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Diethylboron triflate-promoted *anti* aldol additions of Oppolzer's sultam

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Abstract—An excess of diethylboron triflate leads to high *anti* diastereoselectivity (up to 98:2) in aldol additions employing Oppolzer's sultam with both aliphatic and aromatic aldehydes.

1. Introduction

The development of the asymmetric aldol reaction has been proven to be invaluable for the synthesis of complex natural products, especially those bearing multiple contiguous stereogenic centres.[1,2] Although rapid progress has been made in the development of catalytic aldol addition reactions,[3] chiral auxillaries remain a popular choice for asymmetric C–C bond formation. In our work, we are interested in exploring the possibility of employing the same Lewis acid for both enolisation and promotion of *anti* selectivity with aldol precursor **3**. From a practical point of view, this significantly simplifies the execution of the reaction. In addition, the choice of Oppolzer's sultam as an auxilliary was based on the in situ generation of the Lewis acid, again simplifying the experimental procedure.

Recently we reported that Et_2BOTf promoted *anti* selective aldol additions employing Oppolzer's sultam in the synthesis of (+)-nonactic acid **1**[4] and oxatropane **2**[5] (Fig. 1).

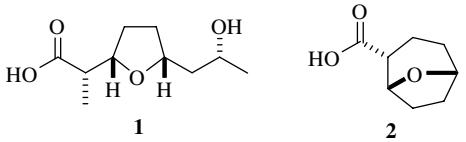

Figure 1. (+)-Nonactic acid **1** and oxatropane **2**.

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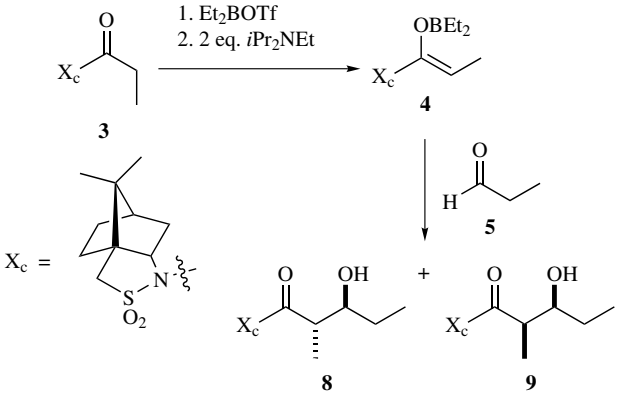
It was observed that an excess of Et_2BOTf present during the reaction was critical in order to promote *anti* selective aldol addition. This is consistent with Heathcock's results using Bu_2BOTf with Evans' acyl oxazolidinones.[6–8] A similar, although more limited, study by Oppolzer showed poor *anti* selectivity with Et_2BOTf and, perhaps, because of the excellent diastereoselectivities obtained with $TiCl_4$ (>99:1 *anti*:*syn*), further investigation of other dialkylboron triflates was not carried out.[10,12] In light of this and of our recent results, we decided to conduct a study in order to determine the scope and utility of Et_2BOTf-promoted *anti* aldol reactions of Oppolzer's sultam. A significant practical advantage in this method when compared to others is that Et_2BOTf can be generated in situ, whereas Bu_2BOTf often requires distillation prior to use.[11]



Scheme 1. *anti* Aldol addition of propionyl sultam **3** with propanal **5**.

2. Results and discussion

In order to determine the precise amount of Et_2BOTf needed for *anti* selective addition, propionyl sultam **3** in DCM at −78 °C was treated with 2 equiv of iPr_2NEt and varying equivalents of Et_2BOTf. Propanal **5** was then added to the resulting solution (Scheme 1).

After reaction for 4 h, excess Et_2BOTf was quenched by adding another equivalent of iPr_2NEt (vide infra) and pH 7 phosphate buffer. The *anti*/*syn* ratio (**8**:**9**) was determined by GC–MS, and the major diastereomer was isolated pure after flash chromatography. The results of these experiments are summarized below (Table 1).

Entry 1 was a control experiment, where 2 equiv each of Et_2BOTf and iPr_2NEt gave the expected *syn* aldol adduct **9**.[12] Entry 2 demonstrates that only a 0.2 excess of Et_2BOTf was required to dramatically reverse the selectivity (85:15) in favour of the *anti* diastereomer **8**. A further increase to 0.5 equiv excess (entry 3) gave even better results (93:7). Further increases (entries 4 and 5) had no impact on yield or selectivity, as was the case with increased amounts of iPr_2NEt (entry 6). Interestingly, by increasing the amount of propanal to 5 equiv (entry 7), a much better yield of **8** was obtained without adversely affecting the stereoselectivity (97:3). The unique work-up of adding an equivalent of iPr_2NEt prior to pH 7 buffer proved critical for obtaining good yields of *anti* adduct **8**. When only the buffer was used in the work-up, a complex mixture of products was obtained where pure **8** could not be isolated. The optimized conditions (entry 7) were then applied to additions of propionyl sultam **3** with a variety of aldehydes (Scheme 2).

The results of these experiments are summarized below (Table 2).

anti Aldol adducts **11a**–**e** were isolated pure after chromatography and identified by measurement and comparison of specific rotation, ^1H and ^{13}C NMR data with the literature values.[9] Acetaldehyde (entry 1) showed the lowest selectivity (88:12), which is consistent with Oppolzer's finding that additions to smaller aldehydes are less selective. As the size of the aldehyde increased (entries 2–5), an increase in selectivity was generally observed. This procedure is applicable to aromatic aldehyhdes as benzaldehyde (entry 5) gave excellent selectivity (96:4).

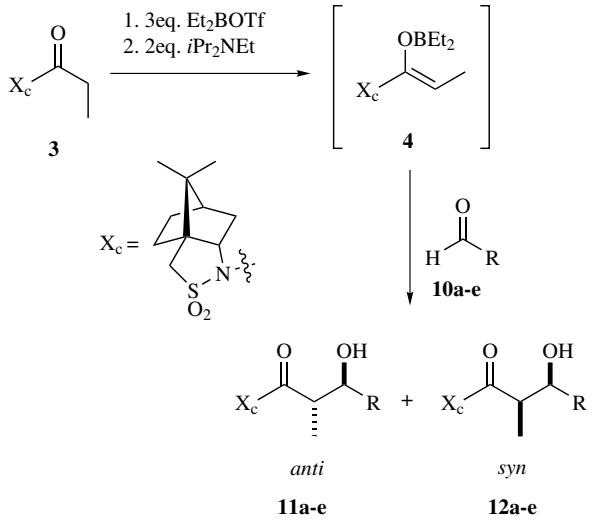
This methodology can be readily applied to more complex substrates, as shown in Scheme 3.

As a result, the reaction of unsaturated acyl sultam **13** with aldehyde **15** under the optimized conditions yielded aldol adduct **16** in 54% yield and with 93:7 *anti*:*syn* diastereoselectivity.

Table 1. Results of *anti* aldol addition of the enolate of propionyl sultam **3** to propanal **5** using varying amounts of Et_2BOTf

Entries	Et_2BOTf (equiv)	iPr_2NEt (equiv)	Propanal (equiv)	Ratio **8**–**9**[b]	Yield of **8** (%)[a]
1	2	2	3	1:99	—
2	2.2	2	3	85:15	68
3	2.5	2	3	93:7	62
4	3	2	3	94:6	68
5	4	2	3	92:8	65
6	3	2.2	3	97:3	64
7	3	2	5	97:3	84

[a] Isolated yield of the *anti* diastereomer after purification by flash chromatography (20% EtOAc/hexanes).
[b] As determined by GC–MS analysis of the crude reaction mixture.

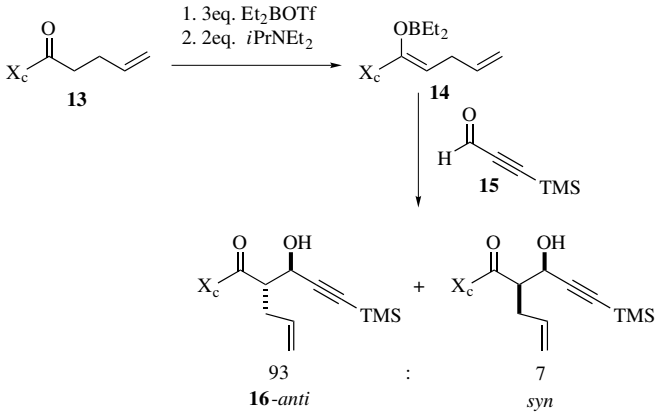


Scheme 2. *anti* Aldol addition of propionyl sultam **3** to aldehydes **10a**–**e**.

Table 2. Results of *anti* addition of propionyl sultam **3** to aldehydes **10a-e**

Entries	R	11:12	Yield[a] (%)	$[\alpha]_D$[b]	Mp[b] (°C)
1	Me	88:12	75	−58.1 (lit.[7] −62.2)	124–126
2	Et	97:3	84	−65.6 (lit.[7] −64.4)	72–74
3	*n*Pr	97:3	66	−23.5	—
4	*i*Pr	91:9	64	−71.5 (lit.[7] −67.2)	145–147
5	Ph	96:4	51	+7.1 (lit.[7] +7.4)	180–181

[a] The isolated yield of the *anti* diastereomer after purification by chromatography (20% EtOAc/hexanes).
[b] Values refer to isolated *anti* adduct.



Scheme 3. Aldol addition of unsaturated acyl sultam **13** to TMS propargylic aldehyde **15**.

3. Conclusion

In conclusion, we have shown that Et_2BOTf promotes *anti* addition of acylated Oppolzer's sultam to various aliphatic, aromatic and propargylic aldehyes with good to excellent diastereoselectivities. This method also offers significant practical advantages, as it (a) obviates the need to precomplex the aldehyde, which can promote unwanted side reactions[1] and (b) generates the Lewis acid in situ.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 300 MHz on a Bruker AM 300 spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AM 300 spectrometer. 2D NMR techniques, such as homonuclear correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple bond coherence (HMBC) and nuclear Overhauser effect Spectroscopy (NOESY) were used to aid with the assignment of some NMR spectra. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High Resolution mass spectra (HRMS) were recorded on a Bruker BioApex 47e FTMS. Infrared spectra (IR) were recorded on a Perkin Elmer 1600 Series Fourier Transform spectrometer. Optical rotations were measured on a PolAAr 2001 automatic polarimeter at the sodium D line (587 nm). Silica gel used for chromatography was 40–63 μm (230–400 mesh) silica gel 60 (Merck No. 9385). GC–MS were performed on a Varian 3700 gas chromatograph using a 30QC5/BPX5 1.0 μm column of internal diameter 0.53 mm and length 30 cm. Solvents were purified as follows: anhydrous diethyl ether (ether) was distilled from sodium/benzophenone ketyl prior to use. Dichloromethane was distilled from calcium hydride. Trifluoromethanesulfonic acid was freshly distilled under nitrogen from P_2O_5 and was used immediately. All reactions were conducted with oven dried glassware under an atmosphere of dry nitrogen or argon.

4.2. Aldehyde purification

Acetaldehyde, propanal, *iso*-butyraldehyde and butyraldehyde were all purified by distillation from $Ca(SO_4)_2$. Benzaldehyde was dissolved in ether, washed with aq 2 M NaOH, dried with $MgSO_4$ and the solvent removed under reduced pressure before use.

4.3. General *anti* aldol procedure for adducts 11a–e

To a stirred solution of triethylborane (1 M in hexanes, 1 mL, 1 mmol,) was added freshly distilled trifluoromethanesulfonic acid (88 μL, 1 mmol). The reaction was stirred for 1 h after which the solution appeared homogenous and pale yellow/orange in colour. The reaction was cooled to −5 °C (ice/acetone bath) and a solution of propionyl sultam **3** (91 mg, 0.34 mmol) in DCM (1 mL) and iPr$_2$NEt (0.12 mL, 0.66 mmol) were added. The reaction was stirred at −5 °C for a further 0.5 h and then cooled to −78 °C (dry ice/acetone bath). A solution of aldehyde (5 mmol) in DCM (2 mL) was then added dropwise to the reaction over a 5 min period ensuring that the temperature did not exceed −70 °C. Stirring was continued for 3 h at −78 °C before additional iPr$_2$NEt (60 μL, 0.33 mmol) and phosphate buffer (pH 7, 4 mL) was added. The reaction was then warmed to rt, and the aqueous and organic phases separated. The aqueous phase was extracted with diethyl ether (3 × 2 mL). The organic phase and extracts were combined, washed with satd NH_4Cl (2 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a colourless crude oil or solid. This was then subjected to GC–MS analysis for determination of the diastereoisomeric ratio and was then purified by flash chromatography (20% EtOAc/hexanes) to yield the appropriate aldol adducts **11a**–**e**.

4.4. (2*R*)-*N*-[(2*S*,3*S*)-3-Hydroxy-2-methylbutan-1-oyl] bornane-10,2-sultam 11a

Following the general *anti* aldol procedure—using the aldehyde acetaldehyde—the title compound was synthesized with 88:12 diastereoselectivity (*anti*:*syn*) and isolated as a colourless crystalline solid in 75% yield. Mp 124–126 °C (lit.[9] 125–126 °C). $[\alpha]_D^{22} = -58.1$ (*c* 0.85, $CHCl_3$) (lit.[9] −62.2 (*c* 1.0, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.17 (s, 3H), 1.19 (d, $J = 6.8$ Hz, 3H), 1.23 (d, $J = 6.3$ Hz, 3H), 1.30–1.43 (m, 3H), 1.84–2.18 (m, 4H), 2.31 (d, $J = 9.2$ Hz, 1H), 3.11 (apparent p, $J = 6.8$ Hz, 1H), 3.43 (d, $J = 13.8$ Hz, 1H), 3.52 (d, $J = 13.8$ Hz, 1H), 3.82 (ddq, $J = 6.8$, 9.2, 8.6 Hz), 3.89 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.0, 20.8, 22.0, 26.5, 33.1, 38.6, 44.8, 47.1, 47.7, 48.2, 53.3, 66.6, 71.8, 176.5.

4.5. (2*R*)-*N*-[(2*S*,3*S*)-3-Hydroxy-2-methylpentan-1-oyl] bornane-10,2-sultam 11b

Following the general *anti* aldol procedure—using the aldehyde propanal—the title compound was synthesized with 97:3 diastereoselectivity (*anti*:*syn*) and isolated as a colourless crystalline solid in 84% yield. Mp 72–74 °C (lit.[9] 75–76 °C). $[\alpha]_D = -65.6$ (*c* 0.99, $CHCl_3$) (lit.[9] −64.4 (*c* 1.65, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 3H), 0.99 (t, $J = 7.4$ Hz, 3H), 1.18 (s, 3H), 1.24 (d, $J = 6.7$ Hz, 3H), 1.31–1.69 (m, 7H), 1.84–2.11 (m, 2H), 3.19 (apparent p, $J = 6.7$ Hz, 1H), 3.44 (d, $J = 10.3$ Hz, 1H), 3.52 (d, $J = 10.3$ Hz, 1H), 3.51 (d, $J = 7.2$ Hz), 3.62 (m, 1H), 3.89 (dd, $J = 5.0$, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 14.4, 20.0, 20.8, 26.6, 28.6, 33.1, 38.6, 44.8, 45.2, 47.9, 48.5, 53.3, 58.1, 65.6, 175.6.

4.6. (2*R*)-*N*-[(2*S*,3*S*)-3-Hydroxy-2-methylhexan-1-oyl] bornane-10,2-sultam 11c

Following the general *anti* aldol procedure—using the aldehyde butanal—the title compound was synthesized with 97:3 diastereoselectivity (*anti*:*syn*) and isolated as a colourless oil in 66% yield. $[\alpha]_D = -23.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.9$ Hz, 3H), 0.95 (s, 3H),

1.15 (s, 3H), 1.19 (d, $J = 6.8$ Hz, 3H), 1.28–1.65 (m, 7H), 1.81–2.10 (m, 4H), 2.35 (d, $J = 7.2$ Hz, 1H), 3.15 (apparent p, $J = 6.8$ Hz, 1H), 3.42 (d, $J = 13.8$ Hz, 1H), 3.50 (d, $J = 13.8$ Hz, 1H), 3.62 (m, 1H), 3.87 (apparent t, $J = 6.3$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.4, 18.8, 20.1, 20.9, 26.6, 33.2, 38.1, 38.7, 44.9, 46.6, 48.0, 48.5, 53.4, 65.7, 75.6, 175.8. IR ν_{max} 3521, 2959, 2876, 1694, 1682, 1674, 1456, 1392, 1332, 1269, 1236, 1213, 1166, 1134, 1117, 1056, 1038, 1011, 965, 848, 775, 644 cm^{-1}. HRMS calcd for $C_{17}H_{29}NO_4SNa^+$ m/z 366.1715, found 366.1717.

4.7. (2*R*)-*N*-[(2*S*,3*S*)-2,4-Dimethyl-3-hydroxypentan-1-oyl] bornane-10,2-sultam 11d

Following the general *anti* selective aldol procedure—using the aldehyde isobutyraldehyde—the title compound was synthesized with 91:9 diastereoselectivity (*anti*:*syn*) and isolated as a colourless crystalline solid in 64% yield. Mp 145–147 °C (lit.[9] 147–148 °C). $[\alpha]_D = -71.7$ (*c* 2.24, $CHCl_3$) (lit.[9] −67.2 (c 1.0 $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, $J = 5.1$ Hz, 3H), 0.95 (s, 3H), 0.97 (d, $J = 7.9$ Hz, 3H), 1.19 (s, 3H), 1.22 (d, $J = 7.1$ Hz, 3H), 1.31–1.43 (m, 2H), 1.51 (m, 1H), 1.83–2.19 (m, 5H), 2.42 (d, $J = 10.3$ Hz, 1H), 3.27 (apparent p, $J = 7.1$ Hz, 1H), 3.39 (m, 1H), 3.43 (d, $J = 10.4$ Hz, 1H), 3.51 (d, $J = 10.4$ Hz, 1H), 3.89 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 15.7, 19.7, 19.9, 20.7, 26.3, 31.0, 33.3, 38.7, 42.9, 44.7, 48.0, 48.6, 53.1, 65.5, 80.5, 175.9.

4.8. (2*R*)-*N*-[(2*S*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropan-1-oyl] bornane-10,2-sultam 11e

Following the general procedure for *anti* selective aldol addition—using the aldehyde benzaldehyde—the title compound was synthesized with 94:6 diastereoselectivity (*anti*:*syn*) and isolated as a colourless crystalline solid in 52% yield. Mp 180–181 °C (lit.[9] 183–184 °C). $[\alpha]_D = +7.1$ (*c* 1.10 $CHCl_3$) (lit.[9] +7.4 (*c* 1.25, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.91 (s, 3H), 1.18 (d, $J = 6.8$ Hz, 3H), 1.21–1.42 (m, 2H), 1.71–2.01 (m, 5H), 3.12 (br s, 1H), 3.38 (d, $J = 13.8$ Hz, 1H), 3.47 (d, $J = 13.8$ Hz, 1H), 3.56 (apparent p, $J = 6.9$ Hz, 1H), 3.83 (m, 1H), 4.72 (apparent d, $J = 7.0$ Hz, 1H), 7.21–7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 20.1, 20.8, 26.6, 33.2, 38.6, 44.9, 46.6, 47.8, 48.8, 53.4, 65.6, 78.0, 126.5, 128.1, 128.6, 142.3, 175.5.

4.9. (2*S*)-*N*-[(2*S*,3*R*)-3-Hydroxy-5-(trimethylsilyl)pent-4-yne-1-oyl] bornane-10,2-sultam 16

Following the general procedure for *anti* selective aldol addition—using acyl sultam **13** and the aldehyde TMS-propynal **15** with a reaction time of 6 h—the title compound **16** was synthesized with 93:7 diastereoselectivity (*anti*:*syn*) and isolated as a colourless solid in 54% yield. Mp 135–136 °C. $[\alpha]_D = +56.4$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 9H), 0.95 (s, 3H), 1.17 (s, 3H), 1.24–1.42 (m, 2H), 1.83–2.23 (m, 5H), 2.51 (dt, $J = 1.0$, 7.0 Hz, 1H), 2.99 (d, $J = 10.0$ Hz, 1H), 3.35 (apparent dd, $J = 6.9$, 14.0 Hz, 1H), 3.44 and 3.52 (AB q, $J = 13.8$ Hz, 2H), 3.89 (dd, $J = 5.0$, 7.8 Hz, 1H), 4.44 (dd, $J = 7.3$, 9.7 Hz, 1H), 5.08 (m, 2H), 5.77 (m, 1H). ^{13}C NMR (75 MHz,$CDCl_3$) δ 172.6, 134.3, 118.1, 104.4, 91.2, 65.6, 64.4, 53.3, 51.2, 48.5, 47.9, 44.8, 38.5, 33.0, 32.7, 26.5, 21.1, 20.0, −0.1. IR (ATR) 3504, 2960, 2362, 2337, 1697, 1654, 1559, 1541, 1457, 1395, 1332s, 1270, 1250, 1214, 1166, 1134, 1068, 1040, 844, 632 cm^{-1}. HRMS calcd for $C_{21}H_{33}NO_4SSiNa^+$ m/z 446.1797, found 446.1794.

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