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Magnesium Bromide Mediated Highly Diastereoselective Heterogeneous Hydrogenation of Olefins

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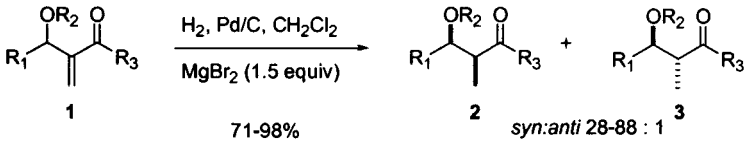
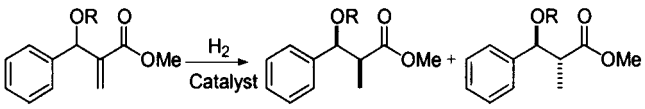
ABSTRACT



Palladium on carbon combined with magnesium bromide catalyzed hydrogenation of Baylis–Hillman olefins to afford the corresponding aldol derivatives in a highly *syn*-diastereoselective manner is described.

Catalytic hydrogenation of a carbon−carbon double bond is a reaction of great importance in organic synthesis, and it can be accomplished in a homogeneous or heterogeneous fashion. While homogeneous hydrogenation of olefins catalyzed by ruthenium, rhodium, and iridium complexes afforded the reduced product with high diastereoselectivity,[1] the heterogeneous counterpart catalyzed by palladium, platinum, and nickel showed generally low selectivity.[2] The difference in reactivity between these two classes of catalysts is attributed to the ability of the soluble catalysts to coordinate with the unsaturation and a neighboring directing heteroatom.[3] For example, the hydrogenation of Baylis−Hillman adduct **1a** in the presence of rhodium catalyst afforded the reduced products **2a:3a** with a high *anti*-selectivity[4] (Scheme 1), whereas the hydrogenation of the same substrate **1a** catalyzed by palladium on carbon produced **2a:3a** without any selectivity.[4] Almeida and Coelho have recently reported a heterogeneous hydrogenation of the derived Bu^{t}Me$_2$Si ether **1b** in the presence of Pd/C in EtOAc to produce **2b:3b** with a moderate *syn*-selectivity[5] (Scheme 1).

Scheme 1



1a, R= H, Rh complex	**2a**	1:99	**3a** (ref. 1b, 4)
1b, R= Bu^{t}Me$_2$Si, Pd/C	**2b**	6:1	**3b** (ref. 5)
1a, R= H, Pd/C, $MgBr_2$, CH_2Cl_2	**2a**	62:1	**3a** (this work)

Although Lewis acids have played an important role in the chelation-controlled ionic,[6] pericyclic,[7] and radical reactions,[8] no report has dealt with the utilization of a Lewis

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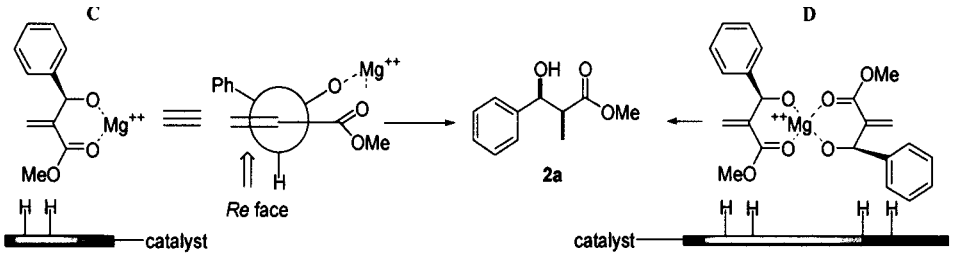
Scheme 2



acid in Pd-catalyzed diastereoselective hydrogenation of olefins. Herein, we would like to report that Pd/C combined with $MgBr_2$ is an excellent system to reduce alkenes with high diastereoselectivity. As a model of our study, we chose Baylis−Hillman[9] adduct **1a**.[10]

Addition of $MgBr_2$ (1.5 equiv) to a solution of **1a** in EtOAc, followed by the addition of Pd/C and subsequent hydrogenation under an atmospheric pressure of H_2, afforded the reduced products in which the *syn*-isomer **2a** predominated by up to 32:1 over the *anti*-isomer **3a** (Scheme 1). The relative stereochemistry of **2a** and **3a** was determined by comparing their ^{1}H NMR spectral data with those reported in the literature.[5a,11] Replacement of EtOAc with THF, a complexing solvent, resulted in a moderate *syn*-selectivity (Table 1, entry 2). Low selectivity and chemical yield were obtained in the case of toluene (entry 3), and complete loss of selectivity was observed when a polar solvent such as methanol was used (entry 4). On the other hand, the use of a noncomplexing solvent such as CH_2Cl_2 enhanced the ratio to 62:1 (entry 5).[12]

Table 1. Diastereoselective Heterogeneous Hydrogenation of **1a** in the Presence of Lewis Acid

entry[a]	solvent	Lewis acid (equiv)	time (h)	yield[b] (%)	ratio **2a:3a**
1	EtOAc	$MgBr_2$ (1.5)	1	95	32:1
2	THF	$MgBr_2$ (1.5)	1	68	7:1
3	toluene	$MgBr_2$ (1.5)	4	42	2:1
4	MeOH	$MgBr_2$ (1.5)	1	81	1:1
5	CH_2Cl_2	$MgBr_2$ (1.5)	1.5	93	62:1
6	CH_2Cl_2	$MgBr_2$ (1.2)	1.5	92	51:1
7	CH_2Cl_2	$MgBr_2$ (1.0)	1.5	92	45:1
8	CH_2Cl_2	$MgBr_2$ (0.5)	1	95	21:1
9	CH_2Cl_2	$MgBr_2$ (0.2)	1	96	7:1
10	CH_2Cl_2	$MgBr_2$ (0.1)	1	98	3:1
11	CH_2Cl_2	none	0.5	97[c]	1:1
12	CH_2Cl_2	$MgCl_2$ (1.5)	5	92	1:1
13	CH_2Cl_2	$ZnCl_2$ (1.5)	5	95	1:1
14	CH_2Cl_2	$ZnBr_2$ (1.5)	24	71	1:1.5
15	CH_2Cl_2	MgI_2 (1.5)	5	*c*	

[a] All reactions were run on 0.5 mmol of **1a** under an atmospheric pressure of H_2. [b] Isolated yields. [c] Only starting material was recovered.

The reaction was found to be highly dependent on the amount of Lewis acid, and the *syn*-selectivity diminished *linearly* with decreasing quantities of $MgBr_2$ (Table 1, entries 5−11). Accordingly, one can conclude that the reaction is stoichiometric and each $MgBr_2$ chelates with one hydroxy-acrylate **1a** as shown in Scheme 2, C. Although the solubility of $MgBr_2$ in CH_2Cl_2 is low,[13] higher ratios were obtained than we expected. For example, the hydrogenation of **1a** in the presence of 0.5 equiv of $MgBr_2$ should afford **2a:3a** with a 3:1 ratio if each $MgBr_2$ chelate with one hydroxy-acrylate **1a**. However, the obtained 21:1 ratio (Table 1, entry 8) indicates that probably each $MgBr_2$ chelates with two hydroxy-acrylates as illustrated in Scheme 2, D. This result would explain the moderate selectivity obtained when THF was employed as the solvent, because of its competition with **1a** in coordinating to the Lewis acid. It is worth noting that no hydrogenation took place in the absence of Pd/C or when it was replaced with Pt/C.

The stereochemical outcome of this hydrogenation reaction can be rationalized on the basis of a chelation of the carbonyl and hydroxy moieties to $MgBr_2$ forcing the molecule into a conformation that exposes the less sterically hindered bottom face (*re* face) to hydrogen delivery and thus providing access

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(10) The starting materials **1a** and **1c**−**f** were prepared according to the Baylis−Hillman procedure;[9] **1g** was prepared by methylation of **1a** in the presence of MeI and Ag_2O in CH_2Cl_2.

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(12) **Typical procedure** for the diastereoselective hydrogenation of **1a** in the presence of $MgBr_2$. To a solution of **1a** (96 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) was added $MgBr_2$ (138 mg, 0.75 mmol). The suspension was stirred for 15 min to allow the formation of the chelate. Pd/C (40 mg) was added, and the reaction was flushed with hydrogen and kept under atmospheric pressure for 90 min. The reaction was diluted with water (3 mL) and CH_2Cl_2 (6 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford cleanly **2a:2b** (90 mg, 93%). **2a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 7.3 Hz, 3H), 2.82 (m, 1H), 3.68 (s, 3H), 5.11 (d, J = 3.3 Hz, 1H), 7.27−7.37 (m, 5H). **3a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, 7.3 H, 3H), 2.96 (m, 1H), 3.74 (s, 3H), 4.75 (d, J = 8.8 Hz, 1H), 7.27−7.37 (m, 5H).

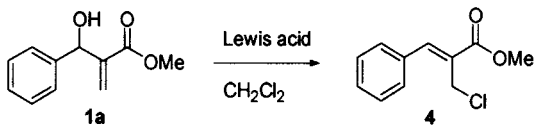
(13) $MgBr_2$ is known to have a low solubility in CH_2Cl_2, and the use of excess (3−5 equiv) is essential to achieve acceptable selectivity. See: Ward, D. E.; Hrapchak, M. J.; Sales, M. *Org. Lett.* **2000**, *2*, 57−60. Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464−10466.

to the *syn*-adduct (Scheme 2). Note that the hydrogenation of **1a** in the presence of $MgBr_2$ is 2−3 times slower than in its absence (entries 5 and 11). This could be explained by the steric hindrance caused by the Lewis acid in the six-membered chelate, which can render difficult its approach to the catalyst surface.

Complete loss of diastereoselectivity was noticed when other Lewis acids, such as $MgCl_2$, $ZnCl_2$, and $ZnBr_2$, were used instead of $MgBr_2$ (entries 12−14), and total inhibition was obtained in the case MgI_2 (entry 15).

As we checked the behavior of each Lewis acid with Baylis−Hillman olefins before every catalytic hydrogenation, we found that treatment of **1a** with $SnCl_4$, $TiCl_4$, and $FeCl_3$ in CH_2Cl_2 led exclusively to Z-allyl chloride **4** in good yields.[14] Such a compound was already obtained by different methods,[15] but to our knowledge, no synthesis of **4** from **1a** has been performed employing the cited Lewis acids.

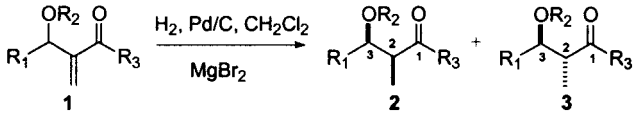
Scheme 3



Lewis acid	
$SnCl_4$	96%
$TiCl_4$	82%
$FeCl_3$	85%

To explore the generality of this highly diastereoselective hydrogenation, other substrates containing an olefin flanked by a carbonyl and a stereogenic hydroxyl group were subjected to our reduction conditions (Table 2). For instance, Pd-catalyzed hydrogenation of hydroxy-acrylate **1c** in the presence of 1.5 equiv of $MgBr_2$ yielded the aldols **2c:3c** with a 28:1 ratio in favor of *syn*-isomer. As predicted, the ratio raised to 88:1 in the case of **1d** where the R_1 group is an isopropyl. Similarly, hydrogenation of vinyl ketone **1e** gave the aldols **2e:3e** with a 83:1 ratio.[16] Low *anti*-selectivity was obtained when **1d** and **1e** were reduced in the absence of Lewis acid. The reaction was extended to alkoxy-acrylate **1g**, and its hydrogenation in the presence of $MgBr_2$ afforded

Table 2. Diastereoselective Heterogeneous Hydrogenation of Baylis−Hillman Adducts



olefin	R_1	R_2	R_3	yield[a] (%)	**2:3** ratio[b]	**2:3** ratio[c]	$^3J_{2,3}$ (Hz)	ref
1a	Ph	H	OMe	93	1:1	62:1	**2a**, 3.2; **3a**, 8.8	11, 5a
1c	Et	H	OMe	71	1:1	28:1	**2c**, *d*; **3c**, *d*	18
1d	^{i}Pr	H	OMe	95	1:2	88:1	**2d**, 3.3; **3d**, 6.0	19
1e	^{i}Pr	H	Me	87	1:1.5	83:1	**2e**, 3.2; **3e**, 6.2	20
1f	Ph	H	OEt	92	1:1	66:1	**2f**, 4.0; **3f**, 9.0	21
1g	Ph	Me	OMe	98	3:1	63:1	**2g**, 7.0; **3g**, 10.0	22

[a] Isolated yields referring to reduced products obtained in the presence of Pd/C/$MgBr_2$. [b] In the absence of $MgBr_2$. [c] In the presence of $MgBr_2$. [d] Value for $^3J_{2,3}$ was difficult to calculate because of the coupling of H-3 with methylenic protons.

the reduced adducts **2g:3g** in good yield and with *syn*-selectivity comparable to that observed with the parent alcohol **1a**. Hydrogenation of **1g** in the absence of $MgBr_2$ showed a slight preference for the *syn*-isomer.

The relative stereochemistry (C-2/C-3) of the reduced products was determined on the basis of ^{1}H NMR (500 MHz); in all cases, the vicinal coupling constant ($^3J_{2,3}$) for the *syn*-isomer is inferior to that of the *anti*-one (Table 2). Moreover, H-3 resonated in all cases downfield for the *syn*-adducts relative to the corresponding resonance of the *anti*-isomers.[17]

In conclusion, we have shown for the first time that Pd/C combined with $MgBr_2$ can catalyze hydrogenation of alkenes in a highly diastereoselective fashion. The ease by which Baylis−Hillman olefins can be prepared[23] followed by the present catalytic hydrogenation in the presence of $MgBr_2$ will constitute an alternative route for the preparation of *syn*-aldol derivatives. Although the present work was restricted to Baylis−Hillman olefins, the chelation-controlled hydrogenation in the presence of $MgBr_2$ could be expanded to other olefin and imine substrates.[24]

(14) To a solution of **1a** (96 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) was added Lewis acid (0.75 mmol). The reaction was stirred until complete consumption of the starting material (15−24 h). It was then diluted with H_2O and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by column to afford Z-allyl chloride **4** (82−96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.49 (s, 3H), 7.40−7.50 (m, 3H), 7.56 (d, J = 7.5 Hz, 2H), 7.89 (s, 1H).

(15) The previous methods used to obtain **4** from **1a** are as follows. NCS−SMe_2, see: Hoffman, H. M. R.; Rabe, J. *Org. Chem.* **1985**, *50*, 3849−3850. NEt_3−MsCl, see: Chavan, S P.; Ethiraj, K. S.; Kamat, S. K. *Tetrahedron Lett.* **1997**, *38*, 7415−7416. Oxalyl chloride−$CHCl_3$, see: McFadden, H. G.; Harris, R. L. N.; Jenkins, C. L. D. *Aust. J. Chem.* **1989**, *42*, 301−314. Treatment of the acetate derived from the corresponding alcohol with $AlCl_3/CH_2Cl_2$, see: Basaviah, D.; Pandiaraju, S.; Padmaja, K. *Synlett* **1996**, *4*, 393−395.

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Supporting Information Available: Preparative procedures and spectroscopic data for **1a**, **1c**−**g**, **2a**, **2c**−**g,** and **3a**, **3c**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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