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Catalytic Redox-Initiated Glycolate Aldol Additions of Silyl Glyoxylates

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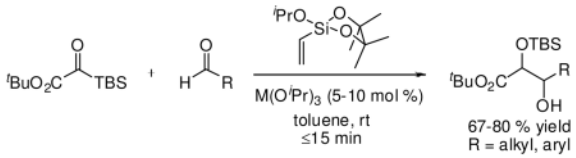
Abstract



Lanthanide triisopropoxides catalyze a rapid, tandem MPV reduction/Brook rearrangement/aldol sequence between silyl glyoxylates and aldehydes that achieves catalytic turnover through alkoxide transfer from a strain-release Lewis acidic silacycle.

Bimolecular chemical reactions that achieve dual symbiotic activation of both reaction partners offer unique and attractive opportunities for efficiency and atom economy. Examples of this unusual reaction mode include aldol reactions initiated by redox reaction between silyl glyoxylates and magnesium alkoxides,[1] and carbonyl allylations initiated by formal H_2 redistribution.[2a–c] The former reaction demonstrated a new means for generating active coupling partners *in situ*, but a challenge that emerged during subsequent studies was the regeneration of the metal alkoxide used as the reducing agent. The absence of a turnover mechanism necessitated the use of a stoichiometric metal alkoxide species (Figure 1). This Letter delineates reaction parameters that are essential in achieving catalysis of the title reaction and we specifically describe the application of strain-release Lewis acidic siloxanes in turnover-enabling alkoxide metathesis.[3]

Key mechanistic features of the projected catalytic reaction are summarized in Figure 1. Following the established silyl glyoxylate reactivity pattern involving a Meerwein-Ponndorf-Verley (MPV) reduction, Brook rearrangement, and aldol addition,[1] our point of departure from the stoichiometric reaction would be the transfer of some undefined moiety Ω from **4** to the terminal metal aldolate **3b**. This proposed alkoxide metathesis would concurrently release the aldolate product and regenerate the MPV reductant **2**.

Preliminary experiments focused on defining two key reaction components. First, the identity of the metal cation would likely prove a determining factor, as previous reactions employing silyl glyoxylates have required the careful selection of a metal that not only promotes MPV reduction but also Brook rearrangement of the intermediate *C*-silyl alkoxides.[4]

Additionally, alkoxide donor **4** must be sufficiently labile in order to facilitate effective catalytic turnover. In an initial screen of a variety of common metal triisopropoxides and acylating or silylating agents (Figure 2), we achieved no greater than 30% conversion to the

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desired aldol product, suggesting that alkoxide transfer from the putative turnover reagents was not occurring.

Realizing that a more reactive turnover agent may be necessary, we turned to strain-release silacycles, which have gained attention through their application in a variety of transformations.[5] The enhanced Lewis acidity of these silacycles is due to their ring constraints and contributes to their ability to function as potent allylating agents and enolate equivalents. We wondered if they might exhibit accelerated subsitution chemistry relative to unconstrained variants. Ethoxysilacycle **6a** was synthesized using a procedure modified from Leighton's published work.[5a] In the presence of **6a** and 5 mol % of erbium(III) isopropoxide, silyl glyoxylate **1** and benzaldehyde reacted completely in under five minutes. Product analysis revealed an important pitfall from this preliminary trial: aldol reaction with the sacrificial equivalent of acetaldehyde generated from the ethoxide transfer and MPV reduction sequence proved competitive with the desired reaction with benzaldehyde (Table 1, entry 1). Isobutoxysilacycle **6b** afforded a similar product ratio, but isopropoxysilacycle **6c** provided the desired coupling product in a 62% yield and with only 3% of the byproduct **8c** present (entries 2 and 3), corresponding to reaction with the sacrificial equivalent of acetone generated. Increased yields could be attained with the use of 10% of the metal catalyst, while catalyst loadings less than 5% provided only trace product formation (entries 4 and 5).

With a successful means for catalytic turnover, we screened additional reaction parameters. Toluene proved to be the optimal solvent choice, providing the desired product in moderate yields and in shorter reaction times than in ether, while incomplete reactions were observed in dichloromethane, THF, and 2-methyl-THF.[6]

Among the cations screened, aluminum[7] and magnesium[1] provided only trace product in this catalytic system. Yttrium and a variety of lanthanides exhibited an inverse relationship between ionic radius[8] and reaction time (Table 2, entries 5–11).

Reactions employing erbium required 30 minutes to reach completion, while praseodymium catalyzed the addition to >98% conversion in approximately 1 minute with benzaldehyde (Table 2, entries 7, 11).

Two reasonable reduction mechanisms could be formulated to account for the observed reductive aldol products (Figure 3). Initial reduction of benzaldehyde could precede reduction of the silylglyoxylate by the resulting benzyl alkoxide (Path A); alternatively, *C*-silyl alkoxide intermediate **9** could arise through a direct MPV reduction of the silylglyoxylate (Path B).

The two mechanisms may be distinguished through the application of the deuterium-labeled isopropylsiloxane **10**. Using 10 mol % of $Pr(2\text{-}d\text{-}O^iPr)_3$ as a catalyst, 99% deuterium incorporation was observed at C_α (Figure 4). This result indicates that hydride scrambling via aldehyde reduction does not contribute appreciably to product formation and that Path B is active in this system. This is consistent with the increased electrophilicity of **1** that is generally observed.[9]

Based on previous studies in related reactions from our laboratory and the results of the labeling experiment, the catalytic cycle in Figure 5 is proposed. Initial MPV reduction of silylglyoxylate **1** results in generation of a transient alkoxide intermediate that undergoes Brook rearrangement to afford ester enolate **13**. Aldol reaction with the aldehyde provides terminal alkoxide **14**, which then attacks the strained silacycle **6c** and expels another isopropoxide equivalent to regenerate the lanthanide triisopropoxide catalyst, possibly facilitated by participation of the ester carbonyl.

A sacrificial equivalent of acetone is generated in the initial step of this cycle; dissociation of acetone from the metal catalyst therefore must proceed more rapidly than its aldol reaction occurs to avoid predominant production of byproduct **8c**. This is consistent with crossover experiments previously conducted in a related system.[1] When the MPV reduction produces a sacrificial aldehyde, however, competitive aldol reactions afford the product ratios observed in Table 1 (entries 1 and 2).

The inverse relationship between ionic radius and reaction time potentially reflects steric limitations in the alkoxide transfer step; the larger coordination sphere of praseodymium likely facilitates the necessary complex formation as well as dissociation of the final product from the metal center.

The reaction worked for the aryl, linear and branched alkyl, and heteroaromatic aldehydes shown in Table 3. In spite of the modest diastereoselectivities observed, reactions were generally quite rapid and gave good yields of the glycolate aldol products. Reaction with acetophenone provided only 17% of the desired addition product, with the remaining silyl glyoxylate consumed by addition to acetone. The background reaction proceeded over 15 minutes to give the coupling product with acetone in 67% yield (Table 3, entry 9).

Notably poor substrates were α,β-unsaturated aldehydes and dihydrocinnamaldehyde (Table 3, entries 6 to 8); no greater than trace quantities of desired product were observed. Although we cannot provide a detailed rationale for the failure of such substrates, they possibly impede reaction through either complexation with or degradation of the metal catalysts.[10]

Preliminary results also suggest the potential for asymmetric catalysis in this system (Table 4). Salen ligands have been shown to be effective in a lanthanide-catalyzed aldol-Tischenko reduction developed by Morken;[11] they provided, therefore, a reasonable starting point. We have verified that ligand → product chirality transfer is feasible, with **17c** ·Pr(O^{i}Pr)$_3$ providing the desired product with no decrease in yield (80%) and with 63:37 e.r. Ongoing studies in our group aim to build upon these preliminary results.

In conclusion, we have developed a new method for the MPV reduction/Brook rearrangement/aldol reaction of silyl glyoxylates. The reactions are catalyzed by lanthanide triisopropoxides and feature a unique turnover step, an alkoxide transfer from a strain-release Lewis acidic silacycle.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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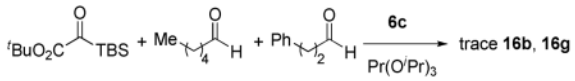
10. A competition experiment using equimolar quantities of these aldehydes and hexanal provided only trace product:



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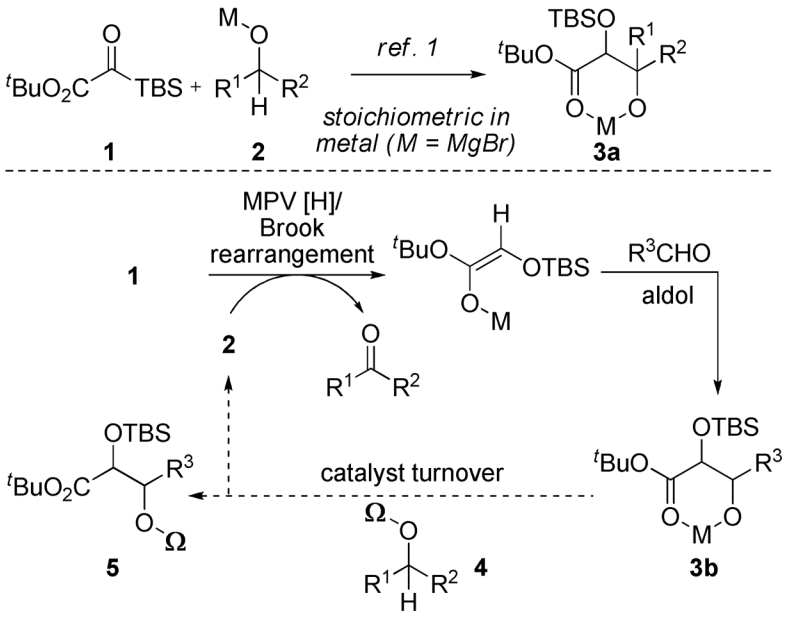


Figure 1.
Catalytic Reductive Aldol Reaction - Proposal

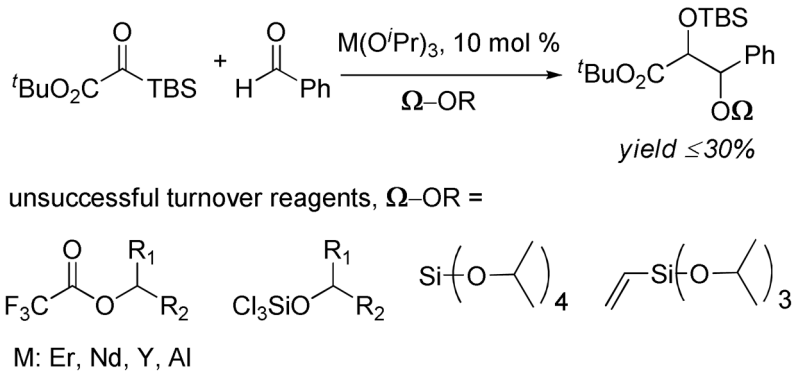


Figure 2.
Summary of Initial Catalyst and Turnover Reagent Screens

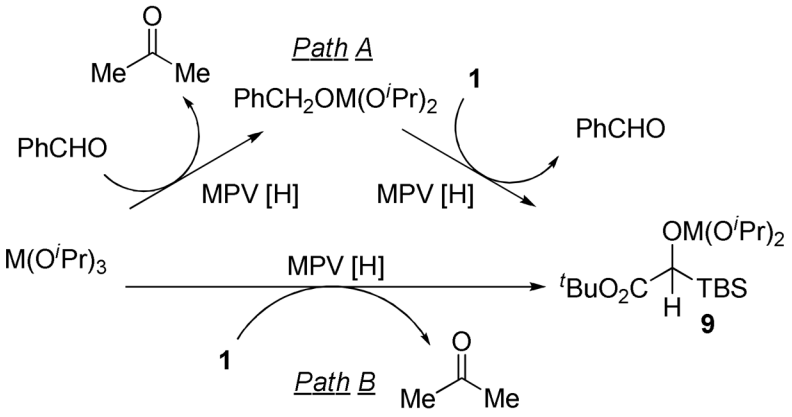


Figure 3.
Possible Hydride Transfer Pathways

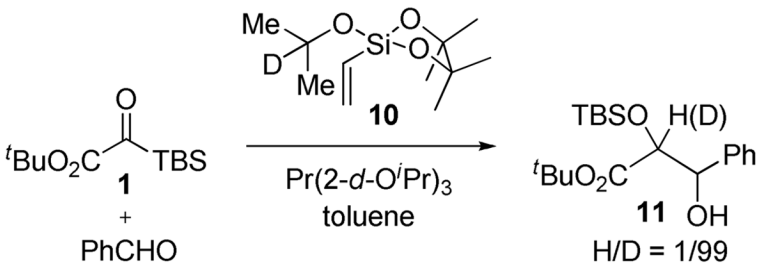


Figure 4.
Isotopic Labeling Study[a]
[a] Conditions: 1.5 equiv of PhCHO, 2 equiv of **10**, $[\mathbf{1}]_0$ = 0.2 M.

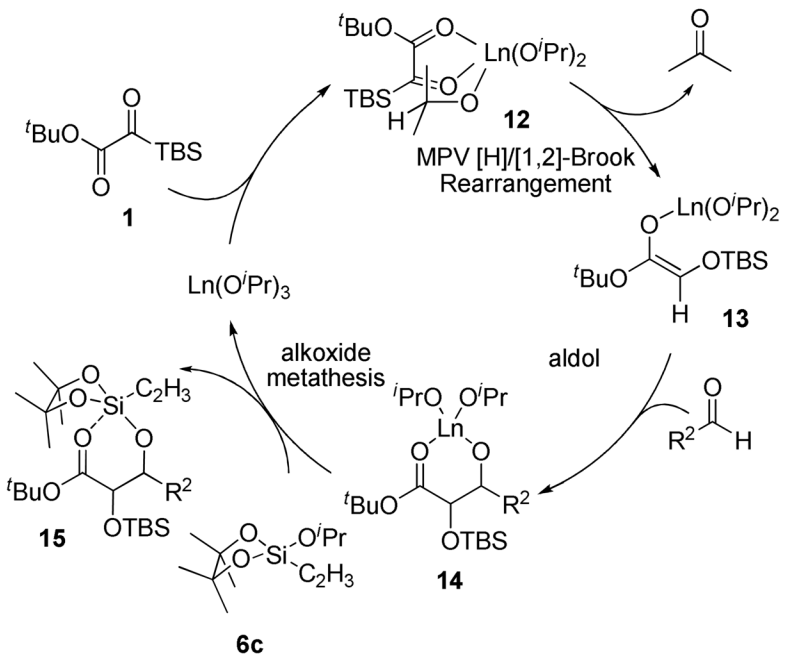
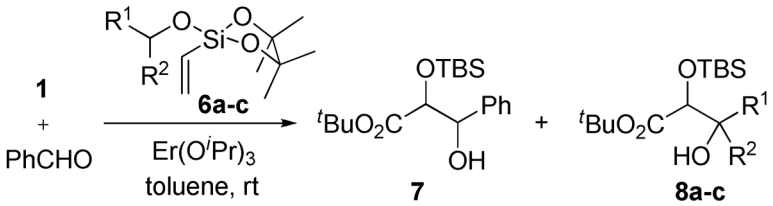


Figure 5.
Proposed Catalytic Cycle Employing Silacycle **6c**

Table 1

Preliminary Trials Using Strain-Release Silacycles[a]



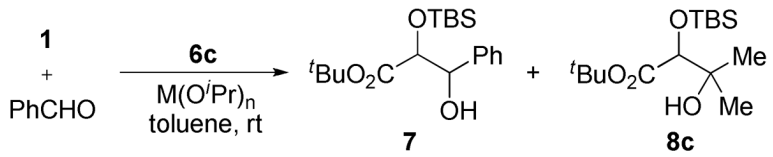
entry	R^1 (silacycle)	R^2	mol %$Er(O^iPr)_3$	% yield 7 (8)[b]	time (min)
1	Me	H (**6a**)	5	50 (32)	5
2	^{i}Pr	H (**6b**)	5	50 (28)	40
3	Me	Me (**6c**)	5	62 (3)	60
4	Me	Me (**6c**)	10	84 (6)	30
5	Me	Me (**6c**)	1	trace	120

[a] Conditions: 1.5 equiv of PhCHO, 2.0 equiv of **6**, $[\mathbf{1}]_0$ = 0.2 M.

[b] Yields determined by ^{1}H NMR versus an internal standard.

Table 2

Screen of Metal Catalysts[a]



entry	M(O^{i}Pr)$_n$ (mol %)	% yield 7 (8)[b]	reaction time (min)	radius (Å)[c]
1	Al(O^{i}Pr)$_3$ (5)	Trace	300	
2	Dy(O^{i}Pr)$_3$ (5)	Trace	300	
3	Zr(O^{i}Pr)$_4$ (5)	Trace	300	
4	Mg(O^{i}Pr)$_2$ (5)	Trace	300	
5	Y(O^{i}Pr)$_3$ (5)	52 (1)	120	0.900
6	Er(O^{i}Pr)$_3$ (5)	62 (5)	120	0.890
7	Er(O^{i}Pr)$_3$ (10)	84 (6)	30	0.890
8	Gd(O^{i}Pr)$_3$ (10)	67 (12)	25	0.938
9	Yb(O^{i}Pr)$_3$ (10)	72 (8)	15	0.868
10	Sm(O^{i}Pr)$_3$ (10)	60 (11)	10	0.958
11	Pr(O^{i}Pr)$_3$ (10)	91 (8)	1	0.997

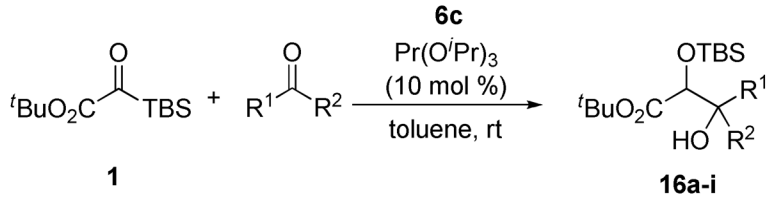
[a] Conditions: 1.5 equiv of PhCHO, 2 equiv of **6c**, $[\mathbf{1}]_0$ = 0.2 M.

[b] Yields determined by ^{1}H NMR spectroscopy versus an internal standard.

[c] Reference 8, for coordination number = 6.

Table 3

Electrophiles for the Reductive Aldol[a]



entry	product	R^1	R^2	yield (%)[b]	time (min)	dr
1	**16a**	Ph	H	80[c]	1	1.5:1
2	**16b**	$CH_3(CH_2)_4$–	H	69	2	1.5:1
3	**16c**	2-furyl	H	73[c]	3	1.3:1
4	**8b**	^{i}Pr	H	71	1	1.5:1
5	**16d**	Ph	Me	17	7	1.3:1
6	**16e**	PhC≡C–	H	Trace	120	n.d.
7	**16f**	(*E*)-PhCH=CH–	H	Trace	120	n.d.
8	**16g**	$PhCH_2CH_2$–	H	Trace	120	n.d.
9[d]	**8c**	Me	Me	67[c]	15	n.a.

[a] Reaction conditions: 1.5 equiv of aldehyde or ketone, 10% $Pr(O^iPr)_3$, 2 equiv of **6c**, $[\mathbf{1}]_0$ = 0.08 M.

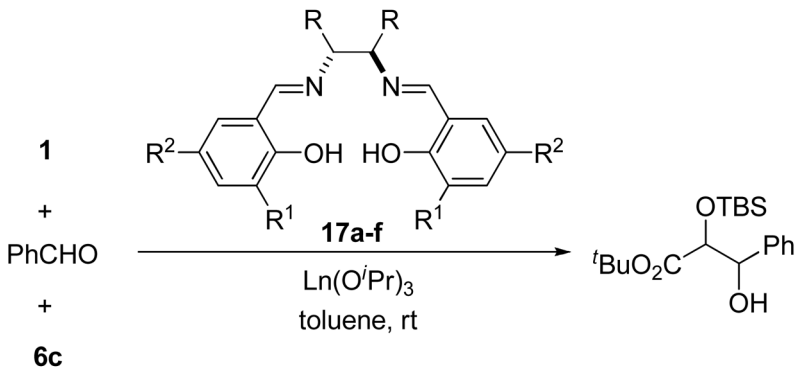
[b] Unless otherwise noted, yields were determined by ^{1}H NMR spectroscopy versus an internal standard.

[c] Isolated yield.

[d] No aldehyde or ketone was added.

Table 4

Asymmetric Aldolization with (salen)Ln Complexes[a]



entry (ligand)	Ln	R	R^1	R^2	% yield	er[b]	dr
1 **(17a)**	Er	-$(CH_2)_4$-	Me	H	18	50:50	1.5:1
2 **(17b)**	Er	-$(CH_2)_4$-	^{t}Bu	^{t}Bu	trace	n.d.	-
3 **(17a)**	Sm	-$(CH_2)_4$-	Me	H	63	61:39	1.4:1
4 **(17c)**	Sm	Ph	^{t}Bu	^{t}Bu	41	55:45	2.1:1
5 **(17d)**	Sm	-$(CH_2)_4$-	H	H	0	n.a.	-
6 **(17e)**	Sm	-$(CH_2)_4$-	^{t}Bu	OMe	45	57:43	2.1:1
7 **(17a)**	Pr	-$(CH_2)_4$-	Me	H	33	58:42	1.9:1
8 **(17c)**	Pr	Ph	^{t}Bu	^{t}Bu	80	63:37	2:1
9 **(17f)**	Pr	naphthyl	^{t}Bu	^{t}Bu	58	53:47	1.7:1

[a] Reaction conditions: 1.5 equiv of PhCHO, 10 mol % of Ln(O^iPr)3, 2 equiv of **6c**, 10 mol % of **17a–f**, $[\mathbf{1}]_0$ = 0.08 M.

[b] For major diastereomer.