Pergamon

Tetrahedron Letters, Vol. 37, No. 52, pp. 9293-9296, 1996
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0040-4039/96 \$15.00 + 0.00

PII: S0040-4039(96)02198-3

Asymmetric Dihydroxylation of Chiral γ-Amino α,β-Unsaturated Esters: Turning the Mismatched into the Matched Case via Protective Group Tuning

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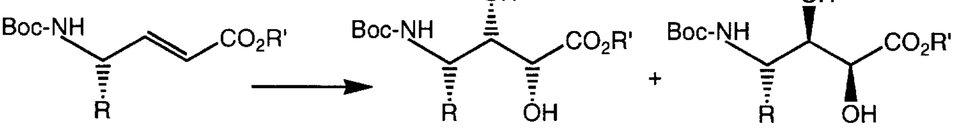
Abstract: Optimal stereoselectivities in the OsO_4-catalyzed dihydroxylation of chiral γ-amino α,β-unsaturated esters are achieved by the proper choice of the protective groups at nitrogen [*t*-butoxycarbonyl (Boc) versus dibenzyl] and the correct choice of the chiral ligand of the catalyst (AD-mix-α versus AD-mix-β). Copyright © 1996 Elsevier Science Ltd

It is well known that prochiral substrates such as aldehydes, ketones, alkenes or dienes having at least one stereogenic center react with achiral reagents or catalysts to provide two possible diastereomeric products. Ideally, variation of reagents, solvents or reaction conditions allows access to either diastereomer on an optional basis. If 1,n-asymmetric induction is poor inspite of such efforts, the principle of double stereodifferentiation using chiral reagents or catalysts offers a way out of the synthetic dilemma.[1] Nevertheless, if the desired diastereomeric product arises from the ''mismatched'' combination, the overall stereoselectivity may be mediocre. In this paper we show that protective group tuning[2] can be a suitable instrument with which to turn the mismatched into the matched case, thereby leading to optimal levels of stereoselectivity.

Upon reacting the N-Boc-protected γ-amino α,β-unsaturated esters **1**[3] with the modified Sharpless AD-mix-α,[4] the expected (2R,3S,4S)-configurated esters **2** were obtained with 94 - 97% stereoselectivity (Table 1). The AD-mix-β afforded the opposite diastereomers **3**, albeit with considerably lower stereoselectivity.[5] Thus, the AD-mix-β represents the mismatched case.



1 **a** $R = CH_3$; $R' = C_2H_5$
b $R = PhCH_2$; $R' = CH_3$
c $R = CH(CH_3)_2$; $R' = C_2H_5$
d $R = CH_2CH(CH_3)_2$; $R' = C_2H_5$

2 (2R,3S,4S)

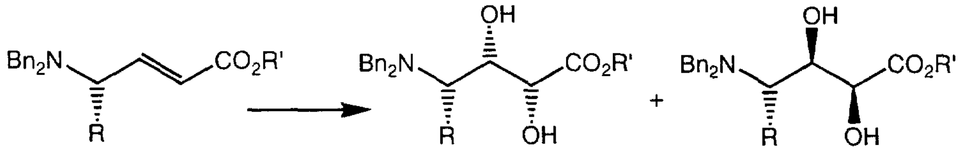
3 (2S,3R,4S)

Table 1. Asymmetric Dihydroxylation of Esters **1** and **4**

Ester	Catalyst system	Reaction time (d)	% Conversion (% isolated)[a]	**2** : **3** or **5** : **6**	
1a	AD-mix-α	1.5	95 (64)	97 : 3	matched
1b	AD-mix-α	0.8	93 (-)	94 : 6	
1c	AD-mix-α	16	80 (-)	95 : 5	
1d	AD-mix-α	5	99 (75)	95 : 5	
1a	AD-mix-β	1.5	90 (63)	9 : 91	mismatched
1b	AD-mix-β	0.8	84 (-)	11 : 89	
1c	AD-mix-β	16	73 (48)	37 : 63	
1d	AD-mix-β	5	99 (88)	14 : 86	
4a	AD-mix-α	4	79 (-)	92 : 8	mismatched
4b	AD-mix-α	10	74 (-)	88 : 12	
4c	AD-mix-α	10	7 (-)	72 : 28	
4d	AD-mix-α	11	15 (-)	75 : 25	
4a	AD-mix-β	4	68 (-)	6 : 94	matched
4b	AD-mix-β	10	49 (-)	14 : 86	
4c	AD-mix-β	10	21 (-)	5 : 95	
4d	AD-mix-β	11	25 (-)	5 : 95	

[a] Yield of major diastereomer; in cases marked by (-), the diastereomers were not separated.

Upon subjecting the N,N-dibenzyl analogs **4**[3] to the AD-mixes, the diastereomers expected on the basis of the Sharpless "mnemonic device" were again obtained (Table 1). However, the extent of the stereoselectivity turned out to be rather different. Indeed, in the N,N-dibenzyl series the AD-mix-α represents the mismatched case. Thus, upon going from the Boc- to the N,N-dibenzyl protected substrates (**1** to **4**, respectively), the mismatched combination turns into the matched case, leading to the highest levels of stereoselectivity in the production of (2S,3R,4S)-configurated products (cf. **6**).



4 **a** R = CH_3; R' = C_2H_5
b R = $PhCH_2$; R' = CH_3
c R = $CH(CH_3)_2$; R' = C_2H_5
d R = $CH_2CH(CH_3)_2$; R' = C_2H_5

5

6

It is instructive to compare the above results with those obtained using the traditional achiral catalyst system OsO_4/N-methylmorpholine-N-oxide (NMO). In the Boc-series poor stereoselectivities in slight favor of the (2R,3S,4S)-configurated diastereomers **2** were observed (**2a** : **3a** = 51 : 49; **2b** : **3b** = 59 : 41; **2c** : **3c** = 81 : 19; **2d** : **3d** = 60 : 40; in all cases >96% conversion). Low facial bias has been reported previously in related reactions of allylic amine derivatives.[6] The sense of diastereoselectivity in our reactions is the same as in the well studied cases of stereoselective dihydroxylation reactions of allylic alcohols and ethers, for which three somewhat different explanations have been proposed:[7] Kishi-model, Stork-Houk-model, Vedejs-model. Formally, all three models, when applied to the present reactions of esters **1**, explain the observed sense of diastereoselectivity. Since we obtained crystals in the case of compound **1c**, an X-ray structural analysis was performed (Fig. 1).[8] Accordingly, atoms N, C6, C10, C11, C12 and O4 are essentially in one plane. This geometry corresponds perfectly to the ''HO-inside'' feature of the Stork-Houk-model (Fig. 2). Thus, the ground state geometry may well correspond to the transition state geometry.

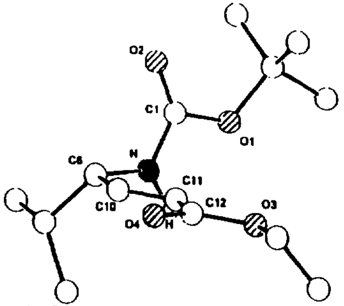


Fig. 1. Crystal structure of **1c**.
Selected bond lengths [Å] and angles [°]:
C10-C11 1.29(1), N···O4* 2.979(7),
N-C6-C10-C11 0(1), C10-C11-C12-O4 -2(1).

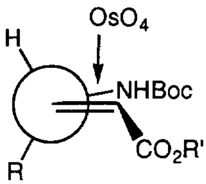


Fig. 2. Stork-Houk-model applied to nitrogen analogs **1**

Finally, the OsO_4/NMO-induced dihydroxylation of the N,N-dibenzylamino esters **4** in the absence of chiral ligands was also studied. In this case better diastereoselectivities resulted, but the sense of stereoselectivity turned out to be opposite to that observed in the N-Boc-series [**5a** : **6a** = 24 : 76; **5b** : **6b** = 8 : 92; **5c**/**6c** (no diol was formed);[9] **5d** : **6d** = 13 : 87; conversion being 100%, 65%, 0% and 99%, respectively]. In the absence of detailed mechanistic studies it is currently difficult to explain these results.

Whatever the true mechanism(s) may be, reversal of diastereoselectivity results upon going from the Boc to two benzyl protective groups at nitrogen. This is the reason why protective group tuning[2] can be used to transform the mismatched into the matched situation in the present cases of asymmetric dihydroxylation using the Sharpless AD-mixes.[10]

Acknowledgement

We thank K. B. Sharpless and M. S. VanNieuwenhze for useful comments.

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8. X-ray analysis of **1c**: $C_{14}H_{25}NO_4$, $M_r = 271.4$ g mol^{-1}, colourless crystals, crystal size 0.18 x 0.46 x 0.49 mm, a = 10.055(1), b = 9.923(1), c = 16.847(1) Å, V = 1680.9 Å^3, T = 293 K, $d_{cal} = 1.07$ g cm^{-3}, $\mu = 6.03$ cm^{-1}, F(000) = 592, Z = 4, orthorhombic, space group $P2_12_12_1$ [No. 19], Enraf-Nonius CAD4 diffractometer, $\lambda = 1.54178$ Å, scan mode ω-2θ, 2014 measured reflections (+h,+k,+l), $[(\sin\theta)/\lambda]_{max} = 0.63$ Å^{-1}, 1991 independent reflections, 1595 observed reflections $[I \geq 2\sigma(I)]$, structure solved by direct methods (SHELXS-86, Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467-473), final refinement by least-squares (GFMLX, a modified version of ORFLS, Busing, W. R.; Martin, K. O.; Levy, H. A. *Report ORNL-TM-305*, Oak Ridge National Laboratory, Oak Ridge, TN, U.S.A. 1962), H-atoms calculated and kept fixed in the final refinement stages (H atom attached to N found and refined isotropically), R = 0.087, $R_w = 0.106$ for 177 refined parameters $[w = 1/\sigma^2(F_0)]$, residual electron density 0.34 eÅ^{-3}. Atomic coordinates and e.s.d.'s have been deposited at the Cambridge Crystallographic Data Centre.
9. In a very sluggish reaction only 17% of **4c** reacted, leading to an unidentified product.[3b]
10. Typical procedure and assignment of configuration: The mixture of an ester **1** (0.1 mmol) and the Sharpless[4] AD-mix-α (Aldrich) (140 mg) modified by additional $(DHQ)_2PHAL$ (3.1 mg) and potassium osmate(VI) (0.3 mg) in *tert*-butanol (1 ml) and H_2O (1 ml) is stirred at room temp. (reaction time: see Table 1). The mixture is treated with Na_2SO_3 (0.2 g). After 0.5 h ethyl acetate (10 ml) is added and the org. phase separated and washed twice with 1 M $KHSO_4$ solution (10 ml) and 5% $NaHCO_3$. The org. phase is filtered through silica gel and dried over $MgSO_4$. Further purification of **2** is possible by chromatography over silica gel (hexane/ethyl acetate 4 : 1). The stereochemical assignments of **2**/**3** and **5**/**6** were made by X-ray structural and NMR analyses.[3b]

(*Received in Germany* 30 *October* 1996; *accepted* 6 *November* 1996)