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Catalytic Silicon-Mediated Carbon−Carbon Bond-Forming Reactions of Unactivated Amides

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Supporting Information

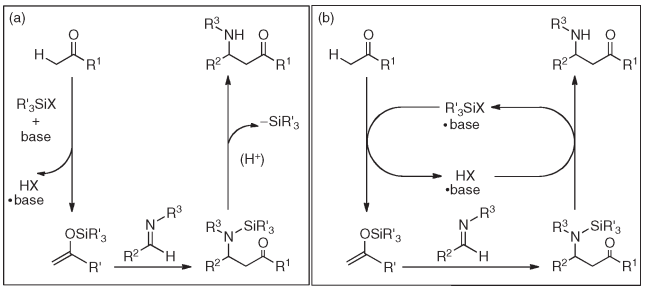
ABSTRACT: In the presence of catalytic amounts of trialkylsilyl triflate and triethylamine, unactivated amides react with imines to afford the corresponding Mannich-type adducts in high yields with high anti selectivities. While silicon enolates have been widely used in organic synthesis for four decades, this is the first example of the catalytic use of the silicon species, to the best of our knowledge. Moreover, it is noteworthy that unactivated simple amides bearing α-protons that are less acidic than those of ketones and aldehydes can be successfully used in catalytic direct-type addition reactions. Finally, a preliminary trial of an asymmetric catalytic version was conducted and showed promising enantioselectivity of the desired product.

Silicon enolates are among the most useful enolates in modern organic chemistry.[1] A variety of silicon enolates have been reported to date,[2] and they serve as convenient carbonyl equivalent donors through nucleophilic additions to aldehydes, imines, α,β-unsaturated carbonyl compounds, etc., in the presence of a substoichiometric amount of a Lewis acid catalyst (i.e., Mukaiyama-type reactions).[3] Asymmetric variants of these reactions have also been intensively studied over the past two decades,[3b,3c,3f,3i] and silicon enolates have played a vital role in the development of many useful chiral Lewis acids.

Despite their versatile utility, there are some drawbacks in silicon enolate chemistry, mainly from the viewpoint of atom economy. While most silicon enolates are isolable and storable, they are prepared from the corresponding carbonyl compounds using stoichiometric amounts of bases such as lithium diisopropylamide (LDA) or tertiary amines. Moreover, adducts of silicon enolates have Si−heteroatom bonds, which are cleaved in many cases by treatment with an acid or a fluoride anion to provide the desired products (Scheme 1a). If catalytic generation of silicon enolates could be attained, these drawbacks would be overcome. An ideal catalytic cycle including in situ generation of silicon enolates using a substoichiometric amount of a silicon Lewis acid and a base[4] is shown in Scheme 1b. However, this catalytic cycle has long been thought to be unlikely because silicon species might be incorporated into products through the formation of a covalent bond between silicon and a heteroatom of the products.

We began with an investigation of the catalytic silicon system in Mannich-type reactions, which provide potentially useful building blocks for nitrogen-containing compounds. First, we chose acetophenone as a nucleophile and treated it with an imino ester in the presence of catalytic amounts of trimethylsilyl triflate (Me_3SiOTf) and pyridine as catalysts (Table 1).

Scheme 1. (a) Conventional Mannich Reaction of Silicon Enolates (Stoichiometric) and (b) Ideal Catalytic Silicon Cycle



When a *p*-methoxyphenyl (PMP) iminoester was employed, the desired adduct was obtained in 31% yield, which was almost the same as the catalyst loading (30 mol %, entry 1). This result may indicate that the product from acetophenone and the PMP iminoester did not release the Si species and thus that catalyst turnover did not occur. A benzyloxycarbonyl (Cbz) iminoester was not productive under these conditions (entry 2), where the imine was assumed to decompose. Interestingly, a *p*-toluenesulfonyl (Ts) iminoester afforded the desired adduct in high yield (84%) in comparison with the catalyst loading (30 mol %) (entry 3). Involvement of the active silicon species is essential; pyridine or pyridinium triflate did not catalyze the desired Mannich reaction at all (entries 4 and 5). We further examined other nucleophiles, such as *S*-ethyl thioacetate, ethyl acetate, *N*-methylacetanilide, and *N*,*N*-dimethylacetamide. Unexpectedly, amides were found to be productive substrates (entries 8 and 9), although more acidic thioesters and esters were not (entries 6 and 7).[5] This is inconsistent with the general reactivity tendency of carbonyl compounds, where more acidic carbonyl compounds can provide nucleophilic species (enolates) more easily. Such a mode of catalytic activation of amides is not only mechanistically novel but also synthetically valuable.[6] Encouraged by these results, we further optimized the reaction conditions, and it was found that the imine derived from benzaldehyde also reacted with the amide using the catalyst system (entry 10) and that

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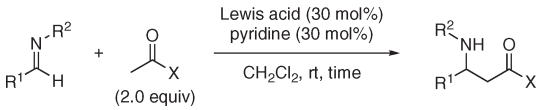
Table 1. Investigation of Catalyst Turnover and Optimization of Reaction Conditions



entry	R^1	R^2	X	Lewis acid	t (h)	yield (%)
1	CO_2Et	PMP	Ph	Me_3SiOTf	30	31
2	CO_2Et	Cbz	Ph	Me_3SiOTf	30	trace
3	CO_2Et	Ts	Ph	Me_3SiOTf	2	84
4	CO_2Et	Ts	Ph	–	48	0
5	CO_2Et	Ts	Ph	TfOH	48	0
6[a,b]	CO_2Et	Ts	SEt	Me_3SiOTf	24	0
7[a,b]	CO_2Et	Ts	OEt	Me_3SiOTf	24	0
8[a,b]	CO_2Et	Ts	NMePh	Me_3SiOTf	24	77
9[a,b]	CO_2Et	Ts	NMe_2	Me_3SiOTf	24	71
10[a,c]	Ph	Ts	NMe_2	Me_3SiOTf	24	51
11[a,d]	Ph	Ts	NMe_2	$^iPr_3SiOTf$	12	quant

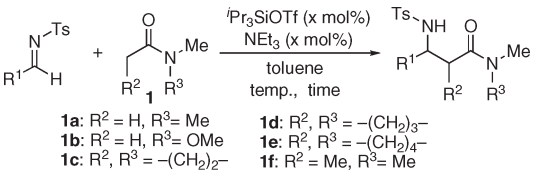
[a] NEt_3 was used instead of pyridine. [b] In THF/CH_2Cl_2. [c] Using 20 mol % Me_3SiOTf and NEt_3 without solvent. [d] Using 5 mol % $^iPr_3SiOTf$ and NEt_3 in toluene.

a bulkier silicon Lewis acid showed high catalytic activity (entry 11).

Under the optimal conditions ($^iPr_3SiOTf$, NEt_3 in toluene), the scope of imines was investigated (Table 2). The desired products were obtained in high yields using a wide range of imines, including aromatic, α,β-unsaturated, and aliphatic imines (entries 1−12).[7] It should be noted that simple amides as well as a Weinreb amide reacted smoothly (entry 3). Addition of α-alkyl-substituted amides led to the construction of two stereogenic centers, which constitute the basic structures of a variety of biologically active compounds. When *N*-methylpyrrolidinone (NMP) was employed as a nucleophile, the imine derived from benzaldehyde did not react at all, even at 60 °C (entry 14); however, the imino ester reacted quantitatively (entry 13). These results indicate that (1) formation of an active silicon species occurred even when NMP is employed as a nucleophile and (2) it is presumably because of poor electrophilicity that the imine derived from benzaldehyde did not afford the desired adduct. A series of Lewis acids were then screened as cocatalysts to activate the imines, and finally it was found that CuOTf emerged as the most active cocatalyst in Mannich-type reactions (entry 15).[8] After optimization of the reaction conditions, 2,4,6-mesitylenesulfonyl imine (**2**) and dichloromethane proved to be the electrophile and solvent of choice, respectively, providing the Mannich-type adduct with high anti selectivity (anti/syn = 27/1) (entry 16). Other cyclic amides (**1d** and **1e**) as well as an acyclic amide (**1f**) also reacted smoothly under the reaction conditions to afford the desired products in high yields with high anti selectivities in most cases (entries 17−19).

The catalytic silicon system could be applied to other reactions. In the presence of $^iPr_3SiOTf$ (10 mol %), NEt_3 (10 mol %), and CuOTf (5 mol %), 4-aminobut-3-en-2-one (**1g**) reacted with the Ts imine derived from benzaldehyde to afford the Mannich-type adduct in high yield. The adduct was further treated with trifluoroacetic acid to give the formal

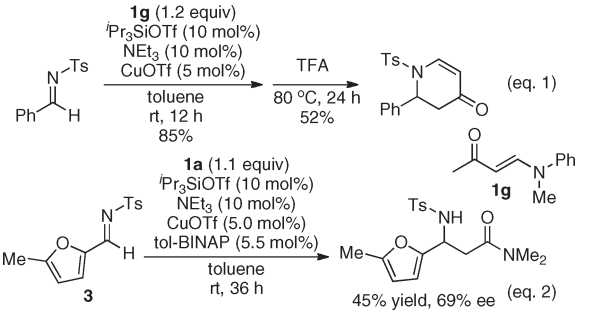
Table 2. Substrate Scope of Catalytic Direct-Type Addition of Amides to Imines



entry	R^1	amide	x	temp. (°C)	time (h)	yield (%)	anti/syn
1	Ph	**1a**	2	rt	24	quant	–
2[a]	Ph	**1a**	5	rt	12	quant	–
3	Ph	**1b**	5	rt	12	quant	–
4	$4\text{-}ClC_6H_4$	**1a**	5	rt	12	quant	–
5	$4\text{-}MeOC_6H_4$	**1a**	5	rt	12	92	–
6	$3\text{-}NO_2C_6H_4$	**1a**	5	rt	12	quant	–
7	1-Nap	**1a**	5	rt	12	98	–
8	2-Nap	**1a**	5	rt	12	quant	–
9	2-thienyl	**1a**	5	rt	12	97	–
10	(*E*)-cinnamyl	**1a**	5	rt	12	81	–
11	^{t}Bu	**1a**	5	rt	12	quant	–
12	cyclopropyl	**1a**	5	rt	12	quant	–
13	CO_2Et	**1c**	10	rt	16	quant	1.5/1
14	Ph	**1c**	10	60	16	0	–
15[b]	Ph	**1c**	10	rt	16	quant	6/1
16[b,c]	Ph	**1c**	10	15	24	81	27/1
17[b,c]	Ph	**1d**	10	0	24	quant	22/1
18[b,c]	Ph	**1e**	10	15	24	30	16/1
19[b,c]	Ph	**1f**	10	0	48	74	4.2/1

[a] 2-Nitrobenzenesulfonyl was used instead of Ts. [b] CuOTf (5 mol %) was used. [c] 2,4,6-Mesitylenesulfonyl imine (**2**) was used instead of Ts in CH_2Cl_2.

aza-Diels−Alder product in moderate yield (eq 1).[9] Moreover, this new methodology could also be extended to asymmetric catalysis (eq 2). Thus, the enantioselective Mannich-type reaction of **1a** with imine **3** proceeded smoothly in the presence of $^iPr_3SiOTf$ (10 mol %), NEt_3 (10 mol %), and CuOTf·(*R*)-*p*-Tol-BINAP[10] (5 mol %) to afford the desired adduct in moderate yield with good enantiomeric excess (ee). It should be noted that in both cases, the active silicon species that were formed catalytically reacted smoothly.



We then conducted several experiments to clarify the mechanism of the catalytic silicon system. Because we hypothesized the catalytic cycle shown in Scheme 1b, we first tried

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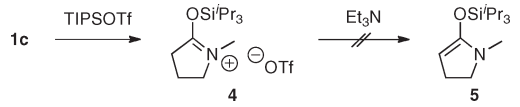
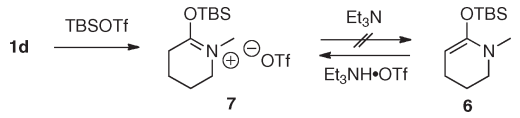
Scheme 2. Formation of Amide/R_3SiOTf Complexes (1)



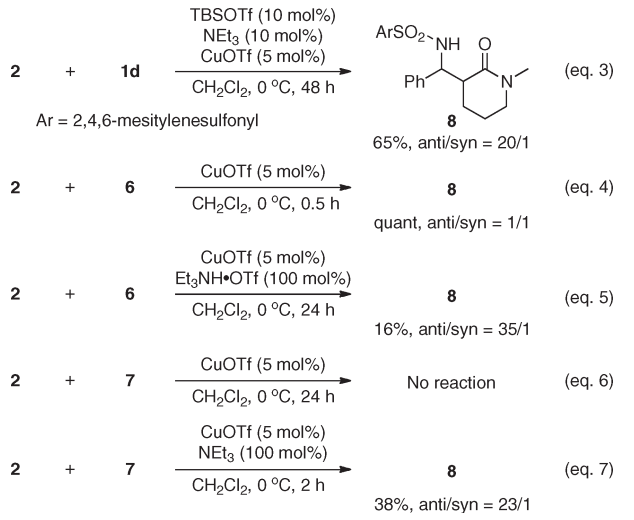
Scheme 3. Formation of Amide/R_3SiOTf Complexes (2)



to detect a silicon enolate. Amides **1a** and **1c** were treated with Me_3SiOTf and Et_3N in CH_2Cl_2 (or CD_2Cl_2) or toluene (or toluene-d_8) independently at 0 °C, room temperature, and 60 °C. However, no clear signals showing formation of silicon enolates were observed by NMR analyses. It was recently reported that amides **1a** and **1c** react with Me_3SiOTf at room temperature to form amide/Me_3SiOTf complexes.[11] We treated **1c** with $^iPr_3SiOTf$ (TIPSOTf) at room temperature and obtained **4** as a white solid. Solid **4** was then combined with Et_3N in toluene or CH_2Cl_2 at the same temperature. However, silicon enolate **5** was not detected by NMR analysis, and independent signals of **4** and Et_3N were observed (Scheme 2).

Because silicon enolates were not detected, we then endeavored to prepare silicon enolates by other methods. According to the literature on formation of silicon enolates of amides, although they can be prepared from the corresponding lithium enolates,[12] the synthesis is strongly dependent on the amide structure. Silicon enolates of amides are unstable, and a mixture of *O*-enolate and *C*-enolate is often formed. Indeed, we tried to prepare the TIPS enolate **5** from the corresponding lithium enolate but failed despite several trials. Instead, we could prepare *tert*-butyldimethylsilyl (TBS) enolate **6** from amide **1d** according to a literature method (LDA, TBSCl).[12,13] It was found that amide/TBSOTf complex **7** was formed from **1e** and TBSOTf (Scheme 3). When **7** and Et_3N were combined, no silicon enolate **6** was detected by NMR analysis, and independent signals of complex **7** and Et_3N were observed. On the other hand, when silicon enolate **6** was treated with $Et_3NH\cdot OTf$, complex **7** was formed immediately. This result shows that **6** is more basic than NEt_3.

We further conducted several control experiments. Imine **2** reacted with amide **1d** in the presence of TBSOTf (10 mol %), NEt_3 (10 mol %), and CuOTf (5 mol %) in dichloromethane at 0 °C for 48 h to afford the desired Mannich adduct **8** in 65% yield with high anti selectivity (anti/syn = 20/1) (eq 3). On the other hand, the reaction of **2** with silicon enolate **6** proceeded rapidly in the presence of CuOTf (5 mol %), and after 30 min, product **8** was obtained quantitatively but with low diastereoselectivity (anti/syn = 1/1) (eq 4). When the same reaction was conducted in the presence of $Et_3NH\cdot OTf$, the reaction proceeded gradually, and the anti product was obtained with high selectivity (eq 5). Furthermore, no reaction occurred between **2** and complex **7** in the presence of CuOTf (5 mol %) (eq 6); however, the reaction proceeded smoothly with anti selectivity when NEt_3 was added to this system (eq 7).



Through these experiments, it was shown that silicon enolates were not detected by NMR analyses and that amide/R_3SiOTf complexes such as **4** and **7** were observed as major silicon species. On the other hand, complex **7** did not react with imine **2** even in the presence of CuOTf. For carbon−carbon bond formation, deprotonation of **7** is needed, and indeed, the reaction with imine **2** proceeded in the presence of NEt_3. A possibility is that **7** and NEt_3 generated a very small amount of silicon enolate **6**, which reacted with imine **2** to afford Mannich adduct **8**. The high anti selectivity may be explained by assuming acyclic transition states, which are often observed in reactions of silicon enolates with imines.[14] When a large amount of silicon enolate exists, another reaction pathway (such as a silicon-cation-mediated reaction)[15] may be dominant (rapid reaction but low diastereoselectivity). Another possibility is that a Cu enolate may be formed from **7**, NEt_3, and CuOTf. While this possibility cannot be denied at this stage, amides **1a**−**c** reacted with imines without CuOTf, and it may be difficult to explain the experimental results that the diastereoselectivities were not dependent on metal triflates.[8]

In summary, we have developed a catalytic silicon system that enables catalytic direct-type addition of unactivated amides to imines. While silicon enolates have been widely used in organic synthesis for four decades, this is the first example of the catalytic use of the silicon species, to the best of our knowledge. In addition, this is also the first successful use of unactivated simple amides in catalytic direct-type addition reactions. Although several trials to detect silicon enolates were unsuccessful, the synthetic advantages of the present catalytic silicon system over the use of stoichiometric silicon enolates are obvious: (1) catalytic use of silicon species; (2) high diastereoselectivities; (3) silicon enolates of amides are unstable and difficult to prepare in many cases. Further investigations to clarify the more detailed mechanism as well as to apply this process to other reactions, including asymmetric catalysis, are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, product characterization, and detailed mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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