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A Mild Procedure for the Lewis Acid-Catalyzed Ring-Opening of Activated Cyclopropanes with Amine Nucleophiles

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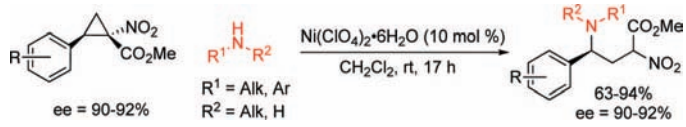
ABSTRACT



The Lewis acid-catalyzed ring-opening of methyl 1-nitrocyclopropanecarboxylates with amine nucleophiles is described. The reaction proceeds at room temperature and with complete preservation of the enantiomeric purity from the electrophilic center of the cyclopropane to the acyclic product. The methodology was applied in an enantioselective synthesis of the dual serotonin/norepinephrine reuptake inhibitor (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine.

The ring opening of activated cyclopropanes provides a versatile route for the construction of functionalized carbon skeletons.[1] The numerous approaches that have been used to fragment the three-membered ring depend on the functionalities present on the cyclopropane and can be broadly divided into two classes. The first class includes the reactions of donor−acceptor cyclopropanes that bear oxygen or amine functionalities as the donor substituents and electron-withdrawing groups as the acceptor substituents.[1b,2] The second class involves the reactions of the electrophilic cyclopropanes, which may be activated by *cation-stabilizing* groups and electron-withdrawing groups in a similar 1,2 relationship.[1a] Within the latter class of reactions, much work has recently been reported on the formal [3 + 2] cycloadditions,[3] which typically employ mild conditions (Lewis acid catalysis and ambient temperature) to yield various cyclic products. However, the generation of acyclic products via strictly nucleophilic processes[4] almost invariably requires elevated temperatures and/or basic conditions,[5] with the exception of organometallic reagents.[6] Such vigorous reaction conditions can lead to various undesired side reactions, such

(1) For reviews, see: (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (d) Burritt, A.; Coron, J. M.; Steel, P. J. *Trends Org. Chem.* **1993**, *4*, 517.

(2) (a) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603. (b) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631. (c) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157.

(3) For recent examples, see: (a) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (b) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (c) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. (d) Perreault, C.; Goudreau, S.; Zimmer, L.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689.

(4) Such processes do not involve an intitial reaction of the cyclopropane with an electrophile. For examples of this class of reactions, see: (a) Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2414, and references therein. (b) Dieter, R. K.; Pounds, S. *J. Org. Chem.* **1982**, *47*, 3174.

(5) Only a 2-unsubstituted and highly activated *gem*-1,1-dinitro-cyclopropane has been ring-opened with amine nucleophiles at ambient temperature and under neutral conditions: Budynina, E. M.; Ivanova, O. A.; Averina, E. B.; Kuznetsova, T. S.; Zefirov, N. S. *Tetrahedron Lett.* **2006**, *47*, 647. For typical conditions, see: (a) Stewart, J. M.; Westberg, H. H. *J. Org. Chem.* **1965**, *30*, 1951. (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313. (c) Vettiger, T.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 195. (d) Seebach, D.; Haener, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507. (e) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron* **1990**, *21*, 7341. (f) Blanchard, L. A.; Schneider, J. A. *J. Org. Chem.* **1981**, *46*, 4042. (g) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561.

(6) See, for example: (a) Bambal, R.; Kemmitt, R. D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 734. (b) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373.

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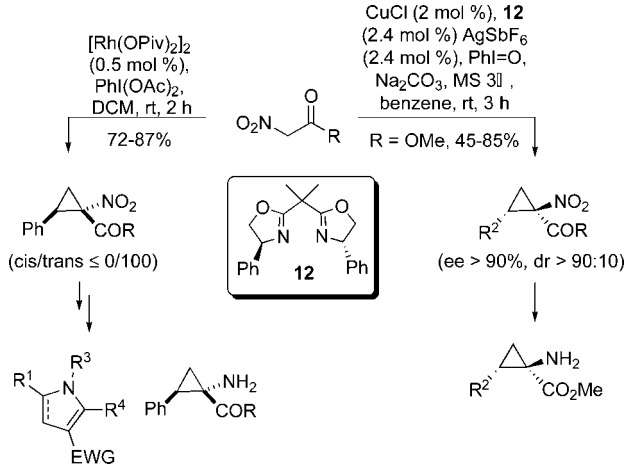
as an intramolecular rearrangement of the cyclopropane.[5a,c–e,7]

Our group has recently developed efficient methodologies to generate diverse 1-nitrocyclopropane-carbonyls in both racemic[8] and enantiomerically enriched[9] forms, which have been used to synthesize substituted dihydropyrroles and pyrroles,[5b] and cyclopropane α-amino acids[10] and esters[9] (Scheme 1).

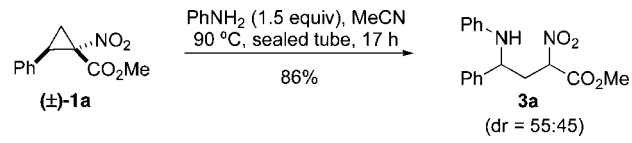
Scheme 1. Synthesis of Racemic and Enantioenriched 1-Nitrocyclopropanecarbonyls and Their Applications[5c,8–10]



To further extend the utility of these cyclopropanes, we sought to develop a procedure for their ring-opening with heteroatom nucleophiles, thereby generating acyclic 1,3-bifunctional molecules. Herein, we report such a method for the ring-opening of methyl 1-nitrocyclopropane carboxylates with amine nucleophiles under Lewis acid catalysis and at ambient temperature, which completely preserves the enantiomeric excess of the cyclopropane at the electrophilic center. The methodology was applied toward the synthesis of a dual serotonin/norepinephrine reuptake inhibitor (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine **9**.[11]

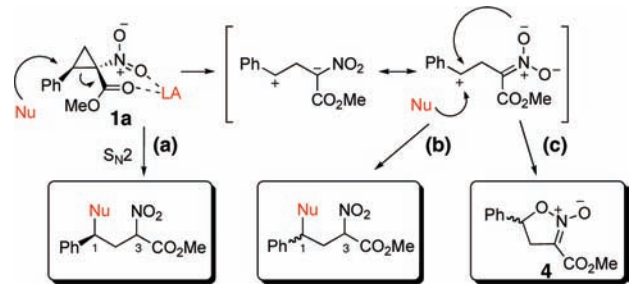
We first tested the ring-opening under thermal conditions, reacting (±)-**1a** with a 5-fold excess of aniline in refluxing methanol. Complete conversion was achieved after 17 h, affording the desired product **3a** in 78% yield. By optimizing the reaction conditions, we found that the aniline loading could be reduced to 1.5 equiv. Carrying out the reaction in acetonitrile at 90 °C suppressed minor side reactions,[12] affording the product cleanly in 86% yield (Scheme 2). However, the reaction of the more sterically hindered

Scheme 2. Ring Opening of (±)-**1a** with Aniline Under Optimized Thermal Conditions



o-bromoaniline under the optimized conditions afforded the ring-opened product in only 15% yield. To overcome this, we turned our attention to the development of a Lewis acid-catalyzed version of this reaction at ambient temperature. It became evident that the relative strength of the Lewis acid was critical in determining the mechanistic pathway of the ring-opening reaction (Scheme 3). Highly activating bidentate

Scheme 3. Possible Mechanisms of a Bidentate Lewis Acid-Catalyzed Cyclopropane Ring Opening



($AlCl_3$, $SnCl_4$) and monodentate (BF_3•Et_2O) Lewis acids generated, in addition to the ring-opened product, the rearrangement product **4** in varying amounts and with loss of enantiomeric excess.[13] This presumably occurs by a Lewis-acid catalyzed ring-opening of the cyclopropane into a zwitterionic species prior to the nucleophilic attack (Scheme 3, pathway c). Such unimolecular ionization[14] could also result in the racemization of the stereogenic center at C-1 in the ring-opened product (pathway b). In contrast, weakly activating Lewis acids ($Cu(OTf)_2$, $ZnCl_2$, $Ti(OiPr)_4$), though preserving the enantiomeric excess at C-1, gave only very low conversion.[13] Although $Y(OTf)_3$ was found to be a good catalyst,[13] the optimal results were obtained with $Ni(ClO_4)_2$•$6H_2O$ (10 mol %),[15] which cleanly catalyzed the ring-opening of **1a** by aniline with full conversion after 17 h and complete preservation of the enantiomeric excess at the

(7) Nitrocyclopropanecarboxylates can isomerize to nitroisoxazoline *N*-oxides by the action of heat, halide ions and certain Lewis and protic acids: Bianchini, L.; Dell'Erba, C.; Gasparrini, F.; Novi, M.; Petrillo, G.; Sancassan, F.; Tavani, C. *Arkivoc* **2002**, 142.

(8) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327.

(9) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014.

(10) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262.

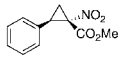
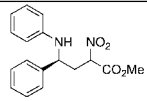
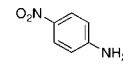
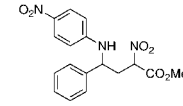
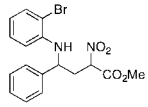
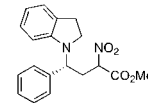
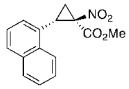
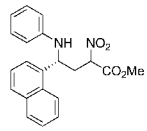
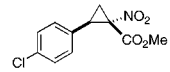
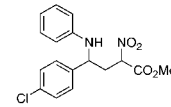
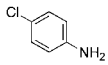
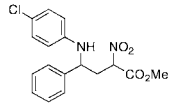
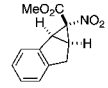
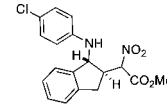
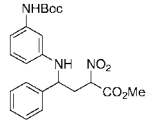
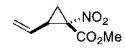
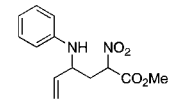
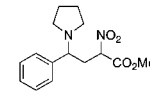
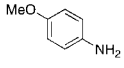
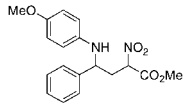
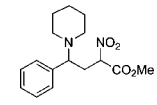
(11) Mahaney, P. E.; Vu, A. T.; McComas, C. C.; Zhang, P.; Nogle, L. M.; Watts, W. L.; Sarkahian, A.; Leventhal, L.; Sullivan, N. R.; Uveges, A. J.; Trybulski, E. J. *Bioorg. Med. Chem.* **2006**, *14*, 8455.

(12) A lactam product resulting from the condensation of the ester and amine moieties in **3a** was observed in small amounts (< 10%) when the reaction was carried out in toluene in a sealed tube at 110 °C for 17 h. Only with longer reaction time (2d) could the lactam product be obtained with significant conversion (78% by ^{1}H NMR, with the remaining material being **3a**), suggesting that temperatures above 90 °C are required for this transformation.

(13) See Supporting information for Lewis acid screening.

(14) (a) Danishefsky, S.; Rovnyak, G. *J. Chem. Soc., Chem. Commun.* **1972**, 821, and references therein. (b) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597.

Table 1. $Ni(ClO_4)_2 \cdot 6H_2O$-Catalyzed Ring Opening of 1-Nitro-cyclopropanecarboxylates by Amine Nucleophiles[a]

entry	cyclopropane (ee%)	amine	product	yield (%),[a,b] (ee%)	entry	cyclopropane (ee%)	amine	product	yield (%),[a,b] (ee%)
1	 **1a** (92)	 **2a**	 **3a**	82 (92)	8	(±)-**1a**	 **2g**	 **3h**	92[c]
2	(±)-**1a**	 **2b**	 **3b**	83	9	*ent*-**1a** (90)	 **2h**	 **3i**	94 (90)
3	 **1b** (92)	**2a**	 **3c**	73 (92)	10	 **1c**	**2a**	 **3j**	74
4	(±)-**1a**	 **2c**	 **3d**	86	11	 **1d**	**2c**	 **3k**	78
5	(±)-**1a**	 **2d**	 **3e**	66	12	 **1e**	**2a**	 **3l**	76
6	(±)-**1a**	 **2e**	 **3f**	80	13	(±)-**1a**	 **2i**	 **3m**	90[c,d]
7	(±)-**1a**	 **2f**	 **3g**	71	14	(±)-**1a**	 **2j**	 **3n**	63[c]

[a] Reaction conditions: **1** (1 equiv), **2** (1.5 equiv), $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol %), CH_2Cl_2 (2.3 M), rt, 16 h. [b] Yield of isolated product. [c] Reaction time 48 h. [d] **2i** (2.1 equiv) was used.

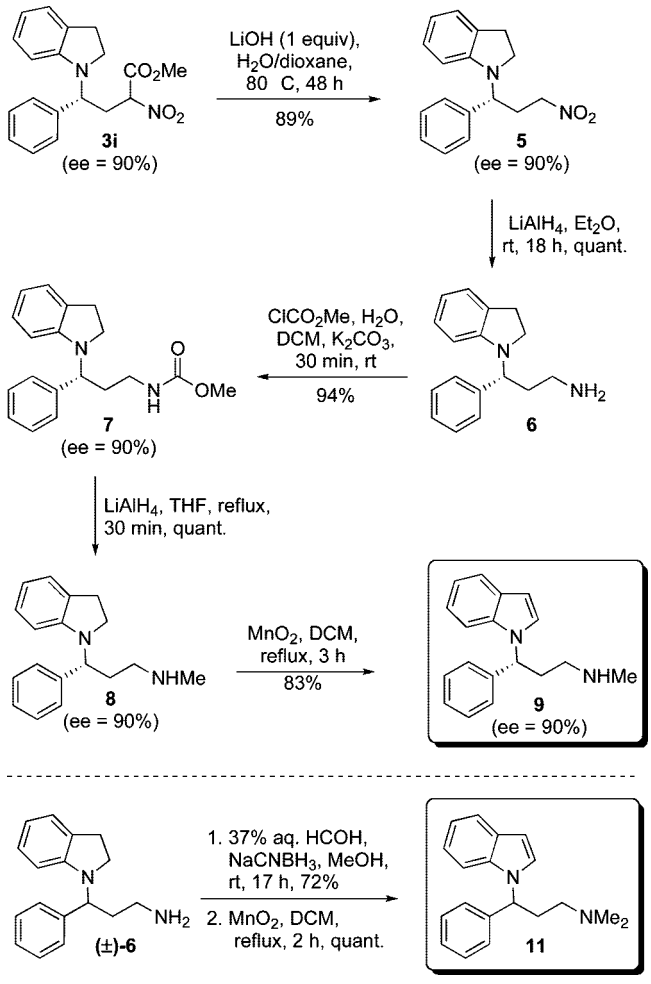
electrophilic center. Interestingly, addition of molecular sieves to the reaction changed the nature of this Lewis acid dramatically, giving only the rearrangement product **4** after 1 h in the absence of the nucleophile, and a sluggish conversion in the presence of the nucleophile.

With the optimal conditions in hand, we examined the substrate scope using various amine nucleophiles (Table 1). Reaction with aniline afforded the ring-opened product in 82% yield and with complete preservation of the cyclopropane's enantiomeric excess at the electrophilic center (Table 1, entry 1). We were pleased to find that the sterically hindered *o*-bromoaniline worked equally well, affording the ring-opened product in 83% yield (entry 2). Secondary aromatic amines (entries 6, 9) similarly gave the ring-opened product in good to excellent yields, as did electron-rich (entry 7) and halogen-substituted (entries 2, 4) aniline derivatives. As expected, the electron-poor *p*-nitroaniline (entry 8) resulted in a slower reaction, but full conversion was achieved after 48 h, with an excellent isolated yield. Boc-protected amines were found to be stable to the reaction conditions, allowing for the introduction of a second amine functionality (entry 5), which could potentially be deprotected and further derivatized. Varying the substituents at the 2-position of the cyclopropane to a *p*-chlorobenzyl (entry 3), naphthyl, indenyl, and vinyl groups (entries 10−12) also gave the addition products in good yields and with the same regioselectivity. Finally, aliphatic amines were tested under the reaction conditions. Unfortunately, their high basicity resulted in a strong complexation to the catalytic Lewis acid, which considerably slowed down the reaction. Only the more nucleophilic pyrrolidine (entry 13) and piperidine (entry 14) gave synthetically useful isolated yields with longer reaction times.

In all cases, a mixture of interconverting diastereomers at C-3 (Scheme 3) was obtained, in approximately a 1:1 ratio, except for the products **3k** (70:30 dr) and **3m** (60:40 dr).

(15) For the use of $Ni(ClO_4)_2$ to activate cyclopropane *gem*-diester derivatives, see ref 3d and: (a) Kang, Y.-B.; Sun, X. L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918. (b) Sibi, M. P.; Ma, Z. H.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764.

Scheme 4. Synthesis of the Dual Serotonin/Norepinephrine Reuptake Inhibitor **9** and its *N*-Dimethyl Analogue **11**



When enantioenriched cyclopropanes were used as starting materials, the reactions proceeded with an S_N2 inversion of the absolute stereochemistry at C-1 (Scheme 3).[16]

We next applied the methodology in an enantioselective synthesis of the dual serotonin/ norepinephrine reuptake inhibitor (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine **9** (Scheme 4).[11] Starting for the readily synthesized adduct **3i** (Table 1, entry 9), saponification and decarboxylation of the methyl ester with aqueous LiOH at 80 °C afforded the nitro compound **5** which was reduced to the primary amine **6** in 89% yield over 2 steps. The amine was *N*-methylated in two steps via a carbamate derivative **7** to give the indoline compound **8** which was oxidized to indole, furnishing the neurotransmitter reuptake inhibitor **9** in an overall 65% yield and 90% ee. A similar approach was used to synthesize the *N*-dimethyl analogue 3-(1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenyl-propan-1-amine **11**.[11] Starting from (±)-**6**, reductive amination and indoline oxidation afforded the neurotransmitter reuptake inhibitor **11** in a 60% overall yield over 5 steps (Scheme 4). By varying the substituents on the cyclopropane and the indole reagents which have been shown to impart different biological activity,[11] various enantioenriched derivatives of the inhibitor could in principle be easily accessed.

In conclusion, we developed a very mild and efficient Lewis acid-catalyzed ring opening reaction of methyl 1-nitrocyclopropanecarboxylates with amine nucleophiles. The reaction proceeds at room temperature and with complete preservation of the enantiomeric excess at the electrophilic center of the cyclopropane, tolerating a variety of amine nucleophiles as well as substituents in the 2-position of cyclopropane ring. The racemic or enantioenriched 1,3-bifunctional molecules generated can serve as useful synthetic precursors for further functionalization. A dual serotonin/ norepinephrine reuptake inhibitor was synthesized in an expedient and high-yielding route employing the cyclopropane ring-opening reaction as the first step of the synthesis.

Acknowledgment. This work was supported by the Natural Science and Engineering Research Council of Canada (NSERC), Merck Frosst Canada Ltd., Boehringer Ingelheim (Canada), Ltd., the Canada Research Chairs Program, the Canadian Foundation for Innovation, and the Université de Montréal. O.L. is grateful to NSERC for a postgraduate scholarship (CGSM). We thank Dr. Dino Alberico for helpful discussions and Jad Tannous (Université de Montréal) for SFC analyses.

Supporting Information Available: Experimental procedures, NMR spectra, SFC chromatograms, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Absolute stereochemistry was established by comparing the optical rotation of the compound **9** derived from the ring-opening of cyclopropane ***ent*-1a**, with the literature value (see Supporting information). The observed $[\alpha]_D$ suggests an inversion of the absolute stereochemistry at C-1 (Scheme 3) from the starting cyclopropane (see ref. [9] for absolute stereochemistry of ***ent*-1a**) and hence an S_N2 mechanism.