Diastereofacial Selection in the Conjugate Reduction of γ-Alkyl-α,β-Unsaturated Carbonyl Derivatives. Stereocontrol Dictated by Aromatic Ring–Pd Interaction

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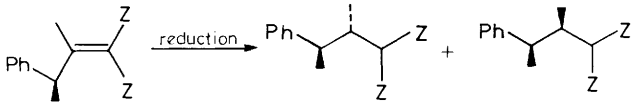
Conjugate reduction of the ethylidene-malonate (**1a**) and -malonitrile (**1b**) bearing the chiral centre at the γ-position with hydride reagents or with Li–NH_3 gives the *anti*-isomer (**2**) preferentially, while the hydrogenation with Pd–C produces the *syn*-isomer (**3**) predominantly: the *syn*-preference is due to a strong interaction between the aromatic π-system and palladium metal.

Diastereoselectivity in nucleophilic addition with organometallic compounds, free radical addition of RI, and allylation *via* photoinduced electron transfer have all been investigated using Michael acceptors bearing a chiral centre at the γ-position:[1] it is revealed that the *syn*/*anti* selectivity is dictated by the electron transfer ability of the nucleophiles and/or by the ability of Michael acceptors to receive an electron. In contrast to the Michael addition of carbon nucleophiles, there are very few examples of diastereofacial selection on Michael hydride reduction.[2] We report that the conjugate reduction of the ethylidene-malonate (**1a**) and malonitrile (**1b**) with ordinary



(**1**) **a**; Z = CO_2Et *anti*-(**2a,b**) *syn*-(**3a,b**)
b; Z = CN

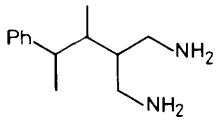
hydride reagents and under Birch conditions gives the *anti*-product (**2a,b**) predominantly, while catalytic hydrogenation on Pd-C affords the *syn*-product (**3a,b**) preferentially.

The results are summarized in the Table. Both Li–NH_3 and

Table. Michael reduction of (**1a**) and (**1b**)

Entry	Michael acceptor	Reagent and conditions	Product ratio[a] *anti*-(**2**):*syn*-(**3**)	Combined isolated yield (%)
1	(**1a**)	Li–NH_3–EtOH, −78 °C, 4 h	78:22	80
2	(**1a**)	$LiAlH_4$, ether, 0 °C, 2 h	89:11	11
3	(**1a**)	H_2/Pd–C, EtOH, 20 °C, 7 h	3:97	72
4	(**1b**)	Li–NH_3–EtOH, −78 °C, 1.5 h	91:9	44
5	(**1b**)	$LiAlH_4$, ether, 20 °C, 7 h	70:30	51
6	(**1b**)	$NaBH_4$, THF, 20 °C, 5 h	74:26	88
7	(**1b**)	L-Selectride, THF, −78→0 °C, 1 h	67:33	92
8	(**1b**)	Bu_3SnH-HMPA, 60 °C, 2 h	45:55	77
9	(**1b**)	H_2/Pd–C, EtOH, 20 °C, 8 h	23:77[b]	87[b]

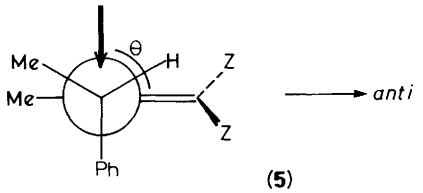
[a] The stereochemistry of (**2**) and (**3**) was determined in comparison with the authentic materials obtained by the Michael addition.[1] The isomeric ratio was determined by capillary g.l.c. (SE-30, 25m). [b] Conjugate reduction was accompanied by formation of (**4**); 69% of (**4**) and 18% of (**3b**) were obtained and the *syn*/*anti* ratio of (**4**) was 71:29; (**2b**) was not obtained. Accordingly, the ratio (23:77) is the average value of (**4**) and (**3b**).



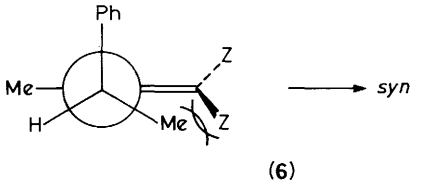
(**4**)

hydride reduction of (**1a**) produced (**2a**) preferentially (entries 1 and 2), while H_2/Pd–C reduction gave (**3a**) with very high diastereoselectivity (entry 3). The reduction of (**1a**) with $LiAlH_4$ was very sluggish, resulting in low yield. The reduction of (**1b**) with hydride reagents (entries 5—7) or with Li–NH_3 (entry 4) also produced (**2a**) predominantly. The hydride reduction of (**1b**) proceeded more rapidly and efficiently than that of (**1a**). Here again, H_2/Pd–C reduction of (**1b**) gave (**3b**) preferentially (entry 9). Slight preference for (**3b**) was observed in the reduction with tributyltin hydride–HMPA[3] (entry 8).

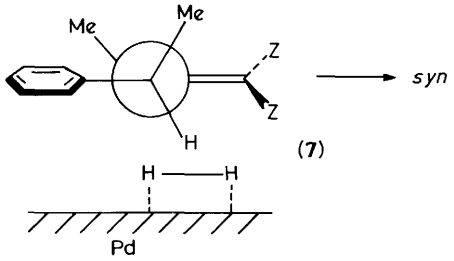
The *anti*-preference in the electron transfer reduction can be explained by the model (**5**) as previously proposed in the electron transfer conjugate addition.[1] Owing to interaction between Me and Z (**6**) is destabilized in comparison with (**5**).



(**5**)



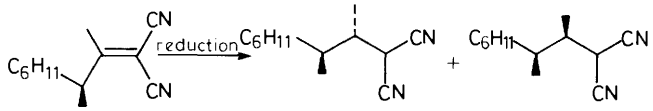
(**6**)



(**7**)

Even after an electron transfer to these two conformers has taken place, the resulting anion radical of (**5**) is more stable than that of (**6**). The protonation of (**5**) occurs from the less hindered direction indicated by the bold arrow. Contrary to expectation, nucleophilic hydride reduction produced *anti*-selectivity; carbon nucleophile Michael addition and electron transfer addition have previously exhibited the opposite diastereoselectivity.[1] There are two possible reasons for this *anti*-selective hydride reduction; (*a*) the conjugate reduction with hydride reagents may proceed through an electron transfer mechanism, or (*b*) since H^- is very small in comparison with the carbon nucleophiles, the interaction between Me and H^- observed in the attack on (**5**) from an obtuse angle ($\theta > 90°$) may be negligible.

More interestingly, the Pd–C catalyzed reduction exhibited *syn*-selectivity.* We expected that palladium metal would interact with the π-electrons of both the aromatic ring and the double bond, and hence conformation (**7**) would be most stable. The hydrogenation of (**7**) must take place from the palladium surface, leading to the *syn*-isomer. To confirm this hypothesis, we examined the hydrogenation of (**8**) with Pd–C catalysis. As expected, the *anti* product (**9**) predominated (70%) [(**9**):(**10**) = 75:25)] under the same conditions as entry 9. Hydride



(**8**) *anti*-(**9**) *syn*-(**10**)

reduction of (**8**) with L-selectride also gave (**9**) preferentially [(**9**):(**10**) = 77:23 in 97% yield]. Accordingly, it is now clear that only the Pd–C catalyzed hydrogenation of Michael acceptors bearing an aromatic ring at the γ-position exhibits *syn*-selectivity; owing to a strong interaction between the aromatic π-electrons and palladium metal.

Experimental

Reduction of (**1**) *and* (**8**).—Catalytic hydrogenation on Pd–C and the ordinary hydride reductions were carried out according to the general procedures. (**2a**) $\delta_H(CDCl_3)$ 0.83 (3 H, d, *J* 7 Hz), 1.29 (6 H, t, *J* 7 Hz), 1.31 (3 H, d, *J* 7 Hz), 2.36 (1 H, m), 2.81

* Homogeneous hydrogenations using catalysis such as $RhCl(PPh_3)_3$ and $HRh(CO)(PPh_3)_3$ were also examined, but reduction did not take place.

(1 H, m), 3.30 (1 H, d, *J* 6 Hz), 4.12 (4 H, q, *J* 7 Hz), and 7.12 (5 H, m); (**3a**); $\delta_H(CDCl_3)$ 1.01 (3 H, d, *J* 7 Hz), 1.23 (3 H, d, *J* 7 Hz), 1.25 (6 H, t, *J* 7 Hz), 2.36 (1 H, m), 2.81 (1 H, m), 3.07 (1 H, d, *J* 6 Hz), 4.08 (4 H, q, *J* 7 Hz), and 7.12 (5 H, m). Accurate mass of (**2a**) and (**3a**) (Found: *m/z* 292.1676. Calc. for $C_{17}H_{24}O_4$ *m/z* 292.1675]. (**2b**) $\delta(CDCl_3)$ 1.13 (3 H, d, *J* 7 Hz), 1.40 (3 H, d, *J* 7 Hz), 2.25 (1 H, m), 2.69—2.93 (1 H, m), 3.58 (1 H, d, *J* 6 Hz), and 7.20 (5 H, m). (**3b**) $\delta_H(CDCl_3)$ 1.38 (3 H, d, *J* 7 Hz), 1.47 (3 H, d, *J* 6 Hz), 2.25 (1 H, m), 2.69—2.93 (1 H, m), 3.25 (1 H, d, *J* 4 Hz), 7.20 (5 H, m). Accurate mass of (**2b**) and (**3b**) (Found: *m/z* 198.1156. Calc. for $C_{13}H_{14}N_2$ *m/z* 198.1157). (**9**) $\delta_H(CDCl_3)$ 0.87 (3 H, d, *J* 8 Hz), 1.17 (3 H, d, *J* 6.6 Hz), 0.91—1.79 (12 H), 2.09 (1 H, m), 3.87 (1 H, d, *J* 4 Hz). (**10**) $\delta_H(CDCl_3)$ 0.90 (3 H, d, *J* 6.6 Hz), 1.32 (3 H, d, *J* 6.6 Hz), 0.91—1.79 (12 H), 2.32 (1 H, m), and 3.70 (1 H, d, *J* 7.3 Hz). Accurate mass of (**9**) and (**10**) (Found: *m/z* 290.1598. Calc. for $C_{13}H_{20}N_2$ *m/z* 204.1626).

References

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