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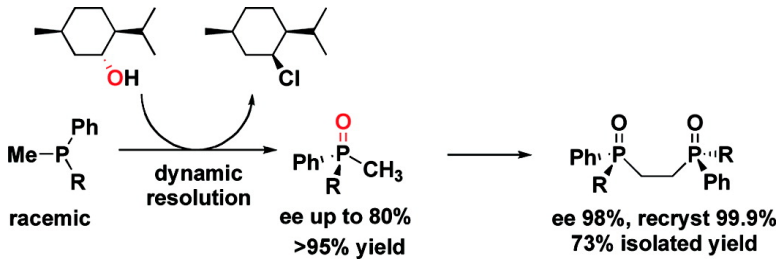

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Synthesis of P-Stereogenic Phosphorus Compounds. Asymmetric Oxidation of Phosphines under Appel Conditions

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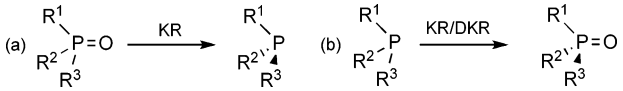
Chiral nonracemic phosphorus compounds are ubiquitous in catalytic asymmetric synthesis, both as ligands in metal-based processes[1] and as organocatalysts in their own right.[2] However, although a very large number of such ligands have been tested, the great majority have their chirality located on the carbon backbone (C-stereogenic, e.g., BINAP and DuPHOS)[1a] instead of on the phosphorus atom (P-stereogenic, e.g., DiPAMP).[1c] This is despite the fact that better chiral induction might be expected by incorporation of chirality as close as possible to the catalytic center.[3] Although P-stereogenic ligands have proven to be effective,[4] relatively few have been studied because they are difficult to synthesize.[5] Early methods were based on resolution and the generation of unequal mixtures of diastereomers,[5a] while more recent strategies include desymmetrization, enzymatic resolution, and catalytic asymmetric synthesis.[5b,6] Some of these methods can be very effective, but most are limited in scope in some way and there remains a clear need for a general solution. Herein we report on our efforts to provide such a methodology.

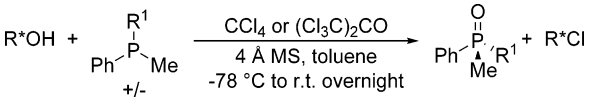
We have been interested in this difficult problem for some time.[7] We felt that there was promise in strategies involving kinetic resolution (KR) or dynamic kinetic resolution (DKR) in P(III)/P(V) interconversions (Scheme 1). Our initial approach centered on KR in asymmetric reduction (Scheme 1a), but this gave uniformly low selectivity,[7a] in line with previous reports,[8] and we turned our attention to asymmetric oxidation (Scheme 1b). There have been very few reported successes at KR/DKR in such systems,[5a,9] most notably by Perlikowska et al.[9a] who reported up to 39% ee in the KR of P-stereogenic tertiary phosphines and 70% ee for a single example of the first DKR of a chlorophosphine. In our early experiments,[7b,c] we reacted racemic phosphines with chiral nonracemic epoxides hoping that the high temperature of the reaction would allow DKR through racemization of the phosphine, but the selectivity was low (20% at best).

A way to achieve facile interconversion of stereogenic phosphorus centers at low temperatures is via pseudorotation of pentavalent pentacoordinate phosphorus compounds (10P5).[10] We therefore explored a variety of processes that could involve 10P5, and we report now our preliminary results on an asymmetric version of the oxidation/reduction/dehydration system known as the Appel conditions.[11] Typically, these conditions involve use of PPh_3/CCl_4 to convert an alcohol to an alkyl chloride in high yield. From our perspective, these conditions are an oxidation of a phosphine involving a potentially chiral reagent (Scheme 2). Therefore, we were encouraged when our first experiments with this system gave some selectivity. Treatment of racemic phenyl-*ortho*-anisylmethylphosphine (PAMP, the precursor of DiPAMP) with CCl_4 and (−)-menthol in benzene at reflux gave the phosphine oxide ((*R*)-PAMPO) in good yields and up to 24% ee.

Scheme 1. Reduction and Oxidation of P(III)/P(V) Compounds



Scheme 2. Racemic Phosphine/Chiral Alcohol in Appel Conditions



Subsequently, we used the more reactive hexachloroacetone (HCA)[12] in place of CCl_4, which allows reaction at much lower temperatures. A wide range of commercially available chiral nonracemic alcohols were screened at room temperature, and it was found that terpineols gave the highest selectivity, although certain diols and amino alcohols were also effective in inducing enantioselectivity in PAMP oxidation.[13] We then focused on cyclic secondary alcohols at −78 °C for studies with a wider range of tertiary phosphines, with results shown in Table 1 and Chart 1.

Table 1 shows that phosphine oxides can be produced in good ee (up to 80%, two cases) and excellent yield. In most cases the highest selectivity was achieved with menthol, an inexpensive, readily available alcohol. In addition, no stereochemical information is lost in the reaction, and (−)-menthol is converted into (+)-*neo*menthyl chloride with a very high selectivity. The cost of (−)-menthol, even in stoichiometric quantities, compares favorably with the cost of typical loadings of a chiral metal-based catalyst.

To show the power of our method, we used it for a simple two-step synthesis of optically pure bisphosphine oxides from racemic monophospine, via dimerization of the enantioenriched monooxide (Scheme 3). In the example shown, chiral dimer (*R,R*)-**6** was produced in 98% ee and the minor amount of *meso* compound formed was easily removed by recrystallization from benzene, which yielded enantiopure (>99.9% ee) bisphosphine oxide in an isolated yield of 73% from the racemic phosphine.

Scheme 4 shows some of the known or likely reaction intermediates under Appel conditions.[11a] Analysis of our reaction mixtures by ^{31}P NMR shows three signals: one corresponding to phosphine oxide, which increases as the reaction progresses, and a transient narrowly spaced unequal pair at ∼65−70 ppm. We propose that these are diastereomeric alkoxyphosphonium salts (**a** and **b**). Stereoselection could occur at several points in Scheme 4. Perhaps most likely is in equilibration between the diastereomeric phosphoranes, which then collapse to produce unequal amounts of salts **a** and **b**, and hence unequal amounts of oxide. This would constitute dynamic thermodynamic resolution.[14] However, if the phosphonium

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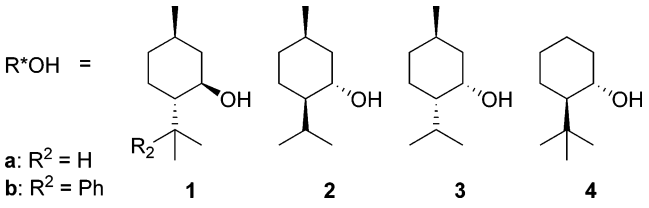
Table 1. Enantiomeric Excesses[a] Obtained in the DKR of Phosphines According to Scheme 2 (using HCA)[b]

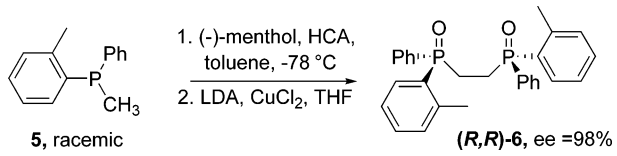
#	R^1	alcohol	% ee	config
1[c]	*o*-anisyl	(−)-menthol **1a**	50	(*R*)
2[c]	*o*-anisyl	(+)-neomenthol **3**	64	(*S*)
3[c]	*o*-anisyl	(+)-isomenthol **2**	42	(*S*)
4[c]	*o*-anisyl	(−)-8-phenylmenthol **1b**	77	(*R*)
5[c]	*o*-anisyl	(+)-*trans*-2-*tert*-butylcyclohexanol **4**	75	(*S*)
6	*o*-tolyl	(−)-menthol **1a**	80	(*R*)
7	*o*-tolyl	(+)-neomenthol **3**	59	(*S*)
8	*o*-tolyl	(+)-isomenthol **2**	71	(*S*)
9	*o*-tolyl	(+)-*trans*-2-*tert*-butylcyclohexanol **4**	58	(*S*)
10	*o*-^{i}PrPh	(−)-menthol **1a**	80	(*R*)[d]
11	*o*-^{i}PrPh	(+)-neomenthol **3**	41	(*S*)[d]
12	*o*-^{i}PrPh	(−)-8-phenylmenthol **1b**	20	(*R*)[d]
13	*o*-ClPh	(−)-menthol **1a**	71	nd[e]
14	^{t}Bu	(−)-menthol **1a**	48	(*S*)
15	^{t}Bu	(+)-neomenthol **3**	6	(*R*)
16	^{t}Bu	(+)-isomenthol **2**	42	(*S*)
17	^{t}Bu	(−)-8-phenylmenthol **1b**	8	(*R*)
18	^{t}Bu	(+)-*trans*-2-*tert*-butylcyclohexanol **4**	7	(*S*)

[a] Determined by CSP HPLC (see SI). [b] Phosphine (0.11 mmol), alcohol (1.2 equiv), HCA (1 equiv), yields >95% (not isolated). [c] No 4 Å MS used, due to decreased yield by product absorption; see SI for details. [d] Assigned by analogy with *o*-anisyl and *o*-tolyl cases. [e] Not determined.

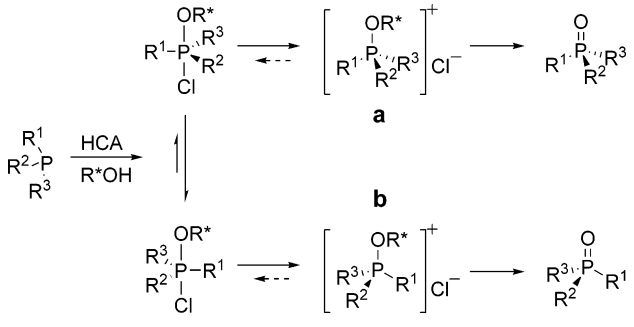
Chart 1. Chiral Nonracemic Alcohols Used in Table 1



Scheme 3



Scheme 4. Proposed Mechanism of Oxidation



salts can equilibrate by re-forming the phosphoranes, the situation is more complex and selection could be by different rates of decomposition of the salts into the phosphine oxides.

The process outlined above is a simple and practical method for the dynamic resolution of P-stereogenic phosphines. Oxidation of phosphines is normally extremely fast, so the introduction of a high level of enantioselection is remarkable. The enantiomeric excesses obtained are, by far, the highest reported for asymmetric phosphine oxidation.

In summary, the results presented here represent a completely unprecedented method for the synthesis of highly enantioenriched P-stereogenic phosphine oxides in excellent yields and opens up a new, facile route for the synthesis of enantiopure bisphosphine oxides. The latter is especially important because many methods exist for their conversion into phosphines with stereocontrol (both retention and inversion),[15] and the resulting bisphosphines have high utility in asymmetric catalysis. We are investigating the reaction mechanism and the use of the products in catalytic asymmetric synthesis, which will be the subject of future reports.

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Supporting Information Available: Procedures for the asymmetric oxidation reactions, phosphine syntheses, and a listing of results of oxidations at room temperature with other chiral alcohols are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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