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Simultaneous Functional Group Manipulation in the Meerwein-Ponndorf-Verley Reduction Process Catalyzed by Bidentate Aluminum Reagent

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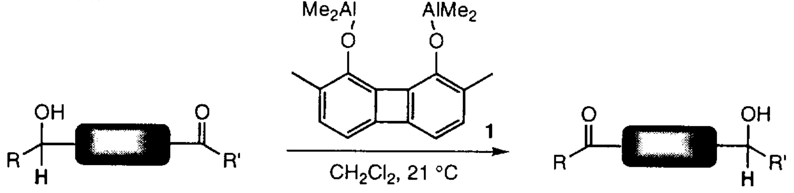
Abstract: Simultaneous reduction/oxidation sequence of hydroxy carbonyl substrates through Meerwein-Ponndorf-Verley reduction can be facilitated in the presence of bidentate aluminum catalyst, (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum). This new approach provides the opportunity for efficient hydride transfer between two remotely situated functional groups.

Despite numerous examples of functional group transformations, little is known of the simultaneous interconversion between different functional groups.[1] We recently introduced bidentate aluminum alkoxide catalysts which allow a modern variant of the Meerwein-Ponndorf-Verley reduction to be carried out under mild conditions based on the double electrophilic activation of carbonyl groups.[2] Various aldehydes and ketones can be reduced efficiently at room temperature in CH_2Cl_2 with *i*-PrOH as a hydride source. This achievement prompted us to examine the catalytic Meerwein-Ponndorf-Verley reduction of carbonyl compounds possessing *sec*-alcohol functionalities as a hydride source, where the oxidation of *sec*-alcohols should coincide with the reduction of carbonyls. Here we wish to report that simultaneous reduction/oxidation sequence of hydroxy carbonyl substrates in the Meerwein-Ponndorf-Verley reduction can be accomplished by use of a catalytic amount of (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum).[3] This new approach represents an efficient hydride transfer from *sec*-alcohol moiety to the remote carbonyl group as illustrated in Scheme 1 and, due to its insensitivity to other functionalities, should find vast potential in the synthesis of complex polyfunctional molecules including both natural and unnatural products.

Scheme 1



Selected results are summarized in Table 1. (2,7-Dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum) (**1**)[3] can be prepared *in situ* from 2,7-dimethyl-1,8-biphenylenediol and Me_3Al (molar ratio = 1:2) in CH_2Cl_2 at 21 °C for 30 min and the subsequent treatment of hydroxy aldehyde **2** with **1** (5 mol%) at 21 °C for 12 h resulted in formation of hydroxy ketone **3** in 78% yield. As expected, the use of 25 mol% of **1** enhanced the rate and the chemical yield was increased to 92% (entries 1 and 2). A similar tendency was observed with cyclohexanone derivative (entries 3-5). *It should be noted that the present reduction/oxidation sequence is highly chemoselective, and can be utilized in the presence of other functionalities such as esters, amides, tert-*

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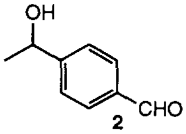
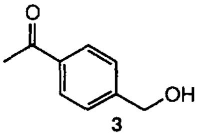
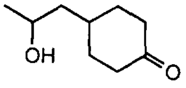
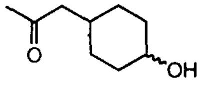
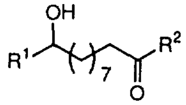
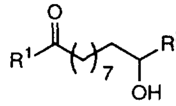
alcohols, nitriles and nitro compounds (entry 4). Aldehyde carbonyl can be reduced more easily than ketone, and the steric demand of the alcohol substituent (R^1 in Table 1) seemed to affect the rate of this reduction/oxidation process rather than its electronic property (entries 6-10).[4]

Table 1. Simultaneous Reduction/Oxidation Sequence of Hydroxy Carbonyl Compounds in the MPV Reduction Process [a]

entry	hydroxy carbonyl compound	mol % of catalyst **1**	condition (°C, h)	product	% yield [b, c]
1	 **2**	25	21, 3	 **3**	92
2		5	21, 12		78
3		25	21, 2		80 [d]
4		25	21, 2		70 [d, e]
5		5	21, 7		51 [f]
					
6	R^1 = Ph, R^2 = H	25	21, 5		87
7	R^1 = Ph, R^2 = CH_3	25	21, 12		34 [g]
8	R^1 = CH_3, R^2 = H	25	21, 3		81
9	R^1 = $CH=CH_2$, R^2 = H	25	21, 3		67
10	R^1 = $C \equiv CPh$, R^2 = H	25	21, 7		51

[a] The reaction of hydroxy carbonyl compound was carried out in the presence of bidentate aluminum reagent 1 in CH_2Cl_2 under the given reaction conditions. [b] Isolated yield. [c] The dicarbony compounds and diols were obtained as the side products in each case. [d] The *cis/trans* ratio was 23:77. [e] The reaction was conducted in the presence of each 0.2 equiv of methyl benzoate, *N*, *N*-dimethylbenzamide, *tert*-butanol, benzonitrile and nitrobenzene. [f] The *cis/trans* = 20:80 [g] 38% of the starting material was recovered.

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References and Notes

(1) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.

(2) Ooi, T.; Miura, T.; Maruoka, K. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2347 and references cited therein.

(3) (a) Ooi, T.; Takahashi, M.; Maruoka, K. *J. Am. Chem. Soc.* **1996**, *118*, 11307. (b) Ooi, T.; Tayama, E.; Takahashi, M.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 7403. (c) Ooi, T.; Takahashi, M.; Maruoka, K. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 835.

(4) The present system takes advantage of the reactivity difference between the substrate carbonyl and the product carbonyl toward MPV reduction in order to attain satisfactory chemical yield. In fact, treatment of (4-hydroxycyclohexyl)methyl methyl ketone (the product in entries 3-5) with 25 mol% of **1** in CH_2Cl_2 at 21 °C for 2 h resulted in 77% recovery of the hydroxy ketone with concomitant formation of 4-(2-hydroxypropyl)cyclohexan-1-one (the starting material in entries 3-5), 4-(2-oxopropyl)cyclohexan-1-one and 4-(2-hydroxypropyl)cyclohexane-1-ol in <1%, 12% and 10% yields, respectively.