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Diastereoselective heterogeneous catalytic hydrogenation of Baylis–Hillman adducts

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Abstract

We describe herein our results concerning a highly diastereoselective heterogeneous hydrogenation of Baylis–Hillman adducts obtained from aromatic aldehydes. The results obtained are complementary to those already described for homogeneous catalytic hydrogenation reactions.

In the last few years the Baylis–Hillman reaction has attracted the attention of many organic chemists,[1] because it is a simple and straightforward method to generate a new C–C σ bond. Moreover, this reaction provides access to multifunctional compounds with high synthetic potential.[2]

In the course of our research directed towards the total synthesis of some pheromones we found it necessary to control the relative configuration of a Baylis–Hillman adduct in a heterogeneous catalytic hydrogenation reaction. There are in the literature several reports[3–7] concerning the utilization of homogeneous catalyst for the hydrogenation reaction of these adducts. In contrast, there is only one report[8] concerning the use of heterogeneous catalyst in a hydrogenation reaction of this type of adduct. Unfortunately, this report provides little information regarding the diastereoselectivity attained in the process.

We are intrigued by this fact and in order to investigate it further we decided to effect a study on the diastereoselectivity of this reduction reaction. As model for our study we have used the Baylis–Hillman adducts originating from aromatic aldehydes that were available in our laboratory.[9]

To evaluate a possible interaction between the hydroxyl group and the catalyst surface in the preferential facial addition of hydrogen onto the double bond, we decided to start the hydrogenation reactions with an unprotected hydroxyl group (Scheme 1).

Table 1 summarizes the results obtained with the hydrogenation reactions,[10] with unprotected Baylis–Hillman adducts.

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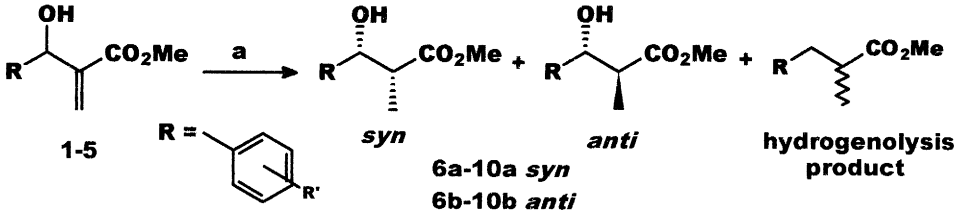


Scheme 1. Reagents and conditions: a. H_2, Pd/C 5%, 1 atm, AcOEt, rt, 3 h

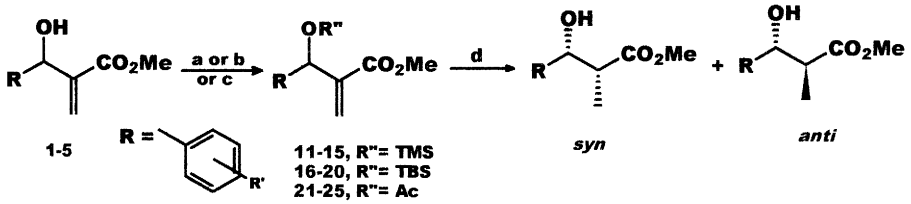
Table 1
Results of heterogeneous catalytic hydrogenation reaction with Baylis–Hillman adducts

Entry	Adduct	*syn:anti* ratio[a] (6-10)	Hydrogenolysis ratio[b]	Yield (%)[c]
1	1, R'=H	50:50	14%	85
2	2, R'= OCH_3	25:75	< 5%	99
3	3, R'= Cl	33:67	17%	99
4	4, R'= NO_2[11]	50:50	-[d]	66
5	5, R'= 3,4-CH_2OCH_2-	28:72	-[d]	98

a. the diastereoisomeric ratio was determined by capillary CG (HP5 column) of the crude reaction products and by ^{1}H NMR (500MHz).[15] The diastereoisomers identification was done by measuring the coupling constants of CHOH and CHCH$_3$;[12] **b**. determined by capillary CG (HP5 column) and by ^{1}H NMR (500 MHz); **c**. isolated products; **d**. no hydrogenolysis products were detected.

For the majority of the adducts tested (Table 1, entries 1–5) it was possible to achieve a modest level of diastereoselectivity. With adduct **2** (entry 2) we have attained the highest level of diastereoselection for this series. In cases where diastereoselectivity is observed, the *anti* product is always the major one.

In order to evaluate the possible influence of a protecting group on the facial preference of addition, we repeated the same reduction procedure introducing an additional modification. The hydroxyl group of all adducts were protected as trimethylsilyl (**11**–**15**) and *tert*-butyldimethylsilyl ethers (**15**–**20**) and also as acetate esters (**20**–**25**). Each derivative was submitted to the hydrogenation reaction conditions[10] (Scheme 2).



Scheme 2. Reagents and conditions: a. TMSCl, THF, Et_3N, 12 h; b. TBSCl, imidazole, DMF, rt, 12 h;[13] c. AcCl, Et_3N, CH_2Cl_2, 3 h; d. H_2, 1 atm, Pd/C 5%, AcOEt, rt 30 min–3 h

The results obtained for the hydrogenation of the adducts with a protected hydroxyl group as silylethers and acetyl esters are summarized in Table 2.

For adducts protected as silyl ethers (Table 2, entries 1–10) there was a dramatic change both in the degree of the diastereoselectivity and in the preferential diastereoisomer formed. In all cases it was possible to achieve a high degree of diastereoselectivity compared to that obtained for the non-protected adducts. However, for the adducts protected as acetate esters the diastereoselectivity achieved is very poor. For this series the *anti* isomer is favored and the results are comparable to those obtained for the non-protected adducts (Table 1, entries 1–5).

For all silylated adducts the preferential diastereoisomer formed was that where the OH and the methyl groups are in a *syn* relationship. The coupling constant (J) for the *syn* diastereoisomer after deprotection

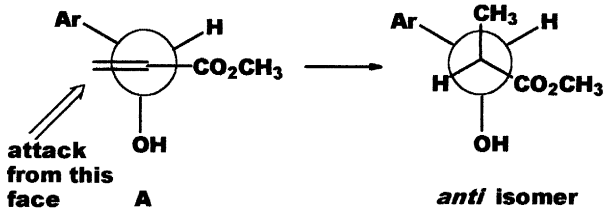
Table 2
Hetereogeneous catalytic hydrogenation of *O*-silylated Baylis–Hillman adducts

Entry	Adduct	Protection yield(%)[a]	*syn:anti* ratio[b]	Yield (%)[c]
1	11, R'=H, R"=TMS	75	85:15	78
2	12, R'= OCH_3, R"= TMS	82	88:12	82
3	13, R'= Cl, R"= TMS	99	84:16	50
4	14, R'= NO_2[11], R"= TMS	70	87:13	70
5	15, R'= 3,4-CH_2OCH_2, R"= TMS	85	85:15	75
6	16, R'=H, R"=TBS	80	91:9	92
7	17, R'= OCH_3, R"= TBS	88	95:5	80
8	18, R'= Cl, R"= TBS	70	83:17	85
9	19, R'= NO_2[11], R"= TBS	80	94:6	82
10	20, R'= 3,4-CH_2OCH_2, R"= TBS	77	91:9	92
11	21, R'=H, R"=Ac	82	25:75	65[d]
12	22, R'= OCH_3, R"= Ac	78	50:50	70[d]
13	23, R'= Cl, R"= Ac	80	37:63	63[d]
14	24, R'= NO_2,[11] R"= Ac	76	40:60	78[d]
15	25, R'= 3,4-CH_2OCH_2, R"= Ac	89	30:70	60[d]

a. Isolated and purified products; **b.** diastereoisomeric ratio determined by capillary CG (HP5 column) and by ^{1}H NMR (500MHz),[12,15] **c.** isolated products; d. hydrogenolysis products has also been detected (30-40%).

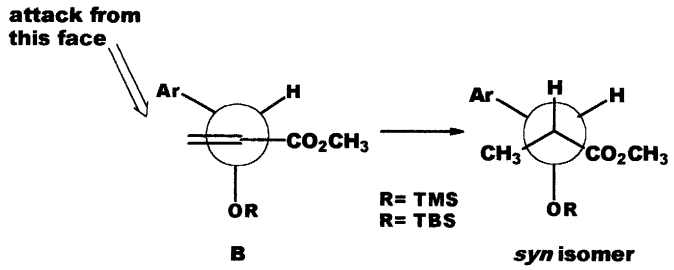
varies between 4–5 Hz and for the *anti* between 8–9 Hz. These values are completely in accordance with that described by Heathcock[12] for identical systems.

The stereochemical outcome of these hydrogenations reactions can be rationalized based on a conformation in which the aryl substituent occupies the inside position and the carbon–oxygen bond is parallel to the π bond.[14,16] This reduces any destablizing interaction between the aryl substituent and the carboxyl group. In the case of the free alcohols (Table 1, entries 1–5) this arrangement allows the delivery of hydrogen from the same face of hydroxyl group (A) and leads to the preferential formation of the *anti* product (Scheme 3).



Scheme 3.

In the case of the silyl ethers (Table 2, entries 1–10), a similar conformation, combined with the attack from the opposite face (B), yields the observed stereoisomers (Scheme 4).



Scheme 4.

The reduction of the adducts protected as acetyl esters (Table 2, entries 11–15) should be occurring by the same model proposed above for the non-protected adducts. Apparently the acetyl group exerts little or no influence in the preferential facial addition of hydrogen onto the double bond.

These models have permitted us to propose an explanation for the diastereoselectivity attained in all conditions. The reactions are very reproducible and the diastereoisomers could be easily separated by conventional column chromatography. The preferential diastereoselectivity obtained for the silylated adducts is the *opposite* of that attained in homogenous catalytic hydrogenation conditions of this type of adduct and in our point of view these results are complementary to them. This simple and efficient methodology associated with the readily chromatographic separation of the diastereoisomers provides a new entry to products which are equivalent to those obtained from an aldol condensation reaction between an aldehyde and a propionate derivative. Additional studies focusing on the generalization of this strategy for other Baylis–Hillman adducts are ongoing in our laboratory.

Acknowledgements

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10. Standard experimental protocol: To a suspension of Pd–C 5% (5 mol%) in ethyl acetate (3mL) was added under nitrogen atmosphere a solution of the adduct (0.1–0.3 mmol) in 3 mL of ethyl acetate. Then the atmosphere reaction was changed for hydrogen and the reaction was maintained for 2–3 h under stirring at room temperature (for the acetylated adducts the reaction was stopped after 30 min). After that the reaction was filtrated over a pad of Celite and the solvent was removed under reduced pressure.
11. In the hydrogenation reaction of the double bond of the nitro derivatives we have observed they were totally reduced to the amine. However the diastereoselectivity achieved is comparable with the other examples.
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15. Spectra data: (^{1}H NMR, 500 MHz, $CDCl_3$) δ **6** *syn*: 1.06 (d, J=6.9 Hz, 3H), 2.54–2.80 (m, 1H), 3.55 (s, 3H), 4.98 (d, J=4.3 Hz, 1H), 7.24–7.26 (m, 5H); **6** *anti*: 0.90 (d, J=7.3 Hz, 3H), 2.54–2.80 (m, 1H), 3.63 (s, 3H), 4.65 (d, J=8,5 Hz, 1H), 7.24–7.26 (m, 5H); **7** *syn*: 1.13 (d, J=6.9 Hz, 3H), 2.58–2.82 (m, 1H), 3.62 (s, 3H), 3.78 (s, 3H), 4.97 (d, J=5.1 Hz, 1H), 6.85–6.88 (m, 2H), 7.23 (d, J=8.7 Hz, 2H); **7** *anti*: 0.95 (d, J=6.9 Hz, 3H), 2.58–2.82 (m. 1H), 3.71 (s, 3H), 3.78 (s, 3H), 4.67 (d, J=8.7 Hz, 1H), 6.85–6.88 (m, 2H), 7.23 (d, J=8.7 Hz, 2H); **8** *syn*: 1.11 (d, H=6.9 Hz, 3H), 2.58–2.82 (m, 1H), 3.64 (s, 3H), 5.02 (d, J=4.3 Hz, 1H), 7.25–7.34 (m, 4H); **8** *anti*: 0.97 (d, J=7.3 Hz, 3H), 2.58–2.82 (m, 1H), 3.69 (s, 3H), 4.70 (d, J=8.4 Hz, 1H), 7.25–7.34 (m, 1H); **9** *syn*: 1.15 (d, J=7.1 Hz, 3H), 2.70–2.82 (m, 1H), 3.64 (s, 3H), 4.94 (d, J=4.6 Hz, 1H), 6.64–6.67 (dd, J= 8.5 and 2.7 Hz, 2H), 7.12 (d, J=7.9 Hz, 2H); **9** *anti*: 0.97 (d, J=7.4 Hz, 3H), 2.70–2.82 (m, 1H), 3.73 (s, 3H), 4.64 (d, J=8.7 Hz, 1H), 6.64–6.67 (dd, J=8.5 and 2.7 Hz, 2H), 7.12 (d, J=7.9 Hz, 2H); **10** *syn*: 1.13 (d, J=7.1 Hz, 3H). 2.70–2.78 (m, 1H), 3.65 (s, 3H), 4.96 (d, J=4.3 Hz, 1H), 5.94 (s, 2H), 6.84 (s, 3H); **10** *anti*: 0.97 (d, J=7.1 Hz, 3H), 2.70–2.78 (m, 1H), 3.04 (broad s, exchangeable with D_2O), 3.72 (s, 3H), 4.65 (d, J=8.7 Hz, 1H), 5.94 (s, 2H), 6.84 (s, 3H).
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