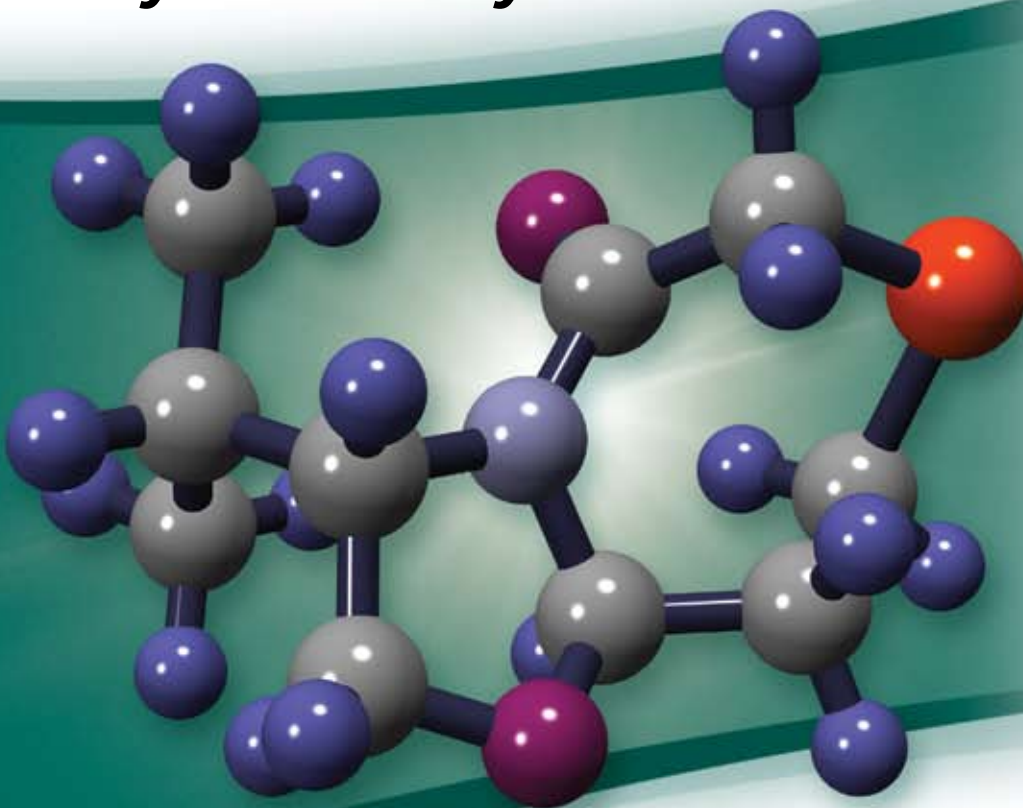


## Asymmetric Synthesis



*(7R,10S)-(+)-1-Aza-10-isopropyl-8-oxa-4-thiabicyclo(5,3,0)-2-decanone  
chiral lactam auxiliary capable of forming chiral quaternary centers*

QUINOXP\* LIGANDS

CARREIRA DOLEFIN  
LIGANDS

VAULTED BIARYL  
LIGANDS AND  
BINOL DERIVATIVES

OXAZOLIDINETHIONE  
AND THIAZOLIDINETHIONE  
AUXILIARIES

GLEASON CHIRAL  
AUXILIARY

SHI EPOXIDATION  
DIKETAL CATALYST

SHVO'S CATALYST

## Introduction

Asymmetric synthesis remains a challenge to synthetic chemists as the demand for enantiomerically pure compounds continues to increase. Many scientists working in chemical synthesis and drug discovery are striving to find new methods for asymmetric synthesis that would lead to the development of new and exciting chiral auxiliaries. In addition, asymmetric catalysis is exploding, as new methods for obtaining enantiomerically pure compounds has fueled a rapidly growing field in chemical synthesis.

This edition of *ChemFiles* describes the applications of new chiral ligands and auxiliaries for use in asymmetric synthesis. Sigma-Aldrich is proud to carry over 5,000 chiral products for the successful construction of complex asymmetric architectures. In most cases, the cutting-edge methodologies illustrated herein exhibit exceptional levels of stereoselectivity. For a complete listing of products related to asymmetric synthesis, please visit us at [sigma-aldrich.com/asymmetric](http://sigma-aldrich.com/asymmetric).

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### About Our Cover

The cover graphic depicts the structure of the Gleason Chiral Auxiliary, (7R,10S)-(+)-1-aza-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone. This chiral lactam auxiliary has been successfully employed in the stereocontrolled synthesis of all carbon quaternary centers. The unique methodology developed by Gleason allows for the creation of either antipode of the product using a single isomer of the auxiliary.

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## QuinoxP\* Ligands

Various optically active phosphine ligands incorporating a chiral center at phosphorus display exceptional enantioselectivities in metal-catalyzed asymmetric synthesis.<sup>1</sup> For instance, known classes of *P*-chiral phosphine ligands offer good to excellent enantiocontrol in Ru- and Rh-catalyzed hydrogenation reactions.<sup>2</sup> The one limitation associated with these ligands is their sensitivity to air, which has impeded widespread applicability in bench-top chemistry. Imamoto and co-workers have addressed this deficiency through the development of QuinoxP\*, which is based on an electron-withdrawing quinoxaline architecture.<sup>3</sup>

Sigma-Aldrich is pleased to offer both enantiomers of QuinoxP\* for the research market.<sup>†</sup> The reactivity profile of these innovative, chiral ligands is covered below and highlights the impressive breadth of valuable transformations mediated by QuinoxP\*. These powerfully efficient ligands exhibit high levels of enantiocontrol in synthetic transformations ranging from metal-catalyzed asymmetric 1,4-additions of arylboronic acids to enantioselective alkylation ring opening to asymmetric hydrogenations.<sup>3</sup> It is worth noting that QuinoxP\* is not oxidized at the stereogenic phosphorus center on standing at ambient temperature in air for more than 9 months.

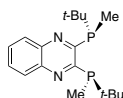
Imamoto has also gone to great lengths to develop enantiomerically pure *P*-chiral ligands for industrially useful transformations such as asymmetric hydrogenation. Impressively, a diverse array of prochiral amino acid and amine substrates were hydrogenated with great efficiency to yield highly enantiopure amine derivatives (**Scheme 1**). These experiments were carried out at room temperature in methanol under low pressures of hydrogen (3 atm). All hydrogenation reactions were complete in 6 hours and with enantiomeric excesses ranging from 96 to 99.9%. Dramatic stereochemical reversal, consistent with the results observed with the related (*S,S*)-*tert*-Bu-BisP\* ligands,<sup>4,5</sup> was obtained when 1-acetyl-amino-1-adamantylethene was hydrogenated to afford the *S*-configuration amine with >96% enantioselectivity (**Table 1**).

Imamoto and co-workers have also exploited the high activity of the QuinoxP\* ligand in rhodium-catalyzed enantioselective 1,4-additions of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyl substrates.<sup>3</sup> High yields of the addition products were obtained by running the reactions between 40 and 50 °C (**Scheme 2**). The exceptional enantiocontrol exerted by this Rh(I)-catalyzed system is evident in the robust performance when compared to the use of BINAP as the chiral ligand.<sup>6</sup>

Additionally, Imamoto and co-workers have succeeded in developing a Pd-catalyzed C–C bond-forming reaction, which displays high enantioselectivities with both dimethyl- and diethylzinc (**Scheme 3**, **Table 2**). This alkylation ring-opening methodology benefits from simply premixing PdCl<sub>2</sub>(cod) and QuinoxP\* for 2 hours at room temperature, leading to a highly active catalyst. This catalyst system affords excellent yields of the ring-opened products and selectivities that rival the highest reported for this transformation. These results, when combined with the outstanding methodologies presented above, indicate that QuinoxP\* is broadly useful for a variety of asymmetric metal-catalyzed transformations.<sup>3</sup>

### (*R,R*)-2,3-Bis(*tert*-butylmethylphosphino)quinoxaline

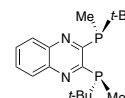
C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>P<sub>2</sub>  
FW: 334.38



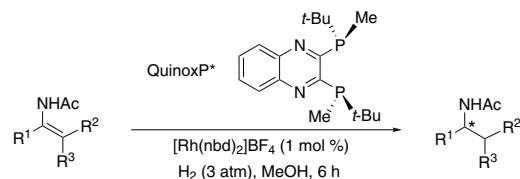
676403-100MG	100 mg
676403-500MG	500 mg

### (*S,S*)-2,3-Bis(*tert*-butylmethylphosphino)quinoxaline

C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>P<sub>2</sub>  
FW: 334.38



676411-100MG	100 mg
676411-500MG	500 mg

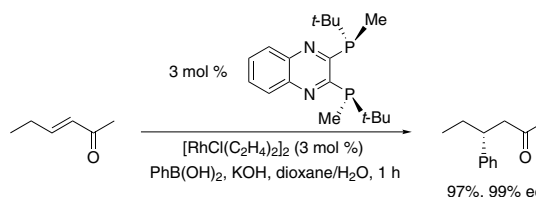


**Scheme 1**

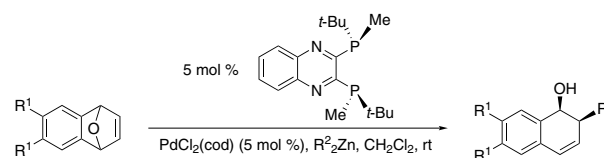
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	ee (%) (config)
1 <sup>a</sup>	CO <sub>2</sub> Me	Ph	H	99.9 ( <i>R</i> )
2	CO <sub>2</sub> Me	4-AcO-3-MeOC <sub>6</sub> H <sub>3</sub>	H	99.6 ( <i>R</i> )
3	Me	H	CO <sub>2</sub> Me	99.7 ( <i>R</i> )
4	Me	CO <sub>2</sub> Me	H	99.2 ( <i>R</i> )
5	Ph	H	H	99.9 ( <i>R</i> )
6	1-adamantyl	H	H	96.3 ( <i>S</i> )

<sup>a</sup>The reaction was completed within 1 h.

**Table 1**



**Scheme 2**



**Scheme 3**

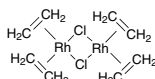
Entry	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Yield (%) <sup>a</sup>	ee (%) (config)
1	H	Me	2	90	95.6 (1 <i>S</i> ,2 <i>S</i> )
2	H	Et	15	88	97.6 (1 <i>S</i> ,2 <i>S</i> )
3	F	Me	2	90	93.8 (1 <i>S</i> ,2 <i>S</i> )

<sup>a</sup> Isolated yield.

**Table 2**

**$\mu$ -Dichlorotetraethylene dirhodium(I)**

C<sub>8</sub>H<sub>16</sub>Cl<sub>2</sub>Rh<sub>2</sub>  
 FW: 388.93  
 [12081-16-2]



656763-100MG	100 mg
656763-1G	1 g

**Dichloro(1,5-cyclooctadiene)palladium(II)**

C<sub>8</sub>H<sub>12</sub>Cl<sub>2</sub>Pd  
 FW: 285.51  
 [12107-56-1]



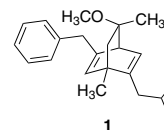
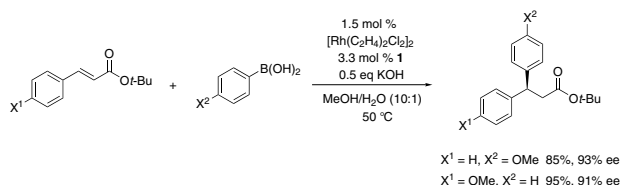
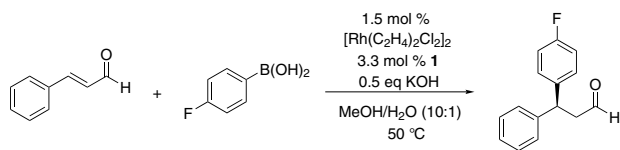
275891-250MG	250 mg
275891-1G	1 g

**Carreira DOLEFIN Ligands**

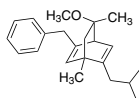
For the past years, the Carreira group has been employing chiral [2.2.2]bicyclooctadienes derived from (*R*)- or (*S*)-carvone in Ir(I)-catalyzed kinetic resolution of allylic carbonates<sup>7</sup> and Rh(I)-catalyzed conjugate addition reactions of boronic acids.<sup>8</sup> More recently, Carreira has developed the ligand **1** (**Figure 1**), which exhibited substantially improved enantioselectivity in the 1,4-addition of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyls.<sup>9</sup> This new ligand facilitates selective preparations of diastereomeric stereogenic centers, even when there is little differentiation between the two aryl groups. Heretofore, the stereoselective synthesis of this motif had been a challenge, with rather limited methods for its preparation.<sup>10</sup>

In one report, *tert*-butyl cinnamate was converted to (*S*)-*tert*-butyl 3-(4-methoxyphenyl)-3-phenylpropanoate in the presence of the Rh(I)-**1** complex in excellent yield and selectivity. Furthermore, from a single enantiomer of the ligand, access to both enantiomers of a product can be achieved simply by switching the aryl acceptor and donor. In this manner, the (*R*)-isomer was prepared from phenylboronic acid and *tert*-butyl 4-methoxycinnamate (**Scheme 4**). Similarly, other 3,3-diaryl- and 3-aryl-3-heteroarylpropanoates were prepared in good to excellent yields and with consistently high enantioselectivity (89–94% ee).

The preparation of chiral 3,3-diarylpropanals has recently been achieved by other researchers via an amine-catalyzed addition of aromatic nucleophiles to 3-substituted acrolein derivatives.<sup>11</sup> Unfortunately, this method does not work well with electron-poor aromatics. However, the Rh(I)-**1**-catalyzed conjugate addition offers a general route independent of the electronic nature of the aryl groups. The addition of 4-fluorophenylboronic acid to cinnamaldehyde provided the 1,4-adduct in 90% yield and 93% ee (**Scheme 5**). Again, other substrates maintained high enantioselectivity in the conjugate addition (89–93% ee).<sup>12</sup>

**1****Figure 1****Scheme 4****Scheme 5****(1*S*,4*S*,8*S*)-5-Benzyl-8-methoxy-1,8-dimethyl-2-(2'-methylpropyl)bicyclo[2.2.2]octa-2,5-diene**

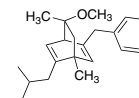
C<sub>22</sub>H<sub>30</sub>O  
 FW: 310.47  
 [862499-50-1]



672254-100MG	100 mg
--------------	--------

**(1*R*,4*R*,8*R*)-5-Benzyl-8-methoxy-1,8-dimethyl-2-(2'-methylpropyl)bicyclo[2.2.2]octa-2,5-diene**

C<sub>22</sub>H<sub>30</sub>O  
 FW: 310.47



669490-100MG	100 mg
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## Vaulted Biaryl Ligands and BINOL Derivatives

BINOL and its derivatives are some of the mostly widely used classes of ligands in asymmetric synthesis, and are utilized in a broad array of reaction classes including: Diels-Alder, ene, carbonyl addition and reductions, Michael additions, as well as many others. While tremendous success has been obtained with the BINOL platform, other  $C_2$ -symmetric diol ligands have attracted considerable attention. Among these are the vaulted biaryl ligands developed by Wulff and co-workers (Michigan State University). Both vaulted 3,3'-biphenanthrol (VAPOL) and vaulted 2,2'-binaphthol (VANOL) have proven to be excellent ligands in catalytic asymmetric Diels-Alder, imine aldol, and aziridination reactions (Figure 2).<sup>13</sup> Additionally, the phosphoric acid derivative of VAPOL was shown to be effective as a chiral Brønsted acid catalyst. In many of the examples illustrated herein, the vaulted biaryls give both higher yields and higher inductions than the same reactions using a BINOL ligand.

Very early on, a catalyst generated from  $\text{Et}_2\text{AlCl}$  and VAPOL was shown to be an effective catalyst for the asymmetric Diels-Alder reactions.<sup>14</sup> As shown in Scheme 6, the cycloaddition of acrolein with cyclopentadiene in the presence of the VAPOL-derived catalyst gave high conversions and excellent stereoselectivities for the *exo* isomer in very high optical purity. Analogous reactions with the BINOL-derived catalyst provided the cycloadduct in high yield, but in very low enantiomeric excess (13–41%).

Aziridines are important building blocks in organic synthesis because they allow for convenient access to amines, amino alcohols, diamines, and other useful nitrogen-containing molecules. Most contemporary methods of chiral aziridine preparation have relied on the chiral pool. Recently, the Wulff group has developed a robust catalytic asymmetric aziridination reaction providing optically active aziridines in high yields and selectivities. The reaction relies on the addition of commercially available ethyl diazoacetate (EDA) to benzhydryl imines in the presence of arylborate catalysts prepared from vaulted aryl ligands and  $\text{B}(\text{OPh})_3$ .<sup>15</sup> The aziridination reaction exhibits excellent selectivities for the *cis* isomer, and high enantiomeric excesses are obtained. The resultant benzydryl-protected aziridines undergo a variety of reactions, including: deprotection, reductive ring opening, and alkylation reactions (Scheme 7, Table 3). The asymmetric synthesis of leukointegrin LFA-1 antagonist BIRT-377 utilized an aziridination/alkylation methodology to provide the hydantoin target in excellent overall yield.

The highly expeditious synthesis of the antibacterial agent (–)-chloramphenicol utilized the asymmetric aziridination reaction, followed by a nucleophilic ring opening of the aziridine with dichloroacetic acid and subsequent acyl group migration (Scheme 8, Table 4). Both VANOL and VAPOL gave higher yields and stereoselectivities than the BINOL-derived catalyst.

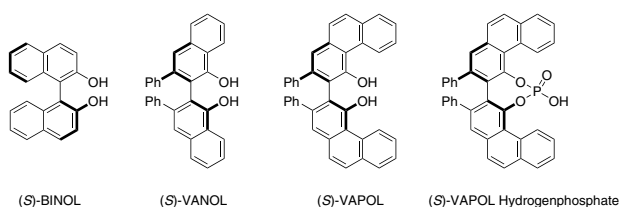
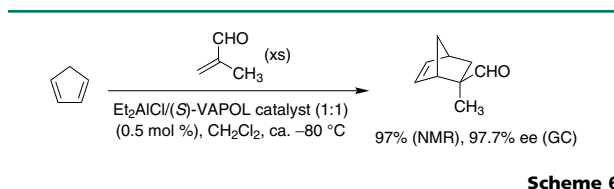
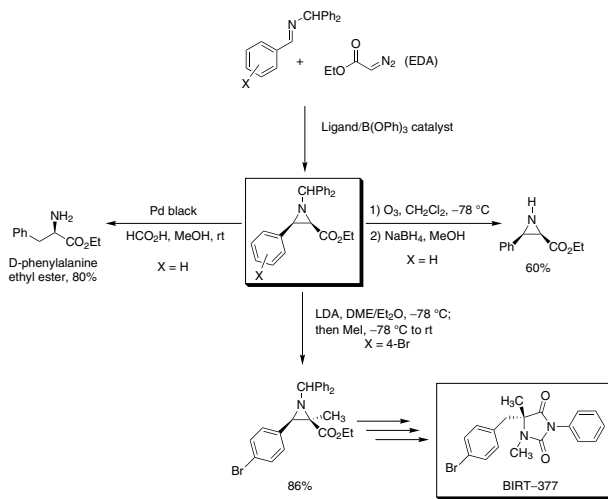


Figure 2



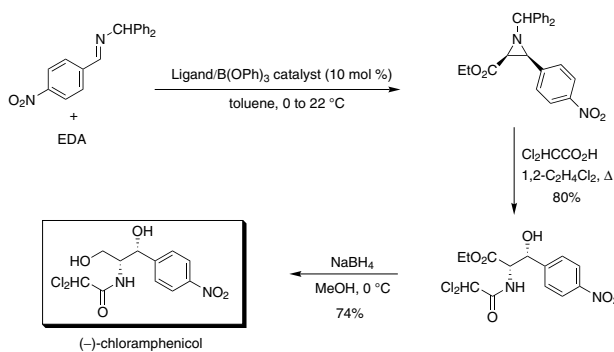
Scheme 6



Scheme 7

Entry	Ligand, Loading	X	Time (h)	Yield (%)	<i>cis:trans</i>	ee (%)
1	(S)-BINOL, 10 mol %	H	3	61	17:1	20
2	(S)-VANOL, 10 mol %	H	0.5	85	>50:1	96
3	(S)-VAPOL, 2 mol %	H	48	77	>50:1	95
4	(S)-VAPOL, 1 mol %	4-Br	20	87	>50:1	94 (>99% ee recryst.)

Table 3



Scheme 8

Entry	Ligand, Time (h)	Yield (%)	<i>cis:trans</i>	ee (%)
1	(R)-BINOL, 26	72	19:1	22
2	(S)-VANOL, 26	77	>50:1	91 <sup>a</sup>
3	(R)-VAPOL, 21	80	30:1	96 (99% ee recryst.)

<sup>a</sup> Product is the enantiomer of aziridine shown.

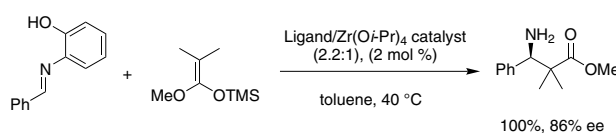
Table 4

Asymmetric imine aldol reactions are also catalyzed by vaulted biaryl-derived catalysts, providing an important method for the synthesis of chiral  $\beta$ -amino esters. The addition of silyl ketene acetals to aryl imines in the presence of either Zr-VANOL or Zr-VAPOL catalysts proceeds with high asymmetric induction and in excellent yield (**Scheme 9, Table 5**). Significantly, both catalysts exhibit substantially higher levels of induction over the analogous BINOL-derived catalyst.<sup>16</sup>

Antilla and co-workers demonstrated VAPOL hydrogenphosphate to be a useful chiral Brønsted acid catalyst in the addition of sulfonamides to Boc-activated aryl imines (**Scheme 10**).<sup>17</sup> The resultant *N,N*-aminal products were prepared in high yields with impressive enantiopurities. The identical reaction with a BINOL-derived Brønsted acid catalyst gave an excellent yield (95%), but a dismal level of asymmetric induction (<5% ee) was obtained. A variety of sulfonamides and aryl imines are active in the imine amidation reaction, and the resultant protected aminals are shelf-stable compounds.

Although a variety of protocols have been developed for the enantioselective reduction of ketimines to the corresponding chiral amines, these methods require the use of preformed, bench-stable imines. MacMillan and co-workers recently reported the first direct enantioselective organocatalytic reductive amination reaction, relying on the silylated BINOL phosphoric acid derivative depicted in **Figure 3**.<sup>18</sup>

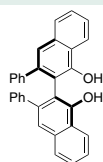
In the presence of this phosphoric acid derivative and ethyl Hantzsch ester (HEH), both aryl and alkyl ketones underwent reductive amination, giving secondary amines in good yields (**Scheme 11**). The reaction conditions are tolerant of a variety of ketone substitution motifs, as well as functionalized aryl amines (**Figure 4**). Additionally, the reaction is chemoselective towards methyl ketones, and the catalyst facial selectivity toward prochiral ketones bearing similar alkyl groups is pronounced.



Scheme 9

**(S)-VANOL, 97%**

C<sub>32</sub>H<sub>22</sub>O<sub>2</sub>  
FW: 438.52  
[147702-14-5]

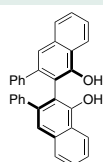


676098-250MG

250 mg

**(R)-VANOL, 97%**

C<sub>32</sub>H<sub>22</sub>O<sub>2</sub>  
FW: 428.52  
[147702-13-4]

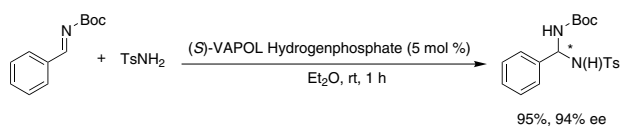


675156-250MG

250 mg

Entry	Ligand	Loading (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	( <i>R</i> )-BINOL	20	CH <sub>2</sub> Cl <sub>2</sub>	25	4	100	28
2	( <i>S</i> )-VAPOL	20	Toluene	25	15	94	89
3	( <i>S</i> )-VAPOL	2	Toluene	40	6	100	86

Table 5



Scheme 10

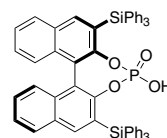
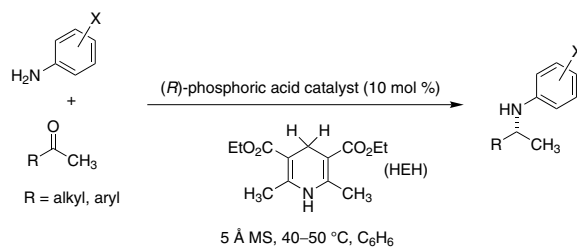


Figure 3



Scheme 11

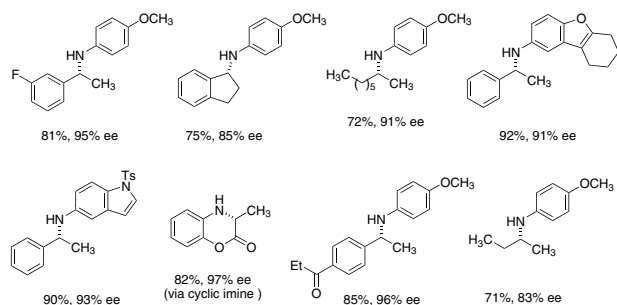
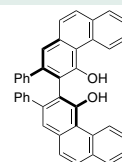


Figure 4

**(S)-VAPOL, 97%**

C<sub>40</sub>H<sub>26</sub>O<sub>2</sub>  
FW: 538.63  
[147702-15-6]

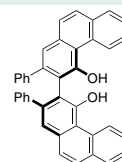


675334-250MG

250 mg

**(R)-VAPOL, 97%**

C<sub>40</sub>H<sub>26</sub>O<sub>2</sub>  
FW: 538.63  
[147702-16-7]

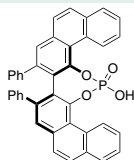


675210-250MG

250 mg

**(R)-VAPOL hydrogenphosphate**

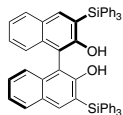
$C_{40}H_{25}O_4P$   
FW: 600.6  
[871130-18-6]



675512-250MG 250 mg

**(R)-3,3'-Bis(triphenylsilyl)-1,1'-bi-2-naphthol, 96%**

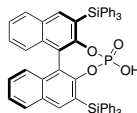
$C_{56}H_{42}O_2Si_2$   
FW: 803.1  
[111822-69-6]



674737-100MG 100 mg

**(R)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate**

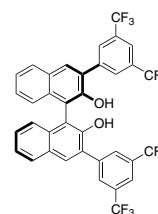
$C_{56}H_{41}O_4PSi_2$   
FW: 865.07  
[791616-55-2]



674745-100MG 100 mg

**(R)-3,3'-Bis(3,5-trifluoromethylphenyl)-1,1'-bi-2-naphthol, 95%**

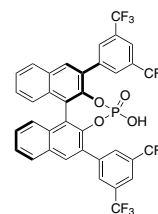
$C_{36}H_{18}F_{12}O_2$   
FW: 710.51  
[756491-54-0]



674591-100MG 100 mg

**(R)-3,3'-Bis(3,5-bis(trifluoromethyl)phenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, 95%**

$C_{36}H_{17}F_{12}O_4P$   
FW: 772.47  
[791616-62-1]



674605-100MG 100 mg

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## Oxazolidinethione and Thiazolidinethione Auxiliaries

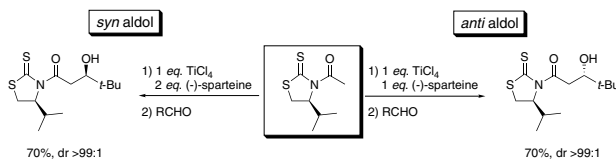
The asymmetric aldol reaction mediated by chiral auxiliaries is considered to be one of the most important methods for asymmetric C–C bond formation. Chiral oxazolidinethiones and thiazolidinethiones, structural variants of the well-known Evans oxazolidinones, have proven to be highly selective and efficient chiral auxiliaries.<sup>19</sup> The acetate aldol reaction of titanium enolates of the *N*-acylated auxiliaries with aldehydes results in excellent diastereoselectivities (**Scheme 12**). Interestingly, the *syn* aldol product was obtained in high diastereomeric ratio when using 1 equivalent of sparteine, while the *anti* aldol product was obtained preferentially when 2 equivalents of base were employed.<sup>20</sup> However, the corresponding oxazolidinones are only able to achieve poor diastereoselectivities in this particular transformation.<sup>21</sup>

In a series of experiments, Crimmins has shown in detail that, by choosing the appropriate reaction conditions, it is possible to selectively synthesize aldol condensation products bearing either “Evans-*syn*” or “non-Evans-*syn*” stereochemistry starting with the same chiral auxiliary (**Scheme 13**)! Both *N*-propionyl oxazolidinethiones and *N*-propionyl thiazolidinethiones can be used to this effect. The change in facial selectivity in the aldol additions is proposed to be a result of switching between chelated and nonchelated transition states in the mechanistic pathway.<sup>22</sup>

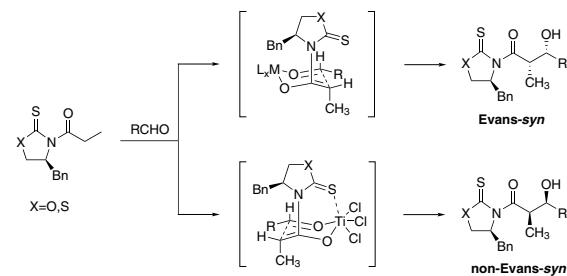
Iterative aldol sequences with high diastereoselectivity can also be accomplished. Crimmins demonstrated the utility of this methodology in an iterative aldol sequence giving access to either the *syn-syn-syn* adduct or *syn-anti-syn* adduct depending on the reaction conditions (**Scheme 14**).

In contrast to the oxazolidinone analogs, the *N*-acyl thiazolidinethiones and *N*-acyl oxazolidinethiones can be directly reduced to their corresponding aldehydes and the chiral auxiliary by reductive cleavage with diisobutylaluminum hydride.<sup>23</sup> Alcoholysis using methanol and imidazole leads to the corresponding esters, while transamination to the Weinreb amides can be accomplished by treatment with *N,O*-dimethylhydroxylamine hydrochloride in the presence of imidazole<sup>22</sup> or organoaluminum compounds (**Scheme 15**).<sup>24</sup>

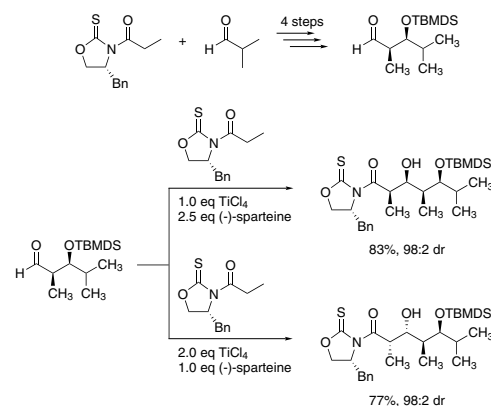
Recently, the thiazolidinethione auxiliary was successfully applied by Crimmins and DeBaillie in a convergent enantioselective total synthesis of Bistramide A, a member of a new class of bioactive molecules isolated from the marine ascidian *Lissoclinum bistratum* with neuro- and cytotoxic properties as well as effects on cell cycle regulation. The pyran ring fragment was constructed diastereoselectively in a total of 10 steps starting from the TIPS-protected aldehyde and the chlorotitanium enolate of (4*S*)-*N*-propionyl-4-benzylthiazolidine-2-thione (**Scheme 16**). This stereoinducing step proceeded in excellent yield (87%) and gave a diastereomeric ratio of >98:2.<sup>25</sup>



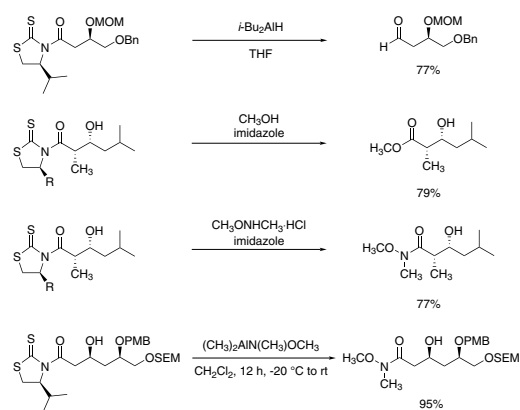
**Scheme 12**



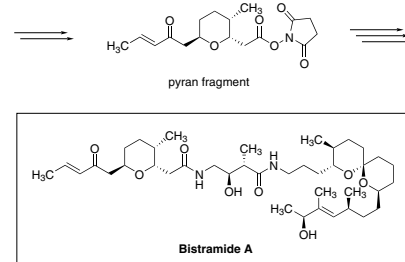
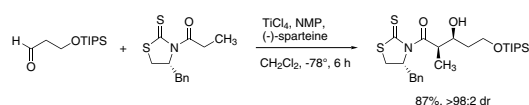
**Scheme 13**



**Scheme 14**



**Scheme 15**



**Scheme 16**

**(S)-4-Isopropyl-1,3-thiazolidine-2-thione**

NEW

C<sub>6</sub>H<sub>11</sub>NS<sub>2</sub>  
FW: 161.29  
[76186-04-4]



39933-500MG-F 500 mg  
39933-2.5G-F 2.5 g

**(S)-4-Isopropyl-1,3-oxazolidine-2-thione**

NEW

C<sub>6</sub>H<sub>11</sub>NOS  
FW: 145.22  
[104499-08-3]



04987-1G-F 1 g  
04987-5G-F 5 g

**(R)-4-Isopropyl-1,3-thiazolidine-2-thione**

NEW

C<sub>6</sub>H<sub>11</sub>NS<sub>2</sub>  
FW: 161.29  
[110199-16-1]



05329-500MG 500 mg  
05329-2.5G 2.5 g

**(R)-4-Isopropyl-1,3-oxazolidine-2-thione**

NEW

C<sub>6</sub>H<sub>11</sub>NOS  
FW: 145.22

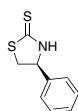


08914-1G-F 1 g

**(S)-4-Phenyl-1,3-thiazolidine-2-thione**

NEW

C<sub>9</sub>H<sub>9</sub>NS<sub>2</sub>  
FW: 195.3  
[185137-29-5]

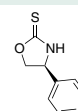


39911-1G-F 1 g  
39911-5G-F 5 g

**(S)-4-Phenyl-1,3-oxazolidin-2-thione**

NEW

C<sub>9</sub>H<sub>9</sub>NOS  
FW: 179.24  
[190970-57-1]

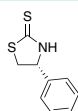


08913-1G-F 1 g  
08913-5G-F 5 g

**(R)-4-Phenyl-1,3-thiazolidine-2-thione**

NEW

C<sub>9</sub>H<sub>9</sub>NS<sub>2</sub>  
FW: 195.3  
[110199-18-3]

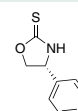


05802-1G-F 1 g  
05802-5G-F 5 g

**(R)-4-Phenyl-1,3-oxazolidine-2-thione**

NEW

C<sub>9</sub>H<sub>9</sub>NOS  
FW: 179.24  
[171877-37-5]

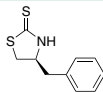


00762-1G-F 1 g  
00762-5G-F 5 g

**(S)-4-Benzyl-1,3-thiazolidine-2-thione**

NEW

C<sub>10</sub>H<sub>11</sub>NS<sub>2</sub>  
FW: 209.33  
[171877-39-7]

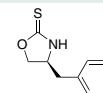


06357-1G-F 1 g  
06357-5G-F 5 g

**(S)-4-Benzyl-1,3-oxazolidine-2-thione**

NEW

C<sub>10</sub>H<sub>11</sub>NOS  
FW: 193.27  
[145588-94-9]

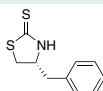


08416-1G-F 1 g  
08416-5G-F 5 g

**(R)-4-Benzyl-1,3-thiazolidine-2-thione**

NEW

C<sub>10</sub>H<sub>11</sub>NS<sub>2</sub>  
FW: 209.33  
[110199-17-2]

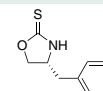


42787-1G-F 1 g  
42787-5G-F 5 g

**(R)-4-Benzyl-1,3-oxazolidine-2-thione**

NEW

C<sub>10</sub>H<sub>11</sub>NOS  
FW: 193.27  
[190970-58-2]



00749-1G-F 1 g  
00749-5G-F 5 g

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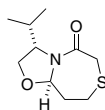


## Gleason Chiral Auxiliary

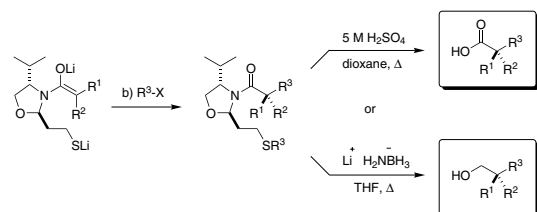
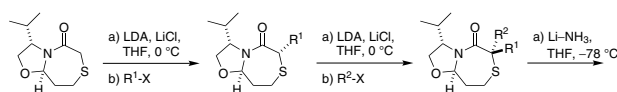
The stereocontrolled synthesis of all-carbon quaternary centers is a formidable challenge in asymmetric synthesis. Alkylation of an enolate is a fundamental reaction that may be used towards this task. While progress has been made using catalytic asymmetric methods in allylation and arylation, the majority of direct alkylation methods continue to require the use of chiral auxiliaries. Professor James Gleason of McGill University has developed an elegant method for preparing quaternary carbons using a chiral thioglycolate lactam auxiliary (**Figure 5**).<sup>26</sup>

The lactam can be alkylated three times; twice using basic enolization and once using reductive enolization, to give  $\alpha$ -quaternary carboxylic acid derivatives (**Scheme 17**). Each alkylation step occurs in excellent yield and with a high degree of diastereoselectivity. Cleavage of the auxiliary via acidic or reductive conditions furnishes the corresponding carboxylic acid or primary alcohol, respectively.

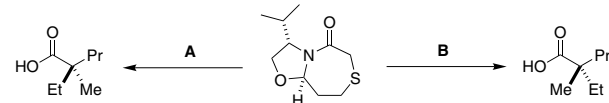
Furthermore, from a single chiral auxiliary, access to both antipodes can be achieved simply by altering the order of enolate alkylation. For instance, both enantiomers of 2-ethyl-2-methylpentanoic acid were synthesized in good overall yield and in excellent optical purity (**Scheme 18**, **Table 6**). Importantly, this example illustrates that the third reductive alkylation step proceeds diastereoselectively for both (*Z*- or (*E*-)disubstituted enolates. Gleason and co-workers have demonstrated that synthetically useful groups such as: allyl, functionalized alkyl, and benzyl groups can be introduced at the quaternary center while maintaining good yields and stereocontrol (**Figure 6**). Sigma-Aldrich is pleased to offer this versatile auxiliary for your research purposes.



**Figure 5**



**Scheme 17**



**Scheme 18**

### (7*R*,10*S*)-(+)-1-Aza-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone, 97%

C<sub>10</sub>H<sub>17</sub>NO<sub>2</sub>S  
FW: 215.31

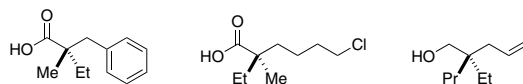


667587-1G

1 g

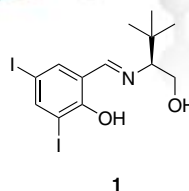
A			B		
Sequence	Yield (%)	dr (%)	Sequence	Yield (%)	dr (%)
1. LDA / EtI	95	99:1	1. LDA / MeI	90	99:1
2. LDA / MeI	90	99:1	2. LDA / EtI	86	99:1
3. Li-NH <sub>3</sub> / PrI	88	99:1	3. Li-NH <sub>3</sub> / PrI	91	99:1
4. H <sub>2</sub> SO <sub>4</sub>	79	n/a	4. H <sub>2</sub> SO <sub>4</sub>	82	n/a

**Table 6**



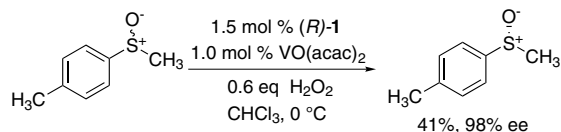
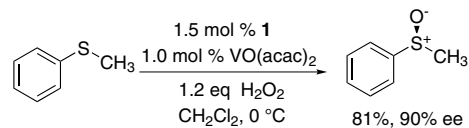
**Figure 6**

## Vanadium-Catalyzed Asymmetric Oxidation



**1**

Anson and co-workers have reported that the 3,5-diiodo Schiff base **1** in combination with VO(acac)<sub>2</sub> gives excellent results in the catalytic asymmetric sulfoxidation of alkyl aryl sulfides.<sup>1</sup> Recently, Jackson and co-workers have demonstrated its use in the kinetic resolution of alkyl aryl sulfoxides with high enantioselectivities.<sup>2</sup>



### (*S*)-2-[(1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl]-4,6-diiodophenol, 97%

C<sub>13</sub>H<sub>17</sub>I<sub>2</sub>NO<sub>2</sub>  
FW: 473.09  
[477339-39-2]

677558-100MG 100 mg  
677558-500MG 500 mg

### Vanadyl acetylacetonate, 98%

C<sub>10</sub>H<sub>14</sub>O<sub>5</sub>V  
FW: 265.16  
[3153-26-2]

550787-10G 10 g  
550787-50G 50 g

**References:** (1) Pelotier, B. et al. *Synlett* **2002**, 1055. (2) (*R*)-isomer used. Drago, C. et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 7221.

## Shi Epoxidation Diketal Catalyst

Catalytic asymmetric epoxidation of alkenes has been the focus of many research efforts over the past two decades, the best known methods probably being those developed by Sharpless<sup>27</sup> and Jacobsen-Katsuki.<sup>28</sup> Shi has also developed a very efficient method for asymmetric epoxidation, using ketone-derived organocatalyst **2** based on D-fructose (Figure 7).<sup>29</sup> This organocatalyst is able to epoxidize *trans* alkenes and certain *cis* alkenes with good to excellent yields and selectivities. More recently, Shi has achieved excellent results using hydrogen peroxide as an oxidant instead of Oxone, which allows a significant reduction in the amount of additional salts introduced and solvent used in the reaction (Scheme 19).<sup>30</sup>

Other groups have found use of Shi's methodology in pursuit of various unique moieties. For example, McDonald and coworkers recently reported a robust and selective synthesis of 2-amino-3,5-diols that employs the Shi epoxidation in a key step (Scheme 20).<sup>31</sup> These 2-amino-3,5-diols are 1-deoxy-5-hydroxysphingosine analogues, which show promise as anticancer agents.

The Shi epoxidation has also appeared in various total syntheses. In one example, Morimoto and coworkers have used Shi's methodology to achieve the *cis* conformation of the D ring in the total synthesis of (+)-aurilol (Scheme 21).<sup>32</sup> (+)-Aurilol has been shown to exhibit significant cytotoxicity against HeLa S<sub>3</sub> cells.<sup>33</sup>

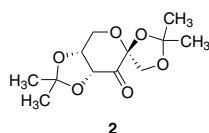
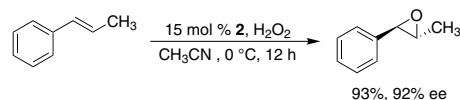
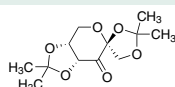


Figure 7



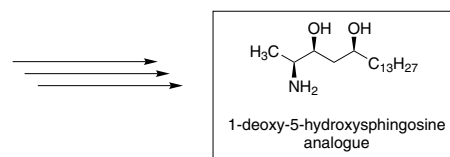
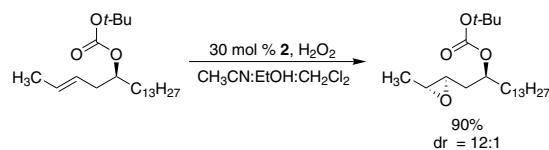
### 1,2:4,5-Di-O-isopropylidene-β-D-erythro-2,3-hexodiulo-2,6-pyranose, 98%

C<sub>12</sub>H<sub>18</sub>O<sub>6</sub>  
FW: 258.27  
[18422-53-2]

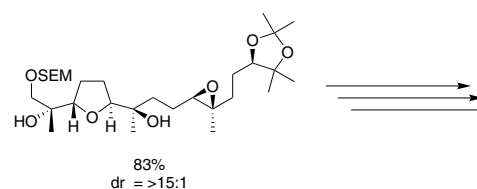
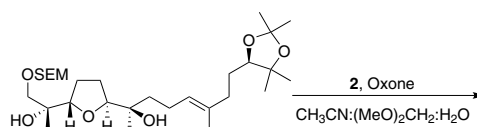


520160-5G

5 g



Scheme 20



Scheme 21



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## Shvo's Catalyst

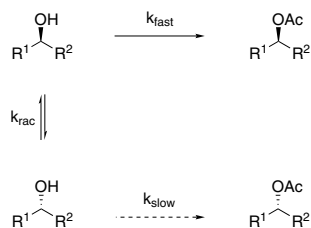
In catalytic asymmetric synthesis enzyme-mediated kinetic resolution is an important area. Lipases are particularly successful in kinetic resolutions and hence are manufactured on commercial scale. However, conventional kinetic resolution has a maximum theoretical yield of 50%. Dynamic kinetic resolution (DKR) circumvents this limitation by epimerizing the slow-reacting enantiomer concurrently with the kinetic resolution. In this way, one enantiomer of the epimerized substrate is converted faster to the product (e.g. by transesterification) by the enzyme, and the yield can theoretically be increased to 100% using DKR (**Scheme 22**).<sup>34</sup>

Diruthenium complex **3**, first reported by Shvo,<sup>35</sup> has found numerous applications as a versatile catalyst in organic synthesis, including the reduction of aldehydes and ketones to alcohols, bimolecular disproportionation reaction of aldehydes to esters, isomerization of allylic alcohols and oxidation of alcohols.<sup>36</sup> Under thermal conditions, the Shvo catalyst dissociates into the catalytically active 16-electron species **4** and 18-electron complex **5** (**Scheme 23**).

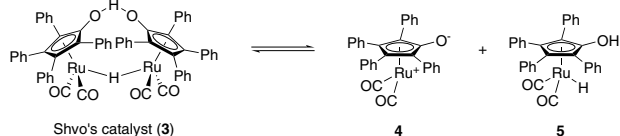
Bäckvall has successfully used Shvo's complex as an efficient epimerization catalyst in several enzyme mediated DKRs.<sup>37</sup> In the first step of the proposed epimerization mechanism of secondary alcohols, one of the oxygens on **4** abstracts a proton (removing the need of an external base as cocatalyst) and the ruthenium metal acts as a hydride acceptor, subsequently leading to ketone formation. The ketone generated is then reduced in reverse fashion, resulting in an overall epimerization of the corresponding alcohol (**Scheme 24**).

The nature of acyl donor is critical to take into account for successful chemoenzymatic DKR, and Bäckvall and co-workers have discovered certain aryl esters are efficient acyl donors in the DKR of several alcohols. An efficient protocol using immobilized *Candida antarctica* lipase B (CALB) is shown in **Scheme 25**. Based on the use of CALB in combination with Shvo's ruthenium catalyst and *p*-chlorophenyl acetate as acyl donor, a number of secondary alcohols were successfully transesterified and obtained in good to high yields and excellent enantioselectivities (**Scheme 26**). In the case of the DKR of the racemic  $\alpha$ -hydroxy esters, immobilized *Pseudomonas cepacia* lipase (PS-C) in cyclohexane was used.

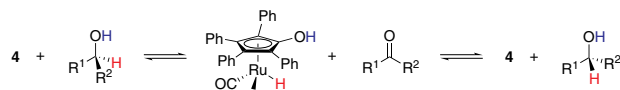
The chemoenzymatic DKR was also applied to symmetrical diols, hydroxy esters, azido alcohols, hydroxy nitriles, halo alcohols and hydroxy phosphonates (**Table 7**). Similarly, using a slightly higher amount of Shvo's catalyst, various  $\beta$ -hydroxy esters were obtained in a tandem aldol-deracemization-transesterification reaction sequence in good yields and enantioselectivities (**Scheme 27**).



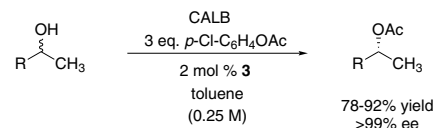
**Scheme 22**



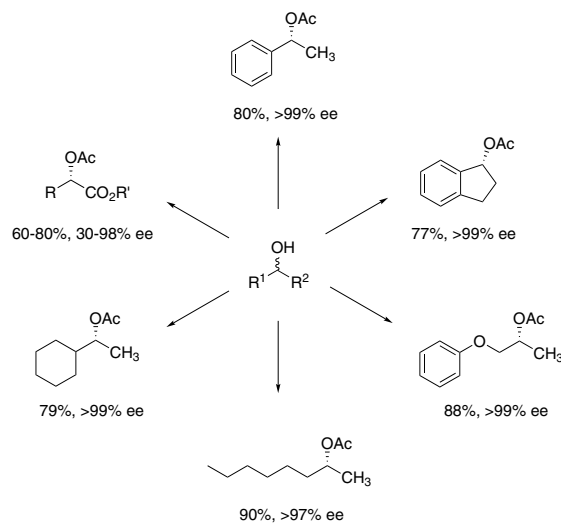
**Scheme 23**



**Scheme 24**



**Scheme 25**

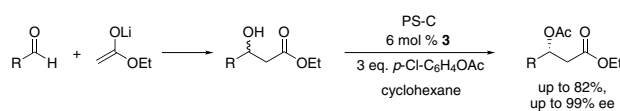


**Scheme 26**

Entry <sup>a</sup>	Starting Material	Product	Yield (%)	Selectivity
1			90	>99% ee ( <i>R,R</i> ), meso 38:62
2			78	>99% ee ( <i>R,R</i> ), meso >99:1
3			64	>96% ee ( <i>R,R</i> ), meso 89:11
4			71–87	85–99% ee
5			72–98	36–99% ee
6			74–98	87–95% ee
7			69–86	>99% ee

<sup>a</sup> Typical reaction conditions: CALB, 4 mol % **3**, 3 eq. *p*-Cl-C<sub>6</sub>H<sub>4</sub>OAc in toluene.

**Table 7**

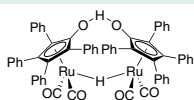


**Scheme 27**

**1-Hydroxytetraphenyl-cyclopentadienyl  
(tetraphenyl-2,4-cyclopentadien-1-one)- $\mu$ -  
hydrotetracarbonyldiruthenium(II)**

NEW

$C_{62}H_{42}O_6Ru_2$   
FW: 1085.13  
[104439-77-2]



668281-100MG	100 mg
668281-500MG	500 mg

**Lipase A, *Candida antarctica*, CLEA**

NEW

12117-1G	1 g
12117-5G	5 g

**Lipase B, *Candida antarctica*, recombinant from *Aspergillus oryzae***

[9001-62-1]

62288-50MG-F	50 mg
62288-250MG-F	250 mg

**Lipase, *Candida antarctica*, CLEA**

16698-100MG-F	100 mg
16698-500MG-F	500 mg

**Lipase from *Candida antarctica***

[9001-62-1]

62299-100MG-F	100 mg
62299-500MG-F	500 mg

**Lipase immobilized from *Candida antarctica***

73940-1G	1 g
73940-5G	5 g

**Lipase, immobilized in Sol-Gel-AK on pumice from *Candida antarctica***

89137-1G-F	1 g
89137-5G-F	5 g

**Amano Lipase PS from *Pseudomonas cepacia***

534641-10G	10 g
534641-50G	50 g

**Lipase from *Pseudomonas cepacia***

[9001-62-1]

62309-100MG	100 mg
62309-500MG	500 mg

**Lipase, immobilized in Sol-Gel-AK from *Pseudomonas cepacia***

62279-1G	1 g
62279-5G	5 g

**Lipase, immobilized on ceramic particle from *Pseudomonas cepacia***

17261-1G	1 g
17261-5G	5 g

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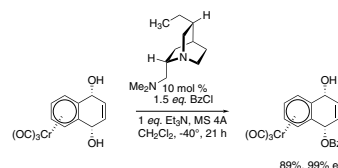
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## Additions and Corrections to ChemFiles Vol. 6 No. 4 "Asymmetric Organocatalysis"

### Cinchona Alkaloids – Desymmetrization

Page 7, Paragraph 4, Scheme 13. The diamine catalysts **07317** and **39867** mentioned in the text do not produce the indicated results. The correct catalysts must have dimethylamino groups (-NMe<sub>2</sub>) instead of amino groups (-NH<sub>2</sub>). These diamine catalysts can easily be synthesized via Eschweiler-Clarke reaction from either **07317** or **39867** (for a method of preparation see reference 28 in this issue). The corrected Scheme 13 is shown in the next column.



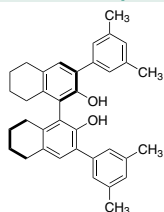
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- Page 14, Reference (5)(c) a-Aminoxylation. The following reference is missing: Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247–4250. Page 14, Reference (28). The following reference is missing: (b) Kündig, E. P.; Enríquez-García, A.; Lomberget, T.; Bernardinelli, G. T. *Angew. Chem. Int. Ed.* **2006**, *45*, 98–101.

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### (R)-(-)-3,3'-Bis-(3,5-dimethylphenyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol

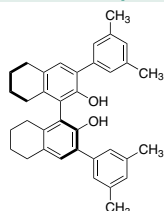
C<sub>36</sub>H<sub>38</sub>O<sub>2</sub>  
FW: 502.69



669180-100MG 100 mg

### (S)-(+)-3,3'-Bis-(3,5-dimethylphenyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol

C<sub>36</sub>H<sub>38</sub>O<sub>2</sub>  
FW: 502.69



669172-100MG 100 mg

### R-(+)-3,3,3-Trifluoro-1,2-epoxypropane

C<sub>3</sub>H<sub>3</sub>F<sub>3</sub>O  
FW: 112.05  
[143142-90-9]



667005-250MG 250 mg  
667005-1G 1 g

### (S)-(-)-3,3,3-Trifluoro-1,2-epoxypropane

C<sub>3</sub>H<sub>3</sub>F<sub>3</sub>O  
FW: 112.05  
[130025-34-2]



665797-250MG 250 mg  
665797-1G 1 g

### (R)-(4-Fluorophenyl)oxirane

C<sub>8</sub>H<sub>7</sub>FO  
FW: 138.14  
[134356-73-3]



41609-250MG-F 250 mg  
41609-1G-F 1 g

### (S)-(4-Fluorophenyl)oxirane

C<sub>8</sub>H<sub>7</sub>FO  
FW: 138.14  
[134356-74-4]



76477-250MG-F 250 mg  
76477-1G-F 1 g

### (R)-(-)-1,2,3,4-Tetrahydro-1-naphthylamine

C<sub>10</sub>H<sub>13</sub>N  
FW: 147.22  
[23357-46-2]



668818-5G 5 g  
668818-25G 25 g

### (S)-(+)-1,2,3,4-Tetrahydro-1-naphthylamine

C<sub>10</sub>H<sub>13</sub>N  
FW: 147.22  
[23357-52-0]



668796-5G 5 g  
668796-25G 25 g

### (R)-1-Boc-3-methylpiperazine

C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>  
FW: 200.28  
[163765-44-4]



08571-1G-F 1 g  
08571-5G-F 5 g

### (S)-1-Boc-3-methylpiperazine

C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>  
FW: 200.28  
[163765-44-4]



63207-1G-F 1 g  
63207-5G-F 5 g

### (R)-(-)-1-Fmoc-3-pyrrolidinol

C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub>  
FW: 309.36  
[215178-39-5]



654639-1G 1 g  
654639-5G 5 g

### (S)-(+)-1-Fmoc-3-pyrrolidinol

C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub>  
FW: 309.36  
[215178-39-4]



654647-1G 1 g  
654647-5G 5 g

### (R)-(-)-1-Cbz-3-pyrrolidinol

C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>  
FW: 221.25  
[100858-33-1]



654655-1G 1 g  
654655-5G 5 g

### Z-D-Prolinol

C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>  
FW: 235.28  
[72597-18-3]



673102-1G 1 g

### (R)-2-Piperazinecarboxylic acid dihydrochloride

C<sub>5</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> · 2HCl  
FW: 203.07  
[126330-90-3]



67176-1G-F 1 g  
67176-5G-F 5 g

### (S)-(+)-3-Piperidinecarboxylic acid

C<sub>6</sub>H<sub>11</sub>NO<sub>2</sub>  
FW: 129.16  
[59045-82-8]



656364-1G 1 g  
656364-10G 10 g

### (R)-(-)-3-Aminopiperidine dihydrochloride

C<sub>5</sub>H<sub>12</sub>N<sub>2</sub> · 2HCl  
FW: 173.08  
[334618-23-4]



666297-250MG 250 mg  
666297-1G 1 g

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