Aza-Nazarov Cyclization Reactions via Anion Exchange Catalysis

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S *Supporting Information*
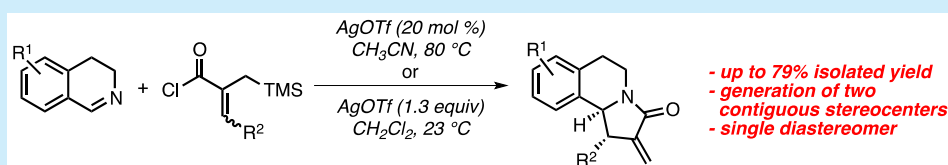
ABSTRACT: A catalytic aza-Nazarov cyclization between 3,4-dihydroisoquinolines and α,β-unsaturated acyl chlorides has been developed to access α-methylene-γ-lactam products in good yields (up to 79%) as single diastereomers. The reactions proceed efficiently when AgOTf is used as an anion exchange catalyst with a 20 mol % loading at 80 °C. Computational studies were performed to investigate the reaction mechanism, and the findings support the role of the −TMS group in reducing the reaction barrier of the key cyclization step.

Heterocyclic chemistry continues to have a pivotal role in various areas of organic chemistry, particularly for the development of new pharmaceuticals and agrochemicals.[1] In a recent perspective article, discovery of new synthetic methods to access substituted aliphatic heterocycles stereoselectively from acyclic precursors has been listed as one of the major synthetic challenges that could contribute significantly to drug discovery.[2] In this respect, cyclization reactions of *N*-acyliminium ions offer a plethora of opportunities for the synthesis of a broad range of nitrogen heterocycles.[3−7] In particular, the aza-Nazarov reaction stands out as a potentially useful transformation for the construction of five-membered, nitrogen-containing heterocyclic structures.[8] However, whereas the catalytic, all-carbon Nazarov reaction has enjoyed remarkable advances within the past two decades,[9] the analogous aza-Nazarov reaction is still in its infancy.[10] Pioneering studies by Würthwein and co-workers demonstrated that aza-Nazarov cyclization could be employed effectively to access a broad range of pyrrole and 2*H*-pyrrole derivatives.[11] For instance, treatment of oxime and hydrazone derivatives **1** with trifluoromethanesulfonic acid (TfOH) followed by trapping with acid anhydrides afforded substituted pyrrole products **2** in good yields (Scheme 1a).[11a] In an elegant work reported by the Klumpp group in 2007, aza-Nazarov reactions of *N*-acyliminium salts **3** were shown to be effectively promoted by TfOH as a superacid (Scheme 1b).[12a] However, the reactions investigated in this study generally required the use of 5 equiv or more of TfOH. This methodology was extended to the aza-Nazarov reactions of in situ generated iminium ions starting from benzamides bearing tethered acetal groups.[12b] Cyclization reactions of pyridine-containing triarylmethanols to

pyrido[1,2-*a*]indoles were achieved by the Klumpp and Sekar groups with the use of TfOH and formic acid, respectively.[13,14]

To our knowledge, the only catalytic enantioselective aza-Nazarov reaction to date was reported by the Tius group in 2010.[15] In this work, the racemic azirine reactant **4** was found to undergo an organocatalytic aza-Nazarov reaction in the form of a kinetic resolution to afford enantiomerically pure product **6** after a ring expansion reaction (Scheme 1c). In 2016, Liao and co-workers reported the aza-Nazarov-type cyclization of in situ formed azaoxyallyl cations leading to the efficient synthesis of *N*-hydroxy oxindoles.[16] In addition to these transformations, aza-Nazarov type cyclizations were proposed to take part in a number of transition-metal-mediated reactions.[17]

In this work, we developed a highly efficient aza-Nazarov reaction between 3,4-dihydroisoquinolines (**7**) and α,β-unsaturated acyl chlorides (**8**) that leads to the formation of a broad range of α-methylene-γ-lactam products (**9**) with two contiguous stereocenters as single diastereomers (Scheme 1d). The α-alkylidene-γ-lactam unit is an important structural motif present in many biologically active molecules and natural products.[18,19] In our reaction design, the aza-Nazarov-type cyclization of the *N*-acyliminium cation **10**, which would be derived from the acylation of imine **7** with acyl chloride **8**, was anticipated to give intermediate **11** that would eventually convert to **9** via desilylation. We envisaged that the trimethylsilyl (−TMS) group at the allylic position of **10** would not only increase the electron density on the alkene moiety toward the
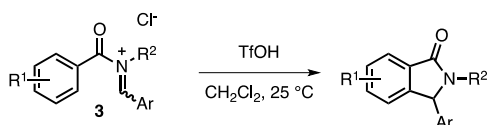
Scheme 1. Examples of Aza-Nazarov Reaction

(a) Würthwein, 2006 (ref 11a)

X = OMe, OBn or NMePh
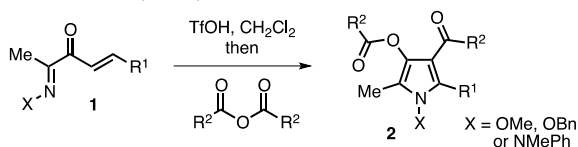
(b) Klumpp, 2007 (ref 12a)

(c) Tius, 2010 (ref 15)

6
28% yield
>99:1 er

(d) *This work:*

9
single diastereomer
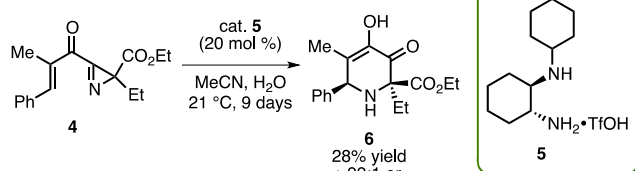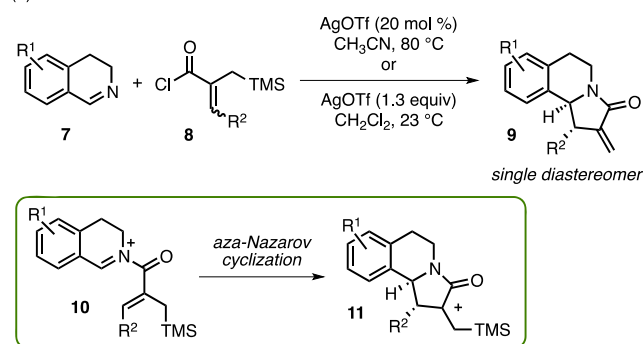

addition to the iminium but also stabilize the carbocation of intermediate **11** through the *β*-silicon stabilization effect.[20−22]

We commenced our studies by the preparation of the *α,β*-unsaturated acyl chloride substrates for which the method developed by Omura and co-workers was followed with slight modifications.[23] The reaction sequence used for the synthesis of acyl chloride **16** is shown in Scheme 2. Alkylation of the

Scheme 2. Preparation of Acyl Chloride 16
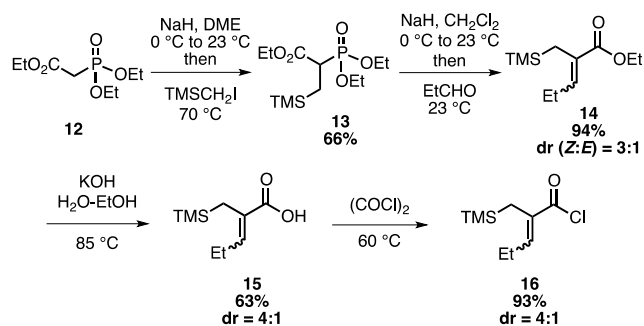
commercially available triethyl phosphonoacetate (**12**) with TMSCH$_2$I gave **13** in 66% yield. Horner−Wadsworth−Emmons reaction of **13** with propanal afforded *α,β*-unsaturated ester **14** in 94% yield and with 3:1 dr (*Z/E*). Acyl chloride **16** was obtained by the saponification of ester **14** followed by treatment with oxalyl chloride.

With the acyl chloride **16** in hand, we next sought to test our hypothesis on the aza-Nazarov reaction using 3,4-dihydroiso-
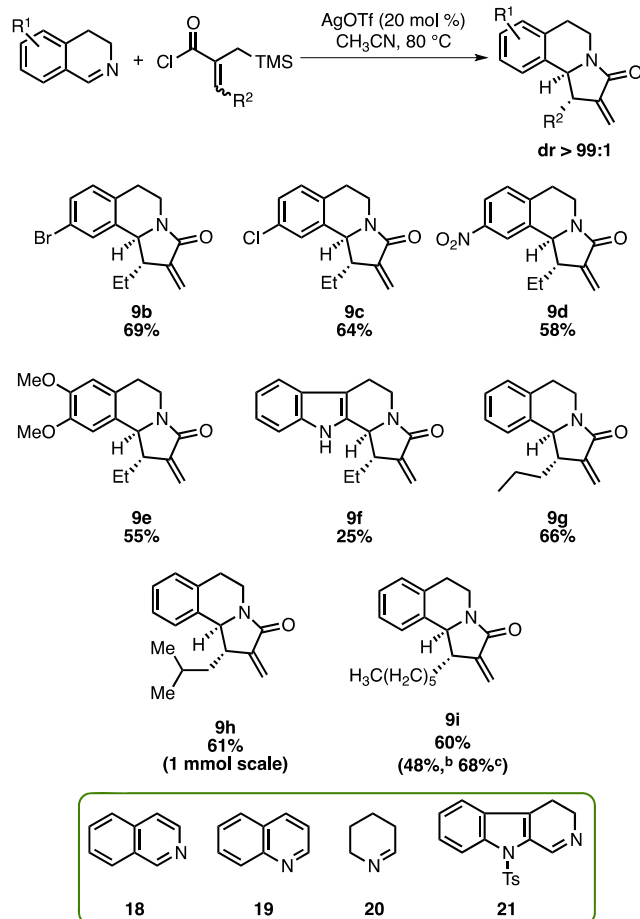
quinoline (**17**) as the imine component. In the absence of any catalyst, a mixture of **16** and **17** did not undergo aza-Nazarov reaction at 23 °C in CH$_2$Cl$_2$ (Table 1, entry 1). On the other

Table 1. Initial Studies on the Aza-Nazarov Reaction

9a
single diastereomer

entry	AgOTf (equiv)	solvent	temp (°C)	isolated yield (%)
1	−	CH$_2$Cl$_2$	23	<1
2	1.3	CH$_2$Cl$_2$	23	57
3	0.2	CH$_3$CN	80	79
4	−	CH$_3$CN	80	13

hand, our initial studies using different Lewis acids for chloride abstraction revealed AgOTf as a highly effective Lewis acid. We were gratified to obtain aza-Nazarov product **9a** as a single diastereomer, and in 57% isolated yield when a mixture of **16** and **17** in CH$_2$Cl$_2$ was treated with a stoichiometric amount of AgOTf (1.3 equiv) at 23 °C (entry 2). We attribute this enhanced reactivity in the presence of AgOTf to the formation of an activated iminium cation due to the more noncoordinating nature of TfO$^-$ compared to the Cl$^-$ anion. Excitingly, the reaction was found to proceed well even with the use of 20 mol % of AgOTf in CH$_3$CN; however, a higher temperature (80 °C) is required for this process. Under these conditions, aza-Nazarov product **9a** was isolated in 79% yield, again as a single diastereomer (entry 3). A control experiment under the same conditions demonstrated that the reaction is much slower when AgOTf was not used (13% yield, entry 4). Overall, these results not only supported our initial proposal on the design of the aza-Nazarov reaction but also showed that the reaction could be performed comparably well under both stoichiometric and catalytic conditions depending on the reaction temperature and solvent. Finally, control experiments between 3,4-dihydroiso-quinoline (**17**) and methacryloyl chloride in the absence and presence of AgOTf at both rt and 80 °C did not result in the formation of any aza-Nazarov product.[24] Hence, our hypothesis on the importance of the −TMS group is supported by these observations.

We next studied the substrate scope of the newly developed aza-Nazarov cyclization (Scheme 3). Initially, the effect of electron-withdrawing and -donating groups present on the imine component was investigated under catalytic conditions. Pleasingly, 3,4-dihydroisoquinolines bearing electron-withdraw-ing −Br, −Cl, and −NO$_2$ substituents at the 7-position were all found to be competent substrates giving aza-Nazarov products **9b**, **9c**, and **9d** as single diastereomers, and in 69%, 64%, and 58% isolated yields, respectively. The reaction was found to tolerate electron-donating MeO− groups on the imine, and product **9e** was isolated in 55% yield. Unsubstituted 3,4-dihydro-*β*-carboline was also observed to undergo the aza-Nazarov cyclization successfully, albeit with a lower yield (**9f**, 25%). Next, we turned our attention to investigate substitution at the *β*-position of acyl halide substrates. When *n*-propyl-substituted acyl chloride was tested, product **9g** was obtained in 66% yield. The aza-Nazarov product **9h** with the branched isobutyl side chain was isolated in 61% yield on a 1.0 mmol reaction scale. In addition, both the catalytic and stoichiometric

Scheme 3. Substrate Scope of the Aza-Nazarov Reaction[a]

Figure 1. X-ray crystal structure of **9e**.

[a]Reaction conditions: 1.0 equiv of imine, 1.3 equiv of acyl chloride, 20 mol % of AgOTf, CH$_3$CN, 80 °C, N$_2$, 22 h. [b]1.3 equiv of AgOTf was used at 23 °C in CH$_2$Cl$_2$. [c]1.3 equiv of AgOTf was used at 80 °C in CH$_3$CN.

catalytic conditions (Scheme 4). These results clearly demonstrate the potential of this methodology in accessing a variety of nitrogen-containing aliphatic heterocycles.

Scheme 4. Aza-Nazarov Reactions Using Acyclic Imines

conditions were tested and found to be successful using the *n*-hexyl-substituted acyl chloride substrate. Whereas aza-Nazarov product **9i** was isolated in 60% yield under the standard catalytic conditions, the yield was found to be slightly lower (48%) with the use of a stoichiometric amount of AgOTf (1.3 equiv) at 23 °C in CH$_2$Cl$_2$. However, the yield increased to 68% when the reaction mixture was heated at 80 °C in CH$_3$CN with the use of 1.3 equiv of AgOTf. Finally, when compounds **18−21** were tested as the imine component of the reaction, aza-Nazarov product formation was not observed. Isoquinoline (**18**) and quinoline (**19**) gave no reaction while complex mixtures of products were obtained in the reactions of imines **20** and **21**.

The relative stereochemistry of the two stereogenic centers of the aza-Nazarov products was initially determined via the NOESY analysis of **9a**.[24] Afterward, this conclusion was confirmed through the single-crystal X-ray diffraction analysis of **9e** (Figure 1).

Encouraged by the results obtained with the dihydroisoquinoline substrates, we next investigated the possibility of using acyclic imines in the aza-Nazarov reaction. To our delight, pyrrolidinone products **24a−c** were obtained in 35−64% yield and with dr values ranging from 10:1 to 5:1, when acyclic imines derived from benzaldehyde derivatives **22a−c** and *n*-propyl-amine (**23**) were subjected to aza-Nazarov cyclization under the
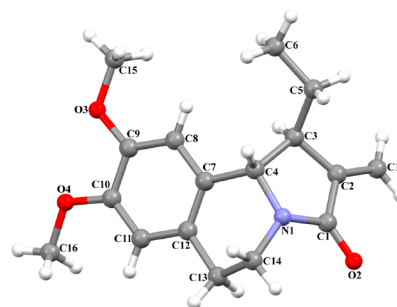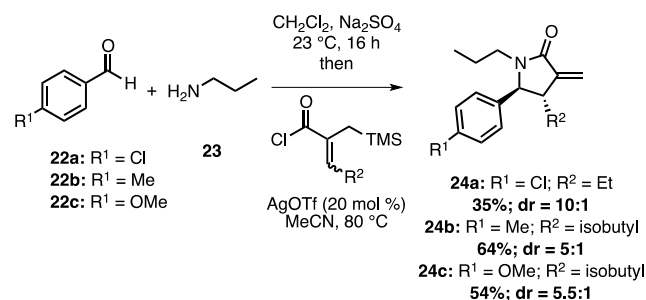
In order to shed light on the reaction mechanism, the key cyclization step was investigated computationally with the density functional theory (DFT). For this purpose, the B3LYP functional[25] was employed along with the 6-311++G(d,p) basis set.[26] Throughout this research, all the relative energies refer to the zero-point vibrational energy (ZPVE) corrected energies. Initially, the reaction barriers and reaction energies (ΔE) for the aza-Nazarov cyclization steps of *N*-acyliminium cations **25a**, **25b**, and **28** were studied (Figure 2). The reaction barrier for the
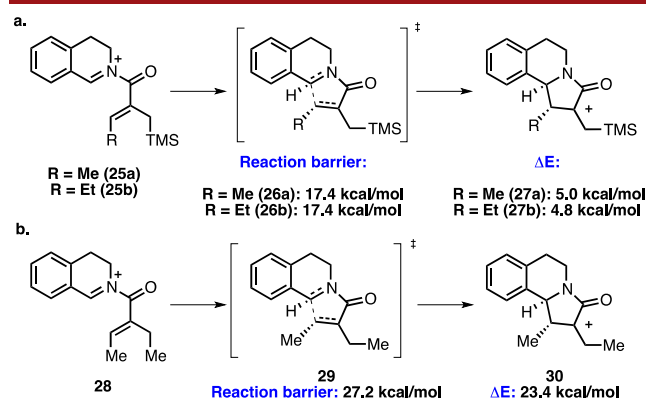

Figure 2. Computational studies (at B3LYP/6-311++G(d,p) level) on the cyclization of **25a**, **25b**, and **28**.

cyclization of **25a** and **25b**, both having a −TMS group, was calculated to be 17.4 kcal/mol, which is 9.8 kcal/mol lower than the barrier of cation **28** (27.2 kcal/mol) that has a −Me in place of the −TMS group.[27] Moreover, the reaction energies (ΔE) for the cyclization of iminium cations **25a** and **25b** were found to be much lower than that of **28** (5.0 and 4.8 kcal/mol compared to

23.4 kcal/mol). These observations are in perfect agreement with our initial hypothesis on the β-silicon effect to be imparted by the −TMS group.

The calculated structures of the transition states (TS) **26b** and **29** with selected interatomic distances are shown in Figure 3.

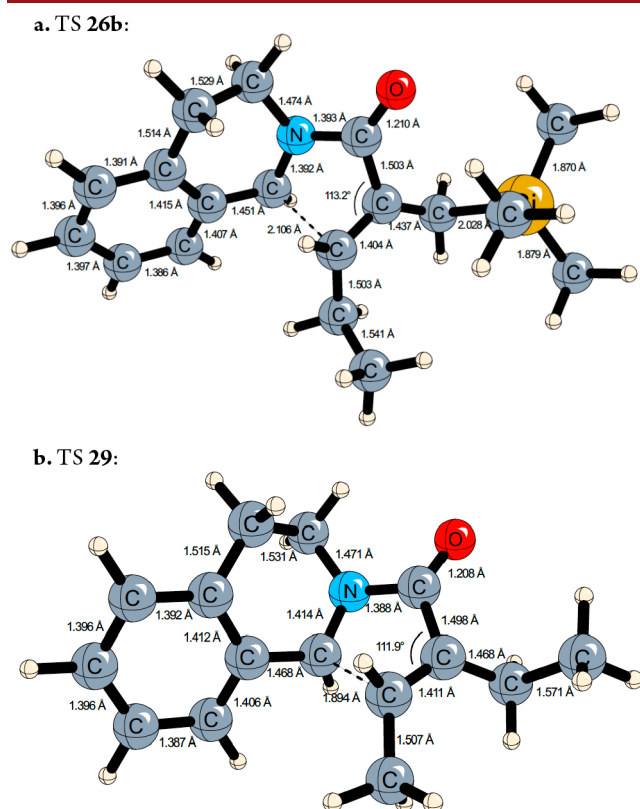**a.** TS **26b**:

b. TS **29**:

Figure 3. Computed structures (at B3LYP/6-311++G(d,p) level) of the transition states **26b** and **29**.

The larger distance of 2.106 Å for the newly forming bond (shown by dashed lines) for TS **26b** compared to 1.894 Å for TS **29** is indicative of an earlier TS for **26b**. This is in accordance with the Hammond−Leffler postulate and the higher reaction energy (ΔE) calculated for the conversion of **28** to **30** compared to that of **25b** to **27b**. In addition, the difference in the C−N bond distances in the TS structures **26b** and **29** (1.392 and 1.414 Å, respectively) lends support to this conclusion. Finally, in the structure of TS **26b**, the β-silicon effect due to the presence of the −TMS group finds reflection in the relatively short C(O)C−CH$_2$TMS bond distance (1.437 Å) and long CH$_2$−SiMe$_3$ bond distance (2.028 Å). This situation is even more pronounced in the calculated structures of **27a** and **27b** (Figures S6 and S10).[24] Finally, we cannot rule out the possibility that the cyclization reaction discussed here may mechanistically be an intramolecular aza-Sakurai-type reaction[22] which involves the nucleophilic attack of an allylsilane moiety to the iminium, even though this would correspond to a disfavored 5-endo-trig cyclization according to Baldwin's rules.[28,29]

In light of our computational studies, observations, and other reactions reported in the field of anion binding catalysis, we propose the mechanism shown in Scheme 5 for the catalytic aza-Nazarov cyclization.[22c,30,31] Treatment of imine **7** with acyl chloride **8** gives iminium chloride salt **31** which may be in equilibrium with **32**.[32] Addition of AgOTf is proposed to induce an anion exchange to afford iminium triflate **33** along with the

Scheme 5. Proposed Reaction Mechanism
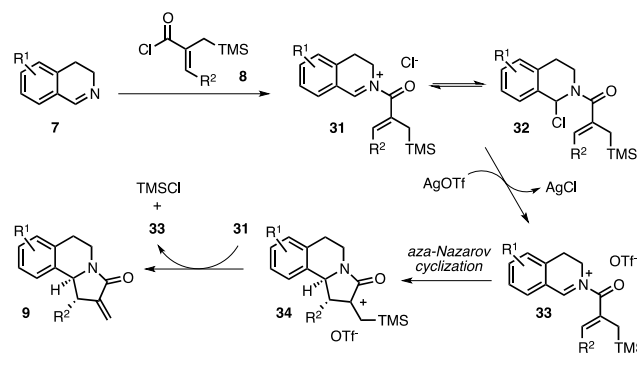
formation of AgCl. Compared to the chloride salt **31**, the iminium salt **33** bearing the OTf⁻ counteranion is expected to be more active toward the aza-Nazarov cyclization to give intermediate **34**. Finally, abstraction of the −TMS group of **34** by the Cl⁻ anion of another molecule of **31** is proposed to yield aza-Nazarov product **9** along with TMSCl and regenerate activated iminium salt **33**.

In summary, we have developed a new aza-Nazarov cyclization between 3,4-dihydroisoquinolines and α,β-unsaturated acyl chlorides, which operates via anion exchange catalysis. α-Methylene-γ-lactam products were obtained in good yields (up to 79%) and with high diastereomeric ratios. The reaction proceeds well at 23 °C when AgOTf is used in a stoichiometric amount, whereas it can be rendered catalytic with the use of 20 mol % of AgOTf at 80 °C. We have also demonstrated the use of acyclic imine substrates in this methodology through the syntheses of pyrrolidinone products **24a**−**c**. The key role of the −TMS group in reducing the reaction barrier of the aza-Nazarov cyclization step was revealed by computational studies. Research to transform this methodology to a catalytic enantioselective process is currently underway in our laboratory.

■ **ASSOCIATED CONTENT**

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03886.

> Experimental procedures, characterization data, ¹H and ¹³C NMR spectra, computational details, coordinates and energies of the computed structures (PDF)

Accession Codes

CCDC 1875287 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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(32) We thank the reviewers for their comments about the reaction mechanism. Our preliminary NMR studies indicate that imine **17** reacts completely with acyl chloride **16** to form the iminium within 10 min, before the addition of AgOTf.