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Synthesis of 1,2-Aminoalcohols by Ti(IV)-Catalyzed Photohydroxymethylation of Chiral Aldimines

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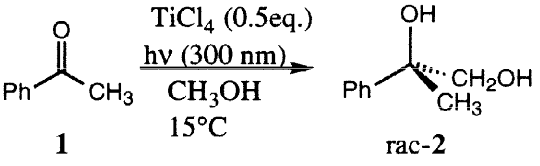
Abstract. *The N-(α-phenylethyl) alkylated aldimines* ***3a-c*** *are conveniently hydroxymethylated with moderate diastereoselectivities by means of irradiation in methanolic solution in the presence of titanium(IV)chloride.*

Photochemical hydroxymethylation of ketones has been studied by Sato et al. in detail for a series of substrates[1] and applied in a two-step synthesis of the well-known pheromone *frontalin*.[2] The authors used titanium(IV)chloride for the activation of methanol. Alternatively, α,β-unsaturated carbonyl compounds can be photochemically hydroxymethylated in the presence of triplet sensitizers[3] or by direct excitation[4,5] of the substrate in methanol. Imines[6] as well as iminium cations[7] can be likewise transformed into β-amino alcohols by excitation of the substrate or by use of titanium(IV)chloride as electron transfer mediator.[8] The latter version is a potentially interesting reaction for the stereoselective synthesis of chiral β-amino alcohols[9] from chiral or prochiral imines. By applying enantiomerically pure imines[10] from the corresponding amines and prochiral aldehydes, we envisaged the preparation of N-alkylated amino alcohols which could be N-dealkylated to give chiral β-aminoalcohols. We determined the optimal reaction conditions for the $TiCl_4$-mediated hydroxy-methylation using acetophenone (**1**) as the substrate. The maximum yield (88%) of the *vic*-diol *rac*-**2** was obtained with 0.5 equivalents of $TiCl_4$ in a 200 molar excess of methanol and irradiation at 300 nm (phosphor-coated mercury low pressure lamps). Reaction progress can be followed by UV/Vis spectroscopy: the initial strong absorption at ca. 240 nm is reduced during irradiation and a new weak absorption at λ_{max}= 362 nm evolved. Additionally, a colored species is formed which is not photochemically reactive, i.e. irradiation at λ > 350 nm did not lead to any conversion. We suggest a Ti(IV)-diol complex to be responsible for this deep blue intermediate which can be used as an indicator for the progress of the hydroxymethylation. Alternatively $Ti(OiPr)_2Cl_2$ or titanocene dichloride could be used as electron transfer mediator. In order to suppress side-reactions induced under the acidic conditions, sodium methoxide could be added. Reducing the amount of methanol below ca. 100 mol-equivalents led to a strong decrease in chemical yields.



1

rac-2

As chiral auxiliary for the imine experiments *(S)*-ß-phenylethylamine was used. The enantiomerially pure imines were synthesized from the corresponding aldehydes by standard condensation conditions.[10] The starting materials **3a-c** were purified by distillation or crystallization as the pure E-diastereoisomers (as determined by NOE spectroscopy). In contrast to the conditions above, the photoinduced hydroxymethylation had to be performed in the presence of 2 equivalents of $TiCl_4$ in order to enable complete conversion of the starting materials.

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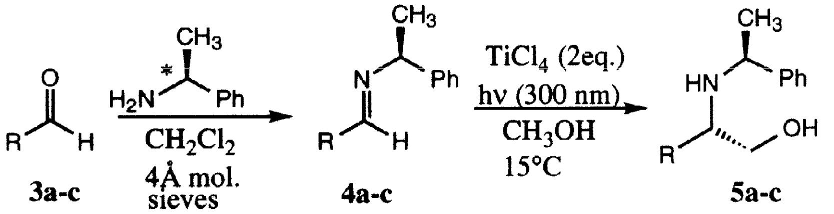
After irradiation of the chiral aldimines **4a-c** for 17-24 hours and aqueous working up, the ß-aminoalcohols **5a-c** were isolated as mixtures of diastereoisomers. No asymmetric induction was observed for the acetaldehyde derivative **4a**, whereas the pivaldehyde substrate **4c** and especially the benzaldehyde substrate **4b** gave moderate diastereoselectivities up to 80%. The yields for purified products were low (12-18% after distillation), but could be scaled up to ca. 50% by continuous extraction of the products from the crude reaction mixture. X-ray structure analysis of **5c** revealed the *like*-configuration[11] of the main diastereoisomer (2*S*,4*S*). Catalytic hydrogenation of **5a-c** following literature procedures[12] led to the corresponding N-deprotected 1,2-aminoalcohols.



R =
a: Me d.r.= 50:50
b: Ph d.r.= 80:20
c: tBu d.r.= 73:27

References and Notes

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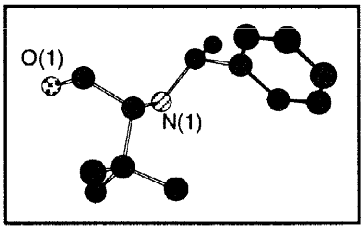
11. The crystals of **5c** ($C_{14}H_{23}NO$, $[\alpha]^{20}_D$= -52.9° (MeOH, c= 1), M = 221.33, from CH_2Cl_2) are monoclinic, space group $P2_1$, a = 794.6(2), b = 2751.6(8), c = 621.5(9) pm; β= 92.35(2)°; V = 1357.7(6)x10^6 pm^3; Z = 4; d_{calc} = 1.083 g/cm^3. Data collection: Enraf-Nonius-CAD4 diffractometer, Mo-K_α, graphite monochromator, Wyckoff-scan, theta range [°] : 1.48-26.9, crystal dimensions: 0.55 x 0.50 x 0.45 mm; no. refl. measd.: 3018, no. unique refl.: 3007, no. refl. $F>3\sigma(F)$: 2265; R, R_w: 0.071, 0.099. Program used: SHELXTL-93. Further details of the crystal structure investigation may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ (UK) on quoting the full journal citation.



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