New Biphenol-based Phosphoramidite Ligands for the Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc

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General Procedures. ^1H (300, 400, and 500 MHz), ^{13}C (75, 100, and 125 MHz), and ^{31}P NMR (122, 162, and 202 MHz) spectra were recorded in CDCl_3 or DMSO-d_6 and chemical shifts (δ) are quoted in ppm relative to tetramethylsilane (0 ppm) and referenced to the residual undeuterated solvent. For convenience, the following abbreviations are used; s - singlet, d - doublet, t - triplet, q - quartet, qn - quintet, m - multiplet, dd - doublet of doublet, dt - doublet of triplet, td - triplet of doublet, ddd - doublet of doublet of doublet. Coupling constants (J) are given in Hertz (Hz).

Optical rotations were measured at 22°C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ (concentration c given as g/100mL). Enantiomeric excesses were determined by chiral GC (capillary column, 10 psi H_2) or chiral SFC with the stated column. Temperature programs are described as follows: initial temperature ($^\circ\text{C}$) – initial time (min) – temperature gradient ($^\circ\text{C}/\text{min}$) – final temperature ($^\circ\text{C}$); retention time (R_T) are given in min. Flash chromatography were performed using silica gel 32-63 μm , 60 $\text{\AA}$.

Phosphorus trichloride was distilled once and then degassed three times *in vacuo* at -78°C to remove the residual HCl . It was stored at -20°C in a Schlenk tube. Triethylamine was in every case freshly distilled. All non-solid phosphorus ligand were dissolved in the appropriate volume of dry toluene to make an about 1 M solution that was used in conjugate addition reactions.

THF and diethyl ether were distilled from sodium using benzophenone ketyl as indicator. Other solvents were purified by standard techniques. Brine refers to a saturated solution of sodium chloride in water and DCM to dichloromethane.

Cyclohexenone **S1**, cycloheptenone **S3**, chalcone **S4**, benzalacetone **S5**, *trans*-5-Me-3-hexen-2-one **S6**, *trans*-3-nonen-2-one **S7**, *trans*- β -nitrostyrene **S8**, *trans*-4-methyl- β -nitrostyrene **S9**, *trans*-4-methoxy- β -nitrostyrene **S9**, 1-(2-furyl)-2-nitroethylene **S12**, 1-nitrocyclohexene **S13** 2,4-dimethylphenol, 2,2'-dihydroxybiphenyl **B1**, 2,4-di-*tert*-butylphenol, 2-methoxy-4-methylphenol and *sec*-butylamine were commercial products and used as received. Cyclopentadecen-2-one **S3** was prepared according to the literature.¹

Melting points are uncorrected.

Ligand synthesis procedure. To a stirred mixture of Et_3N (111.1 mmol, 15.5 mL) and PCl_3 (22.2 mmol, 1.9 mL) at 0°C , a solution of amine (22.2 mmol) in THF (10 mL) was added and the reaction mixture was stirred for 3h at room temperature. Biphenol (22.2 mmol) in a solution of THF (5 mL) was slowly added to the reaction mixture at 0°C and then the suspension was stirred at RT overnight. The suspension was diluted in toluene (8 mL) and filtered on neutral alumina, the solution was concentrated and purified by flash chromatography through neutral alumina using dry toluene as eluent, to give the pure ligand as a white solid or a colorless oil.

Asymmetric conjugate addition procedure. To a solution of copper thiophenecarboxylate (CuTC)² (0.008mmol) in Et_2O (1ml) at room temperature under nitrogen, was added the ligand (0.0166mmol) and 1ml of Et_2O . The solution was stirred at 25°C for 30min and then cooled to -30°C . Et_2Zn (1ml, 0.5 mmol 15% in hexane) was added dropwise in order that temperature did not rise over -30°C . The solution was stirred for 5min, and the Michael acceptor (0.415mmol) was then added dropwise, neat or in solution in 0.5mL of toluene. The reaction mixture was stirred at -30°C for 12h before being quenched by 2N, HCl / Et_2O (aq. sat. NH_4Cl in the case of nitroalkene compounds). Enantiomeric excess was determined by chiral GC or SFC.

¹Engman, L. *J. Org. Chem.* **1988**, 53, 4031-4037.

² CuTC can either be purchased from Frontier Scientific Ltd or prepared according to the literature procedure: Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, 118, 2748-2749.

DP008N02 CDCL3 400MHZ 1H

B2

Integral

2.0000

1.9613

1.8781

12.130

(ppm)

S 3

DP008N02 CDCL3 400MHZ 13C

B2

S4

DP025N02 (400MHz)(DMSO)

B3

*** Current Data Parameters ***

NAME : sm89cr1

EXPNO : 10

PROCNG : 1

*** Processing Parameters ***

SF : 500.1299850 MHz

B4

*** Current Data Parameters ***

NAME : sm89cri1

EXPNO : 11

PROCNO : 1

*** Processing Parameters ***

SF : 125.7577270 MHz

200

180

160

140

120

100

80

60

40

20

0

(ppm)

S8

*** Current Data Parameters ***

NAME : sm95cri1

EXPNO : 11

PROCNO : 1

*** Processing Parameters ***

SF : 125.7577940 MHz

*** Current Data Parameters ***

NAME : sm96fr6b

EXPNO : 11

PROCNO : 1

*** Processing Parameters ***

SF : 125.7578080 MHz

2

S12

1H Spectrum

7.7031
7.6974
7.6627
7.5611
7.5428
7.5232
7.4859
7.4676
7.4480
7.3830
7.3641
7.3458
7.2700

5.9492

7.7031
7.6974
7.6627
7.5611
7.5428
7.5232
7.4859
7.4676
7.4480
7.3830
7.3641
7.3458

*** Current Data Parameters ***

NAME : sm107ext

EXPNO : 10

PROCNO : 1

*** Processing Parameters ***

400.1300170 MHz

B5

Integral

5.8795

1.9780

3.0053

1.0000

0.9175

7.7 7.6 7.5 7.4

(ppm)

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

(ppm)

S13

¹³C CPD Spectrum

*** Current Data Parameters ***

NAME : sm107ext

EXPNO : 11

PROCNO : 1

*** Processing Parameters ***

SF : 100.6127796 MHz

DP082N04 CDCL3 400MHZ 1H

B6

DP121N01 CDCL3 1H 400MHZ

3

S 20

DP123 CDCL3 1H 400MHZ

7.4939
7.4870
7.4800
7.4756
7.3051
7.2995
7.2862
7.2824
7.0936
7.0842
7.0753
7.0570

5.3239

0.3721

7.4977
7.4939
7.4870
7.4800
7.4756

7.3051
7.2995
7.2862
7.2824

7.0936
7.0842
7.0753
7.0570

B8

S21

DP123 CDCL3 13C 100MHZ

B8

DP034N01 (400MHz)(CDCl₃)

4

B9

S25

DPBISALL 400MHZ 13C CDCL3

B9

DP097PUR 400MHZ CDCL3 1H

7.3664
7.3620
7.3531
7.3481
7.3437
7.3361
7.0823
7.0665
7.0640
7.0046
6.9850
6.9825

4.9565
4.8908

4.4248

1.7276

5

S27

DP097PUR 400MHZ CDCL3 13C

5

S28

B10

DP111PUR 400MHZ CDCL3 13C

B10

DPHYDR CDCL3 13C 400MHZ

B11

MT027 CDCL3 1H 400MHZ

7.4898
7.4841
7.3389
7.3326
7.2928
7.2865
7.2600
7.1394
7.1268

L3a

4.6796
4.6619
4.6518
4.6341

1.7892
1.7715

7.5391
7.5328

7.4898
7.4841

7.3389
7.3326

7.2928
7.2865

7.2600

S33

MT027 CDCL3 13C 400MHZ

L3a

MT027 CDCL3 31P 400MHZ

L3a

S35

DP193 CDCL3 1H 400MHZ

L4a

DP193 CDCL3 13C 400MHZ

157.6076
148.5246
147.3624
135.8974
135.6336
132.6499
132.6087
131.8174
131.0097
127.8859
126.9050
118.5556
117.5747
117.4016
116.1735
77.4017
77.0885
76.7670
53.1198
53.0044
26.9752

DP193 CDCL3 31P 400MHZ

147.8431

260

220

180

140

100

60

20

-20

-60

-100

-140

(ppm)

S 38

*** Current Data Parameters ***

NAME : sm109fr1

EXPNO : 11

PROCNO : 1

*** Processing Parameters ***

SF : 100.6127730 MHz

DP098N02 CDCL3 400MHZ 13C

L6a

DP098N02 CDCL3 400MHZ 31P

L6a

146.0828
145.0101

11.8038

DP084N04 CDCL3 1H 400MHZ

7.5036
7.4979
7.4247
7.4190
7.2182
7.2119
7.1463
7.1406

L7a

1.6496
1.3819
1.1356

7.5036
7.4979

7.4247
7.4190

7.2182
7.2119

7.1463
7.1406

7.50

(ppm)

7.2

(ppm)

Integral

0.8988
0.9869
1.1085
10.028

1.6733

9.0000
18.545
8.4764

7.5

6.5

6.0

5.5

5.0

4.5

4.0

3.5

3.0

2.5

2.0

1.5

1.0

0.5

(ppm)

S 45

DP084N04 CDCL3 13C 400MHZ

L7a

DP084N04 CDCL3 31P 400MHZ

L7a

149, 122.1

S 47

DP124N03 CDCL3 400MHZ 1H

L8a

DP124N03 CDCL3 400MHZ 13C

L8a

240 220 200 180 160 140 120 100 80 60 40 20 0 -20
(ppm)

S 49

DP124N03 CDCL3 400MHZ 31P

L8a

149.3972

DP077N22 CDCL3 300MHZ 1H

L9a

DP077N22 CDCL3 300MHZ 13C

L9a

DPSR1234 CDCL3 500MHZ 1H

L9b

S 54

DPSR1234 CDCL3 500MHZ 13C

L9b

DPSR1234 CDCL3 500MHZ 31P

L9b

S 56

DPSR1231 CDCL3 300MHZ 1H

L10a

S 57

DPSR1231 CDCL3 300MHZ 13C

L10a

DPSR1231 CDCL3 300MHZ 31P

L10a

DPSR1232 CDCL3 300MHZ 1H

L10b

*
N
E
F
*
S
*
S
*

DPSR1232 CDCL3 300MHZ 13C

L10b

DPSR1232 CDCL3 300MHZ 31P

L10b

S 62

DP194N06 CDCL3 400MHZ 1H

L11a

DP194N06 CDCL3 400MHZ 13C

L11a

DP194N06 CDCL3 400MHZ 31P

L11a