Enantioselective Henry reaction catalyzed by C_2-symmetric chiral diamine–copper(II) complex†

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A copper(II) complex of C_2-symmetric diamine has been proved to be an efficient catalyst for the enantioselective Henry reaction between nitroalkanes and various aldehydes to provide β-hydroxy nitroalkanes in high yields (up to 97%), moderate diastereoselectivities (up to 71:29) and excellent enantiomeric excesses (up to 96%). The chiral nitroaldol adduct obtained has been further converted into chiral aziridine in few steps.

Introduction

The Henry[1] (nitroaldol) reaction remains one of the most widely utilized transformations in synthetic organic chemistry. The enantioselective version of this reaction can provide access to important enantiomerically enriched β-nitroalkanols, which are versatile precursors for a wide range of important organic intermediates.[2] The nitro group in the product can be converted into amines (reduction), carbonyl compounds (Nef reaction),[3c] azides (S_N2 displacement),[2d] and other bifunctional compounds.[3] However, despite its importance, the asymmetric Henry reaction was not explored until 1992. Shibasaki *et al.* reported the first example of asymmetric addition of nitromethane to aldehyde using a BINOL derived heterobimetallic complex.[4] Since this pioneering work, the enantioselective Henry reaction has gained much attention and various types of chiral metal catalyst and organocatalyst[5] have been extensively studied. Copper complexes of chiral ligands such as bis(oxazoline),[6] (–)-sparteine,[7] bisimidazoline,[8] diamine,[9] sulfonyldiamine,[10] aminopyridine,[11] tetrahydrosalen,[12a] and *N*,*N*′- dioxide[12b] have been developed for this reaction. Although a reasonable number of catalysts having metals other than copper, such as dinuclear zinc,[13a] zinc triflate-amino alcohol,[13b] zinc-bisoxazolidine,[13c] zinc-fam catalyst,[13d] cobalt-ketoimino complexes,[14] nano-crystalline MgO,[15] and salen-chromium complex[16] have also been developed. Some of these methods have certain limitations such as high catalyst loading, the use of activated silylnitronates, low substrate scope, expensive starting materials, and long synthetic sequences for the ligand synthesis and the use of additives such as molecular sieves. Besides these, only a few catalytic systems have been tested for the diastereoselective Henry reaction. In this paper, we address some of these issues and delineate full details of our work in this area.

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Results and discussion

The design, synthesis, and tuning of a suitable chiral ligand around a metal center is an important task in asymmetric synthesis.[17] As a part of our research programme towards the application of versatile and fine tunable chiral non-racemic diamines in enantioselective reactions,[18] we intended to evaluate similar kinds of amino acid derived diamine ligands (Fig. 1) for the enantioselective Henry reaction.

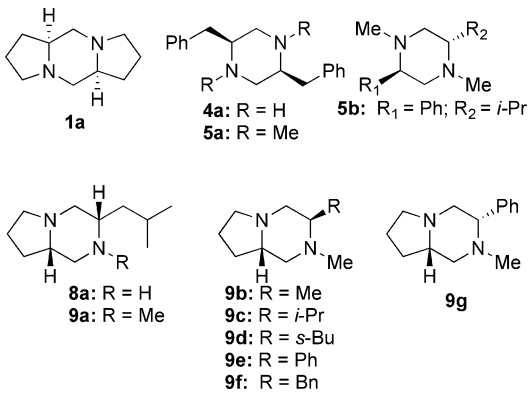
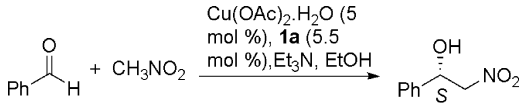


Fig. 1 Chiral diamine ligands.

A chiral C_2-symmetric diamine **1a** is known in the literature and has been used for enantioselective alkylation of carbonyl compounds,[19a] asymmetric benzoylation of 1,2-meso diols,[19b] and enantioselective Baylis–Hillman reactions.[19c,d] At the outset, it appeared logical to test this diamine in the Henry reaction. It was synthesized according to the known literature procedure starting from L-proline.[19b] In order to optimize the reaction conditions, a series of reactions were carried out between nitromethane and benzaldehyde in ethanol with **1a**–$Cu(OAc)_2 \cdot H_2O$ complex as the catalyst. The reaction was complete in 28 h at room temperature and the nitroaldol adduct was obtained in 74% ee (Table 1, entry 1). However, on decreasing the reaction temperature from rt to 0 °C and then to –20 °C, enantioselectivity increased remarkably with a decrease in the rate of the reaction (Table 1, entries 2 and 3). In order to improve the chemical yield of the reaction, without affecting the enantioselectivity, base promoter[7] such as Et_3N were added for the activation of nitromethane. Thus, the catalyst

Table 1 Effect of the amount of Et_3N on the enantioselective Henry reaction[a]



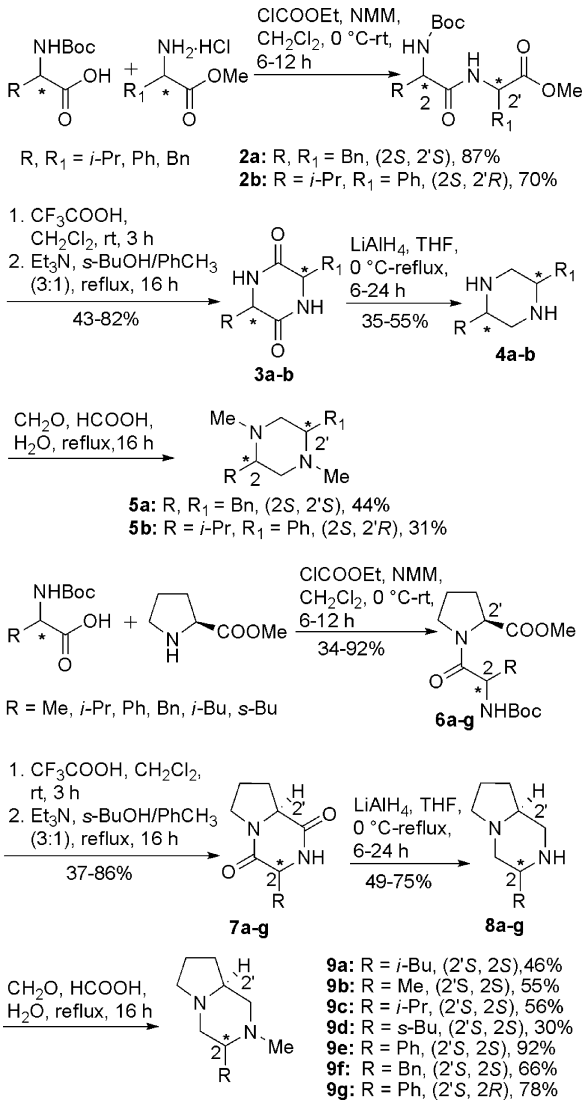
entry	Et_3N (mol%)	temperature (°C)	time (h)	yield (%)	ee[b] (%)
1	–	rt	28	86	74
2	–	0	62	28	86
3	–	–20	48	24	90
4	2	–20	62	32	90
5	5	–20	72	46	86
6	10	–20	36	70	88
7	20	–20	36	98	86
8	50	–20	24	97	75
9	100	–20	24	98	65
10	10	–40	96	75	92

[a] Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane in 2 mL of ethanol. [b] Determined by chiral HPLC using Chiralcel OD-H column. The absolute configurations were established by comparison with literature data.

1a–Cu(II) complex was activated towards the Henry reaction under dual acid/base catalysis[20] conditions. It was gratifying to note that Et_3N increased the rate of the reaction without having a significant effect on the enantioselectivity. With 2 mol% of Et_3N at –20 °C, the reaction took longer and the corresponding product was obtained in 32% yield and 90% ee (Table 1, entry 4). However, on increasing the amount of Et_3N from 5 mol% to 20 mol%, the chemical yield of the reaction increased rapidly without affecting the enantioselectivity (Table 1, entries 5–7). Further increases in the amount of base resulted in the depletion of enantioselectivity (Table 1, entries 8 and 9). It was also observed that the use of 10 mol% of Et_3N and a reaction temperature of –40 °C are optimum for achieving high enantioselectivity in the reaction (Table 1, entries 6 and 10).

Having achieved good results in the above reaction with the ligand **1a**, it was logical to evaluate similar kinds of chiral piperazine derivative having mono- and bicyclic skeletons. With this aim, a variety of chiral diamines were synthesized. The generality of the synthesis was demonstrated in the preparation of these diamines in four steps from commercially available α-amino acids. The nature of the substituent at the stereocenter is dictated by the selection of the starting amino acid (Scheme 1). The coupling reaction of *N*-Boc amino acids with appropriate amino esters was carried out in the presence of ethylchloroformate and *N*-methylmorpholine. The Boc protecting group was then cleaved using TFA in CH_2Cl_2, which on subsequent reflux with Et_3N in 2-butanol:toluene (3:1) afforded diketopiperazine[21] derivatives **3a–b** and **7a–g**. The diketopiperazines **3a–b** and **7a–g** obtained in this way were reduced to diamines **4a–b** and **8a–g** by using $LiAlH_4$. *N*-Methyl ligands **5a–b** and **9a–g** were synthesized by reductive amination[21a] of formaldehyde with the diamines **4a–b** or **8a–g** in the presence of formic acid.

After successful completion of ligand synthesis, the chiral piperazines with monocyclic skeletons (Fig. 1) were first examined in the enantioselective Henry reaction under optimized conditions. Interestingly, the substituents on the nitrogen atoms of

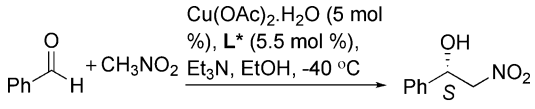


Scheme 1 Synthesis of chiral diamines.

phenylalanine-based diamines (**4a** *vs* **5a**) showed a significant effect on the enantioselectivity (Table 2, entries 2 and 3). Furthermore, only a trace amount of product was obtained in low enantioselectivity with diamine **5b** having different absolute stereochemistry (Table 2, entry 4). This clearly indicated that the matched chirality between the two amino acids is crucial for the high catalytic efficiency.

In order to study the effect of cyclic structures of diamine on enantioselectivity, diamines with bicyclic skeletons were then screened (Table 2, entries 5–12). A similar trend in enantioselectivity (*vide supra*) was observed after introducing a substituent on the nitrogen atom (Table 2, entries 2–3 *vs* 5–6). Next, the effect of variation in the substituents at the chiral centers of the bicyclic diamine ligands on the Henry reaction was studied. When the isobutyl group of the ligand **9a** was replaced by methyl, isopropyl, *sec*-butyl, benzyl or phenyl, the asymmetric induction in the reaction was scarcely affected (Table 2, entries 6–11). The absence of any asymmetric induction with ligand **9g** (Table 2, entry 12) indicated that both the stereogenic centers (*S*,*S*) of the diamine skeleton were essential for the chirality transfer in the catalytic

Table 2 Enantioselective Henry reaction of benzaldehyde with nitromethane in the presence of different ligands[a]

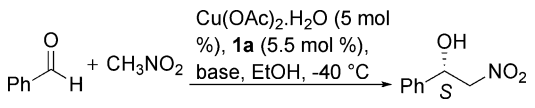


10a

entry	ligand	time (h)	yield (%)	ee[b] (%)
1	**1a**	96	75	92
2	**4a**	96	22	40
3	**5a**	102	47	77
4	**5b**	120	36	*rac*
5	**8a**	98	21	46
6	**9a**	102	61	89
7	**9b**	96	58	69
8	**9c**	96	63	75
9	**9d**	96	86	83
10	**9e**	144	53	39
11	**9f**	102	79	79
12	**9g**	144	44	*rac*

[a] Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane and 0.05 mmol of base in 2 mL of ethanol. [b] Determined by chiral HPLC using Chiralcel OD-H column.

Table 3 Effect of different bases on the enantioselective Henry reaction[a]



10a

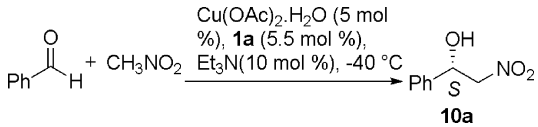
entry	base	time (h)	yield (%)	ee[b] (%)
1	Et_3N	96	72	92
2	$Et(iPr)_2N$	72	86	82
3	*N*-methylmorpholine	72	14	87
4	pyridine	72	14	52
5	DMAP	48	11	17
6	1-methyl-1*H*-imidazole	96	12	04
7	K_2CO_3	48	34	18
8	DBU	96	72	59

[a] Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane and 0.05 mmol of base in 2 mL of ethanol. [b] Determined by chiral HPLC using Chiralcel OD-H column.

Henry reaction (*vide supra*). From these results (Table 2), it was concluded that (*S*)-proline derived diamine **1a** with a tricyclic skeleton is superior in terms of yield and stereoinduction (Table 2, entry 1) and was thus chosen for further studies.

The drastic effect of Et_3N on the rate of the reaction prompted us to examine the effect of other bases for this reaction. Among the bases screened, Et_3N gave the best result (Table 3, entry 1). The use of bulky tertiary amines like iPr_2NEt and *N*-methylmorpholine gave lower enantioselectivity (Table 3, entries 2 and 3). Strong coordinating bases *viz* pyridine, DMAP and 1-methyl-1*H*-imidazole gave the product in poor chemical and optical yield (Table 3, entries 4–6). An inorganic base, K_2CO_3, gave poor results (Table 3, entry 7). Interestingly, the bulkier and more basic DBU gave the nitroaldol adduct in moderate yield and enantioselectivity (Table 3, entry 8).

Table 4 Effect of solvent on the enantioselective Henry reaction[a]

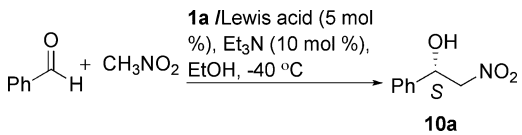


10a

entry	solvent	yield (%)	ee[b] (%)
1	methanol	59	63
2	ethanol	75	92
3	*n*-propanol	83	89
4	2-propanol	92	90
5	*n*-butanol	66	83
6	THF	39	83
7	acetonitrile	41	71
8	nitromethane	94	27[c]
9	dichloromethane	24	73

[a] Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane in 2 mL of solvent for 4 d. [b] Determined by chiral HPLC using Chiralcel OD-H column. [c] Reaction was carried out at –20 °C.

Table 5 Screening of Lewis acids for the enantioselective Henry reaction[a]



10a

entry	Lewis acid	yield (%)	ee[b] (%)
1	$Cu(OAc)_2{\cdot}H_2O$	75	92
2	$CuCl_2$	98	75
3	CuCl	51	37
4	$Cu(OTf)_2$	94	75
5	$Zn(OTf)_2$	17	*rac*
6	$Zn(OAc)_2{\cdot}2H_2O$	20	*rac*
7	$Pd(OAc)_2$	06	16

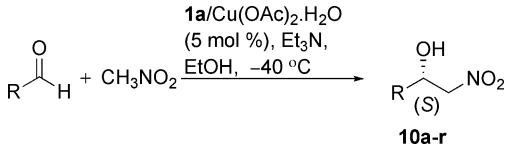
[a] Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane in 2 mL of ethanol for 4 d. [b] Determined by chiral HPLC using Chiralcel OD-H column.

The effect of solvent on the enantioselectivity in the Henry reaction catalyzed by diamine **1a** was also studied (Table 4). Among the different solvents screened, protic solvents were found to be superior to the aprotic ones, and of the different protic solvents screened, ethanol was the solvent of a choice (Table 4, entry 2).

A series of Lewis acids were then screened in combination with **1a** and Et_3N in ethanol (Table 5). $Cu(OAc)_2{\cdot}H_2O$ turned out to be the most suitable Lewis acid for the reaction. $CuCl_2$ and $Cu(OTf)_2$ also facilitated the reaction and afforded the nitroaldol adduct in excellent yield and moderate enantioselectivity (Table 5, entries 2 and 4). With other metal salts such as $Zn(OTf)_2$, $Zn(OAc)_2{\cdot}2H_2O$ and $Pd(OAc)_2$, reaction was sluggish and the product was almost racemic (Table 5, entries 5–7).

The scope and limitations of the Henry reaction catalyzed by **1a**–Cu(II) complex were then examined. A wide range of aldehydes including both aromatic and aliphatic aldehydes reacted smoothly with nitromethane under the optimized conditions, to give nitroaldol adduct in good yield and enantioselectivity[22] (Table 6). The rate of the reaction with aromatic aldehydes

Table 6 Enantioselective Henry reaction of nitromethane with different aldehydes[a]



10a-r

entry	R	time (h)	product	yield (%)	ee[b] (%)
1	C_6H_5	96	**10a**	75	92
2	2-$NO_2C_6H_4$	78	**10b**	91	87[c]
3	4-$NO_2C_6H_4$	78	**10c**	69	78[c]
4	4-$CF_3C_6H_4$	72	**10d**	60	90[c]
5	4-FC_6H_4	88	**10e**	97	89
6	3-MeC_6H_4	94	**10f**	91	84
7	4-ClC_6H_4	94	**10g**	93	85
8	4-MeC_6H_4	116	**10h**	94	87
9	2-$OMeC_6H_4$	90	**10i**	93	88
10	1-naphthyl	98	**10j**	70	80
11	2-MeC_6H_4	94	**10k**	77	87
12	2-thienyl	98	**10l**	66	84
13	2-ClC_6H_4	96	**10m**	94	84
14	3,5-$OMeC_6H_3$	106	**10n**	88	87
15	3,4,5-$OMeC_6H_2$	96	**10o**	90	83
16	$PhCH_2CH_2$	120	**10p**	91	87[d]
17	cyclohexyl	144	**10q**	42	93[d]
18	3-pentyl	144	**10r**	51	96[d]

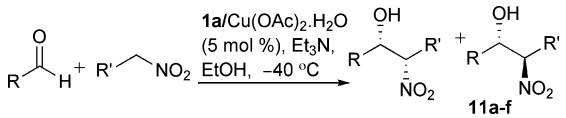
[a] Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane and 0.05 mmol of base in 2 mL of ethanol, unless noted otherwise. [b] Determined by HPLC using chiral column. [c] Reaction was carried out at –20 °C and in the absence of base. [d] 10 mol% of catalyst was used at 0 °C and in the absence of base.

containing electron-withdrawing groups (Table 6, entries 2–5) was faster in comparison to aldehydes having an electron-donating group (Table 6, entries 6–15). Under these conditions, the rate of the reaction was much slower for the aliphatic substrates. This was overcome by carrying out the reaction at 0 °C with 10 mol% of the catalyst and in the absence of Et_3N (Table 6, entries 16–18).

The catalytic activity of the **1a**–Cu(II) complex was tested for the diastereoselective Henry reaction, for which there are not many reports in the literature.[9d,10,11b,13c] Under the optimized reaction conditions, aromatic aldehydes reacted with nitroethane to give nitroaldol product in moderate diastereoselectivity (up to 71: 29, *anti*/*syn*) and the *anti* product was formed predominantly, with an ee of 79% (Table 7, entry 1). On the other hand, reaction of nitroethane with aliphatic aldehyde afforded the *syn* isomer predominantly, with lower diastereoselectivity (54:46, *syn*/*anti*) and higher ee than the reaction of aromatic aldehydes (Table 7, entry 6).

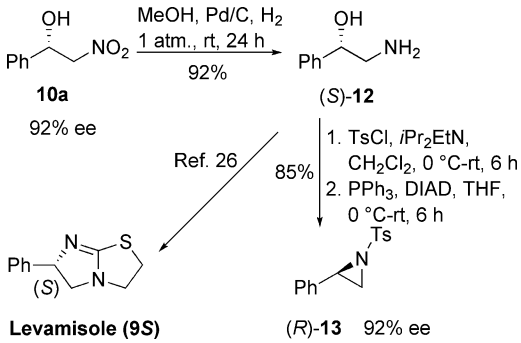
With the nitroaldol adduct **10a** in hand, we found that it could be further elaborated into chiral amino alcohol (*S*)-**12**[23] through catalytic hydrogenation using 10% Pd/C in good yield (Scheme 2). The chiral amino alcohol thus obtained was then cyclised *via* sulfonylation followed by Mitsunobu reaction[24] with DIAD and PPh_3 readily furnished the corresponding aziridine (*R*)-**13** without loss of optical purity.[25] These aziridines constitute the key structural feature of several N-containing natural products and also serve in synthesis as chiral building blocks, auxiliaries, and ligands.[26] The chiral amino alcohol (*S*)-**12** is also a key intermediate in the synthesis of Levamisol (9S), an anthelmintic agent.[27]

Table 7 Diastereoselective Henry reaction of nitroalkane with different aldehydes[a]



entry	R	R′	time (h)	product	yield (%)	*syn*/*anti*[b]	ee (%)[c] *syn*/*anti*
1	C_6H_5	Me	96	**11a**	78	38/62	80/79
2	2-MeC_6H_4	Me	76	**11b**	70	29/71	79/66
3	2-$OMeC_6H_4$	Me	72	**11c**	86	32/68	86/73
4	4-ClC_6H_4	Me	78	**11d**	73	48/52	64/64
5	C_6H_5	Et	144	**11e**	64	40/60	85/82
6[d]	$PhCH_2CH_2$	Me	144	**11f**	45	54/46	90/95

[a] Reactions were carried out on a 0.5 mmol scale with 5 mmol of nitromethane and 0.05 mmol of base in 2 mL of ethanol, unless noted other-wise. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC using chiral column. [d] 10 mol% of catalyst was used at 0 °C and in the absence of base.



Scheme 2

Conclusions

In conclusion, the chiral Cu(II)–**1a** complex prepared from $Cu(OAc)_2 \cdot H_2O$ and the C_2-symmetric diamine ligand **1a** was found to be an effective catalyst for the enantioselective Henry reaction between nitroalkanes and aldehydes. The procedure is operationally very simple and can provide a variety of *β*-hydroxy nitroalkanes in good to excellent yields with excellent enantioselectivities (up to 96% ee). In addition, the chiral nitroaldol adduct has been derivatized to synthetically useful chiral aziridine in few steps.

Experimental section

General Methods

^1H and ^{13}C NMR spectra were recorded on JEOL JNM-LA 400 and Jeol ECX 500 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in Hz. Mass spectrometric analyses were done on Waters Q Tof Premier Micromass (ESI) spectrometer. Routine monitoring of reactions was performed by TLC, using 0.2 mm Kieselgel 60 F_{254} precoated aluminium sheets, commercially available from Merck. Visualization was done by fluorescence quenching at 254 nm, exposure to iodine vapor, and/or 2,4-dinitrophenylhydrazine solution. All the column chromatographic

separations were done by using silica gel (Acme's, 60–120 mesh). HPLC was done on a Daicel chiral column having 0.46 cm internal diameter × 25 cm length. Petroleum ether used was of boiling range 60–80 °C. Reactions that needed anhydrous conditions were run under an atmosphere of nitrogen or argon using flame-dried glassware. The organic extracts were dried over *anhydrous* sodium sulfate. Evaporation of solvents was performed at reduced pressure. CH_2Cl_2, $CHCl_3$ and triethylamine (Et_3N) were distilled from CaH_2.

General procedure for the coupling of *N*-Boc amino acid with amino esters

A solution of (*S*)-*N*-Boc amino acid (10 mmol) and *N*-methylmorpholine (12 mmol) in CH_2Cl_2 (30 mL) was treated with ethyl chloroformate (12 mmol) at 0 °C for 10 min. Amino ester (12 mmol) was then added dropwise at the same temperature and the mixture was stirred for 16 h (0 °C to rt). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water and brine. The organic layer was dried, and the solvent was evaporated in vacuo. Purification by column chromatography over silica gel gave pure coupled product **2** or **6**.

(*S*)-Methyl-1-((*S*)-2-(*tert*-butoxycarbonylamino)-4-methyl-pentanoyl)pyrrolidine-2-carboxylate (6a). Yield 80%; Yellow liquid; $[\alpha]_D^{25}$ −7.8 (*c* 1.0, $CHCl_3$); TLC R_f 0.60 (40%, EtOAc/Pet ether); IR ν_{max}/cm^{-1} (film) 3313, 2956, 1748, 1709, 1650; ^1H NMR (500 MHz, $CDCl_3$): δ 0.96 (m, 6H), 1.27 (m, 1H), 1.45 (s, 9H), 1.96 (m, 1H), 2.04 (m, 3H), 2.22 (m, 1H), 3.60 (m, 1H), 3.72 (s, 3H), 3.77 (m, 1H), 4.52 (m, 2H), 5.12 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 23.4, 24.5, 24.9, 28.3, 28.9, 41.9, 46.7, 50.2, 52.2, 58.6, 79.5, 155.7, 171.9, 172.5. Anal. Calcd. for $C_{17}H_{30}N_2O_5$: C, 59.63; H, 8.83; N, 8.18. Found: C, 59.79; H, 8.85; N, 8.20.

General procedure for the synthesis of diketopiperazines

A solution of amide **2** or **6** (2.0 mmol) in dry CH_2Cl_2 (6 mL) was treated with TFA (800 µL) at rt for 3h. Solvent was then evaporated and the reaction mixture was dissolved in 2-butanol:toluene (4:2 mL) followed by addition of triethylamine (2 mmol). The mixture was allowed to reflux for 16 h. After the evaporation of solvent, diketopiperazines **3** or **7** precipitated as a white solid, which was filtered off, washed with MeOH, and used for next step without further purification.

(3*S*,8a*S*)-3-Isobutylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (7a). Yield 75%; White solid; mp 164 °C; $[\alpha]_D^{25}$–137.2 (*c* 0.5, DMSO); TLC R_f 0.50 (5%, MeOH/CH_2Cl_2); IR ν_{max}/cm^{-1} (pellet) 3429, 2993, 1670, 1634; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (m, 6H), 1.54 (m, 1H), 1.78–2.15 (m, 5H), 2.35 (m, 1H), 3.57 (m, 2H), 4.02 (m, 1H), 4.12 (m, 1H), 6.30 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 22.8, 23.3, 24.7, 28.1, 38.6, 45.5, 53.4, 59.0, 166.3, 170.3; HRMS (ES+) calc. for $C_{11}H_{18}N_2O_2$ 211.1446, $[M + H]^+$ found 211.1445.

General procedure for the synthesis of piperazine

To a solution of amide (2 mmol) **3** or **7** in dry THF (8 mL) was added LAH (10 mmol) in portions at 0 °C and the reaction stirred for 10 min. The reaction mixture was warmed slowly to room temperature and refluxed for 6–24 h. Reaction mixture was then cooled slowly to 0 °C and excess of LAH was destroyed by the addition of few drops of EtOAc. Water (200 µL) was added, followed by the same amount of 4*N* NaOH. After 5 min, 600 µL of water was again added and the mixture stirred for 15 min. The white precipitate formed was filtered off, the filtrate was dried, and solvent was evaporated. The crude product was purified by column chromatography using neutral alumina.

(3*S*,8a*S*)-3-Isobutyloctahydropyrrolo[1,2-*a*]pyrazine (8a). Yield 74%; Colorless liquid; $[\alpha]_D^{25}$ +12.8 (*c* 1.0, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 3286, 2953; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (m, 6H), 1.28 (m, 1H), 1.47 (m, 1H), 1.62–1.83 (m, 5H), 2.02 (m, 1H), 2.2–2.33 (m, 2H), 2.64–2.77 (m, 2H), 2.91–2.97 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7, 22.2, 23.1, 24.9, 26.7, 41.0, 45.6, 50.4, 54.6, 57.0, 63.2; HRMS (ES+) calc. for $C_{11}H_{22}N_2$ 183.1861, $[M + H]^+$ found 183. 1861.

General procedure for the reductive amination of piperazines

To a solution of amine **4** or **8** (2.5 mmol) in water (2.5 mL) was added formaldehyde (8.5 mmol, 39% in w/v) and formic acid (27.5 mmol) at room temperature. The reaction mixture was allowed to reflux for 16 h. It was cooled and then basified by the addition of saturated $NaHCO_3$ and 10*N* NaOH solution. Aqueous layer was extracted with EtOAc and the organic layer was then washed with brine and dried over *anhydrous* Na_2SO_4. Solvent was removed in vacuum and the residue was purified by column chromatography using neutral alumina.

(3*S*,8a*S*)-3-Isobutyl-2-methyloctahydropyrrolo[1,2-*a*]pyrazine (9a). Yield 46%; Colorless liquid; $[\alpha]_D^{25}$ +26.3 (*c* 0.6, $CHCl_3$); TLC R_f 0.50 (100%, MeOH); IR ν_{max}/cm^{-1} (film) 2954, 2794; ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (m, 6H), 1.25–1.84 (m, 7H), 2.10 (m, 2H), 2.27–2.38 (m, 5H), 2.61 (m, 2H), 2.81 (dd, J = 2.4, 10.8 Hz, 1H), 2.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 22.0, 23.6, 26.3, 27.4, 32.9, 42.2, 53.9, 54.0, 54.9, 57.3, 62.2; HRMS (ES+) calc. for $C_{12}H_{24}N_2$ 197.2018, $[M + H]^+$ found 197.2018.

General procedure for the enantioselective/diastereoselective Henry reaction

A solution of ligand **1a** (4.6 mg, 0.0275 mmol) and $Cu(OAc)\cdot H_2O$ (5 mg, 0.025 mmol) in dichloromethane (2 mL) was stirred overnight at room temperature. Solvent was removed under reduced pressure and the residue was dissolved in dry EtOH (2 mL). To the resulting blue solution, nitroalkane (5 mmol), Et_3N (7 µL, 0.050 mmol) and aldehyde (0.5 mmol) were added at –40 °C. The reaction mixture was stirred for appropriate time and the progress of the reaction monitored by TLC. After completion of the reaction, the volatile components were removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/Petroleum ether) to afford the nitroaldol product. The enantiomeric excess was determined by chiral HPLC and diastereoselectivity was determined by ^1H NMR spectroscopy.

Synthesis of (*S*)-2-amino-1-phenylethanol (12). β-Nitro alcohol **10a** (0.4 mmol) in methanol (2 mL) was hydrogenated (H_2, 1 atm) in the presence of 10% Pd/C (20 mg) for 24 h. The solution was filtered over celite, and the methanol was removed under

reduced pressure. The crude material was used without further purification. Yield 92%; white solid; mp 54–56 °C; $[\alpha]_D^{25}$ +9.1 (*c* 1.68, EtOH); [lit.[23] (*S*) ee = 100%; $[\alpha]_D^{20}$ +47.9 (*c* 2.4, EtOH)]; IR ν_{max}/cm^{-1} (film) 3384, 2925, 2855; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.79 (m, 1H), 3.0 (m, 1H), 3.46 (bs, 1H), 4.63 (m, 1H), 7.25–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.3, 74.4, 125.9, 127.6, 128.5, 128.6, 142.6; HRMS (ES+) calc. for $C_8H_{11}NO$ 138.0920, $[M + H]^+$ found 138.0919.

Synthesis of (*R*)-2-phenyl-1-tosylaziridine (13). *p*-Toluene sulfonyl chloride (1.2 mmol) was added in portions to a solution of amino alcohol **12** (1 mmol) and diisopropylethylamine (2 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The ice bath was then removed, and the reaction was allowed to warm to rt and further stirred for 6 h. The reaction mixture was then washed with water, brine and dried over *anhydrous* Na_2SO_4. The organic layer was then concentrated and the crude product was purified by column chromatography on silica gel to afford the sulfonylated amino alcohol. To this *N*-sulfonyl-substituted amino alcohol in dry THF (4 mL) was added triphenylphosphine (1.2 mmol) in one portion at rt. The reaction mixture was then cooled to 0 °C, and treated slowly with diisopropylazodicarboxylate (1.2 mmol). The ice bath was removed and the yellow solution was stirred at rt for 6 h. THF was evaporated, and the residue was purified by column chromatography to yield the chiral aziridine **13**. Yield 85%; white solid, mp 82–84 °C; TLC R_f 0.8 (40% EA in petroleum ether); $[\alpha]_D^{25}$ –86.4 (*c* 1.0, $CHCl_3$); IR ν_{max}/cm^{-1} (pellet) 3038, 1385; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (m, 1H), 2.42 (s, 3H), 2.98 (m, 1H), 3.77 (m, 1H), 7.2–7.33 (m, 7H), 7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 36.1, 41.1, 126.7, 128.0, 128.4, 128.7, 129.9, 135.0, 135.1, 144.8; HRMS (ES+) calc. for $C_{15}H_{15}NO_2S$ 274.0902, $[M + H]^+$ found 274. 0903.; Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (*n*-hexane/2-propanol 90:10, λ = 254 nm); flow rate 0.8 mL/min; $t_{R(minor)}$ = 37.47 min (*S*), $t_{R(major)}$ = 44.43 min (*R*).

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