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STEREOSELECTIVE ALDOL REACTIONS OF β-CHLOROVINYL KETONES USING DIENOL BORINATES: A NEW SYNTHESIS OF DIHYDROPYRONES.

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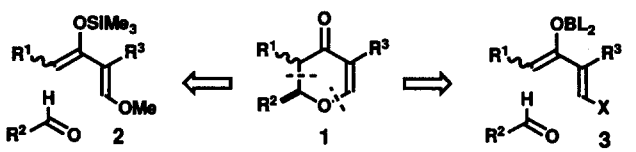
Summary: The *syn*-selective aldol reaction of β-chlorovinyl ketones using dienol borinates can be coupled with a trimethylsilyltriflate promoted cyclisation to give *cis*-dihydropyrones, **4** → **6** → **7**. Use of dienol diisopinocampheylborinates leads to an enantioselective synthesis of dihydropyrones.

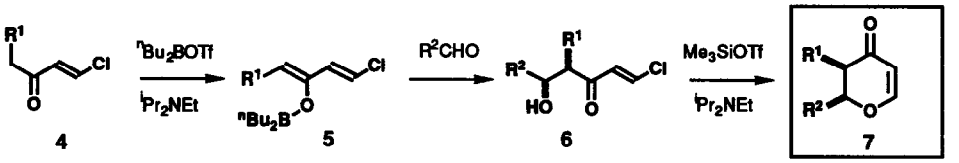
Dihydropyrones like **1** are useful intermediates for access to a wide range of substituted tetrahydropyran rings.[1] Their diastereoselective synthesis is usually based on the Lewis acid catalysed reaction of siloxydienes **2** with aldehydes (**Scheme 1**), as developed by the Danishefsky group.[1a,b,2,3] For the asymmetric synthesis of **1**, chiral aldehydes,[2] chiral auxiliaries[3] attached to the diene and chiral Lewis acids[3,4] have all been used with varying success in this cyclocondensation reaction. We have investigated an alternative stereocontrolled construction of dihydropyrones from aldehydes by use of dienol borinates **3** (X = Cl, I, SPh, OMe, *etc.*). This approach exploits the high levels of enantio- and diastereoselectivity associated with boron enolate aldol reactions.[5]

Scheme 1



We now report our results for the aldol reaction of β-chlorovinyl ketones **4** with aldehydes *via* the dienol dibutylborinates **5** (**Scheme 2**), which leads to *syn* adducts **6** in good yield and with high diastereoselectivity (≥97%). A subsequent cyclisation step, promoted by trimethylsilyltriflate and diisopropylethylamine, gives the corresponding *cis*-dihydropyrones, **6** → **7** (R^1 = Me; R^2 = saturated alkyl). Use of the corresponding dienol diisopinocampheylborinates leads on aldol addition and cyclisation to the enantioselective formation of dihydropyrones.

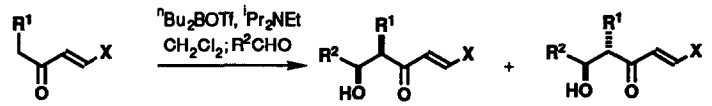
Scheme 2



We first examined the aldol reactions of a range of readily available[6] β-substituted vinyl ketones **4**, **9**, **10** and **11** (**Scheme 3**), where the β-X group (Cl, OMe, SPh, or I) was intended as a leaving group in a subsequent cyclisation reaction. Under the normal conditions ($^nBu_2BOTf/^iPr_2NEt$, CH_2Cl_2, -78 °C, 5 h; ^{n}PrCHO, -5 °C, 16 h), the vinylogous ester system **9** (X = OMe for R^1 = H) failed to undergo an aldol addition. However, successful *syn*-selective aldol reactions were obtained with the chloride, iodide and phenylsulphide, as shown in **Table 1**.[7] In the case of the phenylthio substituted system **10** (entry 1), the aldol reaction was complicated by equilibration to the

double bond isomers of **12** and **8** (X = SPh). Best results were obtained with the chlorides **4**, which are also the most readily available ($AlCl_3$ catalysed addition of R^1CH_2COCl to acetylene[6]). For R^1 = Me (entries 4-9), the boron-mediated aldol reaction of **4** with a range of aldehydes produced the *syn* adduct **6** in good yield (53-84%) with high *syn* selectivity (97%) *via* the *Z* dienol dibutylborinate **5**.[8] Selective production of the *anti* isomer **8**, X = Cl (*via* the corresponding *E* dienol borinate), however, proved unsatisfactory.[9] For R^1 = H, the corresponding aldol reactions of **4** also proceeded well (entries 10-12).

Scheme 3



4 X = Cl; **9** X = OMe; **10** X = SPh; **11** X = I

6 (*syn*); **12** X = SPh; **13** X = I

8 (*anti*)

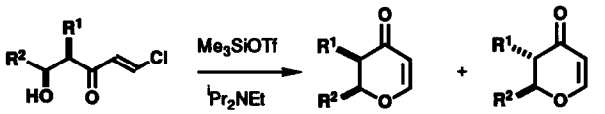
Table 1. Aldol reactions of vinyl ketones **4**, **10** and **11** using $^nBu_2BOTf/^iPr_2NEt$ in CH_2Cl_2.[a]

entry	ketone	X	R^1	R^2	syn:anti[b]	% yield[c]
1	**10**	SPh	Me	^{n}Pr	81:19[d]	61
2	**11**	I	Me	^{n}Pr	≥95:5	54
3	**11**	I	Me	MeC=CH_2	≥95:5	60
4	**4**	Cl	Me	^{n}Pr	97:3	81
5	**4**	Cl	Me	Ph	97:3	84
6	**4**	Cl	Me	$BnOCH_2$	97:3	84
7	**4**	Cl	Me	*c*-C_6H_{11}	97:3	53
8	**4**	Cl	Me	*E*-MeCH=CH	97:3	83
9	**4**	Cl	Me	MeC=CH_2	97:3	53
10	**4**	Cl	H	^{n}Pr	-	95
11	**4**	Cl	H	Ph	-	91
12	**4**	Cl	H	$BnOCH_2$	-	90

[a] Enolisation at -78 °C (5 h) followed by addition of aldehyde and warming to -5 °C (16 h), unless otherwise stated. See footnote 8 for representative reaction. [b] *Syn:anti* ratios from ^{1}H NMR or HPLC. [c] Isolated yield after chromatography. [d] Mixture of four isomers: *E-syn*, *Z-syn*, *E-anti*, *Z-anti*.

The cyclisation of the aldol products **6** and **13** to give the required dihydropyrones was then investigated using a range of reagents (Lewis acids, protic acids, bases). Preliminary work was carried out on the butanal *syn* aldol adducts (*i.e.* **6** and **13**, R^1 = Me, R^2 = ^{n}Pr). Best results were obtained for the chloride series[10] using trimethylsilyltriflate with diisopropylamine (**Scheme 4**), which gave 44-90% yield of dihydropyrone depending on the exact reaction conditions (**Table 2**, entries 1-6)). Equilibration of the *cis*-dihydropyrone **7** (the kinetic product) to the *trans* isomer **14** was found to be an added complication (entries 1-2). The amount of *trans*-dihydropyrone produced could usually be minimised by using less than one equivalent of amine base and conducting the reaction at -15 °C in CH_2Cl_2 or CCl_4 (entries 3-7). Even under these conditions, however, extensive equilibration was obtained with R^2 = $BnOCH_2$ (entry 8). A typical experimental procedure for **6** → **7** (R^1 = Me; R^2 = ^{n}Pr) follows: to a stirred solution of **6** (222 mg, 1.17 mmol) in dry CH_2Cl_2 (6 ml) at -78 °C was added diisopropylethylamine (0.12 ml, 0.69 mmol, 0.6 eq.) followed by trimethylsilyltriflate (0.24 ml, 1.24 mmol, 1.07 eq.). The solution was stirred at -78 °C for 30 min, then kept at -15 °C (freezer) for 15 h. The reaction mixture was then quenched with $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with saturated brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (5% Et_2O/CH_2Cl_2) gave the separated *cis*- and *trans*-pyrones, **7** and **14** (147 mg, 82%; *cis*:*trans* = 91:9).[11]

Scheme 4



6 **7** (*cis*) **14** (*trans*)

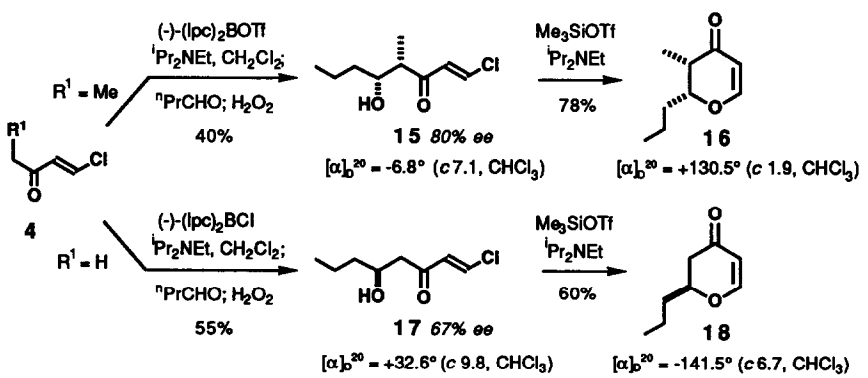
Table 2. Cyclisation reactions of vinyl ketones **6** using Me_3SiOTf (1.1 eq.) and $^iPr_2NEt$ (0.1-1 eq.).[a]

entry	R^1	R^2	solvent (conditions)	equiv. $^iPr_2NEt$	*cis:trans*[b]	% yield[c]
1	Me	^{n}Pr	CH_2Cl_2 (-78 → 20 °C, 30 min)	1.0	70:30	44
2	Me	^{n}Pr	CH_2Cl_2 (-78 → -15 °C, 15 h)	1.0	68:32	80
3	Me	^{n}Pr	CH_2Cl_2 (-78 → -15 °C, 15 h)	0.1	89:11	73
4	Me	^{n}Pr	CH_2Cl_2 (-78 → -15 °C, 15 h)	0.6	91:9	82
5	Me	^{n}Pr	CCl_4 (-78 → -15 °C, 15 h)	0.8	95:5	90
6	Me	^{n}Pr	PhMe (-78 → -15 °C, 15 h)	0.8	90:10	55
7	Me	*c*-C_6H_{11}	CH_2Cl_2 (-78 → -15 °C, 15 h)	0.8	93:7	62
8	Me	$BnOCH_2$	CH_2Cl_2 (-78 → -22 °C, 15 h)	0.8	74:26	62[d]
9	H	^{n}Pr	CH_2Cl_2 (-78 → -15 °C, 15 h)	0.8	-	60
10	H	$BnOCH_2$	CH_2Cl_2 (-78 → -15 °C, 15 h)	0.6	-	66

[a] Reaction conditions as described in text, unless otherwise stated. [b] *Cis:trans* ratios from ^1H NMR or by weighing after chromatography. [c] Isolated yield after chromatography. [d] Yield based on recovered **6**.

Using these conditions, a further four dihydropyrones were prepared (entries 7-10). Unfortunately, the cyclisation could not be extended to the situation where R^2 is phenyl or alkenyl as competitive dehydration occurred. We believe that this new reaction proceeds through the trimethylsilyl ether derivative of **6**, which then undergoes acid (or trimethylsilyl triflate) catalysed cyclisation to the dihydropyrone. In one experiment, the trimethylsilyl ether of **6** was preformed for R^1 = Me, R^2 = ^{n}Pr (Me_3SiCl, $^iPr_2NEt$, CH_2Cl_2) and then subjected directly to catalytic acid (0.1 equiv. triflic acid, CH_2Cl_2, 0 °C), which gave the corresponding *cis*-dihydropyrone **7** (44%).

Scheme 5



We have briefly looked at extending this procedure to give an asymmetric synthesis of dihydropyrones by using chiral boron reagents for the initial aldol reaction (**Scheme 5**). Use of (-)-$(Ipc)_2BOTf$ (1.3 equiv.)[12] for enolisation of **4**, R^1 = Me, ($^iPr_2NEt$, CH_2Cl_2, -78 °C, 16 h) and addition of butanal (-20 °C, 22 h; H_2O_2, aq. THF, 0 °C, 20 min) gave the *syn* aldol product **15**[13] (40%, >97% diastereoselectivity) in 80% ee (^1H NMR with $Eu(hfc)_3$). Cyclisation of **15** with $Me_3SiOTf/^iPr_2NEt$, under the standard conditions, gave a 78% yield of the *cis*-

dihydropyrone **16**[13] also in 80% ee ($Eu(hfc)_3$). Hence no detectable racemisation occurred on the cyclisation step. Similarly, the (-)-$(Ipc)_2BCl$[12,14] mediated aldol reaction of **4**, R^1 = H, with butanal gave **17**[13] in 67% ee, which was cyclised up to give the dihydropyrone **18**.[13]

In summary, we have developed a new and convenient two step synthesis of dihydropyrones from readily available β-chlorovinyl ketones and aldehydes, which exhibits useful levels of enantio- and diastereoselectivity.

Acknowledgement: We thank the SERC and ICI Pharmaceuticals Division for support (CASE Studentship to S.O.) and Dr Peter Harrison (ICI) for helpful discussions. I.P. thanks the Royal Society of Chemistry for a Hickinbottom Research Fellowship.

References and Notes

1. For reviews, see: (a) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Eng.* **1987**, *26*, 15; (b) Danishefsky, S. J. *Aldrich. Acta* **1986**, *19*, 59; (c) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250.

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4. Maruoka, K.; Itoh, T.; Sirasaki, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.

5. For example, see: (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127; (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099; (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174; (d) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279; (e) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121 and ref. 2 therein for literature survey of enol borinate aldol reactions.

6. The parent β-chlorovinyl ketones **4**, R = H and Me, were prepared by $AlCl_3$ promoted addition of the appropriate acid chloride to acetylene in CCl_4, see: Price, C. C.; Pappalardo, J. A. *J. Am. Chem. Soc.* **1950**, *72*, 2613; **11** was prepared from **4** by NaI in Me_2CO (reflux, 1.5 h); for the preparation of **10**, see Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235.

7. All new compounds gave spectroscopic data in agreement with the assigned structures.

8. Representative aldol reaction for **4** → **6** (R^1 = Me; R^2 = ^{n}Pr): To a stirred solution of diisopropylethylamine (1.1 ml, 6.3 mmol), di-n-butylboron triflate (5 ml of a 1M soln in CH_2Cl_2, 5 mmol) in dry CH_2Cl_2 (10 ml), at -78 °C under Ar, was added (*E*)-1-chloro-1-penten-3-one (0.45 ml, 4.06 mmol). After 5 h, butanal (1.0 ml, 10 mmol) was added and the reaction was maintained at -78 °C for 0.5 h then at -5 °C (fridge) for 16 h. The reaction mixture was then poured into pH7 buffer solution (30 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic layers were washed with saturated brine (50 ml), dried ($MgSO_4$) and eluted through a silica plug with 10% Et_2O/CH_2Cl_2. (*NB* this workup was used in place of the conventional H_2O_2 oxidative workup) Evaporation *in vacuo* and flash chromatography (5% Et_2O/CH_2Cl_2) gave **6** as a pale yellow oil (625 mg, 81%). δ (250 MHz, $CDCl_3$) 7.34 (1H, d, *J* = 13.3 Hz), 6.60 (1H, d, *J* = 13.3 Hz), 3.95 (1H, td, *J* = 8.2, 3.5 Hz), 2.66 (1H, qd, *J* = 7.2, 3.5 Hz), 1.23-1.58 (4H, m), 1.15 (3H, d, *J* = 7.2 Hz), 0.92 (3H, t, *J* = 7.1 Hz).

9. Aldol reactions of **4**, R^1 = Me, with butanal using $(c\text{-}C_6H_{11})_2BCl/Et_3N$ in Et_2O gave at best a 60:40 *syn:anti* ratio. For the *E*-selective enolisation of simple ketones using these conditions, see: Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

10. The corresponding iodide **13** cyclised in poorer yield (40%) to the dihydropyrone.

11. Representative ^1H NMR data (250 MHz, $CDCl_3$) for *cis* and *trans* pyrones (R^1 = Me, R^2 = ^{n}Pr): **7** had δ 7.30 (1H, d, *J* = 5.9 Hz), 5.31 (1H, dd, *J* = 5.9, 0.8 Hz), 4.33 (1H, ddd, *J* = 3.5, 8.1, 8.1), 2.33 (1H, qdd, *J* = 7.4, 3.5, 0.8), 1.3-1.6 (4H, m), 1.05 (3H, d, *J* = 7.4 Hz), 0.95 (3H, t, *J* = 7.2 Hz); **14** had δ 7.31 (1H, d, *J* = 5.9 Hz), 5.35 (1H, d, *J* = 5.9 Hz), 4.06 (1H, td, *J* = 7.0, 13 Hz), 2.43 (1H, qd, *J* = 7.0, 13 Hz), 1.41-1.75 (4H, m), 1.10 (3H, d, *J* = 7.0 Hz), 0.95 (3H, t, *J* = 7.4 Hz).

12. (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 0000; (b) Paterson, I.; Goodman, J. M. *Tetrahedron Letters* **1989**, *30*, 997; (c) Paterson, I., Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585; (d) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787.

13. The configurations of the aldol adducts and the derived dihydropyrones shown are based on our earlier findings for ethyl (ref 12a,d) and methyl (ref 12b) ketone aldol reactions using (-)-$(Ipc)_2BOTf$.

14. Diisopinocampheylchloroborane can be used instead of the triflate for the aldol reactions of methyl ketones (ref 12a). For ketone reductions, see: Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.

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