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EFFICIENT ASYMMETRIC HYDROGENATIONS OF CAMPHOR-SULTAM-IMIDE-CONJUGATED ALKENES.

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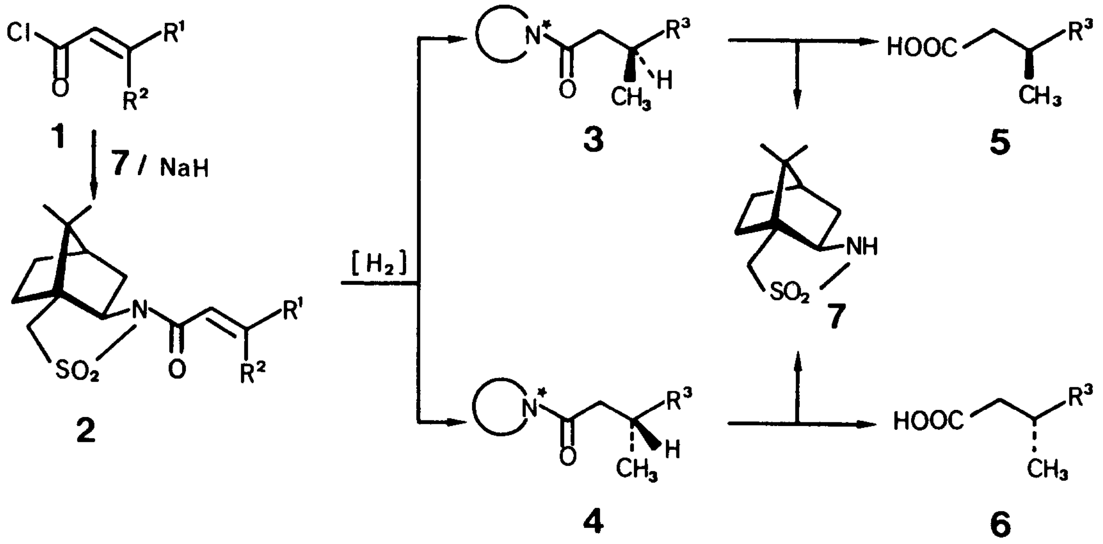
Abstract: The trisubstituted olefinic bond of sultam-imides 2 was hydrogenated in the presence of Pd/C with >90% diastereoface discrimination to give after saponification recovered auxiliary 7 and the β-substituted carboxylic acids 5 or 6 in high e.e..

The stereoface-selective addition of hydrogen to various olefinic bonds remains a practical and intellectual problem despite the striking achievement of enantioselective hydrogenations of prochiral Z-α-acylaminoacrylic acids and esters [1].

As an extension of previous work revealing highly π-face selective Diels-Alder additions of 1,3-dienes to the chiral dienophiles 2 (R^1,R^2=H and R^1=Me,R^2=H) [2] we examined the hydrogenation of the trisubstituted alkenes 2 (R^1,R^2 = CH_3, Alkyl). Our results are summarized in Scheme 1 and the Tables 1 and 2.

Scheme 1



Successive treatment of sultam 7 with NaH and the corresponding acid chloride 1 [3] gave the imides 2 [6] in 50 to 84% yield after crystallization (2a, 2b, 2g, 2h) or flash chromatography. Choosing imide 2b as the substrate a variety of reagents and reaction conditions for the hydrogenation were first explored (Table 1).

Table 1: Asymmetric Hydrogenation of 2, R^1= nPr, R^2=Me: Variation of the Reaction Conditions.

Entry	Reaction Conditions					Ratio[a)] 3b : 4b
1	LAH/$CoCl_2$		THF	-78° → RT	1 h	92 : 8
2	LAH solution/$CoCl_2$		Et_2O	-78° → RT	3 h	16 : 84
3	$[Ir(cod)py\ (PCy)_3]^+\ PF_6^-$,	1 atm H_2	CH_2Cl_2	RT	1 h	61 : 39
4	10% Pd/C	30 psi H_2	EtOH	RT	48 h	95 : 5
5	10% Pd/C	95 psi H_2	EtOH	RT	1.5h	98 : 2
6	10% Pt/C	90 psi H_2	EtOH	RT	17 h	89 : 11

After addition of 2b (E/Z = 98:2) to a slurry of $LiAlH_4$ (2.4 moleq.) and $CoCl_2$ [7] (2.4eq.) in THF at -78° the mixture was allowed to warm to r.t. over 90 min affording a 92:8-mixture of 3b+4b in good yield (entry 1). Apart from this high degree of topological control it is worth noting that the imide group remained intact under these reaction conditions [7] Unexpectedly, the topicity of the reaction was reversed but less distinct on analogous reduction of 2b with a solution of $LiAlH_4$ (2.0 moleq) and $CoCl_2$ (2.0 eq) in Et_2O (-78°, 1h →r.t., 3h, entry 2). Hydrogenation of 2b using the soluble Felkin-Crabtree catalyst $Ir(cod)pyP(Cy_3)PF_6$ [8] displayed only poor stereoface discrimination (entry 3). By contrast and to our surprise, conventional, heterogenous catalysis with Pd/C under 30 psi H_2 (48h) provided 3b with >90% π-face selection (entry 4). On increasing the H_2 pressure to 95 psi the reaction was complete within 1.5h [9] to give 3b [7] with virtually quantitative topological control (accounting for the 98:2-E/Z-ratio of 2b, entry 5). Under similar conditions the Pt-catalyzed hydrogenation was slower and less stereoselective (entry 6).

To examine the scope and limits of the strikingly simple and efficient reaction conditions described in entry 5 [9] the hydrogenation of a series of β,β-disubstituted imides 2 were studied (Table 2).

Table 2: Asymmetric Hydrogenation of 2 with H_2 (100 psi), Pd/C, EtOH: Variation of R^1 and R^2.

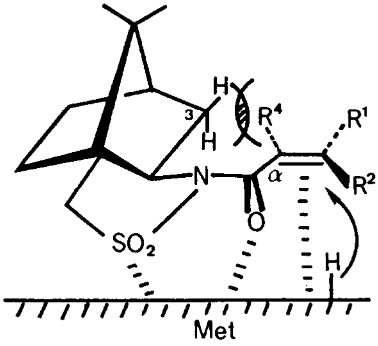
Entry	Substrate			Product[6]		
	R^1 /	R^2	E/Z[a)]	R^3	Yield[b)] 3 + 4	Ratio[b)] 3 : 4
a	C_2H_5	CH_3	>99.9: 0.1	C_2H_5	99(88)	(>99.5:<0.5)[d)]
b	nC_3H_7	CH_3	99 : 1	nC_3H_7	95	98 : 2[c,e)]
c	iC_3H_7	CH_3	99 : 1	iC_3H_7	97	95.5: 4.5[c,d)]
d	nC_4H_9	CH_3	97.7: 2.3	nC_4H_9	95	95 : 5[c,e)]
e	nC_6H_{13}	CH_3	98 : 2	nC_6H_{13}	99	96 : 4[c,d,e)]
f	nC_8H_{17}	CH_3	99.8: 0.2	nC_8H_{17}	93	96.2: 3.8[c,d,e)]
g	$(CH_2)_2CH{=}C(CH_3)_2$	CH_3	99.2: 0.8	$(CH_2)_3C(CH_3)_2$	96(69)	95(>99.5): 5(<0.5)[c,d,e)]
h	CH_3	$(CH_2)_2CH{=}C(CH_3)_2$	1.7:98.3	$(CH_2)_3C(CH_3)_2$	96	4.3:95.7[c,d,e)]

a) capillary GC; b) crude (crystalline); c) capillary GC of the mixture 3+4. The amides derived from 5+6 and(+)-(R)-α-naphthylethylamine were analyzed d) by capillary GC and e) by HPLC

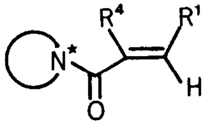
The extent of chiral induction was conveniently determined by direct capillary GC analyses of the crude reaction mixtures. Saponification of products 3 and 4 with 1.23 N LiOH (8 eq) in THF/H_2O (7:3, r.t. 18h) afforded the β-substituted carboxylic acids 5 [6] and 6 [6] in 92 to 100% yield after distillation. Their absolute configurations were assigned based on chiroptic comparison with published values [10]. The enantiomeric purities of acids 5 and 6, as determined by GC and analyses of their α-ethylnaphthylethylamides [12] parallel the diastereoisomer ratios 3:4.

Several aspects of Table 2 are noteworthy. Entries a and g show that products 3a and 3g can be purified by crystallization and thus obtained efficiently in virtually 100% diastereomeric purity . Comparison of entries g and h illustrates the expected correlation of topological control with olefin geometry. Accordingly, the E-alkene 2g furnished the (R)-dihydrocitronellic acid 5g whereas the Z-alkene 2h gave the antipodal (S)-acid 5h with the same level of 90% stereoface discrimination.

Scheme 2



A



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The observed direction and extent of diastereoface differentiation on Pd/C.catalyzed hydrogenations of imides 2 may be rationalized by figure A, R^4=H (Scheme 2). Thus, we assume coordination of the SO_2- and C=O oxygens as well as of the olefinic bond to the metal surface from the sterically less hindered Cα-Re face followed by H-transfer to the same face. Consistent with this postulate the analogous hydrogenations of α-branched acrylimides 8, R^4=$n C_3H_7$, R^1=H and of 8, R^4=CH_3, R^1=C_2H_5 showed only 32% and 23% face differentiation, respectively; apparently, C=C/C=O synplanarity is excluded here for reasons of steric repulsion between R^4/C(3).

In conclusion we believe that the employment of covalently bound but easily recoverable chiral auxiliaries enlarges significantly the scope of asymmetric alkene hydrogenations [13]. This issue is currently subject of further investigation in this laboratory.

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[10] Reported $[\alpha]_D$-values: "Stereochemistry, Fundamentals and Methods" Vol. 4, Ed. H.B. Kagan, G. Thieme, Stuttgart 1977; see also 5a, 5d, 5f [11] 5g, 5h, [5].

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