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Chemoselective amide-forming ligation between acylsilanes and hydroxylamines under aqueous conditions

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Dedicated to the memory of Professor Chris Abell

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Abstract: We report the facile amide-forming ligation of AcylSilanes with HydroxylAmines (ASHA ligation) under aqueous conditions. The ligation is fast, chemoselective, mild, high-yielding and displays excellent functional group tolerance. Late-stage modifications of an array of marketed drugs, peptides, natural products and biologically active compounds showcase the robustness and functional group tolerance of the reaction. The key to the success of the reaction could be the possible formation of the strong Si-O bond *via* a Brook-type rearrangement. Given its simplicity and efficiency, this ligation has the potential to unfold new applications in the areas of medicinal chemistry and chemical biology.

Amide bond formation is among the most extensively employed reactions in chemical industries and academic settings[1] due to the prevalence of this functional group in numerous life-saving pharmaceutical products,[1,2a] peptides,[2b] biological conjugates,[2c,2d] agrochemicals[2e] and materials such as polymers,[2f,2g] MOFs[2h] and hydrogels.[2i] Recent cheminformatics analysis of around 420,000 bioactive molecules from the ChEMBL database has identified the amide bond as the most occurring functional group in 40.3% of all molecules.[3] Furthermore, amide bonds are known to be crucial for modulating the structures and functions of proteins and other small molecule-based drugs.[4] Hence, amide functionality is of central importance in modern research, and new methods to generate amide bonds in sustainable and chemoselective ways are in demand.

The most common method to access amide bonds is by condensing a carboxylic acid and amine in the presence of stoichiometric amount of a coupling reagent and a base in organic solvent.[5] The lack of chemoselectivity, aqueous incompatibility and the generation of copious amounts of organic waste along with other safety complications[6] makes this method less appealing or even unfit, especially for chemical biology and chemical library synthesis applications. Numerous non-classical amide-bond forming reactions have been reported in the last two decades that overcome the limitations associated with the traditional methods.[7] Among these reactions, native chemical ligation (NCL),[8] α-ketoacid-hydroxylamine (KAHA)[9] and potassium acyltrifluoroborate (KAT)[10] ligations are in the frontline when it comes to applications pertaining to peptide and protein chemistry, bioconjugation and inhibitor discovery.[11,12] These reactions are highly chemoselective, can take place under mild aqueous conditions and are capable of stitching protein fragments together.[12] However, the slower reaction rate is the major limitation of NCL and KAHA ligations. Conversely, KAT ligation is rapid with a second-order rate constant of up to 100 $M^{-1}s^{-1}$ and can occur under dilute concentrations with equimolar reactants, thus making it ideal when dealing with macromolecules;[11d] however, the lack of rapid methods to access diverse KATs limits its wider application, especially in the areas of fragment-based drug discovery and compound library synthesis, where a few hundreds to thousands of diverse small-molecule fragments are usually involved.

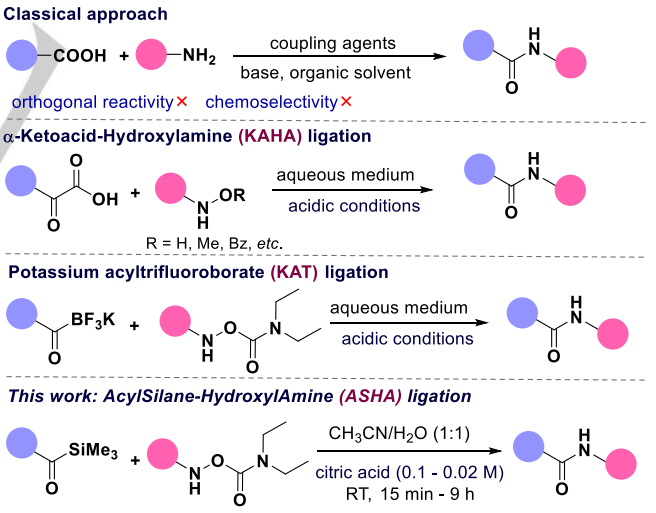

Figure 1. Traditional amide bond formation reaction, KAT and KAHA ligations, and the present work.

In our quest to discover efficient amide-forming ligation from easily accessible starting materials, we considered acylsilanes (also called silyl ketones), a class of fascinating compounds with established chemistry[13] yet underexplored in medicinal chemistry and chemical biology. In many instances, these compounds behave entirely different from ketones in terms of reactivity and

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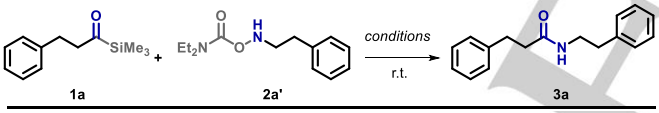
spectroscopic properties due to the positive inductive effect of the silicon atom.[13e] It is known that ketones condense with *N*-alkylhydroxylamines, generally under harsh conditions to generate hemiaminals *via* nitrone intermediates,[14] but similar reactions with acylsilanes are unknown. Other distinct reactions of acylsilanes in forging amide-based linkages are also known. The electrochemical oxidation of acylsilanes with the derivatives of *N*-methylcarbamate and *p*-toluenesulfonamide furnished the respective diamide and *N*-tosylamide derivatives.[15] Recently, Yu *et al*. reported an elegant amide synthesis method *via* an intermolecular Schmidt reaction of acylsilanes with alkyl azides mediated by trifluoromethanesulfonic acid.[16] However, the requirement of a strong acid, use of undesirable dichloromethane as the solvent, a narrow substrate scope consisting of mostly unfunctionalized simple alkyls and aryls, and requirements of an excess of azide reactant severely limits the application of this method. Apart from these studies, acylsilanes are unexplored in the amide-bond forming reaction. Interestingly, Denmark *et al*. had speculated on the possibility of ligation of acylsilanes with hydroxylamines.[17] Further, inspired by Bode's work on KAHA and KAT ligations, we questioned whether hydroxylamines could react with acylsilanes in a similar fashion to that of α-ketoacids/KATs to deliver amide linkages. We hypothesized that this new acylsilane-hydroxylamine (ASHA) ligation could be driven by the formation of a strong Si-O bond *via* a Brook-type rearrangement [18] (Figure 3, pathway A). Moreover, boron and silicon show diagonal relationships [19] and as such, acylsilanes could behave in a similar fashion to acylboronate derivatives, including KATs and MIDA acylboronates, upon treatment with hydroxylamines under suitable conditions. [20]

Table 1. Optimization of ASHA ligation[a]

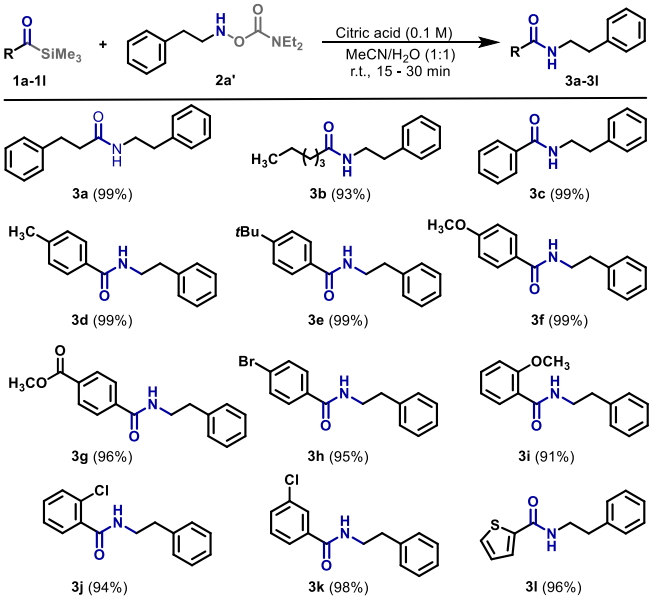


1a 2a' 3a

Entry	solvent	Additive (%)	Yield(%)[b]
1	DMSO (or) CH_3CN (or) *t*-BuOH	nil	N.R.
2	CH_3CN	0.5 N HCl (aq.)	60
3	CH_3CN	HCOOH	78
4	CH_3CN	Oxalic acid	92
5	CH_3CN	Citric acid	96
6[c]	CH_3CN/H_2O (1:1)	Citric acid	99
7	*t*-BuOH/H_2O (1:1)	Citric acid	85
8	DMSO/H_2O (1:1)	Citric acid	72
9	DMF/H_2O (1:1)	Citric acid	75
10	H_2O	Citric acid	61

[a] Reaction condition: acylsilane **1a** (0.2 mmol, 1.0 equiv), *O*-diethylcarbamoyl-*N*-phenethylhydroxylamine **2a'** (0.2 mmol, 1.0 equiv, acid additive (0.1 M, 0.2 mmol, 1.0 equiv), solvent(s) (2 mL), r.t., 2 h; [b] isolated yield; [c] reaction time: 15 min. DMSO = Dimethyl sulfoxide, DMF = Dimethylformamide. N.R. = no reaction.

At the outset of the study, we quickly investigated any possible reactions of acylsilane **1d** with a simple hydroxylamine (*i.e.*, benzylhydroxylamine hydrochloride) and *O*-Me-hydroxylamine (*i.e.*, *N,O*-dimethylhydroxylamine hydrochloride). Although the desired amides were observed, the conversions were either poor or not clean. Hence, we turned our attention towards *O*-diethylcarbamoyl-derived hydroxylamines, which are known to be robust coupling partners in KAT ligation.[10b] For the optimization studies, we used 3-phenylpropionyltrimethylsilane **1a** and *O*-diethylcarbamoyl-*N*-phenethylhydroxylamine **2a'** as model substrates (Table 1). The reactions were performed at room temperature. No measures were taken to exclude air and moisture from the reaction flask. Initially, we screened polar solvents such as DMSO, CH_3CN and *t*-BuOH in the absence of any additives (entry 1). However, the starting materials remained intact and no traces of the desired product formation were observed in all these cases even after two hours. Next, we explored the reaction in CH_3CN using 0.5 N aq. HCl (0.4 mL) as an additive and isolated 60% of the desired product **3a** after two hours of the reaction (entry 2). Encouraged by the product formation, we chose CH_3CN as a solvent and screened various organic acids, including formic, oxalic and citric acids. To our delight, the reaction was completed within two hours, and the desired amide product **3a** was isolated in 78, 92 and 96% yields, respectively (entries 3-5). When the reaction was performed in CH_3CN/H_2O in a 1:1 ratio and in the presence of 0.1 M of citric acid, the reaction proceeded to completion within 15 minutes in quantitative yield (entry 6). When acetonitrile co-solvent was replaced with other polar solvents such as *t*-BuOH, DMSO and DMF, the yield dropped to 85, 72 and 75%, respectively (entries 7-9). Finally, it was encouraging to note that the reaction can be performed in water in the absence of any organic co-solvent furnishing the desired amide in 61% yield, yet the reaction was incomplete even after 2 hours as the starting materials were not soluble in water. In general, we found that the acylsilanes are quite stable under aqueous conditions. No noticeable decomposition of acylsilane **1d** was observed at 40 °C in the presence of 1 equiv. of citric acid for over 2 days in CH_3CN:H_2O (1:1). However, the presence of a strong acid (table 1, entry 2) compromised the stability of the acylsilane **1a** to a certain extent.



Scheme 1. Substrate scope of acylsilanes. Reactions were carried out on a 0.2 mmol scale. Acylsilane (1 equiv.) and hydroxylamine (1 equiv.).

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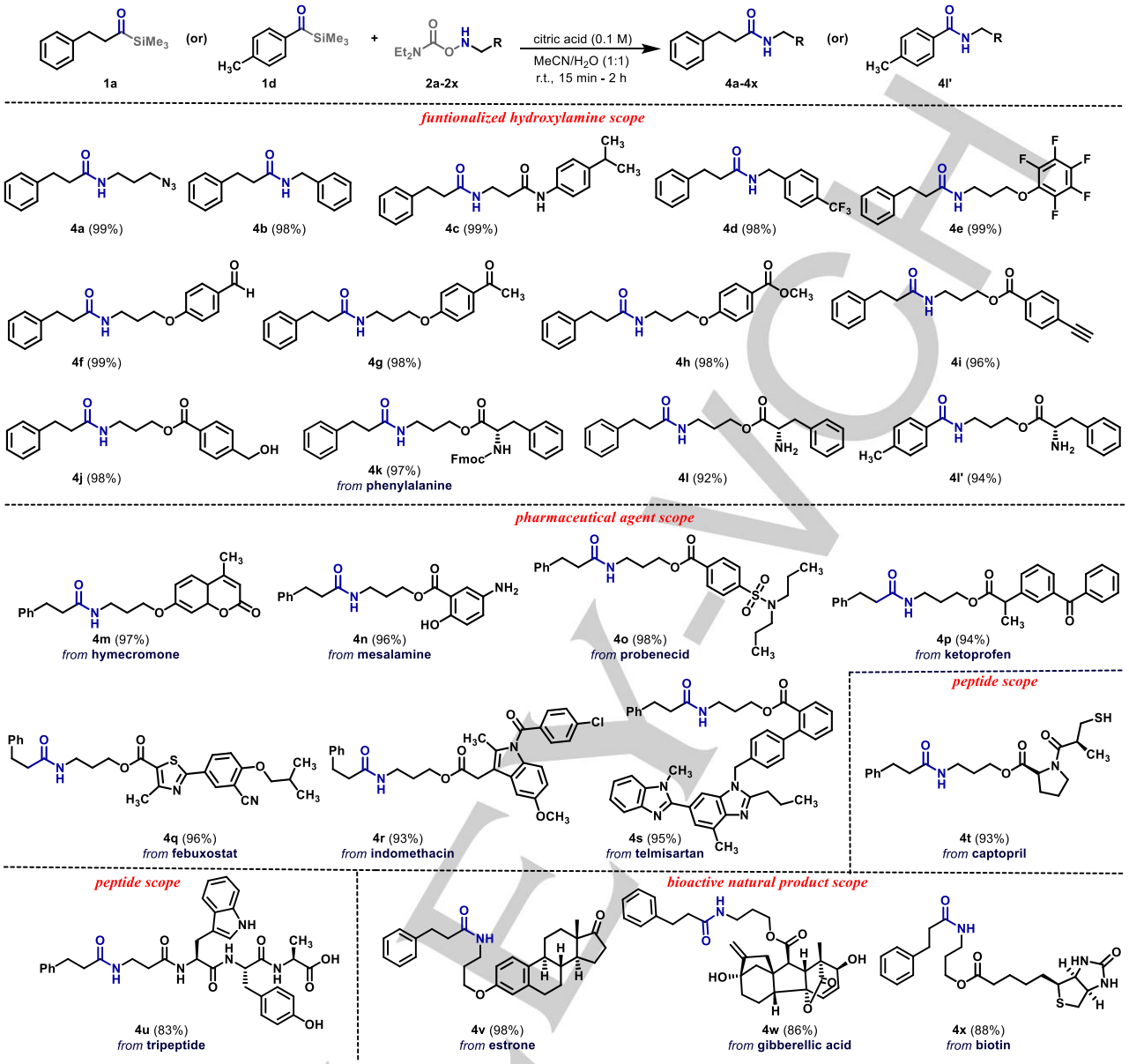

Scheme 2: Scope of hydroxylamines and late stage modifications of drugs, peptides and biologically active natural products. Reactions were carried out with acylsilane (1.05 equiv, 0.21 mmol) and hydroxylamine (1 equiv, 0.2 mmol).

Having optimized the reaction conditions (Table 1, entry 6), we studied the substrate scope of diverse acylsilanes **1a**-**1l** with hydroxylamine **2a'** (scheme 1). These acylsilanes can be easily prepared from their acid or aldehyde derivatives using established procedures.[13] *O*-Diethylcarbamoyl protected hydroxylamine was prepared following Bode's protocol.[10b] Aralkyl acylsilane **1a** reacted with **2a'** to furnish the desired amide **3a** in quantitative yield in just 15 min Similarly, alkyl acylsilane **1b** furnished the amide **3b** in 93% yield in 15 min. Aryl acylsilanes **1c**-**1k** consisting of substituents with varying steric and electronic properties (-CH_3, -*t*Bu, -OCH_3, -$COOCH_3$, -Cl and -Br) underwent the reaction smoothly to afford the desired amides **3c**-**3k** in 91-99% yields. Thiophene acylsilane **1l** also underwent the reaction smoothly to furnish the desired amide **3l** in 96% yield. All these reactions were completed within 30 min.

Impressed by the efficiency of this ligation, we next investigated the chemoselectivity of the reaction by using various *O*-diethylcarbamoyl-derived hydroxylamines tethered to diverse substrates, including approved drugs, peptides, complex molecules and natural products containing unprotected functionalities (scheme 2). The tethering was achieved by either a ether, ester or amide linkage. A total of 24 hydroxylamines **2a**-**2x** were synthesized for this purpose (see supporting information). Hydroxylamine **2a** bearing azide moiety, reacted smoothly with acylsilane **1a** to furnish amide **4a** in quantitative yields. It is interesting to note that the competing intramolecular Schmidt

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reaction was not observed between the azide functionality and acylsilane. Hydroxylamines **2b**-**2e** underwent the ligation with acylsilane **1a** smoothly to furnish amides **4b**-**4e** in quantitative yields. Hydroxylamines bearing reactive functional groups such as aldehyde (**2f**), ketone (**2g**), ester (**2h**), alkyne (**2i**), alcohol (**2j**) and Fmoc- protected amine (**2k)** underwent the reaction smoothly with acylsilane **1a** to afford the desired amides **4f**-**4k** in 94-99% yield. Further, it is interesting to note the hydroxylamine **2l**, derived from *L*-phenylalanine bearing a free amino group, underwent the reaction smoothly with acylsilanes **1a** and **1d** to afford the desired amides **4l** and **4l'** in 92 and 94% yield, respectively, leaving the free amino group untouched. In all these cases, the reaction completed within 15-25 minutes.

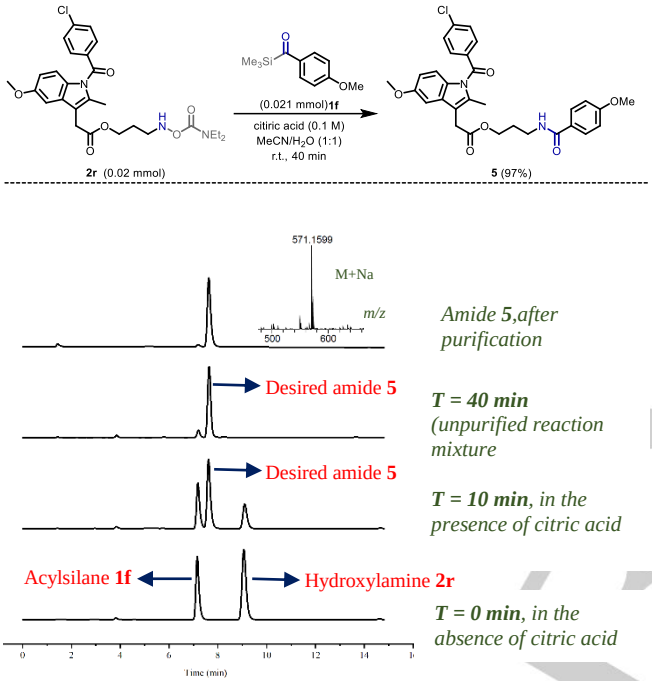
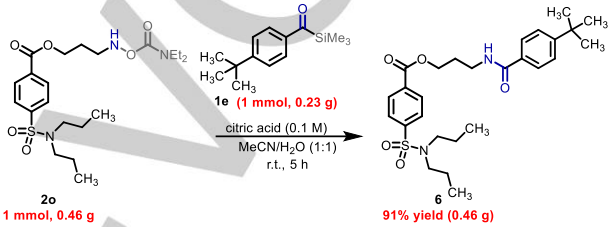


Figure 2. ASHA ligation of indomethacin derivative **2r** with acylsilane **1f**, and HPLC monitoring of the reaction at different time intervals

Subsequently, hydroxylamine-tethered small molecule drugs (**2m**-**2s**) were treated with acylsilane **1a** under standard conditions to furnish the amide modified drugs **4m**-**4s** in 93-98% yield. All these reactions were completed within an hour with complete functional group tolerance, thus reinforcing the potential of this ligation in the late-stage modification of complex molecules. Various heterocyclic scaffolds present in the drugs were also well-tolerated. Next, a dipeptide-based angiotensin-converting enzyme (ACE) inhibitor, captopril, functionalized to hydroxylamine, underwent the ligation with acylsilane **1a** smoothly to afford the amide product **4t** in 93% yield and leaving the free thiol group intact. Further, a tripeptide **2u** bearing a free carboxylic acid group underwent the ligation efficiently with acylsilane **1a**. Other reactive groups, including the free –NH of the indole moiety in tryptophan and the phenolic –OH in the tyrosine unit, were completely unaffected under the ASHA ligation conditions. The desired modified peptide **4u** was obtained in 83% yield. Finally, hydroxylamines tethered to other biologically active compounds (**2v**-**2x**), including estrone, gibberellic acid and biotin, all underwent the ligation effectively with acylsilane **1a** to afford the respective amides (**4v**-**4x**) in excellent yield of 86-98%. The above substrates showcase the promising aspects of ASHA ligation in terms of orthogonal reactivity, chemoselectivity, aqueous compatibility, fast kinetics, mostly near-perfect yields and the capability to modify complex molecules in a late-stage fashion under mild conditions. As such, this new ligation holds the potential to open up new applications. HPLC monitoring of the ligation between acylsilane **1f** and indomethacin derived hydroxylamine **2r** and is shown in figure 2 for different time intervals. The reaction was completed cleanly within 40 min.

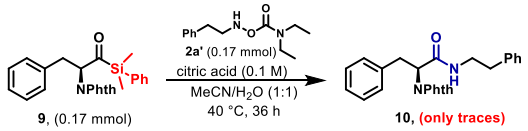
Further, the antigout drug, probenecid-derived hydroxylamine **2o**, underwent the ligation with acylsilane **1e** in 1-mmol scale to furnish the desired amide **6** in 91% yield in 5 h, thus demonstrating the amenability of the reaction for scale-up operations (Scheme 3).



Scheme 3. Evaluation of a scale-up reaction

Next, we investigated the ligation (0.2 mmol scale) between acylsilane **1d** and hydroxylamine **2a'** at different concentrations at 25 °C (refer SI, section 12) to find out the amenability of the reaction for bioconjugation applications. At 20 mM concentration, the reaction was promising and completed in 9 hours to furnish the amide **3d** in 96% yield. On further dilution to 2 mM, we observed only traces of the product even after three days of reaction. However, on warming the reaction to 40 °C for three days, 36% of the desired product was isolated, whilst the reaction remained incomplete.

Subsequently, we subjected a *N*-Phth protected α-amino acyl(dimethylphenyl)silane,[21] **9** derived from *L*-phenylalanine to ASHA ligation with hydroxylamine, **2a'** at 40 °C for over 36 h (Scheme 4). Nevertheless, we observed only traces of the desired amide **10**. We speculate the –$SiPhMe_2$ could be too hindered to effect the ligation, coupled with the steric congestion from the *N*-phthalimide group. Practical and rapid synthetic methods to access diverse α-amino acyl(trimethyl)silanes are necessary for the further development of ASHA ligation for peptide synthesis applications



Scheme 4. Unsuccessful ASHA ligation of α-amino acylsilane **9**

When ASHA ligation was carried out in the presence of one equivalent of TEMPO, the yield was unaffected, suggesting that the reaction does not operate *via* a free radical pathway. Two general mechanistic pathways (**A** and **B**) for the amide formation can be postulated (Figure 3). In both pathways, the first step is the nucleophilic addition of the hydroxylamine nitrogen to the activated carbonyl of the acylsilane to form a tetrahedral hemiaminal intermediate **a**. In pathway **A**, intermediate **a** undergoes a Brook-type rearrangement *via* a [1,2]-silyl migration forging a new Si-O bond to form imine **b**, which can be hydrolyzed

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to the desired amide **e** *via* the imine **c**. The formation of the strong Si-O bond could be the driving force for this ligation.

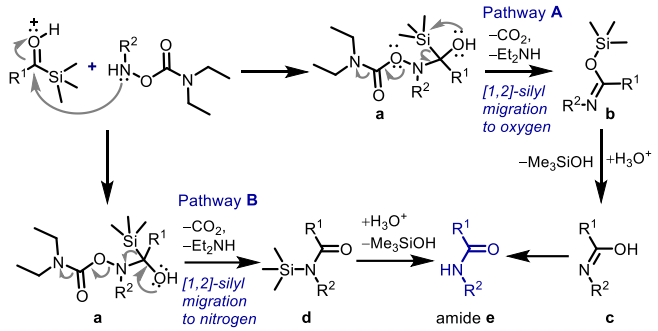

Figure 3. Proposed reaction pathways for ASHA ligation

In conclusion, we have disclosed a chemoselective amide-forming ligation between acylsilane and hydroxylamine under aqueous conditions. The key to the success of the reaction could be the potential formation of the strong Si-O bond. The reaction is high-yielding, operationally simple and can be carried out open to the air. Further, the reaction is fast and tolerates a wide range of reactive functional groups such as alkene, alkyne, aldehyde, ketone, ester, lactone, acid, nitrile, amine, aniline, azide, alcohol, phenol and thiol. The electronics of the substitutes on the starting materials had no observable influence on the ligation and should therefore be generally applicable. A suite of marketed drugs, unprotected peptides, natural products and other biologically active compounds was modified using the developed ligation in a late-stage fashion demonstrating the robustness of the reaction. Acylsilanes are established functionalities but are underappreciated in chemical biology and medicinal chemistry. This ligation could potentially revive the use of acylsilanes and lead to new applications in multiple research areas, including fragment-based drug discovery, chemical biology and materials science. Further development of this ligation and its variants (including acylgermanes) as well as detailed mechanistic studies are underway in our laboratory.

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Keywords: ligation reactions • acylsilanes • amides •chemoselectivity • aqueous reactions

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Entry for the Table of Contents

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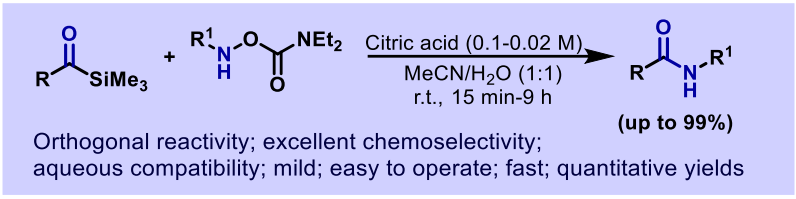

ASHA ligation: A fast, easy-to-perform, mild and high-yielding chemoselective amide-forming ligation of acylsilanes with *O*-diethylcarbamoyl-derived hydroxylamines under aqueous conditions is reported. The reaction is mediated by citric acid and tolerates a wide range of reactive functional groups as demonstrated by the late-stage modifications of a panel of drugs, peptides, natural products and biologically active molecules. We believe this ligation will revive the use of acylsilanes and be a valuable addition to the synthetic toolbox of medicinal chemists and chemical biologists for creating amide linkages between diverse chemical fragments.