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The formal [4+3] cycloaddition between donor-acceptor cyclobutanes and nitrones.

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The Formal [4+3] Cycloaddition Between Donor-Acceptor Cyclobutanes and Nitrones

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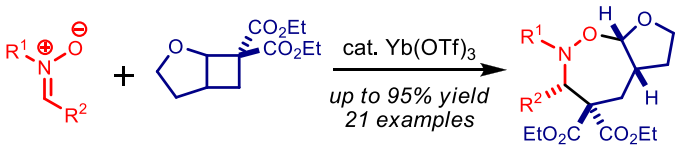
ABSTRACT



The formal [4+3] cycloaddition of 2-alkoxy-1,1-dicarboxylate activated donor-acceptor cyclobutanes with nitrones is disclosed. The reaction forms structurally unique oxazepines in moderate to high yield with a wide scope of nitrones. In most cases either a diastereomeric mixture or a single diastereomer may be formed, depending on the reaction conditions.

Cycloaddition chemistry persists as one of the premiere methods for the rapid formation of highly complex molecular scaffolds.[1] New dipolar cycloadditions continue to be developed to address the need for tailored reactivity and the synthesis of unique or intriguing structural motifs.[2] Nitrones, which are versatile 1,3-dipolarophiles, have been shown to undergo highly enantio- and regioselective [3+2] cycloadditions with olefins to form functionalized oxazolines.[3] Additionally, reactions of nitrones with alkynes, ynamides, or ynolates have been used to prepare β-lactams,[4] α-amino-β-lactams[5] or 5-isoxazolidinones,[6] respectively. However, it was not until the seminal reports of Kerr and coworkers that demonstrated highly strained donor-acceptor (DA) cyclopropanes could engage in nitrone cycloadditions.[7]

While DA cyclopropanes have been extensively studied in cycloaddition chemistry,[8] only recently have DA cyclobutanes, which share a similar degree of bond

(1) For reviews see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H.; John Wiley & Sons, Inc. New York, NY, 2002. (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev*. **2008**, *108*, 2887-2902.

(2) For recent examples see: (a) Sumiya, T.; Ishigami, K.; Wantanabe, H. *Angew. Chem. Int. Ed*. **2010**, *49*, 5527-5528. (b) Creech, G. S.; Kwon, O. *J. Am. Chem. Soc*. **2010**, *132*, 8876-8877. (c) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc*. **2010**, *132*, 14418-14420. (d) Spiteri, C.; Kelling, S.; Moses, J. E. *Org. Lett*. **2010**, *12*, 3368-3371. (e) Gryko, D. T.; Rogacki, M. K.; Klajn, J.; Gałęzowski, M.; Stępień, K.; Cyrański, M. K. *Org. Lett*. **2010**, *12*, 2020-2023.

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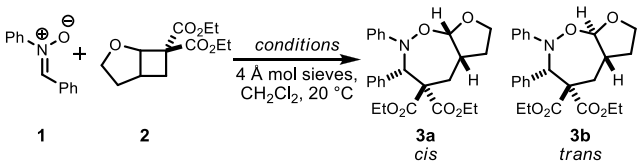
(8) For reviews see: (a) Reissig, H.-U. *Top. Curr. Chem*. **1988**, *144*, 73–135. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev*. **2003**, *103*, 1151–1196. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (d) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051–3060. (e) De Simone, F.; Waser, J. *Synthesis* **2009**, *20*, 3353–3374.

strain,[9] been explored for related modes of reactivity. To date, only a handful of dipolarophiles have been shown to undergo reactions with cyclobutanes, including aldehydes,[10] ketones,[10a,10b] imines,[11] silylenolethers,[12] and allylsilanes.[13] In this letter we disclose the first example of a formal [4+3] cycloaddition between alkoxy-substituted DA cyclobutanes and nitrones for the generation of structurally unique oxazepines.[14] This intriguing structural motif, though not naturally occurring, has been shown to be relevant as analogs of eudistomin natural products that display antiviral[15] and antiproliferative[16] activity.

$Yb(OTf)_3$ has previously been shown to be an effective catalyst for the reaction between nitrones and cyclopropanes activated by geminal diesters,[7,17] as well as in recent work for cyclobutane cycloadditions,[10e,11b] and thus was selected initially for optimization studies (Table 1). Much to our delight, upon addition of cyclobutane **2** to a solution of nitrone **1** and 10 mol % $Yb(OTf)_3$ in dichloromethane, the anticipated cycloadduct **3a** was formed as a single diastereomer in 60% isolated yield (Table 1, entry 1).[18] Control tests demonstrated that a metal catalyst was not required for the reaction to occur; however, extended reaction times were necessary and a mixture of two apparently non-equilibrating diastereomers resulted (entry 2). A modest increase in yield was observed when the nitrone, rather than the cyclobutane, was used as the limiting reagent (compare entries 1 and 3). When the catalytic loading was decreased from 10 mol % to 5 mol % a mixture of two diastereomers was found if the reaction was stopped after 10 minutes (entry 4), and the diastereomeric ratio reversed when the reaction was conducted at 0 °C (entry 5). In all cases, increasing the reaction time or catalyst loading led ultimately to the single diastereomer **3a** (entry 6) and, as expected, exposure of **3b** to $Yb(OTf)_3$ resulted in isomerization to **3a**. To date conditions have not been identified that allow for exclusive formation of the *trans* diastereomer **3b** despite exploring various temperatures, catalysts and solvents. Interestingly, decreasing the catalytic loading of $Yb(OTf)_3$ to 1 mol % resulted in the formation of three diastereomers.[19]

Table 1. Optimization of the [4+3] cycloaddition of DA cyclobutanes and nitrones.

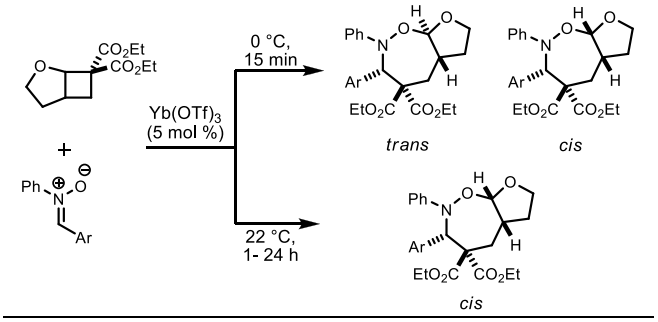


1 **2** **3a** *cis* **3b** *trans*

entry	**1** (equiv)	**2** (equiv)	$Yb(OTf)_3$ (mol %)	time (min)	**3a:3b**	yield (%)
1	1.5	1.0	10	10	1.0:0.0	60
2	1.5	1.0	0	60	1.3:1.0	87[a]
3	1.0	1.2	10	10	1.0:0.0	81
4	1.0	1.2	5	10	1.7:1.0	78
5	1.0	1.2	5	10	1.0:2.2	91[a]
6	1.0	1.2	5	60	1.0:0.0	76

[a]Reaction conducted in the presence of 4 Å molecular sieves. In the absense of both molecular sieves and Lewis acids, no reaction occurs. [b]Reaction conducted at 0 °C.

Table 2. Effect of *C*-substitution on the cyclobutane/nitrone cycloaddition.



trans *cis* *cis*

entry	nitrone	diastereomeric mixture[a] yield (%)	diastereomeric mixture[a] d.r. (*trans*:*cis*:3rd)	single *cis* diastereomer[b] yield (%)
1	Ar = C_6H_5	91	69:31	76[c]
2	Ar = *p*-$C_6H_4OCH_3$	88	63:37	74[c]
3	Ar = *p*-C_6H_4Cl	82	71:29	73[c]
4	Ar = *p*-C_6H_4CN	95	57:15:27	76[d]
5	Ar = *p*-$C_6H_4NO_2$	90	63:11:26	73[d]

[a]Conditions: 0 °C, 15 min. [b]Conditions: 22 °C, reaction allowed to proceed until only a single product was observable by TLC. [c]Reactions required less than 1 hour to form single diastereomers. [d]Reactions required 24 h to form single diastereomers.

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(12) Matsuo, J.-I.; Negishi, S.; Ishibashi, H. *Tetrahedron Lett*. **2009**, *50*, 5831–5833

(13) Matsuo, J.-I.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822-3825.

(14) Oxazepines have been made by the reaction of 1-(1-alkynyl) cyclopropyl ketones with nitrones, Zhang, Y.; Liu, F.; Zhang, J. *Chem. Eur. J*. **2010**, *16*, 6146-6150.

(15) Kurihara, T.; Sakamoto, Y.; Kimura, T.; Ohishi, H.; Harusawa, S.; Yoneda, R.; Suzutani, T.; Azuma, M. *Chem. Pharm. Bull*. **1996**, *44*, 900-908.

(16) van Maarseveen, J. H.; Scheeren, H. W.; De Clercq, E.; Balzarini, J.; Kruse, C. G. *Bioorg. Med. Chem*. **1997**, *5*, 955-970.

(17) (a) Hu, B.; Zhu,J.; Xing, S.; Fang, J.; Du, D.; Wang, Z. *Chem. Eur. J.* **2009**, *15*, 324-327. (b) Wu, L. Shi, M. *Chem. Eur. J.* **2010**, *16*, 1149-1152.

(18) 4 Å molecular sieves were needed to prevent hydrolysis of the nitrone.

(19) A mixture of three diastereomers was formed, *cis*:*trans*:3rd 1.0:1.4:1.4, 95% yield.

The breadth of the cycloaddition reaction was then examined, and separate experiments were conducted to obtain both diastereomeric mixtures and a single diastereomer. The electronics of the nitrone were first investigated, and a significant impact on the length of time required for single diastereomer formation was found (Table 2). While electron rich nitrones required less than an hour for the reaction to yield a single diastereomer (entries 1-3), electron deficient nitrones required extended reaction times (up to 24 h) to allow for full equilibration (entries 4 and 5). Additionally, with electron deficient nitrones (entries 4 and 5) the formation of an apparent third inseparable/transient diastereomer (not isolated) was observed with short reaction times. The yields were found to be consistent regardless of the electronic nature of the nitrone, though the extended times required for equilibrating the diastereomeric mixtures resulted in lower yields due to competing background decomposition.

The stereochemistry of the *cis* and *trans* diastereomers were assigned according to nOe interactions. In the case of entry 3, the stereochemistry of both diastereomers was unambiguously confirmed by single crystal X-ray analysis (Figure 1).

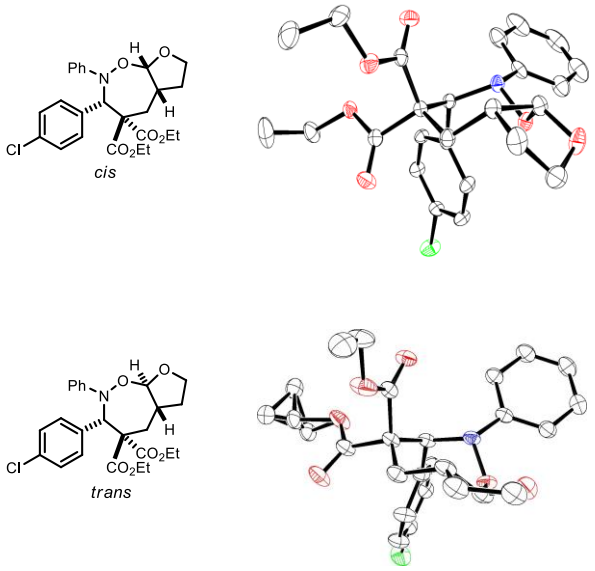
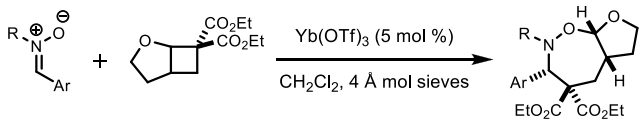


Figure 1. X-ray structure of the *cis* and *trans* diastereomers of Table 2, entry 3.

Next, the effect of *N*-substitution on the nitrone was examined (Table 3). Nitrones bearing an electron deficient *N*-aryl group were found to be viable reaction partners (entries 2 and 3). Electron rich *N*-PMP nitrones underwent the cycloaddition to afford PMP-protected oxazepines (entries 4 - 6). It was also discovered that *N*-benzyl nitrone reacts to provide a single diastereomer (entry 7).

Table 3. Effect of *N*-substitution of the cycloaddition of DA cyclobutanes and nitrones.

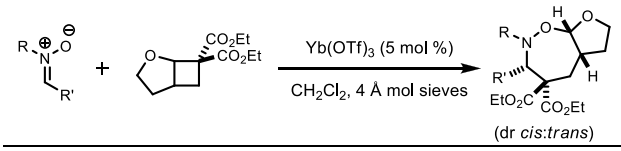


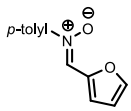
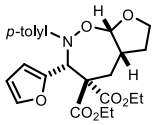
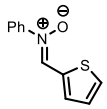
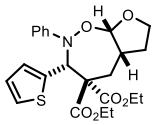
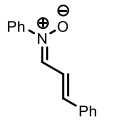
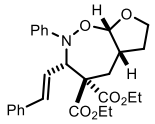
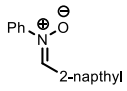
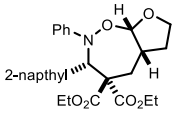
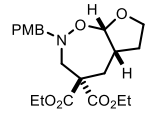
entry	nitrone	diastereomeric mixture[a] yield (%)	diastereomeric mixture[a] dr (*cis*:*trans*:3rd)	single *cis* diastereomer[b] yield (%)
1	R = C_6H_5 Ar = C_6H_5	91	31:69	76
2	R = *p*-$C_6H_4CO_2Me$ Ar = C_6H_5	68	16:40:44	52[c]
3	R = *p*-$C_6H_4CO_2Me$ Ar = *p*-$C_6H_4NO_2$	74	7:58:35	68
4	R = *p*-C_6H_4OMe Ar = C_6H_5	69	34:66	43
5	R = *p*-C_6H_4OMe Ar = *p*-C_6H_4CN	66	32:68	55
6	R = *p*-C_6H_4OMe Ar = *p*-C_6H_4OMe	70	56:44	54
7	R = Bn Ar = C_6H_5	-	-	60

[a]Conditions: 0 °C, 15 min. [b]Conditions: 22 °C, reaction allowed to proceed until only a single product was observable by TLC. [c]Incomplete conversion, 72:28 *cis*:*trans* after 24 h and 10 mol % $Yb(OTf)_3$.

Having found the reaction to be compatible with a variety of nitrones, additional functionalities of the *C*-substituents were explored (Table 4). It was discovered that heteroaromatic nitrone substituents worked well in the cycloaddition (entries 1 and 2). Surprisingly, when napthyl- or cinnamyl- substituted nitrones were subjected to the reaction conditions only single diastereomers were observed rather than diastereomeric mixtures, similar to the results obtained with *N*-alkyl substitution (Table 4, entries 3 and 4 vs table 3, entry 7). It was found that *C*-substitution was not necessary for the reaction as a *C*-unsubstituted benzyl nitrone underwent the reaction to form exclusively the *cis* adduct (entry 5).

Table 4. Exploration of nitrone functionality tolerance in the cycloaddition

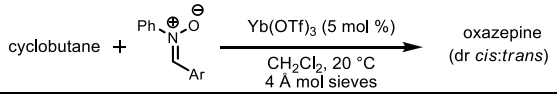


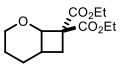
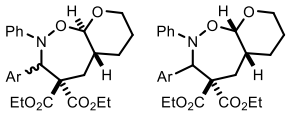
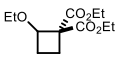
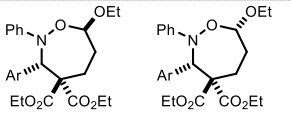
entry	nitrone	oxazepine	diastereomeric mixture[a] yield (*cis*:*trans*)	single *cis* diastereomer[b] yield
1			85% (55:45)	75%
2			77% (55:45)	67%
3			N/A	70%
4			N/A	74%
5			N/A	78%

[a]Conditions: 0 °C, 15 min. [b]Conditions: 22 °C, reaction allowed to proceed until only a single product was observable by TLC.

Lastly, two additional cyclobutanes were subjected to the reaction conditions with several nitrones (Table 5). A pyran-fused cyclobutane was found to react with nitrones to produce diastereomeric cycloadducts (Scheme 1, entries 1-3). An ethoxy-substituted cyclobutane also successfully formed the oxazepines in good yield (entries 4 and 5). The highly crystalline material of entry 5 allowed for the collection of single crystal X-ray data which permitted unambiguous assignment of the two diastereomers formed during the reaction.

Scheme 1. Alternative cyclobutanes in the cycloaddition



entry	cyclobutane	oxazepine (ratio)		yield
				
1	Ar = C_6H_5	78:22	3	65%
2	Ar = *p*-C_6H_4OMe	56:21	23	51%
3	Ar = *p*-C_6H_4Cl	46:46	8	60%
				
4	Ar = C_6H_5	79	21	85%
5	Ar = *p*-C_6H_4OMe	69	31	82%

In conclusion, we have reported the formal [4+3] cycloaddition between alkoxy-activated DA cyclobutanes and nitrones to afford structurally unique, 2,3,4,6,7-substituted oxazepines. The reaction, in most cases, initially affords a diastereomeric mixture which equilibrates to a single diastereomer. To date, all nitrones examined successfully participated in the cycloaddition reaction. Efforts are currently underway to develop asymmetric variants of this methodology, identify new dipolarophile partners for the reaction with DA cyclobutanes, and exploit this new cycloaddition for the synthesis of natural products.

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Supporting Information Available: Detailed experimental procedures, copies of NMR spectra, and X-ray crystal data. This information is available free of charge via the Internet at http://pubs.acs.org.