

Strong and Confined Acids Enable a Catalytic Asymmetric Nazarov Cyclization of Simple Divinyl Ketones

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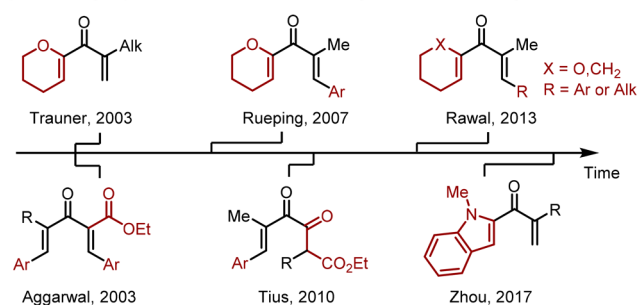
Supporting Information

ABSTRACT: We report a catalytic asymmetric Nazarov cyclization of simple, acyclic, alkyl-substituted divinyl ketones using our recently disclosed strong and confined imidodiphosphorimidate Brønsted acids. The corresponding monocyclic cyclopentenones are formed in good yields and excellent regio-, diastereo-, and enantioselectivities. Further, the chemical utility of the obtained enantiopure cyclopentenones is demonstrated.

Enantiopure cyclopentenones are frequently used as key building blocks toward, and are themselves present within, a variety of bioactive and/or complex natural products.¹ Chemists have consequently devoted considerable effort to the development of enantioselective approaches to these important compounds. Commonly used techniques today include chemical or enzymatic resolutions,^{2,3} asymmetric functionalizations of existing cyclopentenone units,^{1c} or derivatizations of chiral-pool reagents.⁴ While effective, each of these strategies is conceptually inferior to synthetic methods that introduce chirality during the construction of the cyclic unit from simple starting materials, such as asymmetric Pauson–Khand reactions or Nazarov cyclizations.^{5,6} Unfortunately, the relatively underdeveloped methodology of the latter techniques has limited their application. In fact, despite being considered one of the most direct and atom-economical transformations for the synthesis of cyclopentenones, the asymmetric Nazarov cyclization is arguably one of the least employed methods toward chiral cyclopentenones.⁷ The limited application of this strategy is likely an effect of systematic substrate specificity for given variants and, therefore, a lack of generality.

Since the first catalytic asymmetric Nazarov cyclization emerged from the Trauner group in 2003,^{7c} this and subsequent methods have largely depended on designed substrates to overcome the relatively low reactivity of divinyl ketones and/or to circumvent challenges in regio- and stereoselectivity (Figure 1a). More specifically, these substrates are usually activated by adjacent heteroatoms to stabilize the oxyallyl cation, neighboring electron-withdrawing groups, and/or β -aryl substituents to polarize the divinyl ketone.^{5b} Notably, in 2013, Rawal and co-workers disclosed two Nazarov cyclizations of electronically unactivated divinyl ketones; however, in each of these substrates, one of the olefins was within a cyclohexane unit, compromising the overall generality of the method.⁷ⁱ As such, we recognized that simple alkyl-substituted, acyclic divinyl ketones still remain an extremely

a) Previously-reported substrate classes in asymmetric Nazarov cyclizations



b) This work: asymmetric Nazarov cyclizations of simple divinyl ketones

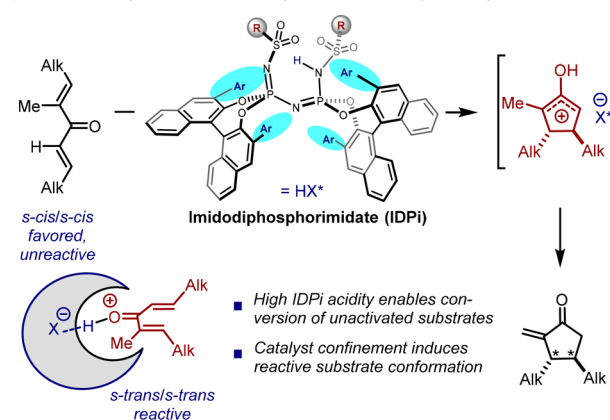


Figure 1. (a) Previously reported systems for asymmetric Nazarov cyclizations. (b) Highly acidic and confined acid enables catalytic asymmetric Nazarov cyclization of simple divinyl ketones.

challenging class of substrates for asymmetric Nazarov cyclizations and thereby undermine its synthetic application.

Recently, our group disclosed a novel class of chiral, highly acidic, and confined Brønsted acids, i.e., imidodiphosphorimidates (IDPis), and demonstrated their success in a variety of asymmetric transformations.⁸ We envisioned that these highly reactive catalysts might be uniquely suited for the Nazarov cyclization of unbiased divinyl ketones, as the confined chiral microenvironment not only induces asymmetry but furthermore may enhance reactivity by increasing the population of the reactive *s-trans/s-trans* conformer of the divinyl ketone (Figure 1b). Here, we report the fruition of these concepts with a unique catalytic asymmetric Nazarov

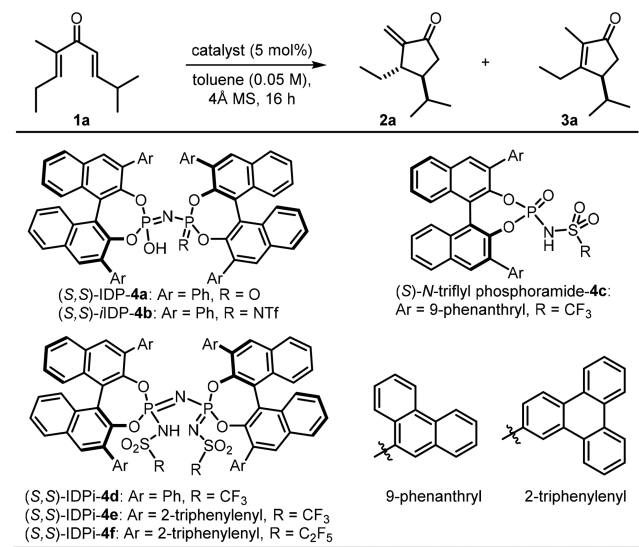
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cyclization of simple, acyclic, and alkyl-substituted divinyl ketones.

We initiated our studies by evaluating acyclic divinyl ketone **1a** as a model substrate using a variety of chiral Brønsted acid catalysts in toluene at 25 °C (Scheme 1). As we anticipated,

Scheme 1. Reaction Development^a



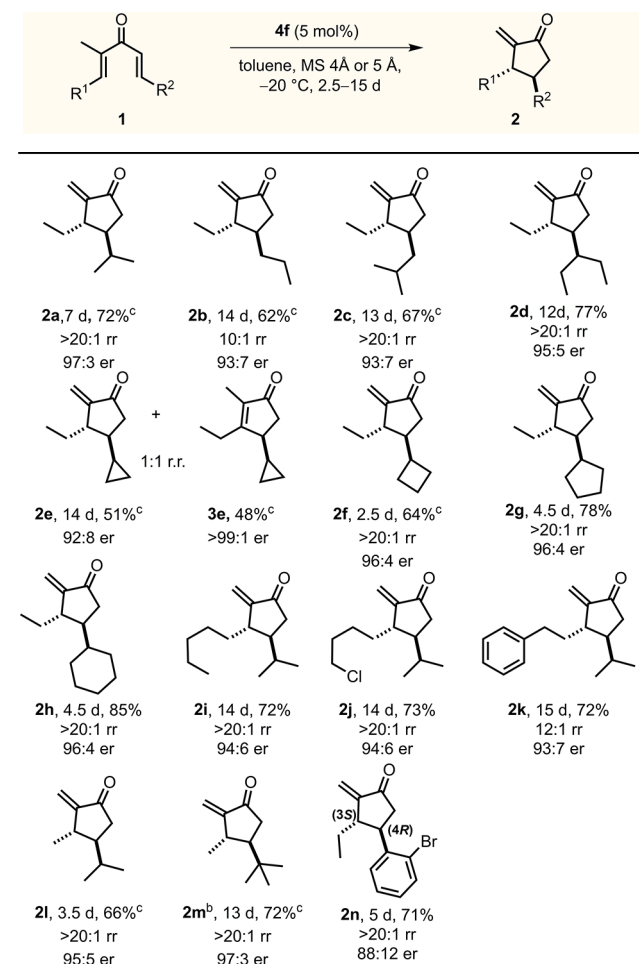
Entry	catalyst	T (°C)	conv. (%)	rr	er _{2a}	er _{3a}
1	4a	25	NR	-	-	-
2	4b	25	NR	-	-	-
3	4c	25	13	1.7:1	56:44	67:33
4	4d	25	NR	-	-	-
5	4e	25	70	>20:1	81:19	ND
6	4f	25	>99	>20:1	86:14	ND
7 ^b	4f	-20	>99	>20:1	97:3	ND

^aReactions were performed with substrate **1a** (0.02 mmol), catalyst (5 mol %), 4 Å MS (10 mg) in toluene (0.4 mL); conversions (conv) and regioisomeric ratios (rr of **2a**:**3a**) were obtained by ¹H NMR analysis with Ph₃CH as an internal standard; enantiomeric ratios (er) were measured by GC, unless otherwise indicated; all diastereomeric ratios (dr) of product **2a** were >20:1. ^bReaction was run for 3.5 days. NR = no reaction; ND = not determined.

relatively weakly acidic and confined Brønsted acids, such as imidodiphosphoric acid (IDP) **4a** and iminoimidodiphosphate (iIDP) **4b**, did not provide any of the desired products (Table 1, entries 1 and 2). Interestingly, *N*-triflyl phosphoramidate **4c**, which Rueping and co-workers have already shown to be an efficient Brønsted acid of Nazarov cyclizations, resulted in poor conversion and regioselectivity (**2a**/**3a** = 1.7:1) and an enantiomeric ratio of 56:44 for **2a** and 67:33 for **3a** (entry 3).

Remarkably, even highly acidic IDPi catalyst **4d** (where Ar = Ph) proved to be inactive under the reaction conditions. However, based on our hypothesis that the confinement of the IDPi scaffold would be critical for the increased population of the necessary *s-trans/s-trans* conformer, we tested IDPi catalysts with sterically larger π -substituents in the 3,3' positions. Indeed, upon testing IDPi catalysts **4e** and **4f** (where Ar = 2-triphenylenyl), **2a** was formed in good yields with excellent diastereo- and regioselectivity (both >20:1) and moderate enantioselectivity (entries 5 and 6). IDPi catalyst **4f**

Table 1. Scope of the Reaction^{a,b}



^aReactions were carried out with 0.2 mmol of substrates **1**, catalyst **4f** (5 mol %), and 100 mg molecular sieves in 4 mL of toluene (0.05 M) at -20 °C for the specified reaction time. Regioisomeric ratios (rr of **2**/**3**) and diastereomeric ratios (dr) were detected by ¹H NMR of the crude reaction mixture. All diastereomeric ratios (dr) were >20:1. The enantiomeric ratios (er) were determined by GC or HPLC analysis. ^b7 mol % catalyst was used. ^cYields of the volatile products were determined by ¹H NMR analysis of the mixtures after column chromatography to remove toluene.

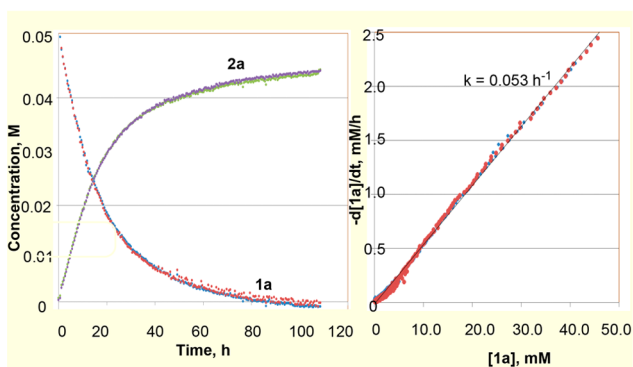
was found to be the best catalyst for this transformation in terms of enantioselectivity and was therefore selected for further optimizations. Gratifyingly, when the reaction was performed at -20 °C, full conversion of substrate **1a** to enone **2a** was observed with excellent regio- (>20:1), diastereo- (>20:1), and enantioselectivity (97:3).

With the optimized conditions in hand, we next explored the scope of this reaction.⁹ Substituents at R² with linear (**1b**), branched (**1c**, **1d**), and cyclic (**1e**–**1h**) aliphatic groups were well tolerated, providing the corresponding enones in good yields with excellent regio- and enantioselectivities. Interestingly, cyclopropyl-substituted substrate **1e** resulted in two regioisomers, **2e** and **3e** (rr = 1:1), under the reaction conditions. We suspect that the poor regioselectivity is a result of a relative increase in the thermodynamic stability of the endocyclic isomer **3e** by virtue of the unique π -character of the cyclopropyl unit. The successful application of substrate **1j**, containing an alkyl chloride, potentially allows for subsequent

cyclization or functionalization. In the case of substrate **1k**, a Friedel–Crafts-type interrupted Nazarov cyclization was not observed.¹⁰ We next turned our attention toward divinyl ketones **1l** and **1m** with a methyl substituent at R¹. The desired enone **2l** was obtained as a single regioisomer (rr > 20:1) and with an excellent enantiomeric ratio of 95:5. As for the more bulky substituted divinyl ketone **1m** (R² = *t*-Bu group), a slightly higher catalyst loading (7 mol %) was required to give cyclopentanone **2m** in good yield (72%) and excellent enantioselectivity (97:3). Notably, *o*-bromophenyl divinyl ketone **1n**, as a representative of an aryl-substituted substrate, was converted with a reasonable er of 88:12. The absolute configuration of the produced ketone **2n** was determined to be 3*S*,4*R* following derivatization (see the SI). The relative configuration of all other products was assigned by analogy.

Encouraged by the success of our reaction design, we were eager to investigate the mechanism of this catalytic, asymmetric Nazarov cyclization. We envisioned two plausible scenarios, the first in which the free catalyst is the resting state and the second involving a covalent intermediate formed in a reaction between the oxyallyl cation and the anion of catalyst **4f**, similar to that which was found in the imidodiphosphoric acid (IDP) catalyzed carbonyl–ene cyclization previously reported by our group.^{8i,11} In order to distinguish these two possible mechanisms, a kinetic study was performed using ¹H NMR analysis. As shown in Figure 2a, the linear correlation

a) Kinetic study (¹H NMR)



b) Proposed catalytic cycle

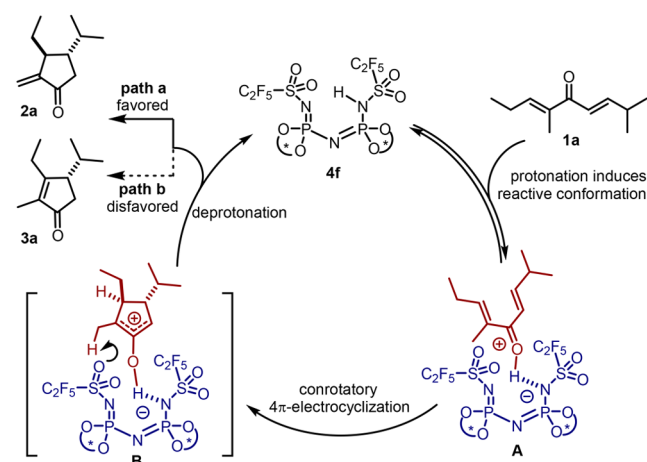
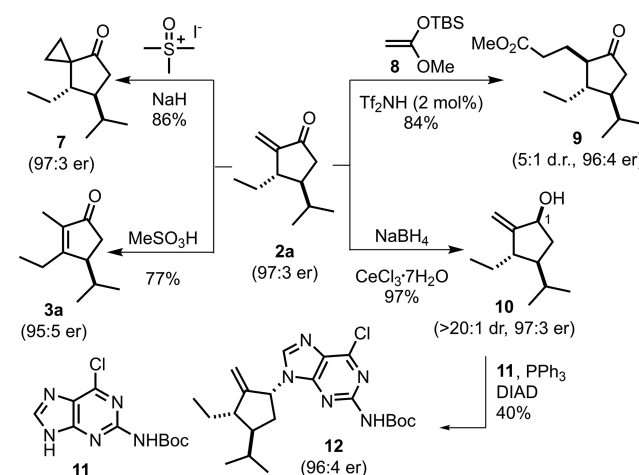


Figure 2. (a) Reaction profile for the reaction of substrate **1a** with catalyst **4f** in the presence of 4 Å molecular sieves at $-20\text{ }^{\circ}\text{C}$ in toluene- d_8 and CH_2Br_2 as external standard. (b) Proposed mechanism.

between reaction rate and concentration of starting material suggests the reaction to be first order in substrate under the steady state approximation. We therefore propose that the free catalyst is the resting state in the catalytic cycle and coordinates to the substrate to form the complex **A** (Figure 2b). Subsequently, a conrotatory 4π -electrocyclization occurs to generate the oxyallyl ion pair **B**, followed by a kinetically controlled deprotonation (path a), presumably by the moderately basic O atoms of the sulfonyl group, which regenerates the catalyst and releases the product.

We also explored the synthetic utility of our enone products (Scheme 2). Indeed, unsaturated ketone **2a** reacted as a

Scheme 2. Functionalization of Nazarov Cyclization Product 2a



Michael acceptor in a cyclopropanation and in a Mukaiyama–Michael addition. The resulting products, ketone **7** and cyclopentanone **9**, were obtained without deterioration of enantioselectivity. The α -methylene unit of **2a** could be isomerized to the fully substituted, thermodynamically more stable cyclopentenone **3a** with an excess amount of methanesulfonic acid, again retaining the excellent enantioselectivity. Moreover, a Luche reduction of **2a** furnished allylic alcohol **10** in excellent diastereoselectivity (dr > 20:1), which could then be utilized in a Mitsunobu reaction to install a purine-derivative and afford compound **12** with excellent C1 enantiopurity.¹²

In conclusion, we have developed a powerful catalytic, asymmetric Nazarov cyclization of simple, acyclic, aliphatic-substituted divinyl ketones using a strong and confined Brønsted acid. We propose that the confinement of the IDPi scaffold induces the reactive *s-trans/s-trans* conformation of the divinyl ketone substrate, thereby promoting the cyclization to give a variety of versatile enones in good yields and excellent enantio-, regio-, and diastereoselectivities. Our approach could be useful in other conformation-dependent transformations, and the developed Nazarov reaction may aid in the asymmetric synthesis of several biologically active natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13899.

Additional detailed synthetic protocols, analytical data for all compounds, and computational strategy (PDF)

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Notes

The authors declare the following competing financial interest(s): A patent, WO2017037141 (A1), has been filed by the MPI für Kohlenforschung covering the IDPi catalyst class and their applications in asymmetric synthesis.

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