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Samarium dienolate mediated stereoselective synthesis of *anti*-1,3-diol monoesters via aldol-Tishchenko reaction

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Abstract—The reaction of an (*E*)-samarium dienolate, generated by the regioselective reductive cleavage of a phenylsulfonyl activated cyclopropyl ketone with samarium(II) iodide, with aliphatic and aromatic aldehydes gives the 2-substituted *anti*-1,3-diol monoester derivatives, stereoselectively, in good to excellent yields. The results represent the first report of a dienolate in the aldol-Tishchenko reaction and also provide an optically active polyol with (*R*)-glyceraldehyde.
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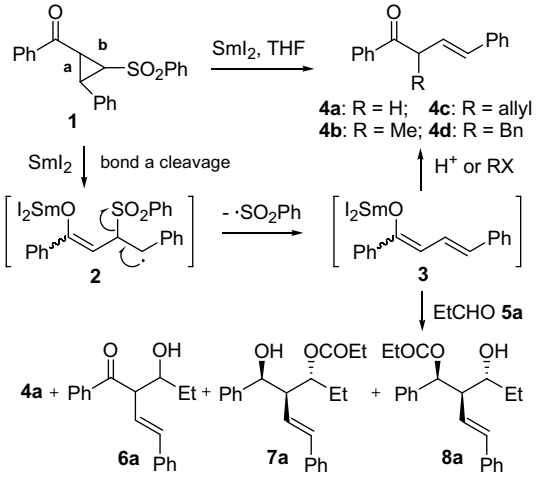
The Tishchenko reaction is a powerful tool in organic synthesis that allows the highly effective synthesis of many natural products[1] such as polyketides, macrolides, and coalescing agents in the paint industry.[2] In general, the tandem aldol-Tishchenko reaction is employed to access *anti*-1,3-diol monoesters from the intermediate metal-enolates (e.g., M = Li^{+}, Zn^{2+}, Al^{3+}, Sm^{2+}, Sm^{3+}, Yb^{3+}, Y^{3+}, Ga^{3+}, La^{3+}, Ti^{4+}, Zr^{4+}, or Hf^{4+}) with 2 mol of aldehyde through intramolecular hydride transfer in the hemiacetal formed from the aldehyde and the β-metaloxy carbonyl compound.[3,4] Among these metal complexes, samarium(II) iodide is one of the most effective agents for catalyzing both the Tishchenko reduction and the tandem aldol-Tishchenko reaction of β-hydroxy ketones and ketones or aliphatic aldehydes with aldehydes, respectively, to give *anti*-1,3-diol monoester adducts in high yields and excellent stereoselectivity.[1,3b,h,5]

Recently, we reported the synthetic applications of samarium(II) iodide-mediated regioselective cleavage of phenylsulfonyl activated cyclopropyl ketone **1** to give the (*E*)-β,γ-unsaturated ketone **4a** in high yield. Samarium dienolate **3** was proposed as the intermediate, which could be electrophilically trapped with alkylating agents. Only α-alkylated products **4b–d** were isolated (Scheme 1).[6] To the best of our knowledge, there are only a few reports on the reactions of samarium dienolates with various electrophiles.[6,7] In this letter, we report the first example of the tandem aldol-Tishchenko reaction of samarium dienolate **3** with various aldehydes to afford 2-substituted *anti*-1,3-diol monoesters in high yields and excellent stereoselectivity.

We first examined and optimized the reaction of samarium dienolate **3** with propanal in THF (Scheme 1 and



Scheme 1. Possible mechanism for the SmI_2-mediated formation of samarium dienolate **3** from activated cyclopropyl ketone **1** and its reactions with electrophiles.

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Table 1). With 10 equiv of propanal and stirring the reaction at −78 °C for 15 min and then at room temperature for an additional 5 h (entry 1), the aldol-Tishchenko adducts **7a** and **8a** were isolated in 44% and 30% yields, respectively. The addition of HMPA as cosolvent (entry 2) caused a reduction of the yields. We then searched extensively for the optimum conditions for the reaction. In Table 1, the conditions giving the highest yield of the aldol-Tishchenko adducts **7a** (68%) and **8a** (17%) are shown in entry 5. A longer reaction time caused equilibration (transesterification of **7a**) of the adducts **7a** and **8a**.[3a,e]

The generality of the reaction was secured through experiments with different aldehydes as electrophiles (Table 2) under the optimum conditions (Table 1, entry 5).[8] All the aldehydes studied gave the aldol-Tishchenko adducts in good to excellent yields, except for *p*-bromobenzaldehyde (entry 8) and the less electrophilic anisaldehyde (entry 10), as might be expected. Comparable levels of diastereoselection [**7**:**9** and **8**:**10** (>99:1)] were obtained with all long chain aliphatic, aromatic and β-alkyl substituted aldehydes. However, the α-alkyl substituted aldehyde, isobutyraldehyde (entry 4), appeared to exhibit lower diastereoselectivity under the current reaction conditions, compounds **7** and **9** were isolated in almost equal amounts.

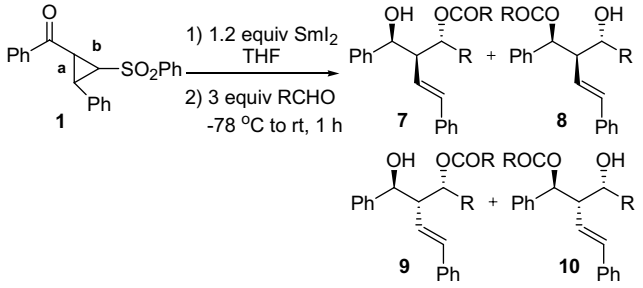
The structures and relative stereochemistries of the *anti*-1,3-diol monoesters **7**–**10** were established based on their ^{1}H NMR spectra. The relative stereochemistry of the unusual aldol-Tishchenko adduct **9d** (Table 2, entry 4) was confirmed by X-ray crystallographic analysis as shown in Figure 1. The mechanism of the aldol-Tishchenko reaction has been proposed in both stepwise[3b,g,h,j,4a,9,10] and concerted[3c] manners. Based on previous reports and our current studies, a possible mechanistic pathway of the aldol-Tishchenko reaction of the samarium dienolate **3** with an aldehyde is illustrated in Scheme 2. The aldol reaction is reversible, whereas the stereospecific Tishchenko reaction is irreversible.[3a,g,h,5a] The rate difference of these two reactions is an important factor that determines the stereochemical outcome of the final diol monoester adducts. Previous studies[3h,m] firmly established that the fast interconversion of *anti*- and *syn*-aldolates occurred via a dissociation–recombination pathway. The formation of products **7** and **8** for all entries except entry 4, Table 2, could be explained by the fast and irreversible reaction of *anti*-aldolate **A** with a second mole of aldehyde via the favorable transition state **C** compared to the less energetically favorable transition state **F** due to the axial position of the styryl group. In these cases, presumably the fast isomerization from *syn*-aldolate **B** to *anti*-aldolate **A** surpasses the rate of Tishchenko reaction. Thus *syn*-aldolate **B** can isomerize to an *anti*-aldolate **A**, which undergoes subsequent Tishchenko reduction via the more favorable transition state **C** to afford the desired product **7** and its transesterification isomer **8** (via a six-membered intermediate **E** and **D′**).[3a,g]

Table 1. Optimization studies[a]

Entry	EtCHO (equiv)	Temp (°C)	Time (h)	Products (% yield)[b]				
				4a	**6a**	**7a**	**8a**	**7a**+**8a**
1	10.0	−78 to rt	5	—	—	44	30	74
2[c]	10.0	−78 to rt	5	5	—	36	11	47
3	1.5	−78 to rt	1	10	—	49	7	56
4	2.0	−78 to rt	1	3	—	61	12	73
5	3.0	−78 to rt	1	—	—	68	17	85
6	3.0	−78 to rt	5	—	—	48	29	77
7	4.0	−78 to rt	1	—	—	61	18	79

[a] All reactions were performed using 1.2 equiv of SmI_2 (0.1 M) in THF.
[b] Isolated yield.
[c] HMPA (10 equiv) was used as cosolvent.

Table 2. The aldol-Tishchenko reaction of samarium dienolate **3** with various aldehydes[8]



Entry	Aldehyde **5**		Products (% yield)[a]				Overall yields (%)
	R		**7**	**8**	**9**	**10**	
1	Ethyl	**a**	68	17	—	—	85
2	*n*-Butyl	**b**	63	22	—	—	85
3	*n*-Heptyl	**c**	62	27	—	—	89
4	*i*-Propyl	**d**	33	3	32	10	78
5	*i*-Butyl	**e**	55	14	—	—	69
6	Phenyl	**f**	28	28	—	—	56
7	4-ClC_6H_4	**g**	21	34	—	—	55
8	4-BrC_6H_4	**h**	10	22	—	—	32
9	4-$CH_3C_6H_4$	**i**	27	26	—	—	53
10	4-$CH_3OC_6H_4$	**j**	30	6	—	—	36

[a] Isolated yield.

In the case of isobutyraldehyde (Table 2, entry 4), the steric effect caused by the isopropyl group resulted in both a slow down in equilibration of the *anti*-aldolate **A** and *syn*-aldolate **B**, and a lowering of the energy difference between the transition states **C** and **F**.[3h] These combined effects, presumably, led to the formation of **7**, its transesterification isomers **8** and **9** and its transesterification isomer **10** (via a six-membered intermediate **H** and **G′**).

The tandem aldol-Tishchenko reaction of the samarium dienolate **3** is also applicable to the stereoselective synthesis of optically pure polyoxygenated organic compounds. The reaction of cyclopropyl ketone **1** with (*R*)-glyceraldehyde acetonide **11** in the presence of SmI_2 in THF (Scheme 3) gave only the transesterified aldol-Tishchenko adducts **13** [5%, $[\alpha]_D^{29}$ −61.82 (*c* 0.11, $CHCl_3$)] and **15** [38%, $[\alpha]_D^{31}$ +70.00 (*c* 0.10, $CHCl_3$)]. The results indicated that three stereogenic centers of the corresponding *anti*-diol monoester could be created in a single operation.

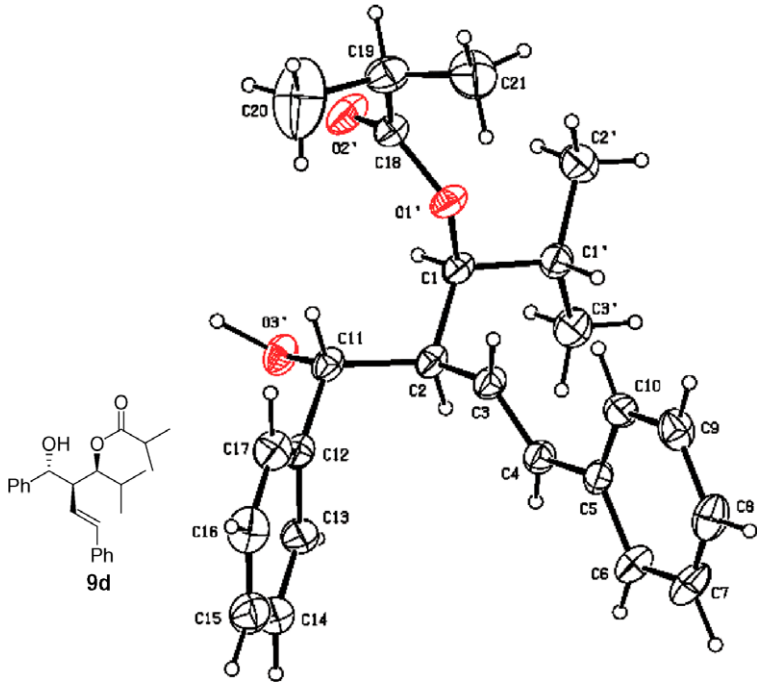
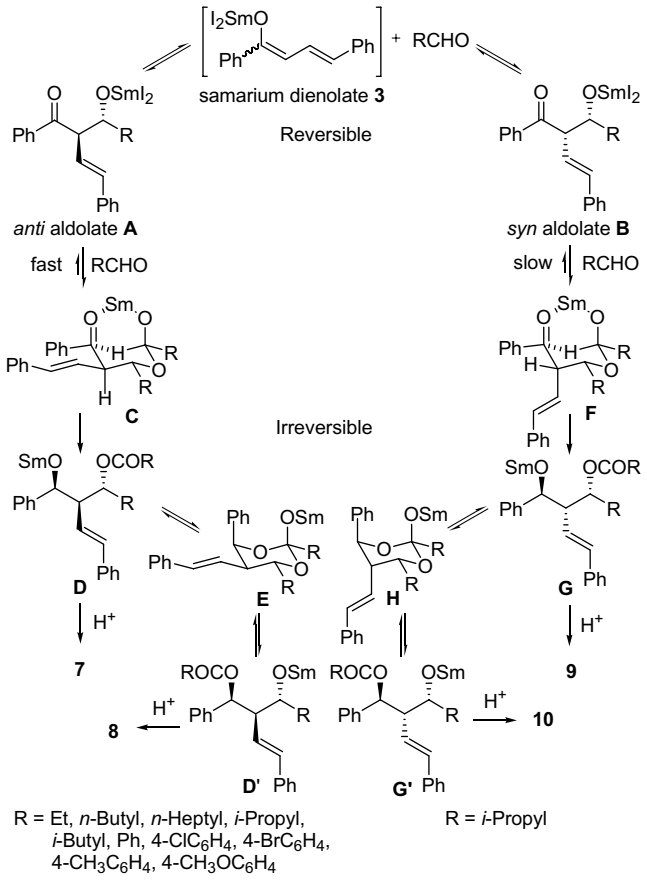
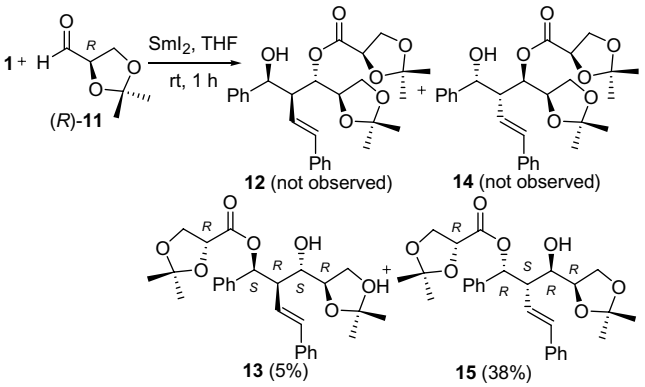


Figure 1. ORTEP plot of the X-ray crystal structure of compound **9d**.



Scheme 2. Possible mechanism for the tandem aldol-Tishchenko reaction of samarium dienolate **3** with aldehydes.



Scheme 3. The aldol-Tishchenko reaction of samarium dienolate **3** with (*R*)-glyceraldehyde acetonide **11**.

The relative and absolute stereochemistries of compound **15** were established by spectroscopic techniques and confirmed by X-ray crystallographic analysis of compound **16** derived from 3,5-dinitrobenzoylation of alcohol **15** (Fig. 2). The origin of the 1,3-*anti* stereoselectivity can be rationalized by two consecutive stereoselective reactions, that is the *anti* selective aldol condensation of samarium dienolate **3** with the enantiomerically pure aldehyde (*R*)-**11** (via chelated transition state **I**) followed by the *anti* stereoselective Tishchenko reduction (via **K**) to afford transition state **L** (Scheme 4).[11] Intramolecular acyl migration in **L** decreases the steric effect and dipole–dipole interaction between the two acetonide groups (via **M** and **L′**). The absolute configuration at the C-3 and C-4 positions in the transition state **L** was attributed to the chelation control of the oxophilic Lewis acid, samarium salt to the oxygen atom of the carbonyl group and the oxygen atom in the α position of the acetonide (via **I** and **J**). Therefore, the samarium dienolate **3** would attack preferentially at the *re* face of (*R*)-glyceraldehyde acetonide **11**.

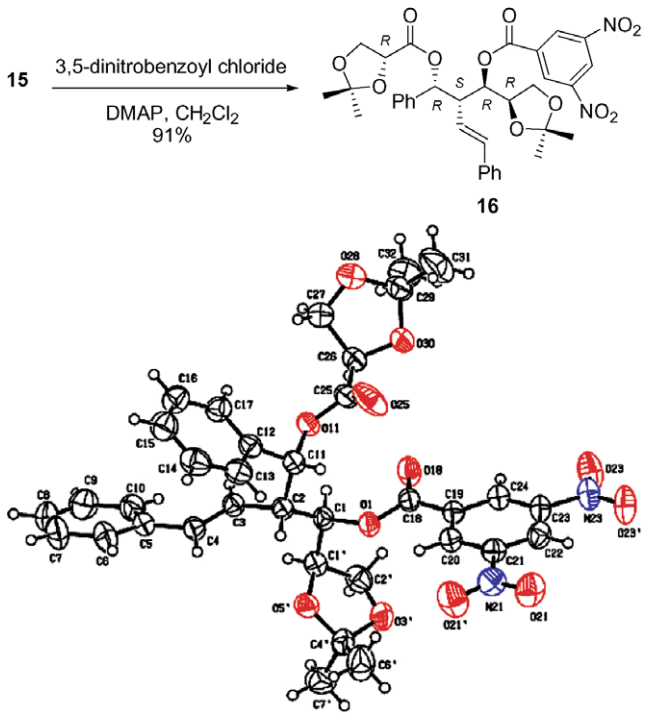
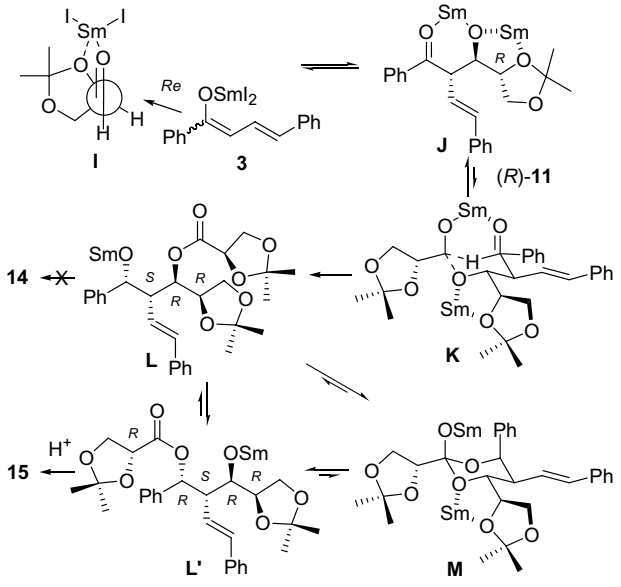


Figure 2. ORTEP plot of the X-ray crystal structure of compound **16**.



Scheme 4. Possible transition state for the formation of compound **15** through tandem aldol-Tishchenko reaction of samarium dienolate **3** with (*R*)-glyceraldehyde acetonide **11**.

In summary, the stereoselective synthesis of *anti*-1,3-diol monoesters could be smoothly carried out via the reaction of samarium dienolate with various aldehydes via the tandem aldol-Tishchenko reaction. Our results also provide a complementary insight of the reaction mechanism. Moreover, the aldol-Tishchenko process is also applicable to the stereoselective synthesis of optically active *anti*-1,3-diol monoesters in one step. Further investigations into the scope and limitations of this reaction are in progress.

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8. Typical procedure for the tandem aldol-Tishchenko reaction (Table 2): Under an atmosphere of argon at −20 °C (MeOH–ice), a solution of phenylsulfonyl activated cyclopropyl ketone **1** (362 mg, 1 mmol) in THF (5 mL) was added to a deep blue SmI_2 (1.2 mmol) solution freshly prepared from samarium (60 mesh, 300 mg, 2 mmol) and diiodomethane (0.1 mL, 1.2 mmol) in THF (10 mL). The reaction mixture was stirred at −20 °C for 15 min and then was allowed to warm to rt for an additional 15 min. The reaction mixture was cooled to −78 °C before a solution of freshly distilled aldehyde (3 mmol) in THF (1 mL) was added. Stirring was continued at −78 °C for 15 min, then at rt for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layer was washed with water (3×50 mL), saturated NaCl (50 mL), dried over anhydrous $MgSO_4$, and evaporated to give an oil or a solid as a crude product.
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