Calcd for $C_9H_6N_6S_3$: C, 36.72; H, 2.05; N, 28.55. Found: C, 36.71; H, 2.17; N, 28.20.

The S_3N_3 Tris(lactam) 26 was prepared as reported by Grandolini and Martani.[29] The yield of crude product was 1.357 g. Analysis of the product mixture by NMR spectroscopy revealed it to be a ca. 1:1 mixture of the desired product **26** and the bis(lactam) **29**.

Recrystallization of the crude product mixture from ethylene glycol gave the tris(lactam) **26** as tan needles in 31% yield. Drying the product at 111 °C under vacuum (20 μmHg) over P_2O_5 for 12 h gave analytically pure material: mp >350 °C (lit.[29] mp >350 °C); NMR (DMSO-d_6) 9.980 (s, 3 H), 3.352 ppm (s, 6 H); IR (KBr) 3345 (w), 3220 (w, br), 2920 (w), 1675 (s), 1575 (m), 1460 (m), 1400 (w), 1355, 1335 (d, m), 695 (w) cm^{-1}. Anal. Calcd for $C_{12}H_9N_3O_3S_3$: C, 42.47; H, 2.67; N, 12.38; S, 28.34. Found: C, 42.41; H, 2.72; N, 12.21; S, 28.11.

Extraction of the crude product mixture with hot ethanol followed by cooling of the hot filtrate gave the bis(lactam) **29** in 29% yield as a light brown granular solid: mp 282–286 °C dec (lit.[29] mp 315 °C dec); NMR (DMF-d_7) 9.728 (s, 2 H), 5.659 (s, 2 H), 3.700 (s, 2 H), 3.554 ppm (s, 4 H); IR (KBr) 3415 (w), 3320 (m), 3215 (w), 3000 (w), 2920 (w), 1710 (s), 1675 (s), 1610 (s), 1515 (m), 1470 (m), 1430 (m), 1400 (m), 1335 (s), 1255 (m), 1145 (m), 900 (w), 660 (m) cm^{-1}; MS (CI, CH_4) (M + 1) 358 (78), (M + 3) 360 (10), (M + 18) 375 (100), (M + 20) 377 (17).

Conversion of the Bis(lactam) 29 to the Tris(lactam) 26. Compound **29** (36.2 mg, 0.10 mmol) was suspended in 20 mL of absolute ethanol. A trace (ca. 0.25 mL) of 1 N HCl was added to the reaction mixture, and it was brought to reflux. After 48 h, the reaction was cooled to room temperature, and the white precipitate was collected by vacuum filtration and washed with methanol. The yield of tris(lactam) **26**, judged to be pure by NMR, was 30.0 mg (88%).

Preparation of the Trimethylated S_3N_3 Tris(lactam) 31. Tris(lactam) **26** (0.325 g, 0.958 mmol) was dissolved in 20 mL of DMSO (dried over activated 4-Å molecular sieves). To this solution was added 3.90 mL (2.88 mmol) of 0.739 M sodium ethoxide in ethanol, the suspension was stirred for 1.5 h, and 0.6 mL (9.6 mmol) methyl iodide was added to the reaction mixture. The resulting clear solution was stirred for an additional 1 h, and then it was poured into 75 mL of distilled H_2O. The resulting suspension was cooled in an ice bath, and after 0.5 h the tan crystals were collected by vacuum filtration and washed with several portions of distilled H_2O. The yield was 0.327 g (89%). Samples were purified for elemental analysis by flash chromatography with CH_2Cl_2/methanol (97:3) as the eluent: mp >320 °C; NMR ($CDCl_3$) 3.394 (s, 3 H), 3.33 ppm (br, s, 2 H); IR (KBr) 3010 (w), 2945 (w), 1675 (s), 1535 (m), 1430 (w), 1395 (m), 1335 (s), 1255 (w), 1235 (w), 1215 (w), 1150 (w), 1095 (s), 995 (w), 900 (w, br), 885 (w), 775 (w), 720 (w), 695 (w), 650 (w) cm^{-1}; MS (CI, NH_3) (M + 1) 382 (60); (M + 3) 384 (11), (M + 18) 399 (100), (M + 2) 401 (17). Anal. Calcd for $C_{15}H_{15}N_3O_3S_3$: C, 47.23; H, 3.96; N, 11.01; S, 25.21. Found: C; 47.00, 47.83; H; 4.16, 4.06; N; 10.13, 10.90; S; 24.67.

BSNM (25). A reaction vessel was charged with 0.3124 g (0.819 mmol) of **31** and 12.0 mL (12.0 mmol) of 1 M BH_3 in THF. The resulting suspension was brought to reflux for 2 h. The excess BH_3/THF was then removed under reduced pressure, and the residue was dissolved with heating in 10 mL of 6 N HCl for 15–30 min at 60 °C. The solution was cooled in an ice bath and made basic by the addition of 15 mL of 6 N NaOH. A white precipitate was collected by vacuum filtration and washed with several portions of H_2O. The yield of crude BSNM (**25**) as an off-white powder was 0.226 g (81%). Purification by flash chromatography with CH_2Cl_2 as the eluent gave 0.169 g (61%) of **25**. A sample purified by flash chromatography was submitted for elemental analysis: mp 252–253 °C; NMR ($CDCl_3$) 3.228 (m, 2 H), 3.08 (m, 2 H), 2.689 ppm (s, 3 H); IR (KBr) 2940 (d, m), 2870 (d, w), 2820 (w), 1380 (s), 1360 (w), 1265 (w), 1215 (m), 1185 (w), 1120 (w), 1100 (m), 1050 (m), 950 (w), 830 (m), 730 (m) cm^{-1}; MS (CI, NH_3) (M + 1) 340 (100), (M + 3) 342 (17). Anal. Calcd for $C_{15}H_{21}N_3S_3$: C, 53.06; H, 6.23; N, 12.38. Found: C, 52.96; H, 6.75; N, 12.73.

Oxidation of this species with $NO^+SbF_6^-$ produced a cation radical with a broad ESR signal. No triplet ESR signal could be seen with an excess of the oxidant.

BSNH (24). A reaction vessel was charged with 49.5 mg (0.146 mmol) of tris(lactam) **26** and 4.0 mL (4.0 mmol) of 1 M BH_3 in THF. The suspension was brought to reflux for 2 h, and the excess BH_3/THF was removed under reduced pressure leaving a yellow solid. The residue was taken up in 6 mL of 6 N HCl and the solution was warmed to 60 °C for 15 min. It was then cooled in an ice bath and made basic by the addition of 7 mL of 6 N NaOH. An off-white precipitate formed; after being stirred for 15 min in the ice bath, it was collected by vacuum filtration and washed with several portions of H_2O. The yield of crude BSNH (**24**) was 36.3 mg (84%). Purification by flash chromatography with CH_2Cl_2/methanol (98:2) as the eluent and with argon pressure gave 30.9 mg (71%) of **24** as an off-white solid: mp 202–204 °C; NMR ($CDCl_3$) 4.170 (br s, 1 H), 3.697 (m, 2 H), 2.931 ppm (m, 2 H); IR (KBr) 3380 (w), 2920 (w), 2860 (w), 1565 (s), 1490 (m), 1450 (w), 1410 (w), 1375 (w), 1330 (m), 1285 (w), 1215 (w), 1155 (w) cm^{-1}; MS (CI, NH_3) (M + 1) 298 (100), (M + 3) 300 (47).

Treatment of this material with I_2 led to a poorly defined doublet ESR signal. No triplet ESR spectrum could be elicited under various oxidizing conditions.

Acknowledgment. This work was supported by a grant from the U.S. National Science Foundation.

N,*N'*-Dibenzyl-*N*,*N'*-ethylenetartramide: A Rationally Designed Chiral Auxiliary for the Allylboration Reaction

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Abstract: The chiral auxiliary designated in the title was designed as a probe of our previously suggested mechanism of asymmetric induction with tartrate allylboronates **1–3**, namely that n/n electronic repulsive interactions between electron pairs on the aldehydic oxygen atom and an ester carbonyl disfavor transition-state C relative to A. The results reported for the new reagent **5** strongly support this thesis and suggest that the convergence of functional groups toward a metal center can be an exceedingly useful strategy for achieving a topological bias in the enantioselective functionalization of a carbonyl group.

Recent publications from several laboratories have demonstrated the potential of the allylboration reaction as a method for acyclic diastereoselective synthesis.[2,3] We have concentrated on tartrate allylboronates **1–3** and have shown that good to excellent stereoselectivity is obtained with a range of chiral and achiral aldehydes (typically 60–88% ee). While this level of stereoselection

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(1) On leave from the Universitā di Genova, Italy and recipient of a grant from the Consiglio Nazionale delle Ricerche.

(2) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Halterman, R. L. *Ibid.* **1986**, *108*, 294. (c) Roush, W. R.; Palkowitz, A. D. *Ibid.* **1987**, *109*, 953. (d) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316.

(3) (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *Ibid.* **1986**, *51*, 432. (c) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (d) Ditrich, K.; Bube, T.; Sturmer; R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1028. (e) Hoffmann, R. W.; Presely, S. *Ibid.* **1986**, *25*, 189. (f) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 2013.

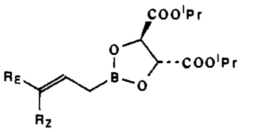
0002-7863/88/1510-3979$01.50/0

Table I. Reactions of (*R*,*R*)-**5** and Achiral Aldehydes[a,b]

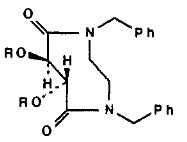
entry	aldehyde	conditions		% conv[c]	% yield[d]	% ee[e,f]	config[g]	$\Delta\Delta G^{\ddagger}$[f,h]
		temp, °C	time, h					
1	c-$C_6H_{11}CHO$	−78	47	80	40[i]	97 (87)	*S*	−1.61 (−1.03)
2	c-$C_6H_{11}CHO$	−50	17	84		94 (82)	*S*	−1.53 (−1.02)
3	c-$C_6H_{11}CHO$	25	2	97		87 (50)	*S*	−1.55 (−0.65)
4	C_6H_5CHO	−78	47	75		85 (60)	*S*	−0.97 (−0.54)
5	*t*-C_4H_9CHO	−78	67	60		96 (86)	*S*	−1.50 (−1.00)
6	(TBDPS)$OCH_2CH_2CH_2CHO$	−78	37	80	58	94 (82)	*R*	−1.34 (−0.89)
7	BzlOCH_2CHO	−78	46	62	45	86 (60)	*S*	−0.97 (−0.54)

[a] Reactions were performed in toluene (typically 0.03 M) with 1–1.3 equiv of **5** and 4-Å molecular sieves as described in ref 2a. Reactions were quenched with $NaBH_4$ in EtOH to reduce any unreacted aldehyde. [b] The reactions with cyclohexanecarboxaldehyde and benzaldehyde were examined in six solvents (toluene, THF, Et_2O, CH_2Cl_2, CH_3CN, $CHCl_3$), and in both cases the best selectivity was realized in toluene. [c] Determined by GC analysis following reaction workup. [d] Isolated yield of homoallyl alcohol, *uncorrected* for recovered RCH_2OH. The total mass recovery in each case was 73–83%. [e] Enantiomeric purities of homoallyl alcohols in entries 1–5 were determined by the chiral capillary GC method.[10] Percent ee data in entries 6 and 7 were determined by the Mosher ester technique.[11] [f] Values in parentheses are those obtained by using (*R*,*R*)-**1**. [g] Absolute configurations of the products in entries 6 and 7 are by analogy to the other cases that are known unambiguously.[2a] [h] $\Delta\Delta G^{\ddagger}$ values are in kilocalories per mole. These values provide a convenient means of comparing enantioselectivity in energetic terms. [i] Product from an experiment that proceeded to 48% conversion.

is certainly useful synthetically,[2c,d] we recognized that considerable room for improvement existed. We also were intrigued by the mechanism of asymmetric induction with **1–3** and, consequently, initiated studies on the rational design of new auxiliary systems. We are pleased to describe here, therefore, the design and synthesis of *N*,*N*′-dibenzyl-*N*,*N*′-ethylenetartramide (DBETA, **4**) and to *report that the derived allylboronate **5** exhibits substantially improved enantioselection relative to the parent reagent **1***. These experiments provide strong support for a novel stereoelectronic effect that may find broad application as a stereochemical control element in asymmetric synthesis.

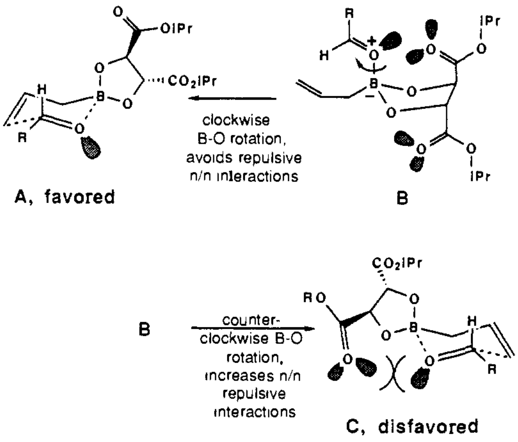


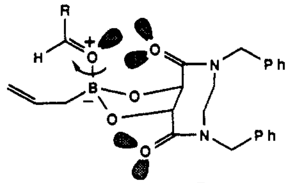
(**R**,**R**)–**1**, $R_E = R_Z = H$
(**R**,**R**)–**2**, $R_E = Me$, $R_Z = H$
(**R**,**R**)–**3**, $R_E = H$, $R_Z = Me$



(**R**,**R**)–**4**, R = H
(**R**,**R**)–**5**, $R = BCH_2CH{=}CH_2$

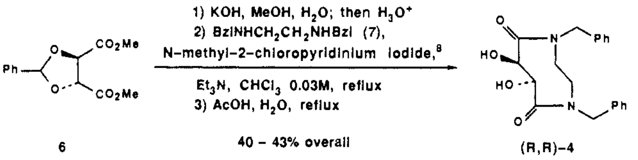
Our decision to explore conformationally restricted auxiliary systems like **4**[4] derives from our earlier suggestion that the origin of asymmetry with **1–3** involved an unprecedented[5] n/n electronic repulsive interaction between the nonbonding lone pair on the aldehydic oxygen and an ester carbonyl as indicated in transition-state C.[2a] For this mechanism to be correct, the dioxaborolane system must exist in conformation B with the two CO_2R units pseudoaxial and the ester carbonyls syn-coplanar to the adjacent ring oxygens.[6] Furthermore, the level of enantioselection would be expected to depend on the extent of conformational homogeneity at these sites. As long as the tartrate unit is held within an eight-membered ring (cf., **5**), however, these critical conformational features become structural constants, and intermediate aldehyde complexes have no choice but to exist in conformations analogous to B (e.g., D).





D

Bis(lactam) (*R*,*R*)-**4** [mp 202–203 °C; $[\alpha]_D^{25}$ −73.9° (*c* 1, dioxane)] was readily synthesized from commercially available precursors **6** and **7** by a three-step sequence in 40–43% overall yield. It is noteworthy that the amidation–lactamization step[8] proceeds in a preparatively useful yield (52–56%) in view of the poor results previously reported for the synthesis of eight-membered lactams from ω-amino acid precursors.[7,17] Reagent **5** was



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(4) We have thus far been unsuccessful in attempts to synthesize the bis(lactone) auxiliary related to **4**.

(5) After our first publication (ref 2a) appeared, Ojima and co-workers submitted a paper in which a similar stereoelectronic effect was invoked to explain diastereoselectivity in the [2 + 2] cycloadditions of azidoketene to chiral 3-imino-β-lactams: Ojima, I.; Nakahashi, K.; Brandstadter, S. M.; Hatanaka, N. *J. Am. Chem. Soc.* **1987**, *109*, 1798.

(6) Conformation B represents the ground-state Lewis acid aldehyde complex, stabilized by a boron-centered anomeric effect (n–σ* interactions between the axial lone pairs of the ring oxygens and the B—O═CHR single bond. For a previous example of a boron-centered anomeric effect, see: Shiner, C. S.; Garner, C. M.; Haltiwanger, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 7167.) The actual transition state for the allyl transfer probably occurs during a flipping motion of the dioxaborolane O–B–O unit that moves the allyl group toward a pseudoaxial position with development of two anti n_O–σ^*_{B-C} interactions that facilitate cleavage of the B–C bond. Note, however, that reasonable transition states for C–C bond formation are inaccessible if the aldehyde is symmetrically disposed with respect to the dioxaborolane system. Clockwise rotation about the B–O bond as indicated in B moves the aldehyde nonbonding lone pair away from the proximate ester carbonyl and leads to the favored transition-state A. Rotation of the B–O bond in the reverse direction increases the n/n interactions and leads to disfavored transition-state C.

(7) (a) Steliou, K.; Poupart, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 7130. (b) Collum, D. B.; Chen, S. C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393.

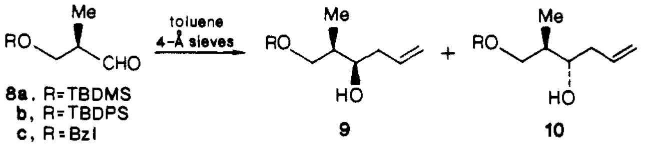
(8) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. Bald, E.; Saigo, K.; Mukaiyama, T. *Ibid.* **1975**, 1163.

(9) Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1986**, *51*, 427.

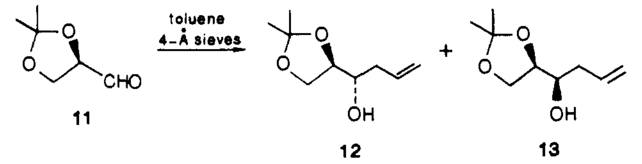
(10) Halterman, R. L.; Roush, W. R.; Hoong, L. K. *J. Org. Chem.* **1987**, *52*, 1152.

(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Table II. Reactions of **5** with Chiral Aldehydes[a]



entry	RCHO	reagent	conditions temp, C	conditions time, h	% conv[b]	% yield[c]	diastereoselectivity[d,e]
1	**8a**	(*S*,*S*)-**5**	-78	37	50	46	$\boxed{97:3}$ (89:11)
2	**8a**	(*S*,*S*)-**5**	-50	21	95	76	95:5
3	**8a**	(*R*,*R*)-**5**	-78	36	45	43	$\boxed{3:97}$ (19:81)
4	**8b**	(*S*,*S*)-**5**	-78	44	50	48	$\boxed{95:5}$ (79:21)
5	**8b**	(*R*,*R*)-**5**	-78	25	45	35	$\boxed{3:97}$ (13:87)
6	**8b**	(*R*,*R*)-**5**	-50	21	90	68	5:95
7	**8c**	(*S*,*S*)-**5**	-50	23	85	56	93:7 (83:17)
8	**8c**	(*R*,*R*)-**5**	-50	23	84	53	7:93 (20:80)



entry	RCHO	reagent	conditions temp, °C	conditions time, h	% conv[b]	diastereoselectivity[d,e]
9	**11**	(*R*,*R*)-**5**	-78	43	81	$\boxed{99.7:0.3}$ (96:4)
10	**11**	(*S*,*S*)-**5**	-78	43	84	$\boxed{2:98}$ (8:92)

[a] Reactions were performed with 1.5 equiv of **5** as described in Table I. [b] Conversions in entries 7–10 were determined by GC analysis. All others were determined by product isolation. [c] Isolated yields of homoallyl alcohol, *uncorrected* for recovered RCH_2OH. The total mass recovery in each case was 73–95%. [d] Diastereoselectivities were measured as described previously.[2a,d] [e] Values in parentheses are those previously reported for reactions involving **1**.[2a,d]

then prepared by treatment of **4** with triallylborane[2a,9] (CH_2Cl_2, 23 °C; then evaporated at 0.1 mmHg).

Results of reactions of **5** with several achiral aldehydes are summarized in Table I; also included are comparative data obtained with **1**. In every instance it is readily apparent that **5** greatly outperformed its predecessor. In energetic terms, **5** is at least 50% more enantioselective on a case by case basis. Significantly, **5** is as selective in reactions at 25 °C as is **1** at -78 °C (entries 1 and 3), the $\Delta\Delta G^{\ddagger}$ of reactions of **5** appear to be independent of temperature within experimental error (entries 1–3), and the sense of asymmetric induction of **5** and **1** is identical.

The increased enantioselectivity of **5** also pays dividends in reactions with chiral aldehydes (Table II). The allylborations of **8a**,**b** now proceed with ~30:1 selectivity for either diastereomer **9** or **10**, whereas by using **1** the maximum diastereoselectivity was 8:1. Even better results were obtained with glyceraldehyde acetonide (**11**): 300:1 selectivity for **12** in the matched double-asymmetric reaction, 50:1 selectivity for **13** in the mismatched combination.

These data strongly support our original thesis regarding the origin of asymmetry with reagents **1**–**3**[12] and establish **5** as the most highly enantioselective allylmetal reagent yet devised.[3,13] While the poor solubility of **5** in toluene especially at low temperatures, no doubt contributing to the incomplete conversions even at long reaction times, remains a problem we are striving to solve,[14] the present study clearly demonstrates the importance of functional group convergence toward an active metal center as a means of achieving a topological bias in the enantioselective functionalization of a carbonyl group.[6,15] Attempts to extend this concept to other classes of enantioselective C–C bond-forming processes will be reported in due course.

Experimental Section

All reactions were performed in oven-dried glassware under an atmosphere of dry argon or nitrogen. The following reaction solvents were purified before use: ether and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2; toluene was distilled from sodium metal; $CHCl_3$ was distilled from K_2CO_3 after washing with water to remove ethanol.

Dimethyl 2,3-*O*-benzylidenetartrate (**6**; mp, 72–72.5 °C) is commercially available (Aldrich) but is also easily prepared in 87–92% yield with the procedure reported by Tanaka et al.[16]

2,3-*O*-Benzylidenetartaric Acid. Diester **6** (19.6 g, 73.4 mmol) was dissolved in a mixture of 210 mL of MeOH and 90 mL of H_2O containing 16.8 g (300 mmol) of KOH. The mixture was stirred at 25 °C for 6 h; then MeOH was removed in vacuo. The remaining aqueous solution was treated with KH_2PO_4 (13.6 g, 100 mmol) and carefully acidified with 3 N HCl until pH 3. The resulting suspension was extracted with EtOAc. The organic phase was dried (Na_2SO_4) and evaporated, and the crude solid (17.7 g) was recrystallized from EtOAc–hexane to give the pure diacid (15.5 g, 89%) as white crystals. This material slowly decomposes to benzaldehyde and tartaric acid when stored at room temperature, so it is recommended that it be stored in a freezer under an inert atmosphere unless it is used immediately following preparation: mp 128.5–129.5 °C; $[\alpha]_D^{25}$ -37.0° (*c* 1.0, acetone) for the (*S*,*S*) isomer, $[\alpha]_D^{25}$ +39.4° for the (*R*,*R*) isomer; ^1H NMR (DMSO-d_6, 250 MHz) δ 13.43 (2 H, br s), 7.50–7.60 (2 H, m), 7.35–7.45 (3 H, m), 5.98 (1 H, s), 4.91 (d, J = 4.0 Hz, 1 H), 4.75 (d, J = 4.0 Hz, 1 H); IR

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(12) The increased enantioselectivity of **5** is not simply the result of the ester to lactam functional group modification. A series of acyclic tartramides have been examined [e.g., bis(*N*,*N*′-dibenzyl)tartramide], and their allylboron derivtives are *significantly* less enantioselective than **1**.

(13) Reagent **5** also ranks among the most highly enantioselective chiral acetate aldol enolate equivalents: (a) Braun, M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 24 and literature cited therein. (b) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.

(14) Although **5** is substantially more enantioselective than **1**, it is not, however, a superior reagent for organic synthesis. The poor solubility/reactivity characteristics of **5** are highly unattractive. Thus, efforts are underway to develop a reagent that combines the reactivity of **1** with the enantioselectivity and ease of preparation of **5**. This species, if successfully developed, should be ideally suited for use in organic synthesis.

(15) The significance of convergent functional groups on the design of molecular receptors and clefts has been described: (a) Rebek, J., Jr.; Askew, B.; Ballester, P.; Doa, M. *J. Am. Chem. Soc.* **1987**, *109*, 4119. (b) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *Ibid.* **1987**, *109*, 2432. (c) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *Ibid.* **1987**, *109*, 2426.

(16) Tanaka, A.; Otsuka, S.; Yamashita, K. *Agric. Biol. Chem.* **1984**, *36*, 2135.

(KBr) 3300–2500 (br), 1728, 1462, 1430, 1408, 1270, 1253, 1225, 1104, 760, 695, 676 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23. Found: C, 55.34; H, 4.24.

2,3-*O*-Benzylidene-*N*,*N'*-dibenzyl-*N*,*N'*-ethylenetartramide.[17] A solution of benzylidenetartaric acid (1.19 g, 5.0 mmol), dibenzylethylenediamine (1.18 mL, 5.0 mmol, Aldrich), and Et_3N (4.2 mL, 30 mmol) in dry $CHCl_3$ (80 mL) was added dropwise over 5 h to a refluxing solution of *N*-methyl-2-chloropyridinium iodide (3.83 g, 15.0 mmol) in dry $CHCl_3$ (80 mL). The solution was refluxed overnight, extracted with saturated aqueous $NaHCO_3$ (150 mL), washed with water (2 × 150 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (on several occasions the product crystallized at this stage) and filtered through 50 g of 60–230-mesh silica gel, using 1:1 hexane–EtOAc as eluant, to give 1.15 g (52%) of the title compound as a crystalline solid. This material was generally recrystallized from CH_2Cl_2–hexane before the next step. This reaction is somewhat less efficient when performed in CH_3CN (35–40% yield; 20-mmol scale): mp 110–111 °C; $[\alpha]_D^{25}$ +58.6° (*c* 1, $CHCl_3$) for the (*R*,*R*) isomer; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.7–7.74 (m, 2 H), 7.20–7.45 (m, 13 H), 6.24 (s, 1 H), 4.96 (A of AB, J = 6.7 Hz, 1 H), 4.84 (B of AB, J = 6.7 Hz, 1 H), 4.77 (d, J = 14.7 Hz, 1 H), 4.75 (d, J = 14.7 Hz, 1 H), 4.44 (d, J = 14.8 Hz, 2 H), 3.15–3.44 (m, 4 H); ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ 170.6, 168.4, 136.6, 136.4, 134.9, 129.9, 129.0, 128.9, 128.4, 128.3, 128.1, 128.0, 127.6, 106.6, 76.6, 76.4, 52.0, 51.7, 49.2; IR ($CHCl_3$) 1680, 1495, 1470, 1455, 1435, 1235, 1110 cm^{-1}; mass spectrum (EI, 270 °C) m/z 442 (M^+). Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.29; H, 5.92; N, 6.33. Found: C, 72.91; H, 5.89; N, 6.30.

***N*,*N'*-Dibenzyl-*N*,*N'*-ethylenetartramide (DBETA, 4).** A solution of the benzylidene acetal (3.35 g, 7.57 mmol) in HOAc (30 mL) and H_2O (10 mL) was heated at reflux for 17 h. The solvent was then removed at reduced pressure and dried by coevaporation with heptane and absolute EtOH. The crude product was crystallized from 30 mL of 2:1 $CHCl_3$–Et_2O, giving 2.32 g (87%) of **4**. A second crystallization from 21 mL of 7:3 EtOH–H_2O gave analytically pure material that was used in all allylboration experiments: m.p. 202–203 °C; $[\alpha]_D^{25}$ −73.9° (*c* 1, dioxane, after 15-min equilibration) for the (*R*,*R*) isomer; ^1H NMR (DMSOd_6, 90 °C) δ 7.18–7.38 (m, 10 H), 4.31 (s, 2 H), 4.27 and 4.13 (AB system, J = 14.7 Hz, 4 H, CH_2Bzl), 3.65–3.80 (m, 2 H), 3.40–3.60 (m, 2 H); IR (KBr) 3375, 1620, 1452, 1066, 743, 698 cm^{-1}; mass spectrum (EI, 250 °C) m/z 354 (M^+). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.56; H, 6.43; N, 8.04.

Allylboronate 5. A suspension of **4** (200 mg, 0.56 mmol) in dry CH_2Cl_2 (5 mL) was treated with triallylborane (98 μL, 0.56 mmol) at 23 °C. The suspension became a clear solution within a few minutes and was stirred for 3 h before being concentrated in vacuo with exclusion of moisture. The resulting white foam was stripped overnight at 0.1 mmHg to give reagent **5**, which was used directly in the experiments described in Tables I and II: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.33 (m, 10 H), 5.87–6.05 (m, 1 H), 5.11 (d, J = 17.1 Hz, 1 H), 4.96–5.02 (m, 1 H), 4.98 (s, 2 H, C*H*O), 4.73 (d, J = 14.0 Hz, 2 H), 4.40 (d, J = 14 Hz, 2 H), 3.35 (d, J = 15.0 Hz, 2 H), 3.14 (d, J = 15 Hz, 2 H), 2.01 (d, J = 7.3 Hz, 2 H, CH_2B); ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ 169.7, 136.4, 132.8, 129.0, 128.4, 128.1, 115.9, 77.0, 52.0, 49.3.

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Registry No. (*R*,*R*)-**4**, 112897-01-5; (*R*,*R*)-**5**, 112897-02-6; **6**, 38270-72-3; **7**, 140-28-3; **8a**, 97826-89-6; **8b**, 112897-04-8; **8c**, 79026-61-2; **9a**, 112897-05-9; **9b**, 112897-06-0; **9c**, 94233-73-5; **10a**, 112897-07-1; **10b**, 112897-08-2; **10c**, 94233-74-6; **11**, 15186-48-8; **12**, 79364-35-5; **13**, 87604-46-4; *c*-$C_6H_{11}CHO$, 2043-61-0; C_6H_5CHO, 100-52-7; *t*-C_4H_9CHO, 630-19-3; (TBDPS)OCH_2CH_2CHO, 112897-03-7; BzlOCH_2CHO, 60656-87-3; (*S*)-c-$C_6H_{11}CH(OH)CH_2CH{=}CH_2$, 94340-22-4; (*S*)-$C_6H_5CH(OH)CH_2CH{=}CH_2$, 77118-87-7; (*S*)-*t*-$C_4H_9CH(OH)CH_2CH{=}CH_2$, 67760-86-5; (*R*)-(TBDPS)-$OCH_2CH_2CH(OH)CH_2CH{=}CH_2$, 112897-09-3; (*S*)-Bzl$OCH_2CH(OH)CH_2CH{=}CH_2$, 88981-35-5; 2,3-*O*-benzylidene tartaric acid, 83529-41-3; *N*-methyl-2-chloropyridinium iodide, 14338-32-0; 2,3-*O*-benzylidene-*N*,*N'*-dibenzyl-*N*,*N'*-ethylene tartrate, 112897-00-4; *N*,*N'*-ethylene tartrate triallylborane, 688-61-9.

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On the Electron–Proton–Electron Mechanism for 1-Benzyl-1,4-dihydronicotinamide Oxidations

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Abstract: The reaction of 1-benzyl-1,4-dihydronicotinamide (BNAH) with several ferrocenium (Fc^+) salts in aqueous propanol was studied. The mechanism was shown to involve electron–proton–electron transfer with rate-limiting electron transfer from BNAH to Fc^+. From the rate constants and $E°(Fc/Fc^+)$ values, the $E°(BNAH/BNAH^{\cdot+})$ was estimated to be 0.89 V (SCE). The electrochemistry of BNAH was investigated in order to evaluate a previously determined $E°(BNAH/BNAH^{\cdot+})$. A reconsideration of the literature data for (non-DDQ) quinone oxidations of reduced nicotinamide adenine dinucleotide (NADH) in water and BNAH in CH_3CN shows that the data are consistent with a hydride-transfer mechanism and inconsistent with an electron–proton–electron mechanism involving free $NADH^{\cdot+}$. A mechanism in which the hydride is transferred by electron–proton–electron transfer within one complex cannot be excluded.

The mechanisms of nonenzymatic oxidations of reduced nicotinamide adenine dinucleotide (NADH) and NADH model compounds like 1-benzyl-1,4-dihydronicotinamide (BNAH) have attracted continuing attention.[1] An issue of particular interest has been the three-step mechanism involving sequential electron–proton–electron transfer (e–p–e) as an alternative to a one-step hydride transfer for conversion of NADH to NAD^+. Evidence has been reported to support the e–p–e mechanism for reactions involving thermal,[2-5] photochemical,[5-10] and electrochemical[10-15] oxidation. Each of these cases involved strong

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[1] Fukuzumi, S.; Koumitsu, S.; Hironaka, K.; Tanaka, T. *J. Am. Chem. Soc.* **1987**, *109*, 305. This paper contains an extensive list of references.

[2] Carlson, B. W.; Miller, L. L.; Neta, P.; Grodkowski, J. *J. Am. Chem. Soc.* **1984**, *106*, 7233.

[3] (a) Powell, M. F.; Wu, J. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 3850. (b) Sinha, A.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 7291.

[4] Fukuzumi, S.; Konda, Y.; Tanaka, T. *J. Chem. Soc., Perkin Trans. II* **1984**, 673. Fukuzumi, S.; Nishizawa, N.; Tanaka, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3482.

[5] Okamoto, T.; Ohno, A.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1977**, 784; **1977**, 181.

0002-7863/88/1510-3982$01.50/0