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Remote Substituent Effects on Regioselectivity in Rhodium(I)-catalyzed Hydroborations of Norbornenes

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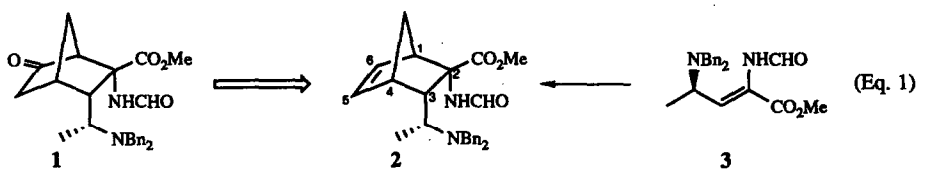
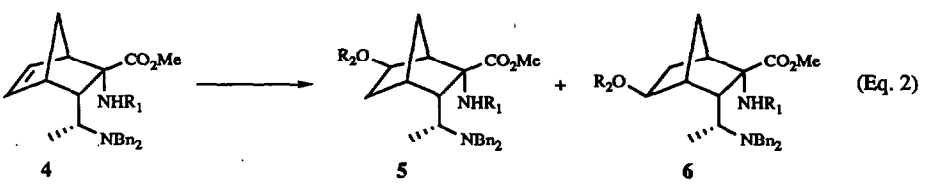
Abstract: Remote substituent effects on the regioselectivity of both the conventional and the rhodium(I)-catalyzed hydroborations of some norbornene derivatives are discussed.

In the course of an alkaloid synthesis we required access to enantiomerically pure norbornanone derivative **1**. We envisioned a strategy in which this compound was obtained via a regioselective hydroboration of norbornene **2**. The latter was readily available through a highly stereoselective Et_2AlCl-mediated Diels-Alder reaction of enantiopure dienophile **3** with cyclopentadiene (Equation 1).[2] This paper describes how we achieved this goal as well as some efforts to rationalize our results.



(Eq. 1)

As anticipated, conventional hydroboration of formamide **2** (Table 1, entry 1) gave only a modest C-6 (*exo*) selectivity, in accord with reported electronic effects on hydroboration reactions.[3, 4] The corresponding deformylated amine (entry 4) was next treated with BH_3.THF, anticipating a regioselective "intramolecular" hydroboration from the more crowded *endo* face via a coordinated amine-borane complex. While a higher reaction temperature was indeed required, consistent with amine-borane coordination, only *exo* alcohols[5] were obtained with marginal regioselectivity.



(Eq. 2)

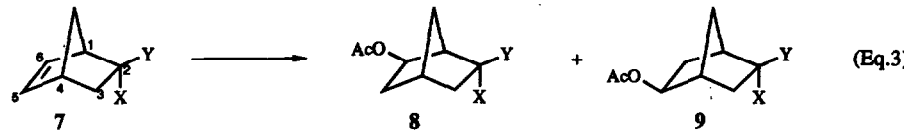
Table 1: Hydroboration of norbornene derivatives **4** (eq. 2).

entry	R_1	R_2	conditions[a]	temp. in °C	yield[b] in %	**5 / 6** [c]
1	CHO	Ac	A	RT	50	72 / 28
2	CHO	Ac	B	RT	52	91 / 9
3	CHO	Ac	B	-5	56[d]	96 / 4
4	H	H	A	67	61	61 / 39[e]
5	H	H	B	-5	79	84 / 16[e]
6	CO_2Me	Ac	B	-5	83	> 98 / 2[7]

a) A 1 moleq. BH_3.THF in THF (0.2 M), 16h; 50 % H_2O_2/ 3M NaOH, RT, 1h; $Ac_2O/Et_3N/DMAP/CH_2Cl_2$, RT, 4h; B 2-3 equivalents of catecholborane, 5 mol% $1/2[Cl(COD)_2Rh]_2.4Ph_3P$ in THF (0.2 M), 16 h; oxidative workup and acetylation as in A; *b*) yields are not optimized and refer to the combined isolated regioisomers after flash chromatography; *c*) determined by HPLC (Spherisorb® silica 3µm column; hexane/ethanol 95/5 eluent) unless indicated otherwise; *d*) based on recovered starting material; *e*) ratio based on pure chromatographed regioisomers

Recognizing that transition metal-catalyzed hydroborations offer an important alternative to conventional techniques,[6] we reacted formamide **2** and also the free amine (entries 2-3, 5) with 2-3 molar equivalents of catecholborane in the presence of 5 mol% of 1/2[Cl(COD)$_2$Rh]$_2$.4Ph$_3$P. For all examples a significant enhancement in C-6 regioselectivity was observed. The most striking selectivity was observed for the carbamate (entry 6).[7]

Intrigued by these results, we set out to determine the structural factors that governed the observed selectivity in the rhodium(I)-catalyzed reactions of this system (Table 2). For comparison, a number of our substrates were also subjected to BH$_3$.THF hydroborations. Some literature examples are also included (entries 2,3 and 5-9). The stereo- and regiochemistries of all reported products were readily determined by both ^{1}H and ^{13}C-NMR.[5, 8]



7 8 9 (Eq.3)

Table 2: Hydroboration of norbornene derivatives **7** (eq. 3).

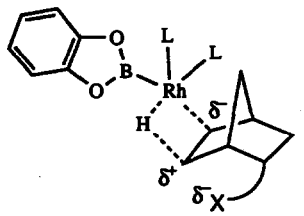
entry	X	Y	uncatalyzed hydroboration [a] yield [c]	**8** / **9** [d]	catalyzed hydroboration [b] yield [c]	**8** / **9** [d]
1	CO_2Bn	H[12]	55	56 / 44	72	30 / 70
2	CO_2Me	H	85	60 / 40[4e]		
3	H	CO_2Me	97	60 / 40[4c]		
4	CO_2Me	CO_2Me[13]	56	65 / 35	54	38 / 62
5	H	NO_2	83	75 / 25[4c]		
6	OAc	H	75	60 / 40[4f]		
7	H	OAc	60	65 / 35[4c]		
8	OMe	H	52	52 / 48[4f]		
9	Br	H	85	40 / 60[4f]		
10	$CONBn_2$	H[12]			62	16 / 84
11	H	$CONBn_2$[12]			78	46 / 54
12	CONHBn	H[12]			61	24 / 76
13	SO_2Ph	H[14]	77	56 / 44	73	13 / 87
14	H	SO_2Ph[14]	66	63 / 37	86	57 / 43
15	CH_2NBn_2	H[12]	60	50 / 50	83	20 / 80
16	H	CH_2NBn_2[12]			76	50 / 50
17	NHCHO	CO_2Et[15]			NR[e]	
18	CO_2Et	NHCHO[15]			NR[e]	
19	$NHCO_2Bn$	CO_2Et[16]	58	62 / 38	75	22 / 78
20	NHCOPh	CO_2Et[16]			51	23 / 77

a) 1 moleq. BH$_3$.THF in THF (0.2 M), RT, 16h; 50 % H_2O_2/ 3M NaOH, RT, 1h; Ac_2O/Et_3N/DMAP/CH_2Cl_2, RT, 4h; *b)* 2-3 eq catecholborane; 5 mol% 1/2[Cl(COD)$_2$Rh]$_2$.4Ph$_3$P in THF (0.2 M); RT, 16 h; oxidative workup and acetylation as in before; *c)* yields are in %, are not optimized and refer to the combined isolated regioisomers after flash chromatography; *d)* literature ratios are referenced; all other stated ratios were determined by us using NMR on both crude and purified products. Error margin is ±5; *e)* entries 17 and 18 used together as a 3/1 mixture of the inseparable isomers, with the isomer of entry 18 as the major one (cf. note 15).

Table 2 shows that the conventional and rhodium(I)-catalyzed hydroboration reactions generally have opposite regioselectivities. A similar observation has been noted by Evans et. al. in cyclohexenyl systems.[9] Since oxidation of organoboranes occurs with retention of configuration, all of our hydroborations must have occurred from the *exo* face. This makes a directing role for polar substituents, as has recently been reported for iridium(I) catalyzed hydroborations in conformationally more flexible systems,[10] unlikely in our cases.

It is clear from Table 2 that the preference for the formation of the 2,6 substituted isomers **8** in the conventional sequence is only very modest. When the polar substituents are *exo*, there seems to be a qualitative correlation between their field effect[11] and the regioselectivity (entries 3, 5, 7, 14; and also 4 vs. 19), as is expected for a reaction dominated solely by electronic effects. The relation between *endo* substituent polarity and regioselectivity appears much less straightforward (entries 1, 2, 6, 8, 9, 13).

For the rhodium(I) catalyzed hydroborations the *endo* substituents seem to be far more important in enhancing the regioselectivity than their *exo* counterparts (entry 10 vs. 11; 13 vs. 14). It is also clear that the correlation goes beyond a pure inductively withdrawing effect of the *endo* substituents (entry 1 vs. 10 and 12; 4 vs. 19 and 20). Very informative are entries 15 and 16, which show that for catalyzed hydroboration a dibenzylaminomethyl substituent only affects the regiochemistry when it has the *endo* orientation. Empirically, the regioselectivity of the catalyzed reaction increases in the following order of *endo* substituents: ester < amide ≈ carbamate ≈ dibenzylaminomethyl < sulfone. Entries 15 and 19 indicate that the *endo* carbamate and dibenzyl-aminomethyl groups are equipotent in favoring regioisomer **8**. Yet, in the case of **4** (R_1 = CO_2Me; entry 6 of Table 1) complete selectivity was observed. At this point we cannot offer an adequate explanation for these observations. It must also be noted that formamide esters (entries 17 and 18) failed to react under the catalyzed conditions.



A

The mechanism of transition metal-catalyzed hydroboration reactions is still unclear, and could be highly dependent on the structure of the substrate olefin.[17, 18] However ensemble **A** can account nicely for the observed remote substituent effects. It incorporates both the postulated complex formed by oxidative insertion of rhodium(I) into the boron hydrogen bond of catecholborane,[6] and also the experimentally demonstrated small charge separation effects in the insertion of olefins into transition metal hydride bonds (or its microscopic reverse, β-hydride elimination).[19]

We conclude that useful regioselectivities can be attained in transition metal-catalyzed hydroboration reactions of norbornenes containing certain polar functional groups on the *endo* face. The mechanistic origin and broader synthetic applicability of this selectivity remain to be further investigated.[20]

References and notes:

1 Present address: Merck, Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, NJ 07065.

2 We thank Professor Manfred Reetz (Max Planck Inst. f. Kohlenforschung, D-4330 Mülheim, Germany) for providing us with his unpublished results and experimental conditions for this reaction, as well as structural evidence (including X-ray analysis) for the adduct; see Reetz, M.T.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1992**, *33*, 3453-3456.

3 Pelter, A. ; Smith, K., in *"Comprehensive Organic Chemistry "* (Barton, D.H.R.; Ollis, W.D., Eds.), Vol. 3, Part 14, Pergamon: Oxford, 1979, p. 695, 713. See also reference 9.

4 For examples in norbornene hydroborations: a) Henkel, J.G.; Spurlock, L.A. *J. Am. Chem. Soc.*, **1973**, *95*, 8339; b) Malinovsky, M.S.; Kas'yan, L.I.; Ovsyanik, V.D.; Ivchenko, O.V.; Tkachenko, V.S. *Zh. Org. Khim.*, **1972**, *8*, 982-984; c)

Fischer, W.; Grob, C.A.; Sprecher, G. von *Helv. Chim. Acta*, **1980**, *63*, 806-815; d) Fischer, W.; Grob, C.A.; vonSprecher, G. *Helv. Chim. Acta*, **1980**, *63*, 816-823; e) Grob, C.A.; Günther, B.; Waldner, A. *Helv. Chim. Acta*, **1981**, *64*, 2709-2720; f) Grob, C.A.; Günther, B.; Hanreich, R. *Helv. Chim. Acta*, **1982**, *65*, 2288-2298.

5 The *exo* stereochemistry of all product alcohols was apparent from their NMR spectra (cf. Flautt, T.J.; Erman, W.F. *J. Am. Chem. Soc.*, **1963**, *85*, 3212-3218). In selected cases (entries 1-3 of Table 1; entries 4, 10, 15 and 16 of Table 2) this was further corroborated by oxidation (with TPAP/NMO; cf. Griffith, W.P.; Ley, S.V.; Whitcombe, G.P.; White, A.D. *J. Chem. Soc. Chem. Comm.*, **1987**, 1625-1627) and reduction (L-Selectride®; cf. Brown, H.C.; Krishnamurthy, S. *J. Am. Chem. Soc.*, **1972**, *94*, 7159), which gave a different alcohol (*endo*) in all those cases. For the major acetate **5** derived from entries 1-3 of Table 1: Anal. calc for $C_{28}H_{34}O_5N_2$ (478.58): C, 70.27; H, 7.16; N, 5.85. Found: C, 70.26; H, 7.16; N, 5.57.

6 For a recent review: Burgess, K.; Ohlmeyer, M.J. *Chem. Rev.*, **1991**, *91*, 1179-1191.

7 Spectroscopic data for these regioisomers are representative.
Regioisomer **5** (R_1=CO_2Me, R_2=Ac) was obtained by the catalyzed hydroboration sequence; m.p. 144-145°C; $[\alpha]_D$ -0.40° (c 1.0; $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.2-7.4 (m, 10H), 4.67 (br, 1H), 4.60 (d, *J* 6.4, 1H), 3.74 (br d, 2H), 3.72 (s, 3H), 3.65 (s, 3H), 3.33 (d, *J* 13.6, 2H), 3.19 (m, 1H), 2.71 (m, 1H), 2.61 (dq, *J* 11.1, *J* 6.3, 1H), 2.07 (m, *J* 11.0, 1H), 1.97 (s, 3H), 1.84 (m, *J* 10.5, 1H), 1.73 (m, *J* 10.5, 1H), 1.43 (m, 1H), 1.27 (m, 1H), 1.17 (d, *J* 6.3, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz): 174.38 (s), 170.28 (s), 156.41 (s), 139.17 (s), 128.88 (d), 128.34 (d), 127.22 (d), 73.18 (d), 62.71 (s), 53.50 (d), 53.21 (t), 50.77 (q), 49.34 (d), 49.25 (d), 37.74 (d), 34.85 (t), 32.22 (t), 21.24 (q), 10.62 (q); Anal. calc.for $C_{29}H_{36}N_2O_6$ (508.60): C, 68.48; H, 7.14; N, 5.51. Found: C, 68.98; H, 6.98; N, 5.20.
Regioisomer **6** (R_1=CO_2Me, R_2=Ac) was obtained by treatment of the minor isomer of entries 4/5 of Table 1 with *i*) methyl chloroformate; *ii*) acetic anhydride; $[\alpha]_D$ -3.12° (c 1.0; $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.2-7.4 (m, 10H), 4.77 (br, 1H), 4.27 (m, 1H), 3.80 (br d, 2H), 3.72 (s, 3H), 3.62 (s, 3H), 3.35 (d, *J* 13,7, 2H), 3.12 (m, 1H), 2.74 (m, 1H), 2.70 (m, 1H), 2.18 (dd, *J* 11.1, J 3.0, 1H), 2.12 (s, 3H), 2.09 (m, 1H), 1.86 (m, *J* 10.6, 1H), 1.72 (m, *J* 10.6, 1H), 1.15 (d, *J* 16.3, 3H), 1.13 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz): 174.79 (s), 170.02 (s), 156.17 (s), 138.86 (s), 128.69 (d), 128.44 (d), 127.21 (d), 72.57 (d), 63.06 (s), 53.50 (t), 52.48 (q), 52.39 (d), 52.22 (q), 49.01 (d), 46.34 (d), 43.65 (d), 36.20 (t), 35.06 (t), 21.29 (q), 10.84 (q).

8 In particular various small ^4J long range couplings, which could be clarified by extensive decoupling experiments, were very informative. Table 2, entry 1 is a representative case. The 2*endo* / 6*exo* isomer has ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.38 (m, 5H, ArH), 5.17 (m, *J* 12.3, 2H, OCH_2Ar), 4.73 (m, *J* 7.0, 1H, 6H*endo*), 2.84 (m, 1H, 2H*exo*), 2.67 (m, 1H, 1H), 2.35 (m, 1H, 4H), 2.01 (s, 3H, Ac), 1.90 (ddd, *J* 13.6, *J* 7.0, *J* 2.4, 1H, 5H*endo*), 1.60-1.75 (m, 3H, 3H*endo* and 3H*exo* and 7H), 1.48 (m, 1H, 5H*exo*), 1.35 (m, 1H, 7H); By decoupling experiments small long range couplings were established between 1H and 5H*exo*, 1H and 3H*exo*, 3H*exo* and 5H*exo*, 5H*endo* and 7H*anti*; ^{13}C-NMR ($CDCl_3$, 75 MHz): 173.69 (s), 170.14 (s), 136.02 (s), 128.49 (d), 128.28 (d), 128.10 (d), 73.74 (d), 66.52 (t), 45.19 (d), 42.67 (d), 39.45 (t), 37.06 (t), 36.25 (d), 30.76 (t), 21.23 (q); Anal. calc. for $C_{17}H_{20}O_4$ (288.33): C, 70.81; H 6.99; Found C, 71.08; H, 6.93. The 2*endo*/5*exo* isomer has ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.36 (m, 5H, ArH), 5.12 (s, 2H, OCH_2Ar), 4.66 (m, *J* 6.6, 1H, 5H*endo*), 2.76 (m, 1H, 2H*exo*), 2.62 (m, 1H, 1H), 2.37 (m, *J* 4.7, 1H, 4H), 2.01 (s, 3H, Ac), 1.85 (ddd, *J* 14.3, *J* 7.0, *J* 2.5, 1H, 6H*endo*), 1.74 (dd, *J* 11.1, *J* 5.2, 1H, 3H*exo*), 1.66 (m, 1H, 7H), 1.62 (m, 1H, 3H*endo*), 1.37 (m, 2H, 6H*exo* and 7H); By decoupling experiments small long range couplings were established between 2H*exo* and 6H*exo*, 2H*exo* and 4H; ^{13}C-NMR ($CDCl_3$, 75 MHz): 173.87 (s), 170.43 (s), 136.10 (s), 128.51 (d), 128.14 (d), 128.09 (d), 76.52 (d), 66.19 (t), 44.47 (d), 42.05 (d), 39.42 (d), 36.90 (t), 34.60 (t), 27.23 (t), 21.26 (q).

9 Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.*, **1988**, *110*, 6917-6918.

10 Evans, D.A.; Fu, G.C. *J. Am. Chem. Soc.*, **1991**, *113*, 4042-4043.

11 Charton, M. *Prog. Phys. Org. Chem.*, **1981**, *13*, 119-252.

12 The starting esters and amides were prepared from commercially available 5-norbornene-2-carbonyl chloride (Pfaltz & Bauer; 2/1 mixture of *endo*/*exo* isomers). In all cases *exo* and *endo* isomers were readily separated by flash chromatography. The tertiary amines were obtained by $LiAlH_4$ reduction of the corresponding tertiary amides.

13 The starting geminal diester was obtained from the corresponding mono ester by *i*) LDA, THF, -78°C; *ii*) MeO_2CCN, HMPA in 75 % yield, after chromatography.

14 Starting sulfones prepared according to Maccagnani, G.; Montanari, F.; Taddei, F. *J. Chem. Soc. (B)*, **1968**, 453-458. For *exo*-acetate (**8**) derived from *endo*-sulfone of entry 13: Anal. calc. for $C_{15}H_{18}O_4S$ (294.35): C, 61.15; H, 6.16; S, 10.87. Found: C, 61.47; H, 5.86; S, 10.67.

15 The starting formamide ester was obtained by a Diels-Alder between ethyl *N*-formyl dehydroalaninate (Hellmann, H; Teichmann, K.; Lingens, F. *Chem. Ber.*, **1958**, *91*, 2427-2431) and cyclopentadiene. Both thermal (110°C, 5 h) and Lewis acid catalyzed reactions (1 eq.Et_2AlCl, -10°C, 10 h) gave in 70-80 % yield an inseparable mixture of *endo* and *exo* formamides in a ratio of 3.5 / 1.

16 Starting materials were obtained by treating the formamide ester mixture of note 15 with HCl/MeOH, followed by benzyl chloroformate or benzoyl chloride. The *exo* and *endo* isomers were readily separated by flash chromatography.

17 Evans, D.A.; Fu, G.C. *J. Org. Chem.*, **1990**, *55*, 2280-2282.

18 Burgess, K.; van der Donk, W.A.; Kook, A.M. *J. Org. Chem.*, **1991**, *56*, 2949-2951 and 7360.

19 a) Doherty, N.M.; Bercaw, J.E. *J. Am. Chem. Soc.*, **1985**, *107*, 2670-2682; b) Burger, B.J.; Santarsiero, B.D.; Trimmer, M.S.; Bercaw, J.E. *J. Am. Chem. Soc.*, **1988**, *110*, 3134-3146 and references therein; c) Burger, B.J.; Thompson, M.E.; Cotter, D.; Bercaw, J.E. *J. Am. Chem. Soc.*, **1990**, *112*, 1566-1577.

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