Face Selectivity in the Borohydride Reduction of 4-eq,6-ax-Diaryl-5-azaadamantan-2-ones

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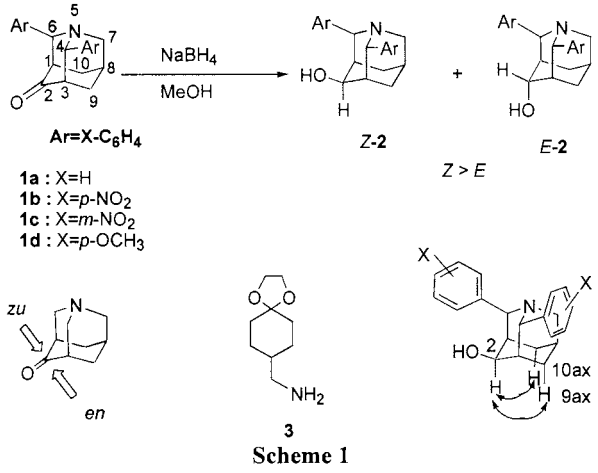
The highly preferential attack at the *en* face in the reduction with sodium borohydride of 4-eq,6-ax-diaryl-5-azaadamantan-2-ones in methanol is described. Steric and electronic effects are involved.

Facial selection in the different rigid ketones such as adamantanone,[1] azaadamantanone[2] and its *N*-oxide[3] have been explained in terms of either Cieplak[4] or Anh–Felkin[5] proposals. In azaadamantanone, the hydride attack occurred at the *en* face in THF ($LiAlH_4$) and at the *zu* face with protic solvents ($NaBH_4$);[2] but in the *N*-oxide a preferred *zu* attack (96%) was observed. According to le Noble,[3] the Cieplak model operates in both examples. However, Gung suggested that the observed diasterofacial selectivity should be explained in terms of steric effects,[6] because of azaadamantanone and its *N*-oxide have distorted structures which differentiate the two faces, outlined in Scheme 1.



Scheme 1

We describe here our preliminary results on the facial selectivity in the nucleophilic addition of sodium borohydride to the novel 4-eq,6-ax-diaryl-5-azaadamantan-2-ones **1a–d** (Scheme 1), which were prepared by Mannich condensation of the amino acetal **3**[7] with the corresponding substituted benzaldehyde.[8] The ketones **1** were characterized by IR, EIMS and elemental analysis. The NMR assignations were performed with the aid of the corresponding COSY, HETCOR, DEPT and NOESY experiments.

The reductions were done at 25 °C by adding a solution of 4.5 mg of sodium borohydride in 0.5 mL of methanol to a solution of each ketone (0.05 mmol in 0.5 mL of methanol). After evaporating the dried extract (anhydrous sodium sulfate), the solid mixture of alcohols was analyzed by ^{1}H and ^{13}C-NMR techniques. In the case of **2b** and **2c**, we were able to assign all ^{1}H and ^{13}C signals in both isomers, but in **2a** and **2d** only the *Z* isomer is reported (Table 1). The NOESY experiment was performed and both isomers were clearly differentiated in agreement with the prominent H-2/H-9ax and H-2/H-10ax NOE correlations in the *Z*-isomer (Scheme 1).

Table 1. ^{1}H and ^{13}C-NMR ($CDCl_3$) δ (ppm) values of *Z* and *E* 4-eq,6-ax-diaryl-azaadamantanols **2** on the tricyclic framework[a]

	Z-**2a**	*Z*-**2b**	*E*-**2b**	*Z*-**2c**	*E*-**2c**	*Z*-**2d**
H1[b]	2.77	2.85	2.73	2.87	2.74	2.69
H2[c]	4.30	4.40	4.10[b]	4.42	4.13[b]	4.26
	(3.0)	(3.3)		(3.3)		(3.0)
H3[b]	2.31	2.35	2.43	2.36	2.45	2.24
H4[b]	4.60	4.53	3.77	4.51	3.78	4.51
H6[b]	4.42	4.47	4.59	4.48	4.60	4.35
H7[e]	3.33	3.26	3.24	3.26	3.26	3.28
	(13.2)	(13.8)	(13.5)	(13.8)	(13.8)	(13.5)
H7'[e]	2.94	3.00	3.04	3.01	3.04	2.89
	(13.2)	(13.8)	(13.5)	(13.8)	(13.8)	(13.5)
H8[b]	1.53	1.64	1.58	1.64	1.58	1.48
H9[e]	1.71	1.75	1.89	1.77	1.89	1.68
ax	(12.9)	(13.5)	(12.9)	(13.8)	(12.6)	(12.6)
H9[d]	2.13	2.02	2.59	2.06	2.60	2.08
eq	(3,6,13)	(3,5.7,	(3, 6,	(2.7,5.7	(2.7,6,	(2.7,6,
		13.5)	12.9)	,13.8)	12.6)	12.6)
H10[d]	2.08	2.11	2.11	2.11	2.11	2.03
ax	(3,6,12.6)	(2.4,5.4,	(2.4,5.4,	(2.7, 6,	(2.7, 6,	(3,6,12)
		12.9)	12.9)	12.9)	12.9)	
H10[d]	2.22	2.24	2.24	2.24	2.24	2.17
eq	(3, 6, 12.6)	(2.4,5.4,	(2.4,5.4,	(2.7, 6,	(2.7, 6,	(3,6,12)
		12.9)	12.9)	12.9)	12.9)	
C1	35.9	34.8	33.7	34.3	33.6	35.9
C2	76.3	75.1	69.9	75.1	69.7	76.6
C3	35.3	34.7	34.9	34.5	34.8	35.4
C4	52.6	52.1	58.0	51.5	57.4	52.0
C6	66.9	65.5	66.7	65.2	66.3	66.6
C7	54.9	54.0	53.9	53.9	53.7	54.9
C8	27.3	25.4	25.8	25.5	25.9	27.5
C9	31.4	30.0	24.6	29.9	24.6	31.6
C10	38.0	36.6	31.1	36.6	31.2	38.2

[a] Assignations in the aromatic moeity: ^{1}H NMR: *Z*-**2a**: 7.63 (d, *J*=8.1 Hz, 2H), 7.59 (d, *J*=8.1 Hz, 2H), 7.38 (dd, *J*=7.5, 8.1 Hz, 2H), 7.26 (dd, *J*=7.5, 8.1 Hz, 2H), 7.20 (d, *J*=7.5 Hz, 1H), 7.12 (d, *J*=7.5 Hz, 1H); (*Z*+*E*)-**2b**: 8.30-8.16 (m, 8H), 7.82-7.73 (m, 8H); (*Z*+*E*)-**2c**: 8.54-8.44 (m, 4H), 8.17-8.12 (m, 2H), 8.06-7.96 (m, 6H), 7.65 (dd, *J*=7.8, 8.1 Hz, 1H), 7.64 (dd, *J*=7.8, 8.1 Hz, 1H), 7.61 (dd, *J*=7.8, 8.1 Hz, 1H), 7.51 (dd, *J*=7.8, 8.1 Hz, 1H); *Z*-**2d**: 7.50 (d, *J*=9.0 Hz, 2H), 7.49 (d, *J*=9.0 Hz, 2H), 6.93 (d, *J*=9.0 Hz, 2H), 6.83 (d, *J*=9.0 Hz, 2H), 3.79 (s, 3H) 3.77 (s, 3H). ^{13}C NMR: *Z*-**2a**: 126.4, 126.6, 126.9, 127.4, 128.7, 129.3, 143.2, 144.1; *Z*-**2b**: 123.4, 123.8, 126.4, 127.3, 146.3, 146.6, 149.6, 150.3; *E*-**2b**: 123.8, 123.9, 126.9, 127.5, 146.7, 146.8, 148.3, 148.5; *Z*-**2c**: 121.1, 121.2, 121.5, 121.6, 129.0, 129.6, 131.8, 132.8, 144.0, 144.7, 148.3, 148.9; *E*-**2c**: 121.1, 121.7 (2C), 121.9, 129.7, 132.3, 133.0, 142.1, 142.8; *Z*-**2d**: 114.3, 114.8, 127.8, 128.6, 135.3, 136.3, 159.1, 159.4. [b]Broad singlet. [c]Broad triplet. [d]ddd. [e]Broad doublet. [f]*J* (Hz) values between parenthesis.

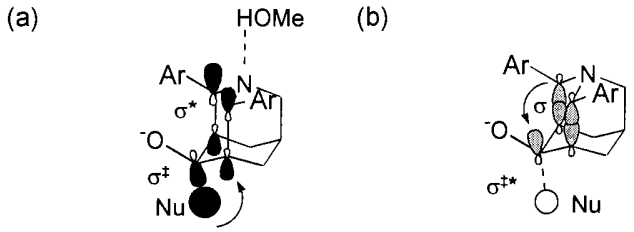
Table 2. Product distributions in the reduction of **1a-d** with $NaBH_4$ in methanol

Entry	X	σ^a	% *Z*	% *E*
1a	H	0	94	6
1b	*p*-NO_2	0.78	75	25
1c	*m*-NO_2	0.71	79	21
1d	*p*-CH_3O	-0.27	92	8

[a]Hammett substituent constants from Ref. 10.

The product distribution of the isomers was determined by integration of the H-2 signals (CHOH) in the ^{1}H-NMR spectra (Table 2). Although in **2a** and **2d** the signals of *Z*-isomer (the major product) are clear in contrast with the corresponding *E*-isomer, 2-, 3- and 1- positions are enough observable for the integral evaluation. These results show that the preferential product is the *Z*-alcohol (75–94%).

Apparently, the diasteroselectivity is influenced by the configuration of the aryls in 4- and 6- positions in the framework (steric), the electron donation from nitrogen lone pair (hyperconjugation) and the substituent remote effect in the aryls. The two possible explanations can be described according to the TS models, Ahn–Felkin (a) and Cieplak (b) outlined below.



Senda[2] claimed that the solvent effect is responsible for the preferential *zu* attack on azaadamantanone because of hydrogen-bond formation between the protic solvent and the n_N orbital, then a corresponding withdrawal of electrons from σ_{CC} orbitals. Thus, in our molecular probes, σ_{C3C4} and σ_{C1C6} would be poor electronically and in this way hyperconjugative assistance in TS and the steric effects will point toward Ahn–Felkin model. On the other way, we can suppose that the N in the congested aryls–side has less ability in complexing with the solvent and allow the electronic transfer from the lone pair through σ_{C3C4} and σ_{C1C6}, in this case Cieplak model operates in better way.

The plot in Figure 1 shows the correlation between the diastereoselectivity and the Hammett substituent constant.[9] The electron withdrawing groups as NO_2 led to a less *en* selectivity than H and *p*-OCH_3, their modulation in the charge transfer is manifested in the selectivity. At the present, we are studying these probes with different models recently proposed (Tomoda's EFOE[10] and Yadav's cation-complexation[11]).

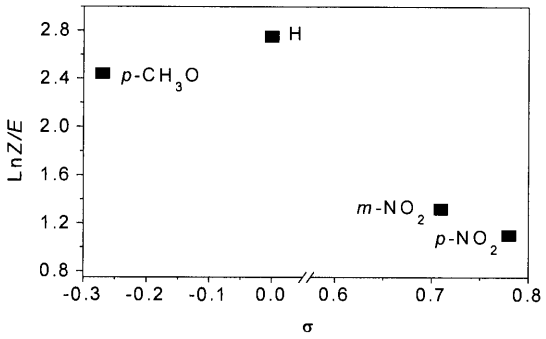


Figure 1. Plot of ln *Z*-**2**/*E*-**2** vs Hammett substituent constant (σ).

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References and Notes

1 a) C. K. Cheung, L. T. Tseng, M.-H. Lin, S. Srivastava, and W. J. le Noble, *J. Am. Chem. Soc.*, **108**, 1598 (1986). b) W. Adcock and N. A. Trout, *J. Org. Chem.*, **56**, 3229 (1991). c) W. Adcock, J. Cotton, and N. A. Trout, *J. Org. Chem.*, **59**, 1867 (1994).
2 Y. Senda, M. Morita, and H. Itoh, *J. Chem. Soc., Perkin Trans. 2*, **1996**, 221.
3 a) J. M. Hanh and W. J. le Noble, *J. Am. Chem. Soc.*, **114**, 1916 (1992), b) J. Lau, E. M. Gonikberg, J. Hung, and W. J. le Noble, *J. Am. Chem. Soc.*, **117**, 11421 (1995).
4 A. S. Cieplak, *J. Am. Chem. Soc.*, **103,** 4540 (1981).
5 a) N. T. Ahn and O. Eisenstein, *Nouv. J. Chim.***, 1**, 61 (1977) b) M. N. Paddon-Row, Y. D. Wu, and K. N. Houk, *J. Am. Chem. Soc.*, **114**, 10638 (1993).
6 B. W. Gung and M. A. Wolf, *J. Org. Chem.*, **61**, 232 (1996).
7 D. P. Becker and D. L. Flynn, *Synthesis*, **1992**, 1080.
8 Typical Procedure for the Preparation of ketones **1**: 0.746 mmol of the amino acetal **3** was dissolved in 5 mL of ethanol and 3 drops of 10% aqueous HCl. After refluxing for 20 minutes, an ethanolic solution of 4-substituted benzaldehyde (1.492 mmol) was added in hot, and the reflux continued by 24–72 h. Further treatment with 20% aqueous NaOH to pH = 8.5–9.0, the crude was extracted with chloroform (3 × 5 mL), then was dried over anhydrous sodium sulfate and evaporated in vacuo. After chromatographic purification, 4,6-diarylazaadamantanones were obtained and characterized.
9 C. Hansch, A. Leo, and R. W. Taft, *Chem. Rev.*, **91**, 165 (1991).
10 S. Tomoda and T. Senju, *Tetrahedron*, **55**, 5303 (1999).
11 V. K. Yadav, G. Senthil, and D. A. Jerayaj, *Tetrahedron*, **55**, 14211 (1999).