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Syntheses with organoboranes. Part 14: Enolization–aldolization of conjugated cyclohexenones via dienolborinates†

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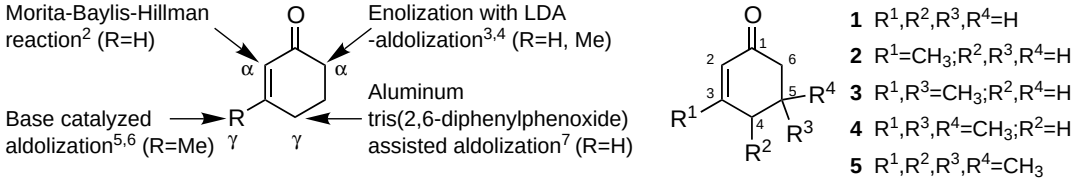
Abstract—Enolization of cyclohex-2-enone (**1**), 3-methyl- (**2**), 3,5-dimethyl- (**3**), 3,5,5-trimethyl- (**4**), and 3,4,5,5-tetramethylcyclohex-2-enone (**5**) with chlorodicyclohexylborane proceeds by deprotonation at the 6-position. Aldolization of the dienolborinates with benzaldehyde, and acetaldehyde, provides the corresponding *anti* aldols with 87–95% selectivity. Ketones **4** and **5** undergo competitive deprotonation at the 3-methyl group and aldolization at the 2-position. In contrast, lithium dienolates derived from **4** and **5** gave *syn* aldols with 95% selectivity.

The directed aldol reaction is a powerful methodology for the stereoselective construction of new carbon–carbon bonds. Boron mediated aldolizations play an important role in the methodology, and are widely used for asymmetric synthesis.[1] In spite of extensive studies in this area, surprisingly little is known on the directed aldol reactions of dienolborinates derived from conjugated ketones. Generally, the ketones may undergo aldolization at α- or γ-positions depending on the reaction employed (Scheme 1).

Enolization of **1** and **2** with LDA and the reaction with benzaldehyde affords the corresponding aldols in 81/19 and 82/18 *anti*/*syn* ratios, respectively.[3,4] The ratio is reversed to 35/65 and 25/75 for titanium and zirconium dienolates obtained from **1**.[3] Enolization of **1** with chlorodicyclohexylborane (Chx_2BCl) in carbon tetrachloride was reported to give >97% of the dienolborinate by deprotonation at the 6-position, however, its aldolization was not studied.[8] The unexplored aldolization of dienolborinates derived from conjugated cycloalkenones is synthetically attractive since differences in stereoselectivity, as compared to lithium dienolates, may be expected. Consequently, we decided to examine enolization of representative conjugated cyclohexenones **1**–**5** (Scheme 1) with Chx_2BCl and LDA followed by aldolization with benzaldehyde, and acetaldehyde. The composition of dienolborinates obtained is presented in Table 1.

The ^1H NMR spectrum of the dienolborinate obtained from **1** showed that clean enolization had occurred to give **6**, in agreement with the earlier report.[8] However, the spectra of dienolborinates obtained from **2**–**5** showed in addition to **6** the competitive formation of **7** by proton abstraction from the 3-methyl group. Deprotonation of a conjugated system in the γ-position, in the absence of a C–H bond in the α-position, was also observed in the formation of butylchloroboran-2-furanolates.[9] Decreasing enolization at the 6-position for



Scheme 1.

Keywords: conjugated ketones; enolborinates; aldols.

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† Dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

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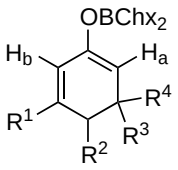
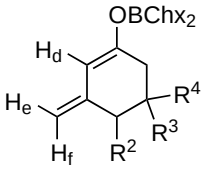
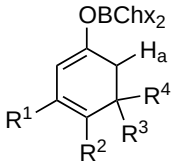
Table 1. Enolization of **1**–**5** with chlorodicyclohexylborane in carbon tetrachloride[a]

Ketone	Dienolborinates composition, %; ^{1}H NMR δ, (J in Hz)				
					
	6		**7**		**8**
	%	δ (J)	%	δ (J)	%
1	97	H_a 4.94 (m) H_b 5.60 (dd, 1.8, 9.9)			3[b]
2	89	H_a 4.76 (m) H_b 5.34 (m)	11	H_d 5.48 (bs) H_e,H_f 4.62 (m)	
3	80	H_a 4.70 (dd, 1.4, 3.9) H_b 5.33 (m)	20	H_d 5.48 (bs) H_e,H_f 4.65 (m)	
4	50	H_a 4.57 (bs) H_b 5.34 (m)	50	H_d 5.48 (bs) H_e,H_f 4.65 (bs), 4.71(bs)	
5	30	H_a 4.45 (bs) H_b 5.27 (m)	70	H_d 5.43 (bs) H_e,H_f 4.69 (bs), 4.71 (bs)	

[a] Chx_2BCl (5.15 mmol) was dissolved in CCl_4 (17 ml) at 0°C, triethylamine (5.16 mmol) was added followed by the ketone (5.0 mmol), the mixture was stirred at 0°C for 1 h, and analyzed by ^{1}H NMR (Varian Gemini 200).
[b] Ref. 8, not observed in this study.

2–**5** may reflect the increasing steric hindrance at this position. Enolization of **1**–**5** with Chx_2BCl and aldolization with benzaldehyde, and acetaldehyde, was carried out in diethyl ether.[11] The product aldols, and the aldols obtained via lithium dienolates, are presented in Table 2.

anti Aldols were consistently the favored products obtained from dienolborinates derived from **1**–**5**. The *anti*/*syn* ratio 81/19 obtained from **1** and benzaldehyde increased to ~90/10 for **2**, **4**, and *anti* isomers were obtained from **3** and **5**. Lithium dienolates formed from **1** and **2** gave the corresponding *anti*/*syn* aldols in 91/9 and 78/22 ratios, respectively.[12]

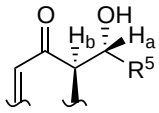
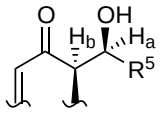
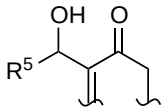
The dienolborinate obtained from **3** gave two products with benzaldehyde. The major one was a crystalline compound, and its X-ray analysis revealed the *anti* aldol **18** with the methyl group at C-5 in the *trans* position (Fig. 1). The ^{1}H NMR spectrum of the minor product showed $J_{Ha–Hb}$ 9.48 Hz indicating the *anti* aldol **17**, with the methyl group at C-5 in the *cis* position. Two aldols were also obtained from the lithium dienolate of **3** and benzaldehyde. The major product was **18**, and the minor product showed $J_{Ha–Hb}$ 5.19 Hz indicating the *syn* aldol **19** with the methyl group at C-5 either *cis* or *trans*.

The dienolborinates derived from **4** gave three aldolization products with benzaldehyde. The major one was the *anti* aldol **20**, and a small amount of the *syn* aldol **21** was also formed. The third aldol **22** was produced by aldolization at the 2-position. As shown in Table 1, enolization of **4** with Chx_2BCl proceeds competitively producing **7**. Although the amount formed in diethyl ether may not be the same as in carbon tetrachloride, aldolization of **7** at the 2-position followed by double bond migration accounts for the formation of **22**. Similarly, the dienolborinate derived from the more hindered **5** reacted with benzaldehyde producing the *anti* aldol **26** as a mixture of *cis*/*trans* isomers at C-4. In contrast, the reaction of lithium dienolates derived from **4** and **5** showed the opposite stereoselectivity. The major products were the *syn* aldol **21**, and the *syn* aldol **27** with the methyl group at C-4 in the *trans* position, identified by X-ray analysis (Fig. 1).

The reactions of dienolborinates and lithium dienolates derived from **1**, **2**, and **4** were also carried out with acetaldehyde (Table 2). The dienolborinates reacted with high *anti* selectivity. Aldols **11**, **15**, and **23** obtained by aldolization at the 6-position were the only products. Aldolization of the lithium dienolates derived from **1** and **2** was less selective. In contrast, the lithium dienolate prepared from **4** produced the *syn* aldol **24**, similar to the reaction with benzaldehyde.

The results presented above demonstrate the preferential enolization of **1**–**5** with Chx_2BCl by deprotonation at C-6. When this position is hindered, deprotonation at the 3-methyl group becomes competitive. Aldolization of the dienolborinates **6** with benzaldehyde, and acetaldehyde, consistently produces the corresponding *anti* aldols with 87–95% selectivity. Aldolization of the competitively formed dienolborinates **7** proceeds at the 2-position, leading to the Morita–Baylis–Hillman type of products. Lithium dienolates obtained from the less hindered **1**–**3** react with benzaldehyde, and acetalde-

Table 2. Aldols prepared by enolization of **1**–**5** with Chx_2BCl/Et_3N and LDA, aldolization with benzaldehyde and acetaldehyde[11,12]

Ketone	Enolate[a]	Aldehyde[b]	Product aldols[c]									
			Composition[d] %; ^{1}H NMR δ (J in Hz); melting point									Yield[e]
			 (R^5=Ph, Me)									
			anti	%	δ_{H_a} ($J_{H_a-H_b}$)	Mp (°C)	*syn*	%	δ_{H_a} ($J_{H_a-H_b}$)	Mp (°C)	%	
1	C	B	**9**	81	4.82 (8.9)		**10**	19	5.55 (2.8)			58
	L	B	**9**	91			**10**	9				73
	C	A	**11**	>95	3.95 (7.9)							24
	L	A	**11**	86			**12**	14	4.23 (3.5)			45
2	C	B	**13**	90	4.80 (9.0)		**14**[f]	10	5.53 (3.0)	114–115		72
	L	B	**13**	78			**14**	22				96
	C	A	**15**	>95	3.93 (8.0)							45
	L	A	**15**	95			**16**	5				66
	L	A	**15**	65[g]			**16**	35[g]	4.22 (3.6)			66
3	C	B	**17**	32	4.95 (9.48)							51
	C	B	**18**[f,h]	68	4.77 (8.36)	98–99						
	L	B	**18**	78			**19**	22	4.99 (5.2)			75
4	C	B	**20**[f,i]	68	5.02 (3.0)	65–68	**21**[f,h]	10	5.10 (5.4)	64–66	**22**[i] 22	39
	L	B	**20**	6			**21**	94				76
	C	A	**23**[f]	51	4.10 (6.6)						**25** 49	55
	L	A	**23**	15			**24**	85	4.02 (4.6)			84
5	C	B	**26**[j]	73	5.02 (2.2)						**28**[k] 27	53
	L	B	**26**[j]	5			**27**[f,h]	95	5.16 (4.4)	108–109		52

[a] C enolized with Chx_2BCl; L enolized with LDA.
[b] B, benzaldehyde; A, acetaldehyde.
[c] All products gave ^{1}H and ^{13}C NMR spectra consistent with their assigned structures.
[d] The *anti*/*syn* ratios were determined by HPLC analysis, and by ^{1}H NMR (Varian Gemini 200), according to the procedure based on the coupling constants.[10]
[e] Isolated yields after chromatography on SiO_2.
[f] Satisfactory elemental analysis.[13]
[g] Time of aldolization = 1 h.
[h] Structures determined by X-ray analysis, **18** (Nonius Kappa CCD, Mo lamp), **21** and **27** (Kuma KM 4 CCD, Mo lamp) (Fig. 1).
[i] Isolated by preparative HPLC (LC-5B chromatograph, ODS dp 10 μm 250×8 mm column, eluent MeOH/H_2O (90/10)).
[j] A mixture of *cis*/*trans* isomers.
[k] A 1:1 mixture of diastereomers.

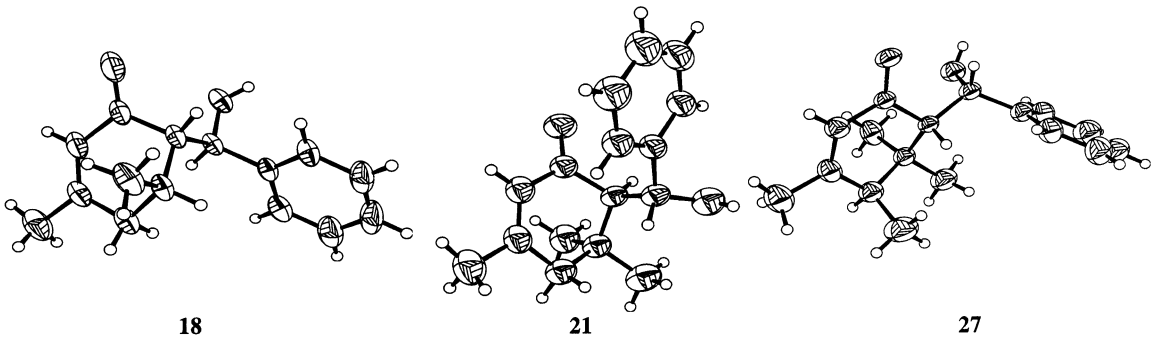


Figure 1. X-Ray structures of **18**, **21** and **27**.[14]

hyde, producing preferentially *anti* aldols, whereas *syn* selectivity predominates for the dienolates derived from the more hindered **4** and **5**. Consequently, the dienolborinates derived from conjugated cyclohexenones may serve as useful reagents for the synthesis of *anti* aldols, often showing higher selectivity as compared to the

corresponding lithium dienolates. The opposite stereoselectivity of aldolization of dienolborinates and lithium dienolates derived from the more hindered ketones makes these reagents complementary.

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11. To a solution of Chx_2BCl (3.18 g, 15.0 mmol) and Et_3N (1.51 g, 15.0 mmol) in Et_2O (50 ml), the ketone (15.0 mmol) was added dropwise at 0°C, and the mixture was stirred for 1 h. A white precipitate of $Et_3N{\cdot}HCl$ was formed. The mixture was cooled to −78°C, and the aldehyde (15.0 mmol) was added dropwise. The mixture was stirred at −78°C for 4 h and was left overnight to attain room temperature. Methanol (100 ml) was added to dissolve the precipitate followed by 30% H_2O_2 (5.1 ml), added at 0°C, and the mixture was stirred for 8 h at room temperature. Solvents were removed under water aspirator vacuum, and the mixture was extracted with Et_2O (2×50 ml). The extracts were washed with water (25 ml) and dried over anhydrous magnesium sulfate. Products were isolated by flash chromatography on silica gel or by preparative HPLC.
12. To a solution of LDA (1.61 g, 15.0 mmol) in tetrahydrofuran (50 ml), the ketone (15.0 mmol) was added dropwise at −78°C. The mixture was stirred for 30 min, and the aldehyde (15.0 mmol) was added. After 60 s the reaction was quenched with a saturated aqueous solution of ammonium chloride (9.0 g in 25 ml). The mixture was extracted with Et_2O (3×30 ml), washed with water (50 ml), saturated brine (50 ml), and dried over anhydrous magnesium sulfate. Aldols were isolated by flash chromatography on silica gel.
13. Anal.: **14**, $C_{14}H_{16}O_2$ calcd (216.28): C, 77.75; H, 7.46. Found: C, 77.53; H, 7.36. **18**, $C_{15}H_{18}O_2$ calcd (230.31): C, 78.23; H, 7.88. Found: C, 78.49; H, 7.78. **20**, $C_{16}H_{20}O_2$ calcd (244.34): C, 78.65; H, 8.25. Found: C, 78.32; H, 8.26. **21**, $C_{16}H_{20}O_2$ calcd (244.34): C, 78.65; H, 8.25. Found: C, 78.93; H, 8.15. **23**, $C_{11}H_{18}O_2$ calcd (182.26): C, 72.49; H, 9.95. Found: C, 72.87; H, 9.81. **27**, $C_{17}H_{22}O_2$ calcd (258.36): C, 79.03; H, 8.58. Found: C, 79.09; H, 8.48.
14. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 178064 for **18**, 178152 for **21**, and 178153 for **27**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
Crystal data: Compound **18**: $C_{15}H_{18}O_2$, crystal system triclinic, space group, $P1$; $a=7.0111(6)$, $b=9.3633(6)$, $c=10.693(1)$ Å, $\alpha=70.320(4)$, $\beta=76.320(4)$, $\gamma=89.259(6)$, $V=640.50(9)$ Å^3; $Z=2$; $F(000)=248$; $\mu=0.078$ mm^{-1}; $R_1=0.038$, $wR_2=0.092$; $S=1.060$; compound **21**: $C_{16}H_{20}O_2$, crystal system tetragonal, space group, $P4(1)$; $a=8.031(1)$, $b=8.031(1)$, $c=22.197(4)$ Å, $V=1431.6(4)$ Å^3; $Z=4$; $F(000)=528$; $\mu=0.073$ mm^{-1}; $R_1=0.080$, $wR_2=0.236$; Flack $x=0.1(3.0)$; $S=1.007$; compound **27**: $C_{17}H_{22}O_2$, crystal system monoclinic, space group, $P2(1)/c$; $a=8.633(2)$, $b=26.796(5)$, $c=12.902(3)$ Å, $\beta=90.44(3)$, $V=2984.5(11)$ Å^3; $Z=8$; $F(000)=1120$; $\mu=0.074$ mm^{-1}; $R_1=0.070$, $wR_2=0.186$; $S=1.107$.