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Synthesis of a Novel Chiral 1, 3-Benzoxazinone Auxiliary and Its Application to Highly Diastereoselective Aldol Reaction

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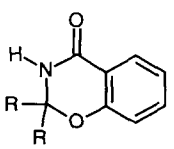
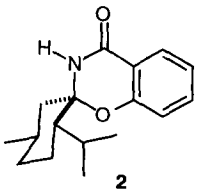
Abstract: Condensation of *l*-menthone with salicylamide followed by isomerization of the adduct withDBU afforded a novel chiral 1, 3-benzoxazinone auxiliary, the usefulness of which was demonstrated by highly diastereoselective aldol reaction with aldehydes. Copyright © 1996 Elsevier Science Ltd

Since the discovery of 2-oxazolidones[1] and camphor sultams,[2] an auxiliary-mediated second generation method of asymmetric synthesis has been recognized as one of the steadiest access to optically active compounds.[3] As a part of our project to develop a carbapenem antibiotic, the 2, 2-disubstituted 1, 3-benzoxazinones **1** have been shown to induce a high level of stereoselectivity in the Reformatsky reaction of *N*-α-bromopropionyl derivative with acetoxyazetidinone.[4] The successful result prompted us to synthesize a chiral 1, 3-benzoxazinone auxiliary and examine its efficacy in the asymmetric synthesis. We report herein synthesis of a novel chiral 1, 3-benzoxazinone auxiliary **2** and its induction of excellent diastereoselectivities in aldol reaction.



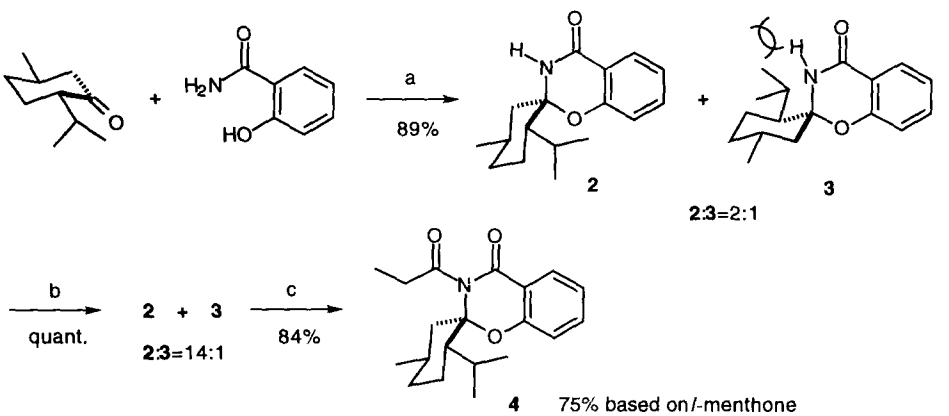
1



2

Synthesis of the chiral auxiliary **2** was carried out by dehydrative condensation of *l*-menthone with salicylamide (Scheme 1). Refluxing equimolar amount of *l*-menthone and salicylamide in toluene for 24 h in the presence of *p*-TsOH (5 mol%) in a Dean-Stark apparatus gave a mixture of the chiral 1, 3-benzoxazinones **2** and its diastereomer **3** (**2**/**3**=2:1).[5] The predominant formation of **2** may be due to a repulsive interaction between the isopropyl group and the amide hydrogen atom observed in **3**.[6] Since the 1, 3-benzoxazinones **2** and **3** are acetal-type compounds, it seemed likely that there is an equilibrium between **2** and **3** under certain conditions, and consequently the attempt to shift the equilibrium to **2** by isomerization was undertaken. Although acid-catalyzed isomerization of **3** was not fruitful (Table 1, entries 1 and 2), base-catalyzed counterpart using DBU in *N*-methylpyrrolidone (NMP) was found to be very effective (Table 1, entry 3). Treatment of **3** with a catalytic

Scheme 1



a: *p*-TsOH (0.05 eq.), toluene, reflux, 24 h; b: DBU (0.1 eq.), NMP, 25°C, 24 h, -20°C, 24 h; c: EtCOCl, *i*-Pr_2EtN, CuCl (cat.), toluene, 50°C, 3 h.

amount of DBU (10 mol %) in NMP at 25°C for 24 h then at -20°C for 24 h yielded **2** in predominance over **3** (**2**:**3**=14:1). A mixture of **2** and **3** (**2**:**3**=2:1) was subjected to the same isomerization to afford the same ratio of the mixture (**2**:**3**=14:1). In addition, a mixture of **2** and **3** was kinetically differentiated in subsequent acylation. *N*-Propionyl 1, 3-benzoxazinone **4** was exclusively formed from a mixture of **2** and **3** under the acylation conditions using a weak base[7] [EtCOCl, *i*-Pr_2EtN, CuCl (cat.), 50°C, 3 h]. It seems plausible that the exclusive formation of **4** may also be accounted for by repulsive interactions between the isopropyl group and incoming base and/or acid chloride encountered in the case of **3**. Combination of these three chemical transformations (steps a-c) furnished the *N*-propionylbenzoxazinone **4** in 75% yield based on *l*-menthone.

Table 1

3 ⟶ **2** + **3**

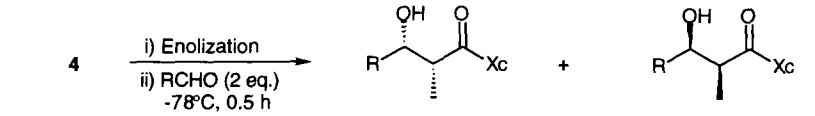
Entry[a]	Reagent (eq.)	Solvent	Conditions	**2**:**3**[b]
1	*p*-TsOH (0.1)	Toluene	reflux, 6 h	2:1
2	PPTS (0.1)	Toluene	reflux, 24 h	3:1
3	DBU (0.1)	NMP	25°C, 24 h -20°C, 24 h	14:1

[a]All the reactions were conducted in 1 mmol scale. [b]Determined by HPLC.

In order to examine the utility of the chiral auxiliary **2** in the asymmetric synthesis, aldol reaction of *N*-propionyl derivative **4** was next carried out. Enolization of **4** with LDA followed by addition of benzaldehyde afforded the aldol in favor of the *syn*-isomer **5a**[8] in moderate yield (Table 2, entry 1). The yield and the *syn*-selectivity were remarkably improved by the use of the sodium enolate generated by reaction of **4** and $NaN(TMS)_2$ yielding the aldol in 85% yield with a ratio of **5a**:**6a**=91:2 (Table 2, entry 2). Transmetallation of the sodium enolate of **4** into the titanium enolate with $ClTi(O\textit{i}\text{-}Pr)_3$ and subsequent addition of benzaldehyde

gave the *syn*-isomer **6a**[8, 1e] in high yield with high stereoselectivity (81% yield, **5a**:**6a**=3:94) (Table 2, entry 3). Direct generation of the more reactive chlorotitanium enolate[1f] of **4** by deprotonation of the $TiCl_4$-complexed **4** with Et_3N followed by the reaction of the enolate with benzaldehyde as well gave rise to the *syn*-isomer **6a** in high yield with high selectivity (Table 2, entry 4). To check the further versatility of the chiral auxiliary, the aldol reaction of **4** with acetaldehyde, an example of an alkanal, was also examined and observed that the *syn*-aldol **6b** yielded both in high yield and with high stereoselectivity (Table 2, entry 5). In all cases, the products were easily obtained in >99% d.e. by simple column chromatography on silica-gel.

Table 2



5a,b **6a, b**

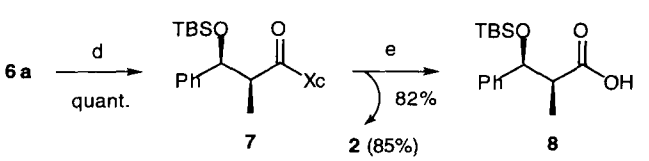
Xc: Chiral auxiliary **a**: R=Ph; **b**: R=Me

Entry[a]	R	Enolization			Yield (%)[b]	**5** : **6**[c]	Major Product[d] Yield (%)
		Reagent (eq.)	Solvent	Conditions			
1	Ph	LDA (1.1)	THF	-78°C, 2 h	45	66:10 (24)	-[e]
2	Ph	$NaN(TMS)_2$ (1.1)	THF	-78°C, 0.5 h	85	91:2 (7)	72
3	Ph	$NaN(TMS)_2$ (1.6)[f] $ClTi(O\,i\text{-}Pr)_3$ (1.6)[g]	THF	-78°C, 0.5 h[f] -40°C, 0.2 h[g]	86	3:94 (3)	75
4	Ph	$TiCl_4$ (2.0), Et_3N (2.0)	CH_2Cl_2	-78°C, 2 h	84	2:96 (2)	76
5[h]	Me	$TiCl_4$ (2.0), Et_3N (2.0)	CH_2Cl_2	-78°C, 0.5 h	98	2:97 (1)	91

[a]All the reactions were conducted in 1 mmol scale. [b]Combined isolated yields. [c]The ratio was determined by HPLC. The figures in the parenthesis denote the combined isolated yields of *anti*-products. [d]Isolated yields of the pure major product (>99% d.e.). [e]The major product was not isolated. [f]The conditions for enolization. [g]The conditions for transmetallation. [h]10 eq. of aldehyde was used for the reaction.

Additional usefulness of the novel chiral auxiliary is demonstrated by its facile recovery from the product, which is shown in Scheme 2. Conversion of **6a** into the silyl ether **7** followed by treatment with $LiOH/H_2O_2$ in aqueous THF afforded the optically pure *O*-TBS acid **8**[1d, 9] in 82% yield and the chiral auxiliary in 85% yield.

Scheme 2



d: TBS-Cl, imidazole, DMF, 25 °C, 17 h; e: H_2O_2, LiOH, THF, H_2O, 0°C, 20 min

In summary, the newly synthesized 1, 3-benzoxazinone auxiliary **2** has the following distinct advantages: 1) easy accessibility of the starting materials, *l*-menthone and salicylamide; 2) facile preparation; 3) high yield in *N*-acylation by the use of a weak base (*i*-Pr2EtN); 4) high level of asymmetric induction observed in aldol reaction; 5) facile recovery of the auxiliary without affecting the developed chiral centers. Owing to these excellent features, the 1, 3-benzoxazinone auxiliary **2** represents a new entry of a chiral auxiliary for the auxiliary-mediated asymmetric synthesis. Utilization of the present auxiliary to the asymmetric synthesis of natural products are under way which will be described elsewhere in due course.

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5. **2**: mp 82-83°C. IR (KBr) ν_{max}: 1677, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.93 (dd, *J*=7.7, 1.7 Hz, 1H); 7.44 (ddd, *J*=8.0, 7.5, 1.7 Hz, 1H); 7.05 (ddd, *J*=7.7, 7.5, 1.0 Hz, 1H); 6.92 (dd, *J*= 8.0, 1.0 Hz, 1H); 6.08 (brs, 1H); 2.38-2.44 (m, 2H); 1.61-1.76 (m, 5H); 1.26-1.33 (m, 1H); 1.02-1.09 (m, 1H); 0.97 (d, *J*=7.1 Hz, 3H); 0.93 (d, *J*=6.8 Hz, 3H); 0.79 (d, *J*=6.7 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ: 163.07, 155.49 (2s); 134.42, 127.68, 121.52, 117.15 (4d); 117.01, 91.59 (2s); 49.95 (d); 45.92, 34.31 (2t); 28.81, 26.14 (2d); 23.39, 21.58 (2q); 21.29 (t); 18.00 (q). Mass *m/z*: 273 (M^+). $[\alpha]_D^{25}$ -82.3° (*c*, 1.1, MeOH). **3**: mp 159-160°C. IR (KBr) ν_{max}: 1673, 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.91 (dd, *J*=7.7, 1.7 Hz, 1H); 7.44 (ddd, *J*=8.0, 7.5, 1.7 Hz, 1H); 7.04 (dt, *J*=7.7, 7.5, 1.0 Hz, 1H); 6.90 (dd, *J*=8.0, 1.0 Hz, 1H); 7.75 (brs, 1H); 2.25-2.38 (m, 2H); 1.50-1.90 (m, 5H); 1.08-1.24 (m, 2H); 1.03 (d, *J*=7 Hz, 3H); 0.91 (d, *J*=6.8 Hz, 3H); 0.83 (d, *J*=6.7 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ: 162.79, 156.11 (2s); 134.50, 127.65, 121.29, 116.97 (4d); 116.89, 91.82 (2s); 49.94 (d); 46.32, 34.31 (2t); 28.75, 26.11 (2d); 23.73 (q); 22.66 (t); 21.77 (q); 18.84 (q). Mass *m/z*: 273 (M^+). $[\alpha]_D^{25}$ +64.8° (*c*, 1.0, MeOH). The structure of **2** and **3** was unequivocally confirmed by X-ray crystallographic analysis. The X-ray data have been deposited at Cambridge Crystallographic Data Center.
6. Similar steric interactions found in *l*-menthonide, see: Harada, T.; Ueda, S.; Yoshida, T.; Inoue, A.; Takeuchi, M.; Ogawa, N.; Oku, A. *J. Org. Chem.* **1994**, *59*, 7575- 7576.
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8. **5a**: colorless oil. $[\alpha]_D^{25}$ +87.5° (*c*, 1.0, MeOH). **6a**: colorless oil. $[\alpha]_D^{25}$ +41.4° (*c*, 1.0, MeOH). **6b**: colorless oil. $[\alpha]_D^{25}$ +19.1° (*c*, 1.0, MeOH). The structure of compounds **5a** and **6a** was substantially confirmed by X-ray crystallographic analysis of corresponding racemic derivatives. The X-ray data have been deposited at Cambridge Crystallographic Data Center. The structure of **6b** was confirmed on corresponding hydroxy acid by comparison with the reported physicochemical properties.[2b]
9. **8**: colorless oil. IR (KBr) ν_{max}: 1700, 2956 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.16-7.30 (m, 5H); 5.07 (d, *J*=5.0 Hz, 1H); 2.61-2.75 (m, 1H); 1.09 (d, *J*= 7.0 Hz, 3H); 0.66 (s, 9H); 0.03 (s, 3H); -0.21 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 179.9, 142.5 (2s); 128.1, 127.5, 126.5, 75.6, 48.5 (5d); 25.8 (q), 18.2 (s); 10.9 (q); 0.01 (q); -4.6 (q). Mass *m/z*: 295 (M^++1). $[\alpha]_D^{25}$ -31.5° (*c*, 1.1, MeOH). The corresponding hydroxy acid obtained by removal of the TBS group of **8** (TBAF, THF, 25°C, 30 min, 95%) had an optical rotation {$[\alpha]_D^{24}$ -26.4° (*c*, 1.13, CH_2Cl_2)}in good accordance with the reported value {$[\alpha]_D^{24}$ -26.4° (*c*, 1.04, CH_2Cl_2)}.[1d]

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