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Enantioselective Synthesis of Chiral Oxime Ethers: Desymmetrization and Dynamic Kinetic Resolution of Substituted Cyclohexanones

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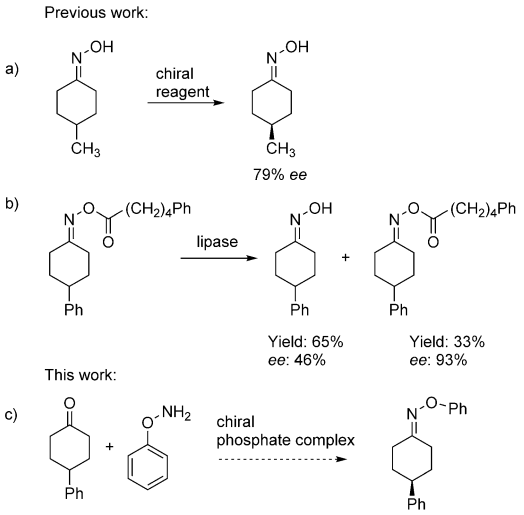
Abstract: *Axially chiral cyclohexylidene oxime ethers exhibit unique chirality because of the restricted rotation of C=N. The first catalytic enantioselective synthesis of novel axially chiral cyclohexylidene oximes has been developed by catalytic desymmetrization of 4-substituted cyclohexanones with O-arylhydroxylamines and is catalyzed by a chiral BINOL-derived strontium phosphate with excellent yields and good enantioselectivities. In addition, chiral BINOL-derived phosphoric acid catalyzed dynamic kinetic resolution of α-substituted cyclohexanones has been performed and yields versatile intermediates in high yields and enantioselectivities.*

The development of novel asymmetric reactions has been one of the prime foci of modern synthetic organic chemistry. Substantial advances have been made in asymmetric synthesis of compounds with central chirality by using transition metals and organocatalytic methods. In addition, compounds with axial chirality, planar chirality, and helical chirality have attracted recent attention because of their importance in synthesis and asymmetric catalysis.[1] Axially chiral compounds, also known as atropisomers, exhibit unique chirality because of the non-coplanar arrangement of groups about an imaginary axis. This arrangement is attributed to the restricted rotation around either a single or double bond.[2] Although the first axially chiral compound was observed in 1910,[3] their importance was not realized until recently as a consequence of their occurrence in natural products and their application as chiral ligands.[4] Over the last decade, tremendous progress has been made for the synthesis of axially chiral biaryls, allenes, spiranes, and cyclohexylidenes.[5] However, methods for catalytic enantioselective synthesis of cyclohexylidene oximes and its analogues are scarce.

Oximes and oxime ethers are versatile intermediates and key structural motifs present in several biologically active compounds which exhibit medicinal properties.[6] Recent progress in C–H activation proved that oxime ethers are efficient directing groups in several synthetic transformations.[7] Chiral cyclohexylidene oximes contain stereogenic axes which arise from the restricted rotation about the C=N bond and high activation energy barrier for nitrogen inversion.[8] To date, only two reports have described the enantioselective resolution of chiral cyclohexylidene oximes. In 1990, Toda first reported the successful isolation of optically active oximes by the conventional second-order asymmetric transformation starting from racemic compounds (Scheme 1a)[9]



Scheme 1. Synthesis of chiral cyclohexylidene oximes.

Later, in 1994, Hoshino et al. demonstrated the kinetic resolution of phenylcyclohexanone oxime esters by lipase-catalyzed transesterification[9b] to give optically active oximes and oxime esters (Scheme 1b). Herein, we report the first enantioselective synthesis of chiral cyclohexylidene oxime ethers by desymmetric condensation of 4-phenylcyclohexanone with aryloxyamine catalyzed by a chiral BINOL phosphate complex (Scheme 1c). We further applied this methodology in the dynamic kinetic resolution of 2-substituted cyclohexanones.

Desymmetrization and dynamic kinetic resolution (DKR) processes are represented as powerful synthetic tools for converting *meso* or prochiral substrates into enantiopure compounds.[10] Versatile desymmetrization reactions of prochiral cyclohexanones by Michael addition,[10c–e] aldol reaction,[10f–h] Schmidt reaction,[10i,j] and Baeyer–Villiger oxidation[10k–m] have been reported. The group of List[11] developed elegant strategies for catalytic asymmetric Fischer indole synthesis and chiral indoline synthesis with substituted cyclohexanone-derived phenylhydrazones using chiral phosphoric

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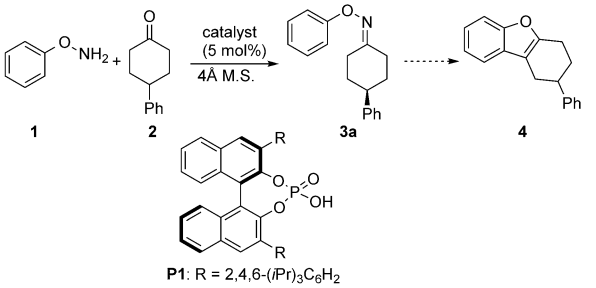
acid.[12] Inspired by these results, and our continuous interest in chiral BINOL-derived phosphoric acid and phosphate complexes,[13] we envisioned the asymmetric synthesis of benzofurans could be feasible by reacting 4-substituted cyclohexanones with phenoxyamines in a similar fashion.

To investigate our hypothesis, we started with the reaction of *O*-phenylhydroxylamine (**1**) with 4-phenyl cyclohexanone (**2**) in dichloromethane at 45 °C using **P1**. Unfortunately, we did not observe the benzofuran product **4**, but full conversion of the starting materials into the condensed product, the cyclohexylidene oxime ether **3** was obtained (Table 1). To our

Table 1: Optimization of reaction conditions for desymmetrization of 4-phenyl cyclohexanone.[a]

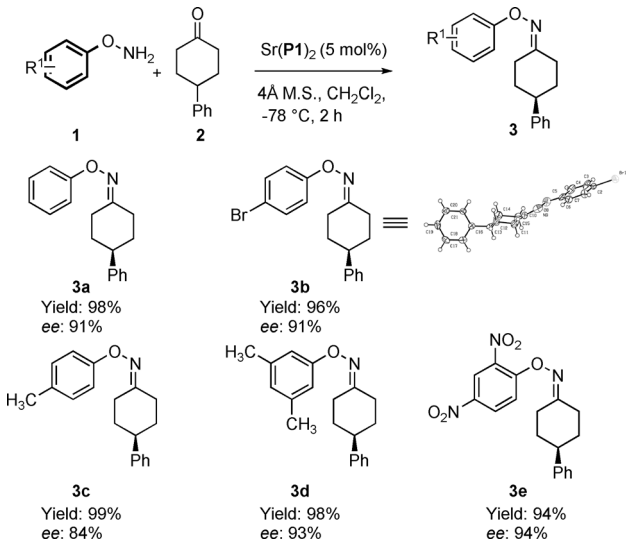


Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	*ee* [%][b]
1[c]	**P1**	CH_2Cl_2	45	16	10
2[c]	Mg(**P1**)$_2$	CH_2Cl_2	45	16	54
3[c]	Mg(**P1**)$_2$	CH_2Cl_2	RT	2	62
4	Ca(**P1**)$_2$	CH_2Cl_2	RT	0.5	62
5	Mg(**P1**)$_2$	CH_2Cl_2	RT	0.5	64
6	Mg(**P1**)$_2$	Et_2O	RT	0.5	40
7	Mg(**P1**)$_2$	toluene	RT	0.5	64
8	Mg(**P1**)$_2$	THF	RT	0.5	58
9	Mg(**P1**)$_2$	$CHCl_3$	RT	0.5	52
10	Mg(**P1**)$_2$	CH_2Cl_2	−78	2	70
11	Sr(**P1**)$_2$	CH_2Cl_2	−78	2	91
12	**P1**	CH_2Cl_2	−78	2	83

[a] Reaction conditions: **1** (0.15 mmol), **2** (0.22 mmol), catalyst (5 mol%) [b] Determined by chiral-phase HPLC analysis. [c] Without molecular sieves. M.S. = molecular sieves, THF = tetrahydrofuran.

surprise Mg(**P1**)$_2$ gave **3** with 54% enantiomeric excess (*ee*). Intrigued by the unique stereoselectivity of these unprecedented compounds, we proceeded to optimize the reaction conditions. The condensation of **1** and **2** proceeds smoothly at room temperature with Mg(**P1**)$_2$ in presence of molecular sieves, and showed slightly better selectivity than Ca(**P1**)$_2$ (entries 4 and 5). Screening of solvents was not helpful increasing the stereoselectivity compared to that for dichloromethane (entries 6–9). Lowering the reaction temperature to −78 °C improved the enantioselectivity to 70% (entry 10). To our delight, Sr(**P1**)$_2$ in dichloromethane at −78 °C proved to be the ideal conditions for the axially chiral **3** with good enantioselectivity.

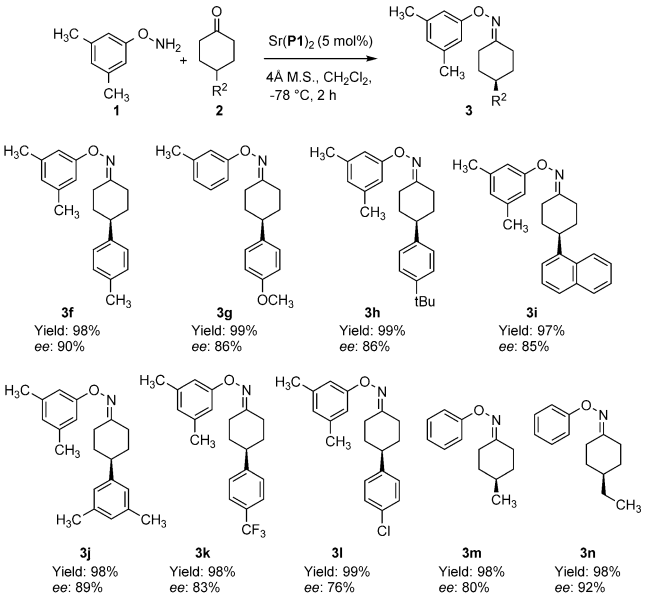
With the optimal reaction conditions in hand, we then explored the substrate scope for this desymmetrization reaction. As shown in (Scheme 2), substituents on the *para* position of the phenyl ring of **1** gave good enantioselectivity



Scheme 2. Substrate scope for the synthesis of chiral cyclohexylidene oximes.[20]

and excellent yields (**3b**,**c**). The 3,5-disubstituted and 2,4-disubstituted phenyl substrates offered little improvement in selectivity (**3d**,**e**). The absolute configuration for **3b** was assigned based on the X-ray crystal structure[20] and all other compounds were assigned analogously. It is noteworthy that the phenyl group of **1** is pivotal for enantiomeric induction, as using aliphatic oxyamines afforded only racemic products.

Similarly, the scope for 4-substituted cyclohexanones, substrates with both electron-releasing and electron-withdrawing groups on the phenyl group are well tolerated (Scheme 3). Even the aliphatic groups, 4-methyl and 4-ethyl, afforded good enantioselectivities (**3m**,**n**). Our efforts to further extend the utility for these novel chiral compounds in asymmetric benzofuran synthesis failed to retain the enantioselectivity.[14]



Scheme 3. Substrate scope for the synthesis of chiral cyclohexylidene oximes.

To gain additional insight into the origin of stereoselectivity, we examined entry 12 of Table 1 at the PCM-ωB97X-D/def2-TZVP//PCM-B97-D/def2-TZVP level of theory,[15] thereby computing free energies within the quasi-RRHO approximation of Grimme.[16] The stereocontrolling step is the dehydration of the intermediate alcohol in the presence of the chiral phosphoric acid in an E1-like process, as depicted in Figure 1. In this transition state (TS), the substrate is bound to

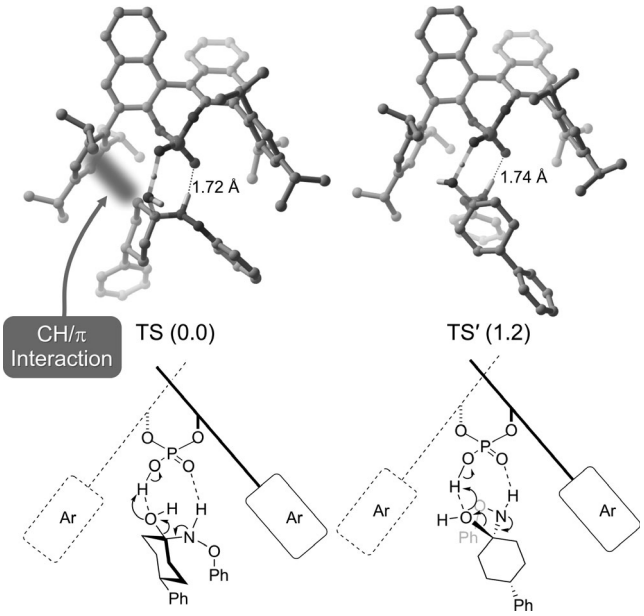
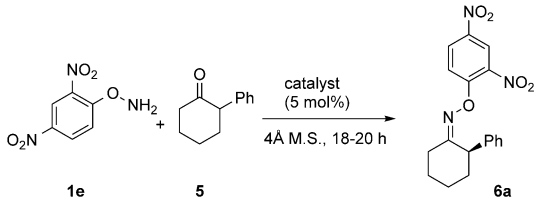


Figure 1. Computed TS structures leading to the favored (TS) and disfavored (TS′) stereoisomeric oxime ethers, along with relative free energies in kcal mol^{-1}.

the catalyst by an NH···O hydrogen-bonding interaction. The phosphoric acid simultaneously protonates the hydroxy group as it leaves as a water molecule. An extensive conformational search (see Table S2 in the Supporting Information) yielded the lowest-lying TS structures leading to the favored and disfavored stereoisomers of the oxime ether shown in Figure 1. The corresponding free-energy difference between these two structures (1.2 kcal mol^{-1}) leads to a computed *ee* value of 91%, which is in reasonable agreement with the experimental value. This computed *ee* value is improved to 80% upon consideration of a Boltzmann weighted sum of all TS conformations, and is in excellent agreement with the experimental value (83%; Table 1). Upon examining the lowest-lying structures in Figure 1, the favored TS exhibits greater shape complementarity between the substrate and chiral binding pocket of the catalyst, thus leading to a more favorable NH···O interaction (as reflected in the H···O distances; see Figure 1), as well as stabilizing CH···π interactions with one of the aryl substituents of the catalyst.

We envisioned, this methodology could also be used in the DKR of 2-substituted cyclohexanones. The group of List[17] reported an efficient direct reductive amination of α-branched ketones by a DKR process catalyzed by chiral BINOL phosphoric acid. Screening of different O-protecting

Table 2: Optimization of reaction conditions for dynamic kinetic resolution of 2-phenyl cyclohexanones.[a]



1e **5** **6a**

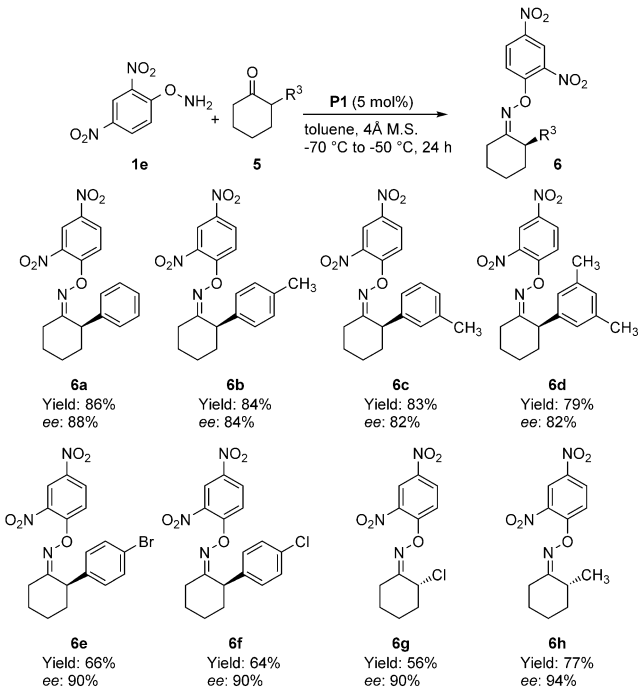
Entry	Catalyst	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**P1**	CH_2Cl_2	−78	84	20
2	Mg(**P1**)$_2$	CH_2Cl_2	−78	76	38
3	Sr(**P1**)$_2$	CH_2Cl_2	−78	80	13
4	Mg(**P1**)$_2$	toluene	−78	60	97
5	Ca(**P1**)$_2$	toluene	−78	56	90
6	Mg(**P1**)$_2$	toluene	−30	74	60
7	Mg(**P1**)$_2$	toluene	−50	75	82
8	Mg(**P1**)$_2$	toluene	−65	58	94
9	Mg(**P1**)$_2$	toluene	−65 to −50	75	93
10	**P1**	toluene	−70 to −50	86	88

[a] Reaction conditions: **1e** (0.07 mmol), **5** (0.05 mmol), catalyst (5 mol%) [b] Yield of isolated product. [c] Determined by chiral-phase HPLC analysis.

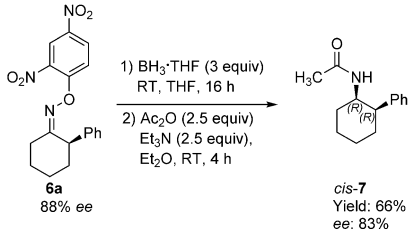
groups showed that *O*-(2,4-dinitrophenyl)hydroxylamine (**1e**) in dichloromethane at −78°C showed improvement in selectivity with moderate yield (Table 2, entry 2). Interestingly, by changing the solvent to toluene both Mg(**P1**)$_2$ and Ca(**P1**)$_2$ furnished products with excellent enantioselectivity but with moderate yields (entries 4 and 5). Upon screening various conditions, it became clear that there was strong temperature dependence for this reaction. Lower yields could be attributed to decomposition of the starting hydroxylamine because of subdued kinetics in the condensation process, under lower temperatures. However, raising the temperature often afforded poorer stereoinduction. To our delight, by slowly increasing the temperature from −70°C to −50°C in toluene with **P1** as a catalyst, good yield and enantioselectivity of **6** could be attained. Having established the optimized reaction conditions, a variety of substrates **5** were synthesized. Electron-releasing groups and electron-withdrawing groups are tolerated and lead to good yields and enantioselectivities (Scheme 4; **6a**–**f**). Even an alkyl and chloro group in the α-position of the cyclohexanone gave excellent enantioselective products.

Further utility of these compounds was demonstrated by the reduction of **6a** with BH_3·THF followed by N-acetylation to yield *cis*-**7** (Scheme 5).[18] The absolute configuration for the 2-substituted cyclohexanone oxime ethers **6** was assigned by comparison with **7**, which was reported in literature.

In conclusion, we have developed an efficient catalytic asymmetric reaction for the desymmetrization of 4-phenyl cyclohexanones to novel axially chiral cyclohexylidene oxime ethers. To show the utility of this methodology, we have demonstrated the DKR[19] process of α-branched cyclohexanones to yield useful products. A computational study of the desymmetrization of a 4-substituted cyclohexanone is in excellent agreement with the obtained experimental *ee* values, and provides insight into the mode of stereoinduction.



Scheme 4. Substrate scope for the synthesis of chiral 2-substituted cyclohexanone oxime ethers.



Scheme 5. Synthesis of *N*-((1*R*,2*R*)-2-phenylcyclohexyl)acetamide.

Additional studies of the dynamic kinetic resolution of 2-substituted cyclohexanones are currently underway.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chirality · enantioelectivity · kinetic resolution · organocatalysis · oximes

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[20] CCDC 1491317 (**3b**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Communications

Organocatalysis

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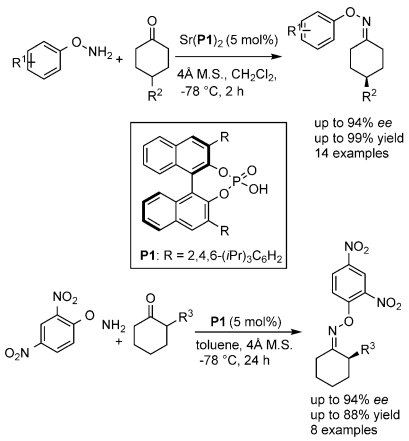
Enantioselective Synthesis of Chiral Oxime Ethers: Desymmetrization and Dynamic Kinetic Resolution of Substituted Cyclohexanones



An ax to grind: A enantioselective synthesis of axially chiral cyclohexylidene oximes has been developed by catalytic desymmetrization of 4-substituted cyclohexanones with O-arylhydroxylamines in the presence of a chiral BINOL-derived strontium phosphate. In addition, the dynamic kinetic resolution of α-substituted cyclohexanones has been performed and yields versatile intermediates in high yields and enantioselectivities. M.S. = molecular sieves.

