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Synthesis of Acylsilanes via Nickel-Catalyzed Reactions of α-Hydroxyallylsilanes

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ABSTRACT

The redox isomerization processes and tandem isomerization−aldolization reactions, mediated by nickel catalysts, offer new versatile entries to acylsilanes. For the second reaction, high diastereoselectivities, up to 98:2, have been obtained with bulky substituents on silicon.

Acylsilanes are versatile intermediates in organic synthesis,[1,2] used mainly as umpolung reagents for the preparation of carbonyl derivatives, employing the Brook rearrangement.[3] With regard to the activation of acylsilanes in 1,2 benzoin-type additions and 1,4 Stetter reactions, new types of catalysts have been developed, e.g. cyanides,[4] thiazolium salts,[5] and metallophosphites,[6] along with successful extensions to enantioselective reactions.[7] Yet, new applications of acylsilanes have been demonstrated recently with additions of enolates,[8] Pd-catalyzed coupling reactions,[9] or photochemical transformations for instance.[10] Many routes have been proposed for the preparation of acylsilanes, including the hydroboration−oxidation of alkynylsilanes,[11] the use of dithianes[12] or benzotriazoles[13] as intermediates, and reactions using various silyl anions.[1]

These methodologies appear satisfactory for unfunctionalized compounds, but there are difficulties in the case of more complex derivatives.[1] Thus, there is still a need for new, versatile methods for the synthesis of acylsilanes. Based on our previous work in the area of transition-metal-mediated

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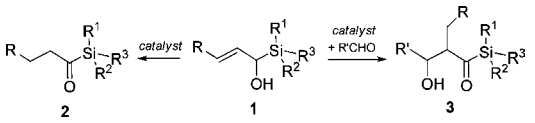
Scheme 1. New Synthetic Strategy towards Acylsilanes

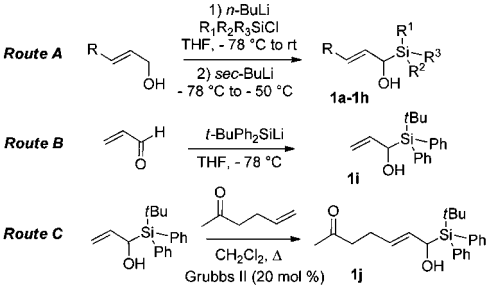


isomerization of allylic alcohols[14] and the corresponding tandem isomerization–aldolization process,[15] we envisaged a new strategy for the preparation of acylsilanes (Scheme 1).

Starting from type **1** α-hydroxyallylsilanes, the isomerization process should lead to the corresponding acylsilanes **2** while, on reaction with aldehydes, the tandem process should afford aldol-type derivatives **3**. Both series of acylsilanes appear as attractive intermediates for further synthetic applications. This strategy requires first an easy access to type **1** α-hydroxyallylsilanes with sufficient flexibility to introduce the different substituents, especially around silicon. Then appropriate catalysts and reaction conditions, compatible with the sensitive acylsilane moiety, must be designed for the transition-metal-mediated reactions. Further, we considered it interesting to study the effect of the different silyl groups on the diastereoselectivity of the tandem isomerization–aldolization process.

Three different strategies have been used to prepare the desired α-hydroxyallylsilanes, and the results are reported in Scheme 2. In one avenue, allylic alcohols are silylated and then submitted to a retro-Brook rearrangement to give the desired products.[16] This versatile method allows the introduction of different alkyl substituents around the silicon (R_{Si}), from trimethyl to triisopropyl and dimethyl *tert*-butyl, as demonstrated by the preparation, in good yield, of **1a** to **1h**. A second method (route B) involves the addition of a silyl anion to an enal. Moreover, this direct method requires at least one aryl substituent on silicon to prepare the lithium anion.[17] It is therefore complementary to the previous one and has been employed for the preparation, in moderate yield, of **1i**. Further, in the case of **1i**, route A gives only a very poor yield (11%). The third route uses a cross metathesis reaction[18] between the preceding α-hydroxyallylsilane **1i** and an alkene. It is useful in the case of derivatives with substituents R not compatible with the previous, strongly basic, reaction conditions and has been demonstrated with ketone **1j**.

Scheme 2. Synthesis of α-Hydroxyallylsilanes



entry	route	R	R_{Si}	product	yield[a,b] (%)
1.	A	H	TMS	**1a**	77
2.	A	H	TES	**1b**	81
3.	A	H	TPS	**1c**	86
4.	A	H	TBS	**1d**	72
5.	A	H	TIPS	**1e**	68
6.	A	n-C_4H_9	TES	**1f**	78
7.	A	n-$C_{10}H_{21}$	TES	**1g**	85
8.	A	C_6H_5	TES	**1h**	68
9.	B	H	TBDPS	**1i**	40
10.	C	$CH_3CO(CH_2)_2$	TBDPS	**1j**	46

[a] Isolated yield; [b] all products were characterized by ^{1}H NMR, ^{13}C NMR and Mass Spectral data.

With this series of intermediates in hand, it was possible to study the transition-metal-mediated reactions. The isomerization of allylic alcohols to saturated carbonyls is a well-known process,[19] but to the best of our knowledge, it has never been employed for the preparation of acylsilanes. Various types of catalysts could be used for this isomerization, but in this particular case, they must be compatible with the sensitive acylsilane moiety.[20] We have selected nickel hydride since it proved to be very mild and efficient in our recent work for the tandem isomerization–aldolization or isomerization–Mannich reactions.[15] After optimization of the reaction conditions, with 10 mol % of this catalyst at 30 to 60 °C, the isomerization proved to be efficient affording the desired acylsilanes **2a**–**2j** in good to excellent yields (Table 1). For the most difficult cases, an increase in catalyst quantity to 20 mol % (**2f**, **2g**) or 40 mol % (**2h**) and higher temperatures were required to obtain the products in fair-to-good yields and short reaction times. All these silanes have spectral and analytical data in agreement with the indicated structures.

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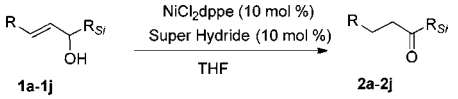
Table 1. Transition-Metal-Catalyzed Isomerization of the α-Hydroxyallylsilanes to Acylsilanes



1a-1j 2a-2j

entry	R	R_{Si}	temp (°C)	time (h)	product	yield[a,b] (%)
1	H	TMS	30	3	**2a**	78
2	H	TES	30	3	**2b**	92
3	H	TPS	30	3	**2c**	89
4	H	TBS	30	3	**2d**	84
5	H	TIPS	30	3	**2e**	88
6	n-C_4H_9	TES	40	3	**2f**	80[c]
7	n-$C_{10}H_{21}$	TES	40	3	**2g**	78[c]
8	C_6H_5	TES	60	24	**2h**	58[d]
9	H	TBDPS	30	3	**2i**	72[c]
10	$CH_3CO(CH_2)_2$	TBDPS	60	24	**2j**	56[d]

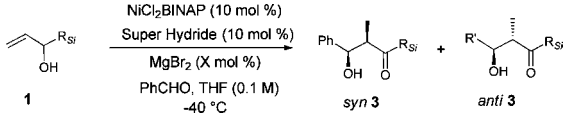
[a] Isolated yield. [b] All products were characterized by ^1H NMR, ^{13}C NMR, and mass spectral data. [c] 20 mol % of Ni catalyst and super hydride was used. [d] 40 mol % of Ni catalyst was used.

Table 2. Optimization of the Reaction Conditions between **1a** and PhCHO with $NiCl_2$dppe (10 mol %)

entry	time (h)	concn[a]	temp (°C)	dr[b] (*syn*-**3a**/*anti*-**3a**)
1	3	0.018	rt	42:58
2	3	0.025	rt	46:54
3	3	0.043	rt	55:45
4	3	0.062	rt	60:40
5	18	0.018	−40	72:28
6	18	0.1	−40	80:20

[a] Concentration in THF (mol/L). [b] dr established by ^1H NMR on the crude product.

Table 3. Diastereoselectivity Studies for the Tandem Isomerization−Aldolization Starting from α-Hydroxyallylsilanes **1**



entry	R_{Si}	time (h)	$MgBr_2$ (mol %)	yield[a,b] (%)	*dr* (*syn*/*anti*)
1	TMS	18	10	88	85:15 (**3a**)
2	TES	24	10	82	91:09 (**3b**)
3	TPS	24	10	79	80:20 (**3c**)
4	TBS	24	10	85	75:25 (**3d**)
5	TIPS	24	10	83	95:05 (**3e**)
6	TBDPS	30	20	70[c]	95:05 (**3i**)
7	TBDPS	30	40	77[c]	92:08 (**3i**)
8	TBDPS	24	60	82[c]	98:02 (**3i**)
9	TBDPS	24	100	83[c]	98:02 (**3i**)

[a] Isolated yield. [b] All products were characterized by ^1H NMR, ^{13}C NMR, and mass spectral data. [c] 20 mol % of Ni catalyst and Super Hydride were used.

The stage was thus set for study of the tandem process toward the aldol products **3**. To the best of our knowledge, only a few derivatives of this type have been described until now by direct addition of acylsilane enolates on aldehydes.[21] The first step of our study was to define the best reaction conditions for the catalyst, solvent, and temperature. These experiments were performed using the α-hydroxyallylsilane **1a** as a model and benzaldehyde as the acceptor (Table 2). In a first series of experiments, we have shown that increasing the concentration gave slightly better selectivities (up to 60:40, entries 1−4). Lowering the temperature further increased the selectivity to 72:28, and by working at 0.1 M concentration and −40 °C, good selectivity (*syn*/*anti* = 80:20) was obtained (entry 6). Further experiments that changed the nature of the ligand and counteranion gave only little improvement with $NiCl_2$/BINAP (see Supporting Information (SI)).

The next step was to study the effect of the substituents on the silyl group on the tandem reaction, most especially on the *syn*/*anti* diastereoselectivity (Table 3). Under the previously defined conditions, the tandem reaction worked well for all types of substituents on the silyl group, the aldols **3a** to **3i** being obtained in 70−88% yields. The ^1H NMR data give excellent indications for the stereochemistry: the *syn* isomers have $^3J_{HH}$ from 1.5 to 3.3 Hz while the *anti* has $^3J_{HH}$ from 6.5 to 8.3 Hz. This was further confirmed by X-ray analysis of **3i**.[22] It is noteworthy that the diastereoselectivity in favor of the *syn* isomer was excellent (95:05), in the case of the more bulky substituents (**1e** and **1i**).

Finally, by using **1i** as a model, the amount of $MgBr_2$ was also found to play a role in the reaction (entries 7−9) with an increase in the quantity of additive up to 60 mol % (entry 8) giving the desired products **3i** in good yield and with excellent *syn*/*anti* selectivity (98:2). A mechanism can be proposed for the tandem process (Scheme 3). The nickel catalyst performs the isomerization to the enols which react with the aldehydes, in the presence of $MgBr_2$, through a Zimmerman−Traxler transition state. The amount of the *Z* and *E* enols is related to the size of the R_{Si} groups, and the bulky substituents give the maximum of *Z* enols (R^1 = H) and thus of *syn* adducts. This is in full agreement with our previous studies using allylic alcohols with bulky substituents (like a *tert*-butyl group) on the carbinol center.[15b]

Taking into account its good reactivity and diastereoselectivity, **1i** was selected as a α-hydroxyallylsilane model

(22) CCDC 912880 (**3i**) and CCDC 912881 (**15i**) contain the supplementary crystallographic data for this paper, which can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif and are included in the SI.

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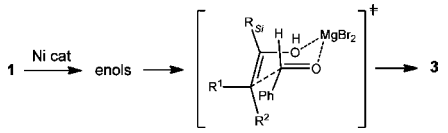
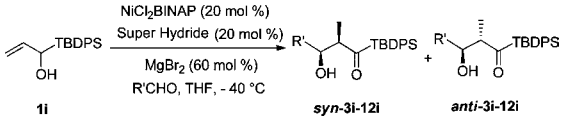
Scheme 3. Postulated Mechanism for the Tandem Process



to study the scope of the reaction with various types of aldehyde (Table 4). Under previously optimized reaction conditions, the tandem reaction worked well with different aromatic aldehydes (entries 1−4) and with heteroaromatic systems (entries 5−6). It also gave the desired aldol products with aliphatic aldehydes (entries 7−8) and with enals (entries 9−10). All *syn* derivatives have been isolated by SiO_2 chromatography and the *syn*/*anti* stereochemistry was established by NMR, as with the previous examples. The overall yields range from fair-to-excellent, and except in the case of enals (entries 9−10), the *syn*/*anti* stereoselectivities are also good to excellent (up to 98:2).

Next, face selectivity studies were performed with α-hydroxysilane **1i** and the easily accessible aldehyde **13**.[23] This reaction afforded *anti*−*syn* aldol product **15i**, along with other diastereoisomers in small amounts (Table 5, entry 1). The major compound **15i** was isolated in 62% yield by chromatography, and its stereochemistry was secured by X-ray analysis.[22] Complementary studies have shown that complete facial selectivity, together with good *syn*/*anti* diastereoselectivity, were obtained from the reaction of **1i** with aldehyde **14** which bears a TBS ether (entry 2). In contrast, α-hydroxyallylsilane **1e** gave significant amounts of *syn*−*syn* derivatives **19e** and **20e** with both aldehydes (entries 3 and 4).

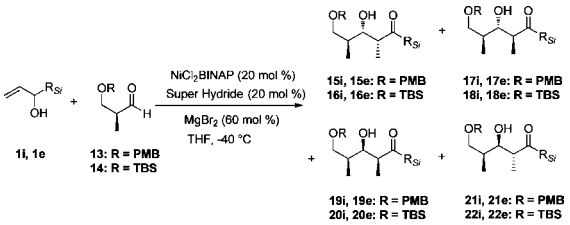
Table 4. Scope of the Tandem Isomerization−Aldolization Starting from **1i** and Using Different Aldehydes



entry	R^1	time (h)	yield[a,b] (%)	product	dr (*syn*/*anti*)
1	C_6H_5	24	83	**3i**	98[c]:02
2	4F-C_6H_4	24	64	**4i**	94:06
3	4MeO-C_6H_4	24	60	**5i**	94:06
4	4Br-C_6H_4	24	90	**6i**	89:11
5	2-thiophene	24	78	**7i**	92:08
6	3-Py	30	62	**8i**	84:16
7	*i*-Pr	24	65	**9i**	91:09
8	*t*-Bu	24	64	**10i**	90:10
9	(*E*)-CH_3CHCH	24	78	**11i**	60:40
10	(*E*)-C_6H_5CHCH	24	85	**12i**	60:40

[a] Isolated yield. [b] All products were characterized by ^1H NMR, ^{13}C NMR, and mass spectral data. [c] Stereochemistry determined by X-ray crystallography.

Table 5. Face Selectivity Studies with α-Substituted Aldehydes



			dr ratio[a]				
entry	R	R_{Si}	**15**, **16**	**17**, **18**	**19**, **20**	**21**, **22**	yield[b] (%)
1	PMB	TBDPS	68(**15i**)	12(**17i**)	19(**19i**)	1(**21i**)	92
2	TBS	TBDPS	88(**16i**)	12(**18i**)	−(**20i**)	−(**22i**)	91
3	PMB	TIPS	74(**15e**)	−(**17e**)	26(**19e**)	−(**21e**)	81[c]
4	TBS	TIPS	76(**16e**)	−(**18e**)	24(**20e**)	−(**22e**)	91[c]

[a] Diastereomeric ratios established by ^1H NMR. [b] Isolated yields. [c] $MgBr_2$ used at 20 mol %.

These results, combined with several previous examples on the use of Pd-catalyzed reactions,[24,9] confirm that transition metal catalysis could be of much interest to develop acylsilane chemistry.

In summary, two complementary strategies have been successfully demonstrated for the preparation of acylsilanes. Starting from easily accessible α-hydroxyallylsilanes, and using a nickel hydride system as a catalyst, an isomerization process gave acylsilanes in good yields. Moreover, with the same catalyst, along with $MgBr_2$ and in the presence of carbonyl derivatives, a tandem isomerization−aldolization process afforded aldol-type acylsilanes in good yields. This method allows good flexibility in the choice of substituents around the silicon. The nature of these substituents plays an important role in this process, and more bulky groups, e.g. TIPS and TBDPS, give aldol derivatives with up to 98:2 *syn* diastereoselectivity. These results should expand the synthetic potential of this tandem aldol process by taking advantage of the versatility of the newly introduced acylsilane moiety. Corresponding studies are under development and will be reported in due course.

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Supporting Information Available. Detailed experimental procedures and complete characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.