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A Highly Efficient Gold(I)-Catalyzed Mukaiyama–Mannich Reaction of α-Amino Sulfones with Fluorinated Silyl Enol Ethers To Give β-Amino α-Fluorinated Ketones

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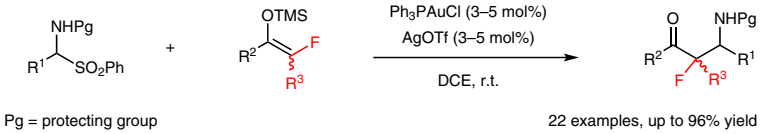

Pg = protecting group

22 examples, up to 96% yield

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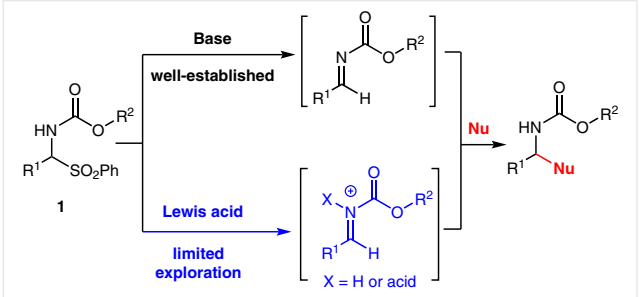
Abstract $Ph_3PAuOTf$ was identified as a powerful catalyst for the Mukaiyama–Mannich reaction of fluorinated silyl enol ethers with α-amino sulfones. This provides ready access to β-amino α-fluorinated ketones in good to excellent yields.

Key words Mukaiyama–Mannich reaction, fluorinated silyl enol ethers, amino sulfones, amino fluorinated ketones, gold catalysis

The Mannich-type reaction is a powerful C–C bond-forming reaction for the synthesis of β-amino carbonyl compounds of high synthetic value.[1] However, because imine substrates are often unstable and prone to decompose during the purification process or prolonged storage, the use of imines generated *in situ* for reaction development is highly desirable. In this context, α-amino sulfones have emerged as a class of stable precursors that can be readily prepared by a three-component reaction of an aldehyde, a carbamate, and a sulfinate.[2] They can be converted into imines by treatment with a stoichiometric amount of base[3] or into the corresponding reactive *N*-(alkoxycarbonyl)iminium species in the presence of an acid (Scheme 1).[4] In particular, it is possible to use catalytic amounts of Lewis acids for reaction development.

When it comes to Lewis acid catalyzed Mukaiyama–Mannich reactions using α-amino sulfones **1**, known methods are largely based on the use of a stoichiometric amount or a large excess of a Lewis acid such as $TiCl_4$ or $SnCl_4$.[5] The



Scheme 1 Synthetic approaches to the conversion of α-amino sulfones

use of a catalytic amount of Lewis acid for reaction development is very attractive in terms of both cost and atom utilization. However, only two examples are known. The Ollevier[4a] and List[4i] groups independently reported that catalytic amounts of $Bi(OTf)_3$ or disulfonimide, respectively, catalyze Mukaiyama–Mannich reactions of the imine precursor **1**. On the other hand, while fluorinated silyl enol ethers are useful synthons for selective fluoroalkylation[6] and Shi and Akiyama have developed the Mannich reaction of difluoroenoxysilanes to aldehyde-derived hydrazone and *N*-Boc imines,[6e–g] respectively, the corresponding reaction using readily available stable *N*-amino sulfones **1** is unprecedented. Because the selective introduction of a fluoroalkyl group is often effective in modulating the properties of organic bioactive compounds,[7] β-amino α-fluorinated carbonyl derivatives are valuable for the synthesis of difluorinated analogues of bioactive molecules to secure enhanced

properties.[8] For example, difluorinated docetaxel[8a] and rhodopeptin[8b] (Figure 1) both exhibit enhanced physical and biological properties. Therefore, it is important to develop Mannich reaction of α-amino sulfones **1** with fluorinated silyl enol ethers.

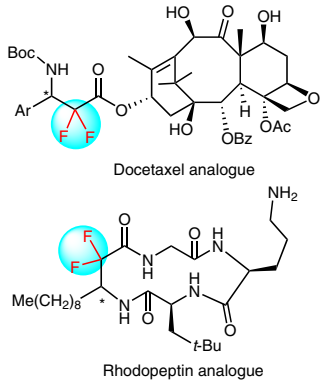
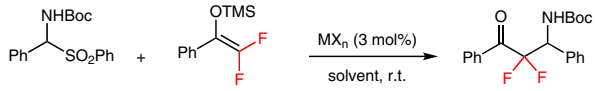


Figure 1 Selected bioactive compounds

Recently, we carried out a program to explore the potential of fluorinated silyl enol ethers in fluoroalkylation,[9] because both monofluorinated and *gem*-difluorinated silyl enol ethers can be easily prepared.[10] The necessity of using such fluorinated enolate equivalents is justified by the fact that the corresponding α-fluorinated ketones are not readily activated by deprotonation under mild conditions.[9a,b] In the past few years, we have successfully developed aldol,[9a–e] Mannich,[9f–g] and Michael reactions[9h] and olefinations[9j] by using fluorinated silyl enol ethers. Recently, we found that Au(I) efficiently catalyzes the Mannich reaction of difluoroenoxysilanes with activated ketimines,[9f] so we hoped to extend Au(I) catalysis[11] to the reaction of α-amino sulfones **1** with fluorinated silyl enol ethers, because the use of Au(I) to generate acyliminium intermediates *in situ* from amino sulfones is unprecedented.[12]

Inspired by the work of Ollevier,[4a] we first examined the use of $Ph_3PAuOTf$ in the reaction of *tert*-butyl [phenyl(phenylsulfonyl)methyl]carbamate (**1a**) and the difluoroenoxysilane **2a** in CH_2Cl_2, and we found the reaction was complete within six hours, giving adduct **3a** in 79% yield (Table 1, entry 1). Encouraged by this result, we examined the effect of the solvent. Good yields for **3a** were also obtained when toluene or 1,2-dichloroethane (DCE) was used as the solvent (entries 2 and 3). When the reaction was carried out in solvents of stronger coordinating ability, such as Et_2O, ethyl acetate, or MeCN, poor results were obtained (43, 41, and 58% yield, respectively). DCE proved to be the solvent of choice in terms of the reaction time and yield of **3a** (entry 3). Previously, we found that $Ph_3PAuOTf$ was most active among a range of metal triflates in the Mukaiyama–Mannich reaction of difluoroenoxysilanes **2** with activated ketimines.[9f] Accordingly, we compared the performance of Au(I) with some other metal triflates in this reaction. $Bi(OTf)_3$, which Ollevier et al. used for the reaction of α-amino sulfones **1** with nonfluorinated silyl enol ethers,[4a] mediated the reaction well to give **3a** in 79% yield, but increasing its loading to 10 mol% led to a lower yield (entry 4). $Al(OTf)_3$, $Fe(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, and $Yb(OTf)_3$ were also examined, but all gave **3a** in inferior yields regardless of whether the catalyst loading was 3.0 or 10.0 mol% (entries 5–9). An increased loading of some Lewis acids might have led to diminished yields of **3a** due to hydrolysis of the difluoroenoxysilane **2a**. These results indicated it would be worthwhile exploring the potential of Au(I) as a σ-Lewis acid in organic synthesis,[12] a field still full of synthetic opportunity. The effectiveness of cationic Au(I) was also confirmed by some control experiments. First, only a trace amount of **3a** was detected after four hours in the presence of Ph_3PAuCl (entry 11). Secondly, HOTf alone promoted the reaction, albeit in a lower 65% yield (entry 12). Thirdly, $Hg(OTf)_2$,[13] in which Hg(II) is isoelectronic with Au(I), mediated the present reaction to give **3a** in 81% yield (entry 13). These results suggested that Au(I) might play a role in facilitating this reaction.

Table 1 Reaction Optimization for the Reaction of α-Amino Sulfone **1a** with Difluoroenoxysilane **2a**



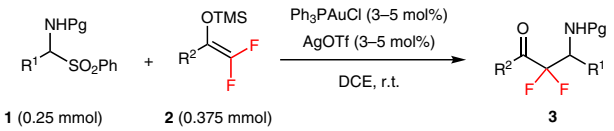
1a (0.25 mmol) **2a** (0.375 mmol) **3a**

Entry	MX_n	Solvent	Time (h)	Yield[a] (%)
1	$Ph_3PAuOTf$	CH_2Cl_2	6	79
2	$Ph_3PAuOTf$	toluene	4	79
3	$Ph_3PAuOTf$	DCE	4	89
4	$Bi(OTf)_3$	DCE	4	79 (71)[b]
5	$Al(OTf)_3$	DCE	4	75 (79)[b]
6	$Fe(OTf)_3$	DCE	4	78 (76)[b]
7	$Zn(OTf)_2$	DCE	4	67 (82)[b]
8	$Cu(OTf)_2$	DCE	4	68 (78)[b]
9	$Yb(OTf)_3$	DCE	4	77 (72)[b]
10	AgOTf	DCE	4	42
11	Ph_3PAuCl	DCE	4	trace
12	HOTf	DCE	4	65
13	$Hg(OTf)_2$	DCE	4	81

[a] Isolated yield.
[b] The results in parentheses were obtained with 10 mol% catalyst.

Because Au(I) was identified as the most efficient catalyst, and Au(I)-catalyzed Mukaiyama–Mannich reactions are relatively unexplored,[9f,14] we examined the substrate scope of our protocol by running the reaction in DCE at room temperature in the presence of 3–5 mol% of $Ph_3PAuOTf$, as shown in Table 2.

Table 2 Substrate Scope for Difluoroenoxysilanes **2**[a]



1 (0.25 mmol) **2** (0.375 mmol) **3**

Pg = protecting group

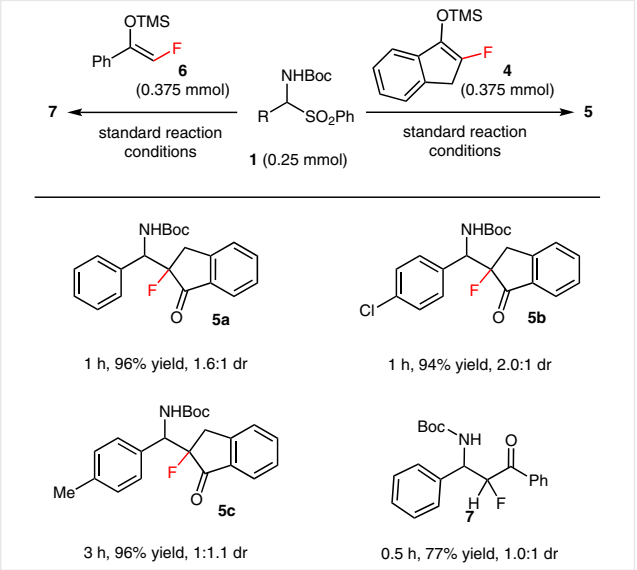
Entry	Amino sulfone	R^1	Pg	Enoxysilane	R^2	Time (h)	Product	Yield[a] (%)
1	**1a**	Ph	Boc	**2a**	Ph	4	**3a**	89
2[b]	**1b**	4-FC_6H_4	Boc	**2a**	Ph	1	**3b**	81
3[b]	**1c**	4-BrC_6H_4	Boc	**2a**	Ph	7	**3c**	68
4	**1d**	4-ClC_6H_4	Boc	**2a**	Ph	3	**3d**	74
5[b]	**1e**	3-ClC_6H_4	Boc	**2a**	Ph	6	**3e**	64
6[b]	**1f**	2-ClC_6H_4	Boc	**2a**	Ph	5	**3f**	69
7	**1g**	4-Tol	Boc	**2a**	Ph	12	**3g**	79
8[b]	**1h**	4-$MeOC_6H_4$	Boc	**2a**	Ph	22	**3h**	74
9[b]	**1i**	2-thienyl	Boc	**2a**	Ph	24	**3i**	66
10[b]	**1j**	2-furyl	Boc	**2a**	Ph	24	**3j**	63
11[b]	**1k**	*n*-Pr	Boc	**2a**	Ph	9	**3k**	42
12[b]	**1l**	*i*-Bu	Boc	**2a**	Ph	9	**3l**	36
13[b]	**1m**	Ph	Cbz	**2a**	Ph	28	**3m**	61
14	**1a**	Ph	Boc	**2b**	4-ClC_6H_4	9	**3n**	78
15	**1a**	Ph	Boc	**2c**	4-$MeOC_6H_4$	8	**3o**	86
16	**1a**	Ph	Boc	**2d**	CH_2Bn	5 (0.5)[c]	**3p**	50 (61)[c]
17	**1d**	4-ClC_6H_4	Boc	**2d**	CH_2Bn	5	**3q**	35
18	**1g**	4-Tol	Boc	**2d**	CH_2Bn	7	**3r**	47

[a] Isolated yield.
[b] 5 mol% of Au was used.
[c] With 10 mol% catalyst.

α-Amino sulfones **1b–h** with electron-donating or electron-withdrawing groups on the phenyl ring all reacted smoothly with difluoroenoxysilane **2a** to provide the desired adducts **3b–h** in good yields (Table 2, entries 2–8). Notably, electron-withdrawing groups obviously accelerated the reaction (entries 2–6 versus entries 7 and 8). Hetaryl-substituted sulfones **1i** and **1j** furnished the corresponding products **3i** and **3j** in moderate yields (entries 9 and 10). Aliphatic substituted α-amino sulfones were also viable substrates, as exemplified by the synthesis of adducts **3k** and **3l** from **1k** and **1l** in modest yields (entries 11 and 12). The *N*-Cbz-protected sulfone **1m** also readily reacted with **2a** to afford the corresponding product **3m** in 61% yield (entry 13). Aryl-substituted difluoroenoxysilanes **2b** and **2c** with various aromatic substituents worked well with **1a** to provide adducts **3n** and **3o** in good to high yields (entries 14 and 15). When the aliphatic difluoroenoxysilane **2d** was used, the desired products **3p–r** were obtained in modest yields (entry 16–18). The relatively lower yield obtained by the aliphatic difluoroenoxysilane might possibly be due to its hydrolysis. We also tried using 10 mol% of catalyst to mediate the reaction, which was complete within half an hour, with a slightly improved yield of 61% (entry 16).

To our delight, when monofluorinated silyl enol ethers **4** and **6** were used, this permitted a facile synthesis of the desired products **5a–c** and **7** in excellent yields, albeit in moderate dr values (Scheme 2). The much higher observed reaction rate of the monofluorinated silyl enol ethers was in accordance with our previous work on the Au(I)-catalyzed Mannich reaction of an isatin-derived *N*-Boc ketimine.[9f] The reason for this is unclear at this stage, because we found the difference in the activity between mono- and difluorinated silyl enol ethers to be dependent on the reaction conditions.[9d,f]

In conclusion, we have developed the first Mukaiyama–Mannich reaction of α-amino sulfones with fluorinated silyl enol ethers. A cationic Au(I) catalyst once again exhibited promising catalytic properties in the reaction.[15] The use of 3–5 mol% of $Ph_3PAuOTf$ can mediate the reaction well, affording β-amino α-fluorinated ketones in good to excellent



Scheme 2 Reactions of α-amino sulfones with monofluorinated silyl enol ethers

yields.[16] The resulting β-amino α-fluorinated ketones are useful synthons, and can be applied in the synthesis of β-amino α-fluorinated esters or 3,3-difluoroazetidin-2-ones by methods reported in the literature.[6g] The development of an enantioselective version of the reaction is now in progress in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588475.

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(15) Because $Bi(OTf)_3$ was slightly inferior to $Ph_3PAuOTf$ in terms of the yield of **3a** (Table 1), we also examined its performance in other solvents, such as ethyl acetate, toluene, or MeCN, but no better result was obtained (the yields of **3a** were 21, 55, and 58%, respectively). When $Bi(OTf)_3$ was used to mediate the reaction of the aliphatic aldehyde-derived sulfones **1k** and **1l**, the desired products **3k** and **3l** were obtained in 15 and 10% yield, respectively, which were much lower than those obtained by using the Au(I) catalyst.

(16) ***tert*-Butyl (2,2-Difluoro-3-oxo-1,3-diphenylpropyl)carbamate (3a); Typical Procedure**

Under N_2, a 25 mL dry Schleck tube was charged with Ph_3PAuCl (0.0075 mmol, 3.7 mg) and AgOTf (0.0075 mmol, 1.9 mg), followed by anhyd DCE (2.5 mL). The solution was stirred at r.t. for about 15 min, and then the α-amino sulfone **1a** (0.25 mmol) and the fluorinated silyl enol ether **2a** (0.375 mmol) were added sequentially. The mixture was stirred at r.t. until **1a** was fully converted (TLC), and then purified directly by flash column chromatography to give a white solid; yield: 80.4 mg (89%); mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.98 (m, 2 H), 7.65–7.60 (m, 1 H), 7.50–7.45 (m, 2 H), 7.36–7.34 (m, 5 H), 5.62–5.54 (m, 2 H), 1.40 (s, 9 H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –105.86 (d, J_{F-F} = 275.8 Hz, 1 F), –107.06 (d, J_{F-F} = 275.2 Hz, 1 F). ^{13}C NMR (100 MHz, $CDCl_3$): δ =188.88 (t, J_{C-F} = 28.5 Hz), 154.70, 134.37, 133.90, 132.34 (t, J_{C-F} = 1.9 Hz), 129.83 (t, J_{C-F} = 3.5 Hz), 128.67, 128.56, 128.36, 116.78 (t, J_{C-F} = 258.3 Hz), 80.47, 57.08 (t, J_{C-F} = 24.5 Hz), 28.14.