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Allenes in Asymmetric Catalysis: Asymmetric Ring Opening of *meso*-Epoxides Catalyzed by Allene-Containing Phosphine Oxides

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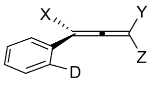
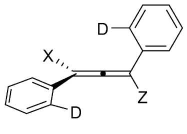
Asymmetric catalysis has revolutionized the synthesis of chiral, nonracemic materials. It has been the subject of academic inquiry and industrial implementation. The last several decades have witnessed continued introduction and development of chiral organic catalysts and ligands for transition- and main-group metals.[1] Most existing ligands and organic catalysts are characterized by one of two types of chirality: some species owe their chirality to stereogenic atoms, usually tetrahedral carbon or phosphorus; many others are chiral by virtue of hindered rotation around a carbon−carbon single bond, the exemplar of which is the binaphthyl backbone. Some of the most successful catalysts combine the elements of both central and axial chirality.[2,3]

Allenes can be chiral but have made only limited contributions to asymmetric catalysis to date. They were predicted to display chirality by van't Hoff over a century ago,[4] but to the best of our knowledge, allenes have been used only once in catalytic quantities to control the stereochemical outcome of a reaction. In that report, Soai and co-workers[5] demonstrated that optically active disubstituted allenes induced asymmetry in the addition of diisopropyl zinc to a pyrimidine carboxaldehyde. The actual effectiveness of the allene as a chiral modulator was difficult to gauge because other experiments with the same system indicated that a strong nonlinear effect coupled with autocatalysis conspire to amplify even unmeasurable enantiomeric excesses.[6]

We hypothesized that allenes having the general structure **A** or **B** might represent attractive frameworks for developing ligands for asymmetric catalysis:[7] The unique architecture of the allene projects functionality differently than either tetrahedral carbon or chiral biaryls and therefore may create a complementary chiral environment. Additionally, the ortho relationship between the donor group and the allene might facilitate asymmetric induction by orienting metals or sites of reactivity toward the source of chirality. Finally, this basic platform could be amenable to introduction of a variety of donor groups and could find utility in main-group and transition-metal catalysis or organocatalysis. Here we demonstrate that the chirality of an allene can indeed be communicated effectively to a transition state in the context of an enantioselective transformation. This observation suggests the possibility of a new class of ligands and catalysts for use in asymmetric synthesis.



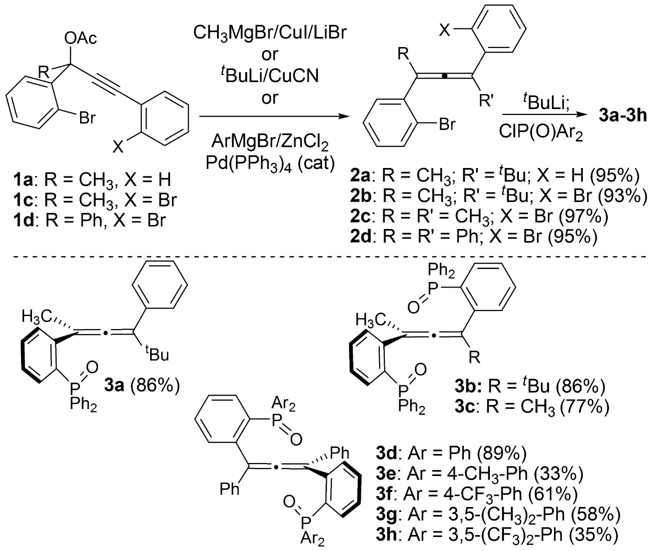
A: D = donor group



B: D = donor group

Since phosphine oxides have shown promise as chiral Lewis bases,[8] we prepared a series of optically active mono- and bisphosphine oxides that contain an allene backbone (Scheme 1). Thus, proparygylic acetates **1** were prepared from the corresponding alcohols, which had previously been generated in optically active form through either asymmetric addition of terminal alkynes to the corresponding ketones[9] or resolution of the racemic tertiary alcohols.[10,11] Propargylic substitution with diorganocuprate reagents or aryl zinc halides then generated the tetrasubstituted allenes **2**. The aryl bromides were treated with *tert*-butyllithium, and the corresponding aryl lithium intermediates were trapped with diarylchlorophosphine oxides. In this way, we synthesized several mono- and bisphosphine oxides displaying diverse substitution patterns on both the allene backbone and the phosphorus. Most of the prospective catalysts were prepared in optically pure form through recrystallization of the bisphosphine oxide (**3b**, **3c**) or the dibromoallene (**3d**−**h**).[12]

Scheme 1



In the solid state, bisphosphine oxide **3d** adopts a conformation characterized by π-stacking interactions involving two phenyl rings of the phosphine oxides and one of the backbone phenyl rings (Figure 1). A consequence of this arrangement is that the two oxygen atoms project in roughly the same direction. The signifi-

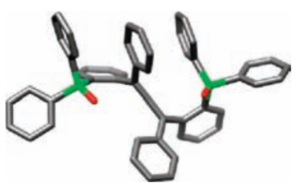


Figure 1. X-ray crystal structure of **3d**. Hydrogen atoms, an identical molecule of **3d**, and a molecule of water have been removed for clarity.

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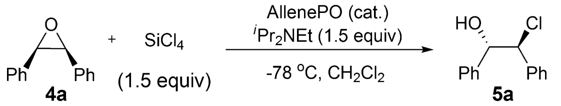
cance of this conformation is not clear, however, as the bisphosphine oxide appears to be C_2-symmetric on the NMR time scale.

We initiated our studies of catalysis by considering the asymmetric addition of $SiCl_4$ to *meso*-epoxides. The Denmark group demonstrated that optically active phosphorus triamides could catalyze this transformation;[13] subsequent reports revealed the utility of pyridine *N*-oxides and phosphine oxides.[14] Mechanistically, these reactions are thought to involve coordination of one or more Lewis bases to $SiCl_4$ to generate a more Lewis acidic species $(LB)_nSiCl_3^+$ (LB = Lewis base) capable of activating the epoxide toward ring opening.[13b]

cis-Stilbene oxide was exposed to $SiCl_4$ and $^iPr_2NEt$ in the presence of catalytic allene-containing mono- or bisphosphine oxides **3** (AllenePO, Table 1). These experiments revealed several aspects of the ring-opening reaction: (1) Allene-containing ligands can induce enantioselectivity in catalytic reactions. (2) In general, bisphosphine oxides (e.g, **3b**) displayed higher reactivities and enantioselectivities than the monophosphine oxide (**3a**). (3) Substantial variation on the allene itself was tolerated, as both the methyl- and phenyl-substituted catalysts (**3c**, **3d**) were reactive and enantioselective. (4) The ring opening is sensitive to the aryl rings on the phosphine oxide. Both electron-donating groups (entries 6 and 8) and, more profoundly, electron-withdrawing groups (entries 7 and 9) decreased the reactivity and, where measurable, the selectivity. (5) *The diphenyl-substituted catalyst* **3d** *is a highly reactive and enantioselective catalyst, displaying nearly 1000 turnovers and generating the chlorohydrin in 94% ee* (entry 10).

Table 1. Evaluation of Phosphine Oxides as Catalysts for the Addition of $SiCl_4$ to *cis*-Stilbene Oxide[a]

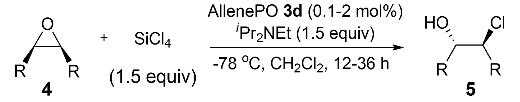


entry	AllenePO	loading (mol %)	% yield	% ee[b] (+/−)
1	**3a**[c]	10	39	<10
2	**3a**[c]	2	<10	---
3	**3b**[d]	2	47	54 (−)
4	**3c**	2	76	84 (−)
5	**3d**	2	93	89 (+)
6	**3e**	2	86	84 (+)
7	**3f**	2	<5	---
8	**3g**	2	58	78 (+)
9	**3h**	2	<5	---
10[e]	**3d**	0.1	97	94 (+)

[a] Reactions were carried out with [**4a**] = 0.02 M unless otherwise noted. [b] Determined by HPLC. [c] **3a** was 70% ee. [d] **3b** was 79% ee. [e] [**4a**] = 0.2 M.

A set of *meso*-epoxides were opened with $SiCl_4$ in the presence of catalyst **3d** (Table 2). In general, the reaction is effective for substituted stilbene oxides. Both electron-releasing and electron-withdrawing substituents are tolerated in the meta or para position, although the electron-poor substrates tended to require increased catalyst loadings (entries 4, 7, 8). In contrast, ortho-substituted stilbene oxides were not reactive (entry 10). Finally, the chlorohydrins derived from linear, cyclic, or bicyclic aliphatic epoxides were isolated in high yield but with rather unimpressive enantiomeric excesses (entries 11−13).

Table 2. Asymmetric Ring Opening of *meso*-Epoxides[a]



entry	R	**3d** (mol %)	yield (%)[b]	ee (%)[c]
1	Ph[d] (**4a**)	0.1	97	94
2	4-F-Ph (**4b**)	0.1	96	93
3	4-CH_3-Ph (**4c**)	0.1	92	89
4	4-CF_3-Ph (**4d**)	2	97	87
5	4-Cl-Ph (**4e**)	0.1	89	82
6	3-CH_3−Ph (**4f**)	0.2	89	91
7	3-Cl-Ph (**4g**)	2	96	90
8	3-CF_3-Ph (**4h**)	2	91	88
9	3-CH_3O-Ph (**4i**)	0.2	95	88
10	2-Br-Ph (**4j**)	2	<5	---
11	$BnOCH_2$ (**4k**)	2	90	60
12	$(CH_2)_4$ (**4l**)	0.1	95	29
13	*exo*-2,3-norbornyl (**4m**)	0.1	76	50

[a] All of the reactions were quenched with propylene oxide and KF/KH_2PO_4 buffer. See the Supporting Information for details. [b] Isolated yields. [c] For entries 1−12, the ee was determined by HPLC; for entry 13, the ee was determined by GC. [d] Ph = phenyl.

Allenes have attracted attention from the synthetic community because, among other reasons, they react with both nucleophiles and electrophiles, often under mild conditions. In the present circumstance, however, this reactivity profile represented a potential liability inasmuch as catalyst stability would be critical for a practical synthetic method. In this regard, we were encouraged that we could recover catalyst **3d** in 94% yield from a reaction involving the ring opening of epoxide **4a**.[11]

More than a century after van't Hoff recognized that allenes could be chiral, we have demonstrated that their chirality can be harnessed in the service of asymmetric catalysis. In the present example, we have prepared organic Lewis bases and shown that they can activate $SiCl_4$. However, this design principle may extend equally well to other classes of organic catalysts or ligands for transition metals.[7] The utility of allenes in these contexts is the subject of current investigations.

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Supporting Information Available: Complete experimental details and characterization data, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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