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Cascade Reactions

A Triple-Aldol Cascade Reaction for the Rapid Assembly of Polyketides**

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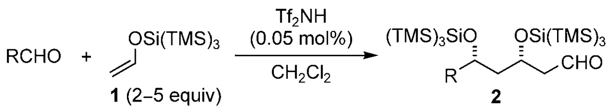
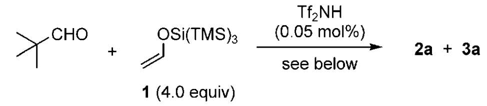
Polyketides have long provided synthetic organic chemists with a variety of complex architectures to construct and develop new chemical tools for, and provided medicine with, many useful drugs. About 1% of polyketides display drug activity, which is five times the average for natural products.[1] A common strategy in the synthesis of polyketides is the cross-aldol reaction, although it can be complicated by uncontrolled oligomerization and dehydration reactions.[2] There has been significant advances in the development of the asymmetric aldol and allylation reactions of aldehydes.[3,4] However, further manipulations, such as alcohol protection or redox reactions, are often required before the next iteration can proceed. Therefore, there has been increasing interest in one-pot cascade aldol reactions;[5,6] however, only one example successfully proceeded to the third aldol iteration, and in low yields.[5a] Inspired by the seminal work of Mukaiyama et al.,[2a] our research group reported an aldol cascade reaction using tris(trimethylsilyl)silyl enol ethers, such as the easily prepared **1**,[7] to give versatile aldehyde products **2** (Scheme 1). Moreover, these aldehydes can be treated with Grignard or polyhalomethyllithium reagents in the same reaction pot to generate mono-protected diols.[8] The formation of these compounds is highly diastereoselective because of the extreme steric bulk of the tris(trimethylsilyl)silyl group.[7a,8a,9] Significantly, further addition of **1** to **2** is strictly prevented, because of the steric bulk of the $(TMS)_3SiNTf_2$·**2** complex.



Scheme 1. Synthesis of 3,5-disilyloxyaldehydes utilizing silyl enol ether **1**. TMS = trimethylsilyl; Tf = trifluoromethanesulfonyl.

We set out with the challenging aim of extending this aldol cascade reaction to three or more additions of **1** to an aldehyde for the construction of polyketides in a minimal number of steps. Despite several attempts, treatment of dimethylpropanal with **1** (4.0 equivalents) and Tf_2NH in dichloromethane gave only the double-aldol product **2a** (R = *t*Bu), without the formation of any triple-aldol product **3a** (Table 1, entry 1). Heating the reaction mixture also failed to produce the desired triple aldol adduct. Evidently, a new approach was required. Simple solvent screening had interesting effects on the reaction: performing the reaction in hexane or toluene gave only the mono-aldol adduct (Table 1, entries 2 and 3), whilst when chlorobenzene or perfluorooctane were used, **2a** was obtained in 60 and 20% yields, respectively, with little or no formation of **3a** (Table 1, entries 4 and 5).

Table 1: Optimization of the triple aldol reaction.



Entry	Solvent	T [°C]	Additive [mol%]	Yield of **2a** [%][a]	Yield of **3a** [%][a,b]
1	CH_2Cl_2	0 to 40	none	75	0
2	hexanes	23 to 65	none	< 5	0
3	toluene	−78 to 80	none	< 5	0
4	PhCl	0 to 50	none	60	< 5
5	C_8F_{18}	0 to 60	none	20	< 5
6	CH_2Cl_2	0 to 23	ICH_2CH_2I (10)	37	31
7	CH_2Cl_2	−78 to 23	MeI (10)	71	13
8	CH_2Cl_2	−40 to 0	PhI (10)	30	52
9	CH_2Cl_2	−40 to 23	1,2-$C_6H_4I_2$ (10)	49	27
10	CH_2Cl_2	−40 to 23	2-I-py (10)	< 5	0
11[c]	CH_2Cl_2	−40 to 23	I_2 (5.0)	65	7
12[c]	CH_2Cl_2	−40 to 23	PhI (10)	< 5	85
13[c]	CH_2Cl_2	−40 to 0	PhI (10)	64	32
14[c]	CH_2Cl_2	0	PhI (10)	29	51
15[c]	CH_2Cl_2	23	PhI (10)	15	47
16[c]	CH_2Cl_2	−40 to 0	PhI (2.0)	12	77
17[c]	CH_2Cl_2	−40 to 0	PhI (0.5)	46	26

[a] Yield of combined isolated diastereomers. [b] d.r. = 87:10:2:< 1 as determined by crude ^1H NMR spectroscopic and HPLC analyses. [c] 5.0 equivalents of **1**.

Because the solvent seemed to be playing a critical role in affecting the active catalytic species, different additives were then screened. The use of a substoichiometric amount of 1,2-diiodoethane, which was chosen because **3a** was formed in low yield when 1,2-dichloroethane was used as the reaction solvent, gave **2a** and **3a** in 37 and 31% yields, respectively (Table 1, entry 6). Surprised by the large effect that the iodine-containing additive had on the reaction, other iodides were screened. Iodomethane gave **2a** and **3a** in 71 and 13% yields, respectively, and iodobenzene afforded the products in

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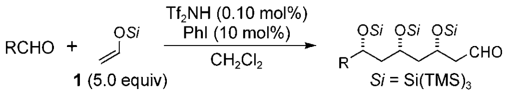
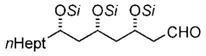
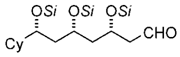
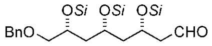
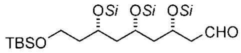
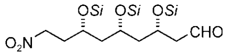
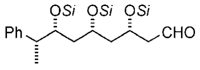
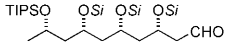
30 and 52 % yields, respectively (Table 1, entries 7 and 8). The use of two other aryl iodides, 1,2-diiodobenzene and 2-iodopyridine, were less successful (Table 1, entries 9 and 10). Finally, the use of I_2 as an additive proved ineffective in forming **3a** (Table 1, entry 11). Therefore, iodobenzene was chosen to be the optimal additive for our investigation.

This reaction was optimized using iodobenzene as an additive and dichloromethane as the solvent. Gratifyingly, **3a** was obtained in a remarkable 85 % yield when the reaction was performed at −40 to 0 °C, using 5.0 equivalents of **1** (Table 1, entry 12). The temperature played a critical role in the generation of **3a**. Too low a reaction temperature did not allow the third aldol reaction to occur, whereas too high a temperature caused decomposition of **1**, **2a**, and **3a** (Table 1, entries 13–15). Although, the amount of iodobenzene could be lowered (Table 1, entries 16 and 17), it caused a decrease in the yield of **3a**.

With our optimized triple-aldol reaction conditions in hand, the aldehyde substrate scope was then investigated (Table 2). Octanal and cyclohexanecarboxaldehyde were good substrates for the triple-aldol reaction, giving **3b** and **3c** along with their minor diastereomers in 84 and 87 % yields, respectively (Table 2, entries 1 and 2). This reaction was tolerant of different functionalities on the aldehyde. Benzyloxyacetaldehyde and 3-*tert*-butyldimethylsilyloxypropanal gave **3d** and **3e** in 75 and 87 % yields, respectively (Table 2, entries 3 and 4). Furthermore, 3-nitropropanal produced **3f** and its minor diastereomers in 89 % yield (Table 2, entry 5). Chiral aldehydes 2-phenylpropanal and 3-triisopropylsilyloxybutanal afforded **3g** and **3h** in 54 % and 57 % yields, respectively, as a mixture of easily separated diastereomers (Table 2, entries 6 and 7).

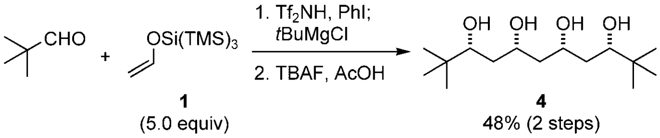
Table 2: Scope of the aldehyde substrate in the triple-aldol reaction with **1**.



Entry	Product		Yield [%][a]	d.r.[b]
1		**3b**	84	79:10:9:<2
2		**3c**	87	81:9:8:<2
3		**3d**	75	81:9:8:<2
4		**3e**	87	71:14:12:2
5[c]		**3f**	89	87:8:3:2
6		**3g**	54	–[d]
7[e]		**3h**	57	–[d]

[a] Yield of combined isolated diastereomers, unless otherwise noted. [b] The diastereomeric ratios were determined by crude ^{1}H NMR spectroscopic and HPLC analyses. [c] 0.2 mol% Tf$_2$NH was used. [d] this yield is for the diastereomer shown only; [e] 10 mol% 1-iodo-3,3-dimethyl-1-butyne was employed in this reaction. Cy = cyclohexyl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

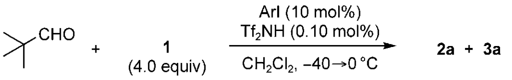
The relative configurations for aldehydes **3** were elucidated from their reduction and subsequent deprotection with TBAF or UV light,[10] utilizing the powerful NMR spectroscopy method described by Kishi and Kobayashi (for full details, see the Supporting Information).[11] Furthermore, **3a** could be treated with *t*BuMgCl in the same reaction vessel to generate a *meso* tetraol (**4**) after deprotection (Scheme 2). This method is able to create four C–C bonds and four stereocenters in high efficiency in a one-pot operation.



Scheme 2. One-pot preparation of tetraol **4**. TBAF = tetrabutylammonium fluoride.

Intrigued by the critical role of iodobenzene in the promotion of the third aldol reaction in this cascade, the following experiments were designed. With the hypothesis in mind that iodobenzene is acting as a Lewis base towards $(TMS)_3SiNTf_2$, the steric and electronic environments of iodobenzene were varied. Somewhat sterically more-hindered aryl iodides had little effect on the synthesis of **3a** (Table 3, entries 2 and 3), whereas a very bulky aryl iodide gave diminished reactivity (Table 3, entry 5). The electronically less-Lewis-basic 1-iodo-3,5-bis(trifluoromethyl)benzene was also less effective as an additive (Table 3, entry 4). Indeed, the mass spectra of $(TMS)_3SiNTf_2$ in the presence of iodobenzene showed signals at *m*/*z* 536 and 656, which correspond to $[(TMS)_3Si + IPh + CH_2Cl_2]^+$ and $[(TMS)_3Si + (IPh)_2]^+$, respectively. These results are supported by the previously reported crystal structure of 1,2-dichlorobenzene and $i\mathrm{Pr}_3\mathrm{Si}^+\,[\mathrm{CHB}_{11}\mathrm{Cl}_{11}]^-$.[12] Although ^{29}Si NMR spectroscopy experiments with $(TMS)_3SiNTf_2$ did not show a significant difference on addition of iodobenzene ($\Delta\delta = 0.4$ ppm of the central silicon atom), this could be due to the rapid equilibration or a screening effect of the multiple TMS groups.

Table 3: Perturbation of the aryl iodide.

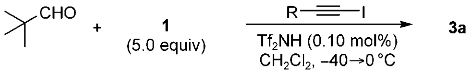


Entry	ArI	Yield [%][a]	
		2a	**3a**
1[b]	iodobenzene	29 (<5)	51 (85)
2	1,3-dimethyl-2-iodobenzene	73	24
3	3,5-dimethyl-1-iodobenzene	52	40
4	1-iodo-3,5-bis(trifluoromethyl)benzene	78	12
5	1-iodo-2,4,6-triisopropylbenzene	87	7

[a] Yield of combined isolated diastereomers. [b] Yields in parentheses refer to when 5.0 equivalents of **1** are employed.

In the search for a better co-catalyst for the triple-aldol cascade reaction, we required a smaller yet electronically stabilized organoiodide. Towards this end, a 1-iodo-2-phenylacetylene was prepared, and it proved to be a more effective additive than iodobenzene for the production of **3a**, effective as low as 0.1 mol% (Table 4, entries 1–4). 1-Iodo-3,3-dimethyl-1-butyne further improved the production of **3a** to 85 and 77% yields, when employed in 0.5 and 0.1 mol%, respectively. These results showed little drop-off in the yield of **3a**, as compared to the yields in Table 2, and clearly demonstrate the power of using organoiodides in this reaction.

Table 4: Improved organoiodide co-catalysts.



Entry	R [mol%]	Yield [%][a]
1	Ph (10)	80
2	Ph (2.0)	71
3	Ph (0.5)	65
4	Ph (0.1)	56
5	*t*Bu (0.5)	85
6	*t*Bu (0.1)	77

[a] Yield of combined isolated diastereomers.

We propose that organoiodides (RI) can react with $(\mathrm{TMS})_3\mathrm{SiNTf_2}$, to afford the cationic and sterically less-demanding complex **5** [Eq. (1)], in analogy with the crystal structure reported by Reed and co-workers.[12] This more-reactive complex is able to promote the reaction of **1** and **2**.

$$\mathrm{Tf_2N{-}Si(TMS)_3} \xrightleftharpoons{\mathrm{RI}} \underset{\mathbf{5}}{\mathrm{RI{-}Si(TMS)_3}^{+}} \quad {}^{-}\mathrm{NTf_2} \qquad (1)$$

In summary, we have developed an efficient triple-aldol cascade reaction for the preparation of 3,5,7-trisilyloxy aldehydes in high diastereoselectivities from a diverse set of simple aldehydes. This method can produce these complex structures with unprecedented ease. The key to allowing the triple-aldol reaction to proceed efficiently was the addition of iodobenzene or 1-iodoalkynes, which generated a more reactive catalytic system. However, as an asymmetric version of this reaction is not yet available, simple chiral aldehydes can be employed in this reaction to generate enantiopure complex aldehydes **3** with unmatched speed.

Experimental Section

Representative procedure for the triple aldol condensation of aldehydes and silyl enol ether **1**: A stirred solution of **1** (729 mg, 2.50 mmol), PhI (5.6 μL, 0.050 mmol), and dimethylpropanal (55 μL, 0.50 mmol) in $\mathrm{CH_2Cl_2}$ (2.5 mL) was cooled to −40°C before $\mathrm{Tf_2NH}$ (0.010 M in $\mathrm{CH_2Cl_2}$, 50 μL, 0.50 μmol) was added to the mixture. The reaction mixture was stirred for 30 minutes at the same temperature, then warmed to 0°C. After an additional 30 minutes at the same temperature, the reaction was quenched by the addition of a pH 7 buffer (5 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 mL). The combined organic layers were dried over $\mathrm{Na_2SO_4}$, filtered through cotton, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (50 mL) eluting with dichloromethane/hexanes (1:19→1:4) to give **3a** (409 mg, 85%) as a white foam.

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Keywords: aldol reaction · diastereoselectivity · Lewis acids · organocatalysis · polyketides

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