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Lewis acid-catalyzed [3+3] cycloadditions of donor–acceptor aziridines with *N*,*N*-dialkyl-3-vinylanilines via carbon-carbon bond cleavage

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ABSTRACT

A Lewis acid-catalyzed [3 + 3] cycloaddition reaction of donor–acceptor aziridines with *N*,*N*-dialkyl-3-vinylanilines has been developed for the stereoselective synthesis of tetrahydroisoquinolines (THIQs). The reaction performed using $Gd(OTf)_3$ as the Lewis acid catalyst was tolerant to various *N*-tosylaziridine and *N*,*N*-dialkyl-3-vinylaniline substrates and provided access to highly functionalized THIQs in typically high yields with moderate-to-excellent diastereoselectivities.

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1. Introduction

Nitrogen-containing heterocycles are key structural elements in various natural products and pharmaceutically relevant molecules.[1] Cycloaddition of activated aziridine is an attractive method for the synthesis of various nitrogen-containing heterocycles.[2] Aziridines, highly ring strained the smallest *N*-containing heterocyclic compounds, have been extensively studied in the field of organic synthesis in the past years. The most widely reported reaction of aziridines is the Lewis acid-catalyzed C–N bond cleavage to act as a masked $1_C,3_N$-ylide, which readily reacts with versatile dipolarophiles such alkenes, alkynes, aldehydes/ketones, and nucleophiles.[3] On the other hand, under thermal or photochemical conditions, the C–C bond cleavage of aziridines can also generate $1_C,3_C$-ylides, even though it is difficult because of the higher energy barrier than the C–N bond cleavage. Donor–acceptor (D–A) aziridines can undergo heterolytic C–C bond cleavage in the presence of a Lewis acid under mild conditions to generate $1_C,3_C$-ylides (azomethine ylides), which may further undergo cycloaddition reactions with various dipolarophiles, such as aldehydes, alkenes, alkynes, 2,3-disubstituted indoles, imines, D–A cyclopropanes, isocyanides, etc.[4] Nevertheless, most of these cycloaddition reactions are [3 + 2] cycloadditions, and it is desirable to find proper [3 + 3] cycloadditions for the synthesis of six-membered nitrogen-containing heterocycles.

Tetrahydroisoquinoline (THIQ) is a well-known privileged structural motif that is commonly found in many biologically active natural products and synthetic pharmaceutical compounds.[5] This structural scaffold exhibits pharmacologically relevant promising antitumor, antiviral, antimalarial, and antiinflammatory activities. For example, (−)-Quinocarcin has shown remarkable antiproliferative activity against lymphocytic leukemia and a significant inhibitor of non-small cell lung cancer and adenocarcinoma.[6] 11-Hydroxyerythratidine exhibits sedative, hypotensive, and central nerve system depressant activities.[7] Furthermore, (R)-Carnegine revealed inhibition properties towards human monoamine oxidases A and B.[8] A few natural alkaloids containing THIQ core structures are shown in Fig. 1.

In view of potent biological activities and unique structural features of THIQs, many methodologies have been developed for their synthesis.[9] The classical strategies for the synthesis of THIQs include Pictet–Spengler cyclization, Bischler–Napieralski cyclization/reduction, Pomeranz–Fritsch cyclization, deprotonation/alkylation reaction, and addition of nucleophiles to the C=N bonds

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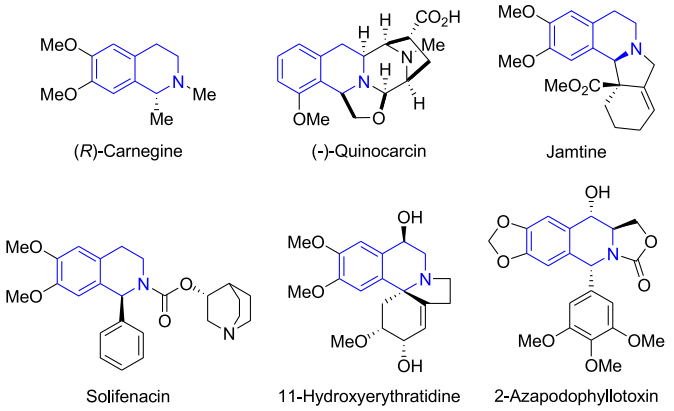
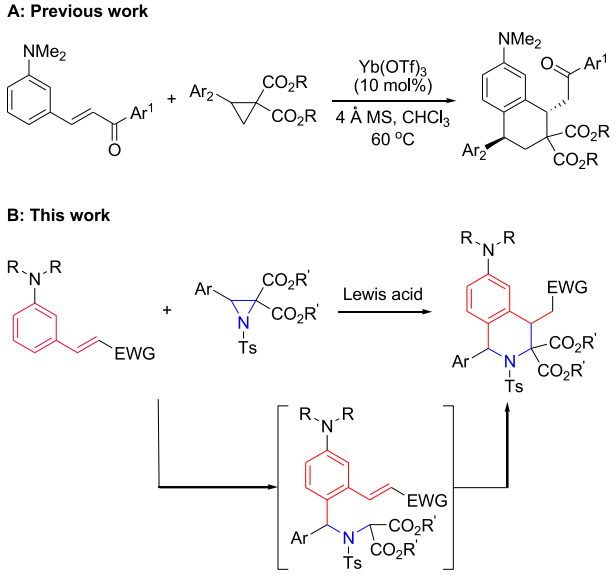


Fig. 1. Selected bioactive naturally occurring tetrahydroisoquinolines.

of dihydroisoquinolines or an iminium ion of the cyclic precursor. Recently, the cross-dehydrogenative coupling reaction of various carbon pronucleophiles and proelectrophiles of simple unfunctionalized THIQ has been developed as a powerful method for constructing functionalized THIQs.[10] However, much synthetic effort has been devoted to the synthesis of 1-substituted or 1,3-disubstituted THIQs. Few examples are known for the synthesis of 1,4-disubstituted and 1,3,4-trisubstituted THIQs, which are even more biologically interesting and important.[9a] Quirion achieved the Bischler-Napieralski cyclization of β-phenylethylamines for the synthesis of 1,4-disubstituted THIQs.[11] Park investigated the $Yb(OTf)_3$-catalyzed ring opening of bridged oxazolines, which were synthesized from Garner aldehydes, to furnish 1,3,4-trisubstituted THIQs.[12] Xing realized a Lewis acid-promoted three-component reaction of aziridines, arenes, and aldehydes involving tandem ring opening/Pictet-Spengler condensation to give 1,4-disubstituted THIQs.[13] Therefore, it is challenging and highly desirable to develop a convenient and general synthetic method for 1,4-disubstituted and 1,3,4-trisubstituted THIQs.

Recently, we developed a [3 + 3] cycloaddition reaction of D–A cyclopropanes with *m*-*N*,*N*-dimethylaminophenyl α,β-unsaturated carbonyls providing a valuable method for the synthesis of tetralin derivatives (Scheme 1A).[14] The reaction of *m*-*N*,*N*-dimethylaminophenyl α,β-unsaturated ketones with D–A cyclopropanes provided tetralins with a *trans* orientation of the 1,4-substituents on the cyclohexyl ring. On the other hand, *m*-*N*,*N*-dimethylaminophenyl substituted methylidenemalonates furnished *cis*-tetralins with high diastereoselectivities. *N*,*N*-Dialkylaniline acts as a good nucleophile without any deactivation or decomposition by Lewis acids like $Yb(OTf)_3$, which was used as the catalyst in this Friedel–Crafts reaction. In the present study, we designed a new synthetic method for highly functionalized THIQs having 1,4-carbon stereocenters by a Lewis acid-catalyzed cascade reaction (Scheme 1B). This [3 + 3] cycloaddition strategy includes stereoselective Friedel–Crafts type ring-opening/intramolecular Michael addition cascade reaction between *m*-*N*,*N*-dialkylaminophenyl α,β-unsaturated carbonyl compounds and azomethine ylides, which are obtained from the selective C–C bond cleavage of D–A aziridines under mild conditions, leading to the formation of the corresponding 1,3,4-trisubstituted THIQs. We earlier communicated the preparative procedure for highly functionalized *trans*-THIQs via [3 + 3] cycloaddition of *N*-tosylaziridines with *m*-*N*,*N*-dialkylaminophenyl methylidenemalonates.[15] Owing to the sustained pharmaceutical significance of the THIQ product classes and our interest in developing novel routes to common heterocycles, we have further explored this [3 + 3] cycloaddition methodology in terms of reactivity and functionality of D–A aziridines with *N*-dialkyl-3-vinylanilines. Herein, we report the comprehensive results of our efforts as an article.

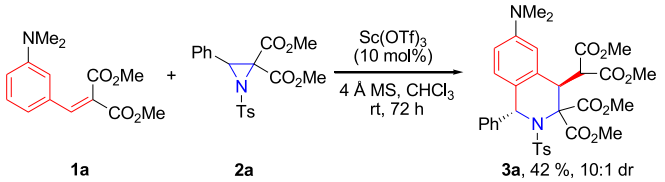


Scheme 1. Lewis acid-catalyzed [3 + 3] cycloaddition of *N*,*N*-dialkyl-3-vinylaniline.

2. Results and discussion

Based on our report on the synthesis of tetralins via [3 + 3] cycloaddition reaction of D–A cyclopropanes with *m*-*N*,*N*-dimethylaminophenyl α,β-unsaturated carbonyls, we envisaged that THIQs could be synthesized via [3 + 3] cycloaddition reaction of D–A aziridines with *m*-*N*,*N*-dimethylaminophenyl α,β-unsaturated carbonyls under the appropriate reaction conditions. To this end, we initiated our investigation with the [3 + 3] cycloaddition reaction of *m*-*N*,*N*-dimethylaminophenyl methylidenemalonate **1a** with 3-phenyl-*N*-tosylaziridinedicarboxylate **2a**[16] using 10 mol% of the Lewis acid catalyst in the presence of 4 Å molecular sieves in $CHCl_3$ at room temperature. The reaction was completed in 72 h and the desired THIQ derivative **3a** was obtained in 42% yield with good diastereoselectivity (10:1 dr, Scheme 2).

In order to optimize the reaction between **1a** and **2a**, various Lewis acids were screened, and the results are shown in Table 1. $Gd(OTf)_3$ was found to be the most effective catalyst. The other commercially available Lewis acids such as $Yb(OTf)_3$, $Sc(OTf)_3$, $Sm(OTf)_3$, and $Cu(OTf)_2$ led to lower yields and diastereoselectivities of **3a** as compared to $Gd(OTf)_3$ (Table 1, entries 1–5). For $Ni(ClO_4)_2$, $FeCl_3$, $Zn(OTf)_2$, $Mg(OTf)_2$, and MgI_2, **3a** was obtained with high diastereoselectivities, albeit in low-to-moderate yields (entries 6–10). The reaction in the presence of 3 Å molecular sieves was afforded slightly inferior results (entry 11). To further optimize the reaction feasibility and yields, various solvents were examined for the $Gd(OTf)_3$-catalyzed reaction (entries 12–18). The reaction



Scheme 2. Synthesis of THIQ **3a** via $Sc(OTf)_3$-catalyzed [3 + 3] cycloaddition of *N*,*N*-dimethyl-3-vinylaniline **1a** with D-A aziridine **2a**.

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