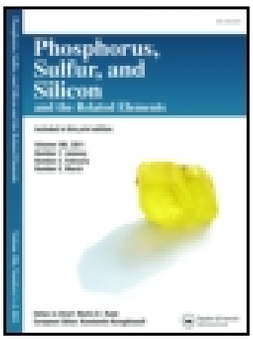

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Phosphorus, Sulfur, and Silicon and the Related Elements

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$TiCl_2(OTf)$-SiO_2: A solid stable lewis acid catalyst for Michael addition of α-Aminophosphonates, Amines, Indoles and Pyrrole

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ABSTRACT

$TiCl_2(OTf)$-SiO_2 is simply prepared by immobilization of $TiCl_3(OTf)$ on silica gel surface and introduced as a non-hygroscopic Lewis acid catalyst for C-N and C-C bond formation *via* Michael addition reaction. A variety of structurally diverse nitrogen nucleophiles including α-aminophosphonates, aliphatic and aromatic amines and imidazole were evaluated as Michael donors. Friedel–Crafts alkylation of indoles and pyrrole was also investigated through Michael addition reaction in the presence of $TiCl_2(OTf)$-SiO_2 as a catalyst. The reactions were conducted at room temperature or 60 °C under solvent-free conditions and the desired Michael adducts were obtained in high to excellent yields.

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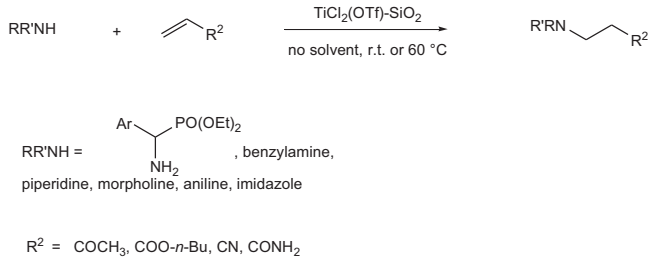
Michael reaction; titanium(IV) triflate; α-aminophosphonates; heterogeneous catalysts; electron deficient olefins

GRAPHICAL ABSTRACT



Introduction

The development of synthetic approaches to β-amino carbonyl compounds has received great attention because of their numerous synthetic applications as versatile intermediates for the synthesis of a variety of complex natural products, antibiotics, chiral auxiliaries and useful building blocks in fine chemicals and pharmaceuticals.[1–4] The Mannich-type reaction is a conventional method for the preparation of these compounds.[5] On the other hand, due to the atom economy and simplicity, the aza-Michael addition reaction provides a special route for the synthesis of β-amino carbonyl compounds.[6,7] Traditionally, aza-Michael addition reactions proceed under strongly acidic[8] or basic conditions,[9] which often lead to undesirable side reactions and are incompatible with green chemistry. In recent decades, various materials including transition metal based catalysts,[10–19] organocatalysts,[20–26] supported reagents,[27–33] ionic liquids,[34–40] metal nitrates,[41–43] and solid heterogeneous materials[44–50] have been developed to promote the aza-Michael addition reaction. This reaction has also been conducted in different media such as water,[51–61] with or without promoters, polyethylene glycol[62] and glycerol[63].

Despite some success achieved, many of the reports suffer from at least one of the following disadvantages: the use of expensive catalysts, stoichiometric amounts of the promoters, using hazardous organic solvents and extended reaction times. In addition, some reactions are limited in substrate scope to aliphatic amines and exhibit poor compatibility with various substrate functional groups.

Indole derivatives occur in many biologically active compounds and natural products.[64–66] Pyrroles are important building blocks in various natural products such as chlorophyll, porphyrin, hemoglobin, vitamin B_{12}, indigo and bile pigment.[67] A useful method for C-alkylation of indoles and pyrroles is the Friedel-Crafts type conjugate addition of these compounds to electron deficient olefins. However, indoles and pyrroles are both acid sensitive compounds and the acid-catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions.

Many useful methods have been reported in the literature to promote C-alkylation of indoles and pyrroles through Michael addition reaction.[68–85] Among them, the use of $CeCl_3.7H_2O$-NaI,[71] $Bi(OTf)_3$,[73,74] iodine,[77] $[Al(DS)_3]$ 3 H_2O,[78]

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and ionic liquid[83] can be mentioned. Although these methods are useful, yet, there is a room for a more practical method.

Carbon-phosphorus bonds are present in many organic compounds and natural products.[86] Among organophosphorus compounds, α-aminophosphonic acid derivatives have attracted much attention and their preparation, reactivity, as well as biological and medicinal applicability has been investigated.[87–95] To the best of our knowledge, functionalization of α-aminophosphonates through Michael addition reaction and C-N bond formation has not yet been reported in the literature.

Titanium tetrachloride, $TiCl_4$, is a highly aggressive Lewis acid, which is extensively used in industrial processes as a catalyst. Handling of $TiCl_4$ needs serious precautions. Exposure of $TiCl_4$ to moisture creates clouds of HCl. In order to overcome these problems, $TiCl_3(OTf)$ is a good alternative for fuming $TiCl_4$,[96] which has been employed as an efficient catalyst in some organic transformations.[97–102]

Due to the ease of handling, easy workup procedure, minimization of waste generation as well as environmental and economical advantages, supported acid catalysts have received much attention in organic synthesis. On the other hand, silica gel has a high surface area and can be easily functionalized, which makes it a well-known support. We have also introduced $TiCl_2(OTf)$-SiO_2 as a moisture insensitive Lewis acid catalyst for silylation of -OH groups and cyanosilylation of aldehydes.[103]

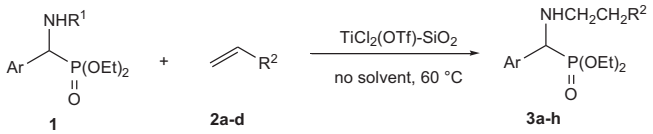
Herein, we describe another application of $TiCl_2(OTf)$-SiO_2 as an effective heterogeneous catalyst for conjugate addition of α-aminophosphonates, amines, imidazole, indoles and pyrrole to electron deficient olefins under neat conditions.

Results and discussion

$TiCl_3(OTf)$ has been reported as a catalyst for the conversion of epoxides to 1,3-dioxolanes,[97] aldol condensation of cycloalkanones with aromatic aldehydes[98] and conversion of acetophenones to 1,3,5-triarylbenzenes.[99] We have also reported some other applications of $TiCl_3(OTf)$ as a catalyst for esterification reactions,[100] protection of aldehydes as their acylals[101] and silylation of hydroxyl groups.[102] We also introduced $TiCl_2(OTf)$-SiO_2 as a moisture tolerant alternative to $TiCl_3(OTf)$, which was further applied as a catalyst for silylation of -OH groups and cyanosilylation of aldehydes.[103] In continuation to our studies, we investigated aza-Michael addition reaction in the presence of $TiCl_2(OTf)$-SiO_2 as a catalyst. Due to the biological and medicinal application of α-aminophosphonates, aza-Michael addition reaction of α-aminophosphonates was first investigated. For this purpose, in a typical experiment, diethyl phenyl (α-amino) methylphosphonate was treated with *n*-butyl acrylate in the presence of $TiCl_2(OTf)$-SiO_2 as a catalyst. We observed that using 1 mol % of the catalyst at 60 °C under solvent-free conditions, the reaction proceeded efficiently and after 48 h the desired *N*-substituted α-aminophosphonate was obtained in 84% isolated yield (Table 1, entry 2).

Next, the reaction was extended to different electron deficient olefins. We observed that only methyl vinyl ketone and *n*-butyl acrylate were reactive towards conjugate addition of diethyl phenyl (α-amino) methylphosphonate, though methyl vinyl ketone was much more reactive than *n*-butyl acrylate (Table 1, entry 1). This observation is consistent with the higher reactivity of α,β-unsaturated ketones towards conjugate addition. However, the reaction of other Michael acceptors such as acrylonitrile and acrylamide was not successful.

Table 1. Aza-Michael addition of α-aminophosphonates[a].



2a (R^2 = $COCH_3$), **2b** (R^2 = COO-*n*-Bu)
2c (R^2 = CN), **2d** (R^2 = $CONH_2$)

Entry	Ar	R^1	2	Product	Time	yield %[b]
1	Ph	H	2a	**3a**	5 min	86
2	Ph	H	2b	**3b**	48 h	84
3	*p*-CH_3-C_6H_4-	H	2a	**3c**	5 min	87
4	*p*-CH_3-C_6H_4-	H	2b	**3d**	40 h	85
5	*p*-Cl-C_6H_4-	H	2a	**3e**	5 min	90
6	*p*-Cl-C_6H_4-	H	2b	**3f**	55 h	89
7	2-Naphthyl	H	2a	**3g**	10 min	84
8	2-Naphthyl	H	2b	**3h**	55 h	87

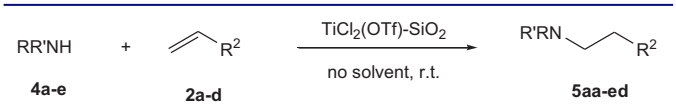
[a]The molar ratio of α-aminophosphonate: Michael acceptor: catalyst was 1: 1.1: 0.01. The products have been fully characterized based on their spectral data.
[b]Yield of isolated product.

Next, aza-Michael reaction of structurally different α-aminophosphonates with electron deficient olefins was investigated and similar results were obtained (Table 1, entries 3–8). In addition, secondary α-aminophosphonates were inert under this reaction conditions.

Then, the generality of the method was explored through the reaction of different amines with various Michael acceptors in the presence of $TiCl_2(OTf)$-SiO_2 (1 mol %) under solvent-free conditions. Herein, the reactions were conducted at room temperature unless otherwise stated. First, Michael reaction of benzyl amine to methyl vinyl ketone was investigated. The reaction resulted in a mixture of mono and disubstituted products. Attempts to obtain the monosubstituted compound as the major product even using an excess of benzyl amine remained unsuccessful. On the other hand, the reaction of benzyl amine with weaker Michael acceptors such as *n*-butyl acrylate and acrylonitrile provided only the monosubstituted product in high yields (Table 2, entries 1,2). Aza-Michael addition reaction of piperidine and morpholine to *n*-butyl acrylate and acrylonitrile also proceeded with good yields (Table 2, entries 3–5).

Due to the weaker nucleophilicity of aniline, conjugate addition of aniline to electron deficient olefines at room temperature was a rather difficult task. Therefore, Michal addition reaction of aniline was conducted at higher temperature. The reaction with Michael acceptors such as methyl vinyl ketone, *n*-butyl acrylate and acrylonitrile was performed at 60 °C in high yields (Table 2, entries 6–8). The reaction of imidazole with the same Michael acceptors was performed at room temperature (Table 2, entries 9–11). However, conjugate addition of imidazole to acryl amide was accomplished at 60 °C (Table 2, entry 12).

Table 2. Amine and Michael acceptor scope[a].



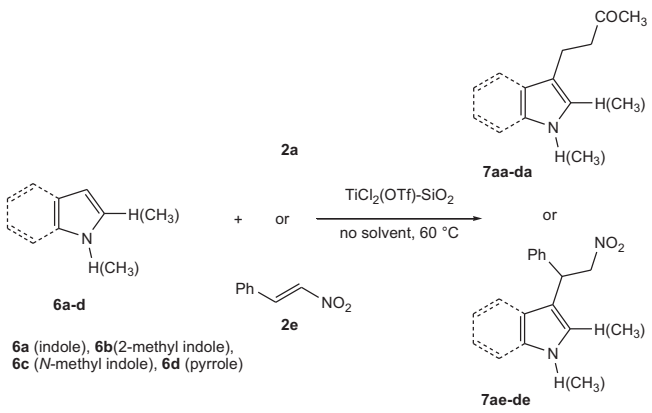
4a (RR'NH = $PhCH_2NH_2$), **4b**(RR'NH = piperidine), **4c** (RR'NH= morpholine), **4d** (RR'NH = $PhNH_2$), **4e** (RR'NH = imidazole)

Entry	RR'NH	2	Product	Time	Yield %[b]
1	4a	2b	**5ab**	10 min	92
2	4a	2c	**5ac**	10 min	88
3	4b	2b	**5bb**	10 min	89
4	4c	2b	**5cb**	10 min	90
5	4c	2c	**5cc**	10 min	80
6	4d	2a	**5da**	10 min	87[c]
7	4d	2b	**5db**	5 h	95[c]
8	4d	2c	**5dc**	12 h	84[c]
9	4e	2a	**5ea**	1 h	85
10	4e	2b	**5eb**	1.5 h	84
11	4e	2c	**5ec**	1.5 h	87
12	4e	2d	**5ed**	2 h	89[c]

[a] All products were identified by comparison of their spectral data with those of known samples.[20,22,25,26,47,48] The molar ratio of nucleophile: Michael acceptor: catalyst was 1: 1.1: 0.01. [b] Isolated yield of the product. [c] The reaction was performed at 60 °C.

Indoles and pyrroles are important building blocks in many biologically active compounds and natural products. Both are acid sensitive structure units. Therefore, introducing mild reaction procedure for Michael addition reaction of these compounds is advantageous. In this regard, conjugate addition of indoles and pyrrole in the presence of $TiCl_2(OTf)$-SiO_2 was investigated. Using $TiCl_2(OTf)$-SiO_2 (1 mol %), indole, 2-methylindole and *N*-methylindole were treated with methyl vinyl ketone under neat reaction conditions at 60 °C. The corresponding 3-alkylated indole derivatives were obtained in high yields after appropriate reaction times (Table 3, entries 1–3). However, due to the higher reactivity of pyrrole, preparation of monoalkylated product upon treatment of pyrrole with methyl vinyl ketone was not successful. In addition, Michael addition reaction of indoles and pyrrole to β-nitrostyrene was satisfactory and provided the corresponding products in high to excellent yields (Table 3, entries 4–7).

Table 3. Michael addition of indoles and pyrrole[a].



6a (indole), **6b**(2-methyl indole), **6c** (*N*-methyl indole), **6d** (pyrrole)

Entry	Donor	Acceptor	Product	Time	yield %[b]
1	6a	2a	**7aa**	10 min	84
2	6b	2a	**7ba**	5 min	87
3	6c	2a	**7ca**	10 min	85
4	6a	2e	**7ae**	45 min	82
5	6b	2e	**7be**	15 min	85
6	6c	2e	**7ce**	30 min	87
7	6d	2e	**7de**	30 min	85

[a] All products were identified by comparison of their spectral data with those of known samples.[12,69,77,81] The molar ratio of nucleophile: Michael acceptor: catalyst was 1: 1.5: 0.01. [b] Isolated yield of the product.

In order to show the merit of $TiCl_2(OTf)$-SiO_2 we compared the catalytic activity of $TiCl_2(OTf)$-SiO_2 with that of some other promoters used for 1,4-conjugate addition of aniline, imidazole and 2-methylindole to electron deficient olefins (Table 4). As the results in Table 4 show, $TiCl_2(OTf)$-SiO_2 is an efficient catalyst for a broad range of substrates, which provides the corresponding Michael addition product in high yields at a reasonable time.

Recyclability of the catalyst was also investigated upon the reaction of imidazole with *n*-butyl acrylate. After completion of the reaction, the catalyst was simply separated by addition of ethyl acetate to the reaction mixture and filtration. The recovered catalyst was dried in oven and reused for a similar reaction. For the first run, either the reaction time or the conversion yield was unchanged. However, for further runs, the reaction time was increased and after four consecutive runs, the catalytic activity was considerably decreased (Table S 1, Supplemental Materials).

Due to the Lewis acidic nature of $TiCl_2(OTf)$-SiO_2, the possible mechanism of the reaction might be the activation of conjugated β carbon atom towards nucleophiles through a resonance form which accommodates positive charge on C_β. Then, nitrogen or carbon nucleophile reacts with Michael acceptor at C_β and enol equivalent intermediate is obtained which simultaneously releases the catalyst and tautomerizes to the keto-form product (Scheme 1).

Conclusions

In conclusion, in this study we have introduced another application of solid $TiCl_2(OTf)$-SiO_2 as a new heterogeneous and recyclable catalyst for aza-Michael addition reaction. The generality of the catalyst for C–C and C–N bond formation reactions through 1,4-conjugate addition of structurally diverse nitrogen nucleophiles to electron deficient C-C double bonds has been shown. By this method, the reactions proceeded in short reaction times and the desired Michael adducts were obtained in high to excellent yields. Herein, for the first time, we have reported *N*-derivatization of α-aminophosphonate *via* Michael addition reaction. The use of solid heterogeneous easy handling catalyst and its tolerance towards moisture combined with an easy work-up procedure are the strong points of the presented catalytic protocol for C–C and C–N bond formation *via* Michael addition reactions.

Experimental section

Chemicals were either prepared in our laboratories or were purchased from Fluka and Merck Chemical Companies. The purity determination of the products was accomplished by GC on a Shimadzu model GC-14A instrument or by TLC on silica gel polygram SIL G/UV 254 plates. The IR spectra were recorded with a Perkin Elmer 781 spectrophotometer.

Table 4. Comparison data.

Entry	Catalyst[ref]	Molar ratio of donor: acceptor: cat.	Condition, Time, Yield[a]
	imidazole + n-butyl acrylate		
1	$Y(NO_3)_3 \cdot 6\,H_2O$[43]	1: 1: 0.1	r.t., 24 h, 87%
2	Polyaniline supported CuI[30]	1: 1.1: 0.025	r.t., 8 h, 92%
3	$TiCl_2(OTf)$-SiO_2	1: 1.1: 0.01	r.t., 1.5 h, 84%
	aniline + acrylonitrile		
4	Na_2CO_3(aq.)[61]	1: 1: 0.1 M	r.t., 20 h, 72%
5	CuCl, Ligand, KO*t*-Bu[19]	1: 1.5: 0.07	22 °C, 15 h, 94%
6	$TiCl_2(OTf)$-SiO_2	1: 1.1: 0.01	60 °C, 12 h, 84%
	2-methyl indole + methyl vinyl ketone		
7	$CeCl_3 \cdot 7\,H_2O$-NaI/ SiO_2[71]	1: 1: 0.3	r.t., 20 h, 98%
8	$InCl_3$[69]	1: 1: 0.1	r.t., 2.5 h, 92%
9	$TiCl_2(OTf)$-SiO_2	1: 1.1: 0.01	60 °C, 5 min, 87%

[a]Isolated yield of the product.

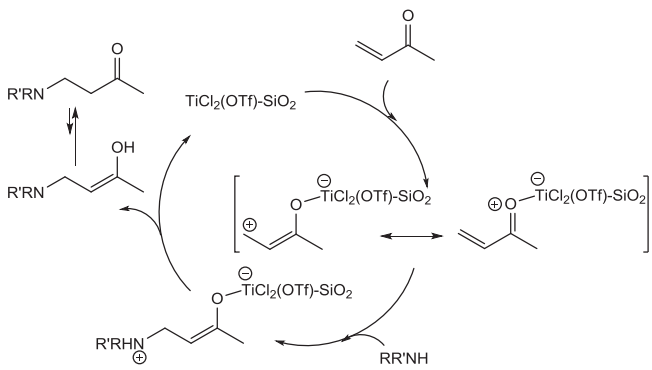
The NMR spectra were recorded with a Bruker Avance DPX 250 MHz spectrometer. Elemental analyses were obtained using ThermoFinnigan Flash EA 1112 Series. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra of the products 3 and 5 (Figures S 1 – S 11).

Preparation of the catalyst

$TiCl_3(OTf)$ was prepared according to the literature upon reaction of $TiCl_4$ with TfOH.[96] As we have reported previously,[103] $TiCl_2(OTf)$-SiO_2 was also obtained through treatment of $TiCl_3(OTf)$ with dry silica gel in dry CH_2Cl_2 under nitrogen atmosphere at room temperature.

General procedure for aza-Michael addition of α-amino phosphonates

To a mixture of α-amino phosphonate[104] **1** (1 mmol) and Michael acceptor **2** (1.1 mmol) $TiCl_2(OTf)$-SiO_2 (30 mg, 1 mol %) was added and the resulting mixture was stirred at 60 ºC for the appropriate time. Then, EtOAc (10 mL) was added to the reaction mixture and the reaction mixture was filtered off. The solvent was evaporated *in vacuo* and the resulting crude material was purified by chromatography on a short column of silica gel (EtOAc: petroleum ether, 1: 3) to give the desired *N*-substituted aminophosphonate **3a-h**.



Scheme 1. Suggested mechanism for $TiCl_2(OTf)$-SiO_2 catalyzed aza-Michael addition to methyl vinyl ketone.

Diethyl [(3-oxo-butylamino)-phenyl-methyl] phosphonate (3a)

Oil, 86% yield. ^{1}H NMR ($CDCl_3$, 250 MHz), δ = 1.14 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 2.12 (s, 3H), 2.55–2.65 (brs, 1H), 2.60 (t, J = 6.1 Hz, 2H), 2.69–2.76 (m, 2H), 3.74–4.08 (m, 4H), 4.01 (d, J = 19.5 Hz, 1H), 7.25–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ = 14.1, 16.1 (d, $^4J_{PC}$ = 5.7 Hz), 16.3 (d, $^4J_{PC}$ = 5.7 Hz), 30.0, 42.6 (d, $^3J_{PC}$ = 17.8 Hz), 61.1 (d, $^1J_{PC}$ = 153.4 Hz), 62.7 (d, $^3J_{PC}$ = 6.3 Hz), 62.8 (d, $^3J_{PC}$ = 6.6 Hz), 127.8 (d, $^4J_{PC}$ = 3.1 Hz), 128.1, 128.4 (d, $^3J_{PC}$ = 5.8 Hz), 135.6 (d, $^2J_{PC}$ = 4.0 Hz), 207.9; IR (neat): 3317, 2981, 2904, 1712 cm^{-1}; Anal. Calcd. for ($C_{15}H_{24}NPO_4$): C, 57.54; H, 7.66; N, 4.47; Found: C, 57.44; H, 7.69; N, 4.46%.

Butyl 3-[(diethoxy-phosphoryl)-phenyl-methyl]amino-propanoate (3b)

Oil, 84% yield.^{1}H NMR ($CDCl_3$, 250 MHz), δ = 0.89 (t, J = 7.3 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.28–1.34 (m, 2H), 1.53–1.58 (m, 2H), 2.29 (s, 1H), 2.43 (t, J = 6.6 Hz, 2H), 2.68–2.77 (m, 2H), 3.70–4.23 (m, 6H), 4.01 (d, J = 20.9 Hz, 1H), 7.22–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ = 13.6, 16.2 (d, $^4J_{PC}$ = 5.7 Hz), 16.3 (d, $^4J_{PC}$ = 5.7 Hz), 19.0, 30.5, 34.6, 43.4 (d, $^3J_{PC}$ = 17.8 Hz), 60.0 (d, $^1J_{PC}$ = 153.3 Hz), 62.7 (d, $^3J_{PC}$ = 6.9 Hz), 62.9 (d, $^3J_{PC}$ = 7.1 Hz), 64.3, 127.8 (d, $^4J_{PC}$ = 3.2 Hz), 128.4, 128.4 (d, $^3J_{PC}$ = 4.7 Hz), 135.6 (d, $^2J_{PC}$ = 4.3 Hz), 172.4; IR (neat): 3317, 2931, 2869, 1732 cm^{-1}; Anal. Calcd. for ($C_{18}H_{30}NPO_5$): C, 58.25; H, 8.08; N, 3.77; Found: C, 58.19; H, 8.05; N, 3.78%.

Diethyl [(3-oxo-butylamino)-p-tolyl-methyl] phosphonate (3c)

Oil, 87% yield. ^{1}H NMR ($CDCl_3$, 250 MHz), δ = 1.15 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 2.11 (s, 3H), 2.32 (s, 3H), 2.43 (s, 1H), 2.58 (t, J = 6.1 Hz, 2H), 2.67–2.75 (m, 2H), 3.80–4.26 (m, 4H), 3.97 (d, J = 19.9 Hz, 1H), 7.16 (AA′, 2H), 7.28 (BB′, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ = 16.2 (d, $^4J_{PC}$ = 5.6 Hz), 16.3 (d, $^4J_{PC}$ = 5.7 Hz), 21.0, 30.0, 42.6 (d, $^3J_{PC}$ = 17.8 Hz), 43.4, 60.8 (d, $^1J_{PC}$ = 154.1 Hz), 62.6, 62.7 (d, $^3J_{PC}$ = 6.9 Hz), 128.2 (d, $^3J_{PC}$ = 6.1 Hz), 129.0 (d, $^4J_{PC}$ = 2.4 Hz), 132.4 (d, $^2J_{PC}$

= 4.2 Hz), 137.4 (d, $^5J_{PC}$ = 3.3 Hz), 207.9; IR (neat): 3325, 2981, 2904, 1712 cm^{-1}; Anal. Calcd. for ($C_{16}H_{26}NPO_4$): C, 58.74; H, 7.94; N, 4.28; Found: C, 58.72; H, 7.95; N, 4.29%.

Butyl 3-[(diethoxy-phosphoryl)-p-tolyl-methyl]amino-propanoate (3d)

Oil, 85% yield. ^{1}H NMR ($CDCl_3$, 250 MHz), δ = 0.92 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.30–1.34 (m, 2H), 1.56–1.59 (m, 2H), 2.33 (s, 3H), 2.34 (s, 1H), 2.46 (t, J = 6.6 Hz, 2H), 2.60–2.81 (m, 2H), 3.8–4.21 (m, 6H), 4.00 (d, J = 19.8 Hz, 1H), 7.22 (AA′, 2H), 7.32 (BB′, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ = 13.6, 16.2 (d, $^4J_{PC}$ = 5.9 Hz), 16.4 (d, $^4J_{PC}$ = 5.7 Hz), 19.0, 21.1, 30.5, 34.5, 43.3 (d, $^3J_{PC}$ = 17.9 Hz), 60.6 (d, $^1J_{PC}$ = 153.9 Hz), 62.7 (d, $^3J_{PC}$ = 7.3 Hz), 62.8 (d, $^3J_{PC}$ = 8.4 Hz), 64.3, 128.3 (d, $^4J_{PC}$ = 6.1 Hz), 129.1 (d, $^3J_{PC}$ = 2.5 Hz), 132.4, 137.6, 172.5; IR (neat): 3317, 2931, 2869, 1732 cm^{-1}; Anal. Calcd. for ($C_{19}H_{32}NPO_5$): C, 59.25; H, 8.30; N, 3.63; Found: C, 59.19; H, 8.33; N, 3.62%.

Diethyl [(4-chloro-phenyl)-(3-oxo-butylamino)-methyl] phosphonate (3e)

Oil, 90% yield. ^{1}H NMR ($CDCl_3$, 250 MHz), δ = 1.19 (t, J = 7.0 Hz, 3H), 1.7 (t, J = 7.0 Hz, 3H), 2.13 (s, 3H), 2.32 (s, 1H), 2.60 (t, J = 4.5 Hz, 2H), 2.67–2.71 (m, 2H), 3.91–4.30 (m, 4H), 3.95 (d, J = 20.1 Hz, 1H), 7.30–7.40 (m, 4H). ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ = 16.2 (d, $^4J_{PC}$ = 6.5 Hz), 16.3 (d, $^4J_{PC}$ = 6.2 Hz), 30.1, 42.6 (d, $^3J_{PC}$ = 17.6 Hz), 43.4, 60.6 (d, $^1J_{PC}$ = 153.4 Hz), 62.8 (d, $^3J_{PC}$ = 7.2 Hz), 62.9 (d, $^3J_{PC}$ = 7.2 Hz), 128.5 (d, $^4J_{PC}$ = 2.6 Hz), 129.7 (d, $^3J_{PC}$ = 6.0 Hz), 133.6, 134.3 (d, $^2J_{PC}$ = 4.7 Hz), 207.9; IR (neat): 3325, 2970, 2858, 1712 cm^{-1}; Anal. Calcd. for ($C_{15}H_{23}NPO_4Cl$): C, 51.83; H, 6.61; N, 4.03; Found: C, 51.72; H, 6.64; N, 4.01%.

Butyl 3-[(4-chloro-phenyl)-(diethoxy-phosphoryl)-methyl]amino-propanoate (3f)

Oil, 89% yield. ^{1}H NMR ($CDCl_3$, 250 MHz), δ = 0.89 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.3 Hz, 3H), 1.24–1.37 (m, 3H), 1.56–1.62 (m, 2H), 2.42–2.52 (brs, 1H), 2.47 (t, J = 6.3 Hz, 2H), 2.73–2.78 (m, 2H), 3.99–4.09 (m, 6H), 4.05 (d, J = 18.1 Hz, 1H), 7.19–7.84 (m, 4H). ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ = 13.6, 16.2 (d, $^4J_{PC}$ = 6.2 Hz), 16.3 (d, $^4J_{PC}$ = 6.7 Hz), 19.1, 30.5, 34.4, 43.4 (d, $^3J_{PC}$ = 17.4 Hz), 60.4 (d, $^1J_{PC}$ = 153.4 Hz), 62.9 (d, $^3J_{PC}$ = 6.9 Hz), 63.0 (d, $^3J_{PC}$ = 9.8 Hz), 64.4, 128.6 (d, $^4J_{PC}$ = 2.6 Hz), 135.6 (d, $^2J_{PC}$ = 6.0 Hz), 172.4; IR (neat): 3317, 2931, 2869, 1728 cm^{-1}; Anal. Calcd. for ($C_{18}H_{29}NPO_5Cl$): C, 53.43; H, 7.16; N, 3.46; Found: C, 53.45; H, 7.19; N, 3.44%.

Diethyl [(naphthalen-2-yl)-(3-oxo-butylamino)-methyl] phosphonate (3g)

Oil, 84% yield. ^{1}H NMR ($CDCl_3$, 250 MHz), δ = 1.13 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 2.08 (s, 3H), 2.60 (t, J = 6.1 Hz, 2H), 2.55–2.65 (brs, 1H), 2.72–2.77 (m, 2H), 3.85–4.08 (m, 4H), 4.20 (d, J = 20.1 Hz, 1H), 7.43–7.50 (m, 2H), 7.56–7.60 (m, 1H), 7.80–7.85 (m, 4H). ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ = 16.2 (d, $^4J_{PC}$ = 5.7 Hz), 16.4 (d, $^4J_{PC}$ = 5.7 Hz), 30.0, 42.8 (d, $^3J_{PC}$ = 17.8 Hz), 61.4 (d, $^1J_{PC}$ = 153.3 Hz), 62.8 (d, $^3J_{PC}$ = 7.2 Hz), 62.9 (d, $^3J_{PC}$ = 7.4 Hz), 126.0, 126.1, 127.6, 126.7, 127.8, 127.9, 128.1, 128.2, 133.1, 133.2, 208.0; IR (neat): 3317, 2948, 2908, 1712 cm^{-1}; Anal. Calcd. for ($C_{19}H_{26}NPO_4$): C, 62.84; H, 7.16; N, 3.85; Found: C, 62.74; H, 7.19; N, 3.84%.

Butyl 3-[(diethoxy-phosphoryl)-(naphthalen-2-yl)-methyl]amino-propanoate (3h)

Oil, 87% yield. ^{1}H NMR ($CDCl_3$, 250 MHz), δ = 0.90 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H), 1.22–1.35 (m, 5H), 1.55–1.58 (m, 2H), 2.49 (t, J = 6.2 Hz, 2H), 2.42–2.54 (brs, 1H), 2.72–2.88 (m, 2H), 4.02–4.10 (m, 6H), 4.22 (d, J = 20.1 Hz, 1H), 7.45–7.53 (m, 2H), 7.60–7.65 (m, 1H), 7.82–7.90 (m, 4H). ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ = 13.6, 16.2 (d, $^4J_{PC}$ = 6.2 Hz), 16.4 (d, $^4J_{PC}$ = 6.7 Hz), 19.1, 30.5, 34.4, 43.4 (d, $^3J_{PC}$ = 17.4 Hz), 61.3 (d, $^1J_{PC}$ = 153.4 Hz), 62.9 (d, $^3J_{PC}$ = 6.9 Hz), 63.0 (d, $^3J_{PC}$ = 9.8 Hz), 64.4, 126.0, 126.1, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 133.1, 133.2, 172.4; IR (neat): 3317, 2927, 2869, 1732 cm^{-1}; Anal. Calcd. for ($C_{22}H_{32}NPO_5$): C, 62.73; H, 7.59; N, 3.32; Found: C, 62.67; H, 7.58; N, 3.31%.

General procedure for Michael addition of amines and imidazole

To a mixture of amine or imidazole **4a-e** (1 mmol) and Michael acceptor **2a-d** (1.1 mmol), $TiCl_2(OTf)$-SiO_2 (30 mg, 1 mol %) was added. The reaction mixture was stirred at room temperature or 60 °C. After completion of the reaction, EtOH (8 mL) was added to the reaction mixture and stirred for 15 min, followed by filtration and evaporation of the solvent. The resulting crude product was purified by crystallization or column chromatography to provide pure Michael adducts **5**.

General procedure for Michael addition of indoles and pyrrole

$TiCl_2(OTf)$-SiO_2 (30 mg, 1 mol %) was added to a mixture of indoles or pyrrole **6a-d** (1 mmol) and Michael acceptor **2a** or **2e** (1.5 mmol) at 60 °C. The mixture was stirred for appropriate time. After completion of the reaction CH_2Cl_2 (15 mL) was added to the reaction mixture and filtered. Evaporation of the filtrate gave the crude product, which was further purified by column chromatography, eluting with the appropriate solvents to furnish pure Michael adduct **7**.

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Author contribution statement

The data of this manuscript are taken from the corresponding author PhD Thesis, Shiraz University: 'New applications of trichlorotitanium(IV) trifluoromethanesulfonate, $TiCl_3(OTf)$ & preparation and application of silica bound Ti(IV), $TiCl_2(OTf)$-SiO_2 as a heterogeneous catalyst in organic transformations'. Professor Habib Firouzabadi: Thesis Director.

Supplementary material

Electronic Supplementary Information (ESI) available: copies of NMR spectra of the new compounds and characterization data of known compounds.

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