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Enantioselective Silicon-Directed Nazarov Cyclization

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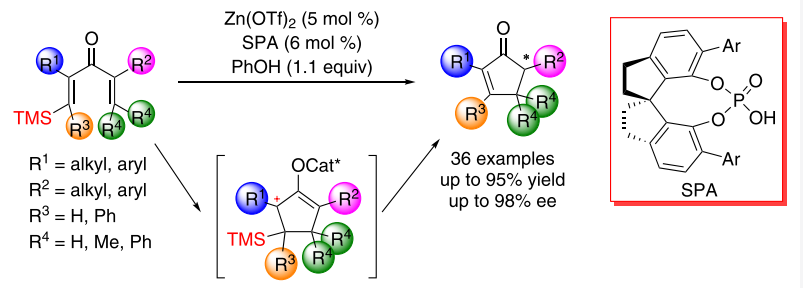

ABSTRACT: The Nazarov electrocyclization reaction is a convenient, widely used method for construction of cyclopentenones. In the past few decades, catalytic asymmetric versions of the reaction have been extensively studied, but the strategies used to control the position of the double bond limit the substituent pattern of the products and thus the synthetic applications of the reaction. Herein, we report highly enantioselective silicon-directed Nazarov reactions which were cooperatively catalyzed by a Lewis acid and a chiral Brønsted acid. The chiral cyclopentenones we synthesized using this method generally cannot be obtained by means of other catalytic enantioselective reactions, including previously reported methods for enantioselective Nazarov cyclization. The silicon group in the dienone substrate stabilized the β-carbocation of the intermediate, thereby determining the position of the double bond in the product. Mechanistic studies suggested that the combination of Lewis and Brønsted acids synergistically activated the dienone substrate and that the enantioselectivity of the reaction originated from a chiral Brønsted acid promoted proton transfer reaction of the enol intermediate.

INTRODUCTION

Chiral cyclopentenones are key intermediates in asymmetric synthesis and present in many natural products and pharmaceuticals as core structures.[1−8] Nazarov cyclization, a classic 4π electrocyclization reaction, is considered as a powerful tool that offers easy access to multifunctionalized cyclopentenones in one step.[9−12] In recent decades, extensive work on catalytic asymmetric versions of the Nazarov cyclization have resulted in important progress. However, the cyclization proceeds via a carbocation intermediate, which can rearrange readily; thus, if the substrate molecule has multiple β-hydrogens for elimination, the reaction produces many different cyclization products with double bonds in various positions. A number of strategies have been developed to control the position of the double bond. For example, a cyclic olefin moiety can be introduced into the dienone substrate to increase the stability of one of the possible carbocations and thus determine the location of the double bond in the resulting bicyclic product (Scheme 1a).[13−17] Alternatively, introduction of an electron-donating group to one of the double bonds of the dienone and an electron-withdrawing group to the other results in generation of a carbocation on the side bearing the electron-donating group and thus determines the position of the double bond in the product (Scheme 1b).[18−30] Although the above-mentioned strategies have met with great success, the requirements imposed on the substitution pattern of the substrate limit the diversity of the products that can be obtained. For example, neither strategy permits enantioselective synthesis of any α,α'-disubstituted cyclopentenones (Scheme 1c), including α-alkyl-α'-aryl cyclopentenones (**CPK1**), α,α'-dialkyl or α,α'-diaryl cyclopentenones (**CPK2**, **CPK3**), or α-alkenyl or α-alkynyl cyclopentenones (**CPK4**, **CPK5**). Therefore, accurate control of both the regio- and stereoselectivity of Nazarov reaction to synthesize multifunctionalized cyclopentenones with high generality is a highly desired but challenging task.[31−36]

In 1982, Denmark and Jones[37] reported a method for silicon-directed Nazarov cyclization, and considerable research on this method has been conducted since then.[38−43] In this method, a silicon group installed on the dienone substrate stabilizes the carbocation intermediate by means of the β-silicon effect and thus acts as a directing group. Subsequent

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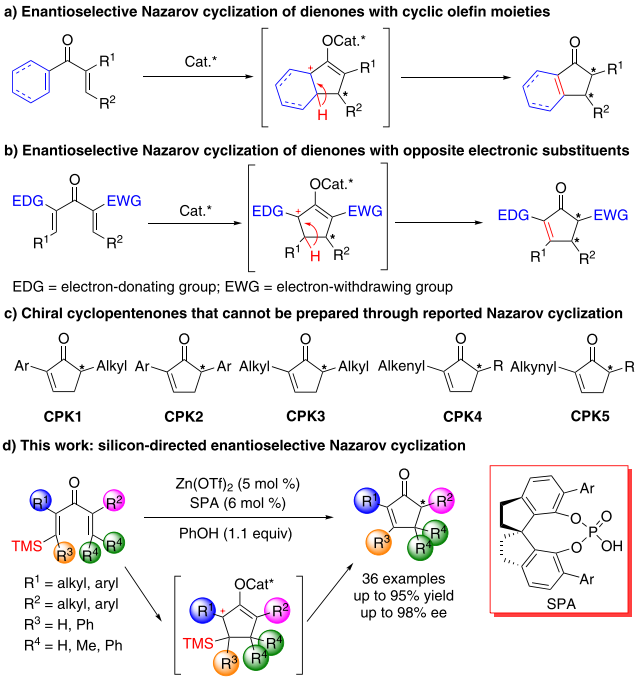
Scheme 1. Regioselectivity-Control Strategies in Enantioselective Nazarov Cyclization

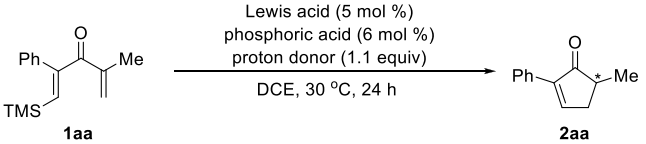


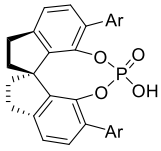
elimination of the silicon group forms the double bond exclusively at the desired position. This traceless silicon-directing strategy minimizes the restrictions on the substrate substituents and thus provides an effective method for synthesizing a diverse array of cyclopentenones. Further work revealed that Sn and F can also be used as directing groups in Nazarov cyclizations.[44,45] However, silicon-directed Nazarov cyclizations generally require the use of stoichiometric or substoichiometric amounts of strong Lewis or Brønsted acids as promoters, and an enantioselective version of this reaction has not been developed. Herein, we report a highly enantioselective silicon-directed Nazarov cyclization reaction, which we achieved by using a synergistic catalyst system consisting of an achiral Lewis acid and a chiral Brønsted acid (Scheme 1d). This system significantly increased the reaction rate and allowed us to effectively control its enantioselectivity. Using our newly developed protocol, we prepared chiral cyclopentenones with unprecedented structural diversity in good yields with high enantioselectivities, which have never been accessed by means of other catalytic enantioselective reactions, including previously reported enantioselective Nazarov cyclization reactions.

RESULTS AND DISCUSSION

We began by evaluating chiral spiro phosphoric acids (SPAs) **3** (6 mol %) as Brønsted acids[46−48] in Nazarov cyclization reactions of **1aa** in 1,2-dichloroethane (DCE) at 30 °C with $Zn(OTf)_2$ (5 mol %) as the Lewis acid catalyst and phenol (1.1 equiv) as the proton source (Table 1, entries 1−7). In all cases, the regioselectivity of the reaction was completely controlled, with the double bond attached to the silicon group being retained to afford product **2aa**. The 6,6′-diaryl moieties of the chiral SPA markedly affected the enantioselectivity of the reaction. Sterically bulky aryl-substituted ligand (*R*)-**3d** gave the highest enantioselectivity (94% ee) and a high yield (entry 4). The Lewis acid had a substantial effect on both the yield

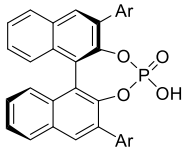
Table 1. Catalytic Asymmetric Silicon-Directed Nazarov Cyclization: Optimization of Reaction Conditions[a]





SPA

3a Ar = Ph
3b Ar = 3,5-(^{t}Bu)$_2$C$_6$H$_3$
3c Ar = 2,4,6-(Me)$_3$C$_6$H$_2$
3d Ar = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
3e Ar = 1-pyrenyl
3f Ar = 10-Ph-9-anthracenyl



4, Ar = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$

entry	Lewis acid	phosphoric acid	proton donor (pK_a)[b]	yield[c] (%)	ee (%)
1	$Zn(OTf)_2$	(*R*)-**3a**	PhOH (18.0)	74	−11
2	$Zn(OTf)_2$	(*R*)-**3b**	PhOH (18.0)	84	1
3	$Zn(OTf)_2$	(*R*)-**3c**	PhOH (18.0)	77	48
4	$Zn(OTf)_2$	(*R*)-**3d**	PhOH (18.0)	87	94
5	$Zn(OTf)_2$	(*S*)-**3e**	PhOH (18.0)	89	−78
6[d]	$Zn(OTf)_2$	(*R*)-**3f**	PhOH (18.0)	64	−52
7[d]	$Zn(OTf)_2$	(*R*)-**4**	PhOH (18.0)	81	26
8[e]	$FeCl_3$	(*R*)-**3d**	PhOH (18.0)	89	45
9[e]	$AuCl_3$	(*R*)-**3d**	PhOH (18.0)	93	36
10[e]	$Sm(OTf)_3$	(*R*)-**3d**	PhOH (18.0)	88	91
11	$ZnCl_2$	(*R*)-**3d**	PhOH (18.0)	89	90
12	$MnCl_2$	(*R*)-**3d**	PhOH (18.0)	<5	NA
13[e]	$Zn(OTf)_2$	(*R*)-**3d**	$PhCO_2H$ (10.6)	90	73
14[e]	$Zn(OTf)_2$	(*R*)-**3d**	CH_3CO_2H (12.6)	92	68
15	$Zn(OTf)_2$	(*R*)-**3d**	$CH_3SO_2NH_2$ (17.5)	74	93
16[e]	$Zn(OTf)_2$	(*R*)-**3d**	CF_3CH_2OH (23.5)	93	89
17	$Zn(OTf)_2$	(*R*)-**3d**	H_2O (31.4)	50	72
18[f]	$Zn(OTf)_2$	(*R*)-**3d**	PhOH (18.0)	92	93
19	$Zn(OTf)_2$	none	PhOH (18.0)	28	NA
20	none	(*S*)-**3d**	PhOH (18.0)	0	NA
21	$Zn(OTf)_2$	(*S*)-**3d**-Na	PhOH (18.0)	<5	NA

[a]Reaction conditions: Lewis acid/phosphoric acid/**1aa**/proton donor = 0.01:0.012:0.2:0.22 (mmol), in 3 mL of DCE at 30 °C, 24 h. NA = not analyzed. [b]pK_a value in DMSO.[49] [c]Isolated yield. [d]Reaction time: 20 h. [e]Reaction time: 12 h. [f]Performed at 40 °C, 12 h.

and the enantioselectivity (entries 8−12); the weak Lewis acid $MnCl_2$ failed to promote the reaction (entry 12). There was a clear correlation between the pK_a of the proton source and the reaction outcome (entries 13−17). Specifically, H_2O, which is a weak acid, decreased both the yield and the enantioselectivity (entry 17). Carboxylic acids, which are more acidic than phenol, substantially accelerated the reaction but decreased the enantioselectivity (entries 13 and 14). Trifluoroethanol and methanesulfonamide, which have acidities close to that of phenol, gave ee values similar to those obtained with phenol (entries 15 and 16). Evaluation of a variety of solvents (Table S1) revealed that the reaction exhibited higher yields in chlorinated solvents than in other types of solvents. Solvents with low polarity (e.g., toluene and *n*-hexane) greatly reduced the yield and the enantioselectivity. In highly polar solvents and in coordinative solvents, the reaction was completely suppressed. Increasing the temperature to 40 °C markedly increased the reaction rate but had little effect on the ee (entry

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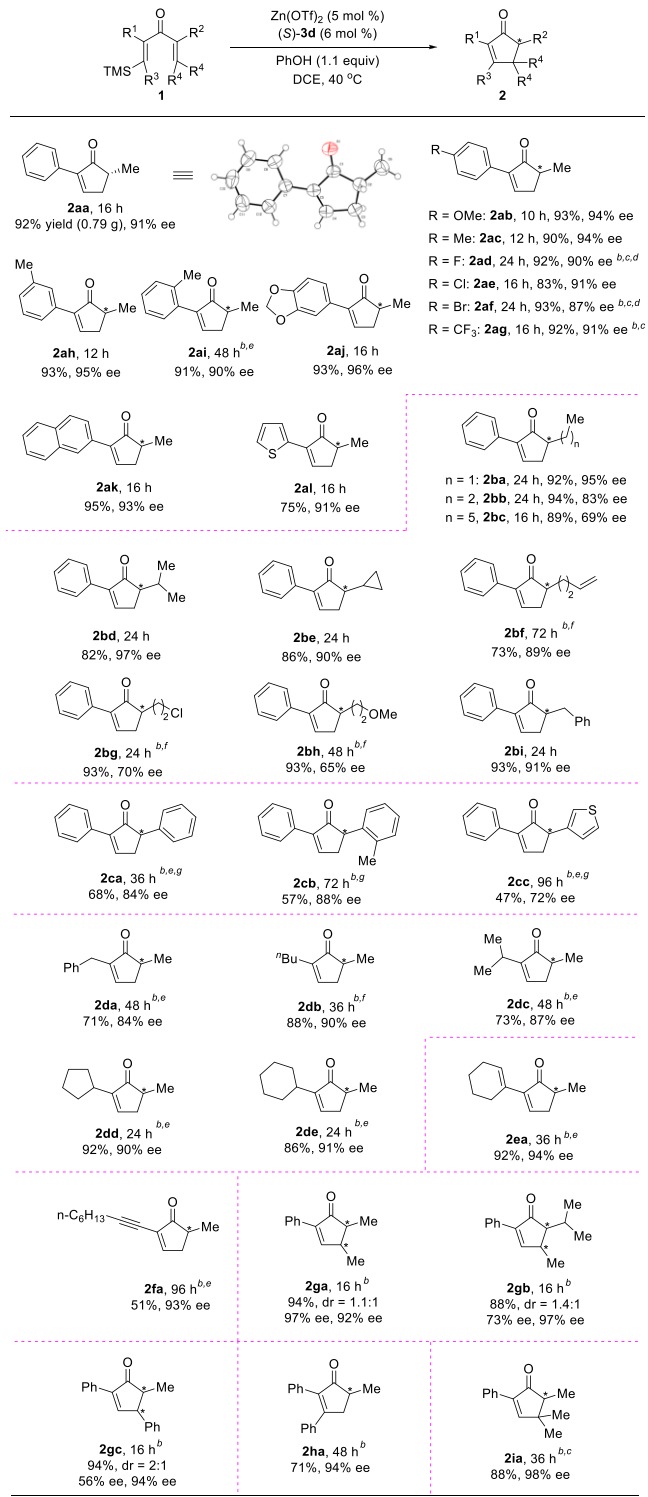
18). Therefore, we carried out all subsequent reactions at 40 °C.

Control experiments were performed to elucidate the roles of $Zn(OTf)_2$ and the SPA. In the absence of (*R*)-**3d**, $Zn(OTf)_2$ independently catalyzed the cyclization (entry 19), but the yield was much lower than when both catalysts were used (entry 18). This result indicates that the SPA has a significant acceleration effect on the reaction. No reaction occurred in the presence of the SPA alone at 40 °C (entry 20). When we used the sodium salt of the SPA, (*S*)-**3d**-Na, only trace **2aa** was detected (entry 21). This result may be interpreted as the formation of zinc(II) phosphate (*S*)-**3d**-Zn, which cannot activate the **1aa** due to the large steric hindrance or low Lewis acidity.

Under the optimal conditions, Nazarov cyclization reactions of various substituted *β*-silyl dienones **1** were evaluated (Table 2). When R^1 was a phenyl or substituted phenyl group, the corresponding products (**2aa**–**2ai**) were obtained in good yields (83–93%) with high enantioselectivities (87–95% ee). Substrates with electron-withdrawing groups were less reactive than other substrates and required a stronger Lewis acid, a higher temperature, and a larger amount of phenol to get satisfactory yields of the corresponding products (**2ad**, **2af**, **2ag**). A gram-scale reaction of **1aa** afforded **2aa** with no decrease in yield or ee value. X-ray single-crystal diffraction analysis confirmed that the absolute configuration of **2aa** was (*R*).[50] Substrates with a fused ring (**2aj**), a condensed ring (**2ak**), or a heteroaromatic ring (**2al**) at R^1 also gave good results. When R^1 was phenyl and R^2 was systematically varied, we found that R^2 could be a linear alkyl group (**2ba**–**2bc**), a branched alkyl group (**2bd** and **2be**), a functionalized alkyl group (**2bf**–**2bh**), or a benzyl group (**2bi**); all these reactions proceeded smoothly, giving satisfactory yields (73–94%) and enantioselectivities (65–97% ee). Increasing the length of the alkyl group adversely affected the enantioselectivity (**2ba**, **2bb**, **2bc**). When R^2 was isopropyl, **2bd** was obtained with 97% ee. When both R^1 and R^2 were aryl groups (**2ca**–**2cc**), good results were obtained, even when the two *α*-substituents were identical (**2ca**). Both R^1 and R^2 could also be alkyl groups. In addition, we investigated substrates with a methyl group as R^2 and a linear alkyl group (**2da** and **2db**), a branched alkyl group (**2dc**), or a cyclic alkyl group (**2dd** and **2de**) as R^1; by reducing the reaction temperature and increasing the amount of phenol, we could obtain the corresponding products with good yields (71–92%) and enantioselectivities (84–91% ee). The R^1 substituent could even be an alkenyl or alkynyl group; reactions of these substrates gave the corresponding functionalized chiral cyclopentenones (**2ea** and **2fa**) in satisfactory yields and enantioselectivities. Finally, we also investigated highly substituted dienones. The reactions of dienones with substituents other than H at R^3 and R^4 (**2ga**–**2gc**, **2ha**, and **2ia**) showed high yields and enantioselectivities but required 3 equiv of phenol or a stronger Lewis acid catalyst, $Sm(OTf)_3$. When one of the R^4 was a methyl group (**2ga**), the reaction gave a mixture of diastereomers (dr = 1.1:1), indicating that the stereochemistry at the *β*-position was not controlled well under the tested conditions. Increasing the difference between R^2 and R^4 (**2gb** and **2gc**) exhibited a minor impact on yield, ee, and dr.

Chiral cyclopentenone units are present in a wide variety of bioactive molecules and are versatile synthons as well.[1−8] To demonstrate the potential utility of the protocol reported herein, we also performed several transformations of cyclopentenone **2aa** (Scheme 2). First, we used it as a Michael acceptor in a Mukaiyama–Michael addition reaction to generate stable enol silyl ether **5**, which has two chiral centers;

Table 2. Catalytic Asymmetric Silicon-Directed Nazarov Cyclization: Substrate Scope[a]



[a]Reaction conditions: $Zn(OTf)_2$/(*S*)-**3d**/**1aa**/PhOH = 0.01:0.012:0.2:0.22 (mmol), in 3 mL of DCE at 40 °C. [b]PhOH (3.0 equiv). [c]$Sm(OTf)_3$ instead of $Zn(OTf)_2$ was used as Lewis acid catalyst. [d]Performed at 50 °C. [e]Performed at 15 °C. [f]Performed at 0 °C. [g](*R*)-**3f** instead of (*S*)-**3d** was used as Brønsted acid catalyst.

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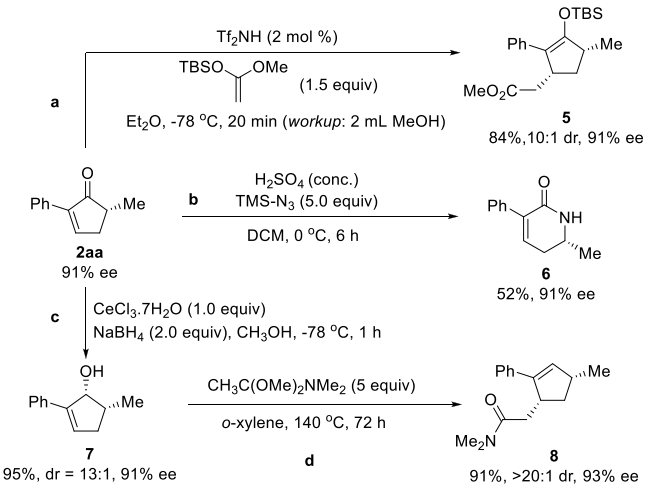
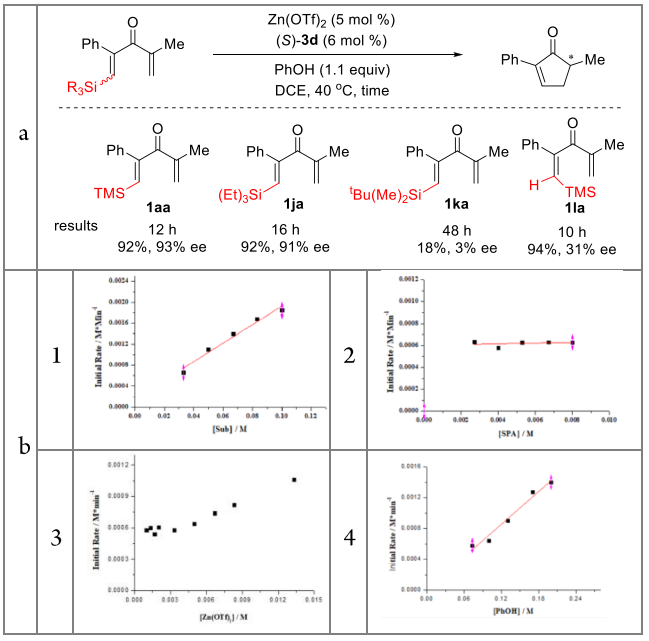
Scheme 2. Transformations of Nazarov Cyclization Product



the dr was high, and there was no loss in ee. We also converted **2aa** to δ-lactam **6** by means of a Schmidt reaction with no decrease in ee. Moreover, **2aa** could be reduced to allyl alcohol **7** with a high dr, and an Eschenmoser−Claisen rearrangement of **7** afforded a product with two chiral centers (**8**).

To elucidate the reaction mechanism, we investigated the effect of varying the silicon group on the substrate (Scheme 3a). Increasing the size of the silyl substituents markedly reduced the yield and the enantioselectivity. The configuration of the silyl-substituted double bond also strongly affected the enantioselectivity (comparing the results of **1aa** and **1la**,

Scheme 3. Control Experiments for Understanding the Mechanism

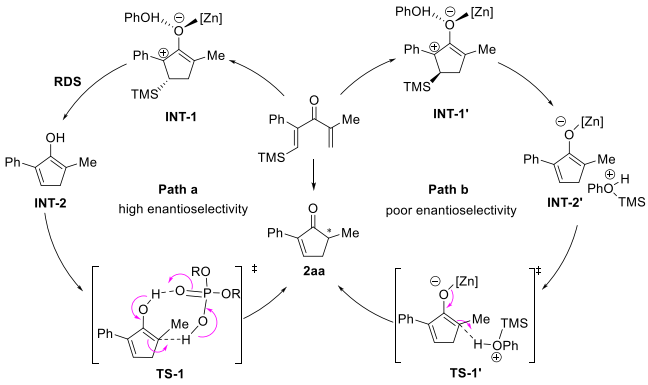


[a]Silicon effect on the Nazarov cyclization. [b]Kinetic studies through in situ IR technique: (1) Kinetic profiles of different initial concentrations of **1aa** (from 0.033 to 0.1 M). (2) Kinetic profiles of different initial concentrations of (*S*)-**3d** (from 0.0027 to 0.008 M). (3) Kinetic profiles of different initial concentrations of $Zn(OTf)_2$ (from 0.001 to 0.013 M). (4) Kinetic profiles of different initial concentrations of PhOH (from 0.073 to 0.2 M).

Scheme 3a). We studied the kinetics of the reaction by varying the concentrations of the reactants and observing the initial rate of the reaction by means of in situ IR spectroscopy (Scheme 3b). The reaction was first order with respect to both the substrate and the phenol. In contrast, the reaction was zero order with respect to chiral SPA **3d**. At low $Zn(OTf)_2$ concentrations, the reaction appeared to be zero order with respect to this component, but the reaction clearly accelerated as the $Zn(OTf)_2$ concentration was increased. We deduced that the mechanism of the reaction likely depended on the $Zn(OTf)_2$/**3d** ratio. When the $Zn(OTf)_2$ concentration was less than the **3d** concentration, the substrate and phenol participated in the rate-determining step ($r = k$[**1aa**][PhOH]), whereas when the $Zn(OTf)_2$ concentration was greater than the **3d** concentration, the substrate, phenol, and $Zn(OTf)_2$ were involved in the rate-determining step ($r = k$[**1aa**][$Zn(OTf)_2$][PhOH]).

On the basis of the above-described results, we propose the reaction mechanism shown in Scheme 4. First, the substrate is

Scheme 4. Proposed Mechanism



activated by $Zn(OTf)_2$ and PhOH to undergo a 4π electrocyclization reaction to afford carbocationic enol intermediate **INT-1**. The trimethylsilyl group has two possible configurations toward coordinated phenol as shown in **INT-1** and **INT-1′**, respectively. In the *cis*-configuration (**INT-1**), an intramolecular attack of coordinated phenol to the silyl group might happen to release a free enol intermediate **INT-2**. Finally, protonation of **INT-2** by SPA generates the target product. Throughout the catalytic cycle, the carbocation remains localized at the β-position relative to the silyl group owing to the unique electronic properties of the silicon atom; this is the fundamental reason for the highly controllable regioselectivity. The proton transfer step that generates target product from **INT-2** is the enantioselectivity-determining step. In this step, the chiral SPA acts as a chiral proton shuttle,[51−58] promoting transfer of the phenol proton to the enol via a hydrogen-bonding network and thus controlling the stereochemistry (**TS-1**). According to the above kinetic studies, the elimination of the silicon group is likely to be the rate-determining step of the reaction, and both $Zn(OTf)_2$ and phenol participate in this step. When the SPA concentration exceeds that of $Zn(OTf)_2$, the SPA may promote the dissociation of $Zn(OTf)_2$ from **INT-1** through complexation, resulting in the observed zero-order kinetics with respect to $Zn(OTf)_2$ at low concentrations. Although SPA does not directly promote in the rate-limiting step, it may accelerate the overall reaction rate through significant lowering of the energy

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barrier of the proton transfer of enol intermediate as previously reported.[58] However, when the silyl group is *trans* toward the coordinated phenol as shown in **INT-1′**, the elimination of the silyl group most likely assists with another phenol and thus generates a zinc enolate and an oxonium of phenol. Because the oxonium of phenol has a high acidity proton, it may directly protonate the zinc enolate without the assistance of SPA (**TS-1′**) and thus result in low enantioselectivity. Since different silyl groups as well as their initial configurations may lead to different ratios of **INT-1** to **INT-1′**, the two possible pathways may explain the significant silyl effect on enantioselectivity of this reaction. Because of the high complexity of the mechanism,[59] more studies are needed for deep understanding of this reaction.

CONCLUSION

In summary, we have realized the first highly enantioselective silicon-directed Nazarov reaction by using a combination of Lewis and Brønsted acid catalysts. Using this mild reaction, we efficiently synthesized chiral cyclopentenones with unprecedented structural diversity and high regio- and stereoselectivity. Preliminary mechanistic studies showed that the chiral Brønsted acid promotes a proton transfer reaction of the enol intermediate via a hydrogen-bonding network to achieve asymmetric induction. Detailed mechanistic studies and investigation of synthetic applications of this reaction are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01194.

Experimental procedures, spectral data, and computational study results (PDF)

Accession Codes

CCDC 1986102 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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