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On the stereoselective hydrogenation of chiral cyclobutyl dehydro-amino acid derivatives: influence of the catalyst in the π-facial diastereoselection

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Abstract—Several optically active cyclobutyl dehydro-amino acid derivatives have been hydrogenated employing Wilkinson, (*S*,*S*)-chiraphos-Rh and Et-duphos-Rh (both enantiomers) as catalysts. The use of a chiral catalyst has been revealed to be crucial for the production of saturated amino acids with high stereoselectivity from substrates in which the chiral cyclobutyl unit is separated from the double bond by a methylene group.

The catalytic hydrogenation of dehydro α-amino acid derivatives, usually enamido esters (enamides), is one of the procedures widely employed for the stereoselective synthesis of natural or unnatural saturated α-amino acids. The incorporation of homochiral ligands in the catalyst[1,2] was a remarkable improvement allowing the formation, from prochiral precursors, of saturated amino acids in modest to excellent enantiomeric excesses.[3] Despite the number of reports on the hydrogenation of achiral olefins, there are few reports on the use of chiral catalysts in the hydrogenation of chiral, optically active, substrates as an instance of double asymmetric induction.[4] Products are obtained in a high diastereomeric excess (d.e.) when the double induction due to the chiral catalyst on the one hand, and the stereogenic centers of the substrate on the other, are complementary. However, poor d.e.'s result when these inductions are mutually opposed.[4b]

In this communication, we describe our preliminary results on the stereoselective hydrogenation of several cyclobutyl enamides. These compounds, with (*Z*)-double bond configuration, have been synthesized through the Wittig–Horner condensation of suitable phosphonates and aldehydes prepared in our laboratory from (−)-α-pinene or (−)-verbenone as chiral precursors.[5] The results derived from the use of achiral catalysts, both under heterogeneous and homogeneous conditions, are compared with those obtained with commercially available (*S*,*S*)-chiraphos-Rh[1,2,3a] and both (*R*,*R*)- and (*S*,*S*)-Et-duphos-Rh.[6]

The enamides studied, **1**–**4**, and the products obtained, **5**–**8**,[7] are shown in Scheme 1. It is noteworthy that **3** has inverse configuration at C-(1′) and C-(3′) with respect to **1** and **2**. In these three molecules, the double bond is directly linked to one stereogenic center of the cyclobutane ring, while in **4** the double bond is separated from the carbocycle by a methylene group.

As expected, hydrogenation of **1**–**4** in the presence of palladium on charcoal afforded a 1:1 mixture of both diastereomers in each case. In contrast, the use of Wilkinson catalyst afforded good diastereomeric excesses in the hydrogenation of **1**, **2** and **3** (Table 1, entries 1, 4 and 7). The stereochemistry of the major isomers of amino acids **5** and **6** was initially assigned, in agreement with the mechanism proposed by Halpern,[2] by considering preferential coordination of the catalyst, and a subsequent intramolecular hydrogen transfer to the *Si*-face of the double bond which is the opposite to the *gem*-dimethyl substitution of the cyclobutane ring. This is the same argument previously invoked by us to justify the stereochemical outcome of the 1,3-dipolar cycloaddition of diazomethane to similar dehydro-amino acids.[8] Actually, X-ray structural analysis of **5a** (Fig. 1) confirmed this hypothesis.[9] The use of (*S*,*S*)-chiraphos or (*R*,*R*)-Et-duphos as ligands in the catalytic hydrogenation of enamides **1** and **2** led to the

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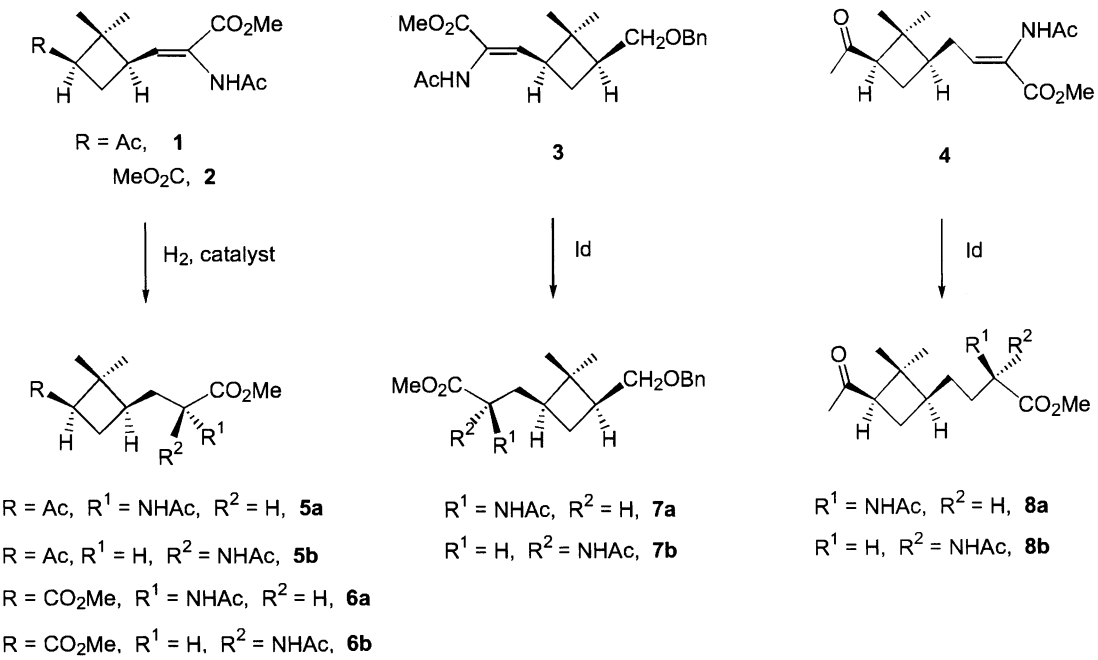


Scheme 1.

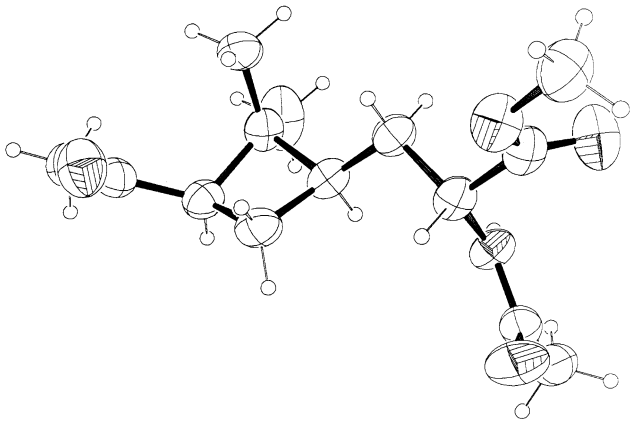
production of amino acids **5a** and **6a**, respectively, as the major stereoisomers, which are the same as those obtained with Wilkinson's catalyst.[10] Similarly, in the case of enamide **3**, compound **7b** was obtained as the major stereoisomer from hydrogenation in the presence of both (*S*,*S*)-chiraphos-Rh and Wilkinson's catalyst (Table 1, entries 7 and 8). This fact allowed us to assign tentatively (*S*)-configuration to C-(2) in **7b** by assuming that hydrogen is transferred by the less hindered *Re*-face of the double bond.

In the case of **4**, a 1:1 mixture of both diastereomers was obtained when reduction was carried out with Wilkinson's catalyst.[11] In contrast, high stereoselectivity was observed in the hydrogenation of **4** in the presence of chiral catalysts (compare entry 9 with entries 10–12 in Table 1). When (*R*,*R*)-duphos-Rh was employed only one isomer, **8a**, was detected in the ^{1}H NMR spectrum of the hydrogenation crude. Its (*R*)-configuration at the new stereogenic center C-(2) was unambiguously determined by X-ray analysis (Fig. 1).[9] The same

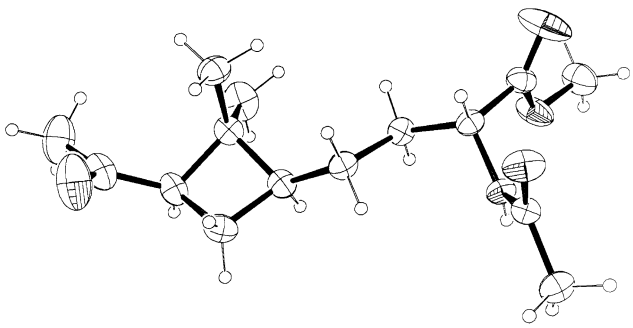
Table 1. Hydrogenation of dehydro-amino acids **1**–**4** and diastereomeric ratio[a] of products with catalysts $(Ph_3P)_3RhCl$ **9**, [Rh((*S*,*S*)-chiraphos)]ClO_4 **10**, [(COD)Rh((*R*,*R*)-Et-duphos)]OTf (*R*,*R*)-**11**

Entry	Substrate	Catalyst	Product	Configuration[b]	Isomer ratio[c]
1	**1**	**9**[d,e]	**5a**	*R*	80:20
2	**1**	**10**[e,f]	**5a**	*R*	83:17
3	**1**	(*R*,*R*)-**11**[g,h]	**5a**	*R*	80:20
4	**2**	**9**[d,e]	**6a**	*R*	75:25
5	**2**	**10**[e,f]	**6a**	*R*	95:5
6	**2**	(*R*,*R*)-**11**[g,h]	**6a**	*R*	85:15
7	**3**	**9**[d,e]	**7b**	*S*	77:23
8	**3**	**10**[e,f]	**7b**	*S*	68:32
9	**4**	**9**[d,e]	**8a**/**8b**	*R*/*S*	50:50
10	**4**	**10**[e,f]	**8a**	*R*	92:8
11	**4**	(*R*,*R*)-**11**[g,h]	**8a**	*R*	>98:2
12	**4**	(*S*,*S*)-**11**[g,h]	**8b**	*S*	>98:2

[a] Determined by ^{1}H NMR.
[b] Refers to the new stereogenic center in the major diastereomer.
[c] At 100% conversion.
[d] In 1:1 EtOH–benzene.
[e] Under 4 atm. pressure.
[f] In EtOH.
[g] In MeOH.
[h] Under 2 atm. pressure.



5a

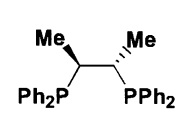


8a

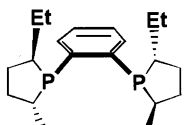
Figure 1. An ORTEP view of the molecular structures of **5a** and **8a**. The thermal ellipsoids enclose 30% probability.

isomer resulted as the major product (92:8) from the hydrogenation catalyzed by (*S*,*S*)-chiraphos-Rh (Table 1, entries 10 and 11). On the contrary, diastereomer **8b** with (*S*)-configuration at C-(2) resulted from reduction of **4** using (*S*,*S*)-Et-duphos-Rh as catalyst (Table 1, entry 12, Fig. 2).

These results point out that the use of chiral catalysts is crucial to stereoselective induction in the hydrogenation of enamides such as **4**, where the stereogenic center is too remote from the double bond to influence the π-facial diastereoselection. In these cases the configuration of the stereogenic center created in the hydrogenation is clearly determined by the chirality of the catalyst. However, for enamides, **1**–**3**, it is too early to conclude whether the configuration of the newly formed stereogenic center depends on the catalyst, the substrate, or if it results from double asymmetric induction promoted by both reactants.



(*S*,*S*)-chiraphos



(*R*,*R*)-Et-duphos

Figure 2.

Experimentation is being carried out in our laboratory in order to establish the main factors governing the diastereoselection for enamides such as **1**–**3**. A knowledge of the above factors will be useful for predicting the predominant product configuration resulting from the hydrogenation of similar substrates.

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7. The new compounds **5a**, **6a** and **8a** were fully characterized and exhibited correct microanalysis. The major iso-

mer **7b**, from the reduction of **3**, could not be isolated neither by chromatography nor by crystallization.
8. Moglioni, A. G.; García-Expósito, E.; Alvarez-Larena, A.; Branchadell, V.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, *11*, 4903.
9. Crystallographic data will be published elsewhere.
10. The optimal conditions to achieve 100% conversion in the hydrogenation with Wilkinson's catalyst involved 4 atmospheres pressure at room temperature for 10–12 days. Higher pressures resulted in a decreasing stereoselectivity. Reduction was completed in 5–6 days when (*S*,*S*)-chiraphos-Rh was used. Et-duphos-Rh was the most active catalyst affording quantitative yields of reduction products after hydrogenation under 2 atmospheres for 1 day.
11. In the case of the reaction of **4** with diazomethane a 1:1 diastereomeric mixture of pyrazolines was obtained.[8]