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Tetrahedron Letters 45 (2004) 3035–3037
Tetrahedron Letters

Chelation-controlled highly diastereoselective catalytic hydrogenation of γ-hydroxy-α-methylenecarboxylic acid esters

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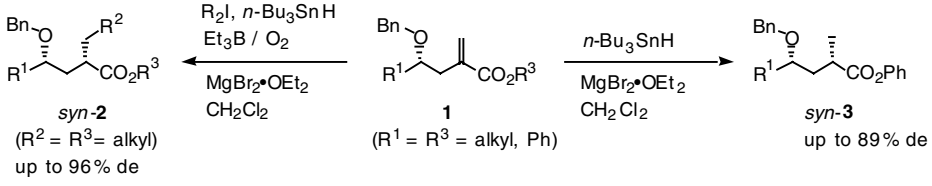
Received 2 February 2004; revised 16 February 2004; accepted 20 February 2004

Abstract—We report the catalytic hydrogenation of γ-hydroxy-α-methylenecarboxylic acid esters over Pd/C in the presence of 4 equiv of $MgBr_2$ in tetrahydrofuran yielding predominantly the corresponding *syn*-γ-hydroxy-α-methylcarboxylic acid esters.

The use of chelation with Lewis acids is one of the most efficient and practical means to control stereochemistry in acyclic reactions.[1] Recently, the concept has been applied to the stereoselective acyclic radical reactions.[2] We have reported the chelation-controlled 1,3-asymmetric induction in the radical-mediated additions to γ-benzyloxy-α-methylenecarboxylic acid esters **1** (R^3=alkyl; Scheme 1).[3] Furthermore, we applied the chelation control to the diastereoselective conjugate reduction of **1** (R^3=Ph) with tributyltin hydride.[4] To expand the scope and utility of the stereocontrol based on the seven-membered chelate ring formation, we have examined the heterogeneous catalytic hydrogenation of γ-hydroxy-α-methylenecarboxylic acid esters in the presence of Lewis acids. Very recently, Bouzide has reported the chelation-controlled stereoselective catalytic hydrogenation of α-methylene-β-oxycarboxylic acid esters (Baylis–Hillman adducts),[5] but to our knowledge, little is known about chelation-controlled heterogeneous catalytic hydrogenation reactions despite their importance in organic synthesis.

Initially, we carried out the hydrogenation of γ-hydroxy esters **4a** over Pd/C (10%) under an atmospheric pressure of hydrogen in various solvents (Scheme 2 and Table 1).[6] The hydrogenation of **4a** over Pd/C in THF showed no diastereoselectivity (entry 1).[7] However, the reaction performed in the presence of 3 equiv of $MgBr_2$ gave **5a** with high *syn*-selectivity (entry 2). In the radical reactions of **1** (Scheme 1), 3 equiv of $MgBr_2$ was sufficient to attain the highest diastereoselectivity,[3] but in the hydrogenation, the addition of 4 equiv of $MgBr_2$ further improved the diastereoselectivity to *syn*:*anti*=29:1 (entry 3). The use of dichloromethane as solvent showed lower *syn*-selectivity (entry 4),[8] although the solvent was very effective in the chelation-controlled radical reactions of **1**.[3] The addition of THF to dichloromethane increased the *syn*-stereoselectivity (entries 5 and 6). Surprisingly,



Scheme 1.

Keywords: Catalytic hydrogenation; Acrylic acid esters; Chelation control; Lewis acid; Solvent effect.
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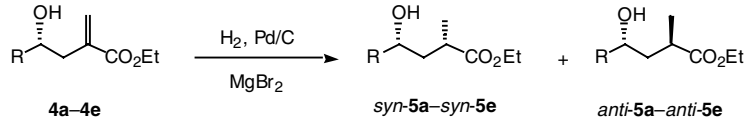
doi:10.1016/j.tetlet.2004.02.111



4a–4e *syn*-**5a**–*syn*-**5e** *anti*-**5a**–*anti*-**5e**

a R = *i*-Pr
b R = *c*-C_6H_{11}
c R = *n*-C_7H_{15}
d R = *t*-Bu
e R = Ph

Scheme 2. Chelation-controlled catalytic hydrogenation of **4**.

Table 1. Diastereoselectivity in the catalytic hydrogenation of **4a–e** over Pd/C

Entry	Substrate	$MgBr_2$ (equiv)	Solvent	Product	Yield (%)	*syn*:*anti*
1	**4a**	—	THF	**5a**	78	1:1
2		3	THF		72	16:1
3		4	THF		79	29:1
4		3	CH_2Cl_2		77	5.5:1
5		4	CH_2Cl_2[a]		73	7.1:1
6		4	THF–CH_2Cl_2[b]		69	12:1
7		3	1,4-Dioxane		92	1:1
8		4	CH_2Cl_2[c]		74	1.6:1
9		3	Et_2O		78	7.2:1
10		4	CH_3CN		82	8.8:1
11		3	AcOEt		59	3.5:1
12		3	MeOH		65	1.7:1
13	**4b**	4	THF	**5b**	90	21:1
14	**4c**	4	THF	**5c**	86	10:1
15	**4d**	3	THF	**5d**	86	>50:1
16	**4e**	4	THF	**5e**	85	3.9:1

[a] Additive: 4 equiv of THF.
[b] Ratio 1:10 v/v.
[c] Additive: 4 equiv of 1,4-dioxane.

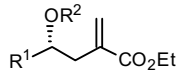
the diastereoselectivity was completely lost in 1,4-dioxane (entry 7) and even in dichloromethane containing 4 equiv of 1,4-dioxane (entry 8). Diethyl ether and acetonitrile were less effective compared to THF (entries 9 and 10). Entries 11 and 12 show that ethyl acetate and methanol were not suitable for the stereocontrol.

The selectivity did not increase on lowering the temperature to 0 °C. Neither $Mg(ClO_4)_2$ nor $ZnCl_2$ was effective. The hydrogenation of **4a** over platinum(IV) oxide in dichloromethane showed no diastereoselectivity even in the presence of $MgBr_2$.

Under the optimized reaction conditions (entry 3), we subsequently carried out the hydrogenation using various γ-hydroxy-α-methylenecarboxylic acid esters **4b–e**. γ-Cyclohexyl-substituted **4b** showed high *syn*-selectivity (entry 13), but the selectivity in the hydrogenation of **4c** was lower (entry 14). Substrate **4d**[3d] bearing a bulky *tert*-butyl group showed excellent *syn*-selectivity (*syn*:*anti*=>50:1; entry 15). These results suggest that the *syn*-selectivity increased with increasing the bulk of γ-substituent. γ-Phenyl-substituted substrate **4e**,[3d] however, gave **5e** with low *syn*-selectivity (entry 16).

The reaction of **4** affording *syn*-**5** and the catalytic hydrogenation of γ-substituted-α-methylene-γ-lactones affording the corresponding *syn*-α-methyl-γ-lactones[9] are complementary to each other with respect to diastereoselectivity.

The catalytic hydrogenation of MOM ether derivatives **6** and methyl ether **7** over Pd/C in the presence of $MgBr_2$ in THF or dichloromethane showed poor diastereoselectivity. This suggests that the hydrogen bonding between the γ-hydroxy group and a THF molecule may play an important role for the stereocontrol in the hydrogenation of hydroxy esters **4** in THF. However, the solvation of the magnesium center cannot be neglected to account for the differing selectivities observed with different solvents. Further investigation on the origin of the diastereoselectivity is now in progress.



6 R^1 = *i*-Pr, *c*-C_6H_{11}, *n*-C_7H_{15}, Ph
R^2 = MOM
7 R^1 = Ph, R^2 = Me

In summary, we reported the catalytic hydrogenation of γ-hydroxy-α-methylenecarboxylic acid esters **4** over Pd/

C in the presence of 4 equiv of $MgBr_2$ in tetrahydrofuran yielding predominantly the corresponding *syn*-γ-hydroxy-α-methylcarboxylic acid esters **5**.

References and notes

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6. Typical procedure of hydrogenation. To a solution of **4a** (21 mg, 0.11 mmol) in 3.0 cm^3 of dry THF was added $MgBr_2$ (86 mg, 0.47 mmol, 4.2 equiv), and the mixture was stirred at room temperature for 15 min. To the suspension was added Pd/C (10%; 26 mg, 0.2 equiv) and the mixture was stirred under an atmospheric pressure of H_2 at room temperature for 3.5 h. After filtration, the crude product was chromatographed on silica gel (2 g; eluent: hexane–ethyl acetate (6:1)) to give **5a** (16.7 mg, 79% yield) as an inseparable diastereomeric mixture.
7. The α-methin proton of *syn*-**5** resonated in lower field compared to that of *anti*-**5** (see, Ref. 3). The diastereomer ratio of **5** was determined by the integration of α-methin protons.
8. For recent palladium-catalyzed heterogeneous hydrogenation, see: King, A. O.; Larsen, R. D.; Negishi, E.-i. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley: New York, 2002; Vol. 2, pp 2719–2752.
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