Published in final edited form as:

Adv Synth Catal. 2020 October 6; 362(19): 4092–4097. doi:10.1002/adsc.202000831.

Asymmetric Nazarov Cyclizations of Unactivated Dienones by Hydrogen-Bond-Donor/Lewis Acid Co-Catalyzed, Enantioselective Proton-Transfer

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Abstract

We report an enantioselective Nazarov cyclization catalyzed by chiral hydrogen-bond-donors in concert with silyl Lewis acids. The developed transformation provides access to tri-substituted cyclopentenones in high levels of enantioselectivity (up to 95% e.e.) from a variety of simple unactivated dienones. Kinetic and mechanistic studies are consistent with a reversible 4π -electrocyclization C–C bond-forming step followed by rate- and enantio-determining proton-transfer as the mode of catalysis.

Graphical Abstract

Keywords

Nazarov; catalysis; enantioselective; Lewis acid; electrocyclization; physical organic

Catalysis with weakly acidic, chiral dual-hydrogen-bond-donors (HBDs) such as ureas, thioureas, and squaramides has emerged as a versatile platform for a wide variety of important enantioselective organic transformations.¹ While several different modes of substrate activation^{1,2} have been identified for this subclass of organocatalysis,³ the pool of reactive substrates is generally limited by the acidity of the hydrogen-bond-donor species.⁴ In an effort to extend the scope of electrophiles that may be engaged in asymmetric HBD

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

catalysis, our group recently reported that the combination of chiral squaramides and silyl triflates results in enhanced reactivity relative to either catalyst operating individually.⁵ The cooperative action of Lewis acid and HBD was thus shown to enable the generation of cationic intermediates from acetals and tertiary acetates, as well as their capture in enantioselective addition pathways.^{5,6} Following these proofs of concept, we considered whether Lewis acid-HBD co-catalysis could promote valuable transformations of simple carbonyl compounds that typically require strong metal-based Lewis acid or Brønsted acid catalysis.⁷

We selected the Nazarov cyclization as an especially interesting target for development of the dual catalysis principle. Since its discovery in the 1940s,⁸ the Nazarov reaction has become one of the most studied and useful carbocyclization processes due to the efficient access it provides to versatile cyclopentenone scaffolds.⁹ The reaction typically involves activation of divinylketones by strong Lewis or Brønsted acids to generate pentadienyl cation equivalents that can undergo a 4π -electrocyclization-deprotonation/reprotonation sequence to yield cyclopentenone products.⁹ Racemic versions of the Nazarov reaction,¹⁰ including so-called interrupted variants involving in situ-capture of the oxallyl cation intermediate,¹¹ have found widespread application in the synthesis of complex organic scaffolds.¹² Given the possibility of generating multiple stereocenters in the cyclization, significant effort has also been devoted to the development of asymmetric, catalytic variants, with early successes achieved with certain classes of highly activated dienones,¹³ and more recent breakthroughs in cyclizations of electronically unactivated dienones reported by Rawal and List.¹⁴ Herein, we describe enantioselective Nazarov cyclizations of unactivated dienones catalyzed by the combination of a chiral squaramide (**3a**) and trimethylsilyl triflate (TMSOTf). On the basis of kinetic isotope effect and other mechanistic studies, an unanticipated basis for enantioinduction is proposed, with the reaction proceeding via reversible electrocyclization and rate- and enantiodetermining proton transfer.¹⁵

A systematic survey of potential model substrates for HBD-TMSOTf co-catalyzed Nazarov reactions led to the identification of the diaryl-substituted dienone **1a** as a promising and previously unstudied class of dienones for the HBD/TMSOTf co-catalyzed asymmetric Nazarov cyclization (Figure 2).^{13,14} Multiple factors had to be taken under consideration in the reaction optimization, including not only maximization of product yield and enantioselectivity, but also minimization of byproduct formation, overcoming product inhibition due to TMSOTf binding to the ketone product, and avoidance of product racemization. The structure of the HBD and Lewis acid were naturally critical, with squaramide **3a** and TMSOTf proving optimal (see Table S11 for full catalyst optimization studies). Other crucial factors included solvent choice, ratio of the co-catalysts, and the work-up procedure (Figure 2). Reactions carried out in ethereal solvents led to formation of the desired product in good yields and excellent enantioselectivity (up to 54% yield and 90% e.e. in Et₂O), but with commensurate generation of a byproduct that was isolated after workup as the novel dimeric hydroperoxide **4a** (**2a**:**4a** = 1.3:1).¹⁶ The extent of formation of **4a** was the same in reactions performed with either degassed or oxygen-saturated ether. Performing the reaction in toluene suppressed formation of **4a** (**2a**:**4a** = 33:1), but resulted in slightly decreased enantioselectivity (86% e.e.) in the formation of **2a**. Ultimately, 1:1

mixtures of toluene and *n*-butyl ether were found to afford the best compromise of product yield and e.e. (**2a:4a** = 8:1, 33% yield of **2a**, 92% e.e.).

The ratio of squaramide **3a** to TMSOTf was revealed to be another critical reaction parameter. Reaction rates were impractically slow when **[3a]** > **[TMSOTf]**, suggesting the possible formation of inactive aggregates (see Figures S12 and S13). Under conditions where **[TMSOTf]** > **[3a]**, a straightforward first-order kinetic dependence on **[TMSOTf]** was observed, however, the presence of excess TMSOTf relative to **3a** led to slight decreases in the e.e. of **2a**. Reactions carried out with **[3a]** = **[TMSOTf]** were found to stall at moderate conversions of **1a**, a phenomenon that was traced to product inhibition due to binding of TMSOTf to **2a** (see Figure S14 for details). Improved substrate conversion and product yields were achieved by addition of a second portion of TMSOTf.

A series of dienones was subjected to the optimal conditions for the enantioselective Nazarov cyclization, and the reaction was found to exhibit a broad scope within the specific context of substrates bearing diaryl substitution (Figure 3). The α -alkyl substituent R^1 could be varied while maintaining high product e.e. (entries 1 and 19), but alkyl substitution at the R^3 position resulted in a significant decrease in enantioselectivity (entry 18). While the scope studies were executed on 0.3 mmol scale, the reaction was scaled up effectively to the 1.0 mmol scale with a slight improvement in product e.e. (entries 4 and 5). The HBD catalyst **3a** was recovered and isolated in 98% yield from the preparative-scale reaction.

The observation of high enantioselectivity in squaramide/TMSOTf co-catalyzed cyclizations of **1** raises intriguing questions about the identity of the rate- and enantio-determining step(s) in these processes, since the key C–C bond-forming step is not directly coupled to the ultimate stereocenter-forming event. A similar concern was encountered in Trauner's pioneering work on Lewis acid-promoted enantioselective Nazarov reactions.^{13b} Consistent with the well-accepted understanding of the Nazarov cyclization, the reaction is expected to involve a 4π -electrocyclization, followed by a formal 1,4-proton transfer to generate the enone product **2** (Figure 4). A large, primary kinetic isotope effect ($k_H/k_D = 5.3$) for the migrating proton was determined experimentally (Figure 5, top). Since no intermediates are observed to build up under the reaction conditions, it can be concluded from the KIE that the 4π -electrocyclization step must therefore be reversible and that the proton transfer includes the rate- and enantio-determining step.

The proton transfer was confirmed to be intramolecular in a crossover experiment between fluorinated dienone **1d** and deuterated dienone **1a-d₁** (Figure 5, middle). Among conceivable modes for intramolecular proton transfer, a concerted [1,4]-shift would be forbidden suprafacially and sterically inaccessible antarafacially,¹⁸ so that possibility may be excluded out of hand. The proton transfer can therefore be concluded to be intramolecular, stepwise, and to involve the chiral HBD catalyst since it includes the enantiodetermining step.

Consequently, either the deprotonation or reprotonation steps could be enantiodetermining. In the former case, enantioselectivity could arise from a formal dynamic kinetic resolution of intermediate **I-2** (Figure 4), with the racemization pathway provided by the reversible

electrocyclization. In the latter case, protonation of prochiral siloxydiene **5** by the HBD·HOTf complex would have to occur enantioselectively and within a tight solvent cage to ensure the overall intramolecularity of the process.

Experimental evidence against reprotonation as the enantiodetermining step was obtained by subjecting siloxydiene **5d** to an equimolar mixture of squaramide **3a** and HOTf under the conditions of the catalytic reaction, in an attempt to enter the catalytic cycle at the reprotonation step. Enone **2d** was generated quantitatively but with low enantioselectivity in the opposite absolute sense as that obtained in the cyclization of **1d** (Figure 5, bottom). The same outcome was obtained regardless of the order of addition of acid and **5d**.

On the basis of the results summarized above, the most likely mechanism for the HBD/TMSOTf co-catalyzed Nazarov cyclization involves reversible 4π -electrocyclization to siloxy-allyl cation **I-2** followed by HBD-promoted deprotonation in a dynamic kinetic resolution and subsequent highly stereoretentive reprotonation to afford the enone product **2** (Figure 6). Deprotonation by a chiral HBD-anion complex is an unusual mode of enantioinduction, but it finds direct precedent in thiourea/carboxylic acid co-catalyzed Pictet–Spengler reactions, where reversible C–C bond formation followed by enantiodetermining deprotonation was also demonstrated.¹⁹

In conclusion, an enantioselective, TMSOTf/HBD co-catalyzed Nazarov cyclization of unactivated dienones was developed. Trisubstituted cyclopentenones were accessed in good yields and high enantioselectivity (up to 76% yield and 95% e.e.). The reaction was demonstrated on millimole scale with almost quantitative catalyst recovery. Mechanistic analysis is consistent with reversible electrocyclization and rate- and enantio-determining deprotonation. We envision the reactivity principles identified in this study may serve as the basis for the development of new asymmetric, HBD/Lewis acid co-catalyzed reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the NIH through GM132571 and GM43214, and by the Alexander von Humboldt Foundation (Feodor Lynen Research Fellowship to J.B.M). We thank Dr. Shao-Liang Zheng (Harvard University) for determination of the X-ray crystal structures.

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Cooperative Hydrogen-Bond Donor / Lewis Acid Catalysis

This work: Hydrogen-Bond-Donor-Catalyzed Nazarov Cyclization

Figure 1.

(top) Generation of highly reactive intermediates from stable, sp^3 -hybridized electrophiles via cooperative action of hydrogen-bond-donor catalysts and silyl triflate Lewis acids (LG = leaving group). (bottom) Development of an asymmetric, hydrogen-bond-donor/silyl triflate co-catalyzed Nazarov cyclization of unactivated dienones via enantioselective proton transfer.

Variation from conditions listed above	Yield [%]	e.e. [%]
None	33	92
100% Et ₂ O as solvent	54 ^a	90
100% toluene as solvent	48	86
100% <i>n</i> Bu ₂ O as solvent	31	82
Reaction Temperature -40 °C ^b	90	32
10 mol% TBSOTf	32	91
10 mol% TfOH	5	90
20 mol% 3a	7	91
20 mol% TMSOTf	48	90
48 h Reaction Time	38	91
10 mol% TMSOTf + 10 mol% after 24 h ^c	60 ^d	89
10 mol% TMSOTf + 5 mol% after 48 h ^e	59 ^f	90
Work-up with aq. NaHCO ₃ sol. ^g	45-56	88-90
No TMSOTf	0	-
No 3a	<5	-

Figure 2.

Reaction optimization of the HBD/silyl triflate co-catalyzed Nazarov cyclization. Reactions carried out on 0.1 mmol scale. ^aSide product **4a** generated as a major by-product (**2a**:**4a** 1.3:1). ^bReaction performed in Et₂O. ^cReaction time 48 h and reaction performed on 0.3 mmol scale. ^d**2a**:**4a** 5:1. ^eReaction time 96 h and reaction performed on 0.3 mmol scale. ^f**2a**:**4a** 9:1. ^gReactions performed with second addition of TMSOTf (5 mol%) after 48 h and on 0.3 mmol scale. Reaction time 96 h. The aqueous NaHCO₃ biphasic work-up led to poor reproducibility on the small screening scale, but afforded optimal results on larger scale (e.g. 1 mmol; Figure 3, entry 5).

Entry	R ¹	R ²	R ³	Yield [%]	e.e. [%]
1a	Me	Ph	Ph	59	90
1b	Me	4-MeC ₆ H ₄	Ph	76	90
1c	Me	3-MeC ₆ H ₄	Ph	59	88
1d	Me	4-FC ₆ H ₄	Ph	71	93
1d^a	Me	4-FC ₆ H ₄	Ph	59	95
1e	Me	3-FC ₆ H ₄	Ph	45	89
1f	Me	2-FC ₆ H ₄	Ph	60	88
1g	Me	4-ClC ₆ H ₄	Ph	54	93
1h	Me	4-BrC ₆ H ₄	Ph	61	93
1i	Me	3-BrC ₆ H ₄	Ph	35	83
1j	Me	4-MeOC ₆ H ₄	Ph	60	87
1k	Me	3-MeOC ₆ H ₄	Ph	55	86
1l	Me	2-Naphthyl	Ph	44	85
1m	Me	Ph	4-MeC ₆ H ₄	61	85
1n	Me	Ph	3-MeC ₆ H ₄	53	89
1o	Me	Ph	4-FC ₆ H ₄	58	92
1p	Me	Ph	2-FC ₆ H ₄	40	79
1q	Me	Ph	Me	65	64
1r	Et	Ph	Ph	65	92

Figure 3.

Substrate scope for the HBD/TMSOTf co-catalyzed Nazarov cyclization of unactivated dienones. Unless noted otherwise, reactions were run on a 0.3 mmol scale, with standard reaction work-up. The absolute configuration of the product of entry 4 was assigned by X-ray crystallographic analysis, and that of all other products was assigned by analogy.^{17a} Reaction carried out on 1.0 mmol scale. Work-up was accomplished with aq. NaHCO₃.

Figure 4.
General mechanistic considerations in the HBD/TMSOTf co-catalyzed enantioselective Nazarov cyclization.

Figure 5.

(top) One-pot competition kinetic isotope effect experiment with dienones **1a** and **1a-d₁** revealing a large, primary kinetic isotope effect in the proton-transfer step. (middle) Crossover experiment between dienones **1d** and **1a-d₁** demonstrating the intramolecular nature of the proton-transfer step. The reaction was interrupted after 24 h, resulting in incomplete consumption of the dienone starting materials. (bottom) Enantioselective protonation of TBS-protected enol ether **5d** with HOTf/**3a**. The observation of low enantioinduction and in the opposite sense of that observed in the reaction of **1d** catalyzed by TMSOTf/**3a** rules out asymmetric protonation as the enantiodetermining step in the Nazarov cyclization. Conditions: Reactions were run on a 0.2 mmol (top & middle) and 0.05 mmol (bottom) scale.

Figure 6. Proposed catalytic cycle for the HBD-Lewis acid co-catalyzed enantioselective Nazarov cyclization.