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Conjugate reduction of aryl acrylates with tributyltin hydride in the presence of magnesium bromide diethyl etherate

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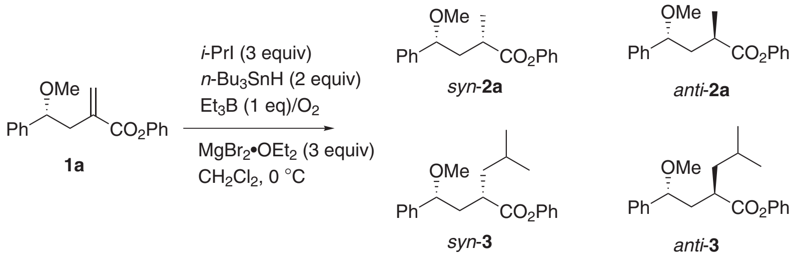
Abstract—The conjugate reduction of aryl acrylates performed with tributyltin hydride in the presence of magnesium bromide diethyl etherate in dichloromethane gave the corresponding saturated esters in moderate to high yields. The reduction of α-methylene-γ-benzyloxycarboxylic acid esters proceeded *syn*-selectively, but α-methylene-β-oxycarboxylic acid esters afforded reductive elimination products under the reaction conditions.

Organotin hydrides are effective for the conjugate reduction of α,β-unsaturated aldehydes and ketones.[1] However, the reagents undergo radical addition reaction to α,β-unsaturated carboxylic acid alkyl esters.[1d,2] Recently, Wu et al. have reported the radical-mediated conjugate reduction of *N*-(α-arylacryloyl)oxazolidinones with tributyltin hydride.[3] We now report the conjugate reduction of aryl acrylates with tributyltin hydride in the presence of $MgBr_2 \cdot OEt_2$ and the chelation controlled 1,3-asymmetric induction.[4–6] The conjugate reduction with the mild and neutral organotin reagent is of interest from the point of view that the reduction of aryl acrylates would proceed chemoselectively without affecting the unsaturated bond such as isolated double bond C=C and alkyl acrylate moieties.[7,8] Furthermore, the chelation controlled diastereoselective reduction would be an alternative to catalytic hydrogenation being used commonly for the diastereoselective reduction of acrylic acid esters.[9]

During the investigation on the diastereoselectivity in the alkyl radical addition to α-methylene-γ-oxycarboxylic acid esters,[4d] we found that the reaction of phenyl ester **1a** with isopropyl iodide gave the conjugate reduction products **2a** (21%, *syn*:*anti* = 1:1) together with radical adducts **3a** (40%, *syn*:*anti* = 2.8:1) (Scheme 1 and Table 1, entry 1).[10] The reaction of **1a** performed without isopropyl iodide gave **2a** in 51% yield with a diastereomer ratio *syn*:*anti* = 1.5:1 (entry 2).[5] Entry 3 shows that 2 equiv of $n\text{-}Bu_3SnH$ are required to attain high yield. The reaction proceeded without Et_3B, a radical initiator, and gave **2a** in 65% yield (entry 4):[11] this indicates that the conjugate reduction should proceed through an ionic mechanism. The Lewis acid



Scheme 1.

Keywords: Aryl acrylate; Conjugate reduction; Tributyltin hydride; Lewis acid.

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Table 1. Reduction of **1a** with n-Bu_3SnH[a]

Entry	n-Bu_3SnH (equiv)	Lewis acid (3 equiv)	Et_3B (equiv)	Yield of **2a** (%)
1[b]	2	$MgBr_2{\cdot}OEt_2$	1	21
2	2	$MgBr_2{\cdot}OEt_2$	1	51
3	1.2	$MgBr_2{\cdot}OEt_2$	1	45
4	2	$MgBr_2{\cdot}OEt_2$	0	65
5	2	$MgBr_2$	0	42
6	2	MgI_2	0	39

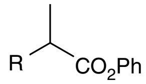
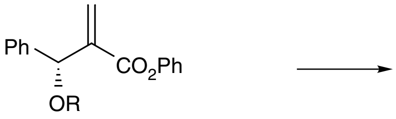
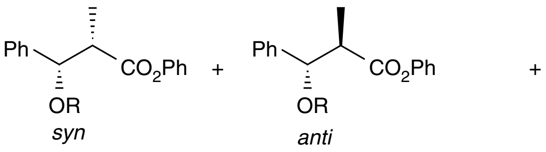
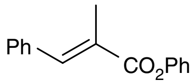
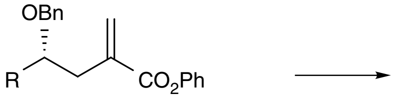
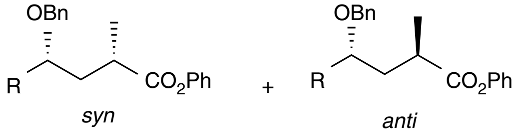
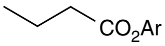
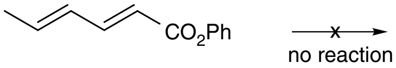
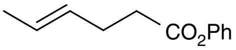
[a] Diastereomer ratio of **2a**: *syn*:*anti* = 1.5:1.

[b] The reaction was performed with *i*-PrI to give **3a** (40% yield; *syn*:*anti* = 2.8:1).

$MgBr_2{\cdot}OEt_2$ was indispensable for the reduction[1c] and in fact, a complex mixture was yielded in the absence of the Lewis acid. However, the use of $MgBr_2$ or MgI_2 as Lewis acid gave **2a** in lower yield (entries 5 and 6). $Mg(ClO_4)_2$, $ZnCl_2$, $Yb(OTf)_3$, and $LiClO_4$ were ineffective. The reduction of **1a** using Ph_3SnH instead of n-Bu_3SnH did not proceed.

Under the optimized reaction conditions (Table 1, entry 4), we next carried out the reduction using various aryl acrylates **1b**–**l** (Table 2).[10,11] The reduction of phenyl acrylate **1b** gave **2b** in poor yield due to the dimerization of **1b**. The yields in the reduction of α-substituted acrylates **1c**[12] and **1d** were 66% and 87%, respectively, but β-hydroxy-α-methylenecarboxylic acid ester (Baylis–Hillman adduct) **1e**[6] afforded **2e** (*syn*:*anti* = 2.2:1)[9] and the reductive dehydroxylation product **4**[13] in 25% and

Table 2. Conjugate reduction of aryl acrylates **1b**–**l** with n-Bu_3SnH in the presence of $MgBr_2{\cdot}OEt_2$

Substrate **1**	Product **2** (yield/%)	Other product (yield/%)
		
1b R = H	**2b** (25)	
1c R = Me	**2c** (66)	
1d R = $PhCH_2CH_2$	**2d** (87)	
		
1e R = H	**2e** (25; *syn*:*anti*= 2.2:1)	**4** (21)
1f R = MOM	**2f** (0)	**4** (96)
		
1g R = n-C_7H_{15}	**2g** (87; *syn*:*anti*= 18.0:1)	
1h R = Ph	**2h** (56; *syn*:*anti*= 8.2:1)	
		
1i Ar = Ph	**2i** (14; conversion yield 37) (49) [a]	
1j Ar = p-$O_2NC_6H_4$	**2j** (32; conversion yield 38) (40) [a]	
1k Ar = 1-naphthyl	**2k** (41; conversion yield 58) (74; conversion yield 84) [a]	
		
1l	**2l**	

[a] Reaction time: 27 h.

21% yields, respectively. In the case of the corresponding MOM ether **1f**, the α,β-unsaturated ester **4** was yielded exclusively in 96% yield. The reduction of benzyl ethers **1g** and **1h** proceeded in good yields with high *syn*-selectivities.[5] In contrast to the methyl ether **1a** (Table 1), the benzyl ethers showed higher diastereoselectivity.

Although the reduction of α-substituted acrylates proceeded in moderate to high yields as mentioned above, the reduction of phenyl crotonate **1i**[12] was sluggish and gave **2i** in only 14% yield. A longer reaction time (27 h) was required to increase the yield of **2i** (49%). *p*-Nitrophenyl crotonate **1j** gave **2j** in 32% yield, but in this case only a slight increase of yield was observed even after 27 h of the reaction. Further improvements were observed for the reduction of 2-naphthyl crotonate **1k**, although the reaction was not completed even after 27 h. The reduction of aryl crotonates (= nonterminal olefins) is very slow because the access to β-reaction center is hindered. With phenyl sorbate **1l**, no reaction occurred.

The LUMO energy of phenyl acrylates is lower than that of the corresponding alkyl acrylates (semiempirical AM1 calculations).[7,14] Furthermore, the coordination of the carbonyl oxygen atom of phenyl acrylates to the Lewis acid lowers their LUMO energy. The synergistic effects lowering the LUMO energy of acrylates may accelerate the conjugate reduction. The higher reactivity of *p*-nitrophenyl crotonate **1j** and 2-naphthyl crotonate **1k** compared to phenyl crotonate **1i** is due to the LUMO energies of **1j** and **1k** being lower than that of **1i**.

In summary, the phenyl esters of α-substituted acrylic acids (= terminal olefins) were reduced with tributyltin hydride in the presence of magnesium bromide diethyl ether to give the corresponding saturated esters in moderate to high yields. However, the β-substituted acrylic acids (= nonterminal olefins) were less reactive.

References and notes

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5. The chelation-controlled stereoselective catalytic hydrogenation of γ-hydroxy-α-methylene carboxylic acid esters will be reported elsewhere.
6. It has been reported that aryl acrylates react much faster than their alkyl counterparts in the Baylis–Hillman reactions. (a) Perlmutter, P.; Puniani, E.; Westman, G. *Tetrahedron Lett.* **1996**, *37*, 1715–1718; (b) Lee, W.-D.; Yang, K.-S.; Chen, K. *Chem. Commun.* **2001**, 1612–1613; (c) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* **2003**, *68*, 915–919.
7. No reduction of alkyl acrylate was observed under the reaction conditions.
8. It has been reported that the catalytic hydrogenation of methyl acrylate proceeds much faster than octyl, cyclohexyl or cyclododecyl acrylate over montmorillonitediphenylphoshinepalladium(II) chloride. Choudary, B. M.; Rao, K. K. *Tetrahedron Lett.* **1992**, *33*, 121–124.
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10. All new compounds showed satisfactory IR, ^{1}H NMR, ^{13}C NMR, MS, and HRMS spectroscopic data. The stereochemistries and diastereomer ratios of **2a**, **2g**, and **2h** were determined based on the chemical shift values and integrations of their α-protons.
11. Typical procedure: To a solution of **1** in dry dichloromethane (0.1 mol dm^{-3}) was added $MgBr_2{\cdot}OEt_2$ (3 equiv) under nitrogen atmosphere. The mixture was stirred at room temperature for 15 min and then was cooled to 0 °C. *n*-Bu_3SnH (2 equiv) was added and the mixture was stirred at 0 °C for 5 h. After treatment with KF and water and subsequent filtration through a column of Florisil, product was purified by column chromatography on silica gel to afford **2**.
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