

Diastereoselectivity-Switchable and Highly Enantioselective 1,3-Dipolar Cycloaddition of Nitrones to Alkylidene Malonates

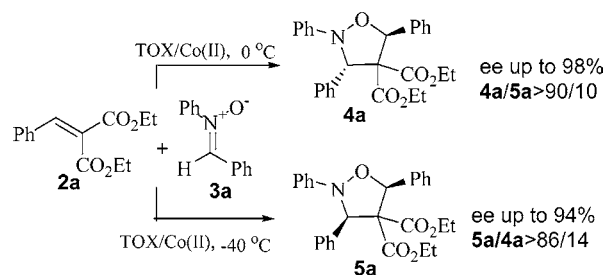
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Received March 23, 2004

ABSTRACT



Trisoxazoline 1/Co(ClO₄)₂·6H₂O catalyzed the 1,3-cycloaddition between nitrones **3** with alkylidene malonates **2** at 0 °C to give the isoxazolidines with both high enantioselectivity and high exo selectivity. However, when the temperature was lowered from 0 to -40 °C, the same cycloaddition afforded endo isomers as the major products with good to high enantioselectivity. A mechanism is provided.

The control of stereoselectivity is of special interest and is still a challenging problem in asymmetric catalysis. Of the strategies developed,¹ the most promising is probably to access different isomers by employing the same starting materials and the same reagent/catalyst, just by changing reaction conditions. Additives,² temperature,³ and solvent⁴ have been used for reversing the enantioselectivity, and thus

both enantiomers could be prepared using the same chiral catalyst in some cases. Several examples on switching diastereoselectivity by reaction conditions have been reported,⁵ however, few reported on the synthesis of optically active diastereomers, particularly in asymmetric catalysis.⁶ In a previous study on this subject, we reported that the diastereoselectivity of the cyclopropanation of chiral tellu-

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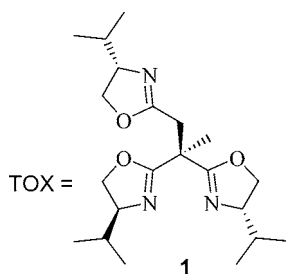
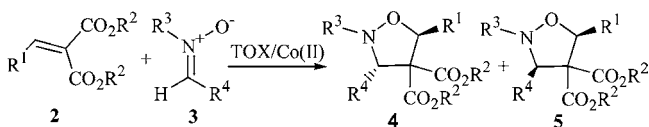


Figure 1.

ronium allylides with α,β -unsaturated esters or amides could be controlled by the choice of the base used for the formation of ylide and two diastereomers could be obtained at will with high enantioselectivity in some cases.⁷ In this communication, we wish to report a diastereoselectivity-switchable and highly enantioselective cycloaddition between nitrones and alkylidene malonates. Simply by changing the temperature of this reaction, both *cis* and *trans* cycloaddition adducts can be prepared with high enantioselectivity when trisoxazoline (TOX)⁸ **1**/Co(ClO₄)₂·6H₂O is employed as the catalyst (Figure 1).

The reaction of nitrones with olefinic dipolarophiles yields highly substituted isoxazolidines with multiple stereocenters.⁹ This versatile and atom-economical process has been applied toward the preparation of both β -lactams¹⁰ and β' -hydroxy- β -amino acids,^{9a,11} which are important motifs in many biologically active molecules. Usually, electron-rich alkenes were reported to react with nitrones to give *exo* selectivity¹² with high enantioselectivity, while *endo* selectivity¹³ is favored for electron-deficient alkenes.¹⁴ We are pleased to find that TOX **1**/Co(ClO₄)₂·6H₂O catalyzed the 1,3-cycloaddition

Table 1. Enantioselective 1,3-Dipolar Cycloadditions between Alkenes **2** and Nitrones **3**^a



entry	R ¹ /R ²	R ³ /R ⁴	yield (%)	4/5 ^b	ee (%) ^c
1	Ph/Et	<i>p</i> -CH ₃ C ₆ H ₄ /Ph	93	>99/1	91
2 ^d	Ph/Et	<i>p</i> -BrC ₆ H ₄ /Ph	76	>99/1	95 ^d
3	Ph/Et	Ph/Ph	94	97/3	95
4	<i>p</i> -CH ₃ C ₆ H ₄ /Et	Ph/Ph	95	95/5	92
5	<i>p</i> -NO ₂ C ₆ H ₄ /Me	Ph/Ph	93	97/3	94
6 ^e	<i>p</i> -BrC ₆ H ₄ /Et	Ph/Ph	99	95/5	95
7	Ph/Me	Ph/ <i>p</i> -CF ₃ C ₆ H ₄	100	92/8	98
8	Ph/Me	Ph/ <i>p</i> -CH ₃ OC ₆ H ₄	94	95/5	96
9	Ph/Me	<i>p</i> -BrC ₆ H ₄ /Ph	92	>99/1	98
10	Ph/Bu ⁱ	<i>p</i> -BrC ₆ H ₄ /Ph	95	>99/1	96
11 ^d	<i>c</i> -Hex/Et	<i>p</i> -BrC ₆ H ₄ /Ph	91	90/10	89

^a Reactions were carried out at 0 °C using 3.3 mol % ligand **1** unless noted otherwise.¹⁶ ^b Determined by ¹H NMR. ^c For **4** by chiral HPLC. ^d Using 6.7 mol % ligand **1**. ^e Absolute configuration was determined by X-ray crystallography.

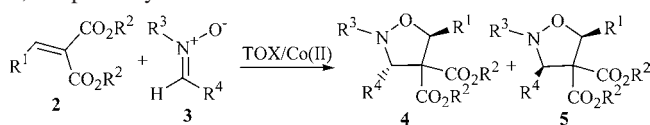
between nitrones **3** between alkylidene malonates **2** at 0 °C to give the desired products with both high enantioselectivity and high *exo* selectivity. As shown in Table 1, a variety of nitrones and alkylidene malonates with different structures proved to be good substrates for this reaction, and all reactions gave the desired products with high to excellent enantioselectivity in high yields. The enantiomeric excess ranged from 89 to 98%. Regardless of the dimethyl, diethyl, or diisobutyl malonate used, this cycloaddition proceeded well to give almost perfect *exo* selectivity (*exo/endo* > 99/1) with excellent enantioselectivity (entries 2, 9, 10). Further studies showed that the substituents R³ and R⁴ of nitrones had almost no effect on the enantioselectivity or yield. Furthermore, all reactions favored high *exo* selectivity.¹⁵

Remarkably, the diastereoselectivity of this reaction is temperature-dependent. When the temperature was lowered from 0 to –40 °C, the cycloaddition afforded *endo* isomers as the major products with good to high enantioselectivity. To determine the generality of this reversal, both alkylidene and arylidene malonates were evaluated as substrates in a low-temperature reaction. As shown in Table 2, all screened substrates shifted from *exo* selectivity to *endo* selectivity when the reaction temperature was lowered. The ratio of *endo/exo* products could be tuned from <1/99 at 0 °C to >86/14 at –40 °C. In both conditions, the enantioselectivity is good to excellent. Thus, either one of the *trans* and *cis* products could be enantioselectively synthesized at will just by the choice of reaction temperature using the same catalyst TOX **1**/Co(ClO₄)₂·6H₂O. These results revealed a remarkable

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(15) *Endo* and *exo* are defined relative to amido or ester carbonyl group located in the *trans* position of the 3-substituent (phenyl) of the dipolarophile alkene and the N–O function of nitrones.

Table 2. Temperature-Reversed Diastereoselectivity of 1,3-Dipolar Cycloadditions between Alkenes **2** and Nitrones **3**^a



entry	R ¹ /R ²	R ³ /R ⁴	yield (%) ^b	4/5 ^c	ee (%) ^d
1	<i>p</i> -BrC ₆ H ₄ /Et	Ph/Ph	88	5/95	80
2 ^e	<i>p</i> -NO ₂ C ₆ H ₄ /Et	Ph/Ph	99	10/90	83
3	<i>p</i> -MeC ₆ H ₄ /Et	Ph/Ph	99	14/86	88
4 ^f	Ph/Et	Ph/Ph	81	11/89	93
5	Ph/Et	<i>p</i> -MeC ₆ H ₄ /Ph	77	14/86	87
6 ^{e,f,g}	Ph/Et	<i>p</i> -BrC ₆ H ₄ /Ph	90	10/90	80
7 ^f	Ph/Bu ⁱ	<i>p</i> -BrC ₆ H ₄ /Ph	38	12/88	94
8 ^e	<i>c</i> -Hex/Et	<i>p</i> -BrC ₆ H ₄ /Ph	99	14/86	71

^a Reactions were carried out at -40 °C using 3.3 mol % ligand **1** unless noted otherwise.¹⁶ ^b Isolated yield for **4** + **5**. ^c Determined by ¹H NMR. ^d For **5** by chiral HPLC, %. ^e At -50 °C. ^f Using 6.7 mol % ligand **1**. ^g Absolute configuration was determined by X-ray analysis.

advantage of the trisoxazoline in delivering stereoselectivity to the products in this cycloaddition.

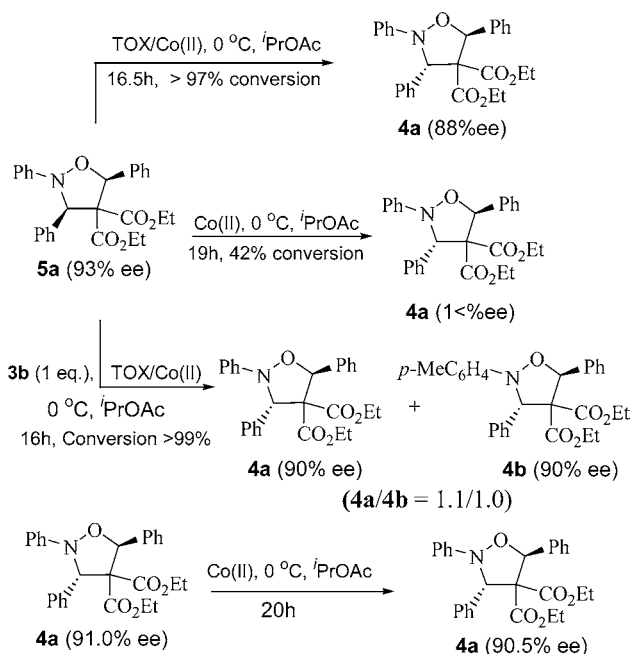
To understand the mechanism of this reversal of the diastereoselectivity, the *cis* isomer **5a** (93% ee) was treated with catalytic TOX **1**/Co(ClO₄)₂·6H₂O and Co(ClO₄)₂·6H₂O, respectively. It was found that the *cis* isomer **5a** was smoothly transformed into the *trans* isomer **4a** in the presence of Co(II) catalyst at 0 °C. 88% ee was obtained in *i*PrOAc when TOX **1** was used. Without TOX, however, only racemic *trans* isoxazolidine **4a** was afforded under the same reaction conditions (Scheme 1). These results suggested that the 1,3-cycloaddition of nitrones with alkylidene malonates to form *cis*-isoxazolidine **5** at low temperature was reversible. Further studies showed that the reaction of *cis*-isoxazolidine **5a** at 0 °C with compound **3b** gave *trans* products **4a** and **4b** in almost equal proportions (1.1/1.0, mol/mol) in 90% ee (Scheme 1), similar to the result from nitrones and alkylidene as starting materials.¹⁶

Moreover, the enantiomeric excess was maintained when optically pure *trans*-isoxazolidine **4a** (91% ee) was treated with catalytic Co(ClO₄)₂·6H₂O at 0 °C without TOX for 20 h.

On the basis of this experimental evidence, it was concluded that reaction to form *cis*-isoxazolidine is reversible and subject to kinetic control at -40 °C. In the case of the reaction at 0 °C, the cycloaddition is subject to thermodynamic control, favoring the *trans* isomer (Scheme 2).

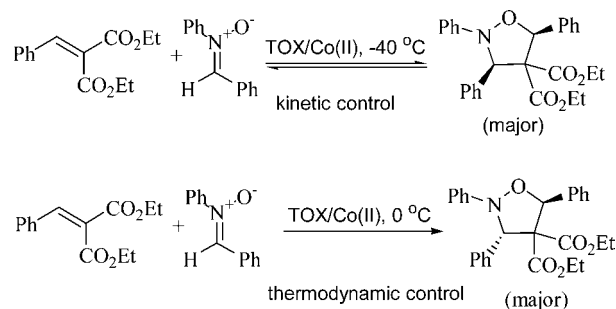
In summary, we have developed the first example of enantioselective cycloadditions between nitrones and alkylidene malonates. The outstanding character of this reaction is that the endo/exo selectivity could be controlled effectively by reaction temperature and thus both *cis*- and *trans*-

Scheme 1



isoxazolidine could be prepared enantioselectively. The mild reaction conditions, cheap and easy synthesis of the catalyst, the synthetically useful products, the controllable diastereoselectivity, and high enantioselectivity make this method potentially useful in organic synthesis.

Scheme 2



Acknowledgment. We are grateful for the financial support from the National Natural Sciences Foundation of China. This paper is dedicated to professor Li-Xin Dai on the occasion of his 80th birthday.

Supporting Information Available: Characterization data for all new compounds, absolute configuration of compounds noted in Tables 1 and 2, and experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(16) For more details, please see Supporting Information.

OL049460D