

Samarium Ion-Promoted Cross-Aldol Reactions and Tandem Aldol/Evans–Tishchenko Reactions

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Cross-aldol reactions of carbonyl compounds were achieved by the catalysis of SmI_2 or SmI_3 , together with molecular sieves, at ambient temperature. 1,3-Dichloroacetone and 1-chloroacetone can be used as acceptor substrates in the cross-aldol reactions with donor substrates such as acetone, cyclopentanone, and cyclohexanone. The cross-aldol reactions with (*R*)-glyceraldehyde acetoneide gave optically pure compounds **25–32**, the stereochemistry of which was in agreement with a chairlike chelate transition state of dipolar mode. SmI_2 –molecular sieves or SmI_3 –molecular sieves also functioned as effective Lewis acids to catalyze tandem aldol/Evans–Tishchenko reactions. The aldol/Evans–Tishchenko reactions of methyl ketones with aldehydes occurred at 0 °C to give α,γ -anti diol monoesters **53a–59a**. When the reactions were conducted at room temperature, a certain degree of transesterification took place. The aldol/Evans–Tishchenko reactions of ethyl or benzyl ketones with aldehydes yielded α,β -anti– α,γ -anti diol monoesters **60a–65a**. However, the aldol/Evans–Tishchenko reactions of cyclic ketones with benzaldehyde occurred with a different stereoselectivity to give α,β -syn– α,γ -anti diol monoesters **66a–76a**. The structures of products were determined by chemical and spectroscopic methods including an X-ray diffraction analysis of **72a** derived from the reaction of 4-*tert*-butylcyclohexanone and benzaldehyde. A reaction mechanism involving dissociation–recombination of aldols followed by intramolecular stereoselective hydride shift is proposed, based on some experimental evidence, to explain the dichotomous stereoselectivity using acyclic or cyclic ketones as the reaction substrates.

Introduction

The use of lanthanide metal is beneficial to aldol reactions¹ because lanthanide enolates are less basic than alkali enolates and the aldol products are stabilized by lanthanide ions.² Cross-aldol reactions using samarium enolates have not been extensively studied.³ In most reports, α -haloketones are reduced with SmI_2 to generate samarium enolates (Reformatsky-type reactions), but the aldol reactions are usually limited to those using aldehydes as the acceptor substrates. α -Haloketones, such as 1,3-dichloroacetone (**4**) and 1-chloroacetone (**5**), have almost never been used as the aldol acceptors.⁴ This may be due to (i) a lower reactivity of the ketones (compared with aldehydes) due to steric effect, (ii) facile enolization of α -chloroketones due to the electron-withdrawing prop-

erty of the α -substituent, and (iii) reductive dehalogenation of the α -chloroketones by SmI_2 . However, we have found that cross-aldol reactions using α -haloketones **4** and **5** as the acceptor substrates were effectively promoted by SmI_2 , in contrast to the general opinion that SmI_2 functions as a one-electron reducing agent.^{2,3}

Under such reaction conditions, we also found that the samarium ion-catalyzed aldol reactions of aldehydes usually proceeded further to give 1,3-diol monoesters via an in situ Tishchenko reaction.⁵ Many natural products such as polyketides and macrolides contain 1,3-diol moieties.⁶ Either anti- or syn-1,3-diols are generally prepared by stereoselective reductions of aldols.⁷ The intramolecular Tishchenko reaction of β -hydroxy ketones has been carried out stereoselectively by samarium ion catalysis to give anti-1,3-diol monoesters.^{7c} Ketone enolates (with Li^+ , Zn^{2+} , or Ga^{3+} counterion) are known to undergo tandem aldol–Tishchenko reactions with alde-

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Table 1. Lewis Acid-Promoted Aldol Reactions of Cyclopentanone (**7**) and 1,3-Dichloroacetone (**4**)^a

entry no.	Lewis acid (equiv)	additive	method ^a	reaction time/h	products (yield/%) ^b	recovered reactants (yield/%)
1	ZnI ₂ (1.0)		B	24		7 (99) + 4 (97)
2	TiCl ₄ (1.0)	MS ^c	B	0.7	16 (7) + 14 (19)	7 (78) + 4 (70)
3	SmCl ₃ (1.0)		B	24	14 (9)	7 (92) + 4 (82)
4	SmCl ₃ (1.0)	MS	B	24	14 (11)	7 (90) + 4 (77)
5	SmCl ₃ (0.1)		B	48	14 (6)	7 (95) + 4 (84)
6	SmI ₃ (1.0)		B	0.7	16 (48) + 11 (49)	7 (25)
7	SmI ₃ (1.0)	MS	B	0.7	16 (50) + 11 (50)	7 (18)
8	SmI ₃ (0.1)		B	0.7	16 (5) + 11 (2)	7 (81) + 4 (78)
9	SmI ₂ (2.0)	MS	B	0.5	16 (58) + 11 (17)	7 (10)
10	SmI ₂ (1.0)		B	0.7	16 (40) + 11 (36)	7 (20)
11	SmI ₂ (2.0)	MS	A	0.5	16 (86)	
12	SmI ₂ (1.0)	MS	A	0.5	16 (63) + 11 (4)	7 (5)
13	SmI ₂ (0.5)	MS	A	0.5	16 (48) + 11 (10)	7 (30)
14 ^d	SmI ₂ (0.5)	MS	A	1.3	16 (70) + 11 (7)	

^a The reaction was conducted in THF solution at room temperature (20–25 °C). Cyclopentanone (3.58 mmol) and 1,3-dichloroacetone (3.94 mmol, 1.1 equiv) were used. Method A: Cyclopentanone was mixed with Lewis acid to form the metal enolate, and then 1,3-dichloroacetone was added. Method B: A mixture of cyclopentanone and 1,3-dichloroacetone was added to the Lewis acid solution.

^b Compound **16** is the cross-coupling product of cyclopentanone and 1,3-dichloroacetone; compound **14** is the self-coupling product of 1,3-dichloroacetone, whereas compound **11** is a dechlorination derivative of **14**. ^c MS represents molecular sieves (4 Å, 200 mg). ^d The aldol reaction was conducted at 0 °C.

hydres to give anti-1,3-diol monoesters.⁸ By the catalysis of BuTi(*i*-OPr)₄Li,^{8e} a tandem aldol–Tishchenko reaction between 3-pentanone and benzaldehyde also occurs in a stereoselective manner. We report herein that tandem aldol/Evans–Tishchenko reactions are generally achieved in a highly stereoselective manner by the catalysis of SmI₂ or SmI₃. However, the stereoselectivity varies depending on whether acyclic or cyclic ketones are utilized as the donor substrates.

Results and Discussion

In this study, a dark blue THF solution of SmI₂ was prepared from Sm and ICH₂CH₂I (1 equiv) in the presence of molecular sieves.^{9a,10} On the other hand, a yellow THF solution of SmI₃ was prepared from Sm and I₂ (1.5 equiv) in the presence of molecular sieves.^{9b,10} Molecular sieves (abbreviated MS in this paper) were used in order to facilitate the formation of SmI₂ and SmI₃.¹⁰

Aldol Reactions with α -Chloroketones. We first examined the cross-aldol reactions of 1,3-dichloroacetone (**4**) and cyclopentanone (**7**) (Table 1). Lewis acids ZnI₂, TiCl₄, and SmCl₃ were ineffective for the cross-aldol reactions (entries 1–5). A self-aldol **14** (9–19%) (Figure 1) was formed by the aldol reaction of 1,3-dichloroacetone, and in one case, the desired cross-aldol **16** was obtained in a small amount (7%). On the other hand, treatment of ketones **4** and **7** (1:1 mixture) with SmI₂ or SmI₃ (method B, entries 6–10, Table 1) gave reasonable yields of **16** (up to 58%), accompanied by variable amounts of

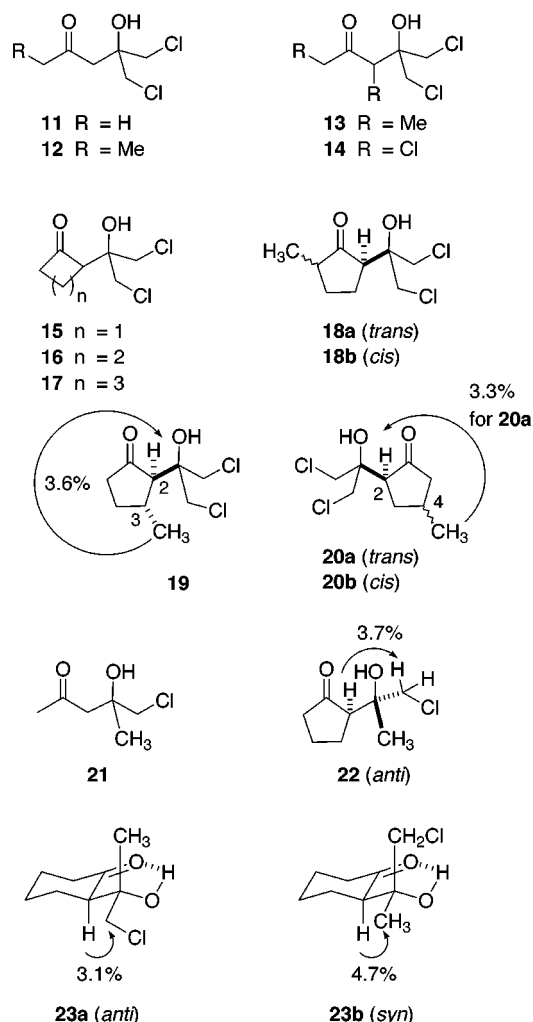


Figure 1. Samarium ion-promoted cross-aldol reaction products of ketones (Tables 1 and 2). For comparison, syn-aldol **23b** was prepared from cyclohexanone lithium enolate and 1-chloroacetone.

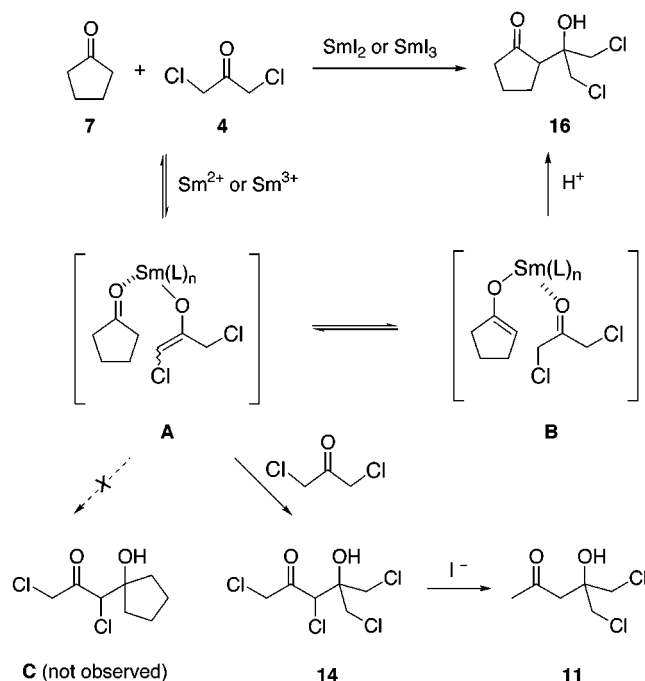
aldol **11** (2–50%). Compound **11** was formed by reductive removal of the α -chlorine atoms from **14** (see below). No products (secondary alcohols or vicinal diols) formed by reduction or pinacol coupling of ketone **4** or **7** were observed. Reduction and pinacol coupling of aliphatic

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Scheme 1



ketones with SmI_2 usually require the presence of a proton source (e.g., *t*-BuOH) or a polar solvent (e.g., HMPA); otherwise, these reactions are sluggish.¹¹ In THF solution (this study), enolization of ketones and the subsequent aldol reactions appeared to be faster than reduction and pinacol coupling.

According to this procedure (method B), SmI_2 and molecular sieves functioned as a combined Lewis acid catalyst. Compound **16** was conceivably derived by addition of cyclopentanone enolate to 1,3-dichloroacetone via a transition state **B** (Scheme 1). The alternative cross-aldol reaction, giving **C** by addition of 1,3-dichloroacetone enolates to cyclopentanone, did not occur. Since the acidity of α -proton in 1,3-dichloroacetone is higher than in cyclopentanone, we presume that the samarium enolates of 1,3-dichloroacetone (*E*- or *Z*-forms) were primarily generated (transition state **A**). The samarium enolates would be less basic and less reactive than the corresponding lithium enolates. Thus, the 1,3-dichloroacetone enolates **A** could not add to the less reactive carbonyl center of cyclopentanone. Instead, the samarium enolates might undergo a transenolization by abstraction of an α -proton of cyclopentanone (from **A** to **B**). The cyclopentanone enolate generated as such reacted readily with 1,3-dichloroacetone to give the cross-aldol **16**. On the other hand, 1,3-dichloroacetone enolates could also react with another molecule of 1,3-dichloroacetone to afford a self-aldol **14**. Reductive removal of α -chlorine atoms from **14** would afford **11**. We consider that the I^- ion,¹² not SmI_2 , is responsible for the dechlorination, as compound **11** was also obtained from the reaction with SmI_3 (entries 6–8, Table 1).

The yield of aldol **16** was increased by treatment of a preformed cyclopentanone enolate with 1,3-dichloro-

acetone at room temperature (method A). Accordingly, the reaction using 2.0 equiv of SmI_2 (entry 11) in the presence of molecular sieves afforded an 86% yield of **16**. The reaction using a substoichiometric amount of SmI_2 (entries 13 and 14) gave lower yields of **16** together with small amounts of **11** (Figure 1).

The SmI_2 -MS-mediated cross-aldol reactions of 1,3-dichloroacetone with other cyclic or acyclic ketones were successfully carried out (Table 2). These reactions using preformed enolates (method A) were complete in 40 min at ambient temperature. The reaction of 2-butanone occurred exclusively at C-1 (the methyl site), giving aldol **12**. The reaction of 2-methylcyclopentanone also occurred at the less substituted α -carbon, giving the product **18** (80%) as a mixture of two isomers (4:1). The major isomer might have a trans configuration by analogy with the result of the reaction of 3-methylcyclopentanone. The reaction of 3-methylcyclopentanone occurred at both α - and α' -carbons, giving aldols **19**, **20a**, and **20b** in a ratio of 27:63:10, as shown by the ^1H NMR spectrum (300 MHz). Although **19**, **20a**, and **20b** were not completely separated, the detailed NMR spectral analyses (500 MHz) indicated that **19** and **20a** had trans configurations. Their proton resonances were assigned by assistance of the H–H COSY and TOCSY spectra. Thus, irradiation of the methyl group (at δ 1.22) of compound **19** caused a 3.6% NOE of H-2 (at δ 2.17, d, J = 9.5 Hz). When the methyl group (at δ 1.02) of compound **20a** was irradiated, a 3.3% enhancement of H-2 (at δ 2.63, t, J = 7.6 Hz) was also observed.

An unsymmetric ketone, 1-chloroacetone (**5**), was also utilized as an acceptor substrate for the SmI_2 -MS-mediated cross-aldol reactions. The reactions using cyclopentanone or cyclohexanone as donor substrates afforded anti-aldols **22** and **23a**. To determine the configuration, we also prepared a mixture of **23a** and its syn isomer **23b** (1:1) by addition of 1-chloroacetone to the lithium enolate of cyclohexanone. The NOE experiments clearly indicated the configurations of **23a** and **23b**. Irradiation of the axially oriented H-2 (at δ 2.82, dd, J = 12.4, 5.5 Hz) of **23a** caused a 3.1% enhancement of the CH_2Cl signal (at δ 3.40 and 3.62 as an AB quartet), whereas irradiation of the axially oriented H-2 (at δ 2.66, dd, J = 12.4, 5.4 Hz) of **23b** caused a 4.7% enhancement of the methyl group (at δ 1.28). The anti configuration of aldol **22** was similarly determined; that is, irradiation of H-2 (at δ 2.58) caused a 3.7% NOE of the CH_2Cl group.

Aldol Reactions with (*R*)-Glyceraldehyde Acetonide. The samarium ion-catalyzed aldol reactions using (*R*)-glyceraldehyde acetonide (**24**) as the acceptor substrate led to optically pure products **25**–**32** (Table 3, Figure 2). The cross-aldol reactions were carried out by either method A with preformed enolate or by method B with concurrent addition of a mixture of substrates. For example, compound **25** with the (4*S*,5*R*)-configuration,^{13a} [α]_D²⁶ –27 (CHCl_3 , c = 1.0), was obtained in 70% yield simply by treatment of a mixture of acetone and **24** (1:1) in the THF solution of SmI_2 -MS (method B). The reaction of 1-chloroacetone and **24** (method A, entry 5 of Table 3) also afforded **25** (74%) after in situ removal of the α -chlorine atom. Our present method is superior to

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Table 2. Aldol Reactions Promoted by SmI₂ (2.0 equiv) and Molecular Sieves (THF, 20–25 °C)^a

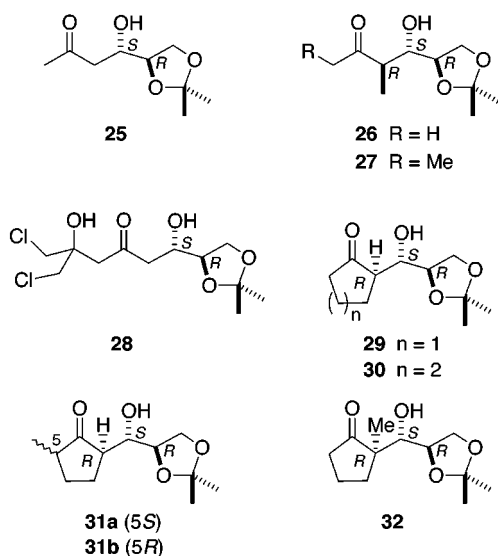
entry no.	donor	acceptor	reaction time/min	products (yield%)
1	acetone (1)	1,3-dichloroacetone (4)	15	11 (90)
2	2-butanone (2)	4	40	12 (75)
3	3-pentanone (3)	4	40	13 (81)
4	cyclobutanone (6)	4	40	15 (53)
5	cyclopentanone (7)	4	30	16 (86)
6	cyclohexanone (8)	4	30	17 (63)
7	2-methylcyclopentanone (9)	4	40	18a/18b (80) ^b
8	3-methylcyclopentanone (10)	4	40	19a/20a/20b (68) ^c
9	1	1-chloroacetone (5)	15	21 (87)
10	5	5	20	21 (86)
11	7	5	20	22 (75)
12	8	5	30	23a (63)

^a The reaction was conducted by addition of the acceptor substrate (1.1 equiv) to the preformed samarium enolate of the donor substrate (1.0 equiv) according to method A described in Table 1. ^b The ratio of trans- and cis-isomers **18a/18b** = 4:1. ^c The ratio of **19a/20a/20b** = 27:63:10.

Table 3. Aldol Reactions of Ketones (1.1 equiv) and (*R*)-Glyceraldehyde Acetonide (24**) (1.0 equiv) Promoted by SmI₂ (2.0 equiv) and Molecular Sieves (THF, 20–25 °C)^a**

entry no.	ketone	additive	method	reaction time/min	products (yield%)
1	acetone (1)	<i>t</i> -BuOH	B	15	25 (70)
2	2-butanone (2)		A	40	26 (77)
3	3-pentanone (3)		A	40	27 (85)
4	1,3-dichloroacetone (4) ^b		A	20	28 (61)
5	1-chloroacetone (5)		A	20	25 (74)
6	cyclopentanone (7)		A	30	29 (47)
7	7		B	30	29 (45)
8	7	<i>t</i> -BuOH	B	20	29 (78)
9 ^c	7		A	300	29 (70)
10	7 ^d	<i>t</i> -BuOH	B	30	29 (68) ^d
11	cyclohexanone (8)		A	30	30 (50)
12	8	<i>t</i> -BuOH	B	30	30 (62)
13	2-methylcyclopentanone (9)		A	40	31 (60) ^e + 32 (16)

^a The reaction was conducted according to methods A or B described in Table 1, whereas *t*-BuOH (2.0 equiv) was added in appropriate entries. ^b 1,3-Dichloroacetone (2 equiv) was used. ^c Substoichiometric amount of SmI₂ (0.5 equiv) was used. ^d Cyclopentanone (2 equiv) was used. The self-aldol product of cyclopentanone was also isolated in 18% yield. ^e It contained two C-5 epimers **31a/31b** = 4:1.

**Figure 2.** Cross-aldol reaction products of ketones and (*R*)-glyceraldehyde acetonide (Table 3).

the previous nonselective preparation,^{13a} which requires a multistep sequence to produce a mixture of **25** and its (4*R*,5*R*)-isomer.

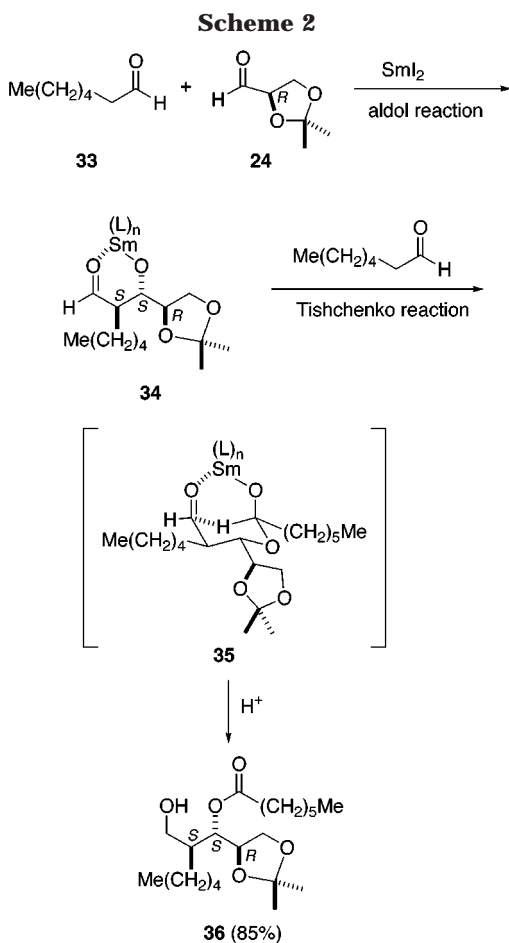
The cross-aldol reaction of 2-butanone occurred at the more substituted α'-site to give **26** (77%) with the (3*R*,4*S*,5*R*)-configuration. Compound **26** exhibited an optical rotation, [α]_D²⁶ +24 (CHCl₃, *c* = 0.35), close to the reported value.¹³ The C-3 methyl group of **26** appeared at δ_C 14.1 ppm, a typical position for 4,5-anti aldols.¹⁴

The corresponding signals of 4,5-syn aldols usually appeared at higher fields (δ_C < 10 ppm).¹⁴ The regioselectivity was different from the reaction with 1,3-dichloroacetone, which occurred at the methyl site of 2-butanone to give **12**. The addition of a rather bulky ketone (1,3-dichloroacetone) at the methylene site (C-3) of 2-butanone was presumably disfavored. A different process of transesterification (Scheme 1) might also change the regiochemistry.

The cross-aldol reaction between 3-pentanone and **24** yielded an aldol **27** with the (4*R*,5*S*,6*R*)-configuration. The resonance of the C-4 methyl group of **27**, appearing at δ_C 14.3 ppm, is diagnostic for the stereochemical assignment.¹⁴ When 1,3-dichloroacetone (2 equiv) was treated with SmI₂ (2.1 equiv) in THF followed by addition of (*R*)-glyceraldehyde acetonide (1 equiv), an uncommon double cross-aldol product **28** (61%) was obtained after in situ removal of four α-chlorine atoms.

The SmI₂-promoted cross-aldol reactions of cyclopentanone and cyclohexanone with (*R*)-glyceraldehyde acetonide were carried out by either method A or method B (with or without *t*-BuOH) to give the enantiomerically pure aldols **29** and **30**. Their structures were inferred from mechanistic considerations (see Scheme 4). The cross-aldol reaction of 2-methylcyclopentanone occurred at both α- and α'-carbons, giving **31** (60%) and **32** (16%). Though the addition of (*R*)-glyceraldehyde acetonide at the more substituted α'-carbon was a minor pathway, this

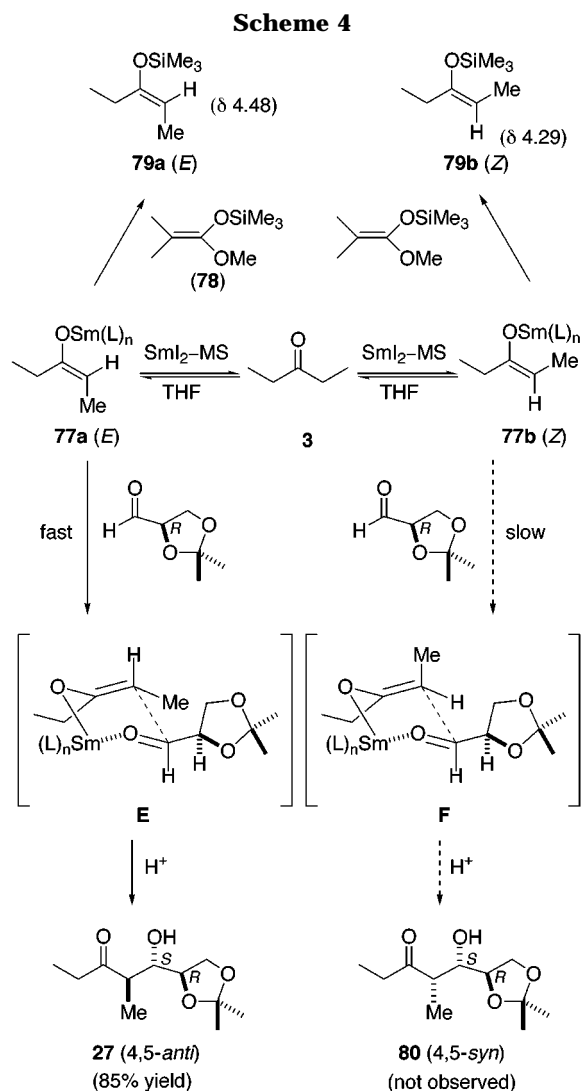
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reaction showed the feasibility for construction of a new quaternary carbon center.

Aldol/Evans-Tishchenko Reaction of Heptanal and (*R*)-Glyceraldehyde Acetonide. The SmI_2 -catalyzed aldol reaction of heptanal (2 equiv) with (*R*)-glyceraldehyde acetonide (1 equiv) proceeded with a subsequent Tishchenko reaction to give a diol monoester **36**, which was considered to have the (2*R*,3*S*,4*S*)-configuration (Scheme 2). The 3,4-anti relationship in the aldol intermediate **34** was established by a mechanism similar to that operating in the reaction of 3-pentanone with (*R*)-glyceraldehyde acetonide (see Scheme 4). Under such samarium ion-catalyzed conditions, an acetal intermediate **35** formed and underwent an intramolecular hydride shift to give the observed product **36**.

Aldol/Evans-Tishchenko Reactions of Acyclic Ketones. Both SmI_2 and SmI_3 were effective catalysts for tandem aldol/Evans-Tishchenko reactions (Tables 4



and 5). For example, acetophenone was treated with SmI_2 (30 mol %) in the presence of molecular sieves at 0 °C, followed by addition of benzaldehyde (2.5 equiv), to afford a diol monoester **53a** (Figure 3) in 84% yield. Saponification of **53a** led to a known compound **53c** having the α,γ -anti configuration.^{15a,b} Greeks α - γ are used in this paper to avoid confusion with carbon numbering in products. The tandem aldol/Evans-Tishchenko reaction of acetophenone with isobutyraldehyde proceeded similarly to give the known α,γ -anti diol **55c**,^{7b} after a subsequent hydrolysis. The characteristic C-1 and C-3 resonances of **55c** appeared at higher fields (δ 73.86 and 71.83), due to the γ -gauche effect, than the corresponding carbons in the α,γ -syn isomer (at δ 76.97 and 74.89).^{7b} The

(15) For compound **53c**: (a) Yamamoto, K.; Ando, H.; Chikamatsu, H. *J. Chem. Soc., Chem. Commun.* **1987**, 334. (b) Corey, E. J.; Chen, Z. *Tetrahedron Lett.* **1994**, 35, 8731. For compound **55c**: see ref 7b. For compounds **67c** and **68c**: (c) Thompson, S. H. J.; Mahon, M. F.; Molloy, K. C.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 379.

Table 4. Tandem Aldol/Evans–Tishchenko Reactions Promoted by SmI₂ (0.3 equiv) in the Presence of Molecular Sieves (THF, 0 °C)^a

entry no.	donor ^a	acceptor ^a	reaction time/h	products (yield/%)
1 ^b	heptanal (33)	(<i>R</i>)-glyceraldehyde acetonide (24)	0.5	36 (85)
2	acetophenone (40)	benzaldehyde (37)	2	53a (84)
3 ^c	40	propionaldehyde (38)	2	54a/54b (68) ^d
4	40	isobutyraldehyde (39)	2	55a (72)
5	3,3-dimethyl-2-butanone (41)	37	4	56a (80)
6	41	39	4	57a (80)
7	cyclohexyl methyl ketone (42)	37	3	58a (80)
8	2-butanone (2)	37	2	59a/59b/60a/60b (83) ^e
9	3-pentanone (3)	37	1	61a (77) + 61b (9)
10 ^c	3	37	2	61a (12) + 61b (76)
11	3	38	0.5	62a (79)
12 ^c	3	39	2	63a (50) + 63b (28)
13	propiophenone (43)	37	4	64a (90)
14	deoxybenzoin (44)	37	4	65a (88)
15	cyclobutanone (6)	37	1	66a (80)
16	cyclopentanone (7)	37	2	67a (85)
17	cyclohexanone (8)	37	3	68a (88)
18	1,4-cyclohexanedione (45)	37	4	69a (80)
19	1,4-cyclohexanedione monoethylene acetal (46)	37	5	70a (93)
20	4-methylcyclohexanone (47)	37	3	71a (95)
21	4- <i>tert</i> -butylcyclohexanone (48)	37	4	72a (85)
22	tetrahydro-4 <i>H</i> -pyran-4-one (49)	37	4	73a (84)
23	2-cyclohexenone (50)	37	5	74a (92)
24	α-tetralone (51)	37	2	75a (77)
25	<i>trans</i> -1-decalone (52)	37	6	76a (81)

^a The dark blue SmI₂ (0.1 M)–THF (3 mL) suspension was prepared by treatment of Sm (0.3 mmol) with diiodoethane (0.3 mmol) in the presence of molecular sieves (4 Å, 100 mg). The enolate of donor substrate (1 mmol) was formed at 0 °C, after which the acceptor substrate (2.5 mmol) was added. ^b Heptanal (2.0 mmol), (*R*)-glyceraldehyde (1.0 mmol), and SmI₂ (2.1 mmol) were used. ^c The reaction was conducted at room temperature (20–25 °C). ^d Isomers **54a** and **54b** (1:3) were not separated. ^e The ratio **59a/59b/60a/60b** = 49:4:40:7.

Table 5. Tandem Aldol/Evans–Tishchenko Reactions Promoted by SmI₃ (0.3 equiv) in the Presence of Molecular Sieves (THF, 0 °C) Using Benzaldehyde (2.5 equiv) as the Acceptor^a

entry no.	donor (1.0 equiv)	reaction time/h	products (yield/%)
1	acetophenone	6	53a (80)
2	3,3-dimethyl-2-butanone	14	56a (78)
3	cyclohexyl methyl ketone	8	58a (84)
4 ^b	2-butanone	14	59b (41) + 60b (41)
5	3-pentanone	14	61a (85)
6	propiophenone	10	64a (90)
7	deoxybenzoin	10	65a (87)
8	cyclobutanone	4	66a (81)
9	cyclopentanone	6	67a (87)
10	cyclohexanone	8	68a (89)
11	1,4-cyclohexanedione	10	69a (90)
12	1,4-cyclohexanedione monoethylene acetal	10	70a (89)
13	4-methylcyclohexanone	8	71a (91)
14	4- <i>tert</i> -butylcyclohexanone	12	72a (84)
15	tetrahydro-4 <i>H</i> -pyran-4-one	13	73a (81)
16	2-cyclohexenone	14	74a (89)
17	α-tetralone	6	75a (77)
18	<i>trans</i> -1-decalone	12	76a (79)

^a The yellow SmI₃ (0.06 M)–THF (5 mL) suspension was prepared by treatment of Sm (0.3 mmol) with I₂ (0.45 mmol) in the presence of molecular sieves (4 Å, 100 mg). The enolate of donor substrate (1 mmol) was formed at 0 °C, after which the acceptor substrate (2.5 mmol) was added. ^b The reaction was conducted at room temperature (20–25 °C).

samarium ion-catalyzed reaction of 3,3-dimethyl-2-butanone (**41**) with benzaldehyde gave a diol monoester **56a** (ca. 80%) at 0 °C, whereas the nickel-bound enolate of **41** has been shown to react with benzaldehyde to give a mixture of **56a** and its transesterification isomer.^{8a}

The tandem aldol/Evans–Tishchenko reaction of cyclohexyl methyl ketone with benzaldehyde occurred in a regio- and stereoselective fashion to give the diol monoester **58a** with anti configuration. However, the tandem aldol/Evans–Tishchenko reaction of 2-butanone occurred at both α- and α'-carbons, giving **59a,b** and **60a,b** in nearly equal amounts. Compounds **59b** and **60b** were the transesterification products of **59a** and **60a**. The structures were deduced from their ¹H NMR spectra, in

which the signals of methyl groups and the chemical shifts of H-1 and H-3 were most diagnostic. The methyl groups of **60a** and **60b** exhibited as doublets, whereas the methyl groups of **59a** and **59b** displayed as triplets. The H-1 signals of the transesterification products **59b** and **60b** showed at lower fields (δ 4.67 and 4.29) than the H-3 signals of **59a** and **60a** (at δ 3.68 and 4.17). On the other hand, the H-3 signals of **59b** and **60b** appeared at higher fields (δ 5.38 and 5.82) than the H-1 signals of **59a** and **60a** (at δ 6.37 and 5.98). A mixture of **59a**, **59b**, **60a**, and **60b** (49:4:40:7) was subjected to hydrolysis (NaOH, MeOH) to give the (1*S**,3*R**)-diol **59c** and (1*S**,2*S**,3*R**)-diol **60c** in a ratio of 53:47, in agreement with the stereochemical assignment.

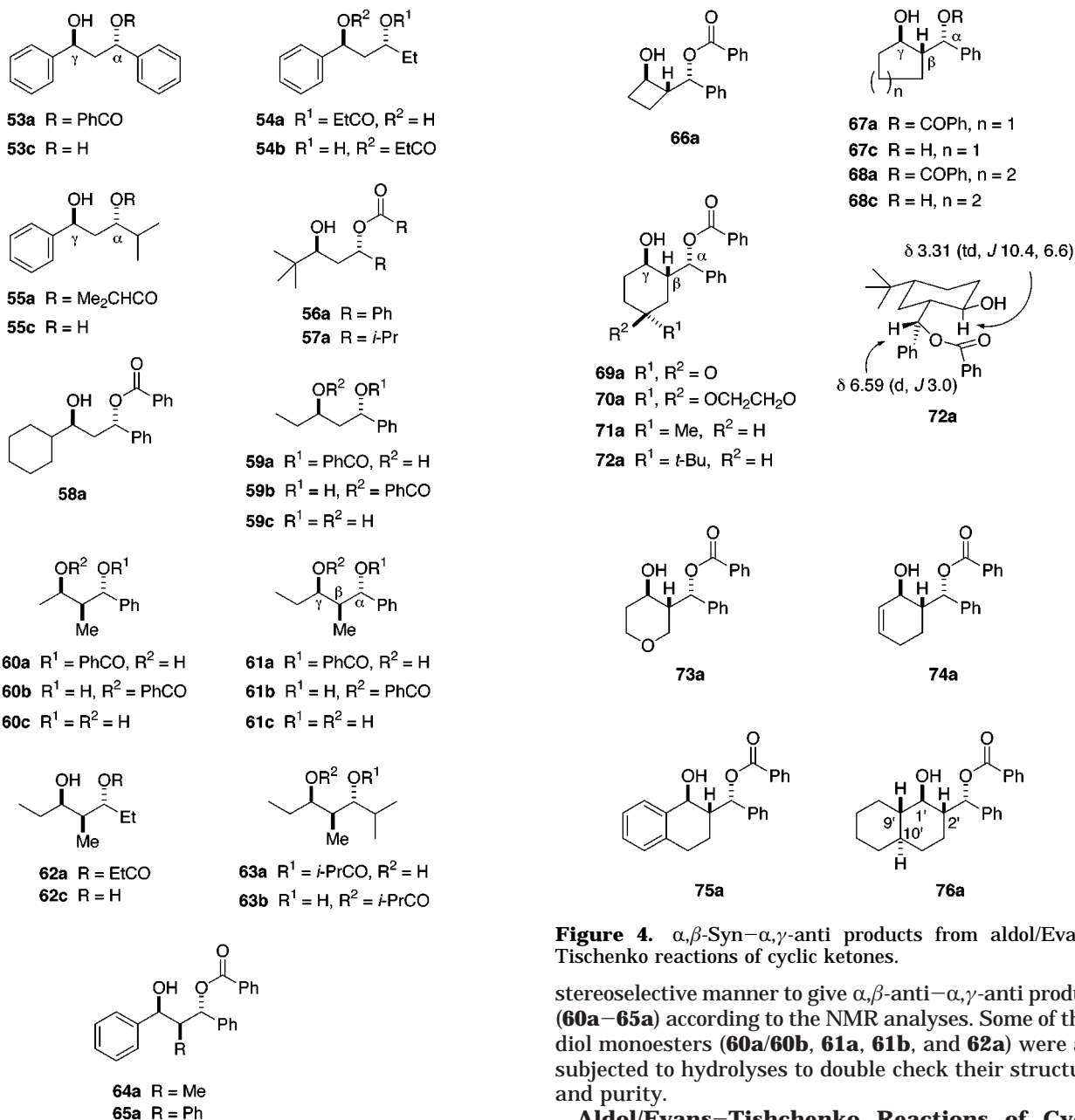


Figure 3. α,γ -Anti and α,β -anti- α,γ -anti products from the aldol/Evans-Tishchenko reactions of acyclic ketones.

The samarium ion-catalyzed reaction of 3-pentanone with benzaldehyde proceeded in a highly stereoselective manner at 0 °C to give the diol monoester **61a** (85%). The reaction at room temperature yielded a mixture of **61a** and its transesterification product **61b** (14:86). Transesterification tended to occur at room temperature for a prolonged period (compared entries 9 and 10 of Table 4). A similar reaction using a titanium complex BuTi(O*i*-Pr)₄Li as the catalyst has been reported.^{8c} Hydrolysis of either **61a** or **61b** gave a diol **61c**, which had the α,β -anti- α,γ -anti configuration. The characteristic carbon resonances of **61c** occurred at δ 10.6 (C-5), 11.4 (Me-2), 73.9 (C-3), and 76.6 (C-1), compatible with chemical shifts of known analogues.^{8a} In our study, all tandem aldol/Evans-Tishchenko reactions of acyclic ketones (2-butanone, 3-pentanone, propiophenone, and deoxybenzoin) with aldehydes (benzaldehyde, propionaldehyde, and isobutyraldehyde) occurred in a highly

Figure 4. α,β -Syn- α,γ -anti products from aldol/Evans-Tishchenko reactions of cyclic ketones.

stereoselective manner to give α,β -anti- α,γ -anti products (**60a**–**65a**) according to the NMR analyses. Some of these diol monoesters (**60a**/**60b**, **61a**, **61b**, and **62a**) were also subjected to hydrolyses to double check their structures and purity.

Aldol/Evans-Tishchenko Reactions of Cyclic Ketones. To our surprise, cyclic ketones reacted with benzaldehyde to give diol monoesters with α,β -syn- α,γ -anti configuration, differing from the stereochemistry in the reactions of acyclic ketones. As a direct comparison of the configuration of products, the β -carbon in compounds **66a**–**76a** (Figure 4), obtained from the aldol/Evans-Tishchenko reactions of cyclic ketones, is viewed as the carbon bearing a methylene substituent. For example, the reaction of cyclopentanone and benzaldehyde by the catalysis of SmI₂ or SmI₃ in the presence of molecular sieves afforded **67a** in 85–87% yields. Hydrolysis of **67a** yielded an α,β -syn- α,γ -anti diol **67c**,^{15c} mp 78.5–79.5 °C. A similar aldol/Evans-Tishchenko reaction of cyclohexanone with benzaldehyde afforded **68a**, of which axial H-1' (at β -carbon) exhibited as a triplet of doublet (*J* = 10.0, 4.2 Hz) in the ¹H NMR spectrum. The assignment was confirmed by transformation of **68a** to a known α,β -syn- α,γ -anti diol **68c**,^{15c} mp 106–107 °C. Cyclohexane-1,4-dione underwent an aldol/Evans-Tishchenko reaction to give the diol monoester **69a**, the other carbonyl group remaining unattacked. The

aldol/Evans–Tishchenko reaction of 2-cyclohexenone occurred at the α' -site (C-6), giving **74a**, but not at the α - or γ -sites (C-2 or C-4). The aldol/Evans–Tishchenko reaction of *trans*-1-decalone yielded **76a**, of which the carbinyl proton (H-1') displayed at δ 3.03 as a triplet ($J = 9.4$ Hz), indicating that H-1', H-2', and H-9' all had axial orientation. The aldol/Evans–Tishchenko reaction products **69a–76a** of cyclohexanone-derived ketones all exhibited 1,2-*trans* configurations as inferred from the characteristic patterns of their axial C-1' protons in the ^1H NMR spectra. An X-ray diffraction analysis of **72a** not only confirmed this stereochemical assignment (α,β -syn– α,γ -anti configuration) but also showed the equatorial disposition of the hydroxy, *tert*-butyl, and (α -benzoyloxy)-benzyl groups.

Reaction Mechanism. In this study, we have demonstrated that either SmI_2 or SmI_3 promoted cross-aldol and aldol/Evans–Tishchenko reactions in a highly stereoselective manner. SmI_2 has been employed as a catalyst in aldol and other reactions.^{3d,f} SmI_2 and SmI_3 have also been used to promote intramolecular Tishchenko reactions of β -hydroxy ketones with aldehydes.^{5c} The nature of the samarium catalysts in these reactions remains unclear, although some reports suggest that only the trivalent samarium ion plays the real catalytic role.^{3d}

The stereochemical outcome of an aldol reaction depends on several factors, such as the steric effect of substrates, the configuration of the enolate, the type of transition state, and the reversibility of the reaction. For example, steric effects were operative in the aldol reaction of 3-methylcyclopentanone with 1,3-dichloroacetone to give predominantly the 2,4-disubstituted cyclopentanone **20** (55%) over the 2,3-disubstituted isomer **19** (23%).

The preference in formation of an anti-aldol **22** can be explained by addition of 1-chloroacetone onto the enolate of cyclopentanone (**7**) via a cyclic transition state **D** (Scheme 3). The samarium enolate of **7** can only exist as the *E*-form. The other possible cyclic transition state, which places the bulkier CH_2Cl group in the ring, is energetically unfavorable.

Cyclic ketones can form only *E*-enolates, but acyclic ketones and aldehydes may form either *E*- or *Z*-enolates.¹⁶ On treatment with SmI_2 (0.3 equiv) and molecular sieves in THF, 3-pentanone was presumably to form the corresponding samarium enolates of *E*- and *Z*-configurations. Attempts to trap the samarium enolates with acetic anhydride or $\text{Me}_3\text{SiCl}-(i\text{-Pr})_2\text{NEt}$ failed. Instead, the ring-opening products of THF,¹⁷ 4-iodobutyl acetate and 4-iodobutanol trimethylsilyl ether, were obtained. The samarium enolates were, however, successfully trapped by the trimethylsilyl ketene acetal prepared from methyl isobutyrate (**78**) to give the corresponding enol silyl ethers **79a** (*E*-form) and **79b** (*Z*-form) in a ratio of 7:3, according to the intensity of their vinyl protons (δ 4.48 for *E*-enolate and δ 4.29 for *Z*-enolate) in the ^1H NMR spectrum (Scheme 4). Noteworthy, similar experiments of 5-nonanone using $\text{SmI}_2(\text{THF})_2$, $\text{SmI}_3(\text{THF})_3$, or $\text{SmI}_2(\text{O}t\text{-Bu})(\text{THF})_3$ in CH_2Cl_2 are reported to give preferentially the *Z*-enol silyl ether ($Z/E = 3$).¹⁸ The change of *E/Z* ratio

may be attributable to the different nature of Lewis acids, solvent systems, and reaction substrates.

The aldol reactions of (*R*)-glyceraldehyde acetonide (or related cyclohexanone ketal) with metal enolates,¹⁹ e.g., Li(I)-, Sn(II)-, and Sm(III)-enolates, are believed to follow the Conforth dipolar mode.²⁰ This reaction mode accounts for the formation of (*S*)-carbinyl centers in aldols **26** and **27** and **29–32**. The aldol reactions with samarium enolates often proceed with Zimmerman–Traxler chair-like transition states (Scheme 4).¹ Accordingly, an *E*-enolate **77a** should yield an anti-aldol **27**, via the transition state **E**, whereas a *Z*-enolate **77b** should yield a syn-aldol **80**, via the transition state **F**. However, the aldol reaction of 3-pentanone with (*R*)-glyceraldehyde acetonide actually results in a single product **27**, even if both *E*- and *Z*-enolates are present at an early stage of this reaction. How can one interpret this phenomenon? We may assume that the transition state **F** is energetically less favorable than **E** due to steric effects such as the pentane-*gauche* repulsions of the methyl group with the dioxolane ring or the repulsion of the methyl group with the ligands attached to the samarium ion. Thus, addition of (*R*)-glyceraldehyde acetonide to the *Z*-enolate (via **F**) is conceivably slow. Instead, the *Z*-enolate **77b** may revert to the *E*-enolate **77a**, which reacts rapidly with (*R*)-glyceraldehyde acetonide via the energetically favorable transition state **E** to give the anti-aldol **27**. In this case, the anti-aldol **27** is also likely more stable than the corresponding syn isomer.

Intramolecular Tishchenko reactions are believed to proceed with bicyclic transition states to give α,γ -anti diol monoesters in a stereospecific manner. Evans and Hoveyda^{5c} have shown that the Tishchenko reactions of β -hydroxy ketones using SmI_2 as promoters are stereospecific processes with α,β -configuration unchanged. For example, the reaction of α,β -syn aldol **86** was treated with isobutyraldehyde (4–8 equiv) at -10 °C for 0.5–0.75 h in the presence of SmI_2 (15 mol %) to give an α,β -syn– α,γ -anti diol monoester **90** (entry 2, Table 6). On the other hand, Mahrwald and Costisella^{8c} have demonstrated that treatment of an α,β -syn aldol **82** with benzaldehyde in the presence of $\text{BuTi}(\text{O}i\text{-Pr})_4\text{Li}$ at room temperature for 24 h led to the α,β -anti– α,γ -anti diol monoester **61a** and its transesterification isomer **61b**, but no α,β -syn– α,γ -anti product **87** (entry 1, Table 6; Scheme 5). This stereochemical outcome is different from that observed by Evans and Hoveyda. It seems that syn-aldol **82** isomerizes to anti-aldol **81** prior to the Tishchenko reaction, though no evidence is provided.

To gain insight into this problem, we prepared a mixture of aldols **85** and **86** (anti/syn = 64:36) from isobutyraldehyde and the lithium enolate of 3-pentanone. The mixture of **85/86** in THF solution was then treated with isobutyraldehyde (2.5 equiv) in the presence of SmI_2 (0.3 equiv) and molecular sieves. After stirring at 0 °C for 1 h, compounds **63a** and **90** were isolated in a ratio of 76:24 (entry 3, Table 6). After additional stirring at 22 °C for 1 h, the content of **90** further decreased (**63a/90** = 82:18). This result may account for a partial

(16) For ytterbium enolates: Fukuzawa, S.-i.; Tsuchimoto, T.; Kanai, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2227.

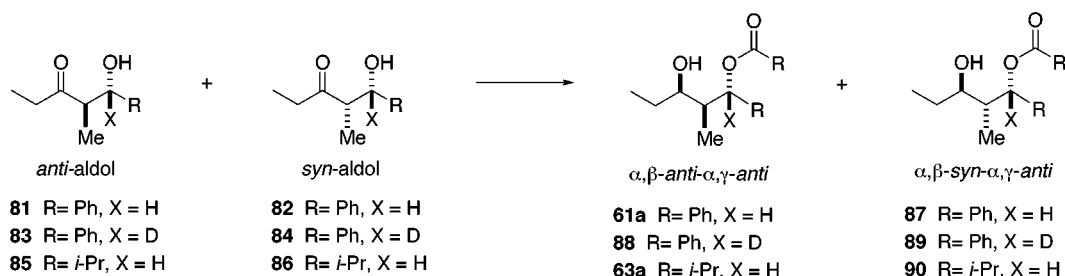
(17) Examples of related reactions: (a) Oku, A.; Harada, T.; Kita, K. *Tetrahedron Lett.* **1982**, 681. (b) Yu, Y.; Zhang, Y.; Ling, R. *Synth. Commun.* **1993**, *23*, 1973.

(18) Hydrio, J.; Van de Weghe, P.; Collin, J. *Synthesis* **1997**, 68.

(19) For reviews of the reactions of (*R*)-glyceraldehyde acetonide: (a) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447. (b) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. (c) Murakami, M.; Kawano, T.; Ito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2437.

(20) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 2, pp 125–155.

Table 6



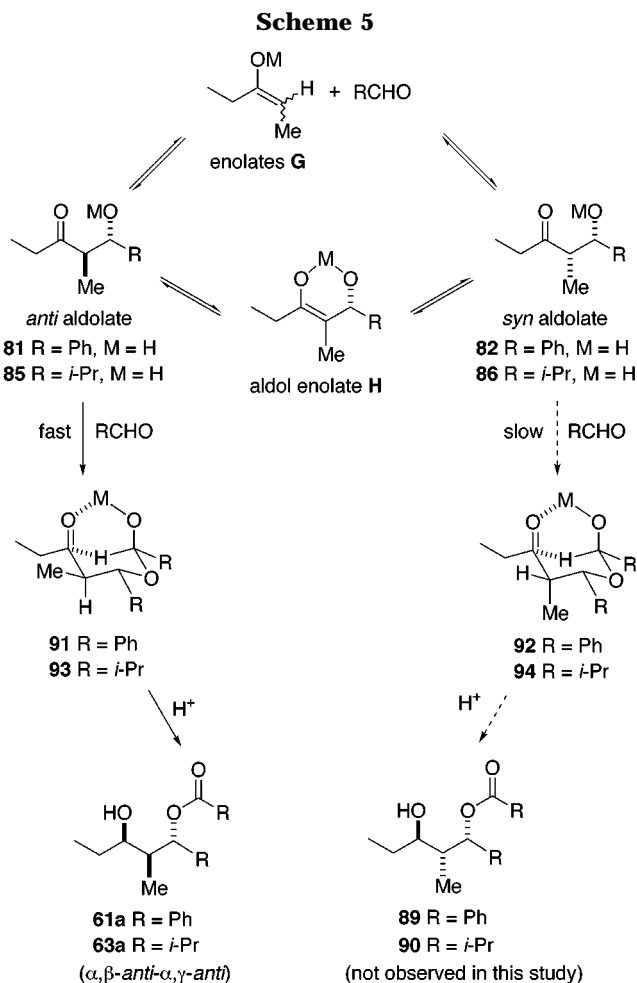
entry no.	reactants	reaction conditions	products
1 ^a	82 + PhCHO	BuTi(O <i>i</i> -Pr) ₄ Li, rt, 24 h	61a + 61b
2 ^b	86 + <i>i</i> -PrCHO (4–8 equiv)	SmI ₂ (15 mol %), –10 °C, 0.5–0.75 h	90
3	85/86 (64:36) + <i>i</i> -PrCHO (2.5 equiv)	SmI ₂ (30 mol %), MS, 0 °C, 1 h	63a/90 (76:24)
4	85/86 (64:36) + <i>i</i> -PrCHO (2.5 equiv)	SmI ₂ (30 mol %), MS, 0 °C (1 h), 22 °C (1 h)	63a/90 (82:18)
5	81/82 (50:50) + PhCHO (2.5 equiv)	SmI ₂ (30 mol %), MS, 0 °C, 0.5 h	61a
6	83/84 (50:50) + PhCHO (2.5 equiv)	SmI ₂ (30 mol %), MS, 0 °C, 0.5 h	61a (>80%)

^a The data are adapted from ref 8e. Compound **61b** is the transesterification isomer of **61a**. ^b The data are adapted from ref 5c.

isomerization of syn-aldol **86** to anti-aldol **85** prior to the Tishchenko reaction. Furthermore, we prepared a 1:1 mixture of **81** and **82** and treated it with benzaldehyde (2.5 equiv) in the presence of SmI₂ (0.3 equiv) and molecular sieves at 0 °C for 0.5 h. Only the α,β -anti- β,γ -syn diol monoester **61a** was obtained, indicating a very rapid isomerization of syn-aldol **82** to anti-aldol **81**. These results were in agreement with the higher reversibility of benzaldehyde than that of isobutyraldehyde in retro-aldol reactions.

Isomerization between anti and syn aldols (or corresponding metal aldolates) may proceed with enolization–protonation (via aldol enolate **H**) or dissociation–recombination (via enolates **G**) pathways (Scheme 5). We thus designed the following experiment to distinguish these two possible pathways. We prepared a 1:1 mixture of deuterated compounds **83** and **84** from PhCDO and the lithium enolate of 3-pentanone. The THF solution of this deuterium-containing mixture was then treated with PhCHO (2.5 equiv) in the presence of SmI₂ (0.3 equiv) and molecular sieves at 0 °C for 0.5 h (entry 6, Table 6). After which, compound **61a** (containing no deuterium) was obtained as the major product according to the ¹H NMR analysis. Thus, dissociation of **83/84** occurred to give the enolates **G**, and recombination of **G** with PhCHO led to aldols **81/82**. This dissociation–recombination process proceeded until an equilibrium was reached, presumably in favor of the anti aldolate.

From the previous reports^{5c,8c} and our current studies, a picture of the tandem aldol–Tishchenko reaction can be drawn: (i) A Lewis acid catalyst (such as titanium complex, SmI₂, SmI₂–MS, or SmI₃–MS) can promote interconversion between anti and syn aldols under appropriate reaction conditions. (ii) Such interconversion follows a dissociation–recombination pathway. (iii) The rate of isomerization of aldols depends on several factors. The aldols derived from benzaldehyde (e.g., **81/82**) reached equilibrium faster than the isobutyraldehyde counterpart (e.g., **85/86**). (iv) The isomerization of aldols and the subsequent Tishchenko reactions are facilitated at a higher temperature (compared entries 2–4 in Table 6). (v) Aldol reaction is reversible, whereas Tishchenko reaction is irreversible. The difference of rates in these two reactions is an important factor to determine the stereochemical outcome of the final diol monoester



products. (vi) Tishchenko reactions are stereospecific processes. An α,β -anti aldol (e.g., **81** or **85**) proceeds with a bicyclic transition state (e.g., **91** or **93**) to give an α,β -anti- α,γ -anti diol monoester (e.g., **61a** or **63a**). An α,β -syn aldol (e.g., **82** or **86**) can undergo a similar Tishchenko reaction with a slower rate through the transition state **92** or **94**, the methyl group of which occupies an energetically unfavorable axial position, to give an α,β -syn- α,γ -anti diol monoester (e.g., **89** or **90**). In such cases, a fast isomerization from syn-aldol to anti-

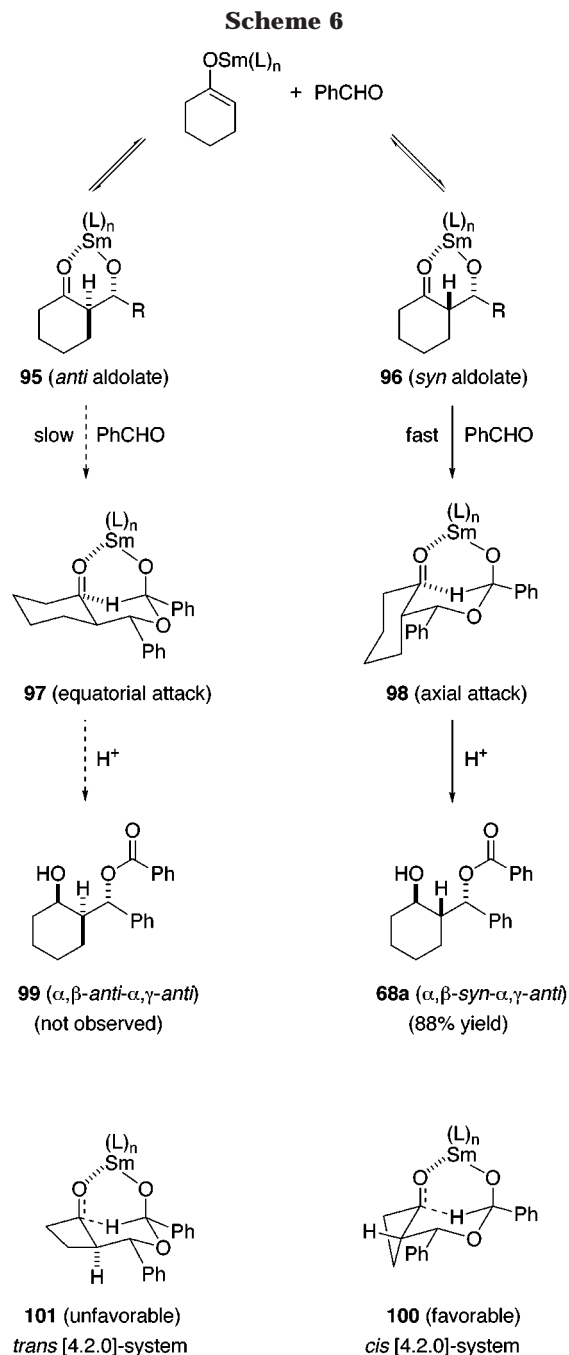
aldol may surpass the rate of Tishchenko reaction. Thus, a syn-aldol may isomerize to an anti-aldol and undergoes a subsequent Tishchenko reaction via the more favorable transition state (e.g., **91** or **93**) to afford the observed α,β -anti- α,γ -anti products. (vii) Transesterification of diol monoesters can occur, but this process can also be avoided by lowering the reaction temperature (e.g. transesterification of **61a** to **61b** occurred at room temperature but was inhibited at 0 °C).

At first glance, one is perplexed that aldol/Evans–Tishchenko reactions of cyclic and acyclic ketones show a dichotomous stereochemical course. The exclusive formation of α,β -syn- α,γ -anti diol monoesters must result from the Tishchenko reactions of α,β -syn aldols. Addition of the *E*-enolates of cyclic ketones to benzaldehyde hardly gives only syn-aldols;²¹ however, anti-aldols (e.g., **95**) can isomerize to syn-aldols (e.g., **96**) via a dissociation–recombination pathway (Scheme 6). If one assumes that syn-aldol **96** undergoes an intramolecular Tishchenko reaction faster than anti-aldol **95**, the preferable formation of α,β -syn- α,γ -anti diol monoester **68a** can be realized. We speculate that the transition state **98**, having H^- attack the cyclohexanone moiety from the axial direction, is superior to an equatorial H^- attack in the transition state **97**. Many previous studies support that axial H^- delivery to cyclohexanones is a kinetically favored process.²² This selective axial addition is very likely applicable to the Tishchenko reactions exemplified in this paper. Under such circumstances, a product development control also favors the formation of the more stable equatorial alcohol (e.g., **68a**). The aldol–Tishchenko reactions of substituted cyclohexanones, 2-cyclohexenone, tetrahydropyranone, α -tetralone, and *trans*-decalone, with benzaldehyde all follow a similar mechanism to give α,β -syn- α,γ -anti products **69a**–**76a**. Formation of **67a** (α,β -syn- α,γ -anti configuration) in the aldol/Evans–Tishchenko reaction of cyclopentanone is also consistent with a preferable pseudoaxial hydride shift. In the reaction of cyclobutanone, the *cis*-developing [4.2.0]bicyclic transition state **100** is considered more favorable than the *trans*-developing transition state **101**; the reaction thus leads to the α,β -syn- α,γ -anti product **66a**. Interestingly, Curran and Wolin^{8b} have proposed a similar transition state for an aldol–Tishchenko reaction in a *cis*-bicyclo[3.3.0]octan-3-one system, though the configuration of the diol monoester product is not rigorously determined.

Conclusion. Although the nature of SmI_2 –MS or SmI_3 –MS is not fully understood, they do function differently, at least to a certain degree, from using SmI_2 or SmI_3 alone. This study shows that SmI_2 –MS can function as an effective Lewis acid to promote cross-aldol and aldol/Evans–Tishchenko reactions. The reactions occur in highly stereoselective manners under mild conditions (0–25 °C). Highly enolizable ketones, such as

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(22) (a) Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 1.1, pp 5–7. (b) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, 75, 521.



1,3-dichloroacetone, are successfully used as the acceptor substrates in the cross-aldol reactions. The dichotomous stereochemistry in aldol/Evans–Tishchenko reactions of cyclic and acyclic ketones is an unprecedented finding. When (*R*)-glyceraldehyde acetonide is employed as the acceptor substrate, the cross-aldol and aldol/Evans–Tishchenko reactions occur in a stereoselective fashion to afford enantiomerically pure compounds. Application of this method to the synthesis of complex natural products is promising.

Experimental Section

Melting points are uncorrected. Optical rotations were measured on a digital polarimeter with a cuvette of 1 cm length. ¹H NMR spectra were recorded at 200, 300, or 500 MHz; ¹³C NMR spectra were recorded at 50, 75, or 125 MHz. CHCl₃ ($\delta = 7.24$ ppm) was used as an internal standard in ¹H

NMR spectra. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. Merck silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on silica gel (70–230 mesh) or alumina (neutral); gradients of EtOAc and *n*-hexane were used as eluents. HPLC was performed on a Hibar Lichrosorb Si 60 (7 μ m) column (25 cm \times 1 cm i.d.) with the indicated eluent at a 5 mL/min flow rate. THF was distilled from sodium benzophenone ketyl under N₂.

General Procedure for Aldol Reactions Promoted by Samarium Diiodide and Molecular Sieves (Tables 1–3). In an oven-dried round-bottomed flask (50 mL) was placed samarium metal (1.13 g, 7.51 mmol), 1,2-diiodoethane (2.10 g, 7.45 mmol), and molecular sieves (4 Å, 200 mg). The air was evacuated by pump. The flask was inflated with argon and capped with a septum. Anhydrous THF (12 mL) was added via syringe. The mixture was vigorously stirred at room temperature (20–25 °C) for 15–20 min to give a deep blue suspension (0.36 M).

Method A. A donor substrate (3.72 mmol) in THF (2 mL) was added dropwise to the deep blue suspension, and the mixture was stirred at room temperature for 5–20 min, after which, an acceptor substrate (4.09 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for an appropriate period, the septum was removed, and the mixture was stirred for additional 10 min in the air to give a yellow suspension. The mixture was filtered and rinsed with CH₂Cl₂ (2 \times 25 mL). The filtrate was concentrated by rotary evaporation. The residue was passed through a short column packed with alumina (neutral, 20–25 g) and eluted with gradients of EtOAc and hexane to give the desired aldol products.

Method B. A mixture of donor (3.72 mmol) and acceptor (4.09 mmol) substrates in THF (4 mL) was added to the deep blue suspension. In certain cases (Table 3), *t*-BuOH (0.71 mL, 7.45 mmol) was added. The workup procedure was similar to that described in method A.

General Procedure for Tandem Aldol/Evans–Tishchenko Reactions Promoted by Samarium Ions (Tables 4 and 5). (i) The dark blue SmI₂ (0.1 M)–THF (3 mL) suspension was prepared by treatment of Sm (45.1 mg, 0.3 mmol) with diiodoethane (84.5 mg, 0.3 mmol) in the presence of molecular sieves (4 Å, 100 mg) by the above-mentioned procedure. (ii) The yellow SmI₃ (0.06 M)–THF (5 mL) suspension was prepared by treatment of Sm (45.1 mg, 0.3 mmol) with I₂ (114.2 mg, 0.45 mmol) in the presence of molecular sieves (4 Å, 100 mg). (iii) A donor substrate (1.0 mmol) in THF (0.5 mL) was added at 0 °C to the SmI₂ or SmI₃ suspension prepared from steps (i) or (ii). The mixture was stirred for 40 min, and an acceptor substrate (2.5 mmol) in THF (1.5 mL) was added dropwise. The mixture was stirred for an appropriate period at 0 °C and then warmed to room temperature. The mixture was filtered and rinsed with CH₂Cl₂. The filtrate was concentrated by rotary evaporation. The residue was passed through a short column packed with alumina (neutral) and eluted with gradients of EtOAc and hexane to give the desired products of diol monoesters.

2-(1-Chloro-2-hydroxyprop-2-yl)cyclopentanone (22). Treatment of cyclopentanone (301 mg, 3.58 mmol) with 1-chloroacetone (364 mg, 3.94 mmol) according to the general procedure (method A) gave the title compound (474 mg, 75%) having the (1'*S*',2'*R*')-configuration: oil; TLC (EtOAc/hexane (20:80)) *R*_f = 0.82; IR (neat) 3342, 1739 cm⁻¹; ¹H NMR (CDCl₃) δ 1.19 (3 H, s), 1.58–1.80 (2 H, m), 2.03–2.47 (4 H, m), 2.58 (1 H, dd, *J* = 8.2 Hz, 8.7 Hz), 3.48, 3.58 (2 H, AB quartet, *J* = 11.5 Hz), 3.97 (1 H, s, OH); ¹³C NMR (CDCl₃) δ 20.1 (q), 22.3 (t), 26.1 (t), 39.4 (t), 52.0 (t), 54.3 (d), 73.4 (s), 222.6 (s); MS *m/z* (rel intensity) 140 (32, M⁺ – HCl), 83 (100). HRMS Calcd for C₈H₁₂O₂ (M⁺ – HCl): 140.0837. Found: 140.0836.

2-[1-Hydroxy-2,3-(isopropylidenedioxy)prop-1-yl]-cyclohexanone (30). Treatment of cyclohexanone (387 mg, 3.94 mmol) with (*R*)-glyceraldehyde acetone (465 mg, 3.58 mmol) in the presence of *t*-BuOH (530 mg, 7.16 mmol) according to the general procedure (method B) gave the title compound (557 mg, 62%) having the (1'*S*',2'*R*',2'*R*')-configuration. The reaction using method A gave a 50% yield of **30**: oil; TLC (EtOAc/hexane (50:50)) *R*_f = 0.5; [α]_D²⁰ –66 (CHCl₃, *c* = 1.0); IR (neat) 3432, 1702 cm⁻¹; ¹H NMR (CDCl₃) δ 1.34 (3 H, s), 1.39 (3 H, s), 1.18–2.44 (9 H, m), 2.62–2.80 (1 H, m), 3.28–3.42 (1 H, m), 3.90–4.22 (3 H, m); ¹³C NMR (CDCl₃) δ 25.3 (2 C), 26.8 (q), 28.2 (t), 32.3 (t), 43.2 (t), 51.7 (d), 67.7 (t), 70.4 (d), 75.0 (d), 109.3 (s), 216.1 (s); MS *m/z* (rel intensity) 228 (3, M⁺), 101 (100); HRMS Calcd for C₁₂H₂₀O₄ (M⁺): 228.1361. Found: 228.1359.

5-Hydroxy-4-methylhept-3-yl Propanoate (62a) and 4-Methylheptane-3,5-diol (62c). The SmI₂-promoted aldol–Tishchenko reaction of 3-pentanone (86 mg, 1.0 mmol) and propionaldehyde (145 mg, 2.5 mmol) at 0 °C, according to the general procedure, gave **62a** (149 mg, 79%; 3*R*',4*S*',5*R*'-configuration). Saponification of **62a** in saturated aqueous NaOH (5 mL) and MeOH (1 mL) for 2 h gave the corresponding diol **62c** (3*R*',5*R*'-configuration). **62a**: oil; TLC (EtOAc/hexane (5:95)) *R*_f = 0.3; IR (neat) 3438, 1725 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 0.79–0.97 (9 H, m), 1.14–1.71 (8 H, m), 2.37 (2 H, q, *J* = 7.5 Hz), 3.04 (1 H, m), 3.36 (1 H, d, *J* = 4.1 Hz, OH), 5.14 (1 H, m); ¹³C NMR (CDCl₃, 75 MHz) δ 9.2, 9.5, 9.8, 10.2, 24.7, 27.7 (2 C), 38.8, 64.2, 74.8, 175.6; MS *m/z* (rel intensity) 201 (1, M⁺ – 1), 57 (100). HRMS Calcd for C₁₁H₂₁O₃ (M⁺ – 1): 201.1491. Found: 201.1502. **62c**: oil; ¹H NMR (CDCl₃, 200 MHz) δ 0.86 (3 H, d, *J* = 7.4 Hz), 0.92 (6 H, t, *J* = 7.4 Hz), 1.30–1.88 (4 H, m), 1.98–2.06 (1 H, m), 2.81 (2 H, br s), 3.60–3.70 (2 H, m); ¹³C NMR (CDCl₃, 75 MHz) δ 9.9, 10.5 (2 C), 26.8 (2 C), 38.6, 67.0, 75.9. Anal. Calcd for C₈H₁₈O₂: C, 65.7; H, 12.4. Found: C, 65.5; H, 12.6.

α -(2-Hydroxycyclohex-1-yl)benzyl Benzoate (68a) and 2-(α -Hydroxybenzyl)cyclohexanol (68c). The SmI₂-promoted aldol–Tishchenko reaction of cyclohexanone (98 mg, 1.0 mmol) and benzaldehyde (265 mg, 2.5 mmol) at 0 °C, according to the general procedure, gave **68a** (273 mg, 88%) having the (1*S*',1'*R*',2'*R*')-configuration. The reaction promoted by SmI₃ gave **68a** in 89% yield. Saponification of **68a** in saturated aqueous NaOH (5 mL) and MeOH (1 mL) for 2 h gave the corresponding diol **68c** (1*R*',1'*R*',2'*R*'). **68a**: oil; TLC (EtOAc/hexane (10:90)) *R*_f = 0.6; IR (neat) 3438, 1720 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 0.99–1.26 (3 H, m), 1.31–1.42 (5 H, m), 1.99–2.93 (1 H, m), 3.33 (1 H, br s), 3.38 (1 H, td, *J* = 10.0, 4.2 Hz), 6.62 (1 H, d, *J* = 2.1 Hz), 7.25–7.61 (8 H, m), 8.12–8.18 (2 H, m); ¹³C NMR (CDCl₃, 50 MHz) δ 23.3, 24.7, 25.3, 34.5, 51.9, 70.1, 74.2, 125.7 (2 C), 127.1, 128.1 (2 C), 128.2, 128.5 (2 C), 129.7, 129.8, 133.3, 139.3, 166.5; MS *m/z* (rel intensity) 310 (10, M⁺), 105 (100). HRMS Calcd for C₂₀H₂₂O₃ (M⁺): 310.1568. Found: 310.1566. **68c**: solid (recrystallized from Et₂O–hexane), mp 106–107 °C, lit.^{15c} 106–107.5 °C; ¹³C NMR (CDCl₃, 75 MHz) δ 24.3, 25.3, 26.1, 35.7, 50.0, 71.4, 76.9, 126.7 (2 C), 127.2, 127.9 (2 C), 141.9.

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Supporting Information Available: Additional experimental procedures, spectral data, and NMR spectra of new compounds, as well as the crystal data, bond distances, bond angles, and an ORTEP drawing of compound **72a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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