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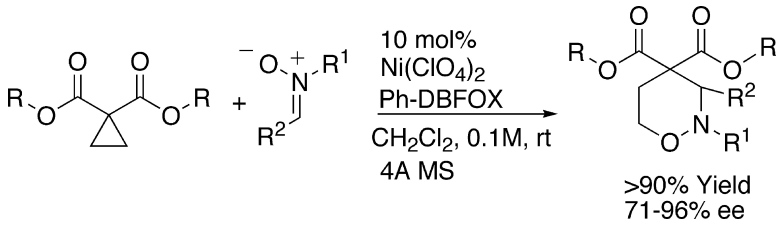
J. Am. Chem. Soc., **2005**, 127 (16), 5764-5765• DOI: 10.1021/ja0421497 • Publication Date (Web): 29 March 2005



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Enantioselective Addition of Nitrones to Activated Cyclopropanes

Mukund P. Sibi,* Zhihua Ma, and Craig P. Jasperse

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105

Received December 30, 2004; E-mail: Mukund.Sibi@ndsu.edu

Diactivated cyclopropanes undergo nucleophile addition, which results in ring-opened products, ordinarily under forcing conditions.[1] Several groups have shown that Lewis acids can effectively activate addition of electron-rich olefins, indoles, and β-ketoesters.[2] Recently, Young and Kerr reported the $Yb(OTf)_3$-mediated addition of nitrones, resulting in the formation of racemic tetrahydro-1,2-oxazine products.[3] Tetrahydro-1,2-oxazines[4] have potential as therapeutic agents[5] and as chiral building blocks,[6] and their substructure is part of bioactive natural products.[7] In this paper, we demonstrate the first examples of chiral Lewis acid catalysis in the formation of tetrahydro-1,2-oxazines with very high enantioselectivity.

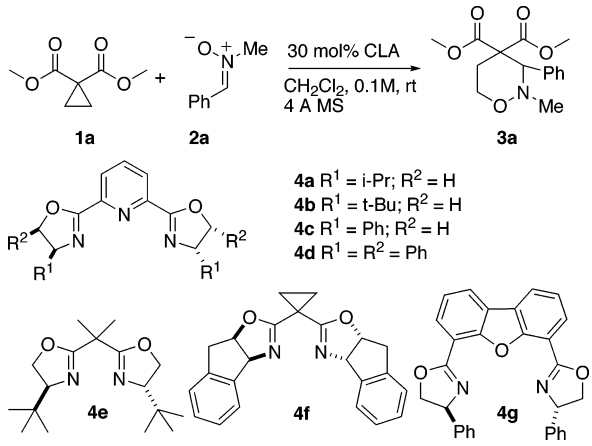
Our experiments began with the identification of an optimal chiral Lewis acid system for the reaction of cyclopropane **1a** with nitrone **2a** (Table 1).[8] For initial experiments, we used 30 mol % catalyst loading in dichloromethane with 4 Å molecular sieves at room temperature. Reactions with ytterbium triflate as a Lewis acid and a variety of PyBox ligands led to low enantioselectivity for the tetrahydro-1,2-oxazine product **3a** (entries 1−4).[9] The use of bisoxazoline ligands **4e** and **4f** with $Cu(OTf)_2$ and MgI_2 was also ineffective (entries 5−7). Recently, Kanemasa has developed a highly effective chiral Lewis acid system derived from nickel perchlorate and ligand **4g** and demonstrated its broad-based utility.[10] This chiral Lewis acid proved to be very effective (96% yield, >80% ee, entry 8). Molecular sieves were important for obtaining good yield (entry 9). THF as a solvent also gave good results, as long as molecular sieves were included (entry 10).

Having identified a promising chiral Lewis acid for tetrahydro-1,2-oxazine formation, we evaluated the effect of the diester substituents on yield and selectivity (Table 2). The diethyl substrate **1b** showed the best characteristics with both *N*-methyl nitrone **2a** (entries 1−3) and *N*-phenyl nitrone **2b** (entries 4−6), giving high yield and selectivity (entries 2 and 5). Reaction with the bulky *tert*-butyl ester **1c** was slow (entries 3 and 6). The more reactive *N*-phenyl nitrone **2b** gave higher enantioselectivities than did nitrone **2a** (compare entries 4 versus 1, and 5 versus 2). Using ethyl ester **2b**, the catalyst loading could be lowered to 10 mol % without compromising selectivity or yield (compare entry 2 with entries 7 and 8).

The breadth and scope for the reaction involving different nitrones was investigated next, using cyclopropane **1b** and the optimal catalyst (Table 3, 10% catalyst). A variety of nitrones added in high yields (entries 1−7). The enantioselectivity for the products was very high (entries 1−5) except with nitrones derived from cinnamyl aldehyde (entry 6) and furfural (entry 7).

Table 4 shows results with mono- and disubstituted cyclopropane diesters. Methyl- and phenyl-substituted cyclopropanes **1d** and **1e** (racemic mixtures) reacted in high yields (entries 1−3). As observed by Kerr,[3a] the additions were completely regioselective, with the oxygen end of the dipole adding to the substituted rather than the unsubstituted carbon of the cyclopropane. For monosubstituted cyclopropanes **1d** and **1e**, trans/cis mixtures resulted under chiral

Table 1. Evaluation of Reaction Conditions[a]



entry	Lewis acid	ligand	time (days)	yield (%)[b]	ee (%)[c]
1	$Yb(OTf)_3$	**4a**	3	50	28
2	$Yb(OTf)_3$	**4b**	6	90	10
3	$Yb(OTf)_3$	**4c**	3	76	02
4	$Yb(OTf)_3$	**4d**	3	87	18
5	$Cu(OTf)_2$	**4e**	7	−	−
6	$Cu(OTf)_2$	**4f**	6	47	37
7	MgI_2	**4f**	6	75	34
8	$Ni(ClO_4)_2$	**4g**	2	96	89
9[d]	$Ni(ClO_4)_2$	**4g**	2	51	89
10[e]	$Ni(ClO_4)_2$	**4g**	2	88	90

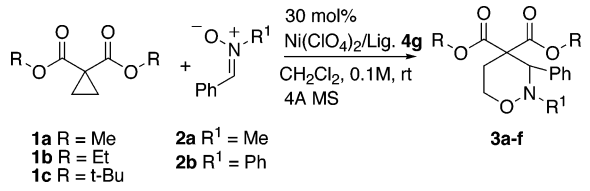
[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Determined by chiral HPLC. [d] No MS 4 Å. [e] THF as a solvent with MS.

$Ni(ClO_4)_2$-**4g** catalysis (entries 1−3). The low diastereoselectivity under chiral $Ni(ClO_4)_2$-**4g** catalysis contrasts the strong cis-selectivity using achiral $Yb(OTf)_3$ (entry 4).[3a] More importantly, the chiral catalyst gave good enantioselectivity for both diastereomers, particularly for the trans isomers (≥95% ee, entries 1−3). Addition to dimethyl- and cyclohexyl-disubstituted substrates **1f** and **1g** was also completely regioselective and proceeded with superb enantioselectivity (entries 5 and 6), although yields were somewhat lower. In terms of reactivity, the substituted cyclopropanes **1d**−**1g** in Table 4 are much more reactive than the unsubstituted substrates **1a**−**1c**, reacting completely within hours. In a study using nitrone **2a**, the relative reactivity was found to be **1e**, **1f** > **1d** > **1a**.

Young and Kerr[3a] postulated three scenarios for the addition of nitrones to activated cyclopropanes: (1) stepwise attack by nitrone oxygen on the cyclopropane ring (S_N2), followed by malonate attack on the resulting iminium; (2) a concerted cycloaddition of the nitrone across the cyclopropane σ-bond; and (3) ring opening of the activated cyclopropane to a dipolar species which is trapped by the nitrone (S_N1). A mechanism involving extensive or total ring opening to a zwitterionic species appears to be operative under

10.1021/ja0421497 CCC: $30.25

Table 2. Effect of Ester Substituent on Selectivity



1a R = Me
1b R = Et
1c R = t-Bu

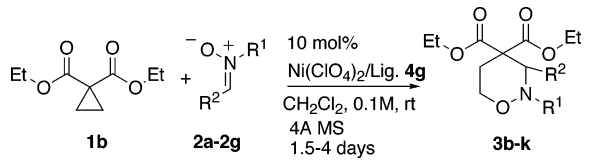
2a R^1 = Me
2b R^1 = Ph

3a-f

entry	substituent	nitrone	product	time (days)	yield (%)[a]	ee (%)[b]
1	**1a**	**2a**	**3a**	2	96	89
2	**1b**	**2a**	**3b**	2	99	92
3	**1c**	**2a**	**3c**	3	<5	–
4	**1a**	**2b**	**3d**	2	97	91
5	**1b**	**2b**	**3e**	2	99	94
6	**1c**	**2b**	**3f**	3	39	95
7[c]	**1b**	**2a**	**3b**	2	99	92
8[d]	**1b**	**2a**	**3b**	2	99	91

[a] Isolated yield. [b] Determined by chiral HPLC or chiral GC. [c] With 20 mol % catalyst. [d] With 10 mol % catalyst.

Table 3. Reaction with Different Nitrones

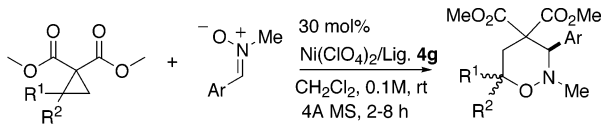


1b **2a-2g** **3b-k**

entry	R^1	R^2	nitrone	product	yield (%)[a]	ee (%)[b]
1	Me	Ph	**2a**	**3b**	99	92
2	Me	4-BrPh	**2c**	**3g**	99	95
3	Ph	Ph	**2b**	**3e**	99	94
4	Bn	Ph	**2d**	**3h**	99	93
5	Bn	4-MeO−Ph	**2e**	**3i**	99	90
6	Me	cinnamyl	**2f**	**3j**	99	71
7	Me	2-furyl	**2g**	**3k**	95	79

[a] Isolated yield. [b] Determined by chiral HPLC.

Table 4. Reactions with Substituted Cyclopropanes[a]



1d R^1 = Me, R^2 = H
1e R^1 = Ph, R^2 = H
1f R^1 , R^2 = Me
1g R^1, R^2 = -$(CH_2)_5$-

2a Ar = Ph
2c Ar = 4Br-Ph

3l Ar = 4Br-Ph, R^1 = Me, R^2 = H
3m Ar = 4Br-Ph, R^1 = Ph, R^2 = H
3n Ar = Ph, R^1 = Ph, R^2 = H
3o Ar = Ph, R^1 , R^2 = Me
3p Ar = 4Br-Ph, R^1, R^2 = -$(CH_2)_5$-

entry	substituent	R^1	R^2	product	yield (%)[b]	trans/cis[c]	ee trans (cis)[d]
1	**1d**	Me	H	**3l**	99	0.8/1	96 (90)
2	**1e**	Ph	H	**3m**	99	1.4/1	95 (90)
3[e]	**1e**	Ph	H	**3n**	99	1.4/1	96 (90)
4[f]	**1e**	Ph	H	**3n**	84	0/100	–
5	**1f**	Me	Me	**3o**	73	–	96
6	**1g**	$-(CH_2)_5-$		**3p**	54	–	99

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Ratio determined by NMR. [d] Determined by chiral HPLC. [e] Nitrone **2a** was used. [f] Racemic reaction using achiral $Yb(OTf)_3$ as catalyst and nitrone **2a**, without MS (ref 3a).

our conditions. The relative reactivity of mono- and disubstituted substrates **1d**−**1g** reflects the degree to which the cationic end of a zwitterion is stabilized and correlates standard S_N1-type reactivity. The regioselective preference for nitrone addition to the more substituted carbon also fits mechanism 3.[11] The Lewis acid assists ring opening by stabilizing the malonate anion. The low cis/trans diastereoselectivity (but high enantioselectivity) contrasts the cis-selectivity observed using achiral $Yb(OTf)_3$[3a] and suggests that capture of the zwitterion by nitrone occurs stepwise.[12] The chiral nickel is probably able to control the stereocenter proximal but not distal to the malonate.[13] Work to expand the utility of enantioselective additions to activated cyclopropanes is ongoing.

Acknowledgment. Our research program is supported by grants from the NIH and NSF.

Supporting Information Available: Characterization data for compounds **1**−**4** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) That reversible formation of a zwitterion can occur is supported by a control experiment in which racemic substrate **1e** becomes optically active (39% ee) following exposure to $Ni(ClO_4)_2$-**4g**.

(12) When racemic product **3a** was exposed to $Ni(ClO_4)_2$-**4g**, no enantiomeric enrichment was observed. This suggests that nitrone addition is irreversible with stereoselectivity under kinetic control.

(13) Nonselective C−O bond formation probably occurs first, remote from and uncontrolled by the chiral nickel malonate, followed by nickel-controlled formation of C3. An alternative possibility is that C−C bond formation may occur first, but neither the nickel nor C3 stereocenters provide high stereoinduction at the C−O bond forming step.

JA0421497