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A Versatile One-Pot Synthesis of Polysubstituted Cyclopent-2-enimines from α,β-Unsaturated Amides via Imino-Nazarov Reaction

Ting Fan,[a] Ao Wang,[a] Jia-Qi Li,[a] Jian-Liang Ye,*[a] Xiao Zheng*[a] and Pei-Qiang Huang*[a,b]

Abstract: The imino-Nazarov cyclization of polysubstituted pentan-1,4-diene-3-imines is realized. To this aim, a one-pot procedure involving reductive alkenyliminylation of α,β-unsaturated secondary amides with potassium organotrifluoroborates followed by acid-catalyzed imino-Nazarov cyclization of the polysubstituted pentan-1,4-diene-3-imine intermediates is studied systematically. This mild, operationally simple, flexible, and high-yielding protocol efficiently affords polysubstituted pentan-1,4-diene-3-imines, cyclopentenimines, and α-amino cyclopentenones, which are useful scaffolds in organic synthesis. The substituent effect at the *C-2* position of polysubstituted pentan-1,4-diene-3-imines was studied by means of density functional theory calculations. The results suggested that the electron-donating group facilitates the imino-Nazarov cyclization process.

Polysubstituted cyclopentylamines are structural skeletons found in many natural products and pharmacologically active molecules, such as cytotoxic flavagline analogs,[1] immunosuppressive marine alkaloid palau'amine,[2] and the novel influenza antiviral drug peramivir[3] (Figure 1). Thus, there is ongoing interest in developing flexible and efficient protocols for accessing this structure, and many methods have been reported.[4]

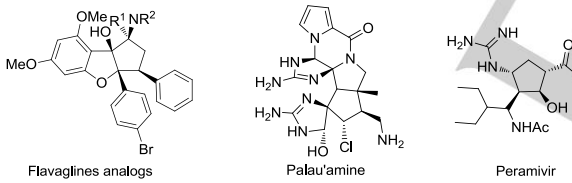

Figure 1. Polysubstituted cyclopentylamine-containing natural products and drugs.

The Nazarov (cyclization) reaction is a powerful method for the construction of cyclopentenones.[5] The aza analog of a Nazarov reaction, if it could be accessed, would provide a convenient route to polysubstituted cyclopentylamines.[6] However, in 1997, on the basis of ab initio calculations, Smith and Ulmer predicted that this process is disfavored because of the higher stability of the pentadienyl cation **I** compared to the cyclopentenyl cation **II** (Figure 2, a).[7] Nevertheless, in 2001, Tius et al. reported the first imino-Nazarov cyclization via acidifying lithioallenylimine **III**.[8] Subsequent to this pioneering work, the following have been reported: a gold(I)-catalyzed [4 + 1] cyclization of internal alkynes and imines,[9] a chiral vicinal diamine-catalyzed cyclization of α-ketoenones,[8b] a gold(I)-catalyzed annulation of α-aryl-substituted allenamides,[10] a silver-assisted cyclization of vinyl cyclopropylamines,[11] and a Lewis acid-catalyzed cyclization cascade of a 2,4-dienal with secondary aniline[12]. It was assumed that these reactions pass through the 4π-electrocyclizations of postulated intermediates **III~VIII**, respectively (Figure 2b).

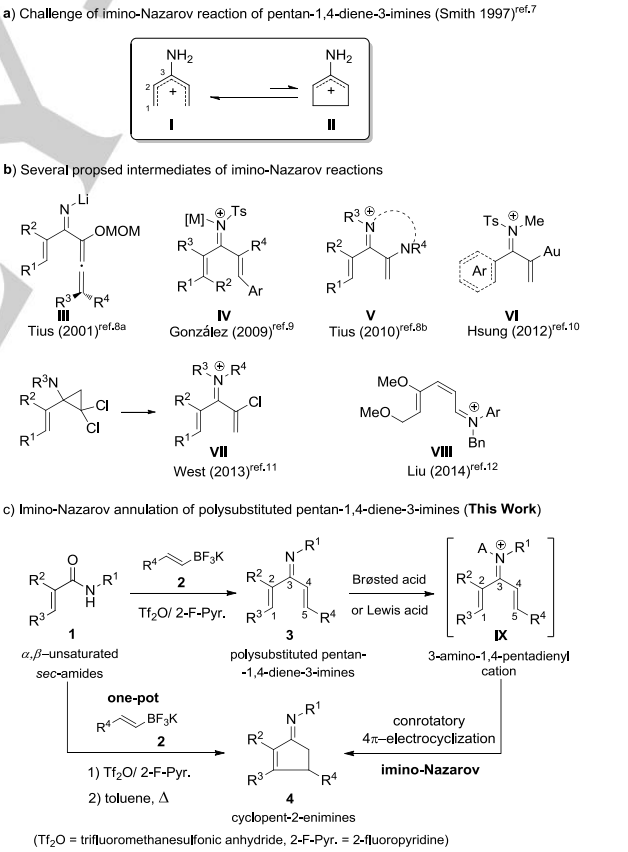

Figure 2. Postulated intermediates of imino-Nazarov reactions and our proposed work.

To clarify the contradiction between the theoretical prediction and experimental results, there is an urgent need to study the imino-Nazarov cyclization of polysubstituted pentan-1,4-diene-3-imines **3** (Figure 2c). Surprisingly, this cyclization reaction has never yet been reported. This may be partly

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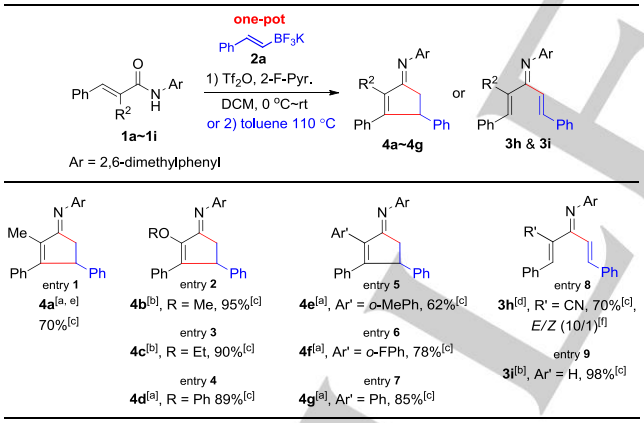
because polysubstituted pentan-1,4-diene-3-imines **3** are not readily available. Indeed, very few methods have been reported for their preparation.[13–16] Thus, based on the development of a simple and versatile method for the synthesis of polysubstituted pentan-1,4-diene-3-imines **3** from α,β-unsaturated secondary amides **1**, we herein report a metal-free one-pot transformation of amides **1** to polysubstituted cyclopentenimines **4** via a tandem reductive alkenyliminylation–imino-Nazarov cyclization sequence (Figure 2, c), together with a mechanism deciphering 4π-electrocyclization of polysubstituted pentan-1,4-diene-3-imines **3**.

We first focused on establishing an easy access to polysubstituted pentan-1,4-diene-3-imines **3**. For this purpose, the coupling reaction of secondary amides with alkenes was used to yield α,β-unsaturated ketimines.[17] This is one of the methods we recently developed in our laboratory for the direct transformation of secondary amides.[18] To develop a general and flexible entrance to polysubstituted pentan-1,4-diene-3-imines **3**, the use of readily available potassium organotrifluoroborates **2** as alternative nucleophiles[19] was investigated. Thus, we have established not only a protocol for the synthesis of polysubstituted pentan-1,4-diene-3-imines **3**, but also the one-pot synthesis of polysubstituted cyclopent-2-enimines **4** from α,β-unsaturated amides **1** and potassium organotrifluoroborates **2** (see the Supporting Information, Scheme S1). Furthermore, the intermediacy of **3** in the one-pot synthesis of **4** from **1** was also confirmed (see the Supporting Information, Table S1).

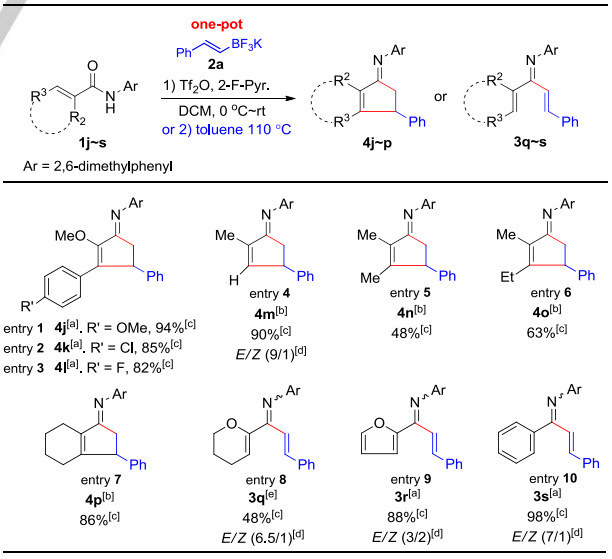
Table 1: Effect of α-substituted groups R^2 of *sec*-amides **1a~1i**.



[a] **General method**: To a DCM solution (0.05 M) of amide (1.0 equiv) and RBF_3K (2.0 equiv) was added 2-F-Pyr. (0.6 equiv) and Tf_2O (1.1 equiv), successively, at 0°C. After stirring in DCM at 0°C for several minutes, the reaction mixture was stirred in DCM at rt for 0.5–3 h. Then DCM was removed in vacuo, toluene was added. The reaction mixture was stirred at 110°C for 0.5–1 h. [b] **Protocol 1**: To a DCM solution (0.05 M) of amide (1.0 equiv) and RBF_3K (2.0 equiv) was added 2-F-Pyr. (0.6 equiv) and Tf_2O (1.1 equiv), successively, at 0°C. After stirring in DCM at 0°C for several minutes, the reaction mixture was stirred in DCM at rt for 0.5–3 h. [c] Isolated yield. [d] **Protocol 2**: To a DCM solution (0.05 M) of amide (1.0 equiv) and RBF_3K (2.0 equiv) was added 2-F-Pyr. (0.6 equiv) and Tf_2O (1.1 equiv) successively at –20°C. The reaction mixture was stirred at –20°C for 3 h. [e] The structure and stereochemistry of **4a** were confirmed by single crystal X-ray diffraction analysis.[20] [f] *E/Z* ratio of enimine **3h** was determined by ^{1}H NMR analysis.

The easy access to polysubstituted pentan-1,4-diene-3-imines **3** and cyclopentenimines **4** provided us with a rare opportunity to investigate the substituent effect of substrates in the imino-Nazarov cyclization reaction. Firstly, the one-pot cascade annulations of *N*-substituted 2-methyl-3-phenylacrylamides with potassium *trans*-styryltrifluoroborate **2a** were studied. *N*-2,6-Dimethylphenyl 2-methyl-3-phenylacrylamide **1a** gave the best results (see the Supporting Information, Table S2). We next investigated the influence of various α-R^2-substituents on *N*-2,6-dimethylphenyl α,β-unsaturated *sec*-amides **1a~i** (Table 1). Various R^2-substituents exhibited significant influence on the yield of one-pot cascade annulations. When the R^2-substituent was a strong electron-donating group, such as a methoxyl or ethoxyl group, the desired cyclopentenimine **4b** or **4c** was generated in excellent yield within about 1 h at rt (Table 1, entries 2 and 3). In contrast, for α-phenyloxyl, α-(*o*-substituted)phenyl, and α-phenyl-α,β-unsaturated *sec*-amides **1d~g**, the reactions with potassium *trans*-styryltrifluoroborate **2a** must be carried out at rt for about 1 h, followed by one-pot solvent exchange, and then refluxed in toluene for about 1 h to afford **4d~g** in moderate to good yields. (Table 1, entries 4–7). Notably, pentan-1,4-diene-3-imine **3h**[20] was obtained from α-cyano-α,β-unsaturated *sec*-amide **1h** in moderate yield at –20°C, but a complex mixture formed at a higher temperature (Table 1, entry 8). Moreover, the reaction of α-unsubstituted α,β-unsaturated *sec*-amide **1i** afforded **3i** in nearly quantitative yield under general conditions, yet no imino-Nazarov product was observed under either heating or acid-catalyzed conditions (Table 1, entry 9).

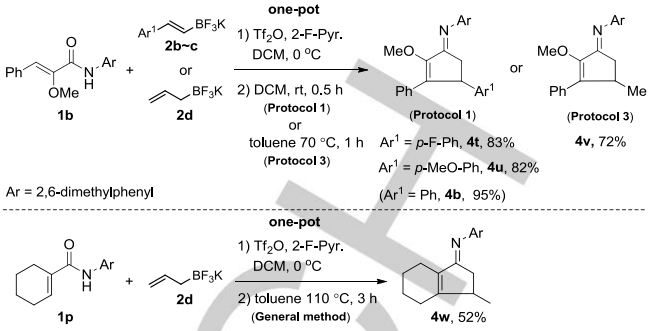
Table 2: Effect of β-substituted groups R^3 of *sec*-amides **1j~s**.



[a] **Protocol 1**. [b] **General method**. [c] Isolated yield. [d] *E/Z* ratio of enimine was determined by ^{1}H NMR analysis. [e] **Protocol 2**.

Then a wide array of α-R^2- and β-R^3-substituted *N*-2,6-dimethylphenyl α,β-unsaturated *sec*-amides **1j~s** were investigated. As shown in Table 2, when α-R^2 is a methoxyl group, the reactions of β-aryl-α,β-unsaturated *sec*-amides **1-j~l** afforded desired cyclopentenimines in good to excellent yields. The reaction of electron-rich β-aryl amide **1j** gave a higher yield than reactions of electron-deficient β-aryl amides **1k** and **1-l** (Table 2, entries 1–3). When α-R^2 is a methyl group, the reaction of β-unsubstituted α,β-unsaturated *sec*-amide **1m** gave cyclopentenimine **4m** in 90% yield. The reactions of β-methyl and β-ethyl α,β-unsaturated *sec*-amides **1n** and **1o** produced the desired cyclopentenimines **4n** and **4o** in moderate yields, along with complex mixtures (Table 2, entries 5 and 6). The observed attenuated yields in the case of entries 5 (β-methyl) and 6 (β-ethyl) deserves comments. According to our observation, for all the amide substrates, the reductive olefination reactions proceeded smoothly to give the corresponding enimines **3** in excellent yields. The difference in yield comes from the second step, namely, the imino-Nazarov cyclization. Among several possible factors that may affect the yield, the stability of the products under the reaction conditions appears to play an important role. In fact, while other products were formed cleanly, the formation of **4o** and in particular **4n** was accompanied with many un-identified by-products. Moreover, a prolonged reaction resulted in a decrease in yield. The product stability may be in related with the kinetic acidity of the proton at β-alkyl substituents. Possessing the most acidic proton, β-Me derivative **4n** is easier to form a more nucleophilic dienamine tautomer, and thus causes side reactions, which results in the lowest yield. The reaction of cyclohexenyl *sec*-amide **1p** also provided the imino-Nazarov product **4p** in 86% yield, while reactions of 3,4-dihydro-2*H*-pyran-6-yl, 2-furyl, and phenyl carboxamides **1q~s** only afforded substituted enimines **3q~s**. The failure for the former is due to the lability of enimine **3q** which was stable only at −20 °C under the acidic reaction conditions (Table 2, entry 8). The lability of enimine **3q** could be attributed to the high reactivity arisen from its resonance structure: 2,3-dihydropyrylium. On the other hand, **3r** and **3s** are too stable to undergo the desired imino-Nazarov cyclization reaction (Table 2, entries 9 and 10).

Furthermore, the one-pot cascade annulations of α,β-unsaturated *sec*-amide **1b** with potassium 2-arylvinyltrifluoroborates **2b** and **2c** were investigated (Scheme 1). Both electron-rich and electron-deficient aryl conjugated vinyltrifluoroborates reacted well in DCM at rt to give the desired cyclopentenimines **4t** and **4u** in good yields (yields were lower than **4b** from **2a**, Table 1). In addition, the one-pot cascade annulation of α,β-unsaturated *sec*-amide **1b** with potassium allyltrifluoroborate **2d** afforded cyclopentenimine **4v** in 72% yield after a one-pot solvent exchange and heating in toluene at 70 °C for about 1 h. Notably, the reaction of amide **1p** with potassium allyltrifluoroborate **2d** afforded cyclopentenimine **4w** in 52% yield. This means a β-aryl group on polysubstituted pentan-1,4-diene-3-imine is not critical for this imino-Nazarov cyclization.



Scheme 1. Other organotrifluoroborates suitable for this one-pot reaction.

To rationalize the crucial substituent effect shown in Table 1-2 and Scheme 1, density functional theory (DFT) calculations on the selected 3-amino pentadienyl cations **I** (Figure 3a), **IX-a**, **IX-b**, and **IX-c** (Figure 3b) were conducted. Figure 3a shows that our DFT calculated free energies are essentially consistent with those of Smith and Ulmer obtained by *ab initio* calculation.[7] In the case of polysubstituted pentan-1,4-diene-3-imines, the disrotatory transition state ($\mathbf{TS_D}$) barriers are higher than those of the corresponding conrotatory $\mathbf{TS_C}$. The results are in line with polysubstituted pentan-1,4-diene-3-imine **3** undergoing a 4π-electrocyclization process; and demonstrated that an electron-rich substituent (such as methoxyl) at the α-position of 3-imino-pentadienyl cation **IX** can lower the activation energy of the transition state $\mathbf{TS_C}$ and stabilize the π_3^2 cyclopentenyl cation **X**, thus facilitating the imino-Nazarov cyclization. Both our experimental and DFT calculation results are consistent with the substituent effects observed in normal Nazarov reactions.[21]

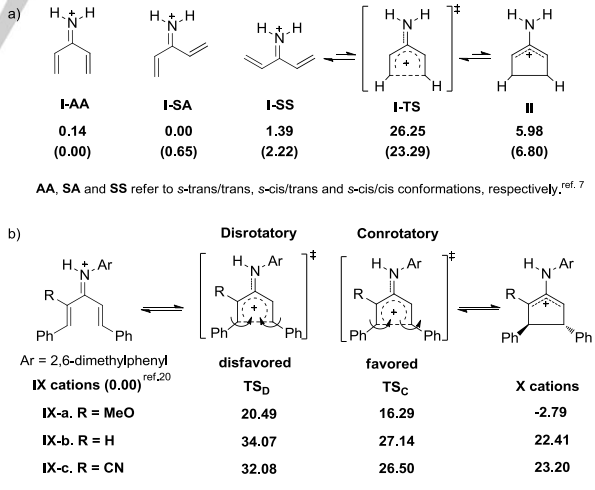
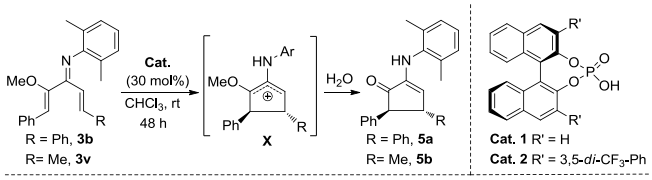


Figure 3. a) The DFT calculated free energies and Smith and Ulmer's ab initio calculated energies (in parentheses) for the 3-amino pentadienyl cation **I**; b) The DFT calculated free energies for acid-promoted imino-Nazarov cyclization of some pentan-1,4-diene-3-imines. All energies are reported in Kcal/mol.

Finally, to obtain further insight into this reaction, preliminary investigations were carried out into the chiral BINOL-derived phosphoric acid-catalyzed imino-Nazarov cyclization of pentan-

1,4-diene-3-imines **3b** and **3v** (Scheme 2). [22] Interestingly, by using **Cat. 1**, racemic α-amino cyclopentenones **5a** and **5b** were



R = Ph, **5a** for **Cat. 1**: 74% yield; 0% ee; for **Cat. 2**: 76% yield; 24% ee

R = Me, **5b** for **Cat. 1**: 30% yield; 0% ee; for **Cat. 2**: 0% yield

Scheme 2. The imino-Nazarov cyclization of pentan-1,4-diene-3-imines **3b** and **3v** catalyzed by chiral BINOL-derived phosphate acids.

obtained as a single diastereomer in 74% and 30% yields, respectively. Notably, the bulkier **Cat. 2**-catalyzed imino-Nazarov cyclization of **3b** also yielded **5a** as a single diastereomer in 76% yield but with 24% *ee*. Because cyclopentenimines **4b** and **4v** were not observed during these reactions, we speculated that the α-amino cyclopentenones were produced by hydrolysis of the intermediate π_3^2 cyclopentenyl cations **X**. The *trans* stereochemistry of **5a** was confirmed by single-crystal X-ray diffraction analysis,[20] while that of *trans*-**5b** was established via the NOESY technique (see Supporting Information for details).

In summary, a one-pot cascade reductive alkenyliminylation–imino-Nazarov cyclization was established based on a novel reductive alkenyliminylation of α,β-unsaturated secondary amides with potassium organotrifluoroborates. This expeditious protocol features easy operation, broad substrate scope, a high-yielding synthesis of polysubstituted pentan-1,4-diene-3-imines, and an acid-promoted cascade 4π-electrocyclization, hence providing flexible and efficient access to a series of polysubstituted cyclopentenimines. Of particular significance was that a study of substituent effect of substrates and DFT calculations revealed that an electron-donating substituent at the *C-2* position of pentan-1,4-diene-3-imine can promote the imino-Nazarov cyclization and stabilize the cyclopentenyl cation. The possibility of enantioselective organocatalytic imino-Nazarov cyclization also emerged.

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Keywords: imino-Nazarov reaction • cyclization • potassium organotrifluoroborates • pentan-1,4-diene-3-imines • one-pot reaction

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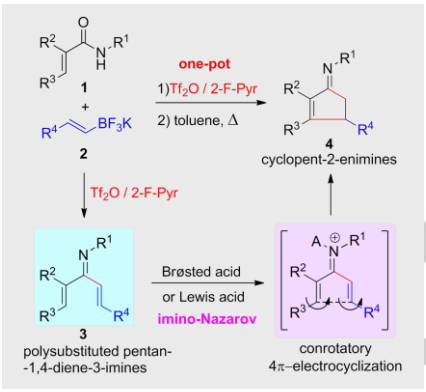
An imino-Nazarov cyclization of polysubstituted pentan-1,4-diene-3-imines **3** to prepare polysubstituted cyclopentenimines **4** is established, which features a one-pot reductive alkenyliminylation of α,β-unsaturated secondary amides **1** with potassium organotrifluoroborates–acid-catalyzed 4π-electrocyclization of enimines **3**.



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A Versatile One-Pot Synthesis of Polysubstituted Cyclopent-2-enimines from α,β-Unsaturated Amides via Imino-Nazarov Reaction