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Lewis acid-catalyzed Friedel-Crafts/Michael cascade reaction of *N*,*N*-dialkyl-3-vinylanilines with *N*-tosylaziridines for the stereoselective synthesis of highly functionalized tetrahydroisoquinolines

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ABSTRACT

A Lewis acid-catalyzed Friedel-Crafts/Michael cascade reaction between *N*-dialkyl-3-vinylanilines and *N*-tosylaziridines has been developed for the stereoselective synthesis of tetrahydroisoquinolines (THIQs). The reaction using $Gd(OTf)_3$ as the Lewis acid catalyst was tolerant to the various *N*-dialkyl-3-vinylaniline and *N*-tosylaziridine substrates and provided access to 28 new, highly functionalized THIQs in typically high yields with moderate- to- excellent diastereoselectivities.

Introduction

Tetrahydroisoquinoline (THIQ) is a well-known privileged scaffold that is commonly encountered in many biologically active natural products and synthetic pharmaceutical compounds.[1] This structural motif exhibits promising pharmacologically relevant antitumor, antiviral, antimalarial, and antiinflammatory activities. A few natural alkaloids containing THIQ core structures are shown in Fig. 1.

In view of their potent biological activities and unique structural features, extensive efforts have been made to construct this ring system and several different approaches have been developed (Scheme 1).[2] The classical strategies for the synthesis of functionalized THIQs include Pictet-Spengler cyclization, Bischler-Napieralski cyclization/reduction, Pomeranz-Fritsch cyclization, deprotonation/alkylation reaction, and addition reaction of nucleophiles to the C=N bonds of dihydroquinolines. 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.[3] While much synthetic effort has been devoted to the synthesis of 1-substituted or 1,3-disubstituted THIQs, there

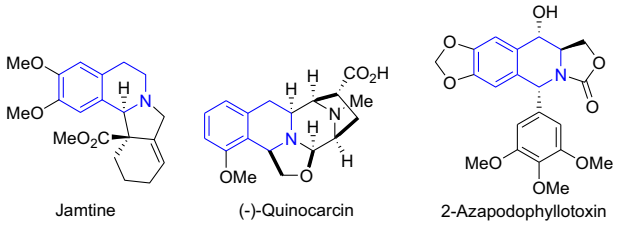

Figure 1. Examples of bioactive naturally occurring tetrahydroisoquinoline.

are very few examples of the synthesis of 1,4-disubstitued and 1,3,4-trisubstituted THIQs, which are even more biologically interesting and important.[4] Therefore, a direct, convenient, and general synthetic method of 1,4-disubstituted and 1,3,4-trisubstituted THIQs is highly desirable.

Owing to our interest in developing novel routes to common heterocycles,[5] we designed a new synthetic method for highly functionalized THIQs having 1,4-carbon stereocenters by a Lewis acid-catalyzed cascade reaction (Scheme 2). In this manner, THIQs could be formed from *N*,*N*-dialkyl-3-vinylanilines by the Friedel-Crafts/Michael cascade reaction with azomethine ylides, which are obtained from the selective C—C bond cleavage of donor-acceptor (D-A) aziridines under mild conditions.

D-A aziridines are highly ring strained but readily accessible three membered amines and have been extensively studied in

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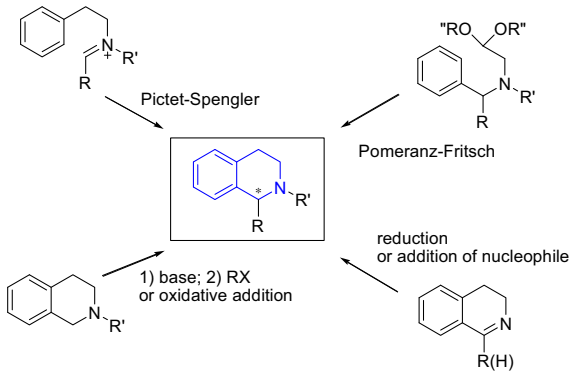
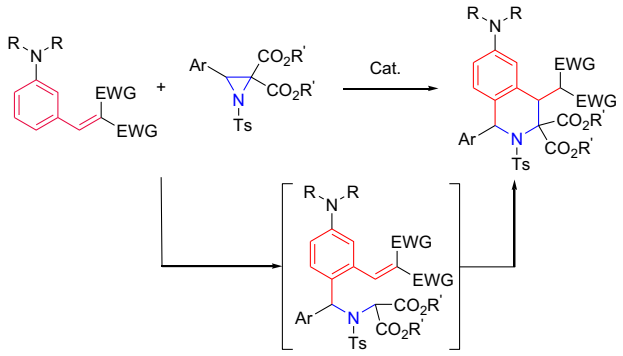


Scheme 1. Representative strategies for the synthesis of THIQ skeleton.



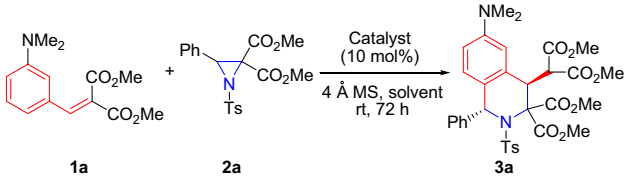
Scheme 2. Friedel-Crafts/Michael cascade reaction of *N,N*-dialkyl-3-vinylaniline with *N*-tosylaziridine as a new synthetic approach of THIQs.

organic synthesis in the past years.[6] The most widely encountered reaction of aziridines is 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.[7] However, the selective C—C bond cleavage of aziridines generating $1_C,3_C$-ylide has been rarely explored because of the relatively high energy barrier. Nevertheless, D-A aziridines can undergo heterolytic C—C bond cleavage in the presence of a Lewis acid to generate $1_C,3_C$-ylides (azomethine ylides) which may further react with various dipolarophiles in cycloaddition reactions.[8]

Results and discussion

Based on our previous research results,[5c,9] we initiated our investigation on the cascade reaction of *m-N,N*-dimethylaminophenyl methylidenemalonate **1a** with 3-phenyl-*N*-tosylaziridinedicarboxylate **2a**,[10] which were chosen as the model substrates, to afford THIQ **3a** using 10 mol% of the Lewis acid catalyst in the presence of 4 Å molecular sieves in $CHCl_3$ at rt (Table 1). In order to optimize the reaction between **1a** and **2a**, various Lewis acids were employed, and $Gd(OTf)_3$ was found to be the most effective. 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). In the cases of $Ni(ClO_4)_2$, $FeCl_3$, $Zn(OTf)_2$, and MgI_2, **3a** was obtained with high diastereoselectivities, albeit in low to moderate yields (Table 1, entries 6–9).[11] To further optimize the reaction feasibility and yields, various solvents were examined in the $Gd(OTf)_3$-catalyzed reaction (Table 1, entries 10–15). The reaction medium was found to have substantial impact on the conversion efficiency and stereoselectivity of the reaction. The reaction proceeded well with CH_2Cl_2 and $ClCH_2CH_2Cl$, and while **3a** was

Table 1
Optimization of the reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Solvent	Yield (%)[b]	dr[c]
1	$Yb(OTf)_3$	$CHCl_3$	26	9:1
2	$Sc(OTf)_3$	$CHCl_3$	42	10:1
3	$Sm(OTf)_3$	$CHCl_3$	61	9:1
4	$Gd(OTf)_3$	$CHCl_3$	87	25:1
5	$Cu(OTf)_2$	$CHCl_3$	24	20:1
6	$Ni(ClO_4)_2$	$CHCl_3$	57	>30:1
7	$FeCl_3$	$CHCl_3$	25	>30:1
8	$Zn(OTf)_2$	$CHCl_3$	35	>30:1
9	MgI_2	$CHCl_3$	46	25:1
10	$Gd(OTf)_3$	CH_2Cl_2	88	6:1
11	$Gd(OTf)_3$	$ClCH_2CH_2Cl$	65	10:1
12	$Gd(OTf)_3$	Toluene	35	8:1
13	$Gd(OTf)_3$	CH_3CN	41	15:1
14	$Gd(OTf)_3$	EtOAc	20	3:1
15	$Gd(OTf)_3$	MeOH	–[d]	–[e]

[a] The reactions were carried out in solvent (0.2 M) with **1a** (0.1 mmol) and **2a** (0.15 mmol) in the presence of 4 Å molecular sieves and 10 mol% catalyst at room temperature for 72 h.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^1H NMR analysis of the crude product.
[d] No reaction.
[e] Not determined.