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Enantioselective 1,2-Anionotropic Rearrangement of Acylsilane through Bisguanidinium Silicate Ion Pair

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ABSTRACT: Highly enantioselective bisguanidinium-catalyzed tandem rearrangements of acylsilanes are reported. The acylsilanes were activated *via* an addition of fluoride on the silicon to form a penta-coordinate anionic silicate intermediate. The silicate then underwent alkyl or aryl group migration from the silicon atom to the neighboring carbonyl carbon atom (1,2-anionotropic rearrangement), followed by [1,2]-Brook rearrangement to provide the secondary alcohols in high yields with excellent enantioselectivities (up to 95% ee). The isolation of an α -silylcarbinol intermediate as well as DFT calculations revealed that the 1,2-anionotropic rearrangement occurred *via* a bisguanidinium silicate ion-pair, which is the stereo-determining step. The chiral center formed is then retained without inversion through the subsequent [1,2]-Brook rearrangement. Crotyl acylsilanes were smoothly transform into homoallylic linear crotyl alcohols with retention of E/Z geometry and no branched alcohols were detected. This clearly suggested that the 1,2-anionotropic rearrangement occurred through a three-membered instead of a five-membered transition state.

■ INTRODUCTION

Hypervalent silicon have been widely applied to organic synthesis and catalysis due to its unique structure and reactivity.¹ Penta- and hexa-coordinate silicon are known to be crucial intermediates in many reactions. A representative reaction involving pentavalent silicon intermediate is the Brook rearrangement.² This process generally requires base and its putative reaction mechanism is an intramolecular anionic migration of the silyl group from carbon to oxygen. Acylsilanes are carbonyl derivatives and behave similarly to aldehydes or ketones and are susceptible to nucleophilic additions.³ Addition of a nucleophile to acylsilane, catalyzed with a chiral metal-complex, generates an enantiopure α -silyl alkoxide, which is a precursor to Brook rearrangement (Scheme 1). This is the most common strategy towards catalytic enantioselective Brook rearrangements. For example, Johnson^{4a} reported a chiral (salen)-Al(OiPr) catalyzed cyanation of acylsilanes and Marek^{4c} reported a Zn-mediated enantioselective alkylation of acylsilanes. Both reactions are followed by stereoselective Brook rearrangements. Alternatively, the enantiopure α -silyl alkoxide can be generated through hydride reduction of alkynoylsilane using stoichiometric chiral amide, as demonstrated by Takeda.^{4e} Several other chemoselective and diastereoselective variants of this nucleophilic addition strategy have also been reported.^{2d-e, 5}

Acylsilanes can also be activated *via* a nucleophilic attack on the silicon to form a penta-coordinate anionic silicate intermediate (Scheme 2). The silicate can then undergo alkyl or aryl group migration from the silicon atom to the neighboring carbonyl carbon atom (1,2-anionotropic rearrangement), followed by [1,2]-Brook rearrangement to provide a secondary alcohol. Brook⁶ and others⁷ reported this tandem rearrangement of acylsilanes using alkoxide or fluoride salts. To the best of our knowledge, the enantioselective catalytic variant of this reaction, has not been realized.

Ion-pairing catalysis,⁸ comprising of chiral cation working synergistically with metal-centered anions, has been reported for several enantioselective transformations.⁹ Specifically, dicationic bisguanidinium has been used to direct permanganate, diphosphatobisperoxotungstate and dinuclear oxodiperoxomolybdatesulfate anions in enantioselective oxohydroxylation and sulfoxidation reactions.^{9a-c} Bisguanidinium silicates have also been proposed to be key intermediates in enantioselective alkylations using silylamide.^{9d} In this study, we hypothesized that the silicate intermediate derived from acylsilane can be mediated using a chiral cation to promote enantioselective 1,2-anionotropic rearrangement and followed by stereoselective Brooks rearrangement, lead to chiral secondary alcohols (Scheme 2).

Scheme 1. Tandem nucleophilic addition/[1,2]-Brook rearrangement of acylsilane (previous works).

Scheme 2. Tandem 1,2-anionotropic/[1,2]-Brook rearrangement of acylsilane (current strategy).

■ RESULTS AND DISCUSSION

Enantioselective 1,2-Anionotropic Rearrangement of Acylsilane. In the initial study, acylsilane **1a** was selected as the model starting substrate. When **1a** was used in the presence

of CsF and bisguanidinium catalyst **BG-*t*Bu** (5 mol %), no reaction was observed (Table 1, entry 1; see SI, Table S1). Trace amount of the desired product **3a** was obtained, after 48 h, when H₂O was added as a proton source (entry 2). As a result, we further probed the use of alcohols as the proton source, which led to improve reactivities and enantioselectivities (entries 3-5). The use of a bulky silyl alcohol *i*Pr₃SiOH was found to be the best proton source (entry 5) and at this stage we were intrigued by the influence of the proton source on enantioselectivity. We initially suspected that the reaction might to be an enantioselective protonation reaction of the carbanion but further investigations refuted this hypothesis as a silylated alcohol intermediate **2a** was isolated and spectroscopically identified. Various solvents were screened and TBME was found to furnish the best yield and enantioselectivity (entries 5-8). Lower reaction temperatures led to improve enantioselectivities but at a cost, i.e. longer reaction times and reduced yields (entries 9-11). Increasing the catalyst loading to 10 mol % and amount of CsF gave the optimal reaction conditions (entry 12). By employing a newly developed bisguanidinium catalyst **BG-TMS**, enantioselectivity was further improved (entry 13).

Table 1. Optimization of the Reaction Conditions.^a

entry	ROH	solvent	T/°C	time (h)	yield (%) ^b	ee (%) ^c
1	-	TBME	rt	48	NR ^d	-
2	H ₂ O	TBME	rt	48	trace	-
3	MeOH	TBME	rt	48	80	15
4	<i>t</i> BuOH	TBME	rt	12	87	21
5	<i>i</i> Pr ₃ SiOH	TBME	rt	1	93	55
6	<i>i</i> Pr ₃ SiOH	Et ₂ O	rt	2	87	51
7	<i>i</i> Pr ₃ SiOH	DCM	rt	1	86	9
8	<i>i</i> Pr ₃ SiOH	Toluene	rt	1	88	26
9	<i>i</i> Pr ₃ SiOH	TBME	0	4	91	69
10	<i>i</i> Pr ₃ SiOH	TBME	-40	14	93	81
11	<i>i</i> Pr ₃ SiOH	TBME	-50	72	51	89
12 ^e	<i>i</i> Pr ₃ SiOH	TBME	-50	36	89	87
13 ^f	<i>i</i> Pr ₃ SiOH	TBME	-50	48	83	90

^a Unless otherwise noted, reactions were carried out with **BG-*t*Bu** (5 mol %), CsF (0.1 mmol, 1.0 equiv.), **1a** (0.10 mmol), ROH (0.2 mmol, 2.0 equiv.) in solvent (0.5 mL) at indicated temperature, rt = room temperature. ^b Isolated yield of **3a**. ^c Determined by HPLC using chiral OD-H column. ^d NR = No reaction. ^e **BG-*t*Bu** (10 mol %) and CsF (4.0 equiv.) were used. ^f **BG-TMS** (10 mol %) and CsF (4.0 equiv.) were used.

Using the optimized reaction condition, a series of aryl substituted acylsilanes were investigated (Table 2). The reaction tolerated migrating aryl groups bearing substituents with varying electronic or steric properties. The corresponding chiral second alcohols **3a-3k** were furnished with good yields (69-93%) and high enantioselectivities (84-95% ee).¹⁰ Substrates bearing electron withdrawing groups on the migrating aryl group were

more reactive,¹¹ presumably due to increased Lewis acidity of silicon and facilitating the formation of the hypervalent silicate intermediate. In the subsequent anionotropic shift, electron withdrawing groups also stabilized the migratory aryl anion. Furanyl group was well tolerated and provided the furanyl alcohol **3l** in 69% yield with 84% ee. The substituents on benzyl group of the acylsilane had little effect on the yields and enantioselectivity (**3m-3p**).

Table 2. Enantioselective 1,2-Anionotropic Rearrangement of Aryl Acylsilane.^a

^a Reactions were carried out with **BG-TMS** (10 mol %), CsF (0.4 mmol, 4.0 equiv.), **1** (0.10 mmol), *i*Pr₃SiOH (0.2 mmol, 2.0 equiv.) in TBME (0.5 mL) at -50 °C. ^b Isolated yields of **3**. ^c Determined by chiral HPLC.

Scheme 3. Enantioselective 1,2-anionotropic rearrangement of allyl and crotyl acylsilanes.

Intermolecular asymmetric allylation of carbonyl compounds or imine using silane reagents typically requires activation of the silane reagent with Lewis bases or the electrophiles with Lewis acids.¹² For this intramolecular rearrangement, allyl acylsilane **1q** could smoothly transform into allylic alcohol **3q** (Scheme 3a). Fortuitously, (*Z*)-homoallylic linear crotyl alcohol **3r** was obtained from (*Z*)-crotyl acylsilane **1r** using this protocol (Scheme 3b). We initially predicted that a branched alcohol¹³ would be derived through a five-membered ring transition state but retention of stereochemistry clearly suggested that the

1,2-anionotropic rearrangement proceeded through a three-membered transition state instead (Scheme 3c). We also explored the use of vinyl acylsilanes, and only trace product was achieved under the optimized conditions (Table 1, entry 13; see SI for details). Further investigations are required to determine if other mediator besides fluoride could facilitate this sluggish migratory process.

MECHANISTIC STUDIES

Identification of Reaction Intermediates. In order to fully understand this tandem 1,2-anionotropic/Brook rearrangement, it was indispensable to verify the enantio-determining step. Fortunately, we were able to isolate α -silyl carbinol **4** and delighted to find it to be in high enantiopurity (Scheme 4a). When treated with TBAF solution, **4** underwent the [1,2]-Brook rearrangement with complete conversion to allylic alcohol **3q** without diminished enantiopurity (Scheme 4b).^{4d,14} Similarly, when silylated allylic alcohol **2q** was treated with TBAF solution, allylic alcohol **3q** was obtained while retaining both its enantiopurity and absolute configuration (Scheme 4c). These experiments indicated that the 1,2-anionotropic rearrangement to be the enantio-determining step and was indirect evidence for the presence of a tight bisguanidinium silicate ion pair (Scheme 2). We also found that the amount of CsF used had no effect on enantioselectivity but had a positive correlation to the reactivity (Scheme 5).

Scheme 4. Investigation of the enantio-determining step.

Scheme 5. The role of fluoride.

Theoretical Modelling Studies. Protic additives like alcohol are important to the reaction, with the bulky silyl alcohol having significant effect on enantioselectivity (Table 1, entries 2-5). Furthermore, the isolation of α -silyl carbinol **4** and silylated allylic alcohol **2q** as reaction intermediates (Scheme 4) serve to suggest R_3SiOH as an important mediator early in the reaction. It is proposed that once halide exchange occurs with the original bisguanidinium chloride catalyst, a pentavalent silyl complex **intA** is formed (Figure 1; BG_s is truncated version of $BG-rBu$). Our DFT model predicts that Me_3SiOH is able to stabilize **intA** by 2.4 kcal/mol through non-covalent hydrogen bonding to the F-Si bond generating **intB** (See SI for DFT methods and detailed discussion). A low energy barrier involving three-membered transition state **TSB-3m** ($\Delta G^\ddagger = +11.6$ kcal/mol) was found to be more energetically plausible over a five-membered ring transition state for the anionotropic rearrangement process (See SI). Subsequently the α -silylalkoxide **intC** is able to form two nearly iso-energetic intermediates: ring closure to give a siloxirane intermediate **intE** ($\Delta G = -15.3$ kcal/mol),¹⁵ and O⁻...H bound **intD** ($\Delta G = -15.5$ kcal/mol). Direct proton transfer from

intD between the alkoxyl group and Me_3SiOH affords α -silyl-carbinol **4**. Tandem Brook rearrangement and protonation through transition state **TSE** ($\Delta G^\ddagger = +6.5$ kcal/mol) leads to a pentavalent precursor **intF**, which upon facile fluoride dissociation generates silylated allylic alcohol **2q**. It is thus interesting to observe that ion pair catalysis can work synergistically with hydrogen bonding and this will have significant implication in the understanding and design of ion pair-mediated reactions.

Figure 1. Proposed hydrogen bonding-assisted tandem 1,2-anionotropic rearrangement. Values in kcal/mol are calculated solution free energies of minimum and TS electronic structures optimized at B3LYP-B3/def2TZVP/SMD//B3LYP/6-31+G(d) level of theory (see SI on DFT methods).

CONCLUSIONS

In summary, the first catalytic asymmetric tandem 1,2-anionotropic/Brook rearrangements of acylsilane furnishing highly enantio-enriched secondary alcohols has been described. Isolation of reaction intermediates such as α -silyl carbinol **4** and silylated allylic alcohol **2q**, coupled with theoretical calculations, a bisguanidinium hypervalent silicate ion pair was proposed to be the key intermediate for the stereo-determining 1,2-anionotropic rearrangement. In addition, experimental and computational results suggested that the 1,2-anionotropic rearrangement proceeded through a three-membered ring transition state. This new synthetic strategy in ion pairing catalysis is important to expand the repertoire of reactions for acylsilanes. This also points to the future use of chiral cations as an approach to mediate reactions containing silicates as intermediates.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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