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Investigation of a novel diamine based chiral auxiliary in the asymmetric alkylation of ketones

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ABSTRACT

A novel chiral auxiliary containing a pyrrolidine ring has been utilised in the preparation of various chiral ketones with good to excellent enantioselectivities (up to 92%). It has been successfully employed in aldol and Michael reactions giving moderate to high selectivity.

1. Introduction

The α-alkylation of ketones is a fundamental reaction in organic synthesis. However there exists a very limited number of methods to carry out this transformation in an asymmetric manner. The use of SAMP/RAMP methodology almost exclusively accounts for these types of transformations.[1] SAMP/RAMP hydrazones have been widely employed as key steps in the synthesis of numerous natural products, for example, indanomycine,[2] (+)-eremophilenolide[3] and stigmatellin A.[4] Previous alteration of the basic SAMP/RAMP framework has included the use of more sterically hindered groups on the arm to give chiral auxiliaries such as SADP, SAEP, SAPP[5] and RAMBO.[6] Replacement of the terminal methoxy group with a trimethylsiloxy group showed comparable enantioselectivities to SAMP in asymmetric α-alkylation reactions and very good selectivities with aldol reactions.[7] More recently, Coltart has successfully used chiral *N*-amino cyclic carbamate hydrazones as an alternative to SAMP-type hydrazones, allowing the preparation of both α-alkylated and α,α-bisalkylated ketones in a convenient and scalable manner.[8]

With such a limited number of routes available to chiral α-alkylated ketones, there remains significant scope for the exploration of new, easily prepared chiral auxiliaries for use in their synthesis. We set out to investigate if a nitrogen (as part of a pyrrolidine system) could ligate to lithium as effectively as in the SAMP/RAMP system (where a –OMe group is utilised). We herein report the chromatography-free synthesis of a novel chiral auxiliary incorporating a pyrrolidine ring. The chiral hydrazine is available in four steps from N-protected proline **1** or only two steps from commercially available (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **3**. Subsequent reaction with symmetrical and unsymmetrical ketones followed by deprotonation, alkylation (using both alkyl and the rarely reported benzyl electrophiles) and hydrolysis gave valuable chiral ketones in very good ee and moderate yields. The chiral auxiliary can be applied to both aldol and Michael reactions.

2. Results and discussion

Chiral auxiliary **5** was formed in a five step sequence from commercially available (*S*)-*N*-(benzyloxycarbonyl)proline **1** via DCC coupling to provide amide **2** in 81% yield. Two reduction steps afforded chiral diamine **3** in good yield. Nitrosation gave **4** and a final $LiAlH_4$ reduction furnished hydrazine **5**. Chiral auxiliary **5** was reacted with 3-pentanone to give chiral hydrazone **6** in 80% yield (46% yield after purification by distillation) (Scheme 1). In a similar manner, **5** was combined with propiophenone, *p*-methoxypropiophenone and *p*-fluoropropiophenone to afford hydrazones **7a**, **7b** and **7c** in 52%, 54% and 48% yields, respectively (Scheme 2).

Chiral hydrazone **6** was then subjected to LDA (5 h, room temperature) deprotonation and alkylated with benzyl bromide (addition at −110 °C, temperature held for 1 h at −110 °C then for 5 h at −70 °C) in either diethyl ether, toluene or tetrahydrofuran. The resultant alkylated hydrazone **8** was hydrolysed using a biphasic 4 M HCl/diethyl ether system and ketone **9** was analysed for enantioselectivity using chiral gas chromatography (Scheme 3). The use of diethyl ether as the solvent for the alkylation step afforded **9** with very good enantioselectivity (89% ee) in comparison to toluene and tetrahydrofuran (66% and 61% ee, respectively) albeit in moderate yields (20–30%).[9]

Improved yields were obtained on extension of the deprotonation time to 16 h and by decreasing the temperature to 0 °C. In these cases complete conversion to the alkylated hydrazone was observed. Yields remained moderate, most likely due to the high volatility of the resulting ketones.[10]

Various methods for the cleavage of α-substituted hydrazones to the corresponding ketones have been utilised.[11] Oxalic acid is reported as a convenient, high yielding, racemisation-free method for the hydrolytic cleavage of SAMP hydrazones.[12] However, when

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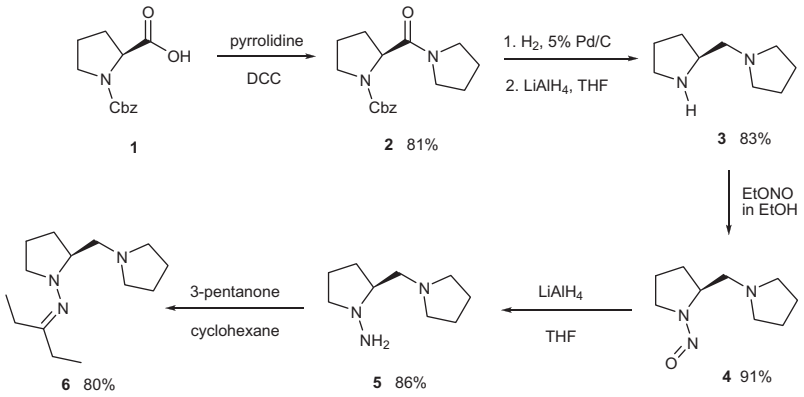
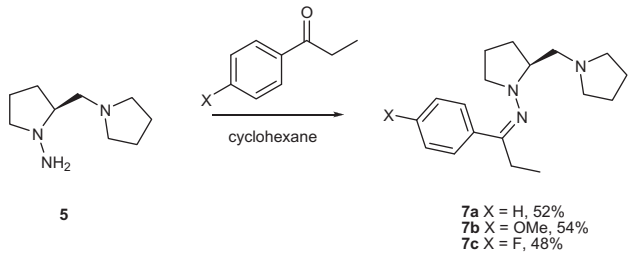


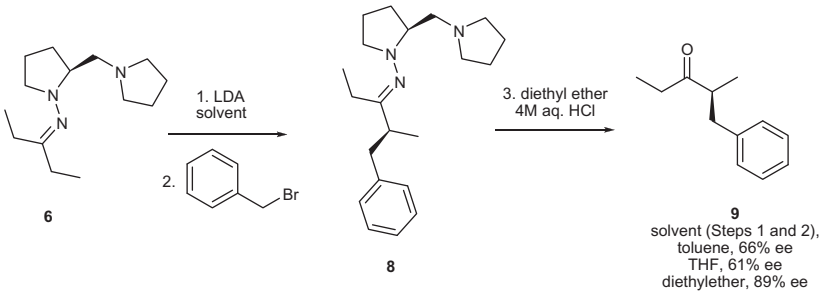
Scheme 1. Synthesis of the chiral auxiliary and the corresponding 3-pentanone hydrazone.



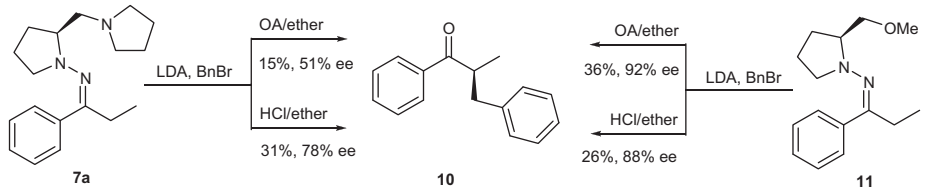
Scheme 2. Synthesis of propiophenone-based hydrazones.

we employed oxalic acid as a hydrazone cleavage method only moderate enantioselectivity was observed in the chiral ketones.[13] We suspected that racemisation was occurring, possibly due to some protonation of the pyrrolidine and increased solubility and exposure to the aqueous acidic layer. In order to investigate this possibility, both chiral hydrazone **7a** and the corresponding SAMP variant **11** were prepared and subjected to LDA and benzylbromide (Scheme 4). Both hydrazones were hydrolysed using oxalic acid and HCl/diethyl ether. Using the SAMP hydrazine, benzylated propiophenone **10** was obtained in 92% and 88% ee using oxalic acid and HCl/diethyl ether cleavage methods, respectively. A larger variation in the enantioselectivity was observed between the two cleavage methods when chiral auxiliary **7a** was employed in the reaction (51% and 78% ee). This clearly indicates that racemisation does occur when oxalic acid is used in combination with our chiral auxiliary and underlines the need for a thorough investigation of cleavage methods in such cases. To the best of our knowledge, the enzymatic cleavage of chiral hydrazones has not been reported. Porcine pancreatic lipase (PPL) was chosen as an appropriate enzyme because of its use in the cleavage of dimethylhydrazones.[14] Its use furnished ketone **9** in low (ca. 10%) yield (over two steps) albeit in 83% ee (Table 1, entry 8). Finally, a biphasic hydrolysis method (HCl/diethylether) was attempted. Clean conversion from alkylated hydrazones to ketones was observed with little or no racemisation occurring.

With usable hydrolysis conditions in hand, a variety of electrophiles were reacted with the azaenolate derived from **6**. The reaction of 3-pentanone hydrazone **6** with LDA and pentyliodide gave ketone **12** with 92% ee, albeit in moderate yield (Table 1, entry 1). When *t*-BuLi was employed as the base instead of LDA, the selectivity dropped to 82% ee (entry 2). Various other aliphatic electrophiles were employed to afford ketones **13**–**16** (entries 3–6) with very good enantioselectivities. We next turned our

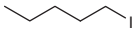
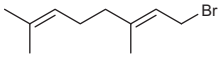
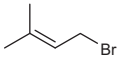
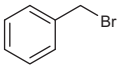
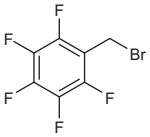
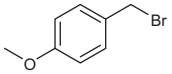
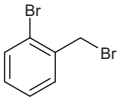
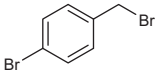
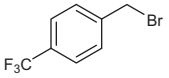
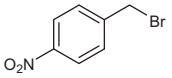
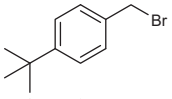
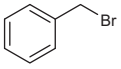


Scheme 3. Solvent screen for the alkylation step of a chiral hydrazone.



Scheme 4. Racemisation studies of chiral hydrazone **7a** and the SAMP variant **11** using oxalic acid (OA) or a biphasic 4 M HCl mediated cleavage. Isolated yields quoted over two steps.

Table 1
Results of alkylation reactions of hydrazones

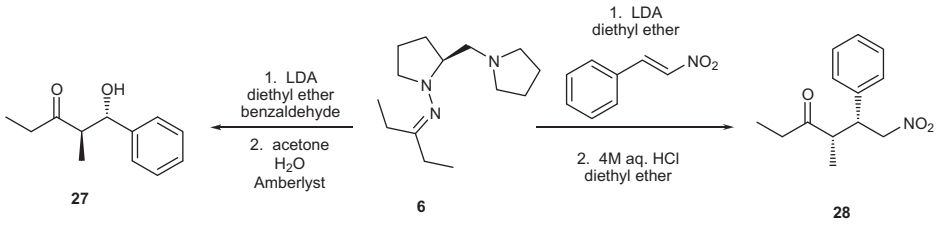
Entry	Hydrazone	Electrophile	Product ketone	% Yield (over two steps)	% ee[e]
1	**6**		**12**	13	**92**[a]
2	**6**		**12**	29	82[a,b]
3	**6**		**13**	**63**	55[c]
4	**6**		**14**	23	90[a]
5	**6**		**15**	15	86[a]
6	**6**		**16**	19	89[a]
7	**6**		**9**	7	89[a]
8	**6**		**9**	10	83[d]
9	**6**		**17**	34	48[a]
10	**6**		**18**	24	84[a]
11	**6**		**19**	21	86[a]
12	**6**		**20**	19	62[c]
13	**6**		**21**	14	73[c]
14	**6**		**22**	6	58[a]
15	**6**		**23**	28	87[a]
16	**7a**		**10**	15	78[a]
17	**7a**		**24**	25	89[a]
18	**7b**		**25**	29	79[a]
19	**7c**		**26**	33	90[a]

Yield is calculated over two steps; alkylation of the parent hydrazone and hydrolysis of the alkylated hydrazone to the product ketone. Alkylated hydrazone is not isolated.
[a] HCl/diethyl ether hydrolysis.
[b] *t*-BuLi used as the base.
[c] Satd aq oxalic acid/diethyl ether hydrolysis.
[d] PPL hydrolysis. The ketone products have been assigned as (*S*) by comparison of the specific rotation value of **24** with that reported in the literature and others by analogy.[15]
[e] All ee values were determined using chiral GC analysis and confirmed by comparison with independently prepared racemic ketones.

attention to the use of benzyl bromides as electrophiles. Their use in hydrazone chiral auxiliary methodology has been very limited. In fact, no thorough investigation of benzyl based electrophiles has been reported using chiral hydrazone methodology. A plethora of electrophiles were used affording ketones **9**, and **17**–**23**, all with good enantioselectivity. Substituted benzyl groups allowed us to probe the effect of electron withdrawing and donating groups present on the electrophiles. The presence of electron withdrawing groups on the benzyl moiety caused a decrease in the enantioselectivity of the resultant ketone when compared to the unsubstituted benzyl bromide (entry 7, 89%), which is most apparent with the use of perfluorobenzyl bromide (entry 9, 48%). The presence of an electron donating group, for example the use of *p*-methoxybenzyl bromide (entry 10, 84%), had little effect on the enantioselectivity observed.

Further to these studies it was decided to investigate the effect of the electronic substituents on the hydrazone moiety. Propiophenone, *p*-methyoxypropiophenone and *p*-fluoropropiophenone hydrazones **7a**–**c** were chosen as substrates and subjected to the standard conditions using allyl bromide as the electrophile. The resultant ketones **24**–**26** demonstrate that the presence of an electron donating substituent on the ring (entry 18, 79% ee) results in a decrease in the enantioselectivity when compared to the unsubstituted ketone (entry 17, 89% ee). The presence of an electron withdrawing substituent (entry 19, 90% ee), had little effect on the enantioselectivity.

We then applied our methodology to an aldol reaction (Scheme 5). Hydrazone **6** was deprotonated using LDA, reacted with benzaldehyde and hydrolysed using Amberlyst® to afford **27** in 39% yield over two steps. Enantiomeric excesses of 63% and



Scheme 5. Aldol and Michael reactions. Absolute stereochemistry unknown.

15% were obtained for *anti*- and *syn*-**27**, respectively. A diastereomeric ratio of 86:14 *anti*/*syn*, determined by GC, was identical to that observed by ^{1}H NMR.[16] The relative stereochemistry observed (*anti*) was opposite to that usually seen in aldol reactions using SAMP (*syn*).

Our novel chiral auxiliary was then applied to a Michael reaction (Scheme 5). Hydrazone **6** was treated with LDA and *trans*-β-nitrostyrene followed by subsequent hydrolysis to afford crude **28**, which was subjected to GC analysis. Enantiomeric excesses of 84% and 47% were determined for *syn*- and *anti*-**28**, respectively, with an excellent diastereomeric ratio of 94:6 *syn*/*anti* as determined by GC and NMR analysis. Again the relative orientation was opposite to that usually formed when using a SAMP chiral auxiliary in Michael reactions.[1c,17] Purification using column chromatography allowed isolation of *syn*-**28** in 84% ee and 13% yield over two steps.

3. Conclusion

A novel hydrazone-based chiral auxiliary has been established involving a pyrrolidine arm. The chiral auxiliary has been formed in good yields in five steps from commercially available (*S*)-*N*-(benzyloxycarbonyl)proline **1** (or only two steps from commercially available (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **3**) without the need for silica column chromatography purification. Enantiomeric excesses of up to 92% were achieved in the α-alkylated aliphatic ketones formed and up to 89% in the less studied aromatic ketones. While the overall yields were moderate (in many cases due to product volatility), comparison studies with the SAMP chiral auxiliary showed comparable yields (Scheme 4). However, given the remarkably few methods available to access these compounds and the excellent enantioselectivities observed, we are pleased to report our novel chiral auxiliary as a viable route to these chiral synthons. Initial unoptimised studies into the use of our chiral auxiliary in Michael reactions have proven to be successful.

4. Experimental

4.1. Procedure for synthesis of the chiral auxiliary:

4.1.1. (*S*)-1-[*N*-(benzyloxycarbonyl)proly]-pyrrolidine 2[18]

To a CH_2Cl_2 solution (120 mL) of (*S*)-*N*-(benzyloxycarbonyl)proline (74.57 g, 0.3 mol) was added dropwise a CH_2Cl_2 solution (120 mL) of DCC (61.69 g, 0.3 mol) at 0 °C under a nitrogen atmosphere. After stirring for 30 min, a CH_2Cl_2 solution (120 mL) of pyrrolidine (24.7 mL, 0.3 mol) was slowly added dropwise to the reaction mixture at 0 °C via an addition funnel. The reaction mixture was allowed to warm to room temperature overnight. The precipitate was removed by filtration through a pad of Celite® and washed with CH_2Cl_2. The filtrate was washed with 0.5 M HCl (2 × 150 mL), satd aq $NaHCO_3$ solution (150 mL), H_2O (150 mL) and brine (150 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo and the crude product recrystallised from ethyl acetate to yield product **2** as a white, crystalline solid (73.52 g, 81% yield). $[\alpha]_D^{22} = -13.3$ (*c* 1.60, MeOH) {lit.[19] $[\alpha]_D^{22} = -14.1$ (*c* 1.61, MeOH)}. Mp 123–125 °C [lit.[19] 130–130 °C]. δ_H ($CDCl_3$, 300 MHz) (mixture of rotamers) 1.56–2.20 (8H, m, 4× CH_2), 3.25–3.75 (6H, m, 3× CH_2), 4.39–4.54 (1H, m, CH), 4.97–5.22 (2H, m, CH_2), 7.28–7.37 (5H, m, ArH). δ_C ($CDCl_3$, 75.5 MHz) (mixture of rotamers) 23.8, 23.9 (CH_2), 24.1, 24.4 (CH_2), 26.0, 26.3 (CH_2), 29.5, 30.5 (CH_2), 46.0, 46.0 (CH_2), 46.1, 46.3 (CH_2), 46.7, 47.3 (CH_2), 57.7, 58.2 (CH_2), 66.9, 67.1 (CH), 127.8, 127.9 (2× ArCH), 128.0, 128.1 (ArCH), 128.4, 128.4 (2× ArCH), 136.7, 136.8 (quaternary C), 154.2, 154.9 (C=O), 170.7, 171.0 (C=O). *m*/*z* (ES+) 303 [$(M+H)^+$, 100%].

4.1.2. (*S*)-2-(1-Pyrrolidinylmethyl)-pyrrolidine 3[20]

To a methanol (350 mL) solution of **2** (75.40 g, 250 mmol) was added Pd/C (5%, 4.78 g). The reaction mixture was then stirred under hydrogen at atmospheric pressure for 22 h while monitoring the reaction progress by TLC analysis. The crude reaction mixture was filtered through a pad of Celite® and washed with methanol to elute the product. The filtrate was concentrated in vacuo to yield the crude amide as a yellow oil (39.84 g, 95% yield). $[\alpha]_D^{26} = -89.6$ (*c* 1.7, EtOH) {lit.[21] $[\alpha]_D^{26} = -112.2$ (*c* 1.7, EtOH)}. δ_H ($CDCl_3$, 300 MHz) 1.60–2.02 (7H, m, 7× CH_2), 2.05–2.14 (1H, m, CH_2), 2.77–2.85 (1H, m, CH_2), 2.93 (1H, br s, NH), 3.15–3.22 (1H, m, CH_2), 3.36–3.57 (4H, m, 2× CH_2), 3.73–3.77 (1H, dd, *J* = 6.5, 8.6 Hz, CH). δ_C ($CDCl_3$, 75.5 MHz) 24.0, 26.0, 26.5, 30.4, 45.9, 46.0, 47.7 (7× CH_2), 59.5 (CH), 172.7 (C=O). *m*/*z* (ES+) 169 [$(M+H)^+$, 100%]. A solution of amide (19.02 g, 113 mmol) in dry THF (80 mL) was added dropwise over 3 h to $LiAlH_4$ (15.00 g, 396 mmol) in dry THF (140 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to stir at room temperature overnight, heated at reflux for 4 h, then allowed to stir at room temperature overnight. The reaction mixture was quenched by the dropwise addition of satd aq Na_2SO_4 solution (20 mL). The crude reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate. The mother liquor was concentrated in vacuo to give the crude product as a yellow oil (14.54 g, 83% yield). Additional purification was achieved by Kugelrohr distillation yielding **3** as a colourless oil (11.22 g, 64% yield). $[\alpha]_D^{20} = +5.2$ (*c* 2.4, EtOH) [lit.[21] $[\alpha]_D^{20} = +8.9$ (*c* 2.4, EtOH)]. δ_H ($CDCl_3$, 300 MHz) 1.22–1.43 (1H, m, CH_2), 1.68–1.81 (6H, m, 3× CH_2), 1.82–1.95 (1H, m, CH_2), 2.31–2.37 (1H, dd, *J* = 5.2, 11.9 Hz, CH_2), 2.45–2.61 (6H, m, 3× CH_2, NH), 2.81–2.89 (1H, m, CH_2), 2.94–3.02 (1H, m, CH_2), 3.17–3.26 (1H, m, CH). δ_C ($CDCl_3$, 75.5 MHz) 23.4 (2× CH_2), 25.0, 30.1, 46.1 (3× CH_2), 54.6 (2× CH_2), 57.4 (CH), 62.1 (CH_2). *m*/*z* (ES+) 155 [$(M+H)^+$, 100%].

4.1.3. (*S*)-1-Nitroso-2-(pyrrolidin-1-ylmethyl)pyrrolidine 4

At first, 10–20% ethyl nitrite in ethanol (taken to be 15%) (5.45 mL, 8.63 mmol) was added to **3** (1.065 g, 6.90 mmol). The reaction vessel was covered in aluminium foil and allowed to stir at room temperature with progress monitored by ^{1}H NMR spectroscopy. After 45 h, ethanol was removed in vacuo to yield **4** as a yellow oil (1.15 g, 91% yield). δ_H ($CDCl_3$, 300 MHz) 1.76–

1.81 (4H, m, 2× CH_2), 1.91–2.25 (4H, m, 2× CH_2), 2.54–2.67 (4H, m, 2× CH_2), 2.80 (1H, dd, J = 8.8, 12.2 Hz, CH_2), 3.00 (1H, dd, J = 5.1, 12.2 Hz, CH_2), 3.52–3.75 (2H, m, CH_2), 4.59–4.67 (1H, m, CH). δ_C ($CDCl_3$, 75.5 MHz) 20.7 (CH_2), 23.5 (2× CH_2), 28.7, 45.6 (2× CH_2), 54.7 (2× CH_2), 59.5 (CH_2), 60.3 (CH). Since nitrosamines are potentially carcinogenic, no further data was obtained and the crude reaction mixture was used without purification in the next step.

4.1.4. (*S*)-2-(Pyrrolidin-1-ylmethyl)pyrrolidin-1-amine 5

To a solution of $LiAlH_4$ (2.61 g, 69 mmol) in dry THF (120 mL) was added dropwise a solution of **4** (6.30 g, 34 mmol) in dry THF (60 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to stir at 0 °C for 1 h, then at room temperature for 1 h before being heated at reflux for 4.5 h and stirred at room temperature overnight. The reaction progress was monitored by ^1H NMR spectroscopy. On completion, the reaction vessel was transferred to an ice bath and quenched by the dropwise addition of H_2O (2.6 mL), 3 M aq NaOH (2.6 mL) and H_2O (7.2 mL). The reaction mixture was filtered through a pad of Celite® using ether to elute the product. The mother liquor was concentrated in vacuo to yield **5** as a yellow oil (4.98 g, 86%). $[\alpha]_D^{20} = -11.4$ (c 1, EtOH). ν_{max}/cm^{-1} (KBr): 3306 (N–H stretch, m), 1591 (N–H bending, m), 1137 (C–N stretch, m). δ_H ($CDCl_3$, 300 MHz) 1.41–1.54 (1H, m, CH_2), 1.68–1.85 (6H, m, 3× CH_2), 1.93–2.07 (1H, m, CH_2), 2.26–2.41 (3H, m, 2× CH_2), 2.45–2.53 (2H, m, CH_2), 2.54–2.62 (2H, m, CH_2), 2.69–2.72 (3H, m/br s, CH_2/NH_2), 2.85–2.91 (1H, m, CH_2), 3.22–3.29 (1H, m, CH). δ_C ($CDCl_3$, 75.5 MHz) 20.6 (CH_2), 23.5 (2× CH_2), 28.7 (CH_2), 54.8 (2× CH_2), 59.6 (CH_2), 61.5 (CH_2), 67.8 (CH). Exact mass calcd for $C_8H_{11}IO_2$ [(M+H)$^+$], 170.1657. Found 170.1674.

4.1.5. (*S*)-*N*-(Pentan-3-ylidine)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-amine 6

3-Pentanone (9.34 mL, 88 mmol) was added dropwise to a stirred solution of **5** (4.98 g, 29 mmol) in cyclohexane (8 mL) under an atmosphere of nitrogen. The reaction mixture was then allowed to stir at room temperature overnight and reaction progress monitored by ^1H NMR spectroscopy. On completion, the reaction mixture was poured into 6:1 DCM/H_2O and the organic layer extracted. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude product as a yellow oil (5.61 g, 80% yield). Purification was achieved by Kugelrohr distillation to yield the product as a colourless oil (4.52 g, 65% yield). $[\alpha]_D^{20} = +114$ (c 1, EtOH). ν_{max}/cm^{-1} (NaCl): 1637 (C=N stretch, s), 1342, 1138 (C–N stretch, m). δ_H ($CDCl_3$, 300 MHz) 1.07 (6H, q, 2× CH_3), 1.53–1.66 (1H, m, CH_2), 1.69–1.91 (6H, m, 3× CH_2), 2.02–2.14 (1H, m, CH_2), 2.17–2.29 (2H, m, CH_2), 2.30–2.55 (9H, m, 4× CH_2, CH), 2.97–3.10 (2H, m, CH_2). δ_C ($CDCl_3$, 75.5 MHz) 10.9 (2× CH_3), 11.8, 21.8, 23.5, 23.5, 28.6, 28.7, 54.8, 55.0, 61.4 (10× CH_2), 66.1 (CH), 173.3 (CN). Exact mass calcd for $C_{14}H_{27}N_3$ [(M+H)$^+$], 238.2277. Found 238.2283.

4.2. General procedure for synthesis of racemic ketones

To THF (5 mL) was added commercially available LDA (1.1 equiv) at −78 °C. The reaction was stirred for 5 min and 3-pentanone was added dropwise. The reaction was stirred at −78 °C for 30 min and the electrophile (1.1 equiv) was added (in 3 mL THF if solid). The reaction was allowed to warm to room temperature overnight. Next, at. aq NH_4Cl solution (10 mL) was added and the crude product extracted with ethyl acetate or ether (3× 15 mL), dried over $MgSO_4$ and concentrated in vacuo to yield the crude product, which was purified by silica column chromatography.

4.3. General procedure for HCl/diethyl ether hydrolysis

At first, 4 M HCl (0.5 mL) and water (0.5 mL) were added to a vigorously stirred solution of alkylated hydrazone in diethyl ether (5 mL). The reaction progress was monitored by TLC analysis every 10 min. On completion, water (10 mL) was added, followed by extraction with diethyl ether (3× 25 mL). The organic layers were combined and washed with water (2× 10 mL), dried over $MgSO_4$ and concentrated in vacuo to yield the ketone, which was purified by silica column chromatography.

4.4. Procedure for PPL hydrolysis

To a solution of PPL (100 mg) in water (10 mL) was added a solution of alkylated hydrazone (1.05 mmol) in acetone (6 mL). The reaction was allowed to stir at room temperature for 23 h, diluted with diethyl ether (20 mL), washed with brine (3× 15 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification was achieved using silica column chromatography to yield **9** as a yellow oil (19.3 mg, 10% yield over two steps).

4.5. General procedure for oxalic acid hydrolysis

At first, satd aq oxalic acid (1.5 vol with respect to mmol hydrazone) was added to a vigorously stirred solution of alkylated hydrazone in diethyl ether (4 vol with respect to mmol hydrazone). The reaction progress was monitored by TLC analysis and on completion were added water (5 mL) and diethyl ether (3× 20 mL). Organic extracts were combined, dried over $MgSO_4$ and concentrated in vacuo to yield the ketone which was purified by silica column chromatography.

4.6. Example procedure for the alkylation of chiral hydrazone

To a stirred solution of dry diisopropylamine (0.16 mL, 1.16 mmol) in dry diethyl ether (4 mL) in an N_2 filled Schlenk tube at −78 °C was added 1.6 M *n*-BuLi (0.86 mL, 1.21 mmol). The solution was allowed to stir at 0 °C for 30 min to generate a solution of LDA. Hydrazone **6** (250 mg, 1.05 mmol) was added slowly dropwise at −78 °C and allowed to stir at 0 °C for 16 h. A solution of *n*-pentyl iodide (250 mg, 1.26 mmol) in dry diethyl ether (2 mL) in a separate Schlenk, which was previously evacuated and filled with N_2 three times, was added dropwise to a solution of deprotonated hydrazone at −110 °C. The temperature of the reaction was kept at −110 °C for 1 h, then at −70 °C for 5 h before being allowed to warm gradually to room temperature overnight. Next, satd aq NH_4Cl solution (10 mL) was added to quench the reaction followed by extraction with diethyl ether (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo to yield the crude alkylated hydrazone as a yellow oil, which was hydrolysed using HCl/diethyl ether to yield the crude product as a yellow oil. Purification was carried out using silica column chromatography eluting with 95:5 hexane/diethyl ether to afford **12** as a pale yellow oil (22 mg, 13% and 92% ee). $[\alpha]_D^{20} = +5.5$ (c 0.2, Et_2O). ν_{max}/cm^{-1} (film) 2961, 2932 (alkane CH stretches), 1714 (C=O). δ_H ($CDCl_3$, 300 MHz) 0.88 (3H, t, J = 6.8 Hz, CH_3), 1.04 (3H, t, J = 7.3 Hz, CH_3) 1.06 (3H, d, J = 6.9 Hz, CH_3), 1.17–1.35 (8H, m, 4× CH_2), 2.46 (2H, dq, J = 1.5, 7.3 Hz, CH_2), 2.48–2.58 (1H, m, CH). δ_C ($CDCl_3$, 125 MHz) 7.8, 14.1, 16.5 (3× CH_3), 22.5, 27.0, 31.9, 33.1, 34.2 (5× CH_2), 46.1 (CH), 215.7 (C=O). Exact mass calcd for $C_{10}H_{21}O$ [(M+H)$^+$], 157.1592. Found 157.1584. Sample for GC made up at 1 mg/mL in dry dichloromethane and run on Agilent Technologies 7820A GC System using G4513A Injector and Astec Chiraldex G-TA fused silica capillary column purchased from Sigma Aldrich Supelco using conditions 105 °C hold 10 min, ramp 10 °C/min to 140 °C hold 5 min, flow 1 mL/min, inj. vol. 0.2 μL, split ratio 10:1, front inlet 150 °C, detector 155 °C. Retention time: 3.63 min (minor), 3.87 min (major).

4.7. Example of the procedure for the Michael reaction

To a stirred solution of dry diisopropylamine (0.2 mL, 1.39 mmol) in dry diethyl ether (4 mL) in an N_2 filled Schlenk tube at −78 °C was added 1.6 M *n*-BuLi (0.91 mL, 1.45 mmol). The solution was then allowed to stir at 0 °C for 30 min to generate a

solution of LDA. Hydrazone **6** (299 mg, 1.26 mmol) was slowly added dropwise at −78 °C and allowed to stir at 0 °C for 16 h. Next, *trans*-β-nitrostyrene (245 mg, 1.64 mmol) was dissolved in dry diethyl ether (3 mL), cooled to −78 °C and then slowly added dropwise to a solution of deprotonated hydrazone at −110 °C via a cannula. The temperature of the reaction was kept at −110 °C for 1 h, then at −70 °C for 5 h before being allowed to warm gradually to room temperature overnight. Next, satd aq NH_4Cl solution (10 mL) was added to quench the reaction followed by extraction with diethyl ether (3× 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo to yield a product as a dark yellow solid, which was hydrolysed using HCl/diethyl ether to yield the crude product as a pale brown oil (GC analysis of crude obtained), which was purified using silica column chromatography eluting with 90:10 hexane/diethyl ether to afford *syn*-**28** as a yellow oil (37 mg, 13% and 84% ee). $[\alpha]_D^{22} = +3.5$ (*c* 0.2, $CHCl_3$). {lit.[22] $[\alpha]_D^{22} = +8.9$ (*c* 0.2, $CHCl_3$)}. δ_H ($CDCl_3$, 300 MHz) 0.97 (3H, d, *J* = 7.1 Hz, CH_3), 1.07 (3H, t, *J* = 7.3 Hz, CH_3), 2.41 (1H, dq, *J* = 7.3, 18.0 Hz, CH_3CH_2), 2.61 (1H, dq, *J* = 7.3, 18.0 Hz, CH_3CH_2), 2.94–3.05 (1H, m, CH_3CH), 3.66–3.73 (1H, m, *CH*Ar), 4.57–4.71 (2H, m, CH_2NO_2), 7.14–7.17 (2H, m, ArH), 7.29–7.33 (3H, m, ArH). δ_C ($CDCl_3$, 75.5 MHz) 7.6, 16.3 (2× CH_3), 35.4 (CH_2), 46.1, 48.3 (2× CH), 78.3 (CH_2), 127.9, 129.0 (5× ArC), 137.6 (quaternary C), 213.6 (C=O). *m*/*z* (ES+) 235 [$(M+H)^+$, 78%]. Samples for GC made up at 1 mg/mL in dry dichloromethane and ran on Agilent Technologies 7820A GC System using G4513A Injector and Astec Chiraldex G-TA fused silica capillary column purchased from Sigma Aldrich Supelco using conditions 140 °C hold 70 min, flow 1 mL/min, inj. vol. 0.2 μL, split ratio 10:1, front inlet 150 °C, detector 155 °C. *anti*-**28** could not be isolated. Retention times: 44.95 min (*syn*), 51.05 min (*anti*), 52.40 min (*syn*), 55.53 min (*anti*).

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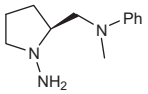

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