

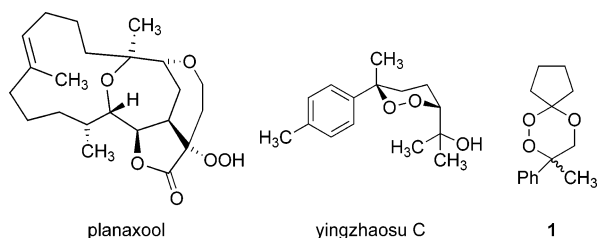
Kinetic Resolution of Hydroperoxides with Enantiopure Phosphines: Preparation of Enantioenriched Tertiary Hydroperoxides

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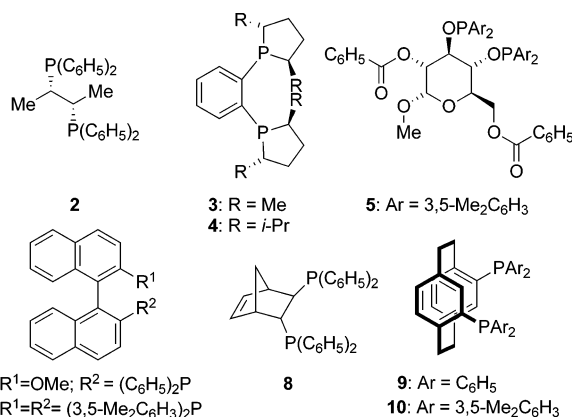
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Hydroperoxides can serve as both biologically active agents and precursors to therapeutically valuable endoperoxides.¹ For example, planaxool is a cytotoxic agent representative of the complex tertiary hydroperoxides found in nature.² In addition, appropriately substituted tertiary hydroperoxides have been utilized as intermediates in the syntheses of antimalarial agents such as the natural product yingzhaosu C³ and the synthetic 1,2,4-trioxane **1**.⁴



Applications of these compounds and related structures in medicinal chemistry would benefit from a method capable of obtaining enantiopure tertiary hydroperoxides. The accessibility of racemic hydroperoxides, often available in one step from the corresponding alcohol, has spurred the exploration of kinetic⁵ and classical⁶ resolution strategies to synthesize these compounds. Although enzymatic kinetic resolutions of a few secondary benzylic⁷ and α -hydroxy allylic hydroperoxides⁸ proceed with excellent selectivities, these systems are limited in substrate scope. To date, all resolutions of tertiary hydroperoxides occur with selectivity factors of less than three.⁹



In this communication, we demonstrate that a reductive kinetic resolution strategy, employing commercially available enantiopure phosphines, can provide optically pure tertiary hydroperoxides with high efficiency. The use of phosphines in stoichiometric quantities is mitigated by the ease with which the resulting phosphine oxide can be recycled (*vide infra*). In addition, this strategy can be applied to secondary hydroperoxides as a complementary method to those reported.⁷

Table 1. Kinetic Resolution of Hydroperoxide **11** with Various Enantiopure Phosphines

entry	phosphine	% conv ^a	% ee of 11 ^a	<i>k</i> _{rel} ^b
1	(2 <i>S</i> ,3 <i>S</i>)-CHIRAPHOS (2)	47	0	1.0
2	(<i>R,R</i>)-Me-DuPHOS (3)	39	0	1.0
3	(<i>S,S</i>)- <i>i</i> -Pr-DuPHOS (4)	50	19	1.2
4	CARBOPHOS (5)	41	13	1.3
5	(<i>S</i>)-MOP (6)	28	6	1.5
6	(<i>S</i>)-xylyl-BINAP (7)	56	23	1.7
7	(<i>S,S</i>)-NORPHOS (8)	55	36	2.5
8	(<i>R</i>)-PHANEPHOS (9)	50 ^c	45	3.5
9	(<i>S</i>)-xylyl-PHANEPHOS (10)	50	86	37

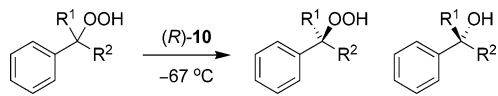
^a Conversion and ee were determined by HPLC or SFC analysis using Chiracel OD-H columns. ^b See ref 11. ^c Conversion was determined by ¹H NMR spectroscopic analysis.

The reduction of chiral tertiary hydroperoxides by chiral phosphines was examined using compound **11**. This substrate contains three sterically different substituents, including a chromophore to facilitate HPLC analysis. Although all of the phosphines screened are effective at enantioselective transformations in metal-mediated syntheses,¹⁰ most gave low selectivities for the reduction of hydroperoxide **11** (Table 1, entries 1–8). The cyclophane-derived phosphine **10**, however, reduced hydroperoxide **11** with a *k*_{rel} of 37, providing recovered starting material with 86% ee at 50% conversion (Table 1, entry 9).^{11,12}

The kinetic resolution of benzylic tertiary hydroperoxides is general using the optimized bisphosphine, xylyl-PHANEPHOS (**10**) was effective in resolving hydroperoxides containing three sterically different substituents (Table 2, entries 1–5). In all cases, (*R*)-**10** reduced the (–)-(*S*)-hydroperoxide preferentially, and the enantiomer, (*S*)-**10**, had the opposite selectivity.¹³ Phosphine (*R*)-**10** also resolved the functionalized hydroperoxide **18**, although the selectivity was lower (Table 2, entry 6).

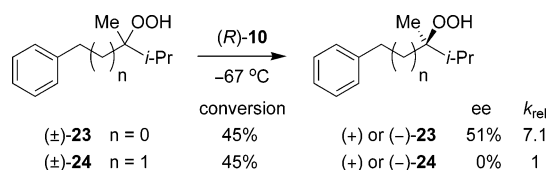
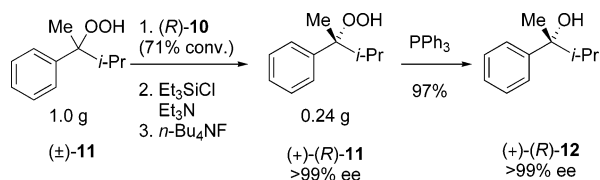
The phosphine optimized for tertiary benzylic hydroperoxides is less efficient for the resolution of secondary benzylic and non-benzylic hydroperoxides. The reduction of secondary benzylic hydroperoxides with phosphine (*R*)-**10** proceeded with moderate selectivity. This process, however, complements other methods of obtaining these compounds in enantiopure form (Table 2, entries 6–9).⁷ Selectivities diminished with increasing length of the alkyl linker in the resolutions of non-benzylic hydroperoxides **23** and **24** with (*R*)-**10** (Scheme 1). Presumably, as the tether length increases, the steric differentiation decreases at the reactive center.

The kinetic resolution of racemic tertiary hydroperoxides is amenable to preparative scale reactions. One gram of hydroperoxide (±)-**11** was subjected to resolution conditions with commercially

Table 2. Generality of Kinetic Resolution


entry	substrate	R ¹	R ²	% conv ^a	% ee ^a	k _{rel} ^b
1	13	Me	Et	43	63	21
2	14	Me	<i>n</i> -Pr	46 ^c	71	23
3	15	Me	<i>n</i> -Bu	57	90	16
4	16	Me	<i>i</i> -Bu	39	58	37
5	17	Me	<i>c</i> -C ₆ H ₁₁	56	95	25
6	18	Me	CH ₂ OSiMe ₂ <i>t</i> -Bu	49 ^c	42	3.8
7	19	H	Me	84	77	2.6
8	20	H	Et	75	76	3.4
9	21	H	<i>i</i> -Pr	50	62	6.9
10	22	H	<i>c</i> -C ₆ H ₁₁	43	42	5.2

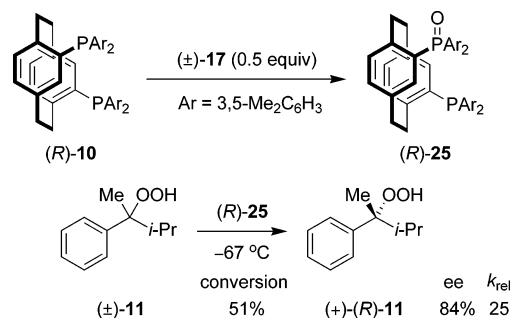
^a Conversion and ee were determined by HPLC or SFC analysis using Chiralcel OD-H columns. ^b See ref 11. ^c Conversion was determined by ¹H NMR spectroscopic analysis.

Scheme 1**Scheme 2**

available phosphine (*R*)-**10** (71% conversion, Scheme 2). The resulting enantiopure hydroperoxide (+)-(R)-**11** and enriched alcohol (–)-(S)-**12** could not be separated by physical means, but a strategy was developed to facilitate purification. When the mixture of hydroperoxide (+)-(R)-**11** and alcohol (–)-(S)-**12** was treated with Et₃SiCl, the hydroperoxide was protected selectively,¹⁴ and the resulting silylperoxy ether could be separated from the alcohol by column chromatography. Subsequent desilylation provided enantiopure (>99% ee) hydroperoxide (+)-(R)-**11** in 24% overall yield. This route also allows access to enantiopure tertiary alcohol (+)-(R)-**12** by reduction with triphenyl phosphine (Scheme 2).

Preliminary mechanistic studies reveal that the two phosphines of *xylyl*-PHANEPHOS (**10**) operate independently.¹⁵ The supposed intermediate, mono(phosphine oxide) (*R*)-**25**, was isolated from the reaction of phosphine (*R*)-**10** and 1 equiv of hydroperoxide **17**. Utilizing this compound in the resolution of hydroperoxide **11** afforded starting material with 84% ee at 51% conversion (*k*_{rel} = 25, Scheme 3). This experiment demonstrates that the monophosphine intermediate (*R*)-**25** reduces hydroperoxides with a similar selectivity to that of *xylyl*-PHANEPHOS. It also suggests that less complex monophosphines may also be useful for this type of resolution.

In conclusion, we have described a method for the stoichiometric kinetic resolution of hydroperoxides employing commercially available phosphines. The reaction provides access to enantiopure hydroperoxides and, therefore, the corresponding alcohols as well.

Scheme 3

In addition, the resulting bis(phosphine oxide) can be converted back to the phosphine in high yield.¹⁶

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Supporting Information Available: Complete experimental procedures, product characterization, and HPLC/SFC traces (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (11) Theoretically, starting material with >99% ee can be recovered in ~43% yield utilizing a kinetic resolution method that proceeds with a *k*_{rel} of 37. Selectivity values (*k*_{rel}) were calculated using the equation *k*_{rel} = ln[(1 - C)(1 + ee)]/ln[(1 - C)(1 - ee)]. See: Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry*; Wiley: New York, 1988; pp 249–330.
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