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Enantioconvergent Nucleophilic Substitution Reaction of Racemic Alkyne–Dicobalt Complex (Nicholas Reaction) Catalyzed by Chiral Brønsted Acid

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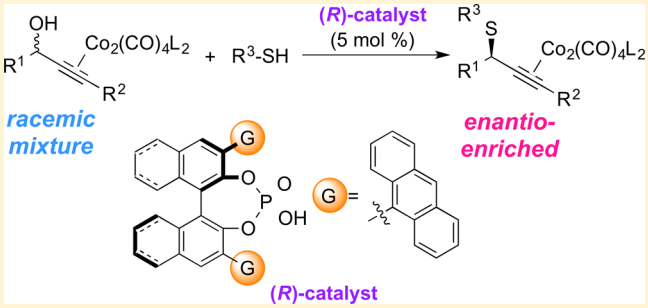
Supporting Information

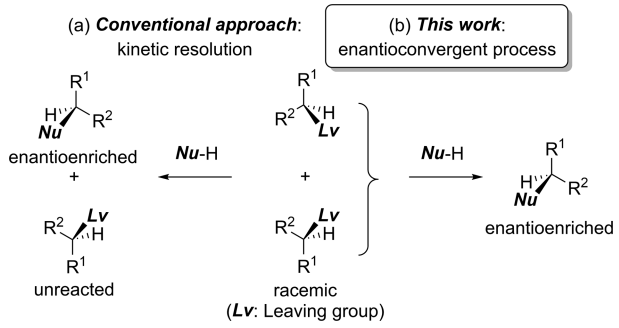
ABSTRACT: Catalytic enantioselective syntheses enable a practical approach to enantioenriched molecules. While most of these syntheses have been accomplished by reaction at the prochiral sp^2-hybridized carbon atom, little attention has been paid to enantioselective nucleophilic substitution at the sp^3-hybridized carbon atom. In particular, substitution at the chiral sp^3-hybridized carbon atom of racemic electrophiles has been rarely exploited. To establish an unprecedented enantioselective substitution reaction of racemic electrophiles, enantioconvergent Nicholas reaction of an alkyne–dicobalt complex derived from racemic propargylic alcohol was developed using a chiral phosphoric acid catalyst. In the present enantioconvergent process, both enantiomers of the racemic alcohol were transformed efficiently to a variety of thioethers with high enantioselectivity. The key to achieving success is dynamic kinetic asymmetric transformation (DYKAT) of enantiomeric cationic intermediates generated via dehydroxylation of the starting racemic alcohol under the influence of the chiral phosphoric acid catalyst. The present fascinating DYKAT involves the efficient racemization of these enantiomeric intermediates and effective resolution of these enantiomers through utilization of the chiral conjugate base of the phosphoric acid.



INTRODUCTION

During the past half century, significant progress has been made toward the asymmetric synthesis of molecules in an enantioenriched form. Effort has been devoted to the chemical synthesis of these molecules because of increasing demand for enantioenriched molecules in medicine and material science. Among the methods for asymmetric synthesis, enantioselective catalysis is one of the representatives to produce these molecules in an efficient and practical manner, most of which has been accomplished by reaction at the prochiral sp^2-hybridized carbon atom of double bonds (e.g., C=O, C=N, and C=C). Enantioselective nucleophilic addition to prochiral electrophiles such as aldehydes, ketones, imines, and electron-deficient double bonds is one of the most extensively investigated reactions, and substantial achievements have been reported using chiral metal catalysts, enzymes, and organocatalysts.[1] In contrast, despite being one of the most fundamental and powerful methods for the formation of covalent bonds, enantioselective nucleophilic substitution at the sp^3-hybridized carbon atom has received much less attention than the enantioselective nucleophilic addition reactions. In particular, substitution reaction at the chiral sp^3-hybridized carbon atom of racemic electrophiles has rarely been exploited as a catalytic enantioselective transformation, presumably because the chiral information on racemic electrophiles is transferred to the corresponding substitution product through inversion at the stereogenic center via the S_N2 pathway. Therefore, in the conventional approach, kinetic resolution of racemic electrophiles has been used to afford the substitution product in an enantioenriched form (Scheme 1a).[2] In an alternative approach to the S_N2 pathway (i.e., the S_N1 protocol), the cationic intermediate generated as an electrophile forms a contact ion pair with a leaving group that makes enantiocontrol of the substitution product difficult. To

Scheme 1. Enantioselective Substitution Reaction of a Racemic Electrophile



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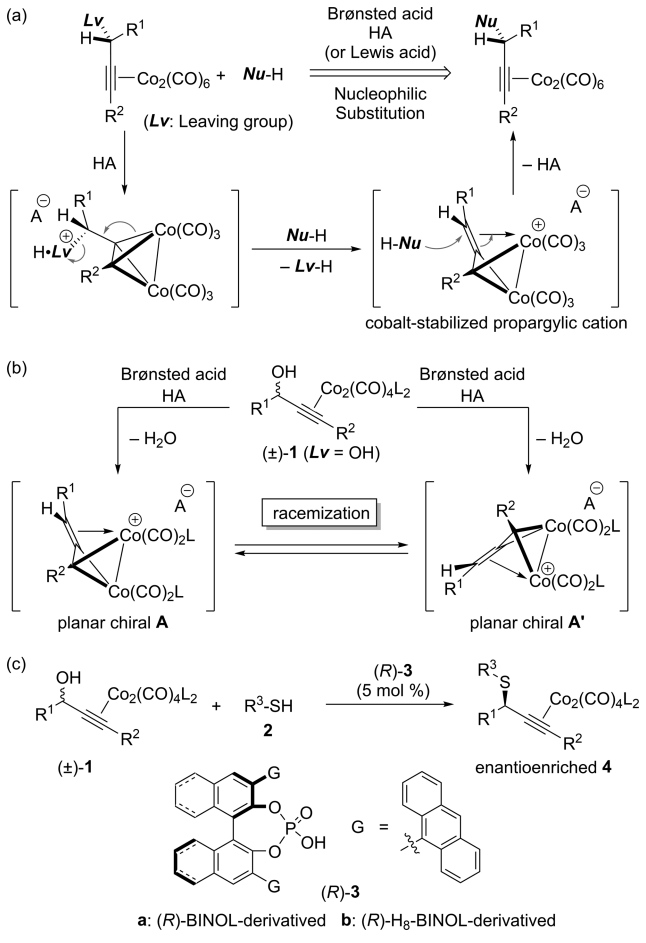
circumvent this intrinsic feature of S_N1 reactions, several specific methods for enantioselective nucleophilic substitution at the racemic stereogenic center have been reported, such as S_N1-type reactions by virtue of contriving the reaction system[3] and allylic substitution[4] as well as cross-coupling reactions[5,6] using transition metal catalysts. The challenge of governing the stereochemical outcome in enantioselective substitution reactions of racemic electrophiles provides a new frontier of enantioselective catalysis for nucleophilic substitution (Scheme 1b), in which enantioconvergence can be achieved from the racemic electrophile to the enantioenriched substitution product without recovering unreacted enantiomer of the electrophile.

Introduction of an effective racemization process to the reaction system is necessary to establish efficient enantioconvergence of the nucleophilic substitution reaction because the initial chirality of the racemic electrophile significantly affects the stereochemical outcome of the substitution product. To overcome this intrinsic problem associated with the use of the racemic electrophile, we envisioned a metal-assisted protocol for realizing efficient racemization of the electrophile and predicted that the Nicholas reaction is beneficial for this purpose (Scheme 2a). The Nicholas reaction,[7,8] in which a propargylic cation stabilized by cobalt complex is involved as a reactive intermediate, is generally promoted by a Brønsted or Lewis acid. In some cases, the Nicholas reaction using enantioenriched propargylic alcohols forms enantioenriched products in a stereoretentive manner under particular reaction conditions,[9] while in diastereofacial selective reactions of nucleophiles having an enantioenriched chiral auxiliary, racemization at the propargylic position of the racemic alcohol is found to occur during the course of the Nicholas reaction (Scheme 2b).[10]

Scheme 2. (a) Nicholas Reaction, (b) Racemization of Cobalt-Stabilized Propargylic Cation, and (c) Enantioconvergent Synthesis of Organosulfur Compounds by Nicholas Reaction Catalyzed by Chiral Phosphoric Acid



We hence postulated that fluxional aspects of the enantiomeric planar chiral intermediates **A** and **A′** result in the racemization at the propargylic position of these enantiomeric species under certain reaction conditions, although a catalytic enantioconvergent Nicholas reaction using racemic substrate **1** had never been reported.[11,12] The synthetic advantages of the Nicholas reaction include (i) high regioselectivity at the propargylic position[13] and (ii) wide scope of nucleophiles in inter- and/or intramolecular reactions. In this study, a thiol (Nu-H = RSH) was used as the nucleophile to yield organosulfur compounds, which are difficult to obtain by conventional asymmetric catalysis using chiral metal complexes because the formation of a relatively stable metal−sulfur bond, especially for transition metal species, prevents efficient turnover of the catalyst.[14] Most of the useful and bioactive organosulfur compounds are enantioenriched and widely present in drugs and relevant molecules.[15] Because of this, enantioselective carbon−sulfur (C−S) bond formation is an especially important and challenging transformation.[16] The present report describes the first enantioconvergent Nicholas reaction of thiol **2** with the dicobalt complex of racemic propargylic alcohols **1** (Lv = OH) catalyzed by chiral phosphoric acid **3** (Scheme 2c), which has recently emerged as a versatile catalyst for a variety of enantioselective transformations.[17,18] In the present enantioconvergent process, enantioenriched thioethers **4** with a broad range of substituent patterns were formed in a highly enantioselective manner. The key to achieving enantioconvergence is the ability of the chiral conjugate base of chiral phosphoric acid (*R*)-**3** to function as a stereodifferentiating agent of enantiomeric intermediates **A** and **A′** generated via dehydroxylation of the starting racemic alcohol **1** (Scheme 2b).[19] The racemization between these enantiomeric intermediates **A** and **A′** coupled with the efficient resolution of these enantiomers, namely, dynamic kinetic asymmetric transformation (DYKAT),[20] was accomplished in the present enantioconvergent substitution reaction.

RESULTS AND DISCUSSION

At the outset of our study, a typical dicobalthexacarbonyl complex of racemic propargylic alcohol with a trimethylsilyl substituent at the alkynyl terminus was used as the racemic electrophile of a substitution reaction with benzenethiol (**2a**). However, initial attempts to promote the substitution reaction with **2a** using 10 mol % of chiral phosphoric acid (*R*)-**3a** in toluene did not result in formation of the desired substitution product, even at 50 °C. We, therefore, introduced the diphosphine ligand, dppm, [1,1-bis(diphenylphosphino)-methane], instead of two carbon monoxide ligands to enhance reactivity of the dicobalt complex of propargylic alcohol **1**.[21] Thus, **1a** complexed with dppm was exposed to **2a** in the presence of (*R*)-**3a** (10 mol %) and 4 Å molecular sieves (used to scavenge the water generated) in toluene at room temperature for 24 h. As expected, the desired substitution product **4a** was obtained in an acceptable yield with fairly good enantioselectivity (Table 1, entry 1). This promising result

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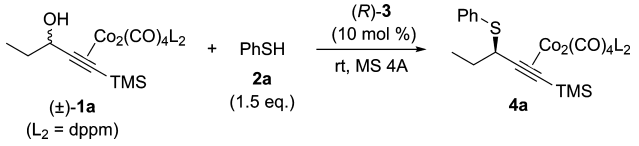
Table 1. Optimization of Reaction Conditions[a]



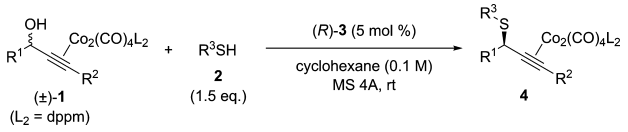
entry	CPA	solvent	time	yield (%)[b]	ee (%)[c,d]
1	(*R*)-**3a**	toluene (0.1 M)	24 h	64	87
2	(*R*)-**3a**	MeCN (0.1 M)	24 h	5	<5
3	(*R*)-**3a**	AcOEt (0.1 M)	24 h	9	<5
4	(*R*)-**3a**	CH_2Cl_2 (0.1 M)	24 h	44	10
5	(*R*)-**3a**	*c*-hexane (0.1 M)	2 h	91	92
6	(*R*)-**3a**	*c*-hexane (0.02 M)	12 h	95	93
7	(*R*)-**3a**[e]	*c*-hexane (0.1 M)	4 h	94	92
8	(*R*)-**3a**[f]	*c*-hexane (0.1 M)	24 h	83	91
9	(*R*)-**3b**[e]	*c*-hexane (0.1 M)	4 h	95	92

[a]Unless otherwise noted, all reactions were performed using 0.10 mmol of **1a**, 0.15 mmol of **2a**, and 0.010 mmol of catalyst (*R*)-**3** (10 mol %) in the indicated solvent (0.1 M) at room temperature. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral stationary phase HPLC analysis. [d]Enantiomeric excess of **4a** was determined after desilylation of **4a** to terminal alkyne derivative. [e]5 mol %. [f]2.5 mol %.

prompted further investigation of the effect of solvent because the Nicholas reaction involves a cationic intermediate that should be responsible for the racemization. The chemical yield and the enantioselectivity were markedly dependent on the solvent used (entries 1−5). Despite stabilization of the cationic intermediate by polar solvents, such as acetonitrile and ethyl acetate, these polar solvents considerably prevented the substitution reaction (entries 2 and 3). More importantly, product **4a** was formed in nearly racemic mixtures. The use of methylene chloride resulted in moderate conversion with low enantioselectivity (entry 4), even though methylene chloride is one of the most common solvents in chiral phosphoric acid-catalyzed reactions.[18] In contrast, the less polar solvent cyclohexane significantly accelerated the reaction, giving rise to the substitution product **4a** in good yield with high enantioselectivity (92% ee) within 2 h (entry 5).[22] Further investigation of reaction conditions by changing the concentration and catalyst loading was conducted (entries 6−8). The enantioselectivity of **4a** slightly increased as the concentration decreased. Catalyst loading could be reduced to 2.5 mol % without a significant decrease in enantioselectivity but required prolonged reaction time and a slight decrease in yield (entry 8). The H_8-BINOL-derived chiral phosphoric acid (*R*)-**3b** also facilitated the reaction to afford **4a** with the same enantioselectivity (entry 9 vs entry 7). Single-crystal X-ray diffraction analysis revealed that the absolute stereochemistry of the major enantiomer of **4a** was the *R*-configuration.[23] Thus, chiral phosphoric acid (*R*)-**3** gave (*R*)-**4a**.

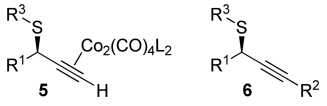
Optimized reaction conditions using chiral phosphoric acid (*R*)-**3a** or (*R*)-**3b** were applied to a broad range of racemic propargyl alcohol dicobalt complexes **1** and a variety of thiols **2**. In most cases, the thioether product **4** was obtained in high yield and enantioselectivity (Table 2). When a trimethylsilyl group was introduced to the alkynyl terminus (entries 1−5), aromatic and aliphatic substituents were tolerated at the propargylic position, yielding thioether **4** in good to excellent enantioselectivity. The substituent effect of the alkynyl terminus was also investigated, and the results showed that bulky *tert*-

Table 2. Substrate Scope[a]



entry	(*R*)-**3**	**4**	R^1	R^2	R^3	time	yield (%)[b]	ee (%)[c,d]
1	**3a**	**4b**	Me	TMS	Ph	2 h	97	85
2	**3b**	**4c**	*n*-pent	TMS	Ph	4 h	>98	84[d]
3	**3b**[e]	**4d**	*i*-Bu	TMS	Ph	40 h	86	96[d]
4	**3b**[e]	**4e**	*i*-Pr	TMS	Ph	48 h	60	97
5	**3b**	**4f**	Ph	TMS	Ph	2 h	>98	84
6	**3b**	**4g**	Me	TBS	Ph	4 h	98	88
7	**3b**	**4h**	Et	*n*-Bu	Ph	6 h	97	87
8	**3b**	**4i**	Et	*c*-hex	Ph	3 h	98	89
9[f]	**3b**	**4j**	Et	Ph	Ph	24 h	92	90[g]
10[f]	**3a**	**4k**	Me	Ph	Ph	24 h	94	73[g]
11	**3a**	**4l**	Et	TMS	4-BrC_6H_4	4 h	97	92[d]
12	**3a**	**4m**	Et	TMS	4-$MeOC_6H_4$	4 h	98	92[d]
13	**3b**[e]	**4n**	Et	TMS	2-BrC_6H_4	6 h	98	87[d]
14	**3b**[e]	**4o**	Et	TMS	2-$MeOC_6H_4$	6 h	94	92[d]
15	**3a**[e]	**4p**	Et	TMS	*n*-C_8H_{17}	8 h	97	84[d]
16	**3b**	**4q**	Ph	TMS	*n*-C_8H_{17}	6 h	>98	84

[a]Reactions were conducted on 0.1 mmol scale. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral stationary phase HPLC. [d]Enantiomeric excess of **4** was determined after desilylation of **4** to **5** (R^2 = H). [e]10 mol %. [f]0.02 M. [g]Enantiomeric excess was determined after removal of cobalt complex from **4** to derivatize propargyl thioether **6**.



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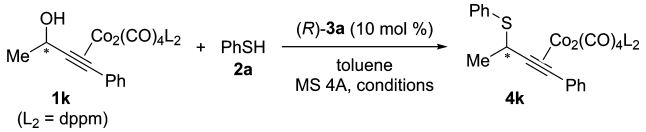
butyldimethylsilyl, aliphatic, and aromatic substituents could be used in the present reaction, affording **4** in high yield with good enantioselectivity (entries 6–9), although the substrate having R^1 = methyl and R^2 = phenyl substituents exhibited a slight reduction in enantioselectivity (entry 10). Further investigation of the thiol substituent demonstrated that a variety of thiols **2** underwent reaction to produce the corresponding products in excellent yield, regardless of the steric bulkiness and acidity of the thiols, including aliphatic thiol (entries 11–16), although a slight reduction in enantioselectivity resulted from reaction of aliphatic thiol (entries 15 and 16).

MECHANISTIC STUDIES

During the course of these studies, anomalous temperature and concentration effects were observed in the enantioconvergent process, particularly when using **1k** as the substrate (R^1 = methyl, R^2 = phenyl) in toluene (Table 3). For entries 1–3, a higher temperature resulted in better enantioselectivity, even though product enantioselectivity increased as reaction temperature decreased for a typical catalytic enantioselective reaction. Furthermore, a lower concentration resulted in better enantioselectivity (entry 4 vs entry 2). In general, enantioselectivity is independent of concentration in a typical enantioselective reaction. These findings prompted investigation of the mechanism behind these intriguing phenomena. We thus conducted the reaction using enantiomerically enriched alcohol **1k** to acquire mechanistic insights into the enantioconvergent reaction. The Nicholas reaction partially involves retention of the chirality at the propargylic position under particular reaction conditions.[9] If reaction of (*R*)-**1k** proceeds in accordance with the retentive manner at the propargylic position, (*R*)-**4k** should be formed. When this stereochemical relation between reactant and product is taken into consideration, (*R*)-**1k** can be expected to be favorable in the present reaction because of the formation of the *R*-product as the major enantiomer under the influence of chiral phosphoric acid (*R*)-**3**. In fact, (*R*)-**1k** was consumed much faster than (±)-**1k** and underwent reaction with enantioselectivity higher than that of (±)-**1k** (entry 5 vs entry 2). In contrast, reaction of (*S*)-**1k** proceeded sluggishly to yield the inversion product (*R*)-**4k** with enantioselectivity much lower than that of (±)- and (*R*)-**1k** (entry 6 vs entries 2 and 5). In the reaction of (*S*)-**1k**, the racemization is apparently indispensable to afford the inversion product (*R*)-**4k**.[24]

To rationalize the anomalous temperature and concentration effects observed (Table 3, entries 1–4), we performed additional reactions using (*S*)-**1k** under different temperatures, concentrations, and equivalents of thiol **2a** (entries 7–9). These parameters significantly affect the stereochemical outcome because of the involvement of the racemization process. Reducing the reaction temperature markedly decreased the enantioselectivity (entry 7 vs entry 6). Reducing the concentration from 0.1 to 0.02 M dramatically enhanced the enantioselectivity (entry 8 vs entry 6), while an increase in equivalents of thiol **2a** led to the formation of the opposite enantiomer (*S*)-**4k** as the major isomer (entry 9). These results clearly indicate that the stereochemical outcomes from the reactions of (*S*)-**1k** are markedly influential in the anomalous temperature and concentration effects observed in the reaction of (±)-**1k**. A plausible mechanism of the present enantioconvergent process is illustrated in Scheme 3. The relative rate between racemization of the cationic intermediates and the nucleophilic addition to these intermediates is the key to achieving efficient enantioconvergence. At lower concentrations, nucleophilic addition is suppressed because of intermolecular processes; therefore, the racemization process (an intramolecular process) predominates over nucleophilic addition in which the chiral information on the unfavorable (*S*)-**1k** disappears efficiently. In this regard, an increase in equivalents of thiol **2a** accelerated the nucleophilic addition, and hence, most of the chiral information on (*S*)-**1k** remained retentive to afford (*S*)-**4k** as the major enantiomer. At higher temperatures, the experimental results strongly suggest that the racemization process is markedly accelerated over nucleophilic addition. To accomplish efficient enantioconvergence, selective reaction of thiol **2a** with one of the enantiomeric cationic intermediates occurs under the influence of the chiral conjugate base of (*R*)-**3a** to afford the corresponding C–S bond formation product (*R*)-**4k**. The other enantiomer is subjected to racemization, followed by thiol addition through the same resolution pathway, and the overall process enables the enantioconvergent Nicholas reaction in a highly stereoselective manner.

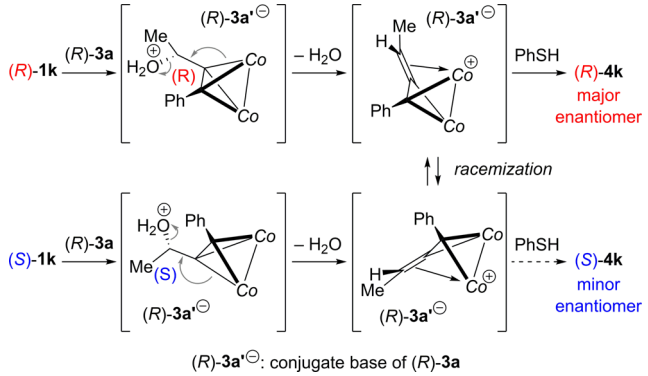
Table 3. Temperature and Concentration Effects[a]



entry	1k	equiv of 2a	conc (M)	conditions	yield (%)[b]	ee (%)[c]
1	(±)-1k	1.5	0.1	0 °C, 24 h	78	57 (*R*)
2	(±)-1k	1.5	0.1	rt, 4 h	97	68 (*R*)
3	(±)-1k	1.5	0.1	50 °C, 1 h	91	74 (*R*)
4	(±)-1k	1.5	0.02	rt, 6 h	95	78 (*R*)
5	(*R*)-1k[d]	1.5	0.1	rt, 1 h	>99	82 (*R*)
6	(*S*)-1k[e]	1.5	0.1	rt, 6 h	>99	34 (*R*)
7	(*S*)-1k[e]	1.5	0.1	0 °C, 48 h	98	3 (*R*)
8	(*S*)-1k[e]	1.5	0.02	rt, 24 h	94	69 (*R*)
9	(*S*)-1k[e]	6.0	0.1	0 °C, 48 h	92	44 (*S*)

[a]Unless otherwise noted, all reactions were conducted using 0.05 mmol **1k**, indicated amount of **2a**, and 0.005 mmol catalyst (*R*)-**3a** (10 mol %) in toluene. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral stationary phase HPLC after removal of cobalt complex from **4k** to derivatize propargyl thioether **6k**. [d]With 97% ee (*R*)-**1k**. [e]With 96% ee (*S*)-**1k**.

Scheme 3. Plausible Mechanism of the Enantioconvergent Nicholas Reaction



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CONCLUSIONS

We have demonstrated the enantioconvergent Nicholas reaction of an alkyne−dicobalt complex derived from racemic propargylic alcohols with thiol catalyzed by a chiral phosphoric acid. The method provides a novel strategy for enantioselective C−S bond formation through an enantioconvergent process of the nucleophilic substitution reaction using racemic alcohols, in which enantioenriched thioethers with a wide range of substituents can be synthesized in a highly enantioselective manner. This enantioconvergent process, namely, DYKAT, is accomplished by efficient racemization of a pair of enantiomeric cationic intermediates as well as by effective resolution of these enantiomeric intermediates through the chiral conjugate base of the phosphoric acid. Further studies on the application of enantioconvergent substitution reactions of racemic substrates are in progress with the aim of developing even more efficient enantioselective transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05948.

Exploratory investigation, experimental procedures, and characterization data (PDF)

X-ray data for $C_{42}H_{42}Co_2O_4P_3SSi$ (CIF)

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Notes

The authors declare no competing financial interest.

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(23) CCDC No. 1459022 [(*R*)-**4a**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. Absolute configurations of other products were assigned by analogy. See the Supporting Information for details.

(24) During the course of the reaction of (*S*)-**1k** with **2a**, the enantiomeric purity of (*S*)-**1k** was maintained at a high level (≥96% ee), and hence, racemization of (*S*)-**1k** did not take place primarily under the standard reaction conditions (Table 3, entry 6).

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