Diastereoselective Hydrogenation of Methyl 2-[α-(Methoxycarbonylamino)-benzyl]acrylate Catalyzed by Ru(II) or Rh(I) Complexes[1]

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Synopsis. The title compound was prepared and hydrogenated by using a Ru(II)- or Rh(I)-phosphine catalyst precursor with excellent *anti*-selectivity, the results indicating that a ligating group, $NHCO_2Me$, may direct the addition of hydrogen to an olefinic diastereoface proximate to this group which binds the catalyst.

Recently, highly anti-selective preparation of the Aldol-type α-substituted β-hydroxy esters has been reported[2] via diastereoselective hydrogenation of α-(hydroxyalkyl)acrylates, and the selectivity stems from the hydroxyl-directed olefin hydrogenation of these chiral allylic alcohols.[3]

We report here that a ligating group, $NHCO_2Me$ in an allylic position of certain olefinic substrates, can bind the catalyst and direct effectively addition of hydrogen from one olefinic diastereoface of the molecule.

Very recently, Brown et al.[4] have reported the same directed hydrogenation of N-substituted α-(aminoalkyl)acrylates closely related to the present substrate, even with the kinetic resolution by using a chiral rhodium(I)–phosphine complex.

Results and Discussion

Methyl 2-[α-(methoxycarbonylamino)benzyl]acrylate (**1**) was readily prepared from methyl benzylidenecarbamate[5] and methyl acrylate (Eq. 1).

$$PhCH{=}NCO_2Me + H_2C{=}CHCO_2Me \xrightarrow{DABCO} PhCH(NHCO_2Me)C(=CH_2)CO_2Me \quad (1)$$

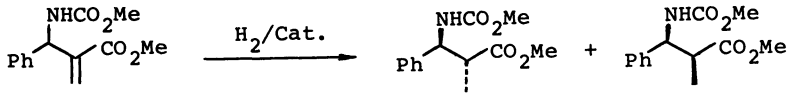
We have found that the amine-catalyzed reaction of acrylates with the imine compound is much faster than that with common aldehydes[6] at room temperature in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to give **1** in ca. 80% yield.

Acrylate **1** thus obtained was hydrogenated under various conditions by using 1 mol% of $Ru(OCOCF_3)_2(PPh_3)_2$ (**2**) or $[Rh(cod)(dppe)]^+ClO_4^-$ (**3**) as a catalyst precursor. The Ru(II) complex **2** was prepared by a reported procedure with slight modification.[7] All data for conversion and selectivity of the present hydrogenation of **1** are given in Table 1.

Hydrogenation of **1** was markedly dependent on the solvent used, less polar solvent such as dichloromethane, benzene or THF being found to behave either inhibitive or a little less selective (Entries 1—3, 8 and 9).

Methanol was generally the best solvent. Hydrogen pressure also played a crucial role for acceptable rate of hydrogenation (at 25 °C in two days) and 30 atm or above of hydrogen pressure was necessary for both catalysts **2** and **3** (Entries 4—6 and 10) or $[Rh(cod)(dppb)]^+ClO_4^-$ (**5**) (Entries 11 and 12). Thus, under selected conditions, excellent diastereoselective hydrogenation was achieved in two cases (99.1% anti

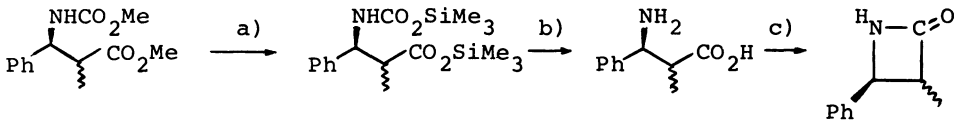
Table 1. Hydrogenation of Methyl 2-[α-(Methoxycarbonylamino)benzyl]acrylate (**1**)



1 **4a** (anti) **4b** (syn)

Entry	Catalyst[a] (1 mol%)	Solvent (5 mL)	H_2 atm	Temp °C	Time h	Conversion[b] %	Selectivity[c] anti/%
1	**2**	CH_2Cl_2	30	50	33	0	
2	**2**	PhH	30	50	34	8	
3	**2**	THF	30	50	48	40	58.3
4	**2**	MeOH	30	25	65	100	99.1
5	**2**	MeOH	5	25	48	8	
6	**2**	MeOH	10	25	48	50	87.5
7	**2**	MeOH	75	25	40	100	97.9
8	**3**	CH_2Cl_2	30	25	48	30	98.9
9	**3**	THF	30	25	48	99	95.0
10	**3**	MeOH	30	25	40	100	98.0
11	**5**	MeOH	30	25	17	100	97.0
12	**5**	MeOH	10	25	16	20	
13	**6**	MeOH	10	25	3	100	30.3—35.7

a) Substrate **1** (1 mmol, 0.2 M) was used. b) GLC analysis (Silicone DC-550, 3 m×3 mm, at 200 °C). c) Determined by capillary GLC (HR-20M, 30 m×0.2 mm, at 200 °C).



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Scheme 1. a) 2 Me_3SiI/MeCN, Δ. b) Silica gel/MeOH. c)  I^-/Et_3N/MeCN, Δ.

in Entry 4 and 98.0% anti in Entry 10, respectively).

As is seen in Entry 13, 5% palladium on charcoal (**6**) was active enough for complete hydrogenation of **1** under 10 atm of hydrogen in 3 h, to result in low but reverse selectivity.

Since stereochemistry of the diastereomeric hydrogenation products **4** was hardly determined on the basis of coupling constants of vicinal protons (5.9 and 6.4 Hz, respectively), they were converted to the corresponding 2-azetidinone derivatives in the following manner: Two samples of **4** obtained from Entries 10 and 13 were independently converted into 3-methyl-4-phenyl-2-azetidinone (**7**) by unambiguous three-step procedures as depicted in Scheme 1.

A sample of **4** from Entry 10 (diastereomer ratio=50:1) afforded *trans*-**7** in exclusive preference (trans:cis=70:1), indicating that the present hydrogenation of **1** proceeded with anti-selectivity.

A plausible explanation of the observed selectivity could derive from the presence of a ligating $NHCO_2Me$ group in **1**, which directs efficiently the attack of the hydrogenation catalyst, Ru(II) or Rh(I)/H_2/MeOH, on one diastereoface of the molecule proximate to the directing group.

It should be noted that an *N*-tosylated analog of **1**[8] was found to be very reluctant to the hydrogenation under conditions employed.

Furthermore, the alkyl analogs of **1**, i.e. methyl (**8**), isopropyl (**9**), isobutyl (**10**), and *t*-butyl (**11**) instead of phenyl group in **1**, were prepared (see **Experimental**). However, these analogs were found, at the present time, to undergo hydrogenation under the comparable conditions with much inferior anti-selectivity (54—93%).

Experimental

General Comments. All boiling and melting points are uncorrected. ^1H and $^{13}C\{^1H\}$ NMR spectra were obtained on a JEOL FX-90Q spectrometer with Me_4Si as an internal standard in $CDCl_3$. IR spectra (mostly neat) were recorded on JASCO IRA-2 spectrophotometer.

Catalyst Precursors. $Ru(OCOCF_3)_2(PPh_3)_2$ (**2**)[7], [Rh(dppe)(cod)]$^+ClO_4^-$ (**3**)[9] (dppe=1,2-bis(diphenylphosphino)ethane, cod=1,5-cyclooctadiene), and [Rh(dppb)(cod)]$^+ClO_4^-$ (**5**)[9] (dppb=1,4-bis(diphenylphosphino)butane) were prepared according to the reported procedures, respectively. Complex **2** was prepared by the reaction of $RuCl_2(PPh_3)_3$ with $AgOCOCF_3$ in acetone.

Preparation of Methyl 2-[α-(Methoxycarbonylamino)benzyl]acrylate (1). Methyl benzylidenecarbamate[5] (7.23 g, 44 mmol) and DABCO (1.00 g, 9 mmol, 20 mol%) were dissolved in methyl acrylate (5 mL) and the mixture was stirred overnight at room temperature. Excess acrylate was removed by evaporation and crystalline materials remained were dissolved in $CHCl_3$ (150 mL). The $CHCl_3$ solution was washed with 3 M† HCl, aq $NaHCO_3$, and water to remove DABCO, and dried ($MgSO_4$). Solvent was removed and fairly clean product (80% yield) was recrystallized (hexane-$CHCl_3$) to give analytically pure **1**: Mp 120—121 °C; ^1H NMR (90 MHz) δ=3.67 and 3.70 (s, MeO×2), 5.67 (br. s, NH and CH-N), 5.91 (br. s, =CH), 6.37 (d, *J*=0.9 Hz, =CH), and 7.28 (br. s, Ph). IR (KBr) 1715 and 1690 cm^{-1}; Found: C, 62.49; H, 6.01; N, 5.53%. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62%.

Preparation of Methyl 2-[α-(Methoxycarbonylamino)alkyl]acrylates (8—11). In a typical reaction, methyl (1-ethoxyethyl)carbamate (2.50 g, 17 mmol), obtained from acetaldehyde diethyl acetal and methyl carbamate, and methyl 3-(dimethylamino)propionate (2.22 g, 17 mmol) were treated with 2 equiv. of lithium diisopropylamide (LDA) (40 mmol) in hexane-THF (1:2, 75 mL) at −78 °C for 15 min.[10] The whole mixture was allowed to warm up to 0 °C and stirred for additional 2 h. Usual workup and removal of the solvents afforded a precursor of the requisite acrylate.

The crude precursor (17 mmol) was treated overnight with excess MeI (90 mmol) in MeOH (5 mL) and the resulting ammonium salt was then treated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (20 mmol) in acetone (15 mL). Workup and distillation as usual gave methyl 2-[α-(methoxycarbonylamino)ethyl]acrylate (**8**) (1.40 g, 43% overall yield): Bp 82—84 °C/2 Torr††; ^1H NMR δ=1.35 (d, *J*=7 Hz, Me), 3.65 and 3.77 (s, MeO×2), 4.60 (m, CH), 5.10 (br. d, NH), 5.76 (s, =CH), and 6.17 (d, *J*=0.9 Hz, =CH); IR (neat) 1715 and 1695 cm^{-1}; Found: C, 51.39; H, 7.30; N, 7.31%. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48%.

In exactly the same manner as above, isopropyl (**9**), isobutyl (**10**), and *t*-butyl (**11**) analogs were prepared starting with respective acetals of *i*-PrCHO, *i*-BuCHO, and *t*-BuCHO. (**9**) (61% yield): Bp 98—100 °C/2 Torr; ^1H NMR δ=0.84 and 0.95 (d, *J*=6.6 Hz, 3H×2), 1.95 (m, 1H), 3.66 (s, 3H), 3.76 (s, 3H), 4.08 (t, *J*=9 Hz, 1H), 5.42 (br. d, 1H), 5.71 (br. s, 1H), and 6.22 (d, *J*=1.1 Hz, 1H); Found: CHN. (**10**) (74% yield): Bp 75—78 °C/2 Torr; ^1H NMR δ=0.94 and 0.96 (d, *J*=6.4 Hz, 3H×2), 1.54 (m, 3H), 3.65 (s, 3H), 3.76 (s, 3H), 4.50 (q, *J*=9 Hz, 1H), 5.33 (br. d, 1H), 5.75 (br. s, 1H), and 6.18 (d, *J*=1.1 Hz); Found: CHN. (**11**) (53% yield): Bp 112—113 °C/2 Torr; ^1H NMR δ=0.90 (s, 9H), 3.66 (s, 3H), 3.76 (s, 3H), 4.39 (d, *J*=10 Hz, 1H), 5.65 (br. s, 1H), 5.90 (br. d, 1H), and 6.28 (d, *J*=1.1 Hz, 1H); Found: CHN.

Hydrogenation Procedures. In a 50-mL micro autoclave containing a glass lining tube and a stirring magnetic bar, under an argon atmosphere, were placed a catalyst precursor (1×10^{-2} mmol) and the substrate **1** (1 mmol) dissolved in a given solvent (5 mL). The inert atmosphere was replaced with hydrogen, the initial pressure of hydrogen being adjusted to 5—30 atm in each run. The reaction mixture was stirred at room temperature for 15—48 h depending on the other reaction conditions. The mixture was then filtered

† 1 M=1 mol dm^{-3}.

†† 1 Torr=133.322 Pa.

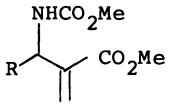
through a short plug of silica gel to remove the catalyst complex and the filtrate was evaporated to leave an oil. Conversion of the reaction was determined by capillary GLC (HR-20M, 30 m×0.2 mm, at 200 °C). Purification of the product by column chromatography (silica gel, hexane–ether) afforded a major component (**4a**) from the diastereomeric mixtures. ^{1}H NMR δ=1.23 (d, J=7.0 Hz, Me), 2.93 (qd, J=7.0 and 5.9 Hz, CH), 3.58 and 3.65 (s, MeO×2), 4.84 (dd, J=9.4 and 5.9 Hz, CHN), 6.00 (br. d, J=9.4 Hz, NH), and 7.26 (br. s, Ph). The vicinal coupling of the minor component (**4b**), J=6.4 Hz. Data of hydrogenation of **1** were given in Table 1. Hydrogenation of alkyl analogs of **1** (**8**—**11**) was also carried out in essentially the same procedure as described above (in methanol). Antiselectivity in each analog was given in parentheses: **8** (93%), **9** (69%), **10** (54%), and **11** (77%).

Preparation of 3-Methyl-4-phenyl-2-azetidinone (7). Iodine (0.76 g, 3 mmol) and hexamethyldisilane (0.51 g, 3.5 mmol) were stirred at 70 °C for 30 min. To trimethylsilyl iodide thus formed was added **4** (obtained from Entry 10) (1 mmol) dissolved in MeCN (5 mL) and the mixture was heated under reflux for 4 h. All volatile materials but disilylated product were evacuated under 2 Torr, and the residue was treated through a short silica gel column with MeOH. The eluent was evaporated to leave crude β-amino acid, $PhCH(NH_2)CHMeCO_2H$. The latter was treated with 2-chloro-1-methylpyridinium iodide (0.28 g, 1.1 mmol) and Et_3N (0.3 mL, 2.2 mmol) in dry MeCN (100 mL) under reflux for 8 h.[11] After evaporation of the solvent, the residue was extracted with ether and the extracts were washed with water and dried ($MgSO_4$). The crude product was purified by column chromatography (silica gel, hexane–ether) to give **7** (86.6 mg, 54% overall yield). The ratio of cis/trans=1/70 was determined by capillary GLC (HR-20M, 30 m×0.2 mm at 200 °C): T_R(trans) 18 min, T_R(cis) 23 min.

In the same manner as above, a sample of **4** from Entry 13 was converted into **7**. In this case, the cis/trans ratio was 80/20, and the isomers were separated by column chromatography. NMR spectral data of *cis*- and *trans*-**7**[12] were given below. *cis*-**7**: ^{1}H NMR δ=0.82 (d, J=7.5 Hz, 3H), 3.58 (ddq, J=1.8, 5.5, and 7.5 Hz, 1H), 4.88 (d, J=5.5 Hz, 1H), 6.14 (br., 1H), and 7.13—7.48 (m, 5H). ^{13}C NMR (22.5 MHz) δ=10.1, 51.0, 55.2, 126.6, 127.9, 128.6, 137.6, and 173.8. *trans*-**7**: ^{1}H NMR δ=1.42 (d, J=7.5 Hz, 3H), 3.06 (dq, J=2.2 and 7.5 Hz, 1H), 3.61 (d, J=2.2 Hz, 1H), 6.20 (br., 1H), and 7.35 (br. s, 5H). ^{13}C NMR δ=13.0, 56.5, 59.3, 125.5, 128.0, 128.8, 140.3, and 171.7.

Appendix

Elemental Analyses for 2-[α-(Methoxycarbonylamino)-alkyl]acrylates.



R=*i*-Pr (**9**) Found: C, 55.60; H, 8.07; N, 6.77% Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51%

R=*i*-Bu (**10**) Found: C, 57.46; H, 8.45; N, 6.36% Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11%

R=*t*-Bu (**11**) Found: C, 57.82; H, 8.60; N, 6.26% Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11%

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