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Published in:
Organic & Biomolecular Chemistry

DOI:
[10.1039/B404996A](https://doi.org/10.1039/B404996A)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2004

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Duursma, A., Lefort, L., Boogers, J. A. F., de Vries, A. H. M., Vries, J. G. D., Minnaard, A. J., & Feringa, B. L. (2004). Synthesis and application in asymmetric C–C bond formation of solution phase ligand libraries of monodentate phosphoramidites. *Organic & Biomolecular Chemistry*, 2(12).
<https://doi.org/10.1039/B404996A>

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SUPPLEMENTARY INFORMATION

Synthesis and application in asymmetric C-C bond formation of solution phase ligand libraries of monodentate phosphoramidites

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General.

All reactions were performed in a dry nitrogen atmosphere using standard Schlenk techniques or in the glove box. Reagent grade dried solvents were purchased from Fluka and used as received. Phosphorochloridites **A**, **B**, and **C** were prepared according literature procedure.¹ Amines and enones were used as provided by Aldrich, Fluka, Acros. Ethyl nipecotate, perhydroisoquinoline and 2,3-dimethyl-2,3-dihydro-1H-indole were used as mixtures of stereoisomers. Triethylamine was stored over KOH pellets. Enantiomeric excesses and conversions were determined by capillary GC analysis on a HP 6890 gas chromatograph with a flame ionisation detector. The library was synthesized using a Zinsser Lissy liquid handling robot equipped with 4 probes and placed inside a glove box. Whatman PKP 2mL 96-well filter plates in combination with the UniVac 3 vacuum manifold were used to perform the parallel filtration of the ligand library. The reactions were carried out in a Premex 96-Multi Reactor that can accommodate 96 reactions vessels at the same temperature.²

Synthesis of the library.

Stock solutions were prepared by dissolving the proper amounts of every reagent necessary for the library synthesis in dry toluene (all by weight). For the phosphorochloridites a concentration of 0.150 M was used, for the amines 0.157 M, and for the triethylamine 0.500 M. Using the liquid handling robot 0.333 mL (1.00 eq) of each of the three phosphorochloridite solutions was transferred into the corresponding 32 wells of the Whatman PKP filter plate. The triethylamine solution 0.100 mL (1.00 eq) was added to each of the 96 wells. Next 0.333 mL (1.05 eq) of each of the 32 amine solutions was added to each of the three blocks of 32 wells. The microplate was placed on an orbital shaker and vortexed for 2 hours at room temperature. The microplate was then placed onto the vacuum manifold and filtration was performed upon application of the vacuum. The filtrates, i.e. 96 solutions of different phosphoramidites in dry toluene (0.766 mL, 0.065M) were collected and stored into a 96-well polypropylene microplate.

Screening of the library.

A stock solution containing the Rh precursor, Rh(acac)(eth)₂ at a concentration of 0.0012 M, and the enone, **1** or **4** at a concentration of 0.0310 M, in absolute ethanol was prepared. Using the liquid handling robot 0.100 mL (0.10 eq) of the 96 ligand solutions was transferred from the microplate into 96 vials, equipped with stirring bars. Then 2.000 mL of the Rh(acac)(eth)₂ and enone stock solution, (0.04 eq and 1.00 eq, respectively) was added to each of the 96 vials. After the addition of 35 mg (4.00 eq) of trifluoroborate **2** the vials were capped and transferred to the parallel reactor. The reactions were left stirring at reflux for the indicated time, and then analyzed by chiral GC in order to determine the conversion and the e.e.

Results of the screening.

For cyclohexenone (**1**) the following results were obtained :

position (ligand)	conv. (%)	e.e. (%)	position (ligand)	conv. (%)	e.e. (%)	position (ligand)	conv. (%)	e.e. (%)
a1	19	79	e1	35	76	i1	4	16
a2	21	73	e2	53	78	i2	9	9
a3	34	64	e3	56	75	i3	6	7
a4	41	73	e4	62	72	i4	6	14
a5	10	18	e5	22	48	i5	24	25
a6	17	16	e6	21	14	i6	16	26
a7	12	41	e7	10	41	i7	12	40
a8	51	75	e8	80	82	i8	4	15
b1	52	84	f1	81	87	j1	4	14
b2	18	22	f2	21	14	j2	13	31
b3	12	19	f3	20	45	j3	22	27
b4	22	64	f4	62	77	j4	2	15
b5	12	21	f5	19	49	j5	23	27
b6	18	58	f6	20	75	j6	17	42
b7	14	44	f7	9	41	j7	19	37
b8	10	21	f8	17	48	j8	16	18
c1	10	34	g1	21	49	k1	7	22
c2	13	25	g2	20	45	k2	19	18
c3	45	67	g3	69	74	k3	4	6
c4	7	24	g4	19	43	k4	11	24
c5	31	31	g5	39	19	k5	21	50
c6	14	36	g6	7	53	k6	19	41
c7	15	33	g7	8	47	k7	10	41
c8	11	76	g8	22	82	k8	1	29
d1	13	11	h1	21	37	l1	12	14
d2	36	77	h2	74	78	l2	8	0
d3	22	52	h3	61	58	l3	3	15
d4	35	82	h4	41	72	l4	8	4
d5	7	28	h5	5	28	l5	8	25
d6	9	26	h6	13	37	l6	24	39
d7	13	49	h7	10	47	l7	14	40
d8	17	37	h8	17	42	l8	11	14

3-Vinyl-cyclohexanone (3). Spectral data were in accordance with literature.³ Enantiomer separation on a ChiralDEX A-TA column, 30m x 0.25 mm, 90°C isothermic, 11.8 / 12.4 min.

For benzylidene acetone (**4**) the following results were obtained :

position (ligand)	conv. (%)	e.e. (%)	position (ligand)	conv. (%)	e.e. (%)	position (ligand)	conv. (%)	e.e. (%)
a1	69	10	e1	92	7	i1	14	10
a2	82	22	e2	84	15	i2	17	12
a3	92	31	e3	88	33	i3	13	4
a4	99	23	e4	96	21	i4	20	13
a5	1	0	e5	6	25	i5	10	9
a6	16	34	e6	42	28	i6	8	6
a7	35	21	e7	52	24	i7	16	5
a8	99	17	e8	96	8	i8	17	4
b1	99	8	f1	88	3	j1	15	5
b2	28	24	f2	49	29	j2	9	6
b3	6	12	f3	1	25	j3	9	10
b4	77	40	f4	99	30	j4	11	4
b5	15	35	f5	26	26	j5	10	10
b6	31	37	f6	24	23	j6	8	4
b7	38	18	f7	35	19	j7	13	7
b8	28	32	f8	44	27	j8	13	10
c1	22	43	g1	49	34	k1	4	5
c2	21	36	g2	2	28	k2	16	11
c3	78	37	g3	99	25	k3	16	4
c4	12	41	g4	16	27	k4	10	9
c5	35	32	g5	49	31	k5	14	6
c6	32	28	g6	36	29	k6	19	7
c7	33	16	g7	40	21	k7	17	5
c8	63	30	g8	83	22	k8	3	8
d1	22	30	h1	13	30	l1	6	10
d2	91	14	h2	99	24	l2	16	15
d3	89	42	h3	99	40	l3	11	24
d4	70	2	h4	99	17	l4	22	29
d5	15	22	h5	36	26	l5	21	8
d6	34	32	h6	52	26	l6	12	3
d7	30	25	h7	70	23	l7	16	4
d8	45	33	h8	37	31	l8	16	8

4-Phenyl-hex-5-en-2-one (5). Spectral data were in accordance with literature.⁴ Enantiomer separation on a Chiraldex G-TA column, 30m x 0.25 mm, 125°C isothermic, 11.2 / 11.5 min.

Large scale preparation of phosphoramidite ligands.

According literature procedure,¹ ligand **8e** was obtained as a white foam in 80% yield. ¹H-NMR (200 MHz, CDCl₃) δ 1.10 (t, *J* = 7.0 Hz, 3H); 1.54 (m, 2H); 1.70-1.84 (m, 6H); 2.18-2.37 (m, 5H); 2.58-3.19 (m, 10H); 7.00 (m, 4H) ppm. ¹³C-NMR (50 MHz, CDCl₃) δ 14.5; 22.5; 22.6; 27.7 (d, *J* = 6.8 Hz); 29.1 (d, *J* = 5.6 Hz); 31.3 (d, *J* = 6.8 Hz); 43.8 (d, *J* = 35.6 Hz); 118.5; 129.2 (d, *J* = 6.8 Hz); 133.9 (d, *J* = 49.7 Hz); 137.9 (d, *J* = 24.3 Hz); 148.7 (d, *J* = 17.0 Hz) ppm. ³¹P-NMR (81 MHz, CDCl₃) δ 142.080 ppm. HRMS calcd for C₂₃H₂₈NO₂P: 318.18575, found 318.18496. EA calcd for C₂₃H₂₈NO₂P: C 72.42 H 7.40 N 3.67, found C 72.50 H 7.42 N 3.59 Mp 88°C [α]_D = + 257°, (*c* = 1.0, CHCl₃). Ligand **8f** was prepared according to a published procedure.¹

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