Highly enantioselective synthesis of isoxazoline *N*-oxides†

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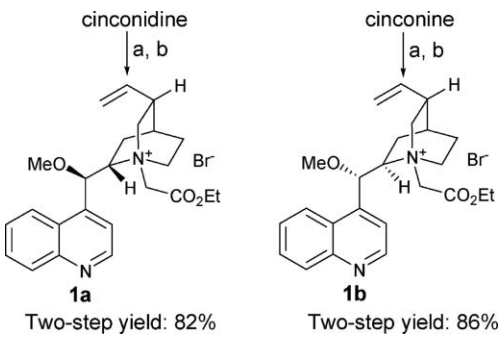
The reaction of cinchonidine (cinchonine)-derived ammonium salts with nitroolefins in the presence of Cs_2CO_3 to afford optically active isoxazoline *N*-oxides with excellent ee and high de values has been developed.

Isoxazoline *N*-oxides and their derivatives are frequently used as intermediates[1] in the synthesis of natural products and several biologically active compounds.[1c,1d,2] Although several synthetic strategies have been developed,[3] methods for the practical synthesis of optically active multi-substituted isoxazoline *N*-oxides with high diastereoselectivities and enantioselectivities remain very limited. As part of our on-going research project on ylide reactions and their applications in organic synthesis,[4] we have found very recently that cinchonidine (cinchonine)-derived ammonium salts **1a** and **1b**[5,6] react with nitroolefins in the presence of Cs_2CO_3 to afford optically active isoxazoline *N*-oxides‡ with excellent ee and high de values. In this Communication, we wish to report the preliminary results.

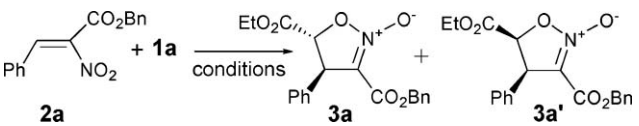
Ammonium salts **1a** and **1b** were readily available from cheap and commercial cinchonidine and cinchonine, respectively, in two-steps and in high yield (Scheme 1).† We were pleased to find that salt **1a** reacted with (*Z*)-benzyl-2-nitro-3-phenylacrylate (**2a**) in the presence of Cs_2CO_3, leading to optically active isoxazoline *N*-oxides with excellent diastereoselectivity (>99/1) and enantioselectivity (98% ee), although the yield was 26% (Table 1, entry 1). To further improve the yield, several of the reaction conditions were optimized. As shown in Table 1, solvents strongly influenced the yield (Table 1, entries 1–5). The optimal solvent was THF, and in this solvent, the yield could be increased to 57% without loss of selectivity. Strong base effects were also observed. Na_2CO_3, DBU and KHDMS did not promote the reaction at all. K_2CO_3 gave 45% yield, but it was lower than that when Cs_2CO_3 was employed (Table 1, entry 5 *vs.* entry 7). The addition of $KF{\cdot}2H_2O$ had almost no effect on this reaction (Table 1, entry 12 *vs.* 10) but 18-crown-6 and 4 Å MS inhibited the cyclization (Table 1, entries 11 and 13). A trace amount of H_2O slightly accelerated the reaction and thus shortened the reaction time. Product **3a** proved to be unstable in silica gel. The addition of triethylamine (0.3% v/v) to the eluent improved the isolated yield from 55 to 65% without loss of de or ee (Table 1, entry 14 *vs.* 15). Thus, by using THF as a solvent with a trace amount of water and Cs_2CO_3 as a base, cinchonidine-derived ammonium salt **1a** reacted with **2a** to afford the desired isoxazoline *N*-oxide, **3a**, in good yield, and with excellent ee and de.



Scheme 1 Synthesis of salts **1a** and **1b**. Reaction conditions and reagents: a: KH, MeI, THF, 0 °C–rt; b: $BrCH_2COOEt$, acetone, rt.

Under the optimal conditions, we studied the generality of this reaction by investigating a variety of 2-nitroacrylate derivatives.§ As shown in Table 2, various 2-nitro α,β-unsaturated esters are good substrates for this reaction, giving the desired products, with no cyclopropanes being observed.¶ The ester group influenced the enantioselectivity slightly (Table 2, entries 1 and 11). Both 3-aryl and 3-heteroaryl-2-nitro acrylates† worked well to afford

Table 1 Effects of reaction conditions on the cyclization



2a

Entry	Solvent	Base	Yield (%)[a]	ee (%)[b]	3a/3′a[c]
1[d]	CH_3CN	Cs_2CO_3	26	98	>99/1
2[d]	DME	Cs_2CO_3	49	97	>99/1
3[d]	DMF	Cs_2CO_3	50	98	>99/1
4[d]	DCE	Cs_2CO_3	49	99	>99/1
5[d]	THF	Cs_2CO_3	57	99	>99/1
6[d]	THF	Na_2CO_3	0	—	—
7[d]	THF	K_2CO_3	45	99	>99/1
8[d]	THF	KHDMS	0	—	—
9[d]	THF	DBU	0	—	—
10[e]	THF	Cs_2CO_3	54	98	>99/1
11[e,f]	THF	Cs_2CO_3	0	—	—
12[e,g]	THF	Cs_2CO_3	56	98	>99/1
13[e,h]	THF	Cs_2CO_3	0	—	—
14[e,i]	THF	Cs_2CO_3	55	>99	98
15[e,i,j]	THF	Cs_2CO_3	65	>99	>99/1

[a] Isolated yield. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC. [d] **2a** (57 mg, 0.2 mmol), base (0.3 mmol), **1a** (105 mg, 0.22 mmol), solvent (2.5 mL), 0 °C. [e] **2a** (57 mg, 0.2 mmol), Cs_2CO_3 (0.22 mmol, 72 mg), **1a** (105 mg, 0.22 mmol), THF (2.5 mL), 0 °C. [f] 18-crown-6 (158 mg) was added. [g] $KF{\cdot}2H_2O$ (35 mg) was added. [h] 4 Å MS (100 mg) was added. [i] H_2O (10 μL) was added. [j] 0.3% (v/v) of NEt_3 was added to the eluent for fast chromatography.

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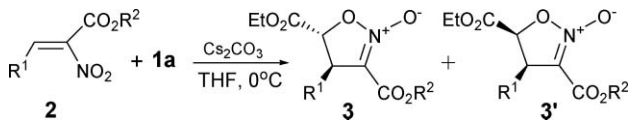
Table 2 Reaction of ammonium salts **1a** with nitroalkenes **2**[a]



2 3 3'

Entry	R^1	R^2	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	Bn (**2a**)	65	>99/1	>99
2	p-BrC_6H_4	Me (**2b**)	74	>99/1	98
3	p-$MeOC_6H_4$	Bn (**2c**)	75[e]	>99/1	99
4[f]	p-$MeOC_6H_4$	Bn (**2d**)	56	>99/1	98
5	p-MeC_6H_4	Bn (**2e**)	77	>99/1	97
6	p-FC_6H_4	Me (**2f**)	79	>99/1	99
7		Bn (**2g**)	67	>99/1	>99
8		Me (**2h**)	79	>99/1	>99
9		Me (**2i**)	68	>99/1	96
10	*o*-$MeOC_6H_4$	Me (**2j**)	54	>99/1	99
11	Ph	Me (**2k**)	62	>99/1	97
12	Ph	Me (**2k**)	69	>99/1	−99[g]
13	*i*-C_3H_7	Me (**2l**)	30[h]	80/20	99

[a] Conditions: **2** (0.2 mmol); Cs_2CO_3 (72 mg, 0.22 mmol); **1a** (105 mg, 0.22 mmol) in THF (0.08 mol/L); 10 μL of H_2O; 0 °C. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC for *trans*-isomer. [e] Cinchonidine derived amine was recovered at the yield of 59%. [f] The ammonium salt of cinchonidine with *tert*-butyl bromoacetate was used. [g] Salt **1b** was employed. [h] Total yield of **3l** and **3l′**.

trans-isoxazoline *N*-oxides as single diastereomers. The enantioselectivity is nearly independent of the substituents on the aryl and heteroaryl groups. In all the cases examined, *trans*-isomers of the desired products were obtained in higher than 96% ee and in good yields (Table 2, entries 1–12),‖ providing easy access to optically active isoxazoline *N*-oxides. Aliphatic nitroalkene **2l** proved to be suitable for this cyclization and gave the desired product in 99% ee, although both the yield and the diastereoselectivity decreased (Table 2, entry 13). Noticeably, the same cyclization was undertaken smoothly using cinchonine-derived salt **1b** instead of **1a**, but gave the opposite enantioselectivity with −99% ee (Table 2, entries 11 and 12). Thus, both enantiomers could be obtained easily by a simple choice of ammonium salt. For simple nitroolefins such as 1-((*E*)-2-nitrovinyl)benzene as the substrate, the desired isoxazoline *N*-oxide was not observed under the same reaction conditions. Attempts to develop a catalytic version of the reaction for these compounds failed. For example, a mixture of ethyl bromoacetate, nitroolefin **2a** and Cs_2CO_3 in presence of 20 mol% of **1a** gave only the desired product in less than 10% yield.

In conclusion, we have developed a highly diastereoselective and enantioselective ylide cyclization for the synthesis of optically active isoxazoline *N*-oxides by the reaction of chiral ammonium salts with nitroalkenes. Both enantiomers can be obtained, simply by choosing which cinchonidine-derived or cinchonine-derived ylide is used. Although a stoichiometric amount of chiral reagent is used, cinchonidine and cinchonine are quite inexpensive and recoverable.**

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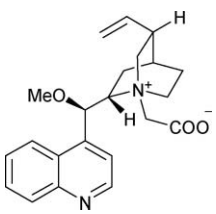
Notes and references

‡ The racemic isoxazoline *N*-oxides were prepared from the corresponding sulfonium ylides.

§ **Representative procedure** (substrate **2a** as an example): A mixture of salt **1a** (105 mg, 0.22 mmol), Cs_2CO_3 (72 mg, 0.22 mmol) and nitroalkene **2a** (57 mg, 0.2 mmol) were cooled to 0 °C under N_2. To the mixture was added H_2O (10 μL) and then THF (2.5 mL). The reaction mixture was stirred at 0 °C for 46 h. After the reaction was complete (monitored by TLC), the mixture was passed rapidly through a glass funnel with a thin layer (20 mm) of silica gel (300–400 mesh), washed with AcOEt (100 mL). The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography (EtOAc/petroleum ether/Et_3N 100/500/1.8 v/v/v). Yield 48 mg (65%). dr > 99/1. HPLC analysis (Chiralcel OD-H, ^{i}PrOH/hexane 30/70, 0.8 mL min^{-1}, 238 nm; t_r (major) = 12.75 min, t_r (minor) = 20.94 min) gave the isomeric composition of the product: >99% ee. $[\alpha]_D^{20}$ = −171.8 (*c* 1.11 in $CHCl_3$). mp. 82–85 °C. IR (film) ν/cm^{-1}: 3064 (m), 3033 (m), 2983 (m), 1743 (s), 1708 (s), 1635 (s), 1207 (m), 1148 (m), 750 (s) and 699 (s). ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 7.36–7.38 (m, 3H), 7.25–7.30 (m, 5H), 7.04–7.08 (m, 2H), 5.20 (d, J = 12.3 Hz, 1H), 5.06 (ABd, J = 12.3 Hz, 1H), 4.92 (d, J = 3.0 Hz, 1H), 4.85 (d, J = 3.0 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H) and 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 157.8, 137.8, 134.5, 129.3, 128.7, 128.4, 128.3, 127.9, 127.0, 108.8, 78.7, 67.2, 62.6, 52.5 and 14.0. MS (ESI, *m/z*): 424.1 $[M + MeOH + Na]^+$, 392.0 $[M + Na]^+$, 387.1 $[M + NH_4]^+$ and 370.1 $[M + H]^+$. Anal. calc. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.21; H, 5.19; N, 3.51%.

¶ To determine the absolute stereoconfigurations of these compounds, we obtained a single crystal of **3b**. Unfortunately, X-ray analysis showed that the crystal system is orthorhombic and that the space group is *Pccn*. And thus, it could not be determined by this way.

‖ When **1a** was treated with ^{n}BuLi or KHMDS, only a hydrolyzed product was isolated. This side reaction might exist in the present cyclization and result in a decreased yield. The hydrolyzed product of salt **1a**:



** 50–60% of the amines were recovered.

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