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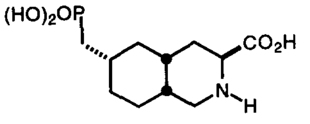
Diastereoselectivity in the Heterogeneous Hydrogenation Reactions of Phosphorous Substituted Olefins

Bret E. Huff,* Vien V. Khau, Michael E. LeTourneau, Michael J. Martinelli,*
Naresh K. Nayyar, and Barry C. Peterson

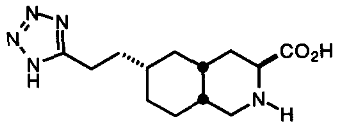
Chemical Process R&D
Lilly Research Laboratories
A Division of Eli Lilly and Company
Indianapolis, Indiana 46285-4813

Phosphorous substituted methylenecyclohexane olefins show enhanced diastereoselectivity in heterogeneous hydrogenation reactions using Pd/C. A model system derived from 4-*t*-butylcyclohexanone was used to explore the effects of solvent polarity and catalyst on the reduction reaction. It was found that olefins hydrogenated with catalytic Pd/C in polar solvents afford the highest diastereoselectivities (>15:1). © 1997 Elsevier Science Ltd.

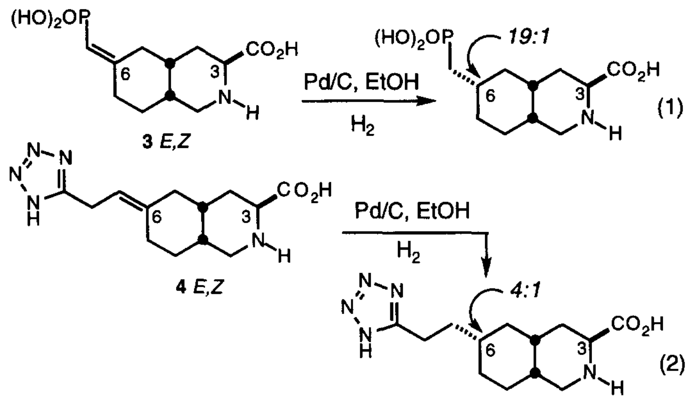
During studies to prepare two pre-clinical drug candidates, LY235959 (**1**) and LY293558 (**2**), the corresponding precursor olefins were subjected to heterogeneous hydrogenation conditions with surprisingly different results (eqn 1 and 2).[1] While olefin **3**, containing a vinyl (*E* and *Z*) phosphonate moiety was reduced with excellent diastereoselectivity at C-6 (19:1), compound **4** was hydrogenated with only fair (4:1) C-6 diastereoselectivity. Although a slight preference for axial hydrogenation of 1,4-disubstituted methylenecyclohexanes to provide the corresponding *trans* products in 2-4:1 selectivity (Table 1) has been demonstrated,[2] the magnitude of the selectivity observed in the reduction of **3** is unprecedented. In this report, we describe our efforts to explore the generality of this observation by the preparation and reduction of a variety of model exocyclic olefins prepared from 4-*t*-butyl cyclohexanone.



LY235959 (**1**)

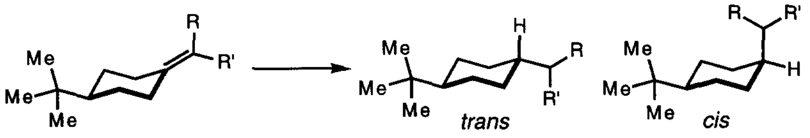


LY293558 (**2**)



Results of the hydrogenation of a series of substituted olefins derived from 4-*t*-butyl cyclohexanone are summarized in Table 1. Compared with olefin substrates **3**-**4**, these model compounds simplify the study by obviating any possible effects of olefin geometry. First, we established that the reaction conditions used in this study (10% Pd/C, 50 psi H_2, EtOH) provided reduction products with the same slight preference for *trans* product as those reported in the literature (entries 1-3). Next, we showed that phosphonate-substituted olefins (entries 8 and 9) provided much higher selectivity than the alkyl substituted olefins (entries 1-3).[3] Indeed, the phosphate ester (entry 8), and even the trifluoroethyl phosphonate (entry 9) provided enhanced diastereoselectivities. Interestingly, substrates containing other polar groups such as ethyl ester (entry 4) and sulfoxide (entries 4-5) did not provide markedly higher selectivities.

Table 1. Reductions of Variously Substituted 4-*t*-Butylcyclohexenes.[a]

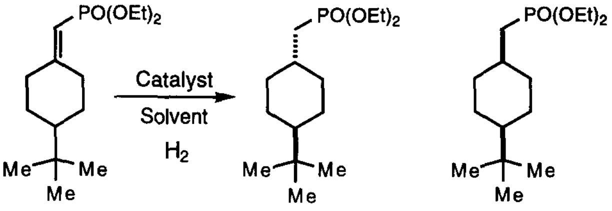


Entry[a]	R, R' =	*trans*	*cis*
1	H, H	2	1
2	H, Me	2.1	1
3	Me, Me	3.8	1
4	H, CO_2Et	3.1	1
5	H, $SO_2(OEt)$	2.9	1
6	H, *t*-Bu	3	1
7	H, $POPh_2$	1.3	1
8	H, $PO(OEt)_2$	14.3	1
9	H, $PO(OCH_2CF_3)_2$	8	1

[a] All reactions were carried out using 10 wt% 10%Pd/C in EtOH at 50 psi H_2 unless otherwise noted. Ratios of products were determined using capillary GC after complete reduction of olefin substrate.

Hydrogenation of **5** was also carried out in solvents of varying polarity with 10% Pd/C, 5% Pt/C, and 3% Rh/C (Table 2). Hydrogenation of **5** proceeded with highest diastereoselectivity in polar solvents with 10% Pd/C (entries 1-2) and with lowest selectivity using 3% Rh/C in EtOAc/Hex (entry 9). As expected, no reaction occurred using homogeneous hydrogenation conditions (Table 2, entry 10).[4]

Table 2. Effect of solvent and catalyst on product ratio.

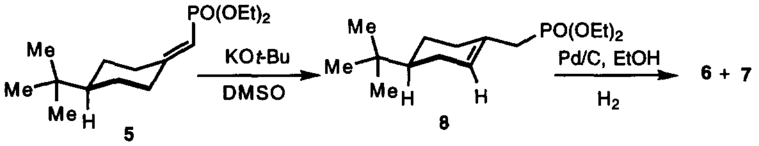


5 **6** **7**

Entry	Solvent[a]	Catalyst (mg/mL)	Yield (%)[b]	Ratio[c] (**6**:**7**)
1	EtOH	10% Pd/C (1.08)	98.9	14.3:1
2	EtOAc	10% Pd/C (1.08)	98.2	9.3:1
3	Hex:EtOAc (3:1)	10% Pd/C (1.12)	98.1	6.6:1
4	EtOH	5% Pt/C (1.09)	97.6	9.5:1
5	EtOAc	5% Pt/C (1.09)	98.2	8.7:1
6	Hex:EtOAc (3:1)	5% Pt/C (1.12)	96.0	7.4:1
7	EtOH	3% Rh/C (0.56)	98.2	1.9:1
8	EtOAc	3% Rh/C (0.54)	97.6	1.2:1
9	Hex:EtOAc (3:1)	3% Rh/C (0.55)	97.6	1.2:1
10	Hex:EtOAc (3:1)	$Rh(PPh_3)_3Cl$ (1.12)	---	---

[a] All reactions were carried out at 50 psi H_2. [b] Isolated yield of purified material. [c] Determined by capillary GC.

Next, we considered the possibility that olefin migration might be responsible for the high diastereoselectivity observed in the reaction (Scheme). Olefin migration during hydrogenation reactions is well documented, particularly with Pd/C.[5] Close analysis of the reaction progress by GC and ^1H NMR established that some olefin migration was indeed occurring under the optimal conditions (Table 2, entry 1). Equilibration of the vinylic phosphonate olefin **5** to the allylic phosphonate **8** with *t*-BuOK[6] followed by hydrogenation with Pd/C in EtOH provided only a 4:1 ratio of **6**:**7**. These results are in agreement with the findings of Sauvage who showed that increasing amounts of *cis* isomer are formed upon isomerization of exocyclic olefins to the internal position of 1,4-substituted cycloalkenes.[7] Further analysis (GC) of the reaction showed that the vinylic phosphonate olefin was rapidly reduced, whereas the internal allylic phosphonate olefin **8** was reduced at a much slower rate.



Scheme.

Conclusion. Phosphonate-substituted olefins provide enhanced diastereoselection in hydrogenations over Pd/C. It appears unlikely that result can be explained by coordination of the phosphonate with the catalyst surface since the effect is greatest in polar solvents. Studies by Thompson on the ability of polar "haptophilic" groups to coordinate with catalytic surfaces would indicate that the polar solvents would decrease the interaction of the catalyst surface and the phosphonate.[8] It is also possible that the phosphonate is somehow stabilizing the half-hydrogenated intermediate in the reduction.[9] Lambert has recently proposed that phosphorous, like silicon, is competent at stabilizing β-charge.[10] Further studies are underway to explore the key control elements of the enhanced diastereoselection described here.

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References and Notes.

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