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A Stereoselective Reductive Hosomi−Sakurai Reaction

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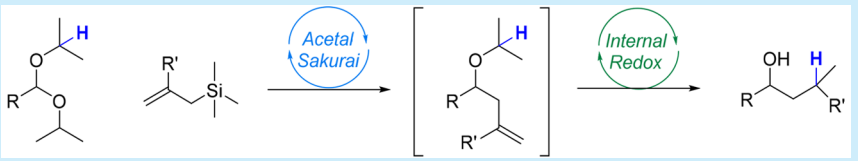
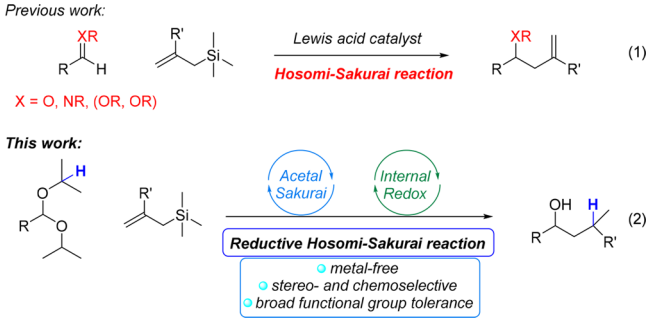
Supporting Information



ABSTRACT: A novel reductive variant of the classical Hosomi−Sakurai reaction is reported. This transformation hinges on a redox-neutral, stereoselective internal reduction event under mild conditions. This operationally simple reaction relies on readily available starting materials and leads to useful products in diastereoselectivities of up to 7:1. The versatility of this new method is demonstrated through the stereoselective one-step synthesis of an AChE inhibitor.

The development of innovative methods for C−C bond formation remains at the heart of contemporary progress in organic chemistry. Allylsilanes emerged in the 1970s as mild, nontoxic carbon nucleophiles which are easy-to-handle and useful reagents for addition to electrophilic carbons in a broad sense.[1] These transformations are now textbook knowledge and are collectively known as "Hosomi−Sakurai reactions", honoring the first observation by those two chemists in 1976 of the Lewis acid promoted nucleophilic attack of an allylsilane to aldehydes and ketones (Scheme 1, eq 1).[1a] Several variations

Scheme 1. Conventional and Reductive Hosomi−Sakurai Reactions



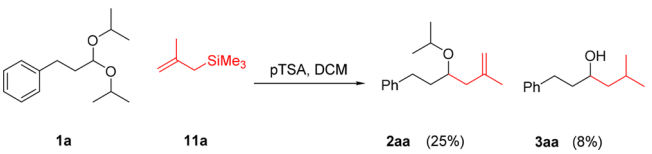
on this theme have been reported ever since,[2] including nucleophilic additions to acceptor alkenes,[1b] diverse carbonyl compounds,[1a,c] epoxides,[1c] imines,[1d,e] and acetals.[1h,j] Nucleophilic displacements of activated alcohols[1f] are also known, and stereoselective[2b,c] Hosomi−Sakurai reactions have also attracted considerable attention.

1,5-Hydride transfer reactions are known to typically occur from C−H bonds adjacent to oxygen or nitrogen toward electron-deficient carbons,[3] and such transformations hold significant potential for the highly regioselective C−H functionalization of simple building blocks.[4] Particularly appealing is their "internal redox" nature that dispenses with external oxidants or reductants. However, in spite of their long history and revival in recent years, a vast majority of the 1,5-hydride transfer reactions known to date still use Michael acceptors and carbonyl derivatives as electropositive fragments.[4a,f−j,l−o]

We were intrigued by the 1,5-relationship between the generated double bond and hydroxy substituents of Hosomi−Sakurai products. In this context, we hypothesized that protonation of the double bond could trigger an internal redox process if a suitable hydroxy derivative was in place. Herein (Scheme 1, eq 2), we report a metal-free, regio- and diastereoselective reductive Hosomi−Sakurai reaction relying on an internal redox event. The process displays noteworthy functional group tolerance.

Initial experiments employing acetal **1a** and allylsilane **11a** using *p*-toluenesulfonic acid (Scheme 2) delivered the desired

Scheme 2. First Observation of the Reductive Hosomi−Sakurai Reaction[a]



[a]Yields determined by H NMR analysis.

product **3aa** in low yield, along with the conventional Hosomi−Sakurai product **2aa**. Focusing more closely on the internal redox step, the homoallylic ether **2aa** was prepared, and its interaction with different acids was investigated (Table 1).

Drawing on the report of List on the use of acetals for the Hosomi−Sakurai reaction,[1h,i] 2,4-dinitrobenzenesulfonic acid (DNBA) and benzenedisulfonimide (BDSI) were tested as

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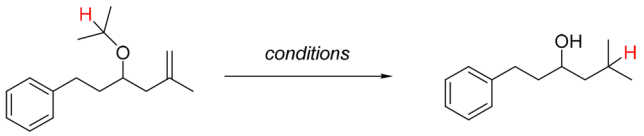
Table 1. Optimization of Conditions for the Internal Redox Event



2aa **3aa**

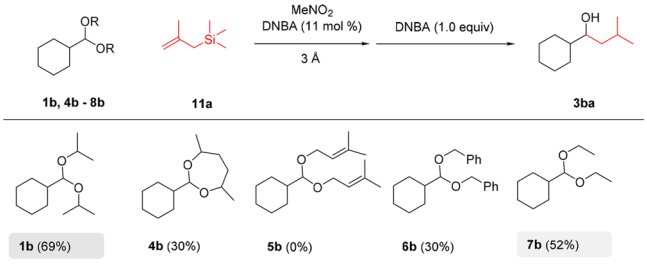
entry	solvent	acid	temp (°C)	time (h)	yield[a] (%)	conv[a] (%)
1	1,2-DCE	BDSI	25−50	3.5	14	68
2	MeCN	BDSI	25−50	3	26	65
3	1,2-DCE	DNBA	25−50	3.5	25	>95
4	MeCN	DNBA	25	3	40	>95
5	THF	DNBA	25	2	<5	21
6	DMF	DNBA	25	2	<5	38
7	MeOH	DNBA	25	2	<5	90
8	$MeNO_2$	DNBA	25	2	73	>95

[a]All reactions carried out on 0.3 mmol scale. Yields determined by H NMR analysis.

Brønsted acids. DNBA showed higher yields at lower temperatures than BDSI (Table 1, entries 1−2 versus 3). Solvent optimization revealed that nitromethane led to the desired product in good yields (Table 1, entries 3−8) with a clean reaction profile.

The high dipolar moment and the low nucleophilicity of nitromethane are likely to be decisive for the stabilization of the cationic intermediates involved (*vide infra*). We eventually found that nitromethane was also a suitable solvent for the Hosomi−Sakurai step under DNBA catalysis. After optimization, a reproducible and efficient one-pot procedure was developed. To this end, the use of 3 Å molecular sieves was important since DNBA is a hygroscopic substance sold as a hydrate.[5] As the nature of the acetal should be important for the internal redox event, we investigated different acetals, a selection of which is shown in Scheme 3.[5] Use of cyclic acetals was generally unproductive, and **4b**, the most promising among those tested, led to a complex reaction mixture containing 30% of product.

Scheme 3. Acetal Screening for the Internal Redox Event[a]



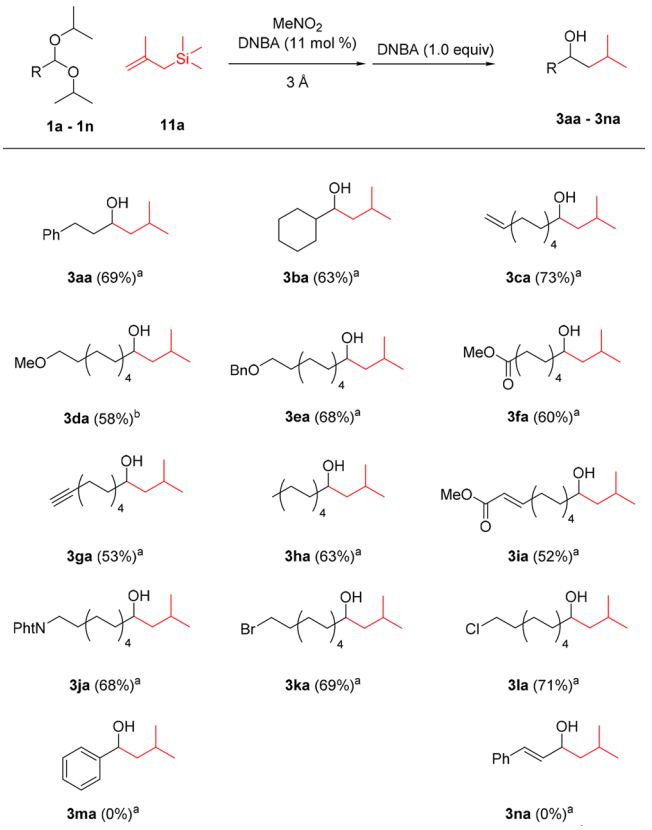
[a]All reactions carried out on 0.3 mmol scale. Yields determined by NMR analysis.

An acetal derived from an electron-rich allylic alcohol **5b** or a dibenzyl acetal **6b**, designed for attempted enhancement of the hydride-transfer step, was also not effective. Surprisingly, a diethyl acetal **7b** was better than most of the other acetals, suggesting that oxacarbenium stability is not the most important element in the efficiency of a 1,5-hydride transfer.[6] However, the highest yields were still observed for the originally assayed diisopropyl acetal **1b**.

With efficient conditions in hand, the substrate scope was surveyed (Scheme 4). First, several acetal backbones were tested. Additional unsaturation on the acetal did not disrupt the internal redox process, be it an alkene or an alkyne (**3ca**, **3ga**). A benzyl-protected alcohol did not interfere in the process (**3ea**). Importantly, these are functionalities that would not have survived a reduction/hydrogenolysis step. A phthalimide substituent was well tolerated (**3ja**), as well as esters (**3fa**) or more electrophilic α,β-unsaturated esters (**3ia**). Chlorides (**3la**) or bromides (**3ka**) are also compatible with these conditions. This body of results outlines a transformation that, while being broadly comparable to the addition of an organometallic species to an aldehyde, is tolerant of several substituents that likely would not be compatible with such reagents. The product **3ba** was also synthesized on a preparative scale (6 mmol starting material) in a comparable yield.[5] At this juncture, we were keen to try different allylsilanes, well aware that the presence of a substituent other than methyl would lead to the creation of an additional stereogenic center. Our results are compiled in Scheme 5. Aromatic and α,β-unsaturated acetals lead to a complex mixture in which no desired product was observed. Competitive elimination, under the acidic conditions, is likely to occur in these cases.

Interestingly, up to 7.3:1 diastereoselectivity in favor of the *anti*-product was observed for diethyl acetals when the allylsilane nucleophilic partner carried an aryl substituent.

Scheme 4. Substrate Scope of Acetals



[a]Reactions carried out on 0.3 mmol scale. Yields refer to isolated products. [b]Reaction carried out on 0.15 mmol scale. Yields refer to isolated products.

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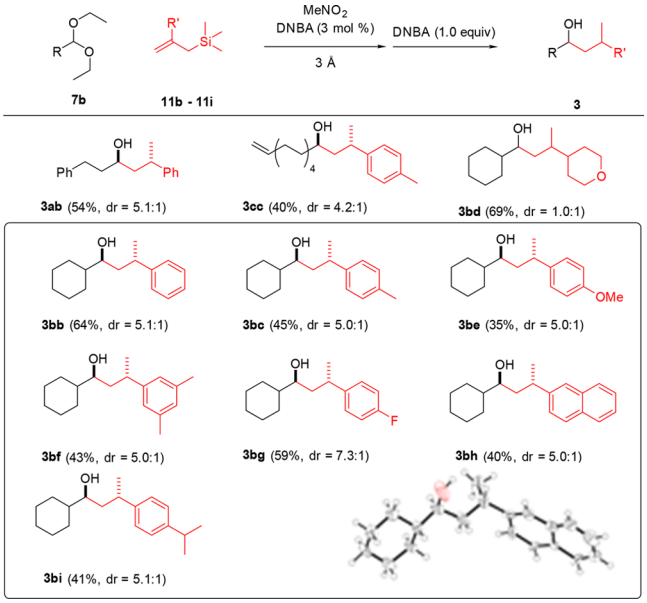
Scheme 5. Allylsilane Scope and Diastereoselectivity[a]



[a]Yields refer to isolated products. diastereoisomeric ratios determined by H NMR analysis. Bottom right: X-ray structure of **3bh**.

This appears to be independent of the electronic nature of that aryl moiety, ranging from electron-rich (**3be**) to neutral (**3bb** or **3bh**) to electron-poor (**3bg**).

Aiming for more information on the mechanism, we carried out an isotopic labeling study with a fully deuterated diisopropyl acetal **5** (Scheme 6, eq 1). The product **10** carries the deuterium label in the anticipated position. This allowed us to put forward a mechanistic proposal whereby, after protonation of the double bond of the transient Hosomi–Sakurai product, a 1,5-hydride transfer takes place (Scheme 6, eq 1, **9ba**) from the ether moiety to generate an oxacarbenium ion.

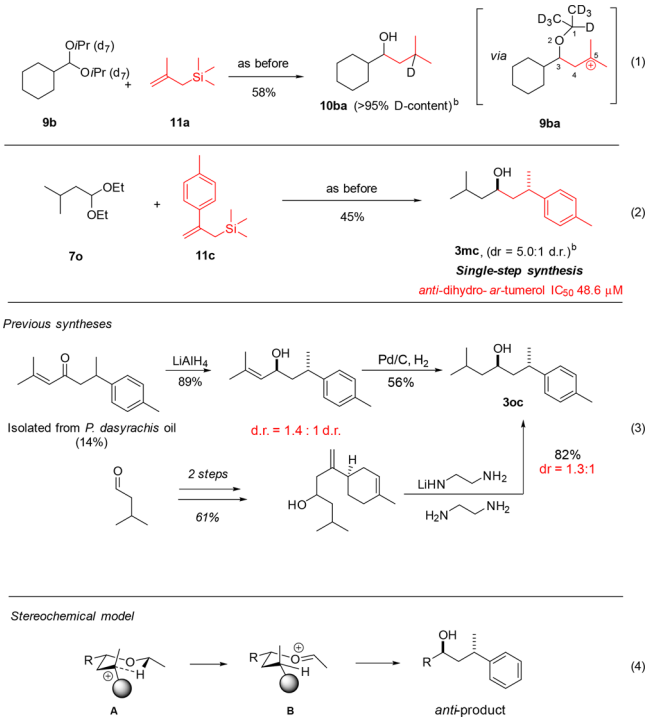
This is likely hydrolyzed to the observed alcohol and acetone during the aqueous workup. Subsequently, we used the reductive Hosomi–Sakurai procedure to synthesize **3oc**, a known acetylcholinesterase inhibitor (Scheme 6, eq 2).[7,8]

The starting acetal **7m**, commercially available (or easily obtained from isovaleraldehyde), was engaged with allylsilane **11c** to provide **3oc** in 45% yield and a 5:1 dr. In spite of the modest yield, the conciseness and diastereoselectivity of this route, a single step from **7m** or two steps from isovaleraldehyde, compare favorably with prior approaches (Scheme 6, eq 3) which involved the poorly selective reduction of a ketone precursor[8] or the redox isomerization of a terpene-derived homoallylic alcohol.[9]

The major diastereoisomer in these reactions is the *anti*-isomer, which probably results from a chairlike six-membered transition state where the bulkier aromatic ring occupies the pseudoequatorial position (Scheme 6, eq 4).[10]

In summary, we have presented a novel reductive Hosomi–Sakurai reaction that relies on an internal redox process triggered by a cheap Brønsted acid under simple conditions. Mechanistic experiments using deuterium labeling and substrate probes provided insight into the factors controlling stereoselectivity and allowed a demonstration of synthetic utility in the synthesis of a potent AChE inhibitor.

Scheme 6. Mechanistic Study and Application in Synthesis[a]



[a](1) Deuterium labeling study, (2) single-step synthesis of a biologically active compound,[5] and (3) comparison with prior approaches.[8,9] (4) Stereochemical model for the diastereoselectivity. Yields refer to isolated products. [b]Determined by NMR analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00276.

Experimental data and spectral characterization for new products (PDF)

Accession Codes

CCDC 1813236 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(5) See the Supporting Information for details.

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(10) This model is in accordance with the observation that secondary ethers (i.e., isopropyl ether) lead to lower diastereoselectivity, which could be due to increased 1,3 repulsion in conformer **A** of Scheme 6d.

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