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Stereoselective Synthesis of α,γ -Diamino Acid Esters

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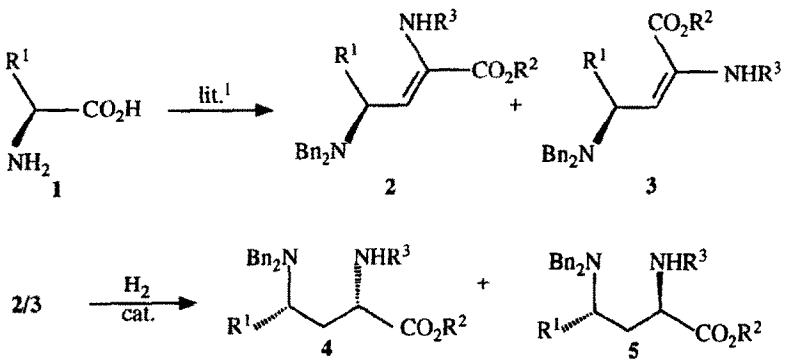
Abstract: Chiral didehydro amino acid esters **2/3** derived from amino acids are hydrogenated stereoselectively with rhodium catalysts based on achiral ligands, the α,γ-diamino acid derivatives **4** being the major products. The sense and degree of stereoselectivity can be influenced to some extent by the use of chiral diphosphines. The iridium-containing Crabtree-catalyst is particularly effective in the case of the serine derivative **2** (R^1 = $HOCH_2$).

Recently we described the synthesis and stereoselective cycloaddition reactions of γ-amino α,β-didehydro amino acid esters **2** and **3** derived from amino acids **1**[1]. In this communication we report on the stereoselective rhodium- and iridium-mediated hydrogenation of these novel olefins using achiral and chiral homogeneous catalysts[2]. The products **4/5**, obtained in quantitative conversions, are derivatives of α,γ-diamino acids, which occur in several natural products and in certain synthetic anti-hypertensive agents[3].



Using achiral diphosphines as ligands, separate hydrogenations of **2** (Table 1) and **3** (Table 2) were conducted under standard conditions[2,4]. Several conclusions can be reached on the basis of the data. Olefins **2** react faster and more selectively than **3**, but both generally afford **4** as the major diastereomer having the S-configuration at the newly created stereogenic center. The degree of 1,2-asymmetric induction decreases as the bulk of R^1 increases, the sense of diastereoselectivity actually inverting in the case of **2** (R = *i*Pr) derived from valine. The sequence of reactions starting from **1** occurs without any racemization (ee >98%)[1b]. The configurational assignments were made on the basis of X-ray and NMR data[1b].

Table 1. Rhodium-mediated Hydrogenation of Olefins **2** in CH_3OH

R^1	R^2	R^3	Ligand	p(atm)/t(h)	**4**	:	**5**
Me	Et	CHO	$Ph_2P(CH_2)_2PPh_2$	25/40	88	:	12
Me	Et	CHO	$Ph_2P(CH_2)_4PPh_2$	70/20	81	:	19
Me	Me	Boc[a)]	$Ph_2P(CH_2)_4PPh_2$	70/72	85	:	15
Me	Me	Cbz[b)]	$Ph_2P(CH_2)_4PPh_2$	75/72	76	:	24
$PhCH_2$	Et	CHO	$Ph_2P(CH_2)_2PPh_2$	35/17	73	:	27
$PhCH_2$	Et	CHO	$Ph_2P(CH_2)_2PPh_2$	35/17	76	:	24
Me_2CHCH_2	Et	CHO	$Ph_2P(CH_2)_2PPh_2$	80/42	68	:	32
Me_2CHCH_2	Et	CHO	$Ph_2P(CH_2)_4PPh_2$	75/80	74	:	26
Me_2CH	Et	CHO	$Ph_2P(CH_2)_4PPh_2$	25/40	48	:	52
Me_2CH	Me	Cbz[b)]	$Ph_2P(CH_2)_4PPh_2$	25/20	22	:	78
t-$BuMe_2SiOCH_2$	Et	CHO	$Ph_2P(CH_2)_4PPh_2$	50/45	79	:	21
$HOCH_2$	Et	CHO	$Ph_2P(CH_2)_4PPh_2$	80/21	87	:	13
$HOCH_2$	Et	CHO	$Ph_2P(CH_2)_4PPh_2$	80/23	88	:	13
$HOCH_2$	Et	CHO	$Ph_2P(CH_2)_2PPh_2$	85/41	90	:	10

a) Boc = t-butoxycarbonyl; b) Cbz = benzyloxycarbonyl

Table 2. Rhodium-mediated Hydrogenation of Olefins **3** using $Ph_2P(CH_2)_4PPh_2$ in CH_3OH

R^1	R^2	R^3	p(atm)/t(h)	**4**	:	**5**
Me	Et	CHO	80/20	68	:	32
Me	Me	Boc[a)]	70/20	77	:	23
Me	Me	Cbz[b)]	30/18	58	:	42
$PhCH_2$	Et	CHO	85/20	64	:	36
Me_2CHCH_2	Et	CHO	85/52	62	:	38
Me_2CH	Et	CHO	80/72	57	:	43
Me_2CH	Me	Cbz[b)]	25/20	58	:	42
t-$BuMe_2SiOCH_2$	Et	CHO	50/45	62	:	38

a) Boc = t-butoxycarbonyl; b) Cbz = benzyloxycarbonyl

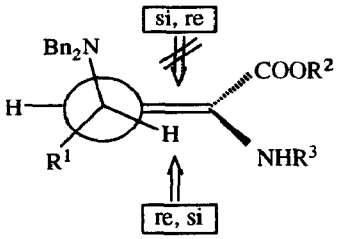
In order to increase stereoselectivity, the Z-olefins **2** were hydrogenated using commercially available chiral ligands[2]. Table 3 shows that R,R-DIPAMP delivers a single product **4** in the case of **2** (R^1 = Me). Using (+)- or (-)-DIOP in the latter case, reagent control is possible, 75 : 25 and 25 : 75 ratios of **4**/**5** being observed. Increasing the bulk of the R^1 group lowers the stereoselectivity. In summary, the present partial optimization shows that each substrate must be studied individually in order to reach maximum stereoselectivity.

Table 3. Rhodium-mediated Hydrogenation of Olefins **2** (R^2 = Et; R^3 = CHO) using chiral Phosphine-Ligands in CH_3OH

R^1	Ligand	p(atm)/t(h)	**4**	:	**5**
Me	S,S-CHIRAPHOS	25/20	78	:	22
Me	(+)-DIOP	30/19	75	:	25
Me	(-)-DIOP	30/19	25	:	75
Me	R,R-DIPAMP	30/42	>98	:	<2
Me	(-)-BINAP	85/22	73	:	27
Me	(+)-BINAP	85/22	39	:	61
$PhCH_2$	S,S-CHIRAPHOS	30/100	72	:	28
$PhCH_2$	(+)-DIOP	50/20	63	:	37
$PhCH_2$	(-)-DIOP	50/20	52	:	48
$PhCH_2$	R,R-DIPAMP	50/41	65	:	35
$PhCH_2$	(-)-BINAP	85/21	.....		*)
Me_2CHCH_2	(+)-DIOP	45/56	79	:	21
Me_2CHCH_2	(-)-DIOP	45/56	53	:	47
Me_2CHCH_2	R,R-DIPAMP	80/58	71	:	29
Me_2CH	(+)-DIOP	50/32	55	:	45
Me_2CH	(-)-DIOP	50/32	.....		*)
t-$BuMe_2SiOCH_2$	(+)-DIOP	50/21	78	:	22
t-$BuMe_2SiOCH_2$	(-)-DIOP	50/22	25	:	75
t-$BuMe_2SiOCH_2$	R,R-DIPAMP	50/21	90	:	10
$HOCH_2$	R,R-DIPAMP	80/20	97	:	3

*) No reaction under these conditions

We refrain from a detailed mechanistic discussion at this time[1b], except to point out that 1,3-allylic strain[5] may be operating in the preferred re,si attack (cf. **6**). This tendency is enhanced in the case of the serine derivative **2** (R^1 = $HOCH_2$), because the unprotected hydroxyl function can induce additional chelation (cf. **7**). Indeed, Tables 1 and 3 show that this substrate results in exceptionally high stereoselectivities. In a final experiment along these lines, the iridium-containing Crabtree-catalyst[6] was used to hydrogenate **2** (R^1 = $HOCH_2$; R^2 = Et; R^3 = CHO) in THF (85 atm/26 h), the **4** : **5** ratio being 96 : 4 (quantitative conversion). Starting from unnatural serine, this type of chemistry may be of use in the stereoselective synthesis of certain anti-leukaemic and anti-fungal amino-carbohydrates (3-desoxyprumycin derivatives)[7]. It remains to be seen whether reversal of diastereoselectivity can be achieved by protective group tuning (e.g., Cbz instead of dibenzyl protective groups) in **2**, rather than reagent (catalyst) control. Finally, we point out that very few other cases are known in which chiral didehydro amino acid derivatives have been hydrogenated[8].



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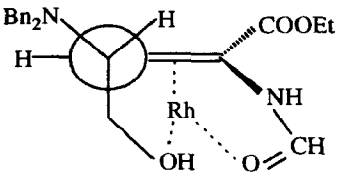

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4. In a normal hydrogenation apparatus the substrate **2** or **3** is dissolved in methanol. After flushing with argon, a catalyst (10-15 mol-%) is added. The catalyst is prepared as the rhodium-norbornadiene/diphosphine complex with BF_4^- or OTf^- counterions[2]. The apparatus is flushed several times with hydrogen, and then the pressure is adjusted (cf. Tables). After completion of the reaction, the solvent is removed and a small amount of ether is added. Following filtration through a SiO_2 column (ether/pet ether), the solvent is removed and the crude product is purified by flash chromatography (SiO_2; pet ether/ethyl acetate 95:5).
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8. a) Schmidt, U.; Lieberknecht, A.; Kazmaier, U.; Griesser, H.; Jung, G.; Metzger, J. *Synthesis* **1991**, 49-55; b) We have performed related reactions[1b]: Glyceraldehyde acetonide was converted into **8** using the Schöllkopf procedure[1] (62%; >95% Z). Hydrogenation (Rh/R,R-DIPAMP) delivered a single diastereomer **9**.