Diamine Catalysed Asymmetric Michael Additions of Aldehydes and Ketones to Nitrostyrene

Supporting information

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Formation of catalyst 3.

(7R,8R)-2,2-Dimethyl-1,3-diazatricyclo[6.3.0.0^{3,7}]undecane (2): To a solution of 2,2'-bipyrrolidine **1**¹ (1.0 eq., 3.57 mmol 500 mg) in THF (15 mL) was added molecular sieves 4Å (~ 0.5 g) and acetone (2.5 mL). The mixture was stirred overnight, then K₂CO₃ was added and the mixture was filtered. Solvent was removed to give the crude aminal as a pale yellow oil (644 mg, 81 %) which is used without purification for the next step.
¹H NMR (400MHz, C₆D₆) : δ = 3.27-3.21 (m, 2H), 2.86-2.76 (m, 4H), 1.80-1.67 (m, 6H), 1.36-1.29 (m, 2H), 1.26 (s, 6H).
¹³C NMR (100.6 MHz, C₆D₆) : δ = 80.34 (C_{quat.}), 70.52 (2 CH), 47.45 (2 CH₂), 30.30 (2 CH₂), 27.57 (2 CH₂), 26.47 (2 CH₃).

(2R,2'R)-1-(1-Methylethyl)-2,2'-bipyrrolidine (3): To a solution of aminal **2** (1.0 eq., 2.66 mmol, 480 mg) in MeOH (10 mL) was added by portion at 0°C NaBH₄ (1.5 eq., 4.0 mmol, 151 mg) then acetic acid (4eq., 10.6 mmol, 0.61 mL). The solution was stirred 3h at 0°C and then diluted with ether (20 mL) and hydrolysed with NaOH_{aq.} 30% (5 mL) and water (10 mL). The solution was decanted, the aqueous phase was extracted two times with AcOEt. The combined organic phases were washed with brine, dried over K₂CO₃, filtered, concentrated in vacuo and purified by bulb to bulb distillation (0.2 mbar, 70°C) to give a colourless oil (427 mg, 88 %).

[α]_D²⁵ = +29.6 (c = 4.8, CHCl₃)

¹H NMR (400 MHz, CDCl₃) : δ = 3.12 (hept, 1H, J = 6.6), 3.01-2.96 (m, 1H), 2.85-2.70 (m, 4H), 2.63-2.56 (m, 1H), 2.06 (s br, 1H, NH), 1.77-1.60 (m, 6H), 1.52-1.46 (m, 1H), 1.33-1.25 (m, 1H), 1.08 (d, 3H, J = 6.8), 0.92 (d, 3H, J = 6.3).

¹³C NMR (100.6 MHz, CDCl₃) : δ = 64.85 (CH), 64.55 (CH), 51.27 (CH), 46.40 (CH₂), 46.27 (CH₂), 29.25 (CH₂), 28.28 (CH₂), 24.573 (2 CH₂), 22.79 (CH₃), 15.10 (CH₃).

IR (CHCl₃) : 3163b, 2959s, 2875s, 2495w, 1458w, 1384w, 1263w, 1165w, 1096w, 1059w cm⁻¹.

MS (EI): 113 (13), 112 (100), 111 (1), 98 (4), 97 (1), 96 (2), 71 (2), 70 (38), 69 (1), 68 (2).

HRMS Calcd for C₁₁H₂₂N₂ 182.1783, found 182.1780.

¹ Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4093.

(2*R*,2'*R*)-1-(1-Methylethyl)-2,2'-bipyrrolidine hydrochloride : To a solution of diamine (**3**) (80 mg, 0.44 mmol) in ether (3 mL) was added at 0°C a solution of hydrochloric acid 1.25M in MeOH (0.37 mL, 0.46 mmol). After a few minutes the solvent was removed in vacuo to give a yellow viscous solid (87 mg, 90%). The product was purified by crystallisation in a mixture of cyclohexane and ethyl acetate to afford a white solid (41 mg, 43%).

m.p. (c-hexane/ethyl acetate) : 133-136°C

1H NMR (400 MHz, $CDCl_3$) : δ = 7.61 (s br, 2H), 3.71-3.61 (m, 2H), 3.36-3.30 (m, 1H), 3.23-3.09 (m, 2H), 3.02 (dt, 1H, J = 10.6, 7.0), 2.87-2.81 (m, 1H), 2.08-1.72 (m, 7H), 1.55-1.46 (m, 1H), 1.32 (d, 3H, J = 6.6), 1.11 (d, 3H, J = 6.3).

^{13}C NMR (100.6 MHz, $CDCl_3$) : δ = 66.91 (CH), 60.80 (CH), 54.88 (CH), 47.02 (CH_2), 46.11 (CH_2), 29.65 ($2CH_2$), 25.21 (CH_2), 24.46 (CH_2), 20.67 (CH_3), 15.91 (CH_3).

Typical procedure for addition of aldehydes and ketones to nitrostyrene.

To a mixture of aldehyde **4a-d** (10 eq., 3.35 mmol) or ketone **7a-f** (30% vol.) and diamine **3** (0.15 eq., 0.05 mmol, 9.2 mg) in chloroform (3 mL) was added nitrostyrene (1.0 eq., 0.335 mmol, 50 mg). The mixture was then stirred at the appropriate temperature until TLC indicated the reaction was complete. The solution was quenched at 0°C with 1N HCl (3 mL) and extracted with CH_2Cl_2 (3x3 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography on silica gel using a mixture of *c*-Hexane, EtOAc as eluent to furnish products **6a-d** and **8a-f**.

Characterisation of adducts.

Compounds **6a**², **6b**², **6d**², **8a**³, **8b**⁴, **8d**⁵, **8e**⁶ and **8f**⁷ are known and our spectroscopic data are in agreement with published data.

2-(2-nitro-1-phenylethyl)-pentanal (**6c**) :

$[\alpha]_D^{25}$ = -24.04 (c = 8.9, $CHCl_3$, 72% ee).

1H NMR (400 MHz, $CDCl_3$) : δ = 9.74 (d, 1H, J = 2.2), 7.41-7.32 (m, 3H), 7.23-7.22 (m, 2H), 4.75 (dd, 1H, J = 4.4, 10.2), 4.69 (dd, 1H, J = 4.7, 10.2), 3.83 (dt, 1H, J = 4.3, 7.8), 2.75 (tt, 1H, J = 2.6, 7.6), 1.56-1.47 (m, 1H), 1.25-1.17 (m, 1H), 0.84 (t, 3H, J = 5.7).

^{13}C NMR (100.6 MHz, $CDCl_3$) : δ = 203.40 (C=O), 136.88 ($C_{quat.}$), 129.19 (2 CH), 128.21 (CH), 128.08 (2 CH), 78.52 (CH_2), 53.86 (CH), 43.20 (CH), 29.52 (CH_2), 19.82 (CH_2), 14.02 (CH_3).

MS (EI): 188(M^+ - HNO_2 , 4), 146(23), 145(88), 131 (10), 118(13), 117(37), 115(13), 105(42), 104(100), 103(17), 91(99), 86(13), 78(14), 77(15), 71(15), 57(30), 55(27).

² Betancort, J. M.; Barbas III, C. F. *Org. Lett.* **2001**, 3, 3737

³ Schionato, A. ; Paganelli, S. ; Botteghi, C. ; Chelucci, G. J. *Mol. Catal.* **1989**, 50, 11.

⁴ Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, 53, 3597.

⁵ Enders, D.; Seki, A. *Synlett* **2002**, 26.

⁶ Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.

⁷ Moorjani, M. C. ; Trivedi, G. K. *Ind. J. Chem.* **1978**, 16B, 405.

1-Nitro-2-phenylheptan-4-one (8c) :

m.p. (pentane) : 32-34°C.

¹H NMR (400 MHz, CDCl₃) : δ = 7.36-7.22 (m, 5H), 4.72 (dd, 1H, J = 6.8, 12.4), 4.62 (dd, 1H, J = 7.8, 12.4), 4.04 (quint, 1H, J = 7.2), 2.91 (dd, 1H, J = 6.8, 17.7), 2.87 (dd, 1H, J = 7.1, 17.7), 2.38 (dt, 1H, J = 16.9, 7.3), 2.32 (dt, 1H, J = 16.9, 7.1), 1.56 (hex, 2H, J = 7.4), 0.86 (t, 3H, J = 7.5).

¹³C NMR (100.6 MHz, CDCl₃) : δ = 207.91 (C=O), 139.05 (C_{quat.}), 129.13 (2CH), 127.95 (CH), 127.49 (2CH), 79.61 (CH₂), 45.38 (CH₂), 45.28 (CH₂), 39.18 (CH), 17.12 (CH₂), 13.67 (CH₃).

IR (CHCl₃) (isomer mixture): 3033w, 2973m, 2876w, 1713s, 1555s, 1495w, 1455w, 1428w, 1378m cm⁻¹.

GC-MS (EI): 188(18), 145(30), 117(18), 104(33), 103(12), 91(12), 71(100), 43(46).

Chiral separation of adduct by chiral SFC and chiral GC.

Compound	Apparatus ^a	Column	Conditions ^c	t _R [min]
6a	SFC GC	Chiralcel OD-H Hydrodex-B-3P ^b	2%-2-1-15 / 30°C 135°C isotherm	6.13(major) / 6.76 56.40 / 57.56(major)
6b	GC	Hydrodex-B-3P ^b	145°C isotherm	42.95 / 43.90(major)
6c	SFC	Chiralcel OD-H	2%-10-2-15 / 10°C	5.57(major) / 6.22
6d	SFC GC	Chiralcel OD-H Hydrodex-B-3P ^b	1%-6-2-15 / 30°C 150°C isotherm	7.00(major) / 7.53 38.42 / 39.79(major)
8a	GC	Lipodex E ^b	120°C-0-2-170	18.27 / 18.76(major)
8b	SFC	Chiralcel OB-H	1%-10-1-15 / 30°C	7.11(major) / 9.36 ^d 10.08(major) / 11.75
8c	SFC	Chiralpak AD	2%-4-2-15 / 30°C	^d 6.59 / 7.83(major)
8d	SFC	Chiralcel OB-H	2%-2-1-15 / 30°C	4.38(major) / 5.69
8e	SFC	Chiralpak AD	10%-6-1-15 / 30°C	4.86(major) / 5.69
8f	SFC	Chiralpak AD	10%-5-2-15 / 30°C	5.01(major) / 5.89

^a SFC : Supercritical Fluid Chromatography (CO₂); GC : Gas Chromatography.

^b 25 meters lenght.

^c SFC conditions : 2 mL/min, 200 bar, 2%-2-1-15 means 2% MeOH modifier during 2 min then concentration gradient of 1%/min until 15%.

GC conditions : 120°C-0-2-170 means 120°C isotherm during 0 min then gradient temperature of 2 °C/min until 170°C.

^d Kinetic regioisomer.

Stereochemistry

Relative (*syn*) and absolute configuration of aldehydes (-)-**6a**, (-)-**6b** and (-)-**6d** was determined by comparison with known ¹H-NMR data and optical rotation values². The stereochemistry of aldehyde (-)-**6c** ([α]_D²⁵ = -24.04 (c = 8.9, CHCl₃, 72% ee)) has been tentatively assigned by comparison to analogous compounds.

The relative and absolute configuration of (+)-**8e** has been assigned by comparison with literature data⁶. The stereochemistry of ketones (+)-**8a**, **8b**, **8c**, (-)-**8d** and **8f** has been assigned by assuming an identical reaction pathway and according to literature results^{5,8}.

⁸ List, B. ; Pojarliev, P. ; Martin, H. J. *Org. Lett.* **2001**, 3, 2423.

¹H Spectrum

¹³C CPD-Spectrum

¹H Spectrum

¹³C CPD-Spectrum

¹H Spectrum

· HCl

¹³C CPD-Spectrum

File : C:\HPCHEM\2\DATA\OA484.D
Operator : olivier a
Acquired : 6-8-02 00:20:37 using AcqMethod FOA135.M
Instrument : HP G1530A
Sample Name: oa484
Misc Info : hydrodex 135-60-10-170
Vial Number: 8

Area Percent Report

Data File : C:\HPCHEM\2\DATA\OA484.D	Vial: 8
Acq On : 6-8-02 00:20:37	Operator: olivier a
Sample : oa484	Inst : HP G1530A
Misc : hydrodex 135-60-10-170	Multiplr: 1.00
	Sample Amount: 0.00

IntFile : EVENTS.E

Method : C:\HPCHEM\2\METHODS\B60-60.M (Chemstation Integrator)
 Title :

Signal : OA484.D\FID1A								
peak #	R.T. min	Start min	End min	PK TY	peak height	peak area	peak % max.	% of total
1	56.399	55.822	56.690	M	21608	6477327	8.22%	7.592%
2	57.559	56.712	58.020	M	246346	78843952	100.00%	92.408%
Sum of corrected areas:						85321279		

OA484.D B60-60.M Sat Jun 08 01:36:36 2002 CHEMSTATION

File : C:\HPCHEM\2\DATA\EE8(1.D
Operator : olivier a
Acquired : 1-22-02 17:11:06 using AcqMethod FOA145.M
Instrument : HP G1530A
Sample Name: EE8
Misc Info : hydrodex 145-45-10-170
Vial Number: 8

Area Percent Report

Data File : C:\HPCHEM\2\DATA\EE8(1.D) Vial: 8
 Acq On : 1-22-02 17:11:06 Operator: olivier a
 Sample : EE8 Inst : HP G1530A
 Misc : hydrodex 145-45-10-170 Multiplr: 1.00
 Sample Amount: 0.00
 IntFile : EVENTS2.E
 Method : C:\HPCHEM\2\METHODS\F65-70.M (Chemstation Integrator)
 Title :

Signal : EE8(1.D\FID1A

peak #	R.T. min	Start min	End min	PK TY	peak height	peak area	peak % max.	% of total
1	42.951	42.226	43.342	BV	20105	4329301	17.48%	12.693%)
2	43.904	43.342	44.946	VB	113786	24763446	100.00%	72.603%
3	46.332	45.533	47.186	BB	33402	5015249	20.25%	14.704%
Sum of corrected areas:						34107997		

EE8(1.D F65-70.M Fri Jan 25 10:07:56 2002 CHEMSTATION

OD-H 2-10-2-15 2 ml/min 200 Bar 10 C

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Acq. Method	: OD-H2-6.M	Seq. Line	:
Acq. Operator	: KARINE	Vial	: 1052
Injection Date	: 25-01-02 10:16:01	Inj	:
Sample Name	: OA315	Inj Volume	: Unknown

Analysis Method : C:\BERGER\1\METHODS\OJ1-4.M
(modified after loading)

CHIRALCEL OJ

LDAD1 B, Sig=220,15 Ref=450,40 of OA\OA315(2.D

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Area Percent Report

Data File C:\BERGER\1\DATA\OA\OA315(2.D

Sorted by Signal
Multiplier : 1.000000

Signal 1: LDAD1 B, Sig=220,15 Ref=450,40

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	5.568	MM	0.223	13129.22852	983.34363	86.5059
2	6.225	MM	0.198	2048.03491	171.96095	13.4941

Totals : 15177.26367 1155.30457

File : C:\HPCHEM\2\DATA\OA471(1.D
Operator : OLIVIER A
Acquired : 5-27-02 21:08:49 using AcqMethod FOA150.M
Instrument : HP G1530A
Sample Name: OA471
Misc Info : HYDRODEX 150-41-10-170
Vial Number: 1

Area Percent Report

Data File : C:\HPCHEM\2\DATA\OA471(1.D
Acq On : 5-27-02 21:08:49
Sample : OA471
Misc : HYDRODEX 150-41-10-170

Vial: 1
Operator: OLIVIER A
Inst : HP G1530A
Multiplr: 1.00
Sample Amount: 0.00

IntFile : EVENTS.E

Method : C:\HPCHEM\2\METHODS\B60-60.M (Chemstation Integrator)
Title :

Signal : OA471(1.D\FID1A

peak #	R.T. min	Start min	End min	PK TY	peak height	peak area	peak % max.	% of total
1	38.422	37.927	38.910	M	80686	18436477	19.37%	15.174%
2	39.794	38.944	40.758	M	381553	95158538	100.00%	78.319%
3	42.332	41.826	42.539	M	38005	7906404	8.31%	6.507%

Sum of corrected areas: 121501418

OA471(1.D B60-60.M

Mon May 27 22:00:37 2002

CHEMSTATION

File : C:\HPCHEM\2\DATA\OA461B.D
Operator : OLIVIER A
Acquired : 5-14-02 22:55:10 using AcqMethod BOA120.M
Instrument : HP G1530A
Sample Name: OA461
Misc Info : LIPODEX E 120-0-2-170
Vial Number: 8

Area Percent Report

Data File : C:\HPCHEM\2\DATA\OA461B.D
 Acq On : 5-14-02 22:55:10
 Sample : OA461
 Misc : LIPODEX E 120-0-2-170

Vial: 8
 Operator: OLIVIER A
 Inst : HP G1530A
 Multiplr: 1.00
 Sample Amount: 0.00

IntFile : EVENTS.E

Method : C:\HPCHEM\2\METHODS\B60-60.M (Chemstation Integrator)
 Title :

peak #	R.T. min	Start min	End min	PK TY	peak height	peak area	peak % max.	% of total
1	17.297	17.158	17.599	M	298729	21274402	60.17%	37.565%
2	17.768	17.646	18.144	M	472509	35359045	100.00%	62.435%
Sum of corrected areas:						56633447		

OA461B.D B60-60.M Tue May 14 23:26:00 2002 CHEMSTATION

OB-H 1%-10-1-15 2 ml/min 200 Bar 30 C

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Acq. Method      : OBH2-6.M                      Seq. Line :   -
Acq. Operator    : Karine                        Vial      : 1007
Injection Date   : 14-03-02 12:43:55             Inj       :   -
Sample Name      : OA387                         Inj Volume: Unknown
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Analysis Method : C:\BERGER\1\METHODS\OBH2-6.M
                  (modified after loading)
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CHIRALCEL OB-H

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Area Percent Report
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Sorted by Signal

Multiplier : 1.000000

Signal 1: LDAD1 B, Sig=220,15 Ref=450,40

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %	
1	7.119	MM	0.275	2943.08203	178.05360	25.0863	32% ee.
2	9.364	MM	0.316	1528.97107	80.71362	13.0327	
3	10.082	MM	0.292	6157.10693	351.54492	52.4822	
4	11.750	MM	0.197	1102.64832	93.07005	9.3988	70% ee

Totals : 11731.80859 703.38220

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*** End of Report ***
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OB-H 2%-2-1-15 2 ml/mn 200 Bar 30 C

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Acq. Method      : OBH1-4.M                      Seq. Line :   -
Acq. Operator    : STEF                          Vial      : 1003
Injection Date   : 27-06-02 11:26:50             Inj       :   -
Sample Name      : OA479                        Inj Volume: Unknown
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Analysis Method : C:\BERGER\1\METHODS\OD-H1-4.M
(modified after loading)

CHIRALCEL OD-H

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Area Percent Report
=====

Sorted by Signal

Multiplier : 1.000000

Signal 1: LDAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	4.378	MM	0.200	15954.57715	1330.97681	83.2322
2	5.685	MM	0.193	3214.16968	276.93564	16.7678

Totals : 19168.74609 1607.91248

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*** End of Report ***
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AD 10%-5-2-15 2 ml/mn 200 Bar 30 C

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=====
Acq. Method      : AD2-6.M                      Seq. Line :   -
Acq. Operator    : Karine                      Vial      : 1025
Injection Date   : 16-05-02 07:52:18          Inj       :   -
Sample Name      : OA463                      Inj Volume: Unknown
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Analysis Method : C:\BERGER\1\METHODS\AD2-6.M
(modified after loading)

CHIRALCEL AD

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Area Percent Report
=====
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Sorted by Signal

Multiplier : 1.000000

Signal 1: LDAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	5.014	MM	0.232	22312.15430	1599.86548	87.0354
2	5.886	MM	0.254	3323.56348	218.04329	12.9646

Totals : 25635.71875 1817.90881

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*** End of Report ***
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