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Synthesis of Tertiary β-Hydroxy Amides by Enolate Additions to Acylsilanes

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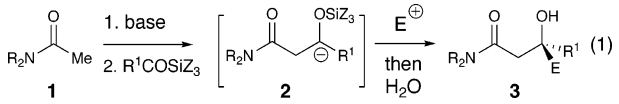
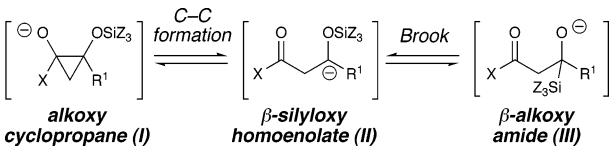
The synthesis of β-hydroxy carbonyl compounds is an important goal due to their prevalence in bioactive molecules.[1] The most convergent strategy to construct this motif is the aldol reaction. Over the last three decades, highly stereoselective additions of enolates to aldehydes have been widely developed.[2] While aldol methodology involving aldehydes is highly advanced, methods for enolate additions to ketones are limited.[3] The efficiency of aldol reactions with enolizable ketones can be compromised by deprotonation of the ketone by the metalloenolate instead of carbon−carbon bond formation. Herein, we report an approach to accessing tertiary β-hydroxy amides by the addition of an amide enolate to an acylsilane. This process utilizes a 1,2-silyl group migration from carbon to oxygen to form β-silyloxy homoenolates (**2**). The subsequent addition of an electrophile delivers tertiary β-hydroxy amides (**3**) in good yields and high levels of stereoselectivity with chiral acetamides (eq 1).



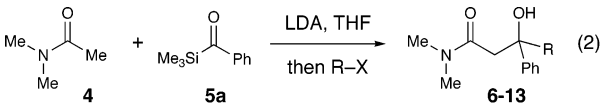
(1)

The addition of organometallic nucleophiles to acylsilanes typically induces a reversible 1,2-silyl group migration from carbon to oxygen (1,2-Brook rearrangement).[4] The additions of alkynyl lithium reagents or alkenyl Grignard reagents to acylsilanes trigger this rearrangement to access useful silyloxy carbanions.[5] Interestingly, the addition of enolates to acylsilanes has seen much less development.[6] Takeda has reported on the addition of ketone enolates to acylsilanes.[7] When the acylsilane lacks α,β-unsaturation, the major product is the hydroxy cyclopropane (**I**, X = alkyl) which arises from the internal attack of the β-silyloxy homoenolate (**II**) generated in situ. With our interest in acylsilanes and Umpolung reactivity,[8] we chose to explore the combination of amide enolates and acylsilanes to access homoenolates.[9] This approach would favor generation of **II**/**III** (X = NR_2) that could undergo intermolecular addition to an electrophile to produce tertiary β-hydroxy amides (**3**). However, the success of this single-flask process depended on controlling the intermediates in the reaction (**I**−**III**) to favor reactivity via the β-silyloxy homoenolate (i.e., *C*-alkylation).

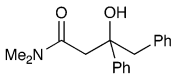
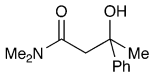
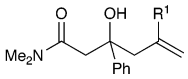
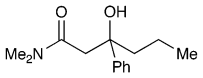
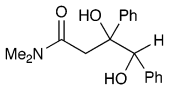
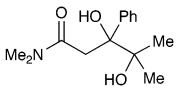
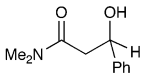


Our initial reaction was conducted with dimethylacetamide (**4**) and benzoyltrimethylsilane (**5a**), with benzyl bromide as the electrophile (Table 1, eq 2). Amide enolate formation with lithium diisopropylamide (LDA) in THF was followed by the addition of **5a**. After 15 min at −78 °C, the alkyl halide was added. To our delight, this three-component reaction provided β-hydroxy amide **6** in 86% after desilylation. Notably, amide **6** (the *C*-alkylation product resulting from **II**) was the major product under these conditions. The corresponding cyclopropane (from **I**) or *O*-alkylation compound (from **III**) were not observed. The absence of cyclopropanes confirmed our hypothesis that the reduced electrophilicity of the amide carbonyl favors a reaction pathway via **II**/**III**.[10] Encouraged by these results, a range of electrophiles was surveyed (Table 1).

Table 1. Reaction with Electrophiles (R−X)[a]



(2)

entry	R–X	product		yield (%)
1			**6**	86
2			**7**	77
3			**8** (R^1 = H)	68
4			**9** (R^1 = Me)	77
5			**10**	69
6			**11**	81[b]
7			**12**	78
8	AcOH/MeOH		**13**	80

[a] Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF at −78 °C. Initial silyl ether products treated with *n*-Bu_4NF in THF prior to purification. [b] 1:1 mixture of diastereomers.

Primary, allylic, and benzylic halides all afford the corresponding tertiary alcohols **6**−**10** in good yields (entries 1−5). The β-silyloxy homoenolate intermediate also undergoes addition to aldehydes and ketones (entries 6 and 7). In cases where elimination (entry 5) or deprotonation (entry 7) is a possibility, the reaction proceeds without complication.

We have also examined the acylsilane scope of the reaction (Table 2, eq 3). The reaction proceeds in good yields in the presence of both electron-deficient (entries 3, 4, and 6) and electron-rich (entry 5) aromatic systems. Unfortunately, a complex mixture is observed when an aliphatic acylsilane is employed (entry 7). This observation is not surprising since an aromatic substituent should stabilize a β-silyloxy homoenolate intermediate (**II**). Also, the deprotonation of an enolizable acylsilane by the enolate is a potentially competitive process.

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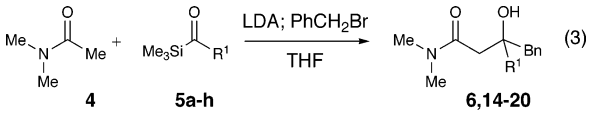
Table 2. Acylsilane Scope[a]

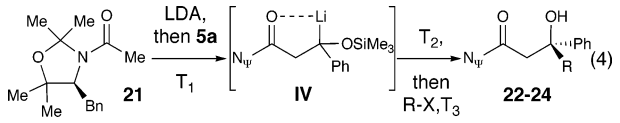


entry	acylsilane	R^1	product	yield (%)
1	**5a**	Ph	**6**	86
2	**5b**	4-MePh	**14**	73
3	**5c**	4-ClPh	**15**	73
4	**5d**	4-BrPh	**16**	69
5	**5e**	4-OMePh	**17**	75
6	**5f**	2-ClPh	**18**	67
7	**5g**	CH_3	**19**	0[b]

[a] See Table 1 for reaction details. [b] Complex mixture.

The success of dimethylacetamide provided the foundation to develop a stereoselective version of this process. The addition of the enantiopure lithium enolate of **21**[11] to **5a**, followed by quenching with benzyl bromide, affords the desired carbinol (**22**, after desilylation) with moderate diastereoselectivity under the established kinetically controlled reaction conditions (−78 °C, entry 1, Table 3). However, when this sequence is conducted completely at 0 °C (entries 2, 4−5), the selectivities improve to ≥10:1. Interestingly, higher levels of selectivity are only observed when the initial adduct (**IV**) is subjected to 0 °C (see entry 3), indicating the need for an equilibration process to generate the most stable carbanion intermediates (entry 3).

Table 3. Diastereoselective Enolate/Acylsilane Reactions[a]



entry	R–X	T_1 (°C)	T_2 (°C)[b]	T_3 (°C)	yield (%)	dr[c]	product
1	BnBr	−78	−78	−78	80	3:1	**22**
2	”	0	0	0	79	10:1	”
3	”	−78	0	−78	79	10:1	”
4	AllylBr	0	0	0	76	10:1	**23**
5	MeI	0	0	0	78	15:1	**24**

[a] Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF. Silyl ether products treated with *n*-Bu_4NF in THF prior to purification. [b] Reaction temp after consumption of **5a** and before the addition of R−X.[12] [c] Determined by ^1H NMR spectroscopy.

The current model for diastereoselection involves enolate addition to **5a** and subsequent Brook rearrangement with stereochemical retention[4,13] to give internally coordinated diastereomeric **IV-(*S*)** and **IV-(*R*)**.[14] Importantly, *O*-alkylation is not observed when the reactions are conducted at −78 or 0 °C, suggesting that the Brook rearrangement occurs rapidly to generate carbanions (**IV**). The unusual inverse relationship of selectivity on temperature suggests that performing the reaction under thermodynamically controlled conditions (0 °C) facilitates interconversion of **IV** prior to alkylation. Since carbanion **IV-(*R*)** is destabilized by nonbonded interactions between the trimethylsilylether and benzyl groups of the auxiliary, the reaction proceeds via intermediate **IV-(*S*)** (Figure 1.

In summary, we have developed a strategy for the synthesis of tertiary β-hydroxy amides using β-silyloxy homoenolates accessed from amide enolates and acylsilanes. These unconventional nucleophilic species undergo addition to alkyl halides, aldehydes and ketones. Importantly, amide enolates strongly favor *C*-alkylation of the homoenolate over *O*-alkylation or the formation of alkoxy cyclopropanes. The use of chiral acetamides affords high levels of diastereoselection for the tertiary alcohol products. Investigations of this Umpolung strategy integrating enolates and the unique reactivity of acylsilanes are ongoing and will be reported in due course.

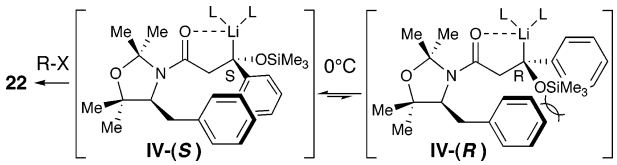


Figure 1. Model for diastereoselection.

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Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information for details.
(13) Absolute stereochemistry of **22** determined by X-ray crystallography with **23** and **24** assigned by analogy.
(14) Strongly coordinating additives (e.g., DMPU, HMPA) reduce the diastereoselectivity and yield of the reactions.

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