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CHIRAL SYNTHESIS VIA ORGANOBORANES. 25. B-(Z AND E)-CROTYLBIS-(2-ISOCARANYL)BORANES AS VALUABLE REAGENTS FOR THE ASYMMETRIC CROTYLBORATION OF ALDEHYDES†

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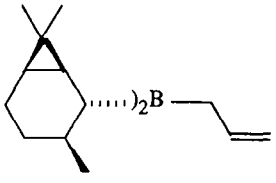
Abstract: The asymmetric crotylboration of representative aldehydes, RCHO (R = Me, Et-), with B-[Z and *E*]-crotylbis(2-isocaranyl)boranes (**4** and **5**) proceeds with remarkably high enantioselectivity (>94-98% ee) and diastereoselectivity (>99% de) at –78 °C in ethyl ether.

The construction of β–hydroxy-α–methylcarbonyl structural units, present in a number of important natural products, such as the 6-deoxyerythronolide B, calcimycin, milbemycins and avermectins, in a highly enantio- and diastereoselective fashion (≥99% ee and de), continues to offer a major synthetic challenge.[1] While the aldol methodology is highly useful in this regard, asymmetric crotylboration has recently emerged as a powerful alternative for achieving this synthetic objective.[2] Recently, we reported a new reagent, *B*-allylbis(2-isocaranyl)borane (2-^{d}Icr$_2$BAll, **1**), which achieves the asymmetric allylation of a variety of aldehydes at –78 °C in Et_2O and affords homoallylic alcohols of 94-99% ee.[3] The enantioselectivities achieved by this reagent are significantly higher than those realized by our previous reagents, *B*-allyldiisopinocampheylborane (^{d}Ipc$_2$BAll, **2**, 83-94% ee) and *B*-allylbis(4-isocaranyl)borane (4-^{d}Icr$_2$BAll, **3**, 88-95% ee) at –78 °C in Et_2O. Therefore, in order to test the efficiency of our new chiral auxiliary, 2-^{d}Icr$_2$B-, we examined the asymmetric crotylboration of representative aldehydes (RCHO, R = Me or Et-) with *B*-[*Z*]-crotylbis(2-isocaranyl)borane (**4**, 2-^{d}Icr$_2$BCrt^Z and *B*-[*E*]-crotylbis(2-isocaranyl)borane (**5**, 2-^{d}Icr$_2$BCrt^E) at –78 °C in Et_2O.



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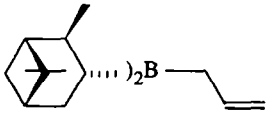

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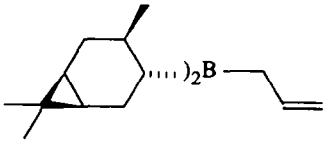

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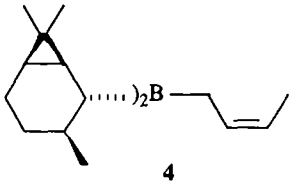

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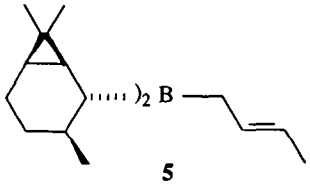

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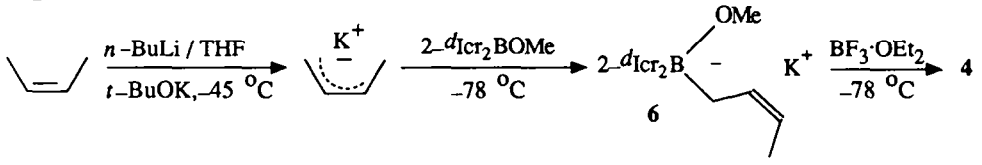
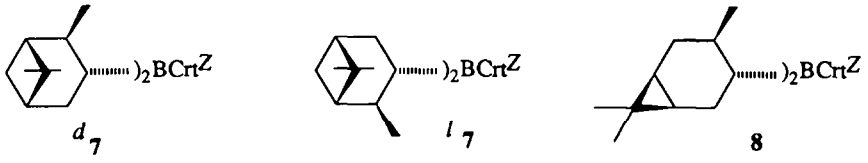
†This paper is dedicated to Professor W. D. Ollis in appreciation of his many outstanding contributions to organic chemistry and to the highly stimulating, annual Sheffield Stereochemistry Symposium.

The preparation of 2-^{d}Icr$_2$BCrt^{Z}(**4**) is conveniently achieved as follows[4] (Scheme I): *cis*-2-butene is metallated by potassium *tert*-butoxide and *n*-butyllithium in THF at –45 °C and the resulting [*Z*]-crotyl potassium is treated with *B*-methoxybis(2-isocaranyl)borane at –78 °C. The ate complex **6** is next treated with BF_3·OEt_2 to obtain **4**. The same procedure provides 2-^{d}Icr$_2$BCrt^{E} (**5**) from *trans*-2-butene.

Scheme I

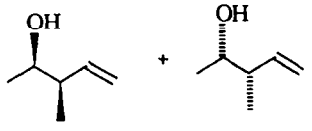
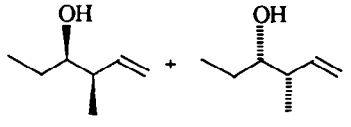


We then examined the crotylboration of representative aldehydes (MeCHO and EtCHO) with 2-^{d}Icr$_2$BCrt^{Z} (**4**) and 2-^{d}Icr$_2$BCrt^{E} (**5**) at –78 °C in Et_2O. 2-^{d}Icr$_2$BCrt^{Z} (**4**) undergoes reaction with acetaldehyde and affords [2*S*,3*S*]-3-methyl-4-penten-2-ol in 94% ee and ≥99% diastereoselectivity. Similarly, **4** reacts with propionaldehyde and yields [3*S*,4*S*]-4-methyl-5-hexen-3-ol in 96% ee and ≥99% diastereoselectivity. In the past, we have reported crotylborations of these aldehydes with *B*-[*Z*]-crotyldiisopinocampheylboranes (^{l} and ^{d} Ipc$_2$BCrt^{Z}, ^{l}**7** and ^{d}**7**) and *B*-[*Z*]-crotylbis(4-isocaranyl)borane (4-^{d} Icr$_2$BCrt^{Z}, **8**)[5]. Table 1 lists these results.



^{d}**7** ^{l}**7** **8**

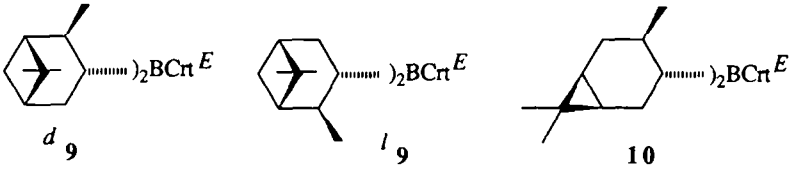
Table 1. A Comparison of the Asymmetric Crotylboration of Representative Aldehydes with 2-^{d}Icr$_2$BCrt^{Z} (4) and Other Reagents ^{d}7, ^{l}7 and 8 at –78 °C in Et_2O

Aldehyde	*syn*-Products	Reagent, Ratio of Enantiomers[a]			
		^{d}Ipc$_2$BCrt^{Z} ^{d}**7**	^{l}Ipc$_2$BCrt^{Z} ^{l}**7**	4-^{d}Icr$_2$BCrt **8**	2-^{d}Icr$_2$BCrt^{Z} **4**
CH_3CHO		95:5 (≥99)[b]	4:96 (≥99)[b]	97:3 (≥99)[b]	3:97 (≥99)[b]
CH_3CH_2CHO		95:5 (≥99)[b]	4:96 (≥99)[b]	97:3 (≥99)[b]	2:98 (≥99)[b]

[a]Determined by capillary GC analysis of the MTP esters. See ref. 7. [b]Values in parentheses are % de observed.

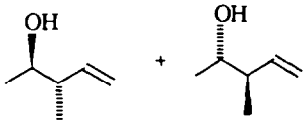
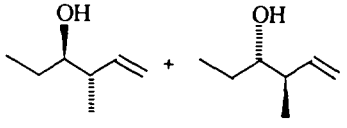
While these reagents are exceptionally diastereoselective (≥99% de), the enantioselectivities achieved in the crotylborations with 2-^{d}Icr$_2$BCrt^{Z} (**4**) are superior to those realizedwith the reagents ^{d} or ^{l}**7** and comparable to those obtained with 4-^{d}Icr$_2$BCrt^{Z} (**8**).

Similarly, the crotylboration of acetaldehyde with *B*-[*E*]-crotylbis(2-isocaranyl)borane (2-^{d}Icr$_2$BCrt^{E} **5**) at –78 °C in Et$_2$O affords [2*S*,3*R*]-3-methyl-4-penten-2-ol in 96% ee and ≥99% de. The crotylboration of propionaldehyde with **5** under identical conditions yields [3*S*,4*R*]-4-methyl-5-hexen-3-ol in 98% ee and ≥99% diastereoselectivity. This time the enantioselectivities achieved in the crotylboration of the representative aldehydes (MeCHO and EtCHO) with 2-^{d}Icr$_2$BCrt^{E} (**5**) are significantly higher than those obtained with *B*-[*E*]-crotyldiisopinocampheylboranes (^{l} and ^{d}Ipc$_2$BCrt^{E}, ^{l}**9** and ^{d}**9**),and *B*- [*E*]-Crotylbis(4-isocaranyl)borane (4-^{d}Icr$_2$BCrt^{E}, **10**) Table 2 summarizes these results.



^{d}**9** ^{l}**9** **10**

Table 2. A Comparison of the Asymmetric Crotylboration of Representative Aldehydes with 2-^{d}Icr$_2$BCrt^{E} (5) and Other Reagents ^{d}9, ^{l}9 and 10 at –78 °C in Et$_2$O

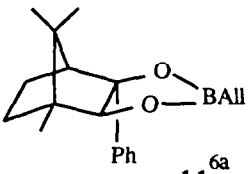
Aldehyde	*anti*-Products	Reagent, Ratio of Enantiomers[a]			
		^{d}Ipc$_2$BCrt^{E} ^{d}**9**	^{l}Ipc$_2$BCrt^{E} ^{l}**9**	4-^{d}Icr$_2$BCrt^{E} **10**	2-^{d}Icr$_2$BCrt^{E} **5**
CH_3CHO		95:5 (≥99)[b]	4:96 (≥99)[b]	97:3 (≥99)[b]	2:98 (≥99)[b]
CH_3CH_2CHO		95:5 (≥99)[b]	4:96 (≥99)[b]	97:3 (≥99)[b]	1:99 (≥99)[b]

[a]Determined by capillary GC analysis of the MTP esters. See ref. 7. [b]Values in parentheses are % de observed.

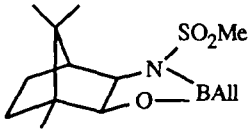
Previously, numerous other chiral auxiliaries have been utilized for asymmetric allylboration[6] (see **11-17**). For such allylborations, the data clearly show that *B*-allylbis(2-isocaranyl)borane (**1**) is not only easier to prepare, but superior in achieving exceptionally high enantioselectivities to most of the reagents.[3] Some of these chiral auxiliaries have also been utilized in crotylboration.[6e,h] Unfortunately, the crotylborations have been applied to far fewer aldehydes (Table 3). Consequently, it is difficult to make direct comparisons. However,

examination of the available data shows that the reagents **4** and **5** are superior to **14b, 14c** as well as **16b, 16c** in % de.

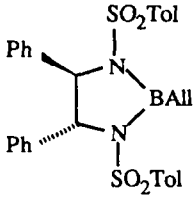
Evidently, further studies with a common set of representative aldehydes will more definitely establish the relative effectiveness of the various crotylboron reagents.



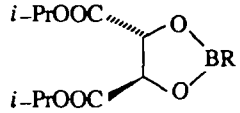
11[6a]



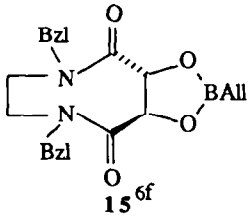
12[6b]



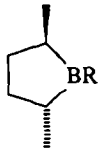
13[6c]



14 a (R = Allyl)[6d]
b (R = Z − Crotyl)[6e]
c (R = E − Crotyl)[6e]



15[6f]



16 a (R = Allyl)[6g]
b (R = Z − Crotyl)[6h]
c (R = E − Crotyl)[6h]

17[6g]

Table 3. A Comparison of the Relative Effectiveness of Various Reagents in the Crotylborations of Achiral Aldehydes at −78 °C

	Reagent, % ee					
Aldehyde	**14b**[a]	**14c**[a]	**16b**[b]	**16c**[b]	**4**	**5**
CH_3CHO					94	96
					(≥99)[c]	(≥99)[c]
CH_3CH_2CHO			86	96	96	98
			(86)[c]	(86)[c]	(≥99)[c]	(≥99)[c]
$CH_3(CH_2)_8CHO$	82	88				
	(98)[c]	(98)[c]				
i-PrCHO			94	98		
			(92)[c]	(92)[c]		
t-BuCHO	70	73	97	95		
	(98)[c]	(90)[c]	(90)[c]	(92)[c]		
C_6H_5CHO	55	67				
	(96)[c]	(98)[c]				

[a]See ref. 6e. [b]See ref. 6h. [c]Values in parentheses are% de observed.

In summary, we describe a highly enantioselective (≥94-98% ee) and diastereoselective (≥99% de) crotylboration of aldehydes with 2-^{d}Icr$_2$BCrt^{Z} (**4**) and 2-^{d}Icr$_2$BCrt^{E} (**5**) at –78 °C in Et_2O. We predict that our reagents will find many applications in the future.

Experimental Section

The reaction flasks and other glass apparatus were dried in an oven at 150 °C, assembled while hot, and cooled under a stream of nitrogen. All air-sensitive manipulations were carried out under N_2, according to the procedures described elsewhere.[7] The diastereoselectivities were determined by capillary GC analysis of the alcohols on a Supelcowax 10 column (15 meters x 0.25 mm). The enantioselectivities were determined by capillary GC analysis of the MTP esters[8] of alcohols on a methylsilicone column (50 meters x 0.25 mm).

***B*-Methoxybis(2-isocaranyl)borane (2-^{d}Icr$_2$BOMe)**[3]: To borane-methyl sulfide (10.3 mL, 9.8 M, 100 mmol) in tetrahydrofuran (200 mL), cooled to -10 °C, was added (+)-2-carene (30 g, 220 mmol), $\alpha^{23}D$ = +92° (neat), over a period of 10 minutes while stirring the reaction mixture. After the addition, stirring was discontinued, and the flask containing the reaction mixture was stored at 0 °C for 24 h. White needles of 2-^{d}Icr$_2$BH separated out. The supernatant liquid was then decanted out and the crystals were washed with anhydrous pentane (2 x 100 mL) at 0 °C. The solid was then dried under aspirator vacuum (15 torr) to obtain 2-^{d}Icr$_2$BH (24.3 g, 85%) of practically 100% optical purity. Next, 2-^{d}Icr$_2$BH (8.58 g, 30 mmol) was suspended in anhydrous ether (100 mL) and methanol (3 mL) was added at 0 °C, in a dropwise manner , while the reaction mixture was stirred. After the evolution of hydrogen ceased (0 °C, ≤ 2 h),a clear solution was formed indicating the completion of methanolysis. The solvent was stripped off under vacuum (15 torr) to obtain a quantitative yield of B-methoxybis(2-isocaranyl)borane.

***B*-[*Z*]-Crotylbis(2-isocaranyl)borane (2-Icr$_2$BCrt^{Z}, 4)**: To a well-stirred mixture of *cis*-2-butene (4.5 mL, 50 mmol), THF (7 mL) and potassium *tert*-butoxide (2.8 g, 25 mmol, dried at 80 °C/0.5 mm for 12 h prior to use), *n*-butyllithium in THF (25 mmol) was added at –78 °C. Following completion of addition, the mixture was stirred at –45 °C for 10 min and once again cooled to –78 °C. To this mixture, *B*-methoxybis(2-isocaranyl)borane[3] (9.5 g, 30 mmol) in ether (30 mL, prepared as described above) was added dropwise and the resulting mixture was stirred for 0.5 h at –78 °C to obtain a white precipitate of the ate-complex **6**. The addition of boron trifluoride etherate (4.78 g, 33.5 mmol) to this ate-complex and stirring the reaction mixture at –78 °C for 15 min afforded a quantitative yield of *B*-[*Z*]-crotylbis(2-isocaranyl)borane (**4**), which was used in the crotylboration experiments at –78 °C without the removal of the salts.

***B*-[*E*]-Crotylbis(2-isocaranyl)borane (2-^{d}Icr$_2$BCrt^{E}, 5)**: By utilizing the procedure described above for the preparation of **4**, and using *trans*-2-butene (4.5 mL, 50 mmol) instead of *cis*-2-butene, the reagent **5** was prepared in essentially quantitative yield. Once again, in order to prevent any isomerization, 2-^{d}Icr$_2$BCrt^{E} (**5**) was used as such, at –78 °C, without isolation in all crotylborations.

Reaction of *B*-[*Z*]-Crotylbis(2-isocaranyl)borane (4) with Aldehydes. A Typical Procedure: To *B*-[*Z*]-crotylbis(2-isocaranyl)borane (**4**), prepared as described above, acetaldehyde (1.54 g, 35 mmol) was added dropwise at –78 °C and the mixture stirred for 3 h at this temperature. Subsequently, methanol (4 mL) was added, the reaction mixture was brought to room temperature and oxidized by alkaline hydrogen peroxide. After the usual workup and distillation (bp 78 °C/85 mm), [2*S*,3*S*]-3-methyl-4-penten-2-ol was isolated, yield 1.88 g (75%). The alcohol was determined to be of 94% ee and ≥99% de by capillary GC analysis.

The reaction of *B*-[*Z*]-crotylbis(2-isocaranyl)borane (**4**) with propionaldehyde, by the procedure described above, provided [3*S*,4*S*]-4-methyl-5-hexen-3-ol (bp 105 °C/80 mm), yield 2.50 g (78%). By capillary GC analysis, the alcohol was 96% ee and ≥99% de.

Reaction of *B*-[*E*]-Crotylbis(2-isocaranyl)borane (5) with Aldehydes: The procedure is the same as described for the reagent **4** with acetaldehyde. Thus, by conducting crotylboration of acetaldehyde and propionaldehyde with 2-^{d}Icr$_2$BCrt^{E} (**5**), [2*S*,3*R*]-3-methyl-4-penten-2-ol (bp 78 °C/85 mm, 75% yield, 96% ee, ≥99% de) and [3*S*,4*R*]-4-methyl-5-hexen-2-ol (bp 105 °C/80 mm, 76% yield, 98% ee, ≥99% de) were obtained.

Acknowledgement

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