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Stereoselective Rh-Catalyzed Hydrogenation of Cyclobutyl Chiral Enamides: Double Stereodifferentiation vs Catalyst-Controlled Diastereoselection

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The hydrogenation reactions of several cyclobutyl enamides derived from (−)-α-pinene or (−)-verbenone have been investigated by using different catalysts. The chiralities of both the substrate and the catalyst as well as the *Z*/*E* stereochemistry of the double bond have been considered, and the observed diastereoselectivity has been rationalized. For enamides with the double bond separated from the cyclobutane by a methylene, the Wilkinson catalyst did not induce any diastereoselection, but excellent diastereoselectivity was observed when using Et-DuPHOS-Rh and ChiraPHOS-Rh. The configuration of the new stereogenic center was catalyst-dependent and can be rationalized according to the Halpern mechanism. For (*Z*)-enamides with the double bond directly linked to the cyclobutane ring, the chirality of the substrate governed the diastereoselection and the Halpern mechanism seemed not to be operative in the hydrogenation with ChiraPHOS, with the configuration of the new stereogenic center being determined by steric effects. On the contrary, the chirality of the catalyst was the factor determining the stereochemistry of the major products with alkyl-DuPHOS-Rh. *Z*/*E* stereochemistry influenced the stereodifferentiation, and a different behavior for each *Z* or *E* stereoisomer was found. For both (*Z*)- and (*E*)-enamides, some instances of match/mismatch between the chirality of the substrate and that of the catalyst were observed. As a result of all of these studies, a series of new cyclobutyl α-amino acids has been synthesized. These products are interesting to incorporate into conformationally constrained peptides.

Introduction

Stereoselective catalytic hydrogenation is a very powerful tool in organic synthesis for the preparation of several types of products through the reduction of C=C or C=O double bonds. The use of chiral ligands resulted in a great improvement of this reaction with respect to the use of achiral complexes such as the Wilkinson catalyst.[1] Among the chiral catalysts, rhodium phosphine complexes have been the most studied, with (*S*,*S*)-ChiraPHOS-Rh being the first catalyst whose mode of action in the mechanism and whose stereochemical outcome of the catalytic hydrogenation were investigated and systematized. Halpern, indeed, studied the asymmetric hydrogenation of achiral enamido esters (enamides) to afford optically active α-amino acids and proposed a mechanism to explain the stereoselectivity of the whole process based on the kinetic control of the addition of hydrogen to the substrate−catalyst complex. Halpern showed that, in many cases, the resultant major stereoisomer is produced from the less stable substrate−catalyst complex, which reacts with hydrogen faster than the most stable one.[2]

Later, Burk introduced the phospholane-based catalysts, alkyl-DuPHOS-Rh, which also present C_2 symmetry.[3] In addition, some of these catalysts, such as rhodium Et-DuPHOS, are commerically available in both enantiomeric forms. These reagents have been used for the asymmetric synthesis of α-, β-, and γ-amino acids. A very recent example is the enantioselective synthesis of (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (Pregabalin) via the asymmetric hydrogenation of 3-cyano-5-methylhex-3-enoic acid salt with [(*R*,*R*)-(Me-DuPHOS)-Rh-(COD)]BF_4 as a catalyst.[4] Usually, these catalysts allow the reactions to proceed quickly under mild temperature and pressure conditions in such a way that the *N*-Cbz amino protecting group remains unaltered.

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(1) See, for instance: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1993.

(2) (a) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952. (b) Halpern, J. *Science* **1982**, 217. (c) Halpern, J. In *Asymmetric Synthesis*; Morrison, J., Ed.; Academic Press: New York, 1985; Vol. 5, pp 41−68.

(3) For some leading works, see: (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (c) Burk, M. J.; Gross, M. F.; Harper, G. P.; Kalberg, C. S.; Lee, J. R.; Martínez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37.

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The influence of the Z/E stereochemistry of the enamides on the stereoselectivity of the process has been scarcely investigated. In general, (E)-olefins react slower than their (Z)-olefin counterparts and afford saturated products with lower enantiomeric excesses. In reference to the asymmetric induction, results vary with the use of different catalysts. Thus, for instance, the configuration of the α-amino acids resulting from the hydrogenation with BINAP-Rh depends on the Z/E configuration of the substrate enamide.[1] In contrast, Burk reported that the configuration of the major isomer resulting from the hydrogenation is not dependent on the Z/E geometry of the double bond when a DuPHOS-Rh catalyst is used.[5] Similar results have been described by other authors.[6]

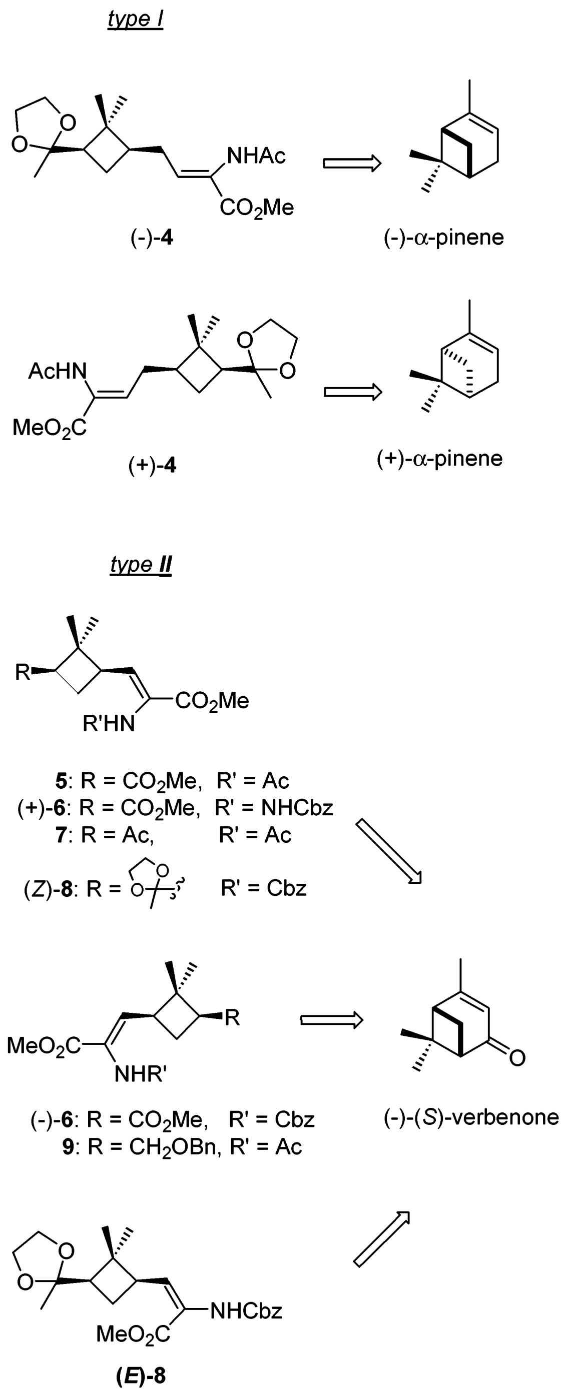
Data found in the literature about asymmetric hydrogenations mainly refer to the reduction of achiral substrates. Nevertheless, only a few examples on the hydrogenation of chiral substrates with chiral catalysts, displaying double stereodifferentiation,[7] have been reported.[8]

In a preliminary communication, we described our first results on the hydrogenation of some of the cyclobutyl chiral (Z)-enamides shown in Scheme 1 using $(Ph_3P)_3RhCl$, Wilkinson catalyst, **1**; [(S,S)-ChiraPHOS-Rh]ClO_4, **2**; and [(R,R)-(Et-DuPHOS)-Rh-(COD)]OTf, (R,R)-**3**, respectively.[9] The type I enamides were prepared from (−)-α-pinene, and those of type II proceed from (−)-(S)-verbenone. These substrates differ in that a methylene group is intercalated between the double bond and the cyclobutane moiety in type I substrates, whereas the double bond is directly linked to the carbocyclic ring in substrates of type II. This feature is crucial in the control of the diastereoselectivity in addition reactions to the double bond of these substrates, as has been previously shown.

High diastereomeric ratios (dr) were obtained in the hydrogenation of type II enamides by using **1**, **2**, and (R,R)-**3** as catalysts, affording amino acids with R configuration for the new stereogenic center in all cases. On the other hand, whereas no stereoselectivity was observed in the hydrogenation of type I enamides with the Wilkinson catalyst, R diastereoisomers were obtained as major products (98:2 dr) when using (S,S)-ChiraPHOS. Moreover, only one diastereomer resulted from the hydrogenation with Et-DuPHOS-Rh, with the configuration depending on the chirality of the catalyst used.[9]

In this article, we present the complete results of our exhaustive study on the hydrogenation of types I and II enamides with several catalysts. The chiralities of both the substrate and the catalyst have been considered, as well as the Z/E stereochemistry of the double bond. A model based on theoretical calculations is proposed to explain the stereochemistry of the produced compounds.

SCHEME 1



These hydrogenation reactions have allowed the synthesis of a collection of new cyclobutyl α-amino acids useful for their incorporation into conformationally constrained peptidomimetics and other complex molecules.

Results and Discussion

1. Synthesis of the Enamides. Compound (+)-**4** was synthesized from (+)-α-pinene as the chiral precursor following the same route as that previously reported for enantiomer (−)-**4** from (−)-α-pinene (Scheme 1).[10,11] The

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(5) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931.

(6) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159.

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SCHEME 2

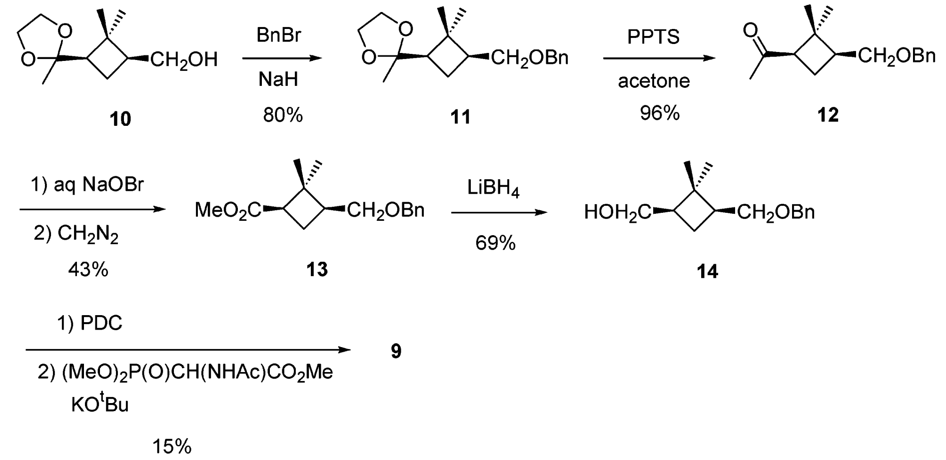
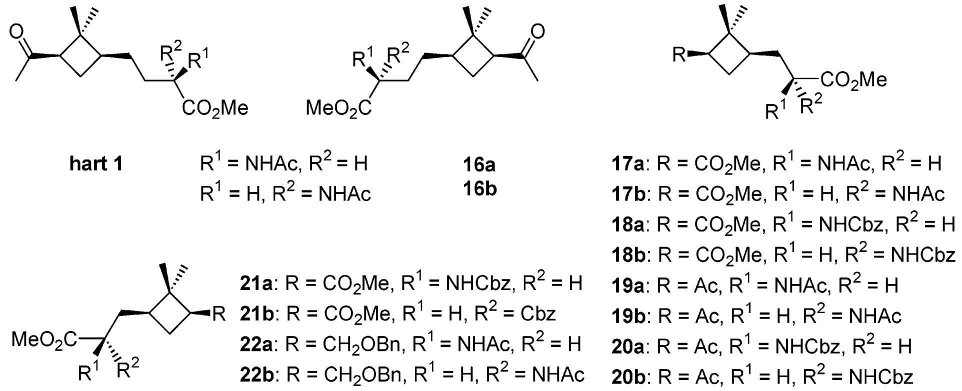


CHART 1


hart 1
R^1 = NHAc, R^2 = H 16a
R^1 = H, R^2 = NHAc 16b
17a: R = CO_2Me, R^1 = NHAc, R^2 = H
17b: R = CO_2Me, R^1 = H, R^2 = NHAc
18a: R = CO_2Me, R^1 = NHCbz, R^2 = H
18b: R = CO_2Me, R^1 = H, R^2 = NHCbz
19a: R = Ac, R^1 = NHAc, R^2 = H
19b: R = Ac, R^1 = H, R^2 = NHAc
20a: R = Ac, R^1 = NHCbz, R^2 = H
20b: R = Ac, R^1 = H, R^2 = NHCbz
21a: R = CO_2Me, R^1 = NHCbz, R^2 = H
21b: R = CO_2Me, R^1 = H, R^2 = Cbz
22a: R = CH_2OBn, R^1 = NHAc, R^2 = H
22b: R = CH_2OBn, R^1 = H, R^2 = NHAc

pair (+)- and (−)-**6** were synthesized from (−)-(*S*)-verbenone as the only chiral starting material through the selective manipulation of functional groups.[12] The other enamides, **5** and **7**−**9**, were also synthesized from this precursor. Compounds **5**[12] and (*Z*)-**8**[11] have previously been described. (*E*)-**8**, resulting as a minor isomer in the preparation of the *Z* counterpart, as well as **7**, prepared from (*Z*)-**8** by hydrolysis of the ketal, has not been reported. The synthesis of the new product **9** is shown in Scheme 2. The known alcohol **10**[11] was protected as a benzyl ether, and then ketal was removed under mild conditions by treatment of **11** with PPTS in acetone. The resultant ketone was submitted to Lieben degradation with sodium hypobromite in aqueous dioxane, affording a carboxylic acid that was methylated with diazomethane. Ester **13** was reduced with lithium borohydride to give alcohol **14**, which was oxidized to aldehyde with PDC in dichloromethane. We had found in our laboratory that direct reduction of esters such as **13** to aldehydes was not satisfactory because it provided mixtures of products.[11] Finally, Wittig−Horner condensation of the prepared aldehyde with a suitable phosphonate,[13] in the presence of potassium *tert*-butoxide as a base, allowed the obtainment of enamide **9**.

TABLE 1. Hydrogenation of Enamides (+)- and (−)-4 and Diastereomeric Ratios (dr)[a] of Products with Catalysts Wilkinson, 1; (*S*,*S*)-ChiraPHOS-Rh, 2; (*R*,*R*)-Et-DuPHOS-Rh, (*R*,*R*)-3; and (*S*,*S*)-Et-DuPHOS-Rh, (*S*,*S*)-3

entry	substrate	catalyst	product	configuration[b]	% dr[c]
1	(−)-**4**	**1**	**15a/15b**	*R*/*S*	<50.5:49.5
2	(−)-**4**	**2**	**15a**	*R*	96:4
3	(−)-**4**	(*R*,*R*)-**3**	**15a**	*R*	>99.9:0.1
4	(−)-**4**	(*S*,*S*)-**3**	**15b**	*S*	>99.9:0.1
5	(+)-**4**	**2**	**16a**	*R*	85:15
6	(+)-**4**	(*R*,*R*)-**3**	**16a**	*R*	>99.9:0.1
7	(+)-**4**	(*S*,*S*)-**3**	**16b**	*S*	>99.9:0.1

[a] Determined by high-resolution ^{1}H NMR. [b] Refers to the new stereogenic center in the major diastereomer. [c] At 100% conversion.

2. Hydrogenation Reactions and Stereochemical Assignment. The produced amino acids are shown in Chart 1.

(a) Type I Enamides. Table 1 summarizes the reactions performed on substrates (+)- and (−)-**4**. With achiral catalyst **1**, no diastereoselectivity was observed (entry 1). In contrast, moderate to excellent diastereomeric ratios were observed with chiral catalysts. The isomer ratio was determined from the 500-MHz ^{1}H NMR spectra of the reaction crudes by considering the area of the signals for the *gem*-dimethyl group at δ 0.79/1.27 and 0.80/1.28, respectively. The major diastereomers from the hydrogenation of both (−)- and (+)-**4** with (*S*,*S*)-ChiraPHOS, **2**, presented the *R* configuration in the newly created stereogenic center (entries 2 and 5). The config-

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[11] Moglioni, A. G.; García-Expósito, E.; Aguado, G. P.; Parella, T.; Branchadell, V.; Moltrasio, G.; Ortuño, R. M. *J. Org. Chem.* **2000**, *65*, 3934.

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[13] Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.

TABLE 2. Hydrogenation of Enamides 5−9 and Diastereomeric Ratios (dr)[a] of Products with Catalysts Wilkinson, 1; (*S*,*S*)-ChiraPHOS-Rh, 2; (*R*,*R*)-Et-DuPHOS-Rh, (*R*,*R*)-3; (*S*,*S*)-Et-DuPHOS-Rh, (*S*,*S*)-3; and (*R*,*R*)-Me-DuPHOS-Rh, 21

entry	substrate	catalyst	product	configuration[b]	% dr[c]
1	**5**	**1**	**17b**	*R*	75:25
2	**5**	**2**	**17b**	*R*	95:5
3	**5**	(*R*,*R*)-**3**	**17b**	*R*	85:15
4	(+)-**6**	**2**	**18b**	*R*	90:10
5	(+)-**6**	(*R*,*R*)-**3**	**18b**	*R*	88:12
6	(+)-**6**	**21**	**18b**	*R*	83:17
7	(+)-**6**	(*S*,*S*)-**3**	**18a**	*S*	80:20
8	(−)-**6**	**2**	**21a**	*S*	90:10
9	(−)-**6**	(*R*,*R*)-**3**	**21b**	*R*	83:17
10	(−)-**6**	**21**	**21b**	*R*	81:19
11	(−)-**6**	(*S*,*S*)-**3**	**21a**	*S*	90:10
12	**7**	**1**	**19b**	*R*	80:20
13	**7**	**2**	**19b**	*R*	83:17
14	**7**	(*R*,*R*)-**3**	**19b**	*R*	80:20
15	**9**	**1**	**22a**	*S*	77:23
16	**9**	**2**	**22a**	*S*	68:32
17	(*Z*)-**8**	**2**	**20b**	*R*	87:13
18	(*Z*)-**8**	(*R*,*R*)-**3**	**20b**	*R*	85:15
19	(*Z*)-**8**	(*S*,*S*)-**3**	**20a**	*S*	80:20
20	(*E*)-**8**	**2**	**20a**	*S*	*d*
21	(*E*)-**8**	(*R*,*R*)-**3**	**20a/20b**	*R*/*S*	<50.5:49.5
22	(*E*)-**8**	(*S*,*S*)-**3**	**20a**	*S*	87:13

[a] Determined by high-resolution ^{1}H NMR. [b] Refers to the new stereogenic center in the major diastereomer. [c] At 100% conversion. [d] Complex mixture showing isomer **20a** as the major product.

uration was catalyst-dependent when the two enantiomers were hydrogenated by using (*R*,*R*)- and (*S*,*S*)-Et-DuPHOS, **3**, respectively (entries 3, 4, 6, and 7). In all cases, the methyl ketone was deprotected under the hydrogenation conditions but no epimerization was observed. The stereochemistry of the new stereogenic centers was determined by X-ray structural analysis of **15a**.[9]

(b) Type II Enamides. Table 2 shows the reactions performed on enamides **5**−**9** with catalysts **1**−**3** and (*R*,*R*)-Me-DuPHOS-Rh, **21**. In some instances reported in the literature, this last catalyst afforded better diastereoselection than Et-DuPHOS-based reagents when sterically hindered substrates were hydrogenated.[14]

In the hydrogenation of enamides **5**, (+)- and (−)-**6**, **7**, and (*Z*)-**8**, Wilkinson catalyst, **1**; (*S*,*S*)-ChiraPHOS-Rh, **2**; (*R*,*R*)-Et-DuPHOS-Rh, (*R*,*R*)-**3**; and (*R*,*R*)-Me-DuPHOS-Rh, **21**, behave similarly, affording saturated amino acids with the *R* configuration and variable dr. (*S*,*S*)-Et-DuPHOS-Rh, (*S*,*S*)-**3**, induced the opposite *S* configuration in these substrates. Diastereomeric ratios were lower when (*R*,*R*)-Me-DuPHOS was used with respect to those in the reactions catalyzed by (*R*,*R*)-Et-DuPHOS (compare entries 6 and 10 with entries 5 and 9 in Table 2). The comparison of the results from the hydrogenations of the enantiomers (+)-**6** (entries 4−7) and (−)-**6** (entries 8−11) with chiral catalysts allowed us to conclude that the configuration is substrate-dependent in the reactions with ChiraPHOS but the stereochemistry of the new products is governed by the configuration of the catalyst in the reductions with DuPHOS. The predominance of the chirality of the substrate in the diastereoselectivity of the reactions with **1** and **2** is also pointed out in entries 15 and 16, which refer to the hydrogenation of enamide **9** with the same chirality as that of (−)-**6** (compare entries 8 and 16) but the reverse of (+)-**5**, **6**, **7**, and (*Z*)-**8**.

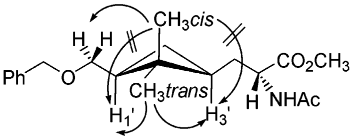

FIGURE 1. Assignment of cis stereochemistry on the basis of NOEDIFF experiments on **22a**.

Results from the hydrogenation of (*Z*)-**8** (entries 17−19) and (*E*)-**8** (entries 20−22) do not agree with those previously reported in the literature. In the reaction with **2**, the configuration of the products was dependent on the *Z*/*E* stereochemistry of the starting material and dr was very different in both cases. Thus, **20b** was obtained from (*Z*)-**8** in 87:13 dr, favoring the *R* configuration (entry 17). Hydrogenation of (*E*)-**8** afforded a complex mixture of substances, with **20a**, with the *S* configuration, being the major identified product (entry 20). Otherwise, a mixture of compounds **20b** and **20a** in 85:15 dr resulted from the hydrogenation of (*Z*)-**8** with (*R*,*R*)-**3** (entry 18), but no diastereoselectivity was observed in the reduction of the *E* isomer with the same catalyst (entry 21). Finally, amino acid **20a** was the major isomer resulting from the hydrogenation of both (*Z*)- and (*E*)-**8** with (*S*)-**3** (80:20 and 87:13 dr, respectively). In all of these cases, dioxolane removal under the reaction conditions was observed. In a separate experiment, hydrolysis of the ketal in (*Z*)-**8** followed by hydrogenation with (*R*,*R*)-**3** also afforded compound **20b**.

The stereochemical assignment of **a** and **b** diastereomers was made by comparison of the ^{1}H NMR pattern for the different products with that of **19b**, whose configuration was unambiguously assigned by X-ray structural analysis.[9] Diastereomeric ratios were determined on the basis of significant peaks in the respective high-resolution ^{1}H NMR spectra of the reaction crudes. The signals of the *gem*-dimethyl group at 0.4−0.7 ppm and of HC_2 at 4.0−4.2 ppm were mainly considered. The cis relationship between the two side chains of the cyclobutane ring showing that epimerization did not take place was established by NOEDIFF experiments. As an example, Figure 1 shows the results for amino acid **22a**.

3. Stereochemical Outcome of These Reactions: Double Stereodifferentiation or Catalyst−Substrate-Governed Diastereoselection. In enamides (+)- and (−)-**4**, a methylene group is intercalated between the double bond and the bulky cyclobutane moiety containing the *gem*-dimethyl group and the two stereogenic centers. Thus, the achiral Wilkinson catalyst did not induce any diastereoselectivity (entry 1 in Table 1). In contrast, with (*S*,*S*)-ChiraPHOS-Rh, **2**, a major diastereomer was obtained. The predominant induced *R* configuration can be interpreted on the basis of the Halpern mechanism, as depicted in Scheme 3. The major diastereomer comes from the presumably less stable catalyst−substrate

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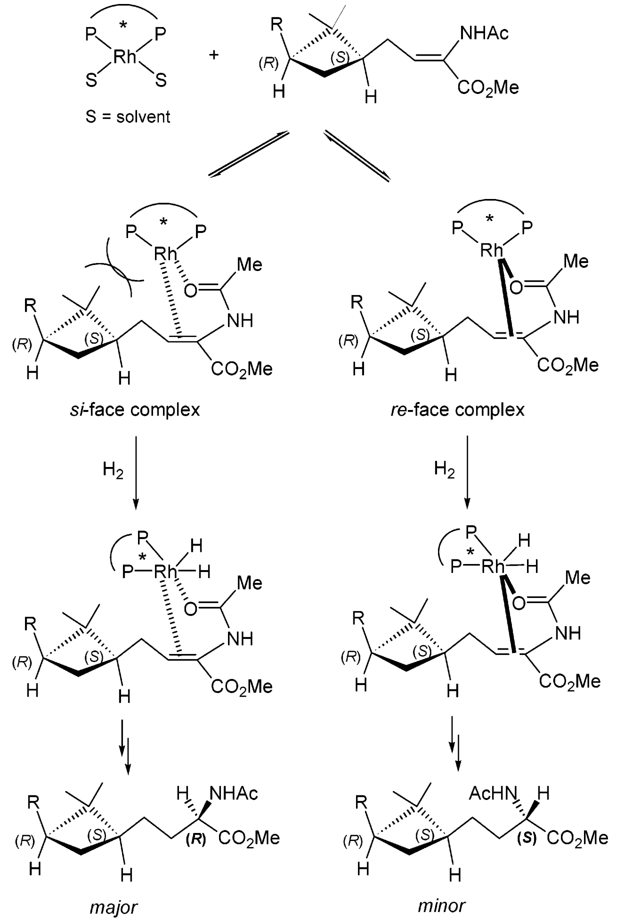
[14] (a) Albrecht, J.; Nagel, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *24*, 407. (b) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martínez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37. (c) Burk, M. J.; Gross, M. E.; Martínez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (d) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (e) Debenhamm, S. D.; Debenham, J. S.; Burk, M. J.; Toone, E. J. *J. Am. Chem. Soc.* **1997**, *119*, 9897. (f) Hoermer, R. S.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3455.

SCHEME 3



complex and results from the addition of hydrogen to the *si* face of the double bond. The chirality of the substrate also influences the π-facial diastereoselection because the diastereomeric ratios from (−)- and (+)-**4** were 96:4 and 85:15, respectively, favoring the *R* isomer in both cases (entries 2 and 5 in Table 1). On the contrary, the configuration of the reduction products using Et-DuPHOS as a catalyst was determined exclusively by the chirality of the catalyst, affording saturated amino acids with 99.9:0.1 dr in all cases (entries 3, 4, 6, and 7 in Table 1).

In enamides **5**−**9**, the double bond is directly linked to the cyclobutane ring and both steric hindrance and the chirality of the substrate were expected to exert influence on the π-facial discrimination. In other addition reactions to the double bond in these substrates, we had previously observed that the major induced configuration could be explained by assuming that the reagent attacks the less hindered π face opposite to the *gem*-dimethyl group in a preferential conformation for the substrate.[15] To provide a more accurate model to explain the diastereoselectivity observed in the hydrogenation reactions, we carried out theoretical calculations by considering the rotation around the C_3-C_4 bond of a model (*Z*)-enamide with R = H. The corresponding potential energy curve obtained at the AM1 level of calculation is shown in Figure 2. We can observe that there is a very flat region in the 150−250° range with two energy minima at $\Phi = 168$ and 228° with an energy difference of only 0.2 kcal mol^{-1}. Beyond this region, energy rapidly increases so that the rotation is hindered. Two energy minima have also been located at the BPW91/6-31G(d) level of calculation at $\Phi = 224.1$ and 236.9°, with the latter being 0.4 kcal mol^{-1} higher in energy than the former. We have also located the most stable conformers for (*Z*)-enamides **5** (R = COOMe, $\Phi =$ 224.7°), **7** (R = Ac, $\Phi = 224.6$°), and (*Z*)-**8** (R = dioxolane, $\Phi = 223.5$°). The structure of the most stable conformer of the latter is shown in Figure 3.

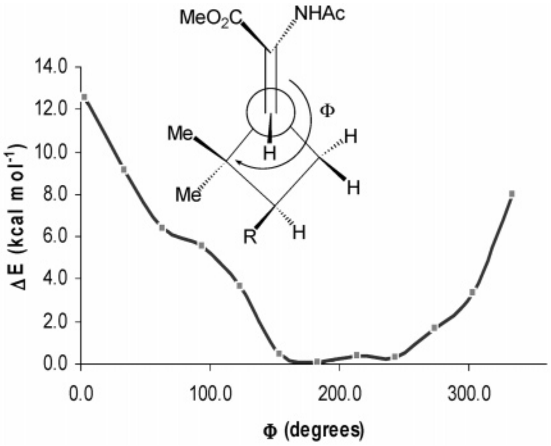


FIGURE 2. Energy curve corresponding to the rotation around the C_3-C_4 bond obtained at the AM1 level of calculation for a model (*Z*)-enamide with R = H.

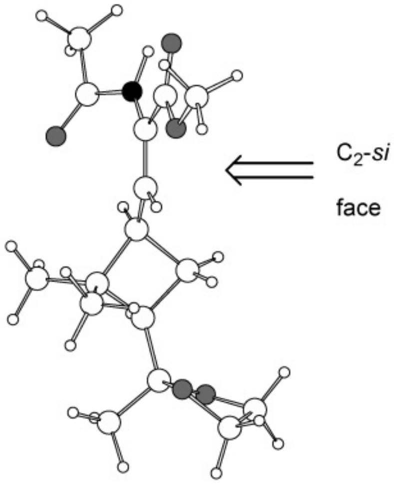


FIGURE 3. Minimum energy structure of (*Z*)-**8** obtained at the BPW91/6-31G(d) level of calculation.

Assuming that this is the preferred conformation for the (*Z*)-enamides, the reaction is favored by the C_2 *si* face, leading to **b** stereoisomers with *R* configuration in the new stereogenic center (Chart 1).

For the model (*E*)-enamide (R = H), only one conformational minimum was found corresponding to a dihedral angle $\Phi = 246.6$°, which also favors the production of **b** stereoisomers. For (*E*)-**8**, the most stable structure corresponds to $\Phi = 236.9$° (see the Supporting Information).

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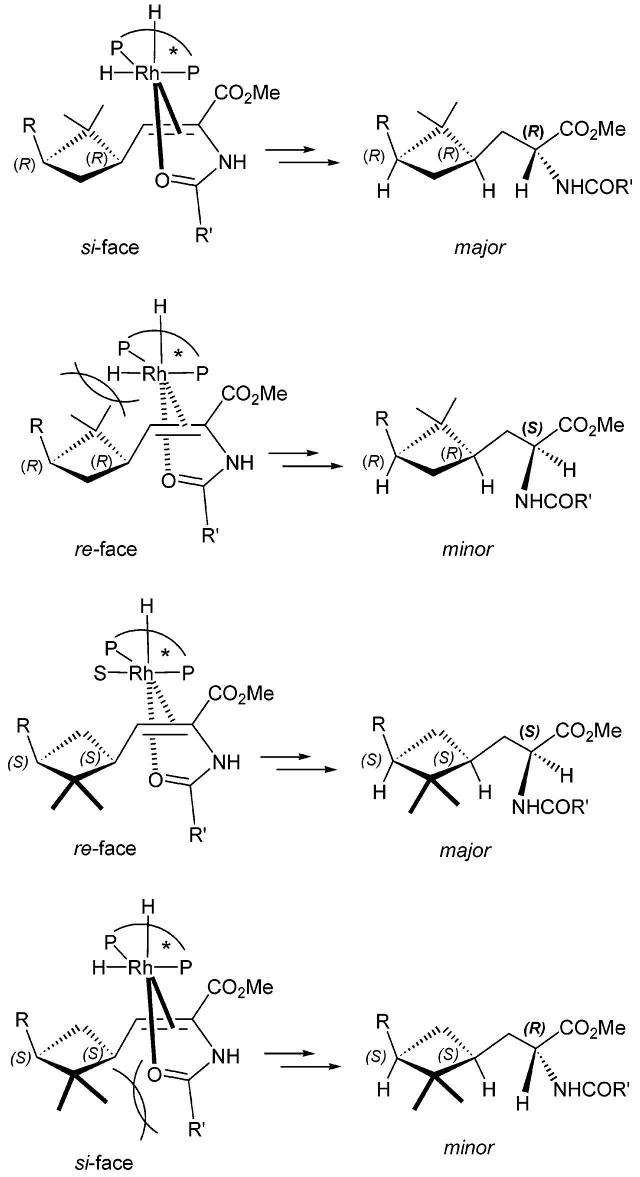
[15] (a) Moglioni, A. G.; García-Expósito, E.; Álvarez-Larena, Á.; Branchadell, V.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, *11*, 4903. (b) Moglioni, A. G.; Muray, E.; Castillo, J. A.; Álvarez-Larena, Á.; Moltrasio, G. Y.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2002**, *67*, 2402. (c) Moglioni, A. G.; Brousse, B. N.; Álvarez-Larena, Á.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2002**, *13*, 451.

SCHEME 4



Inspection of Table 2 leads to the following considerations. Moderate diastereoselectivity was induced when Wilkinson catalyst, **1**, was used (entries 1 and 12), affording *R* diastereomers. When (*S*,*S*)-ChiraPHOS, **2**, was used in the hydrogenation of (*Z*)-enamides **5**, (+)-**6**, **7**, and (*Z*)-**8**, *R* diastereomers were also produced in higher dr (entries 2, 4, and 13). On the contrary, *S* diastereomers prevailed when both **1** and **2** were used in the hydrogenation of substrates (−)-**6** and **9** with opposite chirality of the former enamides (entries 8, 15, and 16). In all of these cases, (*S*,*S*)-ChiraPHOS, **2**, does not follow the Halpern mechanism. The formation of the major adducts can be explained on the basis of the steric congestion of the catalyst−substrate complexes favoring the production of *R* diastereomers as the result of the *si* attack to (*R*,*R*)-substrates **5**, (+)-**6**, **7**, and (*Z*)-**8** (Scheme 4). Similarly, *S* diasteromers were the major products resulting from (*S*,*S*)-enamides (−)-**6** and **9**.

In contrast, when using DuPHOS-Rh, the stereochemistry is governed by the catalyst, which follows the Halpern mechanism. From the reactions of (+)- and (−)-**6** with (*R*,*R*)- and (*S*,*S*)-**3** (entries 5, 7, 9, and 11), we can deduce that (+)-**6**/(*R*,*R*)-**3** and (−)-**6**/(*S*,*S*)-**3** are matching pairs. In these cases, the configurations of the major stereoisomers result from a cooperative effect of the chiralities in the substrate and in the catalyst, also called double stereodifferentiation. On the contrary, (+)-**6**/(*S*,*S*)-**3** and (−)-**6**/(*R*,*R*)-**3** are the mismatching pairs. Diastereoselectivity decreased when catalyst **21** was employed (entries 6 and 10 in Table 2). In general, the determined dr for the obtained products was lower than that for the reduction of enamides (+)- and (−)-**4** and the values reported in the literature for the hydrogenation of achiral olefins with DuPHOS catalysts. Nevertheless, we have recently reported the hydrogenation of a chiral cyclobutyl dehydrodipeptide with (*R*,*R*)-Et-DuPHOS to afford a major product in >99.9:0.1 dr showing a clearly defined instance of double asymmetric induction.[16]

The behaviors of (*Z*)- and (*E*)-enamides toward (*S*,*S*)-ChiraPHOS, **2** (entries 17 and 20 in Table 2), were similar because in both cases the chirality of the substrate governed the diastereoselection. With DuPHOS catalysts, the match/mismatch is not very marked for (*Z*)-**8** (compare 85:15 vs 80:20 dr in entries 18 and 19 in Table 2). This effect is noteworthy, however, for (*E*)-**8** because the chiralities of the substrate and (*R*,*R*)-**3** are strongly mismatching (entry 21). These results contrast with others previously reported in the literature, accounting for a similar behavior of achiral *Z* and *E* substrates toward DuPHOS catalysts.[5,6]

Conclusions

All of these results shed light on the use of chiral catalysts in the stereoselective hydrogenation of chiral olefins. High stereodifferentiation resulted in the hydrogenation of type I enamides when ChiraPHOS or DuPHOS-Rh was employed. Diastereoselection was substrate-dependent when either Wilkinson catalyst or ChiraPHOS-Rh was used in the hydrogenation of type II (*Z*)-enamides. DuPHOS catalyts, however, always controlled the configuration of the amino acids resulting from both types of substrates. In general, diastereoselectivity was lower in the hydrogenation of type II enamides and, in some instances, matching/mismatching effects have been found. Finally, different behavior has been observed in the hydrogenation of a chiral (*Z*)-olefin with respect to the *E* isomer toward different catalysts, contrary to the examples reported in the literature on the hydrogenation of achiral olefins.

Experimental Section

Methyl (1′*R*,3′*R*)-2-Acetylamino-3-(3′-acetyl-2′,2′-dimethylcyclobutyl)-(*Z*)-2-propenoate, 7. Oil. $[\alpha]_D$: −9.2 (*c* 1.09, MeOH). IR (film): 3288, 1725, 1703, 1671 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 0.89 (s, 3H), 1.31 (s, 3H), 1.87−2.30 (complex absorption, 2H), 1.98 (s, 3H), 2.01 (s, 3H), 2.89−3.03 (complex absorption, 2H), 3.67 (s, 3H), 6.46 (d, J = 8.8 Hz, 1H), 8.26 (broad s, 1H). ^{13}C NMR (acetone-d_6): δ 18.6, 22.7, 23.6, 30.1, 30.7, 40.5, 45.8, 52.1, 54.1, 128.5, 137.4, 165.5, 169.1, 206.8. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.62; H, 7.87; N, 5.02.

Methyl (1′*R*,3′*R*)-2-Benzyloxycarbonylamino-3-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-(*E*)-2-

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(16) Aguado, G. P.; Moglioni, A. G.; Brousse, B.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2003**, *14*, 2445.

propenoate, (*E*)-8. Oil. $[\alpha]_D$: −14.3 (*c* 0.28, MeOH). IR (film): 3330, 1729, 1705 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 1.04 (s, 3H), 1.10 (s, 3H), 1.17 (s, 3H), 1.54−2.22 (complex absorption, 3H), 3.18 (m, 1H), 3.71 (s, 3H), 3.72−3.92 (complex absorption, 4H), 5.09 (s, 2H), 6.15 (d, J = 10.0 Hz, 1H), 7.20−7.49 (complex absorption, 5 H), 7.90 (broad s, 1H). ^{13}C NMR (acetone-d_6): δ 17.8, 23.0, 25.6, 30.7, 39.7, 43.8, 49.8, 51.0, 63.2, 65.0, 66.0, 109.2, 126.9, 127.8, 128.2, 129.9, 136.7, 153.7, 164.1. Anal. Calcd for $C_{22}H_{29}O_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.24; H, 7.41; N, 3.17.

(1*S*,3*R*)-2,2-Dimethyl-3-(2′-methyl-1′,3′-dioxolan-2′-yl)-cyclobutylmethanol Benzyl Ether, 11. Sodium hydride (485 mg, 20.2 mmol) was added to a solution of the known alcohol **10**[11] (570 mg, 2.8 mmol) in freshly distilled DMF (9.6 mL), and the mixture was stirred for 1 h under a nitrogen atmosphere. Then benzyl bromide (2.7 g, 15.8 mmol) was added dropwise, and the resultant solution was stirred at room temperature for 96 h. The solvent and much of the excess benzyl bromide were removed under reduced pressure, and the residue was diluted with CH_2Cl_2 (35 mL). The solution was washed with three 30-mL portions of water and dried over $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography (1:1 CH_2Cl_2−hexane, CH_2Cl_2, and 1:1 EtOAc−hexane as the successive eluents) to afford ether **11** (665 mg, 80% yield) as a pale yellow oil. $[\alpha]_D$: −12.54 (*c* 4.6, MeOH). IR (film): 2952, 2876, 1456, 1365, 1177, 1074 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 1.06 (s, 3H), 1.14 (s, 3H), 1.15 (s, 3H), 1.48−1.61 (m, 1H), 1.72−1.82 (m, 1H), 2.05−2.15 (complex absorption, 2H), 3.31−3.50 (complex absorption, 2H) 3.74−3.94 (complex absorption, 4H), 4.44 (s, 2H), 7.31 (complex absorption, 5H). ^{13}C NMR (acetone-d_6): δ 17.3, 22.4, 24.0, 32.4, 41.1, 42.4, 50.55, 64.2, 66.0, 71.9, 73.3, 110.3, 128.0, 128.2, 129.0, 140.1. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.21; H, 8.99.

(1*R*,3*S*)-3-Benzyloxymethyl-2,2-dimethylcyclobutyl Methyl Ketone, 12. A mixture of ketal **11** (140 mg, 0.48 mmol) and PPTS (64 mg, 0.25 mmol) in wet acetone (6.5 mL) was heated to reflux for 6 h. Then the reaction mixture was cooled to room temperature, and the solvent was removed at reduced pressure. The residue was diluted with 25 mL of ether, washed twice with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed, and the crude ketone **12** was purified by column chromatography (3:2 CH_2Cl_2−hexane) to afford pure **12** (114 mg, 96% yield) as a pale yellow oil. Ot: 105−110 °C (0.03 Torr). $[\alpha]_D$: −42 (*c* 3.4, MeOH). IR (film): 1705 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.87 (s, 3H), 1.34 (s, 3H), 1.71−1.99 (complex absorption, 2H), 2.02 (s, 3H), 2.21−2.34 (m, 1H), 2.84 (dd, J = 7.5 Hz, J' = 10.0 Hz, 1H), 3.31−3.43 (complex absorption, 2H), 4.44 (s, 2H), 7.30 (complex absorption, 5H). ^{13}C NMR (acetone-d_6): δ 17.1, 20.3, 30.0, 31.2, 41.7, 43.0, 53.9, 71.4, 73.2, 128.0, 128.1, 128.9, 139.9, 206.9. Anal. Calcd for $C_{16}H_{22}O_2\cdot{}^1/_2H_2O$: C, 75.26; H, 8.68. Found: C, 75.42; H, 8.67.

Methyl (1*R*,3*S*)-3-Benzyloxymethyl-2,2-dimethylcyclobutane-1-carboxylate, 13. An ice-cooled aqueous solution of sodium hypobromite prepared from Br_2 (1.25 mL, 25 mmol) and NaOH (4.3 g, 107 mmol) was added to a stirred solution of ketone **12** (2 g, 8.1 mmol) in dioxane (25 mL) cooled at −5 °C. The mixture was subsequently stirred at 0 °C for 3 h and at room temperature for 4 h and was extracted with two 50-mL portions of ether. Forty percent aqueous $NaHSO_3$ and concentrate HCl were subsequently added to reach pH 2. Then the acid aqueous solution was extracted with ether (5 × 50 mL), and the organic extracts were dried over $MgSO_4$. The solvent was removed at reduced pressure, affording a crude acid (0.9 g, 45% yield), which was used in the next step without further purification. To an ice-cooled solution of this acid (0.9 g, 3.6 mmol) in ether (50 mL) was added a freshly distilled ethereal solution of diazomethane. The mixture was stirred at room temperature for 1 h, excess diazomethane was destroyed by addition of benzoic acid, the resultant mixture was filtered, and the solvent was removed to afford an oil that was chromatographed on silica gel (3:1 hexanes−EtOAc) to provide pure ester **13** (0.9 g, 95% yield). $[\alpha]_D$: −21 (*c* 0.67, MeOH). IR (film): 1734 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 0.92 (s, 3H), 1.22 (s, 3H), 1.91 (complex absorption, 2H), 2.25 (m, 1H), 2.74 (dd, J = 8.2 Hz, J' = 10.0 Hz, 1H), 3.33−3.52 (complex absorption, 2H), 3.60 (s, 3H), 4.45 (s, 2H), 7.31 (complex absorption, 5H). ^{13}C NMR (acetone-d_6): δ 17.6, 21.9, 31.0, 42.1, 42.6, 46.2, 51.1, 71.4, 73.3, 128.0, 128.2, 128.9, 139.9, 173.3. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.20; H, 8.45. Found: C, 73.42; H, 8.58.

(1*R*,3*S*)-3-Benzyloxymethyl-2,2-dimethylcyclobutylmethanol, 14. A 2 M solution of $LiBH_4$ in THF (8 mL, 16 mmol) was added to a solution of ester **13** in freshly distilled dry THF (10 mL), and the mixture was heated to reflux for 24 h under a nitrogen atmosphere. Then the reaction mixture was cooled to room temperature, and the excess hydride was destroyed by slow addition of methanol. Water was added, and the resultant solution was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed at reduced pressure. The residue was purified by column chromatography (EtOAc) to give alcohol **14** (364 mg, 69% yield). Oil. $[\alpha]_D$: +8.9 (*c* 0.89, MeOH). IR (film): 3510−3250 (broad) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3H), 1.16 (s, 3H), 1.23 (m, 1H), 1.91−2.25 (complex absorption, 3H), 3.30−3.64 (complex absorption, 5H), 4.45 (s, 2H), 7.30 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): δ 16.3, 23.3, 31.4, 39.1, 41.3, 44.1, 63.78, 71.1, 72.8, 127.4, 128.2, 138.6. Anal. Calcd for $C_{15}H_{22}O_2\cdot{}^1/_2H_2O$: C, 74.04; H: 9.11. Found: C, 74.48; H, 9.07.

Methyl (1′*S*,3′*S*)-2-Acetylamino-3-(3′-benzyloxymethyl-2′,2′-dimethylcyclobutyl)-(*Z*)-2-propenoate, 9. A mixture of alcohol **14** (0.8 g, 3.4 mmol) and PDC (1.4 g, 3.6 mmol) in dry CH_2Cl_2 (23 mL) was stirred at room temperature for 6 h under a nitrogen atmosphere. Then a small portion of Florisil was added, and stirring was continued for 30 min. The mixture was filtered through Celite that was washed with ether (50 mL), and solvents were removed at reduced pressure to provide a crude aldehyde (0.5 g, 70% yield), which was used in the next step without further purification.

Methyl 2-*N*-acetylamino-2,2-dimethoxyphosphinyl acetate (0.6 g, 2.6 mmol) in dry dichloromethane (5 mL) was slowly added to a solution of KO^{t}Bu (0.3 g, 2.5 mmol) in dry dichloromethane (6 mL) at −78 °C under a nitrogen atmosphere. The resultant solution was stirred at −78 °C for 30 min, and aldehyde (0.2 g, 0.9 mmol) in dry dichloromethane (3 mL) was added. The mixture was warmed to room temperature and stirred for 6 days under a nitrogen atmosphere. Then water (10 mL) was added, layers were separated, and the aqueous phase was extracted with dichloromethane (4 × 25 mL). The combined organic phases were dried over $MgSO_4$, and solvent was removed. The residue was chromatographed (2:1 EtOAc−hexane) to give the enoate **9** (50 mg, 17% yield). Oil. $[\alpha]_D$: −7.3 (*c* 0.82, MeOH). IR (film): 3267 (broad), 1725, 1668 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 1.00 (s, 3H), 1.11 (s, 3H), 1.56 (ddd, $J = J' = J''$ = 10.2 Hz, 1H), 1.97 (s, 3H), 2.07−2.92 (complex absorption, 3H), 3.30−3.53 (complex absorption, 2H), 3.66 (s, 3H), 4.45 (s, 2H), 6.49 (d, J = 8.8 Hz, 1H), 7.20−7.40 (complex absorption, 5H), 8.25 (broad s, 1H). ^{13}C NMR (acetone-d_6): δ 17.5, 22.2, 26.3, 30.8, 40.8, 42.4, 42.9, 51.6, 71.1, 72.8, 127.6, 127.7, 128.5, 137.7, 139.5, 165.2, 168.6. Anal. Calcd for $C_{20}H_{27}O_4N$: C, 69.50; H, 7.88; N, 4.06. Found: C, 69.80; H, 7.87; N, 4.04.

(1′*S*,2*R*,3′*R*)-2-Acetylamino-4-(3′-acetyl-2′,2′-dimethylcyclobutyl)butanoate, 15a. Crystals. Mp: 127−131 °C (from acetone−pentane). $[\alpha]_D$: −18.9 (*c* 0.79, MeOH). IR (film): 3303 (broad), 1746, 1702, 1659 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): δ 0.79 (s, 3H), 1.27 (s, 3H), 1.31−2.10 (complex absorption, 7H), 1.90 (s, 3H), 1.97 (s, 3H), 2.87 (dd, J = 7.9 Hz, J' = 9.8 Hz, 1H), 3.65 (s, 3H), 4.35−4.40 (m, 1H), 7.32 (broad s, 1H). ^{13}C NMR (acetone-d_6): δ 16.7, 22.1, 23.1, 26.2, 30.1, 30.6, 30.4, 41.8, 42.9, 51.60, 52.6, 53.7, 169.5, 173.0, 206.4. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.24; H, 8.56; N, 4.86.

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Supporting Information Available: General experimental methods; full description of compounds **15b**, **16a**, **16b**, **17a**, **17b**, **18a**, **18b**, **19a**, **19b**, **20a**, **20b**, **21a**, **21b**, **22a**, and **22b**; computational details; Cartesian coordinates of all optimized structures; and energy curve corresponding to rotation around C_3-C_4 bond for a model (*E*)-enamide (R = H). This material is available free of charge at http://pubs.acs.org.

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