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Rapid, Stereochemically Flexible Synthesis of Polypropionates by "Super-Silyl"-Governed Aldol Cascades**

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Keywords

aldol reaction; cascade reactions; diastereoselective reactions; polyketides

The polypropionate motif is an important structural unit present in polyketide natural products, many of which are of great interest due to their wide range of biological activities.[1] For instance, members of the erythromycin and rifamycin families have long been used as commercial antibiotics.[2] The importance of these pharmaceutical agents, as well as the potential to discover new biologically active polypropionates, makes their efficient, stereoselective chemical synthesis an important ongoing challenge. The polypropionate structure is recognized by its characteristic carbon chain decorated with alternating methyl- and hydroxyl- groups. The numerous stereogenic centers allows for many possible stereochemical permutations. Even in the case of a simple dipropionate bearing four stereogenic centers, up to 16 diastereomers are possible. This structural complexity has inspired numerous methods for stereoselective synthesis.[3] Of these methods, the aldol reaction is perhaps the most well studied and widely used in the synthesis of polypropionate natural products.[4] Other methods include crotylation,[5,6] epoxide opening,[7] [2+2] cycloaddition,[8] borylative aldehyde-diene coupling[9] and reductive aldol addition.[10]

While many of these methods have been developed to synthesize polypropionates with high enantio- and diastereo- control, the synthesis of complex polypropionates by these methods usually requires a great deal of steps. For instance, a conventional aldol synthesis of polypropionates begins with an aldol reaction of an ester enolate and an aldehyde (Scheme 1). In order to install a second propionate unit, the resulting β-hydroxyl must first be protected, and the ester reduced to the corresponding aldehyde oxidation state. As a result, in this route each carbon-carbon bond forming event requires numerous additional step-consuming protective group manipulations, redox adjustments, and purifications.

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. CCDC … contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Additionally, control of the stereochemistry in subsequent aldol reactions is often complicated.

Recently, the efficiency of complex molecule synthesis has been evaluated by the concepts of redox economy,[11] which strives to build molecules with minimal oxidation and reduction steps, and step economy,[12] which emphasizes reactions that build complexity and avoid extraneous chemical steps. Under these considerations, a more efficient aldol route to polypropionates would be the aldehyde crossed-aldol reaction, in which the nucleophilic species is derived from an aldehyde rather than an ester. The product of the reaction is therefore also an aldehyde, circumventing the need for a redox adjustment. However, aldehyde crossed-aldol reactions,[13] especially those employing metalloenolates[14] and silyl enol ethers[15] are uncommon, due to the instability of the product and side reactions. Toward this end, we have developed the aldol addition of the *tris*(trimethylsilyl)silyl "super silyl" enol ether of acetaldehyde with simple aldehydes (Scheme 2, X= H).[16] The product of the reaction is a protected β-hydroxy aldehyde, and is stable yet suitable for nucleophilic addition. Careful choice of reaction conditions allowed for the controlled, stereoselective single, double and triple aldol reactions in a one-pot manner. Using this methodology, polyketides including the natural product EBC-23 were synthesized in a short sequence of steps, with minimal protecting group manipulations and functional group interconversions. The super silyl group plays a critical role in these polyaldol cascades, acting as both a reactive group and a stereodirecting group, allowing for high yields and diastereoselectivities. In this report, we describe our approach to the challenging polypropionate structure by stereoselective aldol cascades utilizing the silyl enol ethers derived from propionaldehyde (Scheme 2, X = CH_3).

The first challenge was to develop a diastereoselective single aldol reaction between propionaldehyde derived silyl enol ethers and simple aldehydes. In preliminary experiments, we reported the stereoselective synthesis of the *Z* silyl enol ether **1*Z*** and found that it reacted smoothly with simple aldehydes to generate 2,3-*syn* products in high diastereoselectivity.[16a] We hypothesized that the unique steric and electronic properties of the super silyl group would allow for control of the 2,3- stereochemistry based on the enol ether geometry. The *E* silyl enol ether **1*E*** was generated as a single diastereomer by iridium-catalyzed isomerization of the corresponding allyl silyl ether following Miyaura's protocol.[17] When treated with 0.1 mol% triflimide ($HNTf_2$) in CH_2Cl_2 at −78°C, **1*E*** underwent smooth aldol addition with simple aldehydes (Table 1). Gratifyingly, the 2,3-*anti* adducts were obtained, complementing the *syn*-selective addition using **1*Z***. This remarkable stereospecific *Z-syn*, *E-anti* correlation is not usually observed in Mukaiyama-type aldol reactions. Rather, the diastereoselection is usually substrate controlled due to an open transition state.[18]

The *anti*-selective propionaldehyde aldol reaction displays a wide substrate scope with simple achiral aldehydes (Table 1, entries 1−13). Good yields and high *anti*-selectivity are obtained for linear and branched aliphatic aldehydes (entries 1−3), as well as unsaturated aldehydes (entries 4 and 5). Aromatic aldehydes of varying electronic and steric properties give excellent selectivity and good yields. The *anti*-selectivity of the reaction could be further improved by using the *E* enol ether of propionaldehyde bearing the larger *tris*(triethylsilyl)silyl "TES-type super silyl" group (entries 11−13, compared to entries 1−3). [19]

To further expand the scope of the reaction, and to examine its potential use in the synthesis of molecules of greater stereochemical complexity, we investigated the propionaldehyde aldol addition to chiral aldehydes (Table 1, entries 14−20).[20] Reaction of **1*Z*** with β-triisopropylsiloxy hexanal resulted in good yield and high selectivity (entry 14). After

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derivatization, the major diastereomer was found have 2,3,5- *syn-syn* stereochemistry, demonstrating 1,3-*syn* asymmetric induction. Use of **2*E*** resulted in 2,3,5- *anti-syn* as a single diastereomer (entry 15). Aldehydes bearing a stereocenter in the α-position were also investigated (entries 16–20). Remarkably, in all cases the major product was 3,4-*syn*, following the Felkin model of stereocontrol.[21] Both the challenging 2,3-*syn*, [22] and the 2,3-*anti*[23] products can be obtained, even when aldehydes bearing similarly-sized alkyl groups were used (entries 18 and 19). Importantly, the use of enantiopure α-substituted chiral aldehydes led to products with high enantiopurity, indicating no substantial racemisation under the reaction conditions (entries 18, 20).

With highly selective *syn* and *anti* propionaldehyde aldol additions in hand, we turned our attention to multi-component aldol reactions for the one-pot synthesis of highly complex molecules.[24] Our first goal was to see if a one-pot propionaldehyde/acetaldehyde cascade addition could be accomplished. Benzaldehyde was treated with **1*E*** under standard conditions and monitored by TLC analysis. After the first aldol reaction was judged complete, acetaldehyde- derived enol ether **5** was added (Table 2, entry 1), to generate the double addition product in 67% yield and in excellent dr (95:5). The high diastereoselectivity indicates that the second addition step is nearly completely selective. The product was determined to have 2,3-*syn* stereochemistry, consistent with the Felkin model of 1,2- stereocontrol. Alternatively, the super silyl enol ether of acetone **6** could be employed as the second nucleophile, producing the methyl ketone double aldol adduct in high yield and selectivity on preparative scale (7.0 mmol) (Table 2, entry 2).

Consecutive aldol additions to aliphatic aldehydes proved to be more challenging. Mono-aldol adducts varied greatly in reactivity, with small R groups displaying the highest reactivity. Use of $HNTf_2$ alone did not result in double aldol addition to more sterically demanding aldehydes. However, after optimization of reaction conditions, it was found that $HNTf_2$ or our previously developed carbon acid $C_6F_5C(H)Tf_2$[25] promoted the acetaldehyde addition to propionaldehyde adducts when paired with 5 mol% *tert*-butyl iodoacetylene.[16d] Still higher reactivity was observed with ≤0.5 mol% of Lewis acid $AlMe_2NTf_2$. Thus, under optimized reaction conditions, cyclohexane carboxaldehyde underwent propionaldehyde addition followed by double acetaldehyde addition to give the *syn-syn-syn* triple aldol product in one pot (entry 3). Alternatively, the order of silyl enol ether addition could be changed to give double acetaldehyde addition to pivalaldehyde followed by propionaldehyde addition (entries 4 and 5). Both **1*Z*** and **1*E*** gave triple aldol products **10** and **11**, which were isolated after facile separation from their minor diastereomers in 43% and 45% yields, respectively.

We then turned our attention to consecutive propionaldehyde additions. Double aldol addition of **1*Z*** with a range of aldehydes gave the 2,3,4,5-*syn-syn-syn* stereochemistry (entries 6−9). Interestingly, when acetaldehyde was used as a substrate, limiting the amount of **1*Z*** to just 1.5 equivalents resulted in 48% yield of the *syn-syn-syn* double aldol adduct in excellent dr (95:5) along with 22% yield of the predominantly *anti* mono aldol adduct (dr = 85:15) (entry 8). When >1.5 equivalents was used, the yield of the double aldol product increased but the diastereomeric ratio of the product decreased. This observation can be explained by a kinetic resolution of diastereomers: the first aldol reaction is non-selective, resulting in a ~1:1 mixture of **3a-*anti*** and **3a-*syn***. However, **3a-*syn*** undergoes a selective second aldol addition more rapidly than **3a-*anti***.

Double propionaldehyde aldol addition of **1*E*** to aldehydes was also possible (entries 10–12). Addition of **1*E*** to alanine-derived (*S*)-*N*-benzyl-*N*-tosyl 2-amino-propanal[26] (entry 11) showed excellent selectivity, producing predominantly one out of 16 possible diastereomers (dr = 97:3). After derivatization, the stereochemistry of **17** was determined by

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X-ray crystallographic analysis. Curiously, the *anti-anti-anti-anti* stereochemistry was obtained, indicating the first aldol addition takes place with anti-Felkin selectivity.[27] The *anti-anti-anti* stereochemistry was also obtained by double addition of **1*E*** to benzaldehyde and benzyloxy-acetaldehyde (entries 10 and 12).

Having generated double aldol products with 2,3,4,5- *syn-syn-syn* stereochemistry and 2,3,4,5- *anti-anti-anti* stereochemistry, we wondered if it would be possible to generate other stereotetrads with high diastereoselection by sequential addition of **1*Z*** followed by **1*E*** or vice versa. Gratifyingly, benzaldehyde underwent addition of **1*E*** followed by **1*Z*** in one pot in excellent yield (92%) and diastereoselectivity (dr = 89:7:4) (entry 13). After derivatization, product **19** was found to have 2,3,4,5- *syn-syn-anti* stereochemistry. Using 2-methyl butanal as a substrate, we reversed the order of addition (first **1*Z*** then **1*E***), and obtained the 2,3,4,5,6-*anti-syn-syn-syn* product **20** in good yield (80%) and high selectivity (84:7:3:2).

In summary, we have developed a general propionaldehyde crossed-aldol reaction affording *syn* or *anti* aldol products with high diastereoselectivity and wide substrate scope. These aldol products can themselves undergo acetaldehyde- acetone-, and double-acetaldehyde aldol additions to rapidly assemble polyketide fragments in excellent step economy and without redox manipulations. Double-propionaldehyde aldol reactions were also developed, producing molecules with up to five contiguous stereogenic centers with high control of diastereoselectivity. The **Z**/***E*** geometry of the silyl enol ether and the order of addition are convenient handles for controlling the stereochemistry of the product, making this method highly flexible. Overall, this report represents a highly efficient alternative to lengthy classical aldol syntheses of polypropionates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. a) Rohr J. Angew. Chem. 2000; 112:2967–2969.Angew. Chem. Int. Ed. 2000; 39:2847–2849.b) Koskinen AMP, Karisalmi K. Chem. Soc. Rev. 2005; 34:677–690. [PubMed: 16186897]
2. a) Baerson, SR.; Rimando, AM., editors. Polyketides : Biosynthesis, Biological Activity, and Genetic. Engineering. Washington, DC: American Chemical Society; 2006. b) Stauton J, Wilkinson B. Chem. Rev. 1997; 97:2611–26030. [PubMed: 11851474] c) Floss HG, Yu T. Chem. Rev. 2005; 105:621–632. [PubMed: 15700959]
3. Li J, Menche D. Synthesis. 2009:2293–3215. and references therein.
4. a) Schetter B, Mahrwald R. Angew. Chem. 2006; 118:7668–7686.Angew. Chem. Int. Ed. 2006; 45:7506–7525.b) Mahrwald, R., editor. Modern Aldol. Reactions. Weinheim: WILEY-VCH; 2004.
5. Selected examples: Roush WR, Ando K, Powers DB, Halterman RL, Palkowitz AD. Tetrahedron Lett. 1988; 29:5579–5582. Rauniyar V, Huimin Z, Hall DG. J. Am. Chem. Soc. 2008; 130:8481–8490. [PubMed: 18540580] Kim H, Ho S, Leighton JL. J. Am. Chem. Soc. 2011; 133:6517–6520. [PubMed: 21486033] Gao X, Han H, Krische MJ. J. Am. Chem. Soc. 2011; 133:12795–12800. [PubMed: 21739988]
6. Selected reviews: Ramachandran PV. Aldrichchimca Acta. 2002; 35:23–35. Denmark SE, Fu J. Chem. Rev. 2003; 103:2763–2793. [PubMed: 12914480]
7. Chow KY, Bode JW. J. Am. Chem. Soc. 2004; 126:8126–8127. [PubMed: 15225048]
8. a) Zhu C, Shen X, Nelson SG. J. Am. Chem. Soc. 2004; 126:5352–5353. [PubMed: 15113194] b) Shen X, Wasmuth AS, Zhao J, Zhu C, Nelson SG. J. Am. Chem. Soc. 2006; 128:7438–7439. [PubMed: 16756287]
9. Cho HY, Morken JP. J. Am. Chem. Soc. 2010; 132:7576–7577. [PubMed: 20481451]

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10. Selected review: Nishiyama H, Shiomi T. Krische MJ. Metal Catalyzed. Reductive C–C Bond Formation. 2007Berlin, HeidelbergSpringer Berlin Heidelberg:105–137.
11. Burns NZ, Baran PS, Hoffman RW. Angew. Chem. 2009; 121:2896–2890.Angew. Chem. Int. Ed. 2009; 48:2854–2867.
12. a) Wender PA, Bi FC, Gamber GG, Gosselin F, Hubbard RD, Scanio MJC, Sun R, Williams TJ, Zhang L. Pure Appl. Chem. 2002; 74:25–31.b) Wender PA, Verma VA, Paxton TJ, Pillow TH. Acc. Chem. Res. 2008; 41:40–49. [PubMed: 18159936] c) Wender PA, Miller BL. Nature. 2009; 460:197–201. [PubMed: 19587760]
13. For selected organocatalytic methods, see: List B, Verma RA, Barbas CF. J. Am. Chem. Soc. 2000; 122:2395–2396. Northup AB, MacMillan DWC. J. Am. Chem. Soc. 2002; 124:6798–6799. [PubMed: 12059180] Chowdar NS, Ramachary DB, B D, Cordova A, Barbas CF. Tetrahedron Lett. 2002; 43:9591–9595. Northup AB, Mangion IK, Hettche F, MacMillan DWC. Angew. Chem. 2004; 116:2204–2206. Angew. Chem. Int. Ed. 2004; 43:2152–2154. Kano T, Sugimoto H, Maruoka K. J. Am. Chem. Soc. 2011; 133:18130–18133. [PubMed: 21999103]
14. a) Heathcock CH, Buse CT, Kleschick WA, Pirrung MC, Sohn JE, Lampe J. J. Org. Chem. 1980; 45:1066–1081.b) Kohler BAB. Synth. Commun. 1985; 15:39.c) Mahrwald R, Costisella B, Gündogan B. Tetrahedron Lett. 1997; 38:4543–4544.
15. Selected examples: Mukaiyama T, Banno K, Narasaka N. J. Am. Chem. Soc. 1974; 96:7503–7509. Kato J, Mukaiyama T. Chem. Lett. 1983:1727–1728. Denmark SE, Ghosh SK. Angew. Chem. 2001; 113:4895–4898. Angew. Chem. Int. Ed. 2001; 40:4757–4762. Denmark SE, Bui T. J. Org. Chem. 2005; 70:10190–10193. [PubMed: 16292871]
16. a) Boxer M, Yamamoto H. J. Am. Chem. Soc. 2006; 128:48–49. [PubMed: 16390115] b) Boxer M, Yamamoto H. J. Am. Chem. Soc. 2007; 129:2762–2763. [PubMed: 17309266] c) Boxer M, Yamamoto H. J. Am. Chem. Soc. 2008; 130:1580–1582. [PubMed: 18193878] d) Albert BJ, Yamamoto H. Angew. Chem. 2010; 122:2807–2809.Angew. Chem. Int. Ed. 2010; 49:2747–2749.e) Albert BJ, Yamaoka Y, Yamamoto H. Angew. Chem. 2011; 123:2658–2660.Angew. Chem. Int. Ed. 2011; 50:2610–2612.f) Saadi J, Akakura M, Yamamoto H. J. Am. Chem. Soc. 2011; 133:14248–14251. [PubMed: 21815682]
17. Ohmura T, Yamamoto Y, Miyaura N. Organometallics. 1999; 18:413–416.
18. Mahrwald R. Chem. Rev. 1999; 99:1095–1120. [PubMed: 11749441]
19. Yamaoka Y, Yamamoto H. J. Am. Chem. Soc. 2010; 132:5354–5356. [PubMed: 20349994]
20. a) Roush WR. J. Org. Chem. 1991; 56:4151–4157.b) Lodge EP, Heathcock CH. J. Am. Chem. Soc. 1987; 109:3353–3361.c) Mori I, Ishihara K, Heathcock CH. J. Org. Chem. 1990; 55:1114–1117.
21. Anh, NT. Organic Chemistry Syntheses and Reactivity. Berlin/Heidelberg: Springer-verlag; 1980. p. 145-162.
22. a) Ward DE, Guo C, Sasmal PK, Man CC, Sales M. Org. Lett. 2000; 2:1325–1328. [PubMed: 10810739] b) Brazeau J, Mochirian P, Prévost M, Guindon Y. J. Org. Chem. 2009; 74:64–74. [PubMed: 19063596]
23. Nakamura M, Mori Y, Okuyama K, Tanikawa K, Yasuda S, Hanada K, Kobayashi S. Org. Biomol. Chem. 2003; 1:3362–3376. [PubMed: 14584800]
24. Hasegawa A, Ishihara K, Yamamoto H. Angew. Chem. Int. Ed. 2003; 115:5909–5911.Angew. Chem. Int. Ed. 2003; 42:5731–5733.
25. Touré BB, Hall DG. Chem. Rev. 2009; 109:4439–4486. [PubMed: 19480390]
26. Reviews: Reetz M. Chem. Rev. 1999; 99:1121–1162. [PubMed: 11749442] Chalko J, Jurczak J. Chirality. 2003; 13:514–541.
27. See supporting information for further discussion.

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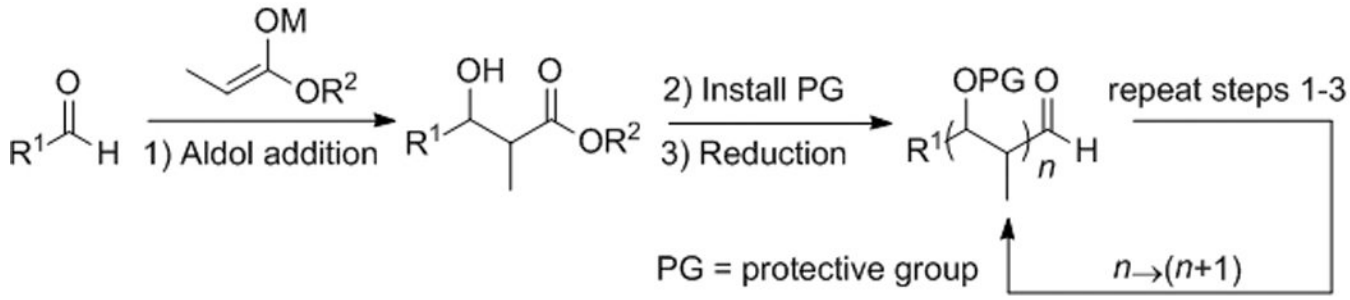
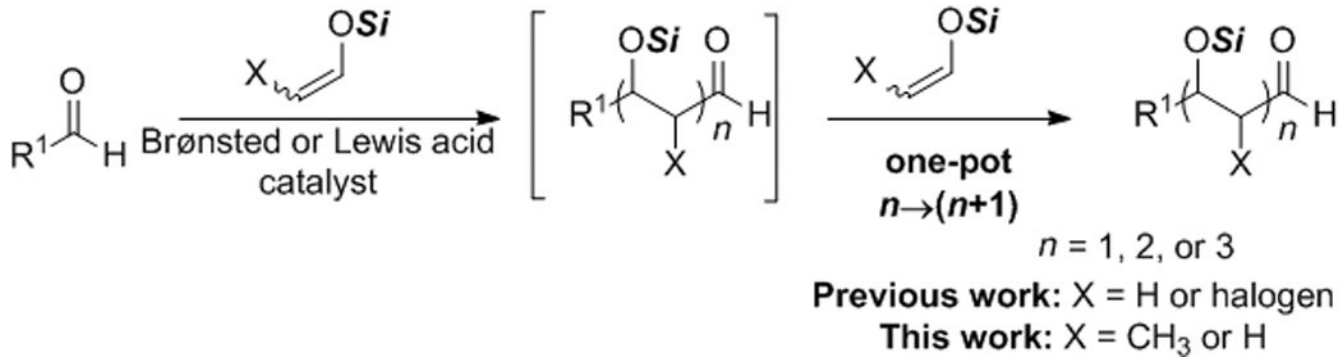


Scheme 1.
Conventional aldol approach to polypropionates.



Scheme 2.

Synthesis of polypropionates by one-pot aldol cascades using aldehyde-derived "super-silyl" enol ethers. ***Si*** =Si(TMS)$_3$

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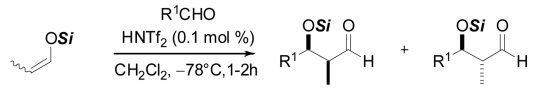
Table 1

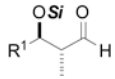
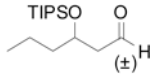
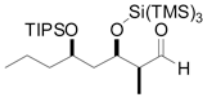
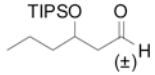
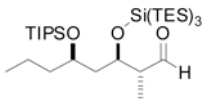
Addition of propionaldehyde enol ethers to aldehydes.



1*E* or **1*Z*** ***Si*** = $Si(TMS)_3$
2*E* ***Si*** = $Si(TES)_3$

3-*syn*: ***Si*** = $Si(TMS)_3$

3-*anti*: ***Si*** = $Si(TMS)_3$
4-*anti*: ***Si*** = $Si(TES)_3$

Entry	Enol Ether	Substrate	Product	% yield	dr[a],[b]
					
1	**1*E***	R^1 = CH_3	**3a-*anti***	74	79:21
2	**1*E***	*n*-Pent	**3b-*anti***	87	87:13
3	**1*E***	*c*-Hex	**3c-*anti***	82	86:14
4	**1*E***	(*E*)-PhCH=CH	**3d-*anti***	58	97:3
5	**1*E***	TMSC≡C	**3e-*anti***	67	79:21
6	**1*E***	Ph	**3f-*anti***	76	96:4
7	**1*E***	4-$(OCH_3)C_6H_4$	**3g-*anti***	54	93:7
8	**1*E***	2-furyl	**3h-*anti***	95	>97:3
9	**1*E***	2-$(Cl)C_6H_4$	**3i-*anti***	91	>97:3
10	**1*E***	4-$(NO_2)C_6H_4$	**3j-*anti***	95	>97:3
11	**2*E***	CH_3	**4a-*anti***	84	90:10
12	**2*E***	*n*-Pent	**4c-*anti***	66	96:4
13	**2*E***	TMSC≡C	**4e-*anti***	63	94:6
14	**1*Z***		 **3k-*syn-syn***	76	88:12
15	**2*E***		 **4k-*anti-syn***	79	>97:3

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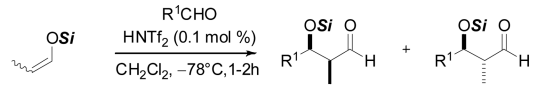
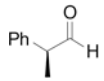
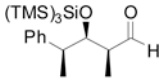
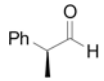
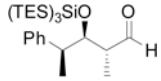
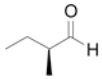
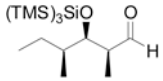
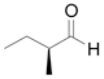
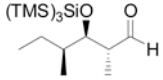
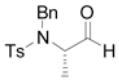
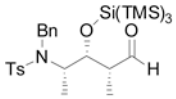


1*E* or **1*Z*** ***Si*** = Si(TMS)$_3$
2*E* ***Si*** = Si(TES)$_3$

3-*syn*: ***Si*** = Si(TMS)$_3$

3-*anti*: ***Si*** = Si(TMS)$_3$
4-*anti*: ***Si*** = Si(TES)$_3$

Entry	Enol Ether	Substrate	Product	% yield	dr[a],[b]
16	**1*Z***		 **3l-*syn-syn***	85	87:10:3
17[c]	**2*E***		 **4l-*anti-syn***	74	90:10
18	**1*Z***		 **3m-syn-*syn***	84	83:13:3:2 (er = 96:4)
19	**1*E***		 **3m-*anti-syn***	77	76:21:3
20	**1*Z***	 (er = >99:1)	 **3n-*syn-syn***	78	>97:3 (er = 99:1)

[a]Ratio of *detectable* diastereomers by ^{1}H NMR integration of the crude reaction mixture.

[b]Enantiomeric ratio of major diastereomer was determined by chiral HPLC.

[c]Me_2AlNTf_2 (0.5 mol%) was used in place of $HNTf_2$. TES = trimethylsilyl; Tf = trifluoromethanesulfonyl; TIPS = triisopropylsilyl; Ts = *p*-toluenesulfonyl.

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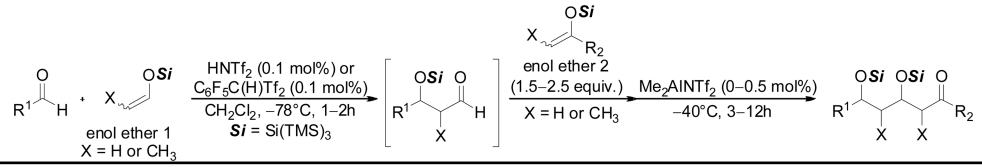
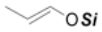
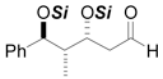
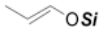
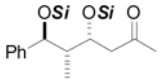
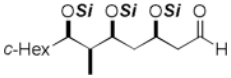
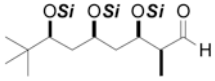
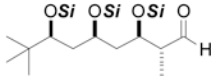
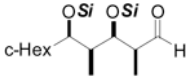
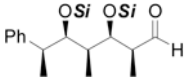
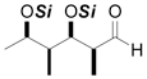
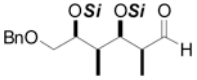
Table 2

One-pot consecutive aldehyde crossed-aldol additions



Entry[a]	R[1]	Enol ether 1		Enol Ether 2		Product		% yield[b]	dr[c]
1	Ph		*1E*		**5**		**7**	67	95:5
2[d]	Ph		*1E*		**6**		**8**	86	96:4
3[e]	*c*-Hex		**1Z**	(2.5 equiv.)	**5**		**9**	57[f]	_[g]
4	*t*-Bu	(2.0 equiv.)	**5**		**1Z**		**10**	43[f]	_[g]
5	*t*-Bu	(2.0 equiv.)	**5**		**1E**		**11**	45[f]	_[g]
6	*c*-Hex		**1Z**	——			**12**	63	81:13:2:4
7			**1Z**	——			**13**	72	94:4:1:1
8	CH_3	(1.5 equiv.)	**1Z**	——			**14**	47	95:5
9	$BnOCH_2$	(1.5 equiv.)	**1Z**	——			**15**	48	89:7:2:2

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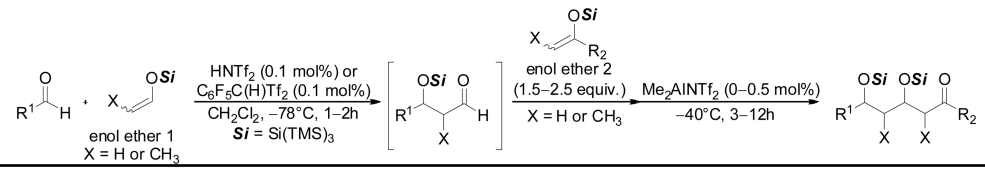
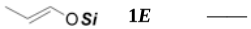
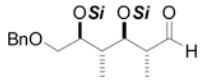
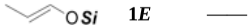
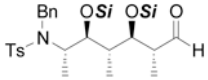
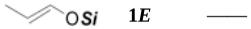
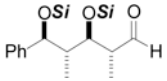
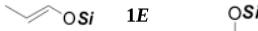
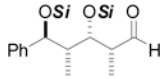
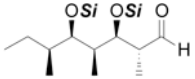


Entry[a]	R^1	Enol ether 1		Enol Ether 2		Product		% yield[b]	dr[c]
10	$BnOCH_2$		**1*E***	——			**16**	63	86:14
11			**1*E***	——			**17**	74	97:3
12	Ph		**1*E***	——			**18**	57	95:5
13	Ph		**1*E***		**1*Z***		**19**	92	89:7:4
14			**1*Z***		**1*E***		**20**	80	84:7:6:3

[a]Reactions conducted at 0.30 mmol scale.

[b]Combined isolated yield of all diastereomers.

[c]Ratio of *detectable* diastereomers by ^{1}H NMR integration of the crude reaction mixture.

[d]Reaction conducted at 7.0 mmol scale.

[e]*t*-BuC≡CI (5 mol%) added with **5**.

[f]Yield shown of isolated single diastereomer after chromatography.

[g]dr could not be determined by ^{1}H NMR analysis of the crude mixture.