Enantioselective Parallel Synthesis Using Polymer-Supported Chiral Co(Salen) Complexes

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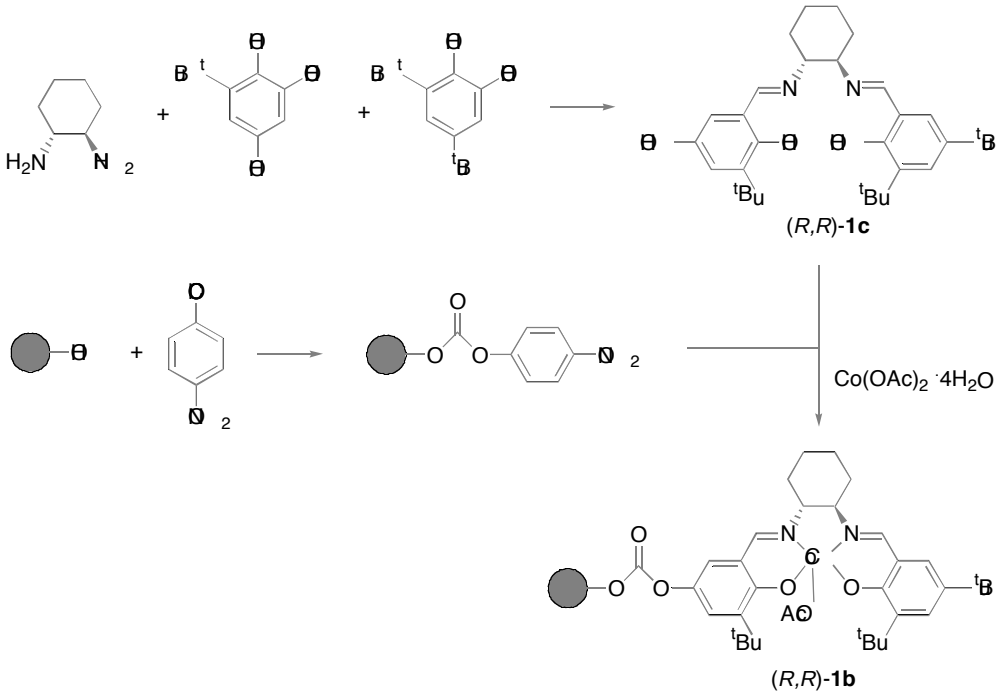
SUPPORTING INFORMATION

General

Dichloromethane was distilled from CaH_2, diethylether from sodium/benzophenon ketyl prior to use. Commercially available starting materials were used as received.

Gas chromatographic analyses were conducted on a Hewlett Packard HP 5890 Series II gas chromatograph. ^{1}H NMR spectra were recorded on a Bruker AM-500 spectrometer. Electronic ionisation (EI) were obtained on a Hewlett Packard HP 5972 Mass Selective Detector. Atmospheric pressure chemical ionisation (APCI) mass spectra were provided by the Mass Spectrometry Laboratory of Harvard University.
HPLC analysis was performed on a Hewlett Packard Series 1100 quaternary pump HPLC system equipped with an HP 1100 autosampler and diode array detector. Chiral HPLC analysis was performed on a Hewlett Packard Series 1050 quaternary pump HPLC system equipped with an HP 1050 diode array detector Chiral HPLC analysis was performed on a Hewlett Packard Series 1050 quaternary pump HPLC system equipped with an HP 1050 diode array detector. Racemic samples for finding chiral HPLC separation conditions were prepared the same way as described below using racemic **1b**. Elemental analysis was performed by H. Kolbe, Mikroanalytisches Laboratorium, Mülheim/Ruhr, Germany.

*Synthesis of (R,R)-**1b***



Chiral salen ligand (*R,R*)-**1c** : To a solution of 3,5-di-*tert*-butylsalicylaldehyde (2.25 g, 9.6 mmol, 1.5 eq.) and 3-*tert*-2,5-dihydroxybenzaldehyde (0.62 g, 3.2 mmol, 0.5 eq.) in CH_2Cl_2 (60 mL) was added (*R,R*)-1,2-diaminocyclohexane (0.73 g, 6.4 mmol, 1 eq). The reaction mixture was stirred at room temperature for 12 h, then concentrated to yield a yellow foam. This product was used without further purification in the synthesis of **1b** by resin capture in the next reaction step. The expected yield of (*R,R*)-**1c** in this mixture is 1.21 g (2.4 mmol).

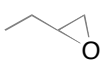
Hydroxymethyl polystyrene (Advanced Chemtech, 2% crosslinked 90μm beads, 0.8 mmol/g, 2.0 g, 1.6 mmol, 1 eq.), 4-nitrophenyl chloroformate (1.29 g, 6.4 mmol, 4 eq.), and DMAP (195 mg, 1.6 mmol, 1eq.) were combined , suspended in CH_2Cl_2 (20 mL), and shaken at room temperature for 3 h. Filtration and rinsing with anhydrous CH_2Cl_2 followed by drying *in vacuo* yielded colorless beads. The IR spectrum (KBr pellet) revealed a strong absorbance at 1767 (C=O) and medium absorbance at 1526 (C-NO_2) cm^{-1}. To a suspension of this material in anhydrous DMF (30 mL) was added (*R,R*)-**1c** (2.4 mmol, 1.5 eq.), DMAP (195 mg, 1.6 mmol, 1 eq.), and DIPEA (0.56 mL, 3.2 mmol, 2 eq.). The resulting yellow suspension was shaken at room temperature 12 h then filtered and rinsed sequentially with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 and dried *in vacuo* to yield the product as yellow beads. The IR spectrum (KBr pellet) showed strong absorbances at 1761 (C=O) and 1630 (C=N) cm^{-1}. The absorbance at 1526 (C-NO_2) cm^{-1} disappeared completely.

Cobalt insertion into the polystyrene-bound ligand was accomplished by adding of a solution of $Co(OAc)_2{\cdot}4H_20$ (0.8 g, 3.2 mmol, 2 eq.) in 20 mL 1:1 MeOH/toluene to the resin beads (2.0 g) with gentle stirring at room temperature. The beads turned red-brown over few minutes. After 2 h the beads were filtered and rinsed sequentially with MeOH, CH_2Cl_2, 9:1 toluene/HOAc, CH_2Cl_2, MeOH, CH_2Cl_2, and then dried *in vacuo* to yield the product as very dark brown beads. The IR spectrum (KBr pellet) contained strong absorbances at 1761 and 1630 cm^{-1}. Elemental analysis indicated 1.43% Co, corresponding to a final loading of 0.24 mmol/g Co.

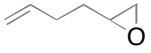
In the same way as described above (*S,S*)-**1b** was prepared from (*S,S*)-1,2-diaminocyclohexane and hydroxymethyl polystyrene (0.97 mmol/g). Elemental analysis indicated 2.16% Co, corresponding to a final loading of 0.37 mmol/g Co.

Building blocks for parallel synthesis

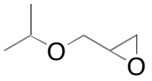
Epoxides



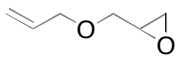
2a



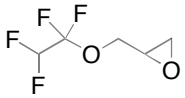
2b



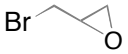
2c



2d

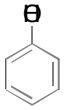


2e

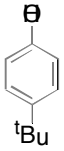


5

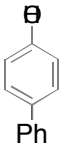
Phenols



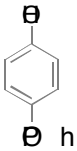
3a'



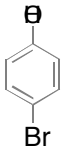
3b'



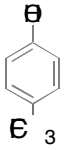
3c'



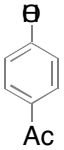
3d'



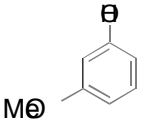
3e'



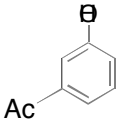
3f'



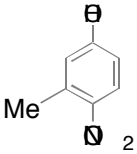
3g'



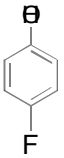
3h'



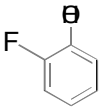
3i'



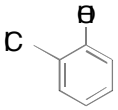
3j'



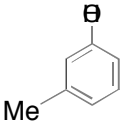
3k'



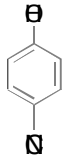
3l'



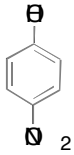
3m'



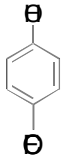
3n'



3o'



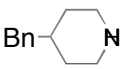
3p'



3q'

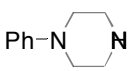
Amines

8a"

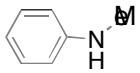


8b"

8c"

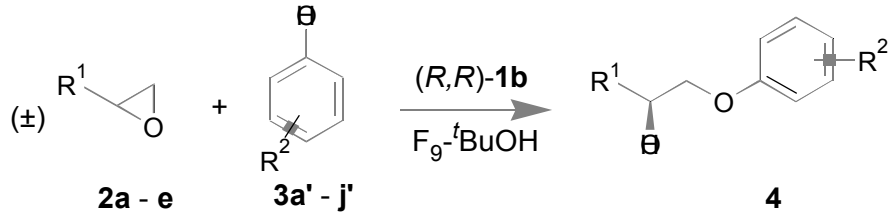


8d"



8e"

*Preparation of compound library **4***



Small vials (2 mL) were charged with catalyst (*R,R*)-**1b** (each 10 mg, 2.4 μmol), epoxides **2** (each 80 μL, 0.6 – 0.9 mmol, 6 – 9 eq.), phenols **3** (each 0.1 mmol, 1 eq.), and F_9-*tert*-butanol (each 3.5 μL, 25 μmol, 0.25 eq.). In cases (see library table below) in which the beads did not swell or the phenols did not dissolve anhydrous dichloromethane (40 μL) was added. The vials were shaken for 6 h at 4˚C and further 2 h at room temperature. The reactions were filtered, the polymer beads rinsed with acetonitrile (2 x 0.1 mL) and the filtrates concentrated in vacuo in a speedvac to yield the 1-aryloxy-2-alcohols **4** as oils or solids.

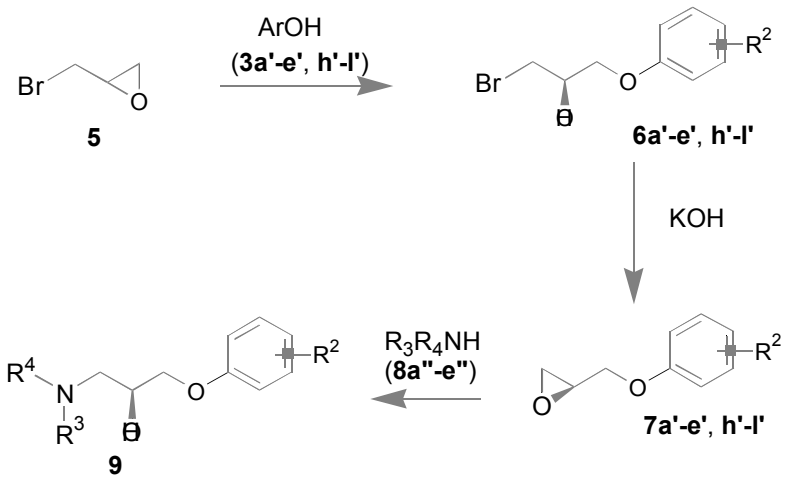
Purity of the compounds was determined by gas chromatography (100˚C [4 min] – 15˚C/min – 200˚C – 25˚C/min – 280˚C [1 min]), molecular mass by EI mass spectrometry, yield by ^{1}H NMR spectroscopy using 0.01 mmol of the internal standard hexamethyldisiloxane (addition of 0.1 mL of a 0.1M solution of hexamethyldisiloxane in $CDCl_3$ to the samples dissolved in $CDCl_3$; integrations to establish yield were performed on the carbinol CH and the aryloxymethylene hydrogen atoms) and enantiomeric excess by chiral HPLC separation (flow rate 1mL/min, **4aa'**: Chiralcel AD, 7.5% 2-propanol/hexanes, t_R = 7.7, 9.3 min; **4ab'**: Chiralcel AS, 2% 2-propanol/hexanes, t_R = 6.2, 7.4 min; **4ad'**: Chiralcel AS, 10% 2-propanol/hexanes, t_R = 10.7, 13.6 min; **4af'**: Chiralcel AD, 7.5% ethanol/hexanes, t_R = 7.6, 8.5 min; **4ah'**: Chiralcel AS, 2.5% 2-propanol/hexanes, t_R = 11.9, 13.7 min; **4bc'**: Chiralcel AD, 7.5% 2-propanol/hexanes, t_R = 12.9, 15.6 min; **4be'**: Chiralcel AD, 5% 2-propanol/hexanes, t_R = 14.8, 16.7 min; **4bf'**: Chiralcel AD, 5% ethanol/hexanes, t_R = 11.3, 12.8 min; **4bi'**: Chiralcel AD, 40% 2-propanol/hexanes, t_R = 5.1, 6.2 min; **4ce'**: Chiralcel AD, 5% 2-propanol/hexanes, t_R = 11.9, 13.4 min; **4ch'**: Chiralcel AS, 2% 2-propanol/hexanes, t_R = 12.9, 14.2 min; **4ci'**: Chiralcel AD, 40% 2-propanol/hexanes, t_R = 4.8, 5.6 min; **4cj'**: Chiralcel AS, 10% 2-propanol/hexanes, t_R = 11.1, 14.2 min; **4dd'**: Chiralcel AD, 7.5% 2-propanol/hexanes, t_R = 13.3, 16.0 min; **4dg'**: Chiralcel AS, 25% ethanol/hexanes, t_R = 7.4, 8.4 min; **4dj'**: Chiralcel AD, 15% ethanol/hexanes, t_R = 13.7, 15.1 min; **4ea'**: Chiralcel AS, 2% 2-propanol/hexanes (0.75 mL/min flow rate), t_R = 18.8, 20.8 min ; **4ec'**: Chiralcel AS, 3% 2-propanol/hexanes, t_R = 17.0, 19.1 min; **4eg'**: Chiralcel AS, 25% 2-propanol/hexanes, t_R = 9.5, 11.0 min).

Table 1. Library **4**

	Compound	yield (%)	purity (%)	ee (%)	mass (calc.)	mass (obs.)
1	**4aa'**	55	100	98	166	M^+
2	**4ab'**	quant.	100	98.5	268	M^+
3	**4ac'**[b]		100		242	M^+
4	**4ad'**	90	100	98.5	258	M^+
5	**4ae'**		98		244	M^+
6	**4af'**	90	98	90	234	M^+
7	**4ag'**		97		208	M^+
8	**4ah'**	95	98	>99	196	M^+
9	**4ai'**		98		208	M^+
10	**4aj'**		97[a]		225	M^+
11	**4ba'**		92		192	M^+
12	**4bb'**		98		192	M^+
13	**4bc'**[b]	95	99	99	268	M^+
14	**4bd'**		100		284	M^+
15	**4be'**	quant.	99	97	270	M^+
16	**4bf'**	quant.	96	93.5	260	M^+
17	**4bg'**		100		234	M^+
18	**4bh'**		92		222	M^+
19	**4bi'**	quant.	97	99	234	M^+
20	**4bj'**		94[a]		251	M^+
21	**4ca'**		96		210	M^+
22	**4cb'**		98		266	M^+
23	**4cc'**[b]		100		286	M^+
24	**4cd'**		100		302	M^+
25	**4ce'**	quant.	98	94	288	M^+
26	**4cf'**		94		278	M^+
27	**4cg'**		99		252	M^+
28	**4ch'**	95	95	>99	240	M^+
29	**4ci'**	quant.	95	98.5	252	M^+
30	**4cj'**	95	97[a]	87	269	M^+
31	**4da'**		92		208	M^+
32	**4db'**	quant.	96		264	M^+
33	**4dc'**[b]		90		284	M^+
34	**4dd'**	90	93[a]	97	300	M^+
35	**4de'**		93		286	M^+
36	**4df'**		91		276	M^+
37	**4dg'**	95	94	84	250	M^+
38	**4dh'**		96		238	M^+
39	**4di'**		90		250	M^+
40	**4dj'**	quant.	95[a]	81	267	M^+
41	**4ea'**[b]	95	100	95	268	M^+
42	**4eb'**[b]		100		324	M^+
43	**4ec'**[b]	90	100	93	344	M^+
44	**4ed'**[b]		100		360	M^+
45	**4ee'**[b]		100		346	M^+
46	**4ef'**[b]		100		336	M^+
47	**4eg'**[b]	95	100	94	310	M^+
48	**4eh'**[b]		100		298	M^+
49	**4ai'**[b]		98		310	M^+
50	**4ej'**[b]		99[a]		327	M^+

[a] purity determined by HPLC, [b] addition of 40 μL dichloromethane to epoxide

*Preparation of compound library **9***



Vials (5 mL) were charged with catalyst (*R,R*)-**1b** (each 25 mg, 6 μmol), phenols **3a' – e', h' – l'** (each 0.5 mmol, 1 eq.), epibromohydrin (**5**) (each 214 μL, 2.5 mmol, 5 eq.) and F_9-*tert*-butanol (each 14 μL, 0.1 mmol, 0.2 eq.). In cases (**3c', j'**) in which the phenols did not dissolve anhydrous dichloromethane (0.2 mL) was added. The vials were shaken for 3 h at 4˚C and further 3 h at room temperature. The reactions were filtered, the polymer beads rinsed with ether (2 ml) and powdered KOH (100 mg) was added. The reactions were shaken for 3 h at room temperature. Filtration through a silica gel plug and concentration yielded the aryl glycidyl ethers **7**. Chiral HPLC indicated the enantiomeric excess (**7a'**: Chiralcel OD, 10% 2-propanol/hexanes, t_R = 7.7, 12.5 min; **7b'**: Chiralcel AS, 15% 2-propanol/hexanes, t_R = 7.4, 9.0 min; **7c'**: Chiralcel OD, 15% 2-propanol/hexanes, t_R = 8.4, 9.2 min; **7d'**: Chiralcel OD, 20% 2-propanol/hexanes, t_R = 7.8, 9.0 min; **7e'**: Chiralcel OJ, 10% 2-propanol/hexanes, t_R = 15.2, 16.9 min; **7h'**: Chiralcel OD, 15% 2-propanol/hexanes, t_R = 9.6, 14.7 min; **7i'**: Chiralcel OD, 5% ethanol/hexanes, t_R = 13.7, 14.7 min; **7j'**: Chiralcel OB, 30% 2-propanol/hexanes, t_R = 26.2, 31.4 min); **7k'**: Chiralcel OD, 5% 2-propanol/hexanes, t_R = 7.2, 8.0 min; **7l'**: Chiralcel OD, 5% 2-propanol/hexanes, t_R = 8.4, 9.2 min).

Aliquots of the aryl glycidyl ethers **7a' – e', h' – l'** (0.1 mmol, 1 eq.) were added to small vials (2 mL), dissolved in dichloromethane (0.2 mL, for alphatic amines) or diethylether (0.2 ml, for aromatic amines), followed by amine (each 0.2 mmol diethylamine and morpholine, 0.15 mmol N-phenylpiperazine, 4-benzylpiperidine and N-methylaniline) and $Yb(OTf)_3$ (6 mg, 0.01 mmol, 0.1 eq., for aliphatic amines), or $Cu(OTf)_2$ (4 mg, 0.01 mmol, 0.1 eq., for aromatic amines) and shaken for 16 h at room temperature. To sequester excess of the non-volatile amines N-phenylpiperazine and 4-benzylpiperidine polystyrene-methyl isocyanate (each 100 mg, 0.15 mmol, 3 eq.) and dichloromethane (1.5 mL) were added for 2 h. The reaction mixtures were filtered through a silica gel plug, eluted with ethanol (1.5 mL, for aliphatic amines) or dichloromethane (1.5 mL, for aromatic amines) and concentrated *in vacuo* to yield compounds **9**.

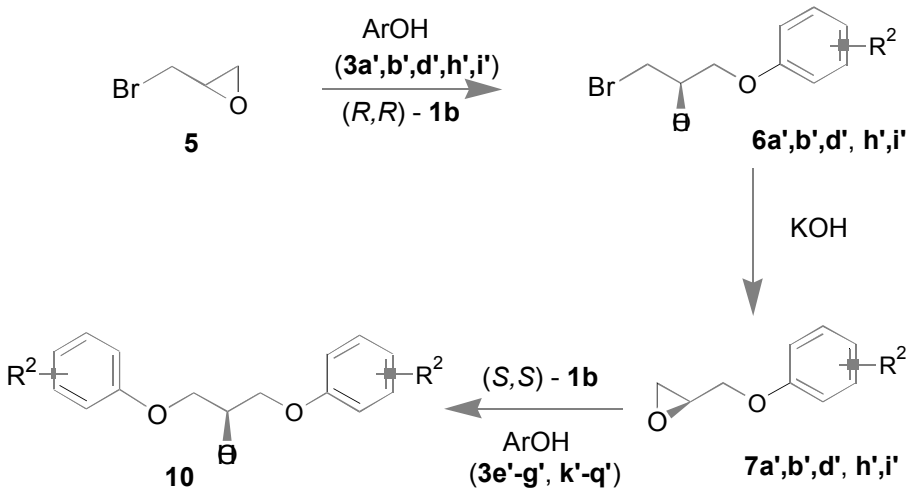
Purity was assayed by RP-HPLC (Microsorb C18, 150 x 4.6 mm, 5μm, 1 mL/min flow rate, 20% B in A – 7 min - 95% B in A[5 min] with A: 0.1%

trifluoroacetic acid in water, B: 0.1% trifluoroacetic acid in MeCN, detection at 220 and 280 nm), molecular mass by APCI mass spectrometry (positive mode gives MH^+ signal) and enantiomeric excess by chiral HPLC separation (**9a'd"**: Chiralcel OD, 40% 2-propanol/hexanes, t_R = 10.4, 14.4 min; **9a'c"**: Chiralcel OD, 40% 2-propanol/hexanes, t_R = 6.8, 15.5 min; **9a'e"**: Chiralcel OD, 30% 2-propanol/hexanes, t_R = 6.6, 8.6 min).

Table 2. Library **9**

	compound	yield (%)	purity (%)	ee (%)	mass (calc.)	mass (obs.)
1	**9a'a"**	quant	96		223	MH^+
2	**9b'a"**	quant.	95		279	MH^+
3	**9c'a"**	98	98		299	MH^+
4	**9d'a"**	quant.	99		315	MH^+
5	**9e'a"**	95	93		301	MH^+
6	**9h'a"**	94	96		253	MH^+
7	**9i'a"**	quant.	97		265	MH^+
8	**9j'a"**	quant.	94		282	MH^+
9	**9k'a"**	quant.	97		241	MH^+
10	**9l'a"**	quant.	96		241	MH^+
11	**9a'b"**	quant.	98		325	MH^+
12	**9b'b"**	93	99		381	MH^+
13	**9c'b"**	74	99		401	MH^+
14	**9d'b"**	79	99		417	MH^+
15	**9e'b"**	98	99		403	MH^+
16	**9h'b"**	quant.	98		355	MH^+
17	**9i'b"**	98	93		367	MH^+
18	**9j'b"**	85	99		384	MH^+
19	**9k'b"**	quant.	98		343	MH^+
20	**9l'b"**	quant.	97		343	MH^+
21	**9a'c"**	85	96	98	237	MH^+
22	**9b'c"**	quant.	98		293	MH^+
23	**9c'c"**	quant.	96		313	MH^+
24	**9d'c"**	93	96		329	MH^+
25	**9e'c"**	quant.	99		315	MH^+
26	**9h'c"**	quant.	98		267	MH^+
27	**9i'c"**	quant.	98		279	MH^+
28	**9j'c"**	quant.	98		296	MH^+
29	**9k'c"**	91	98		255	MH^+
30	**9l'c"**	quant.	98		255	MH^+
31	**9a'd"**	81	95	97.5	312	MH^+
32	**9b'd"**	68	100		368	MH^+
33	**9c'd"**	83	99		388	MH^+
34	**9d'd"**	92	96		404	MH^+
35	**9e'd"**	74	100		390	MH^+
36	**9h'd"**	95	99		342	MH^+
37	**9i'd"**	67	93		354	MH^+
38	**9j'd"**	60	93		371	MH^+
39	**9k'd"**	71	96		330	MH^+
40	**9l'd"**	77	97		330	MH^+
41	**9a'e"**	87	95	98	257	MH^+
42	**9b'e"**	75	95		313	MH^+
43	**9c'e"**	72	95		333	MH^+
44	**9d'e"**	72	97		349	MH^+
45	**9e'e"**	83	97		335	MH^+
46	**9h'e"**	82	95		287	MH^+
47	**9i'e"**	53	87		299	MH^+
48	**9j'e"**	72	97		316	MH^+
49	**9k'e"**	86	97		275	MH^+
50	**9l'e"**	81	95		275	MH^+

*Preparation of compound library **10***



Vials (5 mL) were charged with catalyst (*R,R*)-**1b** (each 50 mg, 12 μmol), phenols **3a' , b', d', h', i'** (each 1 mmol, 1 eq.), epibromohydrin (**5**) (each 428 μL, 5 mmol, 5 eq.) and F_9-*tert*-butanol (each 28 μL, 0.2 mmol, 0.2 eq.). The vials were shaken for 3 h at 4˚C and further 3 h at room temperature. The reactions were filtered, the polymer beads rinsed with ether (4 mL) and powdered KOH (200 mg) was added to the ether filtrates. The reactions were shaken for 3 h at room temperature. Filtration through a silica gel plug and concentration yielded the aryl glycidyl ethers **7**.
Aliquots of the aryl glycidyl ethers **7** (0.1 mmol 1 eq.) were added to small vials (2 mL) and dissolved in dichloromethane (0.1 mL). Phenols **3e' – g', k' – q'** (each 0.2 mmol, 2 eq.), (*S,S*)-**1b** (each 10 mg, 3.7 μmol) and F_9-*tert*-butanol (each 3.5 μL, 25 μmol, 0.2 eq.) were added and the reactions shaken for 6 h at room temperature. Resin-bound catalyst was removed by filtration and excess phenol by solid phase extraction (each 3 mL celite mixed with 0.3 ml 4N NaOH over a silica gel plug) with dichloromethane (4 mL) as eluent to give the 1,3-bisaryloxy-2-propanols **10**.

Purity was assayed by HPLC (YMC-Pack Diol-NP, 150 x 4.6 mm, 5μm, 1.5 mL/min flow rate, 5% B in A – 9 min - 25% B in A [3 min] with A: hexanes, B: ethanol, detection at 220 and 280 nm), molecular mass by EI mass spectrometry and enantiomeric excess by chiral HPLC separation (**10a'o'**: Chiralcel AD, 15% 2-propanol/hexanes, t_R = 20.5, 22.6 min; **10b'p'**: Chiralcel AD, 15% 2-propanol/hexanes, t_R = 16.0, 18.2 min; **10d'f'**: Chiralcel AD, 20% ethanol/hexanes, t_R = 10.8, 14.3 min; **10h'e'**: Chiralcel AD, 30% ethanol/hexanes, t_R = 12.7, 17.4 min; **10i'n'**: Chiralcel AD, 30% 2-propanol/hexanes, t_R = 7.9, 9.2 min).

Table 3. Library **10**

	compound	yield (%)	purity (%)	ee (%)	mass (calc.)	mass (obs.)
1	**10a'e'**	83	99		322	M^+
2	**10a'f'**	quant.	96		312	M^+
3	**10a'g'**	87	99		286	M^+
4	**10a'k'**	98	99		262	M^+
5	**10a'l'**	89	98		262	M^+
6	**10a'm'**	99	99		278	M^+
7	**10a'n'**	89	99		258	M^+
8	**10a'o'**	96	98	>99	269	M^+
9	**10a'p'**	84	95		289	M^+
10	**10a'q'**	94	98		328	M^+
11	**10b'e'**	99	99		377	M^+
12	**10b'f'**	quant.	97		368	M^+
13	**10b'g'**	85	99		342	M^+
14	**10b'k'**	quant.	98		318	M^+
15	**10b'l'**	98	97		318	M^+
16	**10b'm'**	96	97		334	M^+
17	**10b'n'**	81	95		315	M^+
18	**10b'o'**	83	98		325	M^+
19	**10b'p'**	94	98	>99	345	M^+
20	**10b'q'**	94	99		384	M^+
21	**10d'e'**	79	97		414	M^+
22	**10d'f'**	83	95	>99	404	M^+
23	**10d'g'**	77	94		378	M^+
24	**10d'k'**	83	95		354	M^+
25	**10d'l'**	95	95		354	M^+
26	**10d'm'**	77	95		369	M^+
27	**10d'n'**	79	94		350	M^+
28	**10d'o'**	73	96		361	M^+
29	**10d'p'**	73	96		381	M^+
30	**10d'q'**	73	95		420	M^+
31	**10h'e'**	96	91	>99	352	M^+
32	**10h'f'**	75	94		342	M^+
33	**10h'g'**	73	97		316	M^+
34	**10h'k'**	quant.	93		292	M^+
35	**10h'l'**	81	95		292	M^+
36	**10h'm'**	94	96		308	M^+
37	**10h'n'**	quant.	97		288	M^+
38	**10h'o'**	85	93		299	M^+
39	**10h'p'**	69	93		319	M^+
40	**10h'q'**	74	97		358	M^+
41	**10i'e'**	79	95		363	M^+
42	**10i'f'**	91	84		354	M^+
43	**10i'g'**	64	94		328	M^+
44	**10i'k'**	90	92		304	M^+
45	**10i'l'**	75	96		304	M^+
46	**10i'm'**	93	94		320	M^+
47	**10i'n'**	92	97	>99	300	M^+
48	**10i'o'**	78	89		311	M^+
49	**10i'p'**	67	93		331	M^+
50	**10i'q'**	84	94		370	M^+