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An efficient and mild bismuth triflate-catalysed three-component Mannich-type reaction

Thierry Ollevier* and Etienne Nadeau

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In the presence of a catalytic amount of $Bi(OTf)_3 \cdot 4H_2O$, aldehydes together with amines react with silyl enolates to afford the corresponding Mannich-type adducts smoothly. A wide variety of silyl enolates derived from ketones, as well as esters and thioesters, react rapidly to afford the β-amino ketones or the β-amino esters in high yields (up to 94%).

Introduction

The development of new methods for the synthesis of β-amino carbonyl derivatives is an important area of synthetic research, because β-amino ketones and esters are extremely important as biologically active molecules.[1] The Lewis acid-mediated reactions of imines with silyl enolates are among the most efficient methods for the synthesis of β-amino carbonyl compounds. Although a wide range of catalytic methods has been developed for the synthesis of β-amino carbonyl compounds,[2] none are both broadly applicable and amenable to large-scale organic synthesis. Moreover, many imines tend to be unstable during purification by chromatography, distillation, or prolonged storage. Thus, it is desirable from a synthetic point of view that imines, formed *in situ* from aldehydes and amines, immediately react with silyl enolates and provide β-amino carbonyl compounds in a one-pot process.[3] Nevertheless, most Lewis acids can not be used in this reaction because they decompose or deactivate in the presence of the amines and water produced during imine formation. Recently, synthetic methods involving rare-earth and lanthanide triflates as catalysts for Mannich-type reactions have been reported.[4] High catalytic activity, low toxicity, moisture and air tolerance make lanthanide triflates attractive catalysts. However, the high cost of these catalysts restricts their use.

Bismuth compounds too have attracted recent attention due to their low toxicity, low cost, and stability.[5] Bismuth salts have been reported as catalysts for the opening of epoxides,[6] allylation of imines,[7] Mukaiyama-aldol reactions,[8] formation and deprotection of acetals,[9] Friedel–Crafts reactions,[10] Diels–Alder reactions,[11] Fries rearrangements,[12] Claisen rearrangements,[13] and intramolecular Sakurai cyclizations.[14] $Bi(OTf)_3$ is particularly attractive because it is commercially available or can be easily prepared from readily available starting materials.[15]

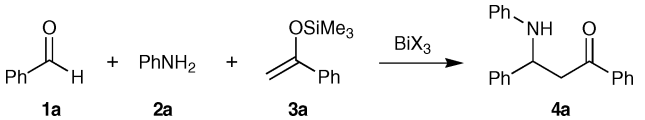
As a part of our ongoing interest in bismuth(III)-catalysed Mannich-type and aza-Sakurai reactions,[7,16] we report herein our results in the three-component bismuth(III)-catalysed Mannich-type reaction. A major merit of the three-component reaction is indeed that many unique structures can be afforded rapidly when three or more reactants are combined in a single step to afford new compounds. We wish to disclose our results in this area, namely, the development of an efficient bismuth-catalysed Mannich-type three-component reaction that combines an aldehyde, an amine, and a silyl enolate to give compounds with a β-amino carbonyl core structure. β-Amino esters and ketones are obtained efficiently in the presence of 1–2 mol% of $Bi(OTf)_3 \cdot 4H_2O$. Since the original communication of our work,[17] the scope and generality of the reaction have been broadened. A large selection of carbonyl compounds and silyl enolates have been examined, and recycling studies are also included in this study. In addition, further insights regarding the mechanism are presented.

Département de Chimie, Université Laval, Québec, G1K 7P4, Canada. E-mail: thierry.ollevier@chm.ulaval.ca; Fax: +1 418 6567916; Tel: +1 418 6565034

Results and discussion

Catalyst screening

Initial investigations of the Mannich-type reaction of silyl enolates with benzaldehyde and aniline employed a series of bismuth(III) salts (Scheme 1, Table 1). These results were promising, as the corresponding β-amino ketone could be obtained in moderate to good yield with bismuth halides except with bismuth fluoride (Table 1, entries 1–4). Bismuth nitrate smoothly afforded the expected product (Table 1, entry 5). While bismuth acetate gave no conversion, bismuth trifluoroacetate provided the product in only moderate yield (Table 1, entries 6 and 7). Phenyl bismuth ditriflate and diphenyl bismuth triflate appeared to be more efficient catalysts than all previously tested ones (Table 1, entries 8 and 9). Bismuth(III) triflate led to the expected product in a good yield and in a short reaction time without any difference between the anhydrous and the hydrated form (Table 1, entries 10 and 11).



Scheme 1 Mannich-type reaction of benzaldehyde, aniline, and (1-phenylvinyloxy)trimethylsilane catalysed by BiX_3 salts.

Solvent screening

With $Bi(OTf)_3 \cdot 4H_2O$ identified as an effective catalyst for the Mannich-type reaction, optimisation of reaction conditions using various solvents was undertaken (Scheme 1, Table 2).

Table 1 Mannich-type reaction of benzaldehyde, aniline, and (1-phenylvinyloxy)trimethylsilane using Bi(III) salts as the catalyst[a]

Entry	Catalyst	Time/h	Yield (%)[b]
1	BiF_3	24	0
2	$BiCl_3$	1.5	59
3	$BiBr_3$	0.3	72
4	BiI_3	7.5	62
5	$Bi(NO_3)_3{\cdot}5H_2O$	0.2	67
6	$Bi(OAc)_3$	23	0
7	$Bi(OCOCF_3)_3$	0.8	36
8	$Ph_2Bi(OTf)$	0.3	85[c]
9	$PhBi(OTf)_2$	0.1	89[c]
10	$Bi(OTf)_3{\cdot}4H_2O$	0.1	89[c]
11	$Bi(OTf)_3$	0.1	90[c]

[a] *Reagents and conditions*: benzaldehyde **1a** (1.0 equiv.), aniline **2a** (1.0 equiv.), (1-phenylvinyloxy)trimethylsilane **3a** (1.0 equiv.), BiX_3 (1 mol%), MeCN, 25 °C. [b] Isolated yield. [c] 1.2 equiv. of (1-phenylvinyloxy)-trimethylsilane was used.

Table 2 Mannich-type reaction of benzaldehyde, aniline, and (1-phenylvinyloxy)trimethylsilane in different solvents[a]

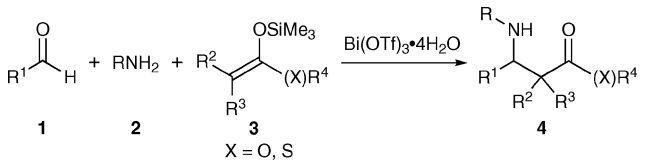
Entry	Solvent	Catalyst loading (x mol%)	Time/h	Yield (%)[b]
1	PhMe	1	3.5	54
2	Et_2O	1	2.5	72
3	CH_2Cl_2	1	1.5	60
4	$MeNO_2$	1	0.1	71
5	EtOH	1	3	80
6	MeCN	1	0.5	82[c]
7	MeCN	0.5	21	68
8	MeCN	2	0.5	84
9	MeCN	5	0.1	85

[a] *Reagents and conditions*: benzaldehyde **1a** (1.0 equiv.), aniline **2a** (1.0 equiv.), (1-phenylvinyloxy)trimethylsilane **3a** (1.0 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (x mol%), 25 °C. [b] Isolated yield. [c] On a 0.1 mol benzaldehyde scale, the yield was 85%.

Benzaldehyde, aniline and (1-phenylvinyloxy)trimethylsilane were chosen as representative substrates. Among various solvents tested, toluene, diethyl ether, dichloromethane, and nitromethane gave moderate yields of the expected product (Table 2, entries 1–4). Ethanol afforded the product in good yield (Table 2, entry 5). The best solvent was found to be acetonitrile, giving 1,3-diphenyl-3-(*N*-phenylamino)propan-1-one **4a** in 82% yield. Scaling up the reaction to 0.1 mol afforded **4a** in 85% yield (Table 2, entry 6). With further optimization of the reaction conditions, we found that a lower catalyst loading gave decreased yields (Table 2, entry 7). Increasing the catalyst loading did not significantly affect the yield (Table 2, entries 8 and 9).

Generality of the reaction

Several examples of $Bi(OTf)_3$-catalysed Mannich-type reactions with various silyl enol ethers are summarized in Table 3. Silyl enol ethers derived from aromatic ketones and from aliphatic ketones were reacted with an equimolar mixture of aldehyde **1** and aniline **2a** (Scheme 2). The corresponding β-amino ketones **4** were obtained in good yields (Table 3, entries 1–4) from aromatic-derived silyl enol ethers except for the more hindered isobutyrophenone derivative. Silyl enol ethers derived from cyclopentanone or cyclohexanone afforded the β-amino ketones in good yields (Table 3, entries 5 and 6).



Scheme 2 $Bi(OTf)_3{\cdot}4H_2O$-catalysed Mannich-type reaction involving various aldehydes, amines, and silyl enolates.

Other aldehydes were tested and, generally, moderate to excellent yields of β-amino ketone were obtained with silyl enol ethers and 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$ at 25 °C in acetonitrile. Aromatic aldehydes reacted smoothly to give the corresponding β-amino ketone derivatives **4** in high yield (Table 3, entries 7–14). The reaction worked well with a variety of aldehydes including those bearing an electron-withdrawing group, and the corresponding β-amino ketones **4** were obtained with very good yields. Several electron-rich aromatic aldehydes led to the desired products in good yields (Table 3, entries 11 and 12). 4-Acetylbenzaldehyde led to the expected product with complete chemoselectivity toward the aldehyde (Table 3, entry 13). Only a moderate yield was obtained with 1-naphthylcarboxaldehyde as the substrate (Table 3, entry 14). With a heterocyclic aldehyde (*e.g.*, furfural) the β-amino ketones were obtained in good yield (Table 3, entries 15–17). However, the reaction with 3-pyridylcarboxaldehyde gave a lower yield due to low conversion (Table 3, entry 18). A conjugated aldehyde was a good substrate as well (Table 3, entry 19). Aliphatic aldehydes did not react under such conditions (probably due to self-condensation), except cyclohexane carboxaldehyde and pivaloyl aldehyde, which afforded product **4** in good yields (Table 3, entries 20 and 21). For enolizable aliphatic aldehydes, it was possible to obtain the corresponding β-amino ketones by a slight modification of the reaction conditions. Decreasing the reaction temperature to 0 °C and adding the aldehyde as the last reagent provided moderate to good yields of the expected products (Table 3, entries 22–24). Interestingly, we never observed side reaction products such as aldol and deamination products.

Silyl ketene acetals as the nucleophilic partner

Several examples of $Bi(OTf)_3$-catalysed Mannich-type reactions with various silyl ketene acetals are summarized in Table 4 (Scheme 2). Due to rapid hydrolysis of silyl ketene acetals under our standard conditions, it was necessary to optimize the reaction parameters. It was found that using 2 mol% of catalyst in THF at −78 °C gave the best yields. Thus, silyl ketene acetals derived from various esters were reacted with an equimolar mixture of benzaldehyde and aniline. The corresponding β-amino esters **4** were obtained in good yields (Table 4). Silyl enolates derived from esters as well as thioesters reacted smoothly to give the adducts. No adducts between aldehydes and the silyl enolates were observed in any reaction according to NMR analysis of the crude reaction mixture. As for the diastereoselectivity of the reaction, good results were obtained with the following substrates. ((*E*)-1-Methoxyprop-1-enyloxy)trimethylsilane afforded the expected product with *syn* stereoselectivity (Table 4, entry 4). Moderate *syn* selectivity was observed with ((*E*)-1-alkoxy-2-phenylvinyloxy)trimethylsilane (Table 4, entries 5 and 6). The geometry of the silyl ketene

Table 3 Mannich-type reaction with silyl enol ethers derived from ketones[a]

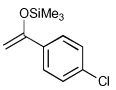
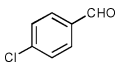
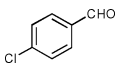
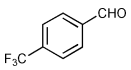
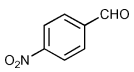
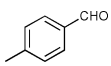
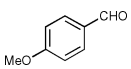
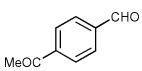
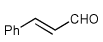
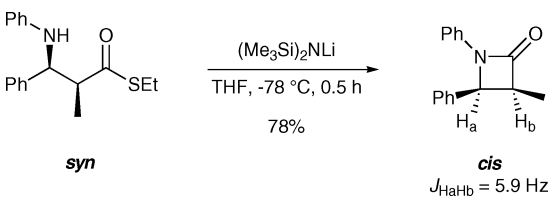
Entry	Aldehyde	Silyl enol ether	Time/h	Yield (%)[b]	*syn*/*anti*
1			0.1	89	—
2			2	94	50 : 50
3			37	45[c]	—
4			0.5	82	—
5			1.5	80	68 : 32
6			0.5	81	61 : 39
7			0.8	82	—
8			1.5	83	—[d]
9			0.5	88	—
10			0.5	87	—
11			1	81	—
12			0.7	86	—
13			0.1	92	—
14			1	44	—
15			1	76	—
16			3	80	—[e]
17			1	78	58 : 42
18			4.5	49	—
19			1.5	72	—

Table 3 (*Contd.*)

Entry	Aldehyde	Silyl enol ether	Time/h	Yield (%)[b]	*syn*/*anti*
20			0.8	77	—
21			1	54	—
22			17	61[f]	—
23			18	51[f]	—
24			3	70[f]	—[g]

[a] Reagents and conditions: aldehyde **1** (1.0 equiv.), aniline **2a** (1.0 equiv.), silyl enol ether **3** (1.0–1.2 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (1 mol%), 25 °C. [b] Isolated yield. [c] $Bi(OTf)_3{\cdot}4H_2O$ (5 mol%). [d] dr = 66 : 34. [e] dr = 61 : 39. [f] Reaction carried out at 0 °C. [g] dr = 85 : 15

acetal did not influence the diastereoisomeric ratio, as (*E*)- and (*Z*)-1-((ethylthio)prop-1-enyloxy)trimethylsilane afforded the β-aminothioester with the same *syn*/*anti* ratios (Table 4, entries 8 and 9). The relative stereochemistry was confirmed by base-cyclization to the corrersponding β-lactam and comparison of the vicinal proton–proton coupling constants with those in the literature (Scheme 3).[18]



Scheme 3 Determination of the relative stereochemistry of a β-amino thioester.

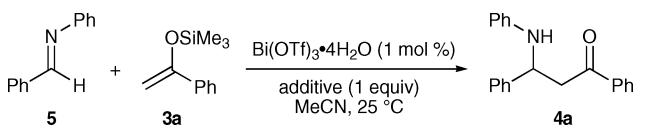
Generally, good yields of β-amino ester were obtained with aromatic aldehydes as well as an α,β-unsaturated aldehyde (Table 4, entries 12–16). Interestingly, we noted that the reaction was sterically sensitive, as *ortho* substitution led to a decreased conversion (compare entries 13 and 14). Aliphatic aldehydes also afforded the corresponding amino esters **4** in moderate to good yields. In all cases, the corresponding aldol derivative was never observed as a by-product.

Reaction scope: amine substrate

The scope of our method could be extended to other amines. Benzaldehyde was chosen in our model reaction (Scheme 2). *Ortho*- and *para*-anisidines gave good yields of the corresponding β-amino carbonyl compounds (Table 5, entries 1 and 2), which are known to be cleavable under oxidative conditions.[19] Other substituted anilines also afforded the β-amino carbonyl compounds in high yields (Table 5, entries 3–5). The reaction with *o*-anisidine or 2-aminophenol and silyl enol ether derived from propiophenone proceeded smoothly, albeit with almost no diastereoselectivity (Table 5, entries 6 and 7). Using benzyl carbamate instead of an aniline gave only a moderate yield of the Cbz-protected β-amino carbonyl compound (Table 5, entry 8). The reaction of the same silyl enol ether with benzaldehyde and α-methylbenzylamine gave no conversion (Table 5, entry 9). For the reactions with a silyl ketene acetal, yields proved to be more dependent on aniline substitution. An excellent yield was obtained with an electron-poor aniline, but lower yields were observed with electron-rich anilines (Table 5, entries 10–12). Changing *p*-anisidine for a more sterically hindered *o*-anisidine also led to a decreased yield (Table 5, compare entries 11 and 12).

Effect of additives

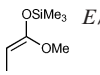
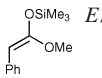
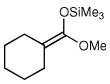
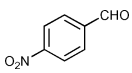
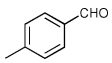
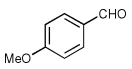
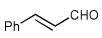
It is interesting to note that the 'two-pot' version of this reaction, *i.e.* with prior formation and isolation of the imine, always occurred in very low conversions in our hands (Scheme 4, Table 6). Knowing that the main difference between the two-pot and the one-pot strategy is the *in situ* formation of water in the latter, the addition of a variety of acidic additives was examined. When the model reaction was studied with *N*-benzilideneaniline **5**, β-aminoketone **4a** was obtained in low yield using 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$ (Table 6, entry 1). However, addition of one equivalent of water or hexafluoroisopropanol provided the expected product (Scheme 4, Table 6, entries 2 and 3) in the usual high yields obtained in the three-component system.



Scheme 4 Use of additives in the $Bi(OTf)_3{\cdot}4H_2O$-catalysed Mannich-type reaction.

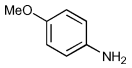
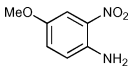
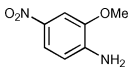
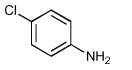
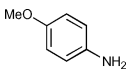
As demonstrated, an aqueous solution of $Bi(OTf)_3$ is acidic,[15a,20] so the true catalyst is apparently HOTf released from the hydrolysis of $Bi(OTf)_3{\cdot}4H_2O$. The observation that the same reaction still occurs in the presence of hindered 2,6-di-*tert*-butylpyridine (1 equiv. of PhCHO **1a**, 1 equiv. of $PhNH_2$ **2a**, 1 equiv. of (1-phenylvinyloxy)trimethylsilane **3a**, 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$, 3 mol% of 2,6-di-*tert*-butylpyridine, 25 °C, 0.3 h, 80% of **4a**)

Table 4 Mannich-type reaction with silyl ketene acetals derived from esters or thioesters[a]

Entry	Aldehyde	Silyl ketene acetal	Time/h	Yield (%)[b]	*syn*/*anti*
1			3.5	84	—
2			1.5	83	—
3			0.8	85	—
4		 $E/Z = 80:20$	2.5	80	74 : 26
5		 $E/Z = 78:22$	2.5	81	78 : 22
6		 $E/Z = 69:31$	24	60	62 : 38
7			1.7	59	—
8		 $E/Z = 5:95$	1	89	76 : 24
9		 $E/Z = 99:1$	1.8	83	78 : 22
10			1	85	—
11			1	90	—
12			2	82	—
13			1	76	—
14			3.5	34	—
15			2	70	—
16			2.5	61	—
17			1	38	—
18			1.3	89	—

[a] *Reagents and conditions*: aldehyde **1** (1.0 equiv.), aniline **2a** (1.0 equiv.), silyl ketene acetal **3** (1.2 equiv.), $Bi(OTf)_3 \cdot 4H_2O$ (2 mol%), THF, −78 °C. [b] Isolated yield.

Table 5 $Bi(OTf)_3{\cdot}4H_2O$-catalysed Mannich-type reaction with amines[a]

Entry	Amine	Silyl enolate	Time/h	Yield (%)[b]
1			2	78
2			1	79
3			0.5	88[c]
4			0.5	85[c]
5			2	78[c]
6			1	92 [d]
7			4	88[e]
8			0.8	49[c]
9			21	0
10			0.8	90
11			2	70
12			22	55

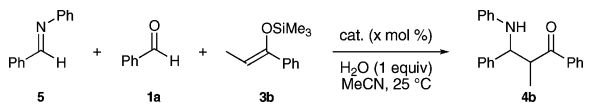
[a] *Reagents and conditions*: benzaldehyde **1a** (1.0 equiv.), amine **2** (1.0 equiv.), silyl enolate **3** (1.2 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (1 mol%), MeCN, 25 °C (entries 1–9) or $Bi(OTf)_3{\cdot}4H_2O$ (2 mol%), THF, −78 °C (entries 10–12). [b] Isolated yield. [c] Reaction at 0 °C. [d] dr = 60 : 40. [e] dr = 50 : 50.

Table 6 Mannich-type reaction of *N*-benzilideneaniline and (1-phenylvinyloxy)trimethylsilane[a]

Entry	Additive	Time/h	Yield (%)[b]
1	—	2	26
2	H_2O	0.1	84
3		0.1	74

[a] *Reagents and conditions*: benzilideneaniline **5** (1.0 equiv.), (1-phenylvinyloxy)trimethylsilane **3a** (1.0 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (1 mol%), additive (1 equiv.), MeCN, 25 °C. [b] Isolated yield.

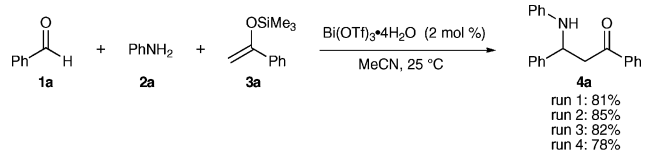
does not indicate unambiguously that a Brønsted acid is not involved in the process, because the pyridinium salt itself also mediates the reaction (1 equiv. of PhCHO **1a**, 1 equiv. of $PhNH_2$ **2a**, 1 equiv. of (1-phenylvinyloxy)trimethylsilane **3a**, 3 mol% of 2,6-di-*tert*-butylpyridinium triflate, 25 °C, 0.3 h, 80% of **4a**). However, replacing $Bi(OTf)_3{\cdot}4H_2O$ by HOTf as catalyst for the three-component model reaction showed that HOTf is indeed as effective as $Bi(OTf)_3{\cdot}4H_2O$ at catalysing the Mannich-type reaction (1 equiv. of PhCHO **1a**, 1 equiv. of $PhNH_2$ **2a**, 1 equiv. of (1-phenylvinyloxy)trimethylsilane **3a**, 3 mol% of HOTf, 25 °C, 0.3 h, 80% of **4a**). The HOTf-catalysed Mannich-type reaction on the preformed imine affords the same product in good yield (1 equiv. of *N*-benzylideneaniline **5**, 1 equiv. of (1-phenylvinyloxy)trimethylsilane **3a**, 1 equiv. H_2O, 3 mol% of HOTf, 25 °C, 0.1 h, 77% of **4a**) (compare with Table 6, entry 2).[21] Moreover, the competition between the Mannich-type and the Mukaiyama aldol reaction was studied using $Bi(OTf)_3{\cdot}4H_2O$ and HOTf with (*Z*)-(1-phenylprop-1-enyloxy)trimethylsilane **3b** as the nucleophile (Scheme 5). In both cases, only the Mannich-type reaction occurred without formation of the corresponding aldol. The β-amino ketone **4b** was obtained in both cases with the same chemical yield, the same diastereoselectivity (1 mol% $Bi(OTf)_3{\cdot}4H_2O$, 0.7 h, 82% of **4b**, dr = 51 : 49; 3 mol% HOTf, 0.6 h, 85% of **4b**, dr = 50 : 50), and the same chemoselectivity. This result, in addition to the previous one, indicates that, most probably, $Bi(OTf)_3{\cdot}4H_2O$ is hydrolysed under these conditions, affording triflic acid, which could be the real catalytic species. Since HOTf is very corrosive and difficult to handle, the practical use of $Bi(OTf)_3{\cdot}4H_2O$ makes our method particularly valuable.



Scheme 5 Competition studies for diastereoselective Mannich-type reaction catalysed by $Bi(OTf)_3{\cdot}4H_2O$ or HOTf.

Catalyst recycling

From an environmental point of view, it is desirable to minimize the amount of waste for each organic transformation. In this context, we recycled the catalyst solution for subsequent runs. We chose the reaction between benzaldehyde, aniline, and (1-phenylvinyloxy)trimethylsilane. As the corresponding β-aminoketone was insoluble in acetonitrile, it could be easily recovered by simple filtration. The catalyst solution was recycled for subsequent cycles. Up to four runs could be achieved without noticeable decrease in yield (Scheme 6).



Scheme 6 Recycling of the catalyst solution.

Conclusions

As an improvement over other catalyst systems, $Bi(OTf)_3{\cdot}4H_2O$ is a versatile catalyst for the Mannich-type reaction of a variety of silyl enolates with imines generated *in situ*. The reaction

affords up to 94% yields of β-amino carbonyl compounds in short reaction times, and using only 1–2 mol% of the catalyst. This method offers several advantages including mild reaction conditions, a highly catalytic process, and no by-products. The conditions are suitable for a variety of aldehydes, aromatic amines and silyl enolates. Also, the practical use of $Bi(OTf)_3{\cdot}4H_2O$ is highly valuable as a surrogate for HOTf since the latter is very corrosive and difficult to handle. Moreover, our protocol does not require prior isolation of the imine. The β-amino carbonyl compound is directly obtained, usually as a crystalline product, in a one-pot process. Because of its numerous benefits, this method for the one-pot synthesis of β-amino esters and ketones using bismuth triflate catalysis should find utility in the synthesis of biologically active compounds.

Experimental

All reactions were carried out in flame-dried test tubes cooled under an atmosphere of argon. Dichloromethane and acetonitrile were distilled from calcium hydride. Tetrahydrofuran and ether were distilled from sodium/benzophenone. Toluene was distilled from sodium. Benzaldehyde, cyclohexylcarboxaldehyde, *n*-butyraldehyde, and isobutyraldehyde were distilled before use. Other reagents and solvents were used as received. Flash column chromatography was performed using silica gel (230–400 mesh) under pressure. Analytical thin layer chromatography (TLC) was carried out using 250 μm commercial silica gel plates, and visualised by ultra-violet irradiation (254 nm) or by staining with aqueous potassium permanganate and developed with appropriate heating. Melting points were recorded on a Mel-Temp apparatus, and are uncorrected. Infra-red spectra were obtained on a FT-IR spectrometer and are reported in cm^{-1}. Mass spectra were obtained on a Waters instrument, by electron impact or electrospray ionisation techniques, at the Department of Chemistry, Université de Sherbrooke, Sherbrooke, Canada. ^1H NMR spectra were recorded at ambient temperature on Varian DPX-400 spectrometer at 400 MHz with tetramethylsilane (TMS) as the internal reference ($\delta_H = 0$ ppm); chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows: δ/ppm (number of protons, multiplicity, coupling constant J/Hz). ^{13}C NMR spectra were recorded at ambient temperature on the same spectrometer at 100 MHz, with the central peak of $CHCl_3$ as the internal reference ($\delta_C = 77.0$ ppm). For ^{19}F NMR, $CFCl_3$ was used as the internal standard ($\delta = 0$). DEPT and two-dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used, where appropriate, to aid the assignments of signals in the ^1H and ^{13}C NMR spectra. Where a compound was characterised as an inseparable mixture of diastereoisomers, the NMR data for the major (maj) and minor (min) isomers have been reported as far as was discernable from the spectrum of the mixture.

General procedure for the bismuth triflate-catalysed three-component reaction with silyl enol ethers

Under an inert atmosphere of argon, the silyl enol ether (2.4 mmol) in 2 mL of dry acetonitrile was added in one portion to a solution of $Bi(OTf)_3{\cdot}4H_2O$ (1 mol%), the aldehyde (2 mmol), and the amine (2 mmol) in 2 mL of dry acetonitrile. The mixture was stirred at room temperature until the reaction was complete as indicated by TLC. The reaction was quenched with water (8 mL) and extracted with diethyl ether (3 × 40 mL). The organic phase was washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated under vacuum (rotary evaporator). When the crude product was a solid, it was triturated with hexane (20 mL) and filtered; otherwise, it was purified by column chromatography (eluent hexane–ethyl acetate). The spectral data for known compounds match with those reported in the literature.[17a,22]

General procedure for the bismuth triflate-catalysed three-component reaction with silyl ketene acetals

Under an inert atmosphere of argon, the silyl ketene acetal (1.2 mmol) in 1 mL of dry THF was added dropwise to a solution of $Bi(OTf)_3{\cdot}4H_2O$ (2 mol%), the aldehyde (1 mmol), and the amine (1 mmol) in 1 mL of dry THF at −78 °C. The mixture was stirred at −78 °C for 0.15 h and then allowed to reach room temperature. The mixture was stirred until the reaction was completed as indicated by TLC. The reaction was quenched with water (4 mL) and extracted with diethyl ether (3 × 20 mL). The organic phase was washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated under vacuum (rotary evaporator). When the crude product was a solid, it was triturated with hexane (10 mL) and filtered; otherwise, it was purified by column chromatography (eluent hexane–ethyl acetate). The spectral data for known compounds match with those reported in the literature.[3g,17b,22c,23]

2,2-Dimethyl-1,3-diphenyl-3-(*N*-phenylamino)propan-1-one. (Table 3, entry 3): Yield 45%; white solid; mp 117–118 °C; R_f 0.54 (hexane–ethyl acetate = 4 : 1); IR (KBr): ν = 3389, 1656; ^1H NMR ($CDCl_3$): δ = 7.20–7.40 (10H, m), 7.01 (2H, m), 6.59 (1H, tt, J = 7.3, 1.0 Hz), 6.43 (2H, m), 4.76 (1H, s), 4.67 (1H, s), 1.32 (3H, s), 1.23 (3H, s); ^{13}C NMR ($CDCl_3$): δ = 210.7, 146.2, 140.1, 138.6, 130.4, 129.2, 129.0, 128.3, 127.8, 126.9, 118.1, 114.1, 63.7, 52.3, 25.5, 20.5; HRMS: Calc. for $C_{23}H_{23}NO$ (M^+) 329.1780, found 329.1783.

3-(4-Chlorophenyl)-2-methyl-1-phenyl-3-(*N*-phenylamino)propan-1-one. (Table 3, entry 8): Yield 83%; major/minor = 66 : 34; white solid; mp 146–149 °C; R_f 0.44 (hexane–ethyl acetate = 4 : 1); IR (KBr): ν = 3417, 3394, 1670; ^1H NMR ($CDCl_3$): δ = 7.92 (maj, 2H, m), 7.75 (min, 2H, m), 7.18–7.59 (7H, m), 7.02–7.09 (2H, m), 6.64 (1H, t, J = 7.3 Hz), 6.51 (min, 2H, d, J = 7.8 Hz), 6.44 (maj, 2H, m), 4.71 (maj, 1H, d, J = 5.3 Hz), 4.69 (min, 1H, d, J = 7.4 Hz), 4.58–4.92 (1H, br s), 3.90–3.99 (1H, m), 1.31 (min, 3H, d, J = 7.0 Hz), 1.22 (maj, 3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 203.9, 202.6, 147.0, 146.8, 140.5, 140.3, 137.1, 136.3, 133.7, 133.6, 133.2, 129.4, 129.2, 129.08, 129.05, 129.0, 128.9, 128.51, 128.47, 128.4, 118.2, 118.0, 114.1, 113.8, 60.9, 59.0, 46.9, 46.4, 16.9, 11.9; HRMS: Calc. for $C_{22}H_{20}ClNO$ (M^+) 349.1233, found 349.1241.

3-(4-Acetylphenyl)-1-phenyl-3-(*N*-phenylamino)propan-1-one. (Table 3, entry 13): Yield 92%; yellowish solid; mp 168–169 °C; R_f 0.18 (hexane–ethyl acetate = 4 : 1); IR (KBr): ν = 3404, 1672; ^1H NMR ($CDCl_3$): δ = 7.89–7.93 (4H, m), 7.54–7.60 (3H, m), 7.45 (2H, t, J = 7.7 Hz), 7.07–7.11 (2H, m), 6.68 (1H, t, J = 7.3 Hz), 6.52–6.55 (2H, m), 5.06 (1H, dd, J = 7.2, 5.4 Hz), 4.64 (1H, br s),

3.52 (1H, dd, $J = 16.5$, 5.4 Hz), 3.46 (1H, dd, $J = 16.5$, 7.2 Hz), 2.57 (3H, s); ^{13}C NMR ($CDCl_3$): $\delta = 198.0$, 197.9, 148.8, 146.9, 136.7, 136.6, 133.9, 129.4, 129.2, 129.0, 128.4, 126.9, 118.4, 114.1, 54.7, 46.1, 26.9; HRMS: Calc. for $C_{23}H_{21}NO_2$ (M^+) 343.1572, found 343.1576.

1-Phenyl-3-(*N*-phenylamino)-3-(3-pyridyl)propan-1-one. (Table 3, entry 18): Yield 49%; yellowish solid; mp 138–139 °C; R_f 0.16 (hexane–ethyl acetate = 1 : 1); IR (KBr): $\nu = 3255$, 1680; ^{1}H NMR ($CDCl_3$): $\delta = 8.70$ (1H, d, $J = 2.1$ Hz), 8.46 (1H, dd, $J = 4.7$, 1.6 Hz), 7.86–7.89 (2H, m), 7.75 (1H, dt, $J = 7.8$, 1.8 Hz), 7.55 (1H, tt, $J = 7.4$, 1.5 Hz), 7.40–7.45 (2H, m), 7.20 (1H, ddd, $J = 7.9$, 4.8, 0.5 Hz), 7.05–7.10 (2H, m), 6.67 (1H, tt, $J = 7.3$, 1.0 Hz), 6.53 (2H, dd, $J = 8.6$, 1.0 Hz), 5.05 (1H, dd, $J = 6.1$, 6.1 Hz), 4.63 (1H, br s), 3.43–3.52 (2H, m); ^{13}C NMR ($CDCl_3$): $\delta = 197.8$, 149.0, 148.8, 146.7, 138.5, 136.6, 134.5, 133.9, 129.5, 129.0, 128.4, 123.9, 118.5, 114.1, 52.6, 45.9; HRMS: Calc. for $C_{20}H_{18}N_2O$ (M^+) 302.1419, found 302.1425.

4,4-Dimethyl-1-phenyl-3-(*N*-phenylamino)pentan-1-one. (Table 3, entry 21): Yield 54%; yellowish solid; mp 102–103 °C; R_f 0.57 (hexane–ethyl acetate = 4 : 1); IR (KBr): $\nu = 3386$, 1663; ^{1}H NMR ($CDCl_3$): $\delta = 7.85$–7.87 (2H, m), 7.53 (1H, tt, $J = 7.3$, 1.5 Hz), 7.40–7.44 (2H, m), 7.05–7.09 (2H, m), 6.56–6.68 (3H, m), 4.02 (1H, dd, $J = 7.1$, 5.1 Hz), 3.30 (1H, dd, $J = 16.0$, 5.1 Hz), 2.97 (1H, dd, $J = 16.0$, 7.1 Hz), 1.01 (9H, s); ^{13}C NMR ($CDCl_3$): $\delta = 199.8$, 148.3, 137.5, 133.2, 129.4, 128.8, 128.3, 117.3, 113.4, 58.6, 40.9, 36.1, 26.9; HRMS: Calc. for $C_{19}H_{23}NO$ (M^+) 281.1780, found 281.1783.

1-Phenyl-3-(*N*-phenylamino)hexan-1-one. (Table 3, entry 22): Yield 61%; yellowish oil; R_f 0.56 (hexane–ethyl acetate = 4 : 1); IR (film): $\nu = 3395$, 1679; ^{1}H NMR ($CDCl_3$): $\delta = 7.90$–7.94 (2H, m), 7.55 (1H, tt, $J = 7.4$, 1.5 Hz), 7.42–7.46 (2H, m), 7.13–7.18 (2H, m), 6.66–6.70 (1H, m), 6.63 (2H, dd, $J = 8.6$, 1.0 Hz), 4.05 (1H, ddt, $J = 7.0$, 7.0, 4.8 Hz), 3.76 (1H, br s), 3.27 (1H, dd, $J = 16.5$, 4.8 Hz), 3.16 (1H, dd, $J = 16.5$, 7.0 Hz), 1.35–1.72 (4H, m), 0.92 (3H, t, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 199.7$, 147.4, 137.4, 133.4, 129.6, 128.8, 128.3, 117.6, 113.6, 50.1, 43.0, 37.8, 19.8, 14.2; HRMS: Calc. for $C_{18}H_{21}NO$ (M^+) 267.1623, found 267.1630.

4-Methyl-1-phenyl-3-(*N*-phenylamino)pentan-1-one. (Table 3, entry 23): Yield 51%; yellowish solid; mp 74–76 °C; R_f 0.68 (hexane–ethyl acetate = 4 : 1); IR (KBr): $\nu = 3392$, 3370, 1668; ^{1}H NMR ($CDCl_3$): $\delta = 7.90$–7.93 (2H, m), 7.55 (1H, tt, $J = 7.3$, 1.5 Hz), 7.43–7.46 (2H, m), 7.10–7.15 (2H, m), 6.65 (1H, tt, $J = 7.3$, 1.1 Hz), 6.58–6.61 (2H, m), 3.93 (1H, ddd, $J = 11.2$, 5.9, 5.9 Hz), 3.78 (1H, br s), 3.20 (1H, dd, $J = 16.4$, 5.9 Hz), 3.09 (1H, dd, 16.4, 5.9 Hz), 1.99–2.07 (1H, m), 1.03 (3H, d, $J = 6.8$ Hz), 0.96 (3H, d, 6.8 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 199.8$, 147.8, 137.4, 133.4, 129.6, 128.9, 128.3, 117.4, 113.6, 55.5, 40.4, 31.9, 19.3, 18.8; HRMS: Calc. for $C_{18}H_{21}NO$ (M^+) 267.1623, found 267.1627.

1,4-Diphenyl-3-(*N*-phenylamino)pentan-1-one. (Table 3, entry 24): Yield 70%; major/minor = 85 : 15; yellowish solid; mp 110–112 °C; R_f 0.69 (hexane–ethyl acetate = 4 : 1); IR (KBr): $\nu = 3409$, 1677; ^{1}H NMR ($CDCl_3$): $\delta = 7.77$–7.80 (min, 2H, m), 7.69–7.72 (maj, 2H, m), 7.47–7.55 (1H, m), 7.12–7.42 (9H, m), 6.61–6.69 (3H, m), 4.28–4.33 (min, 1H, m), 4.12–4.18 (maj, 1H, m), 4.00 (maj, 1H, br s), 3.60 (min, 1H, br s), 3.22–3.27 (min, 1H, m), 3.19 (maj, 1H, dq, $J = 14.4$, 7.2 Hz), 3.11 (min, 1H, dd, $J = 16.5$, 6.5 Hz), 3.10 (maj, 1H, dd, $J = 16.8$, 4.5 Hz), 2.96 (min, 1H, dd, $J = 16.5$, 6.0 Hz), 2.81 (maj, 1H, dd, $J = 16.8$, 6.2 Hz), 1.41 (maj, 3H, d, $J = 7.2$ Hz), 1.37 (min, 3H, d, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 199.9$, 199.5, 147.8, 147.4, 143.9, 142.7, 137.4, 137.0, 133.4, 133.2, 129.6, 128.84, 128.80, 128.7, 128.6, 128.3, 128.2, 128.1, 127.1, 127.0, 117.7, 117.6, 113.80, 113.77, 56.2, 54.7, 43.9, 42.5, 41.1, 40.2, 19.0, 17.0; HRMS: Cald for $C_{23}H_{23}NO$ (M^+) 329.1780, found 329.1783.

Methyl 1-(phenyl-*N*-phenylaminomethyl)cyclohexanecarboxylate. (Table 4, entry 7): Yield 59%; white crystals; mp 98–99 °C; R_f 0.70 (hexane–ethyl acetate = 4 : 1); IR (KBr): $\nu = 3378$, 1721; ^{1}H NMR ($CDCl_3$): $\delta = 7.19$–7.29 (5H, m), 7.02 (2H, dd, $J = 8.7$, 7.3 Hz), 6.57 (1H, tt, $J = 7.2$, 1.1 Hz), 6.45 (2H, dd, $J = 8.7$, 1.1 Hz), 5.01 (1H, br s), 4.32 (1H, s), 3.63 (3H, s), 2.40 (1H, d, $J = 14.1$ Hz), 2.01 (1H, dd, $J = 12.9$, 2.9 Hz), 1.56–1.68 (3H, m), 1.04–1.44 (5H, m); ^{13}C NMR ($CDCl_3$): $\delta = 175.8$, 147.2, 139.6, 129.2, 128.5, 128.1, 127.7, 117.2, 113.3, 65.3, 52.2, 52.0, 33.8, 30.6, 25.7, 23.8, 23.3; HRMS: Calc. for $C_{21}H_{25}NO_2$ (M^+) 323.1885, found 323.1888.

Methyl 2,2-dimethyl-3-(*N*-phenylamino)-3-*o*-tolylpropanoate. (Table 4, entry 14): Yield 34%; yellowish solid; mp 129–130 °C; R_f 0.70 (hexane–ethyl acetate = 4 : 1); IR (KBr): $\nu = 3371$, 1714; ^{1}H NMR ($CDCl_3$): $\delta = 7.19$–7.22 (1H, m), 7.09–7.15 (3H, m), 7.01–7.07 (2H, m), 6.56–6.61 (1H, m), 6.43–6.46 (2H, m), 4.88 (1H, d, $J = 7.1$ Hz), 4.83 (1H, d, $J = 7.1$ Hz), 3.67 (3H, s), 2.54 (3H, s), 1.29 (3H, s), 1.20 (3H, s); ^{13}C NMR ($CDCl_3$): $\delta = 177.5$, 147.4, 138.1, 136.8, 130.8, 129.4, 127.4, 126.2, 117.5, 113.4, 59.4, 52.4, 48.5, 25.0, 20.67, 20.65; HRMS: Calc. for $C_{19}H_{23}NO_2$ (M^+) 297.1729, found 297.1735.

Methyl 2,2-dimethyl-3-(*N*-phenylamino)hexanoate. (Table 4, entry 18): Yield 89%; colorless oil; R_f 0.78 (hexane–ethyl acetate = 4 : 1); IR (film): $\nu = 3397$, 1725; ^{1}H NMR ($CDCl_3$): $\delta = 7.10$–7.14 (2H, m), 6.59–6.63 (3H, m), 3.56–3.66 (2H, m), 3.61 (3H, s), 1.46–1.50 (2H, m), 1.24–1.30 (2H, m), 1.22 (3H, s), 1.19 (3H, s), 0.86 (3H, t, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 177.9$, 149.5, 129.5, 116.8, 112.8, 59.5, 52.0, 48.2, 35.6, 23.1, 22.0, 20.5, 14.4; HRMS: Calc. for $C_{15}H_{23}NO_2$ (M^+) 249.1729, found 249.1733.

3-(*N*-2-Hydroxyphenylamino)-1,3-diphenylpropan-1-one. (Table 5, entry 5): Yield 78%; yellowish solid; mp 112–113 °C; R_f 0.27 (hexane–ethyl acetate = 4 : 1); IR (KBr): $\nu = 3550$, 3392, 1683; ^{1}H NMR ($CDCl_3$): $\delta = 7.92$–8.00 (2H, m), 7.55 (1H, tt, $J = 7.4$, 1.5 Hz), 7.41–7.45 (2H, m), 7.27–7.36 (4H, m), 7.22 (1H, tt, $J = 7.1$, 1.8 Hz), 6.77 (1H, dd, $J = 7.6$, 1.4 Hz), 6.68 (1H, ddd, $J = 7.6$, 7.6, 1.4 Hz), 6.61 (1H, ddd, $J = 7.6$, 7.6, 1.4 Hz), 6.46 (1H, dd, $J = 7.6$, 1.4 Hz), 6.29 (1H, br s), 4.87 (1H, dd, $J = 8.6$, 4.3 Hz), 4.10 (1H, br s), 3.54 (1H, dd, $J = 17.1$, 8.6 Hz), 3.42 (1H, dd, $J = 17.1$, 4.3 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 199.0$, 146.9, 142.9, 136.8, 134.8, 133.8, 129.0, 128.9, 128.5, 127.7, 126.8, 120.9, 120.8, 117.8, 115.0, 56.1, 46.4; HRMS: Calc. for $C_{21}H_{19}NO_2$ (M^+) 317.1416, found 317.1418.

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