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# **Materials and Methods**

All reactions requiring an anhydrous, inert atmosphere were carried out under a nitrogen atmosphere using evacuated carousel or ampules. Unless preparative details are provided, all reagents were purchased from commercial suppliers Acros Organics, Aldrich, Alfa Aesar, Fluka, Lancaster, Maybridge, Strem or TCI UK and used without further purification. Thin layer chromatography was carried out on aluminium or plastic backed silica plates, purchased from Aldrich. The plates were visualised under UV (254 nm) light, followed by staining with phosphomolybdic acid dip or potassium permanganate and gentle heating. During compound separations, column chromatography was carried out using 60 micron dry silica purchased from Aldrich. Organic layers were routinely dried with anhydrous MgSO<sub>4</sub> and concentrated using a Büchi rotary evaporator.

<sup>1</sup>H NMR / <sup>13</sup>C NMR spectra were run in deuterated ( $\geq$ 99.5%) solvents purchased from Fluorochem unless stated otherwise, on either a Bruker Avance 250 (250 MHz) or a Bruker Avance 300 (300 MHz). Any chemical shifts ( $\delta$ ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) ( $\delta$ H = 0.00 ppm) unless otherwise stated. The coupling constants (*J*) are reported in Hz and signal multiplicities are reported as singlet (s) , doublet (d), triplet (t), quartet (q), pentet (p), quintet (qu), sextet (sext), doublet of doublets (dd), doublet of triplets (dt), triplet of triplets (tt), multiplet (m), or broad singlet (br. s).

For mass spectrometry data aquisition a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik, GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10  $\mu$ L of sample was injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10  $\mu$ L of a calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with relevant absorbances quoted as v in cm<sup>-1</sup>. Optical rotations were measured on an AA-10 Automatic Polarimeter. Enantiomeric excess was measured using a Perkin Elmer 200 Series HPLC machine, eluting with HPLC grade Hex and isopropylalcohol using a ratio and Chiracel column as specified for each compound. Melting point's were determined using Stuart SMP10 melting point equipment using closed end glass capillary tubes and are uncorrected.

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### **General Procedures**

*I. Catalyst Screening and Optimisation: N*-Butyramide (87 mg, 1 mmol) was added to an oven dried Radleys carousel tube. To this benzylamine (109  $\mu$ L, 1 mmol), the appropriate catalyst (10 mol%) and solvent (1 mL) was added and the tube sealed and heated for 18 hours at reflux. The reaction mixture was allowed to cool to room temperature before the before the solvent was removed *in vacuo* on a rotary evaporator. Quadrasil AP was added to a suspension of the crude product in DCM and stirred for 1 hour to remove NMR active catalytic species, organics filtered and solvent removed *in vacuo* with the crude reaction mixtures were analysed by their <sup>1</sup>H NMR spectra

*II.* N-Acylation of Amines with Amides: An oven dried Radleys carousel tube was charged with amide species (1 equivalent, if amide was solid), amine (1.2 equivalent, unless otherwise stated, if amine was solid), zirconocene dichloride (5 mol%) and the tube was sealed and purged with nitrogen gas for around 10 minutes. After which a solution of anhydrous cyclohexane or heptane, volume as appropriate, containing the amide species (1 equivalent, if amide was a liquid) and/or the amine species (1.2 equivalents, if amine was a liquid) was added to the reaction tube and the reaction heated at reflux (see Table 2 for time). After being allowed to cool to room temperature the reaction is quenched using around 5 mL of MeOH and the solvent was removed *in vacuo* on a rotary evaporator. Unless otherwise stated, dichloromethane (50 mL) was added and the organics washed with water (20 mL). The organics were separated and the aqueous washed with dichloromethane (2 x 50 mL), the organics were combined and dried over MgSO<sub>4</sub>. Volatiles were removed *in vacuo* and the crude reaction mixture was the analysed by their <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy and mass spectrometry data. Purification by column chromatography and recrystallisation was carried out as necessary.

*III.* **Zirconium Catalysed Coupling of Carbamates and Amines:** Ethyl carbamate (1 mmol, 89 mg) and amine (1.2 mmol), if amine solid, were added to an oven dried Radleys carousel tube, followed by the Cp<sub>2</sub>ZrCl<sub>2</sub> (0.05 mmol, 14.6 mg). The tube was then sealed and purged with nitrogen for around

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10 min. Heptane (1 mL) and the amine species (1.2 mmol) were then added. The carousel tube was then heated at 100 °C (see Table 2 for time). After being allowed to cool to room temperature, the solvent was removed in vacuo on a rotary evaporator and the resulting crude reaction mixtures were analysed by <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy and mass spectrometry data. The monosubstituted ureas were then purified by column chromatography.

# **Metal Catalyst Screen**

O NH <sub>2</sub>	10 mol% Catal <sub>y</sub> st 1 equiv. Benz <sub>y</sub> lamine ——►	O N Ph
	Toluene <sub>(</sub> 1.0 M <sub>)</sub> ,	Н
	110°C 18 h ́	

Catalyst	Amide (%) <sup>a</sup>	Imine (%) <sup>ª</sup>	Catalyst	Amide (%) <sup>°</sup>	Imine (%) <sup>a</sup>
AICI <sub>3</sub>	54	5	Ti( <sup>i</sup> OPr)₄	75	-
FeCl <sub>2</sub>	24	13	NiNO₃·6H₂O	8	
ZrF <sub>4</sub>	49		MnCl <sub>2</sub>	30	12
Co(Ac) <sub>2</sub>	14	31	Cp <sub>2</sub> ZrCl <sub>2</sub>	100 <sup>b</sup>	-
Sc(OTf)₃	88	-	CuBr		32
ZrCl₄	58	4	Zr(Acac)₄	Undetermined Acac side-product	-
ZnCl <sub>2</sub>	4	-	MgBr <sub>2</sub>	35	18
LiBr	4	-	InCl <sub>3</sub>	6	2

<sup>a</sup>Conversion determined by <sup>1</sup>H NMR

<sup>b</sup>Reaction complete within 5 h



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Catalyst	Conversion (%) <sup>a</sup>	Cost (£/mmol)	
Cp <sub>2</sub> TiCl <sub>2</sub>	36	-	
Cp <sub>2</sub> ZrCl <sub>2</sub>	97	1.98	
Cp <sub>2</sub> HfCl <sub>2</sub>	96	13.93	

<sup>a</sup> Determined by <sup>1</sup>H NMR

# Amide and Amine Solvent Screen and Optimisation

0 	5 mol% $C_{p_2}ZrCl_2$ 1 equiv. Benzylamine $\prod_{ll}$	
		า
1 mmol	<sup>*</sup> 80 °C, Solvent (1.0 M), 5 h H	

Solvent	<b>Conversion (%)</b> <sup><i>a</i></sup>	Solvent	<b>Conversion (%)</b> <sup><i>a</i></sup>
Toluene	14	DMSO	16 (39 imine)
Acetonitrile	7	Ethanol	1
Chlorobenzene	17	Cyclohexane	63
Dichloroethane	7	Pyridine	9
Dioxane	3	THF	13

<sup>*a*</sup> Determined by <sup>1</sup>H NMR



Solvent	Benzylamine Equiv.	<b>Conversion (%)</b> <sup>a</sup>
Anhyd. Cyclohexane	1.0	73
Cyclohexane	1.0	63
Anhyd. Toluene	1.0	27
Anhyd. Cyclohexane	1.2	100

Cyclohexane	1.2	81
Anhyd. Cyclohexane	1.4	82
Cyclohexane	1.4	70
1:1 Anhyd. Cyclohexane: Anhyd. Toluene	1.0	69

<sup>*a*</sup> Determined by <sup>1</sup>H NMR

Anhydrous solvents were purchased from commercial suppliers and used without further purification.

# **Carbamate and Amine Solvent Screen and Optimisation**

Solvent	Conversion after 18 h (%) <sup><i>a,b</i></sup>	Conversion after 24 h (%) <sup>a</sup>
Anhydr. Heptane	30	100 <sup>c</sup>
Anhydr. Cyclohexane	42	62 <sup><i>b</i>, <i>d</i></sup>
Ethyl Acetate	45 (side reaction with ester solvent)	-
DMSO	24	-
DCE	28	-
Acetonitrile	27	-
THF	16	

Conditions: Ethyl Carbamate (1 mmol), Benzylamine (1.2 mmol), Cp<sub>2</sub>ZrCl<sub>2</sub> (5 mol%), Solvent (1.0 M) unless otherwise stated

<sup>a</sup>Determined by <sup>1</sup>H NMR.

<sup>b</sup>Reaction carried out at 80 °C

<sup>c</sup>Reaction carried out at 100 <sup>o</sup>C

<sup>*d*</sup>Benzyl carbamate was used as the substrate.

# **Notable Limitations**

Some less successful reaction are tabulated below.

Substrate	Amine	Solvent <sup>a</sup>	Time/temp	Conversion <sup>b</sup> (%)
	H₂N∕́Ph	cyclohexane	18/80	10
O NH <sub>2</sub>	NH <sub>2</sub>	cyclohexane	18/80	0
	H₂N∕́Ph	cyclohexane	18/80	8
Ph OEt	H <sub>2</sub> N <sup>^</sup> Ph	cyclohexane	18/80	17
	H <sub>2</sub> N OH	cyclohexane	18/80	42
Ph OEt	H₂N∕́Ph	heptane	24/100	88
O H <sub>2</sub> N H <sup>Ph</sup> H	H₂N∕́Ph	heptane	24/100	46 <sup>c</sup> (78:22)
	H₂N∕́Ph	heptane	18/100	0 <sup><i>d</i></sup>
O H <sub>2</sub> N NH <sub>2</sub>	H <sub>2</sub> N <sup>^</sup> Ph	heptane	24/100	0

a) Commercially available anhydrous solvents. b) conversion into secondary amide product based on crude <sup>1</sup>H-NMR *c*) Two equivalents of benzylamine were used. Total conversion into all products given. Parentheses show the ratio of mono to di substituted products d) conversion into the unsymmetrical urea.

# <sup>15</sup>N-Labelling Study

<sup>15</sup>N-Benzamide (1.0 mmol, 121 mg) and benzylamine (1.2 mmol, 131 μL) were reacted according to general procedure II. The crude reaction mixture was purified by reversed phase HPLC and mass spectrometry was used to identify the nitrogen isotope present in the secondary amide product.

# 2,2,2-D<sub>3</sub>-acetamide

Based on a modified literature procedure, to a stirring solution of d<sub>3</sub>-MeCN (47.9 mmol, 2.5 mL, >99.5% in D) in a 100 mL round bottomed flask was added TMSCI (96 mmol, 12.24 mL) and the flask was cooled to 0°C in an ice bath. To this deionised H<sub>2</sub>O (144 mmol, 2.59 mL) was added dropwise, after which the reaction was allowed to come to room temperature and left stirring for 4 h. A gelatinous precipitate was noted to form at the bottom of the reaction mixture. The reaction mixture cooled in an ice bath and was neutralised using a sat. NaHCO<sub>3</sub> (approx. 25 ml) and the aqueous was extracted using EtOAc (3 x 150 mL). The organics were dried using MgSO<sub>4</sub>, filtered and evaporated to dryness, giving the title compound as a white fluffy solid (594mg, 20% yield). <sup>1</sup>H NMR (250 MHz,d6-DMSO): 6.62 (1H, br. s), 7.21 (1H, br. s). <sup>13</sup>C NMR (500 MHz,d6-DMSO): 21.9-22.5 (m, J<sub>C</sub>. <sub>D</sub>), 172.0.

## N-Acylation of Benzylamine using 2,2,2-D<sub>3</sub>-acetamide

As with general procedure II, 2,2,2- $D_3$ -acetamide (124 mg, 2 mmol) was used as the amide species and benzylamine (314  $\mu$ L, 2.4 mmol) as the amine species. <sup>1</sup>H NMR Analysis of the product after workup and column chromatography showed an 89/11 (D/H) incorporation at the  $\alpha$ -position.

### **HPLC Kinetic Analysis**



#### **General Summary:**

The formation of S3 as a function of time was monitored by HPLC. Initial rates were calculated for the first ~5% product formation. Initial rates were calculated at four concentrations for each of the substrates, S1, S2 and to determine the order of reaction with respect to each substrate.

#### General Procedure for HPLC Studies:

Benzamide (303 mg, 2.5 mmol), benzylamine (328  $\mu$ L, 3.0 mmol, 1.2 equivalents) and Cp<sub>2</sub>ZrCl<sub>2</sub> (36.7 mg, 0.125 mmol, 5 mol%) were added to anhydrous toluene (10 mL). Naphthalene (13.3 mg, 0.103 mmol) was added as an internal standard and the reaction mixture was stirred at 110 °C. Samples were taken at selected time points, diluted (1000 fold in CH<sub>3</sub>OH) and analysed by reversed-phase HPLC (H<sub>2</sub>O (0.05% TFA) : CH<sub>3</sub>CN (0.05% TFA), gradient elution). The peak ratio of product to naphthalene was converted into a % conversion for each sample using the calibration curve described below.

#### Calibration:

**S3** was added to the reaction mixture in the place of benzylamine and benzamide at 5, 10 and 20% theoretical conversions (5.3 mg, 10.6 mg and 21.2 mg). The reaction mixture was heated to 110 °C and sampled immediately, following the dilutions described above. The peak ratio of product (**3**) to naphthalene was then plotted against theoretical conversion to give a calibration curve (*Figure S1, black circles*). The calibration was verified by <sup>1</sup>H-NMR (*Figure S1, blue diamonds*). During a typical reaction described above, along with HPLC analysis, samples were also analysed by <sup>1</sup>H-NMR to give conversions. The good agreement between the two calibration methods supports the validity of the results.



**Figure S1**. Calibration curve calculated from the HPLC peak ratio of product (**S3**) to naphthalene plotted as a function of known conversion (*black circles*) and <sup>1</sup>H-NMR calculated conversion (*blue triangles*).

#### Order of Reaction with Respect to Benzylamine

Bezylamine was added to the reaction mixture at four concentrations; 0.23, 0.30, 0.46 and 0.70 M (1, 1.2, 2 and 3 equivalents, respectively). Reactions were monitored over 6 h by HPLC (*Figure S2*). Integrated peak ratios were converted into % conversions using the calibration curve. Initial rates for the four experiments were calculated by measuring the gradient of each line. Initial rates (in mol dm<sup>-1</sup> mol<sup>-1</sup>) were then plotted as a function of [benzylamine] and [benzylamine]<sup>2</sup> (*Figure S3* and *S4*, respectively). A plot of initial rate against [benzylamine]<sup>2</sup> gives a linear plot indicating the reaction is second order in benzylamine ( $k_{obs} = 2.90 \times 10^{-4} \text{ mol}^{-1} \text{ dm}^3 \text{ min}^{-1}$ ).



**Figure S2.** Formation of **S3** over six hours at four benzylamine concentrations; 0.23 (*squares*), 0.30 (*diamonds*), 0.46 (*triangles*) and 0.70 M (*circles*) (1, 1.2, 2 and 3 equivalents, respectively).



**Figure S3**. Initial rate as a function of [benzylamine].

**Figure S4.** Initial rate as a function of  $[benzylamine]^2$ .

Similar analysis was carried out for benzamide and  $Cp_2ZrCl_2$  (*Figures S5* and *S6, respectively*). The results show the reaction is first order in both benzamide ( $k_{obs} = 0.18 \text{ min}^{-1}$ ) and  $Cp_2ZrCl_2$  ( $k_{obs} = 0.008 \text{ min}^{-1}$ ).



**Figure S5**. Initial rate as a function of [benzamide].



**Figure S6**. Initial rate as a function of [ZrCp<sub>2</sub>Cl<sub>2</sub>].

# Effect of added Diisopropylethylamine

To investigate the effect of diisopropylamine (DIPEA) upon the initial rate, the following reaction was carried out : benzamide (1 equiv), benzylamine (1 equiv), ZrCp<sub>2</sub>Cl<sub>2</sub> (5 mol%) in toluene (10 mL) with

additional DIPEA (0, 0.2 and 1 equiv, which are 0. 0.05 and 0.25 mol dm<sup>-3</sup>, respectively). Initial rates were calculated as above and plotted as a function of [DIPEA] (*Figure S7, blue diamonds*). No enhancement of rate with additional DIPEA is observed. To allow comparison, the effect upon the initial rate of adding excess benzylamine is also shown (*Figure S7, red squares*).



**Figure S7.** Initial rate as a function of [DIPEA] (*blue diamonds*) and excess [benzylamine] (*red diamonds*). Standard conditions: benzamide (1 equiv), benzylamine (1 equiv), ZrCp<sub>2</sub>Cl<sub>2</sub> (5 mol%) in toluene (10 mL).

## **Binding Constant Determination**

Cp<sub>2</sub>ZrCl<sub>2</sub> (3 mg, 0.0128 M) was dissolved in  $d_8$ -toluene (0.8 mL). Benzamide was added as a solid to give a concentration range of 0 – 0.08 M (0 – 6 equivalents). Benzamide concentrations were calculated using <sup>1</sup>H-NMR integrals. Chemical shift of the Cp ring protons was measured as a function of added benzamide (*Figure S8*). A binding constant of 1.51 ± 0.42 mol<sup>-1</sup> dm<sup>3</sup> was calculated using WinEQNMR2 software.\*



**Figure S8.** Chemical shift variation in the Cp resonance of Cp<sub>2</sub>ZrCl<sub>2</sub> as a function of added benzamide.\*

Cp<sub>2</sub>ZrCl<sub>2</sub> (Figure S9).

The same analysis was carried out to determine a binding constant for benzylamine association with



**Figure S9.** Chemical shift variation in the Cp resonance of Cp<sub>2</sub>ZrCl<sub>2</sub> as a function of added benzylamine.\*

# **Characterisation of Products**

**N-Benzylacetamide**<sup>a</sup> (Table 2, Entry 1)

Following general procedure II, acetamide (236 mg, 4 mmol) was used as the amide species and benzylamine (524 µL, 4.8 mmol). The *title compound* was recovered as an off-white solid (497 mg, 83% yield) after column chromatography eluting with 10:1 DCM:MeOH.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.88 (3H, s), 4.28 (2H, d, *J* = 5.7 Hz,), 6.32 (1H, br. s,), 7.15- 7.24 (5H, m). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 23.1, 43.6, 127.5, 127.8, 128.7, 138.3, 170.2. HRMS (ESI-TOF) calcd for  $C_9H_{11}NOH^+$ : 150.0918. Found: 150.0932. Electronic Supplementary Material (ESI) for Chemical Communications This journal is The Royal Society of Chemistry 2012

# *N*-Benzylbutyramide<sup>b</sup> (Table 2, Entry 2)

Following general procedure II, butyramide (3.0 mmol, 261 mg) was used as the amide species and benzylamine (3.6 mmol, 393  $\mu$ L) as the amine species. The *title compound* was recovered as a white solid (468 mg, 88% yield) after column chromatography (eluting with DCM/MeOH 95:5) and recrystallisation (DCM/hex).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ . 0.92 (3H, t, *J* = 7.4 Hz), 1.61 (2H, sext., *J* = 7.4 Hz), 2.15 (2H, t, *J* = 7.5 Hz), 4.38 (2H, d, *J* = 5.7 Hz), 6.01 (1H, br. s), 7.20 – 7.32 (5H, m). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  13.8, 19.2, 38.6, 43.5, 127.4, 127.8, 128.7, 138.5, 173.0. HRMS(ESI-TOF) calcd for C<sub>11</sub>H<sub>15</sub>NOH<sup>+</sup>: 178.1232. Found: 178.1248.

*N*-Benzyl-2-phenylacetamide<sup>c</sup> (Table 2, Entry 3)

`N^

Following general procedure II, 2-phenylacetamide (3.0 mmol, 405 mg) was used as the amide species and benzylamine (3.6 mmol, 393  $\mu$ L) as the amine species and was reacted for 8 h. The *title compound* was recovered as a white solid (567 mg, 84% yield) after column chromatography (eluting with DCM/MeOH 98:2).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): δ 3.63 (2H, s), 4.42 (2H, d, J = 5.8 Hz), 5.75 (1H, br. s), 7.17 – 7.38 (10H, m). <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>): δ 43.6, 43.8, 127.4, 127.4, 127.5, 128.67, 129.1, 129.5, 134.8, 138.2, 170.9. HRMS(ESI-TOF) calcd for C<sub>15</sub>H<sub>14</sub>NO<sup>-</sup>: 224.1075. Found: 224.1076.

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#### *N*-Benzylbenzamide<sup>a</sup> (Table 2, Entry 4)



Following general procedure II, benzamide (3.0 mmol, 363 mg) was used as the amide species and benzylamine (3.6 mmol, 393  $\mu$ L) as the amine species and was reacted for 18 h. The *title compound* was recovered as a white solid (633 mg, 93% yield) after column chromatography (eluting with DCM/MeOH 98:2).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  4.56 (2H, d, *J* = 5.7 Hz), 6.39 (1H, br. s), 7.18-7.45 (8H, m), 7.71-7.73 (2H, m) <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  44.1, 127.0, 127.6, 127.9, 128.6, 128.8, 131.5, 134.4, 138.3, 167.5. HRMS(ESI-TOF) calcd for C<sub>14</sub>H<sub>13</sub>NOH<sup>+</sup>: 212.1075.Found: 212.1088.

# **N-Benzyl-4-chlorobenzamide**<sup>d</sup> (Table 2, Entry 5)



Following general procedure II, 4-chlorobenzamide (363 mg, 3.0 mmol) was used as the amide species and benzylamine (393  $\mu$ L, 3.6 mmol) as the amine species. The *title compound* was recovered as a white crystalline solid (633 mg, 93% yield) after column chromatography (eluting with DCM/MeOH 98:2).

<sup>1</sup>H  $\delta$  <sup>1</sup>H NMR (300 MHz, d6-DMSO):  $\delta$  4.48 (d, *J* = 6.0 Hz, 2H), 7.07 – 7.35 (m, 5H), 7.43 – 7.60 (m, 2H), 7.81 – 7.97 (m, 2H), 9.11 (t, *J* = 5.8 Hz, 1H).<sup>13</sup>C NMR (75 MHz, DMSO):  $\delta$  43.1, 127.1, 127.6, 128.7, 128.8, 129.6, 133.4, 136.4, 139.8, 165.5. HMRS(ESI-TOF) calcd for C<sub>14</sub>H<sub>11</sub>CINOH<sup>+</sup>: 246.0686. Found: 246.0694.

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#### *N*-Benzylnicotinamide<sup>e</sup> (Table 2, Entry 6)



Following general procedure II, nicotinamide (261 mg, 3 mmol) was used as the amide species and benzylamine (393  $\mu$ L, 3.6 mmol) was used as the amine species. After removal of solvent *in vacuo* the crude reaction mixture was partitioned between DCM and NaHCO<sub>3</sub> before the organics were washed as with general method. The *title compound* was recovered as a off white solid (535 mg, 84% yield) after column chromatography eluting with 90:10 DCM:MeOH.

<sup>1</sup>H NMR (300 MHz, d6-DMSO):  $\delta$  4.55 (2H, d, *J* = 6.0 Hz), 7.20 - 7.43 (5H, m), 7.54 (1H, ddd, *J* = 7.9, 4.8, 0.7 Hz), 8.19 - 8.35 (1H, m), 8.75 (1H, dd, *J* = 4.8, 1.6 Hz,), 9.10 (1H, d, *J* = 1.6 Hz,), 9.28 (1H, br. s). <sup>13</sup>C NMR  $\delta$ : 43.0, 123.8, 127.2, 127.6, 128.7, 130.2, 135.4, 139.7, 152.3, 148.8, 165.2. HMRS(ESI-TOF) calcd for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>ONa<sup>+</sup>: 235.0847. Found: 235.0861.

# **N-Benzylpicolinamide<sup>f</sup> (Table 2, Entry 7)**



Following general procedure II, picolinamide (261 mg, 3 mmol) was used as the amide species and benzylamine (393 µL, 3.6 mmol) was used as the amine species. After removal of solvent *in vacuo* the crude reaction mixture was partitioned between DCM and NaHCO<sub>3</sub> before the organics were washed as with general method II. The *title compound* was recovered as an off-white solid (548 mg, 86% yield) after column chromatography eluting with 90:10 DCM:MeOH

<sup>1</sup>H NMR (300 MHz,d6-DMSO): δ 4.50 (2H, d, *J* = 6.4 Hz), 7.18 – 7.34 (5H, m), 7.55 – 7.61 (1H, m), 7.95 – 8.07 (2H, m), 8.62 – 8.65 (1H, ddd, *J* = 4.7, 1.5, 0.9), 9.31 (1H, t, *J* = 5.8 Hz).<sup>13</sup>C NMR δ: 42.8, 122.3,

126.9, 127.1, 127.7, 128.6, 138.2, 139.9, 148.8, 150.4, 164.3. HMRS(ESI-TOF) calcd for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>OH<sup>+</sup>: 213.1028. Found: 213.1042.

[*N*-(Benzyl)-*N*'-Boc]-L-prolinamide<sup>g</sup> (Table 2, Entry 8)



Following general procedure II, *N*-boc-L-prolinamide (439 mg, 2 mmol) was used as the amide species and benzylamine (262  $\mu$ L, 2.4 mmol) was used as the amine species. The *title compound* was recovered as a white solid (432mg, 71% yield) after column chromatography eluting with 1:1 Hex:EtOAc. The product was observed as two rotamers in its NMR spectra.

<sup>1</sup>H NMR (300 MHz, d6-DMSO):  $\delta$ 1.29 (9H, s, (major rotamer)), 1.43 (9H, s (minor rotamer)) 1.72-1.86 (3H, m), 3.25 -3.44 (1H, m) 4.07-4.38 (3H, m), 7.21 – 7.33 (5H, m), 8.32 -8.40 (1H, m). <sup>13</sup>C NMR (75 MHz, d6-DMSO):  $\delta$  23.5, 24.3, 28.3, 28.5, 30.4, 31.5, 42.2, 42.4, 46.8, 47.0, 60.2, 60.3, 78.8, 79.0, 126.9, 127.1, 127.2, 127.7, 128.5, 140.0, 153.7, 154.1, 172.6, 172.8. HRMS (ESI-TOF) calcd for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>H<sup>+</sup>: 305.1865. Found: 305.1853. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -80.0 (CHCl<sub>3</sub>, *c* = 1.0), literature value [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -80.2°; e.e. > 99%, Chiracel AD column (25 cm) with AD pre-column (5 cm), 0.5 mL min<sup>-1</sup>, 90:10 Hex:IPA, (*L*) enantiomer retention time 25.11 mins, (*D*) enantiomer retention time 16.68 mins

*N*-Benzyl-2,2-diethoxyacetamide<sup>h</sup> (Table 2, Entry 9)



Following general procedure II, 2,2-diethoxyacetamide (439 mg, 3 mmol) was used as the amide species and benzylamine (393 µL, 3.6 mmol) was used as the amine species. The *title compound* was recovered as an light brown oil (598mg, 84% yield) after column chromatography eluting with 1:1 Hex : EtOAc.

<sup>1</sup>H NMR (300 MHz,CDCl<sub>3</sub>):  $\delta$  1.23 (6H, t, *J* = 7.5 Hz), 3.56 – 3.74 (4H, m), 4.47 (2H, d, *J* = 6 Hz), 4.85 (1H, s), 6.92 (1H, br. s), 7.24 – 7.36 (5H, m).<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  15.1, 43.0, 62.6, 98.5, 127.6, 127.8, 128.7, 137.9, 167.9. HRMS(ESI-TOF) calcd for  $[C_{13}H_{18}NO_3]^{-1}$ : 236.1287. Found: 236.1294.

(±)-*N*-Benzyl-2-chloropropionamide<sup>i</sup> (Table 2, Entry 10)



Following general procedure II, ( $\pm$ )-2-chloropropionamide (3.0 mmol, 405 mg) was used as the amide species and benzylamine (3.6 mmol, 393  $\mu$ L) as the amine species. The *title compound* was recovered as a white solid (544 mg, 92% yield) after column chromatography (eluting with DCM/MeOH 96:4).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ. 1.69 (3H, d, J = 7.2 Hz), 4.35 – 4.42 (3H, m), 6.82 (1H, br. s), 7.18 – 7.31 (5H, m). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 22.8, 43.9, 56.0, 127.7, 127.8, 128.8, 137.5, 169.5. HRMS(ESI-TOF) calcd for  $[C_{10}H_{12}CINONa]^+$ : 220.0505. Found: 220.0491.

### **N-Phenethylacetamide<sup>j</sup>** (Table 3, Entry 1)

Following general procedure II, acetamide (236 mg, 4 mmol) was used as the amide species and 2phenyethylamine (605  $\mu$ L, 4.8 mmol). The *title compound* was recovered as an off-white solid (509 mg, 78% yield) after column chromatography eluting with 10:1 DCM:MeOH <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.84 (s, 3H), 2.72 (t, J = 7.1 Hz, 2H), 3.4 (q, J = 7.0 Hz, 2H), 5.98 (1H, br. s), 7.24-7.09 (m, 5H), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  23.3, 35.6, 40.8, 126.5, 128.6, 128.7, 139.0, 170.3.

HMRS(ESI-TOF) calcd of  $C_{10}H_{13}NOH^+$ : 164.1075.Found: 164.1079.

*N*-(4-Methoxybenzyl)acetamide<sup>k</sup> (Table 3, Entry 2)



Following general procedure II, acetamide (236 mg, 4 mmol) was used as the amide species and 4methoxybenzylamine (627 μL, 4.8 mmol). The *title compound* was recovered as an orange solid (581 mg, 81% yield) after column chromatography eluting with 10:1 DCM:MeOH.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.01 (3H, s), 3.80 (3H, s), 4.36 (2H, d, *J* = 5.7 Hz), 5.79 (1H, br. s), 6.87 (2H, d, *J* = 8.7 Hz), 7.21 (2H, d, *J* = 8.7 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  23.2, 43.2, 55.3, 114.0, 129.2, 130.2, 159.1, 169.8. HRMS(ESI-TOF) calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub>H<sup>+</sup>: 180.1025. Found: 180.1017.

# *N*-(4-Chlorobenzyl)acetamide<sup>1</sup> (Table 3, Entry 3)

Following general procedure II, acetamide (236 mg, 4 mmol) was used as the amide species and 4chlorobenzylamine (584 µL, 4.8 mmol). The *title compound* was recovered as a white solid (503 mg, 69%) after column chromatography eluting with 10:1 DCM:MeOH.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.93 (3H, s), 4.29 (2H, d, J = 5.8 Hz,), 6.08 (1H, br. s), 7.12 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 23.2, 43.0, 128.8, 129.1, 136.9, 170.2. HRMS(ESI-TOF) calcd for C<sub>9</sub>H<sub>10</sub>NOClNa<sup>+</sup>: 206.0349. Found: 206.0341.

1-Morpholinoethanonej (Table 3, Entry 4)Error! Bookmark not defined.

Acetamide (236 mg, 4 mmol) was used as the amide species and morpholine (401  $\mu$ L , 4.6 mmol). The crude reaction mixture purified by column chromatography, affording the *title compound* as a light brown oil (449 mg, 87% yield) after column chromatography eluting with 96:4 DCM MeOH <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  2.02 (s, 3H), 3.38 - 3.42 (2H, m), 3.53 - 3.61 (6H, m). <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>)  $\delta$  21.1, 41.7, 46.6, 66.5, 66.7, 169.1. HMRS(ESI-TOF) calcd for C<sub>6</sub>H<sub>11</sub>NO<sub>2</sub>Na<sup>+</sup>: 152.0687 . Found: 152.0692.

# *N*-Allylbutyramide<sup>d</sup> (Table 3, Entry 5)

° ↓ N √

Following general procedure II, butyramide (3.0 mmol, 261 mg) was used as the amide species and allylamine (3.6 mmol, 270  $\mu$ L) as the amine species. The *title compound* was recovered as a orange oil (347 mg, 91% yield) after column chromatography (eluting with DCM/MeOH 95:5).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  0.86 (3H, t, *J* = 7.5 Hz ), 1.60 (2H, sext, *J* = 7.4 Hz), 2.12 (2H, t, *J* = 7.4 Hz), 3.77-3.82 (2H, tt, *J* = 5.7 and *J* = 1.5 Hz), 5.01-5.14 (2H,m ), 5.70-5.83 (1H, m), 6.11 (1H, br. s). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  13.7, 19.2, 38.5, 41.8, 116.0, 134.4, 173.1. HRMS(ESI-TOF) calcd for C<sub>7</sub>H<sub>13</sub>NONa<sup>+</sup>: 150.0895. Found: 150.0913.

*N*-(4-Chlorobenzyl)butyramide<sup>d</sup> (Table 3, Entry 6)



Following general procedure II, butyramide (3.0 mmol, 261 mg) was used as the amide species and 4-chlorobenzylamine (3.6 mmol, 438  $\mu$ L) as the amine species. The *title compound* was recovered as a white solid (564 mg, 89% yield) after column chromatography (eluting with DCM/MeOH 92:8) and recrystallisation (DCM/Hex).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  0.95 (3H, t, *J* = 7.5 Hz), 1.67 (2H, sext, *J* = 7.5 Hz), 2.19 (2H, t, *J* = 7.5 Hz), 4.39 (2H, d, 5.8 Hz), 5.89 (1H, br. s), 7.20 (2H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 8.4 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  13.8, 19.2, 38.6, 42.8, 128.8, 129.1, 133.3, 137.0, 173.0. HRMS (ESI-TOF) calcd for C<sub>11</sub>H<sub>14</sub>CINOH<sup>+</sup>: 212.0842. Found: 212.0842

# *N*-(5-Methylfurfuryl)butyramide<sup>d</sup> (Table 3, Entry 7)



Following general procedure II, butyramide (3.0 mmol, 261 mg) was used as the amide species and 5-methylfurfurylamine (3.6 mmol, 401 µL) as the amine species. The *title compound* was recovered as a brown oil (564 mg, 89% yield) after column chromatography (eluting with DCM/MeOH 97:3). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ . 0.92 (3H, t, *J* = 7.5 Hz), 1.64 (2H, sext, *J* = 7.5 Hz), 2.15 (2H, t, *J* = 7.5 Hz), 2.23 (3H, s), 4.34 (2H, d, *J* = 5.4 Hz), 5.86 (1H, d, *J* = 2.1 Hz), 6.06 (2H, br. m). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  13.5, 13.7, 19.1, 36.5, 38.5, 106.2, 108.1, 149.6, 151.8, 172.8. HRMS(ESI-TOF) calcd for C<sub>10</sub>H<sub>15</sub>NO<sub>2</sub>H<sup>+</sup>: 182.1181. Found: 182.1188. Electronic Supplementary Material (ESI) for Chemical Communications This journal is O The Royal Society of Chemistry 2012

4-(Methoxyphenyl)butyramide<sup>m</sup> (Table 3, Entry 8)



Following general procedure II, butyramide (261 mg, 3 mmol) was used as the amide species and 4methoxyaniline (443 mg, 3.6 mmol) was used as the amine species. The *title compound* was recovered as a light pink solid (313 mg, 54% yield) after column chromatography eluting with 1:1 EtOAc : Hex and multiple recrystallisations from DCM-Hex.

<sup>1</sup>H NMR (300 MHz,CDCl<sub>3</sub>):  $\delta$  0.99 (3H, t, *J* = 7.3 Hz), 1.75 (2H, sext, *J* = 7.5 Hz), 2.31 (2H, t, *J* = 7.5 Hz), 3.78 (3H, s), 6.84 (2H, d, *J* = 9 Hz), 7.31 (1H, br. s), 7.41 (2H, d, *J* = 9 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ 13.8, 19.2, 39.5, 55.5, 114.1, 121.8, 131.1, 156.4, 171.3. HRMS(ESI-TOF) calcd for C<sub>11</sub>H<sub>14</sub>NO<sub>2</sub><sup>-</sup>: 192.1025.Found: 192.1036.

*N*-(Thiazol-2-yl)butyramide<sup>n</sup> (Table 3, Entry 9)

Following general procedure II, butyramide (3 mmol, 261 mg) was used as the amide species and 2aminothiazole (3.6 mmol, 361 mg) as the amine species. The *title compound* was recovered as beige solid (347 mg, 68% yield) after column chromatography eluting with 1:1 Hex: EtOAc) Melting Point: 133-134 °C (lit.: 132-134 °C). <sup>1</sup>H NMR (300 MHz, d6-DMSO):  $\delta$  0.89 (3H, t, *J* = 7.4Hz), 1.59 (2H, sext, *J* = 7.4 Hz), 2.40 (2H, t, *J* = 7.3Hz), 7.16 (1H, d, *J* = 3.6Hz), 7.45 (1H, d, *J* = 3.6Hz), 12.02 (1H, s).<sup>13</sup>C NMR (75 MHz, d6-DMSO):  $\delta$  13.9, 18.5, 37.1, 113.5, 137.9, 158.4, 171.4. HRMS(ESI-TOF) calcd for C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>OSNa<sup>+</sup>: 193.0412 . Found: 193.0421. IR (neat): v (cm<sup>-1</sup>) = 3165, 3081, 2904, 1687 (C=O stretch), 1555, 1443, 1184, 1167, 730. Anal. Calcd for C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>OS: C, 49.39; H, 5.92; N, 16.46 Found: C, 49.40; H, 5.92; N, 16.40.

### (S)-2,2,2-trifluoro-N-(1-phenylethyl)acetamide<sup>o</sup> (Table 3, Entry 10)



Following general procedure II, 2,2,2-trifluoroacetamide (339 mg, 3.0 mmol) was used as the amide species and (*S*)-(–)- $\alpha$ -methylbenzylamine (464  $\mu$ L, 3.6 mmol) as the amine species. The *title compound* was recovered as a white crystalline solid (573 mg, 88% yield) after column chromatography (eluting with DCM/MeOH 98:2).

<sup>1</sup>H NMR (300 MHz, d6-DMSO):  $\delta$  1.45 (3H, d, *J* = 7.1 Hz,) 5.00 (1H, pent, *J* = 7.2 Hz,), 7.00 - 7.54 (5H, m), 9.85 (1H, d, *J* = 7.6 Hz). <sup>13</sup>C NMR (75 MHz, d6-DMSO):  $\delta$  21.7, 49.4, 116.2 (q, *J*<sub>CF</sub> = 287.3 Hz), 126.4, 127.5, 128.8, 143.2, 155.8 (q, *J*<sub>CF</sub> = 36.8 Hz). <sup>19</sup>F (376MHz, d6-DMSO):  $\delta$  -74.09. HMRS (ESI-TOF) calcd for C<sub>10</sub>H<sub>9</sub>F<sub>3</sub>NO<sup>-</sup>: 216.0636. Found: 216.0663. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -137.0 (CHCl<sub>3</sub>, *c* = 1.0), literature value for (*R*) enantiomer [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +137<sup>o p</sup>; e.e. > 99%, Chiracel OD-H column (25 cm), 1.3 mL min<sup>-1</sup>, 98:2 Hex:IPA, (S) enantiomer retention time 11.09 mins, (R) enantiomer retention time 18.15 mins.

#### *N*-Benzyl-*N*-methylformamide<sup>q</sup> (Table 3, Entry 11)



Following general procedure II, formamide (3.0 mmol, 120  $\mu$ L) was used as the amide species and *N*-benzylmethylamine (3.6 mmol, 465  $\mu$ L) as the amine species. The *title compound* was recovered as an orange-brown oil (425 mg, 95% yield) after column chromatography (eluting with DCM/MeOH 96:4). The product was observed as two rotamers in its NMR spectra.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ. 2.66 (3H (major rotamer), s), 2.73 (3H (minor rotamer), s), 4.27 (2H (major rotamer), s), 4.41 (2H (minor rotamer), s), 7.07-7.29 (5H, m), 8.04 (1H (minor rotamer), s),

8.17 (1H (major rotamer), s). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  29.4 (minor rotamer), 34.0 (major rotamer), 47.7 (minor rotamer), 53.4 (major rotamer), 127.4 (major rotamer), 127.6 (minor rotamer), 128.1 (minor rotamer), 128.2 (major rotamer), 128.7 (minor rotamer), 128.9 (major rotamer), 135.8 (major rotamer), 136.1 (minor rotamer), 162.6 (minor rotamer), 162.7 (major rotamer). HRMS (ESI-TOF) calcd for C<sub>9</sub>H<sub>11</sub>NONa<sup>+</sup>: 172.0738. Found: 172.0742.

#### *N*-(4-Methoxybenzyl)formamide<sup>*q*</sup> (Table 3, Entry 12)



Following general procedure II, formamide (3.0 mmol, 120  $\mu$ L) was used as the amide species and 4-Methoxybenzylamine (3.6 mmol, 470  $\mu$ L) as the amine species. The *title compound* was recovered as a white solid (466 mg, 94% yield) after column chromatography (eluting with DCM:MeOH 96:4). The product was observed as two rotamers in its NMR spectra.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ. 3.78 (3H (major rotamer), s), 3.80 (3H (minor rotamer), s), 4.33 (2H, (minor rotamer), d, J = 6 Hz), 4.39 (2H (major rotamer), d, J = 6 Hz), 6.00 (1H, br. s), 6.83 – 6.90 (2H (major and minor rotamer), m), 7.14 – 7.23 (2H, major and minor rotamer), m), 8.14 (1H (minor rotamer), d, J = 12 Hz), 8.21 (1H (major rotamer), s). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 41.7 (major rotamer), 45.2 (minor rotamer), 55.3, 114.2 (major rotamer), 114.3 (minor rotamer), 128.3 (minor rotamer), 129.2 (major rotamer), 129.5 (minor rotamer), 129.7 (major rotamer), 159.2, 161.0 (major rotamer), 164.5 (minor rotamer). HRMS(ESI-TOF) calcd for C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub>H<sup>+</sup>: 166.0868. Found: 166.0879.

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#### 4-Phenylpiperazine-1-carbaldehyde<sup>r</sup> (Table 3, Entry 13)



Following general procedure II, formamide (120  $\mu$ L, 3 mmol) was used as the amide species and 1phenylpiperizine (549  $\mu$ L, 3.6 mmol) was used as the amine species. The *title compound* was recovered as a beige solid (598mg, 84% yield) after column chromatography eluting with 90:10 DCM:MeOH.

<sup>1</sup>H NMR (300 MHz,CDCl<sub>3</sub>): δ 3.08-3.15 (4H, m), 3.48 (2H, t, *J* = 5.4 Hz), 3.66 (2H, t, *J* = 5.4 Hz), 6.85-6.91 (3H, m), 7.19-7.26 (2H, m), 8.04 (1H, s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 39.9, 45.5, 49.6, 50.7, 117.3, 121.2, 129.4, 160.8. HRMS(ESI-TOF) calcd for  $C_{11}H_{14}N_2OH^+$ : 191.1184. Found: 191.1176.

# 1-Benzylurea <sup>s</sup>(Table 4, Entry 1)



Following general procedure III, ethyl carbamate (1 mmol, 89 mg) was used as the carbamate species and benzylamine (1.2 mmol, 0.13 mL) as the amine species. The *title compound* was recovered as a white solid (0.13 g, 87% yield) after column chromatography (eluting with DCM/MeOH 95:5).

<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>-DMSO): δ. 4.17 (2H, d, J = 6 Hz), 5.54 (2H, br. s), 6.42 (1H, t), 7.27-7.33 (5H, m). <sup>13</sup>C NMR (63 MHz, d<sup>6</sup>-DMSO): δ. 126.49, 126.97, 128.16, 140.89, 158.37. HRMS (ESI-TOF) calcd for  $C_8H_{10}N_2ONa^+$ : 173.0691. Found: 173.0704.

### Hexylurea<sup>s</sup> (Table 4, Entry 2)

Hexylamine (121 mg, 1.2 mmol) and ethyl carbamate (89 mg, 1 mmol) were reacted according to general procedure III. Purification by column chromatography (silica,  $CH_2CI_2$  : 0 – 5%  $CH_3OH$ ) S25

afforded the *title compound* as a white solid (115 mg, 80%); <sup>1</sup>H NMR (250 MHz, d6-DMSO):  $\delta$  0.87 (3H, t, *J* = 6.6 Hz), 1.14 – 1.46 (8H, m), 2.94 (2H, q, *J* = 6.3 Hz), 5.37 (2H, br s), 5.91 (1H, t, *J* = 6.3 Hz). <sup>13</sup>C NMR (63 MHz, d6-DMSO)  $\delta$  14.4, 22.6, 26.5, 30.4, 31.5, 159.2. HMRS(ESI<sup>+</sup>-TOF) calcd for C<sub>7</sub>H<sub>17</sub>N<sub>2</sub>O<sup>+</sup>: 145.1336. Found: 145.1458.

1-Phenylurea <sup>t</sup> (Table 4, Entry 3)

Following general procedure III, ethyl carbamate (1 mmol, 89 mg) was used as the carbamate species and aniline (1.2 mmol, 0.109 mL), as the amine species. The *title compound* was recovered as an off-white solid (0.125 g, 92% yield), after column chromatography (eluting with DCM/MeOH 95:5).

<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>-DMSO): δ 6.95 (1H, t, J = 8.2 Hz), 7.32 (2H, t, J= 8.2 Hz), 7.46 (2H, d, J = 8.2 Hz), 8.68 (1H, s). <sup>13</sup>C NMR (63 MHz, d<sup>6</sup>-DMSO): δ 118.15, 121.78, 128.76, 139.67, 152.43. HRMS (ESI-TOF) cald for C<sub>7</sub>H<sub>9</sub>N<sub>2</sub>O<sup>+</sup>: 137.0714. Found: 137.0716.

### (4-Methylphenyl)urea <sup>u</sup> (Table 4, Entry 4)

4-Methylaniline (128 mg, 1.2 mmol) and ethyl carbamate (89 mg, 1 mmol) were reacted according to general procedure III. Purification by column chromatography (silica,  $CH_2CI_2 : 0 - 5\% CH_3OH$ ) afforded the *title compound* as a white solid (133 mg, 89%); <sup>1</sup>H NMR (250 MHz, d6-DMSO):  $\delta$  2.22 (3H, s), 5.78 (2H, br s), (2H, d, *J* = 8.3 Hz), (2H, d, *J* = 8.3 Hz), 8.41 (1H, br s). <sup>13</sup>C NMR (63 MHz, d6-DMSO)  $\delta$  20.2, 117.8, 129.0, 129.8, 137.9, 156.1. HMRS(ESI<sup>+</sup>-TOF) calcd for C<sub>8</sub>H<sub>11</sub>N<sub>2</sub>O<sup>+</sup>: 151.0866. Found: 151.0959.

# Morpholine-4-carboxamide <sup>v</sup> (Table 4, Entry 5)

Morpholine (105 mg, 104  $\mu$ L, 1.2 mmol) and ethyl carbamate (89 mg, 1 mmol) were reacted according to general procedure III. Purification by column chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub> : 0 – 5% CH<sub>3</sub>OH) afforded the *title compound* as a white solid (109 mg, 84%); <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  3.30 (4H, t, *J* = 5.0 Hz), 3.61 (4H, t, *J* = 5.0 Hz), 5.20 (2H, br s). <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>)  $\delta$  44.1, 66.4, 158.8. HMRS(ESI<sup>+</sup>-TOF) calcd for C<sub>5</sub>H<sub>10</sub>N<sub>2</sub>ONa<sup>+</sup>: 153.0640 . Found: 153.0662.

# **HPLC Traces**

### Racemic 2,2,2-trifluoro-N-(1-phenylethyl)acetamide







**Blank HPLC trace** 



[N-(Benzyl)-N'-Boc]-D-prolinamide



[N-(Benzyl)-N'-Boc]-L-prolinamide (Table 2, Entry 8)



# <sup>1</sup>H and <sup>13</sup>C NMR Spectra



# **N-Benzylacetamide (Table 2, Entry 1)**







# N-Benzylbutyramide (Table 2, Entry 2)





# N-Benzyl-2-phenylacetamide (Table 2, Entry 3)





N-Benzylbenzamide (Table 2, Entry 4)





N-Benzyl-4-chlorobenzamide (Table 2, Entry 5)





# **N-Benzylnicotinamide (Table 2, Entry 6)**





N-Benzylpicolinamide (Table 2, Entry 7)





[N-(Benzyl)-N'-Boc]-L-prolinamide (Table 2, Entry 8)





N-Benzyl-2,2-diethoxyacetamide (Table 2, Entry 9)





# (±)-N-Benzyl-2-chloropropionamide (Table 2, Entry 10)





N-Phenethylacetamide (Table 3, Entry 1)





# N-(4-Methoxybenzyl)acetamide (Table 3, Entry 2)





N-(4-Chlorobenzyl)acetamide (Table 3, Entry 3)





1-Morpholinoethanone (Table 3, Entry 4)



0 ∥ 1

N-Allylbutyramide (Table 3, Entry 5)





# N-(4-Chlorobenzyl)butyramide (Table 3, Entry 6)





# N-(5-Methylfurfuryl)butyramide (Table 3, Entry 7)







# 4-(Methoxyphenyl)butyramide (Table 3, Entry 8)





# N-(Thiazol-2-yl)butyramide (Table 3, Entry 9)





(S)-2,2,2-trifluoro-N-(1-phenylethyl)acetamide (Table 3, Entry 10)





# N-Benzyl-N-methylformamide (Table 3, Entry 11)





# N-(4-Methoxybenzyl)formamide (Table 3, Entry 12)





# 4-Phenylpiperazine-1-carbaldehyde (Table 3, Entry 13)









# 1-Benzylurea (Table 4, Entry 1)



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Hexylurea (Table 4, Entry 2)





1-Phenylurea (Table 4, Entry 3)









# (4-Methylphenyl)urea (Table 4, Entry 4)



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(Table 4, Entry 5)





#### **References:**

- <sup>a</sup> C. L. Allen, S. Davulcu and J. M. J. Williams, Org. Lett. 2010, **12**, 5096.
- <sup>b</sup> A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *J. Org. Chem.* 2011, **76**, 2328.
- <sup>c</sup> C. L. Allen, A. R. Chhatwal and J. M. J. Williams, *Chem. Commun.* 2012, **48**, 666.
- <sup>d</sup> C. L. Allen, B. N. Atkinson and J. M. J. Williams, Angew. Chem. Int. Ed. 2012, **51**, 1383.
- <sup>e</sup> B. Roberts, D. Liptrot, L. Alcaraz, T. Luker and M. J. Stocks, *Org. Lett.* 2010, **12**, 4280.
- <sup>f</sup> Y. Zhao and C. Gong *Org. Lett.* 2011, **13**, 4850.

<sup>g</sup> S. K. Davidsen, P. D. May and J. B. Summers, *J. Org. Chem.*, 1991, **56**, 5482.

<sup>h</sup> H. Fukumi and H. Kurihara *Heterocycles*, 1978, **9**, 1197.

<sup>i</sup> M. Murphy, D. Lynch, M. Schaeffer, K. Marcel, M. Kissane, J. Chopra, E. O'Brien, A. Ford, G. Ferguson and A. R. Maguire, *Org. Biolmol. Chem.*, 2007, **5**, 1228.

<sup>j</sup> J. E. Taylor, M. D. Jones, J. M. J. Williams and S. D. Bull, *J. Org. Chem.*, 2012, **77**, 2808.

<sup>k</sup> L. Rubio-Perez, P. Sharma, F. J. Perez-Flores, L. Velasco, A. Cabrera and J. L. Arias, *Tetrahedron*, 2012, **68**, 2342.

<sup>1</sup>Y. Yamamoto, H. Hasegawa and H. Yamataka, *J. Org. Chem.*, 2011, **76**, 4652.

<sup>m</sup> A. Correa, S. Elmore and C. Bolm, *Chem. Eur. J.* 2008, **14**, 3527.

<sup>n</sup> N. A. Kravchenya, *Pharmaceutical Chemistry Journal*, 1983, **17**, 593.

° S. A. Fowler, R. Luechapanichkul and H. E. Blackwell, J. Org. Chem., 2009, 74, 1440.

<sup>p</sup> J.- G. Kim and D. O. Jang, *Tetrahedron Lett.* 2010, **51**, 683.

<sup>q</sup> O. Saidi, J. Lynch, J. M. J. Williams, M. J. Bamford, R. J. Watson, A. J. Blacker, S. P. Marsden and P. Pawel, *Tetrahedron Lett.* 2010, **51**, 5804.

<sup>r</sup> O. Itsenko, E. Blom, B. Långström and T. Kihlberg, *Eur. J. Org. Chem.* 2007, **26**, 4337.

<sup>s</sup> E. Artuso, I. Degani and R. Fochi, *Synthesis*, 2007, **22**, 3497.

<sup>t</sup> L. De Luca, A. Porcheddu and G. Giacomelli , *Synlett*, 2010, **16**, 2439.

<sup>u</sup> J. O'Connor, J. McLennan, J. Calvert and H. Mitha, Aust. J. Chem., 1987, 40, 677

<sup>v</sup> J. Lorenz, C. Busacca, X. Feng, N. Grinberg, N. Haddad, J. Johnson, S. Kapadia, H. Lee, A. Saha, M. Sarvestam, E. Spinelli, R. Varsolona, X. Wei, X. Zeng and C. Senanyake. *J. Org. Chem.* 2010, **75**, 1155.