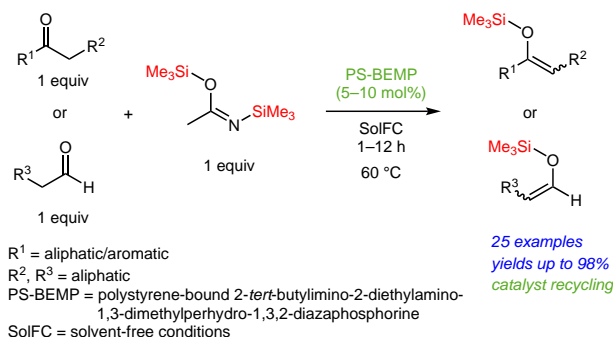C. Morozzi et al.

A Solvent-Free Reaction for Silyl Enol Ethers Synthesis

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R^1 = aliphatic/aromatic
R^2, R^3 = aliphatic
PS-BEMP = polystyrene-bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
SolFC = solvent-free conditions

25 examples
yields up to 98%
catalyst recycling

Abstract Silyl enol ethers are extremely useful nucleophilic intermediates for chemical transformations because they are synthetically versatile substrates for a wide range of C–C bond-forming reactions. Here, we present a new, mild, and solvent-free procedure for the synthesis of silyl enol ethers that employs a catalytic amount of solid-supported base and an equimolar amount of *N,O*-(bistrimethylsilyl)acetamide as a silylating agent.

Sustainable chemistry is a fast-growing area of research in which organic chemists play a critical role in finding efficient and environmentally friendly protocols for organic transformations.[1] During optimization processes for the syntheses of key molecules, great attention is devoted to avoiding the use of toxic solvents, to the use of catalytic protocols, to the development of easily scaled-up procedures, and to the minimization of waste production. Recently, our research group has successfully contributed to this field by employing polystyrene-supported catalysts and solvent-free conditions to promote a variety of organic processes.[2]

Silyl enol ethers are common reaction intermediates whose synthetic utility is already well established and whose preparations have been extensively studied and reviewed.[3] Conventional preparations of silyl enol ethers employ a silyl chloride and an equimolar amount of base to generate an anion enolate and/or to capture HCl, and they require careful attention during the workup of the reaction and the isolation of products. The use of metals and the low temperatures (–78 °C to –10 °C) required to obtain the enolates from the corresponding ketones lead to difficulties in separation of the metal.[3c,4,5] Moreover, complete selectivity to form only one stereoisomer from an unsymmetrical ketone is not always attained.[3c,4] In 2001, Smietana and Mioskowski prepared silyl enol ethers by using *N,O*-(bistrimethylsilyl)acetamide (BSA) in ionic liquids.[6,7] This method employed an excess of BSA, and the ionic liquid was not recovered. Additionally, some methods that use catalytic amounts of bases have appeared in the literature; for example, in 2002 Tanabe and co-workers reported a new method to obtain silyl enol ethers by using various silylating agents and a catalytic amount of NaH,[8] whereas in 2008, Song et al. used N-heterocyclic carbenes as catalysts and trialkylsilyl ketene acetals as silylating agents.[9] Both procedure employed unrecoverable bases and large amounts of silylating agents, and involved laborious anhydrous reaction conditions. Therefore, despite the availability of many methods, there is still room for an alternative environmentally friendly method with improved efficiency and with the possibility of recycling and reusing the catalyst.

This work is focused on a new green and easy synthesis of silyl enol ethers to provide a sustainable alternative to the procedures reported in the literature.

We recently reported how the silylating agent BSA, in the presence of a polymer-supported fluoride (Amberlyst fluoride; Amb-F) was able to act as a strong base in promoting the synthesis of a wide array of alkenyl nitriles from aldehydes and alkyl nitriles under solvent-free conditions (SolFC).[10] Inspired by this work, we initially screened the formation of silyl enol ethers under solvent-free conditions by using acetophenone (**1**) as test compound with an equimolar amount of BSA (**2**), and employing various polystyrene-supported bases as catalysts (Table 1). The reaction between acetophenone (**1**) and BSA (**2**) in the absence of a catalyst did not lead to the desired product, demonstrating the need for catalytic activation when the silylating agent is present in an equimolar amount (Table 1, entry 1). Amb-F

has been investigated for its ability to break a chemical bond between carbon or a heteroatom and silicon and to promote the formation of silyl enol ethers, but the reaction in the presence of Amb-F gave a poor yield, probably because the catalyst promoted both the silylation and desilylation processes (Table 1, entry 2). Polystyrene-bound 4-(dimethylamino)pyridine (PS-DMAP), polystyrene-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD), and polystyrene-bound 1,4-diazabicyclo[2.2.2]octane hydrochloride (PS-DABCO) as catalysts showed moderate abilities to form the product **3** (Table 1, entries 3–5). However, the yield of the silyl enol ethers was increased by using polystyrene-bound 1,8-diazabicyclo[5.4.0]undec-7-ene (PS-DBU) as a catalyst (Table 1, entry 6), but increasing the amount of catalyst from 5 mol% to 10 mol% produced a decreased product yield (Table 1, entry 7). The best result was obtained by using 10 mol% of polystyrene-bound 2–*tert*–butylimino–2–diethylamino–1,3–dimethylperhydro-1,3,2-diazaphosphorine (PS-BEMP), which gave the expected product in 78% yield (Table 1, entry 9).

Table 1 Screening of Various Supported Bases in the Formation of a Silyl Enol Ether from Acetophenone (**1**)
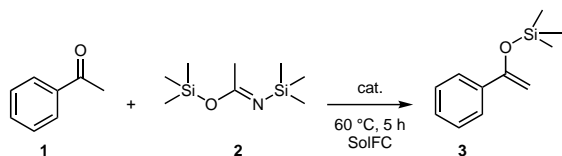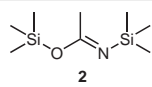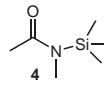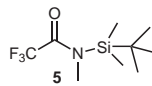
Entry	Catalyst (mol%)	Yield[a] of **3** (%)
1	–	trace
2	Amb-F (5)	26
3	PS-DMAP (5)	49
4	PS-TBD (5)	41
5	PS-DABCO (5)	57
6	PS-DBU (5)	68
7	PS-DBU (10)	52
8	PS-BEMP (5)	55
9	PS-BEMP (10)	78

[a] As determined by ^{1}H NMR analysis.

Other silylating agents were examined to verify whether BSA (**2**) was the best choice of silylating agent for the case study. The PS-BEMP-catalyzed silylation reaction of **1** to yield **3** was therefore also performed by using *N*-methyl-*N*-(trimethylsilyl)acetamide (MTSA, **4**) and *N*-[*tert*-butyl(dimethyl)silyl]-2,2,2-trifluoroacetamide (MTBSTFA, **5**), as summarized in Table 2. Reactant **4** gave a lower yield compared with **2**, and the bulkier **5** was ineffective, the unreacted ketone **1** being recovered after five hours at 60 °C.

Table 2 Comparison of the PS-BEMP-Catalyzed Silylation Reaction of **1** with Various Silylating Agents

Entry	Silylating agent	Yield (%) of **3**
1	**2**	78
2	**4**	24
3	**5**	–

[a] Determined by ^{1}H NMR analysis.

With the optimized reaction conditions in hand, namely PS-BEMP (10 mol%) at 60 °C, the scope of a range of aromatic ketones was investigated (Table 3). Depending on the starting material, the silylating process gave very good to excellent yields. For instance, ketones substituted with an electron-donating group on the aromatic moiety, such as 4-methylacetophenone (**6a**) or 3-methoxyacetophenone (**6b**), were less reactive, but nevertheless gave the desired products in good yields (Table 3, entries 1 and 2). Excellent results were obtained when the reactions were carried out with aromatic ketones **6c–e** bearing electron-withdrawing groups (Table 3, entries 3–5). Moreover, heteroaromatic ketones **6f** and **6g** were smoothly converted into the corresponding silyl enol ethers (Table 3, entries 6 and 7).

Furthermore, the indanones **6h** and **6i** smoothly gave the desired products (Table 3, entries 8 and 9). We further extended this methodology to α-substituted ketones under the optimal reaction conditions, but with the amount of catalyst reduced from 10 mol% to 5 mol%. The reaction was completely stereoselective, leading to the formation of the *Z*-stereoisomers exclusively. Silyl enol ethers were formed quantitatively when ketones **6j** and **6k** were employed as substrates (Table 3, entries 10 and 11), and an excellent yield (85%) was obtained when ketone **6l** was employed (Table 3, entry 12). The use of propiophenone (**6m**) as a starting material gave very good results in terms of both the yield (70%) and the stereoselectivity, as only the *Z*-isomer was detected (Table 3, entry 13). Also the feasibility of using the protocol on sulfone **6n** and enone **6o** was also tested, and very good results were obtained (Table 3, entries 14 and 15).

A further investigation was performed to extend the scope of the work to include aliphatic ketones and aldehydes (Table 4), which showed similar reactivities to the ketones previously discussed. In particular, cyclohexanone (**6p**) gave the corresponding silylated ketone **7p** after three hours in 84% yield (Table 4, entry 1). A very good yield of the silyl enol ether (88%) was obtained from 4-methylcyclohexanone (**6q**) after 12 hours (Table 4, entry 2). A lower

yield of the expected product (51%) was obtained with cyclohex-2-en-1-one (**6r**) (Table 4, entry 3). The more complex heteroatom-containing ketones tetrahydro-4*H*-pyran-4-one (**6s**) and 1-benzylpiperidin-4-one (**6u**) also gave good results (Table 4, entries 4 and 6). The α,β-unsaturated ketone **6t** showed moderate reactivity (Table 4, entry 5). A preliminary study on aldehydes showed that they could be successfully employed as reactants, giving very good results in short reaction times (Table 4, entries 7–9). Unfortunately the purification step for these silylated compounds proved to be more challenging than for those derived from aromatic ketones.[11] Although products **3**, and **7a–o** could be purified by extraction with water to eliminate the acetamide and then, if necessary, by a flash chromatography, the silylated products derived from aliphatic ketones or aldehydes could not isolated by following such a procedure. Instead, distillation worked well for products **7p–s**, **7v**, and **7x** with relatively low boiling points, but failed for the other products which were distilled along with monosilylated acetamides.

Table 3 Scope of the Silyl-Ether-Formation Reaction with PS-BEMP
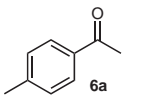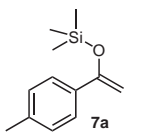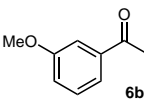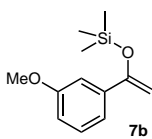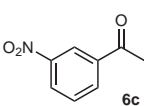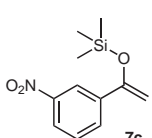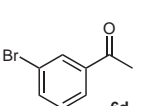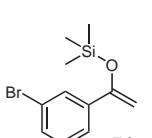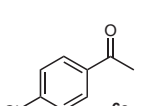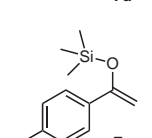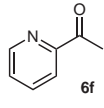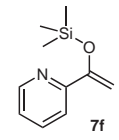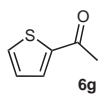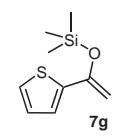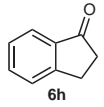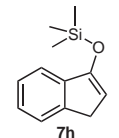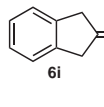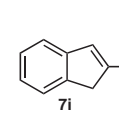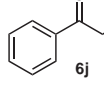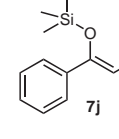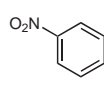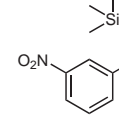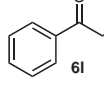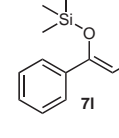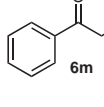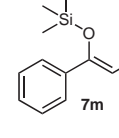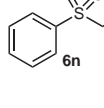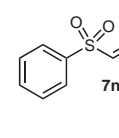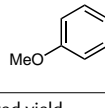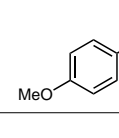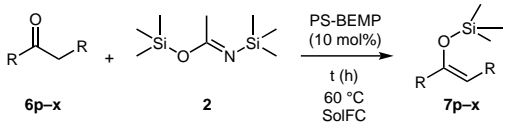
Entry	Ketone	Time (h)	Product	Yield[a] (%)
1	**6a**	7	**7a**	72
2	**6b**	5	**7b**	89
3	**6c**	1	**7c**	92
4	**6d**	5	**7d**	98
5	**6e**	5	**7e**	92
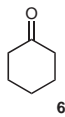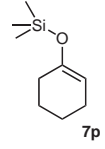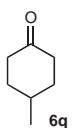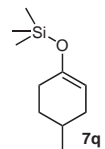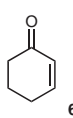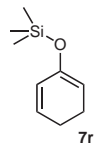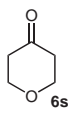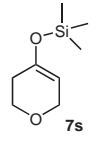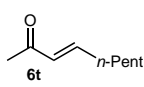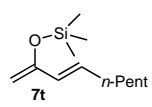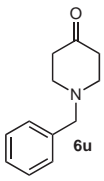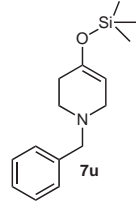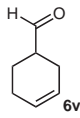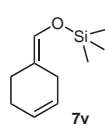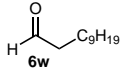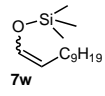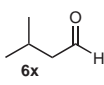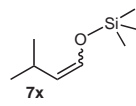
Table 3 (continued)

Entry	Ketone	Time (h)	Product	Yield[a] (%)
6	**6f**	5	**7f**	89
7	**6g**	5	**7g**	87
8	**6h**	3	**7h**	88
9	**6i**	1	**7i**	86
10[b]	**6j**	1	**7j**	98
11[b]	**6k**	2	**7k**	98
12[b]	**6l**	5	**7l**	85
13[b]	**6m**	12	**7m**	70
14	**6n**	1	**7n**	76
15	**6o**	4	**7o**	61

[a] Isolated yield.
[b] PS-BEMP (5 mol%) was used.

Table 4 Reactivity of Aliphatic Ketones and Aldehydes in Forming the Corresponding Silyl Enol Ethers

Entry	Ketone	Time (h)	Product	Yield (%)
1	6p	3	7p	81
2	6q	12	7q	85
3	6r	12	7r	48
4	6s	4	7s	77
5[a]	6t	12	7t	42
6[a]	6u	12	7u	67
7	6v	3	7v	83
8[a]	6w	2	7w	98
9	6x	3	7x	54

[a] Conversion values determined by ^{1}H NMR analysis of the crude mixture.

Finally, to verify the robustness of the protocol, we repeated the reaction of 4-chloroacetophenone (**6e**) on a gram scale by using 50 mmol of the starting material. The yield obtained (95%) was consistent with the result obtained in the reaction performed on a 1 mmol scale (entry 5). Recycling of the catalyst was also investigated in the reaction with 4-chloroacetophenone (**6e**). After three runs, the catalytic ability was not affected and the same yield was consistently obtained.

We have developed a new protocol for the synthesis of silyl enol ethers that employs a stoichiometric amount of the silylating agent and a catalytic amount of a supported base under solvent-free conditions. A wide array of ketones and aldehydes were tested as reactants and consistently gave good to excellent results. Furthermore, the catalyst could be recycled up to three times, making this procedure even more convenient from the point of view of sustainability.

Studies on the incorporation of such a procedure in a one-pot protocol in which the reactant is a silyl enol ether derivative (i.e., Mukaiyama or Mannich reactions) are in progress.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590876.

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(11) **Silyl Enol Ethers 3 and 7a–o; General Procedure**
The appropriate aromatic ketone (1.0 mmol), BSA (244 µL, 1.0 mmol), and PS-BEMP (10 mol%, 45 mg or 5 mol%, 22 mg) were added to a vial, and the mixture was stirred at 60 °C for 5 h. The catalyst was filtered off, the mixture was washed with H_2O (3 × 2 mL), and the aqueous phase was extracted with hexane (3 × 2 mL). The organic phases were combined, washed with brine (2 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to eliminate the acetamide byproduct. The crude mixture was then purified by flash chromatography [silica gel, hexane–Et_2O (99:1)] to remove any residual reagent.

{[(Z)-2-Bromo-1-(3-nitrophenyl)vinyl]oxy}(trimethyl)silane (7k)

Yellow oil; yield: 309 mg (98%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.25 (s, 9 H), 6.15 (s, 1 H), 7.52 (t, J = 8 Hz, 1 H), 7.78 (t, J = 4 Hz, 1 H), 8.16 (d, J = 12 Hz, 1 H), 8.31 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 1.18, 91.33, 120.76, 123.71, 129.96, 131.48, 138.92, 148.78, 151.65. GC/EIMS: *m/z* (%) = 315 (18) [M+], 300 (43), 139 (43), 89 (25), 73 (100), 63 (9). Anal. calcd for $C_{11}H_{14}BrNO_3Si$: C, 41.78; H, 4.46; N, 4.43. Found: C, 41.75; H, 4.60; N, 4.32.

Silyl enol ethers 7p–s, 7v, and 7x: General Procedure

The appropriate aliphatic ketone or aldehyde (1.0 mmol), BSA (244 µL, 1.0 mmol), and PS-BEMP (10 mol%, 45 mg) were added to a vial, and the mixture was stirred at 60 °C for the appropriate time. The products were purified by distillation under pressure.

(3,6-Dihydro-2H-pyran-4-yloxy)(trimethyl)silane (7s)

Colorless oil; yield: 133 mg (77%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.26 (s, 9 H), 2.18–2.22 (m, 2 H), 3.86 (t, J = 5.59 Hz, 2 H), 4.19 (q, J = 2.53, 5.23 Hz, 2 H), 4.87–4.90 (m, 1 H).