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Highly stereoselective synthesis of optically active oxazolinyl oxiranes from azaenolates of a chiral 2-chloromethyloxazoline

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Abstract

Boron and titanium azaenolates **2** and **4**, generated at 0°C and –100°C, respectively, from the optically active chloromethyloxazoline **1**, have been found to couple with aliphatic ketones in a highly diastereoselective fashion ending up with the formation of optically active oxazolinyl oxiranes **3**. Less stereoselective was the reaction with aromatic ketones.

Keywords: boron azaenolate; titanium azaenolate; chiral oxazolines; chiral oxiranyl oxazolines.

The chemistry of azaenolates of 2-alkyloxazolines, which are extremely useful intermediates in synthetic organic chemistry, has been rather exhaustively investigated with pivotal and fundamental achievements from Meyers' research group.[1] In comparison, azaenolates of heterosubstituted 2-alkyloxazolines have been studied much less.[2] Recent results from our laboratory had proved that azaenolates of chloroalkyloxazolines couple efficiently with carbonyl compounds[3] and imines[4] to produce oxazolinyl oxiranes, and then formyl oxiranes by elaboration of the oxazolinyl ring, and aziridines, respectively. In particular, we had found that lithium azaenolates couple with carbonyl compounds with poor diastereoselection,[5] whereas boron azaenolates react with very high and opposite diastereoselection depending upon the ligands on the boron atom.[6] However, we disappointingly found that boron azaenolates of **1**, generated at –78°C, do not couple with aliphatic enolizable ketones probably due to the competing ketone enolization which interferes with the enolization of the chloromethyloxazoline in the generation step of the boron azaenolate.

In the present paper we wish to report that under proper experimental conditions boron azaenolates of the chiral, non-racemic, chloromethyloxazoline **1** also couple efficiently and highly diastereoselectively with enolizable ketones. We also report on the coupling of titanium azaenolates.

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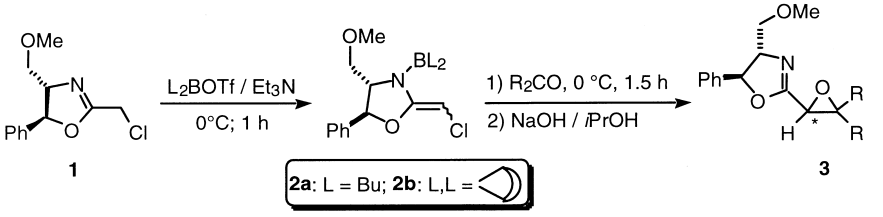
Treatment of a dichloromethane solution of (4*S*,5*S*)-2-chloromethyl-4-methoxymethyl-5-phenyl-2-oxazoline **1** (prepared by chlorination[6–8] of commercially available (4*S*,5*S*)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline) with Bu_2BOTf/NEt_3 at 0°C (1 h) and subsequent addition of 3-pentanone after 1.5 h afforded diastereomeric chlorohydrins, which, without isolation, were converted, under basic conditions (NaOH/*i*PrOH), into oxazolinyl epoxides **3** in high yield and with excellent diastereoselection (dr = 97:3) (Table 1).

Table 1
Reaction of **1**, via boron azaenolates **2a**/**2b**, with ketones



R_2CO	Epoxide (% yield)[a,b]	dr[c,d]	$[\alpha]_D$ (c 1, $CHCl_3$)	R_2CO	Epoxide (% yield)[a,b]	dr[c,d]
	$L_2BOTf = Bu_2BOTf$				***L_2BOTf = 9-BBNOTf***	
3-Pentanone	75	97/3	–25.0			
Cyclopentanone	62	97/3	+17.0	3-Pentanone	70	66/33
Cyclohexanone	70	97/3	–30.6	Cyclohexanone	75	66/33
2-Adamantanone	75	90/10	–9.3	2-Adamantanone	74	30/70
Cyclododecanone	75	97/3	–7.5	Benzophenone	85	7/93[f]
Benzophenone	63[e]	85/15	–8.4			

[a] Based on the conversion of the starting 2-chloromethyl-2-oxazoline **1** which was quantitative in all cases except in the reaction with Ph_2CO (73 % in both cases). Isolated yields. [b] All new oxazolinyl oxiranes **3** showed satisfactory microanalytical data and consistent MS, IR, ^1H and ^{13}C NMR data. [c] Diastereomeric ratio determined by ^1H NMR and GC. [d] The absolute configuration for those epoxides derived from aliphatic ketones has not been determined at present; an X-ray investigation is under way. [e] An *S* configuration was ascertained for this oxazolinyl epoxide. See Ref. 6. [f] An *R* configurated epoxide was obtained in this case with $[\alpha]_D$ –31.2 (c 1, $CHCl_3$). See Ref. 6.

The diastereomeric ratio was determined by gas-chromatography (the main stereoisomer showed the lower retention time) and was confirmed by ^1H NMR (500 MHZ) (usually on the basis of the chemical shift and the integral of the characteristic doublet of each of the two diastereomeric oxazoline ring hydrogens at C-5 in the range of 5.0–5.5 ppm: the main isomer had the higher δ value). Equally highly diastereoselective was the aldol-type reaction of the dibutyl boron azaenolate **2a** with other aliphatic ketones (Table 1). It was interesting to observe that the direction of diastereoselection did not change when the same boron azaenolate **2a** was prepared to 0°C, cooled to –78°C and reacted with the ketone (cyclohexanone).

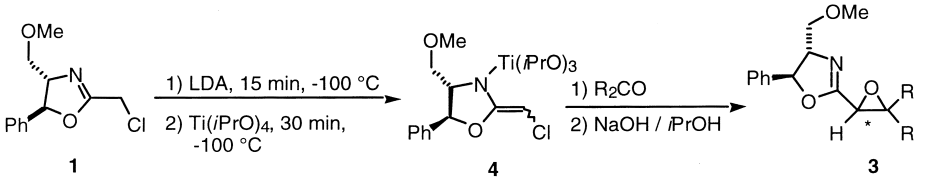
A lower diastereoselection, but showing similar trends, was observed in the coupling reaction of the boron azaenolate **2b** (prepared from **1** and 9-BBNOTf) at 0°C (Table 1). This result seemed intriguing as we had previously found that the aldol-type reaction of the dibutyl boron azaenolate **2a** with aromatic ketones proceeded with high and opposite diastereoselection with respect to the boron azaenolate **2b**.[6] This had been ascribed to the coordination of the boron atom by the methoxymethyl group present on the C_4 of the oxazoline ring,[6] thus driving the carbonyl

to attack the carbanionic center preferentially from the same side of the methoxymethyl appendage. The different behavior observed with aliphatic ketones could be tentatively explained in terms of a competition between the coordination of the boron atom by the methoxymethyl group and the carbonyl compound. The aliphatic ketones (at least those used in the present work) being stronger Lewis bases than the aromatic ketones, one could envisage a weak interaction between the boron atom and the methoxymethyl group with no effect on the stereoselection. It is also useful to point out that when the reaction of **2a** and **2b** with an aromatic ketone (benzophenone) was carried out at 0°C, the measured diastereoselection was exactly the same as for the reaction performed at –78°C.

We have also studied the stereochemical aspects of the aldol-type reaction of the titanium azaenolate of chloromethyl oxazoline **1**. Oxazoline **1** was treated with LDA at –100°C. The lithium azaenolate was then transmetalated with titanium tetraisopropoxide Ti(*i*PrO)$_4$. The resulting titanium azaenolate **4** was treated with cyclobutanone and then with NaOH in *i*PrOH affording the oxazolinyl epoxide in good yield and excellent diastereoselection, the direction of stereoselection being the same of the dibutyl boron azaenolate **2a** (Table 2).

Equally highly diastereoselective was the reaction of **4** with other aliphatic ketones (Table 2). No reaction took place when 2,2,4,4-tetramethyl-3-pentanone was used as the electrophile, probably for steric reasons. In contrast, the reaction of **4** with aromatic ketones occurred with very poor or no stereoselection.

Table 2
Reaction of 1, via titanium azaenolate **4**, with ketones



1 4 3

R_2CO	Epoxide (% yield)[a,b]	dr[c,d]	$[\alpha]_D$ (c 1, $CHCl_3$)	R_2CO	Epoxide (% yield)[a,b]	dr[c,d]
Cyclobutanone	60	98/2	–7.5			
Cyclopentanone	56	90/10	+15.0			
Cyclohexanone	60	97/3	–64.0	R = Ph	74	75/25
2-Adamantanone	75	87/13	–10.5	R = *p*-Me-C_6H_4	68	50/50
Cyclododecanone	50	30/70	–33.8	R = *p*-Cl-C_6H_4	60	59/41
3-Propanone	50	92/8	–42.0	R = *p*-MeO-C_6H_4	68	50/50
3-Pentanone	72	88/12	–27.0			
2,2,4,4-Tetramethyl-3-pentanone	nr[e]	-	-			

[a] Isolated yields. [b] All new oxazolinyl oxiranes **3** showed satisfactory microanalytical data and consistent MS, IR, ^{1}H and ^{13}C NMR data. [c] Diastereomeric ratio determined by ^{1}H NMR and GC. [d] The absolute configuration for those epoxides derived from aliphatic ketones has not been determined at present; an X-ray investigation is under way. [e] No reaction.

In conclusion, in this paper we report a highly stereoselective synthesis of oxazolinyl oxiranes, which are potentially useful synthetic intermediates, based on the coupling reaction of boron and titanium azenolates, easily available from the chiral oxazoline **1**, with ketones. More work is under way in order to razionalize the observed stereoselection.

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