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COMMUNICATIONS

Published on Web 12/13/2005

Tris(trimethylsilyl)silyl-Governed Aldehyde Cross-Aldol Cascade Reaction

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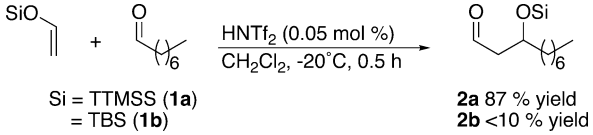
Polyketides constitute a large class of natural products, and approximately 1% exhibit biological activity, which is 5 times higher than the average in natural products.[1] β-Hydroxy carbonyls and/or 1,3-diols are a common motif in this class of biologically important compounds, and the aldol reaction has emerged as a recurrent method for formation of these substructures.[2] Numerous aldol methods utilize ester-, thioester-, or ketone-enolates as the nucleophile to circumvent problems associated with the aldehyde cross-aldol products.[3] Frequently, these products are converted to hydroxy-protected aldehydes for further transformations.[1,4] Although the Mukaiyama aldol synthesis is one of the most powerful approaches for cross-aldol reactions, the most basic aldehyde cross-aldol reaction has never been effectively achieved.[3,4c] Herein we report the first highly diastereoselective Mukaiyama aldehyde cross-aldol reaction of acetaldehyde silyl enol ethers as well as the first cascade Mukaiyama aldol synthesis.

Due to our recent success with the bulky tris(trimethylsilyl)silyl (TTMSS) group for [2 + 2] cyclizations,[5] and its superb reactivity in the presence of acid catalysis, we decided to try the silyl enol ether (SEE) derived from acetaldehyde (**1a**) for the Mukaiyama aldol reaction. Gratifyingly, the 1:1 adduct (**2a**) was obtained as the only isolable product in 87% yield using octanal as the electrophile and triflimide (0.05 mol %) as the catalyst. When the TBS enol ether **1b** was used, the 1:1 adduct (**2b**) was obtained in <10% yield (Scheme 1).

Scheme 1. Mukaiyama Aldol Reaction

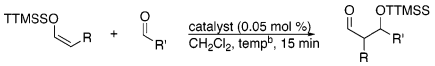


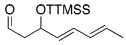
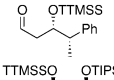
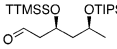
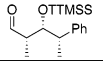
Acid screening (various Ti, Al, Sn, and Brønsted acids) led to the finding that triflimide was superior, and catalyzed the reaction with a loading of 0.05 mol %, giving the 1:1 adducts in high yield. The use of $TTMSSNTf_2$ (0.05 mol %) as the catalyst led to results identical to those obtained by using triflimide, implicating the silyl triflimide as likely the true catalyst (Table 1).[6] Due to these observations as well as the extrememly low catalyst loading (S/C, 2000/1), we propose that the silyltriflimide is a self-repairing catalyst, which can be regenerated even in the presence of water or other protic Lewis bases (Scheme 2). Significantly, triflic acid and TTMSSOTf as catalysts gave a mixture of complex products with only trace amounts of the desired 1:1 adduct, further distinguishing the triflimide anion from the triflate anion.[6c,7b]

The scope of aldehydes for this reaction was tested and showed consistently high yields of 1:1 adducts with primary, secondary, tertiary, benzyl, and even $\alpha,\beta-\gamma,\delta$-unsaturated aldehydes (Table 1, entries 1−5). The use of (*S*)-2-phenylpropanal for diastereoselective aldol additions was tested and showed extrememly high Felkin selectivity (Table 1, entry 6) and syn selectivity for β-substituted aldehydes (Table 1, entry 7).[8] While a previous study showed anti selectivity for open transition state Mukaiyama aldol additions to β-alkoxy aldehydes,[9] we believe our selectivity resides in the extreme size in the TTMSS group (vide infra). The use of propionaldehyde-derived SEE gave comparably high yields with good syn/anti ratios (Table 1, entries 8−11). Importantly, this provides a complementary method to the anti selectivity obtained by MacMillan.[4b] The use of (*S*)-2-phenylpropanal exhibited high Felkin control in conjunction with syn selectivity providing three adjacent stereocenters (Table 1, entry 11).[8]

We became curious as to why the reaction was stopping at the 1:1 adduct in such high yield. The use of anywhere from 2 to 5 equivalents of the SEE all led to a 2:1 adduct isolated in high yield as a single diastereomer when pivalaldehyde was used. The use of

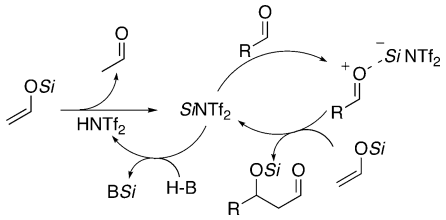
Table 1. Mukaiyama Aldol Reaction[a]



entry	R	R'	catalyst	major product	% yield[d] (*syn*/*anti*)[e]
1	H	$(CH_2)_6CH_3$	$HNTf_2$ $TTMSSNTf_2$		87 (-) 85 (-)
2	H	cyclohexyl	$HNTf_2$ $TTMSSNTf_2$		89 (-) 86 (-)
3	H	^{t}Bu	$HNTf_2$ $TTMSSNTf_2$		90 (-) 91 (-)
4	H		$HNTf_2$ $TTMSSNTf_2$		78 (-) 75(-)
5	H	Ph	$HNTf_2$ $TTMSSNTf_2$		83 (-) 87 (-)
6	H		$HNTf_2$ $TTMSSNTf_2$		86 (>95/5) 85 (>95/5)
7	H		$HNTf_2$ $TTMSSNTf_2$		88 (85/15) 89 (88/12)
8	Me[c]	$(CH_2)_6CH_3$	$HNTf_2$ $TTMSSNTf_2$		82 (80/20) 85 (79/21)
9	Me[c]	cyclohexyl	$HNTf_2$ $TTMSSNTf_2$		72 (85/15) 71 (82/18)
10	Me[c]	^{t}Bu	$HNTf_2$ $TTMSSNTf_2$		78 (95/5) 79 (95/5)
11	Me[c]		$HNTf_2$ $TTMSSNTf_2$		84 (>95/5/0/0) 87 (>95/5/0/0)

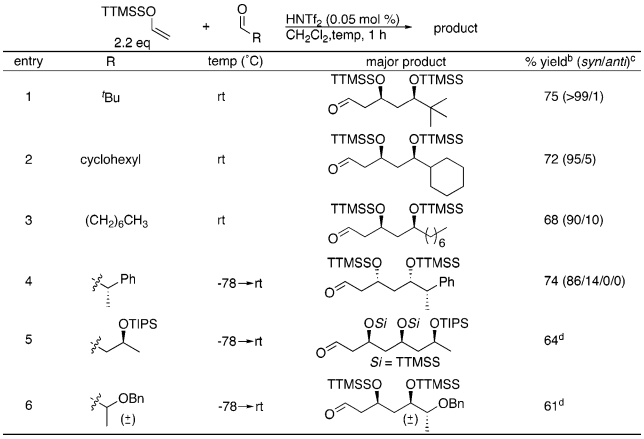
[a] Reactions run by adding acid to 1 equiv SEE (0.1 M) and 1 equiv aldehyde. [b] Entries 1−5 run at room temperature, entries 6−11 were cooled to −78 °C, the catalyst added and the solution removed from cold bath and allowed to warm to room temperature. [c] 95/5 Z/E. [d] Isolated yield. [e] Dr based on ^{1}H NMR of crude material.

Scheme 2. Formation of Silyltriflimide and Its "Self-Repair" Ability



10.1021/ja054725k CCC: $33.50

Table 2. Cascade Mukaiyama Aldol Reaction Catalyzed by $HNTf_2$[a]



entry	R	temp (°C)	major product	% yield[b] (*syn*/*anti*)[c]
1	^{t}Bu	rt		75 (>99/1)
2	cyclohexyl	rt		72 (95/5)
3	$(CH_2)_6CH_3$	rt		68 (90/10)
4		-78→rt		74 (86/14/0/0)
5		-78→rt		64[d]
6		-78→rt		61[d]

[a] Reactions run by premixing 2.2 equiv SEE (0.1 M) and 1 equiv aldehyde and then adding acid. [b] Isolated yield. [c] Dr based on crude ^{1}H NMR. [d] Dr could not be determined through ^{1}H NMR; yield given is isolated yield of pure diastereomer shown.

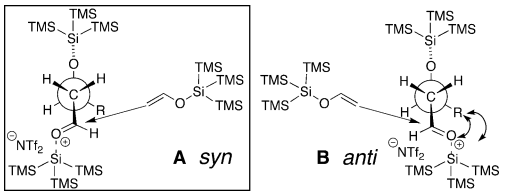


Figure 1. Syn selectivity for β-chiral aldehydes. Conformation **A** leads to syn products, while **B** leads to anti, but contains unfavorable steric interactions including R-carbonyl and R-silyltriflimide.

2.2 equiv of SEE was found to be optimal for the highest yields of 2:1 adduct, and the relative stereochemistry was determined to be syn through single-crystal X-ray analysis (Table 2, entry 1).[8] Cyclohexyl and octyl aldehydes gave similar results with the former giving 95/5 syn selectivity and the latter 90/10 selectivity (Table 2, entries 2 and 3).[8] The cascade reaction using (*S*)-2-phenylpropanal gave high selectivity with all syn stereochemistry as the major product (Table 2, entry 4).[8] The β-TIPSoxy aldehyde afforded the all syn protected β,δ,ζ-tris-siloxyaldehyde in 64% yield (Table 2, entry 5).[8,10] α-Benzyloxy propanal gave the adduct that is consistent with a chelation-controlled first addition followed by a syn-selective second addition furnishing the β,δ,γ-tris-siloxyaldehyde in 61% yield (Table 2, entry 6).[8,10,11]

The exceptional diastereoselectivity and control associated with the TTMSS group can likely be attributed to its steric size. The TTMSS group is extraordinarily bulky[7a,12] and has been determined to shield molecular skeletons with a "H_3C-skin."[12b] After the first addition and silyl transfer, the steric encumberment of this group is likely to kinetically slow the rate of the addition of a second equivalent of SEE to a rate that does not compete with the rate of the first addition. When all of the aldehyde starting material has been consumed, a second addition occurs giving the products in Table 2 with high diastereoselectivity. The reasoning for the syn selectivity is shown in Figure 1 where conformation **A** does not suffer the unfavorable steric interaction between the Lewis acid-coordinated oxygen and the R group that is present in conformation **B**. This explains the higher selectivity obtained with the bulkier R groups (i.e., pivalaldehyde) due to the increased steric interactions in conformation **B**. After this second addition occurs, the aldehyde has β- and δ-TTMSSoxy groups, and if catalyst coordination occurs, the complex is likely too bulky for further additions.

Intrigued by $TTMSSNTf_2$ catalysis, we used ^{29}Si NMR as an indicator of silicon Lewis acidity and found that the central silicon of $TTMSSNTf_2$ was shifted significantly downfield (>6 ppm) compared to TMS and $TBSNTf_2$, and only slightly downfield from pentamethyldisilane-NTf_2 (62.2, 55.9, 55.5, and 60.8 ppm respectively).[7] This trend shows a considerable difference in the cationic nature of silyl groups with only silicon−carbon bonds versus those with silicon−silicon bonds.

In conclusion, we have shown that the tris(trimethylsilyl)silyl group is unique and allows for high-yielding construction of β-hydroxy aldehydes for a very broad range of aldehydes (primary, secondary, tertiary, aromatic, $\alpha,\beta-\gamma,\delta$-unsaturated). Chirality in the aldehyde substrate affords Felkin products when there are nonchelating substituents, chelation products when there is a chelating sbustituent, and syn products when there is β-substitution. *The TTMSS group is distinctive in that it combines the highest Lewis acidity as a silicon catalyst, high nucleophilic reactivity as a SEE, and large steric bulk for superior diastereoselection.* Satisfaction of these conflicting requirements allows for unprecedented one-pot cascade reactions that can create synthetically useful β,δ-bis-, β,δ,γ-tris-, and β,δ,ζ-tris-hydroxy-aldehydes with extremely high selectivity.

Acknowledgment. This work was supported by the SORST project of Japan Science and Technology Agency (JST) and The University of Chicago. Special thanks to Ian Steele for X-ray analysis and Antoni Jurkiewicz for NMR expertise.

Supporting Information Available: Experimental procedures, compound characterization, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA054725K