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The Cycloaddition of Nitrones with Homochiral Cyclopropanes

Katarina Sapeta and Michael A. Kerr*

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

makerr@uwo.ca

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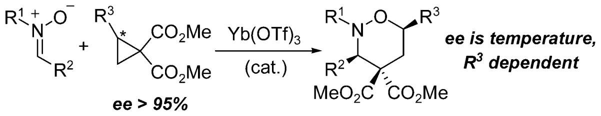
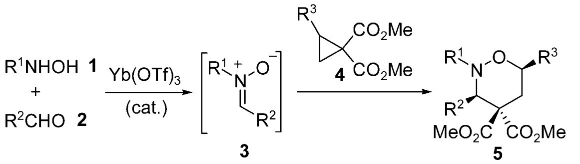


The cycloaddition of nitrones and enantiomerically pure cyclopropane-1,1-dicarboxylates is examined. Transfer of optical activity to the adduct is dictated by thermal reaction conditions and nature of cyclopropane substitution. Optically active 2-substituted cyclopropane-1,1-dicarboxylates are shown to racemize under typical reaction conditions, providing evidence for a zwitterionic ring-opened intermediate.

The 1,3-dipolar cycloaddition reaction is a highly efficient and powerful method for the assembly of a variety of biologically important heterocycles in a convergent fashion from simple precursors.[1] Of particular interest to us is the Lewis acid catalyzed cycloaddition reaction of nitrones **3** and 1,1-cyclopropanediesters **4** to form tetrahydro-1,2-oxazine derivatives **5**, which we have shown to proceed with excellent yields and with high 3,6-*cis* diastereoselectivity using ytterbium triflate as the optimal catalyst (Scheme 1).[2] This account was followed by a simplified three-component protocol in which the reaction proceeds with formation of the nitrone in situ from hydroxylamines **1** and aldehydes **2**[3] and that magnesium iodide was also effective in mediating the reaction.[4]

The 1,2-oxazine motif possesses synthetic utility through reductive N−O bond cleavage to form highly functionalized 1,4-amino alcohols[5] and is found in a number of bioactive natural products.[6] Promoting the nitrone/cyclopropane cycloaddition in an enantioselective sense, either through asymmetric catalytic methods or by virtue of optically active substrates, is consequently desirable to gain access to these useful targets. In this note, we describe results of the examination of the nitrone cycloaddition with enantiomerically pure 1,1-cyclopropanediesters. In brief, the electronic nature of the cyclopropane substituent (R^3 in compound **4**) coupled with reaction temperature dictates translation of optical activity to the adduct. We show that both the cycloadducts **5** and the cyclopropanediesters **4** are subject to racemization under typical Lewis acidic reaction conditions. We believe this provides evidence for a ring-opened zwitterionic intermediate during the reaction.

SCHEME 1. Preparation of Tetrahydro-1,2-oxazines



To date, there have been several asymmetric approaches reported toward the nitrone/cyclopropane cycloaddition. Sibi and co-workers have described a Ni^{II}/DBFOX−Ph chiral Lewis acid system in which tetrahydro-1,2-oxazines are obtained in high ee values but with diminished diastereoselectivity when 2-substituted 1,1-cyclopropanediesters are employed.[7] Very recently, Tang et al. have demonstrated that adducts are obtained in high ee and dr values with a Ni^{II}/trisoxazoline system, and that, cleverly, a kinetic resolution of racemic cyclopropanes could be performed with the same catalyst, providing a straightforward route to either tetrahydro-1,2-oxazine enantiomer.[8] We have used optically active cyclopropanes in the first total synthesis of (+)-phyllantidine[9] and, more recently, the total synthesis of the complex marine alkaloid (+)-nakadomarin A.[10] Both syntheses relied on an enantiospecific nitrone/cyclopropane cycloaddition as the key step. Our motivation in the following account stems from the observation that, when using enantiomerically pure cyclopropanes, a small loss of optical activity was seen in some cases depending on the substrate and reaction conditions.

Recent results from our laboratory indicate that the cycloaddition is likely a stepwise annulative process, with initial S_N2-type displacement of the malonate ion, followed by ring closure of the resultant iminium species.[11] Consequently, formation of enantiomerically enriched oxazines through the use of optically pure cyclopropanes is feasible, assuming that clean inversion at the chiral center occurs without opening of the cyclopropane to a planar zwitterionic intermediate. Loss of optical purity would result if this were the case, either by re-forming the cyclopropane in diminished ee or by reaction to form the racemic adduct. To examine this, a series of cyclopropanes (R^3 = phenyl (*S*)-**4a**, vinyl, (*S*)-**4b**, $-CH_2OBn$, (*R*)-**4c**) were prepared in high enantiomeric excess (ee > 95%)[12] and subjected to typical reaction conditions.[13]

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[11] (a) For a DFT study, see: Wanapun, D.; Van Gorp, K. A.; Mosey, N. J.; Kerr, M. A.; Woo, T. K. *Can. J. Chem.* **2005**, *83*, 1752. (b) Karadeolian, A.; Kerr, M. A. Manuscript in progress.

[12] **4a:** see Supporting Information for preparation; **4b, 4c:** see ref 9 and references within.

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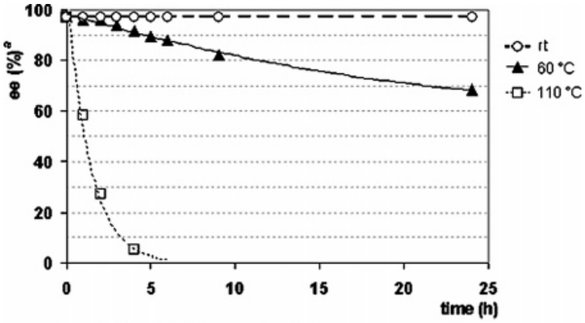

^{a} Determined by HPLC on a chiral phase

FIGURE 1. Racemization of (*S*)-**4a** at various temperatures.

Results for (*S*)-**4a** are shown in Figure 1. No detectable loss of enantiomeric excess at room temperature was observed over the course of 24 h. However, with an increase in temperature, ee values of the cyclopropane decreased; a roughly linear decrease was seen at 60 °C, with **4a** being recovered in 68% ee after 24 h of heating. At reflux in toluene (110 °C), complete racemization was achieved in 4 h. In contrast, exposure of both (*S*)-**4b** and (*R*)-**4c** to harsher conditions exhibited no detectable loss in ee, an unexpected outcome for the vinyl example, as it is predicted to be comparable to the phenyl moiety in regards to stabilization of a positive charge. Retention of optical activity for (*S*)-**4b** and (*R*)-**4c** was a pleasant outcome and offered a rationale for the complete preservation of optical purity in the asymmetric synthesis of both phyllantidine[9] and nakadomarin A,[10] respectively.

We now turned our attention to behavior of the cyclopropanes in the cycloaddition itself using a series of nitrones. Table 1 shows ee values for adducts obtained at various temperatures. Nitrone examples include N-aliphatic and N-aromatic (R^1 = benzyl, phenyl, respectively), with α-aryl groups including electron-poor, -rich, and -neutral (R^2 = 4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, phenyl). Either the two- or three-component procedure for the cycloaddition could be used (see Experimental Section).

Some results from Table 1 are worthy of note. Adducts prepared from cyclopropane (*S*)-**4c** (entries 7, 8) were shown to retain optical integrity throughout the reaction over a broad temperature range, as expected, while adducts derived from the phenyl cyclopropane (*S*)-**4a** exhibited diminished ee values with temperature increases (entries 1−6). This is consistent with results of racemization studies shown in Figure 1 and is a consequence of racemization of (*S*)-**4a** prior to cycloaddition. The electronic character of the α-aryl portion of the nitrone also had an effect on enantioselectivity of the reaction. *N*-Benzyl adducts with an electron-rich group were faster to racemize at elevated temperatures (entry 3), while those containing an electron-poor group were slower (entry 1).

It is worthwhile to note that, while optical integrity of cyclopropane (*S*)-**4a** remains intact at room temperature (Figure 1), no such retention was seen in a number of adducts formed at room temperature, most notably, *N*-benzyl adducts (Table 1, entries 1−3). With regard to this curious result, a plausible scenario for racemization is provided (Figure 2). Ring opening of the adduct is thought to arise via expulsion of the malonate ion through an available retro-Mannich pathway, (i.e., **5** → **I**) at which point a number of events may occur. Attack of a second nitrone on **I**, resulting in double inversion and, hence, racemization to form enantiomer **III** or expulsion of the nitrone to return to planar zwitterionic cyclopropane intermediate **II**, remains a distinct possibility. Such a retro-Mannich event would be most prevalent with the *N*-benzyl nitrones (thus explaining the increased racemization in these cases). The *N*-phenyl adducts would not be as prone to retro-Mannich ring opening due to decreased availability of the nitrogen lone pair. This is reflected in the retention of optical integrity of *N*-phenyl adducts at room temperature and higher (entries 4−6, 8). It must also be noted that temperature was not observed to have influence over reaction diastereoselectivity.[14]

Our interest, given the results above, turned to behavior of isolated adducts and their susceptibility to racemization, if any, when exposed once again to Lewis acidic conditions. Table 2 shows change in ee values of a selection of isolated adducts upon re-exposure to Lewis acid in refluxing conditions. Results are consistent with those of the cycloaddition reaction, namely, that more pronounced losses in ee were observed in adducts prepared from *N*-benzyl nitrones and phenyl cyclopropane (*S*)-**4a** (entries 1−5), while *N*-phenyl adducts fared better under the same conditions (entry 6). The degree of racemization was temperature-dependent: adduct **5c** (R^1 = Bn, R^2 = 4-$OMeC_6H_4$, 78% ee) saw a drastic loss at reflux in toluene over 6 h to 8% ee, while stirring at room temperature over 5 days provided a modest decrease to 69% ee. In comparison with previous observations, neither temperature nor reaction duration was seen to erode diastereomeric ratios of the re-isolated adducts.[15]

In conclusion, we have reported the racemization of optically active 2-substituted 1,1-cyclopropanediesters under the typical nitrone/cyclopropane cycloaddition conditions, implicating a Lewis acid stabilized zwitterionic intermediate. This is observed through diminished optical purity of adducts obtained with enantiopure cyclopropanes. Evidence for reversibility of the ring forming event is provided; optical purity of isolated cycloadducts is shown to erode presumably via a retro-Mannich initiated event. Further investigation into the reaction mechanism is ongoing.

Experimental Section

General Procedure for Tetrahydro-1,2-Oxazines (Three-Component Coupling). 5f: $Yb(OTf)_3$ (10 mg, 0.016 mmol) was added to a solution of *p*-methoxybenzaldehyde (24 mg, 0.22 mmol) and phenylhydroxylamine (22 mg, 0.20 mmol) in dry toluene (2 mL). The solution was stirred over activated 4 Å molecular sieves under argon for 30 min at which time cyclopropane **4a** (37 mg, 0.16 mmol) was added. Mixture was then refluxed for 6 h. After completion as determined by TLC, contents were preadsorbed onto silica and purified by flash column chromatography (silica gel, elution gradient 3−15% EtOAc/hexanes) to afford **5f** in 89% yield (65 mg, 0.14 mmol, cream needles): mp 163−165 °C; R_f = 0.37 (30% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) (major diastereomer) δ = 7.56 (d, J = 7.6 Hz, 2H), 7.53−7.43 (m, 4H), 7.42−7.37 (m, 1H), 7.17−7.13 (tt, J = 8.0, 1.0 Hz, 2H), 7.09 (dd, J = 8.8, 1.2 Hz, 2H), 6.84−6.79 (tt, J = 7.2, 1.2 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 5.75 (s, 1H), 5.05−5.00 (dd, J = 2.8, 8.0 Hz, 1H), 3.92 (s, 3H), 3.71 (s, 3H), 3.50 (s, 3H), 2.90−2.83 (dd, J = 14.4, 12.0 Hz, 1H) 2.80−2.76 (dd, J = 14.0, 2.4 Hz, 2H); ^{13}C NMR

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(13) Toluene, 4 Å molecular sieves, 10 mol % of $Yb(OTf)_3$.

(14) Adducts derived from phenyl cyclopropane were isolated in dr 17−18:1 of 3,6-*cis*:*trans* in all cases at all temperatures, while adducts of $-CH_2$-OBn cyclopropane did not contain detectable traces of the *trans* isomer (^1H NMR).

(15) See ref 14. All adducts were recovered without change in initial dr (^1H NMR).

TABLE 1. Tetrahydro-1,2-oxazine (5) Enantiomeric Excess Values at Various Reaction Temperatures[a]

entry	nitrone	cyclopropane	adduct	yield (%)[c]	enantiomeric excess (%)[b] 22 °C	60 °C	110 °C
1	**3a**, $R^1 = Bn$, $R^2 = 4\text{-}NO_2C_6H_4$	(*S*)-**4a**	**5a**	73	90	80	36
2	**3b**, $R^1 = Bn$, $R^2 = Ph$	(*S*)-**4a**	**5b**	93	84	54	21
3	**3c**, $R^1 = Bn$, $R^2 = 4\text{-}OMeC_6H_4$	(*S*)-**4a**	**5c**	88	78	36	13
4	**3d**, $R^1 = Ph$, $R^2 = 4\text{-}NO_2C_6H_4$	(*S*)-**4a**	**5d**	85	>95	86	79
5	**3e**, $R^1 = Ph$, $R^2 = Ph$	(*S*)-**4a**	**5e**	95	>95	>95	>95
6	**3f**, $R^1 = Ph$, $R^2 = 4\text{-}OMeC_6H_4$	(*S*)-**4a**	**5f**	89	>95	94	88
7	**3b**	(*R*)-**4c**	**5g**	85	>95	>95	>95
8	**3e**	(*R*)-**4c**	**5h**	76	>95	>95	>95

[a] Reactions conducted in toluene, 10 mol % of $Yb(OTf)_3$. [b] Determined by HPLC on a chiral phase. Reaction time 6 h for (*S*)-**4a**, 24 h for (*R*)-**4c**. [c] Optimal yields of isolated adducts. See Supporting Information for conditions.

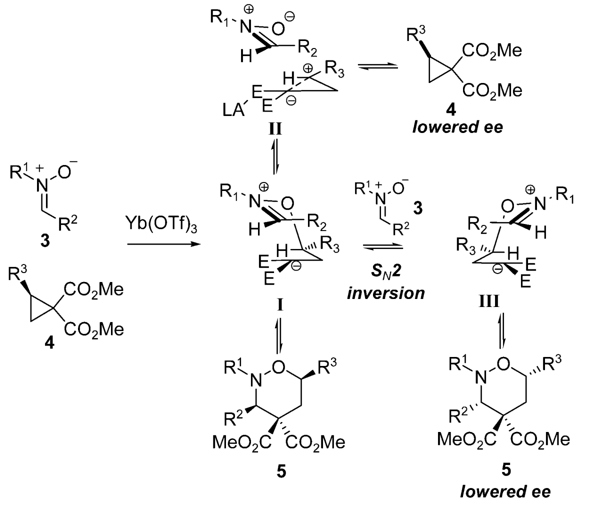

FIGURE 2. A proposed mechanism for racemization.

TABLE 2. Optical Erosion for Selected Isolated Adducts 5[a]

entry	adduct	initial ee (%)[b]	time	temp (°C)	final ee (%)[b]
1	**5a**	90	6 h	110	45
2	**5a**	90	24 h	110	32
3	**5c**	78	6 h	110	8
4	**5c**	78	5 d	22	69
5	**5b**	84	3 d	110	46
6	**5e**	>95	16 h	110	43

[a] Reactions conducted in toluene, 10 mol % of $Yb(OTf)_3$. [b] Determined from re-isolated adducts by HPLC on a chiral phase.

(125 MHz, $CDCl_3$) (major diastereomer) δ = 170.4, 168.6, 159.3, 148.9, 139.7, 131.9, 128.9, 128.7, 128.5, 127.2, 126.7, 121.8, 116.1, 113.6, 79.0, 65.5, 59.8, 55.2, 53.7, 52.9, 31.8; IR (thin film) ν_{max} = 3469, 2954, 2839, 1740, 1609, 1512, 1491, 1454, 1254, 1177, 1032, 952, 884, 841, 755, 698, 601; HRMS calcd for $C_{27}H_{27}O_6N$ 461.1838, found 461.1846; HPLC separation 90:10 hexanes/*i*PrOH, 1.0 mL/min, 220 nm, R_t = 6.5, 8.5 min.

General Procedure for Tetrahydro-1,2-Oxazines (Two-Component Coupling). 5d: $Yb(OTf)_3$ (3 mg, 0.0045 mmol) was added to a solution of nitrone **3d** (15 mg, 0.063 mmol) in dry toluene (2 mL) in the presence of activated 4 Å molecular sieves under argon. Cyclopropane **4a** (11 mg, 0.045 mmol) was then added and the solution stirred at room temperature for 6 h. After completion as determined by TLC, contents were preadsorbed onto silica and purified by flash column chromatography (silica gel, elution gradient 5−15% gradient of EtOAc/hexanes) to afford **5d** in 95% yield (colorless crystals): mp 135−136 °C; R_f = 0.37 (30% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) (major diastereomer) δ = 8.06 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 6.8 Hz, 2H), 7.43 (m, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.85 (t, J = 7.2 Hz, 1H), 5.91 (s, 1H), 5.08 (dd, J = 12.0, 2.4 Hz, 1H), 3.96 (s, 3H), 3.53 (s, 3H), 2.89−2.85 (dd, J = 14.4, 2.4 Hz, 1H), 2.81−2.74 (dd, J = 14.4, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer) δ = 169.6, 168.1, 148.3, 147.5, 142.9, 139.0, 131.6, 129.0, 128.8, 126.6, 123.3, 122.6, 116.0, 79.0, 65.7, 59.4, 54.0, 53.2, 31.8; FTIR (thin film) ν_{max} = 2953, 1741, 1599, 1522, 1493, 1453, 1349, 1261, 1049, 950, 862, 755, 698, 600; HRMS calcd for $C_{26}H_{24}O_7N_2$ 476.1584, found 476.1586; HPLC separation 87:13 hexanes/*i*PrOH, 1.0 mL/min, 220 nm, R_t = 8.4, 10.5 min.

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Supporting Information Available: Full experimental procedures and complete ^1H, ^{13}C NMR, and chromatographic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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