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Zn(II)-Catalyzed Synthesis of Piperidines from Propargyl Amines and Cyclopropanes

Terry P. Lebold, Andrew B. Leduc, and Michael A. Kerr*

Department of Chemistry, The University of Western Ontario, London, Ontario, Canada N6A 5B7

makerr@uwo.ca

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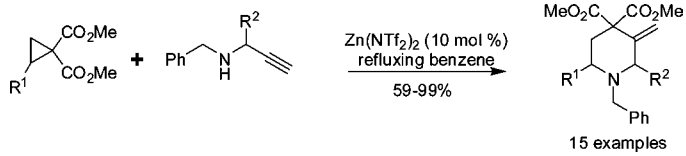
ABSTRACT



The reaction of benzyl-protected propargyl amines and 1,1-cyclopropane diesters in the presence of catalytic $Zn(NTf_2)_2$ allows access to highly functionalized piperidines in excellent yields. The process proceeds via a tandem cyclopropane ring-opening/Conia−ene cyclization.

The prominence of the piperidine ring in both natural products and therapeutic agents cannot be overstated; its ubiquity in both natural and unnatural bioactive compounds is a testament to this[1] (Figure 1 shows several representative examples of interest to our group[2]). New and efficient methods for the preparation of this heterocycle stand to be of great importance to synthetic and medicinal chemists.[3] In this paper, we present a unique process which accesses piperidines in an extraordinarily efficient manner via a tandem cyclopropane ring-opening/Conia−ene cyclization.

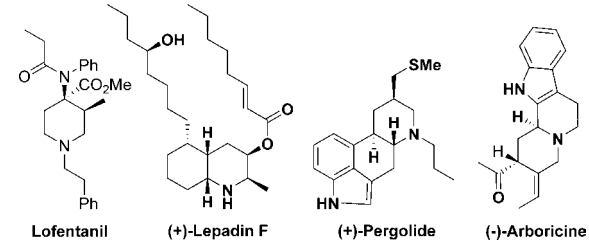


Figure 1. Biologically active piperidines.

The Conia−ene[4] reaction has received much attention in recent years due to its usefulness in C−C bond formation. While there has been considerable advancement of this reaction,[5−8] it has almost exclusively focused on five-membered ring

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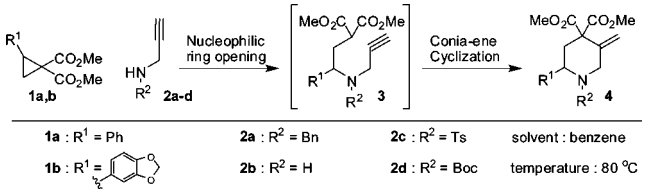
formation[4,5] with only a handful of reports on the formation of larger ring systems.[6,7] It occurred to us that the nucleophilic ring-opening of a 1,1-cyclopropane diester with a propargylic amine would provide a substrate suitable for Conia−ene cyclization, which in turn would furnish a piperidine ring. Furthermore, we surmised that with the judicious choice of Lewis acid catalyst, the process (as illustrated in Table 1) could be made both tandem and

Table 1. Optimization of Tandem Ring-Opening/Conia−Ene Cyclization



entry	cyclopropane	amine	conditions[a]	yield[b] (%)
1	**1a**	**2a**	$Sc(OTf)_3$ (5 mol %), $ZnBr_2$ (2 equiv), amine (2 equiv)	82
2	**1a**	**2a**	$Zn(OTf)_2$ (20 mol %), amine (2 equiv)	77
3	**1a**	**2a**	$Zn(NTf_2)_2$ (20 mol %), amine (2 equiv)	94
4	**1a**	**2a**	$In(OTf)_3$ (5 mol %), amine (2 equiv)	no reaction
5	**1b**	**2a**	$Zn(NTf_2)_2$ (20 mol %), amine (2 equiv)	97
6	**1b**	**2a**	$Zn(NTf_2)_2$ (10 mol %), amine (1.3 equiv)	95
7	**1b**	**2a**	$Zn(NTf_2)_2$ (5 mol %), amine (1.2 equiv)	98
8	**1a**	**2b**	$Zn(NTf_2)_2$ (10 mol %), amine (1.3 equiv)	no reaction
9	**1a**	**2c**	$Zn(NTf_2)_2$ (10 mol %), amine (1.3 equiv)	no reaction
10	**1a**	**2d**	$Zn(NTf_2)_2$ (10 mol %), amine (1.3 equiv)	no reaction

[a] Cyclopropane, propargyl amine, and catalyst were dissolved in 3 mL of benzene, and the reaction was brought to reflux. Upon completion, a small amount of Li_2CO_3 was added and the reaction was purified by column chromatography. [b] Isolated yield.

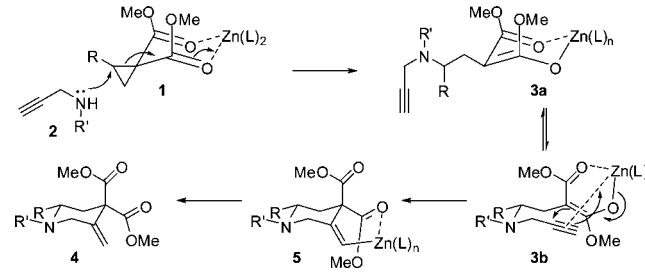
catalytic. Given the considerable interest in the annulation reactions of 1,1-cyclopropane diesters[9] and our work within this field,[9a−c] we felt well-positioned to engage this project. Herein we report an efficient synthesis of piperidines in a catalytic tandem fashion from simple readily available starting materials.

Table 1 outlines both the proof of principle and the search for optimal reaction conditions. Our initial reaction involved treatment of 1,1-cyclopropane diester **1a** and propargyl amine **2a** with 5 mol % of $Sc(OTf)_3$ in refluxing benzene which, after several hours, led only to the ring-opened product **3**.[10] However, treatment of that reaction mixture with 2 equiv of $ZnBr_2$ gratifyingly induced Conia−ene cyclization to give the desired piperidine in an 82% isolated yield.[11] While this two-step, one-pot approach worked well, we still desired a single catalyst capable of inducing both cyclopropane ring opening and subsequent ring closure. While treatment with $In(OTf)_3$ led to no reaction, we were pleased to discover that treatment with 20 mol % of $Zn(OTf)_2$ resulted in a 77% yield of the desired piperidine along with a small amount of unreacted starting material. However, when the more reactive $Zn(NTf_2)_2$[12] was employed, we obtained the desired piperdine in 94% yield.

With the identification of $Zn(NTf_2)_2$ as the superior catalyst we next explored the catalyst loading and amine stoichiometry to find that the reaction would still proceed in excellent yield with just 5 mol % of $Zn(NTf_2)_2$ and 1.2 equiv of the amine (although longer reaction times were required). We therefore settled on the use of 10 mol % of $Zn(NTf_2)_2$ since it allowed for completion of the reaction within 24 h. Neither the primary amine, *N*-Boc, or *N*-tosyl derivatives resulted in the formation of the desired product.

A plausible mechanism for the tandem reaction is presented in Scheme 1. Initial coordination of the diesters by zinc facilitates

Scheme 1. Plausible Mechanism



the nucleophilic ring-opening of the 1,1-cyclopropane diester by the amine to yield intermediate **3**. Subsequent coordination of the alkyne then allows for malonate addition and ring closure. Protonation of the zinc metalate leads to the desired piperidine and regeneration of the zinc catalyst.

With our optimized conditions in hand, we next investigated the scope of the reaction using propargyl amine **2a** and a variety of substituted 1,1-cyclopropane diesters (Table 2). Both simple phenyl substituents (product **4a**) as well as electron-rich aromatics (products **4b**,**c**) performed superbly. While mildly electron-withdrawing groups on the phenyl ring (such as *p*-Br and *p*-Cl) worked well under our standard conditions, yielding **4f** and **4g**, the presence of *p*-CN and *p*-CO_2Me substituents necessitated a higher catalyst loading as well as an increased

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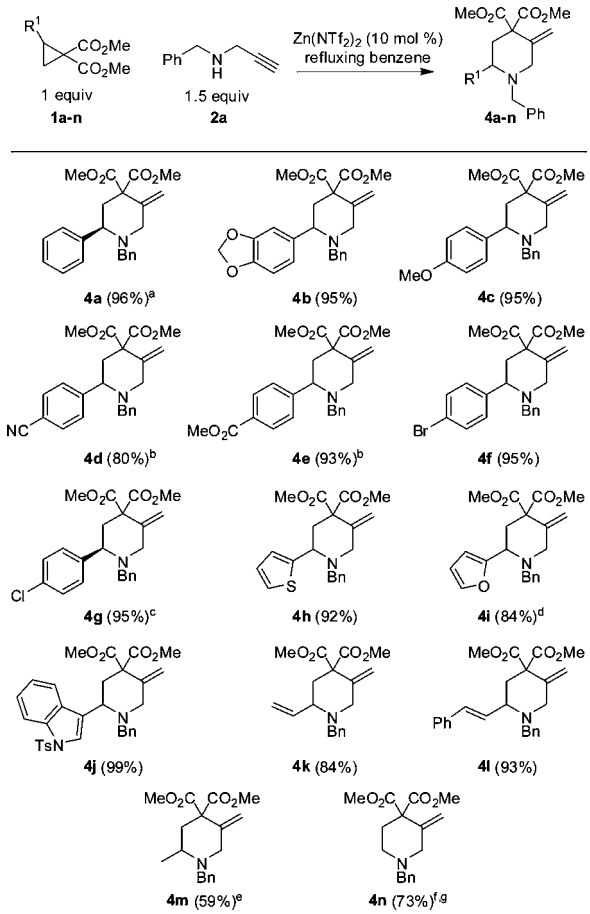
Table 2. Reaction Scope



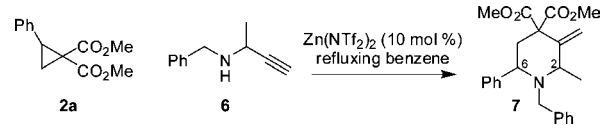
[a] Product obtained in 96% ee. [b] $Zn(NTf_2)_2$ (30 mol %) and amine (3 equiv) were employed. [c] Product obtained in 98% ee. [d] $Zn(NTf_2)_2$ (20 mol %) and amine (3 equiv) were employed in order to avoid decomposition of product which occurred under prolonged heating. [e] $Zn(NTf_2)_2$ (20 mol %) and amine (3 equiv) were employed. [f] Toluene was used as solvent. [g] $Zn(NTf_2)_2$ (15 mol %) and amine (1.5 equiv) were employed.

amount of amine to achieve high yields of **4d** and **4e**. Heteroaromatic substituents could also be employed leading to excellent conversions to piperidines **4h**−**j**. The cyclopropane could also bear alkenyl groups, alkyl groups, or no substitution at all. Furthemore, when homochiral cyclopropanes[13] were employed the chirality was maintained in the piperidine product without erosion of ee (products **4a** and **4g**).

We next investigated the effect of an α chiral amine on the diastereoselectivity of the reaction (Table 3). In order to see if any innate diastereoselectivity could be observed, we treated racemic cyclopropane **2a** with an excess of racemic propargyl amine **6**; however, only a 1:1 mixture of racemic diastereomers was obtained albeit in excellent yield.[14] The use of optically active methyl (*R*)-propargyl amine with either optically active (*R*)-**2a** or (*S*)-**2a** resulted, as expected, in the formation of either the *cis*- or *trans*-2,6-disubstituted piperidines, respectively.

In summary, we have developed a Zn(II)-catalyzed reaction of 1,1-cyclopropane diesters and propargyl amines which allows access to highly substituted piperidines in excellent yields. Notably, the reaction is tandem, catalytic, and atom-economical and occurs under mild reaction conditions. If either optically active amines or 1,1-cyclopropane diesters are employed the chirality is conserved in the piperidine product without erosion of ee.

Table 3. Effects of α-Chirality of the Propargyl Amine



entry	cyclopropane	amine	piperidine	yield (%)
1	*rac*	*rac*	*R,R*:*S,S*:*R,S*:*S,R*	98[d]
2	*R*[a]	*S*[c]	2*S*,6*S*	95[e]
3	*S*[b]	*S*[c]	2*S*,6*R*	96[e]

[a] 98% ee. [b] 98% ee. [c] >99% ee. [d] 1:1 mixture of racemic diastereomers. [e] Diastereomeric purity >97%.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (*R*)-Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate 98% ee, (*R*)-dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate 98% ee.

(14) It is noteworthy that an excess of racemic cyclopropane with optically pure amine showed no kinetic resolution.