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COMMUNICATION

Catalytic asymmetric syntheses of isoxazoline-N-oxides under phase-transfer conditions[†]

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Catalytic asymmetric syntheses of various isoxazoline-*N*-oxides have been accomplished by asymmetric phase-transfer conjugate addition of bromomalonate to nitroolefins and subsequent ringclosing O-alkylation.

Isoxazoline-*N*-oxides serve as versatile building blocks for the preparation of complex molecules,¹ biologically active compounds and natural products.² While a number of synthetic methods have been developed to date,³ there is still a need to expand synthetic approaches for their preparation. Chiral isoxazoline-*N*-oxides are known to be synthesized by using optically pure starting material⁴ or stoichiometric amounts of a chiral reagent;⁵ however, general methods for their preparation based on the catalytic asymmetric reaction are quite rare.⁶ In this context, we have been interested in the development of catalytic asymmetric phase-transfer conjugate addition and ring-closing O-alkylation.⁷ Here we wish to report efficient asymmetric syntheses of isoxazoline-*N*-oxides based on the asymmetric conjugate addition under phase-transfer conditions.



 $\begin{array}{l} (R,R)\mbox{-}1a~(\mbox{Ar}=3,4,5\mbox{-}F_3C_6H_2) \\ (S,S)\mbox{-}1b~(\mbox{Ar}=3,5\mbox{-}fBu_2C_6H_3) \\ (S,S)\mbox{-}1c~(\mbox{Ar}=3,5\mbox{-}[3,5\mbox{-}(CF_3)_2C_6H_3]_2C_6H_3) \\ (S,S)\mbox{-}1d~(\mbox{Ar}=2\mbox{-}naphthyl) \end{array}$

We first examined the synthesis of isoxazoline-*N*-oxide **3a** by the reaction between diethyl bromomalonate and nitroolefin **2a** using 1 mol% of chiral PTC 1^8 as catalyst and K₂CO₃ in THF (Table 1). Among the catalysts used, (*R*,*R*)-**1a** was found to be the most efficient catalyst for the present reaction, and Table 1Asymmetric synthesis of cyclic nitronate with 2a and diethylbromomalonate catalyzed by chiral PTC 1^a

Ph	NO ₂ + BrCH(C Me 2a	chiral PTC (1 mol%) K ₂ CO ₃ THF, 0 °C, 2	$\begin{array}{c} 1 \\ EtO_2C \\ EtO_2C \\ 4 \\ h \end{array}$	
Entry	PTC	$\operatorname{Yield}^{b}(\%)$	ee^{c} (%)	Config.
1^d	(<i>R</i> , <i>R</i>)-1a	95	58	S
2	(<i>S</i> , <i>S</i>)-1b	87	46	R
3	(S,S)-1c	92	56	R
4	(<i>S</i> , <i>S</i>)-1d	73	30	R

^{*a*} The reaction of **2a** (1 equiv.) with diethyl bromomalonate (1 equiv.) was carried out in THF in the presence of chiral PTC **1** (0.01 equiv.) and K₂CO₃ (2 equiv.) at 0 °C for 24 h. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.). ^{*d*} The reaction was performed for 7.5 h.

the desired isoxazoline-*N*-oxide **3a** was obtained in excellent yield with moderate enantioselectivity (entry 1).

Having identified a suitable catalyst, the reaction conditions were then optimized, and the selected results are summarized in Table 2. When reactions were conducted in various solvents, mesitylene gave the highest enantioselectivity (entry 4). In an attempt to further improve enantioselectivity, lowering temperature was effective, although a longer reaction time was required (entry 5). The use of 70% aqueous Cs_2CO_3 as a stronger base successfully increased the reaction rate without loss of enantioselectivity (entry 6). When the reaction was performed at -35 °C for 12 h, the desired product was obtained in excellent yield with good enantioselectivity (entry 8).

With the optimal reaction conditions, catalytic asymmetric syntheses of isoxazoline-*N*-oxides with several other nitroolefins **2** were examined (Table 3). The reaction of nitroolefins **2** having a primary alkyl group ($\mathbb{R}^2 = \mathbb{E}t$ or Bu) at the α -position gave the corresponding isoxazoline-*N*-oxides with good enantioselectivity (entries 2 and 3). On the other hand, the reaction of sterically demanding nitroolefins **2** ($\mathbb{R}^2 = i$ -Pr) proceeded slowly to give the product in lower yield and enantioselectivity (entry 4). We then investigated the effects of the β -substituent on nitroolefins **2**. The reaction of **2** having either electron-deficient or electron-rich phenyl group gave the corresponding isoxazolines in good yield and enantioselectivity

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Table 2 Asymmetric synthesis of cyclic nitronate with 2a and diethyl bromomalonate catalyzed by (R,R)- $1a^a$



Entry	Base	Solvent	Conditions (°C, h)	$\operatorname{Yield}^{b}(\%)$	ee^{c} (%)
1	K ₂ CO ₃	THF	0, 7.5	95	58
2	50% K ₂ CO ₃ aq.	Et ₂ O	0, 8.5	84	63
3	50% K ₂ CO ₃ aq.	Toluene	0, 7.5	94	64
4	50% K ₂ CO ₃ aq.	Mesitylene	0, 7.5	83	70
5	50% K ₂ CO ₃ aq.	Mesitylene	-20, 24	80	77
6	70% Cs ₂ CO ₃ aq.	Mesitylene	-20, 2	70	79
7	70% Cs ₂ CO ₃ aq.	Mesitylene	-30, 8	97	81
8	70% Cs ₂ CO ₃ aq.	Mesitylene	-35, 12	95	83
9	70% Cs ₂ CO ₃ aq.	Mesitylene	-40, 12	29	77

^{*a*} The reaction of **2a** (1 equiv.) with diethyl bromomalonate (1 equiv.) was carried out in a solvent in the presence of (R,R)-**1a** (0.01 equiv.) and a base. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

(entries 6–8). The use of **2** with an alkyl substituent resulted in decreased enantioselectivity (entry 9).

The absolute stereochemistry of the obtained isoxazoline-*N*-oxide (Table 3, entry 6) was confirmed to be *S* by X-ray crystallographic analysis.⁹ Based on the observed stereochemistry, a plausible transition state model can be proposed as shown in Fig. 1. The chiral ammonium enolate, which is generated from diethyl bromomalonate and chiral phase-transfer catalyst (R,R)-1a under basic conditions, approaches the *Si* face of nitroolefins.

The obtained isoxazoline-*N*-oxide was a useful intermediate in organic synthesis and readily converted to the corresponding oxime and isoxazoline (Scheme 1). When isoxazoline-*N*-oxide

Table 3Asymmetric synthesis of cyclic nitronate with 2 with diethylbromomalonate catalyzed by (R,R)-1a^a

R ¹		(<i>R,R</i> (1 m 70% Cs ₂	?)- 1a ol%) EtO₂C ₂ ^{CO} ₃ aq. EtO₂C	⁰ ⊕ 0 [⊖]	
ן R 2	²	² mesitylene –35 °C, 12 h		R^{1} R^{2} R^{2}	
Entry	\mathbb{R}^1	\mathbf{R}^2	$\operatorname{Yield}^{b}(\%)$	$ee^{c,d}$ (%)	
1	Ph	Me	95	83 (99)	
2	Ph	Et	92	86	
3	Ph	Bu	56	86	
4^e	Ph	<i>i</i> -Pr	63	77	
5	Ph	Ph	97	81 (99)	
6 ^e	4-Br-C ₆ H ₄	Et	84	85 (97)	
7	$4-NO_2-C_6H_4$	Et	90	87	
8 ^f	4-MeO-C ₆ H ₄	Et	84	87	
9	Bu	Et	63	77	

^{*a*} The reaction of **2** (1 equiv.) with diethyl bromomalonate (1 equiv.) was carried out in mesitylene in the presence of (R,R)-**1a** (0.01 equiv.) and 70% Cs₂CO₃ aq. at -35 °C for 12 h. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC analysis using chiral column (Chiralpak AD-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd.). ^{*d*} Enantiomeric excesses in parentheses were obtained after a single recrystallization from cold ethanol. ^{*e*} The reaction was performed for 24 h. ^{*f*} The reaction was performed for 36 h.



Fig. 1 Plausible transition state model.



Scheme 1 Transformation of isoxazoline-N-oxide 3b.

3b was treated with Pd/C in MeOH under a H_2 atmosphere, oxime **4** was obtained in good yield with complete retention of stereochemistry. Treatment of **4** with methanesulfonyl chloride and triethylamine in dichloromethane gave isoxazoline **5** in excellent yield without loss of optical purity.¹⁰ Selective reduction of one ester group in **5** with lithium tri(*tert*-butoxy)aluminium hydride gave mono-alcohol **6** exclusively.¹¹

In summary, we have developed efficient asymmetric syntheses of isoxazolidine-*N*-oxides by the asymmetric phase-transfer conjugate addition and the subsequent ring-closing O-alkylation. Further investigations to expand the substrate scope of this reaction are currently underway.

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