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Lewis Acid Catalyzed Annulation of Nitrones with Oxiranes, Aziridines, and Thiiranes

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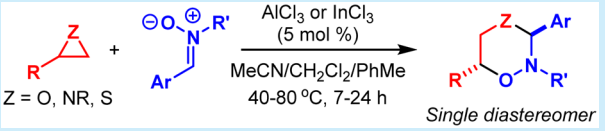
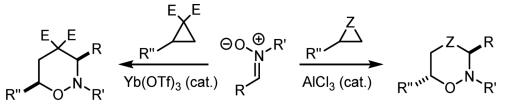
Supporting Information

ABSTRACT: A highly selective Lewis acid catalyzed annulation of three-membered heterocycles with nitrones has been developed. Oxiranes, aziridines, and thiiranes were used as substrates for the synthesis of various six-membered heterocycles using Al or In catalysts. This catalytic protocol demonstrates a broad substrate scope and provides access to new structural motifs in high yields and in excellent selectivity under mild reaction conditions.



Functionalized nitrogen-containing heterocycles are common structural motifs in natural products, pharmaceuticals, and agrochemicals. In particular, the importance of saturated heterocycles (high sp^3-content) in drug discovery has recently been highlighted.[1] One important strategy for the synthesis of a diverse range of heterocyclic (and carbocyclic) compounds is based on transformations of strained rings such as cyclopropanes, oxiranes, and aziridines.[2] For example, the Lewis acid catalyzed formal cycloaddition of donor−acceptor cyclopropanes to nitrones (Scheme 1), olefins, and other unsaturated reaction partners has been extensively explored for the synthesis of a variety of cyclic structures.[3] Furthermore, oxiranes[4] and aziridines[5] have been utilized as analogous heteroatom-containing building blocks for the construction of heterocycles by the selective cleavage of the C−C or the C−heteroatom bond. As a part of our research program based on catalysis with main-group elements, we envisioned that the catalytic activation of strained heterocycles such as oxiranes would enable the synthesis of *N,O*-linked heterocycles such as 1,4,2-dioxazinane derivatives by a catalytic annulation reaction with nitrones (Scheme 1).

Scheme 1. Transformations of Nitrones and Strained Rings



The 1,4,2-dioxazinane and 1,2,4-oxadiazinane products represent a largely unexplored class of saturated heterocycles; only a few multistep preparative methods have been reported for the purpose of conformational studies and for an evaluation of their pharmaceutical activities.[6]

Various dioxazine and oxadiazine derivatives are, however, found in the skeletons of the *Sarcoviolin* family[7] of naturally occurring antioxidants, as intermediates in natural product synthesis,[8] and in biologically active drug candidates.[9] Fused oxadiazines have been shown to exhibit high activity as γ-secretase modulators[9a] for potential use in the treatment of Alzheimer's disease (Figure 1).

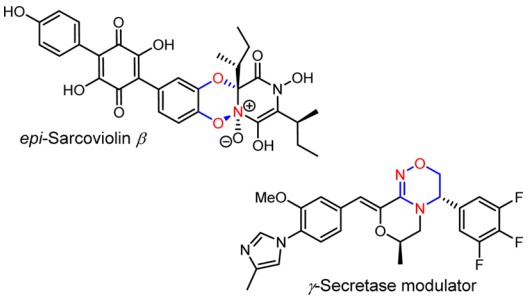


Figure 1. Examples of the dioxazine and oxadiazine motifs.

Herein, we report a new catalytic method for the synthesis of 1,4,2-dioxazinanes (with oxiranes), 1,2,4-oxadiazinanes (with aziridines), and 1,4,2-oxathiazinanes (with thiiranes). At the outset of this study, our focus was directed toward finding an appropriate catalyst and suitable reaction conditions for the annulation of oxirane **1a** with nitrone **2a**. More specifically, we screened for a catalyst and reaction conditions that would suppress the Meinwald rearrangement[10] and the competitive nucleophilic ring opening[11] of the oxirane component. Our initial experiments, using $InCl_3$ (20 mol %) in CH_2Cl_2, afforded the dioxazinane product **3a** in 52% isolated yield after 24 h at 20 °C (Table 1, entry 1).

Interestingly, the product **3a** was obtained as a single diastereomer. The two phenyl groups were found to be positioned in a *trans* relationship (vide infra). When the temperature was increased to 40 °C in the presence of 10 mol % of $InCl_3$, the yield of **3a** increased to 69% after 4 h reaction time

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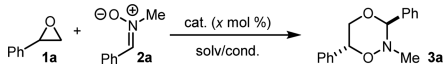
Table 1. Screening of Catalysts and Reaction Conditions[a]



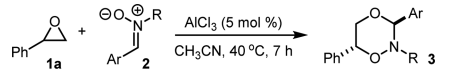
entry	cat. (mol %)	solvent	temp (°C)/time (h)	yield[b] (%)
1	$InCl_3$ (20)	CH_2Cl_2	20/24	52
2	$InCl_3$ (10)	CH_2Cl_2	40/4	69
3	$InBr_3$ (10)	CH_2Cl_2	40/4	80
4	$In(OTf)_3$ (10)	CH_2Cl_2	0/4	70
5	$AlCl_3$ (10)	CH_2Cl_2	40/4	93
6	**$AlCl_3$ (5)**	**CH_3CN**	**40/7**	**98/92**[c]
7	$BF_3{\cdot}OEt_2$ (30)	CH_2Cl_2	40/4	16[d]
8	$FeCl_3$ (10)	CH_2Cl_2	40/4	88
9	$Sc(OTf)_3$ (10)	CH_2Cl_2	0/5	39[d]
10	$ZnCl_2$ (10)	CH_2Cl_2	40/24	62
11	$Zn(OTf)_2$ (10)	CH_2Cl_2	40/4	36[d]
12	TfOH (30)	CH_2Cl_2	40/4	0
13	TfOH (30)	CH_2Cl_2	0/4	20
14	none	CH_3CN	80/24	0[e]

[a]Conditions: oxirane **1a** (0.30 mmol), nitrone **2a** (0.20 mmol), and catalyst were dissolved in the indicated solvent (dry, 0.5 mL) and stirred under Ar atmosphere. [b]Isolated yield unless otherwise stated. [c]5.0 mmol scale. [d]NMR yield. [e]**1a** and **2a** were recovered.

(Table 1, entry 2). Changing the catalyst from $InCl_3$ to $InBr_3$ (Table 1, entry 3) furnished **3a** in 80% yield, whereas $In(OTf)_3$ led to a rapid decomposition of the oxirane (40 °C). However, the product was isolated in 70% yield when the reaction was performed at 0 °C (Table 1, entry 4). Gratifyingly, the use of $AlCl_3$ in CH_2Cl_2 at 40 °C afforded **3a** in 93% yield. MeCN was found to be a slightly better solvent with a 5 mol % catalyst loading (98% yield). Moreover, the reaction could be performed on a 5.0 mmol scale to give an isolated yield of 92% (Table 1, entries 5 and 6). The use of $BF_3{\cdot}$etherate led to a low yield of the desired product (16% yield) (Table 1, entry 7). $FeCl_3$ was found to be an efficient catalyst (88% yield) (Table 1, entry 8), while Sc- and Zn-based catalysts gave moderate yields and/or decomposition of the starting materials (Table 1, entries 9–11). No reaction was observed in the presence of $MgCl_2$ or $Ti(OiPr)_4$. Furthermore, we investigated the capability of a Brønsted acid, which may be generated by hydrolysis of the Lewis acid, to catalyze the annulation reaction.[12] In the presence of TfOH (30 mol %), mainly decomposition of **1a** was observed and only 20% yield of **3a** was obtained at 0 °C (Table 1, entries 12 and 13).[13] In the absence of a catalyst, no product was formed even after a prolonged reaction time at an elevated temperature (Table 1, entry 14).

Using 5 mol % of $AlCl_3$, we then investigated the scope of this reaction with regard to the nitrone component (Table 2). It was found that a wide range of aryl-substituted *N*-methylnitrones (**2b–g**) performed well in the annulation with **1a** to furnish the dioxazinane products **3b–g** in high yields (77–97%) (Table 2, entries 1–6). Electron-withdrawing substituents led to slightly lower yields (Table 2, entries 3, 4, and 6), and the *m*-bromo-substituted nitrone **2h** was found to react more sluggishly (60% yield) (Table 2, entry 7). Upon changing the nitrogen substituent of the nitrone to a benzyl group, the corresponding dioxazine products **3i–k** were obtained in similar, or slightly lower, yields (Table 2, entries 8–10). Moreover, heteroaryl-substituted nitrones **2l** and **2m** gave the corresponding products **3l** and **3m** in 79% and 69% yield, respectively (Table 2, entries 11 and 12).

Table 2. Annulation of Oxiranes with Various Nitrones[a]



entry	nitrone, **2**	product, **3**	yield [%][b]
1	**2b** R' = Me	**3b**	97
2	**2c** R' = OMe	**3c**	92
3	**2d** R' = NO_2	**3d**	82
4	**2e** R' = CF_3	**3e**	81
5	**2f** R' = Cl	**3f**	92
6	**2g** R' = Br	**3g**	77
7	**2h**	**3h**	60
8	**2i**	**3i**	83
9	**2j**	**3j**	92
10	**2k**	**3k**	62
11	**2l**	**3l**	79
12	**2m**	**3m**	69

[a]Conditions: oxirane **1a** (0.45 mmol), nitrone **2** (0.30 mmol), and $AlCl_3$ (5 mol %) were heated at 40 °C for 7 h in CH_3CN (0.8 mL). [b]Isolated yield.

We then applied a selection of substituted oxiranes in the annulation reaction (Table 3). Under the standard reaction conditions, the *para*-substituted phenyl oxiranes **1b–d** were all less efficient compared to their nonsubstituted analogue **1a**. The electron-rich oxiranes **1c** and **1d** were found to undergo a rapid rearrangement and/or polymerization when $AlCl_3$ was applied as the catalyst. However, upon changing the solvent to CH_2Cl_2 and the catalyst to $InCl_3$ for **1c**, moderate yields of dioxazinanes **3n–p** were obtained (Table 3, entries 1–3). In contrast, vinyloxirane **1e** and cyclohexene oxide **1f** reacted with high selectivity using $AlCl_3$ as the catalyst; vinyl-substituted dioxazinanes **3q,r** and *trans*-fused bicyclic products **3s,t** were isolated in excellent yields (Table 3, entries 4–7). The use of cyclohexyl nitrone **2n** with oxirane **1f** and the reaction of chloro-substituted oxirane **1g** required a prolonged reaction time (24 h) for completion and resulted in lower yields (Table 3, entries 8 and 9). For all of the monosubstituted oxiranes, a single diastereomer of the dioxazinane products **3** was obtained. Thus, we were interested in exploring the selectivity with *trans*- and *cis*-disubstituted oxiranes **1h** and **1i**. The reaction of **1h** with nitrone **2a** furnished the fully substituted dioxazinane **3w** in a 3:1 diastereomeric ratio (by crude ^1H NMR). Upon isolation by silica gel chromatography, the ratio changed to 2:1 (Table 3, entry 10). When $InBr_3$ was used in place of $AlCl_3$, a 2:1 ratio of **3w** was observed by crude ^1H NMR analysis. The ratios varied slightly over time though, indicating a rapid epimerization process.

For *cis*-oxirane **1i** with nitrone **2a**, a 2:1 diastereomeric ratio of **3x** was observed by crude ^1H NMR with $AlCl_3$ as catalyst. However, with $InBr_3$, a single isomer of **3x** was isolated in 98% yield (Table 3, entry 11). We speculate that the stereochemical outcome (i.e., the C3 configuration) for **3w** and **3x** is dependent

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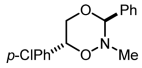
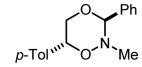
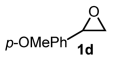
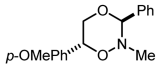
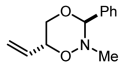
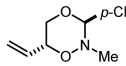
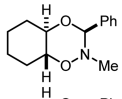
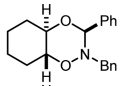
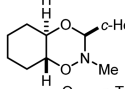
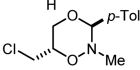
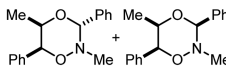
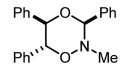
Table 3. Oxirane Substrate Scope[a]

entry	oxirane, 1	nitrone, 2	product, 3	yield [%][b]
1	 1b	2a		3n 65[c]
2	 1c	2a		3o 44[c,d,e]
3	 1d	2a		3p 25[c]
4	 1e	2a		3q 97
5	1e	2f		3r 94
6	 1f	2a		3s 89
7	1f	2i		3t 97
8	1f	 2n		3u 61[d,e]
9	 1g	2b		3v 71[d]
10	 1h	2a		3w 80[f]
11	 1i	2a		3x 98[g]

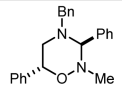
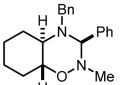
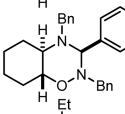
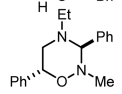
[a]Conditions: oxirane **1** (0.45 mmol), nitrone **2** (0.30 mmol), and $AlCl_3$ (5 mol %) were heated at 40 °C for 7 h in CH_3CN (0.8 mL). [b]Isolated yield. [c]CH_2Cl_2 was used. [d]24 h reaction time. [e]$InCl_3$ was used. [f]Products were obtained in a 2:1 diastereomeric ratio. [g]$InBr_3$ was used.

on the relative stabilities of the two diastereomers (the all-equatorial arrangement of **3x** is energetically favored).

Having established a procedure for the annulation of oxiranes with nitrones, we then investigated the possibility of using aziridines as substrates. In comparison with the oxiranes, we found that the annulation with aziridines required modified reaction conditions with respect to reaction temperature and catalyst. Additionally, aziridines **4a** and **4b** reacted with the applied nitrones also in the absence of a catalyst, albeit in lower yields. As shown in Table 4, both the phenyl-substituted and aliphatic *N*-benzylaziridines **4a** and **4b** led to a selective formation of the 1,2,4-oxadiazinanes **5a–c** in high yields with $InCl_3$ as catalyst. In the absence of a catalyst, 40% of product **5a** and 16% of **5c** were obtained. The use of $AlCl_3$ as catalyst led to a lower yield, 35%, of **5c** at 80 °C, whereas no reaction was observed at 40 °C (Table 4, entries 1–3). *N*-Ethyl-substituted aziridine **4c** did not react without a catalyst; $InCl_3$ furnished the product **5d** in 51% yield (Table 4, entry 4). *N*-Tosyl-substituted aziridines were unreactive under the applied conditions. This lack of reactivity may be explained by a less efficient Lewis acid activation or a low nucleophilicity of the *N*-tosyl group, which impedes the annulation reaction.[14]

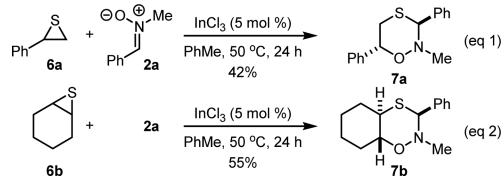
Furthermore, we were pleased to find that not only oxiranes and aziridines but also thiiranes **6** could be employed in the annulation with nitrones (Scheme 2, eqs 1 and 2). The reaction of nitrone **2a** with thiiranes **6a** and **6b** furnished the 1,4,2-oxathiazinane products **7a,b** in moderate yields as single diastereomers. A rapid decomposition of the thiirane was

Table 4. Annulation of Aziridines and Nitrones[a]

entry	aziridine, 4	nitrone, 2	product, 5	yield [%][b]
1	 4a	2a		5a 87/40[c]
2	 4b	2a		5b 90
3	4b	2j		5c 85/16[c]/35[d]
4	 4c	2a		5d 51/0[c]

[a]Conditions: aziridine **4** (0.45 mmol), nitrone **2** (0.30 mmol), and $InCl_3$ (5 mol %) were heated at 80 °C for 24 h in CH_3CN (0.8 mL). [b]Isolated yield. [c]In the absence of catalyst. [d]$AlCl_3$ was used.

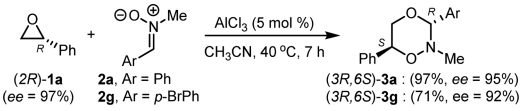
Scheme 2. Reactions with Thiiranes



observed that only partly could be avoided by the use of $InCl_3$ in toluene.

In order to gain insight into the mechanism of the presented transformation, reactions of enantiopure oxirane (2*R*)-**1a** with nitrones **2a** and **2g** were performed (Scheme 3).

Scheme 3. Transfer of Chirality in the Annulation Reaction



The corresponding dioxazinanes **3a** and **3g** were obtained in high yields with only a slight erosion of the enantiomeric excesses. Single-crystal X-ray analysis was used to determine the absolute configuration of **3g** (Figure 2).[15]

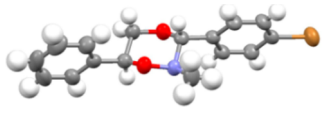


Figure 2. Ellipsoidal representation of compound **3g**.

From these experiments, it can be concluded that the stereocenter of the oxirane was inverted upon reaction with the nitrone. Most likely, these results indicate that the reaction is initiated by an S_N2-opening of the oxirane followed by a selective cyclization.[3c] Alternatively, a rapid epimerization of the second stereocenter, leading to the most stable conformer of the dioxazinane product, can be envisioned on the basis of the results in Table 3, entries 10 and 11.

In summary, we have established an efficient catalytic method for the selective annulation of nitrones with oxiranes, aziridines, and thiiranes. The products were, in almost all cases, obtained as single diastereomers comprising a wide variety of functional

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groups. Thus, this straightforward method provides ready access to structural motifs with a potential biological importance with inexpensive and readily available catalysts and reagents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02195.

Experimental procedures, compound characterization data, and crystallographic data (PDF)

X-ray crystallographic data of **3g** (CIF)

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The authors declare no competing financial interest.

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(14) For a helpful discussion on aziridine opening, see ref 2g.

(15) CCDC 1051506 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For compounds **3a**, **3s**, **3w**, **3x**, **5a**, and **7a**, the relative stereochemistry was established by dNOE experiments; see the Supporting Information for details.

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