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The Catalytic Mannich Reaction of 1,1-Difluoro-2-trialkyl(aryl)silyl-2-trimethylsilyloxyethenes: Preparation of β-Amino Acid Derivatives

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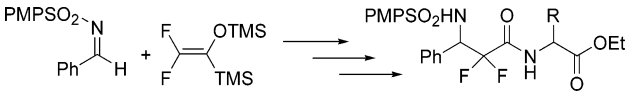

Catalytic Mannich reactions of 1,1-difluoro-2-trialkyl(aryl)-silyl-2-trimethylsilyloxyethenes (**3**) with a variety of sulfonylimines were utilized for the preparation of α,α-difluoro-β-amino acid derivatives (**7**). The influence of the Lewis acid on the reaction was examined. Methods for the conversion of α,α-difluoroacylsilanes to α,α-difluorocarboxylic acids were also explored.

β-Amino acids and derivatives, although less abundant than their α-analogues, have proven utility as building blocks for molecules with applications in pharmaceutical and material science.[1] β-Amino-α-hydroxy acids are of considerable importance as crucial functional groups in taxol[2] and bestatin.[3] β-Peptides, comprised of β-amino acids, have found utility in the investigation of the structure and stabilization of proteins. On substitution of α-amino acids, β-amino acids only very modestly perturb the backbone steric demands yet still form amide bonds capable of participating in intramolecular hydrogen bonds.[4] This utility has led to significant efforts toward the synthesis of β-amino acids.[5]

Selective introduction of fluorine is a well-established strategy for the modulation of the pharmacological properties of biologically active molecules.[6] For example, peptidomimetics in which the scissile amide bond in peptides is replaced by a *gem*-difluoroketone group often exhibit improved activities relative to nonfluorinated compounds. Fluorination at the α-position can promote formation of stable hydrates and hemiacetals, which as

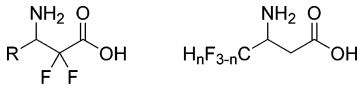

FIGURE 1. Two strategies for the formation of fluorinated β-amino acids.

tetrahedral transition state mimics may competitively inhibit serine proteases such as elastase.[7]

In general, two strategically different approaches to the incorporation of fluorine in β-amino acids have been employed, either the α-carbon can be fluorinated (**1**) or β-fluoroalkyl groups can be introduced (**2**) (Figure 1).

The combination of fluorinated β-amino acid moieties with naturally occurring pharmacophores has led to the construction of new molecules with enhanced medicinal properties.[8]

The synthesis of β-fluoroalkyl-β-amino acids (**1**) is readily tractable via several general approaches.[9] On the other hand, reports of methods for the formation of α,α-difluoro-β-amino acids (**2**) are still limited,[10] even though α,α-difluoro-β-amino acids (**2**) are precursors of fluorinated β-lactam antibiotics.[11] Ethyl bromodifluoroacetate has been utilized in Reformatsky-type reactions with *N-tert*-butylsulfinimines,[10e−g] resin-bound imines,[10d] or oxazolidines[10c] as well as in the formation of difluoroketenesilylacetals[10a,b] that can be utilized in Lewis acid

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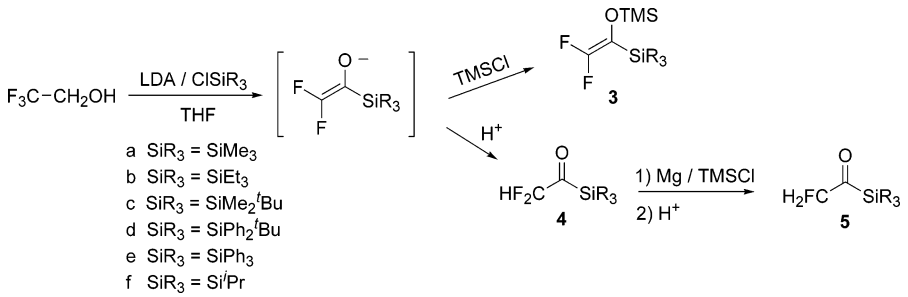
SCHEME 1. Synthesis of Fluorinated Acylsilanes (4−5) and 1,1-Difluoro-2-trialkyl(aryl)silyl-2-trimethylsilyloxyethenes (3)

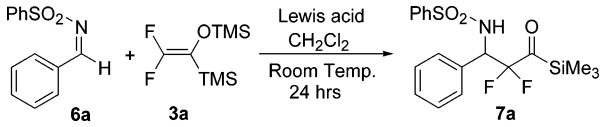


promoted aldol condensations where the aldol product can be subjected to Mitsunobu amination. New fluorinated building blocks based on relatively inexpensive and readily available trifluoroethanol have been developed and the relevant transformations of those materials into α,α-difluoro-β-amino acids are described below.

We recently reported the synthesis of novel 1,1-difluoro-2-trialkyl(aryl)silyl-2-trimethylsilyloxyethenes (**3**) and fluorinated acylsilanes (**4**, **5**) (Scheme 1).[12] Acylsilanes are versatile synthetic intermediates easy to transform to carboxylic acids under basic oxidizing conditions,[13] or to aldehydes under basic conditions[14a−c] or by catalytic reduction.[14d] 1,1-Difluoro-2-trialkyl(aryl)silyl-2-trimethylsilyloxyethenes (**3**) are synthetic equivalents of α,α-difluoroacylsilanes, and therefore synthetic precursors to α,α-difluorocarbonyl compounds such as aldehydes, carboxylic acids, and derivatives.

The Mannich reaction, a classic and attractive method for the synthesis of β-amino acid derivatives involving convergent assembly of two units of similar complexity by carbon−carbon bond formation,[15] can be effected under asymmetric and catalytic protocols as well.[16] In our initial experiments, the condensation of 1,1-difluoro-2-trialkyl-(aryl)silyl-2-trimethylsilyloxyethenes (**3**) and *N*-benzylidineaniline was investigated employing an assortment of Lewis acids and reaction conditions. In contrast to reactions with aldehydes,[17] recovery of **3** without the formation of adduct was observed in every case, while the reaction of **3** with a variety of aldehydes had been shown previously to form aldol adducts in good to moderate yields. It was apparent that the simple aldimines did not possess sufficient reactivity and required activation to react with **3**. This is in contrast to the reported observations that silyl difluoro enamines react well with imines.[18]

TABLE 1. Influence of Lewis Acid



entry	Lewis acid	stoichiometry	yield of **7a**[a] (%)
1	$TiCl_4$	125 mol %	41
2	$BF_3{\cdot}OEt_2$	125 mol %	44
3	$Yb(OTf)_3$	125 mol %	69
4	$Yb(OTf)_3$	10 mol %	66
5	$Sc(OTf)_3$	125 mol %	79
6	$Sc(OTf)_3$	10 mol %	91
7	$Y(OTf)_3$	125 mol %	88
8	$Y(OTf)_3$	10 mol %	87
9	TES-OTf	125 mol %	82
10	TMS-OTf	125 mol %	85
11	TMS-OTf	10 mol %	76
12	Triflic acid	10 mol %	72
13	$Cu(OTf)_2$	10 mol %	72
14	$La(OTf)_3$	125 mol %	0
15	ZnI_2	125 mol %	0
16	$SnCl_2$	125 mol %	0
17	FeI_2	125 mol %	0
18	SmI_2	125 mol %	0

[a] isolated yield; characterized by ^1H, ^{13}C, ^{19}F, and elemental analysis.

Easy to prepare and proven effective, various aromatic and aliphatic *N*-sulfonylaldimines were synthesized by known methods.[19] It is worth noting that aliphatic aldehyde-derived *p*-toluenesulfonylimines were formed in high yields, as solids more easily manipulated and convenient to handle than the corresponding benzenesulfonylimines.

Reaction of *N*-benzylidinebenzenesulfonamide (**6a**, 1 equiv) and 1,1-difluoro-2-trimethylsilyl-2-trimethyloxyethene (**3a**, 1.25 equiv) with $TiCl_4$ (1.25 equiv) in CH_2Cl_2 at room temperature resulted in the formation of adduct in 41% yield. A series of Lewis acids were scrutinized to optimize reaction conditions (Table 1). Reactions with strong Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ (entries 1 and 2) gave the sulfonylamine adduct in low yields. Apparently adventitious hydrolysis of the reactant **6a** to an aldehyde subsequently led to aldol condensation. This competing process was suppressed by employing mild Lewis acids.

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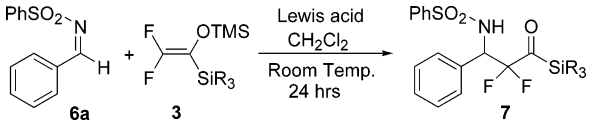
TABLE 2. Influence of Trialkylsilyl Substituents



entry	SiR_3	Lewis acid	stoichiometry	yield of **7**[a] (%)
1	$SiEt_3$	$Sc(OTf)_3$	10 mol %	**7b**: 77
2		TMSOTf	10 mol %	**7b**: 85
3	$SiMe_2{}^tBu$	$Sc(OTf)_3$	10 mol %	**7c:** 80
4		TMSOTf	10 mol %	**7c**: 74
5	$SiPh_2{}^tBu$	$Sc(OTf)_3$	10 mol %	**7d**: 82
6		TMSOTf	10 mol %	**7d**: 84
7	$SiPh_3$	$Sc(OTf)_3$	10 mol %	**7e**: 86
8		TMSOTf	10 mol %	**7e**: 88
9	Si^iPr_3	$Sc(OTf)_3$	10 mol %	**7f**: 0
10		TMSOTf	10 mol %	**7f**: 29
11		$Sc(OTf)_3$	125 mol %	**7f**: 62
12		TMSOTf	125 mol %	**7f**: 68

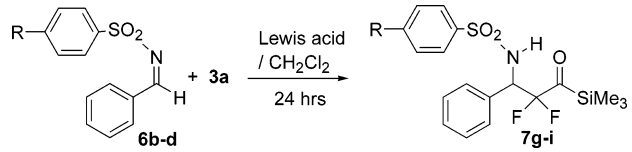
[a] Isolated yield; characterized by ^1H, ^{13}C, ^{19}F, and elemental analysis.

Rare earth triflates and lanthanide triflates have unique properties in comparison with typical Lewis acids.[20] Not only mildly acidic but also stable in aqueous media, rare earth and lanthanide triflates can be employed in catalytic quantities in some cases. $Yb(OTf)_3$, $Sc(OTf)_3$, and $Y(OTf)_3$ mediated reactions in stoichiometric (entry 3, 5, and 7) or catalytic quantities (entry 4, 6, and 8) yielded the desired condensation product without the formation of aldol product. Intriguingly, reaction in the presence of catalytic quantities of triflic acid gave **7a** in good yield (entry 12). Ikeda et al.[21] have postulated that trimethylsilyl triflate, formed by reaction of **3a** with triflic acid, could initiate a catalytic reaction. Trialkylsilyl triflates (entry 9−11) did promote reaction in either catalytic or stoichiometric amounts in good yields. $Cu(OTf)_2$ was also scrutinized in consideration of the potential applicability to asymmetric reactions in the presence of chiral auxiliaries.[22] Other Lewis acids such as $La(OTf)_3$, ZnI_2, $SnCl_2$, FeI_2, and SmI_2 resulted in recovery or decomposition of **3a** without formation of **7a**.

The influence of trialkyl(aryl)silyl substituents on the reactivity and selectivity of **3** was investigated under optimized conditions employing either $Sc(OTf)_3$ or trimethylsilyl triflate (TMS-OTf). As summarized in Table 2, the steric influence of the substituents is particularly noteworthy in the case of the triisopropylsilyl group (entries 9−12). Even with longer reaction times of more than a day, reactions were incomplete with no formation of **7f** or of the aldol product (entry 9) but rather only low yields of **7f** (entry 10). However, with greater than stoichiometric quantities of Lewis acid (125 mol %) **7f** was isolated in moderate yields.

The aryl substituents also modulated the reactivity of the sulfonylimines. Sulfonylimines bearing a 4-methoxy (**6b**) or 4-methyl substituent (**6c**) reacted to form the desired adducts (**7g** and **7h**, respectively) with complete conversion of the sulfonylimines under the optimized conditions. However, reaction of phenylmethylidene-4-nitrobenzenesulfonamide (**6d**) under the same conditions resulted in the formation of only limited quantities of **7i** with a large portion of unreacted **6d** remaining even with extended reaction times (1 week). The best results with **6d** were obtained in reactions with 2 equiv of **3a** and an excess of $Cu(OTf)_2$.

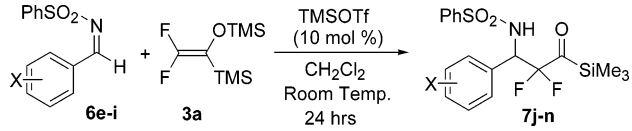
TABLE 3. Influence of Substituents on Aryl of the Sulfonyl Group



entry	R	Lewis acid	yield of **7**[a] (%)
1	OCH_3 (**6b**)	TMSOTf (10 mol %)	**7g**: 75
2	CH_3 (**6c**)	TMSOTf (10 mol %)	**7h**: 79
3	NO_2 (**6d**)	$Cu(OTf)_2$ (200 mol %)	**7i**: 85

[a] Isolated yield; characterized by ^1H, ^{13}C, ^{19}F, and elemental analysis.

TABLE 4. Influence of Substituents on Aromatic Ring



entry	X	yield of **7**[a] (%)
1	4-Cl	**7j**: 72
2	4-CH_3	**7k**: 71
3	4-NO_2	**7*l***: 51
4	4-OCH_3	**7m**: 56
5	2-CH_3	**7n**: 49

[a] Isolated yield; characterized by ^1H, ^{13}C, ^{19}F, and elemental analysis.

The generality of the reactions of **3a** was explored further with various substituted *N*-benzylidinebenzenesulfonamides (**6**). As summarized in Table 4, the desired β-amino acid precursors (**7j**−**n**) were obtained in good to moderate yields. Reaction of substrates bearing substituent at the para position (entries 1−4) resulted in better yields than reaction where there was an ortho substituent (entry 5). Presumably steric inhibition to reaction was significant. Substituents with heteroatoms, either electron donating or withdrawing, gave low yields (entries 3 and 4). The presence of the sulfonyl group led to trouble-free purification of **7** by simple recrystallization in hexane.

As mentioned above, *p*-toluenesulfonylimines derived from aliphatic aldehydes were easier to handle than benzenesulfonylimines. Reaction of **3a** with *N*-cyclohexylmethylene-4-methylbenzenesulfonamide under the conditions previously optimized for reactions of *N*-benzylidinebenzenesulfonamides formed **7o** in low yield due to the higher reactivity of *N*-alkylidine-4-methylbenzenesulfonamide than the *N*-benzylidinebenzenesulfonamide. Better results were obtained on lowering the reaction temperature from −78 °C, whereupon the β-amino acid derivatives (**7o**−**r**) were formed in moderate yields (Table 5).

As mentioned earlier, α,α-difluoroacylsilanes are synthetic precursors of α,α-difluorocarbonyl compounds such

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SCHEME 2

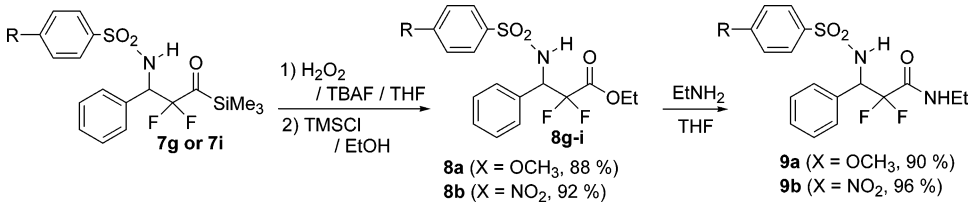
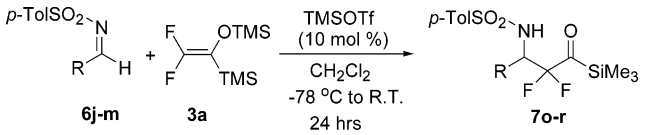


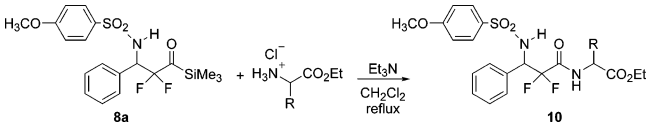
TABLE 5.



entry	R	yield of **7**[a] (%)
1	cyclohexyl	**7o**: 63
2	isopropyl	**7p**: 49
3	isobutyl	**7q**: 51
4	butyl	**7r**: 54

[a] Isolated yield; characterized by ^1H, ^{13}C, ^{19}F, and elemental analysis.

TABLE 6.



entry	R	yield of **10**[a] (%)
1	H	**10a**: 73
2	CH_3	**10b**: 72

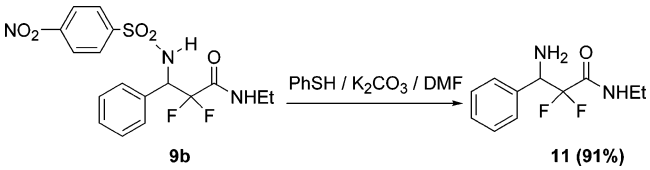
[a] Isolated yield; characterized by ^1H, ^{13}C, ^{19}F, and elemental analysis.

as aldehydes or carboxylic acid derivatives. Conversion of the acylsilane to the ester (**8**) was achieved in good yields by treatment of **7** with tetrabutylammonium fluoride (TBAF) in the presence of hydrogen peroxide (H_2O_2), followed by esterification of the intermediate acid with ethanol under reflux in the presence of chlorotrimethylsilane (TMSCl). Reaction of **8** with ethylamine resulted in the formation of amide (**9**) in good yields (Scheme 2).

Successful conversion of ester (**8**) to amide group (**9**) by simple treatment with ethylamine prompted us to investigate the direct coupling reaction with a *C*-protected amino acid for the formation of dipeptide. Peptide-coupling reaction of **8a** with glycine ethyl ester hydrochloride in the presence of triethylamine in dichloromethane under reflux for 1 day gave dipeptide **10a** in good yield (Table 6, entry 1). However, reaction with L-alanine ethyl ester hydrochloride proceeded more slowly. Longer reaction times were needed to obtain dipeptide (**10b**) in 72% conversion as a mixture of diastereomers (46:54) (Table 6, entry 2).

Excision of the arylsulfonyl group of **9** is required to reveal the β-amino group. Reductive cleavage of sulfonamide with SmI_2 was not suitable for formation of **9** as reaction at the reactive α,α-difluorinated carbonyl led predominately to defluorination under those reaction conditions. However, deprotection in high yield was possible by the reaction of **9b** with thiophenol in the presence of K_2CO_3 to give **11** without defluorination (Scheme 3).[23]

SCHEME 3



In conclusion, we have described a new pathway to α,α-difluoro-β-amino acid derivatives where condensation of **3** with various sulfonylimines (**4**) gave **7** in good to moderate yields. Conversion of the acylsilane moiety of **7** resulted in the formation of β-amino acid ester **8**. Consequent reaction of resultant **8** with either amine or amino acid formed amide (**9**) or dipeptides (**10**). Deprotection of **9b** gave **11** without defluorination. The synthetic applications to obtain chiral **7** and peptide containing α,α-difluoro-β-amino acid moiety are still under investigation.

Experimental Section

General Procedure for the Formation of 7.[24] To a mixture of sulfonylimine (**6,** 0.8 mmol) and trimethylsilyl trifluoromethanesulfonate (18 mg, 0.08 mmol) in 3 mL of dichloromethane was added a solution of **3** (1 mmol) in 2 mL of dichloromethane at 0 °C. The resulting mixture was stirred at room temperature for 24 h, quenched with 10 mL of saturated sodium bicarbonate solution, and then extracted with dichloromethane (2 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. Recrystallization in hexane provided compound **7** as solid.

***N*-(2,2-Difluoro-3-oxo-1-phenyl-3-trimethylsilylpropyl)-benzenesulfonamide (7a)**. White solid: mp 114−115 °C; ^1H NMR ($CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.0 Hz, 1H), 7.27 (t, J = 7.8 Hz, 2H), 7.16−7.05 (m, 5H), 6.00 (d, J = 9.6 Hz, 1H), 4.95 (td, J = 13.1, 9.6 Hz, 1H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 236.3 (t, $^2J_{C-F}$ = 35.9 Hz), 140.1, 132.5, 132.4, 128.7, 128.6, 128.5, 127.0, 115.3 (t, $^1J_{C-F}$ = 259.0 Hz), 57.9 (t, $^2J_{C-F}$ = 24.7 Hz), −3.6; ^{19}F NMR ($CDCl_3$) δ −111.2 (dd, J = 276.2, 12.2 Hz, 1F), −112.8 (dd, J = 276.2, 13.7 Hz, 1F). Anal. Calcd for $C_{18}H_{21}F_2NO_3SSi$: C, 53.39; H, 5.32. Found: C, 54.51; H, 5.49.

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Supporting Information Available: Experimental procedure for the synthesis of compounds **3**, **7**, **8**, **9**, **10**, and **11** as well as characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Full experimental details and compound characterization appear in the Supporting Information.