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RING CONTRACTION OF α,β–UNSATURATED CYCLIC AMINES WITH *cis*-DIHYDROXYLATION AT THE α,β–POSITION

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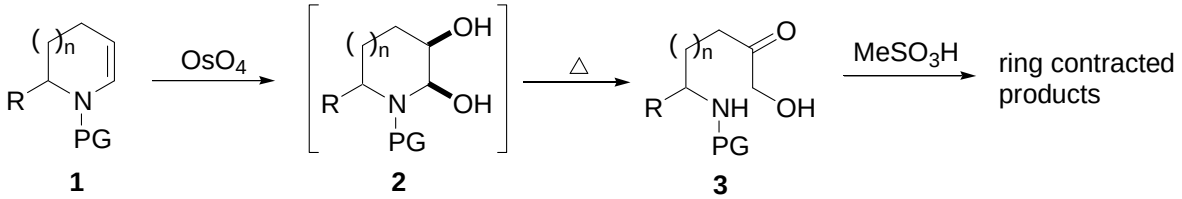
Abstract – α,β–Unsaturated cyclic amines are oxidized by OsO_4 to afford α,β-*cis*-dihydroxylated compounds which are thermodynamically transformed into ring-opened keto-alcohols. The keto-alcohols are then cyclized to form synthetically useful ring-contracted cyclic amines.

INTRODUCTION

Functionalized cyclic amines are versatile building blocks and intermediates for organic synthesis. There are several methods reported to date that achieve these.[1] Ring contraction is one of these methods. Ever since Leonard et al found rearrangement of β-hydroxylated cyclic amines generated from β-oxo cyclic amines during the Clemmensen reduction,[2] some methods for ring contraction via bicyclic aziridinium ion have been exploited.[3] Recently, Sayre et al reported acid catalyzed rearrangement of 1-benzyl-2-methyl-3-piperidone to 1-benzyl-2-acetylpyrrolidine, in which ring-opened keto-alcohol was proposed as a plausible intermediate.[4] Now, we found that *N*-protected α,β–*cis*-dihydroxylated cyclic amines **2** which are formed by oxidation of the corresponding α,β–unsaturated compounds **1** with OsO_4 are thermodynamically unstable and changed to ring-opened keto-alcohols **3**. Acid catalyzed reaction of **3** afforded ring contracted products including functionalized cyclic imines (Scheme 1). Herein, we present the ring contraction of cyclic amines and subsequent formation of functionalized imines.



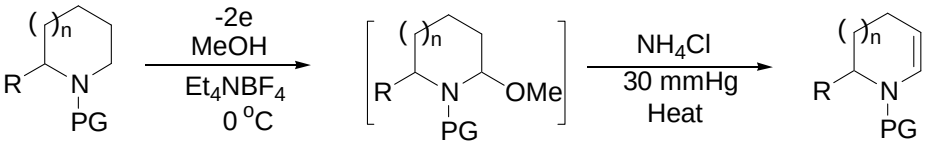
1 **2** **3**

Scheme 1

RESULTS AND DISCUSSION

Starting from readily commercially available cyclic amines **4a-f**, we activated the α-position by electrochemical oxidation in methanol[5] followed by acid catalyzed removal of methanol to afford α,β-unsaturated cyclic amines **1a-f**.[6,7] These results are summarized in Table 1.

Table 1. Preparation of α,β–unsaturated cyclic amines **1a-f**

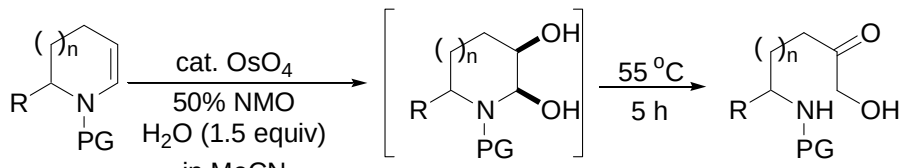


4a-f **1a-f**

Entry	n	R	PG	Substrate	F/mol	Product	Yield (%)
1	0	H	Bz	**4a**	2	**1a**	96
2	1	H	Bz	**4b**	3	**1b**	95
3	1	CO_2Me	Bz	**4c**	5	**1c**	70
4	2	H	Bz	**4d**	3	**1d**	96
5	2	H	CO_2Ph	**4e**	4	**1e**	95
6	2	H	CO_2Me	**4f**	3	**1f**	87

Having successfully prepared **1a-f**, we embarked on the task of functionalizing and subsequent ring opening of the product **2a-f**. First, dihydroxylation of **1a-f** using OsO_4 followed by thermodynamically induced ring opening by use of elevated temperatures afforded **3a-f**. The results are summarized in Table 2.

Table 2. Preparation of keto-alcohols **3a-f**



1a-f **2a-f** **3a-f**

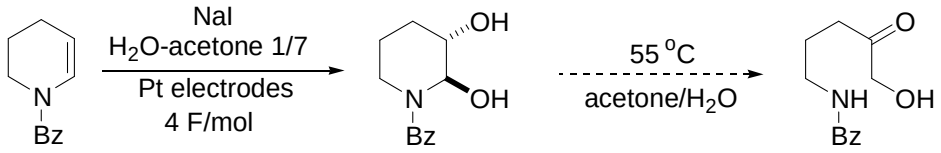
Entry	Substrate	n	R	PG	Product	Yield (%)
1	**1a**	0	H	Bz	**3a**	95
2	**1b**	1	H	Bz	**3b**	74
3	**1c**	1	CO_2Me	Bz	**3c**	62
4	**1d**	2	H	Bz	**3d**	86
5[a]	**1e**	2	H	CO_2Ph	**3e**	82
6[b]	**1f**	2	H	CO_2Me	**3f**	96

[a] Heating at 55 °C for 24 h, [b] Heating at 70 °C for 48 h.

Analysis of the results obtained led us to conclude as follows: protecting groups influenced the ease of keto-alcohol formation, i.e. enamines protected by benzoyl group (Entries 1-4) required only 5 h to convert to keto-alcohols **3** compared to other protecting groups like phenoxycarbonyl and methoxycarbonyl which required 24 h to 48 h for complete reaction (Entries 5 and 6). Furthermore, ring

stability played a role in the reaction. Five and seven membered amines (Entries 1, 4-6) were easily converted to keto-alcohols **3** with comparatively better yields to that of six membered amines (Entries 2 and 3).

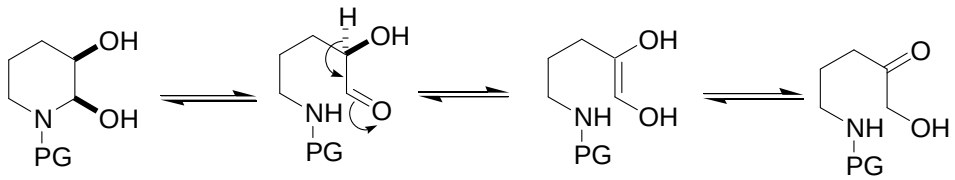
Dihydroxylated products **2** formed by OsO_4 have *cis* orientation. So, to find out if *trans* product can undergo this reaction we prepared *trans* product using electrochemical method.[8] As shown in Scheme 2, the transformation of *trans*-**2b** to keto-alcohol **3b** did not take place even at elevated temperatures of 70 ^{o}C for 48 h.



1b *trans*-**2b** **3b**

Scheme 2

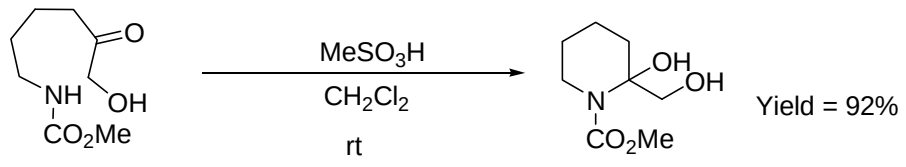
Based on these data, we propose that the mechanism for ring opening is as shown in Scheme 3. Under elevated temperatures, the *cis*-diols **2** are unstable and therefore tautomerize to more stable keto-alcohols **3** (Scheme 3).



2 **A** **B** **3**

Scheme 3

Next, transforming **3a-f** to synthetically useful intermediates or products was examined. We envisioned that in acidic conditions, the carbonyl group on **3f** could be activated leading to an attack by the lone pairs of electrons on the nitrogen group thus forming α-hydroxyl-α-hydroxylmethylpiperidine **5** that has a quaternary carbon at the α-position which might be transformed to pharmaceutically important compounds (Scheme 4).[9]

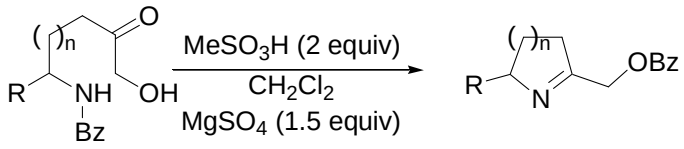


3f **5**

Scheme 4

To test this method, keto-alcohol **3f** was dissolved in CH_2Cl_2 and methanesulfonic acid (1 equiv) was added to it dropwise and left to stir for 12 h. After workup, product **5** was obtained in 92% yield which was determined by NMR analysis. However, when **3b** was subjected to similar reaction conditions, imine **6b** was formed with almost 50% recovery of keto-alcohol **3b**. Therefore, to drive the reaction to completion, $MgSO_4$ was added to remove H_2O. As shown in Table 3, benzoyl group migrated to the terminal hydroxyl group.

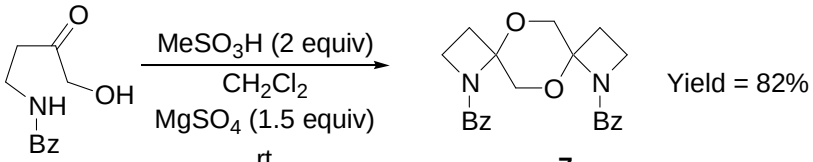
Table 3. Preparation of imines **6b-d** from **3b-d**



3b-d **6b-d**

Entry	Substrate	n	R	Product	Yield (%)
1	**3b**	1	H	**6b**	89
2	**3c**	1	CO_2Me	**6c**	62
3	**3d**	2	H	**6d**	83

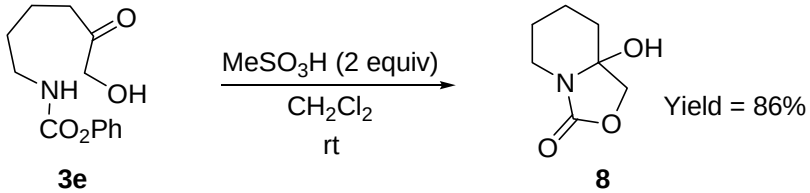
α-Benzoyloxymethylated cyclic imine **6b** was obtained in good yield from **3b** (Entry 1). Methoxycarbonyl substituent on keto-alcohol **3c** was well tolerated (Entry 2). Moreover, 6-membered cyclic imine **6d** was synthesized starting from **3d** with good yield (Entry 3). Interestingly, when **3a** was subjected to these reaction conditions, dimer **7** instead of a 4-membered cyclic imine was exclusively obtained in good yield (Scheme 5). Attempts to vary reaction conditions so as to attain an imine were futile.



3a **7**

Scheme 5

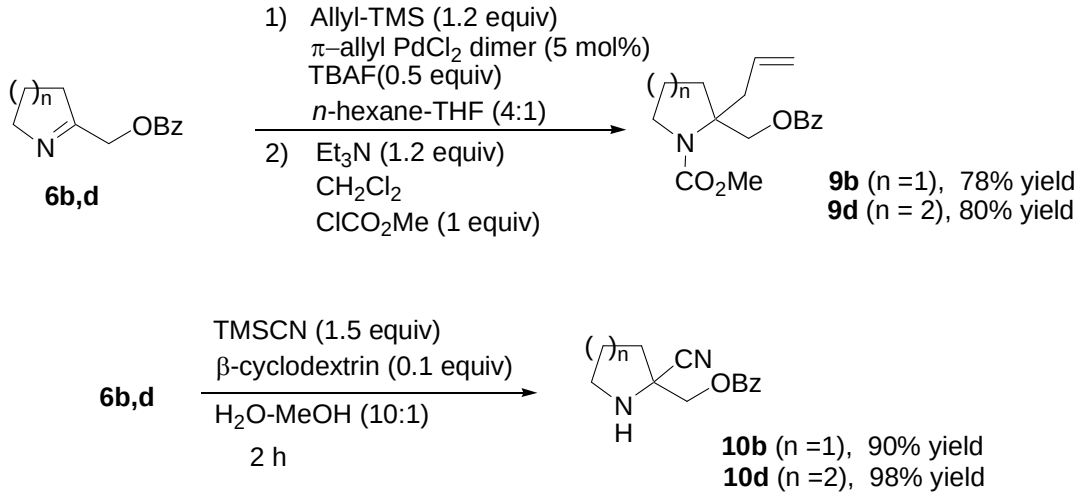
Ketoalcohol **3e** formed bicyclic compound **8** when subjected to acid catalyzed condensation reaction. $MgSO_4$ did not affect the reaction (Scheme 6).



3e **8**

Scheme 6

To demonstrate how the imines can be utilized in organic synthesis,[9] **6b** and **6d** were allylated using allyltrimethylsilane in the presence of π-allylpalladium chloride dimer[10] and cyanated by trimethylsilyl cyanide catalyzed by β-cyclodextrin (Scheme 7).[11]



Scheme 7

In conclusion, starting from simple cyclic amines, we have achieved ring contraction of 5-, 6- and 7-membered ring systems to functionalized 4-, 5- and 6-membered ones respectively through electrochemical and OsO_4 oxidation. Finally, we have demonstrated the use of the imine products by allylation and cyanation.

EXPERIMENTAL

Electrochemical reactions were carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc. ^{1}H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. ^{13}C NMR spectra were measured on a Varian Gemini 400 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Elemental analyses were carried out at the Center for Instrumental Analysis, Nagasaki University. Mass spectra were obtained on a JEOL JMS-DX 303 instrument.

All solvents were used as supplied without further purification.

General procedure for preparation of enecarbamates 1a-f

To a 200 mL beaker containing a stirring bar, **4** (100 mmol), MeOH (200 mL) and platinum electrodes was added Et_4NBF_4 (10 mmol, 2.18 g). The beaker type cell was then placed at 0 ^oC and current passed through as the reaction was monitored by TLC and NMR. Upon completion of reaction, MeOH was removed under *vacuo* and the residue dissolved in AcOEt (100 mL). H_2O (100 mL) was added to the

mixture and the organic layer separated, the aqueous layer was extracted by AcOEt (2 x 100 mL) and the organic layer combined, dried by anhyd. $MgSO_4$, filtered and solvent removed under reduced pressure. The residue was then subjected to flash chromatography to afford methoxylated product. This product was then transferred to 100 mL flask containing a stirring bar and NH_4Cl (10 mmol, 0.535 g). The flask was then transferred to an oil bath already preheated at 100 ^oC to generate MeOH as a side product which was removed under reduced pressure. On completion of reaction as determined by TLC and NMR, the residue was passed through a silica gel column to afford product **1** as oil.

Compounds **1a**,[12] **1b**,[13] **1c**,[6] and **1f**[14] are known compounds.

N-Benzoyl-2,3,4,5-tetrahydroazepin (1d)

^1H NMR (300MHz, $CDCl_3$) δ 7.59-7.34 (m, 5H), 6.80-6.66 and 6.28-6.10 (m, 1H), 5.38-5.20 and 5.13-4.98 (m, 1H), 4.10-3.50 (m, 2H), 2.35-2.20 (m, 2H), 2.00-1.70 (m, 4H). ^{13}C NMR (100Hz, $CDCl_3$) δ 169.58 (1C), 135.86 (1C), 132.69 (1C), 129.96 (1C), 128.26 (1C), 127.86 (2C), 116.56 (1C), 45.95 (1C), 27.71 (1C), 26.99 (1C), 24.58 (2C). IR ν cm^{-1} (neat): 2930, 1636, 1447, 1406, 1387, 1364. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_{13}H_{16}NO$ $[M+H]^+$ 202.1232, found: 202.1243.

N-Phenoxycarbonyl-2,3,4,5-tetrahydroazepin (1e)

^1H NMR (300MHz, $CDCl_3$) δ 7.41-32 (m, 2H), 7.24-7.08 (m, 3H), 6.71-6.57 (m, 1H), 5.23-5.10 (m, 1H), 3.93-3.74 (m, 2H), 2.40-2.20 (m, 2H), 1.95-1.65 (m, 4H). IR ν cm^{-1} (neat): 2928, 1719, 1701, 1497, 1420, 1377, 1196. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$ 218.1181, found: 218.1162.

General procedure for preparation of keto-alcohols 3

To **1** (1 mmol) in MeCN (2 mL) and 50% *N*-methylmorpholine *N*-oxide in H_2O (1.5 mmol) was added 4% OsO_4 in H_2O (0.01 mmol) and the mixture stirred at rt monitored by TLC. On completion of the reaction, the mixture was transferred to an oil bath set at 55 ^oC. The reaction progress was then monitored by TLC and upon completion; H_2O (5 mL) was added and the resulting mixture extracted with AcOEt (3 x 10 mL). The combined organic layer was dried by $MgSO_4$, filtered and solvent removed *in vacuo*.

Recrystallization from AcOEt and *n*-hexane gave white crystalline compounds **3a**,**b**,**d**,**e**. Oily compounds **3c** and **3f** were purified by silica gel column chromatography (*n*-hexane : AcOEt = 1:3).

N-(4-Hydroxy-3-oxobutyl)benzamide (3a)

Mp 82 ^oC; ^1H NMR (300MHz, $CDCl_3$) δ 7.78-7.68 (m, 2H), 7.52-7.38 (m, 3H), 6.88-6.75 (br s, 1H), 4.27 (s, 2H), 3.80-3.70 (m, 2H), 3.21-2.98 (br s, 1H), 2.80 (t, *J*=6.3Hz, 2H). ^{13}C NMR (100Hz, $CDCl_3$) δ

209.68 (1C), 167.68 (1C), 134.00 (1C), 131.62 (2C), 128.54 (1C), 126.87 (2C), 68.30 (1C), 37.88 (1C), 34.45 (1C). IR ν cm^{-1} (neat): 3422, 2900, 1728, 1653, 1603, 1578. Anal. calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.78; H, 6.37; N, 6.70.

N-(5-Hydroxy-4-oxopentyl)benzamide (3b)

Mp 53°C; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.79-7.72 (m, 2H), 7.56-7.40 (m, 3H), 6.45-6.31 (br s, 1H), 4.27 (d, *J*=6.6Hz, 2H), 3.51 (q, *J*=8.4Hz, 2H), 3.03 (t, *J*=6.6Hz, 1H), 2.57 (t, *J*=9.2Hz, 2H), 2.03-1.94 (m, 2H). IR ν cm^{-1} (neat): 3422, 2934, 1719, 1638, 1578, 1541, 1491. Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.51; H, 6.67; N, 6.25.

Methyl 2-(N-benzoylamino)-6-hydroxy-5-oxohexanoate (3c)

Oil; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.80 (d, *J*=7.2Hz, 2H), 7.58-7.39 (m, 3H), 7.20-7.12 (m, 1H), 4.86-4.74 (m, 1H), 4.24 (d, *J*=2.4Hz, 2H), 3.77 (s, 3H), 3.56-3.15 (br s, 1H), 2.71-2.48 (m, 2H), 2.41-2.30 (m, 1H), 2.18-2.03 (m, 1H). IR ν cm^{-1} (neat): 3422, 3063, 2953, 2361, 1747, 1653, 1541, 1491. Anal. calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.51; H, 6.26; N, 4.71.

N-(6-Hydroxy-5-oxohexyl)benzamide (3d)

Mp 102°C; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.78 (d, *J*=6.9Hz, 2H), 7.52-7.39 (m, 3H), 6.41-6.22 (br s, 1H), 4.26 (d, *J*=4.8Hz, 2H), 3.47 (q, *J*=6.6Hz, 2H), 3.13 (t, *J*=4.8Hz, 1H), 2.50 (t, *J*=7.2Hz, 2H), 1.78-1.57 (m, 4H). ^{13}C NMR (100Hz, $CDCl_3$) δ 209.45 (1C), 167.50 (1C), 134.51 (1C), 131.35 (2C), 128.49 (1C), 126.75 (2C), 68.17 (1C), 39.42 (1C), 37.67 (1C), 29.14 (1C), 20.65 (1C). IR ν cm^{-1} (neat): 3422, 2936, 2869, 2357, 1723, 1717, 1682. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_{13}H_{18}NO_3$ $[M+H]^+$ 236.1287, found: 236.1276.

6-Hydroxy-5-oxo-N-phenoxycarbonylhexylamine (3e)

Mp 53-54°C; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 (t, *J*=7.6Hz, 2H), 7.19 (t, *J*=7.6Hz, 1H), 7.11 (d, *J*=7.2Hz, 2H), 5.39-5.31 (br s, 1H), 4.22 (s, 2H), 3.38-3.25 (br s, 1H), 3.23 (q, *J*=6.4Hz, 2H), 2.43 (t, *J*=7.2Hz, 2H), 1.80-1.50 (m, 4H). ^{13}C NMR (100Hz, $CDCl_3$) δ 154.68 (1C), 150.93 (1C), 129.18 (2C), 125.19 (2C), 121.59 (1C), 121.48 (1C), 68.04 (1C), 40.52 (1C), 37.52 (1C), 29.10 (1C), 20.35 (1C). IR ν cm^{-1} (neat): 3328, 3046, 2938, 1744, 1705, 1595. Anal. calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.89; H, 6.53; N, 5.39.

6-Hydroxy-N-methoxycarbonyl-5-oxohexylamine (3f)

^{1}H NMR (300MHz, $CDCl_3$) δ 4.80-4.61 (br s, 1H), 4.25 (d, *J*=4.5Hz, 2H), 3.66 (s, 3H), 3.25-3.11 (m, 2H),

3.08 (t, *J*=3.6Hz, 1H), 2.46 (t, *J*=7.2Hz, 2H), 1.74-1.44 (m, 4H). ^{13}C NMR (100Hz, $CDCl_3$) δ 209.45 (1C), 157.12 (1C), 68.11 (1C), 52.04 (1C), 40.41 (1C), 37.66 (1C), 29.42 (1C), 20.45 (1C). IR ν cm^{-1} (neat): 3430, 3330, 2959, 2884, 1717, 1655, 1539, 1410. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_8H_{16}NO_4$ $[M+H]^+$ 190.1080, found: 190.1078.

General procedure for cyclization of keto-alcohols 3.

To **3** (1 mmol) in CH_2Cl_2 (15 mL) and anhyd. $MgSO_4$ (1.5 mmol) stirring at rt, was added dropwise $MeSO_3H$ (2 mmol) and the mixture left to stir for 9 h. The reaction was then quenched using sat. aq. $NaHCO_3$ (10 mL) and extracted by AcOEt (3 x 10 mL). The combined organic layer was dried using $MgSO_4$, filtered and solvent removed *in vacuo*. The resulting product was purified by silica gel column chromatography (*n*-hexane : AcOEt = 1:2) to afford products **6-8**.

2-Hydroxy-2-hydroxymethyl-N-methoxycarbonylpiperidine (5)

On silica gel **5** is unstable thus decomposes. So, the crude sample was analysed.

^{1}H NMR (300MHz, $CDCl_3$) δ 4.59 (s, 2H), 3.85-3.71 (m, 1H), 3.81 (s, 3H), 3.68-3.57 (m, 3H), 2.20-2.09 (m, 2H), 1.81-1.50 (m, 4H). ^{13}C NMR (100Hz, $CDCl_3$) δ 164.88 (1C), 155.44 (1C), 70.78 (1C), 54.81 (1C), 48.90 (1C), 25.97 (1C), 21.63 (1C), 18.65 (1C). IR νcm^{-1} (neat): 3596, 3430, 2990, 2857, 1800, 1709, 1667. High Resolution Mass Spectrum [EI(+)]: *m/z* calcd for $C_8H_{15}NO_4$ $[M]^+$ 189.1001, found 189.0989.

2-Benzoyloxymethyl-1,2-didehydropyrrolidine (6b)

Oil; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.09 (d, *J*=7.3Hz, 2H), 7.59 (t, *J*=7.3Hz, 1H), 7.46 (t, *J*=7.3Hz, 2H), 5.07 (s, 2H), 3.93 (t, *J*=7.8Hz, 2H), 2.63 (t, *J*=8.3Hz, 2H), 2.04-1.91 (m, 2H). IR ν cm^{-1} (neat): 3063, 3032, 2953, 2349, 1918, 1728, 1662. Anal. calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.67; H, 6.57; N, 6.75.

2-Benzoyloxymethyl-1,2-didehydro-5-methoxycarbonylpyrrolidine (6c)

Oil; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.08 (d, *J*=7.3Hz, 2H), 7.59 (t, *J*=7.8Hz, 1H), 7.46 (t, *J*=7.3Hz, 2H), 5.14 (s, 2H), 4.80 (t, *J*=6.8Hz, 1H), 3.78 (s, 3H), 2.90-2.80 (m, 1H), 2.75-2.65 (m, 1H), 2.33-2.24 (m, 1H), 2.21-2.11 (m, 1H). ^{13}C NMR (100Hz, $CDCl_3$) δ 176.97 (1C), 165.96 (1C), 133.37 (1C), 129.80 (2C), 129.40 (1C), 128.48 (2C), 74.34 (1C), 63.92 (1C), 52.32 (1C), 36.00 (1C), 29.67 (1C), 25.78 (1C). IR ν cm^{-1} (neat): 2955, 2851, 1730, 1653, 1601, 1451, 1435, 1316, 1271. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.1079, found: 262.1103.

2-Benzoyloxymethyl-1,2-didehydropiperidine (6d)

Oil; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.09 (d, *J*=6.9Hz, 2H), 7.60-7.38 (m, 3H), 4.81 (s, 2H), 3.70-3.59 (m, 2H), 2.29-2.19 (m, 2H), 1.81-1.57 (m, 4H). IR νcm^{-1} (neat): 3063, 3032, 2953, 2349, 1918, 1728, 1662. Anal. calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.01; H, 6.75; N, 6.38.

1,10-Diaza-N,N-dibenzoyl-6,12-dioxodispiro[3.2.3.2]dodecane (7)

Mp 128-129 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.00 (d, *J*=6.3Hz, 4H), 7.50-7.33 (m, 6H), 4.11 (d, *J*=12Hz, 2H), 3.92-3.61 (m, 4H), 3.79 (d, *J*=11.7Hz, 2H), 2.00-1.91 (m, 2H), 1.80-1.71 (m, 2H). ^{13}C NMR (100Hz, $CDCl_3$) δ 152.84 (2C), 133.35 (2C), 130.63 (2C), 128.17 (4C), 126.91 (4C), 92.75 (2C), 66.17 (2C), 38.83 (2C), 27.02 (2C). IR ν cm^{-1} (neat): 3306, 2926, 1661, 1443, 1364, 1277, 1186. High Resolution Mass Spectrum [EI(+)]: *m/z* calcd for $C_{22}H_{22}N_2O_4$ $[M]^+$ 378.1579, found 378.1570.

1-Aza-6-hydroxy-8-oxa-9-oxo-[4.3.0]bicyclononane (8)

Mp 115 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) δ 4.29 (d, *J*=9.6Hz, 1H), 4.12 (d, *J*=9.6Hz, 1H), 4.18-3.91 (m, 1H), 3.65 (dd, *J*=9 and 3.9Hz, 1H), 3.16 (td, *J*=9.9 and 3.3Hz, 1H), 2.12-2.02 (m, 1H), 1.90-1.62 (m, 3H), 1.55-1.36 (m, 2H). ^{13}C NMR (100Hz, $CDCl_3$) δ 156.18 (1C), 84.59 (1C), 50.76 (1C), 37.60 (1C), 34.70 (1C), 24.01 (1C), 19.00 (1C). IR ν cm^{-1} (neat): 3370, 2950, 1765, 1597, 1367, 1285, 1242. Anal. calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.78; H, 6.88; N, 8.51.

General procedure for allylation of imines[10]

To a solution of **6b** or **6d** (0.5 mmol) and π-allyl $PdCl_2$ dimer (0.025 mmol) in *n*-hexane (2 mL) was added allyltrimethylsilane (1.0 mmol). The resulting mixture was stirred for about half an hour, and then TBAF (0.25 mmol, 1.0M solution in THF) and THF (0.25 mL) were added. The reaction mixture became two phases: the upper phase was a homogenous *n*-hexane-THF solution and the bottom phase contained a TBAF solution. The mixture was stirred for 24 h at rt. The reaction progress was monitored by TLC. After imine was consumed completely, the reaction was quenched with water. The reaction mixture was extracted with AcOEt. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was then dissolved in CH_2Cl_2 (2 mL), Et_3N (1.2 mmol) was added and the resulting mixture was stirred at room temperature as $ClCO_2Me$ (1.0 mmol) was added dropwise, stirring continued for 1 h as reaction progress was checked by TLC. On completion of reaction, H_2O (3 mL) was added and the mixture extracted using AcOEt. The organic layer was dried over $MgSO_4$, concentrated and then purified over silica gel column chromatography (*n*-hexane : AcOEt = 5 : 1) to afford an oil.

2-Allyl-2-benzoyloxymethyl -N-methoxycarbonylpyrrolidine (9b)

Oil; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.01 (d, *J*=7.3Hz, 2H), 7.57 (t, *J*=7.3Hz, 1H), 7.45 (t, *J*=7.3Hz, 2H), 5.92-5.67 (m, 1H), 5.25-5.00 (m , 2H), 4.72-4.20 (m, 2H), 3.53 and 3.51 (s, 3H), 3.61-3.40 (m, 2H), 2.95-2.70 (m, 1H), 2.53-2.23 (m, 1H), 2.18-1.98 (m, 2H), 1.91-1.73 (m, 2H). IR ν cm^{-1} (neat), 2959, 2878, 1721, 1698, 1640, 1601, 1449, 1375, 1271. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_{17}H_{22}NO_4$ $[M+H]^+$ 304.1548, found: 304.1548.

2-Allyl-2-benzoyloxymethyl -N-methoxycarbonylpiperidine (9d)

Oil; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.99 (d, *J*=3.6Hz, 2H), 7.52 (t, *J*=7.2Hz, 1H), 7.41 (t, *J*=7.6Hz, 2H), 5.88-5.70 (m, 1H), 5.18-5.08 (m, 2H), 4.74 (d, *J*=11.2Hz, 1H), 4.53 (d, *J*=11.2Hz, 1H), 3.62 (s, 3H), 3.68-3.58 (m, 1H), 3.50-3.40 (m, 1H), 2.99 (dd, *J*=7.2 and 6.8Hz, 1H), 2.49 (dd, *J*=8 and 5.6Hz, 1H), 1.88-1.73 (m, 2H), 1.68-1.58 (m, 4H). ^{13}C NMR (100Hz, $CDCl_3$) δ 166.06 (1C), 156.50 (1C), 133.16 (1C), 132.80 (1C), 130.14 (1C), 129.44 (2C), 128.27 (2C), 118.50 (1C), 67.50 (1C), 59.07 (1C), 52.17 (1C), 41.97 (1C), 39.81 (1C), 29.74 (1C), 23.07 (1C), 17.47 (1C). IR ν cm^{-1} (neat), 2951, 1725, 1698, 1603, 1441, 1383, 1275, 1192, 1117. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_{18}H_{24}NO_4$ $[M+H]^+$ 318.1706, found: 318.1700.

General procedure for cyanation[11]

To β-cyclodextrin (0.1 mmol) dissolved in water (10 mL) was added **6b** or **6d** (1.0 mmol) in MeOH (1 mL) followed by trimethylsilyl cyanide (1.0 mmol) and the mixture stirred at rt until the reaction was complete (2 h). The organic material was extracted with AcOEt, dried and concentrated under reduced pressure, and the resulting product, though seen as single compound by TLC, was further purified by passing over a column of silica gel. After extraction with AcOEt, the aqueous phase was lyophilized to get back β-cyclodextrin.

2-Benzoyloxymethyl-2-cyanopyrrolidine (10b)

Oil; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.08 (d, *J*=7.3Hz, 2H), 7.60 (t, *J*=7.3Hz, 1H), 7.46 (t, *J*=7.8Hz, 2H), 4.46 (d, *J*=10.7Hz, 1H), 4.35 (d, *J*=11.2Hz, 1H), 3.31-3.11 (m, 2H), 2.89-2.60 (m, 1H), 2.40-2.22 (m, 1H), 2.13-1.84 (m, 3H). ^{13}C NMR (100Hz, $CDCl_3$) δ 165.77 (1C), 133.44 (2C), 129.74 (2C), 129.13 (1C), 128.46 (1C), 121.58 (1C), 68.37 (1C), 59.74 (1C), 45.63 (1C), 34.38 (1C), 23.43 (1C). IR ν cm^{-1} (neat), 3352, 3067, 2953, 2226, 1725, 1638, 1601, 1451, 1269. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_{13}H_{15}N_2O_2$ $[M+H]^+$ 231.1133, found: 231.1128.

2-Benzoyloxymethyl-2-cyanopiperidine (10d)

Mp 83-85 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.07 (d, *J*=7.3Hz, 2H), 7.60 (t, *J*=7.8Hz, 1H), 7.47 (t,

J=7.8Hz, 2H), 4.44 (d, *J*=10.7Hz, 1H), 4.28 (d, *J*=10.8Hz, 1H), 3.12-2.95 (m, 2H), 2.31-2.12 (br s, 1H), 2.15-1.45 (m, 6H). ^{13}C NMR (100Hz, $CDCl_3$) δ 165.69 (1C), 133.50 (2C), 129.78 (2C), 129.12 (1C), 128.53 (1C), 119.51 (1C), 69.65 (1C), 56.69 (1C), 43.11 (1C), 31.77 (1C), 24.75 (1C), 20.99 (1C). IR ν cm^{-1} (neat), 3333, 3065, 2946, 2863, 2222, 1736, 1601, 1586, 1451, 1379, 1285. High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1290, found: 245.1283.

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