Platinum–catalyzed Michael Addition and Cyclization of Tertiary Amines with Nitroolefins by Dehydrogenation of α , β -sp³ C-H Bonds

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General Remarks:

Column chromatography was carried out on silica gel. Unless noted ^1H NMR spectra were recorded on 400 MHz in CDCl_3 and CD_3COCD_3 , ^{13}C NMR spectra were recorded on 100 MHz in CDCl_3 using TMS as internal standard. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1} . Melting points were determined on a microscopic apparatus and were uncorrected. All new compounds were further characterized by HRMS (high resolution mass spectra); copies of their ^1H NMR and ^{13}C NMR spectra are provided. Commercially available reagents and solvents were used without further purification. The starting material 1-aryl piperidine **1** can be found in previous works.¹

Typical procedure for the preparation of piperidine derivatives 1a-1m²

General Procedure for the Alkylation of Primary Amines to Tertiary Amines with Alkyl Dihalides: Aniline (5 mmol), sodium hydrogen-carbonate (6 mmol) and sodium dodecyl sulfate (SDS, ca. 20 mg) were taken up in water (20 mL) and heated at 80 °C for 5 min. 1, 5-dibromopentane (6 mmol) was added to the reaction mixture and heated for a further period time against each substrate. The reaction mixture was cooled and the alkylated product extracted with ethyl acetate. The crude reaction mixture was purified by passing it through a short column of silica gel and eluting with a mixture of ethyl acetate and hexane to yield the pure product.

General Procedure for 1-(2-benzylphenyl)piperidine 1u.

(i) To a stirred solution of potassium carbonate (3.0 g, 22.0 mmol) in 20 mL DMF was added 2-fluorobenzaldehyde (2.5 g, 20 mmol) and piperidine (1.9 g, 22.0 mmol). After heating the reaction mixture at reflux for 8 h, it was cooled and diluted with diethyl ether. The organic layer was extracted with diethyl ether (2×20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel.

(ii) To a stirring solution of 2-(piperidin-1-yl)benzaldehyde (1 equiv) in THF (1.0 M) was added phenylmagnesium bromide (1.0 M in THF, 2 equiv) at room temperature. After heating the reaction mixture at reflux for 2 h, the reaction mixture was quenched by addition of saturated aqueous ammonium chloride (40 mL) and extracted with ethyl ether (2×40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was purified by flash column chromatography to obtain the pure product.

(iii) A mixture of phenyl-(2-(piperidin-1-yl)-phenyl)-methanol (0.5 g, 2.7 mmol), NaBH_4 (0.5 g, 13.2 mmol), and anhydrous AlCl_3 (1.0 g, 7.4 mmol) in THF (25 mL) is heated under reflux for 2 h. The mixture is then cooled, H_2O (10 mL) is added to give two clear phases, and the whole mixture is extracted with EtOAc (4×50 mL). The extract is dried over sodium sulfate and distilled under reduced pressure to give 1-(2-benzylphenyl)piperidine.

General procedure for 4-phenylmorpholine **1w**³

Copper (I) iodide (200 mg, 1.0 mmol) and potassium phosphate (4.25 g, 20.0 mmol) were put into a 50 mL three-neck flask. The three-neck flask was evacuated and back filled with argon. 2-Propanol (10.0 mL), ethylene glycol (1.11 mL, 20.0 mmol), morpholine (1.31 g, 15 mmol) and iodobenzene (1.12 mL, 10.0 mmol) were added successively by micro-syringe at room temperature. The reaction mixture was heated at 85-90 °C and kept for 24 h and then allowed to cool to room temperature. Diethyl ether (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted with diethyl ether (2 × 20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel (hexane/ethyl acetate = 20:1), and the fraction with an $R_f = 0.7$ was collected to give the desired product **1w** 80 % isolated yield.

Typical procedure for the preparation of nitrostyrene⁴

This procedure is typical: Benzaldehyde (106 mg, 1.00 mmol), was added to a stirred solution of ammonium acetate (19.0 mg, 0.25 mmol) in dry nitromethane (5 mL) at 90 °C. The mixture was heated at reflux for 5 h, poured into water and extracted with diethyl ether (3 × 50 mL). The extract was washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure. The residue was purified by recrystallization from ethanol to give the nitrostyrene as yellow needles (132 mg, 0.88 mmol, 88 % yield).

Typical procedure for the preparation of nitrovinylphenol⁵

2-hydroxybenzaldehyde (3.66 g, 30 mmol), was added to a stirred solution of ammonium acetate (578 mg, 7.5 mmol) and acetic acid (1.9 mL, 7.5 mmol) in dry nitromethane (5 mL) at 90 °C. The mixture was heated at reflux for 5 h, poured into water and extracted with diethyl ether (3 × 50 mL). The extract was washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography to obtain the pure product.

References:

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2. Singh, C. B.; Kavala, V.; Samal, A. K.; Patel, B. K. *Eur. J. Org. Chem.* **2007**, 1369.
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The crystal structure of product 5i:

S-Table 1. Crystal Data and Structure Refinement for **5i**.

Bond precision:	C–C = 0.0031 Å	Wavelength=0.71073
Cell:	a=8.9828(9) b=10.4604(10) c=12.0419(11)	
	alpha=84.888(2) beta=80.135(2) gamma=82.659(2)	
Temperature:	296 K	
	Calculated	Reported
Volume	1103.02(18)	1103.02(18)

Space group	P -1	P-1
Hall group	-P 1	?
Moiety formula	C26 H26 N2 O3	?
Sum formula	C26 H26 N2 O3	C26 H26 N2 O3
Mr	414.49	414.49
Dx, g cm ⁻³	1.248	1.248
Z	2	2
Mu (mm ⁻¹)	0.082	0.082
F000	440.0	440.0
F000'	440.19	
h, k, lmax	10, 12, 14	10, 12, 14
Nref	4112	4067
Tmin, Tmax	0.979, 0.984	0.977, 0.984
Tmin'	0.977	
Correction method=	MULTI-SCAN	
Data completeness=	0.989	Theta(max)= 25.500
R(reflections)=	0.0490(2617)	wR2(reflections)= 0.1435(4067)
S =	1.055	Npar= 281

22.52
22.22
20.97

48.95
45.10

78.07
77.31
77.00
76.68

109.64

115.14

119.67

129.42
129.19
127.25
127.13

136.99
135.78

146.62

xxfma-3-c

0.000

2.335
2.052
2.028
2.012
2.004
1.984
1.962
1.913
1.898
1.888
1.885
1.871
1.866
1.854
1.837

3.435
3.426
3.420
3.411

4.877
4.853
4.847
4.823
4.735
4.718
4.706
4.689
4.160
4.142
4.136
4.119

7.281
7.275
7.263
7.259
7.241
7.231
7.218
7.192
7.177
7.058
7.022
7.006
6.872
6.853
6.834
6.565

XXFMA-14-H

22.57
22.15

48.66
45.12

77.75
77.32
77.00
76.68

108.84

115.26

119.95

137.39
133.18
129.24
128.93
128.77
127.57

146.52

xxfma-4-c

0.000

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3.428

4.865
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4.835
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4.739
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4.692
4.180
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7.287
7.269
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7.239
7.230
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7.119
7.111
7.106
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6.877
6.857
6.565

xxfma-9-h

22.21
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45.13
43.91

77.32
77.00
76.68
76.50

106.34
106.53
110.37
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142.03
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7.054
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6.513

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77.00
76.68

108.61

115.41

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129.15
128.72
127.73
127.39
127.29

138.94

144.54

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77.00
77.32
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108.08

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128.71

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145.55

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6.539

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77.00
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112.45

116.03

120.86

127.70

128.75

128.89

129.06

133.14

137.46

139.03

146.58

xxfma-22-c

22.52
22.26
21.70
20.99

48.97
45.17

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77.32
77.00
76.68

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136.98
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7.347
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76.68

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137.54

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117.07

154.11
150.18

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114.28

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129.03

144.08

154.01
154.18

xxfmacv-1-c

— 20.54
 — 24.16
 — 24.95
 — 35.39
 — 40.92
 — 44.21

— 83.14
 — 80.35
 — 77.32
 — 77.00
 — 76.68

— 131.10
 — 129.60
 — 129.53
 — 129.04
 — 120.87
 — 119.31
 — 117.51
 — 117.10

— 154.18
 — 147.88

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— 20.45
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 — 24.97
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— 116.68
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— 150.27
 — 151.85

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