Organic LETTERS

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Lewis Acid Catalyzed Diastereoselective Cycloaddition Reactions of Donor–Acceptor Cyclopropanes and Vinyl Azides: Synthesis of Functionalized Azidocyclopentane and Tetrahydropyridine Derivatives

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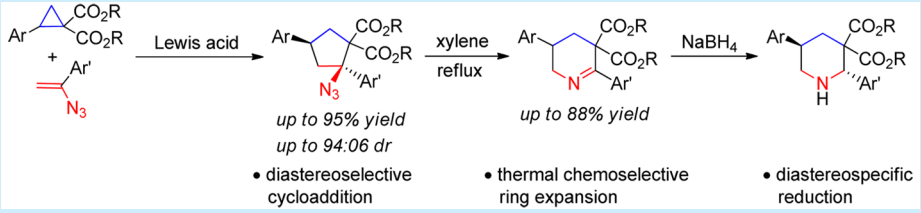
Supporting Information



ABSTRACT: Lewis acid catalyzed [3 + 2]-cycloaddition reaction of donor–acceptor cyclopropanes with vinyl azides has been developed to obtain diastereomerically enriched azidocyclopentane derivatives. In addition, thermal chemoselective ring expansion of azidocyclopentanes to tetrahydropyridine derivatives and further diastereospecific reduction to a substituted piperidine derivative, with an excellent yield, was also achieved.

Nitrogen-containing heterocycles and carbocycles are distinctive structural frameworks present in a wide range of bioactive compounds.[1,2] Among them, *N*-functionalized cyclopentanes and tetrahydropyridines are of particular importance, as these scaffolds constitute the cyclic core structures of varieties of bioactive heterocycles. Pyrazole acids, acting as agonists of G-protein-coupled receptor GPR109a,[3] are representative examples of drugs, containing *N*-functionalized cyclopentane rings (Figure 1). The distinctive

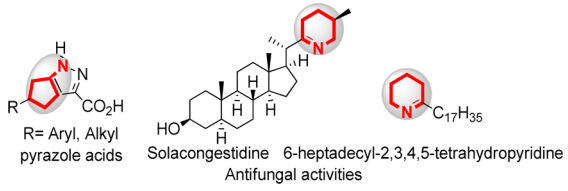


Figure 1. Tetrahydropyridine and *N*-functionalized carbocycles present in natural product.

examples of alkaloids having tetrahydropyridine as a core structural motif are Solacongestidine and 6-heptadecyl-2,3,4,5-tetrahydropyridine, which exhibit antifungal activities.[4] Therefore, the development of efficient protocols for stereoselective construction of these molecular architectures from readily available starting material is of great interest.

In that perspective, due to ease of preparation and foreseeable reactivity, donor–acceptor cyclopropanes (DACs) have frequently been used as building blocks in organic synthesis.[5] In the past few decades, a large number of [3 + *n*]-cycloaddition reactions of DACs with numerous reactive partners[5,6] have been reported. Our group has also explored varieties of annulation and cycloaddition reactions of DACs with oxaziridines, aziridines, nitrosocarbonyls, and epoxides for the synthesis of various heterocyclic and carbocyclic compounds relevant to pharmaceutical applications.[7]

We recently reported a [3 + 2]-cycloaddition reaction of DAC with enamines to synthesize *N*-functionalized cyclopentanes in an enantioselective manner (Scheme 1A).[8] Following the success of this work, we became interested in assessing the reactivity of DACs with vinyl azides (VAs) as they can also act as an enamine.[10] During the preparation of this manuscript, Kerr's group reported an interesting annulation reaction of DACs with VAs for the formation of azabicycles,[9] where they utilized VA as the generator of vinyl nitrene at elevated temperature.

We started the present investigation with the assumption of Lewis acid catalyzed ring opening of DACs resulting from an enamine type nucleophilic attack by VAs, followed by cyclization of the ring opened intermediate. Azidocyclopentanes (**3**) were formed as the sole product in all cases. The structure and geometry of the cycloadduct (**3aa**) were determined by routine spectroscopic techniques and X-ray analysis (Figure 2).[11] The salient feature of these azidocyclopentanes is the attachment of azide functionality to a quaternary carbon atom.[12] This drew our attraction toward investigating the ring expansion through elimination of nitrogen to form tetrahydropyridine derivatives (**4**), as there is no report

Received: November 1, 2016

DOI: 10.1021/acs.orglett.6b03276
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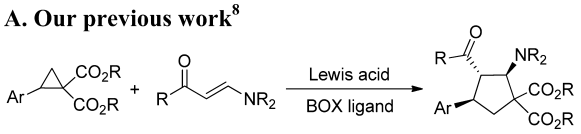
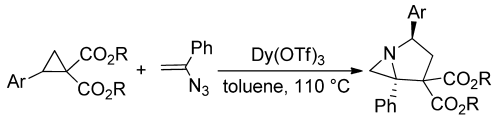
Scheme 1. Reactivity of DACs with Enamines and Vinyl Azides

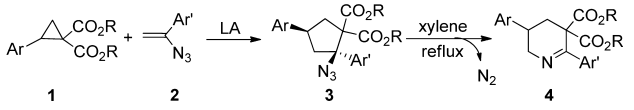
A. Our previous work[8]



B. Kerr's work[9]



C. This work



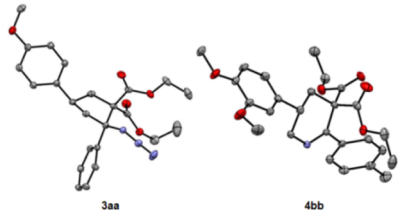


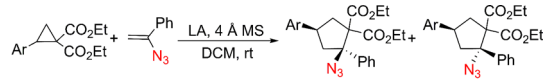
Figure 2. X-ray structure of **3aa** and **4bb** (Hydrogen atoms are omitted for the sake of clarity).

about the cyclopropanes based preparation of tetrahydropyridine. After attempting various conditions, we obtained the expected result in xylene under reflux condition in a facile manner; the transformation did not require any reagent or catalyst and also did not produce any byproduct.

At the beginning of our studies, dimethoxy-substituted phenyl ring containing DAC **1b** and VA **2a** were chosen as model substrates to optimize the conditions for [3 + 2]-cycloaddition reactions. An extensive screening of Lewis acids revealed following two reaction conditions: (1) using MgI_2 (20 mol %) in DCM (condition A) reaction proceeds with excellent diastereoselectivity, but it required a longer time and gave a moderate yield (Table 1, entry 4); (2) with $InCl_3$ (20 mol %) in DCM (condition B) reaction proceeds with low diastereoselectivity within a very short time and gave an excellent yield (Table 1, entry 12).

Under both optimized reaction conditions, the scope and limitations of the reaction were explored with various DACs and VAs, and the results are depicted in Scheme 2. More activated DACs bearing electron-donating functionalities in the vicinal phenyl ring took part in the reaction more effectively. Employing condition B, DAC bearing a mono-, di-, and trimethoxy-substituted phenyl ring (**1a**, **1b**, and **1c**, respectively) gave an excellent yield in a short reaction time although the diastereoselectivity observed was very poor. Whereas, under condition A, these DACs gave a moderate yield with excellent diastereoselectivity. A DAC incorporating heterocycle (**1h**) was also tested in both reaction conditions, and the same result was reflected as in the cases of DACs bearing electron-donating groups. Less activated DACs such as *p*-tolyl, a phenyl ring containing DACs (**1i**, **1j**), did not take part in the reaction under condition A; however, they gave the desired cycloadduct

Table 1. Lewis Acid Catalyzed [3 + 2]-Cycloadditions of VA and DAC: Optimization of Reaction Conditions[a]

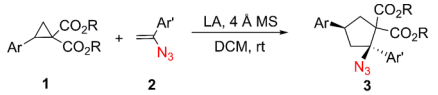


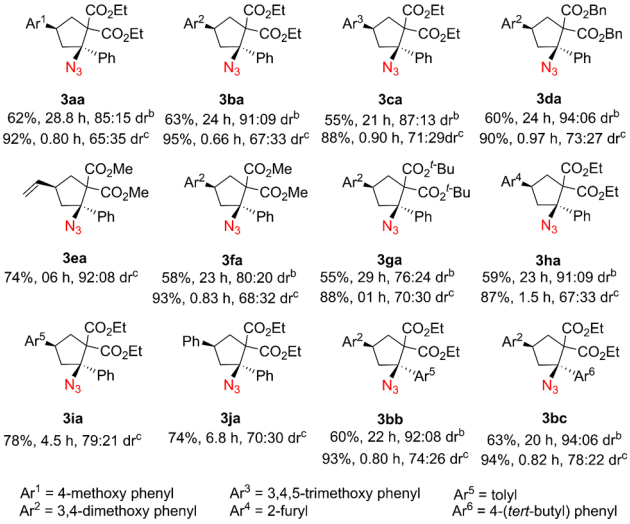
1b Ar = 3,4-dimethoxy phenyl | **2a** | **3ba** *anti* | **3ba** *syn*

entry	Lewis acid	LA (mol %)	solvent	yield (%)[b]	time (h)	dr[e]
1	–	–	DCM	n.r.[c]	48	–
2	MgI_2	05	DCM	20	36	91:09
3	MgI_2	10	DCM	38	36	91:09
4	MgI_2	20	DCM	63	24	91:09
5	$MgBr_2$	20	DCM	58	25	70:30
6	$Mg(OTf)_2$	20	DCM	47	22	70:30
7	$BF_3.OEt_2$	20	DCM	c.m.[d]	4	–
8	$TiCl_4$	20	DCM	48	5	71:29
9	$Cu(OTf)_2$	20	DCM	78	34	78:22
10	$Sc(OTf)_3$	20	DCM	80	3	75:25
11	$Sn(OTf)_2$	20	DCM	83	2	74:26
12	$InCl_3$	20	DCM	95	0.6	67:33
13	$InCl_3$	40	DCM	95	0.6	67:33
14	$InCl_3$	20	xylene	75	3	67:33
15	InI_3	20	DCM	85	1.5	78:22
16	$In(OTf)_3$	20	DCM	89	1	65:35

[a]Reactions were carried out with 1 equiv of **1b** and 1 equiv of **2a** in the presence of molecular sieves (4 Å). [b]Isolated yields. [c]n.r. = no reaction. [d]c.m. = complex mixture. DCM = dichloromethane. [e]dr = diastereomeric ratio was determined by ^1H NMR analysis of the reaction mixture.

Scheme 2. [3 + 2]-Cycloaddition Reaction between VA and DAC: Substrate Scope[a]





Ar^1 = 4-methoxy phenyl; Ar^2 = 3,4-dimethoxy phenyl; Ar^3 = 3,4,5-trimethoxy phenyl; Ar^4 = 2-furyl; Ar^5 = tolyl; Ar^6 = 4-(*tert*-butyl) phenyl

[a]Unless otherwise specified, all reactions were carried out in DCM at rt with 1 equiv of **1** and 1 equiv of **2** in the presence of a Lewis acid (20 mol %) and 4 Å molecular sieves (200 wt %). [b]Isolated yields, reaction time, and diastereomeric ratios with MgI_2. [c]Isolated yield, reaction time, and diastereomeric ratios with $InCl_3$ (for details see the Supporting Information).

DOI: 10.1021/acs.orglett.6b03276
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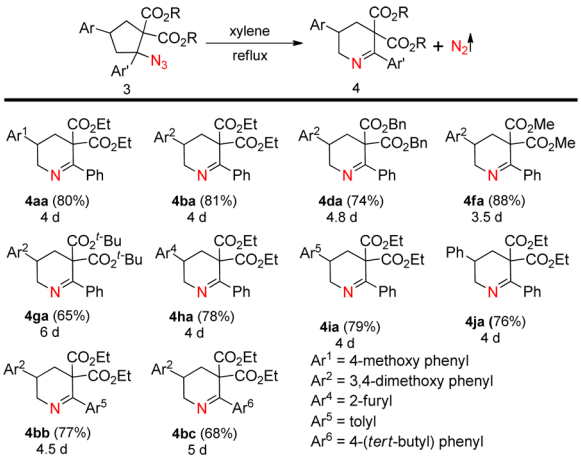
under condition B, with low diastereoselectivity. A DAC bearing *ortho*-substituted phenyl ring, such as *o*-tolyl (**1k**), did not take part in the reaction under both conditions. This may be due to the steric repulsion of substituents. Varieties of other DACs containing different ester groups (**1d**, **1f**, **1g**) were tested to check the effect of the size of ester group in the transformation, but no such profound effect was noticed. Subsequently, the substrate scope with respect to VA was evaluated. Both VAs containing a *p*-methyl (**2b**) and *p*-*tert*-butyl (**2c**) substituted phenyl ring gave almost the same result as VA (**2a**) bearing a simple phenyl ring. A VA containing an *ortho*-substituted phenyl ring (**2d**) did not give the desired product in both conditions. A VA containing a *p*-methoxy-substituted phenyl ring (**2e**) also failed to give the desired product.

Having prepared a series of [3 + 2]-cycloadducts, the feasibility of the rearrangement reaction was examined (Scheme 3). The first aryl (Ar) ring has a minor effect on this

Scheme 3. Ring Expansion of Azidocyclopentanes (3) to Tetrahydropyridines (4)[a]



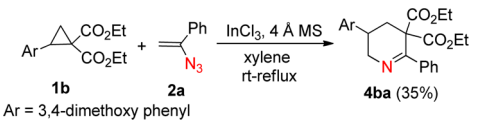
[a]Unless otherwise specified, all reactions were carried out in xylene under reflux conditions.

rearrangement, as in all the cases (**4aa**, **4ba**, **4ha**, **4ia**, and **4ja**) the yields and reaction times are almost the same. In this context, the variation of the ester functionality played a significant role in both the reaction rate and yield. A gradual increase in the size of the ester functionality from methyl ester to *tert*-butyl ester (**4fa**–**4ga**) led to a lower yield and longer reaction time. This might be due to the steric hindrance on the reaction center. The substituent on the second aryl ring (Ar′) (**4bb**, **4bc**) also altered the reaction time and yield of the reaction.

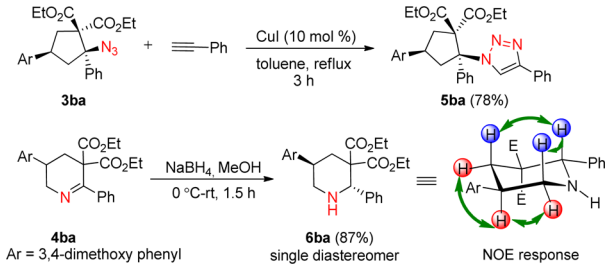
To achieve the formal [3 + 3]-cycloaddition, we led the transformation in one pot by starting the reaction of **1b** and **2a** using $InCl_3$ as the catalyst in xylene (Scheme 4). We could gratifyingly attain the desired product (**4ba**), although the yield (35%) was not impressive.

Furthermore, to show the potential of the developed methodology, the azidocyclopentane **3ba** was subjected to an azide–alkyne click reaction[13] to obtain triazole derivative **5ba** (Scheme 5), which is the structural scaffold for bioactive compounds.[14] A diastereospecific reduction of tetrahydropyridine derivative **4ba** was also performed, using $NaBH_4$,[15] to synthesize piperidine **6ba**, as a single diastereomer. In this

Scheme 4. Formal [3 + 3]-Cycloaddition Reactions of DAC and VA



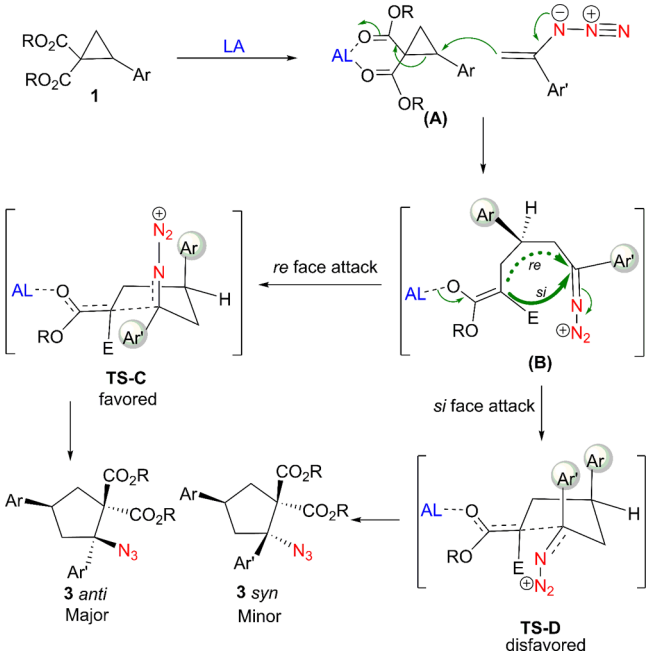
Scheme 5. Chemical Transformations of 3ba and 4ba



transformation, a new stereogenic center was generated. The geometry of **6ba** was determined using NOE studies.

On the basis of previous reports and our observations, a plausible mechanism for both, cycloaddition and ring expansion reactions, is given in Scheme 6. Initially, the Lewis acid activates

Scheme 6. Plausible Mechanism



the DAC to form intermediate **A**. Upon an enamine type nucleophilic attack of VA on intermediate **A**, an open chain intermediate **B** is formed (Scheme 6A). The nucleophilic attack happened in an almost S_N2 fashion which was experimentally proven by carrying the cycloaddition reaction with enantiomercally pure DAC, which in turn gave an enantioenriched cycloadduct (for details see the Supporting Information). Intermediate **B** undergoes a cyclization reaction through either *re*-face or *si*-face attack. In the *re*-face attack, reaction proceeds through **TS-C**, whereas, in the *si*-face attack, reaction proceeds through **TS-D**. **TS-C** contains two bulky substituents (Aryl ring) on different sides, whereas **TS-D** contains two bulky substituents on the same side. Therefore, **TS-C** becomes the

DOI: 10.1021/acs.orglett.6b03276
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favored **TS** and **TS-D** the disfavored one. Subsequently, cyclization through the **TS-C** led to the formation of *anti* isomer **3** as a major diastereomer while cyclization through **TS-D** led to *syn* isomer **3** as a minor diastereomer.

On heating, azidocyclopentane **3** undergoes ring expansion in a chemoselective manner, through elimination of nitrogen, to give tetrahydropyridine **4** (Scheme 6B).

In conclusion, [3 + 2]-cycloaddition reactions between donor−acceptor cyclopropanes and vinyl azides, using various Lewis acid catalysts, have been explored to obtain diastereomerically enriched azide functionalized cyclopentane derivatives. Using the ring expansion of azidocyclopentanes, we report the first DAC-based preparation of tetrahydropyridines. Additionally, we also demonstrate the concise chemical conversion of azidocyclopentane and tetrahydropyridine to a triazole and piperidine derivative, respectively. Further application of this protocol toward natural product synthesis and development of a catalytic enantioselective version of the present transformation are in progress 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.6b03276.

Copies of ^{1}H, ^{13}C NMR, and IR spectra, mass data of all new compounds, single-crystal X-ray data (PDF)
Crystallographic data (CIF, CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to acknowledge financial assistance from the Department of Science and Technology, New Delhi (Project No. EMR/2015/002332). R.D. thanks IIT Ropar for his research fellowship. The authors also acknowledge Dr. C. M. Nagaraja, Department of Chemistry, IIT Ropar, for solving the single-crystal structures presented in this work.

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DOI: 10.1021/acs.orglett.6b03276
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