isolated product after gravimetric chromatography are given. [b]Regioisomeric ratio determined by ^1H NMR analysis.

View Article Online
DOI: 10.1039/C7OB01715D

Scheme 3. Plausible Reaction Mechanism for the Formation of α-Aroylamino Amides 8



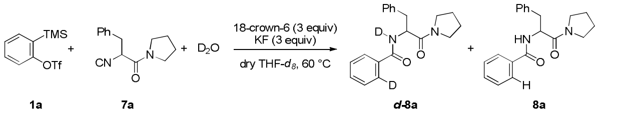
A plausible mechanism of the MCR can be delineated as follows (Scheme 3).

The aryne **9**, formed *in situ* from the precursor **1a**, undergoes a nucleophilic addition of α-isocyanoacetamide **7**, affording the zwitterionic intermediate **10**. The resulting aryl anionic moiety traps the water hydrogen, leading to intermediate **11**. Finally, the nitrilium ion is attacked by hydroxyl ion to give α-aroylamino amide **8**. To our delight, the intermolecular addition to the electrophilic carbon was favored compared to the intramolecular *O*-cyclization. Indeed, no concurrent formation of the 5-amino oxazole **12** (or the corresponding benzyne-oxazole cycloadduct) is observed, even though the nucleophilic attack of the amide oxygen to the nitrilium ion has been exhaustively described in the literature.[9,12] Moreover, we have never detected the formation of phenols as side products, confirming that arynes are not trapped by water under traditional aryne formation conditions.[13]

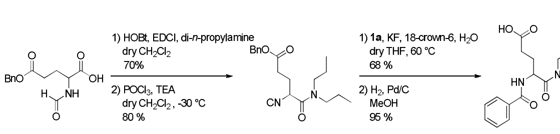
To probe the mechanism explained above, a deuterium-labeling experiment (Scheme 4) was conducted with D_2O as the third component. The structure of ***d*-8a**, confirmed through careful NMR spectroscopy and LC-ESI-MS analysis, demonstrated the trapping of water deuterium by the aryl anionic moiety and its subsequent incorporation at the *ortho* position of the product.

Notably, α-aroylamino amides are substructures relevant to medicinal chemistry and to exemplify the synthetic utility of the reported MCR we carried out the synthesis of proglumide **8o** (Scheme 5), a cholecystokinin antagonist used as a racemate in the treatment of stomach ulcers.[14] *N*-formyl-5-benzyl ester glutamic acid undergoes EDCI-mediated coupling with di-*n*-propylamine. Subsequent dehydration affords the α-isocyanoacetamide **7k**, which triggers the MCR, followed by hydrogenation of the benzyl ester to give the final α-aroylamino amide **8o**.

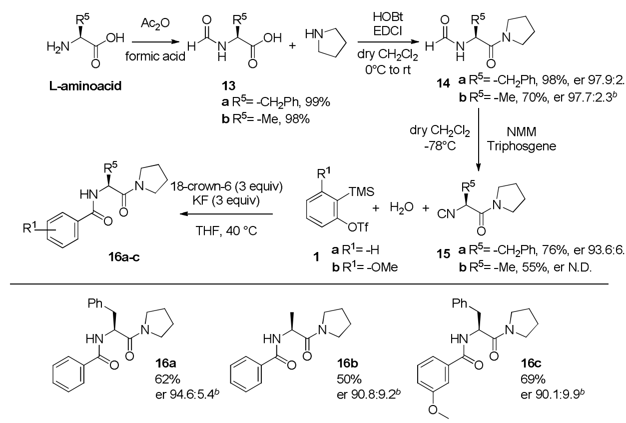
Scheme 4. Deuterium-Labeling Experiment Using D_2O as the Third Component



Scheme 5. Synthesis of Proglumide 8o



Scheme 6. Synthesis of Enantioenriched α-Aroylamino Amides[a]



[a]Reaction conditions for the MCR: **1** (0.75 mmol, 1.5 equiv), **15** (0.50 mmol, 1 equiv), H_2O (1 mmol, 2 equiv), KF (1.50 mmol, 3 equiv), 18-crown-6 (1.50 mmol, 3 equiv), THF (2.5 mL), 40 °C, 4 h. Yields based on isolated product after gravimetric chromatography are given. [b]Enantiomeric ratio determined by HPLC analysis. N.D. not determined.

Compared to the procedure reported in the previous literature where the reaction of di-*n*-propylamine with *N*-benzoyl-DL-glutamic acid anhydride leads to a mixture of two different isomers,[15] our approach represents a convenient way to afford proglumide in four high yielding steps.

To expand the synthetic possibilities of our reaction, we investigated its stereoconservative course when performed among arynes, water and enantioenriched α-isocyanoacetamides. The required α-isocyanoacetamides were synthesized from the corresponding L-aminoacids according to a protocol known in literature (Scheme 6).[16] After formylation, EDCI-mediated coupling reaction and dehydration with triphosgene and *N*-methylmorpholine, products **15a-b** were afforded in high yields. A slight epimerization occurred during the preparation of the precursors, as demonstrated by the enantiomeric ratios displayed by intermediates **14** and **15**. With these compounds in our hands, three α-aroylamino amides **16a-c** were synthesized. The corresponding enantiomeric ratios were higher than 90:10 and consistent with the ones observed for the synthesized precursors, demonstrating that the aryl anion preferentially traps the water hydrogen, without affecting the isocyanoacetamide *alpha*-hydrogen.

Temperature plays a crucial role in the preservation of stereochemistry: when the reaction was performed at 60 °C the er of **16a** was 78.5:21.5. The observed epimerization induced us to perform the reaction at 40 °C, despite in this case the yield is slightly lower (62% *versus* 70%).

Conclusions

In conclusion, we have demonstrated that tertiary α-monosubstituted α-isocyanoacetamides efficaciously react

View Article Online
DOI: 10.1039/C7OB01715D

with water and arynes to afford diverse and highly functionalized α-aroylamino amides in a straightforward and rapid manner. α-Monosubstituted α-isocyanoacetamides are configurationally stable during reaction with water and arynes, despite the formation of the basic aryl anion moiety as a key intermediate. Further studies on related functionalized isocyanides and arynes are ongoing in our laboratory.

Experimental Section

General Experimental Methods. Commercially available reagents and solvents were used without further purification. Potassium fluoride was dried by heating at 100 °C for 12 hours *in vacuo*. 18-Crown-6 was purified by crystallization from distilled acetonitrile. Melting points were determined in open glass capillary. All the target compounds were checked by IR (FT-IR Thermo-Nicolet Avatar), ^{1}H and ^{13}C APT (Jeol ECP 300 MHz), and mass spectrometry (Thermo Finningan LCQ-deca XP-plus) equipped with an ESI source and an ion trap detector. Chemical shifts are reported in parts per million (ppm). Column chromatography was performed on silica gel Merck Kieselgel 70-230 mesh ASTM. Thin layer chromatography (TLC) was carried out on 5 cm × 20 cm plates with a layer thickness of 0.25 mm (Merck silica gel 60 F254). When necessary, TLC plates were visualized with aqueous $KMnO_4$.

Procedure for the synthesis of *N*-benzyl-3-methyl-1-phenyl-1,4-dihydro-1,4-epoxyisoquinolin-4-amine 5. To a flame-dried screw-capped containing a solution of anhydrous KF (3 equiv, 1.5 mmol) and 18-crown-6 (3 equiv, 1.5 mmol) in dry THF (2.5 mL) α-isocyanoacetamide **4** (1 equiv, 0.50 mmol), aryne precursor **1a** (1.5 equiv, 0.75 mmol) and water (2 equiv, 1 mmol) are added under nitrogen atmosphere. After stirring for 8 hours at room temperature, the reaction is filtered over a pad of celite, washed with CH_3CN at 0 °C and the solvent is evaporated. The resulting crude material is purified by gravimetric column using PE/EtOAc 95/5 as eluent to afford compound **5** as a yellow oil (34 mg, 20%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.4 Hz, 2H), 7.56-7.52 (m, 3H), 7.46-7.44 (m, 2H), 7.41-7.32 m, 4H), 7.24-7.23 (m, 1H), 6.98-6.95 (m, 2H), 4.76 (d, *J* = 6.6 Hz, 2H), 1.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.9, 162.2, 139.9, 136.5 (2C), 131.1, 129.9 (2C), 128.9, 128.8, 128.6, 128.3, 127.8, 127.7, 126.9, 125.9, 114.6, 45.1, 26.6; *m/z* (ESI): 341 $[M+H]^+$; ν_{max}/cm^{-1} 3062, 3030, 2925, 1730, 1496, 1447, 1390, 1360, 1074, 756, 697; HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_2O$ $[M+H]^+$: 341.1654, found: 341.1643.

General procedure 1 for the synthesis of α-aroylamino amides 8a-n. To a flame-dried screw-capped containing a solution of anhydrous KF (3 equiv, 1.50 mmol) and 18-crown-6 (3 equiv, 1.50 mmol) in dry THF (2.5 mL), α-isocyanoacetamide **7** (1 equiv, 0.50 mmol) and aryne precursor **1** (1.5 equiv, 0.75 mmol) are added under nitrogen atmosphere and the reaction is heated to 60 °C. After 10 minutes H_2O (2 equiv, 1 mmol) is added and the mixture is stirred for additional 1 h and 30 minutes. In case that the reaction isn't finished after this period, KF (1 equiv, 0.50 mmol), 18-crown-6 (1 equiv, 0.50 mmol), aryne precursor **1** (1 equiv, 0.50 mmol) and H_2O (1 equiv, 0.50 mmol) are added and the mixture is stirred for additional 1 h and 30 minutes at 60 °C. The reaction is then filtered over a pad of celite, washed with CH_3CN at 0 °C and the filtrate is evaporated. The resulting crude material is purified by gravimetric column on silica gel.

N-(1-Oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide (**8a**). The crude material was purified by column chromatography using PE/EtOAc 6/4 as eluent to give a yellow solid (113 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.48-7.38 (m, 3H), 7.26-7.22 (m, 5H), 5.10 (td, *J* = 8.4, 5.4 Hz, 1H), 3.43-3.33 (m, 3H), 3.15 (dd, *J* = 12.9, 5.4 Hz, 1H) 3.09 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.66-2.58 (m, 1H), 1.77-1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 166.8, 136.5, 134.1, 131.7, 129.6, 128.5 (2C), 127.3, 127.1, 53.0, 46.5, 45.9, 39.7, 25.9, 24.1; *m/z* (ESI): 323 $[M+H]^+$; ν_{max}/cm^{-1} 3241, 3025, 2870, 1654, 1619, 1540, 1310, 1039, 756, 690; mp 187-188 °C; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$: 323.1760, found: 323.1754.

N-(1-Oxo-1-(pyrrolidin-1-yl)propan-2-yl)benzamide (**8b**). The crude material was purified by column chromatography using PE/EtOAc 6/4 as eluent to give a white solid (69 mg, 56%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J* = 6.9 Hz, 2H), 7.48-7.36 (m, 3H), 7.29 (br d, *J* = 6.9 Hz, 1 H), 4.91 (quint, *J* = 6.9 Hz, 1H), 3.70-3.62 (m, 1H), 3.56-3.42 (m, 3H), 2.04-1.95 (m, 2H), 1.94-1.85 (m, 2H), 1.44 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 166.5, 134.2, 131.5, 128.5, 127.2, 47.4, 46.5, 46.1, 26.1, 24.2, 18.4; *m/z* (ESI): 247 $[M+H]^+$; ν_{max}/cm^{-1} 3273, 2924, 2875, 1653, 1538, 1455, 1305, 1046, 776, 726; mp 126-127 °C; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$: 247.1447, found: 247.1441.

N-(3-(4-Bromophenyl)-1-oxo-1-(piperidin-1-yl)propan-2-yl)benzamide (**8c**). The crude material was purified by column chromatography using PE/EtOAc 7/3 as eluent to give a yellow solid (108 mg, 52%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.0 Hz, 2H), 7.52-7.37 (m, 5H), 7.18 (br d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 2H), 5.34 (td, *J* = 7.8, 4.3 Hz, 1H), 3.58 (dd, *J* = 13.1, 4.3 Hz, 1H), 3.47 (dd, *J* = 13.1, 4.3 Hz, 1H), 3.40-3.32 (m, 1H), 3.19-2.99 (m, 3H), 1.63-1.42 (m, 5H), 1.26-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 166.6, 135.4, 134.0, 131.7, 131.6, 131.4, 128.6, 127.2, 121.0, 50.0, 46.8, 43.3, 38.8, 26.2, 25.5, 24.3; *m/z* (ESI): 416 $[M+H]^+$; ν_{max}/cm^{-1} 3295, 2993, 2856, 1661, 1616, 1533, 1245, 1011, 854, 812, 718; mp 197-198 °C; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}BrN_2NaO_2$ $[M+Na]^+$: 437.0841, found: 437.0835.

N-(1-Oxo-1-(piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-2-yl)benzamide (**8d**). The crude material was purified by column chromatography using PE/EtOAc 7/3 as eluent to give a yellow solid (129 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.55-7.51 (m, 3H), 7.48-7.40 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.18 (br d, *J* = 7.4 Hz, 1H), 5.39 (q, *J* = 7.4 Hz, 1H), 3.54-3.51 (m, 2H), 3.39-3.32 (m, 1H), 3.27-3.10 (m, 3H), 1.57-1.45 (m, 5H), 1.16-1.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 166.7, 140.6, 133.9, 131.8, 130.1, 129.4 (*J* = 32 Hz), 128.6, 127.2, 125.4, 124.2 (*J* = 270 Hz), 49.9, 46.9, 43.4, 39.2, 26.1, 25.5, 24.3; *m/z* (ESI): 403 $[M-H]^-$; ν_{max}/cm^{-1} 3294, 2946, 2860, 1534, 1448, 1160, 884, 833, 617; mp 189-190 °C; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}F_3N_2O_2$ $[M+H]^+$: 405.1790, found: 405.1784.

View Article Online
DOI: 10.1039/C7OB01715D

N-(1-Morpholino-1-oxopropan-2-yl)benzamide (**8e**). The crude material was purified by column chromatography using PE/EtOAc 4/6 as eluent to give a white solid (85 mg, 65%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.2 Hz, 2H), 7.48-7.39 (m, 3H), 7.34 (br d, *J* = 6.9 Hz, 1H), 5.06 (quint, *J* = 6.9 Hz, 1H), 3.71-3.66 (m, 6H), 3.59-3.53 (m, 2H), 1.42 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 166.4, 134.1, 131.7, 128.6, 127.1, 66.8, 66.6, 46.0, 45.5, 42.6, 19.1; *m/z* (ESI): 263 $[M+H]^+$; ν_{max}/cm^{-1} 3306, 2902, 2863, 1641, 1534, 1461, 1379, 1109, 965, 844, 718; mp 93.5-94.5 °C; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1396, found: 263.1390.

N-(1-Morpholino-3-(4-nitrophenyl)-1-oxopropan-2-yl)benzamide (**8f**). The crude material was purified by column chromatography using PE/EtOAc 5/5 as eluent to give a yellow solid (119 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$, *: referred to the main rotamer): δ 8.15 (d, *J* = 8.7 Hz, 2H)*, 7.75 (d, *J* = 7.6 Hz, 2H), 7.68-7.64 (m, 2H), 7.46-7.36 (m, 3H), 7.11 (br d, *J* = 7.7 Hz, 1H), 5.39 (td, *J* = 7.7, 5.6 Hz, 1H), 3.74-3.70 (m, 4H), 3.65-3.60 (m, 1H), 3.56-3.49 (m, 2H), 3.40-3.32 (m, 1H), 3.30-3.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, *: referred to the main rotamer): δ 169.3, 166.8*, 147.2*, 144.0*, 140.4*, 133.5, 130.5*, 128.7*, 127.1*, 123.7*, 66.9*, 66.5*, 49.7, 46.3, 42.6, 38.9; *m/z* (ESI): 382 $[M-H]^-$; ν_{max}/cm^{-1} 3294, 2976, 1518, 1625, 1438, 1346, 1114, 857, 791; mp 171-172 °C; HRMS (ESI) *m/z* calcd for $C_{20}H_{20}N_3O_5$ $[M-H]^-$: 382.1403, found: 382.1397.

N-(1-(Benzyl(methyl)amino)-1-oxobutan-2-yl)benzamide (**8g**). The crude material was purified by column chromatography using PE/EtOAc 7/3 as eluent to give a yellow oil (96 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$, *: referred to the main rotamer): δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.50-7.41 (m, 3H), 7.33-7.29 (m, 2H)*, 7.24-7.21 (m, 3H)*, 5.16 (dd, *J* = 12.6, 7.5 Hz, 1H)*, 4.77 (d, *J* = 14.7 Hz, 1H), 4.68 (br d, *J* = 2.6 Hz, 1H), 4.47 (d, *J* = 14.7 Hz, 1H), 3.05 (s, 3H)*, 1.82-1.67 (m, 2H)*, 1.00 (t, *J* = 7.5 Hz, 3H)*; ^{13}C NMR (75 MHz, $CDCl_3$,*: referred to the main rotamer): δ 172.2*, 167.0*, 136.7*, 134.2*, 131.7, 128.8*, 128.6*, 128.0*,127.2* (2C), 51.4*, 50.7, 34.9*, 26.0*, 9.7*; *m/z* (ESI): 311 $[M+H]^+$; ν_{max}/cm^{-1} 3306, 2969, 2930, 1628, 1578, 1529, 1452, 1354, 802, 695; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}N_2O_2$ $[M+H]^+$: 311.1760, found: 311.1754.

N-(1-(Isoindolin-2-yl)-1-oxo-3-phenylpropan-2-yl)benzamide (**8h**). The crude material was purified by column chromatography using PE/EtOAc 7/3 as eluent to give a yellow solid (124 mg, 67%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.51-7.38 (m, 3H), 7.29-7.12 (m, 9H), 5.26 (q, *J* = 7.5 Hz, 1H), 4.99 (d, *J* = 13.9 Hz, 1H), 4.84 (d, *J* = 15.9 Hz, 1H), 4.67 (d, *J* = 15.9 Hz, 1H), 4.16 (d, *J* = 13.9 Hz, 1H), 3.21 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 167.0, 136.3, 136.0, 135.6, 133.9, 131.8, 129.5, 128.6, 128.6, 127.8, 127.7, 127.3, 127.2, 122.9, 122.7, 52.7, 52.4, 52.3, 39.3; *m/z* (ESI): 371 $[M+H]^+$; ν_{max}/cm^{-1} 3256, 3028, 2868, 1651, 1533, 1352, 1282, 758, 704; mp 194-196 °C; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_2O_2$ $[M+H]^+$: 371.1760, found: 371.1754.

N-(3-(4-(Tert-butyl)phenyl)-1-oxo-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)propan-2-yl)benzamide (**8i**). The crude material was purified by column chromatography using PE/EtOAc 7/3 as eluent to give an amorphous yellow solid (119 mg, 53%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.51-7.39 (m, 3H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.37 (td, *J* = 8.5, 5.0 Hz, 1H), 3.91-3.81 (m, 5H), 3.48-3.40 (m, 1H), 3.32-3.23 (m, 2H), 3.14 (dd, *J* = 13.0, 5.0 Hz, 1H), 3.04 (dd, *J* = 13.0, 5.0 Hz, 1H), 1.63-1.50 (m, 2H), 1.41-1.37 (m, 1H), 1.29 (s, 9H), 0.85-0.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 166.6, 150.2, 134.1, 133.2, 131.7, 129.4, 128.6, 127.2, 125.6, 106.6, 64.4, 50.2, 43.8, 40.3, 39.6, 34.6, 31.4; *m/z* (ESI): 451 $[M+H]^+$; ν_{max}/cm^{-1} 3272, 2962, 2874, 1624, 1541, 1470, 1360, 1101, 836, 798, 693; HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_2NaO_4$ $[M+Na]^+$: 473.2416, found: 473.2411.

N-(1-(Diethylamino)-1-oxo-3-phenylpropan-2-yl)benzamide (**8j**). The crude material was purified by column chromatography using PE/EtOAc 6/4 as eluent to give a yellow solid (99 mg, 61%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 6.9 Hz, 2H), 7.50-7.40 (m, 3H), 7.29-7.21 (m, 5H), 7.10 (br d, *J* = 8.0 Hz, 1H), 5.27 (td, *J* = 8.0, 6.1 Hz, 1H), 3.57 (dd, *J* = 13.6, 6.1 Hz, 1H), 3.16-3.05 (m, 4H), 3.01 (dd, *J* = 13.6, 6.1 Hz, 1H), 1.07 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 166.6, 136.5, 134.1, 131.6, 129.7, 128.5 (2C), 127.3, 127.0, 50.7, 41.9, 40.7, 39.9, 14.3, 12.9; *m/z* (ESI): 325 $[M+H]^+$; ν_{max}/cm^{-1} 3314, 2984, 2914, 1652, 1628, 1531, 1455, 1364, 1093, 759, 709; mp 98-100 °C; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}N_2NaO_2$ $[M+Na]^+$: 347.1735, found: 347.1730.

3,4-Dimethoxy-N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide (**8k**). The crude material was purified by column chromatography using PE/EtOAc 4/6 as eluent to give a yellow solid (130 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.27-7.23 (m, 5H), 7.04 (br d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 5.09 (td, *J* = 8.5, 5.4 Hz, 1H), 3.92 (s, 6H), 3.46-3.30 (m, 3H), 3.07 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.17 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.65-2.58 (m, 1H), 1.76-1.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 166.3, 151.9, 148.9, 136.6, 129.6, 128.5, 127.1, 126.6, 120.1, 110.6, 110.4, 56.1 (2C), 53.0, 46.5, 45.9, 39.7, 25.8, 24.1; *m/z* (ESI): 383 $[M+H]^+$; ν_{max}/cm^{-1} 3268, 2930, 2880, 1627, 1506, 1454, 1303, 1025, 863, 760, 702; mp 131-133 °C; HRMS (ESI) *m/z* calcd for $C_{22}H_{26}N_2NaO_4$ $[M+Na]^+$: 405.1790, found: 405.1785.

3-Methoxy-N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide (**8l**). The crude material was purified by column chromatography using PE/EtOAc 5/5 as eluent to give a white solid (134 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.27-7.23 (m, 5H), 7.12 (br d, *J* = 8.5 Hz, 1H), 7.05-7.01 (m, 1H), 5.09 (td, *J* = 8.5, 5.4 Hz, 1H), 3.83 (s, 3H), 3.46-3.30 (m, 3H), 3.16 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.07 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.66-2.59 (m, 1H), 1.78-1.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 166.6, 159.8, 136.5, 135.5, 129.6 (2C), 128.5, 127.1, 119.1, 118.1, 112.3, 55.5, 53.0, 46.5, 45.9, 39.7, 25.9, 24.1; *m/z* (ESI): 353 $[M+H]^+$; ν_{max}/cm^{-1} 3256, 2967, 2838, 1615, 1580, 1453, 1365, 1306, 1057, 878, 760, 704; mp 163-165 °C; HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_3$ $[M+Na]^+$: 375.1685, found: 375.1679.

N-(1-Oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)-2-naphthamide and N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)-1-naphthamide (**8m**). The crude material was purified by column chromatography using PE/EtOAc 7/3 as eluent to give an inseparable mixture of *meta* substituted **8m-a** and *ortho* substituted **8m-b** with a ratio *meta:ortho* 1.3:1, respectively,

View Article Online
DOI: 10.1039/C7OB01715D

determined by ^{1}H-NMR (amorphous yellow solid, 127 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) of major isomer: δ 8.32 (s, 1H), 7.90-7.84 (m, 3H), 7.55-7.48 (m, 3H), 7.29-7.26 (m, 5H), 7.03 (br d, *J* = 6.9 Hz, 1H), 5.24 (q, *J* = 6.9 Hz, 1H), 3.52-3.32 (m, 3H), 3.21-3.13 (m, 2H), 2.83-2.75 (m, 1H), 1.78-1.60 (m, 4H); ^{1}H NMR (300 MHz, $CDCl_3$) of minor isomer: 8.20 (d, *J* = 5.3 Hz, 1H), 7.90-7.84 (m, 3H), 7.55-7.48 (m, 3H), 7.29-7.26 (m, 5H), 7.03 (br d, *J* = 6.9 Hz ,1H), 5.18-5.13 (m, 1H), 3.52-3.32 (m, 3H), 3.21-3.13 (m, 2H), 2.68-2.61 (m, 1H), 1.78-1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) of major isomer: δ 169.8, 168.8, 136.5 (2C), 134.9, 133.7, 129.6, 128.5, 128.3, 127.8 (2C), 127.1, 126.7, 126.4, 125.4, 124.7, 52.9, 46.5, 45.9, 39.8, 25.9, 24.1; ^{13}C NMR (75 MHz, $CDCl_3$) of minor isomer: δ 169.6, 166.8, 136.5, 133.9, 132.7, 131.3, 130.8 (2C), 129.6 (2C), 129.1, 128.5, 127.8, 127.1, 125.6, 123.9, 53.1, 46.5, 45.9, 39.8, 25.9, 24.1; *m/z* (ESI): 373 $[M+H]^+$; ν_{max}/cm^{-1} 3268, 3062, 2969, 2875, 1621, 1530, 1451, 912, 779, 730, 700; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}N_2NaO_2$ $[M+Na]^+$: 395.1735, found: 395.1730.

4-Methyl-N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide and 3-methyl-N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide (**8n**). The crude material was purified by column chromatography using PE/EtOAc 6/4 as eluent to give an inseparable mixture of *para* substituted **8n-a** and *meta* substituted **8n-b** with a ratio *para:meta* 1.1:1, respectively, determined by ^{1}H-NMR (white solid, 113 mg, 67%): ^{1}H NMR (300 MHz, $CDCl_3$ of major isomer: δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.31-7.20 (m, 7H), 7.06 (br s, 1H), 5.09 (td, *J* = 8.4, 5.4 Hz, 1H), 7.46-7.32 (m, 3H), 3.17 (dd, *J* = 12.6, 5.4 Hz, 1H), 3.06 (dd, *J* = 12.6, 5.4 Hz, 1H), 2.63-2.56 (m, 1H), 2.38 (s, 3H), 1.77-1.56 (m, 4H); ^{1}H NMR (300 MHz, $CDCl_3$) of minor isomer: 7.59 (s, 1H), 7.57 (br s, 1H), 7.31-7.20 (m, 8H), 5.09 (td, *J* = 8.4, 5.4 Hz, 1H), 7.46-7.32 (m, 3H), 3.17 (dd, *J* = 12.6, 5.4 Hz, 1H), 3.06 (dd, *J* = 12.6, 5.4 Hz, 1H), 2.63-2.56 (m, 1H), 2.38 (s, 3H), 1.77-1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) of major isomer: δ 169.8, 166.7, 142.1, 136.5, 134.0, 129.6, 128.5, 127.9, 127.2, 127.1, 52.9, 46.5, 45.9, 39.8, 25.8, 24.1, 21.5; ^{13}C NMR (75 MHz, $CDCl_3$) of minor isomer: 169.8, 166.9, 138.4, 136.5, 132.4, 131.2, 129.6 (2C), 129.2, 128.5, 127.1, 124.3, 52.9, 46.5, 45.9, 39.8, 25.8, 24.1, 21.4; *m/z* (ESI): 337 $[M+H]^+$; ν_{max}/cm^{-1} 3263, 2972, 2877, 1653, 1614, 1537, 1453, 1310, 833, 752, 703; mp 171-173 °C; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_2O_2$ $[M+H]^+$: 337.1916, found: 337.1911.

Procedure for the synthesis of benzyl 5-(dipropylamino)-4-isocyano-5-oxopentanoate 7k. 5-(benzyloxy)-2-formamido-5-oxopentanoic acid (1 equiv, 5.17 mmol) is dissolved in dry CH_2Cl_2 (15 mL) and TEA (2.2 equiv, 11.37 mmol), HOBt (1.2 equiv, 6.20 mmol), EDCI (1.2 equiv, 6.20 mmol) and di-*n*-propylamine (1.2 equiv, 6.20 mmol) are added. The mixture is stirred overnight. After dilution with saturated aqueous solution of NH_4Cl, the reaction is extracted with CH_2Cl_2 (x 2) and the organic phase is dried over sodium sulfate and evaporated. The resulting crude material is purified by gravimetric column on silica gel using PE/EtOAc 5/5 as eluent to afford benzyl 5-(dipropylamino)-4-formamido-5-oxopentanoate as a yellow oil (1.26 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.35-7.28 (m, 5H), 6.66 (br s, 1H), 5.14 (s, 2H), 5.07 (q, *J* = 6.2 Hz, 1H), 3.49-3.45 (m, 2H), 3.19-3.04 (m, 2H), 2.48-2.41 (m, 2H), 2.11-2.09 (m, 1H), 1.68-1.66 (m, 1H), 1.56 (sext, *J* = 7.4 Hz, 4H), 0.90 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 171.1, 161.3, 135.9, 128.6, 128.3, 128.2, 66.4, 49.2, 47.7, 46.6, 29.7, 28.5, 22.4, 20.8, 11.4, 11.1; *m/z* (ESI): 349 $[M+H]^+$; ν_{max}/cm^{-1} 3315, 3034, 2932, 2858, 1726, 1684, 1455, 1378, 1172, 752, 697.

To a solution of benzyl 5-(dipropylamino)-4-formamido-5-oxopentanoate (1 equiv, 1.58 mmol) in dry CH_2Cl_2 (6 mL) TEA (5 equiv, 7.90 mmol) is added. The reaction is cooled to -30 °C and a solution of $POCl_3$ (1.5 equiv, 2.38 mmol) in dry CH_2Cl_2 (4 mL) is added dropwise. After stirring for 2 hours, a saturated aqueous solution of $NaHCO_3$ is added and the mixture is allowed to reach room temperature. CH_2Cl_2 is added and the organic phase is washed with a saturated aqueous solution of $NaHCO_3$ (x 2), dried over sodium sulfate and evaporated. The crude material is purified by gravimetric column on silica gel using PE/EtOAc 9/1 as eluent to afford product **7k** as a pale yellow oil (418 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.26 (m, 5H), 5.14 (s, 2H), 4.64 (t, *J* = 6.9 Hz, 1H), 3.33-3.22 (m, 4H), 2.64-2.61 (m, 2H), 2.17 (q, *J* = 6.9 Hz, 2H), 1.58 (sext, *J* = 7.1 Hz, 4H), 0.90 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 164.8, 159.1, 135.6, 128.7, 128.5, 128.3, 66.7, 53.1, 49.4, 48.2, 29.3, 28.0, 22.4, 20.7, 11.3, 11.2; ν_{max}/cm^{-1} 2964, 2925, 2143, 1732, 1658, 1453, 1167, 747, 698.

Procedure for the synthesis of 4-benzamido-5-(dipropylamino)-5-oxopentanoic acid 8o (Proglumide). Following the general procedure 1, the crude material was purified by column chromatography using PE/EtOAc 8/2 as eluent to give benzyl 4-benzamido-5-(dipropylamino)-5-oxopentanoate as a yellow oil (144 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.45-7.20 (m, 8H), 5.19 (t, *J* = 7.9 Hz, 1H), 5.10 (s, 2H), 3.54-3.46 (m, 2H), 3.23 (td, *J* = 13.1, 6.6 Hz, 1H), 3.07 (td, *J* = 13.1, 6.6 Hz, 1H), 2.58-2.43 (m, 2H), 2.21-1.15 (m, 1H), 1.98-1.89 (m, 1H), 1.66-1.50 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 171.4, 167.0, 135.9, 133.9, 131.7, 128.6, 128.5, 128.3 (2C), 127.3, 66.5, 49.3, 48.8, 47.8, 29.9, 28.7, 22.5, 20.9, 11.6, 11.4; *m/z* (ESI): 425 $[M+H]^+$; ν_{max}/cm^{-1} 3305, 2963, 2935, 1732, 1626, 1453, 1382, 1167, 1093, 899, 695.

MeOH (1 mL), Pd/C (0.01 eq, $3.4x10^{-3}$ mmol) and benzyl 4-benzamido-5-(dipropylamino)-5-oxopentanoate (1 eq, 0.34 mmol) are added under hydrogen atmosphere. After stirring at room temperature for 1 hour the resulting mixture is filtered under vacuo over a pad of celite, rinsed with MeOH and evaporated. The resulting crude material is purified by gravimetric column using PE/EtOAc 5/5 as eluent to afford compound **8o** as a yellow solid (108 mg, 95%): ^{1}H NMR (300 MHz, CD_3OD): δ 8.41 (br d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.56–7.43 (m, 3H), 7.21 (br d, *J* = 6.6 Hz, 1H), 5.11 (q, *J* = 6.7 Hz, 1H), 3.67-3.57 (m, 1H), 3.54-3.44 (m, 1H), 3.41-3.35 (m, 1H), 3.19-3.10 (m, 1H), 2.47 (t, *J* = 6.7 Hz, 2H), 2.11-1.98 (m, 2H), 1.82-1.70 (m, 2H), 1.62-1.55 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.3 (2C), 168.9, 133.8, 131.6, 128.3, 127.2, 49.5, 49.3 (2C), 47.9 (2C), 22.0, 20.5, 10.3, 10.1; *m/z* (ESI): 335 $[M+H]^+$; ν_{max}/cm^{-1} 2929, 2874, 1793, 1662, 1598, 1528, 1454, 1288,

View Article Online
DOI: 10.1039/C7OB01715D

915, 711; mp 142-143 °C; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}N_2NaO_4$ $[M+Na]^+$: 357.1790, found: 357.1785.

Procedure for the synthesis of enantioenriched *N*-formyl aminoacids 13a-b. To a solution of L-aminoacid (1 equiv, 18.16 mmol) in formic acid (16 mL) at 0 °C, acetic anhydride (8 equiv, 145.28 mmol) is added dropwise. The reaction is left to reach room temperature and is stirred overnight. The mixture is quenched with H_2O and stirred for additional 20 minutes, then the volatile is removed under vacuo. The obtained product **13** is used in the next step without further purification.

(S)-2-Formamido-3-phenylpropanoic acid[17] (**13a**). White solid (3.47 g, 99%).

(S)-2-Formamidopropanoic acid[18] (**13b**). White solid (2.08 g, 98%).

Procedure for the synthesis of enantioenriched α-formamido amides 14a-b. To a solution of secondary amine (2.2 equiv, 14.96 mmol) in dry CH_2Cl_2 (20 mL) at 0°C, HOBt (1.2 equiv, 8.16 mmol), EDCI (1.2 equiv, 8.16 mmol) and compound **13** (1 equiv, 6.80 mmol) are added in order. After stirring 20 minutes, the mixture is left to reach room temperature. The reaction is stirred overnight, then diluted with saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (x 2) and the organic phase is dried over sodium sulfate and evaporated. The resulting crude material is purified by gravimetric column on silica gel.

(S)-N-(1-Oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)formamide (**14a**). The crude material was purified by column chromatography using PE/EtOAc 3/7 as eluent to give a colourless oil (1.64 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.29-7.18 (m, 5H), 6.89 (br s, 1H), 4.98 (q, *J* = 6.3 Hz, 1H), 3.44-3.26 (m, 3H), 3.03 (d, *J* = 6.3 Hz, 2H), 2.62-2.55 (m, 1H), 1.77-1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 161.0, 136.5, 129.4, 128.3, 126.9, 51.0, 46.3, 45.8, 39.2, 25.7, 24.1; *m/z* (ESI): 247 $[M+H]^+$; ν_{max}/cm^{-1} 3217, 2982, 2873, 1667, 1617, 1453, 1378, 760, 704; $[\alpha]_D$: +23.1 (c 1.30 in $CHCl_3$).

(S)-N-(1-Oxo-1-(pyrrolidin-1-yl)propan-2-yl)formamide (**14b**). The crude material was purified by column chromatography using PE/EtOAc 2/8 as eluent to give a pale yellow oil (810 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.49 (br s, 1H), 4.64 (quint, *J* = 7.1 Hz, 1H), 3.48-3.45 (m, 1H), 3.30-3.23 (m, 3H), 1.83 (quint, *J* = 6.9 Hz, 2H), 1.69 (quint, *J* = 6.9 Hz, 2H) 1.20 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 160.7, 46.2, 45.9, 45.2, 25.8, 24.4, 17.9; *m/z* (ESI): 171 $[M+H]^+$; ν_{max}/cm^{-1} 2922, 2852, 1739, 1624, 1457, 1378, 1036, 800; $[\alpha]_D$: -32.6 (c 1.16 in $CHCl_3$).

Procedure for the synthesis of enantioenriched tertiary α-monosubstituted α-isocyanoacetamides 15a-b. The intermediate **14** (1 equiv, 1.62 mmol) is solubilized in dry CH_2Cl_2 (17 mL) and NMM (2 equiv, 3.24 mmol) is added. The reaction is cooled to -78 °C and triphosgene (0.35 equiv, 0.57 mmol) is added in one portion. After stirring for 2-4 hours, a saturated aqueous solution of $NaHCO_3$ is added and the mixture is allowed to reach room temperature. The reaction is quickly extracted with CH_2Cl_2, dried over sodium sulfate and evaporated. The crude material is purified by gravimetric column on silica gel.

(S)-2-Isocyano-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one[19] (**15a**). The crude material was purified by column chromatography using PE/EtOAc 8/2 as eluent to give a dark yellow solid (281 mg, 76%): $[\alpha]_D^{20}$ +25 (*c* 1.5, $CHCl_3$).

(S)-2-Isocyano-1-(pyrrolidin-1-yl)propan-1-one[19] (**15b**). The crude material was purified by column chromatography using PE/EtOAc 7/3 as eluent to give a yellow oil (136 mg, 55%): $[\alpha]_D$: +17.3 (c 1.20 in $CHCl_3$)

General procedure 2 for the synthesis of α-aroylamino amides 16a-c. To a flame-dried screw-capped containing a solution of anhydrous KF (3 equiv, 1.50 mmol), 18-crown-6 (3 equiv, 1.50 mmol) and α-isocyanoacetamide **15** (1 equiv, 0.50 mmol) in dry THF (2.5 mL), aryne precursor **1** (1.5 equiv, 0.75 mmol) and H_2O (2 equiv, 1 mmol) are added under nitrogen atmosphere and the reaction is heated to 40 °C. After stirring for 2 h and 30 minutes, KF (1 equiv, 0.50 mmol), 18-crown-6 (1 equiv, 0.50 mmol), aryne precursor **1** (1 equiv, 0.50 mmol) and H_2O (2 equiv, 1 mmol) are added to complete the reaction, when it is required. After stirring for additional 1 h and 30 minutes at 40 °C, the reaction is filtered over a pad of celite, washed with CH_3CN at 0 °C and the volatile is removed under vacuo. The resulting crude material is purified by gravimetric column on silica gel.

Benzyl 4-benzamido-5-(dipropylamino)-5-oxopentanoate (**8o**). The crude material was purified by column chromatography using PE/EtOAc 8/2 as eluent to give a yellow oil (144 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.45-7.20 (m, 8H), 5.19 (t, *J* = 7.9 Hz, 1H), 5.10 (s, 2H), 3.54-3.46 (m, 2H), 3.23 (td, *J* = 13.1, 6.6 Hz, 1H), 3.07 (td, *J* = 13.1, 6.6 Hz, 1H), 2.58-2.43 (m, 2H), 2.21-1.15 (m, 1H), 1.98-1.89 (m, 1H), 1.66-1.50 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 171.4, 167.0, 135.9, 133.9, 131.7, 128.6, 128.5, 128.3 (2C), 127.3, 66.5, 49.3, 48.8, 47.8, 29.9, 28.7, 22.5, 20.9, 11.6, 11.4; *m/z* (ESI): 425 $[M+H]^+$; ν_{max}/cm^{-1} 3305, 2963, 2935, 1732, 1626, 1453, 1382, 1167, 1093, 899, 695.

(S)-N-(1-Oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide (**16a**). The crude material was purified by column chromatography using PE/EtOAc 6/4 as eluent to give a yellow solid (100 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.48-7.38 (m, 3H), 7.26-7.22 (m, 5H), 5.10 (td, *J* = 8.4, 5.4 Hz, 1H), 3.43-3.33 (m, 3H), 3.15 (dd, *J* = 12.9, 5.4 Hz, 1H) 3.09 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.66-2.58 (m, 1H), 1.77-1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 166.8, 136.5, 134.1, 131.7, 129.6, 128.5 (2C), 127.3, 127.1, 53.0, 46.5, 45.9, 39.7, 25.9, 24.1; *m/z* (ESI): 323 $[M+H]^+$; ν_{max}/cm^{-1} 3241, 3025, 2870, 1654, 1619, 1540, 1310, 1039, 756, 690; mp 187-188 °C; $[\alpha]_D$: +54.5 (c 1.00 in $CHCl_3$).

(S)-N-(1-Oxo-1-(pyrrolidin-1-yl)propan-2-yl)benzamide (**16b**). The crude material was purified by column chromatography using PE/EtOAc 6/4 as eluent to give a white solid (62 mg, 50%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J* = 6.9 Hz, 2H), 7.48-7.36 (m, 3H), 7.29 (br d, *J* = 6.9 Hz, 1 H), 4.91 (quint, *J* = 6.9 Hz, 1H), 3.70-3.62 (m, 1H), 3.56-3.42 (m, 3H), 2.04-1.95 (m, 2H), 1.94-1.85 (m, 2H), 1.44 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 166.5, 134.2, 131.5, 128.5, 127.2, 47.4, 46.5, 46.1, 26.1, 24.2, 18.4; *m/z* (ESI): 247 $[M+H]^+$; ν_{max}/cm^{-1}

View Article Online
DOI: 10.1039/C7OB01715D

3273, 2924, 2875, 1653, 1538, 1455, 1305, 1046, 776, 726; mp 126-127 °C; $[\alpha]_D$: +36.5 (c 1.00 in $CHCl_3$).

(S)-3-Methoxy-N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide (**16c**). The crude material was purified by column chromatography using PE/EtOAc 5/5 as eluent to give a white solid (122 mg, 69%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.27-7.23 (m, 5H), 7.12 (br d, *J* = 8.5 Hz, 1H), 7.05-7.01 (m, 1H), 5.09 (td, *J* = 8.5, 5.4 Hz, 1H), 3.83 (s, 3H), 3.46-3.30 (m, 3H), 3.16 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.07 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.66-2.59 (m, 1H), 1.78-1.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 166.6, 159.8, 136.5, 135.5, 129.6 (2C), 128.5, 127.1, 119.1, 118.1, 112.3, 55.5, 53.0, 46.5, 45.9, 39.7, 25.9, 24.1; *m/z* (ESI): 353 $[M+H]^+$; ν_{max}/cm^{-1} 3256, 2967, 2838, 1615, 1580, 1453, 1365, 1306, 1057, 878, 760, 704; mp 163-165 °C; $[\alpha]_D$: +14.8 (c 1.00 in $CHCl_3$).

Acknowledgements

M.S. and S.A. gratefully acknowledge Compagnia di San Paolo (Grant No. C61J12000280007) for research fellowships.

Notes and references

1 Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.,* 1983, **12**, 1211.
2 Selected recent reviews on aryne chemistry: (a) D. Pérez, D. Peña and E. Guitián, *Eur. J. Org. Chem.,* 2013, 5981; (b) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.,* 2013, **11**, 191; (c) R. W. Hoffmann and K. Suzuki, *Angew. Chem. Int. Ed.,* 2013, **52**, 2655; (d) C. Holden and M. F. Greaney, *Angew. Chem. Int. Ed.,* 2014, **53**, 5746; (e) A. Bhunia and A. T. Biju, *Synlett,* 2014, **25**, 608; (f) E. Goetz, T. K. Shah and N. K. Garg, *Chem. Commun.,* 2015, **51**, 34; (g) H. Miyabe, *Molecules,* 2015, **20**, 12558; (h) S. Yoshida and T. Hosoya, *Chem. Lett.,* 2015, **44**, 1450; (i) J.-A. García-López and M. F. Greaney, *Chem. Soc. Rev.,* 2016, **45**, 6766.
3 Reviews on transition-metal-free aryne-mediated multicomponent coupling reactions: (a) S. S. Bhojgude and A. Biju, *Angew. Chem. Int. Ed.,* 2012, **51**, 1520; (b) A. Bhunia, S. R. Yetra and A. T. Biju, *Chem. Soc. Rev.,* 2012, **41**, 3140; (c) S. S. Bhojgude, A. Bhunia and A. Biju, *Acc. Chem. Res.,* 2016, **49**, 1658. Recent reports on aryne-based multicomponent reactions: (d) S. S. Bhojgude, T. Roy, R. G. Gonnade and A. T. Biju, *Org. Lett.,* 2016, **18**, 5424; (e) T. Roy, S. S. Bhojgude, T. Kaicharla, M. Thangaraj, B. Garai and A. T. Biju, *Org. Chem. Front.,* 2016, **3**, 71; (f) T. Roy, M. Thangaraj, R. G. Gonnade and A. T. Biju, *Chem. Commun.,* 2016, **52**, 9044; (g) A. Bhunia, T. Kaicharla, D. Porwal, R. G. Gonnade and A. T. Biju, *Chem. Commun.,* 2014, **50**, 11389; (h) A. Bhunia, T. Roy, R. G. Gonnade and A. T. Biju, *Org. Lett.,* 2014, **16**, 5132; (i) W.-M. Shu, J.-R. Ma, K.-L. Zheng and A.-X. Wu, *Org. Lett.,* 2016, **18**, 196; (j) T. Roy, D. R. Baviskar and A. T. Biju, *J. Org. Chem.,* 2015, **80**, 11131.
4 (a) H. Yoshida, H. Fukushima, J. Ohshita and A. Kunai, *Angew. Chem. Int. Ed.,* 2004, **43**, 3935; (b) H. Yoshida, H. Fukushima, T. Morishita, J. Ohshita and A. Kunai, *Tetrahedron,* 2007, **63**, 4793; (c) K. M. Allan, C. D. Gilmore and B. M. Stoltz, *Angew. Chem. Int. Ed.,* 2011, **50**, 4488; (d) H. Yoshida, H. Fukushima, J. Ohshita and A. Kunai, *Tetrahedron Lett.,* 2004, **45**, 8659.
5 (a) H. Yoshida, Y. Asatu, Y. Mimura, Y. Ito, J. Oshita and K. Takaki, *Angew. Chem. Int. Ed.,* 2011, **50**, 9676; (b) F. Sha, H. Shen and X.-Y. Wu, *Eur. J. Org. Chem.,* 2013, 2537.
6 (a) F. Sha and X. Huang, *Angew. Chem. Int. Ed.,* 2009, **8**, 3458; (b) F. Sha, L. Wu and X. Huang, *J. Org. Chem.,* 2012, **77**, 3754.
7 (a) J. H. Rigby and S. Laurent, *J. Org. Chem.,* 1998, **63**, 6742; (b) T. Kaicharla, M. Thangaraj and A. T. Biju, *Org. Lett.,* 2014, **16**, 1728.
8 A. Gesù, C. Pozzoli, E. Torre, S. Aprile and Pirali, T. *Org. Lett.,* 2016, **18**, 1992.
9 (a) T. Pirali, G. C. Tron and J. Zhu, *Org. Lett*., 2006, **8**, 4145; (b) T. Pirali, G. C. Tron, G. Masson and J. Zhu, *Org. Lett.,* 2007, **9**, 5275; (c) R. Mossetti, T. Pirali, G. C. Tron and J. Zhu, *Org. Lett.,* 2010, **12**, 820; (d) R. Mossetti, D. Caprioglio, G. Colombano, G. C. Tron and T. Pirali, *Org. Biomol. Chem.,* 2011, **9**, 1627; (e) For a review on functionalized isocyanides, see: M. Giustiniano, A. Basso, V. Mercalli, A. Massarotti, E. Novellino, G. C. Tron and J. Zhu, *Chem. Soc. Rev.,* 2017, **46**, 1295.
10 G. S. Reddy and M. V. Bhatt, *Tetrahedron Lett.,* 1980, **21**, 3627; S. B. Ferguson, E. M. Seward, F. Diederich, E. M. Sanford, A. Chou, P. Inocencio-Szweda and C. B. Knobler, *J. Org. Chem.*, 1988, **53**, 5595; S. E. Whitney, M. Winters and B. Rickborn, *J. Org. Chem.,* 1990, **55**, 929.
11 For a comprehensive review on nonclassical routes for amide bond formation, see: R. M. de Figueiredo, J.-S. Suppo and J.-M. Campagne, *Chem. Rev.,* 2016, **116**, 12029.
12 (a) G. Zhao, X. Sun, H. Bienayné and J. Zhu, *J. Am. Chem. Soc.*, 2001, **123**, 6700-6701; (b) P. Janvier, X. Sun, H. Bienayme and J. Zhu, *J. Am. Chem. Soc.*, 2002, **124**, 2560; (c) A. Fayol and J. Zhu, *Angew. Chem. Int. Ed.,* 2002, **41**, 3633-3635; (d) P. Janvier, H. Bienaymé and J. Zhu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4291-4294; (e) P. Janvier, M. Bois-Choussy, H. Bienaymé and J. Zhu, *Angew. Chem. Int. Ed.,* 2003, **42**, 811-814; (f) A. Fayol and J. Zhu, *Org. Lett.,* 2004, **6**, 115-118; (g) A. Fayol and J. Zhu, *Org. Lett.,* 2005, **7**, 239-242.
13 R. Karkamar, S. Ghorai, Y. Xia and D. Lee, *Molecules*, 2015, **20**, 15860.
14 W. F. Hahne, R. T. Jensen, G. F. Lemp and J. D. Gardner, *Natl. Acad. Sci. USA,* 1981, **78**, 6304.
15 F. Makovec, R. Chisté, M. Bani, L. Revel, I. Setnikar and A. L. Rovati, *Eur. J. Med. Chem.,* 1986, **21**, 9.
16 J. Zhu, X. Wu and S. J. Danishefsky, *Tetrahedron Lett.,* 2009, **50**, 577.
17 U. Chiacchio, G. Buemi, G. Casuscelli, A. Procopio, A. Rescifina, R. Romeo, *Tetrahedron,* 1994, **50**, 5503.
18 U. Chiacchio, G. Buemi, F. Casuscelli, A. Corsaro, V. Librando, A. Rescifina, R. Romeo and G. Romeo, *Tetrahedron,* 1995, **51**, 5689.
19 R. Mossetti, D. Caprioglio, G. Colombano, G. C. Tron and T. Pirali, *Org. Biomol. Chem.,* 2011, **9**, 1627.

View Article Online
DOI: 10.1039/C7OB01715D

A novel multicomponent reaction among arynes, tertiary α-monosubstituted α-isocyanoacetamides and water was discovered to access densely functionalized α-aroylamino amides. The stereoconservative course of the MCR was investigated.