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A Useful Synthetic Equivalent of a Hydroxyacetone Enolate

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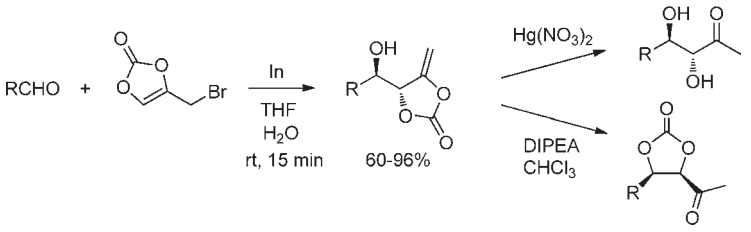
ABSTRACT



Indium promoted allylation of carbonyl compounds with 4-(bromomethyl)-1,3-dioxol-2-one diastereoselectively affords *anti*-α,β-dihydroxyketones, protected as enol carbonates. These initial products can be deprotected to free dihydroxyketones or transformed under mild conditions into the corresponding cyclic carbonates, which constitutes a useful approach to hydroxyacetone aldols.

Initially regarded as a mechanistic curiosity,[1] metal mediated allylations in aqueous media have rapidly evolved into a highly useful synthetic method. Among several metals that may promote such a type of transformation,[2] indium and zinc have found widespread application.[3] Although the allyl group is in principle amenable to various oxidative transformations, which makes it a synthetic equivalent of other nucleophiles, it would be highly desirable to extend the scope of allylation under aqueous conditions to the introduction of more highly functionalized structural subunits into organic compounds. To this aim, allylic halides with an additional halogen,[4] or sulfur,[5] substituent have been employed. Oxygen-substituted allylic halides, such as 3-bromopropenyl benzoate,[6] acetate,[7] or methyl carbonate,[8] have been used as d^1-hydroxyallyl synthons (synthetic equivalents of 1-hydroxyallyl anion). Recently, we introduced 2-(methoxymethyl)allyl bromide as a synthetic equivalent of an acetone enolate.[9]

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(1) (a) Petrier, C.; Einhorn, C.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 1449. (b) Petrier, C.; Luche, L. J. *J. Org. Chem.* **1987**, *50*, 910.

(2) Review article on allylations with allylmetals: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.

(3) Review articles: (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (b) Kargbo, R. B.; Cook, G. R. *Curr. Org. Chem.* **2007**, *11*, 1287. (c) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715. (f) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (g) For an example of the application in the total synthesis of natural products, see: Lee, K.-C.; Loh, T.-P. *Chem. Commun.* **2006**, 4209.

(4) (a) 2,3-Dichloropropene: Oda, Y.; Matsuo, S.; Saito, K. *Tetrahedron Lett.* **1992**, *33*, 97. (b) 1,3-Dichloropropene and 3-iodo-1-chloropropene: Chan, T.-H.; Li, C.-J. *Organometallics* **1990**, *9*, 2649. (c) 2-Chloro-3-iodopropene: Moral, J. A.; Moon, S.-J.; Rodriguez-Tores, S.; Minehan, T. G. *Org. Lett.* **2009**, *11*, 3734. (d) 1,6-Dibromocyclohex-1-ene: Oguro, D.; Watanabe, H. *Tetrahedron* **2011**, *67*, 777.

(5) Marquez, F.; Montoro, R.; Llebaria, A.; Lago, E.; Molins, E.; Delgado, A. *J. Org. Chem.* **2002**, *67*, 308.

(6) Palmelund, A.; Madsen, R. *J. Org. Chem.* **2005**, *70*, 8248.

(7) Lombardo, M.; Morganti, S.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 997.

(8) (a) Lombardo, M.; Pasi, F.; Trombini, C. *Eur. J. Org. Chem.* **2006**, 3061. (b) Lombardo, M.; Capdevila, M. G.; Pasi, F.; Trombini, C. *Org. Lett.* **2006**, *8*, 3303.

(9) (a) Maslak, V.; Tokic-Vujosevic, Z.; Ferjancic, Z.; Saicic, R. N. *Tetrahedron Lett.* **2009**, *50*, 6709. (b) For the extension of this concept to other 2-(alkoxy)allyl bromides, see: Dhanjee, H.; Minehan, T. G. *Tetrahedron Lett.* **2010**, *51*, 5609. See also:(c) 2-acetoxy-3-chloropropene: Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, *49*, 172. (d) (*E*)-Methyl 4-bromo-3-methoxybut-2-enoate: Paquette, L. A.; Kern, B. A.; Mendez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4129.

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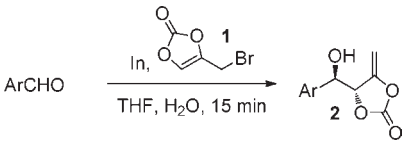
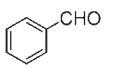
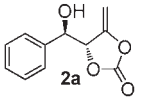
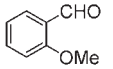
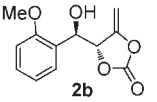
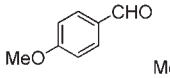
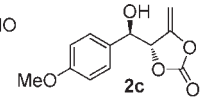
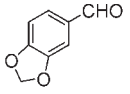
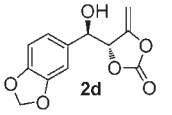
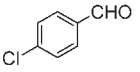
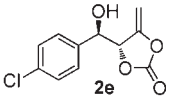
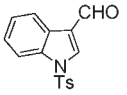
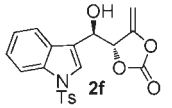
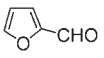
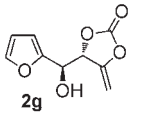
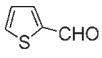
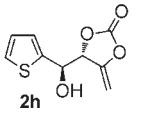
We set out to further enhance the synthetic potential of this method, by increasing the level of functionalization of the allylic reagent, thus making it a synthetic equivalent of more highly functionalized nucleophilic species. To this end, we speculated that 4-(bromomethyl)-1,3-dioxol-2-one **1** would be a reagent of choice, for several reasons: (a) two oxygen substituents make it a synthetic equivalent of an hydroxyacetone enolate; (b) the cyclic structure of the reagent contributes to stereodifferentiation in the transition state, which should result in a diastereoselective allylation reaction; (c) the reaction products are obtained in a protected form, suitable for further synthetic transformations. Literature searching revealed that Wender had reported the allylation with 4-(bromomethyl)-1,3-dioxol-2-one as early as 1990;[10] however, the reaction was only performed with an organochromium reagent and a mixture of regioisomers was obtained. The expected reaction product is a protected form of an α,β-dihydroxy ketone, i.e. a hydroxyacetone aldol – a common structural motif of many natural products and biologically active molecules. It should be noted that, within the past decade, a significant breakthrough in the stereoselective aldol addition of hydroxyacetone has been achieved through organocatalysis. Extensive studies in this field have recently brought about organocatalysts that efficiently promote the formation of hydroxyacetone *syn*-aldols;[11] aldolase antibody 38C2 has also been used for this purpose, with excellent enantioselectivity, but modest diastereoselectivity.[12] *Anti*-isomers seem to be somewhat more difficult to obtain: while proline,[13] DMTC,[13b] and proline derived[14] organocatalysts usually afford *anti*-aldols in high yields and with excellent enantioselectivities, the diastereoselectivities of the reaction are often moderate. Therefore, it would be desirable to have an alternative, mechanistically complementary method for the synthesis of *anti*-configured α,β-dihydroxy ketones and the derivatives thereof.

In our first experiment, 4-(bromomethyl)-1,3-dioxol-2-one **1**[15] was submitted to the reaction with benzaldehyde, in the presence of indium, in aqueous THF. Gratifyingly, within 15 min, TLC indicated full conversion of the starting material into a single product, which was isolated in 96% yield. Spectroscopic characterization showed this

Table 1. Allylation of Aromatic Aldehydes with **1**



entry	aldehyde	product	yield (%)	dr (*anti*:*syn*)
1		 **2a**	96	*11:1*
2		 **2b**	96	*2:1*
3			93[a]	*1:1*
4		 **2c**	82	*8:1*
5		 **2d**	95	*6:1*
6			59[a]	*4.5:1*
7		 **2e**	96	*7:1*
8			57[a]	*4:1*
9		 **2f**	78	only *anti*
10		 **2g**	83	*2:1*
11		 **2h**	91	*6.4:1*

[a] Zn was used instead of In. The reaction time was 45 min.

product to be, as expected, 4-(hydroxy(phenyl)methyl)-5-methylene-1,3-dioxolan-2-one **2a**, with a diastereomeric ratio of *anti*/*syn* = 11:1. The generality of the procedure was tested with a series of aromatic aldehydes, which all afforded the desired products in excellent yields; the results of these experiments are represented in Table 1. The relative stereochemistry of the products was confirmed by X-ray crystallographic analysis of the compound **2e**, which is represented in Figure 1. A drop in diastereoselectivity was observed when there was a proximal oxygen substituent, capable of coordinating the indium ion in the transition state (entries 2 and 10). These reactions could also be performed with zinc, instead of indium. Under

(10) Wender, P. A.; Wisniewski Grissom, J.; Hoffman, U.; Mah, R. *Tetrahedron Lett*. **1990**, *46*, 6605.

(11) (a) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2007**, *129*, 288. (b) Li, J.; Luo, S.; Cheng, J.-P. *J. Org. Chem*. **2009**, *74*, 1747. (c) Wu, X.; Ma, Z.; Ye, Z.; Qian, S.; Zhao, G. *Adv. Synth. Catal*. **2009**, *351*, 158. (d) DBU-catalyzed aldolisation of hydroxyacetone gives aldols in *syn*/*anti* ratios which vary from 9/1 to 7/3: Market, M.; Mulzer, M.; Schetter, B.; Mehrwald, R. *J. Am. Chem. Soc*. **2007**, *129*, 7258.

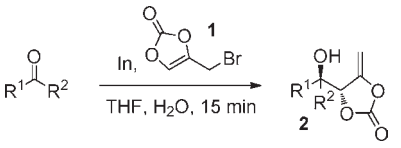
(12) List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. A. *Chem.—Eur. J*. **1998**, *4*, 881.

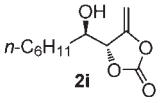
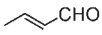
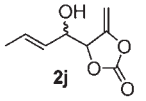
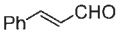
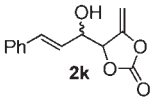
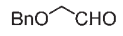
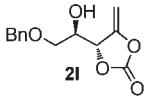
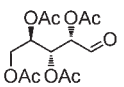
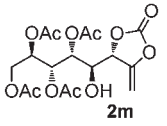
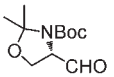
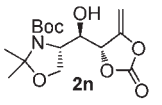
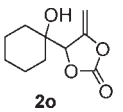
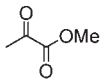
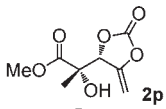
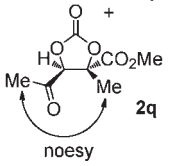
(13) (a) Notz, W.; List, B. *J. Am. Chem. Soc*. **2000**, *122*, 7386. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2001**, *123*, 5260.

(14) Lombardo, M.; Pasi, F.; Easwar, S.; Trombini, C. *Adv. Synth. Catal*. **2007**, *349*, 2061.

(15) This compound was obtained according to the modified literature procedure, in two steps, from hydroxyacetone, according to the procedure described for the 4,5-dimethyl derivative: (a) Alexander, J. U. S. Patent 5,466,811, 1995; *Chem. Abstr*. **1995**, *124*, 176148x. (b) Sakamoto, F.; Ikeda, S.; Tsukamoto, G. *Chem. Pharm. Bull*. **1984**, *32*, 2241. See the Supporting Information for details.

Table 2. Allylations of Aliphatic Carbonyl Compounds with **1**



entry	carbonyl compound	product	yield (%)	dr (*anti:syn*)
1	*n*-C_6H_{13}CHO	 **2i**	88	*6:1*
2			40[a]	*6:1*
3		 **2j**	82	*1:1*
4			38[a]	*1:1*
5		 **2k**	91	*1.4:1*
6		 **2l**	76	*3:1*
7		 **2m**	60	only *anti*[b]
8		 **2n**	81	*both anti*[c]
9		 **2o**	52	
10		 **2p**	52	single isomer
		 **2q** noesy	8	

[a] Zn was used instead of In. The reaction time was 45 min. [b] Represented are the absolute configurations of the reactant and the product. [c] obtained as an equimolar mixture of (*S,R,R*) and (*S,S,S*) isomers (only the (*S,R,R*)-isomer is represented).

these conditions, however, the yields and diastereoselectivities decreased (Table 1, entries 3, 6, and 8).

Next, we examined the reaction with aliphatic carbonyl compounds. In all cases, the desired products were obtained in good/excellent yields (Table 2). The lack of diastereoselectivity was observed with conjugated enals (entries 3, 4, and 5), again, when there was a coordinating oxygen in the α-position (entry 6). In the case of methyl

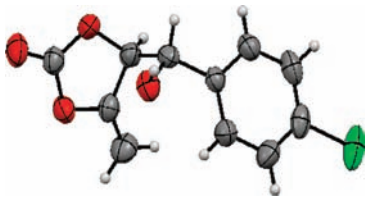


Figure 1. ORTEP diagram for **2e**.

pyruvate, the diastereomerically pure reaction product **2p** contained 15% of the rearranged carbonate **2q**. The relative stereochemistry of this compound (**2q**) was determined by a NOESY experiment, which allowed us to deduce the stereochemistry of **2p**, as well.[16] Allylation of 2,3,4,5-tetra-*O*-acetyl-D-arabinose proceeded with asymmetric induction, providing a single *anti* isomer **2m** (entry 7), as confirmed by X-ray crystallographic analysis (Figure 2). Surprisingly, no asymmetric induction was observed in the reaction with the Garner aldehyde, which furnished equimolar amounts of both *anti* isomers (entry 8).[17]

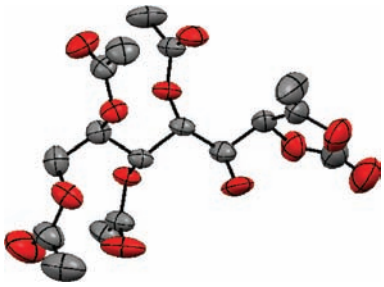
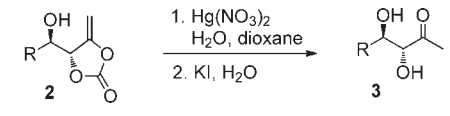


Figure 2. Ortep diagram for **2m**. Hydrogen atoms are omitted for clarity.

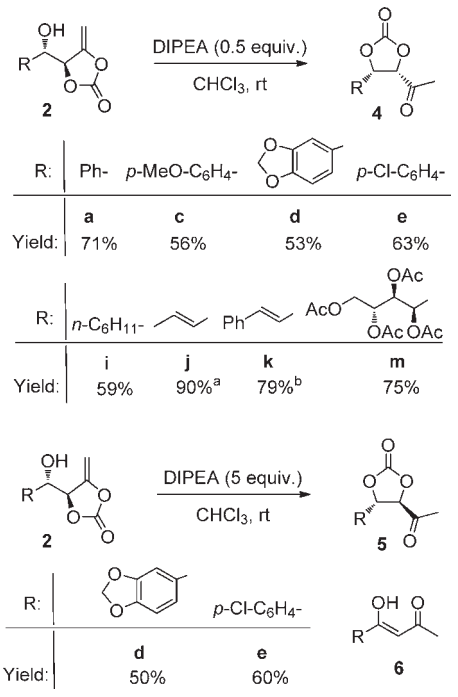
The advantage of our method is that the aldol-like products are obtained in a protected form **2**, suitable for further synthetic manipulation. If, however, free α,β-dihydroxy ketones **3** are needed, the initial products can be deprotected. While the acid- or base-catalyzed hydrolysis

Scheme 1. Deprotection of the Initial Products **2** into α,β-Dihydroxyketones **3**



R:	Ph-	*p*-$MeOC_6H_4$-		*p*-Cl-C_6H_4-	*n*-C_6H_{13}-
	a	**c**	**d**	**e**	**i**
Yield:	67%	64%	49%	75%	67%
(dr)	12:1	10:1	6.4:1	7.7:1	*anti* only

Scheme 2. Base-Promoted Rearrangement and Isomerization Reactions of Enol Carbonates **2**



[a] *Trans*/*cis* = 1.3:1. [b] *Trans*/*cis* = 1:1.

was not successful for this purpose, treatment of **2** with aqueous mercuric nitrate resulted in instantaneous formation of the free aldol products **3**, which retained the initial *anti* configuration (Scheme 1).

(16) **2q** is formed from **2p** by a rearrangement which occurs with the retention of stereochemistry; see below.

(17) Their structures were confirmed by X-ray crystallography; see the Supporting Information for details.

The initial products of type **2** can also be converted into cyclic carbonates **4** – another protected form of *anti*-α,*β*-dihydroxy ketones **3**. This transformation was effected under very mild conditions, by the treatment of **2** with a catalytic amount of DIPEA in chloroform at room temperature. As represented by Scheme 2, the generality of the procedure was tested on a series of compounds, which all gave *cis* products **4** stereoselectively, with the exception of unsaturated derivatives **2j** and **2k**, which gave high yields of diastereoisomeric mixtures. Interestingly, treatment of **2d** (or **2e**) with 5 equiv of the same reagent furnished *trans* isomer **5d** (or **5e**). This finding raised the hope of developing a diastereodivergent synthesis where, starting from carbonyl compounds, either *syn* or *anti* aldols of hydroxyacetone could be obtained at will, protected as cyclic carbonates. Unfortunately, the procedure lacked generality, as other substrates of type **2** gave mixtures of **4**, **5**, and the elimination product **6**.[18]

To summarize, indium mediated allylation of carbonyl compounds with 4-(bromomethyl)-1,3-dioxol-2-one **1** allows for the synthesis of *anti*-α,*β*-hydroxy ketones, in either protected or free form. Research oriented toward the development of a catalytic asymmetric variant of this method is underway.

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Supporting Information Available. Experimental procedures; copies of ^{1}H NMR, ^{13}C NMR, and other relevant spectra of all new compounds; crystal data for **2e**, **2m**, and **2n** (cif files). This material is available free of charge via the Internet at http://pubs.acs.org.

(18) (a) Julia, M.; Binet du Jassonneix, C. *Bull. Soc. Chim. Fr.* **1975**, 751. (b) Mors, W.; Gottliee, O. R.; Djerassi, C. *J. Am. Chem. Soc.* **1957**, *79*, 4507.